VPH Conference 2024

Data-Driven Simulation Technologies for Clinical Decision Making

4-6 September 2024, Stuttgart, Germany

GENERAL INFORMATION

BOOK OF ABSTRACTS

WE THANK OUR SONSORS AND PARTNERS

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WELCOME ADDRESS

WELCOME ADDRESS FROM THE LOCAL ORGANIZERS

A warm welcome to Stuttgart! It is our great pleasure to have you here in our vibrant and innovative city. Stuttgart is the capital of Baden-Württemberg and stands out as a mecca of the automobile industry. Further, it is one of the foremost high-tech centres for mobility, aerospace, engineering, IT, finance and green technology and, from September 4 -6. 2024, also the world capital for the Virtual Physiological Human. As local organizers, we are especially delighted to host the Virtual Physiological Human conference in a city renowned for its strong ties between science, industry, and culture.

Stuttgart offers not only a stunning backdrop of hills, forests, and vineyards but also the University of Stuttgart, which is one of Germany's leading technology-oriented universities. Founded in 1829, it is a place where innovation and interdisciplinarity are at the forefront. With a strong focus on engineering, natural sciences, biomechanics and information technology, it provides an ideal environment for cutting-edge research and the exchange of ideas among scholars from around the world.

The University of Stuttgart has strong roots in the Stuttgart region and is home to numerous non-university research institutions, including two Max Planck Institutes, one location of the German Aerospace Center (DLR), five Fraunhofer Institutes, and the German Literature Archive in Marbach (DLA). Stuttgart is also a global research hub for several major corporations, among them Bosch, Daimler, IBM and Porsche, and hosts a number of small and medium-sized enterprises that are often described as hidden champions in their fields, in particular in the field of biomedical engineering.

We hope you enjoy your time here in Stuttgart and we look forward to the inspiring discussions and fruitful collaborations that this conference will undoubtedly foster.

Enjoy the VPH2024 and your stay in Stuttgart!

Your local VPH2024 Organizing team


Oliver Röhrle


Tim Ricken


Filiz Ates


Nils Karajan


Christian Bleiler


Sina Schorndorfer

PROGRAM AT A GLANCE

Tuesday, Sep 03 Pre-conference Workshops	**Wednesday, Sep 04** Conference Day 1	**Thursday, Sep 05** Conference Day 2	**Friday, Sep 06** Conference Day 3
Registration 08:00am – 06:00pm	**Registration** 08:00am – 04:00pm	**Registration** 08:30am – 04:00pm	**Registration** 08:30am – 12:00pm
	Opening 08:45am – 09:00am		
AAD Part I: Avicenna Alliance Day 09:00am – 12:20am	**Keynote: Dirk Drasdo** 09:00am – 09:55am	**Keynote: Lynne Bilston** 09:00am – 09:55am	**Parallel Session 6** 09.00am – 10.30am
	Coffee Break 10:00am – 10:30am	**Coffee break** 10:00am – 10:30am	**Coffee Break** 10.30am – 11.00am
	Parallel Session 1 10:30am – 12:00pm	**Parallel Session 4** 10.30am – 12.00pm	**Keynote: Natalia Trayanova** 11.00 am – 11.55 am
Lunch Break for AAD delegates 12:20pm – 01:40pm	**Lunch Break** 12:00pm – 1:00pm	**Lunch Break, Meet the Mentor** 12.00pm – 01.00pm	**Closing & Award Ceremony** 12.00pm – 12.30pm
Parallel Workshops **AAD Part II: Avicenna Alliance Day** 01:40 pm – 05:00pm **Final "InSilico World" meeting** 01:00pm – 06:00pm **WS Modeling Software Platforms** 03:00pm – 04:30pm	**Parallel Session 2** 01:00pm – 02:30pm	**VPH Panel Discussion** 01.00pm – 02.30pm	**Parallel Workshops** **WS CompuCell3D** 01.30pm – 03.30pm **WS Public and Patient Involvement** 01.30pm – 04.00pm **ASME V&V 40 training** 01.30pm – 04.30pm **Tools for Implementing the Virtual Human Twin** 01.30pm –04.30pm
	Poster Session 1 02:30pm – 03:30pm	**Poster Session 2** 02.30pm – 03.30pm	
	Parallel Session 3 03:30pm – 05:00pm	**Parallel Session 5** 03.30pm – 05.00pm	
	Keynote: Alfons Hoekstra 05:05pm – 06:00pm	**VPH General Assembly** 05.00pm – 06.00pm	
Student Social Event 06:00pm – 10:00pm	**Welcome Reception** 06:00pm – 10:00pm	**Conference Dinner** 07.00pm – 11.00pm	

SCIENTIFIC COMMITTEE

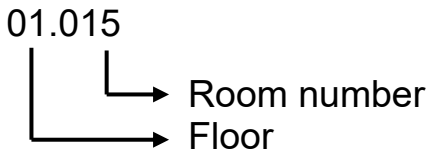
SCIENTIFIC COMMITTEE

The scientific board consists of members of the VPH-Board of Directors, session organizers and the local organizing committee.

David Ackland
Rossana Alessandrello
Filiz Ates
Okan Avci
Prasad Babarenda Gamage
Michèle Barbier
Roberto Benzo
Thor Besier
Annette Birkhold
Christian Bleiler
Silvia Budday
Claudio Capelli
Leo Cheng
Julie Choisne
Marilisa Cortesi
Uta Dahmen
Ahmet Erdemir
Philippe Favre
Emma Fortune
Martin Genet
Liesbet Geries
Leonid Goubergrits
Geoffrey Handsfield
Leif Rune Hellevick
Alfons Hoekstra
Ilse Jonkers
Nils Karajan
Thomas Klotz
Damien Lacroix
Jack Lee
Madeleine Lowery
Luiz Carlos Maia Ladera
Thierry Marchal
Justus Marquetand
David Nickerson
Poul Nielsen
David Nordsletten
Gernot Plank
Nicole Radde
Michael Resch
Tim Ricken
Alina Roitberg
Oliver Röhrle
Michael Sacks
Dominik Schillinger
Syn Schmitt
Reinhard Schneider
Hans-Michael Tautenhahn
Merryn Tawhai
Frans van de Vosse
Peter Varga
Irene Vignon-Clementel
Marco Viceconti
Can Yucesoy

GENERAL INFORMATION

Conference coordinator:
Sina Schorndorfer, conference@imsb.uni-stuttgart.de

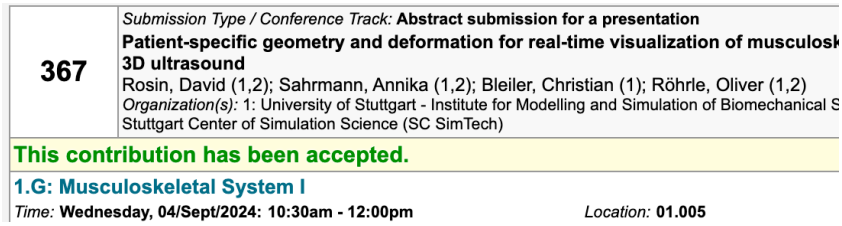
Check-In	All the attendees of the conference must check in at the conference desk at **the foyer of KII (Keplerstraße 17, 70174 Stuttgart)**. Check-In is possible during the scientific program.
Registration	At the conference desk, on-site registration is possible (Payment via PayPal, Stripe or invoice; in EUR). The registration fee includes: • Abstracts (digital) • Final program • Coffee breaks • Welcome reception • Certificate of attendance
Room numbering	
Name badge	Participants are kindly asked to wear their name badges at all times in order to access the conference venue and social events.
Oral presentations	**In preparation for an oral presentation** • Please check the time and lecture room of your presentation in the daily program and in the conference app as there might be some last-minute changes. • All presentations must be prepared and presented in English. • The duration of an oral presentation is 15 minutes maximum (including discussion), ideally 12 minutes presentation + 3 minutes discussion. All presenters are asked to respect this duration. • The chairs are requested to stop the presentation after the time has passed. • There is no template for the presentations, feel free to use your own. **Technical requirements** • Computers are provided. The use of them is recommended. • Please prepare your presentation as pptx or pdf in 16:9 landscape slide format • The computers are state-of-the-art Windows 10 (English) laptops with PowerPoint 2019 and Acrobat Reader. We also provide a presenter. • Films: Embedded video in power point for optimal compatibility (do not forget to embed your fonts and to send your video files separately, as back-up solution, see above).

Uploading your presentation to maximise presenting time:

- Please upload your presentation well in advance of your presentation slot by means of the provided link:
- https://bwsyncandshare.kit.edu/s/awbyyXJ3HMmz8rL, ideally by the day before your presentation. In case of any issues ask for help at the registration desk.
- File name for your uploaded presentation must be: *Format number.Letter_Presenter Last name_Presenter First name*

  Note, the "*Format number.letter"* information can be found in ConfTool under "Your submissions".

  For example, if conftool shows you the following:



  In this case your session is **1.G** (Musculoskeletal System I) and your filename would be: 1.G_Rosin_David.pptx (or .pdf if you have prepared a pdf document).

- After uploading the file, the presentation will then be automatically transferred to the respective computer in the session room. Please check in the break before of your session that the presentation is on the computer in your room.
- If you whish to check your uploaded file in advance of your presentation, you can go to your presentation room during any break, or to the registration desk.
- Should any technical issue arise, there will be in each room a trained staff that can help you further. You recognize the staff person by its yellow polo shirt with an orange smiley on the back.

Poster Presentations

- Size: up to A0 (portrait orientation), classic paper posters
- You must print your poster and bring it with you to the conference site. There is no possibility to print it on-site.
- There is no template for the poster. Feel free to use your own.
- Poster boards will be ready at the venue. We will provide appropriate tape such that you can fix your poster to the poster boards.
- Poster sessions are divided in two parts:
  - Poster session #1: Wednesday, Sep. 4th, 2:30-3:30pm
  - Poster session #2: Thursday, Sep. 5th, 2:30-3:30pm
- In ConfTool you can see whether you have been assigned to poster session #1 or #2.
- ConfTool provides you also with the information on where to mount your poster. There you find a name like Px:y, in which the "P" stands for "Poster", the x refers to the Poster session

number (1= Wednesday or 2=Thursday) and y being the posterboard number.
Example: P1:5 means you present your poster on Wednesday during Poster session 1, on Poster board no. 5.

- Procedure Poster session #1:
  - Posters can be mounted on Sep. 4th in the morning before the program starts. By doing so, you can expose your research to the delegates already during coffee and lunch break.
  - Please remove the posters directly after the poster session (We will need the space for the Welcome Reception).
- Procedure Poster session #2:
  - Posters should be mounted on Thursday, Sep. 5th in the morning before the program starts. By doing so, you can expose your research to the delegates already during coffee and lunch break.
  - Posters should be removed by Friday, Sep. 6th, noon.
- Posters not picked up in time will be collected and destroyed.
- We advise the presenters to be next to their posters not only during the scheduled poster sessions, but also during coffee breaks

Wifi Access

Eduroam network is available all across the campus. An account is required.

Additionally, free access to **uni-stuttgart-open WiFi** is possible.

By using this internet access, you agree with the User Regulations for Digital Information Processing and Communication Equipment (IaC) at the University of Stuttgart.

Conference App	VPH2024 is accompanied by a conference app (Whova) where you find all the necessary information, a schedule and latest changes and notifications. Get in touch with other participants after an easy login. Either use the QR code for the mobile version or check the desktop version via https://whova.com/portal/webapp/vph_202304/.
Coffee breaks	During the coffee breaks coffee, tea, water, soft drinks and snacks will be served.
Conference secretariat/ info point	If you need assistance or have any questions, please contact the conference secretariat at the info point in **the foyer of KII**. There you get information about the technical and social program of the conference as well as on a public transport, Wi-Fi and places of interest in Stuttgart.
Conference staff	Members of the conference staff are present at the conference. You recognize them by the yellow poloshirts with a simle on the back.
Photo policy	Please note that there will be a photographer and a film team during the conference. Please make sure, that mobile phones must be switched off or set to silent mode while attending program slots.
Trains	The nearest train station is "Stuttgart main station (Stuttgart Hauptbahnhof)".
Tourist information	The tourist information center is located next to the main train station at Königsstraße 1A, the main shopping street in Stuttgart.
Stuttgart Wine Festival	During the conference there will be the Stuttgart Wine Festival. It is located between the Schlossplatz and the city hall (Rathaus). Starting from the conference site, this is a 10-15 min walk. It provides a variety of foods, local wines and sweets. In the evenings, it can get very crowded, but everywhere is safe to go, but watch your belongings (as in any crowd). More information can be found online under: https://www.stuttgarter-weindorf.de/en
Wardrobe and luggage	You can leave your jackets and luggage at the information point. It is next to the check-in area in the **foyer of KII**.

VENUE

The VPH2024 takes place at the University of Stuttgart Downtown Campus. The location is very conveniently situated. The events for VPH2024 can be accessed by bus or by feet from Stuttgart main station (Stuttgart Hauptbahnhof) in under 10 minutes.

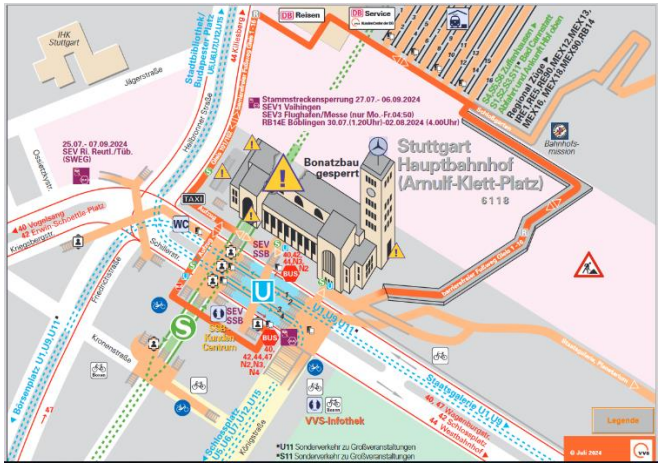
University of Stuttgart
Kollegiengebäude II (K2)
Keplerstr. 17
70174 Stuttgart

From Stuttgart main station ("Hauptbahnhof") you get to the venue:

By bus: The bus stop is located in front of the main train station building on the street side of the building. From there, either take line 42 in the direction of Erwin-Schoettle-Platz or line 40 in the direction of Vogelsang and get off at the Katharinenhospital (Katharinen Krankenhaus) stop. From there it is only a few steps to the conference site.

If you arrive by long-distance train, turn right or left out of the station building and follow the signs for the bus and the green "S-Bahn" signs. You can buy your bus ticket either via the VVS app, on the bus from the driver or at the ticket machine. You need a "KurzstreckenTicket" for one zone, which costs €2.00. You can also buy day or group tickets.

By foot: If you prefer to walk from the main station, it takes about ten minutes.



From Stuttgart Airport you get to the main station ("Hauptbahnhof")

By Light Rail: From the airport, you can take the U6 light rail line in the direction of Rastatter Straße to the main train station (Hauptbahnhof, with stop Arnulf-Klett-Platz). Then take the escalator up and follow the directions from above on how to get from the main train station to the conference venue.

Note for people who previously visited Stuttgart: Due to construction works, the S-Bahn does not run right at the moment directly from the airport to the city center.

By cab: The cabs are located directly in front of the arrival's hall and the journey to the city center costs around 40€.

FOOD

There will be two coffee breaks during the day which you are offered coffee, tea, mineral water, soft drinks and some snacks. The coffee breaks are in the foyer of KII in front of the auditoriums.

Lunch boxes will be provided. Lunch boxes will be provided. NOTE:

Due to the relatively compact program, we will provide lunch boxes including a vegetarian sandwich, e.g. a panini, an apple and some water or soft drinks for every participant.

But there are many locations close to the conference venue where you can buy food as well – either to-go or for dining in e.g. bakeries, restaurants, wine festival. You may check out the lunch flyer or conference App for recommendations of restaurants and bistros nearby.

Alternatively, you can have lunch in the students' cantina – Mensa central. It is located just a few steps away from the venue. You unfortunately cannot pre-purchase meal tickets such that you need to pay on site (only card payment possible)

All coffee breaks, the lunch boxes and the welcome reception are included in the conference fees. The conference dinner is included when you registered for it. Lunch (except lunch boxes) is not included.

STUTTGART

…an innovative, dynamic economy paired with high recreational value

Fascinating and beautiful, cosmopolitan and charming, traditional and future-oriented: the diversity of the Stuttgart region makes it worth visiting more than once. Its economy and its culture are equally thriving – whereby the one is often interlinked with the other, as in the case of the world-famous automobile brands whose names and museums are synonymous with Stuttgart.

There's something to gratify all the senses here. Brilliant achievements and an outstanding inventive spirit are typical of the Stuttgart Region and are evident at every turn: castles and palaces bear witness to a great past – and bold, futuristic architecture to an equally great present. The fine arts have always been given ample room to flourish, and many visitors are astonished at the wealth of outstanding gems which the Stuttgart Region has to offer. International sporting events, an outstanding opera, merry festivals, colorful markets, world-class shopping facilities, traditional cuisine and a countryside defined by a long tradition of viniculture and the River Neckar offer a wide range of leisure activities in the Stuttgart Region.

Information on Stuttgart and the many options available can be found under www.stuttgart-tourist.com

Images courtesy of Regio Stuttgart Marketing- und Tourismus GmbH. Foto Schlossplatz: Sarah Schmid. Foto Fernsehturm: Werner Dieterich

To explore Stuttgart, we recommend the apps **Stuttgart Guide** and **Lauschtour**. In the **Stuttgart Guide** app you will find all the information you need, from events and restaurants to places of interest. The **Lauschtour** (which translates as listening tour) app allows you to go on a self-guided tour through Stuttgart's city center and listen to exciting information and stories about the various sights via the audio guide.

Both apps can be downloaded here:
https://www.stuttgart-tourist.de/en/our-stuttgart-apps.

PLENARY SPEAKERS

Dirk Drasdo

INRIA | Rocquencourt, France

Wednesday, September 4

9:00am – 9:55am

-2.033 (big auditorium)

TOWARDS A FULL DIGITAL LIVER TWIN: DRUG INJURY, REGENERATION AND DISEASE PROGRESSION

The liver is the main detoxifying organ with a significant regenerative capacity. It is composed of smallest repetitive functional tissue units ("lobules") that possess a complex microarchitecture to guarantee optimal contact between blood entering the liver and the hepatocytes that detoxify the blood from toxins. Blood entering the liver enter each lobule by portal conduits and exits the lobule via a vein in the center of the lobule. Liver is zonated: different zones in the liver lobule take over different functions. Overdosage of paracetamol (acetaminophen, APAP) is the main reason for acute liver failure destroying hepatocytes situated close to the central vein. The lesion size is greatest about a day after drug administration, while after this a regeneration process is triggered, the lesion is usually closed within 1-2 weeks. In mice, repetitive administration of APAP can lead to fibrosis, characterized by collagen tissue deposited in the damage zone and forming a network.

In this talk a digital twin model will be represented resolving the liver lobule at microarchitectural level recapitulating the main mechanisms of acute drug induced damage and regeneration. The model includes the key APAP detoxification reactions in each hepatocyte, blood flow and metabolite transport with the blood, the regeneration process with a minimal through still complex network of cell-cell communications, as well as the impaired ammonia detoxification as a consequence of the damage.

Finally, it will be sketched how the model is able to address aspects of fibrosis development and of the ammonia detoxification in presence of fibrotic scar tissue, and, how the model can be used to transfer from one species to another and to inform clinicians. All simulations are confronted with data.

Vita: *Dr. rer. nat. habil. Dirk Drasdo is a Research Director at INRIA Saclay (France). He graduated at RWTH Aachen and performed a PhD in physics at Max Planck Institute (MPI) for Biophysical Chemistry (Göttingen), before joining positions as postdoc or research assistant at MPI for Colloidal and Interfacial Science (Potsdam), at IMISE in Leipzig, and MPI Mathematics in the Sciences (Leipzig), as group leader at IZBI Leipzig (where he performed a habilitation in computer science), and a position as Assistant Prof. (Sen. Lect.) at Univ. of Warwick. He was / is co-PI or participated in multiple research grants in France and Germany, and as member of multiple editorial boards.*

Dirk Drasdo's main research topic is modeling of multi-cellular tissue organization generating virtual twins. He established a number of agent-based model types of growing tissues in various applications. In these models, cells are mimicked as individual agents, parameterized by measurable biophysical and biokinetic parameters. Based on this technology he and his group established a process chain parameterizing single-cell-based tissue models out of histological image data in collaboration with the group of J.G. Hengstler (IfaDo) and other experimental

groups. With a modeling guided experimental strategy it was able to predict a previously unrecognized order mechanism during liver regeneration and more recently to deduce the necessity for an ammonia sink mechanism after drug induced liver damage which subsequently could be identified. This line of research was advanced towards full multi-level virtual twins of liver regeneration, and is being advanced now towards digital virtual twins of liver disease progression.

Alfons Hoekstra

University of Amsterdam | The Netherlands

Wednesday, September 4

5:05pm – 6:00pm

-2.033 (big auditorium)

TOWARDS DIGITAL TWINS IN HEALTHCARE FOR THE CEREBROVASCULAR SYSTEM, APPLIED TO ACUTE ISCHEMIC STROKE

We aim to deliver validated computational models for fundamental understanding and improved treatment of acute strokes, both ischemic and hemorrhagic, and demonstrate added benefit of these models for personalised disease management. To this end we develop validated, integrated multi-scale, multi-organ models for cerebral blood, brain perfusion and metabolism, and blood flow and thrombosis along the heart-brain axis, by integrating available and newly developed dynamic, interoperable, and modular computational models. Here we report on integrated 1D/0D blood flow models for flow from the heart to the major cerebral arteries and from there to the brain surface, and coupled to full blown three-dimensional coarse-grained models for brain perfusion. We demonstrate how to include the leptomeningeal collateral circulation, a very relevant collateral circuit for patients suffering acute ischemic stroke. The perfusion model is coupled to a brain metabolism model, to capture infarction of brain tissue after a stroke event. We also report on applying the model for the Cerebrovascular system to acute ischemic stroke. A stroke event is mimicked by blocking one of the major cerebral arteries. A drop of perfusion in the brain territory that is fed by the blocked artery is observed. Next, infarction is modelled, and the resulting volume of infarcted tissue is measured. Our results are compared to retrospective clinical data from the Mr. Clean trial, demonstrating that on the population level our stroke model is capable of reproducing results from the Mr. Clean trial.

Vita: *Prof. dr. ir. Alfons Hoekstra is a full professor in Computational Science & Engineering at the Computational Science Lab of the Informatics Institute of the University of Amsterdam. His research focusses on the Virtual Human Twin (with applications a.o. in the cardiovascular and cerebrovascular domain), on Multiscale Modeling of Complex Systems, and on High Performance Computing. He is editor of the Journal of Computational Science, member of the Strategy Board for Computational Science NL, and member of the advisory committee on Digitalisation of Research of the Dutch Science Foundation. He served as director of the Informatics Insitute of the University of Amsterdam from 2020 – 2023 and currently serves as scientific director of the technology hub for Molecular and Material Design.*

Lynne Bilston

Neuroscience Research Australia and Graduate School of Biomedical Engineering, UNSW Sydney, Australia

Thursday, September 5

9:00am – 9:55pm

-2.033 (big auditorium)

PERSONALISED MODELLING OF THE PHARYNX: INTEGRATING PHYSIOLOGY, IMAGING, AND COMPUTATIONAL MODELS TO UNDERSTAND PHARYNGEAL IN HEALTHY HUMANS AND PEOPLE WITH OBSTRUCTIVE SLEEP APNOEA

The upper airway, or pharynx, serves multiple functions, including playing a key role in breathing, eating, and speech, and in coordination between these functions. The tongue is the largest muscle in the pharynx, and is a muscular hydrostat made up of eight muscles with complex architecture. It achieves its diverse functions through coordinated contractions of these muscles, requiring fine grained neuromuscular control and reflex responses to adjust to disturbances. In this talk, I will outline our integrated physiology, imaging, and computational modelling approaches to understanding the tongue's task-specific neuromuscular control and its physiological and biomechanical behaviour. I will discuss how tongue function is affected by anatomical variation in the healthy population, and how we can use these integrated approaches to understand abnormal tongue function in people with Obstructive Sleep Apnoea.

Vita: *From a background in biomechanical engineering, the focus of my research is on how the nervous system responds to mechanical loading – both those loads which cause injury and those which are part of normal function. Our approach spans the range from the whole body (e.g. crash testing) through individual tissues, and down to a molecular scale – integrating the data to gain an understanding of the detailed mechanisms of nervous system injury and mechanically influenced physiological functions. I use novel imaging techniques such as tagged MRI and MR elastography to study a diverse range of in vivo mechanical functions, including obstructive sleep apnoea, muscle injury, biomechanical properties of tissues during growth and development, neural tissue mechanics, syringomyelia and hydrocephalus.*

Natalia Trayanova

John Hopkins University | USA

Friday, September 6

11:00am – 11:55am

-2.033 (big auditorium)

ADVANCING ARRHYTHMIA CARE WITH DIGITAL TWINS AND AI

Precision medicine is envisioned to provide therapy tailored to each patient. The rapidly increasing ability to capture extensive patient data, coupled with machine learning, is a pathway to achieving this vision. A different pathway towards precision medicine is the increasing ability to encode known physics laws and physiology knowledge within mathematical equations and to adapt such models to represent the behavior of a specific patient.

Wouldn't it be great to have a digital representation of ourselves that allows doctors to simulate our personal medical history and health conditions using relationships learned both from data and from biophysics knowledge? That virtual replica of ourselves would integrate data-driven machine learning and multiscale physics-based modeling to continuously update itself as our health condition changes and more information about our interaction with the environment is acquired. These digital twins would forecast the trajectory of the patient's disease, estimate risk of adverse events, and predict treatment response so that the potential outcome would inform treatment decision.

This presentation explores the synergies that have been achieved between machine learning and mechanistic physics-based heart models towards enabling precision medicine in cardiology. It showcases how machine learning and multiscale cardiac modeling complement each other in engineering your heart's health. A highlight is the robust prediction of sudden cardiac death risk in different heart diseases. Another application of the heart digital twin technology is illustrated by the development of a precise treatment for patients suffering from arrhythmias. This application prevents future re-hospitalizations and repeat procedures, shifting the treatment selection from being based on the state of the patient today to optimizing the state of the patient tomorrow.

Vita: *Dr. Trayanova holds the inaugural Murray B. Sachs Professorship in the Department of Biomedical Engineering at Johns Hopkins University. She is also a Professor of Medicine at the Johns Hopkins School of Medicine, and a Professor of Applied Mathematics and Statistics. She envisioned, created, and directs the Alliance for Cardiovascular Diagnostic and Treatment Innovation. She is also the Director for AI Research in Health and Medicine at Johns Hopkins University under the Data Science and AI Institute, where she is responsible for directing efforts across the university in developing and deploying AI applications that advance healthcare delivery and improve patient outcomes. She also directs the Computational Cardiology Laboratory. Dr. Trayanova is internationally recognized as a leader in personalized multi-scale computational modeling of whole heart electrophysiology and arrhythmias (heart digital twinning). Her research output includes 450 published papers and book chapters. She has published extensively in the most prestigious journals, such as The Lancet, Nature Cardiovascular Medicine, Nature Communications, Nature BME, Science Advances, Science TM, Physiological Reviews, Nature Reviews Cardiology, eLife, and others. Trayanova's work has received world-wide recognition, and*

she is the recipient of numerous honors and awards. She is the recipient of an NIH Director's Pioneer Award in 2013; in 2019, she was inducted in the Women of Technology International Hall of Fame, an honor conferred only on 5 women each year from around the world. Also in 2019, she received the Distinguished Scientist Award from Heart Rhythm Society. This was followed by the Zipes Distinguished Award by the same society in 2020, and by the Gordon Moe Award by the Cardiac Electrophysiology Society in 2023. In 2025, Trayanova will be the recipient of the Hodgkin-Huxley-Katz Award by the Physiological Society. Trayanova has been named a Fellow of every American and European clinical cardiology society, testifying to her impact in clinical practice. She is also a Fellow of AIMBE, BMES, IAMBE, and IUPS. She has given over 380 invited lectures, majority of them keynotes or plenary lectures. Dr. Trayanova's work has received widespread media coverage and recognition (see recent article in the Wall Street Journal, and she has also given a TEDx talk. Dr. Trayanova is also the inventor on numerous patents and patent applications filed world-wide. In recognition of her innovation, she was named Fellow of the National Academy of Inventors in 2020.

PARALLEL SESSIONS

Overview

Wednesday, September 4

Session 1 10:30am - 12:00pm	Session 2 1:00pm - 2:30pm	Session 3 3:30pm - 5:00pm
1.A Computational Modelling of the Heart 1.B Multi-X Vascular Modelling 1.C Liver & Eye Modelling 1.D Mitral Valve Replacements 1.E Cartilage & Skin 1.F Big Data / Machine Learning I 1.G Musculoskeletal System I 1.H Clinical Imaging	2.A Heart Modelling - Surrogate Modelling 2.B Hemodynamics 2.C COMBINE 2.D CANCELLED 2.E Gastrointestinal Tract, Kidney & Uterus 2.F Big Data / Machine Learning II 2.G Musculoskeletal System II 2.H Computational Knee Biomechanics: Domain-Specific M&S Resources and Translation 2.I Cancer Modelling I	3.A Cardiovascular Digital Twins 3.B Vascular (Re)Modelling 3.C M&S Resources, Infrastructure, and Operationalization 3.D Aortic Valve Replacements 3.E Dental Biomechanics 3.F Big Data / Machine Learning III 3.G Musculoskeletal System - Hard Tissue 3.H Neural Engineering 3.I Cancer Modelling II

Thursday, September 5

Friday, September 6

Session 4 10:30am - 12:00am	Session 5 3:30pm - 5:00pm	Session 6 9:00am - 10:30am
4.A Heart Modelling - Applications I 4.B Vascular CFD Modelling 4.C M&S Reproducibility, Credibility, and Translation 4.D Cellular & Systems Biology I 4.E Lung Modelling I 4.F High-Performance Computing 4.G Musculoskeletal System - Spine 4.H Neurotechnology for Human Movement	5.A Heart Modelling - Applications II 5.B Aneurysms & Appendages 5.C Good Simulation Practice in Healthcare 5.D Cellular & Systems Biology II 5.E Lung Modelling II 5.F Population-based Modelling 5.G In-silico Orthopedics I 5.H Movement Biomechanics and Activity Tracking	6.A Heart Modelling - Perfusion and Blood Flow 6.B Stent Modelling 6.C Experimental Surgery, Animal Models, and Model Transfer 6.D Clinical Decision Support for Cardiovascular Applications 6.E Human Brain Modelling 6.F Pathway to Digital Twins 6.G In-silico Orthopedics II 6.H In-silico Toxicology

Detailed Session Overview

Wednesday, September 4

Session 1, 10:30am – 12:00pm

	1.A Computational Modelling of the Heart | 05.019
10:30am – 10:45am	Computational models of cardiac function – Closing the gaps between virtual and physical reality **Gernot Plank**
10:45am – 11:00am	A multiscale finite element model of cardiac growth and baroreflex regulation **Jonathan Frederick Wenk**
11:00am – 11:15am	Full personalisation of 3D biventricular models from electroanatomical mappings and cardiac MRI to understand the impact of arrhythmic substrate components on electrophysiological function - **Jesus Jairo Rodríguez Padilla**
11:15am – 11:30am	A multi-scale analysis of the impact of measurement and physiological uncertainty on electrocardiograms **Ludovica Cicci**
11:30am – 11:45am	Titin-mediated viscoelastic passive muscle mechanics **Dan A Beard**
11:45am – 12:00pm	

	1.B Multi-X Vascular Modelling | 02.017
10:30am – 10:45am	Multiscale fluid-structure interaction for the effective modeling of vascular tissues **Alfonso Caiazzo**
10:45am – 11:00am	An automated pipeline to investigate the impact of intracranial internal carotid artery calcifications on cerebrovascular events **Federica Fontana**
11:00am – 11:15am	Impact of atrial rotor dominant frequency on flecainide and vernakalant cardioversion ratio **Violeta Puche-García**
11:15am – 11:30am	Predicting chronic cardiac responses to angiotensin receptor/neprilysin inhibitor using a physiological model of heart failure with preserved ejection fraction **John S. Clemmer**
11:30am – 11:45am	Coagulation cascade systems modeling for oral anticoagulant monitorization in atrial fibrillation patients **Maria Segarra-Queralt**
11:45am – 12:00pm	Modeling fluid-structure-chemistry interactions in atherosclerotic arteries **Sharan Nurani Ramesh**

1.C Liver & Eye Modelling | 02.011	
10:30am – 10:45am	A multiscale and multiphase digital twin of function-perfusion processes in the human liver **Tim Ricken**
10:45am – 11:00am	Patient specific prediction of portal vein pressure after liver surgery: Sensitivity, identifiability and uncertainty quantification **Roel Meiburg**
11:00am – 11:15am	A multi-compartment perfusion model for hierarchical vessel networks with application to liver regrowth **Jannes Hohl**
11:15am – 11:30am	Towards sustainable simulation pipelines for human liver decision support **Steffen Gerhäusser**
11:30am – 11:45am	Exploring ethnic diversity in glaucoma surgery efficacy using computational fluid dynamics **Nicol Basson**
11:45am – 12:00pm	A computational fluid dynamic study on graft detachment in the human eye for postoperative endothelial keratoplasty **Eva Cheng**

1.D Mitral Valve Replacements | 09.019	
10:30am – 10:45am	Patient-specific long-term prediction of transcatheter edge-to-edge mitral valve repair **Michael S Sacks**
10:45am – 11:00am	Functional assessment of patients with mitral valve defect augmented by biomechanical modeling: Contractile reserve of the heart and in-silico valve repair - **Radomir Chabiniok**
11:00am – 11:15am	Model reduction for fluid-solid simulations to assess hemodynamics of mitral valve regurgitation and repair **Marc Hirschvogel**
11:15am – 11:30am	Influence of valve shape on mitral valve hemodynamics: An in-silico study **Juliana Franz**
11:30am – 11:45am	Synthetic cohort of mitral valve anatomies based on statistical shape modeling **Katharina Vellguth**
11:45am – 12:00pm	

1.E Cartilage & Skin | 08.019	
10:30am – 10:45am	Articular cartilage systems mechanobiology: A multiscale tissue model of the knee cartilage **Jérôme Noailly**
10:45am – 11:00am	Pixel2Mechanics: Automated biomechanical simulations of high-resolution intervertebral discs from anisotropic MRIs **Estefano Muñoz-Moya**
11:00am – 11:15am	Computational modeling of articular cartilage mechanics: Insights and validation **Franziska S. Egli**
11:15am – 11:30am	Application of an FSI-based model to optimize mechanically stimulated structured hydrogel scaffolds for cartilage cell differentiation **Pedram Azizi**
11:30am – 11:45am	Model investigation of the energy density resulting from the absorption and scattering of radiation in multi-layer skin tissue structures **Seyed Morteza Seyedpour**
11:45am – 12:00pm	Generality and applicability in developing virtual epithelial tissues models **James A Glazier**

1.F Big Data / Machine Learning I | 02.005	
10:30am – 10:45am	A computationally efficient deep learning model for high-resolution transient hemodynamics estimation in complex vascular geometries **Noah Maul**
10:45am – 11:00am	Parameter estimation in cardiac biomechanical models based on physics-informed neural networks **Federica Caforio**
11:00am – 11:15am	Finite volume informed graph attention network for solving partial differential equations — Application to myocardial perfusion **Raoul Sallé de Chou**
11:15am – 11:30am	Machine learning-based models to predict axillary lymph node metastasis in breast cancer patients **Alba Fischer-Carles**
11:30am – 11:45am	Predicting post-traumatic stress disorder (PTSD) symptoms in women suffering from breast cancer using machine learning **Georgios S. Stamatakos**
11:45am – 12:00pm	

1.G Musculoskeletal System Modelling I | 01.005	
10:30am – 10:45am	Shear wave elastography for simulating tibialis anterior muscle forces in vivo **Cemre Su Kaya Keles**
10:45am – 11:00am	Muscle architecture and contractile properties of the human M. tibialis anterior **Lukas Vosse**
11:00am – 11:15am	Predicting passive and active triceps surae muscle forces by integrating magnetic resonance image-based 3D finite element modelling and ultrasound shear wave elastography - **Geoffrey Handsfield**
11:15am – 11:30am	Patient-specific geometry and deformation for real-time visualization of musculoskeletal biomechanics via 3D ultrasound **David Rosin**
11:30am – 11:45am	An activation-driven musculoskeletal finite element model of the human shoulder **Laura Engelhardt**
11:45am – 12:00pm	Investigation of surrogate methods for an electrophysiological skeletal muscle model **Robin Lautenschlager**

1.H Clinical Imaging | 07.017	
10:30am – 10:45am	Digital twins for interventional procedures **Annette Birkhold**
10:45am – 11:00am	
11:00am – 11:15am	Exploring the effect of feto-placental vasculature and oxygenation on T2* MRI using mathematical modelling **Diana M. Cruz de Oliveira**
11:15am – 11:30am	Advanced magnetic resonance imaging techniques offer a virtual tool for assessing physiological mechanisms of human muscular mechanics in vivo **Arda Arpak**
11:30am – 11:45am	Energy-based method for identifying misclassified kidney boundary segmentations using CT scans **Andreea Elena Vântu**
11:45am – 12:00pm	Modelling and dynamic imaging: A few examples for clinical applications **Irene Vignon-Clementel**

Session 2, 1:00pm – 2:30pm

2.A Heart Modelling - Surrogate Modelling | 05.019	
1:00pm – 1:15pm	High-speed real heart simulations using a neural network finite element approach **Michael S Sacks**
1:15pm – 1:30pm	Adaptive reduced-order models for cardiac simulations **Sridhar Chellappa**
1:30pm – 1:45pm	Surrogate modeling of finite deformation hyperelasticity of human myocardial tissue **Osman Gültekin**
1:45pm – 2:00pm	Bridging computational efficiency, sex differences, and clinical accuracy: Surrogate modeling in cardiotoxicity assessment **Alberto Zingaro**
2:00pm – 2:15pm	Physiology-informed machine learning to guide heart failure diagnosis, prognosis, and treatment **Daniel Beard**
2:15pm – 2:30pm	An experimental and modelling pipeline to develop metabolite-sensitive cardiac cross-bridge models **Julia H Musgrave**

2.B Hemodynamics | 02.017	
1:00pm – 1:15pm	Hemodynamics of an implanted pressure sensor in porcine and human pulmonary artery **Leonid Goubergrits**
1:15pm – 1:30pm	Turbulence modeling in aortic blood flow: Traditional models and perspectives on machine learning **Sarah Katz**
1:30pm – 1:45pm	Estimation of exercise-induced pressure drop across aortic coarctations: A comparison of in vitro measurements and FSI simulations **Priya J. Nair**
1:45pm – 2:00pm	Simulation of the hemodynamics of a patient-specific artery at the full-body scale **Xiao-Chuan Cai**
2:00pm – 2:15pm	A detailed 1D model of the feto-placental hemodynamics to investigate hypertensive disorders of pregnancy **Wouter Huberts**
2:15pm – 2:30pm	The impact of clot permeability on thrombus growth in different hemodynamic scenarios **Niksa Mohammadi Bagheri**

2.C COMBINE | 02.011	
1:00pm – 1:15pm	The COmputational MOdelling in BIology NEtwork in 2024: Standards and services for the computational physiology community and beyond **David Phillip Nickerson**
1:15pm – 1:30pm	BayModTS: A FAIR Bayesian workflow to process variable and sparse time series data **Sebastian Höpfl**
1:30pm – 1:45pm	The reproducibility and credibility of biomedical models **Herbert Martin Sauro**
1:45pm – 2:00pm	Reproducible digital twins for personalized liver function assessment **Matthias König**
2:00pm – 2:15pm	The role of standards in defining an ecosystem for virtual human twins (VHTs) **Martin Golebiewski**
2:15pm – 2:30pm	Model reuse - Lessons learned from 20 years of sharing CellML models **Hugh Sorby**

2.E Gastrointestinal Tract, Kidney & Uterus | 09.019	
1:00pm – 1:15pm	Modelling the electrophysiology of the non-pregnant uterus: From interconnected cells to organ **Leo Cheng**
1:15pm – 1:30pm	Computational modeling of the effect of laser tissue soldering on colonic motility **René Thierry Djoumessi**
1:30pm – 1:45pm	Neural stimulation modifies the organ-scale coordination of rat gastric slow waves **Omkar N. Athavale**
1:45pm – 2:00pm	Computational modelling of the human gastric peristalsis **Maire Salina Henke**
2:00pm – 2:15pm	Exploring host-microbiota interactions through mechanistic modelling: Insights into diet impact on beneficial symbiosis resilience in the human gut **Marie Haghebaert**
2:15pm – 2:30pm	Predictive modelling of renal circulation hemodynamic outcomes in hypertensive and diabetic kidney disease **Ning Wang**

2.F Big Data / Machine Learning II | 02.005	
1:00pm – 1:15pm	Virtual anatomical diagnosis of veridical human stroke patients **William W Lytton**
1:15pm – 1:30pm	Interpretable and generalizable mortality prediction in critical care settings: Integrating mechanistic knowledge with machine learning **Moein Einollahzadeh Samadi**
1:30pm – 1:45pm	Explainable machine learning explained in medicine **Karol Przystalski**
1:45pm – 2:00pm	A deep learning approach to discriminate sodium and chloride muscle channelopathies **Emilie Ismailova**
2:00pm – 2:15pm	Hybridising standard reduced-order modelling methods with interpretable sparse neural networks for real-time patient specific lung simulations **Alexandre Daby-Seesaram**
2:15pm – 2:30pm	

2.G Musculoskeletal System II | 01.005	
1:00pm – 1:15pm	Uncovering motor-unit activity in magnetomyography **Nima Noury**
1:15pm – 1:30pm	How distance affects the magnetic muscle signal - An in-vivo and in-silico study **Haodi Yang**
1:30pm – 1:45pm	Clinical possibilities **Justus Carl Marquetand**
1:45pm – 2:00pm	Impact of endomysium on fiber bundle passive and active mechanics for intact and chemically skinned fibers **Paolo Carlo Danesini**
2:00pm – 2:15pm	Exploring the variability in neuromotor control to perform common locomotor tasks **Giorgio Davico**
2:15pm – 2:30pm	Multi-scale modeling approach to determine phrenic nerve activation threshold **Laureen Wegert**

2.H Computational Knee Biomechanics: Domain-Specific M&S Resources and Translation | 07.017	
1:00pm – 1:15pm	Open Knee(s): Computational Knee Biomechanics Resource Growth and Utilization **Ahmet Erdemir**
1:15pm – 1:30pm	
1:30pm – 1:45pm	KNEEHUB: Implementation of the Delphi method to achieve consensus in the modeling and simulation processes and credibility activities in the knee **Jason Halloran**
1:45pm – 2:00pm	Toward an accurate digital twin: In vivo model calibration **Thor E. Andreassen**
2:00pm – 2:15pm	Multi-scale modeling for in silico prediction of patient-specific risk of cartilage degeneration: Insights from a prospective follow-up study in patients with knee OA **Seyed Ali Elahi**
2:15pm – 2:30pm	Distinct knee pathomechanics of females compared to males: A population-based in-silico analysis **Carl Imhauser**

2.I Cancer Modelling I | 08.019	
1:00pm – 1:15pm	Digital twins for oncology and patient-specific simulations: Importance of vascularization **Diego Sainz-DeMena**
1:15pm – 1:30pm	Digital twin of prostate cancer tumour growth: A multiphysics approach **Ángela Pérez-Benito**
1:30pm – 1:45pm	Multiphasic modelling and patient-specific simulation of tumours in soft tissue with OncoFEM **Marlon Suditsch**
1:45pm – 2:00pm	Modeling hypoxia-induced radiation resistance and the impact of radiation sources **Paolo Zunino**
2:00pm – 2:15pm	Efficient radial-shell model for 3D tumor spheroid dynamics with radiotherapy **Anja Voss-Böhme**
2:15pm – 2:30pm	

Session 3, 3:30pm – 5:00pm

	3.A Cardiovascular Digital Twins | 05.019
3:30pm – 3:45pm	Towards a realistic digital twins of coronary artery disease: Is a fluid-structure interaction simulations necessary? **Francesco Migliavacca**
3:45pm – 4:00pm	New perspectives on global sensitivity analysis for the creation of cardiovascular digital twins **Harry Saxton**
4:00pm – 4:15pm	Digital-twin based assessment of atrial arrhythmias: Influence of anatomical and functional personalization strategies **Patricia Martínez Díaz**
4:15pm – 4:30pm	Advancements in multiphysics and multiscale modeling: Connecting computational cardiology with digital twinning **Luca Dede**
4:30pm – 4:45pm	Next generation cardiac care: SimCardioTest cloud-based platform **Alessia Baretta**
4:45pm – 5:00pm	Uncertainty estimation in patient-specific cardiovascular models: The effect of sources of errors in 4D flow MRI and blood pressure **Kajsa Tunedal**

	3.B Vascular (Re)Modelling | 02.017
3:30pm – 3:45pm	Branching exponents of synthetic vascular trees under different optimality principles **Dominik Schillinger**
3:45pm – 4:00pm	Generation of organ-scale synthetic vasculature using mathematical optimization **Etienne Jessen**
4:00pm – 4:15pm	Modelling growth, remodelling and damage of arterial tissue: Application to cerebral vasospasm **Giulia Pederzani**
4:15pm – 4:30pm	Computational modelling of coupled shear-induced NO signalling pathways in endothelial and smooth muscle cells of arterial wall **Fariba Bahadori**
4:30pm – 4:45pm	Do the clot mechanical properties affect the thrombectomy procedures? An in silico study **Giulia Luraghi**
4:45pm – 5:00pm	

	3.C M&S Resources, Infrastructure, and Operationalization | 07.017
3:30pm – 3:45pm	Harmonising historic clinical gait datasets using image-based musculoskeletal models **Thor Besier**
3:45pm – 4:00pm	An in silico world: Resources to accelerate the adoption of in silico trials **Marco Viceconti**
4:00pm – 4:15pm	Computer modelling and simulation in clinics: Longitudinal mapping of usage and clinician's trust in in silico medicine **Zita Van Horenbeeck**
4:15pm – 4:30pm	Energy-based multiscale modelling and system analysis framework **Weiwei Ai**
4:30pm – 4:45pm	Different magic sauce, but same taste? Exploring the social and legal demarcation frictions between artificial intelligence and digital twins in healthcare **Elisa Elhadj**
4:45pm – 5:00pm	

3.D Aortic Valve Replacements | 09.019	
3:30pm – 3:45pm	Patient-specific TAVI thrombosis modelling: Insights from haemodynamic analysis **Maria Isabel Pons Vidal**
3:45pm – 4:00pm	Unveiling the relation between aortic shape and calcification in population with aortic stenosis: Towards better management of TAVI patients **Raphael Sivera**
4:00pm – 4:15pm	Identify transcatheter aortic valve implantation degeneration using computational hemodynamic scores **Luca Crugnola**
4:15pm – 4:30pm	Predicting transcatheter aortic valve implantation procedural outcomes through the development and validation of patient-specific simulations **Benedetta Grossi**
4:30pm – 4:45pm	Virtual cohort generation for in silico trials of transcatheter aortic valve implantation **Sabine Verstraeten**
4:45pm – 5:00pm	Simulation workflow for transcatheter aortic valve replacements: From crimp and deployment to fluid-structure interaction **Nils Karajan**

3.E Dental Biomechanics | 09.033	
3:30pm – 3:45pm	A soft-tissue driven bone remodeling algorithm for mandibular residual ridge resorption **Qing Li**
3:45pm – 4:00pm	
4:00pm – 4:15pm	Morphological and functional aspects in oral rehabilitations – New algorithmic approaches in the era of digital dentistry **Albert Mehl**
4:15pm – 4:30pm	Modeling the spatio-temporal evolution of bone-implant interface stiffness via a stochastic numerical approach **Jing Xie**
4:30pm – 4:45pm	Muscle and joint mechanics during maximum-force biting following total temporomandibular joint replacement surgery **David Ackland**
4:45pm – 5:00pm	Influence of bone quality and dental implant material on stress distribution within the surrounding bone **Iman Soodmand**

3.F Big Data / Machine Learning III | 02.005	
3:30pm – 3:45pm	A computational pipeline for fast surrogates of left atrial appendage occlusion fluid simulations **Marta Saiz Vivó**
3:45pm – 4:00pm	Generative 3D cardiac shape modelling for in-silico trials **Andrei Gasparovici**
4:00pm – 4:15pm	Image segmentation of irradiated tumor spheroids by fully convolutional networks **Steffen Lange**
4:15pm – 4:30pm	Accelerating osteoarthritis progression predictions: A machine learning and finite element analysis approach **Moein Eddin Yousefi**
4:30pm – 4:45pm	Enhancing synthetic medical image fidelity through semantic segmentation guidance in diffusion models **João Pedro Rodrigues**
4:45pm – 5:00pm	Towards multi-scale model selection for rare data applications **Cordula Reisch**

3.G Musculoskeletal System – Hard Tissue | 01.005	
3:30pm – 3:45pm	Improving proximal humerus fracture fixations - Insights from in silico analyses **Peter Varga**
3:45pm – 4:00pm	Predicting lower limb bone geometry in a paediatric population using statistical shape modelling **Laura Carman**
4:00pm – 4:15pm	Automated pose estimation of knee kinematics from fluoroscopy using a differentiable renderer **Jinhao Wang**
4:15pm – 4:30pm	Numerical evaluation of the postoperative primary fixation stability in complex tibial plateau fractures **Simon Comtesse**
4:30pm – 4:45pm	Planning the perfect osteosynthesis: Simulation-assisted decision making in fracture treatment **Lucas Engelhardt**
4:45pm – 5:00pm	Minding the gap: Sex differences influence bone fracture healing **Laura Lafuente-Gracia**

3.H Neural Engineering | 02.011	
3:30pm – 3:45pm	Computational modelling of closed-loop control of deep brain stimulation for Parkinson's disease **Madeleine M. Lowery**
3:45pm – 4:00pm	Group analysis in deep brain stimulation employing simulations of the volume of tissue activated **Simone Hemm**
4:00pm – 4:15pm	Computational modeling of transcranial magnetic stimulation **Thomas R. Knösche**
4:15pm – 4:30pm	Simulation-enhanced magnetomyographic quantum sensor systems to study neuromuscular control **Thomas Klotz**
4:30pm – 4:45pm	Influence of collateral axon parameters on threshold activation during DBS **Karthik Sridhar**
4:45pm – 5:00pm	

3.I Cancer Modelling II | 09.019	
3:30pm – 3:45pm	Computational synthesis of microvascular networks: A precision medicine approach to predict radiotherapy outcome in head and neck cancer **Luca Possenti**
3:45pm – 4:00pm	Development and validation of a computational simulator for treatment outcome prediction in high-grade serous ovarian cancer **Marilisa Cortesi**
4:00pm – 4:15pm	Patient-specific modelling of needle insertion in prostate cancer therapy **Vasileios Vavourakis**
4:15pm – 4:30pm	METASTRA: Computer-aided effective fracture risk stratification of patients with vertebral metastases for personalised treatment through robust computational models validated in clinical settings **Luca Cristofolini**
4:30pm – 4:45pm	Clinical decision support during maintenance therapy for childhood acute lymphoblastic leukemia **Anna Gebhard**
4:45pm – 5:00pm	

Thursday, September 5

Session 4, 10:30am – 12:00pm

	4.A Heart Modelling - Applications I | 05.019
10:30am – 10:45am	Computational modeling of desmoplakin cardiomyopathy **David Nordsletten**
10:45am – 11:00am	
11:00am – 11:15am	Determination of stimulation threshold in a 3D model of a pacemaker **Valentin Pannetier**
11:15am – 11:30am	Development of an automated pipeline for large-scale in silico trials in patient-specific electromechanical ventricular models **Ruben Doste**
11:30am – 11:45am	A strongly coupled electromechanical model of heart failure as a benchtest for proarrhythmia assessment and drug testing **Sergi Picó**
11:45am – 12:00pm	Personalisation of action potentials based on activation recovery intervals in post-infarcted pigs: A simulation study **Jesus Jairo Rodríguez Padilla**

	4.B Vascular CFD Modelling | 02.017
10:30am – 10:45am	Efficient multiscale fluid flow modelling by a Stokes-enforcing boundary condition **David Nolte**
10:45am – 11:00am	An investigation into cerebral perfusion sensitivity under different haemodynamic and anatomical variations **Stephen A. Creamer**
11:00am – 11:15am	Inverse modelling approach to identify model parameters in 0D pulmonary haemodynamic simulation models **Yufei Wang**
11:15am – 11:30am	Neural networks for efficient sensitivity analysis and parameter estimation of dynamical systems for blood and solute whole-body circulation **John M. Hanna**
11:30am – 11:45am	Comparison of 4D flow magnetic resonance imaging with blood flow simulations before and after left atrial appendage occlusion **Paula Casademunt**
11:45am – 12:00pm	Quantitative perfusion assessment: A mechanistic model to interpret dynamic imaging **Jérôme Kowalski**

4.C M&S Reproducibility, Credibility, and Translation | 07.017	
10:30am – 10:45am	A rubric for assessing conformance to the ten rules for credible practice of modeling and simulation in healthcare **Rajanikanth Vadigepalli**
10:45am – 11:00am	The automated construction and verification of physically plausible models of physiological systems **Mehran Akbarpour Ghazani**
11:00am – 11:15am	From clinical measurements to parameter personalisation: An end-to-end standardised framework to navigate computational physiology workflows **Mathilde A. Verlyck**
11:15am – 11:30am	Multiscale agent-based virtual-tissue models: Working towards reproducible and reusable models **James A Glazier**
11:30am – 11:45am	Influence of dependent parameters on the predictive uncertainty of biomechanical models: Insights from global sensitivity analysis **Sebastian Brandstaeter**
11:45am – 12:00pm	KNEEHUB: A Resource for end-to-end modeling & simulation workflows in computational knee biomechanics **Jason Halloran**

4.D Cellular & Systems Biology I | 02.005	
10:30am – 10:45am	Use of bond graphs and scaffolds for modelling physiology **Peter Hunter**
10:45am – 11:00am	
11:00am – 11:15am	Using a systems biology approach to construct adverse outcome pathway networks aligned with the FAIR principles **Luiz Ladeira**
11:15am – 11:30am	Agent-based modelling of cell biomechanics using the open-source platform BioDynaMo **Vasileios Vavourakis**
11:30am – 11:45am	Metabolic digital twins of people with diabetes **Ryan de Vries**
11:45am – 12:00pm	A computational analysis of coupled glycolytic, oxidative ATP synthesis, and energy and pH balance in contracting fast-twitch muscle fibres **Jana Disch**

4.E Lung Modelling I | 02.011	
10:30am – 10:45am	Multiscale modelling and estimation of lung poromechanics **Martin Genet**
10:45am – 11:00am	A coupled multi-dimensional multiphase porous media approach for modeling the respiratory and circulatory system of the human lungs including gas exchange **Lea J. Köglmeier**
11:00am – 11:15am	Personalised computational models of paediatric lung structure from novel lung MRI **Ho-Fung Chan**
11:15am – 11:30am	A framework to characterize phenotype-specific models of the lung from CT imaging **Merryn Tawhai**
11:30am – 11:45am	Identification of expiratory WOB in active expiration with imposed non-linear resistance **Jaimey A. Clifton**
11:45am – 12:00pm	

4.F High-Performance Computing | 09.019	
10:30am – 10:45am	HPC in Biomechanics - Challenges, Current Research and Future Opportunities **Johannes Gebert**
10:45am – 11:00am	A user interface to facilitate visualization and integration of predictions for mechanical femur strength **Massimiliano Mercuri**
11:00am – 11:15am	Enhancing large-scale cohort simulations through integrated HPC infrastructure and model execution environment **Karol Zając**
11:15am – 11:30am	Code verification of contact analysis using a micro-finite-element solver **Frederik Max Trommer**
11:30am – 11:45am	Classification of retinal vein occlusion and diabetic macular edema with deep learning in OCT images **Guilherme Barbosa**
11:45am – 12:00pm	

4.G Musculoskeletal System - Spine | 01.005	
10:30am – 10:45am	A novel in silico approach for the analysis of muscular loads in the lumbar spine **Linda Carpenedo**
10:45am – 11:00am	A novel in silico parametric tool for surgical-decision in lumbar spine fixation and fusion **Luigi La Barbera**
11:00am – 11:15am	Spine surgery planification to avoid proximal junctional failure: A multi-criteria approach using finite element modelling **Morteza Rasouligandomani**
11:15am – 11:30am	In silico functional assessment of a new bio-degradable cage for lumbar interbody fusion through a fully-parametric spine model generator **Davide Ninarello**
11:30am – 11:45am	Modelling percutaneous vertebroplasty (and other processes) using the theory of porous media **Jan-Sören Lennart Völter**
11:45am – 12:00pm	

4.H Neurotechnology for Human Movement | 08.019	
10:30am – 10:45am	From novel muscular mechanics principles to neurotechnology for human movement **Can A. Yucesoy**
10:45am – 11:00am	Integrating intraoperative testing with musculoskeletal modeling: Muscle force-length relationship in patients with cerebral palsy **Cemre Su Kaya Keles**
11:00am – 11:15am	The development of LSTM-based ankle position and moment estimator for powered ankle prosthesis using nonnormalized sEMG and feature inputs **Ahmet Dogukan Keles**
11:15am – 11:30am	Boosting the performance of lightweight deep learning models with attention in human activity recognition **Özlem Durmaz**
11:30am – 11:45am	Joint angle generation for human walking using conditional neural movement primitives **Emre Ugur**
11:45am – 12:00pm	Smartphone application for quantitative assessment of gait and balance impairments in stroke patients **Otar Akanyeti**

Session 5, 3:30pm – 5:00pm

	5.A Heart Modelling - Applications II | 05.019
3:30pm – 3:45pm	Instantaneous biomechanical model of the heart to characterize ventricular remodeling in complex congenital heart disease **Maria Gusseva**
3:45pm – 4:00pm	Construction and manufacturing of an MRI-ready experimental left heart phantom model **Moritz Wiegand**
4:00pm – 4:15pm	Predicting cardiac conduction disturbances during balloon aortic valvuloplasty from patient-specific computational models **Benjamin Ayo Matheson**
4:15pm – 4:30pm	Hierarchical VVUQ strategy for the development and credibility assessment of a pulmonary heart valve model **Nils Götzen**
4:30pm – 4:45pm	Predictive model for the assessment of the TEVAR procedure **Sara Barati**
4:45pm – 5:00pm	Alterations of the in vivo myocardium mechanical properties in aortic stenosis: Finite element analysis in a rat model **Mohammad Javad Sadeghinia**

	5.B Aneurysms & Appendages | 02.017
3:30pm – 3:45pm	In silico pre-operative TEVAR planning: Application to a patient-specific case **Anna Ramella**
3:45pm – 4:00pm	The role of secondary flow activities in the emergence of sidewall intracranial aneurysms **Benjamin Csippa**
4:00pm – 4:15pm	Use of shape analysis and computational fluid dynamics for identification of factors relevant for aneurysm rupture **Ivan Benemerito**
4:15pm – 4:30pm	Virtual particle tracking in geometries with cerebral aneurysms **Dániel Gyürki**
4:30pm – 4:45pm	Left atrial appendage occlusion: A virtual model to simulate the implant procedure in patient-specific scenarios **Francesca Danielli**
4:45pm – 5:00pm	Left atrial wall dynamics in in-silico fluid simulations of atrial fibrillation patients **Nerea Arrarte Terreros**

	5.C Good Simulation Practice in Healthcare | 07.017
3:30pm – 3:45pm	Saving lives today while building the personal digital avatar: An ambitious yet pragmatic digital transformation of healthcare **Thierry Marchal**
3:45pm – 4:00pm	
4:00pm – 4:15pm	PyAnsys-heart: A python library for LS-DYNA multi-physics heart simulations **Karim El Houari**
4:15pm – 4:30pm	Toward good simulation practice: Best practices for the use of computational modelling and simulation in the regulatory process of biomedical products **Vincenzo Carbone**
4:30pm – 4:45pm	AlmaHealthDB: A digital infrastructure for secure management, interoperability and reuse of health research data **Antonino A. La Mattina**
4:45pm – 5:00pm	An in silico medicine info kit for effective stakeholder engagement **Martina Contin**

5.D Cellular & Systems Biology II | 02.005	
3:30pm – 3:45pm	Physiome: Encouraging the publication and reuse of reproducible models **David Phillip Nickerson**
3:45pm – 4:00pm	Development of a computational inflammation model of osteoarthritis including obesity **Damien Lacroix**
4:00pm – 4:15pm	Modeling the interplay among TIMP, proteases and proinflammatory cytokines within the human intervertebral disc **Laura Baumgartner**
4:15pm – 4:30pm	Building a digital twin for rheumatoid arthritis, one cell at a time **Anna Niarakis**
4:30pm – 4:45pm	A sympathetic neuron computational model for hypertension treatment **Finbar John Argus**
4:45pm – 5:00pm	Computational modelling for mechanistic explorations of biomarkers and biomechanical cues in atherosclerosis **Mané Sarkissian**

5.E Lung Modelling II | 02.011	
3:30pm – 3:45pm	The use of rapid expiratory occlusion (REO) to simultaneously identify lung elastance, airway resistance, and muscular effort **Ella F. S. Guy**
3:45pm – 4:00pm	Pulmonary elastance identification and predictive methodology for PCV in a digital twin **Trudy L. Caljé-van der Klei**
4:00pm – 4:15pm	Bridging micro to macro in pulmonary mechanics: Interpretable neural networks for surrogate modelling **Katerina Skardova**
4:15pm – 4:30pm	Integrating macro-vascular and micro-vascular models to elucidate wall shear stress dynamics in pulmonary hypertension: A novel approach to understanding CTEPH development **Behdad Shaarbaf Ebrahimi**
4:30pm – 4:45pm	A virtual asthma patient successfully predicts patient-specific impact of bronchial thermoplasty **Himanshu Kaul**
4:45pm – 5:00pm	

5.F Population-based Modelling | 09.019	
3:30pm – 3:45pm	Classification of glenoid bone loss patterns using statistical shape modelling **Julie Kim**
3:45pm – 4:00pm	Strain analysis in the right ventricular outflow tract using non-parametric deformable shape modelling **Liam David Swanson**
4:00pm – 4:15pm	Hexahedral mesh fitting using scaffolds and statistical shape modelling to reproduce the cortical bone morphology of the femur **Ted Yeung**
4:15pm – 4:30pm	Development of a statistical shape and density model of the paediatric femur for personalised FE models in children **Julie Choisne**
4:30pm – 4:45pm	Generation of digital genetic twins satisfying utility and privacy metrics for robust post-hoc analyses **Igor Faddeenkov**
4:45pm – 5:00pm	Domain adaptation methods for emotion and pain recognition via synthetic data **Alina Roitberg**

5.G In-silico Orthopedics I | 01.005	
3:30pm – 3:45pm	In-silico analysis of physiological joint mechanics within a complex musculoskeletal leg-system and its application to biomechanical evaluation of implants **Okan Avci**
3:45pm – 4:00pm	
4:00pm – 4:15pm	Development of a validated software framework for in-silico clinical trials of orthopedic devices **Lukas Connolly**
4:15pm – 4:30pm	In silico clinical trial to predict the efficacy of alendronate for preventing hip fractures **Sara Oliviero**
4:30pm – 4:45pm	Assessing hip implant stability: A parametric surrogate modelling approach **Marlis Reiber**
4:45pm – 5:00pm	In silico clinical trial for a regulatory submission of a total shoulder arthroplasty system **Christine Mueri**

5.H Movement Biomechanics and Activity Tracking | 08.019	
3:30pm – 3:45pm	Estimating daily dynamic skeletal loading from ankle-worn activity monitors after menopause **Emma Fortune**
3:45pm – 4:00pm	
4:00pm – 4:15pm	Validating the Fitbit Charge 6 wearable activity monitor for use in physical activity interventions in lung cancer: Study protocol **Roberto Benzo**
4:15pm – 4:30pm	Accelerating clinical decision making: Tailoring generic MSK models with subject-specific information is a good approximation to the personalized models **Pratik Nag**
4:30pm – 4:45pm	Gait analysis of patients with spinal cord injury: Influence of postoperative rehabilitation **Sanyam Phutela**
4:45pm – 5:00pm	

Friday, September 6

Session 6, 9:00am – 10:30am

	6.A Heart Modelling - Perfusion and Blood Flow | 05.019
9:00am – 9:15am	Data-driven analysis of modelling approaches for distal vessel trees in coronary blood flow **Jack Lee**
9:15am – 9:30am	An integrated computational model for coronary and myocardial blood flow applied in a clinical diagnostic setting **Giovanni Montino Pelagi**
9:30am – 9:45am	Computational modeling of myocardial perfusion and oxygen transport in coronary venous retroperfusion treatments **Haifeng Wang**
9:45am – 10:00am	Integrating time-varying resistance in a lumped parameter model of the coronary circulation **Enhui Yong**
10:00am – 10:15am	Biventricular modelling of human heart with right ventricular outflow tract **Hao Gao**
10:15am – 10:30am	Examining flow dynamics after left atrial appendage occlusion using CFD simulations: Influence of device implant depth **Carlos Albors**

	6.B Stent Modelling | 02.017
9:00am – 9:15am	Multiscale computational model of blood flow of deployed vascular stents **Gabor Zavodszky**
9:15am – 9:30am	Optimizing surgical outcomes in infants with ductal-dependent pulmonary blood flow conditions **Kevser Banu Köse**
9:30am – 9:45am	Optimization of braided stent deployment techniques **Reza Abdollahi**
9:45am – 10:00am	Virtual coronary stenting simulations: On the use of data from patient-specific imaging for validation and clinical interpretation **Francesca Berti**
10:00am – 10:15am	Effect of oversize stenting using a measurement-driven numerical approach for sidewall aneurysms **Levente Sándor**
10:15am – 10:30am	

6.C Experimental Surgery, Animal Models, and Model Transfer | 07.017	
9:00am – 9:15am	Exploring hepatic vascular dynamics and function in metabolic syndrome and steatotic liver disease: Insights from human and rat models **Sandra Nickel**
9:15am – 9:30am	In-silico enhanced animal experiments for evaluation of cardiovascular implantable devices **Jan Brüning**
9:30am – 9:45am	Computer modelling of cortical pathophysiology in parkinsonism **William Lytton**
9:45am – 10:00am	Induction of steatohepatitis in large animals – An example of successful collaboration between medical doctors, veterinarians, and basic scientists… **Philipp Felgendreff**
10:00am – 10:15am	Reduced lifespan in rats with low intrinsic exercise capacity is associated with reduced complex I threshold in females in aging **Alena Spagnolo**
10:15am – 10:30am	

6.D Clinical Decision Support for Cardiovascular Applications | 09.019	
9:00am – 9:15am	Improved patient classification from 2D cardiac ultrasound using multi-modal transfer learning **Joshua R. Dillon**
9:15am – 9:30am	Bayesian inversion enables personalised septic shock treatment guided by noisy arterial pressure waveforms **Finneas JR Catling**
9:30am – 9:45am	Enhancing ECMO device development through machine-learned virtual patient data **Micha Landoll**
9:45am – 10:00am	Towards an in silico clinical trial on the use of fractional flow reserve based on a data-driven modeling approach **Pjotr Hilhorst**
10:00am – 10:15am	Predicting ventricular tachycardia, taking time into the equations **Carlijn Buck**
10:15am – 10:30am	Patient-specific hemodynamic effect of acute exercise in hypertensive subjects and controls revealed by 4D flow MRI and cardiovascular modeling **Gunnar Cedersund**

6.E Human Brain Modelling | 02.011	
9:00am – 9:15am	Multiscale modelling in deep brain stimulation **Ursula van Rienen**
9:15am – 9:30am	
9:30am – 9:45am	Holography-assisted simulation of brain function **Wieslaw Nowinski**
9:45am – 10:00am	Multiscale model of spreading depolarization in neocortical microcircuits **Adam John Hunter Newton**
10:00am – 10:15am	Investigation of intracranial dynamics using a personalised computational model **Alireza Sharifzadeh-Kermani**
10:15am – 10:30am	Challenges and perspectives in human brain tissue modeling **Silvia Budday**

6.F Pathway to Digital Twins | 02.005	
9:00am – 9:15am	From clinical research to digital twins: How personalised computational modelling can add value in clinical care **Robyn Walker May**
9:15am – 9:30am	A demonstrator of the EDITH virtual human twin platform **Marian Bubak**
9:30am – 9:45am	12 Labours DigitalTWINS platform: Enabling development and clinical translation of virtual human twins **Thiranja P Babarenda Gamage**
9:45am – 10:00am	AI-CARE: Digital twin for cancer research **Daniele Tartarini**
10:00am – 10:15am	OSS-DBS v2.0: Adaptive meshing for deep brain stimulation modelling **Jan Philipp Payonk**
10:15am – 10:30am	

6.G In-silico Orthopedics II | 01.005	
9:00am – 9:15am	Experimental validation of in silico models of orthopaedic implants **Luca Cristofolini**
9:15am – 9:30am	
9:30am – 9:45am	InSole: An in-silico workflow towards personalized prescription of corrective insoles during walking **Bryce Adrian Killen**
9:45am – 10:00am	In-silico analysis of dropfoot disease and biomechanical evaluation of ankle-foot orthoses **Armagan Can Yildiz**
10:00am – 10:15am	Verification of finite element wear models of a total ankle replacement **Cristina Curreli**
10:15am – 10:30am	Digital orthopedic methods for total knee arthroplasty: Insights from comparative analysis and validation studies **Kevser Banu Köse**

6.H In-silico Toxicology | 08.019	
9:00am – 9:15am	Prediction of higher airway particle deposition in children compared with adults: A modelling study **Ge Jin**
9:15am – 9:30am	Towards a virtual embryo: Computational modeling of neural tube closure defects **Job H. Berkhout**
9:30am – 9:45am	Development of a multiscale data-driven lung model to understand the health effects of vaping **Marzieh Aghababaie**
9:45am – 10:00am	Building disease ontology maps: In silico tools for applications in toxicology **Bernard Staumont**
10:00am – 10:15am	Modelling toxicity after prostate cancer radiotherapy using genetically guided pixel-wise analysis **Tiziana Rancati**
10:15am – 10:30am	Virtual Cornea: A computational approach for predicting corneal injury and recovery from chemical exposures **Joel Vanin**

POSTER SESSION

At the VPH2024 conference, young researchers take the opportunity to present their recent work during the poster sessions.

Poster sessions will take place on Wednesday and Thursday (Sep. 4th and 5th), from 2:30 pm to 3:30 pm in the foyer of KII (in front of auditoriums).

At the end of the conference the VPHi Best Poster Award will be presented.

Poster Session 1

Wednesday, September 4

2:30pm – 3:30pm

Foyer of KII, in front of the auditoriums

P1:1	Virtual tissue constructs to assess the potential of electrical impedance spectroscopy as a method for tissue identification and pathology diagnosis **Malwina Matella**
P1:2	Can riot-control water cannon be lethal? **Yinze Lei**
P1:3	In silico modelling of the effect of vaping on pulmonary surfactant dynamics from alveolus to whole lung **Ruobing Li**
P1:4	How does utero-placental vascular structure drive Doppler ultrasound? **Nipuni D. Nagahawatte**
P1:5	Exploring the interaction between electrical stimulation and cells by an image-based digital twin **Vien Lam Che**
P1:6	Using sequential nephron segment simulation to understand mechanisms of diuretic resistance **Robert L. Hester**
P1:7	Agent-based simulation of diffusion-MRI for the characterization of NASH **Charles Boulitrop**
P1:8	Role of conduction channels in ventricular arrhythmias: Insights from in silico simulation and clinical data **Javier Villar-Valero**
P1:9	Electrical power and energy distributions in AF activation could direct to areas of rotor stabilization **Guadalupe Garcia-Isla**
P1:10	Inform design of a pulmonary artery pressure sensor using virtual cohorts **Jan Brüning**
P1:11	Modelling sodium transport in kidney tubuloids **Sangita Swapnasrita**
P1:12	Utilising self-similarity to model the morphometry of the pulmonary arteries **Atefeh Rahimi**
P1:13	3D model of the iliac vein unification – Sensitivity analysis **Magdalena Otta**
P1:14	Evaluating the flow convergence method in mitral regurgitation analysis: Insights from computational fluid dynamics and pulsatile in-vitro studies **Alexander Stroh**

P1:15	In-silico design of wearable- and model-driven digital twins for cardiovascular disease monitoring **Bianca Maria Laudenzi**
P1:16	Parameter estimation from undersampled MRI in frequency space **Miriam Löcke**
P1:17	Computational study of the assessment of atria vulnerability to mutation-induced AF in 3D human atria **Lucia Romero Perez**
P1:18	Mapping persistent atrial fibrillation dynamics: Insights from electro-optic flow analysis in a virtual patient population **Ovais Ahmed Jaffery**
P1:19	Virtual physiological human research requires macro theory **Genggeng Ye**
P1:20	Integrating care: Abalietas as a bridge between clinical quality registers and electronic medical records for enhanced machine learning applications in healthcare **Krzysztof Gądek**
P1:21	PyPopSim: Form single simulation to population studies **Jeremy Laforet**
P1:22	AlmaHealthDB: A digital infrastructure for secure management, interoperability and reuse of health research data **Antonino A. La Mattina**
P1:23	Towards international standardization of computational modeling and simulation in the field of medical devices **Charlott Danielson**
P1:24	A physiologically based digital twin for alcohol consumption – Predicting real-life drinking responses and long-term plasma Peth **Henrik Podéus**
P1:25	Hipathia and metabolizer: Unveiling disease mechanisms and enabling personalized medicine **Kinza Rian**
P1:26	In silico modeling of cell migration over texturally treated curved surfaces **Majid Nazemi**
P1:27	Systematic understanding and categorization of modeling & simulation context of use in knee biomechanics **Snehal Chokhandre**
P1:28	Sensitivity analysis of a finite element model predicting the fixation stability of tibial plateau fractures **Simon Comtesse**
P1:29	Designing a single-use novel surgical kit for a cervical facet cage implantation through iterative FE simulations **Luca Ciriello**
P1:30	3D optical scanning toward personalised whole-body models **Alexander Dixon**
P1:31	A machine learning-based in silico assessment to predict human respiratory irritants and toxicity **Yunendah Nur Fuadah**
P1:32	Unsupervised learning for MRI cross-scanner harmonization **Grace Wen**

Poster Session 2

Thursday, September 5

2:30pm – 3:30pm

Foyer of KII, in front of the auditoriums

P2:1	Incorporating wearable sensor data into research workflows **Gregory B Sands**
P2:2	Modelling the neural regulation of gastric motility at the tissue level **Omkar N. Athavale**
P2:3	Efficient numerical simulation of effective micro-macro models for reactive transport in elastic perforated media **Jonas Knoch**
P2:4	The development of the phantom fiber to mimick muscle fibre activity for the validation of magnetomyography sensors **Ahmet Dogukan Keles**
P2:5	A multiscale network model of tumor microenvironment to predict immunotherapeutic response of head and neck cancers **Rajanikanth Vadigepalli**
P2:6	Mechanobiological modelling to capture relative effects of deviatoric and volumetric stresses on epiphyseal bone growth **Jorge Mateos Arriola**
P2:7	Sensory perturbation due to blood flow restriction leads to change in active MU pool **Franziska Bubeck**
P2:8	A graphic representation of arterial pulse pressure vs. mean arterial pressure time series may be used for clinical decision support during intraoperative hypotension **Estefanía Žugelj Tapia**
P2:9	Development of a hemodynamic model to simulate heart failure patients **Arina Borzistaia**
P2:10	Hypertensive signature in the photoplethysmography signal by combining a whole-body cardiovascular model and optical simulations **Clement Vasseur**
P2:11	Pre-procedural planning of transcatheter heart valve interventions using imaging and in silico modelling Shelly Singh-Gryzbon
P2:12	A 0D-1D global, closed-loop model of the cardiovascular system **Stefano Costa**
P2:13	In silico validation of TAG-based coronary blood flow distribution methods for patient-specific computational iFR prediction **Ester Bergantin**
P2:14	A comparative study between 3D segmentation methods of aorta in contrast enhanced MR acquisitions **Horia Andrei Leonte**
P2:15	Simulation workflow for stent-assisted coiling of brain aneurysms **Felix Borges**
P2:16	Atmospheric pollutants and atrial arrhythmias: An in silico study **Javier Saiz**
P2:17	In-silico assessment of hemodynamics in stenoses of the fontan circulation **Adriano Schlief**

P2:18	A clinical decision support tool for patient management **Adam Nowak**
P2:19	Creation and regression analysis of a hemodynamic virtual patient database **Richard Weber**
P2:20	Towards a prostate cancer radiotherapy digital twin: Simulating the response of prostate cancer to external radiotherapy through mechanistic multiscale modelling. Sensitivity analysis and clinical adaptation **Georgios S. Stamatakos**
P2:21	Recommendations and requirements for implementing computational models in clinical integrated decision support systems (ISO/TS 9491-2) **Martin Golebiewski**
P2:22	Benchmarking computational models of peritoneal dialysis in pigs and patients **Sangita Swapnasrita**
P2:23	Toward multiscale lymph node model: T cell search strategy study **Sára Štráchalová**
P2:24	Software infrastructure tools for biomedical models in systems biology **Herbert Martin Sauro**
P2:25	Probabilistic Boolean modelling highlights neural tube closure dynamics and molecular signalling insights **Ahmed Hemedan**
P2:26	Explanatory models of human physiology to teach pathophysiology of diabetic ketoacidosis with simulators **Tomas Kulhanek**
P2:27	In silico clinical trial to predict the efficacy of alendronate for preventing hip fractures **Sophie Nguyen**
P2:28	Comparative assessment of lower limb joint angle estimation between BTS system and OpenSim **Kaushik Mukherjee**
P2:29	Quantification of periprosthetic bone loss using electrical impedance tomography **Lisa Krukewitt**
P2:30	Machine learning framework to study the impact of metastatic cancer in the spine **Simão Laranjeira**
P2:31	A sustainable neuromorphic framework for disease diagnosis using AI **Rutwik Gulakala**
P2:32	Limits and capabilities of diffusion models for the anatomic editing of digital twins **Karim Kadry**
P2:33	Cross-disease predictive analysis for pandemic preparedness **Joana Elena Meyer**

ABSTRACTS: POSTER

Virtual tissue constructs to assess the potential of electrical impedance spectroscopy as a method for tissue identification and pathology diagnosis

Malwina Matella[1,2], Keith Hunter[3], Zi-Qiang Lang[1,2], Zhicheng Lin[1,2], Dawn Walker[1,2]
[1]Department of Computer Science, University of Sheffield, United Kingdom; [2]Insigneo Institute of in silico Medicine, University of Sheffield, United Kingdom; [3]Liverpool Head and Neck Centre, Molecular and Clinical Cancer Medicine, University of Liverpool

Electrical Impedance Spectroscopy (EIS) has been demonstrated as a non-invasive method to differentiate between healthy and potentially malignant tissue types, e.g. in the case of early cervical cancer detection. We describe how computational simulation using "Virtual Tissue Constructs" consisting of multiscale finite element models, were created and selected features varied in line with data derived from histological images to generate virtual EIS spectra. Machine Learning methods can then be applied to the latter to explore the potential of to distinguish between specific sets of tissue types in vivo. In an exemplar study, we focus on the challenge of differentiating between healthy thyroid and parathyroid tissue during thyroidectomy, where erroneous excision of the parathyroid tissue can cause post-operative complications for the patient. A previous pilot study had reported similarities in the spectra measured from these tissues, suggesting that separation based on EIS measurements may not be straightforward. In order to explore this further, we developed "Virtual Tissue Constructs" representing healthy thyroid and parathyroid tissue structures based on histological images. By adapting aspects of the model meshes at micro-, meso- or macro- in line with realistic variability in certain aspects of the tissue structures, we were able to simulate sets of virtual electrical impedance spectra for both thyroid and parathyroid tissues. Global sensitivity analysis identified the potential presence of a surface layer of connective tissue or *fascia*, as a factor that could "contaminate" EIS measurements and confound the separation of the two tissue types. Separability analysis on these simulated data sets using machine-learning based methods suggested that in the case that the fascia was completely removed, it should theoretically be possible to distinguish between the two tissue types with a high classification performance of over 0.99 AUC. We are now applying a similar approach to the study of oral tissues in order to explore the potential of EIS to differentiate between normal and potentially pre-malignant lesions in the context of oral cancer.

Can riot-control water cannon be lethal?

Yinze LEI[1], Jing XIE[1], María González García[2], Daniel Rittel[3]
[1]Beijing Institute of Technology, 100081, Beijing, China; [2]Department of Biomechanics and Accident Research, Ludwig-Maximilians-University Munich, Munich, Germany.; [3]Faculty of Mechanical Engineering, Technion - Israel Institute of Technology, 32000 Haifa, Israel

A riot-control water cannon is a large, supposedly nonlethal apparatus that uses pressurized water to control and disperse crowds. However, riot-control water cannons may cause personal injury if directly aimed at the human forehead, for example. Because of the absence of well-defined safety standards, the effect of waterjet impact in relation to the dynamic response and injury pattern of the human head at different impact distances, impact locations and angles is investigated here. The direct correlation of the human head response to the corresponding injury potentials for various situations is critically evaluated to render the water cannon a truly nonlethal weapon, or at least raise the awareness about its limitations. In this investigation, the research framework is divided into two steps: calculating the waterjet impact pressure (also called equivalent pressure) and simulating the dynamic response of the head. In the 1st step, the water chamber theoretical model was used to verify the numerical model of waterjet, and the impact equivalent pressure was obtained by considering the time-space evolution of the

waterjet velocity. Subsequently, the equivalent pressure was set as the boundary condition for the human body dynamic response simulation in the 2nd step (ABAQUS/Explicit). Based on a comprehensive parametric investigation, the head impact injury risk was estimated by integrating different injury criteria. The simulation results suggest that 10 m is a critically dangerous working distance because the impact of a water cannon can lead to skull, cervical vertebra and brain injuries. In addition, compared to side/back impacts, frontal impacts are much more dangerous due to a more extensive range of head movement. Oblique impact induces rotational movement on the human body, resulting in a significant risk of injury. A quantitative injury risk analysis is presented to provide safety guidance for water cannon usage.

In silico modelling of the effect of vaping on pulmonary surfactant dynamics from alveolus to whole lung

Ruobing Li, Alys Clark, Merryn Tawhai, David Nickerson, Kelly Burrowes
Auckland Bioengineering Institute, University of Auckland, New Zealand

The lungs provide an interface between inhaled air or aerosols and our internal systems. During breathing, there is a complex interplay between tissue, air, and surfactant governing the dynamic mechanical properties of the lungs. Pulmonary surfactant forms part of the air-liquid interface in each alveolus and plays a crucial role in modulating surface tension and overall lung mechanics. Recent studies have raised concerns about the potential adverse effects of e-cigarette (EC) aerosols on pulmonary surfactant and overall lung health. Exposure to EC aerosols has been shown to disrupt surfactant's ability to maintain low surface tension, thus affecting lung function. This study aims to develop a computational model to understand the impact of vaping on alveolar and whole lung function due to surfactant. We implemented the model of Otis et al. [*J Appl Physiol. 1994; 77(6):2681-2688*] which described the behaviour of alveolar surfactant based on Langmuir kinetics and the 'squeeze-out' relationship of surfactant molecules. The Young-Laplace equation is used to calculate the recoil pressure generated by the surfactant layer. This pressure was coupled with the ventilation model of Swan et al. [*J Theor Biol. 2012; 300:222-31*] to enable simulation of the impact of surfactant on regional and whole lung ventilation. This model can be solved within subject-specific geometric models and used to simulate the dynamic changes in pulmonary compliance in healthy normal conditions and after EC exposure. A sensitivity analysis of the model demonstrated that the adsorption coefficient, minimum surface tension, and isotherm slope were important contributors to lung mechanics for healthy surfactant concentrations. Comparison with data from the literature was used to verify the physiological predictions of both the alveolar and organ level models. When altering the surfactant properties to reflect EC exposure, minimum surface tension was increased. This resulted in higher pressures due to surface forces, reduced lung compliance, and increased work of breathing.

How does utero-placental vascular structure drive Doppler ultrasound?

Nipuni D. Nagahawatte[1], Toby Jackson[1], Joanna James[2], Alys R. Clark[1]
[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand

Doppler ultrasound is commonly used in obstetric care to assess the health of the placenta. Better understanding of what drives Doppler could help to detect indices that are better at predicting placental dysfunction, or improve sensitivity of Doppler in detecting complications. This study aims to provide a computational model of the utero-placental vasculature, with personalised data fitting, to provide new insights into drivers of Doppler waveforms. The model incorporates uterine, arcuate, radial, and spiral

arteries, the intervillous space, and arterio-venous anastomoses. It was fitted to 5 (4 healthy, 1 abnormal) uterine artery Doppler waveforms from open-source resources and published studies. All parameters were free to vary within physiologically defined ranges. Variability across heartbeats within individuals and across different subjects was assessed. A parameter sensitivity analysis showed most sensitivity to the uterine and radial artery radii. The fit parameters with highest variability between subjects were radii of uterine (1.49±0.08 mm), arcuate (1.85±1.03 mm), and radial (0.23±0.02 mm) vessels. The uterine artery, nearest to the measurement site was most influential, correlating with systolic to diastolic flow velocities = 2.38±0.74 and resistance index = 0.55±0.11 ($p<0.05$). Notching in the waveform was influenced by downstream effects of anastomoses and the radius of the radial artery. Intervillous space resistance was a relatively minor contributor to waveforms, highlighting the importance of maternal utero-placental factors in clinical assessment. Fitted parameters showed a standard deviation of <25% across heartbeats in an individual subject, a factor that should be assessed in larger cohorts to determine uncertainty in predictions. The model does not extend beyond the uterus and fitting could be improved in the future by incorporating the wider maternal circulation. Work on this project is supported by Wellcome Leap as part of the In Utero Program.

Exploring the interaction between electrical stimulation and cells by an image-based digital twin

Vien Lam Che[1], Meike Bielfeldt[2], Nils Arbeiter[1], Barbara Nebe[2], Ursula van Rienen[1], Julius Zimmermann[1,3]
[1]University of Rostock, Germany; [2]Rostock University Medical Center; [3]University of Pavia

Electrical stimulation has garnered considerable attention for promoting bone, cartilage, and nerve tissue healing and regeneration. To gain insight into the interaction mechanism between the electric field and the cells, it is essential to determine the actual field strength at the cellular scale and the induced transmembrane potential (iTMP). Here, the digital twin of an electrical stimulation device *in vitro* was used to inform fine-grained numerical simulations of cells based on 3D fluorescent images. The entire setup was represented by an equivalent circuit considering the electrochemical interactions at the electrode interface. This impedance model was experimentally characterised and updated based on electrochemical impedance spectroscopy data and voltage-current measurement. The stimulation voltage, predicted by the equivalent circuit, was incorporated into a numerical model of the electrical stimulation, coupling macro- and microscale. The influence of input parameters in the numerical model was also examined through uncertainty quantification (UQ) and sensitivity analysis. The impedance model could predict stimulation voltages and currents reliably. Based on the potential distribution within the stimulation chamber, the boundary conditions for a sub-model containing the cells were set to 0.4214 V and 0.4279 V. The electric field across the 3D image volume ranged from 31.3 V/m to 33.8 V/m. The iTMP was relatively small at 0.6 mV. It is below the commonly accepted threshold of a few mV, which may lead to ion migration across the membrane. Based on our UQ study, the cellular parameters, such as the dielectric properties and thickness, had no significant impact on the observables. Instead, only the conductivity of the cytoplasm notably influences the iTMP and the electric fields. In future research, we want further to explore the biological implications of electrical stimulation by leveraging digital twins. The goal is to develop a rational choice of the iTMP and test if it is the variable representing the efficacy of electrical stimulation.

Using sequential nephron segment simulation to understand mechanisms of diuretic resistance

W Andrew Pruett[1], Marion Wofford[2], John S Clemmer[1], Robert L Hester[1]
[1]Department of Physiology, University of Mississippi Medical Center, United States of America; [2]Department of Medicine, University of Mississippi Medical Center, United States of America

Congestion is the major factor leading to hospital admission in acute decompensated heart failure (ADF), and diuretic resistance (DR) is associated with worse outcomes and increased length of stay. Continuous loop diuretic use can lead to an emergent DR, where previously effective doses become ineffective, and further increases in dosage have no effect. One hypothesis is that compensatory reabsorption in the distal nephron underlies DR. We utilized HumMod, an integrated model of human physiology, to investigate furosemide DR in hypertensive virtual patients. Furosemide blocks NKCC2 and is utilized in acute congestion to reduce patient fluid volume. Control systems working through WNK kinase modulate sodium reabsorption in the distal nephron on intracellular chloride. Modulation of sodium reabsorption in a nephron segment alters reabsorption distally through changes in lumenal fluid, intracellular electrolyte levels, and activation of kinases. In these simulations, hypertensive virtual patients were subjected to furosemide (at 20, 40 and 80 mg four times daily on subsequent days). In each case, furosemide led to a compensatory increase in sodium reabsorption through NCC in the distal and connecting tubules (CNT), and through ENaC in the CNT and collecting duct. NCC reabsorption was blunted by increases in intracellular Cl and subsequent reduction in phosphorylation of WNK1, WNK4, and SPAK. ENaC transport increases were blunted by increases in intracellular Na. These effects persisted at all dosage levels. Continued use of furosemide was associated with a decrease in serum [Cl], and in some virtual patients, hypochloremia resulted in removal of inhibition of NCC and ENaC in the distal nephron, triggering compensatory sodium reabsorption that offset the blockade of NKCC2. This simulation study demonstrates that the recently discovered WNK kinase control system may be responsible for DR in some patients, and draws a clear mechanistic link between serum chloride and DR.

Agent-based simulation of diffusion-MRI for the characterization of NASH

Charles Boulitrop, Jiři Pešek, Dirk Drasdo
Group SIMBIOTX, INRIA Saclay, 91120 Palaiseau, France

Nonalcoholic steatohepatitis (NASH) is a liver disease in which hepatocytes are subject to ballooning i.e., accumulation of lysis vesicles in cytoplasm, swelling and alterations of the cytoskeleton. These morphological changes progressively impact the hepatocytes function and ultimately leads to liver failure, and death. The prevalence of NASH in the world population is increasing alarmingly, which requires better strategies to diagnose NASH and monitor its progression at the individual level of the patient. Currently, the most reliable strategies for diagnosing NASH rely on invasive interventions, such as biopsies, which have many drawbacks, among which cost, sampling error and risk of complications are the main factors. Therefore, imaging techniques, like temporal diffusion spectroscopy (TDS) offer a promising, non-invasive alternative. TDS is an extension of diffusion-weighted magnetic resonance imaging, which enables the identification of an apparent diffusion coefficient, which is determined by the underlying liver morphology. However, identification of cues linked to NASH inside the signal obtained from TDS, is highly non-trivial, due to the complexity of the liver microarchitecture. This difficulty can be overcome by in-silico methods. The goal of this work it to relate and optimize the MRI signals to changes in the microarchitecture typical for NASH, first by simulating a phantom experiment, and then by simulating an experiment in an in-silico liver microarchitecture. The selected approach relies on the framework of agent-based models, which explicitly solve the Bloch-Torrey equation in

the complex environment in a stochastic manner. When compared with traditional mesh-based approaches, our method allows us to model more accurately the diffusion processes by taking into account their stochastic behavior, to incorporate complex boundary conditions which can vary over time, while allowing us to capture necessary details from the microarchitecture, such as cell membranes, blood vessels or bile canaliculi. These advantages allow us to solve efficiently the Bloch-Torrey equation given the constraints of the liver architecture.

Role of conduction channels in ventricular arrhythmias: Insights from in silico simulation and clinical data

Javier Villar-Valero[1], Juan F Gomez[2], David Soto-Iglesias[3], Diego Penela[3], Antonio Berruezo[3], Beatriz Trenor[1]
[1]Centro de Investigación e Innovación en Bioingeniería, Universitat Politècnica de València, Valencia, Spain; [2]Valencian International University, Valencia, Spain; [3]Arrhythmia Department, Heart Institute, Teknon Medical Center, Barcelona, Spain

Patients who have suffered myocardial infarction face a 10% high-risk mortality, half attributed to ventricular arrhythmias. This work aims to quantify the role of conduction channels in the occurrence of reentries through their in silico simulation using specific models of post-myocardial infarction patients. A dataset of 29 post-MI patients from Teknon Medical Center forms the study basis, in addition with quantification of the border zone of the scar forming conduction channels: fiber-shaped isolated border zone which connects two regions of healthy tissue. Myocardial scar after the infarction is characterized by a non-conductive core and a border zone changing cellular density, conduction velocity, and ion channel conductances. Magnetic resonance imaging is used for anatomical segmentation and three-dimensional model construction. The same stimulation protocol is applied in silico, inducing reentry in 12 patients. Results show the mass of ventricular conduction channels significantly differentiates simulated arrhythmia occurrence, indicating a potential non-invasive predictor of reentrant arrhythmia extracted from magnetic resonance imaging.

Electrical power and energy distributions in AF activation could direct to areas of rotor stabilization

Guadalupe Garcia-Isla[1], Yaiza Sánchez[1], Laura Martínes-Mateu[2], Javier Saiz[1], Omer Berenfeld[3]
[1]Universitat Politècnica de València, Valencia, Spain; [2]Universidad Rey Juan Carlos, Madrid, Spain; [3]University of Michigan, Ann Abor, Michigan, USA

Atrial fibrillation (AF) is the most common sustained arrhythmia. Despite its high incidence, its mechanisms and progression are not well understood yet. Better understanding of dynamics and stability of rotors during AF could help in the developing more effective therapies. Toward that end we studied novel relationships between rotor dynamics and the energy domain characteristics of the substrate. We aimed first to characterize the impact of varying membrane ionic currents on the electrical power and energy of the action potential, and secondly, to investigate the impact of the spatial distributions of electric power and energy of propagating action potentials on the drift and stability of rotors in human persistent AF model. Simulations of rotor activity were performed in two-dimensional (2D) anisotropic tissue models of persistent AF with varying heterogenous distributions of ionic currents based on experimental data from the left and right atria. The heterogeneities included gradients in IK1, ICaL and IKAch and across the 2D model. Rotors were initiated and let to drift spontaneously. Instantaneous electrical power was calculated for the ionic, capacitance, and electrotonic currents of all the action potentials across the model. Thereafter the root-mean-square (RMS) of the power time series as well as the power time integral as energy were

calculated for the series of re-entrant cycles. Our simulations with -60% (IK1 and ICaL) and +50% (IKACh) spatial gradient change relative to baseline values, showed that the rotor drifted toward regions with lowest IK1 and IKACh, or to regions with highest ICaL. The core area of the rotor, where its tip pivots, presented lower RMS power and energy values than the surrounding tissue. The action potentials with lower IK1 and IKACh, and higher ICaL than baseline also presented with lower RMS and energy values. We conclude that rotors in our AF model drifted toward lowest electrical RMS power and energy areas, regardless of the specific ionic current gradient. Localizing regions with low electrical RMS power or energy values of activations might help in identifying areas that attract and stabilize rotors.

Inform design of a pulmonary artery pressure sensor using virtual cohorts

Jan Brüning[1,2], Adriano Schlief[1,2], Pavlo Yevtushenko[1,2], Jan Romberg[3], Andreas Arndt[3,4,5], Leonid Goubergrits[1,2]
[1]Institute of Computer-assisted Cardiovascular Medicine, Charité – Universitätsmedizin Berlin; [2]Deutsches Herzzentrum der Charité; [3]Biotronik SE & Co. KG; [4]Technische Universität Dresden, Germany; [5]Kurt-Schwabe-Institut für Mess- und Sensortechnik Meinsberg e.V., Meinsberg, Germany

Computer models and simulations hold the promise to replace expensive and complex in-vitro bench tests and inform medical devices, allowing to save time and accelerate design cycles. For example, the availability of comprehensive 3D model data bases of the respective anatomical structures a device is intended to be implanted into can inform the device design with respect to required sizes, shapes, delivery methods, and many other aspects, ensuring that the device is applicable to a wide variety, if not the entire population. In this study we describe a combined approach using statistical shape modelling and a fast-to-evaluate model mimicking the device implantation procedure for a pulmonary artery pressure sensor. These devices are implanted within the pulmonary artery via a catheter-based procedure. The presented approach is intended as a proof of concept for rapid evaluation of different device designs with respect to the availability of suitable landing sites and the risk of the device obstructing side branches of the pulmonary artery. For this a database of 2,000 synthetic pulmonary artery geometries was created using a statistical shape model, mimicking the overall heterogeneity of the complex vascular anatomy of the pulmonary artery. The virtual device implantation was simplified and used only geometric constraints. A landing site in the left or right pulmonary artery was chosen randomly based on the device diameter specifications. The rotation of the device within the vessel was chosen randomly. The sensor body was then aligned with the vessel wall, mimicking the implantation. Then the device position is assessed with respect to the side branch configuration. The fast-to-evaluate model for device implantation requires only a couple of seconds for each implantation simulation allowing to rapidly evaluate hundreds of different implantation scenarios. In a next step, hemodynamic surrogate parameters for thrombosis, such as wall shear stresses and oscillatory shear indices will be calculated using computational fluid dynamics to assess whether specific configurations are at higher risk for thrombus formation, extending the approach by functional information.

Modelling sodium transport in kidney tubuloids

Sangita Swapnasrita[1,2], Anita Layton[3], Aurelie MF Carlier[1]
[1]Maastricht University, the Netherlands; [2]UMC Utrecht, the Netherlands; [3]University of Waterloo, Canada

Kidney tubuloids and organoids are miniature kidney structures grown in the lab from stem cells under controlled medium changes, mimicking the complexity of real human kidneys. For patients in need of kidney transplantation, these 3D mimics provide a

regenerative platform that are patient-specific and thus immune-compatible. In this work, to complement and reduce the cost and time of experimental kidney organoid research, we create a first-of-its-kind multi-scale (cell-nephron-tubuloid) computational model. Yengej et al. showcased the capability of tubuloids in capturing the apical and basolateral transport of sodium by using inhibitors to block the transport pathways (alone and in combinations), qualitatively similar to that of kidneys. In particular, they inhibit Na+-K+-ATPase by **O**uabain (basolateral), NKCC2 by **B**umetanide (apical), NCC by **T**hiazide (apical) and epithelial sodium channel by **A**miloride (apical). The combinations they used are O, BO, TO, AO and BTAO. To replicate the experimental setup, the model accounts for the following three solutes: Na^+, K^+ and Cl^-. Medium concentrations were set according to the experimental conditions. The model is formulated for steady state and consists of a large system of coupled ordinary differential equations and algebraic equations. Model solution describes the cytosolic solute concentrations, membrane potential, and transcellular and paracellular fluxes of the three solutes and water. Note that, only segments found to be present in tubuloids are simulated here: proximal tubule (PT), distal convoluted Tubule (DCT), medullary and cortical thick ascending limb (mTAL and cTAL), connecting tubules (CNT) and collecting duct (CCD), with the exception of the progenitor cells. We trained the model on the first four (O, BO, TO, AO) and validate it on the last combination (BTAO). We showed enhanced uptake in the simulated tubuloids when exposed to hypotonic Cl^- in O and BTAO condition similar to that in experiments. In addition, we identified relative transporter importance and predicted the most effective inhibitor. This simulation framework is an important step in regenerative kidney research towards *in silico* trials.

Utilising self-similarity to model the morphometry of the pulmonary arteries

Atefeh Rahimi[1], Joyce John[1], Alys Clark[1], Kelly Burrowes[1], Farbod N Rahaghi[2], Raul San Jose Estepar[2], Merryn Tawhai[1]
[1]University Of Auckland, Bioengineering Institute, New Zealand; [2]Brigham and Women's Hospital (BWH) and Harvard Medical School (HMS)

This study aims to construct a comprehensive model of the human pulmonary artery tree, addressing challenges in image segmentation by incorporating the concept of self-similarity demonstrated in pig lung studies. Despite advancements in defining artery tree geometry through CT imaging, a persistent limitation is the oversight of many small lateral arteries, leading to errors in morphometric descriptions and derived models. This underscores the critical need for a nuanced approach to capture the intricate details of the pulmonary vascular system. Data from 10 never-smokers (5F/5M) with normal lung function underwent intra-pulmonary vessel segmentation and artery/vein separation using the Chest Imaging Platform. Subsequently, the data were transformed into 3D 'graphs' using Python KDTree functions. The connection of sub-graphs involved recalibrating branches and linking closest trees. Essential metrics such as length to diameter ratio (L/D), child to parent diameter ratio (D/Dp), and branching angle (Θ) were then calculated. Lateral branches were introduced to arteries with an L/D ratio exceeding 5.0, with lateral dimensions determined using values derived for minor branches in the arterial tree (L/D = 2.46, D/Dp = 0.4) under the assumption of self-similarity. Initial examination of the raw, uncorrected data (N = 316 ± 65 branches) revealed crucial metrics for the pulmonary artery tree: 3.57 ± 3.32 for length to diameter ratio (L/D), 0.86 ± 0.43 for child to parent diameter ratio (D/Dp), and 46.2 ± 32.7 for branching angle (Θ). Efforts to address connectivity gaps refined the dataset to N = 330 ± 159 branches. Further augmentation through the addition of lateral branches, guided by an L/D ratio exceeding 5.0, resulted in a total of N = 452 ± 123 branches with refined metrics of 0.80 ± 0.40 for D/Dp, 2.89 ± 1.78 for L/D, and 36.6 ± 31.97 for Θ. Comparative analysis with literature values (L/D = 2.8-3.25, D/Dp = 0.78-0.83, Θ = 15.3-57.0) highlights the alignment of our refined model with established standards, emphasizing its reliability in characterizing the pulmonary artery tree.

3D model of the iliac vein unification – Sensitivity analysis

Magdalena Otta[1,2,3], Jan Meizner[1], Ian Halliday[2,3], Maciej Malawski[1,5], Chung Lim[4], Janice Tsui[4,6], Andrew Narracott[2,3]
[1]Sano Centre for Computational Medicine, Poland; [2]Division of Clinical Medicine, University of Sheffield, United Kingdom; [3]Insigneo Institute for in silico medicine, University of Sheffield, United Kingdom; [4]Royal Free London NHS Foundation Trust, United Kingdom; [5]Institute of Computer Science, AGH University of Science and Technology, Kraków, Poland; [6]University College London, London, UK

Deep vein thrombosis (DVT) of the lower limb is a disease in which blood clots form in the leg due to pathological changes in the blood vessels or the blood itself [1]. A common location for thrombus development is the iliac vein unification. Up to 50% of DVT patients develop post-thrombotic syndrome (PTS). Its variable clinical presentation makes it challenging to treat. Modelling could provide additional information for DVT and PTS handling in the clinic [2]. Building on previous Sobol sensitivity analysis of a 0D model of the lower limb venous network [3], a set of idealised 3D geometries of the iliac vein unification was created to simulate the local blood flow patterns in the steady state using ANSYS Fluent. Preliminary sensitivity analysis of the 3D flow field was conducted by varying the geometry and the boundary conditions to investigate their influence on the wall shear stress (WSS) distribution – a parameter related to thrombus development. The chosen threshold of low WSS was set at 0.15 Pa. The analysis showed that a change in the unification angle from 30 to 60 degrees (literature value of 55) has a modest effect in comparison to the variation in velocity boundary conditions (between 0.08 and 0.26 m/s for both inlets). All considered geometries have a consistent location of the low WSS area, but the distribution over that area differs. The significance of this effect is under investigation. Relatively high flow in the internal iliac side branch tends to significantly increase the area of low shear, but the variation is not linear due to interaction with the external iliac flow field. In the next steps, a transient analysis will be conducted to determine whether these trends persist with time varying inflow conditions, improving understanding of the relative influence of anatomy and inflow conditions prior to extension to patient-specific models.

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[2] doi: 10.1016/j.amepre.2009.12.017
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Evaluating the flow convergence method in mitral regurgitation analysis: Insights from computational fluid dynamics and pulsatile in-vitro studies

Alexander Stroh[1], Robin Leister[1], Roger Karl[2,3], Lubov Stroh[4], Derliz Mereles[3], Matthias Eden[3], Luis Neff[4], Raffaele de Simone[2], Gabriele Romano[2], Matthias Karck[2], Christoph Lichtenstern[4], Norbert Frey[3], Jochen Kriegseis[1], Bettina Frohnapfel[1], Sandy Engelhardt[2,3]
[1]Institute of Fluid Mechanics (ISTM), Karlsruhe Institute of Technology (KIT), Germany; [2]Department of Cardiac Surgery, Heidelberg University Hospital, Heidelberg, Germany.; [3]Department of Internal Medicine III, Heidelberg University Hospital, Heidelberg, Germany; [4]Department of Anaesthesiology, Heidelberg University Hospital, Heidelberg, Germany

Mitral Regurgitation (MR) is a prevalent valvular heart condition characterized by the reverse flow of blood through the mitral valve. The accurate assessment of MR is crucial for effective treatment, yet current diagnostic methods, primarily echocardiography, have significant limitations. This study aims to investigate the precision of MR quantification using **transesophageal echocardiography (TEE)** and **Particle Image Velocimetry (PIV)** in a controlled in-vitro setting and to augment this analysis through **computational fluid dynamics (CFD)**. We utilize Mitral Regurgitation Orifice

Phantoms (MROPs) of different simplified shapes (circular, slit and tear-drop shape) and sizes, constructed to simulate various MR conditions. A hemodynamic left-heart simulator created a controlled environment mimicking physiological conditions. The experimental procedure was meticulously designed to capture the dynamic behavior of regurgitation jets across the MROPs, providing a basis for quantitative and qualitative analysis. The PIV-based fluid flow analysis revealed distinct patterns in regurgitation jets across orifice shapes and sizes, particularly noting the formation of a starting vortex as a dominant feature. Echocardiographic findings showed a consistent trend of underestimating MR compared to PIV, particularly in larger orifice areas. The deviation in regurgitation volume estimates reached up to 52% in some cases, indicating a significant underestimation of MR severity. CFD analysis further supported these findings, highlighting that selecting a suboptimal aliasing velocity during echocardiographic measurements is a one of the major sources of potential underestimation. The study's findings emphasize the limitations inherent in current TEE methodologies for MR assessment, particularly in cases of severe regurgitation. The discrepancy between PIV and echocardiography highlights the need for enhanced diagnostic techniques or the refinement of existing methods to ensure accurate MR quantification. Moreover, the utilization of CFD reveals its high potential in identifying error sources within conventional fluid mechanics-based characterization methods.

In-silico design of wearable- and model-driven digital twins for cardiovascular disease monitoring

Bianca Maria Laudenzi, Lucas Omar Müller
University of Trento, Italy

Cardiovascular disease (CVD) is the leading cause of death worldwide. The construction of **health digital twins** for patient monitoring could represent a fundamental tool in order to reduce invasive procedures, minimize patient hospitalization, design clinical trials and personalize therapies of those affected by CVD. The aim of this study is to investigate the feasibility of **machine learning**-based bio-signals analysis for the monitoring of patients with CVD, using a database of **in-silico** patient data. In particular, this involves generating a **virtual database** representing the physiological characteristics of both healthy individuals and those with CVD. Our database allows us to construct, verify, and choose appropriate **surrogate models**, informed by **wearable-acquired data**, in order to reproduce variables normally acquired only during in-hospital exams. The bio-signals of interest are simulated using a zero-dimensional (0D) **global closed-loop mathematical model** comprising major elements characterizing cardiovascular function. The model's efficacy in simulating **physiological and pathological states**, including hypertension, is verified, establishing its ability to represent the actual patient complexity. For the creation of the **virtual database**, we explore the **sensitivity** of clinically relevant model output variables to model parameters. A database comprising over 50 000 virtual subjects corresponding to the physiology of healthy subjects and of those affected by CVD is created by varying the parameters with major impact on the CVD-relevant signals. We assess the feasibility of creating **machine learning-**powered **surrogate models** for the **prediction of in-hospital data**. Such surrogate models use wearable-acquiarable bio-signals and the selected mechanistic model as inputs for the prediction of signals or indicators of interest. Results of this project will allow for the targeted design of prospective studies based on patient-specific real data, aiming at early detection and monitoring of cardiovascular and cardiorespiratory pathologies.

Parameter estimation from undersampled MRI in frequency space

Miriam Löcke, Cristobal Bertoglio
University of Groningen, The Netherlands

4D Flow MRI is the state of the art technique for measuring blood flow, and it provides valuable information for inverse problems in the cardiovascular system. However, 4D Flow MRI has a very long acquisition time, straining healthcare resources and inconveniencing patients. Due to this, usually only a (small) part of the frequency space is acquired, where then further assumptions need to be made in order to obtain an image. Reconstructing these measurements with Compressed Sensing techniques introduces potential artifacts and inaccuracies, which can compromise the results of the inverse problems. Additionally, there is a high number of different sampling patterns available, and it is often unclear which of them is preferable. Here, we present an inverse problem using highly undersampled frequency space measurements by using a Reduced-Order Unscented Kalman Filter (ROUKF) with a novel objective function. We show that this results in more accurate parameter estimation for boundary conditions in a synthetic aortic blood flow than using measurements reconstructed with Compressed Sensing. We also compare different sampling patterns, demonstrating that the quality of the parameter estimation is strongly dependent on the choice of sampling pattern.

Computational study of the assessment of atria vulnerability to mutation-induced AF in 3D human atria

Rebecca Belletti[1], Joaquín Osca[2], Lucia Romero Perez[1], Javier Saiz[1]
[1]Universitat Politecnica de Valencia, Spain; [2]Hospital Universitari i Politecnic La Fe, Valencia, Spain

Background: Patient-specific 3D models of human atria have been lately used as a tool helping the understanding of different forms of arrhythmia, as atrial fibrillation, and their mechanisms. Moreover, fibrillatory episodes in asymptomatic patients were demonstrated to be induced by potassium channels genetic mutations. **Objective:** This work assesses the effects and the atrial susceptibility to AF of three gain-of-function mutations, KCNH2 T895M, KCNH2 T436M, and KCNE3-V17M which are associated with AF outbreaks, using highly detailed 3D computer models of realistic atria. **Methods:** The atrial model was built by segmenting anatomical structures from CT scans of a patient. The electrophysiological activity of the healthy and of the three mutant cells were simulated using versions of the Courtemanche human atrial model. Sixteen locations across the atria were used as source of ectopic foci and an S1-S2 protocol with two S2 basic cycle lengths was employed with eleven coupling intervals in order to induce arrhythmias, resulting into 1408 simulations. **Results:** The APD_{90} was shortened for the three genetic mutations at 3D level. The KCNE3-V17M mutation provoked the highest shortening, followed by KCNH2 T895M and KCNH2 T436M. The genetic mutation KCNE3-V17M led to the highest number of arrhythmias, all occurring with the S2 BCL set to 100 ms. The KCNH2 T436M and KCNH2 T895M mutations caused a similar increase in vulnerability to AF, although of a lesser extent than KCNE3-V17M mutation, and mostly with S2 BCL set to 160 ms. Overall, the left atrium was the area in which most of the arrhythmic episodes were generated (60%). The mutation KCNE3-V17M caused spiral waves, multiple rotors and disordered electrical pattern, while the mutations KCNH2 T436M and KCNH2 T895M exhibited steady and regular scroll waves. **Conclusions:** The predisposition of atrial tissue to AF-susceptible substrate was demonstrated to increase in presence of the three genetic mutations in different ways, depending on their effects on electrophysiological properties of the atria.

Mapping persistent atrial fibrillation dynamics: Insights from electro-optic flow analysis in a virtual patient population

Ovais Ahmed Jaffery, Alexander Zolotarev, Carlos E. Barrera, Cristobal Rodero, Steven Niederer, Edward J. Vigmond, Wilson W.Good, Gregory Slabaugh, Caroline H. Roney
Queen Mary University of London, United Kingdom

Background: In-silico modelling across virtual populations provides an environment for developing novel therapies and testing these through in-silico trials. An example application area is catheter ablation therapy for persistent atrial fibrillation (AF). We hypothesize that combining electrophysiologic phase and optical flow mapping could offer a novel approach to identify ablation sites in persistent AF and apply the electro-optic flow (EOF) ablation pipeline to a set of 100 x in-silico persistent AF patients. **Aim**: To develop a population of AF ablation therapy models to investigate the efficacy and scalability of an electro-optic flow ablation pipeline. **Methods:** A CT derived bi-atrial in-silico population comprising 100 x virtual patients was curated for simulating AF. A pipeline was developed to assess ablation targets based on simulated AF and to automatically connect targets to the closest inert boundaries. As part of target assessment, phase singularities (PS) and Horn-Schunck average optical flow maps were computed. An intersection of information assessed through PS and curl of average optical flow was utilized to generate EOF maps. 3 x strategies comprising purely anatomical empiric ablations; PS based with empiric lesions; and EOF guided ablations with empiric lesions were simulated. The pipeline was simulated for the entire population of 100 x virtual patients using openCARP solver and Archer2 supercomputing resources. Ablation efficacy was determined by first examining change of rhythm via ablation and second by calculating the amount of tissue area ablated. **Results:** A population of ablation lesion masks based on predicted targets was algorithmically generated using suggested pipeline for all bi-atrial patient geometries. AF termination to ablated tissue area ratio was higher for EOF based ablation targets compared to PS based or empiric ablations. **Conclusion:** EOF represents a promising metric for identifying and ablating AF sources. The suggested pipeline is scalable to larger datasets and can provide training data for developing machine learning tools to advance the precision and efficacy of AF treatment.

Virtual physiological human research requires macro theory

Genggeng Ye
None, People's Republic of China

The VPH has been going on for more than ten years, and there is basically no substantial progress in integrating medical knowledge. The main reason is that modern medicine (MM) lacks macro theory, resulting in similar comprehensive research that cannot integrate medical knowledge from various disciplines, levels, and scales. I provide a macro theory in my book *A Systematology Interpretation of Traditional Medicine* (Chinese ver.), which is inspired by traditional medicine (TM) and macroeconomics, and it can be an important research direction for VPH that is expected to integrate medical knowledge. MM and economics are both complex systems science, and MM has a longer history than economics, however, it has no macro theory (TM has). This is worth pondering for us. In particular, we need to pay special attention to that MM has no "equilibrium theory", but economics does and it is of great practical value in managing the national economy. From a systematics view, balance under the negative feedback is only a local issue of the system, while equilibrium is an overall issue. From a mathematical perspective, balance is of negative feedback, very simple, and equilibrium is of simultaneous equations, very complicated. Human health is not just a matter of each negative feedback, but also depends on the equilibrium of the human system, that is, the degree of coordination between all balances (negative feedbacks). MM pays more

attention to local balance, such as blood sugar balance, but pays less to overall equilibrium. At least, it lacks systematic theories and methods to study equilibrium issues. Although the physiologist Cannon (W. B.) initially mentioned the "*stable states for all parts of the organism*" in his book The Wisdom of the Body in 1932, however, no further explanation was given, and later generations did not continue to delve into this issue. My article focuses on introducing the "**equilibrium theory**", the "**Adaptability Relation of Supply and Demand**" model and the division of the nine hierarchical structures of the human body, which can be used as the top model of VPH. As a starting point, I hope it can start the macro theory research on MM.

Integrating care: Abalietas as a bridge between clinical quality registers and electronic medical records for enhanced machine learning applications in healthcare

Krzysztof Gądek, Rafał Niżankowski, Adam Nowak, Dominik Radziszowski, Joanna Twaróg, Maja Więckiewicz
Sano – Centre for Computational Personalised Medicine International Research Foundation, Poland

Machine learning tools that support medical staff in clinical decision-making could potentially positively influence the care of patients and improve treatment outcomes. The critical condition for developing valuable tools is the trustworthiness of essential data. The quality of data that artificial neural networks could learn from is crucial for achieving valuable AI-based IT tools. Unfortunately, this type of data is not available in countries like Poland. Widely used Electronic Medical Records (EMR) aim is not to deliver high-quality data but primarily for documentation and accountancy purposes. Moreover, EMRs do not collect adequate data on patient risk assessment or long-term treatment results, nor are EMR disease/condition specific. Consequently, collecting sufficient cases of particular problems for machine learning is difficult, if not impossible. However, there is another source of medical data. Clinical Quality Registers (CQRs) are country-wide registers of patients with the same disease, health problem, or specific service subject. The major obstacle in the broad adoption of CQR is redundancy in data collection between EMR and CQR. The work duplication imposes a significant burden on medical staff. Our hypothesis states that a new electronic tool that combines CQR and EMR functions could solve the problem. We call it Abalietas (lat.) - meaning „cooperation”. It should be the primary place for doctors’ notice during patient management, following the Clinical Care Pathways approach as a basis for the construction scheme for patient care in outpatient and inpatient departments. The BPMN2 standard is used to describe medical care processes performed with patients. All the collected information must be transferred to EMR and CQR with minimal medical staff engagement. We decided to validate whether such a tool could be constructed for a particular health problem, functional, and accepted by doctors and other medical staff. Promising preliminary results suggest that the Abalietas concept, especially when introduced widely, could offer good-quality data for machine learning and the development of AI-based doctor-assisting tools.

PyPopSim: Form single simulation to population studies

Jeremy Laforet, Sofiane Boudaoud
Université de Technologie de Compiègne, Alliance Sorbonne Universités, CNRS, UMR 7338 Biomécanique et Bio-ingénierie, Centre de recherche Royallieu, CS 60 319 Compiègne, France

We propose an open-source tool written in Python to perform population wide statistical analysis using models designed for single individual simulations. Indeed, many advanced models still have unknown quantities and may struggle to faithfully reproduce a given

individual while their outputs are in valid margins. At the same time, published data are often only available as statistical data over a given population. Our tool allow to easily translate from single simulations to results at the level of virtual population which can then be matched to real data. Another possible usage is to compare several simulated populations through a single model. The populations will be described by the corresponding probability densities of each model inputs. Then Virtual Individuals (VI) are drawn from these probability densities. Each VI can then be simulated with the model of interest and output quantities can be extracted. The tool will run classical statistical analysis and plot the quantities of interest for the simulated populations. Finally, the tool can also be used to compare different implementations of models with the same population. It can allow to compare models relying on different physiological mechanisms or technologies that would show differences on a single simulation (potentially from stochastic effects). It is then possible to check if the simulations are showing significant differences at the population level or if the models can be equivalent. As an example, we compared RMS amplitude of simulated EMG signals for the biceps brachii in two populations: younger and older men, using 100 VI per population. We observe trends similar to the ones extracted from real signals. A rise of the RMS value with the contraction level and significantly lower values for older men comparing to younger ones. Future improvements will include the definition of constrains between the model parameters as they are drawn from their respective probability densities to ensure physical realism. For example, to maintain one parameter higher than a second even if their probabilities overlap.

AlmaHealthDB: A digital infrastructure for secure management, interoperability and reuse of health research data

Antonino A. La Mattina[1], Sabato Mellone[1,2], Marco Viceconti[1,3]
[1]Medical Technology Lab, IRCCS Istituto Ortopedico Rizzoli, Bologna (IT);
[2]Department of Information Engineering, Alma Mater Studiorum – University of Bologna (IT); [3]Department of Industrial Engineering, Alma Mater Studiorum – University of Bologna (IT)

Balancing the contrasting demands of FAIR research [1] and GDPR requirements [2] is a complex task, especially for collaborative research projects. The university and the three research hospitals of Bologna joined forces to create AlmaHealthDB, a secure digital environment to collect, process, and standardise data in compliance with legal, organizational, and regulatory requirements. Data controllers appoint AlmaHealthDB as data processor for their specific research project. Input data origin, consents and conditions for use are stored as metadata linked to the dataset. The variables collected in the studies are minimised and (if needed) pseudonymised before entering AlmaHealthDB infrastructure. AlmaHealthDB operates as a subnet of the regional healthcare service system network, accessible only by system administrators via nominal VPN connections. Disks are encrypted, and the entire infrastructure is backed up daily. A server is exposed on the Internet to allow uploading of data and files by researchers, after two-factors authentication. In the data ingestion phase, constraints on data type and completeness, file format and associated metadata are enforced to minimise data imputation errors. Basic data manipulations are performed inside the protected AlmaHealthDB subnet, while complex simulations and models are run on GDPR-compliant HPC and Cloud infrastructures of Italian research network. In any case, researchers are asked to provide their processing software in a replicable and possibly portable fashion. Input and derived data are mapped early in the study design phase, thus enabling a prompt reuse and sharing of the dataset in HL7 FHIR and/or OMOP CDM standards, if allowed by the collected consent.

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Towards international standardization of computational modeling and simulation in the field of medical devices

Charlott Danielson
Fraunhofer IMTE, Germany

Computational modeling and simulation (CM&S) has emerged as an indispensable tool in the development and (pre-)clinical evaluation of medical devices, offering numerous benefits in predicting performance, assessing design parameters, and simulating real-world scenarios. However, the lack of globally recognized standardized frameworks for establishing the credibility of computational models hinders their widespread acceptance in regulatory decision-making processes. This poster presents a proposal for international standardization aimed at addressing this crucial gap. Building upon existing standards such as ASME V&V 10, 20, and 40 and ISO 9491 series, the ongoing standardization activities seek to develop a comprehensive framework that encompasses verification, validation, and uncertainty quantification (VVUQ) and credibility assessment for various types of computational models, including knowledge-based, data-based, and hybrid models. The proposed standard will provide recommendations for establishing the credibility of computational models throughout several stages of the lifecycle of medical devices, from design and development to regulatory approval. By establishing a unified approach to CM&S credibility assessment, it is aimed to facilitate global recognition by regulators and streamline the adoption of computational modeling and simulation in medical device development and evaluation, ultimately enhancing patient safety and advancing innovation in healthcare technology.

A physiologically based digital twin for alcohol consumption – Predicting real-life drinking responses and long-term plasma Peth

Henrik Podéus[1], Christian Simonsson[1], Patrik Nasr[1], Mattias Ekstedt[1], Stergios Kechagias[1], Peter Lundberg[1], William Lövfors[1,2], Gunnar Cedersund[1,2]
[1]Linköping University, Sweden; [2]Örebro University, Sweden

Alcohol consumption is associated with a wide variety of preventable health complications and is a major risk factor for all-cause mortality. To reduce dangerous drinking behavior, eHealth applications have shown promise. A particularly interesting potential lies in the combination of eHealth apps with mathematical models that can describe blood alcohol concentration. However, existing mathematical models do not consider all real-life situations, such as combined intake of meals and beverages, and do not connect drinking to clinical markers, such as *phosphatidylethanol* (PEth). Herein, we present such a model. Our model is capable of simulating a variety of real-life drinking scenarios, including the combination of food and alcohol. The model was trained using 8 different datasets taken from different independent studies, the model was also capable of describing independent validation data from several independent studies. Additionally, the model can be personalized using anthropometric data for different individuals and can thus be used as a physiologically based digital twin. Furthermore, the twin connects

short-term consumption of alcohol to the long-term dynamics of PEth levels in the blood, a clinical biomarker of alcohol consumption. Using the twin, we can illustrate how connecting short-term alcohol consumption to long-term alcohol markers allows for a new way to determine patient alcohol consumption, based on the individual drinking habits. This approach utilizes the interconnected short- and long-term perspective and allows for estimation of the required alcohol consumption to obtain the measured PEth levels. This could be valuable as a new complement to patient-reported AUDIT forms as measured PEth levels could be used to validate the self-reported drinking of the patients.

Hipathia and metabolizer: Unveiling disease mechanisms and enabling personalized medicine

Kinza Rian, Joaquin Dopazo
Andalusian Platform for Computational Medicine, Spain

Understanding the intricate functioning of signaling and metabolic networks is crucial for comprehending the underlying molecular mechanisms of diseases. Typically, diseases are complex, and coupling different scales, such as metabolic and signaling, presents a challenge. Mechanistic models have demonstrated their usefulness in elucidating the interplay between disease-related molecules and their mechanisms. We propose two mechanistic pathway analysis (MPA) tools: Hipathia and Metabolizer. These tools are designed to integrate, analyze, and interpret high-throughput data, offering valuable insights into biological networks and aiding in the understanding of disease mechanisms. Hipathia serves as a valuable resource for researchers to identify key cellular phenotypes and pathways associated with specific diseases. It facilitates the exploration of signaling pathways, drawing from biological knowledge databases, providing a high-throughput estimation of functional cell activities. This estimation is derived from omics data and considers the activation and inhibition interactions, thereby aiding researchers in gaining a deeper understanding of the causal relationships within biological systems. Metabolizer plays a crucial role in studying metabolic pathways and identifying potential biomarkers. Using transcriptomic data, Metabolizer calculates the impact of modules on the production of metabolites - these modules are a conserved part of metabolism which start with substrate(s) and end with a product. This approach helps uncover the intricate metabolic interactions within the biological system. The combination of Hipathia and Metabolizer, either for patient cohorts or individual cases, holds immense promise in unraveling disease mechanisms and enabling personalized medicine. By leveraging their causality modeling and metabolomics analysis capabilities, these methods may contribute to the construction of comprehensive digital twin models (on a molecular level), enabling a more accurate representation of the patient's biological processes, facilitating personalized treatment strategies, and improving patient outcomes.

In silico modeling of cell migration over texturally treated curved surfaces

Majid Nazemi[1], Liesbet Geris[1,2,3,4]
[1]Biomechanics Research Unit, GIGA In Silico Medicine, University of Liège, Belgium; [2]Prometheus, division of Skeletal Tissue Engineering , KU Leuven, Belgium; [3]Biomechanics Section, KU Leuven, Belgium; [4]Skeletal Biology & Engineering Research Center, KU Leuven, Belgium

A critical factor in determining the efficacy of bone scaffolds is the migration of bone progenitor cells across their surface, facilitating the formation of neo tissue within the cavity. Cell migration behavior, encompassing speed and direction, is influenced by various factors, including surface curvature and topography. The emergence of hybrid pellet additive manufacturing (hPAM) with added laser texturing system offers a unique opportunity for simultaneous control over surface curvature and topography. However,

the vast design possibilities and the impracticality of evaluating each experimentally pose challenges in achieving optimal scaffold designs. In this study, we present a mathematical framework for modeling cell migration over curved and topographically treated surfaces to expedite scaffold optimization by significantly reducing the number of required experiments. The framework involves numerically solving the Diffusion-Convection-Reaction (DCR) equation over a curved surface using the closest point method and finite element modeling. To incorporate the curvature-dependent migration speed reported in the literature, we introduce a nonuniform and anisotropic coefficient of diffusion. Additionally, we capture the reported migration of cells along the gradient of mean curvature in the convection velocity field. Using existing data in the literature we derive mathematical equations to relate the convection velocity field and diffusion tensor entries to curvature values and principal orientations which are in turn computed at each vertex of a provided surface mesh using quadratic approximation and principal component analysis, respectively. We apply the developed framework to a 3D sinusoid surface and calculate the spatiotemporal distribution of cells. We show that model prediction of spatiotemporal cell distribution is consistent with the observed distribution of cells over the 3D sinusoid surface reported in the literature. Furthermore, we are currently endeavoring to formulate a mathematical relationship linking surface texture patterns and the convection velocity field to incorporate texturing effects into our framework.

Systematic understanding and categorization of modeling & simulation context of use in knee biomechanics

Snehal Chokhandre, Ahmet Erdemir
Cleveland Clinic, United States of America

Decisions in computational modeling rely heavily on the context of use (CoU), whether scientific or clinical. CoU dictates model fidelity and specificity, data to build and validate, and computational strategy and resources. In knee biomechanics, the modeling & simulation (M&S) ecosystem is highly fragmented. Frameworks and guidelines for end-to-end workflows and turnkey solutions, to advance discovery and translation, and to capture community needs, necessitate identification of common contexts of use. This work aims to employ a structured and systematic approach to understand the landscape of use scenarios in knee M&S and thus, to identify the breadth and popularity of contexts of use based on knee biomechanics scientific literature. For this purpose, we identified four databases (PubMed, Google Scholar, Dimensions, Semantic Scholar) and seven combinations of terms to perform literature search (e.g., "knee AND finite element"). For each combination, a list of peer-reviewed articles were obtained for each database, with the default 'relevant' setting used for ranking. First 10 articles from each tool were then pooled to 40 articles for each combination (in total, 280 articles including duplicates). Each article was reviewed to extract: study focus (joint or specific tissue), predicted outcome, clinical question, loading, pathology or injury, and intervention. Ongoing analysis identifies and ranks technical and clinical contexts of use. We also devised alternative strategies: (i) searching multiple databases and combining list of articles based on relevance, extracting citation metrics for each article, and sorting based on cumulative as well as average citation; (ii) surveying subject-matter experts for a ranked list of 10 articles that they consider of significance to their work or community, combining and reviewing. These strategies permit systematic documentation, categorization, and ranking of knee M&S contexts of use. Our findings can be used to build consensus M&S workflows for highly ranked contexts of uses, train AI tools for structured and deep extraction of knowledge from literature search, and can transfer to other domains.

Sensitivity analysis of a finite element model predicting the fixation stability of tibial plateau fractures

Simon Comtesse[1,2], Alexander Crotta[1], Arvind von Keudell[2,3,4], Stephen J. Ferguson[1], Thomas Zumbrunn[2]
[1]Institute for Biomechanics, ETH Zürich, Switzerland; [2]CustomSurg AG, Switzerland; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, USA; [4]Bispebjerg Hospital, Copenhagen, Denmark

Introduction: The surgical treatment of tibial plateau fractures is complex and subjective, resulting in complication rates up to 28% [1]. Hence, an objective method for the optimization of tibial plateau fractures by means of Finite Element Modelling (FEM) has been introduced [2]. However, while simulation parameters are chosen based on best practice, they introduce uncertainties to the model. Therefore, a sensitivity analysis was performed to quantify the influence of each parameter on the simulation results. **Methods:** A cadaveric tibial plateau fracture was segmented, and the bone fragments were aligned to achieve the fracture reduction and further fixed with a medial plate and several locking screws. Hounsfield-Unit-derived bone material properties based on a phantomless calibration method [3], as well as joint and muscle forces from subject-specific musculoskeletal gait models were integrated into the FEM.Modelling parameters were changed systematically and the results were compared relative to the standard simulation in terms of maximum displacement of fracture fragments and von Mises screw stresses. **Results:** Linear geometry and linear elements had no or minimal influence on the results. A similar effect could be observed for the frictional coefficients of the plate-bone and bone-bone interface. Parameters determining the material properties (hardware and bone) showed differences of up to 30%, while the applied load had a direct and proportional influence on the results. **Discussion:** Although the contact in-between bone fragments and the bone and the plate seems to be an important modelling parameter, their actual frictional coefficients are irrelevant. Similarly, the computational costs can be reduced significantly with linear parameters without limitations on the simulation output. A much larger impact on the results arises from the parameters directly determining the material properties of the hardware or the bone. However, most of these parameters can be controlled quite accurately.

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Designing a single-use novel surgical kit for a cervical facet cage implantation through iterative FE simulations

Luca Ciriello[1], Tomaso Villa[1,2]
[1]Department of Chemistry, Materials and Chemical Engineering "Giulio Natta" - LaBS, Politecnico di Milano (Italy); [2]IRCCS Istituto Ortopedico Galeazzi (Italy)

Introduction: The Sharkage Instrument Kit from 2B1 Srl is used for cervical facet cage implantation, mainly for degenerative disc disease from C2 to C7. It consists of stainless-steel Surgical Instruments (SIs) [1]. However, multi-use SI requires thorough sterilization before each surgery, leading to increased administrative complexity, costs, and logistical challenges. There's also a risk of breakage during surgeries [2]. Shifting to single-use instruments could reduce costs, minimize breakage, and have better economic and environmental impacts. To make this shift, steps are needed to identify surgical boundary conditions and optimize the instrument design through a Finite Element Model (FEM). The aim of this work is to design a novel single-use SI through iterative FE simulations using a validated cervical spine FEM and use it to assess the instruments' mechanical performance. **Materials and Methods:** Using an average C1-

C7 human spine model [3], a FEM was created and validated in Abaqus 2022 software with ligaments and material properties assigned based on established literature [3]. The boundary conditions during the usage of SIs for cage implantation, in terms of force and torque, were recorded during a previous in-vitro activity simulating the entire implant. These were applied to SIs in the FEM simulating the entire surgery to assess the mechanical performance (stress and deformations) by comparing three designs: (i) the original multi-use SI (2B1 design), (ii) an optimized multi-use SI with a different geometry and (iii) a single-use SI with different materials and geometry. **Results and Discussion:** Applying the in-vitro values as a boundary condition on the SI in the FEM, the three different designs of SI seem to be reliable enough since during the implant no one of them reaches the yielding stress in any of the components. In particular, for option (iii) the FEM is also able to propose the use of a new SI, based on a new design and new materials both crucial to minimize the economic and environmental impact.

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3D optical scanning toward personalised whole-body models

Alexander Dixon[1], Robin Laven[1], Poul Nielsen[1,2]
[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Department of Engineering Science, University of Auckland, New Zealand

Understanding the arrangement of bone, muscle, and fat tissue in the human body is essential for the diagnosis of diseases and the development of personalised digital twins. While imaging modalities, such as CT and MRI give accurate measurements inside the body, these modalities require bulky and expensive equipment, expert operators, and time-consuming procedures. Optical scanning of the body is a modality that is becoming cheaper and of higher spatial resolution, however it is limited to capturing the anatomy of the skin surface only. By combining optical scanning techniques with statistical models of the human anatomy, based on large datasets of internal body scans, it may be possible to perform rapid and cheap scanning of individuals to estimate their internal anatomy. We have developed a custom optical 3D scanner that consists of an array of inward-looking high-resolution cameras surrounding a human participant in a standing position. The scanner is used to capture quasi-static and dynamic poses of an individual. The external surface of an individual is 3D reconstructed using photogrammetry with a custom calibration method of the cameras. The resulting point cloud from the 3D reconstruction of an individual's skin surface is fitted with a statistical shape model of the body surface (STAR model [1]). From the body surface model, an estimate of the bone anatomy can be made with a coupled body surface and bone statistical shape model (OSSO model [2]) for the individual. We are now evaluating the accuracy of these estimates with full-body MRI of individuals who have been scanned in the optical scanner. The scanner and subsequent model fitting workflow in this work provides a tool for quickly and cheaply estimating subject-specific anatomy. Such a tool has the potential for providing personalised anatomical landmarks to register the 3D coordinate system of whole-body physiological models (or digital twins).

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A machine learning-based in silico assessment to predict human respiratory irritants and toxicity

Yunendah Nur Fuadah, Lulu Firdaus, Ki Moo Lim
Kumoh National Institue of Technology, Korea, Republic of (South Korea)

Human respiratory health is significantly affected by exposure to chemical irritants and toxins, presenting major challenges for public health and regulatory frameworks. This study introduces a machine learning-based in silico approach to predict two end points, including potential respiratory irritants and respiratory toxicity of chemicals. Our objective is to improve risk assessments and reduce reliance on animal testing. We analyzed a comprehensive dataset of 1,850 compounds identified as irritants and 1,817 as non-irritants, along with 342 toxic and 335 non-toxic compounds, all classified based on extensive toxicological data from in silico human inhalation studies. Our methodology incorporated various descriptors, such as Morgan fingerprints, MACCS Keys, a molecular descriptor calculator (Modred), and PubChem, alongside machine learning algorithms including Random Forest (RF), Extreme Gradient Boosting (XGBoost), and Support Vector Machine (SVM). Among these, the MACCS Keys descriptor paired with the SVM classifier achieved the highest performance, with an area under the curve (AUC) score of 0.80 for both respiratory toxicity and respiratory irritants. This model notably improved prediction performance compared to other models and previous studies. Validated according to the organization for economic cooperation and development (OECD) QSAR principles using compounds excluded from the training sets, our models make a significant contribution to toxicology and computational chemistry. This study offers new insights and tools for evaluating chemical risks to respiratory health, highlighting the potential of computational approaches in predicting health impacts while supporting global efforts to adopt more ethical and scientifically rigorous testing methods.

Unsupervised learning for MRI cross-scanner harmonization

Grace Wen[1], Alan Wang[1,3,4], Vickie Shim[1,2,4], Samantha Holdsworth[2,3,4]
[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Mātai Medical Research Institute, Gisborne, New Zealand; [3]Department of Anatomy and Medical Imaging, Faculty of Medical and Health Sciences, University of Auckland, New Zealand; [4]Centre for Brain Research, University of Auckland, New Zealand

Pooling data across multiple centres can enhance the statistical power of neuroimaging research. However, combining datasets from different centres poses challenges due to variations in image acquisition, demographics, imaging devices, acquisition protocols, and image quality. To address these non-biological variations, we propose an unsupervised learning approach based on generative models. Generative models are deep learning architectures capable of learning the mapping between two domains while preserving the original semantic information in the transformed data. This study investigates the feasibility of using a generative model to harmonize volumetric data obtained from T1-weighted MR images. We obtained a public dataset comprising 104 3T scans from GE and SIEMENS MRI scanners sourced from the Parkinson's Progression Markers Initiative database (PPMI) and SRPBS Traveling Subject MRI Dataset. Unpaired scans from the PPMI dataset were used to train the model, with data from SIEMENS scanners as the reference. The model architecture utilized a dual generator-discriminator network, incorporating a U-net generator with L1 loss and patchGAN for the discriminator. After harmonization, visual inspection revealed a similarity in contrast between the harmonized (from GE to SIEMENS) and original SIEMENS sets. Performance indicators noted significant improvements, including mean squared error, structural similarity index metric, peak signal-to-noise ratio, and histogram correlation. Results showed that harmonization significantly reduced site-based differences, decreasing classification accuracy from 0.95 to 0.59. An SVM classifier was trained to distinguish between Parkinson's disease patients and normal controls, aiming to assess the impact

of harmonization on machine learning predictors. The findings demonstrated enhancements in accuracy and AUC, with accuracy increasing from 0.55 to 0.63 and AUC rising from 0.54 to 0.59 after harmonization.

Incorporating wearable sensor data into research workflows

Gregory B Sands, Hayden Randles, Poul M F Nielsen
Auckland Bioengineering Institute, University of Auckland, New Zealand

Many devices and instruments are able to provide physiological data used for the analysis and modelling of human health and disease. In contrast to those devices used in a clinic or research lab, wearable sensors have several unique features that require special attention. Wearables are typically used in an everyday context, with irregular connections to transmit data. The format and content of data are usually different for each type of device, and transmissions will often be minimised to reduce battery consumption. Constructing a robust interface from wearable sensors to research workflows ensures that the data and metadata required for analysis are fully described. Postel's law for software interfaces states "be liberal in what you accept, and conservative in what you send". In this sense, the device interface should be flexible enough to cope with a wide range of incoming data, while ensuring that the output into the workflow or database is strictly defined. The ideal arrangement for achieving this is to separate the interface into two parts. At the front end is a set of three plugins unique to each device based on a common template. A Register plugin implements commands Init and Release, which register a single wearable using a unique identifier linking the device to a database record and perform time synchronisation at the start and end of device use. A Configure plugin contains a device-specific UI and outputs a set of configuration sequences. A Control plugin interacts with the wearable and implements a small number of commands: Start, Stop, Configure (sending the set of configuration sequences), Inquire (device status such as battery or memory available) and Acquire. The interface back-end interacts with the front-end plugins and ensures that all required metadata is defined once for each registration, so minimising data transfer while in use. It also packages the acquired data into the standard IEEE 11073-10206 format for storage together with FHIR-compatible metadata. This structure ensures data provenance and security together with timecoding that fulfils the requirements of a research workflow.

Modelling the neural regulation of gastric motility at the tissue level

Omkar N. Athavale, Recep Avci, Alys R. Clark, Leo K. Cheng, Peng Du
University of Auckland, New Zealand

Gastric motility occurs due to intrinsic electrophysiological slow wave events which are regulated by enteric nerve input. There is a gap in our understanding of how cellular mechanisms interact in response to neuromodulation both under normal physiological conditions, and when affected by neurodegenerative diseases such as diabetes. While devices for nerve stimulation exist, determining protocols that elicit relief from gastric dysfunction requires experimentation across a large parameter space. This study aimed to develop a mathematical model of gastric tissue electrophysiology and tension generation to quantify the relative importance of putative cellular mechanisms for inhibitory and excitatory neural regulation of gastric motility. The model coupled two electrophysiological cell models of interstitial cells of Cajal and smooth muscle cells, and a neural regulation component which modulated five pathways: Anoctamin-1, non-specific cation channels, small conductance K^+ channels, contractile apparatus Ca^{2+} sensitivity, and IP_3R. The neural regulation model was frequency-dependent, and parameter optimisation was performed to minimise the total absolute difference

between the simulated results and existing *in vitro* experimental data. A parameter sweep over the input stimulation frequency parameters was also conducted. The parameter optimisation and model simulations demonstrated that modulation of calcium sensitivity of the contractile apparatus was the more significant than the modulation of slow wave amplitude in inhibiting gastric motility. Furthermore, excitatory stimulation only had a small effect on contraction amplitude with inhibitory stimulation also present (-77% vs -79%), but enhanced the effect on contraction frequency (+66% vs +47%). Parameter sweep results were in consonance with *in vitro* experiments not used in the fitting procedure. These results provided insights regarding gastric cellular pathways that may compensate in response to nerve damage. Furthermore, the developed model can underpin organ-level simulations of neuromodulation therapy, to understand how electroceutical protocols can be used to remedy gastric motility dysfunction.

Efficient numerical simulation of effective micro-macro models for reactive transport in elastic perforated media

Jonas Knoch[1], Nicolas Neuß[1], Markus Gahn[2], Maria Neuss-Radu[1,2]
[1]FAU Erlangen-Nürnberg, Germany; [2]Universität Heidelberg, Germany

In this talk we consider an effective elasticity-transport system of micro-macro type in a unified Lagrangian framework, derived by a formal asymptotic expansion from a microscopic model defined in an elastically deformable perforated medium and formulated in a mixed Eulerian/Lagrangian framework. The effective system, consisting of a macroscopic elasticity-transport problem and associated cell problems, is nonlinearly coupled through reaction terms as well as effective coefficients which take into account the periodic microstructure and, in the case of the transport problem, the deformation of the domain. As a result, the diffusion cell solutions have to be computed in each time step and for each quadrature point of the macroscopic grid, leading to high numerical effort. We develop and study an efficient numerical scheme for our problem, including the approximation of the effective coefficients using a feedforward neural network trained on precomputed coefficients. In the simulations, we reproduce key features of the energy metabolism in deforming tissue (e.g. lung or heart tissue) such as the metabolic reprogramming under hypoxic conditions. This is a well-known characteristic of various diseases including sepsis, cancer or Covid-19.

The development of the phantom fiber to mimick muscle fibre activity for the validation of magnetomyography sensors

Ahmet Dogukan Keles[1], Thomas Klotz[1,2], Justus Marquetand[3], Oliver Röhrle[1,2]
[1]Institute for Modelling and Simulation of Biomechanical Systems, University of Stuttgart, Stuttgart, Germany; [2]Stuttgart Center for Simulation Sciences (SC SimTech), University of Stuttgart, Stuttgart, Germany; [3]MEG-Center Tübingen, University of Tübingen, Tübingen, Germany

Magnetomyography (MMG) enables non-invasive measurement of muscle activity through magnetic signals generated by contractions and holds promise for improved spatial resolution, particularly beneficial for long-term measurements like prosthesis control. The use of surface Optically-Pumped Magnetometer (OPM) sensors has been promising in this context. However, biological tissue heterogeneity and potential measurement errors introduce considerable uncertainty to the data. Thus, well-calibrated sensors or benchmarks are necessary to reduce this uncertainty associated with OPMs. In this study, we introduce the "Phantom Fiber", a skeletal muscle electric board designed to replicate the magnetic field of an individual muscle fiber during

contraction. The phantom fiber consists of a controller and a carrier unit. The controller allows for the adjustment of both action potential conduction velocity and magnetic field strength, while the carrier carries the current generated by the controller, mimicking muscle fiber behavior and producing a magnetic field similar to that generated by a propagating action potential in skeletal muscle tissue. The controller utilizes sample-and-hold components to introduce delays at 20 measurement points along the carrier, mimicking propagation similar to muscle fibers. The input signal and operating parameters are conveyed to the phantom fiber through a data acquisition system controlled by a MATLAB script. OPM sensors were used to measure the PF-induced magnetic field and demonstrate its capability as a benchmark and calibration tool. The phantom fiber is capable of generating an adjustable action potential conduction velocity in the range of 1-5 m/s and a magnetic field ranging in nanoteslas (nT), reaching 10 nT at a distance of 5 mm between the OPMs and the carrier.

A multiscale network model of tumor microenvironment to predict immunotherapeutic response of head and neck cancers

Priyan Bhattacharya[1,4], Andrew South[2,4], My Mahoney[2,4], Adam Luginbuhl[3,4], Rajanikanth Vadigepalli[1,4]

[1]Department of Pathology and Genomic Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania, United States of America; [2]Department of Pharmacology, Physiology and Cancer Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, United States of America; [3]Department of Otolaryngology - Head and Neck Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania, United States of America; [4]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, United States of America

Squamous cell carcinoma of the head and neck (HNSCC) is one of the most common cancers, accounting for over 90% of head and neck carcinoma prevalence. Existing therapies targeting the tumor-cell-intrinsic signaling mechanisms underestimate the tumor-promoting role of the non-tumor cells within the microenvironment (TME). Immune checkpoint inhibition (ICI) has emerged as a critical treatment strategy for HNSCC that halts the immune escape of the tumor cells. Despite a few desirable advantages over traditional therapeutic approaches, ICI remains ineffective for some patients. The present work uses a computational modeling framework to decipher the mechanisms behind the survival, growth, and non-response to ICI treatments in the specific scenario of HNSCC. We constructed a multicellular TME network with relevant molecular factors mediating cell-cell interactions and cell state transitions. Stability analysis over a wide range of model parameter values enabled us to identify the possible TME subtypes which, as determined by the molecular markers, are characterized by the presence or absence of immune and fibroblasts cell types in the following ways: Immune deficient, Fibro-desert, Immune and Fibro-deficient, Immune rich, and Fibro-rich phenotypes. Simulation results suggest that in pre-ICI conditions, the growth and proliferation of the tumor cells critically depend on the reinforcing loop between the pro-invasive cancer-associated fibroblasts (CAFs) and the tumor cells, which is protected by the exhausted T cells from the immune response. Furthermore, our analysis indicates that ICI-based intervention hampers the proliferating effect of the CAF-tumor interaction loop, and the quantitative balance between the CAFs and the cytotoxic T cells governs the post-ICI outcome. Based on these results, we propose that the pre-ICI TME subtype plays a dominant role in determining the post-ICI outcome. The computational predictions closely align with the observations from recent experimental studies and

clinical findings. Finally, the model-guided approach enables us to explore TME subtype-specific molecular interventions to improve the efficacy of ICI therapy.

Mechanobiological modelling to capture relative effects of deviatoric and volumetric stresses on epiphyseal bone growth

Jorge Mateos Arriola[1], Carlos Ruiz Wills[1], Miguel A. González Ballester[1,2], Jérôme Noailly[11]
Universitat Pompeu Fabra, Spain; [2]ICREA, Spain

Paediatric limb irregularities often result from the uneven growth of long bone physis, a process influenced by mechanical loads. However, there is a scarcity of computational growth models to enhance and guide implant-based growth techniques to correct it. Therefore, our objective is to create a computational tool that forecasts epiphyseal growth, considering the heterogeneous distribution of the local stress fields. A 2D axisymmetric finite element model was developed, incorporating reserve, proliferative (PZ), and hypertrophic (HZ) zones to predict long bone growth. It integrates contributions of chondrocytes in each zone, including dependence on mechanical factors. Each zone contributes to regulate a growth layer below the growth plate, simulating new bone formation. Mechanical growth was restricted to not exceed half of the biological growth, and sensitivity to deviator stresses was approximately half the one of volumetric. A novel parameter included in HZ, regulates the maximum growth of the HZ relative to PZ. Model parameters were derived from the literature, and a sensitivity analysis was performed to explore the effect of different reference values for the deviatoric and volumetric stresses in the PZ and their related coefficients under free growth conditions. The effect of deviatoric stress change (Cd) on bone growth was lower than the one of hydrostatic change (Ch). The latter induced a pronounced development of growth. Yet, Cd was a cornerstone to trigger growth. High relative effect of Ch generated high transversal growth of new bone. While HZ allowed simulations of growth arrest under external mechanical stress, this parameter shall be adjusted to further control the effect of Ch relative to Cd. Interestingly, and the lack of Ch led to no physiological curved shape for newly formed bone. The predictive capability of this computational model shall provide insights of growth dynamics over time. The coupling with patient-specific joint geometries where nonlinear bone shapes induce heterogeneous distributions of deviatoric and volumetric stresses might help clinicians to plan treatments in paediatric limb deformities.

Sensory perturbation due to blood flow restriction leads to change in active MU pool

Franziska Bubeck[1,2], Mansour Taleshi[3], Ivan Vujaklija[3], Oliver Röhrle[1,2], Leonardo Gizzi[4]
[1]Institute for Modelling and Simulation of Biomechanical Systems, University of Stuttgart, Stuttgart, Germany; [2]Stuttgart Center for Simulation Science, University of Stuttgart, Stuttgart, Germany; [3]Department of Electrical Engineering and Automation, Aalto University, Espoo, Finland; [4]Department of Biomechatronic Systems, Fraunhofer Institute for Manufacturing Engineering and Automation, Stuttgart, Germany

Purpose: This study aimed to better understand the coping strategy of the neuromuscular system under perturbed afferent feedback. For this purpose, the neuromechanical effects of transitory blood flow restriction (BFR) were investigated compared to atmospheric pressure. It has been hypothesized that the altered environmental conditions resulting from the lack of oxygen lead to a change in the recruitment of motor units.

Method: Subjective discomfort (NRS) and neuromechanical parameters (torque and high-density electromyography) were recorded during submaximal isometric ankle dorsiflexion - before (2x), during (5x) and after (2x) BFR. The tibialis and gastrocnemius muscles were examined in 14 healthy young adults. The HDsEMG data were decomposed and the number of motor units (MUs) and spike trains were estimated by using blind source separation technique. Variables of interest were firing rate (FR), recruitment threshold (RT), and number of trackable MUs.
Results: The pool of active motor units changes, particularly during the last two trials of BFR. New MUs are recruited at lower thresholds with constant firing rates. These MUs stay active until the cuff is deflated, and previously recruited MUs become active again.
Conclusion: BFR must be considered a time-dependent variable, as the investigated neuromechanical parameters changed over time. To maintain the force output, an increased central drive is necessary, which leads to a time-dependent change in the recruitment of motor units due to the changed environmental conditions. The reduced recruitment threshold allows the activation of large MUs at an earlier stage, which suggests that oxygen-independent fast twitch fibers are recruited due to acidification.

A graphic representation of arterial pulse pressure vs. mean arterial pressure time series may be used for clinical decision support during intraoperative hypotension

Estefanía Žugelj Tapia[1], Marko Žličar[2], Borut Kirn[1]
[1]University of Ljubljana, Medical faculty, Ljubljana, Slovenia; [2]University Clinical Centre, Ljubljana, Slovenija

Intraoperative hypotension (IOH) usually defined by mean arterial pressure (MAP) decrease below a threshold value (i.e. 65 mmHg) is a common event associated with mortality and postoperative organ dysfunction. In the attempt to avoid and predict IOH, different algorithms and data presentation have been developed. Common interventions in case of IOH may include administration of inotropes, vasopressors and fluids or blood products to increase cardiac contractility, systemic vascular resistance and intravascular volume, respectively. Which of the interventions will be most effective is often indeterminate due to uncertainty in the trends of cardiovascular system (CVS) dynamics during operation. To facilitate the operator insight into the CVS dynamics in time, we created a 2-dimensional graphic of MAP vs. pulse pressure (PP) and observed if it carries potential to reveal new insights into CVS dynamics. We used anonymized and de-identified records of high-resolution arterial pressure waveforms, and therapeutic interventions effectuated during a major surgery. To extract the MAP and PP, first the onsets of the arterial blood pressure pulses were detected by using an open-source algorithm. Next, the time stamps of the recorded interventions were identified. And by using short sections of the time series of pulses, the generated 2-dimensional graphic allowed us to visualize the behavior of the CVS when interventions were effected, enabling physiologically relevant descriptive analysis. We found that the MAP and PP during IOH events show a linear relationship, however the slope of the relationship may vary and is influenced by the applied intervention to treat hypotension in case of successive IOH events. Based on the physiological principles that produce MAP and PP, this simple graphic representation can reflect in real-time the underlying hemodynamic state during surgery and its changes when therapeutic interventions are applied. The CVS dynamics is complex, thus a quest for clinical decision support systems to avoid and shorten IOH remains challenging.

Development of a hemodynamic model to simulate heart failure patients

Juliana Franz[1,2], Arina Borzistaia[1,2], Titus Kühne[1,2], Leonid Goubergrits[1,2]
[1]Charité - Universitätsmedizin Berlin, Germany; [2]Deutsches Herzzentrum der Charité, Institute of Computer-assisted Cardiovascular Medicine, Berlin, Germany

Heart failure (HF) is a major global health issue, leading to frequent and costly hospital visits. Remote patient monitoring seems promising for reducing hospitalizations and improving quality of life, but current systems lack capabilities for automated, personalized treatment adjustments. Patient-specific hemodynamic models may prove useful in assisting with both monitoring and personalized treatment management. This study introduces a workflow for simulating patient-specific hemodynamics of HF patients using non-invasive data for model personalization. We implemented a lumped parameter model of the cardiovascular system with detailed representations of the systemic and pulmonary circulations, as well as the left and right heart. The model is defined by 109 parameters that are categorized into three groups: (1) patient-specific parameters estimated from routine clinical data, (2) patient-adapted parameters to ensure physiological distributions of flow rates and volumes across the cardiovascular system and (3) constant, population-averaged literature values. An iterative algorithm optimizes the patient-specific parameters for an accurate virtual representation of patient hemodynamics. Based on literature data, we built two typical HF-patient cases with preserved and with reduced ejection fraction, respectively, and applied our developed workflow to demonstrate its feasibility. The developed lumped parameter model simulates clinically relevant hemodynamics, including cardiac output and pulmonary artery pressure, which cannot be assessed non-invasively with current remote monitoring systems. This model sets the foundation for further developments on modelling hemodynamic changes over time and predicting responses to treatment modifications.

Hypertensive signature in the photoplethysmography signal by combining a whole-body cardiovascular model and optical simulations

Clement Vasseur, Xavier Bednarek, Pierre Blandin, Guillaume Blanquer
Univ. Grenoble Alpes, CEA, LETI, DTIS, Grenoble, France

High blood pressure is the main risk factor for mortality worldwide [1]. Numerical approach is a powerful tool to investigate this pathology and for guiding the design of medical devices. Numerical models are often adapted to the region of observation and sometimes to the associated mode of observation (optics, bioimpedance, ultrasound …). We propose in this work a cardiovascular model combined with an optical simulation to study the Photoplethysmography (PPG) signal in a hypertensive case. Using a multilayered skin model, we focus on the forearm to highlight specific optical signature.

Our cardiovascular model includes a short-term regulation based on three baroreceptors in the arterial circulation [2]. Theses baroreceptors are the source for symmetrical sigmoid activities (sympathetic and parasympathetic). This process regulates the pressure by the modification of elastances of heart chambers, heartbeat, and the resistances and compliance of some vessels (veins, or in peripheral or in hepatic vascular beds). A multilayer skin model has been developed [3] to simulate the propagation of light in forearm tissue. In three of the layers, the microvascularisation is modeled by a thickness modulation. The pulsations of the radial artery and vein due to blood circulation are carried out by the variation of diameter of two vessels located in the subcutis. A white Monte Carlo simulation is performed including models for skin, light source and photodetector. It allows us to calculate the reflectance of each layer of the skin, and in particular, its variation due to the pulsation of the artery. The variation of « cardiovascular indexes » (systolic, diastolic, mean and pulse pressure in brachial artery) due to hypertensive scenario will be compared to literature [4]. We will analyze

the ability of PPG to measure hypertensive conditions. At last, the impact of position and wavelength of PPG will be also discussed.

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Pre-procedural planning of transcatheter heart valve interventions using imaging and in silico modelling

Shelly Singh-Gryzbon
University of Cambridge, United Kingdom

Transcatheter heart valve interventions have seen tremendous growth over the last decade. These catheter-based procedures offer a minimally-invasive alternative to surgical heart valve replacements, especially for patients considered too high risk for surgery. The extensive use of transcatheter devices has resulted in a paradigm shift in the clinical workflow for structural heart intervention. Pre-procedural planning, procedural guidance and follow-up care are critical to the success of transcatheter interventions. With the growing number of transcatheter heart valves available and a host of adverse outcomes to avoid, current decision-making processes are guided by clinical imaging, with 3D printing and image-based virtual simulation being recently adopted. However, these modalities cannot adequately capture or predict the dynamic interaction between implanted transcatheter devices and native anatomy. Thus, *in silico* models can be integrated as an additional tool to support the clinical decision-making processes. It can do so by providing insights into potential device-anatomy interactions, including hemodynamics and structural mechanics. The aim of this work is to demonstrate the role of patient-specific *in silico* modelling in avoiding adverse outcomes associated with transcatheter replacements of the aortic, mitral, and (most recently) tricuspid valves.

A 0D-1D global, closed-loop model of the cardiovascular system

Stefano Costa[1], Lucas Omar Mueller[1], Federica Caforio[2,3,4]
[1]Dipartimento di Matematica, Università di Trento, (Italy); [2]Department of Mathematics and Scientific Computing, NAWI Graz, University of Graz (Austria); [3]Gottfried Schatz Research Center: Division of Biophysics, Medical University of Graz (Austria); [4]BioTechMed-Graz, (Austria)

Understanding the complex interactions between the heart and the arterial and venous networks in physiological and pathological scenarios remains a significant challenge in cardiovascular research. Computational cardiovascular models show promise as an effective tool for exploring these complexities, but to tackle such interactions methodological challenges must be addressed. We present a cardiovascular closed-loop model that couples a 1D global vascular model [1] with a 0D cardiac model (namely, the CircAdapt model [2]). This coupling enables detailed analysis of the interaction between the heart and the circulatory system, with emphasis on venous return, while maintaining a low computational cost. In particular, the use of a 1D model of blood flow enables to efficiently analyse wave propagation phenomena. Suitable coupling conditions are considered to ensure the integration of the two models while preserving their coherence and consistency. The model's output is validated against physiological data from literature. Finally, selected cardiovascular pathologies will be simulated to investigate how changes in vascular properties affect the cardiac function.

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In silico validation of TAG-based coronary blood flow distribution methods for patient-specific computational iFR prediction

Ester Bergantin, Lucas Omar Müller
University of Trento, Italy

Coronary artery disease (CAD) is one of the leading causes of death in the world. In recent years, clinicians have shown increasing interest in using computational modeling techniques, such as the model-based **instantaneous wave-free ratio** (iFR) prediction, to assess the hemodynamic significance of coronary stenosis and provide treatment guidance. This study focused on the methodology for **splitting total coronary flow** among terminal outlets, a fundamental part of the modeling strategy used for computational iFR prediction. The objective of the work was to investigate and validate the relationship, hypothesized in literature, between blood flow, **transluminal attenuation gradient** (TAG) and the concentration of contrast medium administered during the non-invasive coronary computed tomography angiography (CCTA) diagnostic tests. Fifty patients with stable coronary artery disease were studied using a **patient-specific 1D model**. In order to model the administration of the contrast medium, the transport of a passive scalar has been included in the model, and a patient-specific concentration curve has been prescribed at the inlet of the domain. We designed **in silico experiments** in which simulations with a predefined flow split were considered as "ground truth" and used, with different methods, to calculate TAG. The resulting flow was then compared with our TAG-based flow estimates. In our study, it was observed that the TAG-based flow distribution methods provides a good estimate of the flow split, with an average relative error of 13% for the best method used. In particular, the methods closer to the clinic practice resulted in slightly higher relative errors (average of 22%). In conclusion, we validated a TAG-based flow distribution method in the context of in silico tests.
The reliability of our TAG-based distribution method could allow to reproduce the actual flow distribution of the patient. Therefore, the next step will be to compute TAG directly from the CCTA scans of a patient and distribute the total coronary flow entering the network with a TAG-based distribution method.

A comparative study between 3D segmentation methods of aorta in contrast enhanced MR acquisitions

Horia Andrei Leonte[1,2], Alexandru Constantin Serban[1,2], Lucian Mihai Itu[1,2]
[1]Electrical Engineering and Computer Science, Transilvania University of Brasov, Romania; [2]Advanta, Siemens SRL, Brasov, Romania

The aorta is the largest artery in the human body. Starting from the left ventricle, it distributes oxygenated blood and nutrients through the systemic circulation. Abdominal Aortic Aneurysm (AAA), if left untreated, may cause a life-threatening issue. It leads to an estimated 150,000 to 200,000 deaths per year worldwide. With the advances in medical imaging, computer vision and artificial intelligence, AAA can be efficiently detected and treated. Semantic segmentation represents one of the most important steps in AAA automatic processing pipelines, to accurately delineate the aorta and the aneurysm. Herein, we systematically evaluate and compare deep learning algorithms for

aorta segmentation on Magnetic Resonance Angiography (MRA) acquisitions. The dataset contains 49 MRA acquisitions, out of which 20 contain an AAA. Several approaches have been tested, starting from a 3D U-Net baseline model, following with different loss functions, augmentation techniques, and binary or distance-based labels. Due to the low data regime, the models have been trained and evaluated using the k-fold cross-validation technique (k=5). The preprocessing pipeline consists of three sequential steps: resampling to a standardized pixel spacing of 1x1x1mm, adjusting the contrast curve to emphasize the aorta, and patching the initial volume into smaller samples, to prevent overfitting and to improve the generalization capacity of the models. Two augmentation techniques have been implemented, a synthetic aneurysm generator and a linear acquisition dropout generator, for improving the segmentation where the MRA acquisitions lack content. The results indicate that the implemented techniques improve the F1 score by 5.4% to 85.7% on the entire aorta, and by 7.3% to 91.7% for the AAA. Hence, we conclude that the proposed pipeline has the capacity to successfully perform aorta and AAA semantic segmentation and can potentially be integrated into a clinical-decision workflow due to its high level of automation.

Simulation workflow for stent-assisted coiling of brain aneurysms

Felix Borges, Alexander Pugachev
Simq GmbH, Germany

Intracranial aneurysms affect roughly 3 % of the adult population and pose the risk of life-threatening consequences due to aneurysm rupture. Stent-assisted coiling is increasingly used for treatment of intracranial aneurysms. It is an endovascular procedure involving the introduction of a platinum coil into the aneurysmal sac, supported by a stent deployed in the parent vessel. The anatomy of the intracranial arteries largely differs between patients, highlighting the potential benefit of patient-specific implants for expanding the group of suitable patients, reducing surgery times and ultimately improving treatment outcomes. For optimizing and verifying patient-specific implants to be safe and reliable, digital twins incorporating sophisticated physics-based computational models can be used.

In the presented work, a computational modeling framework is developed for this purpose. This is done leveraging the computational techniques of finite element modelling, computational fluid dynamics (CFD) and the combination of both, fluid-structure interaction simulation. The simulation framework is developed for a patient-specific geometry of an aneurysm at the bifurcation of the internal carotid artery, the posterior communicating artery and the cerebral artery. The stent treatment is reproduced using a finite element model of a placement procedure, whilst the coiling is modeled in the fluid mechanical model using a porous media formulation. The effect of the coiling on the flow structure, pressure distribution and residual flow in the aneurysmal sac is investigated. A significant reduction of the intra-aneurysmal flow and an altered flow structure is demonstrated. The displacements of the vessel wall resulting from the blood flow and their influence on the blood flow are analyzed by comparison to a rigid wall CFD model. Currently, the computation time of around 20 hours makes the workflow unfeasible in acute clinical settings, however, it is acceptable for the assessment of stent designs.

Atmospheric pollutants and atrial arrhythmias: An in silico study

Catalina Tobon[1], Laura C Palacio[1], Sami F Noujaim[2], Javier Saiz[3]
[1]MATBIOM, Universidad de Medellín, Medellín, Colombia; [2]Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida, Tampa, FL, United States; [3]Centro de Investigación e Innovación en Bioingeniería, Universitat Politècnica de València, Valencia, Spain

Air pollution is responsible for more than 6.5 million deaths per year. Recent studies have demonstrated an increased probability of cardiac arrhythmias, such as atrial fibrillation (AF), and its aggravation after exposure to atmospheric pollutants. AF is characterized by a process of electrical and structural remodeling. Fibrosis is a hallmark of remodeling, and its intensification has been reported to be one of the effects of exposure to pollutants. However, the mechanisms by which pollutants increase the probability of arrhythmias in humans have not been well established. In this work, the effect of the most dangerous pollutants for health (PM, SO_2, CO, and NO) on the generation and aggravation of arrhythmias were evaluated using computational simulations. For this, mathematical equations of the effect of the pollutants under normal physiological conditions and AF were incorporated into two atrial cell models, and their effect on the electrophysiological characteristics was evaluated at different concentrations. Subsequently, in a 3D model of human atria, the effects of the pollutants were studied taking into account structural remodeling by implementing a fibroblast cell model. The generation and aggravation of arrhythmias were evaluated. The main findings of this study indicate that the pollutants generate changes in the morphology and action potential duration (APD) in a concentration-dependent manner, where the pollutant with the greatest effect was SO_2 at high concentration, with an APD shortening by 39% and 46% under normal and AF conditions, respectively. At the 3D scale, pollutants in a concentration-dependent manner favored the generation of chaotic propagation patterns, where aggravation of AF was observed as the pollutant concentration increased, characterized by a greater number of reentries (9 reentries, under AF with fibrosis at high concentration). The pollutant that triggered the most chaotic and disordered propagation was also SO_2 at high concentration (7 reentries). Using computational tools this research examines how air pollution affects health, particularly concerning atrial arrhythmias, aiming to enhance understanding of pollutant impacts.

In-silico assessment of hemodynamics in stenoses of the fontan circulation

Adriano Schlief[1,2], Simon Bender[1,2], Peter Kramer[2,3], Marie Schafstedde[1,2,4], Jan Brüning[1,2,4]
[1]Institute of Computer-assisted Cardiovascular Medicine, Charité – Universitätsmedizin Berlin, Germany; [2]Deutsches Herzzentrum der Charité, Berlin, Germany; [3]Department of Pediatric Cardiology, Charité – Universitätsmedizin Berlin, Germany; [4]DZHK (German Centre for Cardiovascular Research), partner site Berlin, Germany

Several congenital heart defects can result in univentricular physiology precluding biventricular repair. In those cases, Fontan-palliation, during which the venae cavae are directly connected to the pulmonary arteries, is commonly performed. This results in altered hemodynamics, causing several sequelae, such as stenoses of the venous connections which are common late complications. Assessing the severity of these stenoses by conventional clinical methods is challenging due to low pressure levels and complex relationship between stenosis shape and function. Since treatment is associated with additional risks and burdens, proper risk stratification is necessary. Computational fluid dynamics (CFD) is a promising approach to facilitate personalized severity assessment of stenoses. However, there is a lack of standardized approaches and

investigated parameters in the literature, making comparison difficult. In this study, proposed hemodynamic parameters are investigated with respect to their sensitivity and uncertainty. Retrospective MRI data of ten Fontan-palliated patients with potential stenoses was used for this study. The patient-specific anatomy of the Fontan circulation will be reconstructed by 3 independent operators using Mimics Innovation Suite (v26, Materialise). A fixed CFD model implemented in STAR-CCM+ will be used to calculate different hemodynamic parameters. The sensitivity of these parameters will be assessed by variation of both boundary conditions but also model constants and assumptions. Uncertainties introduced during the image reconstruction procedure will be assessed based on the geometries obtained by independent operators. Despite using a common protocol and the same software for image reconstruction, relevant differences in the individual surface geometries are observable. Uncertainties in the surface geometry are known to cause relevant changes in calculated hemodynamic parameters in in-silico studies of other vascular structures. Therefore, standardization of the different steps required for assessing the patient-specific intravascular hemodynamics is urgently necessary to allow comparability of results and accelerate clinical uptake.

A clinical decision support tool for patient management

Krzysztof Gądek, Adam Nowak, Rafał Niżankowski, Dominik Radziszowski, Joanna Twaróg, Maja Więckiewicz
Sano – Centre for Computational Personalised Medicine International Research Foundation, Poland

Introduction. The problem of using outdated knowledge in practice was noted long ago. D. Sackett developed evidence-based medicine (EBM) to make clinical decisions based on valid and actual clinical research. Much effort worldwide is put into extracting current knowledge from best trials using EBM and formulating practice guidelines (PG). However, finding proper advice quickly is difficult and utilized sparsely. The lack of clinical decision support (CDS) embedded in electronic medical records (EMR) influences the quality of care and is an important obstacle in the widespread use of CDS tools. We assumed that delivering proper advice when doctors make decisions could potentially overcome the underuse of CDS.

Methods. Electronic forms for the care of patients undergoing endovascular procedures named Abalietas-Angio were developed according to the care pathway of patients with peripheral ischemia. Dedicated, customizable forms serve to collect data on medical problems. They include several decision points guarding the execution of medical procedures. The decision points include detailed recommendations linked to the most up-to-date PG-eligible information related to the patient's medical context and help the doctor make the proper decision.

Results. With the assistance of an angiologist performing endovascular procedures in the University Hospital Krakow, a description in BPMN2 of management processes was developed as a mobile application. Apart from data collection, each form includes several decision points with in-context pop-up texts selected from current international PG.

Discussion. Knowledge-based CDS embedded in electronic forms built according to the management workflow of medical staff adjusted to the care pathway could be short and properly respond to doctors' or nurses' doubts. CDS with documentation focused on disease or medical services instead of EMR could be easily adjusted to staff needs. It will be necessary to assess this approach's acceptance as far as its clinical value.

Conclusion. Small pieces of advice, just in time, instead of extensive databases for searching for proper support, could be more useful in each busy clinical practice.

Creation and regression analysis of a hemodynamic virtual patient database

Richard Weber, Márta Viharos, Katalin Pálfalvi, Dániel Gyürki, György Paál
Department of Hydrodynamic Systems, Faculty of Mechanical Engineering, Budapest University of Technology and Economics Műegyetem rkp. 3., H-1111 Budapest, Hungary

Numerical modelling of human blood circulation could increase the accuracy of diagnosing and treating cardiovascular diseases, which are still leading causes of death. Low-dimensional, transient models offer a computationally cheap solution for determining the quantities of interest, such as pressure distribution, velocities, stroke volume, or augmentation index. This study introduces a mathematical description of creating a virtual patient database (VPD) with tens of thousands of patients while ensuring physiological relevancy. The literature provides measurement or simulation data to validate the computed distribution of the quantities of interest of this study, that is, six pressures, the cardiac output and four pulse wave velocities. The study utilises an in-house hemodynamic solver called first_blood, a computationally efficient one- and zero-dimensional solver, ensuring the validity of the fluid dynamic equations. The creation of the VPD consists of three individual steps: determining a reference patient, handling the input parameters as stochastic variables, and resampling the database. The reference patient is mimicking a patient with "average" physiological quantities. While giving a distribution of each input parameter creates an original VPD with 50000 VPs, the resampling removes the physiologically irrelevant ones. Although the VPD size is significant, first_blood could keep the overall computational time below XY days. Finally, the VPD includes 34347 VPs. Moreover, the final step of the method assigns sex and age data to most VPs while keeping the biological differences. For example, males tend to have higher blood pressure, and the pulse wave velocities increase with ageing.

At last, regression analysis models, such as multiple linear regression (MLR), are used to estimate the quantities of interest (the outputs) as a function of the input variables. The MLR provides excellent matches with limited computational time. Additional methods, such as support vector regression, gradient boosting, extreme gradient boosting, and random forest, are also applied. Most methods can provide results with sufficient accuracy.

Towards a prostate cancer radiotherapy digital twin: Simulating the response of prostate cancer to external radiotherapy through mechanistic multiscale modelling. Sensitivity analysis and clinical adaptation

Eleni Kolokotroni A.[1], Foteini Panagiotidou[1], Stamatia Tsampa[1], Christos Kyroudis[1], Simon Spohn[2,3,4], Anca-Ligia Grosu[2,3], Dimos Baltas[3,5], Ilias Sachpazidis[3,5], Constantinos Zamboglou[2,3,6], Georgios S. Stamatakos[1]
[1]National Technical University of Athens, School of Electrical and Computer Engineering, Institute of Communication and Computer Systems, In Silico Oncology and In Silico Medicine Group, Greece; [2]University of Freiburg, Faculty of Medicine, University Medical Center Freiburg, Department of Radiation Oncology, Germany; [3]German Cancer Consortium (DKTK). Partner Site Freiburg, Germany; [4]Berta-Ottenstein-Programme, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [5]University of Freiburg, Faculty of Medicine, University Medical Center Freiburg, Department of Radiation Oncology, Division of Medical Physics, Germany; [6]German Oncology Center, European University Cyprus, Limassol, Cyprus

Prostate cancer (PCa) is the most frequent diagnosed malignancy in male patients in Europe and radiation therapy (RT) is a main treatment option. However, current RT concepts for PCa have an imminent need to be rectified in order to modify the radiotherapeutic strategy by considering (i) the personal PCa biology in terms of radio resistance and (ii) the individual preferences of each patient. To this end, a mechanistic

multiscale model (MMM) of prostate tumor response to external radiotherapeutic schemes, based on a discrete entity and discrete event modeling approach has been developed. Tomographic data of the tumor in conjunction with histological and molecular data at baseline time point t1 is used in order to virtually 3-D reconstruct the anatomic region of interest (ARI). The latter is discretized with a cubic mesh and pertinent biological and mechanical laws are applied each time the ARI is virtually scanned. The effect of external irradiation per cell is modelled through the cell kill probability according to the linear quadratic model. The simulated tumor at time point t2 (and t3, t4,… ,if available) is compared with the real tumor at time point t2 (and t3, t4,…, if available) for clinical adaptation (calibration) and clinical validation purposes. A sensitivity analysis of the model parameters has been carried out. Real data has been provided by the University of Freiburg, within the framework of the European Commission (EC) supported project PersoRad (ERAPERMED2019-299) [*]. Indicative aspects of the model addressed by the sensitivity analysis at a given time point include: tumor volume reduction, fraction of terminally differentiated tumor cells and fraction of dead tumor cells. A method of clinical adaptation of the model by addressing these aspects has been developed. The MMM has been technically verified. Following completion of a clinical validation study and certification, the corresponding digital twin is expected to be used for both patient individualized treatment and in silico clinical trials.

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Recommendations and requirements for implementing computational models in clinical integrated decision support systems (ISO/TS 9491-2)

Laura Lopez-Perez[1], Elena Martinelli[2], Marc Kirschner[3], Sylvia Krobitsch[3], Heike Moser[4], Giuseppe Fico[1], Tito Poli[2], Martin Golebiewski[5]

[1]Universidad Politécnica de Madrid-Life Supporting Technologies Research Group, ETSIT, 28040 Madrid, Spain; [2]Unit of Maxillofacial Surgery, Department of Medicine and Surgery, University Hospital of Parma, Parma, Italy; [3]Forschungszentrum Jülich GmbH, Projekt Management Jülich, Jülich, Germany; [4]DIN - German Institute for Standardization, Berlin, Germany; [5]Heidelberg Institute for Theoretical Studies (HITS gGmbH), Heidelberg, Germany

Years of progress in biomedical technology have generated a vast number of omics, medical imaging, and health data in multiple formats and described by corresponding metadata in heterogenous ways. Despite its significant promise for clinical use, this big data remains underutilized. The EU-funded **EU-STANDS4PM** project has established a pan-European expert forum for evaluating existing standards and develop new guidelines for in silico methodologies in personalized medicine. In this context an ad-hoc working group has been created to discuss the practical recommendations and requirements that should be considered for implementing computational models in clinical integrated decision support systems. The outcome of these discussions has resulted in the standard draft **ISO/TS 9491-2 Guidelines for implementing computational models in clinical integrated decision support systems** submitted to and accepted by the ISO committee ISO/TC 276 Biotechnology. Its publication by ISO is anticipated.

This standard draft delivers fundamental requirements for: 1) clinically-driven projects standardization, 2) data handling, 3) assessment of data availability and quality in clinically-driven projects, 4) data modeling and interpretability, 5) validation of existing and development of new models for different populations, 6) uncovering patient-specific and population-related patterns that can improve care, 7) reinforcing a multidisciplinary

decision-making process, 8) creating a virtuous cycle of learning, 9) patient involvement and 10) risk management.

We here introduce a guideline for setting up, detailing, annotating, as well as ensuring the interoperability and integration of health data and resulting models, along with their accessibility and origin, in a way that is both understandable and grounded in evidence. It outlines the integration of these guidelines with the conduct of clinical trials through standard operating procedures. Additionally, it deals with the criteria and advice for the data needed to build or validate these models. These recommendations aim to contribute to the standardization of a framework to regulate the use of data-driven systems for clinical research.

Benchmarking computational models of peritoneal dialysis in pigs and patients

Sangita Swapnasrita[1,2], Joost C deVries[2], Carl Oberg[3], Aurelie MF Carlier[1], Karin GF Gerritsen[2]
[1]Maastricht University, the Netherlands; [2]UMC Utrecht, the Netherlands; [3]Lund University, Sweden

Peritoneal dialysis (PD) is a dialysis mode available to patients with acute or chronic kidney failure. As the need for home-based dialysis grows, PD is gathering interest among clinicians and patients leading to an upsurge in the various PD modalities available in the market. To compare the various PD modalities without excess animal or human trials, a robust, generalisable and personalisation-friendly computational model is required. Despite many PD computational models, what lacks is a rigorous benchmarking of the models on the same clinical dataset to find such a model. In this work, we benchmark the efficiency of four PD models in predicting the time-dependent evolution of six solute dialysate concentrations (urea (U), creatinine (C), sodium (S), potassium (Po), glucose (G) and phosphate (Ph)) in pigs and three solutes (U, C, G). We chose two mechanistic models (Graff et al., Three-pore model, TPM) and two analytical models used in clinical practice (Garred et al., Waniewski et al., WM). The four models, in combination, encompass various mechanisms that are essential to PD (diffusion, convection, lymphatics). We collected dwell session data from pigs (n=29) and patients (n=20). For each dataset, we fit the dialysate solute concentrations simultaneously to predict the mass transfer area coefficients (MTAC) of each solute. From the four models, TPM and WM have the lowest RMSE and also computationally efficient. TPM is generalizable and most plausible. In addition to an extensive benchmarking, we obtained for the first time MTAC values for pigs (U: 9.12±3.23 ml/min; C: 4.06±2.37; G: 10.48±22.43, Po: 26.82±15.15; S: 2.26±7.28; Ph: 2.88±1.98), do an exhaustive comparison with literature data and those fitted in human (U: 21.68±7.67 ml/min; C: 11.67±4.99; G: 10.61±5.92). We also use the TPM model to optimize glucose concentration and dwell time regarding urea clearance and ultrafiltration for a given patient model (fixed MTAC). By benchmarking PD models, this study contributes to future avenues for PD personalisation.

Toward multiscale lymph node model: T cell search strategy study

Tomas Bily, Sára Štráchalová, Alžběta Prášilová
CUNI, Czech Republic

Lymph nodes play several critical roles in the immune system, making it crucial to comprehend their functionality for understanding human health and advancing therapies for various diseases. In silico models have proven to be valuable tools for elucidating the behavior of biological systems. Our objective is to develop a multiscale in silico model of lymph nodes. We construct our modeling framework in the mathematical theory of composability, with a focus on the theory of enriched operads. This approach allows us to consistently couple and integrate various modeling methodologies.

We illustrate our framework with a case study on the T cell search strategy in the T cell zones of lymph nodes. The interaction within lymph nodes between mature dendritic cells and naive T cells, which bear cognate antigen receptors, is vital for initiating the adaptive immune response. Given the high heterogeneity of these receptors among T cells, efficient scanning mechanisms are necessary to ensure successful contact. The precise mechanism of this scanning remains unknown, with two prevailing hypotheses: random walk or chemotaxis. Existing data does not provide a definitive conclusion on the employed strategy. Consequently, this issue has been addressed through modeling studies, which, however, have yielded conflicting interpretations that align with the available data. By employing our modeling toolkit to examine these discrepancies, we found out that T cells can employ different strategies depending on the specific conditions within lymph nodes.

Software infrastructure tools for biomedical models in systems biology

Herbert Martin Sauro
University of Washington, United States of America

The center for reproducible biomedical research as well as other efforts in our group, have generated a wide variety of software tools as well as enhancing the current range of systems biology standards, such as SBML, and SEDML. This presentation will describe our range of reproducibility and credibility tools for the community. Specific focus will be on the availability of a new model verification service, a new model reproducibility portal, a new advanced model editor and a new web based interactive modeling environment based on the Iridium desktop modeling platform.

Probabilistic Boolean modelling highlights neural tube closure dynamics and molecular signalling insights

Ahmed Hemedan[1], Job Berkhout[2], Luiz Ladeira[3], Alessio Gamba[3], Harm Heusinkveld[2], Liesbet Geris[3,4], Bernard Staumont[3], Rudi Balling[5], Marek Ostaszewski[1,6], Venkata Satagopam[1,6], Reinhard Schneider[1,6]
[1]Luxembourg University, Luxembourg; [2]Centre for Health Protection, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; [3]Biomechanics Research Unit, GIGA In Silico Medicine, University of Liège, Belgium; Skeletal Biology and Engineering Research Center, KU Leuven, Belgium; [4]Biomechanics Section, Department of Mechanical Engineering, KU Leuven, Belgium; [5]Institute of Molecular Psychiatry, University of Bonn, Bonn, Germany; [6]ELIXIR Luxembourg, Belvaux, Luxembourg

Neural tube closure contributes to the development of the nervous system, and failure of its closure results in severe birth defects such as spina bifida and anencephaly.

Considering the complex processes taking place in the development of the neural tube, advanced computational approaches, such as Boolean modelling, are required to study the complexity of the associated biological processes. The lack of kinetic parameters of the biological processes involved makes Boolean modelling a powerful approach to analyse the development of the neural tube. Boolean modelling is useful as it abstracts representation of biomolecules status to binary states (ON/OFF). In this study, we applied probabilistic Boolean modelling to analyse the neural tube development. We translated the neural tube closure physiological map into a probabilistic Boolean model in an automatic fashion. Then, we parameterized the model with transcriptomics datasets to perform precise and comprehensive system-level simulations. Our results are highlighted in two main points, emphasising the capability of the model to replicate and predict key aspects of neural tube development. Firstly, the simulation of a WNT-activating gradient replicated the progressive specification of neural regions analogous to the Wnt- and GSK3/β-catenin-dependent biological process of caudalization. This was proven since neural tissues with clear anterior-posterior axis characteristics were generated in the early stage of differentiation. Second, the probabilistic model provides a precise description of the detailed modulation of the BMP and FGF signalling pathways, and their roles in neural tube closure. The model displayed that the configurations of specific genes are key to explaining the successful closure of the neural tube - Emphasising the substantial roles of BMP4 and FGF8 in epidermal formation and the binding of two independent layers of neuroectoderm. This approach helps understand the complexity of neural tube development in support of building an accurate model at the base level for strategies for improved therapies and toxicity assessment.

Explanatory models of human physiology to teach pathophysiology of diabetic ketoacidosis with simulators

Tomas Kulhanek, Jiri Kofranek
First Faculty of Medicine, Charles University Prague, Czech Republic

There is rapid growth of using medical simulators to teach medicine and biology. Some of the medical simulators are scenario based thus a behavior is programmed based on the requirement of specific goal for simulation learning. The other sort of medical simulators are based on mathematical models. We have published enabling technology to transfer simple and complex mathematical models written in Modelica language standard via industrial standard FMI to standard web components using computation in WebAssembly supported by most modern browsers on any device (https://bodylight.physiome.cz) [1]. We present case report of metabolic disorder: metabolic ketoacidosis based on co-simulation of hemodynamics model of cardiovascular system [2] and respiratory and blood gas exchange model based on Physiolibrary v.3 [3]. This case report with simulators and interactive materials are now used to support teaching of complex parts of pathophysiology. The supporting material is web based simulator application written in markdown deployed as github pages and using Bodylight.js framework to operate locally connected hardware manequin giving another option to interact with students of medicine and other interactive materials to bring probelm based learning to seminars. Such explanatory simulators do need further testing and certification in order to be used in clinical decision making, it has potential to address complexity of pathophysiology based on scientific valid models and still keep comprehensibility for decision makers.

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In silico clinical trial to predict the efficacy of alendronate for preventing hip fractures

Sophie Nguyen[1,2,3], Sara Oliviero[1,4], Giacomo Savelli[1,4], Antonino Amedeo La Mattina[4], Marco Viceconti[1,4]

[1]Department of Industrial Engineering, Alma Mater Studiorum, University of Bologna, Italy; [2]Faculty of Applied Sciences, University of Liège, Belgium; [3]Biomechanics Section, Department of Mechanical Engineering, KU Leuven, Belgium; [4]Medical Technology Lab, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

Osteoporosis (OP) exposes patients to a high risk of hip fracture due to a loss of bone mineral density (BMD). Current treatments (e.g. alendronate) have limited efficacy in preventing fractures. While the development of new therapies remains needed, clinical trials are long and costly. *In Silico* trials could be used to improve the drug development process. The aim of this work was to replicate *In Silico* a concluded clinical trial to predict the efficacy of alendronate and validate it against clinical data. A relevant clinical trial was selected and data on BMD changes induced by treatment with alendronate were collected[1][2]. A cohort of 293 patients[3] was generated by replicating the femur BMD distribution of the population. The disease and the treatment were introduced with a decrease or increase in BMD over time, respectively. A Markov chain process was applied to predict fracture incidence over 3 years. A Poisson distribution was sampled to determine the number of falls sustained by each patient and the impact force was estimated with a multiscale stochastic model[4]. Finite Element models were used to predict the failure load of the femur. A patient was considered fractured when the impact force exceeded the failure load. Hip fracture incidence was significantly lower in the treated arm compared to placebo. Risk ratio (RR=0.75) was lower compared to clinical data (RR=0.83)[2], indicating that the current model partially overestimated the drug efficacy. The workflow was fully implemented and this work demonstrated the applicability of the method, which will be further developed. *In Silico* trials have the potential to improve the drug development process in terms of time- and cost-effectiveness.

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Comparative assessment of lower limb joint angle estimation between BTS system and OpenSim

Mahshida Hamid[1], Sanyam Phutela[1], Rounak Bhattacharyya[1], Manish Gupta[2], Bhavuk Garg[2], Rajesh Malhotra[2,3], Madhusudan Pal[4,5], Anoop Chawla[1], Sudipto Mukherjee[1], Kaushik Mukherjee[1]

[1]Indian Institute of Technology Delhi, India; [2]All Indian Institute of Medical Sciences, New Delhi, India; [3]Indraprastha Apollo Hospital, New Delhi, India; [4]Defense Institute of Physiology & Allied Science, Defence Research & Development Organisation, Delhi, India; [5]Center of Excellence, Footwear Design & Development Institute, Noida, India

Introduction

Three-dimensional Motion analysis is pivotal for understanding human biomechanics, analyzing different movement disorders, and improving rehabilitation strategies. For movement analysis, a motion capture system (marker or markerless) and musculoskeletal modeling software (like OpenSim, AnyBody, etc) are used prominently. The objective of this study was to investigate the differences in the predicted lower-limb joint angles during normal walking between a motion capture system like BTS bioengineering and a musculoskeletal modeling platform like OpenSim.

Methods

One Healthy male subject (Age 30, Height 163 cm) was recruited at All India Institute of Medical Sciences, New Delhi, India. The kinematic data was recorded at 200 Hz using 12 BTS SMART DX-7000 cameras (BTS Bioengineering). Eight walking trials at a self-selected pace were carried out for the subject. The lower-limb joint angles were first calculated by the BTS system. Thereafter, a subject-specific musculoskeletal model was developed [2], and inverse kinematic analysis was performed for each walking trial. The mean lower-limb joint angles predicted by the BTS system and OpenSim were compared.

Results

The study revealed findings regarding the mean Root Mean Square Error (RMSE) across all joint angles, averaging at 9.45 ± 6°. Specifically, during hip flexion, a RMSE value of 4.5607 was recorded. The knee displayed the highest RMSE at 15.02 ± 6°. Additionally, the ankle joint exhibited an RMSE of 8.60.

Discussion

The kinematic analyses conducted with both the BTS system and OpenSim showed differences, particularly evident during the stance phase in knee and ankle angles. Hence, future investigations should prioritize comparing various musculoskeletal models with motion capture systems to mitigate such disparities, thus enhancing the accuracy and reliability of biomechanical analyses.

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Quantification of periprosthetic bone loss using electrical impedance tomography

Lisa Krukewitt, Sascha Spors
University of Rostock, Germany

Periprosthetic bone loss is a common cause of aseptic loosening in hip stem implants that is often detected late due to the low sensitivity of current methods. Here, we investigate the feasibility of monitoring periprosthetic bone using electrical impedance tomography (EIT), a non-invasive imaging technique that visualizes conductivity changes. We aim to quantify conductivity changes that accompany bone loss in a human thigh with a hip stem implant. As a proof of concept, we use an in-silico model.
EIT works by injecting weak currents through electrodes placed around a body, recording the resulting voltages, and applying an image reconstruction algorithm to show a conductivity distribution. Since the image resolution is low due to the required regularization of the reconstruction problem, we aim to infer the bone quality directly from the voltages. EIT data for various conductivity changes in a human thigh are simulated using a finite element model (FEM). Difference voltages are calculated between a reference state with the conductivity of healthy bone and muscle, and various scenarios with different changes in the conductivity distribution. Since the conductivity of bone changes over a large timescale, surrounding tissue may change simultaneously. We therefore simulate random changes in the muscle tissue by up to 5 % in addition to bone conductivity change. Conductivity of bone elements is gradually increased up to that of muscle to resemble bone loss in one area. Convolutional neural networks (CNNs) are trained to predict the size of a bone defect as well as the conductivity in the defect region from EIT voltages. Over the entire simulated range of bone conductivity, the CNNs can predict both the number of changed FEM elements and the new bone conductivity with low errors. When noise is added to the voltages, the percentage error of the predicted values increases sharply with decreasing signal-to-noise ratio (SNR). For all scenarios, errors in predicted bone properties are below 5 % for an SNR above 40 dB. These predictions are possible with and without inclusion of a titanium implant, showing the feasibility of using EIT to monitor periprosthetic bone quality.

Machine learning framework to study the impact of metastatic cancer in the spine

Simão Laranjeira[1], Simon Walker-Samuel[2], Rebecca J. Shipley[1]
[1]UCL Mechanical Engineering, London, UK; [2]UCL Centre for Computational Medicine, Division of Medicine, London, UK

In Europe, hundreds of thousands of breast cancer cases are diagnosed per annum. From these patients, 2/3 will develop spinal metastatic bone disease (SMBD). SMBD results in the degradation of the bone in the spine and can lead to vertebra fracture, which causes extreme pain and may result in spinal cord injury. The treatment for the most severe cases consists of major surgery with a recuperation time of 6-8 months, a significant amount of time for patients with short life expectancy. There is an critical need for diagnostic tools which evaluate patient-specific fracture risk and which could inform medical intervention. Currently, fracture risk is informed by imaging, such as CT, and various qualitative scores. Here we propose a novel computational framework where patient-specific simulations ascertain the loading distribution (and thus fracture risk) in a vertebra containing a growing metastasis. Our approach consists of 3 phases. Firstly, each of the vertebrae in the spine are accurately segmented and labeled from patient CT scans, using a convolutional neural network (CNN) architecture trained with hundreds of healthy spine CTs. Secondly, a finite element mesh is constructed from the segmentations by fitting statistical shape models (SSM) to each vertebra and using

them as substrate for computational simulations of the vertebra mechanics. Thirdly, to simulate the loading environment, a finite element based model of the spine was developed using the Firedrake framework in Python, assuming the bone and tumours individually behave as heterogeneous, isotropic and elastic-plastic materials with properties defined based on the literature. As a proof of concept, the framework was applied to simulate the lumbar portion of the spine. Our ambition is to extend the framework to encompass the whole spine and to validate it using SMBD data. With such a framework we hope (in the long term) to provide a quantitative tool to inform clinical decisions for patients at risk of vertebra fracture from SMBD.

A sustainable neuromorphic framework for disease diagnosis using AI

Rutwik Gulakala, Marcus Stoffel
RWTH Aachen, Germany

In the diagnosis of medical images, neural network classifications can support rapid diagnosis together with existing imaging methods. Although current state-of-the-art deep learning methods can contribute to this image recognition, the aim of the present study is to develop a general classification framework with brain-inspired neural networks. Following this intention, spiking neural network models, also known as third-generation models, are included here to capitalize on their sparse characteristics and capacity to significantly decrease energy consumption. Inspired by the recent development of neuromorphic hardware, a sustainable neural network framework and algorithm is proposed, leading to an energy reduction down to a thousandth compared to the current state-of-the-art second-generation counterpart of artificial neural networks. Making use of sparse signal transmissions as in the human brain, a neuromorphic algorithm for imaging diagnostics is introduced. A novel, sustainable, brain-inspired spiking neural network is proposed to perform the multi-class classification of digital medical images. To evaluate the proposed framework, a publicly available multiclass dataset of digital X-rays containing Covid-19, healthy and pneumonia-affected individuals is utilized. An equivalent classical neural network model is also proposed for comparison. The data for the spiking neural network is encoded using a latency encoding strategy to convert the images to binary spikes. The models are trained using pre-processed X-ray images and are evaluated based on classification metrics. The proposed neuromorphic framework had extremely high classification metrics with an accuracy of 99.22% and its second-generation counterpart had an accuracy of 99.55%. Though there is a loss of information due to encoding, the proposed neuromorphic framework has achieved accuracy close to its second-generation counterpart. Therefore, the benefit of the proposed framework is the high accuracy of classification while consuming a thousandth of the power, enabling a sustainable and accessible add-on for the available diagnostic tools, such as medical imaging equipment, to achieve rapid diagnosis.

Limits and capabilities of diffusion models for the anatomic editing of digital twins

Karim Kadry[1], Shreya Gupta[1], Farhad R. Nezami[2], Elazer R. Edelman[1,2]
[1]MIT, United States of America; [2]Brigham and Women's Hospital

Numerical simulations can model the physical processes that govern cardiovascular device deployment. When such simulations incorporate digital twins; computational models of patient-specific anatomy, they can expedite and de-risk the device design process. Nonetheless, the exclusive use of patient-specific data constrains the anatomic variability which can be precisely or fully explored. In this study, we investigate the capacity of Latent Diffusion Models (LDMs) to edit digital twins to create anatomic

variants, which we term digital siblings. Digital twins and their corresponding siblings can serve as the basis for comparative simulations, enabling the study of how subtle anatomic variations impact the simulated deployment of cardiovascular devices, as well as the augmentation of virtual cohorts for device assessment. However, while diffusion models have been characterized in their ability to edit natural images, their capacity to anatomically edit digital twins has yet to be studied. Using a case example centered on 3D digital twins of cardiac anatomy, we implement various methods for generating digital siblings and characterize them through morphological and topological analyses. We specifically edit digital twins to introduce anatomic variation at different spatial scales and within localized regions, demonstrating the existence of bias towards common anatomic features. We further show that such anatomic bias can be leveraged for virtual cohort augmentation through selective editing, partially alleviating issues related to dataset imbalance and lack of diversity. Our experimental framework thus delineates the limits and capabilities of using latent diffusion models in synthesizing anatomic variation for virtual intervention studies.

Cross-disease predictive analysis for pandemic preparedness

Joana Elena Meyer[1], Sebastian Fritsch[2], Andreas Schuppert[1]
[1]Institute for Computational Biomedicine, RWTH Aachen, Germany; [2]Departement of Intensive Care Medicine, University Hospital RWTH Aachen, Germany

Pandemic preparedness has gained high relevance during the COVID-19 pandemic. Early- available predictive modeling is crucial for early disease management and decision support systems, yet it is challenged by the limited availability of disease-specific data and an incomplete understanding of disease mechanisms.

In this study, we propose a concept of rapid predictive modelling for novel diseases, based on the hypothesis that common disease-promoting mechanisms can be leveraged across different diseases.

We conducted a retrospective analysis on 11874 mechanically ventilated patients in four intensive care units, including 593 cases of coronavirus. Rather than clustering patients by diseases, our model profiles cases based on disease progression using common monitoring parameters. This approach enables the translation of information gained from known diseases to novel diseases.

We observe that the accuracy of machine learning-based prognostic systems is impacted by rapidly evolving life-threatening events, such as septic shock, indicating a conceptual limitation in patient-specific outcome prediction. However, our model, focusing on common disease- promoting mechanisms and trained with non-COVID-19 patients, proved to be nearly as effective in predicting COVID-19 outcomes as models trained exclusively with COVID-19 data.

We advocate for the use of retrospective patient data repositories for translational learning based on common disease-driving mechanisms. This approach offers rapid strategy for predicting diseases outcomes of newly emerging diseases.

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SOCIAL PROGRAM

Student Social Event


Tuesday, September 3


6:00 pm


Foyer of KII (in front of the auditorium)
Keplerstraße 17, 70174 Stuttgart

Informal evening exclusively organized for student participants.

Meeting point is the foyer of KII, Keplerstraße 17 in Stuttgart. We will do a 2- hour city walk in Stuttgart and have some food and drinks afterwards in the Foyer of KII.

Welcome Reception


Wednesday, September 4


6:00 pm


Foyer of KII, (in front of the auditorium)
Keplerstraße 17, 70174 Stuttgart

Informal evening exclusively organized all conference participants.

On Wednesday there will be the Welcome Reception in the foyer (in front of the auditoriums) of KII with a finger food buffet. In a pleasant atmosphere, all participants get the perfect opportunity to network and to get to know each other. We look forward to open the conference week with a pleasant evening.

Conference Dinner

Thursday, September 5

7:00 pm

Alte Reithalle, Maritim Hotel, Seidenstraße 34, 70174 Stuttgart

Dinner for everyone, who has registered.

The festive conference dinner takes place near the city center within walking distance from the conference venue. The conference organizers do not provide transportation to and from the dinner location. It is recommended to have a short walk (10 minutes) from the conference venue to the dinner location. Alternatively, you can take the bus 42 from Katharinenhospital to Rosenberg-Seidenstraße. It is our pleasure to invite you to a delicious buffet, as well as wine, beer and soft drinks. Drinks and food are included in the dinner registration fee.

Way to the dinner location by foot:

ABSTRACTS: PRESENTATIONS

1.A: Computational Modelling of the Heart

Wednesday, September 4

10:30am - 12:00pm

05.019

Computational models of cardiac function – Closing the gaps between virtual and physical reality

Gernot Plank
Medical University of Graz, Austria

Computational models of cardiac function are increasingly considered in industry for designing medical device therapies, and, in the clinic for diagnosis and therapy planning to tailor patient-specific therapies. A fundamental concern hampering a broader adoption is the lack of evidence of a close correspondence between the physiology of a virtual heart and physical reality. Creating such evidence remains challenging as biophysically detailed virtual hearts are characterized by high dimensional parameter vectors that must be identified from limited low dimensional, noisy and uncertain observations. Further, even for carefully calibrated models, their ability to provide patient-specific predictions of the cardiac response to therapies based on their mechanistic nature is assumed, but not proven. Finally, generating detailed mechanistic models requires complex computationally costly workflows, requiring operators with significant skill levels. This raises concerns regarding scalability to applications to larger variable patient cohorts, the validity of insights produced by error prone workflows, as well as the reproducibility of in silico studies. These concerns render advanced industrial and clinical applications often unviable from both a regulatory as well as an economic perspective. Here, we report on methodological advances addressing these issues. Specifically, we present methods for i) the automated generation of anatomically and structurally accurate models of whole heart and torso from medical images, with suitable reference frames to support automation of parameter sweeps; ii) full physics real-time enabled whole heart electrophysiology simulations and associated electrograms and ECGs; iii) a calibration technique for whole heart electrophysiology using non-invasive ECG measurements; iv) model calibration techniques for cardiac device therapies replicating device measurement applicable for optimizing device designs in industry and for personalized therapy planning in the clinic; and v) a computational approach for guiding ventricular tachycardia ablation therapies based on electrogram and ECG matching.

A multiscale finite element model of cardiac growth and baroreflex regulation

Hossein Sharifi[1], Kenneth Scott Campbell[1], Lik Chuan Lee[2], Jonathan Frederick Wenk[1]

[1]University of Kentucky, United States of America; [2]Michigan State University, United States of America

The heart functions within a complex system that adapts its performance based on alterations in loading via several mechanisms. For example, the baroreflex is a short-term feedback loop that modulates the heart's function on a beat-to-beat basis to control arterial pressure. On the other hand, cardiac growth is a long-term adaptive response that occurs over weeks or months in response to changes in left ventricular loading. In this study, we investigate the impact of a baroreflex feedback loop on left ventricular growth in simulations of valve disease. To achieve this, we integrated the effects of a short-term baroreflex feedback loop and a long-term growth algorithm into a beating multiscale finite element model of the left ventricle. The baroreflex loop modulates the system from the molecular-level function of myofilaments up to system-level parameters, such as heart rate, to control arterial pressure [1]. Meanwhile, the growth algorithm responds to the altered stress level of the myocardium to drive long-term changes in the geometry of the left ventricle. Specifically, eccentric growth (chamber dilation) is driven by time-averaged passive stress in the myofibers, while concentric growth (wall thickening) is driven by time-averaged total stress along the myofiber direction over the cardiac cycle. Our integrated model replicates clinical measures of left ventricular growth in two types of valvular diseases - aortic stenosis and mitral regurgitation - at two different levels of severity for each case. Furthermore, our results showed that incorporating the effects of baroreflex control in simulations of left ventricular growth not only led to more realistic hemodynamics, but also impacted the magnitude of growth. Specifically, our results highlighted the role of regulating venous compliance (vasoconstriction) by the baroreflex immediately after the onset of valvular diseases, which has a significant role on the extent of LV growth in the long term.

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Full personalisation of 3D biventricular models from electroanatomical mappings and cardiac magnetic resonance imaging to understand the impact of arrhythmic substrate components on electrophysiological function

Jesus Jairo Rodríguez Padilla[1], Buntheng Ly[2], Rafael Silva[1], Mihaela Pop[1,3], Maxime Sermesant[1]
[1]Centre Inria d'Université Côte d'Azur, France; [2]IHU-Liryc, Université de Bordeaux, Pessac, France; [3]Sunnybrook Research Institute, Toronto, Canada

In the European Union alone, annual incidence of sudden cardiac death (SCD) reaches 250,000 cases. In particular, SCD following myocardial infarction poses a significantly critical public health problem. In this context, there is a need to develop more effective and non-invasive predictive tools for arrhythmia risk stratification. Besides clinical and experimental studies, cardiac modeling is a powerful and robust tool that can be used to predict scar-related arrhythmia risk as well as ablation targets, as shown in recent works. We propose to leverage on the ability of computer simulations to virtually study the inducibility of ventricular tachycardia (VT) by replicating clinical stimulation protocols, while changing stimulus location to elucidate its effect on the electrophysiologic response in the presence of scars. Cardiac magnetic resonance (MR) imaging data was obtained from 7 swine at five weeks post-infarction, using a 3D late gadolinium enhanced (LGE) method, at 1.4mm isotropic voxel. The VT substrate in LGE images was identified as a 'grey zone', GZ. The tissue types (i.e., healthy, GZ, and unexcitable scar) were segmented using a full width at half maximum method and used to build 3D biventricular models. For myocardial anisotropy, we used our diffusion tensor-based cardiac pig atlas of fiber directions. Next, a Carto3 system was used to perform electro-anatomical (EA) mapping of LV endocardium in sinus and RV-paced rhythms, as well as VT inducibility tests. In this work we discuss the full pipeline used in the computational study: (i) mesh generation and labelling of zones of interest (healthy tissue, GZ, and scar); (ii) numerical methods (modified Crank-Nicolson Adam-Bashford scheme), variational formulation of a modified Mitchell Schaeffer model and solver description (FEniCSx); (iii) 3D model calibration procedure from EA maps; (iv) exemplary results for VT inducibility; (v) stimulation protocols and computational cost; (vi) first steps on the VT substrate impact on heart electromechanics.

A multi-scale analysis of the impact of measurement and physiological uncertainty on electrocardiograms

Ludovica Cicci[1], Shuang Qian[2], Cristóbal Rodero[1], Fernando O. Campos[2], Marina Strocchi[1,2], Karli Gillette[3], Gernot Plank[3,4], Martin J. Bishop[2], Steven A. Niederer[1,2,5]
[1]Imperial College London; [2]King's College London; [3]Medical University of Graz; [4]BioTechMed-Graz; [5]The Alan Turing Institute

An electrocardiogram (ECG) is a non-invasive diagnostic tool for the evaluation of the electrical activity of the heart where electrodes, usually 10 in a standard 12-lead ECG, are placed on the body surface at specific anatomical locations. The ECG signal morphology is used to monitor and diagnose the heart but is a complex function of electrode location, anatomy, tissue properties and cellular function. Using computational models of cardiac electrophysiology (EP), we are developing a multi-scale model that links whole organ measurements, such as ECG and MRI, down to the cellular level. This will allow us to map non-invasive clinical observations with changes in the proteins that span the cell membrane. Our model of ventricular EP, embedded in a whole torso geometry, consists of hundreds of parameters that represent, e.g., different protein densities and tissue heterogeneity. To simulate the electrical activity of the heart, we employ the reaction-eikonal propagation model with the lead field approach, implemented in the software package *CARPentry* (Vigmond, 2008). We then conduct a multi-scale filtering of the model parameters via global sensitivity analysis. At each step, we rank the sub-model parameters according to their influence on specific sub-model outputs -- i.e., scalar quantities liked to a parametric representation of the action potential or the ECG signal -- and screen out the non-important ones. To mitigate the computational complexity of the model, we rely on Gaussian process emulators implemented in *GPErks* (cemrg.co.uk/software/gperks). This approach enables an efficient exploration of the full parameter space, so that we can look at the interactions between input parameters and outputs of interest and identify key model inputs that have the greatest impact on ECG signal variations. Such insight aids in discerning which parameters in our model are pivotal for a specific output, and thus allow us to determine which inputs are likely to be inferred from the available data.

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Titin-mediated viscoelastic passive muscle mechanics

Filip Jezek[1], Anthony Baker[3], David Nordsletten[2], Dan A Beard[1]
[1]Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI, USA; [2]Departments of Biomedical Engineering and Cardiac Surgery, University of Michigan, Ann Arbor, MI, USA; [3]Veterans Affairs Medical Center, San Francisco, CA, and Department of Medicine, University of California, San Francisco, CA, USA

This study investigates the mechanical properties of titin, a sarcomeric structural protein that links the myosin thick filament to the Z disk. The elastic region of titin, located in the I band of striated muscle sarcomeres, plays a vital role in providing the passive restoring force during muscle stretch. Under stress, serial globular domains within the elastic region of the titin molecule reversibly unfold. This unfolding phenomenon contributes to both hysteresis (a lag in stress between loading and unloading) and preconditioning effects in striated muscle mechanics. Moreover, experiments reveal that stress relaxation in titin follows a power law decay, and that titin's nonlinear stress-strain relationship and hysteresis behavior are calcium dependent. To comprehensively analyze these mechanical phenomena, we develop, analyze, and simulate a mesoscopic-scale ensemble model of titin elastic domain mechanics that accounts for the dynamic unfolding of globular domains along the titin chain. Providing a unified basis for observed viscoelastic and preconditioning effects, calcium dependency, and power-law stress relaxation phenomena, this study introduces a novel theoretical basis for understanding and simulating the role of titin in striated muscle mechanics.

1.B: Multi-X Vascular Modelling

Wednesday, September 4

10:30am - 12:00pm

02.017

Multiscale fluid-structure interaction for the effective modeling of vascular tissues

Luca Heltai[2], Camilla Belponer[3], Alfonso Caiazzo[1], Lucas O. Müller[4], Paolo Zunino[5]
[1]WIAS Berlin, Germany; [2]University of Pisa; [3]University of Augsburg; [4]University of Trento; [5]Politecnico di Milano

We present recent results for the modeling and simulation of a vascularized tissue based on a three-dimensional elastic solid material coupled to thin (one-dimensional) fluid inclusions. The application is motivated by the modeling of vascularized tissues and by problems in medical imaging which target the estimation of effective (i.e., macroscale) material properties, taking into account the influence of microscale dynamics, such as fluid flow in the microvasculature. The elastic model is based on the recently proposed reduced Lagrange multipliers framework [Heltai & Zunino, arxiv 2303.10600 2023, Heltai, Belponer, Caiazzo, arxiv 2309.06797 2023], coupled to a high-order one-dimensional finite volume for blood flow (following the method firstly proposed in [Heltai & Caiazzo, IJNMBE 2019, Heltai, Caiazzo, Müller Ann. Biomed. Engnr. 2021]). In this approach, the interface between solid and fluid domains is not resolved within the computational mesh for the elastic material but it is discretized independently, imposing the coupling condition via non-matching Lagrange multipliers condensed on a low dimensional space on the vessel centerline. This approach allows, on the one hand, to reduce the geometrical complexity of creating a conformal discretization. On the other hand, it naturally fits with a one-dimensional approximation of the fluid dynamics in the vessel network. We present numerical analysis results concerning the well-posedness of the elastic problem, as well as numerical results related to different approaches for the coupling with reduced-order fluid models, considering lumped parameter models as well as time-dependent one-dimensional high-order finite volume methods [Müller et al. JCP, 2016]. We discuss the applications of the model in the context of multiscale inverse problems, when measurements at the coarse scale (effective tissue) are used to infer parameters at smaller scales.

An automated pipeline to investigate the impact of intracranial internal carotid artery calcifications on cerebrovascular events

Federica Fontana[1,2], Fennika S. C. Huijben[1,2], Aikaterini Tziotziou[2], Brian B. P. Berghout[3,4,5], Frank J. H. Gijsen[1,2], Ali C. Akyildiz[1,2], Selene Pirola[1]
[1]Department of Biomechanical Engineering, Delft University of Technology, Delft, The Netherlands; [2]Department of Biomedical Engineering, Erasmus Medical Center, Rotterdam, The Netherlands; [3]Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands; [4]Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands; [5]Department of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands

Numerous clinical studies support a link between intracranial Internal Carotid Artery (ICA) calcifications and adverse cerebrovascular outcomes, including cognitive function impairment (Bos et al. 2012) and stroke (Fote et al. 2022). However, these studies only assess the calcification burden focusing on calcification volume alone, neglecting the impact of hemodynamic alterations linked to the disrupted wall mechanics. This work aims to develop an automated pipeline for patient-specific Fluid-Structure Interaction (FSI) modelling of the intracranial ICA. 3D arterial lumen and calcifications are reconstructed from Computed Tomography Angiography (CTA) images using a semi-automated workflow developed in ITK-SNAP and 3D Slicer. Relevant morphometric measures, such as number, thickness and width of calcifications, as well as ICA diameter, tortuosity and curvature radii, are then automatically computed using an in-house MatLab tool. The 3D FSI simulation is then performed using FEBio and taking advantage of its integration with the GIBBON toolbox. FSI model generation (including meshing), simulations launch, and results processing, are all automated within the same environment. The proposed methodology has been preliminary tested on one patient. FSI simulations were performed in the ICA with and without accounting for calcifications. For this case, the ICA average diameter and tortuosity were 3.77 mm and 1.56 mm, respectively. The total calcification volume was 70 mm^3 with 4 calcific lesions. Calcifications had a maximal thickness of 2.19 mm and a maximal circumferential extension of 97°. The comparison of FSI results between the non-calcified and calcified models highlighted the presence of stress concentrations near the calcium deposits leading to an increase in the max principal stress in the wall (0.14 MPa vs 0.26 MPa, +46%). A limited increase in the pressure drop across the calcified region was found (+2%). Helical flow was observed. The obtained results show the potential of the developed pipeline. Current efforts are focused on application on a larger cohort of patients (~100), allowing to assess the impact of calcifications on the local hemodynamic in the ICA.

Impact of atrial rotor dominant frequency on flecainide and vernakalant cardioversion ratio

Violeta Puche-García[1], Laura Martínez-Mateu[2], David Filgueiras-Rama[3], Lucía Romero[1], Javier Saiz[1]
[1]Centro de Investigación e Innovación en Bioingeniería (Ci2B), Universitat Politècnica de València, Spain; [2]Grupo de investigación de alto rendimiento en Ingeniería Biomédica y Ciencia de Datos (BigMed+), Universidad Rey Juan Carlos, Spain; [3]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

Pharmacological therapy holds great potential for treating paroxysmal atrial fibrillation (pAF), yet its efficacy depends on individual patient characteristics. This study investigates how different ionic profiles and electrophysiological mechanisms influence the effectiveness of two antiarrhythmic drugs (flecainide and vernakalant) in terminating fibrillatory episodes. Atrial electrophysiology was simulated using a modified version of the Courtemanche human atrial model, including the parameters to mimic the pAF electrical remodeling. A population was built by applying individual variations of ±30% and ±40% on each of the 11 parameters related to electrophysiological variability (10 ionic currents and the tissue conductivity). Using a 2D left atrial model, a 5 seconds-long sustained rotor was induced for each profile in the absence of drugs and its dominant frequency (DF) was computed. Then, the drug was applied to test its efficacy in terminating the rotor. Two different therapeutic concentrations (flecainide 1.5 and 3μM, vernakalant 10 and 20μM) were used. Flecainide and vernakalant showed differing efficacy and mechanisms in terminating fibrillatory episodes. Flecainide 1.5 and 3μM terminated 5% and 20% of the episodes, respectively, and vernakalant 10 and 20μM terminated 11% and 42%, respectively. When considering all DF values, vernakalant exhibited higher cardioversion rates than flecainide. Interestingly, at low DF values (first tertile), flecainide 3μM yielded a 31% cardioversion rate, whereas vernakalant at 20μM had a 47% rate. At high DF values (third tertile), flecainide at 3μM demonstrated a 5% cardioversion rate, while vernakalant at 20μM increased the ratio to 35%. Therefore, vernakalant performed better than flecainide at cardioverting fibrillatory episodes, specifically at high frequencies. Our results highlight the complex mechanisms underlying drug efficacy in pAF and the key role of DF in predicting drug cardioversion outcomes. These insights have considerable potential for refining personalized pharmacological strategies in pAF patients.

Predicting chronic cardiac responses to angiotensin receptor/neprilysin inhibitor using a physiological model of heart failure with preserved ejection fraction

John S. Clemmer[1], W. Andrew Pruett[1,2], Robert L. Hester[1,2], Marion R. Wofford[1]
[1]University of Mississippi Medical Center, United States of America; [2]HC Simulation

Heart failure (HF) with preserved ejection fraction (HFpEF), or diastolic failure, accounts for most cases of HF. Most of these patients have chronic kidney disease (CKD) and hypertension (HTN), which increases their risk of cardiovascular morbidity and mortality. Recently, sacubitril/valsartan, a dual angiotensin receptor blocker (ARB) and neprilysin inhibitor (ARNI), has been shown to significantly lower blood pressure (BP) and BNP levels in HFpEF patients as compared to ARB alone, but the role using ARNIs in HFpEF during renal dysfunction is unclear. We performed an *in silico* clinical trial using a mathematical model of human physiology (HumMod) to replicate the PARAGON-HF trial and determine the cardiovascular responses to 9 months of sacubitril/valsartan (400 mg/day) or valsartan (320 mg/day) during HFpEF with or without CKD. Baseline HFpEF conditions were associated with normal (BP) and renal function but elevated cardiac pressures, circulating ANP and BNP, and LV stiffness but normal LV ejection fraction. Simulating HFpEF with CKD further increased cardiac pressures and natriuretic peptides and was associated with salt sensitivity, HTN (139/91 mmHg), albuminuria (330 mg/g creatinine), glomerular HTN, and low renal function (glomerular filtration rate, GFR ~60 mL/min). As compared to the 9-month responses to ARB, the simulation predicted greater falls in LV mass, blood pressure, and NT-proBNP levels with ARNI, similar to the results in HFpEF patients from the PARAGON-HF clinical trial. Despite a relatively greater GFR as compared to ARB, the ARNI simulation was associated with worse glomerular hypertension, glomerulosclerosis and albuminuria. In conclusion, our model replicated clinical findings that ARNI is superior to ARB in cardiac indices but predicted glomerular HTN and albuminuria, warranting further attention for using this therapy in HFpEF with progressive renal disease. To our knowledge, this is the first in silico trial using ARNI in a whole-body physiological model of HFpEF. We hope that such future work will provide more insights into the evolving care for HFpEF and CKD to help better understand and manage this vulnerable population.

Coagulation cascade systems modeling for oral anticoagulant monitorization in atrial fibrillation patients

Maria Segarra-Queralt, Marina Ribera, Andy L. Olivares, Oscar Camara
BCN MedTech, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Spain

Atrial fibrillation (AF) affects 1 in 4 individuals older than 40 years old, increasing the risk of stroke from thrombus formation. Oral anticoagulants (OAC) are the primary therapeutic choice. But, a growing number of AF patients face clinical contraindications to OACs, primarily due to bleeding risks and unexpected drug interactions. Predicting optimal medication intake beforehand could significantly reduce adverse drug effects, improving AF patients monitoring. To this end, a 9-species coagulation cascade model (CCM) (i.e. mapping the intrinsic pathway: Factor XI, IX, X, VIII, V; fibrin, protein C, prothrombin and thrombin) from Zarnitsina *et al.* 2001 is adapted to incorporate the action of classic (e.g., Warfarin) and novel OAC (e.g. Apibaxan). Vitamin K (VK) cycle is integrated following the law of mass action for coagulation factors needing VK as a co-factor. This enables to monitor the effects of Warfarin as it competitively inhibits VCOEX, a protein of the VK cycle. Novel OAC action is introduced by targeting Factor X with a mixed-type inhibitory fashion. Finally, a 13-species CCM is expressed as a system of ordinary differential equations. Initial conditions are set using maximum serum concentration values for OAC and physiological concentrations for the left species. When the system is solved following a three-step Runge-Kutta, results show that Warfarin reduce the peak height of the thrombogram, but not its velocity index. Apibaxan reduces both, leading to lower fibrin levels than Warfarin. Interestingly, results show that high doses of Apibaxan have the same effect as low doses on fibrin steady state. Thus, lower doses of novel OAC would be as beneficial as high doses of classical and novel OAC in preventing thrombus formation. Qualitatively, the trend of the simulated thrombogram under different OAC doses resemble those reported by Rimsans *et al.* 2020. Parameter calibration is needed to integrate the CCM and OAC effects better, while adapting species initial conditions for patient-specific predictions. Coupling CCM with fluid simulations would allow study OAC impact on left atrial appendage occlusion device-related thrombus. Fund: GEMINI (101136438).

Modeling fluid-structure-chemistry interactions in atherosclerotic arteries

Daniel Balzani[1], Alexander Heinlein[4], Axel Klawonn[2], Jascha Knepper[2], Sharan Nurani Ramesh[1], Oliver Rheinbach[3], Lea Saßmannshausen[2]
[1]Ruhr University Bochum, Germany; [2]University of Cologne; [3]TU Bergakademie Freiberg; [4]TU Delft

Hypertension is routinely treated using antihypertensive drugs. However, in certain cases, they have been found to have adverse effects and the probability of stroke may even be increased [1]. Numerical simulations can help better understand the underlying pharmaco-mechanical interactions and the resulting stress distributions in atherosclerotic arteries, which may lead to improved outcomes. A material model that accounts for the extracellular matrix, the smooth muscle cell (SMC) response and the drug transport is paramount to producing meaningful drug-tissue interactions. Accordingly, a fully coupled fluid-structure-chemistry model that adopts the SMC model by Uhlmann and Balzani [2] and a simplified reaction-diffusion model for drug transport along with the fluid-structure interaction is developed. In particular, the effects of Calcium channel blockers on SMC contraction are simulated and the consequent stress distributions in atherosclerotic arteries are studied. A monolithic coupling scheme is employed, and the resulting nonlinear problem is solved using linearization via Newton's method. The linearized problem is then solved using the GMRES (generalized minimal residual) method, the FaCSI block-preconditioner [3], and parallel multi-level Schwarz preconditioners of GDSW type for the individual physics blocks. The software framework [4] is based on FEDDLib (Finite element and domain decomposition library) for the fluid-structure-chemistry interaction simulations, AceGen for the code generation of the material models, as well as Trilinos for the parallel linear algebra with the package FROSch (Fast and Robust Overlapping Schwarz) [5] for the Schwarz preconditioners. Simulation results for atherosclerotic arteries under intravascular pressure as well as for the scalability and the efficiency of the simulation framework will be discussed.

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1.C: Liver & Eye Modelling

Wednesday, September 4

10:30am - 12:00pm

02.011

A multiscale and multiphase digital twin of function-perfusion processes in the human liver

Tim Ricken[1], Steffen Gerhäusser[1], Lena Lambers[1], Luis Mandl[1], Matthias König[2], Uta Dahmen[3], Hans-Michael Tautenhahn[4]
[1]University of Stuttgart, Germany; [2]Humboldt Universität zu Berlin, Germany;
[3]University Hospital Jena, Germany; [4]University Hospital Leipzig, Germany

The human liver is responsible for essential processes like fat storage or the detoxification. Some liver diseases can trigger growth processes in the liver, disrupting important hepatic function-perfusion processes. To understand the interplay between hepatic perfusion, metabolism and tissue in the hierarchically organized liver structure, we have developed a multicomponent, poro-elastic multiphasic and multiscale function-perfusion model, using a multicomponent mixture theory based on the Theory of Porous Media (TPM). The multiscale approach considers the different functional units of the liver, the so-called liver lobules, with an anisotropic blood flow via the sinusoids (slender capillaries between the periportal field and the central vein), and the hepatocytes, where the biochemical metabolic reactions take place. On the lobular scale, we consider a tetra-phasic body, composed of a porous solid structure representing healthy tissue, a liquid phase describing the blood, and two solid phases with the ability of growth and depletion representing the fat tissue and the tumor tissue. To describe the influences of the resulting tissue growth, the model is enhanced by a kinematic growth approach using a multiplicative split of the deformation gradient into an elastic and a growth part, dependent on the fat accumulation and tumor development. To describe the metabolic processes as well as the production, utilization and storage of the metabolites on the cellular scale, a bi-scale PDE-ODE approach with embedded coupled ordinary differential equations (ODE) is used. In order to represent realistic conditions of the liver, experimentally or clinically obtained data such as changes in perfusion, material parameters or tissue morphology and geometry are integrated as initial boundary conditions or used for parametrization and validation [5]. Data integration approaches like machine learning are developed for the identification, processing and integration of data. A workflow is designed that directly prepares the model for clinical application by (semi-) automatically processing the data, considering uncertainties, and reducing computation time.

Patient specific prediction of portal vein pressure after liver surgery: Sensitivity, identifiability and uncertainty quantification

Roel Meiburg[1], Sala Lorenzo[2], Kevin Hakkakian[1,3,4], Nicolas Golse[3,4], Irene Vignon-Clementel[1]
[1]Inria, France; [2]Inrae, France; [3]Université Paris-Saclay, France; [4]Inserm Physiopathogénèse et traitement des maladie du foie, France

Primary liver cancer incidence is increasing world-wide and is considered an important source of cancer-related mortality. For a significant portion of patients, surgical removal (partial hepatectomy) of diseased liver tissue is considered the only curative treatment. However, it will likely significantly alter local hemodynamics, possibly resulting in post-operative portal hypertension (PHT). Post-operative PHT has been associated with a significant increase of 90-day mortality. However, occurrence of PHT is multi-factorial (increasing of pre-existing PHT or de novo PHT) and difficult to predict rom pre-operative data only. Computational models may help integrate pre-operative data with physiological models and create a predictive framework for portal vein pressure on a patient-specific basis. Recently, our group has shown the feasibility of using lumped parameter models in PHT prediction when including peri-operative data. Using sensitivity analyses and uncertainty quantification techniques, we aim to reduce the data available to non-invasive measures only while maintaining a reasonable amount of uncertainty on the predictions. We first performed a variance-based sensitivity analysis using polynomial chaos expansion (PCE) to prioritize the set of model input parameters required for personalization of the hemodynamics model. This set of input parameters can be divided into two groups: one can be derived directly from measurements; the other requires optimization. Parameter optimization was performed using the surrogate model to reduce computational time. To ensure a unique solution to the optimization procedure, a profile likelihood analysis was performed, which led to the inclusion of a new clinical measurement in the optimization procedure. Finally, we used PCE to generate the final patient specific uncertainty quantification comprising measured clinical data, planned degree of hepatectomy and possible peri-operative events such as blood loss. In future work, we aim to further reduce the amount of invasive input data needed, include physiological autoregulation mechanisms and include possible peri-operative events to improve the model's predictive power.

A multi-compartment perfusion model for hierarchical vessel networks with application to liver regrowth

Jannes Hohl, Adnan Ebrahem, Etienne Jessen, Dominik Schillinger
Technical University of Darmstadt, Germany

For many physiological phenomena, such as tissue deformation or growth, an adequate perfusion model of the underlying hierarchical vascular network is of great interest. A fully resolved model on multiple spatial scales is still unattainable due to the mostly unknown complex structure of the vascular network. In order to obtain sufficiently accurate results with practical computational resources, a simpler perfusion model is required that still takes into account the hierarchically complex structure over different scales of the tissue and vessels. For this purpose, the vascular network is partitioned into a coupled multi-compartment model where the various hierarchies are represented by the compartments as continua with macroscopic laws. The approach is to describe both the microscale and the hierarchies above as a porous medium using Darcy-type flow models that account for the different spatial scales. Based on synthetic vascular network model data essential parameters are determined for each compartment using averaging procedures. The interaction between the different compartments is considered via the pressure dependent mass exchange and is applied in an averaged sense as well as the boundary conditions. For the solution of deformation-dependent phenomena, iterative solution methods are usually required. Especially for parameters such as permeability, which depend on the geometry of the vascular network and thus on its deformation, the parameters would have to be determined anew in each iteration step. Since this is not in the interest of efficiency, a model for growth-induced deformations was developed that simply updates the model parameters with deformation-dependent quantities only. This avoids the need for re-determination by averaging in each iteration step. We illustrate an application to the regrowth of the liver after resection. For this, a poro-elastic growth model for the microcirculatory compartment is coupled with the compartments of the different hierarchies of the supplying and draining vascular trees while the upper hierarchies not suitable for homogenization are considered as boundary conditions.

Towards sustainable simulation pipelines for human liver decision support

Steffen Gerhäusser[1], Lena Lambers[1], Luis Mandl[1], Ishaan Desai[2], Benjamin Uekermann[2], Matthias König[3], Tim Ricken[1]
[1]Institute of Structural Mechanics and Dynamics in Aerospace Engineering, University of Stuttgart, Germany; [2]Institute of Parallel and Distributed Systems, University of Stuttgart, Germany; [3]Systems Medicine of the Liver Lab, Institute for Biology, Humboldt-University Berlin, Germany

Simulation-based patient-specific risk assessment within a holistic treatment of liver diseases has an enormous potential for everyday clinical use [1], e.g., personalized drug dosing or therapy decision. We present a flexible software framework for coupling tissue and cellular scale using FEBio [2], libRoadRunner [3], and preCICE [4]. Processes at the tissue scale such as deformation or fluid transport are represented by a system of coupled partial differential equations (PDEs) within the Theory of Porous Media (TPM). The described advection-diffusion system is extended by reaction terms that model cellular functions and processes such as metabolism in the hepatocytes that form the tissue matrix. Each hepatocyte can be modeled as an individual micro simulation using ordinary differential equations (ODEs) encoded in SBML. Robust and efficient coupling between the tissue-scale solver FEBio (PDE) and cellular-scale solver libRoadRunner (ODE) is done using the coupling library preCICE. The micro simulations are controlled and coupled to preCICE by a Python package called the Micro Manager [5]. The Micro Manager can adaptively run micro simulations in parallel. The combination of preCICE, the Micro Manager and SBML allows the flexible exchange between various metabolic models for different clinical scenarios. We demonstrate our framework with a SPT model for substrate (S) to product (P) and toxin (T) detoxification as a showcase. This research also addresses the usability of decision-support systems by reviewing critical aspects like performance, maintainability, and security.

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Exploring ethnic diversity in glaucoma surgery efficacy using computational fluid dynamics

Nicol Basson[1], Patrick Geoghegan[2], Susan Williams[1], Weihua Ho[3]
[1]The University of the Witwatersrand, Johannesburg, South Africa; [2]Aston University, Birmingham, United Kingdom; [3]University of Cape Town, Cape Town, South Africa

Glaucoma is a leading cause of irreversible blindness and presents a significant challenge in ophthalmology. Surgical interventions like trabeculectomy and non-penetrating deep sclerectomy (NPDS) have been fundamental in managing intraocular pressure (IOP) to decrease disease progression. However, the efficacy of these procedures across different ethnic demographics is not fully understood. This study aims to investigate the influence of ethnic-specific eye geometries on the efficacy of trabeculectomy and NPDS using Computational Fluid Dynamics (CFD) simulations. Previous research has demonstrated the potential of CFD in evaluating the IOP reduction in glaucoma surgeries. However, the impact of anatomical variations associated with ethnicity has not been adequately explored. This study aims to create 3D models representing African and European ethnicities based on average ocular biometric measurements, including white-to-white length, anterior chamber depth, and anterior chamber angle. Utilizing 3D modelling software, these models will capture the anatomical variations observed in different ethnic groups. Trabeculectomy and NPDS simulations will be conducted using CFD, integrating the ethnic-specific eye geometries. The simulations will assess postoperative outcomes, including IOP reduction and aqueous humour flow patterns, in African and European eye models. The findings of this study have significant clinical implications for patient-specific glaucoma management and surgical decision-making. Understanding how ethnic diversity influences the efficacy of glaucoma surgeries can inform treatment approaches and mitigate healthcare disparities in ophthalmology.

A computational fluid dynamic study on graft detachment in the human eye for postoperative endothelial keratoplasty

Eva Cheng[1], Nikki Basson[1], Wei Hua Ho[1,2]
[1]University of the Witwatersrand, South Africa; [2]University of Cape Town, South Africa

Graft detachment or dislocation following endothelial keratoplasty (EK), commonly known as corneal transplants, poses a significant challenge in postoperative care, often requiring additional interventions. The adherence of the donor graft to the host posterior stroma is crucial for successful outcomes, and understanding the dynamics of multifluid interactions, particularly involving aqueous humour (AH) and a gas bubble, is paramount in reducing dislocation rates. This study employs advanced simulation techniques to investigate AH flow and its interaction with a gas bubble within an idealized anterior chamber (AC) geometry relevant to postoperative EK procedures. Utilizing the Volume of Fluid (VOF) model in ANSYS Fluent, the simulation incorporates a time-dependent gravity expression to mimic real-world conditions during reorientation movements. Of particular significance is the simulation of the gas bubble, which adds a novel dimension to understanding graft adherence dynamics. Through analysis of corneal wall shear stresses (WSS) and force fields generated by AH-bubble interactions, this study aims to provide valuable insights into the mechanisms underlying graft detachment. Preliminary simulations reveal elevated corneal WSS in the presence of the graft, highlighting the importance of multifluid dynamics in graft adherence. Notably, results show significant shearing and normal forces on the graft, indicative of potential dislocation risks. These findings underscore the clinical relevance of understanding AH-bubble interactions in mitigating graft detachment complications post-EK surgery. The insights gleaned from this study have wide-ranging implications for ophthalmic surgery and postoperative care. By elucidating the intricate dynamics of AH-bubble interactions, clinicians can refine surgical techniques and optimize postoperative management protocols to minimize the risk of graft dislocation. Additionally, the simulation framework developed in this study can be extrapolated to other areas of ophthalmic research, such as intraocular lens implantation and glaucoma treatment, where understanding fluid dynamics within the eye is critical for successful outcomes.

1.D: Mitral Valve Replacements

Wednesday, September 4

10:30am - 12:00pm

09.019

Patient-specific long-term prediction of transcatheter edge-to-edge mitral valve repair

Natalie Simonian, Michael S Sacks
University of Texas at Austin, USA

Mitral regurgitation (MR) is the most common valvular disease in the United States affecting over 2% of the population and is expected to double by 2030 due to population aging. However, MR of any type is a major prognostic factor of mortality: the risk of mortality with severe MR at five years is 36% and even moderate MR nearly doubles the risk of mortality in patients with multiple cardiac comorbidities. Recently, transcatheter MV repair methods such as the MitraClip have been of great interest as the technique is generally safe and improves patient outcomes. However, its efficacy compared to other treatment options has been unclear, with the outcomes largely dependent on MR etiology, MR severity, and existing comorbidities. We have previously demonstrated that the MV *plastically* deforms after myocardial infarction, with permanent distortions in annular dimensions, leaflet size, and leaflet stretch. Therefore, we hypothesize that the MV leaflets will undergo a substantial plastic deformation in response to the device. By integrating our previous work on MV plasticity models with the wealth of patient-specific data contained in these preoperative clinical images, we aim to develop a *long-term predictive MV repair model* to quantitatively optimize treatment strategies and achieve maximum repair durability. First, we developed a finite-element model of the full, patient-specific MV apparatus using our previously published methods. Next, we built on our previous work on MV plasticity to model the long-term consequences of the MitraClip on the MV leaflets. The MV tissue is modeled as an incompressible composite of collagen fibers and an isotropic matrix, and we assume all time-dependent behaviors are constrained to the matrix phase. In the follow-up simulations, we were able to reproduce key effects of repair at the 3-month time point. We noted substantial changes in the MV functional state over time in the ED configuration, where strains are principally induced by permanent distortions in geometry. Our results underscore the importance of a long-term view of repair success in the context of MV function,

Functional assessment of patients with mitral valve defect augmented by biomechanical modeling: Contractile reserve of the heart and in-silico valve repair

Hoang Nguyen[1], Maria Gusseva[1], Sanja Dzelebdzic[1,2], Gerald Greil[1], Tarique Hussain[1], Radomir Chabiniok[1]
[1]UT Southwestern Medical Center Dallas, Texas, USA; [2]The University of Utah, Salt Lak City, UT, USA

Assessment of ventricular function is challenging in patients with mitral valve regurgitation (MR). Ejection fraction (EF) can overestimate function as high EF might arise due to the presence of the regurgitant flow. This study applies biomechanical heart modeling to assess the contractile reserve of two patients with MR undergoing inotropic activation. Secondly, we perform an in-silico mitral valve (MV) repair to predict an immediate response of the left ventricle (LV) to ceasing the MR. Two patients (Pt1, Pt2) with MR underwent cardiac MRI (exam included cine MRI with low dose dobutamine stress, 10 μg/kg/min, dob10). Arterial brachial cuff pressures were recorded at each condition. Biomechanical models of the heart were created from patients' clinical data providing estimates of myocardial contractility at rest and dob10 (Gusseva et al, Can J Card 2021). The backward resistance of the mitral valve in the model controls the level of regurgitation and was adjusted according to the measured MR (Chabiniok et al, FIMH 2017). The systemic circulation was represented by Windkessel. For in silico repair, MR was ceased and contractility was recalibrated to obtain two scenarios: (S1) LV end-systolic volume as at rest; and (S2) arterial peak pressure as at rest via additional adjustment of periphery vascular resistance (PVR) in the model. Measured EF was Pt1 [58%; 66%] and Pt2 [55%; 62%] at [rest; dob10]. The measured blood pressure was Pt1 [120/63; 178/59] mmHg, Pt2 [109/46; 138/46] mmHg at [rest; dob10]. LV contractility was Pt1 [110; 198] kPa and Pt2 [118; 196] kPa at [rest; dob10]. In silico MV repair scenario (S1) suggests that LV contractility would become 148kPa, 130 kPa (and predicted blood pressure would be Pt1 168/84 mmHg and Pt2 122/49 mmHg) for Pt1, Pt2, respectively. Assuming the adjustment of PVR (S2) the predicted contractility would decrease to 110 kPa, 110kPa for Pt1, Pt2, resp. LV contractile reserve is estimated to be 1.80 and 1.66 for Pt1, Pt2, resp., a magnitude not visible from standard EF analysis. In silico MV repair predicts the LV contractility to remain within patients' contractile reserve, suggesting patients' readiness to undergo the repair.

Model reduction for fluid-solid simulations to assess hemodynamics of mitral valve regurgitation and repair

Marc Hirschvogel[1], Mia Bonini[3], Maximilian Balmus[2], David Nordsletten[3,4]
[1]MOX, Dipartimento di Matematica, Politecnico di Milano, Milan, Italy; [2]TRIC-DT, The Alan Turing Institute, National Heart and Lung Institute, Imperial College London, London, UK; [3]Department of Biomedical Engineering, University of Michigan, Ann Arbor, USA; [4]Department of Cardiac Surgery, University of Michigan, Ann Arbor, USA

Mitral valve regurgitation represents a serious health issue, where the atrioventricular valve of the left heart is unable to close properly. This condition leads to a backward leakage of blood into the atrium during ventricular systole, reducing the amount of oxygenated blood that can be supplied to the body. This is accompanied by a higher work rate of the ventricle, eventually resulting in heart failure due to the increased amount of blood load the heart has to compensate for. Transcathetermitral valve repair is a minimally invasive surgery technique that allows restoration of mitral valve function. However, contraindications for certain patients remain and the indication for more invasive procedures can be inconclusive. Computational models and tools therefore can help understand the patient-specific pathology of mitral valve leakage and provide insights into possible treatment outcomes from a hemodynamic perspective. We present a recently proposed dual model reduction methodology for fluid-solid coupling to assess the hemodynamics of mitral regurgitation in the left heart, denoted as fluid-reduced-solid interaction (FrSI). The approach leverages imaging data to construct a lower-dimensional subspace for the left heart's boundary, whose physics are described using a structural surface model. We investigate blood flow simulations for three patient-specific casesof severe mitral regurgitation, and demonstrate that the FrSI model allows to predict meaningful left heart hemodynamics along with ventricular unloading in consequence of mitral valve repair. Our results illustrate the potential of model reduction approaches in patient-specific hemodynamics simulations and may promote a better understanding of valve-related diseases in the heart.

Influence of valve shape on mitral valve hemodynamics: An in-silico study

Juliana Franz[1,2], Jan Brüning[1,2], Leonid Goubergrits[1,2], Alexandra Groth[3], Titus Kühne[1,2], Valentina Lavezzo[4], Irina Waechter-Stehle[3], Katharina Vellguth[1,2]
[1]Charité - Universitätsmedizin Berlin, Germany; [2]Deutsches Herzzentrum der Charité, Institute of Computer-assisted Cardiovascular Medicine, Germany; [3]Philips Innovation Technologies, Hamburg, Germany; [4]Philips, Eindhoven, The Netherlands

As a first step towards model-based treatment decision support for mitral regurgitation patients undergoing transcatheter edge-to-edge repair (TEER), we aim to accurately personalize a lumped parameter model (LPM) of cardiovascular hemodynamics using routinely measured mitral valve data. This involves (1) the translation of geometric mitral valve measurements (e.g. orifice area) into a valve resistance parameter and (2) the translation of the Doppler-measured maximum pressure gradient into a net pressure gradient after pressure recovery distal to the vena contracta, which is used as a model optimization target. With this study, we aim to better understand how valve resistance and pressure recovery are influenced by valve shape to improve our model personalization and subsequent patient-specific simulations. We used mitral valve reconstructions of ten TEER patients from 3D transesophageal echocardiography to analyze the mitral valve orifice area and shape in three distinct valve states: (1) early diastole pre-TEER, (2) early diastole post-TEER and (3) systolic regurgitation pre-TEER. Computational fluid dynamics (CFD) simulations were performed to simulate blood flow through the reconstructed valves across a physiological range of net pressure gradients and compute valve resistance and pressure recovery for each simulation. Valve resistance and pressure recovery varied significantly between the three different valve states. Besides orifice area, valve resistance was influenced by the orifice-to-annulus area ratio and the orifice orientation. Pressure recovery was significantly reduced (45%) in diastolic post-TEER compared to pre-TEER valves, and was strongly correlated with the orifice-to-annulus area ratio. We developed shape-based equations for patient-specific estimations of the valve resistance and net pressure gradient using data available from echocardiography. Limits of agreement between the CFD results and the shape-based model results were 7% for the valve resistance and 12% for the net pressure gradient. Our study demonstrates the importance of accounting for valve shape during model personalization to accurately simulate patient hemodynamics.

Synthetic cohort of mitral valve anatomies based on statistical shape modeling

Katharina Vellguth[1,2], Lukas Obermeier[1,2], Jonathan Nestmann[3], Serdar Akansel[1,4], Leonid Goubergrits[1,2]
[1]Charité - Universitätsmedizin Berlin, Germany; [2]Deutsches Herzzentrum der Charité, Institute of Computer-assisted Cardiovascular Medicine, Germany; [3]ETH Zürich, Department of Information Technology and Electrical Engineering, Switzerland; [4]Deutsches Herzzentrum der Charité, Department of Cardiothoracic and Vascular Surgery, Germany

In silico methods are becoming an indispensable tool in personalized medicine and treatment planning, as well as development and approval regulation of medical devices. Lacking quality, quantity or completeness of real-world data remains one of the major challenges for model development and validation. Further obstacles in working with patient data are data privacy regulations, complicating and limiting data sharing, or usage for new purposes. Therefore, the focus is widely set on the creation of synthetic data, allowing to obtain an abundance of data representing the characteristics of a desired cohort or an initial patient group. In our work, we built a statistical shape model (SSM) of mitral valve anatomies in the diastolic (open) and systolic (closed) states based on retrospective echocardiographic data of 104 patients with mitral valve regurgitation. All patients received surgical annuloplasty and mitral valve repair. A synthetic dataset was created applying different strategies, such as linear and non-linear SSMs for the shape analysis, combined and separated processing of states, as well as Gaussian and Copula statistics as resampling strategies. The mitral valve anatomies were segmented in the CE-certified Software Tomtec-Arena (TOMTEC Imaging Systems GmbH). For being processed in our in-house developed code, all geometries must be aligned in space and have nodal correspondence in their meshes. We found the best practice in the combined processing of diastolic and systolic mitral valve states within a linear SSM, and Copula statistics for resampling the synthetic cohort. The Copula approach further allows the integration of demographic data into the resampled cohort, like sex, age, height, and weight. The creation of a data set of 2000 mitral valve geometries, each in diastolic and systolic state takes only a few minutes. Synthetic cohorts are already widely used in in-silico modeling and can circumvent many of the obstacles with patient data. As mitral valve geometries are often badly visible in cardiac imaging, SSMs and virtual cohorts can also enhance the representation and integration of anatomical structures in computational modeling approaches.

1.E: Cartilage & Skin

Wednesday, September 4

10:30am - 12:00pm

08.019

Articular cartilage systems mechanobiology: A multiscale tissue model of the knee cartilage

Andreu Pascuet-Fontanet, Maria Segarra-Queralt, Jérôme Noailly
BCN MedTech, Universitat Pompeu Fabra, Spain

Articular cartilage (AC) degradation in osteoarthritis (OA) involves complex biochemical, genetic, and mechanical interactions at chondrocyte (CC) and tissue levels. Regulatory network-based models (RNM) describe CC biochemical regulation and mechano-transduction, while finite element models (FEM) quantify tissue mechanics. Yet, the impact of CC activity on AC volumetric regulation remains challenging to quantify. Hence, a new multiscale knee AC model is proposed to simulate CC regulation and soluble molecule transport in the AC, to unravel cell-tissue interactions. A 2D FEM depicted a 0.47 mm wide knee AC plug, with CC distribution based on local cellular density. An existing mechanosensitive CC RNM was translated into 21 reaction terms in a diffusion model. FEM nodes with RNM terms represented reactive CC surface, in a pericellular matrix (PCM) with reduced diffusion coefficients. Diffusion through the bone or CC was zero, and concentrations were null in the synovial fluid (SF). Models were initialized with fixed healthy CC RNM-based phenotypes, evolving until steady concentrations were reached in the AC. Then, each CC RNM was regulated over a month based on local FEM concentrations, with or without stimulation of physio-osmotic (PO) mechano-sensors. Diffusion streamlines revealed CC communication, with varying gradients among CC clusters. After initialization, CC had high anabolic activity. Over one-month regulation, CC without PO stimulation shifted towards a pro-catabolic phenotype, while those with PO stimulation kept a pro-anabolic profile. These semi-quantitative CC profiles were translated into quantitative tissue concentrations, enabling intercellular communication. Results indicate that without proper SF contextualization, paracrine signaling is not strong enough to keep CC anabolism, and mechanical stresses must be considered. The FEM simplifies tissue load integration, with early results suggesting a significant role of PCM in CC load transmission. Future tests with patient-specific SF concentrations and tissue loads shall unveil new OA dynamics.

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Pixel2Mechanics: Automated biomechanical simulations of high-resolution intervertebral discs from anisotropic MRIs

Estefano Muñoz-Moya[1], Sai Natarajan[1,2], Morteza Rasouligandomani[1], Carlos Ruiz Wills[1], Francis Chemorion[1,4], Ludovic Humbert[2,3], Miguel A. González Ballester[1], Gemma Piella[1], Jérôme Noailly[1]
[1]BCN MedTech, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, Spain; [2]Galgo Medical S.L., Barcelona, Spain; [3]3D-Shaper Medical S.L., Barcelona, Spain; [4]IT, Department of Information Technology, InSilicoTrials Technologies, Trieste, Italy

1 Introduction

IVD degeneration challenges diagnosis and treatment personalization. Biomechanical simulations offer insights into functional mechanobiology but require complex workflows to generate suitable meshes from clinical MRI data. Pixel2Mechanics proposes a novel pipeline for biomechanical FE simulation of IVD meshes directly from low-resolution clinical MRI, aiming to improve personalized IVD modeling.

2 Methods

Utilizing a geometrical deep learning framework with cross-level feature fusion and optimization based on differentiable rendering, we generate high-resolution meshes of the lumbar Annulus Fibrosus and Nucleus Pulposus from L1-L2 to L4-L5 IVDs. A custom morphing algorithm based on the Bayesian Coherent Point Drift++ (Hirose (2020b)) generates calibrated volumetric FE meshes (Ruiz et al. (2013)), with simulations conducted under daily load conditions (Wilke et al. (1999)) to evaluate mechanical responses, comparing these with manual segmentation outcomes. A set of five IVD models with heights ranging from ~8-16 mm was selected for this study.

3 Results

Pixel2Mechanics outperforms Voxel2Mesh in mesh reconstruction accuracy, with lower average Hausdorff and Point-to-Surface distances (15% and 20% of improvement). Biomechanical simulation comparisons reveal over 88% similarity with manually segmented models, showing the same trend: as average height increases, maximum stress increases, while minimum stress decreases.

4 Conclusions

Pixel2Mechanics offers a fully automated, patient-personalized simulation pipeline for L1-L2 to L4-L5 IVD levels from clinical MRIs, facilitating the exploration of IVD degeneration while minimizing manual effort, being a valuable tool for future clinical integration, diagnosis, and treatment of personalization for IVD degeneration.

5 Foundings

MSCA-ITN-ETN-2020-Disc4All-955735

Computational modeling of articular cartilage mechanics: Insights and validation

Franziska S. Egli, Seyed Morteza Seyedpour, Tim Ricken
University of Stuttgart, Germany

Understanding the intricate mechanical behavior of articular cartilage is essential for grasping joint functionality. This study introduces a computational framework aimed at simulating its response under diverse loading conditions. The model adopts a biphasic approach, treating cartilage as a porous medium composed of a solid, fiber-reinforced phase and a fluid phase incorporating osmotic pressure. Calibration using experimental data from tensile and confined compression tests ensures accurate representation across various loading regimes. Prior to employing computational models for cartilage disease research, validation of predictive accuracy is crucial. A sensitivity analysis is conducted identifying key parameters significantly impacting the model output and thus enhancing the comprehension of underlying mechanisms. The computational model effectively simulates articular cartilage's complex mechanical response under diverse loading scenarios, offering valuable predictive insights into physiological and pathological states. Integration of experimental data and sensitivity analyses enhances reliability, advancing musculoskeletal biomechanics and clinical interventions.

Application of an FSI-based model to optimize mechanically stimulated structured hydrogel scaffolds for cartilage cell differentiation

Pedram Azizi, Christoph Drobek, Ursula van Rienen, Hermann Seitz
Universität Rostock, Germany

Introduction: 3D hydrogel scaffolds have the potential to be utilized in the regenerative treatment of cartilage and bone defects. In tissue engineering, the formation of cartilage can be specifically stimulated by mechanical stimulation.

Objective: The study aims to optimize cartilage cell differentiation on porous hydrogel scaffolds due to mechanical compression stimulation using a fluid-structure interaction (FSI) model.

Methods: A previously developed model [1] was utilized for this study. The geometry of the scaffold from the study [1], which has a regular structure and was designed using CAD, was optimized for cartilage cell differentiation at 5% compression. Strands have been added or removed to each horizontal layer in the first step. Therefore, the horizontal span between strands and the scaffold's porosity was varied. Finally, the best geometry from Step 1 was selected and modified by adding or removing strand layers vertically. The strand diameter had to be changed to keep the scaffold height constant.

Results: The optimal scaffold design could be created in the first step by adding two strands in the horizontal direction. This design could increase cartilage cell differentiation by about 15 % and decrease bone cell differentiation by approximately 24 % compared to the study's original design [1]. The selected scaffold from step 1 was further optimized in step 2, increasing cartilage cell differentiation by around 2 % and decreasing bone cell differentiation by about 5 % compared to the geometry selected in step 1.

Conclusion: Pore design can significantly influence cell differentiation on the surface of structured scaffolds. However, geometric constraints must be considered when designing manufacturable scaffolds.

This study was funded by the Deutsche Forschungsgemeinschaft (German Research Foundation)– SFB 1270/2-299150580.

[1] Azizi, Pedram, et al. "Simulating the mechanical stimulation of cells on a porous hydrogel scaffold using an FSI model to predict cell differentiation." Frontiers in Bioengineering and Biotechnology 11 (2023).

Model investigation of the energy density resulting from the absorption and scattering of radiation in multi-layer skin tissue structures

Seyed Morteza Seyedpour[1,2], Lena Lambers[1,2], Hans-Michael Tautenhahn[3], Franziska Tautenhahn[4], Tim Ricken[1,2]

[1]Institute of Structural Mechanics and Dynamics in Aerospace Engineering, Faculty of Aerospace Engineering and Geodesy, University of Stuttgart, Pfaffenwaldring, 27 Stuttgart, 70569, Germany; [2]Biomechanic Lab, Institute of Structural Mechanics and Dynamics in Aerospace Engineering, Faculty of Aerospace Engineering and Geodesy, University of Stuttgart , Pfaffenwaldring 27, Stuttgart, 70569, Germany; [3]Department of Visceral, Transplantation, Thoracic and Vascular Surgery, Leipzig University Hospital, Liebigstraße 20, Leipzig, 04103, Germany; [4]Clinic and OPD for Oral and Maxillofacial Surgery / Plastic Surgery, Am Klinikum 1, Jena 07747, Germany

Laser therapies embody cutting-edge advances in non-invasive medical techniques. This study concentrates on enhancing precision thermal therapy via a modeling approach to investigate the intricate interplay between laser radiation and the complex layers of human skin. Our method represents the skin as three layers: epidermis, dermis, and subcutaneous tissue. The density of energy absorbed from radiation by multilayer structures is numerically simulated. Our model is based on the Beer model, using functions resembling scattering particles' energy profiles. These scattering particles are simulated numerically throughout the material structure. This study improves the understanding of energy absorption processes and opens up new possibilities for designing and optimizing multilayer structures with optical significance.

Generality and applicability in developing virtual epithelial tissues models

Lorenzo Veschini[1], Joel Vanin[1], Michael Getz[1], Alison Stephens[2], Catherine Mahony[2], James A Glazier[1]
[1]Indiana University, United Kingdom; [2]Procter & Gamble

Computational models of cell assemblies, or Virtual Tissues, are key tools in advancing our understanding of complex biological systems. They allow simulating and studying key interactions at the cellular and subcellular level which ultimately drive all tissue functions and will likely be foundational components of medical digital twins. Formalisms like the GHH or physics-based models like Compucell 3d, TissueForge, and others, can be used to implement VTs and to address current challenges in cellular biophysics and molecular crosstalk. However, comprehensive implementation of generalist cell-based models able to capture most aspects of biologic or engineered tissues are prohibitively expensive computationally. When deciding which biological details to incorporate, modelers should prioritize those directly pertinent to the research question, ensuring a balance between relevance, applicability, and generality. We will discuss these themes using our recent work on virtual Skin (vSkin) and virtual Cornea (vCornea) models as illustrative examples. We will show how a common framework can facilitate the development of generalist epithelium simulations. Through appropriate parameterization, we can then recapitulate the characteristic cellular organization observed in various epithelial tissues. The specific vSkin and vCornea realisation of the model can be used as they are, for example as teaching tools, or further tuned and combined with experimental data to address fundamental research questions or to facilitate drug discovery.

1.F: Big Data / Machine Learning I

Wednesday, September 4

10:30am - 12:00pm

02.005

A computationally efficient deep learning model for high-resolution transient hemodynamics estimation in complex vascular geometries

Noah Maul[1,2], Katharina Zinn[1], Fabian Wagner[1], Mareike Thies[1], Maximilian Rohleder[1,2], Laura Pfaff[1,2], Markus Kowarschik[2], Annette Birkhold[2], Andreas Maier[1]
[1]Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany; [2]Siemens Healthineers AG, Forchheim, Germany

Clinical decision-making for vascular pathologies benefits from hemodynamic information. The coupling of medical imaging with computational models enables the inference of high-resolution flow information. In recent years, machine-learning-based CFD surrogate models have been proposed that can reduce runtime by several orders of magnitude. Model architectures employed in surrogates often rely on conventional networks designed for regular grids and static data. Hence, real-world simulation data, comprising non-uniform spatial resolution and an additional temporal dimension, poses a challenge to conventional architectures. Our deep-learning-based surrogate model approximates the solution operator for the incompressible Navier-Stokes equations, given the vascular geometry and the associated boundary and initial conditions. We utilize octree-based spatial discretization combined with implicit neural function representation to efficiently predict high-resolution time-dependent 3D fields [1]. We apply the model to test set simulation cases based on geometries that were not seen during training and validation. We observe that the velocity field for complex synthetic vascular geometries can be estimated with a mean absolute error of 0.024 m/s compared to CFD simulations. The runtime reduces from several hours on a high performance cluster to a few seconds on a consumer graphical processing unit. We further show results of experiments on anatomical cerebral vasculature and pressure prediction. The computational requirements of numerical CFD simulations limit the application in clinical environments. We present a deep-learning-based surrogate model for high-resolution transient hemodynamic simulations in complex vascular geometries. The concepts and information presented are based on research and are not commercially available.

[1] Maul et al., Transient Hemodynamics Prediction using an Efficient Octree-Based Deep Learning Model, in: Information Processing in Medical Imaging, 2023, pp. 183–194.

Parameter estimation in cardiac biomechanical models based on physics-informed neural networks

Federica Caforio[1,2,3], Francesco Regazzoni[4], Stefano Pagani[4], Matthias Höfler[1], Elias Karabelas[1,2,3], Christoph Augustin[2,3], Gernot Plank[2,3], Gundolf Haase[1,3], Alfio Quarteroni[4,5]
[1]Department of Mathematics and Scientific Computing, NAWI Graz, University of Graz (Austria); [2]Gottfried Schatz Research Center: Division of Biophysics, Medical University of Graz (Austria); [3]BioTechMed-Graz (Austria); [4]MOX, Department of Mathematics, Politecnico di Milano (Italy); [5]Institute of Mathematics, EPFL (Switzerland) (Professor Emeritus)

Biophysical models of cardiac function are gaining popularity due to their capacity to predict patient outcomes and optimising treatment plans. Nonetheless, the development and personalisation of these models entail significant computational costs and extensive calibration, rendering their application in clinical settings challenging. This presentation investigates the use of a novel approach [1] that combines physics-informed neural networks [2] with detailed three-dimensional nonlinear cardiac biomechanical models to reconstruct displacement fields and estimate patient-specific biophysical characteristics (such as passive stiffness and active contractility). The physics of the problem is represented by a mathematical model based on partial differential equations. Moreover, the learning algorithm integrates displacement and strain data that can be routinely acquired from clinical settings. A series of benchmark tests demonstrate the method's accuracy, robustness and promising potential for precisely and efficiently determining patient-specific physical properties in nonlinear, time-dependent biomechanical models.

[1] Caforio, F., Regazzoni, F, Pagani, S., Karabelas, E., Augustin, C., Haase, G., Plank, G. and Quarteroni, A. (2023). Physics-informed neural network estimation of material properties in soft tissue nonlinear biomechanical models. arXiv preprint arXiv:2312.09787.

[2] Raissi, M., Perdikaris, P., and Karniadakis, G. E. (2019). Physics-informed neural networks: A deep learning framework for solving forward and inverse problems involving nonlinear partial differential equations. Journal of Computational Physics, 378:686-707.

Finite volume informed graph attention network for solving partial differential equations — Application to myocardial perfusion

Raoul Sallé de Chou[1,2], Matthew Sinclair[3], Sabrina Lynch[3], Nan Xiao[3], Laurent Najman[4], Hugues Talbot[2], Irene Vignon-clementel[1]
[1]Inria, Palaiseau, France; [2]CentraleSupelec, Inria, Université Paris-Saclay, France; [3]HeartFlow Inc., Redwood City, USA; [4]ESIEE, Université Gustave Eiffel, France

In the past decades, computational fluid dynamics has played an important role in quantifying blood flow in cardiovascular diseases. However, the computational complexity associated with such models can often hinder their practical application in clinical settings. Recent advancements in graph neural networks have gained attention due to their efficacy in handling non-Euclidean data, such as meshes, offering a potential solution to accelerate fluid simulations. Nevertheless, these methods require large amounts of training data and pose challenges in training and generalizing across diverse patient morphologies. In this study, we introduce a novel approach: a physics-informed graph attention network tailored for solving Darcy equations to simulate myocardial perfusion. Our model integrates finite volume discretization into a physics-informed loss function, enabling learning without explicit simulation solutions. Trained on a synthetic dataset resembling left ventricular myocardial shapes, the model demonstrates robustness when validated on myocardium meshes derived from patient Computed Tomography images. Our findings highlight promising outcomes and underscore the model's ability to generalize across varied geometries, contrary to classical physics-informed neural network. Moreover, the incorporation of physics-based loss functions mitigates data dependency, thus fostering its applicability in medical contexts.

Machine learning-based models to predict axillary lymph node metastasis in breast cancer patients

Alba Fischer-Carles[1,2,4], Carlos López Pablo[1,2,3], Esther Sauras-Colón[1,2], Noèlia Gallardo-Borràs[1,2], Alessio Fiorin[1,2,3], Mikel R. Ortiz de Uriarte[1,2], Laia Reverté Calvet[1,2], Marylène Lejeune[1,2,3], Elena Goyda[2], Laia Adalid Llansa[2], Daniel Mata Cano[2], Ramon Bosch Príncep[2], Jérôme Noailly[4], Gemma Piella[4]

[1]Oncological Pathology and Bioinformatics Research Group, Institut d'Investigació Sanitària Pere i Virgili, Tortosa, Spain; [2]Department of Pathology, Hospital de Tortosa Verge de la Cinta, Institut Català de la Salut, Tortosa, Spain; [3]Department of Computer Engineering and Mathematics, Universitat Rovira i Virgili, Tarragona, Spain; [4]BCN MedTech, Department of Information and Communications Technologies, Universitat Pompeu Fabra, Barcelona, Spain

Background: Breast cancer (BC) leads cancer mortality in women. BC survival rate declines with tumour cells spreading beyond the primary site, producing regional or distant metastases. Regional metastases usually occur in the axillary lymph node (ALN), a key factor associated with worse prognosis in BC patients. Artificial intelligence (AI) shows great promise in BC patient stratification. Thus, as tumour cells can alter the immune response in the primary tumour and in the ALN, the present study aims to identify the clinicopathological (CP) and immune population variables most associated with ALN metastases (ALN^+) using Machine Learning (ML) models for the design of new AI stratification tool in BC. **Material and methods:** This study involved 83 women diagnosed with luminal BC between 1995 and 2008 (41 ALN^- and 42 ALN^+). Two ML models were developed using the Random Forest algorithm. Model 1 integrated CP data exclusively, and Model 2 integrated CP data and immune response from the primary tumour and ALN. We applied an identical computational procedure in both models, including data pre-processing, variable selection using recursive feature elimination with cross-validation (CV), algorithm optimization using random search CV, and results interpretability using Shapley additive explanations values. **Results and discussion:** Model 1 achieved a median accuracy of 0.65 and a median area under the curve of 0.63. Model 2 outperformed with a 0.71 and a 0.79, respectively. Tumour diameter and the immune marker intratumoral $CD21^+$ were the variables most associated with ALN^+ in Model 2. Tumour diameter is known to be a prognostic factor in BC. Interestingly, $CD21^+$, follicular dendritic cells, has never been pointed out so far, and might stand for a novel biomarker candidate. Results underscore the need to consider mechanistic features such as a mediating inflammation in BC stratification. **Conclusions:** The proposed ML models revealed the importance of considering the immune response for future AI-based BC stratification tools based on the prediction of the ALN^+ prognosis factor.

Predicting post-traumatic stress disorder (PTSD) symptoms in women suffering from breast cancer using machine learning

Konstantinos N. Rizavas[1], Eleni A. Klokotroni[1], Paula Poikonen-Saksela[2], Georgios S. Stamatakos[1]
[1]National Technical University of Athens, Athens, Greece; [2]Helsinki University Hospital, Helsinki, Finland

(1). Introduction. Patient resilience is an often-overlooked but important aspect of breast cancer treatment. Thus, investigating the factors that can be bolstered to support those living with breast cancer is becoming an important part of cancer research. In this context, the European Commission (EC) funded BOUNCE project (GA: 777167) has explored i.a. the potential of using machine learning (ML) algorithms to predict Post Traumatic Stress Disorder (PTSD) symptoms in women suffering from early breast cancer. (2) Materials and Methods. Data from 578 patients were collected at four oncology centers: the European Institute of Oncology in Milan, the Helsinki University Hospital, the Hebrew University of Jerusalem and the Champalimaud Foundation in Lisbon. The preprocessing method formulated has taken into account the expected heavy imbalance of medical data, the limited number of samples and the high number of features to consider. Model training has leveraged repeated cross-validation in order to tune model hyper-parameters. The best models have been evaluated on a separately-held test set to simulate unknown real-world data. (3). Results. A number of experiments have been conducted in order to test out the best balancing methods and the usage of reduced features as predictors. As soon as the best hyperparameters were decided on, a final experiment was conducted in order to test the generalisability of the results by evaluating model performance through the use of one hospital's data as testing (unseen) data and training on the rest. The results, being remarkably promising, have revealed that the balancing method is of key importance, whereas the models' generalisation is excellent. While no single classifier has stood out, the Voting classifier with ample resources is preferrable; otherwise, the Support Vector Machine or the Random Forest techniques are viable options. (4). Conclusions. This study highlights the potential of ML in predicting the course of psychological disorders across diverse hospitals.

ACKNOWLEDGMENTS

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1.G: Musculoskeletal System - Continuum Mechanics

Wednesday, September 4

10:30am - 12:00pm

01.005

Shear wave elastography for simulating tibialis anterior muscle forces in vivo

Cemre Su Kaya Keles, Jennifer Hiller, Manuela Zimmer, Filiz Ates
Institute of Structural Mechanics and Dynamics in Aerospace Engineering, University of Stuttgart, Stuttgart, Germany

Understanding skeletal muscle mechanics is crucial for grasping musculoskeletal diseases and refining treatments. While modeling and simulation provide valuable insights, validating them in vivo poses challenges. Directly measuring muscle forces from its tendon would be optimal [e.g., 1], but this approach is invasive and not universally applicable. Surface electromyography (sEMG) quantifies muscle electrical activity but does not capture the passive state. Shear wave elastography (SWE), however, offers a non-invasive approach, promising to reflect local muscular properties in both active and passive states [2-3]. This study investigates SWE's utility in understanding active and passive force production of the tibialis anterior (TA) muscle. We tested if SWE reflects changes in TA during a passive state and isometric ramp contractions. Ten healthy volunteers (five females, 26.6 ± 3.9 years) participated. Simultaneous sEMG and SWE of the TA and ankle torque measurements were performed at -15° dorsiflexion, 0°, and 15°, 30°, and 45° plantar flexion positions during rest, maximum voluntary contractions (MVC) and isometric ramp contractions (25%, 50%, and 75% MVC). Muscle length was measured at each ankle angle using B-mode ultrasound. The TA passive shear elastic modulus increased with its increasing muscle length ($p<0.001$). For submaximal isometric ramp contractions, a significant effect of only the contraction intensity ($p<0.001$) on the TA active shear elastic modulus was shown, with no significant effect of ankle angle ($p=0.219$), whereas both factors had significant effects on TA sEMG amplitude ($p<0.001$). Thus, unlike sEMG, SWE characterizes length-dependent passive muscle mechanical properties, and their combined use improves tracking muscular alterations during activity. Developing them as muscle force indexes, validated with direct force measurements, can improve muscular models better simulating neuromuscular conditions or treatments, and illuminating joint functions.

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Muscle architecture and contractile properties of the human M. tibialis anterior

Lukas Vosse[1,2], Annika Sahrmann[2], Oliver Röhrle[2], Tobias Siebert[1]
[1]University of Stuttgart, Department of Motion and Exercise Science, Allmandring 28, 70569 Stuttgart, Germany; [2]University of Stuttgart, Department of Continuum Biomechanics and Mechanobiology

The M. tibialis anterior (TA) is an important contributor to successful locomotion and preserving an upright posture. Its unique function as single-joint and sole ankle dorsiflexor as well as its superficial location allow for clearer determination of muscle architecture and properties and their influence on muscle contraction compared to other muscles of the human body. However, information regarding the contractile and architectural properties of the TA remains scarce. Especially in regards to simulation there are, so far, no validated human 3D muscle models, which realistically predict muscle force generation, muscle deformation and changes in 3D muscle architecture during contraction. To gather data to validate such a muscle model, twenty-eight healthy and physically active males (n=13, a=27±4y, m=75±8kg, h=179±5cm) and females (n=15, a=25±3y, m=62±10kg, h=166±8cm) performed maximum voluntary isometric and isokinetic dorsiflexions in a dynamometer (ISOMED2000). Ankle joint angles were measured with a 3D high speed camera system (Baumer VLXT-Series). Information on the architectural changes of the TA between relaxed and contracted state as well as during dynamic contraction was obtained with an ultrasound system (Aixplorer MACH30). Based on this data the force-length-relationship (FLR), force-velocity-relationship (FVR), contraction history-dependent effects (HDE), muscle thickness, pennation angle and fascicle length of TA were characterized. FLR and FVR are in accordance with results of other studies on skeletal muscles. The physiological working range of the TA is on the ascending branch and the plateau of the FLR. Changes in generated forces for the HDE are within the expected range for mammalian skeletal muscles. In addition to the 3D data on muscle architecture (Sahrmann 2024, accepted for publication), the results serve as input and validation data for a 3D muscle model of the tibialis anterior that is intended to predict changes in 3D muscle architecture, shape and force during contraction. In further studies, the model should then be adapted to specific subject groups to take into account the influence of age or sport.

Predicting passive and active triceps surae muscle forces by integrating magnetic resonance image-based 3D finite element modelling and ultrasound shear wave elastography

Manuela Zimmer[1,2], Geoffrey Handsfield[2], Filiz Ates[1]
[1]University of Stuttgart, Germany; [2]Auckland Bioengineering Institute, New Zealand

One of the oldest goals in biomechanics is understanding and modeling human movement, with the prediction of passive and active forces in individual muscles as its key component. This target remains essential to understanding neuromuscular diseases and improving treatment strategies. Finite element models (FEM) aim to simulate muscle using a continuum mechanics framework, allowing the study of muscle behavior, such as stress or strain distribution in 3D. Recent work has shown the importance of modeling more realistic and complex muscle architecture properties, in addition to the passive musculoskeletal structures [1]. One challenge in predicting muscle force production is that model validation is not straightforward, as techniques for direct force measurements are limited [2]. We aim to confront this challenge by combining musculoskeletal FEM with ultrasound shear wave elastography (SWE) to simulate and validate *in vivo* human muscle and tendon mechanics. Using diffusion magnetic resonance imaging (MRI) and ultrashort echo time MRI, we extract 3D muscle shape and fiber architecture of the triceps surae muscle group together with the Achilles tendon and aponeurosis geometry. We build a FEM and simulate passive muscle lengthening and isometric muscle contraction. The model was informed by experimental data collected at different ankle positions in passive and active states. We use information from SWE [e.g. 3] and intraoperative Achilles tendon forces [e.g. 2] for model validation. Validated with *in vivo* muscle mechanics data, our model predicts individual muscle forces and provides comprehensive insights into complex muscle behavior. Continued development will enable greater probing of relationships between muscle length, activation, joint moment, and individual muscle force. This will aid the study of force-sharing strategies, joint function, and muscular adaptation, demonstrating the potential of combining SWE with computational modeling for clinical application.

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Patient-specific geometry and deformation for real-time visualization of musculoskeletal biomechanics via 3D ultrasound

David Rosin[1,2], Annika Sahrmann[1,2], Christian Bleiler[1], Oliver Röhrle[1,2]
[1]University of Stuttgart - Institute for Modelling and Simulation of Biomechanical Systems, Germany; [2]Stuttgart Center of Simulation Science (SC SimTech)

Realistic prediction of soft-tissue behavior, like the deformation of skeletal muscles due to contraction, is the basis for applications like computer-aided surgery [Cotin, et al., Springer Handbook Aug. Reality, 2023]. In a time-constraint clinical setting, this requires a trade-off between model fidelity and performance [Allard, et al., MMVR 15, 2007]. Our previous work focused on providing a proof-of-concept for predicting real-time muscle deformations and interactive on-body visualization of a continuum-mechanical musculoskeletal system model [Rosin, et al., PerSiVal, arXiv preprint, 2023]. By pre-computing a range of deformation states using such a model, during the so-called offline phase, and using the results for training a neural network, we successfully achieved real-time musculoskeletal system simulations. A drawback, however, was that we based our application on a generic model geometry – a major limitation for real-world applications. As validated, subject-specific, continuum-mechanical musculoskeletal system models are essentially non-existent, yet, we aim to prove the applicability of our workflow to individuals. Towards this end, we propose to replace the pre-computed deformations of the offline phase with deformation maps directly obtained through a novel time-dependent 3D ultrasound imaging methodology [Sahrmann, et al., IEEE, 2024]. The deformation is extracted using different optical flow methods, here, a 3D implementation of the classic Horn-Schunck-method [Horn and Schnuck, 1980] and hyperelastic warping [Weiss, et al., Laser-Tissue Interaction IX, 1998]. We show that a limited number of deformation maps is sufficient to capture the overall contractile characteristics of the m. tibialis anterior, and can provide enough data to train a neural network capable of predicting these deformations in real-time. In this work, we present the feasibility of this approach, its implementation, and use in an augmented reality environment. We conclude with a discussion on the limitations and future research aspects of this new technology.

An activation-driven musculoskeletal finite element model of the human shoulder

Laura Engelhardt[1], Renate Sachse[1], Rainer Burgkart[2], Wolfgang A. Wall[1]
[1]Institute for Computational Mechanics, Technical University of Munich, Germany;
[2]Department of Orthopaedics and Sports Orthopaedics, University Hospital rechts der Isar, Technical University of Munich, Germany

The shoulder joint is one of the functionally and anatomically most sophisticated articular systems in the human body. While the ball-socket design of the glenohumeral joint allows for an extensive range of motion, passive and active soft tissues ensure the joint's integrity. Actively contracting muscles not only drive movement but also stabilize the joint by fine-tuning its position. Maintaining the balance between mobility and stability is crucial for proper joint function. Since injuries, pathologies, or muscular imbalances easily disrupt this equilibrium, shoulder disorders are common. Limited understanding of the underlying biomechanics and insufficient tools to quantitatively assess joint kinematics present significant challenges in diagnosis and treatment. Computational musculoskeletal models offer great potential for studying shoulder biomechanics, quantitatively assessing potentially pathological movement patterns, objectively predicting and evaluating treatment, and designing rehabilitation equipment for physical therapy. While numerous reduced-dimensional multi body models exist, research on three-dimensional continuum mechanical models is limited. However, three-dimensional interactions between the joint components, e.g., contact and gliding, are central to the shoulder's functionality. Continuum mechanical models can represent such effects, account for complex muscle fiber and tendon arrangements, and model sophisticated material behavior. For biomechanical studies of the shoulder, they are thus particularly relevant. In this contribution, we present a continuum mechanical finite element model of the human shoulder joint, including the skeletal structure, cartilaginous components, and the deltoid and rotator cuff muscles. We model muscle tissue with an active constitutive law fitted to experimental data obtained under diverse loading conditions. Our shoulder model accounts for complex muscle fiber architectures, tendon morphology, and contact interactions between the components. Guided by muscle activation data, we simulate physiological contraction scenarios, providing first insights into the shoulder joint's biomechanical behavior.

Investigation of surrogate methods for an electrophysiological skeletal muscle model

Robin Lautenschlager, Dominik Göddeke, Carme Homs-Pons, Oliver Röhrle, Laura Schmid, Miriam Schulte
University of Stuttgart, Germany

The understanding of muscle movement and interaction in the human body is essential for ensuring the best possible treatment in medical care. In the case of clinical amputation techniques such as the agonist-antagonist myoneural interface (AMI) the investigation of the interaction between multiple muscles is essential, because muscles work in agonist-antagonist pairs. Due to the complexity of the system, AMI can substantially profit from in silico analysis. To this end, we describe the muscle physiology by a multi-X electrophysiological skeletal muscle model. This complex multi-X model contains knowledge about the neural input from the brain transferred by the neural system, the feedback information to the nervous system provided by sensory organs in the muscle and the mechanical behaviour of the muscle, and is based on a coupled system of ordinary and partial differential equations. Clinical applications ultimately require optimal physiological parameters or, in general, the identification of (patient specific) parameters based on experimental data. This is an inverse problem. Obviously, solving inverse problems is costly as it requires repeated solutions of forward problems with varying inputs. However, to facilitate and speed up the development process of the optimization approach, the fully resolved multi-X model needs to be replaced by a surrogate model. The approach of this contribution is to present the development of a suitable surrogate for a complex multi-X muscle simulation for the AMI setting to prevent the simulation from impractical high runtimes and complexity.
In detail the goal is to work towards a surrogate model which retains the subcellular characteristics of the underlying muscle model, as well as feedback mechanisms in terms of muscle interaction by simultaneously speeding up the runtime of the simulation. The presented surrogate model is founded on the theories of Physical Informed Neural Networks, Polynomial Chaos Expansions and Hill-type models. This approach contains the minimisation of the loss function and weighting of loss-terms depending on the available data and the underlying PDEs, as well as the integration of initial and boundary conditions.

1.H: Clinical Imaging

Wednesday, September 4

10:30am - 12:00pm

07.017

Digital twins for interventional procedures

Annette Birkhold
Siemens Healthineers AG, Germany

This research aims at advancing the field of interventional X-ray image-guided procedures, focusing on enhancing patient-specific care and optimizing the use of the C-arm system. Our body of work employs a multiscale perspective – from the whole patient down to individual organs, such as the neurovascular system – and the integration of metadata and image data from the procedures to construct detailed and dynamic digital twins. At the core of this work is the development of patient-specific digital twins, which are virtual models which aim at accurately replicating the unique anatomical and physiological characteristics of individual patients. This approach not only allows for the simulation of personalized interventional procedures but also enables the prediction of X-ray doses during the intervention, thereby optimizing patient safety and procedural effectiveness. Our multiscale approach enriches this process by offering detailed insights at various levels of analysis, from the holistic view of patient anatomy and physiology down to the intricate workings of specific organs. This granularity is particularly crucial when addressing complex interventions, such as those involving the neurovascular system, where precision is paramount. In constructing these digital twins, a crucial step is employing patient meta data and image data derived prior and during actual procedures. This data-driven strategy ensures that the digital twins are not only accurate reflections of the patient's current state but also dynamic models that can evolve with new information. By integrating procedural data, we aim at enhancing the realism and utility of the digital twins, making them in the future invaluable tools for pre-procedural planning, real-time decision support, and post-procedural analysis. Digital twin technology holds tremendous promise for transforming interventional radiology practices. Through our research, we have laid a foundation for future advancements in personalized medicine, enhancing the safety, efficacy, and efficiency of interventional procedures through the innovative use of digital twins. The concepts and information presented are based on research and are not commercially available.

Exploring the effect of feto-placental vasculature and oxygenation on T2* MRI using mathematical modelling

Diana M. Cruz de Oliveira[1], Paddy J. Slator[2,3], ZhuangJian Yang[2], Kelly Payette[4], Jana Hutter[4,5], Lisa Story[6], Joseph V. Hajnal[4], Daniel C. Alexander[2], Rebecca Shipley[1]

[1]Dept. Mechanical Engineering, University College London, London, UK; [2]Centre for Medical Image Computing and Dept. of Computer Science, University College London, London, UK; [3]Cardiff University Brain Research Imaging Centre and School of Computer Science and Informatics, Cardiff University, Cardiff, UK; [4]Centre for the Developing Brain and Biomedical Engineering Department, School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK; [5]Smart Imaging Lab, Radiological Institute, University Hospital Erlangen, Erlangen, Germany; [6]Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK

The placenta is vital for fetal development, enabling oxygen exchange and nutrient transfer between mother and fetus. Complications like pre-eclampsia are linked to placental vascular abnormalities; however, current clinical imaging methods lack sensitivity to small-scale placental features. MRI, particularly T2* MRI, is more sensitive to placental dysfunction *in vivo*. T2* MRI relies on oxygenation and other factors such as the spatial variability of oxygenated blood and magnetic field inhomogeneities. To detect vascular pathologies earlier in pregnancy, we require novel, non-invasive imaging tools with enhanced sensitivity to structural and oxygenation changes. This will enable us to understand the link between these changes and imaging signals. We developed a computational framework to simulate MRI T2', a component of T2* attributable to magnetic field inhomogeneities caused by vascular architecture and function. Our pipeline involves: 1) Defining a binary image of fetal vasculature; 2) Simulating susceptibility-induced magnetic field shift maps using the Finite Perturber Method and input parameters from MRI acquisition and haemodynamic properties; 3) Generating MRI signals by summing accumulated phase shifts; 4) Fitting monoexponentials to the MRI signal, voxel-by-voxel, to derive T2'. We simulated MRI T2' for synthetic fetal trees at 20 weeks gestation, assessing its sensitivity to changes in structural parameters and oxygen saturations, spanning from healthy to disease scenarios. Our results show that increased mean vessel diameters and branching angles are linked to reduced T2', typically seen in placental pathology. Fetal and maternal oxygen saturations close to healthy values result in symmetric T2' distributions with higher mean T2'. Deviations from these baseline values yield skewed T2' distributions with lower mean T2', aligning with clinical findings. These results suggest that optimal oxygen saturation ranges are required for appropriate placental T2' distributions. Future work involves improving the pipeline to include T2 contributions to T2* and regional oxygenation regimes, and explore specific clinical scenarios (e.g. placental hyperoxia).

Advanced magnetic resonance imaging techniques offer a virtual tool for assessing physiological mechanisms of human muscular mechanics in vivo

Arda Arpak[1], Seda Yildiz[2], Agah Karakuzu[3], Can A Yucesoy[1]
[1]Institute of Biomedical Engineering, Boğaziçi University, İstanbul, Turkey; [2]Health Science Faculty, Physiotherapy and Rehabilitation Department, Haliç University, İstanbul, Turkey; [3]Biomedical Engineering Institute, Polytechique Montreal, Montreal, Quebec, Canada

Myofascial integrity means there is a continuous mechanical connectivity between muscle fibers and muscular and non-muscular tissues within and beyond the target muscle and, additional to the tendons. *Myofascial loads* developed across this connectivity affect muscle's force production due to their effects on sarcomere lengths. Assessing local along-muscle fascicle length changes *in vivo* is therefore crucial to comment on changes to muscle's functioning. For that, deformable image registration (DIR) of high-resolution anatomical MR images, and diffusion tensor imaging (DTI) based fiber tracking were combined (MRI-DTI). Medial gastrocnemius after knee angle change showed a heterogeneous distribution of along-muscle fascicle length changes indicating myofascial loads' role. Although the calculated length change amplitudes depend on the DIR tuning parameters, their spatial distribution remained robust [1]. Kinesio taping (KT) is widely used in sports medicine to mitigate injury and improve athletic performance, but the mechanism of action is scarcely investigated. Using MRI-DTI the aim was to test whether provoking myofascial loads via KT results in local length changes along muscle fascicles and shear strains between fascicles. Three conditions were studied (n=5): (i) without tape, (ii) with sham application, and (iii) after KT application [2]. Wilcoxon rank sum test revealed ($p<0.001$) that KT caused significant along-muscle fascicle lengthening (mean±SD, 0.026±0.020 and shortening (0.032±0.027) compared to sham application (0.012±0.010, 0.013±0.015, respectively). KT induced along-muscle fascicle length changes showed spatial distribution. MRI-DTI technique allows a unique virtual assessment tool for muscle function in vivo. Collagen is the main structural element responsible for KT induced myofascial loads to cause the said effects and prospects of integrating MRI-DTI technique and collagen quantification imaging and taking ageing as a case will be discussed in this talk.

TUBITAK grant 22AG016 is acknowledged.

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Energy-based method for identifying misclassified kidney boundary segmentations using CT scans

Andreea Elena Vântu[1,2], Daniel Bunescu[1,2], Alexandru Mihnea Ion[1,2], Lucian Mihai Itu[1,2]
[1]Electrical Engineering and Computer Science, Transilvania University, Brasov, Romania;
[2]Advanta, Siemens SRL, Brasov, Romania

Uncertainty quantification is crucial in AI models because it provides insight into the reliability of predictions, enhances decision-making under uncertainty, and enables risk assessment in various applications. One approach in this area of uncertainty quantification relies on out-of-distribution (OOD) methods to detect samples lying outside of the model's learned distribution. Although OOD methods showed promising results, they do not perform well in all circumstances, omitting the quality of the prediction. In this abstract, we considered an energy-based approach that can be used as a proxy for identifying erroneous predictions. For our experiments, we considered a kidney segmentation problem based on Computed Tomography (CT) scans, available in the KiTS21 public challenge, which provides one dataset. The dataset contains 300 patient CT volumes, including kidney, cyst, and tumour segmentations. The kidney region of interest (ROI) was used as input to train a segmentation model. We chose 3D U-Net as a backbone architecture and trained the model using the k-fold cross-validation technique (k=5), reaching, overall, a dice loss of 0.03. For the OOD analysis, our focus was on the most uncertain region of the kidney, which is the kidney boundary. Thus, we defined a border region using image processing morphological operations such as erosion and dilation. We computed the energies using a free energy function that assigns a non-probabilistic scalar to each logit and calculated the mean energy value according to each kidney boundary. Our results showed a good correlation between the mean energy values and the dice loss scores, both computed in the border region: a Pearson Correlation value of 75% and a ROC-AUC score of 92% were obtained. Hence, we conclude that the free energy function has a discriminative ability to identify erroneous predictions regarding their dice loss values. Additionally, the proposed method can be easily integrated during inference, without requiring any adjustments during the training phase.

Modelling and dynamic imaging: A few examples for clinical applications

Irene Vignon-Clementel
Inria, France

Dynamic contrast-enhanced (DCE) perfusion imaging is a promising modality for evaluating organ perfusion and function, cancer development and treatment response. Yet, often this modality is not embedded in the clinical workflow due to lack of understanding of how the signal intensity over time relates to the underlying vascularized tissue. We will present different clinical applications and how modeling can leverage such data in a more quantitative manner [1,2] or can improve our understanding of this complex relation between vascularized tissue and imaging data [3]. In [1], we found that actually a very simple model is able to quantify the signal from Indocyanine Green dynamic imaging at the end of liver transplantation, and its parameter is predictive more than any existing biomarker, of the graft failure. However, this parameter is difficult to relate to perfusion and function of the organ: this is what we study in [2]. Sensitivity analysis is key to stepwise identify the different model parameters based on pathological and healthy situations. The last study [3] aims to establish an in silico model-based pipeline to assess how DCE imaging parameters correspond to true tissue parameters, aiding interpretation of histology data. In silico vasculatures are constructed to simulate contrast agent spread, with blood flow computed in arterial and venous trees. The model incorporates contrast agent input, intra- and extravascular exchange, and interstitial diffusion, generating in silico dynamic perfusion images. Tumor vascularizations are analyzed, revealing characteristic imaging dynamics. Tracer kinetic models are applied to recover perfusion parameters and compared with in silico ground truth data. Results suggest effective identification of tumor features within certain permeability ranges. Explicit spatial consideration in estimating perfusion parameters could significantly enhance interpretation of current tracer-kinetics models.

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2.A: Heart Modelling - Surrogate Modelling

Wednesday, September 4

1:00pm - 2:30pm

05.019

High-speed real heart simulations using a neural network finite element approach

Shuti Motiwale, Michael S Sacks
University of Texas at Austin, USA

With advances in computational modeling as well as imaging techniques, patient-specific cardiovascular modeling for disease modeling and treatment is being widely explored as a means to improve patient outcomes. However, the slow computational speed for accurately simulating the complex physiology of the heart using traditional finite-element based methods still limits their practical clinical application. Moreover, patient-specific clinical applications require rapid evaluation of a large number of clinical scenarios. While reduced order models are commonly used to speed up simulations in many domains at a small loss of accuracy, the associated risk due to this is unacceptable in clinical applications. We have previously demonstrated the efficacy of the neural network finite element (NNFE) approach for predicting cardiac mechanics of an idealized left ventricle geometry within clinically relevant timeframes without compromising accuracy. In this work, we extend this approach to predict cardiac mechanics using a realistic biventricular ventricle model developed using a comprehensive dataset obtained from single ovine heart, that included geoemtry, pressure-volume, action potentials, and fiber sructure. The NNFE model predicted the displacement field for any P-V loop in the physiological training space with a max nodal error <1%. The trained NNFE model could accurately produce the twisting experienced by the left ventricle under active contraction. The NNFE model took 12 hours for training, but a trained NNFE model took 3 seconds for producing the results for any loading, whereas the equivalent Abaqus model required ~2.5 hours on average for a single loading path. Our results demonstrate the first application of the NNFE approach for a biomedical application at an organ level. We are working on extending this method to study the effects of inotropy on cardiac behavior by varying the slope of the end systolic P-V relationship. While still in its early stages, this approach paves the pathway for high-speed patient-specific clinical simulations in clinically relevant timeframes.

Adaptive reduced-order models for cardiac simulations

Sridhar Chellappa[1], Barış Cansız[2], Lihong Feng[1], Peter Benner[1], Michael Kaliske[2]
[1]Max Planck Institute for Dynamics of Complex Technical Systems, 39106 Magdeburg, Germany; [2]Institute for Structural Analysis, Technische Universität Dresden Germany

Mathematical models of the human heart increasingly play a vital role in understanding the working mechanisms of the heart, both under healthy functioning and during disease. The ultimate aim is to aid medical practitioners diagnose and treat the many ailments affecting the heart. Towards this, modelling cardiac electrophysiology is crucial as the heart's electrical activity underlies the contraction mechanism and the resulting pumping action. Apart from modelling attempts, the pursuit of efficient, reliable, and fast solution algorithms has been of great importance in this context. The governing equations and the constitutive laws describing the electrical activity in the heart are coupled, nonlinear, and involve a fast moving wave front, which is generally solved by the finite element method. The numerical treatment of this complex system as part of a virtual heart model is challenging due to the necessity of fine spatial and temporal resolution of the domain. Therefore, efficient surrogate models are needed to predict the electrical activity in the heart under varying parameters and inputs much faster than the finely resolved models. In this work, we discuss an adaptive, projection-based reduced-order surrogate model for cardiac electrophysiology. We introduce an a posteriori error estimator that can accurately and efficiently quantify the accuracy of the surrogate model. Using the error estimator, we systematically update our surrogate model through a greedy search of the parameter space. Furthermore, using the error estimator, the parameter search space is dynamically updated such that the most relevant samples get chosen at every iteration. The proposed adaptive surrogate model is tested on three benchmark models to illustrate its efficiency, accuracy, and ability of generalization.

Reference:

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Surrogate modeling of finite deformation hyperelasticity of human myocardial tissue

Osman Gültekin, Baris Cansiz, Ahmad Moeineddin, Michael Kaliske
Technische Universität Dresden, Germany

Notwithstanding its rapid development, surrogate models using physics-informed neural networks (PINNs) [1-2] have received less attention in predicting hyperelasticity of soft biological tissues thus far. Their potential applications are yet to be leveraged. In the present contribution, PINNs will be used in predicting the deformations throughout the thickness of the myocardium when only the epicardial and endocardial deformations can be tracked down via echocardiography and cardiac Magnetic Resonance Imaging (cMRI) techniques. In order to find optimal network parameters that best predict a solution, neural networks utilize a loss function between the predicted and the target solution. Here, the loss function will be informed by the balance of linear momentum, constitutive response, Dirichlet and Neumann boundary conditions. Efforts will also be made to demonstrate the improvement of predictions when the weak form of the problem is incorporated into the loss function. Investigations will start with predictions of mechanics on the planar basal region of the left ventricle obtained from 2D short axis views through cMRI. Next, efforts will be geared towards 3D PINNs-simulations on the entire left ventricle where measured displacements on the epicardial and endocardial surfaces serve as Dirichlet boundary conditions [3]. The obtained results will be compared with those from well-established computational techniques such as the finite element method (FEM) [4-5]. It is hoped that such developments towards high-end calibrated surrogate models will shed more light on preventative and therapeutic approaches in medicine.

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Bridging computational efficiency, sex differences, and clinical accuracy: Surrogate modeling in cardiotoxicity assessment

Alberto Zingaro[1], Paula Dominguez[1], Caterina Balzotti[1], Laura Baldo[1], Jazmin Aguado Sierra[1], Mariano Vazquez[1,2]
[1]ELEM Biotech SL, Barcelona, Spain; [2]Barcelona Supercomputing Center, Barcelona, Spain

Drug-induced arrhythmias represent a significant global health concern, accentuated during the COVID-19 pandemic by the utilization of potentially pro-arrhythmic medications in urgent attempts to manage the disease. The development of innovative methodologies capable of rapidly assessing the cardiotoxic risks associated with drugs would furnish scientists and clinicians with a formidable clinical asset. Estimating cardiotoxic risks can be achieved through high-fidelity 3D cardiac electrophysiological simulations. Nonetheless, the computational demands of these tools may constrain their utility, particularly when applied to large virtual populations. Addressing these computational challenges is crucial for broadening their applicability and impact in clinical practice. In this study, we use Gaussian Process Regression (GPR) to provide real-time estimations of drug-induced cardiotoxicity. Our methodology involves training the GPR model using 700 high-fidelity 3D electrophysiology simulations conducted on highly detailed biventricular patient-specific geometries. Notably, we incorporate the drug's effects by modulating the ionic profiles and integrate sex as a phenotypic factor. This enables the development of two distinct GPR models tailored to the male and female populations. Cardiac risk assessment is achieved by quantifying QT interval prolongation with respect to a baseline configuration, given the concentration of a drug. We demonstrate that our surrogate models achieve maximum relative errors of approximately 2% compared to the high-fidelity solution, thus providing highly accurate representations with minimal computational overhead. Our analysis highlights the flexibility afforded by GPR models, enabling the simulation of diverse scenarios at a cost-effective rate without sacrificing precision. Furthermore, we leverage these surrogate models to replicate real clinical trials, showcasing how concentration–response relationships of QT interval changes derived computationally exhibit slopes within the confidence interval of regression analyses from clinical trials.

Physiology-informed machine learning to guide heart failure diagnosis, prognosis, and treatment

Feng Gu, Brian Carlson, Filip Jezek, Daniel Beard
University of Michigan, USA

Heart failure with preserved ejection fraction (HFpEF) is a prevalent form of heart disease with a diverse clinical manifestations and etiologies. To characterize phenotypic subgroups in the heart failure population we have developed a framework to categorize and stratify patients using a combination of physiology-/physics-based simulation and machine-learning approaches. Based on a longitudinal data set that includes imaging (cardiac MRI and transthoracic echocardiography) and invasive hemodynamic measurements (right heart catheterization), we have identified patient-specific digital twins simulating cardiac mechanics and cardiovascular systems function on 346 heart failure patients. Combining model-augmented data with additional clinical data (NT-ProBNP, CPET, ECG, cardiac events, clinical outcomes) we performed unsupervised machine learning to identify clusters of differential phenotypes. Performing longitudinal outcome analysis on identified cluster phenogroups, we have identified optimal predictors of outcomes including death, rehospitalization, heart transplant, and LVAD implantation. By comparing the performance of predictors based on raw data, and based on model-augmented data and parameters, we demonstrate how the model-based precision phenotyping affords additional insight not provided from raw clinical data alone. This physiology-informed machine learning classification approach has the potential to represent a novel and uniquely powerful tool to guide diagnosis, therapy, and clinical trial design in the cardiovascular disease space. Beyond utility in precision phenotyping and diagnostics, our approach yields a comprehensive simulation-based "digital twin" of each patient's dynamic cardiovascular state. Thus this simulation-based framework provides a unique tool for not only identifying differential prognosis and treatment outcomes, but also identifying the major mechanistic functional drivers of differential outcomes.

An experimental and modelling pipeline to develop metabolite-sensitive cardiac cross-bridge models

Julia H Musgrave[1], June-Chiew Han[1], Marie-Louise Ward[2], Andrew J Taberner[1,3], Kenneth Tran[1]
[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Department of Physiology, University of Auckland, New Zealand; [3]Department of Engineering Science and Biomedical Engineering, University of Auckland, New Zealand

The prevalence of metabolic and cardiovascular diseases provides strong motivation to leverage computational modelling techniques to interrogate the interactions between energy supply and work done by cardiac muscle at the cellular level. Central to this endeavour is a cardiac cross-bridge model which can respond to metabolic changes. Development of such a model should take place concurrently with selection of suitable experimental techniques which reveal these key processes and generate a rich data set for model parameterisation. We have used sinusoidal analysis to gather mechanical data from permeabilised cardiac trabeculae. By applying small amplitude length perturbations across a range of frequencies and measuring resulting force, a stiffness spectrum (or complex modulus) can be found, which reflects the underlying cross-bridge kinetics of the muscle. We collected these data from muscles across a range of ATP and Pi concentrations to provide information about their sensitivity to metabolic conditions. Driven by this experimental data, we have developed a biophysical cross-bridge model which simplifies the kinetics while capturing the key cellular mechanisms. Using a model linearisation technique, we further simplified the ODEs comprising the cross-bridge model and performed a systematic analysis investigating how the modelling of metabolite effects and the assignment of strain dependence affect the properties of the cross-bridge cycle. Linearisation also allowed us to directly relate the key features of the complex modulus to the properties of the cross-bridge model. Our experiment-modelling pipeline was applied to rat trabeculae to reveal an ideal combination of strain and metabolite dependencies to fit the gathered data. More recently, we have applied this approach to samples from diabetic and non-diabetic human patients. The resulting human cross-bridge model will ultimately be integrated with calcium dynamics and mitochondrial function data to determine how changes in calcium sensitivity or metabolic state of the muscle influence the measured mechanics under simulation of physiological contraction.

2.B: Hemodynamics

Wednesday, September 4

1:00pm - 2:30pm

02.017

Hemodynamics of an implanted pressure sensor in porcine and human pulmonary artery

Leonid Goubergrits[1], Pavlo Yevtushenko[1], Adriano Schlief[1], Jan Romberg[2], Titus Kuehne[1], Andreas Arndt[2,3,4], Jan Bruening[1]
[1]Deutsches Herzzentrum der Charité, Berlin, Germany; [2]Biotronik, Berlin, Germany; [3]Technische Universität Dresden, Germany; [4]Kurt-Schwabe-Institut für Mess- und Sensortechnik Meinsberg e.V., Meinsberg, Germany

To assess whether in-silico models can be used to predict the risk of thrombus formation in pulmonary artery pressure sensors (PAPS), an in-silico study enhanced porcine animal study with 10 pigs. These sensors are implanted into the pulmonary artery aiming to detect earlier acute decompensation that can ideally be mitigated by pharmaceutical treatment of heart failure patients. 20 PAPS (one in a left and one in a right PA of each subject) were virtually implanted mimicking real implantations in pigs as acquired by CT in frames of an animal trial. First, we investigated hemodynamics by using CFD and assessed changes caused by PAPS. Transient flow simulations were done using STARCCM+. Since porcine and human PA differs, we investigated next the ability to translate these results onto human PA. PAPS were virtually implanted in human PA and CFD analysis of the hemodynamic changes due to PAPS implantation was done and results were compared with porcine results. Furthermore, we compared hemodynamics between optimally (sensors causing causing a minimal flow disturbance) and non-optimally (PAPS reaching from one vessel wall to the other, located within a side branch, or covering a side branch orifice) implanted sensors. Time-averaged wall shear stress (TAWSS), oszillating shear index (OSI) and pressure drop caused by a sensor were evaluated. We found a difference in hemodynamics between porcine and human PA resulting in lower TAWSS and higher OSI in human conditions that is associated with probably lower protection against risk of thrombus formation. PAPS implanted in the human PA causes relatively low averaged pressure drop of 0.84±0.77 mmHg, which non-significantly differs from the pressure drop calculated in porcine PA with 0.70±1.1 mmHg. Despite these differences in morphometry and hemodynamic parameters found in porcine and human PA, no higher risk of thrombus formation can be associated with a changed hemodynamics due to PAPS implantation. Despite the significantly lower TAWSS and significantly higher OSI found for PAPS in human PA both in silico studies (porcine and human) found no higher risk of thrombus formation for non-optimally implanted PAPS.

Turbulence modeling in aortic blood flow: Traditional models and perspectives on machine learning

Sarah Katz[1], Alfonso Caiazzo[1], Volker John[1,2]
[1]Weierstrass Institute for Applied Analysis and Stochastics, Germany; [2]Freie Universität Berlin, Germany

In cardiovascular medicine, computational fluid dynamics has been of increasing importance both for generally understanding the behavior of blood flow and for practically enhancing diagnostics and decisionmaking. The flow in larger vessels, particularly the aorta, is highly variable and complex. It exhibits transitional or turbulent behavior at systole, which flow simulations of moderate size cannot resolve. However, quantities of interest for diagnostic purposes are usually spatially (and often temporally) averaged, and computational resources may be limited; therefore lower-resolution simulations that accurately reproduce such quantities are desirable, introducing the need for turbulence modeling. We compare some traditional LES (large eddy simulation) models and examine the potential uses and limitations of a machine learning based implicit super-resolution model with respect to enhancing lower-resolution computations.

Estimation of exercise-induced pressure drop across aortic coarctations: A comparison of in vitro measurements and FSI simulations

Priya J. Nair[1,2], Emanuele Perra[3], Doff B. McElhinney[1,2], Daniel B. Ennis[1,2,4], Alison L. Marsden[1,2], Seraina A. Dual[3]
[1]Stanford University, USA; [2]Stanford Cardiovascular Institute, USA; [3]KTH Royal Institute of Technology, Sweden; [4]VA Palo Alto Healthcare System, USA

INTRODUCTION Coarctation of the aorta (CoA) is a cardiovascular defect characterized by a narrowing of the aorta. Blood pressure gradient (ΔP) across the CoA measured at rest during catheterization is used to diagnose CoA severity but can underestimate the disease burden. Some patients with insignificant ΔP at rest can develop pathologically high ΔP during exercise, but this varies on a patient-specific basis. This study aimed to predict exercise-induced ΔP using compliant aortic patient-specific phantoms in a hybrid mock circulatory loop (HMCL), validated by fluid-structure interaction (FSI) simulations.

METHODS
Model Generation: 4D-Flow MRI datasets and invasive blood pressure measurements at rest (IRB-approved) were acquired for patients with CoA (N=5). 3D aorta geometries were generated from anatomic images using SimVascular and 3D-printed to generate compliant patient-specific phantoms. **HMCL:** Four hemodynamic states: rest (1×CO), 1.25×CO, 1.5×CO, and 2×CO were evaluated for each model. The aorta phantom was integrated into the pressure-controlled HMCL. Cardiovascular hemodynamics were controlled *in silico* by a closed-loop lumped parameter network tuned to achieve patient-specific hemodynamics. Catheter pressures were measured in the AAo and DAo. **FSI Simulations:** 3D FSI simulations were performed in SimVascular at the same hemodynamic conditions using flow and pressure measurements from the HMCL. Simulated pressures were measured in the AAo and DAo at the experimental catheter locations.

RESULTS The drop in mean pressure from AAo to DAo (ΔP_{mean}) is reported for both systems. The error between the simulated and catheter-derived ΔP_{mean} was 1.36 ± 0.91 mmHg, indicating agreement between the methods. ΔP_{mean} also changes non-linearly with increase in CO and the changes vary on a patient-specific basis.

DISCUSSION This study offers a novel approach to estimate ΔP in patients with CoA using an HMCL in exercise states that are unattainable in clinical practice. It also establishes FSI simulations as a useful tool to determine the likelihood of exercise intolerance and provides a foundation for researching factors that influence the non-linearity of ΔP increase with exercise.

Simulation of the hemodynamics of a patient-specific artery at the full-body scale

Xiao-Chuan Cai
University of Macau, Macau S.A.R. (China)

The numerical simulation of blood flows in the human body with a certain level of clinical accuracy is important for the understanding of the human physiology and the success of the modeling relies on a robust numerical method with the corresponding software that can handle the complex geometry, the complex fluid flows and run efficiently on a supercomputer. In this talk, we present a highly parallel domain decomposition method to solve the three-dimensional incompressible Navier-Stokes equations on a patient-specific artery at the full-body scale from neck to feet with 222 outlets and a minimum diameter around 1.0 mm. An a priori knowledge based, locally refined, unstructured mesh is used to resolve the complex fluid flow. Moreover, a two-level method is introduced to determine the model parameters in the Windkessel outlet boundary condition to guarantee clinically correct flow distributions to 14 major organs/regions. A fully implicit Newton-Krylov-Schwarz method is used to solve the nonlinear algebraic system at each time step and numerical experiments show that the proposed method is robust with respect to the complex geometry, the graph-based partition of the complex mesh, the ill-conditioned sparse systems with locally dense blocks, and different model parameters and is scalable with more than 10,000 processor cores. With the method, one simulation of the blood flow in a full-body arterial network can be obtained in about 8 hours per cardiac cycle, which enables its potential use in a wide range of clinical scenarios. This is a joint work with S. Qin and R. Chen.

A detailed 1D model of the feto-placental hemodynamics to investigate hypertensive disorders of pregnancy

Pascalle Wijntjes[1,2,3,4], Jérôme Kowalski[3], Sjeng Quicken[1], Beatrijs van der Hout-van der Jagt[1,2,4], Irene Vignon-Clementel[3], Frans van de Vosse[1,4], Wouter Huberts[1,4]
[1]Eindhoven University of Technology, Netherlands, The; [2]Máxima Medical Centre, the Netherlands; [3]INRIA, France; [4]e/MTIC, the Netherlands

Hypertensive disorders of pregnancy (HDP), affect a significant number of pregnancies, bringing maternal and fetal health at risk. For better understanding and for improving medical care, the cause of this disorder is increasingly studied. One hypothesis is that HDP patients have an increased placental resistance resulting in insufficient placental perfusion effecting fetal growth. The hypothesis on increased placental resistance can be tested via 1D modelling of the placental hemodynamics. 1D wave-propagation models can provide crucial insights into pathologies by explaining their influence on clinically measurable Doppler waveform characteristics at the umbilical arteries (UA). Therefore, the aim of this study is to develop a 1D model of the feto-placental circulation. A volume-filling algorithm is employed to generate a realistic placental vasculature, imposing constraints on branching parameters. Murray's law is applied to establish vessel diameter distributions that reflect physiology. A 1D model, previously developed by Kroon et al., was refined and adapted for this application. At the inlet of the UA, a realistic, model-based, pressure is imposed, whereas at the placental outlets a constant pressure of 20 mmHg is prescribed. The resulting vasculature mimics real placental statistics and consists of almost 100k 1D elements through which the hemodynamics are calculated. It includes 53 villus trees and 23 generations from UA to capillary. Using a terminal radius at capillary level with a chosen power for Murrays law yields UA diameters of approximately 4 mm. These numbers are all in line with existing literature on healthy placental geometries. By imposing a realistic pressure of 40 mmHg with a pulse of 8 mmHg, a flow wave form that corresponds to Doppler measurements is established. The resulting flow is on average 125 mL/min showing good agreement with literature on the mean flow in the umbilical veins. In summary, our modelling approach results in a realistic feto-placental arterial tree that mimics the flow behavior in the UAs when imposing a realistic pressure. Further studies are focusing on the hemodynamics within pathological vasculatures related to HDP.

The impact of clot permeability on thrombus growth in different hemodynamic scenarios

Niksa Mohammadi Bagheri, Gábor Závodszky, Alfons G. Hoekstra
Computational Science Lab, Informatics Institute, University of Amsterdam, Amsterdam, Netherland

Blood thrombi are complex structures characterized by a dense platelet core surrounded by a loosely bonded outer shell. The clots' permeability shows significant variability, with a range of up to seven orders of magnitude, influenced by factors such as blood flow dynamics and clot composition [1]. Diverse hemodynamic conditions and biomaterial interactions exert a substantial influence on the activation and aggregation of platelets, fundamental processes in the formation of blood clots with varying permeabilities. Therefore, it is crucial to assess the impact of different clot permeabilities on thrombus formation and progression in various hemodynamics. In this study, a modified version of a thrombus formation model, which was initially proposed by [2], was used to investigate this phenomenon. Thrombus formation was modeled numerically using a finite element approach implemented in COMSOL Multiphysics. Clot initiation and growth are promoted at the site of vascular injury through the release of adenosine diphosphate (ADP). By incorporating the Brinkman term, the model effectively incorporates the resistance force due to clot permeability into the Navier-Stokes equations. The present study investigated the impact of enhanced platelet fluxes within the boundary layer of a blood clot on clot growth rate and pattern caused by increased permeability. This research further explores the interplay between clot permeability, hemodynamics, and platelet transport in diverse thrombogenic scenarios. Here, a new mathematical framework is introduced, which aims to minimize the dependence on in vivo hemodynamic evaluations when identifying the thrombogenic pattern of clot formation.

2.C: COMBINE

Wednesday, September 4

1:00pm - 2:30pm

02.011

The COmputational MOdelling in BIology NEtwork in 2024: Standards and services for the computational physiology community and beyond

David Phillip Nickerson[1], Martin Golebiewski[2], Thomas E. Gorochowski[3], Sarah M. Keating[4], Matthias König[5], Chris J. Myers[6], Falk Schreiber[7], Dagmar Waltemath[8], Padraig Gleeson[9]
[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Heidelberg Institute for Theoretical Studies - HITS gGmbH, Heidelberg, Germany; [3]School of Biological Sciences, University of Bristol, Bristol, UK; [4]Advanced Research Computing Centre, University College London, UK; [5]Faculty of Life Science, Institute for Biology, Institute for Theoretical Biology, Humboldt-University Berlin, Berlin, Germany; [6]Department of Electrical, Computer, and Energy Engineering, University of Colorado Boulder, USA; [7]Department of Computer and Information Science, University of Konstanz, Konstanz, Germany; [8]Medical Informatics Laboratory, University Medicine Greifswald, Germany; [9]Department of Neuroscience, Physiology and Pharmacology, University College London, UK

The Computational Modelling in Biology Network (https://co.mbine.org/) coordinates the development and dissemination of community standards and formats in systems biology and related fields. It ensures that previously independent standardisation initiatives develop a set of interoperable and non-overlapping standards covering all aspects of modelling in biology and medicine. The global effort is led by the COMBINE coordination board with representatives of all COMBINE standards. Building on the experience of mature projects, which already have stable specifications, software support, user-base and community governance, COMBINE helps foster and support fledgling efforts. As those efforts mature, they may become part of the core set of COMBINE standards. Our presentation will introduce the COMBINE governance and core standards for modelling (CellML, NeuroML, SBOL, SBML), graphical network representation (SBGN, SBOL Visual), simulation encoding (SED-ML), dissemination of modelling studies (COMBINE archive), and handling of metadata (OMEX). We will discuss the available resources and community support specifically for the computational physiology community. An overview of ongoing projects and open challenges to extend the COMBINE standards will be given, as well as examples for implementation in tools and models, e.g. in the context of Virtual Human Twins and personalized medicine. We invite the audience to participate in the standards' development and evaluation. COMBINE supports FAIR and TRUSTed efforts and infrastructures in systems medicine, thereby fostering reuse of simulation studies, reproducibility and interoperability of model-based results. We share our experiences of cooperating with model repositories such as Biomodels or the Physiome Model Repository, and with international efforts such as the Reproducibility Center or the Disease Map community. The development of open software and libraries, standard-enabled workflows, and the contribution to open science efforts (EOSC, FAIRsharing) are also part of our work. We also contribute to formal ISO standards for data sharing in life sciences (ISO 20691) and modelling in personalised medicine (ISO/TS 9491-1).

BayModTS: A FAIR Bayesian workflow to process variable and sparse time series data

Sebastian Höpfl, Nicole Radde
University of Stuttgart, Germany

The generation of biomedical data is often constrained by cost and ethical considerations, resulting in sparse time series with only a limited number of replicates. The inter-individual variability of organisms and the variability within a single organism over time further complicates accurate inference of kinetic parameters. Bayesian Modeling of Time Series Data (BayModTS) processes sparse and highly variable time series data. The workflow is Findable, Accessible, Interoperable, and Reusable (FAIR) through adhering to model standards like the Systems Biology Markup Language (SBML) and state-of-the-art Python toolboxes. Further, a public GitHub repository contains all the information needed to apply BayModTS. Storage of results in a public repository is encouraged. BayModTS employs the retarded transient functions of C. Kreutz as a universal simulation model and can be easily adapted to user-specified SBML models. A parameter posterior distribution, quantifying the uncertainty of the data, is inferred via Markow-Chain-Monte-Carlo sampling. Posterior predictive distributions transfer parameter samples from the posterior to model predictions, providing continuous predictions with filtered noise. We first demonstrate BayModTS' feasibility on rats' in vivo liver perfusion after 60% Portal Vein Ligation. BayModTS transforms MRI perfusion measurements into time-continuous predictions for the perfusion of individual liver lobes equipped with credibility tubes. These can be used as input for liver function models. Second, we apply BayModTS to Caffeine, Midazolam, and Codeine metabolization dynamics of mice with different degrees of steatosis. Here, the noise-filtering property is used to identify the impact of different steatosis degrees on the metabolization of the test drugs. In summary, BayModTS is a FAIR Bayesian workflow to analyse variable and sparse time series data. A user-friendly toolbox can be found on GitHub.

The reproducibility and credibility of biomedical models

Herbert Martin Sauro
University of Washington, United States of America

As computational models begin to be considered for translational purposes, there is a need to be able to assess more formally, and preferably in an automated way, a model's fitness for a given task. Software engineering has a long history of formalizing the development and testing of source code. Biomodelling less so. In this talk I will describe the work of the Center of Reproducible Biomedical Modeling, it's efforts to improve the reproducibility of biomedical models and a new initiative to focus on model credibility. In addition, I will discuss a new set of guidelines, called CURE, which were inspired by FAIR, that is focused on models. Finally, a few words will be said about the role of AL/ML and it implications for the scientific method.

Reproducible digital twins for personalized liver function assessment

Matthias König
Humboldt University Berlin, Germany

Essential prerequisites for the practical application and translation of computational models include: i) reproducibility of results; ii) model reusability and extensibility; iii) data availability; and iv) strategies for model stratification and individualization. Here, we present a modeling workflow built around these foundational prerequisites, with a focus on liver function tests.

Despite the paramount significance of liver function assessment in hepatology, reliable quantification remains a clinical challenge. Dynamic liver function tests offer a promising method for non-invasive in vivo assessment of liver function and metabolic phenotyping. By leveraging whole-body physiologically-based pharmacokinetic (PBPK) models, we're simulating these tests and positioning PBPK models as digital twins for metabolic phenotyping and liver function assessment. To develop and validate our models, we established the open pharmacokinetics database, PK-DB, containing curated data from 600+ clinical studies [10.1093/nar/gkaa990, 10.3389/fphar.2021.752826]. Our models are individualizable and stratifiable, enabling simulation of lifestyle factors and co-administration effects on drug metabolism. Our models have been instrumental in clinical scenarios: from predicting individual outcomes post-hepatectomy [10.3389/fphys.2021.730418, 10.3389/fphys.2021.757293] to discerning the impact of CYP2D6 gene variants on liver function tests [10.3389/fphar.2022.1029073]. These models are constructed hierarchically, describing metabolic and other biological processes in organs like the liver and kidneys, seamlessly integrated with whole-body physiology. Notably, all models and data are readily available and reproducible for reuse, encoded in the Systems Biology Markup Language (SBML) [10.15252/msb.20199110]. We will provide an overview of these PBPK models and demonstrate how SBML and FAIR principles can facilitate model development, coupling, and reuse.

The role of standards in defining an ecosystem for virtual human twins (VHTs)

Martin Golebiewski, Gerhard Mayer, Wolfgang Müller
Heidelberg Institute for Theoretical Studies (HITS), Heidelberg, Germany

The European **EDITH infrastructure** is building an ecosystem for **Virtual Human Twins (VHTs)** for health applications. This requires interoperability of the computational models of different kinds, as well as of their underlying data. Therefore, a high degree of standardization of data, models, provenance information and applied workflows is needed, and the applied standards must be interoperable. In our presentation we will give an overview of the different classes of standards used for the construction, validation, integration and simulation of VHTs and provide insights into some important examples of such standards. Some of the standards are defined by Standard Defining Organizations (**SDOs**) such as **ISO**. At HITS we are leading the drafting of ISO standards that are relevant for VHTs and for clinical decision support systems (CDSSs) that will build on them: **ISO 20691** provides a framework for the development and application of domain-specific and interoperable (meta-)data standards in the life sciences. It defines requirements and rules for the application of standards for formatting, description, and documentation of data, as well as for the design of interoperable data formats and terminologies for semantic annotation. In contrast, **ISO TS 9491-1** "Recommendations and requirements for predictive computational models in personalised medicine research" provides guidelines for constructing, verifying, and validating models, especially for modelling in the field of personalized medicine. **ISO TS 9491-2** "Guidelines for implementing computational models in clinical integrated decision support systems" contains recommendations for computational models and their application in the clinical research context. The **ISO 23494 series** "Provenance information model for biological material and data" describes how to document the provenance information for biological data to trace it back to their original sources. These ISO standards also refer to a whole bunch of grass-roots standards from the scientific community, e.g. defined by the **COMBINE** network (e.g. **SBML, SBGN, Cell ML, SED-ML,** etc.) or **ASME** (e.g. **ASME V&V 40** for assessing the quality and model credibility of medical devices).

Model reuse - Lessons learned from 20 years of sharing CellML models

Hugh Sorby, Alan Garny, Tommy Yu, David Nickerson
University of Auckland, New Zealand

CellML has been used successfully for nearly 25 years, allowing modelers and model users to work in accordance with the FAIR principles. Initially, CellML focused on being able to share reproducible descriptions of mathematical models. As CellML usage grew, it became clear that the initial version was not ideal for model reuse - extending or integrating existing models into new models. As CellML has evolved over these 20+ years, we have learnt much about how to best archive and share models in a manner that facilitates model reuse. In this presentation, we will summarize what we have learnt with CellML, and discuss how the same concepts, methods, and tooling could be applied more broadly to sharing, archiving, and publishing computational models to support future reusability. This discussion will include version control and the propagation of model fixes; communicating understanding of a model; and guidelines for constructing reusable models.

2.E: Gastrointestinal Tract, Kidney & Uterus

Wednesday, September 4

1:00pm - 2:30pm

09.019

Modelling the electrophysiology of the non-pregnant uterus: From interconnected cells to organ

Alys Clark, Mathias Roesler, Shawn Means, Amy Garrett, Leo Cheng
University of Auckland, New Zealand

The uterus contracts regularly, with changes in contraction strength and propagation patterns throughout the menstrual cycle (estrus cycle in animals). Like any muscular organ, uterine contractions are influenced by electrical signals that are modulated by cell-to-cell connectivity, the anatomical structure of the organ, as well as endocrine and nervous system influences. This integrated function prepares the uterus for pregnancy, and dysfunction can contribute to infertility and conditions such as endometriosis, which has a significant impact on quality of life. Here, we propose mathematical models of uterine function which aim to robustly scale from cell to tissue to organ via platforms developed as part of the 12 Labours Project at the Auckland Bioengineering Institute. We aim to develop integrated models that are consistent across scales, and tested against data. We also present an experimental approach in the rodent uterus designed to collect comprehensive data to guide model development and test model performance. This includes: micro-CT imaging of the muscular anatomy of the uterus, confocal microscopy of gap junction connectivity between uterine smooth muscle cells, and novel assessment of electrical wave propagation on the uterus in vivo. We propose an ordinary differential equation model incorporating key ion channels in the uterine smooth muscle cell, including theorised hormonal (estrogen and progesterone) influences on these cells. We then demonstrate scaling of this cell model to a whole organ model that incorporates variable cell-to-cell communication. This whole organ model is defined via a scaffold finite element mesh which allows consistent definition of anatomical landmarks between individuals and species. We focus on aligning model development, anatomical and electrophysiological data acquisition at a high resolution in rodent models, as well as a vision to the future on data collection and integration to assess the human uterus.

Computational modeling of the effect of laser tissue soldering on colonic motility

René Thierry Djoumessi[1], Pietro Lenarda[1], Pietro Alduini[2], Marco Paggi[1], Alessio Gizzi[3]
[1]IMT School for Advanced Studies Lucca, Italy; [2]Hospital of Saint Luca, Italy; [3]Università Campus Bio-Medico di Roma, Italy

Anastomotic leakage after resection of gastrointestinal lesions is a major source of concern for clinicians and patients alike. To address this problem, several technologies have been developed, including laser tissue soldering. However, a clinical rationale still needs to be improved, and computational biomechanics is required to support clinical decisions. The present contribution proposes an electromechanical framework for colonic motility integrating electrophysiology and smooth muscle contractility. The modeling framework comprises three main elements: (1) a material model describing the geometry and composition of four reinforcing fiber families (two active, reproducing the smooth muscle fibers, and two passive, representing collagen sheets referential directions); (2) an electrophysiological model describing the spatiotemporal propagation of slow waves, based on a phenomenological approach; (3) a finite elasticity continuum mechanics model describing the different energetic contributions of the tissue. The active strain approach has been used to enforce tissue electro-mechanics couplings, exploiting the multiplicative decomposition of the gradient deformation tensor [1]. The problem is solved via a finite element staggered solution scheme in the FEniCS software. The present computational framework is capable of computing the intraluminal pressure in a gastrointestinal tract under different physiological and pathological scenarios, considering multiple soldering shapes and material properties. Numerical resuts have been compared with high-resolution manometry signals obtained in clinical practice [2].

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[2] Paskaranandavadivel, N, Lin, AY, Cheng, LK, Bissett, I, Lowe, A, Arkwright, J, Mollaee, S, Dinning, PG, O'Grady, G. ManoMap: an automated system for characterization of colonic propagating contractions recorded by high-resolution manometry. Medical & Biological Engineering & Computing (2021) 57: 417-429.

Neural stimulation modifies the organ-scale coordination of rat gastric slow waves

Omkar N. Athavale, Recep Avci, Alys R. Clark, Leo K. Cheng, Peng Du
University of Auckland, New Zealand

Stomach contractions are governed by bioelectrical slow waves that propagate through excitable cell networks in the stomach. While slow waves are spontaneously generated, the enteric and peripheral nervous systems also influence slow wave activity. Changes in gastric motility due to nerve stimulation have been measured in vitro, but the effects of stimulation on slow wave propagation in the whole organ have not been measured. Interest in nerve stimulation therapy for relieving gastric dysfunction necessitates the development of predictive models so that effects on the organ are precise and specific. An ODE cell model of slow waves incorporating the response to neural stimulation was developed and embedded into a continuum model comprised of triangular elements with 23510 vertex nodes, representing the stomach. The cell model was solved to obtain the membrane potential. The monodomain equation was solved in CHaSTE to simulate propagation of slow waves. Inhibitory, excitatory, or both inhibitory and excitatory neural stimulation was applied at 5 Hz for 60 s to all nodes. Initial conditions were prescribed such that slow waves propagated in a stable, physiological manner. Before stimulation, coordinated slow waves propagated proximal to distal at a speed of 0.8 mm/s, and a frequency of 2.7 cycles per minute. Purely inhibitory stimulation and combined inhibitory and excitatory stimulation decreased slow wave amplitude (-32%, -22%), and changed slow wave frequency (-5%, +43%) but the entire stomach continued to experience coordinated slow waves. However, purely excitatory stimulation caused slow waves to propagate in a decoupled manner in the corpus and antrum stomach regions. The simulations demonstrated that neural stimulation can be applied in a manner that modifies propagation patterns or decreases the amplitude of slow waves. This shows that gastric dysfunction due to poor slow wave coordination may be corrected or mitigated by nerve stimulation. A parameter search for the appropriate stimulation protocols will be conducted to selectively activate excitatory or inhibitory neurons.

Computational modelling of the human gastric peristalsis

Maire Salina Henke[1], Sebastian Brandstaeter[2], Alessio Gizzi[3], Roland Can Aydin[1,4], Christian Johannes Cyron[1,4]
[1]Institute for Continuum and Material Mechanics, Hamburg University of Technology, Germany; [2]Institute for Mathematics and Computer-Based Simulation, University of the Bundeswehr Munich, Germany; [3]Department of Engineering, Campus Bio-Medico University of Rome, Italy; [4]Institute of Material Systems Modeling, Helmholtz-Zentrum Hereon, Germany

The stomach is a complex organ responsible for the digestion of food. This vital process depends on gastric peristalsis, which mixes, grinds, and propels chyme. Gastric peristalsis refers to the coordinated contraction and relaxation of the muscles in the stomach wall controlled by an intricate electromechanical system. We present a computational multiphysics framework to model gastric peristalsis with patient-specific geometries derived from magnetic resonance images. The framework builds upon a robust gastric electrophysiological model with an active-strain finite elasticity model to account for tissue mechanics [1, 2, 3]. Incorporating of an algorithm that maps a two-dimensional parameter distribution onto a general tube-like surface facilitates the determination of spatially varying model parameters capturing the individual anatomical and physiological characteristics of each patient's stomach. The proposed framework can reproduce essential phenomena of gastric electromechanics, including slow wave entrainment and the propagation of ring-shaped peristaltic contraction waves. The combination of computational techniques with patient data provides a powerful tool for large- scale in-silico studies of physiological and pathological mechanisms of gastric electromechanics. This can enhance the accuracy of diagnosing and treating various gastrointestinal disorders.

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Exploring host-microbiota interactions through mechanistic modelling: Insights into diet impact on beneficial symbiosis resilience in the human gut

Marie Haghebaert[1,2,3], Béatrice Laroche[1,2], Lorenzo Sala[1,2], Stanislas Mondot[4], Joel Doré[4,5]

[1]Université Paris-Saclay, INRAE, MaIAGE, Jouy-en-Josas, 78350, France; [2]Université Paris-Saclay, INRIA, MUSCA, Palaiseau, 91120, France; [3]Université Paris-Saclay, INRIA, SIMBIOTX, Palaiseau, 91120, France; [4]Micalis Institute, INRAE, AgroParisTech, University Paris-Saclay, Jouy-en-Josas, 78350, France; [5]Université Paris-Saclay, MGP, INRAE, Jouy-en-Josas, 78350, France

The interactions between an individual and their gut microbiota play a critical role in health and well-being. These interactions are shaped by environmental factors such as diet and health conditions, which influence the composition and functionality of the microbiota. Such changes can lead to shifts between states of beneficial or detrimental symbiotic, indicating alternative stable state within the host-microbiota ecosystem. We introduced a novel mechanistic mathematical model specifically designed to explore the dynamics of host-microbiota interactions within the colonic environment. This model employs partial differential equations (PDEs) to represent the division, differentiation and evolution of crypt cells along the colonic epithelial crypt. It also incorporates a compartmental representation for the dual-layer mucus and lumen environments. By integrating microbial metabolic activities, oxygen presence, inflammation sensitivity, and colonic flows, among others, our model offers a comprehensive framework for investigating the resilience of beneficial symbiosis. We first validated our model against key gut health biomarkers to ensure its accuracy in simulating beneficial gut symbiosis. Then, we investigated how different levels of protein and fiber intake affected these indicators, and compared the impacts of standard and high-protein, low-fiber (HP/LF) diets. Our results showed that a HP/LF diet was particularly detrimental when the epithelial barrier was compromised, exacerbating conditions by promoting the proliferation of facultative anaerobic bacteria, intensifying inflammation, reducing mucus production, and steering the microbiota towards a dysbiotic state. Our study advances the *in silico* understanding of colon host-microbiota symbiosis, offering key insights into oxygen levels, protein degradation, inflammation, epithelial cell and their interactions within the gut ecosystem. Despite potential areas for improvement, our work not only explores the complex dynamics between diet, gut microbiome, and host health but also, sets the stage for data-driven simulations to create personalized nutrition and treatment strategies for gut disorders.

Predictive modelling of renal circulation hemodynamic outcomes in hypertensive and diabetic kidney disease

Ning Wang[1,2], Ivan Benemerito[1,2], Steven Sourbron[1,3], Alberto Marzo[1,2]
[1]INSIGNEO Institute for in silico medicine, The University of Sheffield, UK; [2]Department of Mechanical Engineering, The University of Sheffield, UK; [3]School of Medicine and Population Health, The University of Sheffield, UK

Introduction Hypertension and diabetes are prevalent comorbidities known to independently contribute to the development of chronic kidney disease, often presenting with similar symptoms in the early stages. Non-invasive differentiation between these pathologies currently remains a significant challenge, impacting their effective clinical management. Our research hypothesizes a mechanistic model can identify biomarkers capable of distinguishing between these two pathologies.

Materials and Methods We utilized a multi-dimensional 1D-0D whole-circulation blood flow model (openBF) with a detailed renal network to model an age-based virtual healthy and diseased populations. Our study characterized the effects of diabetes and hypertension on parameters like blood viscosity, lumen radius, vascular stiffness, resistance, and compliance. We calibrated these models by the distribution of the resistive index (RI) values obtained from the literature[1, 2]. Values of RI and mean renal blood flow rate (RBF) were derived from modelled waveforms and used to quantify alterations resulting from these pathological conditions.

Results A virtual population comprising 711 individuals aged between 50-59 years exhibited varying distributions of RI and RBF across different stages of modelled hypertension and diabetes in good alignment with *in vivo* data[1, 2]. Specifically, RI values were 0.69 (SD=0.5) and 0.75 (SD=0.5) in the early and severe stages of diabetes, respectively. Similarly, comparable patterns were noted in hypertension, with RI values ranging from 0.65 (SD=0.4) to 0.72 (SD=0.5) across the same stages. Furthermore, RBF through a single diseased kidney ranged from 320 (SD=45, early) to 305 (SD=92, severe) ml/min in diabetes and 450 (SD=51, early) to 415 (SD=49, severe) ml/min in hypertension.

Conclusions Our results showed RBF is a better biomarker than RI to differentiate these two diseases in the early stage. This finding highlights the potential of utilizing an *in silico* approach to model and develop a deeper understanding of renal circulation damage.

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2.F: Big Data / Machine Learning II

Wednesday, September 4

1:00pm - 2:30pm

02.005

Virtual anatomical diagnosis of veridical human stroke patients

William W Lytton[1,2], Jung-Hyun Lee[1,2], Eunhee Choi[4], Minjae Cho[1,2], Robert McDougal[3]
[1]DHSU, United States of America; [2]Kings County Hospital, USA; [3]Yale University, USA; [4]Lincoln Medical Center, USA

We used a Generative Pre-trained Transformer (GPT-4) as a diagnostic tool to provide a virtual neurologist, asking it to identify the location of ischemic strokes based on published patient History and Physical (H&P). We identified Zero-Shot Chain-of-Thought prompting ("Let's work this out step-by-step") and Text Classification prompting (identify single vs multiple lesions, brain region, side) as effective methods for eliciting an explanation of the clinical reasoning process, as well as the final localization. Localization output was compared with a ground truth based on brain imaging. GPT-4 was queried on 46 cases (3 trials/case) with lesions in cerebral hemisphere, brainstem, cerebellum, or spinal cord. Prompts were followed by the raw text from journal H&P, each reviewed to ensure no references to localization information in the text. Performance was very good: sidedness 0.87, 0.74, 0.75, 0.74 (specificity, sensitivity, precision, F1-score); region: 0.94, 0.85, 0.84, 0.85. Class labels within the 'brain region' were similarly high for all regions except for cerebellum (confusions with brainstem strokes). Errors were largely due to extrinsic causes due to inadequate information in the published cases. Intrinsic failures were rare -- logic error or inadequate knowledge-base. Although GPT-4 has been trained on extensive text datasets, it has not had any specific training regarding brain areas or their associations with patient symptoms or with the signs elicited in the neurological examination, making its success all the more remarkable and suggesting the likelihood of considerably better scores for a large language model (LLM) augmented with additional training on clinical material. We also note that case reports tend to be difficult cases; we would expect better performance using the more typical cases from the electronic medical record. Despite the promise, considerable problems remain for clinical adaptation, due to legal, logistical and patient privacy issues; concerns about adequate accuracy for patient safety; clinical workflow integration; etc.

Interpretable and generalizable mortality prediction in critical care settings: Integrating mechanistic knowledge with machine learning

Moein Einollahzadeh Samadi, Andreas Schuppert
University Hospital RWTH Aachen, Germany

Hybrid modeling, integrating mechanistic knowledge with machine learning, is crucial when the mechanistic details of processes are insufficiently understood, and models relying solely on data become overly complex. Here, we introduce a novel supervised learning strategy wherein classification can be achieved using a tree-structured network with binary input data, such as ICD codes, guided by a priori knowledge. This approach offers advantages over complex data-driven methods by necessitating less data for training due to fewer parameters, and it inherently provides interpretability. The strategy was implemented to develop a mortality predictive model for two case studies involving critically ill patients with COVID-19 and Influenza in the intensive care unit requiring mechanical ventilation [1,2]. The results demonstrate that the proposed learning strategy exhibits extrapolation capability, which is instrumental in enhancing the applicability of machine learning models in medical and clinical research settings characterized by small-sized or biased clinical datasets. Additionally, for multi-hospital studies where model generalizability is paramount, extrapolability is particularly advantageous. Moreover, our learning strategy is designed for interpretability; gaining insights into how factors and their interactions contribute to the final mortality risk offers a clearer understanding of individual patients. This enables clinicians to make more informed decisions and tailor treatments accordingly.

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Explainable machine learning explained in medicine

Karol Przystalski
Codete Global, Poland

Explainable AI (xAI) is a hot topic today. We have seen a boom in AI because deep learning methods made a huge difference in many cases. There are also many more use cases of AI compared to times before Deep Learning was introduced. The problem that we face now is that many methods work and we believe that whatever is done under the hood, we don’t elaborate on the details. The reality is that it's very important to understand the way the prediction is done and not only understand the architecture of the method. There are many scenarios where xAI is very useful. During the talk, we explain the xAI methods with a focus on MedTech cases.

A deep learning approach to discriminate sodium and chloride muscle channelopathies

Emilie Ismailova[1], Alina Roitberg[1], Justus Marquetand[2], Thomas Klotz[1], Zoia Lateva[3], Oliver Röhrle[1]
[1]University of Stuttgart, Germany; [2]University of Tuebingen, Germany; [3]VA Palo Alto Health Care System, CA, USA

Muscle channelopathies are a group of neuromuscular disorders that disturb the cell membrane excitability, which results clinically in myotonia and/or periodic paralysis. The genetic aetiology of some of these disorders can be traced to mutations in the SCN4a or CLCN1 genes, which encode sodium and chloride channels, respectively. Commonly, sodium or chloride channel defects cause muscle hyperexcitability, evident through myotonic discharges in needle electromyography (EMG) recordings, essential for diagnosing channelopathies. Yet, it is debated if myotonic discharge properties can identify the defect type, raising questions about a consistent genotype-to-EMG-phenotype relationship in these disorders. To further clarify this question, we applied a deep learning approach on both simulated and measured pathological needle EMG data, aiming to distinguish between sodium and chloride channelopathies. Using a multiscale model that links membrane dynamics and EMG signals (Klotz et al., Biomechanics and Modeling in Mechanobiology, 2020), we simulated a needle EMG database for sodium and chloride channelopathies. We processed initial time-series data to extract features, specifically by obtaining time-frequency representations of the signals, which were then converted into images. The images were classified with high accuracy by a pre-trained ImageNet network. We applied the method to patient data as reported by Drost et al. (Neuromuscular Disorders, 2015). The limited size of the patient dataset posed a challenge for this deep neural network-based approach. To address this, we employed several strategies for data augmentation, among which MixUp improved our results. Additionally, for enhancing the method's diagnostic reliability we incorporated uncertainty quantification using the Monte-Carlo Dropout technique. For the first time, we show that an automated classification method can correctly identify different channelopathies. Such model trained under controlled conditions could potentially be integrated for a clinical application. Acknowledgements: We extend our gratitude to Dick Steegeman, Kevin McGill, and Jeroen Jeneson for providing the data essential for this study.

Hybridising standard reduced-order modelling methods with interpretable sparse neural networks for real-time patient specific lung simulations

Alexandre Daby-Seesaram[1,2], Kateřina Škardová[1,2], Martin Genet[1,2]
[1]Laboratoire de Mécanique des Solides, École Polytechnique/ CNRS/IPP, France; [2]INRIA, France

Mechanics and, more specifically, stress fields possibly play a crucial role in the development of pulmonary fibrosis. This work aims to provide clinicians with diagnostic and prognostic tools based on mechanical simulation. Personalisation of these tools is critical for clinical pertinence, thus requiring numerical techniques for real-time estimation of patient-specific mechanical parameters. This work proposes hybridising classical model-order reduction methods with machine learning capabilities to provide a fine-tuned surrogate model of the highly non-linear mechanics problem. Similarly to techniques like the Proper Generalised Decomposition (PGD) or the High-Order Singular Value Decomposition (HOSVD), the parametric mechanical field is represented through tensor decomposition, effectively mitigating the curse of dimensionality associated with high-dimensional parameters. Each mode of the tensor decomposition is given by the output of a sparse neural network within the HiDeNN framework, constraining the weights and biases to emulate classical shape functions used in the Finite Element Method. This hybridisation preserves interpretability while affording greater flexibility than standard model-order reduction methods. For instance, it allows for employing diverse meshes for each mode in the tensor decomposition, with the added capability of mesh adaptation during the training stage. Moreover, the model's architecture results directly from the number of nodes and the order of elements used for the interpolation, thus eliminating the arbitrariness in its choice. In this framework, the training stage amounts to solving the minimisation problem classically encountered with classical model reduction methods. However, the automatic differentiation tools naturally available in the neural network framework allow greater flexibility in solving the non-linear problem when its linearisation is not straightforward. Finally, this framework allows for transfer learning between different models with different architectures, leading to high efficiency in the model's design and limiting the wasteful use of resources.

2.G: Musculoskeletal System - Micro Mechanics

Wednesday, September 4

1:00pm - 2:30pm

01.005

Uncovering motor-unit activity in magnetomyography

Nima Noury[1,2,3], Justus Marquetand[1,2,3,4], Markus Siegel[1,2,3]
[1]Department of Neural Dynamics and Magnetoencephalography, Hertie Institute for Clinical Brain Research, University of Tübingen, Germany; [2]Centre for Integrative Neuroscience, University of Tübingen, Germany; [3]MEG Center, University of Tübingen, Germany; [4]Institute for Modelling and Simulation of Biomechanical Systems, University of Stuttgart, Stuttgart, Germany

Studying the discharge patterns of motor units (MUs) is necessary to understand the mechanisms underlying human movement. Traditional intramuscular electromyography (iEMG) allows direct MU study but is invasive. Surface electromyography (sEMG) is a non-invasive method that has been widely used to study muscle activity, although its lower spatial and temporal resolution do not allow it to completely replace iEMG. Advances in optically pumped magnetometers (OPMs) in the last couple of years have significantly increased the interest in a new non-invasive method called magnetomyography (MMG). Interestingly, simulations show that, under ideal situation, MMG is superior to sEMG. However, currently available OPMs have low sensitivity and bandwidth, and it is not clear which information could be extracted from MMG signals recorded with these sensors. In this study, we explored the feasibility of MU detection in MMG signals recorded using three types of magnetometers: SQUID, QuSpin OPMs, and ^{4}He OPMs. We simultaneously recorded iEMG and MMG from abductor digiti minimi muscle (ADM) and asked whether individual MUs could be decomposed from MMG recordings. Using a convolutional independent component analysis (convolutive-ICA) method, we show that MUs are detectable in all our MMG recordings. Importantly, using our simultaneously recorded iEMG recordings, we confirmed the validity of the decomposed MUs. However, the number of decomposed MUs is sub-optimal and only a small amount of their firings was detected, which could be due to suboptimalities in both sensors and our experimental setup. Future studies should correct for the experimental suboptimalities to find the limits of MU decomposition using MMG recordings. In sum, here, for the first time, we showed that MU decomposition is in principle possible with currently available MMG technology.

How distance affects the magnetic muscle signal - An in-vivo and in-silico study

Haodi Yang
University of Tuebingen, Germany

Background: Magnetomyography (MMG) can be utilized as a contactless modality to study the neuromuscular system. On the one hand, being contactless is a practical advantage as one does not need to prepare skin or attach electrodes like in electromyography (EMG). Still, on the other hand, it is also a disadvantage as the magnetic signal decays over distance. However, the effect of sensor-to-source distance in MMG has yet to be studied systematically.

Methods: Comparative studies with changing sensor-to-source distance in-vivo and in-silico were performed. In-vivo, three healthy participants repetitively pressed a button using one finger every 2 seconds within a trial of 60 seconds. The respective muscle activity was recorded using simultaneous surface EMG and one triaxial optically pumped magnetometer (OPM), whereas, after each 60-second trial, the OPM was systematically moved farther away from the skin surface, starting with a 0.4-centimetre distance between the outer shell and skin in one-centimetre steps to four centimetres. Next to the analysis of amplitude, median frequency, and signal-to-noise ratio (SNR), the experimental in-vivo results were compared with the results of an established in-silico model, which was able to predict how maximal proximity would improve the SNR.

Results: The more distant, the more the MMG signal shifts towards the noise level; given a noise level of 0.5-1 pT between 10-350 Hz, the muscle activity of one finger flexor muscle cannot be certainly recorded above a two-centimetre distance using current OPM-technology. For both in-vivo and in-silico datasets, the SNR value decreases to the value of one as the sensor-to-source distance increases above two centimetres.

Conclusion: Amplitude and frequency of MMG signals decay cubically towards noise level when sensor-to-source distance increases. Given that circumstance, below 1 cm sensor-to-source distance, each mm closer significantly improves SNR.

Clinical possibilities

Justus Carl Marquetand[1,2,3]
[1]Institute for Modelling and Simulation of Biomechanical Systems, University of Stuttgart, Stuttgart, Germany, Germany; [2]Department of Neural Dynamics and Magnetoencephalography, Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany; [3]MEG-Center, University of Tübingen, Tübingen, Germany

Magnetomyography (MMG) records muscle-induced magnetic fields and complements electromyography (EMG). Although MMG was first described 50 years ago, its clinical application has only recently been explored. Several challenges limit its practical use, particularly the very low amplitude of MMG signals (pico-Tesla range), which are significantly lower than the earth's magnetic field (micro-Tesla range). This imposes high technical demands on MMG recording systems. However, MMG offers several advantages. Unlike EMG, MMG does not require sensor-tissue contact, reducing measurement noise and facilitating routine clinical use. This also allows for the potential development of implantable MMG sensors that can be encapsulated for long-term biocompatibility. Additionally, MMG is theoretically more spatially selective than surface EMG, which could benefit applications like motor unit decomposition. The advent of novel quantum sensors, particularly optically pumped magnetometers (OPMs), has recently enabled further exploration of MMG as an alternative to EMG. However, only a few preliminary studies have investigated MMG for clinical use. This contribution will overview MMG's current possibilities, future opportunities, and limitations in clinical practice, focusing on the spontaneous activity (SA) of muscle tissue, a diagnostic hallmark of neuromuscular diseases. Surface electromyography (sEMG) cannot detect SA due to skin and subcutaneous fat, necessitating painful needle electrode insertion into the muscle. Given MMG's advantages and proof-of-principle in-vivo experiments, it should be possible to measure five different forms of SA (fibrillations, positive sharp waves, fasciculations, myotonic discharges, complex-repetitive discharges). This overview will explain how and why MMG presents a potential new modality for clinical applications, providing insights from a physician's perspective.

Impact of endomysium on fiber bundle passive and active mechanics for intact and chemically skinned fibers

Paolo Carlo Danesini[1], André Tomalka[2], Tobias Siebert[2,3], Filiz Ateş[1]
[1]Institute of Structural Mechanics and Dynamics in Aerospace Engineering, University of Stuttgart, Germany; [2]Motion and Exercise Science, University of Stuttgart, Germany; [3]Stuttgart Center for Simulation Science, University of Stuttgart, Germany

The extracellular matrix (ECM) forms a continuous structural network in skeletal muscle, playing a crucial role in lateral force transmission [e.g., 1,2]. The relationship between ECM and force production is essential for accurately understanding and simulating muscle performance. However, assessing the impact of individual ECM components, such as the endomysium, remains challenging due to potential interference from experimental procedures, in particular, the chemical skinning [3]. This study aims to assess (i) the impact of endomysium absence on fiber bundle mechanics and (ii) whether the chemical skinning procedure affects this phenomenon. We extracted 16 bundles comprising 4 or 5 rat extensor digitorum longus muscle fibers, 8 of which underwent the chemical skinning procedure. Intact and skinned bundles were mechanically tested by isometric activation, and passive and active force-length characteristics were recorded (i) with intact endomysium and (ii) after one layer of the endomysium was dissected. Skinned fiber bundles produced higher active forces compared to intact ones (24%±9.8%, $p<0.001$), while intact bundles exhibited higher passive forces (19.3±6.2%, $p<0.01$). Dissection of one layer of endomysium caused active forces to drop by 18.8%±2.9% ($p=0.017$) in intact bundles but not in skinned bundles ($p=0.667$). In contrast, passive forces decreased in skinned bundles after endomysium dissection (39%±15%, $p<0.001$), but remained unchanged in intact bundles ($p=0.135$). In conclusion, our findings emphasize the beneficial role of chemical skinning in enhancing active force production potentially by facilitating calcium uptake. Moreover, the significant effects of endomysium dissection, particularly when sarcolemma is intact, indicate the importance of ECM integrity in maintaining active fiber performance by limiting the shape instability of fibers. Further research should focus on modeling ECM-related conditions by considering the role of endomysium in active force production.

References

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Exploring the variability in neuromotor control to perform common locomotor tasks

Giorgio Davico, Alex Bersani, Marco Viceconti
Department of Industrial Engineering, Alma Mater Studiorum - University of Bologna, Italy

The human musculoskeletal system is intrinsically redundant: we have more muscles than degrees of freedom. This gives the central nervous system some flexibility on the selection of the neural strategy (set of muscle activations and forces) to perform a given task, such as walking. To date, such variability is seldomly explored and modelled while performing musculoskeletal dynamics simulations. Recently, a new tool – Myobolica[1] - was developed to enable this, through the implementation of a stochastic exploration of the solution space. Compared to its predecessor (Metabolica[2]), Myobolica includes some constraints to ensure the identification of more physiologically plausible solutions, i.e., to control how quickly the developed muscle forces can vary between consecutive time steps and to account for errors in the experimental data provided as input.

In this work, we tested the Myobolica algorithm to quantify the neuromuscular variability in a healthy young adult during the execution of an overground walking trial. A personalized musculoskeletal model was built off medical imaging data and used to perform biomechanical analyses in OpenSim[3], and Myobolica, where 600k solutions were generated. Our preliminary results showed that, while Myobolica enabled to identify solutions resulting in higher joint contact loads compared to a neural strategy that minimizes the sum of squared muscle activations (classical Static Optimization approach), the median of the 600k Myobolica solutions never exceeded 4 BW – perfectly in line with previous literature data on healthy subjects. These results seem to suggest that a healthy young adult, although technically able to freely select any neural strategy to perform a simple locomotor task, is likely to select a solution that does not overload his joints. This abstract is presented as work in progress, as we plan to perform the simulations on different motor tasks (e.g., squat) and/or more individuals, possibly including elderly subjects, with the final aim to observe whether the width of the band of possible solutions varies.

References

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Multi-scale modeling approach to determine phrenic nerve activation threshold

Laureen Wegert[1], Alexander Hunold[1,2], Marek Ziolkowski[1], Tim Kalla[1], Irene Lange[1], Jens Haueisen[1]
[1]Institute of Biomedical Engineering and Informatics, Technische Universität Ilmenau, Ilmenau, Germany; [2]neuroConn GmbH, Ilmenau, Germany

Ventilator-induced diaphragmatic dysfunction may occur due to inactivity of the diaphragm during mechanical ventilation. Phrenic nerve stimulation can prevent this complication. Realistic models and electromagnetic simulations can provide valuable estimates about the effects of the stimulation and can be used to select appropriate stimulation parameters. We create a detailed anatomical volume conductor model of the neck and the phrenic nerve using a multi-scale approach. The macro-scale volume conductor model of the neck consists of skin, subcutaneous fat, muscles, bones, intervertebral discs, cartilage, thyroid, esophagus, trachea, internal air, blood vessels, and nerves. Two surface electrodes (10 mm by 10 mm, edge-to-edge distance 25 mm) are placed above the posterior border of the sternocleidomastoid muscle to stimulate the phrenic nerve. The electric potential distribution is calculated via the finite element method with COMSOL Multiphysics. The meso-scale volume conductor model of the phrenic nerve represents the nerve with the three fascicles and is coupled to the macro-scale model via boundary conditions and initial values. The tissue types used are epineurium, endoneurium, and perineurium. The micro-scale nerve model from McIntyre, Richardson, and Grill is used to calculate the activation thresholds of the axon fibers inside the fascicles caused by the extracellular potential using the NEURON toolbox. Fiber diameters used are between 7.3 and 12.8 µm. The stimulation signal is a monophasic pulse with a pulse width of 150 µs. The activation thresholds of the phrenic nerve fibers determined by the multi-scale approach are 23.3 mA, 36.3 mA, and 78.7 mA for the exemplary fiber diameters of 12.8 µm, 10 µm, and 7.3 µm. If the meso-scale volume conductor model of the phrenic nerve is not taken into account, the activation threshold changes by 9-23 %, depending on the examined fiber diameter. Larger differences are observed for the smaller fiber diameters. A detailed multi-scale model is provided to investigate the activation threshold of the phrenic nerve due to non-invasive electrical stimulation and can be used to investigate different stimulation signals.

2.H: Computational Knee Biomechanics: Domain-Specific M&S Resources and Translation

Wednesday, September 4

1:00pm - 2:30pm

07.017

Open Knee(s): Computational Knee Biomechanics Resource Growth and Utilization

Ahmet Erdemir, Snehal Chokhandre
Computational Biomodeling (CoBi) Core and Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic

Open Knee(s) is a free and open source modeling and simulation (M&S) project for virtual knee cohorts and related assets (DOI: 10.1007/s10439-022-03074-0). Dissemination strategy of Open Knee(s) encapsulates the whole lifecycle of the M&S workflow including deep in vitro data sets (knee-specific imaging - multi-sequence MRI; knee-specific joint mechanics - laxity and combined loading), derivative data towards virtual representations (tissue geometries and meshes), models of the whole joint for finite element analysis, and workflow specifications. At the moment, Open Knee(s) achieved FAIR dissemination of data and models for 8 knees to support virtual experiments, i.e., for knee biomechanics studies, evaluation of surgical techniques and/or implants, and training. The goal of this study is to describe our roadmap to augment Open Knee(s) resources and harmonize with additional datasets. We will also demonstrate the utility of this resource for technology development. Recently, we have invented Kneeformatics to deliver knee-specific movement capacity and signature directly by processing anatomy and tissue quality obtained from static clinical imaging data such as MRI or CT (patent pending –US App. No. 18226698, International App. No. PCT/US23/28729). Markers such as "movement capacity" (how much a knee can move) and "movement signature" (how the joint actually moves), could improve diagnosis, risk assessment, and planning of individualized treatments. Prototyping strategies to obtain such markers from clinical imaging and evaluating them against measured knee behavior require knee-specific imaging and joint movement data, a need that Open Knee(s) has successfully fulfilled. Our efforts and roadmap will result in diversity and quantity of resources provided through Open Knee(s) cohort, which will lead towards meaningful virtual experiments and in silico trials as demonstrated for development and evaluation of Kneeformatics.

KNEEHUB: Implementation of the Delphi method to achieve consensus in the modeling and simulation processes and credibility activities in the knee

Jason Halloran[1], Snehal Chokhandre[2], Peter Laz[3], Thor Besier[4], Carl Imhauser[5], Kevin Shelburne[3], Ahmet Erdemir[2]
[1]Washington State University, United States of America; [2]Cleveland Clinic, United States of America; [3]University of Denver, United States of America; [4]University of Auckland, New Zealand; [5]Hospital for Special Surgery, United States of America

Modeling of the knee and other joints requires the execution of many modeling tasks, which we have found to lead to variable predictions even when the source data and model intent are controlled [1]. This impacts the reproducibility and credibility of modeling. The purpose of this abstract is to describe our approach to address this shortcoming through the implementation of a Delphi method to establish consensus on processes that define the modeling and simulation workflows. While numerous approaches are available, formal consensus methods such as the Delphi method minimize bias by promoting inclusiveness across the community of stakeholders. Therefore, it provides a structure to combine evidence-based science with expert opinion. It does not require face-to-face meetings, is highly structured, and when properly organized, a high degree of completion can be achieved. Another benefit is the maintenance of anonymity while also allowing iterative feedback to arrive at a statistically measured group response. Our Delphi-based roadmap to achieve consensus in knee modeling is broken down into the following two phases: 1) define two contexts of use and 2) define the context-dependent modeling processes credibility activities. Within each context of use, workflows are influenced by available data, computational resources and subject variability. A panel of experts has been formed to review and prioritize the contexts of use (phase 1) and modeling processes and credibility activities (phase 2). After determination of the two priority contexts of use, the team will design questionnaires to define the modeling processes within each context-dependent workflow that require consensus. Consensus will be achieved by engaging, through an iterative survey-based portal, with the panel of experts. This will include the corresponding credibility activities. Group responses will be analyzed, and further group feedback will be requested until consensus is achieved, as per the Delphi process. The outcome from each round will result in a consensus document for each context of use, which will be published and disseminated to the wider community.

[1] https://simtk.org/projects/kneehub

Toward an accurate digital twin: In vivo model calibration

Thor E. Andreassen, Peter J. Laz, Casey A. Myers, Kevin B. Shelburne
Mechanical and Materials Engineering, University of Denver, United States of America

Human Digital Twins are set to become an integral part of healthcare, including orthopaedics. Yet a challenge for many proposed *in vivo* workflows is the accuracy of the computational model representing the tissues and the personalized material properties with limited data. Most models are calibrated with experimental *in vitro* data that is not possible for *in vivo* subjects. Accordingly, the objective of this work was to develop and demonstrate a novel approach to calibration of a knee model for a healthy living subject. Full-length and knee-specific MRI scans were taken of the lower extremity of a subject (Female, Age=57, BMI=22.6). Segmentation of bones and soft-tissue structures was performed. The subject's movement was measured with high-speed stereo radiography, electromyography, force-plates, load cells, and marker-based motion capture during a series of tasks. Custom devices were used to measure the knee laxity and maximal voluntary contractions of the subject. A subject-specific finite element model was developed in Abaqus Explicit. Ligament geometries were modelled as non-linear tension-only springs with attachment sites rapidly generated from a combination of morphing and Monte Carlo (MC) based techniques. A second MC analysis was used to narrow the possible ranges of material properties for each ligament. Final calibration optimized ligament material properties to match experimental measures of knee laxity and positions of the knee at selected flexion angles. Validation was performed by comparing model predictions of passive knee flexion to experimental measurements. The model accurately predicted passive knee flexion of the subject with root-mean squared errors of less than 2.5 mm for anterior-posterior and 1.5 degrees for internal-external and varus-valgus. This work shows that personalized models developed from *in vivo* data collections can create models with accuracy similar to those from *in vitro* data. Lastly, the efficiency of using the morphing and MC methods make this a viable workflow for creating accurate Digital Twins.

Multi-scale modeling for in silico prediction of patient-specific risk of cartilage degeneration: Insights from a prospective follow-up study in patients with knee OA

Seyed Ali Elahi, Bryce Killen, Yixuan Zhang, Miel Willems, Ikram Mohout, Sabine Verschueren, Frank Luyten, Ilse Jonkers
KU Leuven, Belgium

Knee osteoarthritis (OA) is a major cause of disability, marked by cartilage degeneration. The patient-specific mechanisms of OA progression remain largely unclear. While previous studies suggest that abnormal joint loading is critical in OA initiation and progression, more evidence is needed to confirm the role of mechanical loading in OA progression. This study uses a multi-scale in silico modeling approach to predict patient-specific cartilage degeneration observed during a 4-year follow-up study on a knee OA and healthy control cohort. 3D motion capture data during gait was collected from subjects with medial knee OA at baseline and after 4 years. Musculoskeletal and dynamic simulation workflows estimated contact pressure on the medial tibial cartilage, used as inputs for finite element (FE) cartilage models. These models, built using a fibril-reinforced poro-visco-elastic swelling material, estimated cartilage strains over the thickness. Our Cartilage Adaptive REorientation Degeneration (CARED) model then predicted collagen fibril degradation and reorientation, proteoglycan depletion, and tissue hydration changes using an iterative algorithm. Subjects were categorized into progressor (N=10), non-progressor (N=10), and healthy control (N=10) groups based on radiographic Kellgren Lawrence score changes after 4 years. Our results provide 3D patient-specific insights into the location and magnitude of degradative changes in the cartilage constituents: higher cartilage constituent degradation was confirmed in progressors than non-progressors, mainly affecting the medial compartment's posterior aspect. Minimal changes in cartilage composition were observed in control subjects. Our multi-scale in silico model provides unique insights into subject-specific, 3D progression of degenerative changes in cartilage constituents, enabling prediction of subjects at risk of progressive cartilage degeneration, even based on baseline gait data. In the future, integrating this in silico framework with probabilistic modeling approaches could facilitate the definition of digital twins for earlier disease progression diagnosis, aiding in the development of more effective treatments.

Distinct knee pathomechanics of females compared to males: A population-based in-silico analysis

Carl Imhauser[3], Mitchell Wheatley[3], Mark Amirtharaj[1], David Shamritsky[3], Andrew Pechstein[3], Jacob Zeitlin[3], Jacob Hirth[3], Danyal Nawabi[1], Thomas Wickiewicz[1], Bruce Beynnon[2], Andrew Pearle[1]
[1]Sports Medicine Institute, Hospital for Special Surgery; [2]Larner College of Medicine, University of Vermont; [3]Biomechanics Department, Hospital for Special Surgery

INTRODUCTION: Young, female athletes are disparately vulnerable to first-time, noncontact anterior cruciate ligament (ACL) rupture compared to males [1]. Unfortunately, knee mechanics in young males and females remains poorly understood. In vivo measurement of knee mechanics, such as ACL force, is difficult to accomplish. Thus, we developed a rapidly implementable, computational modeling pipeline and leveraged a unique clinical data set of male and female high school and collegiate athletes to investigate sex-specific knee biomechanics. We asked the following question: Do in silico estimates of ACL force differ between females and males when their knees are subjected to multiplanar loads, which are known to stress the ACL? **METHODS:** MRI data of high school and collegiate athletes consisting of 60 female (Age: 17.1 ± 2.3 years) and 24 male (Age: 18.0 ± 2.5 years) matched pairs of cases who suffered first-time noncontact ACL injury and uninjured controls matched by age, sex, and team were obtained under IRB approval [2]. We then employed our computational modeling pipeline to these MRI data [3]. Loads were applied to the tibia in series and consisted of compression (100 N), then a valgus moment (8 Nm), and finally an anterior force (30 N) (ADAMS, Hexagon, Inc.). ACL force was estimated at the peak applied loads. Unpaired t-tests were used to identify differences in ACL force between male and female cohorts and between ACL-injured and uninjured females ($\alpha = 0.05$). **RESULTS:** Female knees exhibited 35% greater ACL force than male knees (28.4 N, $p < 0.001$). ACL-injured females exhibited 26% greater ACL force than uninjured females (24.9 ± 55 N, $p < 0.001$). **DISCUSSION:** Our rapidly implementable computational modeling pipeline revealed stark differences in the mechanics of the male and female knee. Since ligament properties were standardized, knee geometries likely contribute to these differences. Our findings can inform sex-specific, mechanics-based injury screening tools. **REFERENCES:** [1] Beynnon 2014 AJSM. [2] Vacek 2016 AJSM. [3] Kia 2016 J Biomech Eng.
ACKNOWLEDGEMENTS: Steers and Gosnell Families, Clark and Kirby Foundations, R21AR073388, R01AR050421

2.I: Cancer Modelling I

Wednesday, September 4

1:00pm - 2:30pm

08.019

Digital twins for oncology and patient-specific simulations: Importance of vascularization

Diego Sainz-DeMena, Silvia Hervas-Raluy, Ángela Pérez-Benito, Maria Jose Gomez-Benito, José Manuel García-Aznar, María Ángeles Pérez
Department of Mechanical Engineering, Aragon Institute for Engineering Research (I3A), University of Zaragoza, Zaragoza, Spain

Cancer is a major global health challenge that requires the development of innovative tools to improve our understanding and treatment of the disease. Patient-specific modeling stands as one of the key techniques in this quest. The field of *in silico* medicine holds great promise for predicting patient-specific cancer progression, treatment response and overall prognosis. Over the last years, our research group has focused on the development of patient-specific models to predict the prognosis and treatment efficacy of different types of solid tumors. These models describe the biological processes that drive tumor progression through a set of mathematical equations applied on different temporal and spatial scales. To apply these models to clinical cases, we must first feed them with patient-specific data. These data come mainly from clinical images, specifically MR sequences. The tumor geometry is obtained from the segmentation of the lesion. Next, cellularity and vascularization data are extracted from diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) sequences, respectively. Vascularization plays a key role not only in cancer progression, but also in the efficacy of chemotherapy treatments. A quantitative description of this variable can be obtained by fitting pharmacokinetic (PK) models to DCE sequences. To overcome the limitations of conventional models, we have focused on developing new PK models that increase their precision and range of application. These models have been applied to both Neuroblastoma and prostate cancer, where chemotherapy is commonly applied. The good results obtained show the potential of these models to be included in clinical practice.

Ackowledgements

This work is part of the project PLEC2021-007709 (ProCanAid), funded by MCIN/AEI/10.13039/501100011033/ and by the European Union NextGenerationEU/PRT and in collaboration with IISLAFE and QUIBIM. Authors acknowledge the Aragon Government (T50_23R).

Digital twin of prostate cancer tumour growth: A multiphysics approach

Ángela Pérez-Benito, María José Gómez-Benito, José Manuel García-Aznar, María Ángeles Pérez
Universidad de Zaragoza, Spain

Prostate cancer (PCa) is a major European health concern. Current diagnostic methods involve prostate specific antigen (PSA) blood tests, biopsies, and Magnetic Resonance Imaging (MRI) to assess cancer aggressiveness and guide treatment decisions. MRI aligns with *in silico* medicine, as patient-specific image biomarkers can be obtained, contributing towards the development of digital twins for clinical practice. This work presents a novel framework to create a personalized PCa model by integrating clinical MRI data, such as the prostate and tumour geometry, the initial distribution of cells and the vasculature, so a full representation of the whole prostate is obtained. On top of the personalized model construction, our approach simulates and predict temporal tumour progression in the prostate through the Finite Element method, coupling the dynamics of tumour growth and the mechano-transport of oxygen, and incorporating cellular processes such as proliferation, differentiation, and apoptosis. In addition, our approach includes the simulation of the PSA dynamics, which allows to evaluate tumour progression through the PSA patient's levels. This framework is validated by means of data from two patients with several MRI follow-ups. The diagnosis MRI allows the model creation and initialization, while subsequent MRI-based data provide additional information to validate computational predictions. The model predicts prostate and tumour volumes evolution, along with serum PSA levels. Broadly, the simulations offer valuable clinical insights into tumour growth and cancer aggressiveness. This work is a novel contribution to the creation of digital twins for prostate cancer patients, providing personalized insights into disease dynamics. Future goals involve integrating diverse cancer treatments into the digital twin to create a personalized tool for clinical decision-making. This work is part of the project PLEC2021-007709 (ProCanAid), funded by MCIN/AEI/10.13039/501100011033/ and by the European Union NextGenerationEU/PRT and in collaboration with IISLAFE and QUIBIM. Authors acknowledge the Aragon Government (T50_23R).

Multiphasic modelling and patient-specific simulation of tumours in soft tissue with OncoFEM

Marlon Suditsch[1], Tim Ricken[1], Arndt Wagner[2]
[1]Institute of Structural Mechanics and Dynamics, in Aerospace Engineering, University of Stuttgart, Germany; [2]Institute of Applied Mechanics (CE), University of Stuttgart, Germany

In critical tissue areas such as in the brain, additional chemo- and radiation therapy is essential in conjunction with resection of a tumour or remains as the only possible form of a therapy at all. In this regard, the decision on a suitable form of therapy is extremely challenging. The presented simulation tool OncoFEM aims to support clinicians in a decision-making process by combining data- and knowledge-driven approaches and predicting a tumor evolution from inputs of imaging techniques such as magnetic resonance imaging. The position of the tumour and relevant information on the microstructural composition of the healthy tissue are identified with different machine learning tools, such as convolutional neural networks. Prepared referential states are simulated with the relevant processes by embedding a continuum-mechanical, multi-phasic model in the framework of the Theory of Porous Media, cf. Wagner [1]. Based on Wolf et al. [2], the tumour is divided into its necrotic and active solid core, which is enclosed by an edema in the surrounding tissue, that consists of an extracellular matrix and interstitial fluid. The latter includes additive components, e.g. glucose, growth factors or an applied therapeutic agent. In addition to the basic effects of diffusive spreading and the mass effect, actual situations from the tumour's emergence growing up to the pre-operative state, its resection and the application of a drug can be simulated with a well parametrised model. Relevant clinical questions can be studied from multi-scientific perspectives by consideration of multiple solids and fluid-resolved additive components.

1 A. Wagner. Continuum mechanics of multicomponent materials: modelling, numerics and applications for biological materials in the framework of the theory of porous media. Habilitation. University of Stuttgart (2021)

2 K. J. Wolf et al.. Dissecting and rebuilding the glioblastoma microenvironment with engineered materials. Nature Reviews Materials (2019) 10: 615-668

Modeling hypoxia-induced radiation resistance and the impact of radiation sources

Luca Possenti[1], Piermario Vitullo[2], Alessandro Cicchetti[1], Paolo Zunino[2], Tiziana Rancati[1]
[1]Data Science Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Italy; [2]MOX, Department of Mathematics, Politecnico di Milano, Italy

Radiotherapy is a common treatment for cancer, used to treat more than half of patients. Despite significant advances, cancer control continues to grapple with the complexities arising from both intratumor and intertumor heterogeneity. Central to these challenges is the interaction between oxygenation and radiation therapy, which also involves possible heterogeneity in tumor oxygenation. Knowing that hypoxia contributes significantly to resistance in radiotherapy, this work rigorously examines the influence of microvascular morphology on radiotherapy outcome, specifically focusing on how microvasculature shapes hypoxia within the microenvironment and affects resistance to a standard treatment regimen. Leveraging on advanced multiphysics approaches, which encompass vascular and interstitial flow, red blood cell transport, oxygen transport, and allow mesoscale analysis of the vascular microenvironment, we address here a computational model that extends to the effects of different radiation sources, such as photons, protons and heavy ions. Within this framework, our objective is to analyze the effect of microvasculature on radiation therapy using the proposed state-of-the-art computational model. For photons and protons, our analysis establishes a clear correlation between hypoxic volume distribution and treatment effectiveness, with vascular density and regularity playing a crucial role in treatment success. On the contrary, heavy (carbon) ions exhibit distinct effectiveness, even in areas of intense hypoxia and poor vascularization. This finding points to the potential of carbon-based hadron therapy in overcoming hypoxia-induced resistance to RT. Considering that the spatial scale analyzed in this study is closely aligned with that of imaging data voxels, we also address the implications of these findings in a clinical context envisioning the possibility of detecting subvoxel hypoxia and assessing its effect on treatment outcomes.

Efficient radial-shell model for 3D tumor spheroid dynamics with radiotherapy

Florian Franke[1], Sona Michlikova[2,3], Sebastian Aland[1,4,5], Leoni Kunz-Schughart[2,6], Anja Voss-Böhme[1], Steffen Lange[1,2]

[1]Faculty of Informatics/Mathematics, HTW Dresden - University of Applied Sciences (HTWD), Germany; [2]OncoRay - National Center for Radiation Research in Oncology, Technische Universität Dresden; [3]Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology—OncoRay, Germany; [4]Faculty of Mathematics and Computer Science, TU Freiberg, Germany; [5]Center for Systems Biology Dresden (CSBD), Germany; [6]National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany

Understanding the complex dynamics of tumor growth is one of the most challenging problems in biomedicine. Three-dimensional (3D) tumor spheroids, reflecting avascular microregions within a tumor, are an advanced in vitro model system to assess the curative effect of combinatorial radio(chemo)therapy. Tumor spheroids exhibit particular crucial pathophysiological characteristics such as a radial oxygen gradient that critically affect the sensitivity of the malignant cell population to treatment. However, spheroid experiments remain laborious, and determining long-term radio(chemo)therapy outcomes is challenging. Mathematical models of spheroid dynamics have the potential to enhance the informative value of experimental data, and can support study design; however, they typically face one of two limitations: while non-spatial models are computationally cheap, they lack the spatial resolution to predict oxygen-dependent radioresponse, whereas models that describe spatial cell dynamics are computationally expensive and often heavily parameterized, impeding the required calibration to experimental data. Here, we present an effectively one-dimensional mathematical model based on the cell dynamics within and across radial spheres which fully incorporates the 3D dynamics of tumor spheroids by exploiting their approximate rotational symmetry. We demonstrate that this radial-shell (RS) model reproduces experimental spheroid growth curves of several cell lines with and without radiotherapy, showing equal or better performance than published models such as 3D agent-based models. Notably, the RS model is sufficiently efficient to enable multi-parametric optimization within previously reported and/or physiologically reasonable ranges based on experimental data. Analysis of the model reveals that the characteristic change of dynamics observed in experiments at small spheroid volume originates from the spatial scale of cell interactions. Based on the calibrated parameters, we predict the spheroid volumes at which this behavior should be observable. Finally, we demonstrate how the generic parameterization of the model allows direct parameter transfer to 3D cell-based models.

3.A: Cardiovascular Digital Twins

Wednesday, September 4

3:30pm – 5:00pm

05.019

Towards a realistic digital twins of coronary artery disease: Is a fluid-structure interaction simulations necessary?

Vittorio Lissoni, Marco Stefanati, Gabriele Dubini, Jose Felix Rodriguez Matas, Giulia Luraghi, Francesco Migliavacca
Department of Chemistry, Materials and Chemical Engineering, Politecnico di Milano, Italy

Computational simulations have emerged as a valuable tool to investigate coronary artery disease (CAD). Structural (FEA) and computational fluid-dynamic (CFD) simulations have been used to investigate, respectively, the risk of plaque rupture, through plaque structural stress and arterial shear stress and the risk of infarction, through the calculation of fractional flow reserve. Only a few studies in the literature investigated pathological conditions through fluid-structure (FSI) interaction models. This work describes a methodology to assess CAD by calculating patient-specific coronaries blood flow with FSI simulations. Coronary models accounting for the main epicardial branches and plaque elements were segmented using Medis Medical Imaging Systems B.V. from patient-specific images and then meshed using BETA CAE Systems ANSA. To account for the arterial pre-stress, the zero-pressure configuration was loaded up to diastolic condition in the first simulated cardiac cycle. Simulations were implemented with an ALE, strong and two-way coupling method using the commercial finite element solver Ansys LS-DYNA. Physiological aortic pressure curve was prescribed at the inlet of each coronary, while a five-elements lumped parameter model retrieved from the literature was used to simulate the distal microvasculature behaviour. The resulting pressure/flow rate curves were compared against the theoretical ones retrieved from the literature (maximum flow error in the peak flow instant of 4.2%). Our initial results indicate accurate quantification of both structural and fluid dynamic results. The highest stress values were found in the calcium plaque elements with peak first principal stress of 0.9 MPa in systole for the first left coronary vessel investigated. Shear stress values on the coronaric lumen are consistent with the ones found in a similar work with an average value of 3.0 Pa. This methodology quantifies blood flow in patient-specific diseased coronary vessels. Comparing results with standalone CFD or FEA suggests FSI implementation for accurate CAD risk assessment. This study is being carried out within the MUSA project, NRRP Mission 4 Component 2 Investment Line 1.5

New perspectives on global sensitivity analysis for the creation of cardiovascular digital twins

Harry Saxton[1], Xu Xu[2], Torsten Schenkel[3], Ian Halliday[4]
[1]Materials & Engineering Research Institute, Sheffield Hallam University, Sheffield, United Kingdom; [2]Department of Computer Science, University of Sheffield, Sheffield; [3]Department of Engineering and Mathematics Sheffield Hallam University Sheffield, S1 1WB; [4]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom

The primary aim of this study is to assess the efficacy of examining physiologically relevant measurements during global sensitivity analysis (GSA) within the context of creating a virtual representation of a patient's cardiovascular health, commonly termed a digital twin (DT). Understanding and quantifying the inevitable uncertainty inherent within a DT is a necessary part of the process of identifying clinical biomarkers characterising a particular patient's cardiovascular well-being. Traditionally, during GSA, clinical biomarkers are varied across the assumed physiological range, to determine their respective impacts, on selected clinical outputs. Using a single ventricle model of the systemic circulation, we select typical clinical outputs and confine model inputs to what we assume, a priori is a healthy range, then proceed address the quantification of uncertainty in our simple cardiovascular digital twin. We then address deceptively simple question. What is the effect upon filtered model output metrics, of changing /screening the healthy range? We present data obtained by restricting model outputs to a healthy range; our results illustrate how failing to confine outputs to clinically relevant ranges may inadvertently lead to the quantification of effects of clinical biomarkers contributing to physiological states outside the scope of interest. Consequently, our findings are poised to introduce a novel methodological approach to quantifying uncertainty within cardiovascular digital twins, thereby enhancing their clinical utility and reliability.

Digital-twin based assessment of atrial arrhythmias: Influence of anatomical and functional personalization strategies

Patricia Martínez Díaz[1], Jorge Sánchez[2], Albert Dasí[3], Christian Götz[1,4], Laura Anna Unger[1,5], Nikola André Fitzen[1], Annika Haas[5], Ursula Ravens[6], Armin Luik[5], Olaf Dössel[1], Axel Loewe[1]

[1]Institute of Biomedical Engineering, Karlsruhe Institute of Technology (KIT); [2]Institute of Information and Communication Technologies (ITACA), Universitat Politècnica de València (UPV), Valencia, Spain; [3]Department of Computer Science, University of Oxford, Oxford, United Kingdom; [4]Department of Cardiology, University Hospital Heidelberg, Heidelberg Germany; [5]Städtisches Klinikum Karlsruhe, Karlsruhe, Germany; [6]Universitätsklinikum Freiburg, Freiburg, Germany

Introduction: Personalization means translating patient-specific data into model parameters reflecting specific biophysical properties of the individual. Yet, the impact of different personalization approaches, whether anatomical or functional, on the vulnerability to arrhythmia in personalized atrial computer models remains incompletely understood. **Methods:** In a cohort of 8 patient-specific models, we assessed the effect of incorporating the right atrium (RA) on arrhythmia vulnerability across 3 substrate conditions: healthy (H), mild (M), and severe (S). We developed 2 models: a monoatrial comprising only the left atrium (LA) and a biatrial incorporating the RA and LA. In another cohort of 7 patient-specific models, we examined the impact of incorporating effective refractory period (ERP) measurements on arrhythmia vulnerability across 4 configurations: homogeneous (A), heterogeneous (B), regional (C), and continuous (D). The first 2 configurations were non-personalized based on literature data, the latter 2 were personalized based on measurements. **Results:** Incorporating the RA increased the mean LA vulnerability ratio by 115.8% in state M and 29.0% in state S. No arrhythmia was induced in the H models. RA inclusion increased LA inducibility revealing 5.5±3.0 new inducing stimulus points per patient in the LA for the biatrial model, which did not induce reentry in the monoatrial model. ERP scenario A was the least vulnerable to arrhythmia (3.4±3.9%), while scenario C was the most vulnerable (9.0±5.1%). Compared to the standard non-personalized approach (B), incorporating ERP as a continuous distribution (D) decreased the vulnerability slightly (7.6±3.4% vs. 7.0±3.6%). **Conclusions:** LA arrhythmia vulnerability in biatrial models is higher than in LA monoatrial models. Incorporating the RA unmasked potential inducing points in the LA. Incorporating patient-specific ERP values impacts the assessment of arrhythmia vulnerability and the type of personalization affects the likelihood of arrhythmia inducibility. Using anatomically and functionally detailed models may enhance the evaluation of substrate vulnerability for patient-specific therapy planning tools.

Advancements in multiphysics and multiscale modeling: Connecting computational cardiology with digital twinning

Luca Dede'
MOX-Mathematics Department, Politecnico di Milano, Italy

Recent advances in computational modeling have significantly enhanced our understanding of the complex interplay of electrophysiological, mechanical, and fluid phenomena in the human heart. Here, we present recent contributions in multiphysics and multiscale modeling in computational cardiology, aiming to unravel the intricate dynamics governing cardiac function. We integrate advanced models encompassing electrophysiology, mechanical activation, passive mechanical response of cardiac muscle, and blood flow dynamics into a unified electro-mechano-fluid model. This model seamlessly couples 3D and 0D models at mathematical and numerical simulation levels. Additionally, we incorporate the coupling of the 3D electromechanical and fluid models with a 0D closed-loop representation of systemic and pulmonary circulations, perfusion dynamics, and torso models, providing a biophysically detailed understanding of cardiac function. To address numerical challenges, we employ the FE method for space approximation of the Partial Differential Equations governing cardiac electromechanics, realized through partitioned-staggered schemes. Through extensive simulations on high-performance computing platforms, we offer insights into cardiac function across various conditions, focusing on clinical problems where our model provides meaningful answers. These simulations deepen theoretical understanding and offer a computational framework for guiding therapeutic interventions. Additionally, we introduce a Scientific Machine Learning approach aimed at real-time simulations of cardiac electromechanics, paving the way for patient-specific digital twins. These digital replicas hold potential in personalized medicine, empowering clinicians with predictive tools for improving patient outcomes. Results from constructing cardiac digital twins demonstrate their utility in informing clinical decisions and enhancing patient care.

Next generation cardiac care: SimCardioTest cloud-based platform

Alessia Baretta[1], Yves Coudière[2], Oscar Camara[3], Beatriz Trenor[4], Hermenegild Arevalo[5], Irene Balelli[6], Romano Setzu[7], Liesbet Geris[8], Sylvain Benito[9], Michele Barbier[6], Maxime Sermesant[6]

[1]InSilicoTrials Technologies, Italy; [2]Universite de Bordeaux, Bordeaux, France; [3]Universidad Pompeu Fabra, Barcelona, Spain; [4]Universitat Politecnica de Valencia, Valencia, Spain; [5]Simula Research Laboratory, Oslo, Norway; [6]Institut National De Recherche En informatique et Automatique, Sophia Antipolis, France; [7]Microport CRM, Clamart, France.; [8]VPH Institute, Leuven, Belgium; [9]Exact Cure, Nice, France

Cardiovascular diseases are the leading cause of death globally, claiming an estimated 18 million lives every year, according to the World Health Organization. While numerous solutions have been proposed to develop safe and effective drugs and devices, finding answers that both streamline clinical trials and provide the necessary data to demonstrate safety and efficacy has been challenging. In silico trials have the potential to transform the current system of clinical trials, reducing costs and accelerating the development process of medical drugs and devices. These trials, utilizing individualized simulations of specific patients and sub-populations, hold promise in reducing, refining, and partially replacing traditional clinical trials. Regulatory bodies are increasingly recognizing the validity of in silico trials, highlighting the need for standardized frameworks to ensure reliability and compliance. SimCardioTest, a project funded by the EU Horizon 2020 R&I programme, brings together partners from across Europe in a collaborative effort to revolutionize cardiac treatment. The project's cornerstone is a standardized cloud-based platform integrating different use cases: pacing leads and catheters, left atrial appendage occluders, and drug cardiac safety and efficacy. The SimCardioTest cloud-based in silico trial platform has been meticulously designed to host and execute trials across all three use cases. The platform features a user-friendly interface, bridging the gap between model development and user interaction. Crucially, the platform safeguards the integrity of original models, preventing unauthorized access or modification. SimCardioTest represents a pioneering effort in standardizing and democratizing in silico trials within the realm of cardiac care. By fostering collaboration, adherence to protocols, and user-friendly accessibility, the project aims to accelerate the adoption of in silico methodologies, ultimately enhancing the efficacy and efficiency of cardiac treatment evaluation.

Acknowledgements

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Uncertainty estimation in patient-specific cardiovascular models: The effect of sources of errors in 4D flow MRI and blood pressure

Kajsa Tunedal[1,2], Tino Ebbers[2,3], Gunnar Cedersund[1,2]
[1]Department of Biomedical Engineering, Linköping University, Linköping, Sweden; [2]Center for Medical Image Science and Visualization (CMIV), Linköping University, Linköping, Sweden; [3]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

Mechanistic models can provide new insights into both physiological and pathological cardiovascular mechanisms of blood flow and blood pressure – but only if we can trust the model predictions. To utilize the potential of patient-specific cardiovascular models, the uncertainty of model predictions needs to be determined. When finding the model uncertainty, a crucial aspect is comparison to hemodynamic data. Common methods for uncertainty quantification such as global sensitivity analysis and uncertainty quantification are useful to determine the effect of individual parameters on the model output, and many guides for applying this to cardiovascular models are available. However, to estimate the parameter distribution accurately and to provide confidence intervals for model predictions, one needs to consider the data and its uncertainty. Here, we use parametric bootstrapping to investigate if the parameter estimation-based profile likelihood method can produce accurate confidence intervals also to cardiovascular models based on patient-specific hemodynamic data with systematic errors. First, the uncertainty of the data used to personalize the model was estimated, where the resulting errors in 4D flow MRI-derived stroke volumes were around 5-20% and the errors in blood pressure were 0+-8 mmHg. Secondly, the model uncertainty was estimated with profile likelihood for 100 simulated datasets sampled from the estimated data uncertainty. The true parameter values were found within a 95% confidence interval in 98% of the cases – showing that correct intervals can be found despite the simplified statistic assumptions. The same method can be applied also to model predictions, providing data-based confidence intervals for model predictions. A thoroughly determined model uncertainty allows for more reliable model-based conclusions on patient-specific cardiovascular function, providing the basis for model validation and model credibility assessment which are needed to take the patient-specific cardiovascular models to a clinical setting.

3.B: Vascular (Re)Modelling

Wednesday, September 4

3:30pm – 5:00pm

02.017

Branching exponents of synthetic vascular trees under different optimality principles

Etienne Jessen[1], Marc C. Steinbach[2], Charlotte Debbaut[3], Dominik Schillinger[1]
[1]Technical University of Darmstadt, Germany; [2]Leibniz University Hannover, Germany; [3]Ghent University, Belgium

The cardiovascular system is responsible for transporting blood to and from all cells in the human body, leading to hierarchical networks of vessels inside many organs. According to Murray, this hierarchy obeys scaling relations based on the minimization of the total energy expenditure of the system. His observation resulted in Murray's law that establishes a relationship between the radius of a parent vessel and the radii of its children vessels as a power law, parametrized by a branching exponent. In this talk, we investigate the validity of Murray's law using synthetic vascular trees generated computationally under global optimization criteria. To this end, we first develop a synthetic tree model that does not incorporate Murray's law explicitly. We then investigate the effects of different physical constraints and optimization goals on the branching exponent that is now allowed to vary locally per junction. In particular, we include variable blood viscosity due to the Fåhræus–Lindqvist effect and enforce an equal pressure drop between inflow and the micro-circulation. Using our global optimization framework, we generate vascular trees with over one million terminal vessels and compare them against a detailed corrosion cast of the portal venous tree of a human liver. We show that Murray's law is fulfilled when no additional constraints are enforced, indicating its validity in this setting. Variable blood viscosity or equal pressure drop lead to different optima, but the branching exponent remains within the experimentally predicted range of 2.0 and 3.0. The validation against the corrosion cast shows good agreement from the portal vein down to the venules. Based on these results, we argue that not enforcing Murray's law increases the predictive capabilities of synthetic vascular trees, and in addition reduces the computational cost. In addition, we argue that the ability to study optimal branching exponents across different scales can improve the functional assessment of organs.

Generation of organ-scale synthetic vasculature using mathematical optimization

Etienne Jessen[1], Marc C. Steinbach[2], Dominik Schillinger[1]
[1]TU Darmstadt, Germany; [2]Leibniz University Hannover, Germany

The functional assessment of organs is essential for increasing the success of treatment strategies. Detailed information on the organ's vasculature could critically improve this assessment. Extending our previous work [1,2], we introduce a new framework to generate the complete vasculature of an organ synthetically. Our main contribution is the formulation of a nonlinear optimization problem (NLP) with super-linear time complexity. We further show how the problem of multiple, non-intersecting trees inside a non-convex perfusion domain can be naturally included into NLP. We compare our results against benchmarks for multiple anatomic regions of brain tissue and show that our framework outperforms current state-of-the-art algorithms [3] by an order of magnitude. Furthermore, we generate the complete liver vasculature with over five million vessels and compare them against measurements from the literature [4].

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Modelling growth, remodelling and damage of arterial tissue: Application to cerebral vasospasm

Giulia Pederzani[1], Anne M. Robertson[2], Alfons G. Hoekstra[1], Paul N. Watton[2,3,4]
[1]Computational Science Lab, Informatics Institute, University of Amsterdam, Netherlands; [2]Department of Mechanical Engineering and Materials Science, University of Pittsburgh, USA; [3]Department of Computer Science, University of Sheffield, UK; [4]INSIGNEO Institute for in silico Medicine, University of Sheffield, UK

Cerebral vasospasm (CVS) is a prolonged constriction of a cerebral artery which can impair the blood supply to the brain. It is usually addressed first pharmacologically via vasodilators, and if these fail, via balloon angioplasty. In 2017 the successful use of stent-retrievers challenged the understanding of the disease due to the lower forces applied, but represented a potential safer treatment [1]. We propose a computational model of cerebral vasospasm to gain insight into the underlying processes. We model the artery as a nonlinear elastic cylinder using a constrained mixture approach that explicitly accounts for load bearing, remodelling and damage of individual constituents [2]. The central hypothesis is that, following an initial chemically driven contraction of the vascular smooth muscle cells (VSMCs), they undergo a remodelling process to adapt to the reduced diameter. Assuming that mechanical treatment is successful when VSMCs are stretched beyond a failure threshold, we use experimental data on the force exerted by stent-retrievers to compare three models that evaluate their effectiveness: (1) a 1D membrane model, (2) a 3D finite element (FE) model with internal pressure increase, and (3) a 3D FE model with explicit stent deployment. The models describe the mechanical response of an artery in health, vasospasm and following VSMC damage. They predict that stent-retrievers are generally successful in smaller arteries (<3mm) but fail in larger ones and in general the necessary pressure is an order of magnitude smaller than balloon angioplasty. The predictions are consistent with clinical observations [1] and support the use of stent-retrievers in some cases with significant clinical benefits. The result that a much lower pressure is sufficient to resolve CVS promotes the design of dedicated stents for larger arteries.

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Acknowledgements:
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Computational modelling of coupled shear-induced NO signalling pathways in endothelial and smooth muscle cells of arterial walls

Fariba Bahadori, Merryn Tawhai, Alys Clark
University of Auckland, New Zealand

Blood flow induces shear stress, causing morphological and biochemical changes in the arterial wall through the endothelial cell (EC) and smooth muscle cell (SMC) layers, crucial for regulating vascular tone and overall vascular health. ECs and SMCs work together and have interconnected roles in modulating arterial function through factors such as nitric oxide (NO). We are developing a computational model to provide insights into the complexity underlying arterial behaviour by considering the interplay between EC and SMC during SMC contraction, particularly in response to shear stress. The SMC is modelled, including three main components, each tailored to address specific aspects of cell behaviour: actin-myosin cycling, the intracellular Ca2+, and NO signalling pathways. The EC is modelled to capture the process of transforming the biomechanical force of shear stress into biochemical responses through NO. The SMC model is coupled with the EC model to predict cellular force generation in response to various levels of shear stress. The model comprises 28 ordinary differential equations and is implemented in CellML. Results of NO concentration variability obtained from EC components of our models compared well with experimental data, including that used in prior isolated EC models, describing shear-induced NO across shear stress levels and time frames. Stress levels obtained from our SMC model components compared well with predicted data from previous SMC models that incorporate actin-myosin cycling and force generation. Our results demonstrate the potential of in-silico modelling to predict cellular responses to local biomechanical stimuli in the arteries, such as shear stress, by dynamically tracking the exchange between biomechanical and biochemical processes within the layers of the arterial wall. In the future, we aim to be able to scale these cell-level models to describe arterial function in response to shear stress in complex vascular systems.

Do the clot mechanical properties affect the thrombectomy procedures? An in silico study

Virginia Fregona[1], Behrooz Fereidoonnezhad[2], Frank JH Gijsen[2,3], Jose Felix Rodriguez Matas[1], Francesco Migliavacca[1], Giulia Luraghi[1,2]
[1]Department of Chemistry, Materials and Chemical Engineering 'Giulio Natta', Politecnico di Milano, Italy; [2]Department of Biomechanical Engineering, Delft University of Technology, Delft, The Netherlands; [3]Department of Biomedical Engineering, Erasmus MC, Rotterdam, The Netherlands

Endovascular thrombectomy (EVT) with stent-retriever is a minimally invasive treatment for acute ischemic stroke, aiming at removing a clot from a large cerebral vessel. After being navigated up to the occlusion site crimped in a microcatheter, the stent-retriever is deployed, and the stent with the captured clot is retrieved. Literature suggests that clots are formed mainly by red blood cells (RBCs), platelets, and fibrin, in variable percentages among patients. Fibrin-rich clots may be more difficult retrieve while RBC-rich clots may be more prone to fragmentation. Here, after the development of a material model for clots of different compositions, finite-element simulations of the EVT are performed varying the clot composition. With a methodology validated through the comparison with in vitro experiments, the entire EVT procedure with stent-retriever was replicated in silico in Ansys LS-DYNA. An ideal cerebral vasculature anatomy is created taking the average values of the morphological features reported in and modelled as a rigid shell. A clot of 13.5 mm of length is positioned in the distal M1. The clot is modelled as a hyperelastic foam exploiting the experimental uniaxial stress-strain curves in compression and tension. Three different clot compositions are considered (0%, 1% and 40% RBCs). For each composition three simulations are run changing the design of the stent-retriever. Preliminary data show that the clot composition and the device design have an impact on the in silico EVT outcome, in terms on success of the retrieval. EVTs performed on identical clot but with different stent-retriever design do present different outcomes, as for EVTs performed with the same device and different clots. In some cases, indeed, the clot is lost during the retrieval or fragmented. As expected, fragmentation is more likely to happen for the RBCs-rich clots (here, 40% RBCs). Having the clot a central role in the procedure, knowing its mechanical properties and its interaction with different devices is crucial to improve the selection of retrieval devices and intervention strategies. This project has received funding from the EU Horizon under grant agreement No 101136438.

3.C: M&S Resources, Infrastructure, and Operationalization

Wednesday, September 4

3:30pm – 5:00pm

07.017

Harmonising historic clinical gait datasets using image-based musculoskeletal models

Thor Besier[1], Laura Carman[1], Julie Choisne[1], Elyse Passmore[2], Luca Modenese[3], Chris Carty[4]
[1]University of Auckland, Auckland, New Zealand; [2]Royal Childrens Hospital, Melbourne, Australia; [3]University of New South Wales, Sydney, Australia; [4]Griffith University, Brisbane, Australia

Clinical gait analysis is an important tool for planning paediatric orthopaedic surgery. However, the evidence supporting surgical interventions is sparse, as orthopaedic treatments cannot be tested in randomised controlled trials. Analysis of historic gait and clinical data using causal inference modelling has the potential to identify the best orthopaedic treatments and the optimal timing of those interventions [1]. Such data-driven approaches rely upon large datasets and would benefit from the combination of data across multiple sites. However, these data currently cannot be compared, as clinical gait laboratories use different hardware, markersets, processes, and models to produce their kinematic and kinetic output data. We present a new initiative to create a research platform and data linkage for multicentre benchmarking for clinical gait analysis data across Australia and New Zealand. Our approach is to harmonise kinematic and kinetic gait data from a combined database of >6,000 clinical assessments of 4,000 individuals over a 10-year period. To achieve this, we have developed a musculoskeletal modelling workflow that uses statistical shape modelling to predict lower limb bone morphology from sparse anatomical landmarks [2]. Our shape model scaling can produce reproducible kinematic data that is agnostic to the marker set and marker placement [3] and is capable of fitting to medical imaging-data where available. The workflow re-processes raw marker and ground reaction force data, providing consistent signal processing and model outputs. A client-side application will be provided to each centre for automated throughput of data, which will be de-identified and deployed to the Australian Research Data Commons (ARDC) Nectar Research Cloud. Translation of the project outcomes into clinical practice will be enabled by each hospital's partnership on the Australia-New Zealand Clinical Motion Analysis Group.

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An in silico world: Resources to accelerate the adoption of in silico trials

Marco Viceconti[1], Alfons Hoekstra[2], Frans de Vosse[3], Francesco Pappalardo[4], Liesbet Geris[5], Marian Bubak[6], Jos Vander Sloten[7], Vincenzo Carbone[8], Elisabetta Biasin[9]
[1]Alma Mater Studiorum - University of Bologna, Italy; [2]Computational Science Lab – University of Amsterdam, the Netherlands; [3]Technical University of Eindhoven, Department of Biomedical Engineering, Netherlands; [4]Department of Drug and Health Sciences, University of Catania, Italy; [5]University of Liège, KU Leuven, VPH institute, Belgium; [6]Sano Centre for Computational Medicine: Krakow, Poland; [7]KU Leuven – Mechanical Engineering Department, Biomechanics section, Belgium; [8]InSilicoTrials Technologies SpA, Trieste, Italy; [9]KU Leuven Centre for IT & IP Law – imec

In Silico World is an EU-funded project that will be completed at the end of 2024. It aims to lower the barriers slowing down the adoption of In Silico Trials and the use of computer modelling and simulation in developing and de-risking new medical products. During the project, we further developed 11 in silico trial solutions. Among them are solutions to evaluate the safety and/or the efficacy of new osteoporosis and sarcopenia drugs, tuberculosis and carcinoma vaccines, treatments for multiple sclerosis, cardiac valves, corrective insoles, flow diverters, or treatments to repair osteochondral defects. Two are already commercially available as SaaS through the InSilicoTrials Technologies cloud-based platform; two more are offered as part of consulting services by Mimesis, while Materialise will integrate one into their software solution. Through Zenodo we shared five validation collections to test hip fracture predictors, tuberculosis simulators, stent hemodynamic predictors, valvectomy simulators, and dynapenia predictors. The largest collection includes the cleared data collection out of 1200 angiograms from the FAME1 study. On the regulatory front, we drove the publication of the Open Access Book on Good Simulation Practice, we facilitated the creation of an IEC/ISO work group to develop an EU-harmonised equivalent of the ASME VV-40 standard, and we made available in open access the entire documentation of two qualification advice procedures with EMA. On Zenodo, we also share a complete Legal and Ethical Inventory and Policy Brief on In Silico Trials. Last, on the educational and communication & dissemination side, we shared on Zenodo a complete analysis of the intended learning outcomes, the curriculum revision, and some teaching materials to include in silico medicine in various university curricula and to provide re-training to various professional groups. We also made a 'Do-It-Yourself' info kit available to the community. Adopting in silico methodologies in the de-risking of medical products is not only a technological but also a cultural revolution; it will take years for a full-scale adoption, but the final result is unavoidable.

Computer modelling and simulation in clinics: Longitudinal mapping of usage and clinician's trust in in silico medicine

Zita Van Horenbeeck[1,2], Raphaëlle Lesage[1], Artem Platonov[1], Martina Contin[1], Michiel van Oudheusden[2], Elisa Lievevrouw[2], Bernard Staumont[4], Janaki Raman Rangarajan[1], Silvia Schievano[3], Ine Van Hoyweghen[2], Claudio Capelli[3], Liesbet Geris[1,4,5]

[1]Virtual Physiological Human Institute (VPHi), Belgium; [2]Centre for Sociological Research, KU Leuven, Belgium; [3]Institute of Cardiovascular Science, University College London, London, UK; [4]GIGA Research Institute, University of Liège, Belgium; [5]Division of Biomechanics, KU Leuven, Belgium

INTRODUCTION: *In silico* medicine encompasses Computational Modeling and Simulation (CM&S) for disease prevention, diagnosis, prognosis, treatment, and biomedical product development. However, barriers still hinder the effective uptake of CM&S due to factors like regulatory gaps, limited training/resources, and stakeholder awareness. As the field of *in silico* medicine continues to evolve, it becomes imperative to understand perceptions, concerns, and expectations regarding its integration into clinical practice. To this end, we conducted longitudinal surveys, aiming to gather personal insights of clinicians, who are at the forefront of bringing CM&S for patients' benefit. **MATERIALS & METHODS:** The first online survey[1] was carried out between 2020 and 2021, the follow up survey was launched at the end of 2023 [2]. Both surveys counted about 25 questions, assessing among others, the level of awareness with CM&S techniques, trust, perceived barriers and opportunities for the uptake of *in silico* medicine. The second round probes deeper on trust levels and made available in multiple languages. **RESULTS & DISCUSSION**: Over 80% of the respondents from the first survey foresaw the need for CM&S expertise in their team. Interestingly, they counted on their positive personal experience over regulatory approval, to trust the evidence from CM&S. With a rapidly evolving domain, the follow-up survey aims to track changes in above trends. Moreover, capture a broader representation (different medical fields, geographies, demographics) including from those who have little or never experienced CM&S. Subsequently develop effective stakeholder engagement strategies.

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Energy-based multiscale modelling and system analysis framework

Weiwei Ai, David Nickerson, Peter Hunter
Auckland Bioengineering Institute, University of Auckland, New Zealand

Digital twins play a crucial role in clinical decision making by providing real-time, personalized simulations of individual patients based on their physiological data. Physiological systems involve many processes interacting over various physical domains, such as mechanics, electrical potentials, biochemical reactions, and metabolic energetics. The need arises for a comprehensive framework that supports multi-physical domain modelling and integrating the underlying processes. Additionally, efficient model reduction techniques for real-time simulation and a systematic approach for exploring subsystem dynamics are essential. To address these challenges, we introduce an innovative energy-based framework. This framework leverages the bond graph approach to bridge these diverse domains and integrate them using energy-flows. This physically plausible framework enables structure-preserving model reduction based on the energetic significance of components. The resulting reduced models can be readily assembled into a larger network for exploring more intricate functions. The incorporation of energetic features facilitates system integration through physiological regulation with the free energy principle. Additionally, we can decompose existing complex systems based on the energetic coupling strength of interconnections to analyze subsystem dynamics. Our framework, capturing traceable energy storage, dissipation, and transduction, offer comprehensive insights into the systems under investigation, which allows us to assess the thermodynamic consistency of models not formulated using bond graphs, providing valuable feedback for model and experiment design. Our focus extends to automating the processes of model construction, reduction, decomposition and integration, which is achieved through the application of graph and network algorithms and our standard modelling software platform, enhancing the efficiency of both the modelling process and analysis. Further development will support broader research community in the pursuit of developing digital twins for clinical applications.

Different magic sauce, but same taste? Exploring the social and legal demarcation frictions between artificial intelligence and digital twins in healthcare

Elisa Elhadj[1], Elisabetta Biasin[2]
[1]Life Sciences and Society Lab, KU Leuven, Belgium; [2]Center for IT & IP Law (CiTiP), KU Leuven, Belgium

As we navigate the shift towards data-driven healthcare, a new buzz has emerged through digital twins, playing with the attractiveness of the digital double. In medicine, digital twins have recently gained traction, driven by the efforts of the in silico medicine field. Yet, what a digital twin consists of and how it differs from AI remains unclear for various stakeholders, as well as its differing social and legal implications. In this presentation, we explore the demarcation frictions between AI and digital twins from a social and legal perspective. On the first layer, we observe that there is no standard legal or regulatory definition of digital twins in the EU (which would benefit taxonomies and distinctions from a legal perspective). In light of this, we suggest that, most likely, digital twins qualify as medical device software under the EU Medical Device Regulation (MDR). At the same time, we observe that when these tools entail the use of AI, many legal complexities arise. These concern the interrelationships between the MDR and the recently agreed AI Act, which vary depending on the risk and use of the digital twins. We argue that these differentiations are not yet comprehensively described in legal literature and are not sufficiently acknowledged by relevant stakeholders. On the second layer, we turn our gaze to the in silico community itself and analyze their hype discourses and their discourses on the intersection of AI with digital twins. We conduct a thematic analysis of official documents and reports, and 'grey' literature of actors within the in silico field. The aim is to assess if the in silico community itself, meaning those involved in the making of the field, are contributing (un)willingly to the demarcation frictions. The overlooking of specific nuances, sometimes hidden behind the hype wave, can make different technologies appear as the same 'magic sauce' for healthcare. This can have implications for the development of the field as well as society itself. We shed light on what might be the (un)intended effects of these blurred demarcations, and with that facilitate further sociological and legal inquiry into this buzzing field.

3.D: Aortic Valve Replacements

Wednesday, September 4

3:30pm – 5:00pm

09.019

Patient-specific TAVI thrombosis modelling: Insights from haemodynamic analysis

Maria Isabel Pons Vidal, Harriet Hurrell, Tiffany Patterson, Jack Lee
King's College of London, United Kingdom

Aortic stenosis (AS) represents a prevalent valvular heart disorder among the elderly population. Transcatheter Aortic Valve Implantation (TAVI) stands as the preferred treatment for aortic valve replacement, with its adoption steadily increasing. However, TAVI poses risks of leaflet thrombosis, detectable on computed tomography (CT) scans as hypo-attenuation and leaflet thickening (HALT). Current methods for evaluating post-TAVI thrombus formation lack comprehensive haemodynamic insights. Computational modelling, particularly fluid-structure interaction (FSI) simulations, holds great potential in enhancing the short-term performance of the device. However, existing studies lack a comprehensive exploration of the mechanisms using patient-specific data, including the implanted prosthetic valve. This research aims to investigate the role of blood flow around the valve to gain a better understanding of the hemodynamic determinants of thrombus formation after TAVI. We present our preliminary work in building patient-specific models and conducting FSI simulations. The proposed methodology involves the geometrical characterisation of the TAV device, the generation of patient-specific anatomy, and FSI simulation to integrate valve motion with aortic fluid dynamics. The ongoing project is analysing a cohort of 30 patients who underwent TAVI and attended a follow-up visit within 3 to 6 months post-procedure. The TAVI device in current use, encompasses both Sapien 3 (S3) and S3 Ultra variants belonging to the SAPIEN series from Edwards Lifesciences. The valve reverse engineering process involved 2D imaging of leaflets and contact mechanics simulations. Through this simulation, a model of a closed valve was achieved by applying a constant physiological pressure, serving as the model for the subsequent FSI analysis. FSI, using isogeometric analysis and variational multiscale, run within patient-specific aortic anatomies from pre-TAVI CT scans. For precise device positioning, we have developed an interactive platform that utilizes the vessel centreline for guidance, also enabling commissure alignment. Future work applies machine learning to find pro-HALT fluid indices.

Unveiling the relation between aortic shape and calcification in population with aortic stenosis: Towards better management of TAVI patients

Raphael Sivera[1], Ebba Montgomery-Liljeroth[1], Andrew Cook[1], Silvia Schievano[1], Kush Patel[2], Claudio Capelli[1]
[1]Institute of Cardiovascular Science, University College London, London, UK; [2]Bart's Heart Centre, St Bartholomew's Hospital, London, UK

Introduction: Transcatheter aortic valve implantation (TAVI) is a well-established and minimally invasive procedure to treat patients with aortic stenosis (AS). It is a therapeutic option for an increasing number of patients but its complications, such as mild paravalvular regurgitation, may still have a undesirable impact on the long-term outcome. Aortic valve calcification evaluation and modelling can be crucial to understand evolution of AS, improve TAVI outcomes or develop non-surgical treatments [1,2]. This work aims to unveil the relation between the aortic root shape and calcification in the AS population. **Method:** Clinical data were retrospectively collected from a population (n=130) that underwent TAVI at our clinical centre. Large-deformation atlas modelling [3] based on CT images was used to characterize the aortic shape variability and to standardize the position of the 3D segmented calcified areas. The calcification patterns were then projected on 2D surfaces corresponding to the valve and the ascending aorta. Sparse principal component analysis (sPCA) was performed to represent the calcifications using a limited set of spatially localized atoms. Finally, cross-decomposition using partial least squares (PLS) was computed to analyse the relationship between shape and the calcification patterns. Bootstrapping was performed to assess the stability of the results. **Results:** PLS highlighted up to 3 modes of correlation between shape and calcification. First, small and narrow aortas were associated with less calcification with the stronger effect localized on both the right and left coronary cusps (RCC and LCC). The second mode suggested that rounder and short lobes could be associated with less calcification on the RCC-LCC junction. The third mode linked the tilt of the aorta and the average calcification of the valve. **Conclusion:** This work provides new evidence of important morphological properties affecting the pathological processes leading to aortic valve calcification. This can be used to simulate synthetic data for the assessment of personalized TAVI planning strategies.

References:

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Identify transcatheter aortic valve implantation degeneration using computational hemodynamic scores

Luca Crugnola[1], Laura Fusini[2,1], Ivan Fumagalli[1], Giulia Luraghi[1], Alberto Redaelli[1], Gianluca Pontone[2,3], Christian Vergara[1]
[1]Politecnico di Milano, Milan, Italy; [2]Centro Cardiologico Monzino IRCSS, Milan, Italy; [3]Università degli Studi di Milano, Milan, Italy

Structural Valve Deterioration (SVD) is the main limiting factor to the durability of bioprosthetic valves [1], used for Transcatheter Aortic Valve Implantation (TAVI). Nonetheless, SVD is a complex phenomenon whose underlying mechanisms are still incompletely understood [2]. The aim of this computational retrospective study, building on top of [3], is to perform a patient-specific analysis of post-TAVI aortic blood dynamics in order to identify hemodynamic indices that correlate with a premature onset of SVD. The study population comprises two subgroups: patients with and without SVD at 5-10 years follow-up exam after TAVI. Starting from pre-operative clinical images, we reconstruct patient-specific aortic geometries and we create reliable post-TAVI scenarios by virtually inserting a bioprosthetic valve. Blood dynamics numerical simulations are performed in such virtual scenarios imposing patient-specific mean flowrate values. The numerical results are then post-processed to define synthetic scores, obtained by combining different hemodynamic indices, with the aim of discriminating between the SVD and non-SVD groups. We employed the presented approach for fourteen patients. The virtual insertion of the bioprosthetic valve inside the pre-operative geometries was validated using post-TAVI clinical images, showing a good agreement between the position and orientation of the implanted stent and those of the virtual stent. Moreover, we identified a hemodynamic index that individually shows statistically significant differences ($p=0.007$) between the SVD and non-SVD subgroups. Finally, the proposed synthetic scores were able to clearly separate between the two subgroups of patients. The results of this study suggest that post-TAVI aortic blood dynamics may have an influence on the development of SVD. In particular, the proposed synthetic scores could assist clinicians in a patient-specific planning of follow-up exams, aiming to avoid the dispersion of patients showing a high risk of prematurely developing SVD.

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Predicting transcatheter aortic valve implantation procedural outcomes through the development and validation of patient-specific simulations

Benedetta Grossi[1,2], Giulia Luraghi[1], Anna Ramella[1], Ottavia Cozzi[2,3], Sara Barati[1], Alessandro Villaschi[2,3], Josè Felix Rodriguez Matas[1], Gianluigi Condorelli[2,3], Giulio Stefanini[2,3], Francesco Migliavacca[1]
[1]Department of Chemistry, Materials and Chemical Engineering, Politecnico di Milano, Milan, Italy; [2]Department of Biomedical Sciences, Humanitas University, Milan, Italy; [3]Humanitas Research Hospital, Milan, Italy

Introduction: Aortic stenosis (AS) is the most frequent primary valve disease, requiring intervention. Transcatheter aortic valve implantation (TAVI) is becoming the treatment of choice for elderly patients with high surgical risk. However, procedural complications, such as aortic insufficiency due to paravalvular leak, remain critical issues with a negative prognostic impact on rehospitalization and mortality. For this reason, in silico technologies are increasingly used to simulate the implantation, but current simulations have limited capability to predict complications. Our goal is to develop patient-specific in silico simulations of TAVI for optimal treatment indication and outcomes prediction. **Materials and Methods:** Twenty-five patients undergoing TAVI at Humanitas Research Hospital were enrolled. Patient-specific left ventricular outflow tract models were reconstructed from computed tomography (CT) scans. In addition, high-fidelity models of two commonly used prosthetic valves were reconstructed. To determine optimal material properties for the bioprostheses, experimental crimping tests on two real TAVI valves were conducted. Fluid-Structure Interaction (FSI) simulations were performed considering: i) patient-specific anatomical features, ii) the stented valve, and iii) the patient's hemodynamics. Simulations are validated with post-procedural cardiac magnetic resonance imaging (MRI). **Results**: The experimental and computational valve force-diameter curves showed an excellent match, confirming faithful replication of real mechanical valve behaviour. In structural implantation simulations, we accurately reproduced valve positioning in the aortic root, verified with angiographic views. Moreover, a robust quantification of von Mises stress on the aortic wall was achieved. FSI simulations are still underway, but initial results indicate precise quantification of paravalvular leak, where present. **Conclusions:** Our preliminary results are very promising in terms of implantation reproduction and outcome prediction. The refinement of these models could hold significant potential in clinical practice enhancement, offering a robust tool for pre-operative planning.

Virtual cohort generation for in silico trials of transcatheter aortic valve implantation

Sabine Verstraeten[1], Doris Thissen[1], Martijn Hoeijmakers[2], Frans van de Vosse[1], Wouter Huberts[1]
[1]Eindhoven University of Technology, Netherlands, The; [2]ANSYS, The Netherlands

In silico trials can increase the efficiency of development of transcatheter aortic valve implantation devices. They require large virtual cohorts of aortic stenosis (AS) patients, composed of four main components: a stenosed aortic valve geometry; a physiological model, simulating patient's hemodynamics; appropriate boundary conditions; and a distribution of calcifications across the geometry. This study aims to generate synthetic, virtual patients including these components, using a data set of 97 real AS patients. Aortic valve geometries from CT images are parameterized with 33 shape parameters, resulting from a statistical shape model. Left ventricular and aorta pressure signals, invasively measured with pressure wires, are parameterized with 10 parameters, by combining them with a lumped circulation model, through data assimilation. 3D calcification objects from CT images, are mapped to valve geometry elements. These 2D patterns are described by Gaussian random fields (GRFs), modelling the spatial distribution of calcium deposits. Each valve point is a random variable following a joint multivariate normal distribution, with a covariance function capturing spatial correlation between valve locations. A fluid-structure-interaction model is applied to the aortic valve geometries. Left ventricular and aorta pressure signals are prescribed at the inflow and outflow boundaries, respectively. Leaflets are modelled as a linear elastic material. Calcified leaflet elements get a high Young's modulus of 100 MPa, and that of the remaining part is determined by inverse modelling. Each real patient is described by 44 parameters (1 Young's modulus, 33 shape and 10 lumped parameters). Synthetic patients are generated by sampling points from a 44D distribution, fitted to the real data, and generating GRFs for the calcium distribution. These methods are integrated into a single virtual cohort generator, enabling the creation of any number of virtual patients. Being able to generate large, realistic data sets, without depending on patient data, is a significant step towards implementing *in silico* trials in the validation chain for cardiovascular implantable devices.

Simulation workflow for transcatheter aortic valve replacements: From crimp and deployment to fluid-structure interaction

Nils Karajan[1], Facundo Del Pin[2], Rodrigo Paz[2], Sophie Collin[2], Marco Sensale[2], Martijn Hoeijmakers[2], Michel Rochette[2], Mark Palmer[2]
[1]DYNAmore, An Ansys Company, Germany; [2]Ansys, Inc.

The design of a stent frame for transcatheter valve replacements is a challenging task as treatment preparation and deployment have an influence on the final shape and performance of the device. Moreover, a complicated fluid-structure interaction load case is required to assure optimal performance of the valve and to predict stresses and strains in the frame for fatigue life assessment. Typically, one distinguishes between balloon-expandable frame designs mostly made of stainless steel or self-expandable frame designs made of nitinol as shape memory alloy. The focus of this contribution is on self-expandable frames and all simulations are based on a mockup geometry of the Evolute-R System of Medtronic, which is frequently used in literature [1,2]. The goal of this presentation is to simplify these simulations and work toward connecting them in an automated workflow. Simulation steps include a crimping simulation of the stent frame into a delivery capsule as well as a micro catheter insertion simulation into the anatomy to determine a good initial position for the deployment simulation the device into the anatomy. After the device is properly deployed, fluid-structure interaction simulations are carried out to assess the performance of the valve. With such a workflow, these simulations can be repeated at different implant depths to find a position where the performance of the valve is optimized or even repeat the simulations for other anatomies. This will allow design engineers in industry to quickly assess design ideas under real-life loading conditions. A simplified user interface of the workflow will democratize these complicted simulations to make them availbel to clinicians to check the optimal sizing and positioning of the device.

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3.E: Dental Biomechanics

Wednesday, September 4

3:30pm – 5:00pm

09.033

A soft-tissue driven bone remodeling algorithm for mandibular residual ridge resorption

Qing Li[1], Wenwei Huang[1], Rohana Ahmad[2], Junning Chen[3], Chi Wu[1], Jingrui Hu[3], Keke Zheng[3], Michael Swain[1]
[1]University of Sydney, Australia; [2]Universiti Teknologi MARA, Malaysia; [3]University of Exeter, UK

In the current literature, the role of the biomechanical stimulation from soft tissue deformation has not yet been quantified or separated from the self-regulated hard tissue remodeling governed by Wolff's Law. When patients become edentulous, a prosthodontic overdenture is commonly fitted to the residual ridge to restore masticatory functions. Overdentures compress the oral mucosa beneath in a non-physiological way, potentially causing localized ischemia and inflammation. Such significant changes in the biomechanical environment and resultant mucosa metabolism are believed to accelerate the residual ridge resorption (RRR), presenting ongoing clinical challenges. However, the basis for such mechanical induced soft tissue mediated bone resorption has not been determined. Our study followed up on 6 implant-retained overdenture patients over 5 years and developed a computational framework to quantitatively elucidate the governing relationship between the RRR and the local hydrostatic pressures in the mucosa. Our results suggested that the RRR was most severe during the 1st year post treatment with an average bone resorption of 0.68 ± 0.13 *mm*, consisting of both mucosa-driven and self-regulated baseline bone resorptions, and gradually reduced to 0.011 ± 0.02 *mm* afterwards, being dominated only by baseline bone resorptions. Further, in tandem with the patient-specific finite element models and unsupervised machine learning self-organizing map algorithm, we correlated individual patients' 1st year RRR to the local hydrostatic pressure in their mucosa, revealing a relationship governed by power-law functions with constant terms in the range of the self-regulated bone resorptions. The determined governing equation not only enables us to develop a predictive approach for RRR, potentially providing a biomechanical basis for optimizing prostheses for a better outcome, but also extends the current understanding of the mechanobiological responses of the soft-hard tissue interfaces to external forces such as RRR.

Morphological and functional aspects in oral rehabilitations – New algorithmic approaches in the era of digital dentistry

Albert Mehl
Centre for Dental Medicine, University of Zurich, Switzerland

Digital procedures are becoming more and more established in dentistry and are replacing conventional procedures. From intraoral scanning and virtually designing of the restorations to the computer-aided fabrication of these data sets with different materials, various approaches are available. An important step towards the digitalization of these workflows was the automated reconstruction and prediction of the morphology of the missing tooth substances, which was driven forward by the use of knowledge-based processes such as statistical shape models or neural networks. Another current focus is the recording and simulation of individual jaw movements, the consideration of which is of great importance for the design of a functional dental prosthesis. This lecture will present new algorithmic approaches that can replace conventional measurement methods for certain indications. These approaches can reduce the time required for the tedious conventional manual recording of temporomandibular joint parameters and at the same time improve the "functional" fit of the dental restorations. In addition, new electronic registration methods for measuring jaw movements offer new possibilities for diagnostics and therapy. The lecture will therefore also highlight the advantages and limitations of these new techniques and show the prospects for integrating these biomechanical approaches into dental practice.

Modeling the spatio-temporal evolution of bone-implant interface stiffness via a stochastic numerical approach

Jing XIE[1], Furqan A. Shah[2], Keren Shemtov-Yona[3,4], Daniel Rittel[3]
[1]Beijing Institute of Technology, 100081 Beijing, PR China.; [2]Department of Biomaterials, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden; [3]Faculty of Mechanical Engineering, Technion - Israel Institute of Technology, 32000 Haifa, Israel; [4]The Maurice and Gabriela Goldschleger School of Dental Medicine, Department of Oral Biology, Tel Aviv University, Tel Aviv, Israel

Various biochemical, biological, physical and mechanical processes and interactions take place at the bone-implant interface. This interface gradually evolves over time as peri-implant bone gains stiffness. Owing to the multifactorial nature of interfacial processes, a comprehensive numerical model for predicting the mechanical behavior of the bone-implant interface has remained a challenge. Here, we propose a simple mechanical model, starting from an elementary unit cell comprising randomly assigned stiffness (i.e., Young's modulus) and going all the way up to a macroscopic bone-implant interface in a gap healing model (i.e., at the time of implant placement, a space exists between the implant surface and bone). Gap closure and subsequent increase in stiffness are modeled to account for the two main directions of peri-implant bone formation, namely Contact Osteogenesis (CO) and Distance Osteogenesis (DO). This linear elastic stochastic finite element model reveals a highly nonlinear temporal evolution of bone-implant interface stiffness, strongly dictated by the specific kinetics of the contact osteogenesis and distance osteogenesis. Prior to gap closure at the two peri-implant osteogenesis fronts, the bone-implant interface possesses relatively low stiffness. However, following gap closure, the stiffness increases dramatically – reminiscent of a percolation transition whose threshold corresponds to gap closure. Albeit preliminary, the model presented here can be incorporated into future calculations of the bone-implant system where the material properties of bone and biological processes are defined based on quantitative experimental (*in vivo*) data.

Muscle and joint mechanics during maximum-force biting following total temporomandibular joint replacement surgery

Sarah Woodford, Dale Robinson, Jaafar Abduo, Peter Lee, David Ackland
University of Melbourne, Australia

Dynamic, three-dimensional occlusal loading during mastication is clinically relevant in the design and functional assessment of dental restorations and implants, and temporomandibular joint (TMJ) replacements. Unfortunately, dynamic bite force magnitude and direction cannot be measured directly with conventional instrumentation. The aim of this study was to use custom dental plates, high-speed video motion analysis and subject-specific computational modelling to produce accurate dynamic measurements of occlusal loading during biting and chewing in patients following total temporomandibular joint replacement surgery and healthy controls. An optoelectronic tracking system was used to measure jaw kinematics while biting a rubber sample for 5 unilateral total TMJR patients and 8 controls. Finite element simulations driven by the measured kinematics were employed to calculate the resultant bite force generated when compressing the rubber between teeth during biting tasks. Subject-specific musculoskeletal models were subsequently used to calculate muscle and TMJ loading. Unilateral total TMJR patients generated a bite force of 249.6 ± 24.4 N and 164.2 ± 62.3 N when biting on the contralateral and ipsilateral molars, respectively. In contrast, controls generated a bite force of 317.1 ± 206.6 N. Unilateral total TMJR patients biting on the contralateral molars had a significantly higher lateral TMJ force direction (median difference: 63.6°, $p = 0.028$), and a significantly lower ratio of working TMJ force to bite force (median difference: 0.17, $p = 0.049$) than controls. Results of this study may guide future TMJ prosthesis design, and provide insight into the loading of dental structures, which may influence the design and evaluation of dental implants.

Influence of bone quality and dental implant material on stress distribution within the surrounding bone

Iman Soodmand[1], Jan-Oliver Sass[1], Ann-Kristin Becker[1], Maeruan Kebbach[1], Christopher Jabs[1], Michael Dau[2], Rainer Bader[1]
[1]Department of Orthopaedics, Rostock University Medical Center, Rostock, Germany; [2]Department of Oral, Maxillofacial and Plastic Surgery, Rostock University Medical Center, Rostock, Germany

Due to population aging, its link to reduced bone density, and the recently increasing number of teeth lost, the number of osteoporotic patients (OsP) requiring dental care is anticipated to rise in coming years. Nevertheless, the survival rate of dental implants in OsP is contradictorily discussed by clinical studies and meta-analysis [1, 2]. Here, we aim to use a computational approach to study the effect of bone quality on the biomechanical response to applied forces and the effect of different dental implant materials. A full mandible of a 39-year-old male with a missing left first molar was reconstructed from medical images and used for Finite Element Modelling (FEM) in Abaqus v.2022. Heterogenous material properties are assigned to the mandible according to the Hounsfield Unit of each nodal point using the default MIMICS equation $E\ [GPa] = -0.388 + 5.925 \times \rho_{app}\ [g/cm^3]$. Dental implants with Young`s modulus of 110 GPa (case 1) and 210 GPa (case 2) were assigned to commercially pure titanium (cpTi), and zirconium dioxide (ZrO_2) implants, respectively, and identical designs were placed in the missing teeth position. The boundary conditions (441 N loading and resultant muscle forces) from the clenching scenario were derived from a personalized musculoskeletal simulation in AnyBody™ Modeling System v.7.4.4. Material properties of the cortical and trabecular bone of the healthy dataset (case A) are decreased by 67% and 34% [2], respectively to virtually create an osteoporotic dataset (case B). Due to this decreased bone quality, the maximum von Mises stress increased by about 11% for case 1 and 13% for case 2. The chosen implant material led to a variation of 5% for case A and 3% for case B with ZrO_2 leading to lower stresses. These results highlight the significance of considering bone density and dental implant material in FEM. Further computational investigations for implant-bone interactions and additional parameter studies related to the quality of the bone, such as the thickness of cortical bone and varying implant geometry, are required.

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3.F: Big Data / Machine Learning III

Wednesday, September 4

3:30pm – 5:00pm

05.019

A computational pipeline for fast surrogates of left atrial appendage occlusion fluid simulations

Marta Saiz Vivó[1], Carlos Albors Lucas[1], Angel Herrero Díaz[1], Jordi Mill Tena[1], Andy Luis Olivares[1], Benoit Legghe[2], Xavier Iriart[2], Gemma Piella[1], Maxime Sermesant[3], Oscar Camara[1]
[1]Physense, BCN Medtech, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, Spain; [2]IHU Liryc, CHU Bordeaux, Univ. Bordeaux, Bordeaux, France; [3]Inria Centre, Université Côte d'Azur, Epione team, Sophia Antipolis, Valbonne, France

The left atrial appendage occlusion (LAAO) procedure involves placing a device in the left atrial cavity to prevent thrombus formation in patients with atrial fibrillation (AF). However, suboptimal placements may cause device-related thrombus. In-silico fluid simulations can assess blood flow patterns around virtually implanted devices on patient-specific LA morphologies but face long computational times. Our proposed computational pipeline incorporates LA and LAA morphology, along with patient data, to automatically identify the most similar patient from a virtual cohort of pre-computed fluid simulations with different device setups. The aim is to aid in device design and configuration evaluation for complex cases. From a computed tomography scan the LA is segmented via nn-UNet, and the 3D LA mesh is reconstructed. Utilizing the Shape Diameter Function of the CGAL library the LAA region is automatically detected. A centerline from the mitral valve to the LAA tip is also automatically computed for ostium plane estimation, from which the LAA is clipped, enabling the independent estimation of LA and LAA morphological features. Given the extracted features, the 'closest match' algorithm applies a k-nearest neighbor classification (k = 1) to find the most similar LA geometry and output the corresponding fluid simulations. The output may be refined by considering clinical data. The pipeline was evaluated with 128 AF patients from Hospital Haut-Lévêque (Bordeaux, France). The virtual population database included 4 device configurations, covering and uncovering the pulmonary ridge for plug and pacifier device types. The output mesh geometrical similarity was evaluated with a leave-one out cross validation, average Hausdorff distance of 27.7 ± 5.6 mm (LA) and 17.9 ± 8.7 mm (LAA). The input and algorithm output fluid simulation results exhibited similar in-silico hemodynamic indices. For both device types, uncovering the pulmonary ridge led to low blood flow velocities (< 0.2 m/s) and complex flows near the device surface. The pacifier type and uncovered pulmonary ridge represented the most unfavorable scenario for the input patient.

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Generative 3D cardiac shape modelling for in-silico trials

Andrei Gasparovici[1,2], Alex Serban[1], Lucian Itu[1]
[1]Advanta, Siemens SRL, Brașov, Romania; [2]Faculty of Mathematics and Computer Science, Babeș-Bolyai University, Cluj-Napoca, Romania

In-silico trials provide an opportunity to accelerate testing of medical devices, accounting for a wider range of patients compared to in-vitro trials. To enable in-silico trials, it is necessary to have access to a pool of diverse patient data or have the ability to generate synthetic data. For example, the simulation of Transcatheter Aortic Valve Implantation procedures can be performed computationally on distinct aortic shapes representing diverse human anatomies. We propose a deep learning (DL) method to model and generate synthetic shapes. DL has significant advantages over conventional methods like statistical shape models, allowing the reuse of learned representations for various tasks, including conditioning other generative processes, such as calcium deposit generation, and predicting hemodynamic measurements using physics-informed models. The model, consisting of an 8-layer fully-connected network, represents each shape as the zero-level set of an implicit field, conditioned by a trainable embedding vector which encodes the geometric properties of the shape. We train the network on a dataset of 97 aortic root meshes. For each mesh, we sample 500000 surface points with their associated unit normals. The parameters are tuned by making the network vanish on points sampled on the surface, i.e., minimizing the L1 norm of the output, along with minimizing the L2 distance between the sampled normal vectors and the spatial gradient of the output. In addition, we encourage the network to produce a signed distance field by enforcing the spatial gradient of the output to have unit norm, and include an L2 regularization term for the embedding vectors. The same architecture and training objective are used for calcifications. Empirical results show that our model can represent aortic and calcium deposit shapes with high fidelity, including shapes unseen in training, and shapes inferred from partial point clouds. Moreover, by sampling from the learned embedding vectors, we can generate novel shapes with high variability. Finally, the mesh associated with a learned or sampled shape embedding can be recovered with marching cubes and used for in-silico trials.

Image segmentation of irradiated tumor spheroids by fully convolutional networks

Matthias Streller[2], Willy Ciecior[2,3], Soňa Michlíková[1,4], Leoni Kunz-Schughart[1,5], Steffen Lange[1,2], Anja Voss-Böhme[2,3]
[1]OncoRay—National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden—Rossendorf, Germany; [2]DataMedAssist Group, HTW Dresden—University of Applied Sciences, 01069 Dresden, Germany; [3]Faculty of Informatics/Mathematics, HTW Dresden—University of Applied Sciences, 01069 Dresden, Germany; [4]Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology—OncoRay, 01328 Dresden, Germany; [5]National Center for Tumor Diseases (NCT), Partner Site Dresden, 69120 Heidelberg, Germany

Multi-cellular tumour spheroids are advanced in-vitro model system to assess the curative effect of combinatorial radio(chemo)therapy. These three-dimensional cell cultures exhibit crucial patho-physiological characteristics such as a radial oxygen gradient which critically affect radio-sensitivity of the malignant cell population. The therapeutic response of tumor spheroids after treatment is most frequently monitored over time via phase-contrast microscopy imaging. Based on the collected image data, the response is quantified in terms of spheroid control probabilities - analogous to tumor control probabilities in-vivo - Kaplan-Meier curves and volume growth. This analysis requires segmentation of the spheroids in the images, in order to extract their characteristics like diameter, volume and circularity. This is a very laborious process as it entails manual inspection of up to 100.000 images per treatment arm. While several image analysis algorithms have been developed for the automatic segmentation of spheroid images, they focus on compact and circular spheroids with clearly distinguishable outer rim throughout growth. In contrast, treated spheroids are usually obscured by debris of dead cells and might be partly detached and destroyed. We successfully train two Fully Convolutional Networks, UNet and HRNet, and optimize their hyperparameter to develop an automatic segmentation which covers both cases, spheroids with and without therapy. We systematically validate the automatic segmentation on larger, independent datasets of two cell types of head-and-neck cancer. For the majority of images, we find excellent overlap between manual and automatic segmentation, quantified by Jaccard indices around 90%. For images with smaller overlap of the segmentations, we demonstrate that this error is comparable to the variations between segmentations from different biological experts, suggesting that these images represent biologically unclear or ambiguous cases.

Accelerating osteoarthritis progression predictions: A machine learning and finite element analysis approach

Moein Eddin Yousefi[1], Hassan Amini[1], Mohammad Ali Nazari[1], Ilse Jonkers[2], Seyed Ali Elahi[2,3]
[1]School of Mechanical Engineering, College of Engineering , University of Tehran, Iran; [2]Department of Human Movement Sciences, KU Leuven, Belgium; [3]Mechanical Engineering Department, KU Leuven, Belgium

Osteoarthritis (OA), the most common chronic joint disease with limited curative options, is characterized by degenerative compositional changes in articular cartilage. Computer models can simulate cartilage degeneration to predict the patient-specific OA progression. This predictive information can help the provision of the most suitable treatment for the individual patient at the right time. Mechanical driven cartilage degeneration begins when local tissue strains and stresses exceed a threshold level, determined by mechanobiological experiments. Traditional modeling approaches predict cartilage mechanical degeneration using adaptive finite element (FE) simulations, which require iterative runs of time-consuming FE models, deterring their clinical application. Machine learning algorithms offer an alternative approach, replacing FE simulations with trained neural networks (surrogate models) for more computationally efficient predictions. In this study, we explored the use of surrogate models for predicting cartilage FE model outputs. An FE model of a cylindrical cartilage plug subjected to unconfined compression loading was created using a fibril-reinforced poro-elastic (FRPE) material model. The model included key parameters dictating cartilage mechanical behavior: non-fibrillar matrix Young's modulus, strain-dependent and initial fibril network moduli, initial permeability, and compression loading. These five parameters were used as inputs to train a neural network, with the components of deformation gradient and stress tensors as outputs. The network architecture was refined through experimentation and hyperparameter tuning. The developed surrogate model demonstrated high accuracy, with a test loss of 0.003, indicating the accuracy of predictions compared to actual values on the test dataset. Additionally, an R-squared value of 0.917 was obtained, reflecting the goodness of fit of the regression model. This model provides the basis for our ongoing physics-informed neural network developments aiming at more accurate prediction of FE model outputs, even outside the training input ranges.

Enhancing synthetic medical image fidelity through semantic segmentation guidance in diffusion models

João Pedro Rodrigues[1,2], Alexandra Walter[1,2,3], Oliver Jäkel[1,2,4], Jens Fleckenstein[5], Kristina Giske[1,2]

[1]Department of Medical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, Heidelberg, Germany; [2]Heidelberg Institute of Radiation Oncology (HIRO) & National Center for Radiation Research in Oncology (NCRO), Heidelberg/Dresden, Germany; [3]Karlsruhe Institute of Technology (KIT), Scientific Computing Center, Hermann-von-Helmholtz-Platz 1; [4]Heidelberg Ion Beam Therapy Center (HIT), Heidelberg, Germany; [5]Klinik fur Strahlentherapie und Radioonkologie, Universitätsklinikum, Mannheim, Germany

Recent advancements in diffusion models enable new opportunities for the generation of synthetic medical patient images. Synthetic AI-based generation offers enhanced data augmentation and patient pseudonymization for research-sharing applications in which real patient data is scarce. Despite this, in both latent and pixel space diffusion models, when presented to human experts the image quality of generated patient images has not yet reached the level of real patient data. In our study, we explore how a guided-diffusion technique returns an output of higher fidelity when compared to their equivalent unguided generative models and quantify the impact of the guidance process. We utilize semantic segmentation masks with sparse anatomical information as priors for the generation of 2D medical image data. In this study, we focus on bone delineations from a disjunct patient cohort as priors for our models. We utilized radiotherapy planning CT scans of 188 patients in the head and neck region, sourced from The Cancer Imaging Archive (TCIA). Of which a subset of 19 patients was held back for evaluation. With this subset we evaluated the model using average L1 and MS-SSIM similarity between the original patient slices and generated slices, and using distribution metrics (FID, IS and improved precision and recall) evaluated the distance between generated data distributions. Our procedure for the generation of novel data, is firstly, by utilizing the withheld image data, secondly through the applications of spatial transformations (flipping, rotating, mirroring, shearing), and finally, through articulated image registration using a bio-mechanical model. The latter provides a novel way of generating anatomically consistent masks that we show to be effective as priors for the creation of synthetic data. Our results show that segmentation-guided diffusion models outperform unguided models in terms of image quality, while also showing that the synthetic medical images distribution covers a narrower distribution. We achieved on average across multiple resolutions and configurations a change of 9.70%, -18,14%, 9.73% and -44.44% in FID, IS, precision and recall.

Towards multi-scale model selection for rare data applications

Cordula Reisch[1], Sandra Nickel[2], Hans-Michael Tautenhahn[2]
[1]Institute for Partial Differential Equations, TU Braunschweig, Germany; [2]Department of Visceral, Transplant, Thoracic and Vascular Surgery, University of Leipzig Medical Center, Germany

Complex systems in life sciences often suffer from complicated or expensive data, leading to a lack of time- and space-dependent data. Macro-scale models like reaction diffusion equations allow predictions of long-term behavior which can be associated with observations on a larger length scale. An example of those processes with rare data is liver inflammations. The dynamics leading to chronic inflammation are complex, and only the outcome of chronic inflammation is observable. As the scales of mechanistic processes and observations vary widely, the reaction diffusion system is abstract, and a good representation of the mechanisms is not given a priori. One open challenge therefore is the connection of 1) the longtime behavior, 2) the abstract mechanisms in the reaction diffusion system, and 3) the known interactions on the cell-scale. We approach the challenges from two sides. First, a model family of reaction diffusion equations is presented. Based on analytical properties like the longtime behavior of solutions, one model from the family is selected. Secondly, machine learning techniques are used for selecting models based on qualitative data like long-time observations. We present an algorithm for selecting mechanisms in an ordinary differential equation setting and show challenges that arise. The combination of both approaches leads to a coupling of the different scales and takes advantage of all available information, even in cases with little data.

3.G: Musculoskeletal System - Hard Tissue

Wednesday, September 4

3:30pm – 5:00pm

01.005

Improving proximal humerus fracture fixations - Insights from in silico analyses

Peter Varga, Boyko Gueorguiev, Dominic Mischler
AO Research Institute Davos, Switzerland

Treatment of complex and unstable proximal humerus fractures (PHF) remains a clinical challenge with high failure rates, especially in osteoporotic patients. Mechanical failures such as screw cut-out and perforation occur frequently even with state-of-the-art locked plating. With the aim to reduce the mechanical failure risk, we have addressed this multi-factorial problem with a systematic approach by developing and utilizing a validated computational modeling. Finite element (FE) simulations of instrumented PHF were developed and demonstrated to predict experimentally obtained cyclic screw cut-out failure in human humeri (R2=90). The validated FE analyses were implemented in an automated modeling framework and used in a series of in silico studies to investigate various aspects including plate type, plate position, screw length, screw configuration and cement augmentation of a locking implant, involving 24 – 42 virtual specimens and 504 – 4608 simulations for each study. The clinically relevant findings of these studies included the use of longer screws in configurations maximizing spread, augmenting screws at the medial calcar and proximalizing the plate position. Further in silico studies investigated optimization of the implant design by adjusting the trajectories of the locking screws on 19 digital humeri and 5280 analyses, suggesting elevation of the screws especially in the medical calcar region. The computationally optimized implant design was then compared with the standard design in a biomechanical study, confirming the superiority of the former by achieving significantly higher cycle number to cut-out failure in human humeri. The added value of patient specific optimization was investigated in a follow-up study and found moderate compared to the cohort-optimized design. These underline the potential of validated in silico tools in improving the design and use of fracture treatment implants. Clinical investigations are required to confirm these findings.

Predicting lower limb bone geometry in a paediatric population using statistical shape modelling

Laura Carman[1], Thor Besier[1,2], Julie Choisne[1]
[1]Auckland Bioengineering Institute, The University of Auckland, New Zealand;
[2]Engineering Science, The University of Auckland, New Zealand

Musculoskeletal models are important for planning paediatric orthopaedic surgery. However, their clinical adoption is limited by time and cost (for *image-based models*) and inaccurate representation of the anatomy (for *linear scaling of generic models*). Linear scaling produces different outputs to image-based models in both adults and children [1], questioning its clinical application. Statistical shape models can predict complex bone morphology from sparse anatomical landmarks, providing a new approach to customise musculoskeletal models [2]. Here we present an articulated shape model (ASM) to predict lower limb bone geometry in a paediatric population and compare the model to linear scaling. Surface meshes of the pelvis, femora, tibiae, and fibulae were created from segmentations of CT scans of 324 children aged 4 to 18 years (137 F). Each bone was fitted and aligned to a template mesh to achieve nodal correspondence. A shape model combining all bones was created using principal component analysis and included articulations at the hip (3 rotations) and knee (flex/ext and ab/adduction). Bone geometry was predicted by adjusting morphology and orientation to minimise the root mean squared distance of embedded and target landmarks. Eight landmarks were included for prediction: ASIS and PSIS of the pelvis, the medial and lateral epicondyles of the femur, and the medial and lateral malleoli of the tibia/fibula. ASM bone surface RMSE were 2.63 ± 0.90mm, 1.97 ± 0.61mm, and 1.72 ± 0.51mm for the pelvis, femur, and tibia/fibula, respectively. Linear scaling produced bone surface errors of 4.79 ± 1.39mm, 4.38 ± 0.72mm, and 4.39 ± 0.86 for the pelvis, femur, and tibia/fibula, respectively. Clinical bone measurement prediction errors were low across all bones using the ASM, which outperformed linear scaling for all measurements. Overall, the developed ASM is a fast and accurate method to predict lower limb bone geometry in a paediatric population, outperforming linear scaling.

[1] Kainz et al., Clin. Biomech, 2021
[2] Zhang et al., J Biomech, 2016

Automated pose estimation of knee kinematics from fluoroscopy using a differentiable renderer

Jinhao Wang, Florian Vogl, William Taylor
ETH Zurich, Switzerland

1. Introduction: Measurement of knee kinematics is essential for understanding movement patterns and pathologies. While fluoroscopy provides accurate joint kinematics, it requires estimating the 3D pose from 2D X-ray images. This 2D-3D pose estimation is labour-intensive, costly, and subject to operator bias. This study presents an automated 2D-3D pose estimation method using a differentiable renderer which mimics physical X-ray absorption. The differentiability enables gradient-based optimizer to be used in pose estimation from a given starting pose. We assess the accuracy and capture range (i.e. how good of a starting pose is required for the algorithm to converge) when applying our method to single-plane fluoroscopy images of healthy subjects.
2. Methods: We analyzed five similarity metrics ('MSE', MI, 'NCC', 'GCC','LSNPI') using function landscape analysis [1,2]. The metric with the lowest error was used to estimate the pose from 25 x-ray images [3] by five optimizers (Adam, Adagrad, Adamax, SGD, RMSprop). Accuracy was compared to manually estimated poses using L1 error and geodesic loss for translational and rotational components. To evaluate the capture range, the starting pose of each image was perturbed from the true pose within 1mm and 1°.
3. Results: 'GCC' demonstrated the lowest error in landscape analysis. When combined with the Adam optimizer and a 0.1 learning rate, GCC achieved a capture range of 4-6mm for translations and 2-5° for rotations. In more than 80% of the cases, the average errors for translation and rotation were under 1mm and 1°, provided the starting poses were within 5mm and 5° of the true poses.
4. Discussion and Conclusions: Our approach of combining a differentiable renderer with a GCC metric and a gradient-based optimizer showed high capture range and accuracy for knee kinematics estimation from fluoroscopic images. This algorithm holds potential for future integration with deep learning and is applicable for pose estimation of both bone and implants.

5. References

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Numerical evaluation of the postoperative primary fixation stability in complex tibial plateau fractures

Simon Comtesse[1,2], Marco Drago[1], Thomas Zumbrunn[2], Arvind von Keudell[2,3,4], Stephen J. Ferguson[1], Jochen Franke[5], Paul A. Gruetzner[5], Eric Mandelka[5]
[1]Institute for Biomechanics, ETH Zürich, Switzerland; [2]CustomSurg AG, Switzerland; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, USA; [4]Bispebjerg Hospital, Copenhagen, Denmark; [5]Klinik für Unfallchirurgie und Orthopaedie, Berufsgenossenschaftliche Unfallklinik Ludwigshafen, Germany

Introduction
Complex tibial plateau fractures occur with an incidence of ~10 cases per 100'000 people [1]. Open reduction and internal fixation is often very dependent on the surgeon's skillset, leading to complication rates of up to 28% [2]. Moreover, surgeons lack a tool to quantify the postoperative stability of a specific fracture fixation construct. We used intraoperative 3D scans as input to a previously described simulation-based method to quantify the reduction of complex tibial plateau fractures [3].

Methods
The clinical reconstruction in five patients treated at the BG Klinik Ludwigshafen in 2021, classified with AO 41.C3 and 41.B3 fractures, was reverse-engineered using a preoperative CT scan and an intraoperative 3D scan for the segmentation of bone fragments and hardware components (i.e. osteosynthesis screws and plates), respectively. Hounsfield-Unit-derived bone material properties as well as joint and muscle forces from subject-specific musculoskeletal gait models were integrated in the finite element model (FEM).

Results
The two male and three female patients had an average age of 60.0 ± 15.7 years and an average BMI of 26.2 ± 2.4. Three patients were treated with a medial and lateral plate, two patients received treatment with a lateral plate only. One or two lag screws were positioned in four out of the five cases. The average maximum displacement was 1.72 ± 0.56 mm and the von Mises stresses in the screws ranged between 76 and 825 MPa.

Discussion
While most FEM studies focus on the general comparison of different fixation techniques or modeling strategies, our research represents an approach for patient-specific characterization of postoperative stability. Based on pre- and intraoperative imaging, we were able to quantify the construct stability of five tibial plateau fractures. The computational results serve as a biomechanical reference for the objective evaluation of clinical outcomes.

References
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Planning the perfect osteosynthesis: Simulation-assisted decision making in fracture treatment

Andreas Arnegger, Frank Niemeyer, Lucas Engelhardt
OSORA medical GmbH, Germany

Bone healing simulations utilizing the concept of mechanobiologically-driven tissue differentiation for predicting the effect of fracture treatment are well established concepts in computational biomechanics. Making this technology fit for clinical use has been a long-term goal that has yet to be realized. Early adopters in clinical use cases have proven to be crucial on our path to an MVP for a decision support tool to optimize fracture treatment outcomes. This kind of innovation translation has to be accompanied by both, utilizing clinical data for further validation studies, as well as building a sustainable business model at the same time. The effort required for acquiring and utilizing largely unstructured clinical data for training and validation, unclear regulatory requirements and, little surprising, the complexity of clinical decision making of surgeons in the face of the patient turned out to be major hurdles for the development process. While the biomechanical simulation model has been validated in laboratory environments before, patients' co-morbidities as well as varying and largely unknown compliance with post-operative load bearing recommendations affect the predictive quality of the system. Thus, variations of full and partial load bearing were added to the simulation parameters to reflect this added level of uncertainty. By deploying our tool first as a fracture management training and education software, we gained access to over 200 physicians in training as well as 32 course instructors for testing several design iterations of the software platform. This approach via the education route further drives technology adoption and helps developing a user base, forming a market entry with a lower entry barrier than a fully certified clinical decision support tool in a well comparable context of use. A major challenge remains in funding the ongoing commercialization of a regulatory compliant clinical decision support tool.

Minding the gap: Sex differences influence bone fracture healing

Laura Lafuente-Gracia[1,2], Pieter Ansoms[1], Aurélie Carlier[3], Liesbet Geris[1,2,4]
[1]Biomechanics section, Department of Mechanical engineering, KU Leuven, Belgium; [2]Prometheus: Division of Skeletal Tissue Engineering, KU Leuven, Belgium; [3]Department cBITE, MERLN Institute, Maastricht University, The Netherlands; [4]Biomechanics research unit, GIGA in silico medicine, University of Liège, Belgium

Bone regeneration involves the (inter)action of cells, regulated by biochemical and mechanical factors. After fracture, successful healing is usually achieved within weeks. However, fracture severity, anatomical location and host factors can lead to delayed- or non-healing. Among the host factors, the role of sex differences is still poorly investigated, and experiments report contradictory findings. Evidence suggests a less efficient bone healing in females [1] due to a sexually dimorphic inflammatory response [2]. Indeed, M1 macrophages predominate in males, and M2 in females; leading to a not-fully-understood, sex-based macrophages-stem cells crosstalk in osteogenesis [3]. In the repair phase, sex hormones regulate stem cell differentiation and proliferation [4]. A stronger repair response is often found in males due to a higher skeletal stem cell [4] and osteoblast [5] activity, and a more prominent cartilaginous callus [5]; but some studies observed the opposite: higher bone formation in females [3]. It is thus not clear how sex disparities integrate in an emergent outcome. In this study, we used a macrophage-mediated bone healing model [6] to investigate how sex differences influence the healing progress in different fracture types. A sensitivity analysis selected a reduced parameter set: a one-at-a-time approach identified the impactful parameters, and a design of experiments analyzed the joint effect of these. The reduced set was crossed with literature data to create male and female parameter sets. The model was validated with literature data. The predicted union cases revealed no significant sex-specific differences in the bone outcome, but different cell activities were observed. The non-union cases showed that sex differences further amplify impaired healing. This study contributes to an improved understanding of the role of sex differences in fracture healing.

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Ack.: Horizon2020 (874837).

3.H: Neural Engineering

Wednesday, September 4

3:30pm – 5:00pm

02.011

Computational modelling of closed-loop control of deep brain stimulation for Parkinson's disease

Madeleine M. Lowery, Jakub Orlowski
University College Dublin, Ireland

Closed-loop control of deep brain stimulation (DBS), also known as adaptive DBS, offers the potential to automatically adjust stimulation parameters based on patient symptoms and side-effects in order to overcome the limitations of conventional open-loop or continuous DBS. Preliminary pre-clinical and clinical studies indicate that closed-loop DBS can provide similar control of motor symptoms to conventional DBS, with lower power consumption and better control of side-effects (REFs). While closed-loop or adaptive DBS is progressing towards a point where large scale clinical trials can be conducted, fundamental questions remain in terms of the most appropriate biomarkers and control strategies to for safe, effective control of stimulation parameters. Computational models provide a valuable means with which to address these questions and test new approaches for closed-loop neural stimulation. Multiscale neural models spanning the cellular to the system level can be coupled with detailed finite element models to simulate the electric field generated by the stimulation electrodes, allowing the effect of neural stimulation on the activity of individual neurons and populations of neurons to be simulated. The electric fields generated by neural activity within the central and peripheral nervous system can similarly be simulated, enabling simulation of single neuron activity, local field potentials, electrocortographic (ECoG) and electromyographic (EMG) signals. Biomarkers of pathological neural activity derived from these signals can be used to control DBS parameters, providing the required amount of stimulation to suppress symptoms while avoiding stimulation-induced side-effects. Here we present a multiscale model of the neuromuscular system during DBS for Parkinson's disease and demonstrate how it can be used to explore new approaches for closed-loop stimulation including adaptive and multi-variable control.

Group analysis in deep brain stimulation employing simulations of the volume of tissue activated

Simone Hemm[1,2], Dorian Vogel[1], Teresa Nordin[2], Vittoria Bucciarelli[1], Karin Wårdell[1,2]
[1]Institut for Medical Engineering and Medical Informatics, University of Applied Sciences and Arts Northwestern Switzerland, Switzerland; [2]Department of Biomedical Engineering, Linköping University, Sweden

Deep Brain Stimulation (DBS) is today a well-established treatment for movement disorders such as Parkinson's disease. Nevertheless, the symptom dependent anatomical area responsible for the therapeutic effect within the stimulated region is still a matter of discussion. Group analysis based on data from already implanted patients has been introduced and gained importance during the last years for the investigation of the optimal DBS sites. The objective of this work is to present the different steps necessary and parameters to choose to generate probabilistic stimulation maps (PSM). Group analysis can be divided into three main steps. First the volume of tissue activated (VTA) is simulated on a patient level for specific stimulation parameters inducing a specific therapeutic or adverse effect. Tissue conductivity models have to be generated for the different tissue types. During a second step patient's image data are coregistered to a generic or a cohort specific template space. The quality of these templates depends on the type of image registration (linear/ non-linear), the registration settings (e.g. number of iterations), the image data available and used for the generation and the cohort of subjects (healthy/diseased, condition and age-matched). Once registered, VTAs can then be projected into this template space for a patient cohort. The third step consists in summarizing, analyzing and visualizing all patient data in form of PSMs. Different statistical methods such as t-test and Wilcoxon test depending on the available patient data are applied to identify relevant clusters for symptom improvement and adverse effects. The description of the anatomical position of these clusters depends on the available additional anatomical information such as fiber tracts, manually outlined structures or anatomical atlases. The present work provides an overview of the necessary steps for group analysis and the influencing parameters, which should be carefully selected rather than using default settings and workflows. Further studies are essential to better understand the influence of each parameter on the final PSMs.

Computational modeling of transcranial magnetic stimulation

Konstantin Weise[1,4], Ole Numssen[1], Torge Worbs[2], Aaron Miller[1], Vincent Chien[3], Helmut Schmidt[3], Thomas R. Knösche[1,5]
[1]Max Planck Institut für Kognitions- und Neurowissenschaften, Germany; [2]Danish Technical University, Copenhagen, Denmark; [3]Czech Academy of Sciences, Prague, Czech Republic; [4]Hochschule für Technik, Wissenschaft und Kunst, Leipzig, Germany; [5]Technische Universität Ilmenau, Ilmenau, Germany

Transcranial magnetic stimulation (TMS) allows for the direct interference with brain function without any invasive procedure. This makes it an extremely valuable tool both for fundamental brain research and for clinical therapeutic and diagnostic purposes. However, to date, the full potential of the technique cannot be exploited, because the mechanism how the applied magnetic field influences brain function is yet largely uncharted. Here, we will describe, by way of the example of motor evoked potentials (MEP), the entire modeling chain from the magnetic field to the observable effect. First, we will discuss how we can use advanced FEM modeling and non-linear regression for localize the relevant neural populations and determine input-output curves linking the induced electric field to the amplitude of the MEP [1, 2]. This will include recent work about bridging the gap between macroscopic fields, as computed by FEM, and the microscopic field at the cell membranes, which are relevant for activating the neurons. Second, we present detailed modeling work on the excitation of cortical neurons upon exposure to the electric field with emphasis to the direction sensitivity [3] and the generation of cortical responses (DI waves). Third, we discuss the role of signal transmission via spinal fiber bundles and peripheral nerves [4, 5] as well as models of the spinal circuitry. The final building block of our modeling chain is the generation of the MEPs using a detailed numerical model of the hand muscle [6].

References

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Simulation-enhanced magnetomyographic quantum sensor systems to study neuromuscular control

Thomas Klotz[1], Francesco Negro[2], Justus Marquetand[1,3], Ahmed Dogukan Keles[1], Nima Nouri[3], Oliver Röhrle[1]
[1]University of Stuttgart, Germany; [2]University of Brescia, Italy; [3]University of Stuttgart, Germany

Magnetomyography (MMG) is an unexplored alternative to established electromyography (EMG), commonly used to study neuromuscular control. In theory, MMG offers some advantages to EMG. Most importantly, the human body's magnetic permeability is the same as in free space. Thus, MMG can be measured contact-free. Moreover, MMG is potentially less affected by tissue properties than EMG. Recent advances in quantum sensing have enabled the investigation of MMG. Here, we combine simulations and experiments to investigate whether MMG can push the limits of motor unit (MU) decompositions. This is essential to decode motions. We have developed a unique experimental protocol that simultaneously measures high-density MMG and EMG. MMG is recorded with 15 optically pumped magnetometers (OPMs) arranged through a 3D-printed sensor holder (spacing 15 mm). The simultaneous measurement of MMG and EMG required custom high-density EMG electrodes (64 electrodes, spacing 4 mm) with long non-magnetic connector cables. Proof-of-concept experiments recording isometric contractions in a shielded room of the ADM showed that MUs can be decomposed from MMG using convolutive blind source separation. The results are validated by decomposing EMG. However, the experiments provide limited insights to relate decomposition results to tissue properties, detection systems, and decomposition schemes. Thus, we additionally developed an in-silico trial framework that integrates a biophysical muscle model into the spike estimation step of a MU decomposition algorithm. The in-silico trials show that MMG-based MU decomposition is superior to surface EMG-based MU decomposition. The number of decomposable MUs increases by 76%. Decomposing MMG can identify MUs in depths of more than 2 mm. Such MUs are typically not identifiable through surface HD-EMG. Yet, MMG-based decompositions are currently limited by the performance of the detection system. Most importantly, the signal-to-noise ratio of the acquired signals. Further, we can show that unlocking the full potential of MMG-based MU decomposition requires MMG arrays with higher density (spacing below 8 mm) and a bandwidth above 500 Hz.

Influence of collateral axon parameters on threshold activation during DBS

Karthik Sridhar[1], Revathi Appali[1,2], Ursula Van Rienen[1,2,3]
[1]Institute of General Electrical Engineering, University of Rostock, Germany; [2]Ageing of Individuals and Society, Interdisciplinary Faculty, University of Rostock, Germany; [3]Life, Light and Matter, Interdisciplinary Faculty, University of Rostock, Germany

Deep brain stimulation (DBS) in the subthalamic region (STN) represents an effective surgical intervention for restoring motor function in patients with Parkinson's disease (PD). It is well-established that the hyper-direct pathway directly connects the cortex to the STN and plays a crucial role in modulating PD symptoms. Recent studies involving computational models of DBS have shown that collateral axons have lower activation thresholds than the longer axons of passage. However, the morphological properties of these collaterals incorporated into the multi-compartment axon model were taken constant. However, there is a need to quantify their influence on activation thresholds for more accurate tuning of DBS parameters. To determine the extent of activation by STN DBS of collaterals within the STN, we positioned 1000 idealized multi-compartment cable models of an axon and branching collateral with randomized diameters in the range of 0.2-2 µm within the STN. At each time step, the time-dependent extracellular potential, computed from the finite element model of rat DBS, was applied to each node of each collateral segment in NEURON using the extracellular mechanism. The extracellular potential at each node within the volume conductor was calculated using the Fourier method. The activation threshold of each collateral was defined as the minimum current or voltage at which action potential propagation was observed.
Our model simulations show that larger collateral diameters requiring higher current amplitudes than their smaller counterparts. Furthermore, the region of collateral activation exhibited greater sensitivity to collateral diameter rather than its spatial position within the STN domain. These findings emphasize the significance of understanding the morphological variations of collaterals and their impact on action potential generation. This knowledge is crucial for understanding both antidromic and orthodromic neuronal activity during DBS and its potential to suppress beta oscillations, contributing to more effective therapeutic outcomes for PD patients.

3.I: Cancer Modelling II

Wednesday, September 4

3:30pm – 5:00pm

08.019

Computational synthesis of microvascular networks: A precision medicine approach to predict radiotherapy outcome in head and neck cancer

Sophie Materne[1,2], Luca Possenti[1], Alessandro Cicchetti[1], Francesco Pisani[1], Alessandra Catalano[1], Piermario Vitullo[2], Tiziana Rancati[1], Paolo Zunino[2]
[1]Data Science Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Italy; [2]Department of Mathematics, Politecnico di Milano, Milan, Italy

The microvascular system is vital in cancer treatment, participating in immune cell trafficking and delivering nutrients and drugs, eventually impacting tumor control and treatment side effects. Microvascular morphology and regularity determine oxygenation levels in the microenvironment and this highly impacts radiotherapy effectiveness via the oxygen enhancement effect. This study introduces a computational method to generate patient-specific synthetic microvascular networks using data from the sublingual microvasculature of 63 Head and Neck Cancer patients undergoing radiotherapy. Total tumor doses ranged from 60 to 70 Gy, administered in fractions of 1.7-2.12 Gy. We initiated the process by randomly generating a specific number of seeds and employing Voronoi tessellation to create the synthetic microvascular network. Vessel radii were assigned to mirror the distributions measured on patients. Subsequently, blood flow within the synthetic microvasculature was simulated, including the presence of red blood cells (RBCs). This involved solving Poiseuille's equation alongside the conservation and transport equations for RBCs and considering the Fahraeus-Lindqvist and Zweifach-Fung effects. The results illustrate how the computational framework can replicate relevant microvascular conditions. Specifically, synthetic networks emulate microvascular density, vessel diameter distribution, and blood flow across the patient population. The method can generate tailored geometries for a single patient reproducing vascular radius, density, and blood flow (Real velocity vs Synthetic velocity in μm/s, pt1: r=107.8 ± 15.8, s=92.4 ± 26.7, pt2: r= 108.5 ± 0.1, s=100.9 ± 23.1, pt3: r=109.0 ± 6.14, s=103.5 ± 27.7). These synthetic networks enable personalized mechanistic simulations of microvascular flow, including the delivery of drugs and nutrients and the oxygen distribution at the microscale level. This model promises to be a valuable tool for mechanistically examining how the microvasculature influences the microenvironment, contributing to understanding and predicting outcomes after radiotherapy.

Development and validation of a computational simulator for treatment outcome prediction in high-grade serous ovarian cancer

Marilisa Cortesi[1,2], Dongli Liu[2], Elyse Powell[2], Ellen Barlow[2], Kristina Warton[2], Emanuele Giordano[1], Caroline E. Ford[2]
[1]University of Bologna, Italy; [2]University of New South Wales

Treatment personalisation in high-grade serous ovarian cancer (HGSOC) is fundamental to the clinical management of this disease. The effective clinical implementation of precision medicine is complicated by several challenges, including limited access to tissue samples [1] and the rapid evolution of HGSOC, which often leads to genetically distinct sub-clones coexisting within the same patient [2]. To bridge this gap, we have developed ALISON (digitAl twIn Simulator Ovarian caNcer) a computational framework integrating a digital twin simulator and a patient calibration procedure, to recapitulate treatment response in individual patients. Standard clinical information, was used to identify the model parameters best representing each member of our cohort. The simulator combines an agent-based framework and a finite element model to capture both the behaviour of individual cells and the concentration distributions of key molecules (oxygen, glucose, drugs). The combined effect of these two models, together with the integration of features like cell-cell variability and the interaction between cancer and healthy cells enables the simulation of drug response and the quantification of the effectiveness of different drugs on each patient. Our simulations effectively recapitulated the response to cisplatin, carboplatin and paclitaxel for all the patients in our cohort (n=7). Primary cell culture derived from ascites samples were used as reference, providing a reliable and standardised method to evaluate the results of our computational framework. These results demonstrate the feasibility of using ALISON to infer patient-specific treatment response in HGSOC. While simulation of a wider panel of treatments would be necessary to make this tool useful in the clinic, our data provide a valuable proof of concept of the effectiveness of our approach.

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Patient-specific modelling of needle insertion in prostate cancer therapy

Myrianthi Hadjicharalambous[1], Vasileios Vavourakis[1,2]
[1]University of Cyprus, Cyprus; [2]University College London, UK

High-dose-rate brachytherapy (HDR-BRT) constitutes a highly promising therapeutic option for prostate cancer patients, associated with high survival rates and minimal disruption in patients' life. It involves the implantation of catheter needles in the prostate, following a pre-operative plan for optimal distribution of a radioactive dose. However, the efficiency of the treatment is often dependent on the accuracy in needle placement, which, in turn, is affected by the deformation induced on the prostate tissue during needle insertion. In this work, we propose a data-driven meshless modelling framework which simulates needle insertion during HDR-BRT, while accounting for the deformation on the prostate. A meshless methodology is employed which relies on a kinematic condition for modelling needle insertion, while the non-linear nature of the prostate tissue is modelled using a nonlinear (Green-elastic material) constitutive model. Notably, models are personalized using comprehensive medical images at different stages of HDR-BRT, while images at the end of the procedure offer a unique framework for model evaluation. Focus of this contribution is placed on providing patient-specific simulations of the entire HDR-BRT process, including simulating the sequential insertion of multiple catheter needles – a challenging process which has hardly been investigated. Our results show good agreement between model and data, highlighting the potential of our *in silico* modelling procedure to offer a pre-operative planning tool that will enhance the accuracy in needle placement and ultimately improve the efficiency of HDR-BRT.

METASTRA: Computer-aided effective fracture risk stratification of patients with vertebral metastases for personalised treatment through robust computational models validated in clinical settings

Luca Cristofolini[1], Giovanni Barbanti-Bròdano[2], Vincenzo Carbone[3], Enrico Dall'Ara[4], Stephen Ferguson[5], Rudolf Ferenc[6], Jose Manuel Garcia Aznar[7], Niccole Germscheid[8], Jakob Haardt[9], Aron Lazary[10], Marco Palanca[1], Nikolina Lednicki[11], Peter Vajkoczy[12], Jorrit-Jan Verlaan[13], Laszlo Vidacs[14], Emmanuelle Voisin[15]

[1]Alma Mater Studiorum - University of Bologna, Italy; [2]Rizzoli Orthopaedic Institute, Italy; [3]InSilicoTrials Technologies, Italy; [4]University of Sheffield, UK; [5]Federal Institute of Technology ETH Zurich, Switzerland; [6]FrontEndArt, Hungary; [7]University of Zaragoza, Spain; [8]AOSpine, Switzerland; [9]Eurice, Germany; [10]Buda Health Center, Hungary; [11]Rise, Croatia; [12]Charité Universitätsmedizin Berlin, Germany; [13]University Medical Center Utrecht, Netherlands; [14]University of Szeged, Hungary; [15]Voisin Consulting Life Science, France

Cancer patients (2.7M in EU) with a positive prognosis often develop metastases (≈1M) in their remaining lifetime. Metastases spread to the spine in 30-70% cases, reducing the mechanical competence of the affected vertebrae. Fractures occur in ≈30% cases. Clinicians face a dilemma: either operate to stabilise the spine (possibly exposing oncologic patients to an unnecessary surgery), or leave the patient exposed to a high fracture risk (with possibly dramatic consequences). Currently, the decision is based on the surgeon's experience, and is often associated to under- or over-treatment. The standard-of-care to vertebral metastases are scoring systems (e.g. Spine Instability Neoplastic Score) based on radiographic images, with little consideration of the biomechanics of the spine and of the vertebrae involved. Such scoring systems are unable to provide reliable indications in ≈60% cases. The HEU-funded METASTRA project involves 15 partners across Europe, including biomechanicians, modellers, clinicians, experts in verification, validation, uncertainty quantification and certification. We aim to improve the stratification of patients with vertebral metastases evaluating their risk of fracture. METASTRA will develop two groups of computational models: Explainable Artificial Intelligence (AI) and personalised Physiology-based biomechanical (VPH) models. We expect that the METASTRA-AI model will be able to stratify most patients, based on parameters that can be extracted in a quasi-automated way, with limited effort end cost. Those patients that cannot be reliably evaluated through the AI model will be examined through more detailed and personalised VPH model. The METASTRA models will be trained through an unprecedentedly large multicentric retrospective study (2000 cases) and validated against biomechanical experiments (120 ex vivo specimens). A decision support system will be developed and tested in a multicentric prospective observational study (200 patients). The METASTRA approach is expected to reduce the indeterminate diagnoses from the current 60% down to 20% of patients.

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Clinical decision support during maintenance therapy for childhood acute lymphoblastic leukemia

Anna Gebhard[1], Sebastian Sager[1], Jakob Zierk[2], Markus Metzler[2], Manfred Rauh[2]
[1]MathOpt group, Otto von Guericke University Magdeburg; [2]Department of Pediatrics and Adolescent Medicine, University Hospital Erlangen

Acute lymphoblastic leukemia (ALL) is one of the most common pediatric malignant diseases, and is currently treated with a combination of high-dose chemotherapy followed by an oral maintenance therapy with 6-mercaptopurine (6MP) and low-dose methotrexate (MTX), which continues up to two years after diagnosis. Although the survival rate of pediatric ALL is approximately 90%, the dose-response relationships vary widely between patients and necessitate the improvement of personalized treatment. We use the pharmacokinetic-pharmacodynamic (PKPD) model by Gebhard et al. (2023) to simulate different treatment strategies, aiming to aid clinical decision making during maintenance therapy. This model is based on a detailed data set with measurements of thioguanine nucleotides and MTX in red blood cells and the absolute neutrophil count (ANC) and is capable of predicting individual ANC levels, which are the biomarkers currently used in a clinical setting to adjust the treatment schedules of 6MP and MTX. While these measurements already allow for some individualization of the maintenance therapy, modeling the dose-response relationship allows not only to compare different treatment strategies when simulating the effect on the ANC, e.g. steady treatment with different dosage levels, but also to exploit the corresponding dynamics, e.g. taking into account the impact of a feedback mechanism on the ANC trajectories. We show that the latter approach leads to less oscillations in the ANC values and therefore, less risk of neutropenia, testifying to the usefulness of modeling the maintenance therapy response.

Gebhard, A., Lilienthal, P., Metzler, M., Rauh, M., Sager, S., Schmiegelow, K., Toksvang, L. N. & Zierk, J. (2023). Pharmacokinetic–pharmacodynamic modeling of maintenance therapy for childhood acute lymphoblastic leukemia. Scientific Reports, 13(1), 11749.

4.A: Heart Modelling - Applications I

Thursday, September 5

10:30am – 12:00pm

05.019

Computational modeling of desmoplakin cardiomyopathy

Javiera Jilberto, Adam Helms, David Nordsletten
University of Michigan, United States of America

Desmoplakin Cardiomyopathy (DSP-CM) is a genetic condition resulting from abnormal variants of the desmoplakin protein. Serving as one of the primary proteins in the complex linking sarcomeres across cell-cell junctions, the phenotype of DSP-CM is the formation of subepicardial fibrosis that spreads around the heart, penetrating slowly in the transmural direction. While the genetics of DSP-CM are known, the cause of this phenotype, what causes progression, and how progression can be mitigated are not well known. One possible theory extends from the potential mechanics of the heart, leading to elevated stresses that manifest into progressive cell damage and fibrotic remodeling. In this abstract, we explore the diastolic and systolic mechanics of DSP-CM, examining the potential triggers of damage as well as progression of disease. For this study, we examined (N=12) patients with DSP-CM at varying stages in the time course of their disease. Patient's hearts were imaged using magnetic resonance imaging, segmented using neural networks, and used to patient-specific models. A class of virtual patients were formed from the state-space of geometries, fibrosis patterns, and passive / active properties. This virtual cohort provides an understanding of the variance of disease and function. Finally, passive and active stresses were examined throughout the heart, with specific emphasis on the subepicardium – exploring the potential mechanical drivers of DSP-CM. From our study, we observe that the most common sites for fibrotic remodeling – and likely the loci of DSP-CM fibrosis – occur in the sub-epicardium below the tricuspid and pulmonary valves at the LV-RV junction. This region of the heart, undergoes distinct and complex biomechanics throughout the cardiac cycle, with stresses amplified by exercise or other acute stressors. Our results highlight the potential of cardiac biomechanics to elucidate the unique mechanics of the heart in disease. We demonstrate that DSP-CM shows progressive fibrosis that mirrors mechanics, providing potential clues to underlying drivers of damage and progressive fibrotic remodeling.

Determination of stimulation threshold in a 3D model of a pacemaker

Valentin Pannetier[1], Michael Leguèbe[1], Yves Coudière[1], Guilhem Faure[2], Delphine Feuerstein[2]
[1]Université de Bordeaux / IHU Liryc / Inria, France; [2]Microport CRM, France

We present a 3D model which computes the threshold of a pacemaker, i.e. the minimal electrical energy required for a pacemaker stimulation to elicit action potentials throughout the heart muscle. This model was developed during the SimCardioTest European project on in-silico techniques for cardiac medicine. More precisely, a pacemaker device behaves like a pulse generator that locally applies a current to the heart for a short duration via leads inserted in the heart cavities. If sufficient, the delivered energy triggers an action potential in the heart. In that case, the device is said to capture. In the pulse amplitude-duration plane, capturing and non-capturing regions are delimited by the energy threshold curve. To preserve the pacemaker battery, it is necessary to stimulate at the minimal energy that captures. Hence, being able to predict the threshold curve contributes to lead design improvement, capture optimization and the increase of device lifetime. We introduce a new 3D computational model that couples through boundary conditions the cardiac bidomain equations, embedded in a bath, to a model based on an electrotechnic equivalent schematic of the pulse generator and pacemaker leads. These conditions model the capacitive and resistive effects of the metal-tissue interface during pacing. Such an interface model is of paramount importance to evaluate the energy actually delivered to the tissue. For each pulse amplitude and duration, capture is considered achieved if the volume of excited tissue increases during the 10 ms after the pulse ends. Afterwards, the threshold curve is built by dichotomy. Model solutions are approximated with a finite element method, on a given mesh of the cardiac domain and leads, with a fixed time step. We use an iterative method to solve the linear system which arises at each time step. We will show results of the software quality assurance, and numerical convergence verification procedures, which were designed following the ASME V&V40 guidelines. We will notably present convergence of the solution and accuracy of the threshold curve with respect to mesh size, time step, and stopping criteria for the iterative solver.

Development of an automated pipeline for large-scale in silico trials in patient-specific electromechanical ventricular models

Ruben Doste[1], Julia Camps[1], Zhinuo Jenny Wang[1], Lucas Arantes Berg[1], Marcel Beetz[2], Abhirup Banerjee[2], Vicente Grau[2], Blanca Rodriguez[1]
[1]Department of Computer Science, University of Oxford, United Kingdom; [2]Department of Engineering Science, University of Oxford, United Kingdom

In recent years, human *in silico* trials have gained significant attention as a powerful approach supported by industry and regulatory bodies to evaluate drugs, clinical interventions, and medical devices. By utilizing patient-specific modelling and simulations, *in silico* trials not only minimize patient risks but also improve human translation and reduce reliance on animal testing. However, the implementation of in silico trials presents several computational challenges. It requires the generation of a large number of patient-specific models and conducting numerous simulations for each individual geometry, driven by diverse uncertainties such as clinical protocols, drug dosages or variability. These variations lead to an exponential growth of the number of simulations. Therefore, automatic methods for the generation of personalized models and simulation files are crucial for handling these computational demands. In this study, we present an open-source pipeline tailored for automated execution of in silico trials in patient-specific cardiac biventricular geometries, enabling both electrophysiological and electromechanical simulations. The pipeline generates closed biventricular surface meshes and automatically adds labels to the surfaces, apexes, and valves. From the surface it creates tetrahedral and hexahedral meshes with the desired resolution and generates the most common fields required for the simulations such as fibre information, cellular heterogeneity, or heart gradients. Additionally, the pipeline integrates algorithms for Purkinje tree generation and electrophysiological personalization based on patient data. Geometric data generation, such as Cobiveco coordinates and AHA segmentation, is also integrated into the pipeline. We demonstrate the application of the proposed methodology by performing simulations on 100 cases from the UK Biobank, showcasing its potential in effectively handling large databases.

A strongly coupled electromechanical model of heart failure as a benchtest for proarrhythmia assessment and drug testing

Eva Casoni[1], Jazmin Aguado-Sierra[1], Maite Mora[3], Sergi Picó[2], Juan Francisco Gómez[3], Mariano Vázquez[1,2], Beatriz Trenor[3]
[1]ELEM Biotech, Spain; [2]Barcelona Supercomputing Center, Spain; [3]Universitat Politècnica de València, Spain

Heart Failure (HF) is a common cardiovascular disease in which the failing heart undergoes electrical and structural changes that may lead to cardiac arrhythmias. In this study a multiscale model of the human ventricles from single cells to the 3D organ is presented. Computer models can provide a mechanistic knowledge of the physiology and the complex feedback mechanisms involved in cardiac pathologies, such as HF. The model considers the coupling between the electric and mechanical activities of the heart, which is the fundamental physiological process at the basis of the cardiac function. HF conditions are characterised by prolonged action potential and alterations in intracellular calcium handling, therefore the model includes the effects on the contractility and deformation to portray a complete picture of this cardiac pathophysiology. This work presents a detailed 3D coupled electromechanical model to study the effects of contractility on a human biventricular anatomy under healthy and HF conditions. Cardiac electrophysiology, mechanics and hemodynamic were solved to verify the accurate description of this pathophysiology against the normal cardiac activity and quantify the effects caused by drugs according to the cellular properties they modulate.

Personalisation of action potentials based on activation recovery intervals in post-infarcted pigs: A simulation study

Jesus Jairo Rodríguez Padilla[1], Rafael Silva[1], Buntheng Ly[2], Mihaela Pop[1], Maxime Sermesant[1]
[1]Centre Inria d'Université Côte d'Azur, France; [2]IHU Liryc, Université de Bordeaux, France

Cardiac modeling is a powerful and robust tool in electrophysiology (EP), supporting non-invasive arrhythmia diagnosis and therapy planning. Some studies showed that in silico modelling can be used to predict scar-related arrhythmia risk and ablation targets. However, model personalization is still relying on 'average' EP parameters derived from literature, largely due to a paucity of their identification from EP clinical data. We hypothesize that activation-recovery interval (ARI), a surrogate for action potential duration, APD) can be extracted from intracardiac electrograms (iEGMs) and used to parameterize models for more accurate AP wave simulations per individual case. In this work we personalised APDs using ARI values extracted from endocardial electro-anatomical maps recorded in sinus rhythm and during pacing in post-infarcted swine (n=8). Specifically, we sought to investigate the differences in model parameters needed to calibrate simulated APDs in healthy tissue and border zone, BZ (i.e., arrhythmia substrate) when using an 'average' ARI computed from all cases versus those calibrated from ARIs extracted per each case. To simulate AP waves, we used a modified Mitchell Schaeffer model with a FEniCSx implementation. We simulated a 2 cm virtual strand of tissue activated by a stimulus applied 10 times, and then computed an average APD on the strand from the last beat. Results showed that average ARIs in healthy tissue and BZ for all cases during sinus rhythm were 206.12 ±50.18ms and 213.21± 52.1ms, respectively, whereas for pacing cases we obtained 282.5 ± 74.92ms and 310.43 ± 98.16ms, respectively. Figure 1 shows exemplary results of APD personalization using 'average' ARIs vs. per case ARIs, demonstrating significant differences. Furthermore, simulated tissue excitability (λ parameter) was reduced in the BZ compared to healthy myocardium.

This work underlines the importance of model personalisation by case, suggesting that is fundamentally needed to accurately reproduce in silico the experimental observations.

4.B: Vascular CFD Modelling

Thursday, September 5

10:30am – 12:00pm

02.017

Efficient multiscale fluid flow modelling by a Stokes-enforcing boundary condition

Jeremías Garay[1,2], David Nolte[1], Cristóbal Bertoglio[1]
[1]University of Groningen, The Netherlands; [2]Pontificia Universidad Católica, Chile

Lumped parameter models, serving as boundary conditions for 3D fluid flow models, offer flexibility in representing neglected domain influences but pose significant computational challenges. While time-explicit coupling in the forward problem leads to conditionally stable time integration schemes, time-implicit solutions necessitate non-local spatial coupling between 0D and 3D compartments, demanding tailored linear algebra methods and multiple 3D model solutions. Additionally, containing several parameters per boundary exacerbates computational complexity in the solution of the inverse problem. This study introduces a new approach inspired by prior works on "Stokes-consistent" backflow stabilization (Bertoglio & Caiazzo 2016) and the method of asymptotic partial decomposition of a domain (Panassenko 1998, Bertoglio et al 2019). Termed "Stokes-enforcing," this boundary condition incorporates a weak integral term and constrains velocity perpendicular to the boundary, effectively extending outlets virtually with specific lengths. Advantages of the Stokes-enforcing boundary condition over standard lumped parameter models include:
+ Enhanced physical accuracy compared to resistive models.
+ Calibration of a single parameter per outlet, accounting for viscous and transient effects simultaneously.
+ Implicit time coupling between 3D and reduced parts, while locally coupling degrees of freedom at the outlet.
+ Direct backflow stabilization in the case of sufficiently large virtual lengths.
In our presentation, we will discuss in particular:
* Theory: derivation, time stability and asymptotic analysis.
* Accuracy: comparison of Stokes-enforcing versus resistive boundary conditions relative to full geometry simulations
* Discretization: Development, efficiency and accuracy of fractional step methods.
* Parametrization: Sequential parameter estimation of virtual lengths from MRI velocity data.
Blood flow simulations in a left coronary arterial tree serve as a pertinent example to demonstrate the efficacy and applicability of the proposed approach.

An investigation into cerebral perfusion sensitivity under different haemodynamic and anatomical variations

Stephen A. Creamer[1], Finbar J. Argus[1], Debbie Zhao[1], Martyn P. Nash[1,3], Julian F. R. Paton[2], Gonzalo Maso Talou
[1]Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand; [2]Department of Physiology, Translational Cardio-Respiratory Laboratory, School of Medical Sciences, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; [3]Department of Engineering Science and Biomedical Engineering, University of Auckland, Auckland, New Zealand

Cardiovascular disease is a leading cause of morbidity, and can have cerebrovascular implications such as stroke and dementia. As both conditions are linked to cerebral perfusion, a better understanding of how anatomical variations in the circle of Willis (CoW) and changes in mean arterial pressure (MAP) can impact perfusion, is needed. This can be achieved with an in-silico model to investigate the sensitivity of perfusion to certain anatomical variations and changes in haemodynamic state. In this work, a closed-loop 0D cardiovascular model was used to investigate cerebral perfusion under different MAP values, vertebral radii, and anatomical variations of the CoW. A previously validated anatomical model of the cardiac and cerebral vasculature was used as a baseline. This model was modified to represent two common CoW variations: i) an incomplete CoW (iCoW) defined in this study as having missing posterior communicanting arteries, and ii) vertebral artery hypoplasia (VAH). Inclusion of posterior communicating arteries, MAP alteration, and change of vertebral radii were investigated to determine the sensitivity of cerebral perfusion to these factors. Cerebral perfusion was taken as the integral of flow at the posterior cerebral artery over one cardiac cycle. Initial findings indicated that when both an iCoW and VAH were present, a 15 mmHg increase in MAP was required to reach the baseline cerebral perfusion. Although significant changes in perfusion were not found in the presence of an iCoW, an iCoW coupled with VAH led to increased perfusion sensitivity to vertebral radius modulation, with a 20% radius reduction leading to an 11% reduction in flow, and a 50% radius reduction led to a 50% reduction of flow. This was not seen when VAH was present with a complete CoW, for which the reductions in flow were only 6% and 10%, for 20% and 50% radius reductions, respectively. This work demonstrates the coupling of cardiac pressure and cerebral anatomy, showing the benefits of vascular redundancy to maintain system homeostasis. These results align with previous experimental observations, and provide a mechanistic rationale to interpret these findings.

Inverse modelling approach to identify model parameters in 0D pulmonary haemodynamic simulation models

Yufei Wang, James Butterworth, Alejandro Diaz De La O, Rebecca Shipley, Ryo Torii
University College London, United Kingdom

Introduction: Pulmonary hypertension (PH) is a rare but often fatal condition characterised by increased pressure in the proximal pulmonary arteries. Due to the strong adaptability of the lung, PH typically has rapid progression and spatial heterogeneity, which poses challenges in clinical diagnostics and treatment. The aim of this study is therefore to construct computational models of those individuals, i.e. virtual patients, which would offer an opportunity to assist clinicians in understanding their pathophysiology and allow the testing of various treatment options without risking patients.

Methods: A closed-loop lumped parameter model (LPM) is used to simulate the haemodynamics of the pulmonary vascular tree, in which each segment has a length, diameter and elastic modulus. By calibrating the LPM using covariance-matrix adaptation evolution strategy (CMA-ES), we construct an inverse modelling framework to identify the model parameters in the LPM based on given flow and/or pressure waveforms that could come from clinical measurement. In this process, the model parameters are sought such that the difference between the output and target waveforms over one cardiac cycle is minimised. In this proof-of-concept stage, we first generate synthetic patients' data, i.e. synthetic pressure and flow rate waveforms using the LPM with a 3 generation pulmonary vascular network in 'forward' approach with a given set of model parameters. The synthetically generated waveforms are then used as targets in the CMA-ES+LPM framework to locate the parameters of an individual synthetic patient, which can be compared against the originally given parameters.
Results and discussion: The parameters of the synthetic patients were successfully identified with an overall accuracy of 0.1%. The calibration process per patient generally involved 100,000 LPM simulations, conducted over 12 hours. The combination of LPM and CMA-ES therefore allows identification of the parameters in PH-LPM with high accuracy. When applied to haemodynamic observation data in clinic, this method could effectively derive physiological parameters of patients and assist doctors in diagnosis and treatment decision making.

Neural networks for efficient sensitivity analysis and parameter estimation of dynamical systems for blood and solute whole-body circulation

John M. Hanna, Pavlos Varsos, Jérôme Kowalski, Roel Meiburg, Irene E. Vignon-Clementel
Inria, Palaiseau, France

0D cardiovascular models are reduced order models aimed to study the global dynamics of the whole circulation system or transport within it. They are employed to obtain estimates of pressures, volumes, flow rates, concentrations in the circulation, which are important biomarkers for surgery planning or assessment applications, or can provide boundary conditions for high fidelity 3D models. Most 0D models suffer from a high number of independent parameters as inputs, easily reaching 40+ parameters in some cases. Many of these parameters are not clinically measurable and to be tuned from patient-specific data, introducing difficulty in their inference process. In this work, metamodels are built for several 0D models with the aim of alleviating this difficulty: here neural networks are chosen because of their accurate and fast prediction abilities. The neural network models have reduced number of inputs that are mostly clinically relevant or easy to measure, thus simplifying the use of 0D models. The models are trained and tested on synthetic data generated from the 0D models. The built metamodels are differentiable which paves the way to solve inverse problems in seconds or few minutes. Moreover, sensitivity analysis can also be performed on the input parameters. Three different 0D models are studied in this work. The first is a lumped model aimed at predicting the pressure in the portal vein after surgery. Due to the strong interaction between local liver hemodynamics and the global circulation, the full circulation is modeled. The second one is simulating the whole-body circulation under the conditions of Pulmonary Arterial Hypertension. It is targeted for intervention planning, specifically regarding the acquisition of a pulmonary-to-systemic shunt (namely Potts shunt), predicting its impact on cardiac function and overall physiology. The final model is aimed to assess the blood perfusion of an organ after a revascularization surgery, the transport of indocyanine-green (a fluorescent agent) is modeled on top of a simplified 0D hemodynamics model. This work thus provides an efficient framework for sensitivity analysis and parameter estimation.

Comparison of 4D flow magnetic resonance imaging with blood flow simulations before and after left atrial appendage occlusion

Paula Casademunt[1], Xabier Morales Ferez[1], Jordi Mill[1], Carlos Albors[1], Íñigo Anduaga[2], Pedro Cepas[2], Ada Doltra[2], Xavier Freixa[2], Oscar Camara[1]
[1]Pompeu Fabra University, Department of Information and Communications Technologies, Barcelona, Spain; [2]Hospital Clínic, Universitat de Barcelona, Cardiovascular Institute, Barcelona, Spain

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 1/3 of the population over their lifetime. This pathology increases the risk of thrombus formation, particularly in the left atrial appendage (LAA). LAA occlusion (LAAO) can mitigate stroke risk in AF patients, separating the LAA from the rest of the left atrium (LA) with a device. State of the art proposes computational fluid dynamics (CFD) simulations to assess the risk of thrombus formation, as it has a superior resolution than current imaging techniques. However, further verification and validation experiments following V&V40 standards are needed to increase the credibility of flow simulations in the LA. Comparing blood flow simulations including LAAO devices with data such as 4D flow magnetic resonance imaging (MRI) can provide further evidence on the realism of the CFD simulations. Our unique dataset includes 4D flow MRI of the LA, cardiac computed tomography (CT) scans and Doppler ultrasound (US) of the mitral valve (MV) plane for 5 patients (5 pre-LAAO; 5 post-LAAO, 3 of which had leaks). We developed patient-specific CFD simulations integrating CT and US data, which were compared to 4D flow MRI blood flow patterns. Both modalities allowed a clear visualization of blood flow entering the LAA in post-LAAO cases with leak, potentially leading to the development of thrombi. The patterns in Endothelial Cell Activation Potential (ECAP) were consistent between CFD data and 4D flow MRI, although higher mean values were reported by 4D flow MRI. In pre-LAAO cases, the velocity root mean square error (RMSE) between 4D flow MRI and simulations was 0.06 m/s at the LAA ostium plane and 0.09 m/s at the MV. Comparing post-LAAO cases, the velocity RMSE at the pulmonary ridge was 0.11 m/s, and 0.06 m/s at the MV. However, blood flow patterns near the device were compromised in the imaging data due to acquisition noise. Our study underscores the relevance of validating these simulations and performs initial steps by comparing the flow dynamics of CFD models and 4D flow MRI. This is the first study to analyze 4D flow MRI data with implanted LAAO devices and compare it to CFD simulations.

Quantitative perfusion assessment: A mechanistic model to interpret dynamic imaging

Jérôme Kowalski[1], Stefan Koning[2], Lorenzo Sala[3], Roderick C. Peul[2], Mo W. Kruiswijk[2], Joost R. Van der Vorst[2], Irene Vignon-Clementel[1]
[1]Inria Saclay, France; [2]Leiden University Medical Center, The Netherlands; [3]Inrae, France

To assess blood perfusion of an organ, during or after surgery, clinicians can inject a fluorescent agent in the patients' blood and dynamically follow its transport by imaging the region of interest. This technique is however rather qualitative and can be enhanced through the interpretation of dynamic imaging. This consists in taking snapshots through time, and analyzing the obtained time-intensity curves to extract blood flow parameters. We here study the perfusion of the feet, following a revascularization surgery in peripheral artery disease patients. We present a mechanistic model, based on reduced hemodynamic and pharmacokinetic methods. In our approach, key body parts are represented as compartments, here the heart, the legs (as organs of interest), and the other organs connected through other compartments representing the main arterial and venous circulations. The blood circulation is represented by Windkessel models in the closed loop system, driven by the heart as a blood flow generator. On top of that, transport of the substance is calculated, assuming an injection point in the veins before the heart, and the slow uptake of the contrast agent by the liver. Each compartment modifies the received time-concentration profile through a specific transfer function. It fully characterizes the transport behavior and directly correlates to the vascular architecture of the represented organ. The model reproduces the clinically observed behavior with good precision. The biomarkers identified by surgeons in their clinical practice as characterizing the patient feet perfusion, are selected to assess the sensitivity of the model to the patients' characteristics. A variance-based global sensitivity analysis highlights the most impactful parameters: the outcome is coherent with clinical practice. Ultimately the model enables to successfully retrieve foot perfusion. Future plans involve refining the model by including information on vascular architecture for a comprehensive representation of a larger number of vascular anomalies. This innovative approach marks a significant step forward in achieving a more quantitative and informative understanding of perfusion dynamics.

4.C: M&S Reproducibility, Credibility, and Translation

Thursday, September 5

10:30am – 12:00pm

07.017

A rubric for assessing conformance to the ten rules for credible practice of modeling and simulation in healthcare

Alexandra Manchel[1], William W. Lytton[2,3], Jerry G. Myers Jr.[4], Ahmet Erdemir[5], Marc Horner[6], Bruno V. Rego[7], Lealem Mulugeta[8], Joy P. Ku[9], Rajanikanth Vadigepalli[1]

[1]Department of Pathology and Genomic Medicine, Thomas Jefferson University, Philadelphia, PA, USA; [2]Downstate Health Sciences University, Brooklyn, NY, USA; [3]Kings County Hospital, Brooklyn, NY, USA; [4]NASA - John H Glenn Research Center, Cleveland, OH, USA; [5]Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, OH, USA; [6]Ansys Inc. Evanston, IL, USA; [7]Department of Biological & Agricultural Engineering, Louisiana State University, Baton Rouge, LA, USA; [8]InSilico Labs LLC, Houston, TX USA; [9]Department of Bioengineering, Stanford University, Stanford, CA, USA

The power of computational modeling and simulation (M&S) is realized when the results are credible, and the workflow generates evidence that supports credibility for the context of use. The Committee on Credible Practice of Modeling & Simulation in Healthcare was established to help address the need for processes and procedures to support the credible use of M&S in healthcare and biomedical research. Our community efforts have led to the Ten Rules (TR) for Credible Practice of M&S in life sciences and healthcare. This framework is an outcome of a multidisciplinary investigation from a wide range of stakeholders beginning in 2012. Here, we present a pragmatic rubric for assessing the conformance of an M&S activity to the TR. This rubric considers the ability of the M&S to facilitate outreach of the results to a wide range of stakeholders from context-specific M&S practitioners to policymakers. It uses an ordinal scale ranging from Insufficient (zero) to Comprehensive (four) that is applicable to each rule, providing a uniform approach for comparing assessments across different reviewers and different models. We used the rubric to evaluate the conformance of two computational modeling activities: 1. six viral disease (COVID-19) propagation models, and 2. a model of hepatic glycogenolysis with neural innervation and calcium signaling. These examples were used to evaluate the applicability of the rubric and illustrate rubric usage in real-world M&S scenarios including those that bridge scientific M&S with policymaking. The COVID-19 M&S studies were of particular interest because they needed to be quickly operationalized by government and private decision-makers early in the COVID-19 pandemic and were accessible as open-source tools. Our findings demonstrate that the TR rubric represents a systematic tool for assessing the conformance of an M&S activity to codified good practices and enhances the value of the TR for supporting real-world decision-making.

The automated construction and verification of physically plausible models of physiological systems

Mehran Akbarpour Ghazani[1], Michael Pan[2], Kenneth Tran[1], David Nickerson[1]
[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]School of Mathematics and Statistics, Faculty of Science, University of Melbourne, Australia

In recent years, mathematical models have played an increasing role in studying biology, with combinations of numerical and experimental methods being increasingly used. Despite the rapid growth in numerical modelling, rigorously verifying these formulations against physical laws is often overlooked. Computational models of biological systems are intricate and reliant on a deep understanding of complex biophysical processes, often requiring diverse mathematical formulations and encompassing large parameter spaces. As such, they are prone to errors and oversights. Therefore, there is a pressing need to develop pre-emptive tools that can identify and rectify errors before running simulations and applying these models in practical settings. In particular, a verification tool not only saves valuable time but also ensures compliance with the laws of physics. Here, we propose two distinct approaches applicable to CellML models in the Physiome Model Repository. The first approach involves converting models into Bond Graph counterparts. Representing a model through bond graphs guarantees adherence to the principles of physics and thermodynamics. The second approach, which we are currently developing, is for those CellML models not suited to the first approach. Using semantic annotations and analysis of the mathematical expressions defined by the model, we construct stoichiometric and elemental matrices to verify compliance with the conservation of mass. This comprehensive approach enables the identification of errors in formulations and provides specific references to the location of these errors for debugging purposes. Laying the foundation to extend our work to rigorously verify models and produce physically plausible models of physiological systems.

From clinical measurements to parameter personalisation: An end-to-end standardised framework to navigate computational physiology workflows

Mathilde A. Verlyck[1], Debbie Zhao[1], Martyn P. Nash[1,2], David P. Nickerson[1], Thiranja P. Babarenda Gamage[1]
[1]Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand; [2]Department of Engineering Science and Biomedical Engineering, University of Auckland, Auckland, New Zealand

INTRODUCTION: Computational physiology models provide valuable disease detection, diagnosis, and treatment insights. The clinical translation of these models lies in the potential to personalise their parameters based on patient-specific measurements using computational workflows. Yet, multiple workflows may define a given parameter. We aim to simplify the navigation of existing workflows for parameter personalisation by identifying the most suitable workflows based on available clinical measurements.
METHODS: A standardised description layer using the Common Workflow Language (CWL) is added to each computational physiology model, and an accompanying JSON file outlines their standardised inputs and outputs, adhering to the Unified Medical Language System (UMLS) terminology. These established standards facilitate the automatic population of a knowledge graph based on the JSON descriptions. The knowledge graph is built upon a simplified version of the EDAM ontology, featuring two primary classes: Operation and Data. The models are categorised under the Operation class, while the inputs and outputs are assigned to the Data class. Once the knowledge graph is generated, querying a parameter is achieved through its associated UMLS concept unique ID. The query returns workflows described in CWL and their corresponding input combinations for personalisation of the queried parameter. Finally, the workflows can be filtered based on available clinical measurements.
RESULTS: We have established a framework standardised with CWL for model and workflow descriptions and UMLS for data representation. We verified the framework by personalising the cardiac peak global longitudinal strain. Our workflows enable the calculation of peak strain either from the time-varying 3D mesh or the strain curve, depending on the availability of the inputs. This demonstrates the derivation of personalised values using different sets of measurements.
CONCLUSION: This framework enables navigation through available workflows for parameter personalisation. Future work includes integrating additional features like cost, time, and standard errors, alongside the workflow information to inform the selection.

Multiscale agent-based virtual-tissue models: Working towards reproducible and reusable models

James A Glazier
Indiana University, United States of America

The relationship between health, disease, and therapy depends on how molecular states translate into physiological outcomes at tissue and organ levels. Predicting larger-scale outcomes from molecular data is complex due to feedback across cellular, multicellular, organ, and organismal scales. Virtual Tissue simulations, utilizing an Agent-Based, middle-out approach, start by modeling cell behaviors and interactions and then scale up and down to different biological levels. These simulations have helped advance understanding of development, homeostasis, disease mechanisms and toxicology. Integrating Virtual Tissue models into drug-discovery and clinical workflows holds significant potential for therapy discovery and the development of personalized Medical Digital Twins. However, the community is fragmented, with multiple, frameworks with proprietary model-description approaches and back-end APIs, which slows model development and impedes the development of trust. To improve the utility of Virtual-Tissue Models requires the development of a culture of shared model development and reuse, as well as standardized descriptions of biological processes and model implementations and a shift towards community-based development and validation. A number of efforts in Europe and the USA are working to support this transformation, including OpenVT (funded by the US National Science Foundation) and we invite the expertise and participation of the broader biomedical research and translational community to help navigate this journey.

Influence of dependent parameters on the predictive uncertainty of biomechanical models: Insights from global sensitivity analysis

Sebastian Brandstaeter, Alexander Popp
University of the Bundeswehr Munich, Germany

Acknowledging the uncertainty in biomechanical model predictions is paramount, especially when they aid clinical decision-making, given the high stakes involved. This uncertainty stems, among others, from incomplete knowledge of model parameters. Thus, determining the extent to which input parameter uncertainty contributes to overall model output uncertainty is crucial. Our recent research highlights the essential role of variance-based global sensitivity analysis, utilising Sobol indices, in identifying influential and uninfluential parameters within complex biomechanical models [1, 2]. Yet, Sobol's method assumes parameter independence, a notable limitation since dependencies among the parameters – in the form of correlations or algebraic constraints – are known in many models. Hence, a global sensitivity analysis framework that overcomes this restriction is needed. We showcase that Shapley effects [3] can be used for this. The method's properties and capabilities are demonstrated through examples, illustrating its ability to quantify the impacts of dependent parameters on the predictive uncertainty of biomechanical models. In conclusion, the framework presented in this study provides an important tool for the reliable predictive use of biomechanical models by broadening the application of global sensitivity analysis to a large class of models: those featuring dependent input parameters.

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KNEEHUB: A Resource for end-to-end modeling & simulation workflows in computational knee biomechanics

Snehal Chokhandre[1], Peter Laz[2], Thor Besier[3], Jason Halloran[4], Carl Imhauser[5], Kevin Shelburne[2], Ahmet Erdemir[1]
[1]Cleveland Clinic, United States of America; [2]University of Denver, United States of America; [3]University Auckland, New Zealand; [4]Washington State University, United States of America; [5]Hospital for Special Surgery, United States of America

Reproducibility is essential for establishing scientific credibility. Yet, this is particularly challenging in computational modeling approaches due to lack of unified processes. For computational knee biomechanics, our project KNEEHUB [1] set out to understand how modeling decisions influence predictions of modeling and simulation use cases for the same knee, given the same data. We quantified the influence of workflow variations on the reproducibility of joint and tissue level predictions with participation from five knee modeling teams. The activities were staged to include Model Development, Calibration, Benchmarking, and Reuse [2]. The goal of this study is to document and disseminate the diverse array of digital assets from KNEEHUB as a resource. Deep documentation of modelers' choices provides workflow variations and a comprehensive understanding of the art of modeling in computational knee biomechanics. The impact of these variations on the predictive uncertainty of models (of the same knee) raised notable concerns for reproducibility of simulation outcomes. We have shown that even when source data and target simulation scenarios remain the same, modelers exhibit large variations in their choices. These uncertainties collectively reflect on differences in predicted simulation outputs. Thus, dissemination of source data, diverse workflows (x5) to conduct similar M&S tasks (specifications and protocol deviations), and staged outcomes of all these workflows (derivative data, models at different stages, simulation outputs) provide an opportunity for others to learn from, test and reuse different modeling strategies. Our findings imply that without unified modeling and simulation processes, the simulation outputs are dependent upon the subjective decisions of the modeler. Sharing this resource will facilitate efforts to establish unified, and ideally standardized, approaches.

References: [1] https://simtk.org/projects/kneehub [2] DOI: 10.1115/1.4043346

4.D: Cellular & Systems Biology I

Thursday, September 5

10:30am – 12:00pm

02.005

Use of bond graphs and scaffolds for modelling physiology

Peter Hunter
University of Auckland, New Zealand

Bond graphs provide a useful level of abstraction for modelling protein function for a wide range of protein functions … metabolic reactions, membrane transporters and ATPase pumps, myofilament mechanics, receptors and signalling, etc. They can also be used for modelling at the level of systems physiology (e.g. for understanding homeostasis of blood electrolytes, blood pressure and fluid volume, etc). This talk will show how bond graph approaches ensure that the equations of physics (conservation of mass, charge and energy, respectively) are automatically satisfied, and how they can generate CellML-encoded models both at the level of proteins and intracellular mechanisms and at the whole-body systems level. Scaffolds, based on high-order finite element descriptions of anatomical structure, provide a powerful way of capturing spatial fields at multiple physiological scales. The talk will also discuss how scaffolds can be used for obtaining the lengths, areas and volumes of tissue structure that enable protein models to be coupled to systems physiology models.

Using a systems biology approach to construct adverse outcome pathway networks aligned with the FAIR principles

Luiz Ladeira[1], Alexander Mazein[2], Marek Ostaszewski[2,3], Anouk Verhoeven[4], Ahmed Hemedan[2], Eliska Kuchovska[5], Julen Sanz-Serrano[4], Annika Drees[4], Kristin Reiche[6,7], Katherina Sewald[8], Ellen Fritsche[9,10], Venkata Satagopam[2,3], Mathieu Vinken[4], Liesbet Geris[11,12], Bernard Staumont[1]

[1]Biomechanics Research Unit, GIGA In Silico Medicine, University of Liège, Belgium; [2]Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Belvaux, Luxembourg; [3]ELIXIR Luxembourg, Belvaux, Luxembourg; [4]Vrije Universiteit Brussel, IVTD research group, Brussels, Belgium; [5]IUF - Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany; [6]Department of Diagnostics, Fraunhofer Institute for Cell Therapy and Immunology, Leipzig, Germany; [7]Center for Scalable Data Analytics and Artificial Intelligence (ScaDS.AI), Dresden/Leipzig, Germany; [8]Institute of Clinical Immunology, Medical Faculty, University Hospital, University of Leipzig, Leipzig, Germany; [9]DNTOX, Düsseldorf, Germany; [10]Swiss Centre for Applied Human Toxicology, Basel, Switzerland; [11]Skeletal Biology and Engineering Research Center, KU Leuven, Belgium; [12]Biomechanics Section, Department of Mechanical Engineering, KU Leuven, Belgium

Adverse Outcome Pathways (AOPs) connect molecular initiating events to adverse outcomes through key events (KE), which are crucial to understanding chemical exposure and adverse health effects. To comply with FAIR principles, AOP graphical representations are being made machine-readable. The Systems Biology Graphical Notation (SBGN) elements enhance AOPs with standardized graphical notation, improving visualization and interpretability, as introduced by Mazein and collaborators (2023). In addition, van Ertvelde and collaborators (2023) used AI-based systematic review, data screening, and curation, introducing an accelerated way to build large AOP networks. In this sense, we developed a workflow addressing challenges and opportunities in developing SBGN-based AOP networks and proposing scalable solutions that can be adjusted to meet various demands. This approach integrates data acquisition methods with automated network construction, followed by manual graphical improvements. Our workflow consists of: a) data checking, annotation and disambiguation; b) automated data processing; c) conversion into a CellDesigner SBML network, using R scripts applying functions from the minervar package; d) manual design editing for improved layout and human interpretability. The MINERVA platform was used for automated annotation, visualization, and exploration of the network. This approach was applied to extended case-studies with different data acquisition methods highlighting its versatility. The proposed approach leverages established standards and automated methods to expedite machine-readability and ensure FAIR principles compliance in AOP networks. Utilizing the proposed workflow in constructing AOP networks not only boosts reproducibility and interoperability but also facilitates the development of more accurate and biologically relevant networks. The incorporation of KE descriptors and biology enrichment expands mechanistic relevance, improving the overall accuracy and comprehensiveness of the AOP networks.

Agent-based modelling of cell biomechanics using the open-source platform BioDynaMo

Vasileios Vavourakis[1,2], Roman Bauer[3]
[1]University of Cyprus, Cyprus; [2]University College London, UK; [3]University of Surrey, UK

In silico models in computational cell biomechanics are usually confronted with the fact that they need to capture processes across multiple spatial/temporal scales. These processes play out intracellularly, such as for instance gene regulatory dynamics, as well as extracellularly, such as their interactions with the extracellular matrix and parenchymal components. Agent-based modelling (ABM) alone, or via hybrid multiscale procedures, is an attractive approach to explore complex biological processes. ABM is a complex-system modelling method that assumes autonomous, interactive 'agents' that are denoted as particles (i.e., cell bodies) or segments (e.g., neurites, vessels), positioned in 2D/3D-space following an off-lattice approach, and 'agent behavior' is determined by rules as a Markov process. In this contribution, we demonstrate ABM in biomedical applications using the open-source simulation platform BioDynaMo (www.biodynamo.org). It can encompass the interactions with other cells and responses to external stimuli, their ability to secrete and/or take up cytokines, enzymes, etc. Thus, BioDynaMo implements ABM, and it has been designed to leverage modern software engineering techniques for high-performance computing using distributed computing procedures. In this talk, we will present a selection of examples to demonstrate the simulation of biological cell growth and development (e.g., in cancer and wound healing/inflammation), therapy, and cell pathophysiology in chronic diseases.

Metabolic digital twins of people with diabetes

Ryan de Vries[1], Harm Haak[2], Natal van Riel[1]
[1]Eindhoven University of Technology, The Netherlands; [2]Máxima MC, Department of Internal Medicine, Eindhoven, The Netherlands

Diabetes mellitus is a disease characterized by dysregulated blood glucose levels due to insulin deficiency or resistance and deteriorating insulin production capacity. Preventing chronically elevated glycemic levels is imperative to minimize the risk of complications (e.g. cardiovascular diseases and neuropathy), requiring persistent self-management by patients. Nonetheless, glycemic dynamics are impacted by the interplay of everyday behavior like dietary intake, physical activity, and insulin dosing. To gain further insight into daily glycemic dynamics at an individual level, data collected in daily-life settings through wearable devices and applications provide easily acquirable personal information. Therefore, we have measured data from sixty participants (52 type 2 diabetes, 8 type 1 diabetes) using a continuous glucose monitor, smartwatch with in-house software, and public smartphone application acquiring data on blood glucose levels, heart rate, step count, acceleration, participant-reported dietary intake, physical activity, insulin dosing, and mood. Subsequently, these data are used to develop metabolic digital twins. The model we are using to capture glycemic dynamics is a physiology-based mathematical model of the glucose-insulin system. This model describes glucose and insulin concentrations following a mixed meal or glucose drink and has previously been validated on meal tolerance tests in various cohorts (diabetes, obese, overweight). Current work focuses on extending the model to describe the subcutaneous absorption of various insulin analogues and leveraging the multimodal data to create digital twins outside of a clinical setting. Furthermore, the ability of the model to capture glycemic dynamics of people with type 1 diabetes, who lack endogenous insulin production, is evaluated. Future work should consider residual insulin production capacity in people with type 2 diabetes at an individual level. These digital twins elucidate the independent and coherent effects of various lifestyle factors on glycemic dynamics. Ultimately, these digital twins will be employed to aid self-management education through a personalized interactive serious game.

A computational analysis of coupled glycolytic, oxidative ATP synthesis, and energy and pH balance in contracting fast-twitch muscle fibres

Jana Disch[1], Thomas Klotz[1], Daniel Beard[2], Jeroen Jeneson[3,4], Oliver Röhrle[1,5]
[1]Institute for Modelling and Simulation of Biomechanical Systems, University of Stuttgart, Germany; [2]Department of Molecular and Integrative Physiology, University of Michigan, USA; [3]Centre for Child Development and Exercise, Wilhelmina Children's Hospital, University Medical Centre Utrecht, the Netherlands; [4]Biomedical MR Research Lab, Department of Nuclear Medicine and Radiology, Amsterdam University Medical Centre|site AMC, the Netherlands; [5]Stuttgart Centre for Simulation Science (SC SimTech), University of Stuttgart, Germany

The range and variability of motor tasks are afforded by the tight coupling of motor control and an adaptive metabolic network that can manage both 100-fold jumps as well as hour-long elevations in ATP demand. However, the control mechanisms of ATP homeostasis and hence muscle fatigue are not fully understood due to a lack of experimental or theoretical methodologies that afford to simultaneously study muscle contraction and metabolism. In vitro animal studies are ethically controversial and no longer reflect an intact physiological system while in vivo 31P MR spectroscopy is limited to a small number of metabolites. Existing computer models provide limited insights into the physiology or can not capture the whole working range of muscles. To provide essential information for understanding the regulation of ATP metabolism and to investigate how muscle manages perturbations in proton and redox balance, we developed a computational model that sufficiently captures hereto necessary biochemical interactions including redox coupling of glycolysis and oxidative phosphorylation. The model describes the thermodynamically constrained kinetics of a biochemical reaction network by a set of differential algebraic equations to quantify metabolites associated with ATP metabolism and the pH dynamics in an open system. The network was parameterized for a fast-twitch oxidative glycolytic muscle fiber. Parameters were identified through dynamic in vivo recordings of metabolite and pH levels in rodent fast-twitch muscle and validated against independent datasets. The conducted simulations showed that feedback regulation of the metabolic pathways adequately explained energy balance over a 100-fold dynamic range of ATP turnover rates in this in silico fiber. The proposed model provides a new platform to test hypotheses in muscle physiology. Specifically, the model can predict internal variables that are not directly measurable to bridge the gap between the cellular function and in vivo measurements of human muscle performance. This knowledge could provide a new, rational basis for clinical decisions and tailored design of physical training to improve care for (neuro)muscular diseases.

4.E: Lung Modelling I

Thursday, September 5

10:30am – 12:00pm

02.011

Multiscale modelling and estimation of lung poromechanics

Martin Genet, Alice Peyraut
École Polytechnique, France

In this talk, I will present recent and ongoing works first on the modeling of the lungs at both alveolar, tissue, and organ scales; then on the estimation of such model parameters based on clinical data toward clinical applications. More specifically, starting with tissue scale modeling efforts, I will introduce a general theory of poromechanics, and describe constitutive choices suitable for the lungs. Then, at the organ scale, I will introduce various sets of boundary conditions that we proposed for the lungs, describing the organ environment with various levels of details. I will finish the modeling part of the talk with current work at the alveolar scale, including a consistent formulation of the micro-poro-mechanics problem as well as a bridge between micro- and macro- poro-mechanics. In the second part of the talk, I will present the personalization pipeline we designed alongside the model, in order to personalize parts of the model geometry, behavior and boundary conditions based on clinical data. This allows to build digital twins of patient organs, which could serve as biomedical engineering tools to better diagnose, prognose and ultimately treat various diseases. I will also detail our novel undertainty quantification pipeline, which allows to quantifiy the confidence that we can have in the biomarkers estimated by combining the model and images, taking into account both measurement and modeling errors. As an example, I will discuss early results obtained on Idiopathic Pulmonary Fibrosis, a progressive form of interstitial lung disease that has a strong impact on the tissue mechanical properties and could be strongly influence by the tissue stresses and/or strains, but that remains poorly understood, poorly diagnosed, and poorly treated.

A coupled multi-dimensional multiphase porous media approach for modeling the respiratory and circulatory system of the human lungs including gas exchange

Lea J. Köglmeier, Carolin M. Geitner, Buğrahan Z. Temür, Barbara Wirthl, Wolfgang A. Wall
Institute for Computational Mechanics, Technical University of Munich, Garching b. München, Germany

Mechanical ventilation is a life-saving therapeutic tool for treating patients with impaired pulmonary function, yet it carries the risk of ventilator-induced lung injury (VILI). The primary barriers hindering more protective ventilation strategies are still insufficient knowledge and understanding of complex lung mechanics, mainly due to the limited ability for in vivo measurement or imaging techniques. To shed light into this issue, great efforts have been made in developing computational lung models. However, most

of these works only focus on studying the effects of ventilation on tissue strains and stresses, while coupling with the pulmonary circulation is mostly neglected so far. This is despite the fact that the lungs' main function, gas exchange, takes place through a dense network of blood vessels in the alveolar walls, and damage caused by improper ventilation is characterized by the impairment of this vital interface.
In this contribution we therefore present a physics-based coupled approach to computationally model the respiratory and the circulatory system of the human lungs. Motivated by the structure of the lungs, larger airways and blood vessels are modeled as discrete zero-dimensional (0D) networks that are embedded into a three-dimensional (3D), multiphase porous medium, representing the smaller airways, smaller blood vessels and lung tissue. Further, the respiratory gases, oxygen and carbon dioxide, are modeled as chemical subcomponents of air and blood with a suitable exchange model in the porous domain. To connect the homogenized and the discrete representations of airways and blood vessels, respectively, we developed a 0D-3D coupling method that allows a non-matching spatial discretization of both domains.
Such a comprehensive coupled approach allows us to study the complex interplay of tissue deformation and perfusion including pathological conditions such as transcapillary leakage - a hallmark of VILI - and its effects on oxygenation and carbon dioxide release. We consider our model to be a promising base for investigating clinically relevant questions, which will contribute to an improved treatment in respiratory care.

Personalised computational models of paediatric lung structure from novel lung MRI

Ho-Fung Chan[1,2], Megan Soo[1], Haribalan Kumar[1,2,3], Daniel Cornfeld[2], Paul Condron[2,4], Taylor Emsden[2,4], Leigh Potter[2], Samantha Holdsworth[2,4], Merryn Tawhai[1]
[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Mātai Medical Research Institute, Gisborne, New Zealand; [3]GE Healthcare Australia-New Zealand; [4]Faculty of Medical and Health Sciences, University of Auckland, New Zealand

Background: Personalised computational physiology models of the paediatric lung are scarce because existing lung models rely on adult lung CT imaging. The latest lung MRI techniques can provide novel regional lung structure-function information without ionising radiation. This makes MRI a promising clinical tool for paediatric lung disease management and provides an opportunity to derive new computational structure-function lung models for children. Here, we utilise novel lung MRI to develop personalised computational models of paediatric lung structure.
Methods: Nine healthy children (8-11 yrs) underwent novel 3D zero echo time (ZTE) lung MRI (1.5mm isotropic voxel) on a 3T GE SIGNA Premier scanner. The lung cavity and central airways were segmented from ZTE lung MRI. MRI intensity values within the lung cavity were normalised to chest muscle signal and the resultant values approximated true density. Personalised models of the airway tree and lung soft tissue mechanics were then created using in-house code (github.com/LungNoodle/lungsim). Airway trees were generated from a volume-filling branching algorithm that utilised the central airways as initial conditions and the lung cavity as the constraining boundary. A curvilinear volumetric finite element mesh was fitted to the lung cavity for simulation of soft tissue deformation mechanics in the supine posture. The tissue mechanics model was validated by comparing the tissue density in 10mm bins along the dorso-ventral gravitational direction to the equivalent normalised ZTE lung MRI density bins.
Results: Personalised lung airway trees and soft tissue mechanics models were derived from ZTE lung MRI in all nine children. The mean slice bin difference in MRI- and model-derived densities across all subjects was 10.6±4.0% indicating that the tissue mechanics model can simulate regional changes in tissue density.
Conclusion: This work demonstrates the feasibility of creating personalised paediatric lung structure models from novel lung MRI. In future work, MRI-based lung function models of ventilation and perfusion will be developed to simulate different aspects of paediatric lung structure and function.

A framework to characterize phenotype-specific models of the lung from CT imaging

Joyce John, Kelly Burrowes, Merryn Tawhai
Auckland Bioengineering Institute, The University of Auckland, New Zealand

Using computational modelling of lung physiology to understand various pathology is emerging as a powerful tool for optimizing treatment strategies. The existing models are usually generic or patient-specific, with advantages and disadvantages. We seek to develop phenotype-specific models of the healthy never-smoking lung, smokers without lung disease, and pathologies that affect the lung tissue. In this study, we present a novel approach to utilize various quantitative computed tomography (QCT) tools to characterize structural features of the lung, to inform phenotype-specific computational models. Our framework segments the lung and fissure surfaces from volumetric CT imaging, fits a scaffold mesh to the surface data, and derives a statistical shape model for each cohort. Shape is compared between cohorts by projecting individual shape models to the average for another cohort. We then evaluate the distribution of tissue density and tissue heterogeneity on CT imaging using quadtree decomposition (QtD). The spatial distribution of both metrics, mapped to the shape models, are used to validate simulations of soft tissue mechanics deformation. They are also used to derive average representations for each cohort. Graph-based algorithms are then used to extract pulmonary vascular structures, and to quantify arterial and venous morphometry and blood volume. Averaged spatial distribution and tree size are calculated for each cohort, and are used to initiate volume-filling tree generation models. Our shape analysis has revealed clusters of shape that align with pathological cohorts. QtD appears significantly higher than healthy in smoking and in diseases that both increase (fibrosis) and decrease (COPD) mean tissue density, but with different characteristic distributions. And, compared with healthy, pulmonary vessel-like volumes are higher in fibrosis and lower in COPD. In summary, our study demonstrates the capability of QCT tools to characterize models that represent specific cohorts or phenotypes. This provides a tool for studying the interactions between tissue properties, shape and volume change, and tissue perfusion during the evolution of lung disease.

Identification of expiratory WOB in active expiration with imposed non-linear resistance

Jaimey A. Clifton, Ella F. S. Guy, Trudy L. Caljé-van der Klei, Lui Holder-Pearson, J. Geoffrey Chase
University of Canterbury, New Zealand

Background: Respiratory disease is a growing healthcare crisis. Model-based pulmonary assessment methods offer the potential for automation of respiratory care to increase productivity and equity-of-access to care, as well as to personalise care. Single compartment lung models can effectively identify lung mechanics and inspiratory work of breathing (WOB). Previously, WOB has only been determined on inspiration as expiration is assumed passive. This assumption is invalid in some cases of respiratory disease, including Chronic Obstructive Respiratory Disease (COPD), where added expiratory resistance due to flow limitation requires active expiratory effort to overcome.

Methods: This study assesses expiratory WOB identification in 20 healthy subjects with an added (external) resistance to exhalation, and with increasing (0, 4, and 8 cmH_2O) positive end-expiratory pressure (PEEP). The elastic (E) component of the model was identified using the control tests at 0 cmH_2O (ZEEP) and resistance (R) assumed to be constant (2.25 cmH_2Os/L). The additional expiratory resistance and WOB mechanics were identified using 2^{nd} order b-splines, as a Non-linear Resistance WOB (NRWOB) term.

Results: All subject's data showed the NRWOB term decreased exponentially with increasing PEEP, as expected. The NRWOB value normalised by tidal volume was 70.7 at ZEEP, 45.6 at 4cmH20, and 33.4 at 8cmH20.

Discussion: Currently, the added resistance to simulate COPD is indistinguishable from added WOB within the identified NRWOB value. Thus, the NRWOB term is not an accurate estimation of the true WOB value due to the added resistance. Therefore, another method is required to identify the individual contributions of non-linear added expiratory resistance and WOB, as well as to identify passive mechanics (E and R). Future work should examine methods, such as implementing rapid expiratory occlusion (REO) techniques to separately identify the passive mechanics and added expiratory resistance, allowing the identification of WOB without parameter trade-off.

4.F: High-Performance Computing

Thursday, September 5

10:30am – 12:00pm

09.019

HPC in Biomechanics - Challenges, Current Research and Future Opportunities

Johannes Gebert, **Benjamin Schnabel**
High-Performance Computing Center Stuttgart, Germany

In silico models significantly improved our understanding of biomechanics by enabling experiments and predictions that are inaccessible through traditional methods. These patient-specific and generic models advance our understanding of complex systems, such as fluid-structure, musculoskeletal, and bone-implant interactions.
The basis of these models is medical imaging, which includes data acquisition and segmentation. Such data and the corresponding software combined allow for reproducing results anytime. We shed light on our current approach to versioning and referencing software and data with tools and platforms like Git and the data repository of the University of Stuttgart (DaRUS).
Our talk focuses on the biomechanical challenges addressed by the High-Performance Computing Center Stuttgart (HLRS), spotlighting current research on patient-specific mechanical properties in vivo, the process of inserting bone screws, patient-specific aortic models, and future opportunities, e.g., virtual clinical trials. Accurate dynamic and time-dependent systems are an additional near-future field of research.
Developing biomechanical models poses significant challenges, particularly regarding computational demands and the necessity for high-performance computing (HPC) methods and capabilities. HLRS provides and uses its extensive HPC infrastructure to tackle these challenges, employing computational techniques such as virtual clinical trials, computational fluid dynamics, finite element analysis, multibody dynamics, and coupled multiphysics simulations. We also give an insight into enhancing existing software to suit the massively parallel characteristics of HPC systems for solving large-scale simulations.
In conclusion, we highlight how HLRS addresses the biomechanical challenges through its computational resources and improves the state of research in biomechanics.

A user interface to facilitate visualization and integration of predictions for mechanical femur strength.

Massimiliano Mercuri[1], Filippo Nardini[2], Cristina Curreli[3], Antonino A. La Mattina[3], Sabato Mellone[2], Marco Viceconti[1,3]
[1]Department of Industrial Engineering, Alma Mater Studiorum - University of Bologna, Bologna, Italy.; [2]Department of Electrical, Electronic and Information Engineering, University of Bologna, 40126 Bologna, Italy; [3]Medical Technology Lab, IRCCS Istituto Ortopedico Rizzoli, Via di Barbiano 1/10, 40136, Bologna, Italy.

Over the past two decades, there has been extensive research and development in the field of image-based Finite Element (FE) modeling techniques for numerically predicting bone strength arising from pathological conditions such as osteoporosis. While multiple workflows have been adopted to enhance clinical and research translation, many still require manual data handling, limiting their systematic applicability. Here, we present a powerful, customizable, and ergonimic Graphical User Interface developed to set up the FE models, run the analyses and visualize simulation results of surrogate biomarkers for femur fracture endpoints. An application GUI was developed to integrate the BBCT-hip workflow, leveraging the Visualization Toolkit for advanced medical image manipulation. The software integrates five main functionalities:

- Integrates with the medical record software and PACS server to load images and patient data from the list of patients associated with the specific healthcare professional. Data includes height, weight, sex, age, and CT scan images.
- Implements a robust volume-rendering process for visualizing the femur region. Femur geometry can be loaded in STL format or directly obtained through automatic/semi-automatic segmentation using a graph cut approach. Direct comparison with CT slices in 3D and 2D verifies the segmentation strategy.
- Allows the user to identify, visualize, and modify anatomical points in the 3D view, crucial for setting boundary conditions for the numerical solution.
- Allow the user to select the simulation scenario, choosing between risk of fracture at the time of the diagnostic test, effect of antiresorptive treatments, and effect of weight-loss, and to launch the simulation using High Performance Computer (HPC) resources.
- Visualizes the results for the selected surrogate biomarkers of the fracture endpoint.

The suggested user interface functions as an efficient tool for enhancing user experience and comprehension of in-silico methodologies, facilitating their clinical translation even for non-expert users. The software is optimized for HPC resources and supports multiple biomarkers for fracture risk assessment in various scenarios.

Enhancing large-scale cohort simulations through integrated HPC infrastructure and model execution environment

Karol Zając[1], Taras Zhyhulin[1], Piotr Nowakowski[1,2], Jan Meizner[1,2], Bartosz Baliś[1], Konrad Czerepak[1], Marek Kasztelnik[2], Piotr Połeć[2], Sara Oliviero[3], Maciej Malawski[1,2]

[1]Sano - Centre for Computational Personalized Medicine, Kraków, Poland; [2]ACC Cyfronet AGH, Kraków, Poland; [3]Department of Industrial Engineering, Alma Mater Studiorum, University of Bologna, Bologna, Italy

In the realm of high-performance computing (HPC), leveraging modern resources for large-scale cohort simulations is imperative for advancing healthcare research. This abstract explores the integration of HPC infrastructure with a sophisticated Model Execution Environment (MEE), facilitating scientific workflows in patient-based simulations, cohort analyses, and campaign assessments [1]. Our solution not only enables the seamless execution of complex workflows but also provides robust monitoring capabilities to track resource usage by specific patients, pipelines, and steps.

The MEE serves as a centralized platform for orchestrating simulations, allowing researchers to harness the power of HPC resources efficiently. Moreover, our framework streamlines data accessibility by facilitating the data access from public repositories such as Zenodo or Dataverse, thereby enhancing collaboration in scientific endeavors.

A prime example of our approach in action is the BoneStrength In Silico trial, which exemplifies the practical application of our solution to estimate hip fracture incidence. By simulation across large patient cohorts, we demonstrate the scalability of our integrated infrastructure in tackling complex biomedical challenges.

This abstract highlights the pivotal role of integrated HPC and MEE frameworks in driving large-scale cohort simulations, fostering innovation, and accelerating discoveries in healthcare and beyond.

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Acknowledgements:

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Code verification of contact analysis using a micro-finite-element solver

Frederik Max Trommer[1,2], Pinaki Bhattacharya[1,2]
[1]Department of Mechanical Engineering, University of Sheffield, United Kingdom;
[2]Insigneo Institute for in silico Medicine

Micro-finite element analysis solvers, like ParOSol [1] use Cartesian mesh models based on high resolution computed tomography images to efficiently solve problems with billions of degrees of freedom. Such solvers do not accurately compute contact induced stresses due to the artificially jagged mesh surface. The simulated smoothed surface, sliding contact (SS-SC) contact formulation can reduce errors associated with contact from 42% to 2% [2]. Previously, we modified ParOSol to implement a hard, frictionless penalty contact interaction with SS-SC formulation [3]. The present study's aim was to use the Method of Manufactured Solutions (MMS) to conduct code verification of this new version of ParOSol.

A domain consisting of two disjoint unit cubes was defined with regions of the opposing faces as contacting surfaces. Analytical displacement fields are defined so that these regions would conform exactly to a common contact interface. These are also defined throughout the two cubes so that small deformation conditions are met and conform to the displacement on the opposing faces. Strain and stress tensor fields are derived by defining homogeneous, isotropic linear-elastic behaviour for both cubes. The resulting non-zero stress divergence is balanced by a body force field. The total surface traction on the opposing faces is derived and on the contacting regions of the opposing faces, the contribution from the contact-induced surface traction is removed. On the remaining 5 faces of each cube, the known displacement is applied.

The errors and order of convergence are quantified for 4 levels of mesh refinement and 11 penalty contact stiffness values. A minimum root-mean-squared (RMS) error <2% was achieved for all tested discretisations. For each fixed mesh resolution tested, the lower extreme of contact stiffness values corresponded to a zeroth-order of convergence.This asymptotic tendency suggests a low likelihood of coding errors in the tested solver.

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Classification of retinal vein occlusion and diabetic macular edema with deep learning in OCT images

Guilherme Barbosa[1], Eduardo da Silva Carvalho[1], Ana Guerra[1], Nilza Ramião[1], Marco Parente[1,2], Sónia Torres-Costa[3,4], Manuel Falcão[3,4]
[1]INEGI - Institute of Science and Innovation in Mechanical and Industrial Engineering, Porto, Portugal; [2]DEMec - Department of Mechanical Engineering, Faculty of Engineering of University of Porto (FEUP), Porto, Portugal; [3]Surgery and Physiology Department, Faculty of Medicine of University of Porto (FMU; [4]Ophthalmology Department, ULS São Joao, Porto, Portugal

Optical Coherence Tomography (OCT) is crucial to diagnose retinal diseases, such as diabetic macular edema (DME) and retinal vein occlusion (RVO), but their similarities can lead to misdiagnosis. Deep learning (DL) can be used to extract features of images and aid diagnosis. Image preprocessing and transfer learning were applied to train a convolutional neural network, which was used in a multimodal model to classify the OCT images into four classes: Normal, RVO, DME and other pathologies. This multimodal model took the information about diabetes and the OCT image as input. A total of 708 patients from Unidade Local de Saúde São João were selected. Only the 5 scans most centered at the fovea were considered, with 1035 images of normal eyes, 1030 images of eyes with RVO, 1090 images of eyes with DME and 385 images of eyes with other pathologies. After image preprocessing, 3040 images were used for training and validation and 500 images were used for testing. Then, accuracy, precision, recall, specificity, f-beta score, f-score and area under the receiver operating characteristic (AUROC) were calculated. Data augmentation and hyperparameter-tuning were applied to improve the results obtained. The proposed architecture provides an accuracy of 95%, precision of 95.08%, recall of 95%, f-beta score of 95%, f-score of 94.42% and AUROC of 99.03% in distinguishing between the four classes. The trained model could distinguish DME from RVO, and it might be useful in clinical practice and retinal screening. In the future, new studies are needed to improve the accuracy of these models and to extend the application to the diagnosis of other diseases. No images with DME were misclassified, which proves that information related to diabetes is valuable to create a more robust and reliable model.

The present study was developed in the scope of the Project "Agenda I BlockChain PT. Descentralizar Portugal " [C644918095-00000033 | Project nº 51], financed by PRR – Plano de Recuperação e Resiliência under the Next Generation EU from the European Union. Moreover, the authors acknowledge the funding provided by LAETA under protect UBS/50022/2020.

4.H: Neurotechnology for Human Movement

Thursday, September 5

10:30am – 12:00pm

08.019

From novel muscular mechanics principles to neurotechnology for human movement

Can A. Yucesoy
Bogazici University, Turkiye

Human movement is key to individuals' involvement in life and contribution to production and economy. Skeletal muscle is the motor for joint movement empowering bodily motion. Although muscular mechanics is largely characterized as the force production within individual muscle fibers and musculoskeletal mechanics is typically considered to be powered by the force production of individual muscles in isolation, a much more complex system is likely to shape bodily motion. Such system involves intramuscular connective tissues via which muscle fibers comprising the muscle belly interact with each other and epimuscular connective tissues, which interconnects different muscles within and across muscle compartments to interact with each other. Consequently, sarcomere lengths that determine muscles' force and movement production can be manipulated by mechanical interactions between muscle fibers and extracellular matrix and target and adjacent or distant muscles. This yields rather than independent, a condition dependent muscle functioning and contribution to joint moment and movement [1]. Animal experiments revealed this phenomenon and the linked fiber matrix mesh model [2] was used to simulate tested conditions to explain e.g., a sizable shift of peak muscle force production to a longer muscle length. Such novel principles have major clinical implications in cerebral palsy [3], which may explain the pathological knee joint condition that impedes the gait and effect mechanisms of treatments involving surgery [4] or botulinum toxin injections [2]. Note that, neurotechnology is about sensors, data, algorithms and context aware decision making, which can be extremely impactful in developing innovative motion assistive device technologies and rehabilitation robotics. This talk will link novel muscular mechanics principles to muscle sensor systems, powered prostheses and human-robot interfaces for developing neurotechnology for human movement.

TUBITAK grant 22AG016 is acknowledged

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Integrating intraoperative testing with musculoskeletal modeling: Muscle force-length relationship in patients with cerebral palsy

Cemre Su Kaya Keles[1], Filiz Ates[1], Can A. Yucesoy[2]

[1]Institute of Structural Mechanics and Dynamics in Aerospace Engineering, University of Stuttgart, Stuttgart, Germany; [2]Institute of Biomedical Engineering, Boğaziçi University, Istanbul, Türkiye

The clinical perception that physically shortened spastic muscles exert high forces at lower lengths was challenged by intraoperative findings. Measuring spastic knee flexor muscle forces during surgery showed only low forces in flexed positions if the muscle is activated alone, but forces increased upon coactivation of other muscles, explained by epimuscular myofascial force transmission (EMFT) [1,2]. This study aimed at filling the gap between intraoperative data and spastic muscle's force-length characteristics. Spastic semitendinosus (ST) was studied in seven children with CP (9.1±2.9 years old, ten limbs tested). 3D gait analyses were conducted. Subsequently, isometric ST forces were measured intraoperatively at the distal tendon in ten hip-knee joint angle combinations, under three conditions: (1) passive state, (2) exclusive activation of the ST, and (3) simultaneous activation of the ST with other muscles promoting EMFT. The gait_2392 model in OpenSim was used to calculate patient-specific gait-relevant muscle-tendon unit lengths (lMTU) and analyze ST force-lMTU data. ST during gait was 14.1% shorter in patients with CP than in age-matched healthy children. Passive state forces were low at short and higher only at longer lengths. Correlations between operational ST length (mean lMTU) and muscular mechanics (percent force at shortest lMTU of peak force) were weak: ρ=-0.16 P=0.66 for passive, and ρ=-0.15 P=0.68 for active state. Co-activation of other muscles substantially increased ST distal force, suggesting a potential contribution of EMFT to high flexor moment, hence pathological gait. Yet, the correlation was weak (ρ=-0.16 P=0.65) between operational ST length and EMFT. This suggests the role of other factors than muscle length, such as structural proteins and intermuscular mechanics interactions, in joint pathological conditions in CP [3]. Intraoperative tests coupled with modeling present a unique virtual human analysis.

TUBITAK grant 22AG016 is acknowledged.

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The development of LSTM-based ankle position and moment estimator for powered ankle prosthesis using nonnormalized sEMG and feature inputs

Ahmet Dogukan Keles[1], Can A. Yucesoy[2]
[1]Institute for Modelling and Simulation of Biomechanical Systems, University of Stuttgart, Stuttgart, Germany; [2]Institute of Biomedical Engineering, Boğaziçi University, Istanbul, Türkiye

Despite recent substantial advances in powered prosthetic hardware development, controllers still face challenges in achieving autonomous adaptation. The use of surface electromyogram (sEMG) sensors has been promising in this context [1]. Minimizing the number of sEMG inputs allows for building an *economic algorithm*, whereas limited use of lower leg muscles can lead to a *practical algorithm* suitable for different amputation levels. For this, (1) a systematic assessment of various sEMG inputs in estimating ankle position and moment is essential, (2) the use of nonnormalized sEMG amplitude is crucial for overcoming real-time processing complexities. We utilized walking and nonnormalized sEMG data of tibialis anterior (TA), soleus (SO), medial gastrocnemius (MG), peroneus longus (PL), rectus femoris (RF), vastus medialis (VM), biceps femoris (BF), and gluteus maximus (GMax) muscles of healthy participants [2] to develop long short-term memory network (LSTM) algorithms for estimating sagittal ankle position and moment, and ranked muscle combinations based on success. Five features extracted from sEMG amplitudes were studied: integrated EMG (IEMG), mean absolute value (MAV), Willison amplitude (WAMP), root mean square (RMS), and waveform length (WL). Muscle and feature combination variations were ranked using Pearson's correlation coefficient, the root-mean-square error, and one-dimensional statistical parametric mapping between the original data and LSTM response. The results showed that the IEMG+WL feature variation yields the best performance. The best-performing muscle variation was MG+RF+VM (r_position=0.91 and r_moment=0.97) whereas, PL (r_position=0.90, r_moment=0.97) and GMax+VM (r_position=0.90, r_moment=0.97) were distinguished as the economic and practical variations, respectively. This study shows a pioneering approach for the use of nonnormalized sEMG in powered prosthesis controllers.

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Boosting the performance of lightweight deep learning models with attention in human activity recognition

Özlem Durmaz[1], Sümeyye Ağaç[2]
[1]University of Twente; [2]Bogazici University

Deep learning models with automatic feature extraction capabilities have gained prominence in sensor-based human activity recognition (HAR), especially on large datasets. However, the computational and memory demands of deep learning models pose challenges for deployment on resource-constrained mobile and wearable devices. On-device processing offers advantages in terms of privacy and response time. Yet, achieving accurate recognition while maintaining low resource consumption is crucial.

While attention mechanisms have been successful in computer vision, their application in sensor-based HAR, particularly in conjunction with smaller deep-learning models, still needs to be explored. This study investigates the integration of Convolutional Block Attention Modules (CBAM), a widely used computer vision attention mechanism, into DeepConvLSTM, a state-of-the-art deep learning architecture for HAR. We aim to determine if applying attention to a smaller model can achieve accuracy similar to that of a larger model while maintaining lower resource consumption. We analyze the performance of this combination using five publicly available datasets and examine how adding the attention module affects different model sizes. Our focus lies on exploring the potential of boosting performance by adjusting model features rather than expanding the model size, thereby enhancing resource efficiency. The results demonstrate that applying CBAM to the lightweight model allows it to achieve recognition performance similar to the moderate-sized model, significantly reducing resource requirements. Specifically, the lightweight model with CBAM requires approximately 2-13 times fewer parameters and 3.5 times fewer floating-point operations (FLOPs) than the moderate-sized model.

Furthermore, we evaluate the model's performance with sensor data at lower sampling rates and data from fewer sensors attached to different body locations. The results reveal that the attention mechanism mitigates performance degradation under lower sampling rates and missing data from one or more body parts. This finding enhances the model's suitability for sensor-based HAR applications with potential data limitations.

Joint angle generation for human walking using conditional neural movement primitives

Mehmet Selcuk Albayrak, Muhammet Hatipoglu, Evren Samur, Emre Ugur
Bogazici University, Turkiye

Learning human motion and gait patterns is challenging from a few demonstrations. The individualized gait patterns depend on many different factors, such as anthropometric parameters of the individual humans, such as their mass and body size. The gait patterns also depend on factors such as the velocity of the walking person. Learning nonlinear motions that depend on these parameters is challenging. In this paper, we propose a learning-based gait model that learns from a gait data set collected from healthy subjects with varying anthropometric parameters and velocities. The gait database used in this study were constructed by instructing the subjects to walk on a treadmill with speeds varying from 1.0 kph to 6.0 kph at 0.5 kph increments and recording the joint angles via an IMU-based wearable Motion Capture System. Our method is built on top of a recent movement primitive, namely Conditional Neural Movement Primitives, that allows us to learn distributions across the exhibited trajectories. Our system is composed of an encoder-decoder network. The encoder layer of the CNMP learns a representation of trajectory points and other variables conditioned on the time. The decoder layer takes the learned representations and outputs the mean and
variance of a Gaussian distribution as a function of time It can generate the corresponding trajectories given the desired walking speed and anthropometric parameters. We compared the trajectory generation results with a state-of-the-art method that uses Kernelized Movement Primitives and showed that our method can produce more accurate joint trajectories.

Smartphone application for quantitative assessment of gait and balance impairments in stroke patients

Otar Akanyeti[1], Federico Villagra Povina[1], Arshad Sher[1,2], Magali Sganga[1,3,4]
[1]Aberystwyth University, United Kingdom; [2]Nottingham Trent University, United Kingdom; [3]Universidad Maimónides, Argentina; [4]Universidad Nacional de La Matanza, Argentina

Stroke is a life changing event with long-lasting mobility issues which in return increase fall risk and diminish quality of life. Measuring the severity of these issues and whether they get worse over time is important for clinicians to design timely interventions and measure short- and long-term patient outcomes. However, these measurements are not done as often as they could be due to practical issues related to time, costs, and logistics. Advances in miniaturized inertial sensor technologies including those found in mobile devices have paved the way for affordable and portable solutions to complement laboratory-based clinical measurements.

We have been developing a smartphone application for automatic gait and balance assessments, and hope that one day it can be used as a diagnostic, recovery monitoring and follow-up tool to aid clinical decision making. In its core, the app relies on new AI engine which is trained to recognise under which circumstances a recording is made (who is the user, what type of activity, and in what environment the activity takes place), and adjust the data processing workflow accordingly to improve performance. In the last few years, we have been validating the system against gold standard methods by analysing data from various participant groups including sub-acute and chronic stroke patients and young and age-matched healthy controls during various functional fitness tests that are relevant for the activities of daily living (i.e., 10-meter and 6-minute walk, timed-up-and-go, chair sit to stand, and static and dynamic balance tests). In this talk, we will describe the innerworkings of the latest version of the app, and report its performance (in terms of accuracy, reliability, and sensitivity) on various tasks: differentiating stroke gait from healthy gait, detecting gait change events during intensive treadmill training, measuring temporal gait parameters (such as step time, swing-to-stance ratio, and asymmetry between healthy and hemiparetic side) during indoor and outdoor walking, recognising different chair-rise strategies., and predicting centre of pressure during dynamic balance tests.

4.G: Musculoskeletal System – Spine

Thursday, September 5

10:30am – 12:00pm

01.005

A novel in silico approach for the analysis of muscular loads in the lumbar spine

Linda Carpenedo[1], Luigi La Barbera[1,2]
[1]LaBS, Department of Chemistry, Materials and Chemical Engineering "G.Natta", Politecnico di Milano; [2]IRCCS Galeazzi-Sant'Ambrogio Hospital, Italy

Introduction

Musculoskeletal load imbalances strongly impact spinal health. As traditional load measurements are invasive to perform, computational approaches are helpful. Multibody simulations are an affirmed alternative, yet their integration into Finite Element (FE) modelling is problematic. This study aims to propose a novel fully parametric FE model of the T12-S1 spine including muscles.

Material and methods

A validated parametric T12-S1 FE model of the spine is used [1]. Eight muscle groups, namely Ileocostalis, Longissimus Thoracis (LT), Psoas Major (IP), Multifidus (MF), Quadratus Lumborum, Rectus Abdominis, External and Internal Obliques, are modelled to replicate a symmetric architecture. Anatomical data on muscle origin and insertion sites and body weight loads are integrated into the model [2,3]. Standing posture and 10° and 20° forward flexions are simulated. All possible combinations of muscle forces, each varying of 10N in the 0-50N range, are tested to derive range of motions (ROMs). Different acceptability thresholds (0.5°, 1°) on predicted ROMs are set by comparison with experimental measurements and optimal solutions are identified by minimizing an energy criterion (sum of cubic muscle stresses) within a 5% deviation. Results are presented for the L5-S1 level.

Results

Different sets of optimal solutions are identified when changing thresholds on ROMs for standing (minimum energy is found with IP=0N, LT=30N, MF=40N or 30N for 0.5° and 1° thresholds, respectively), while they expand for flexion. MF and LT muscles are the most active during these tasks, while IP force is always <10N. Optimum muscle forces at this level are lower for flexion, while their sum over the whole spine increases.

Discussion

The novel approach allowed to estimate redundant muscle activation patterns closely aligned with both experimental and computational findings from literature [2]. To ensure the method's robustness, sensitivity studies on muscle attachment points and exploration of different optimization criteria will be performed.

References

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A novel in silico parametric tool for surgical-decision in lumbar spine fixation and fusion

Luigi La Barbera[1,2], Emilia Bellina[1,3], Linda Carpenedo[1], Gabriele Capo[3], Maurizio Fornari[3]
[1]LaBS, Department of Chemistry, Materials and Chemical Engineering "G.Natta", Politecnico di Milano, Italy; [2]IRCCS Galeazzi-Sant'Ambrogio Hospital, Italy; [3]Department of Neurosurgery, IRCSS Humanitas Research Hospital, Milan, Italy

Introduction

The treatment of sagittal spine imbalance often involves lumbar fixation and fusion, posing risks of complications like adjacent segment disease (ASD). Predictive tools based on musculoskeletal spine models could enhance the preoperative surgical decision-making. The study aims to showcase the potential of a new parametric spine model generator in assessing the effect of sagittal profile, instrumentation techniques in lumbar spine fixation and fusion in silico.

Material&Methods

A validated parametric spine model generated different spinal profiles varying lumbar lordosis (LL) and spino-pelvic parameters (SS,PI): type 2 (LL,SS,PI=48°,30°,41°), type 3 (58°,39°,53°) and type 4 (69°,49°,62°) according to Roussouly classification. Each profile was virtually instrumented with short (L4-L5) and long (L3-L5) fixation with/without intervertebral cage, techniques often related with ASD. The study examined how spinal alignment and instrumentation technique affect range of motion (RoM), intradiscal pressure (IDP) and spinal loads. Simplified (axial load+bending), hybrid (axial load+rotation) and more realistic loading protocols were analysed.

Results

Simplified loading protocols increased (+11%) global RoM for type 2 profiles compared to type 3, and vice versa for type 4 (-13%). Cages totally constrained the ROM. Fixation decreased (27%) the IDP at the treated level. Type 4 profiles showed higher tensile strains for the posterior ligaments compared to types 3 and 2, with slightly lower compressive strains anteriorly. Hybrid loading protocols led to higher variations particularly at adjacent levels. Including muscles forces introduced shear loads, resulting in unstable kinematics.

Discussion&Conclusion

The study demonstrates the potential of a new parametric spine model as a preoperative tool to assess the biomechanical impact of sagittal profile and instrumentation techniques. The loading protocol to assess adjacent levels' biomechanics remains a crucial decision.

Spine surgery planification to avoid proximal junctional failure: A multi-criteria approach using finite element modelling

Morteza Rasouligandomani[1], Alex del Arco[2], Ferran Pellisé[3], Miguel A. González Ballester[1,4], Fabio Galbusera[5], Jérôme Noailly[1]
[1]BCN MedTech, DTIC, Pompeu Fabra University, Barcelona, Spain; [2]Hospital del Mar, Barcelona, Spain; [3]University Hospital Vall d'Hebron, Barcelona, Spain; [4]ICREA, Barcelona, Spain; [5]Shulthess Klinik, Zurich, Switzerland

Introduction: Proximal Junctional Failure (PJF) is a common mechanical complication following corrective adult spine surgery, while Hardware Density (HD) management is crucial to reduce risk of PJF. Global Alignment and Proportion (GAP) is a potential predictor of PJF with cut-off value 7, but its role in defining safe HD scenarios remains unclear. This study aims to identify safe HD scenarios considering various GAPs, rod materials, and bone properties for Upper Instrumented Vertebra (UIV) at T10 and T3. Patient-personalised Finite Element (FE) thoracolumbar spine models were created, biomechanical indexes were evaluated, and trade-off analyses were conducted to exploit safe surgery plans.

Methods: 42 non-operated spine EOS 3D models were included. A statistical shape model trained on 42 models enabled the generation of unstructured meshes by activating shape modes. These meshes were transformed into structured FE meshes using the BCPD++ algorithm. Ligaments and Intervertebral Discs (IVD) were included. Spinopelvic measurements were validated against images. A virtual cohort of 91 models with GAP ranging from 7 to 13 was created, each instrumented with different HD scenarios and rod materials. Material properties and boundary conditions were introduced. FE simulation steps were adapted to clinical surgery maneuvers. IVD fiber strain and screw pull-out force were calculated and compared to control values. Safe surgery plans were proposed if both biomechanical indexes were below the control.

Results: For UIV at T10, GAP 12 and 13 did not yield safe HD scenarios with Ti or Cr-Co rods. HD reduction in UIV T10 with GAP 11 did not mitigate risk with Cr-Co rods. For UIV at T3, GAP 13 could not benefit from HD reduction regardless of rod material. However, Ti rods may enable HD reduction to de-risk GAP 12 patients with UIV at T3.

Discussions: Results can assist clinicians for selecting sub-optimal HD scenarios and rod properties to avoid PJF for UIV at T10 & T3 across different GAPs. Validation with 23 clinical cases confirmed real-world consistency. Overall, personalised FE modelling and simulation offer unique insights, aiding medical doctors for spine surgery planning.

In silico functional assessment of a new bio-degradable cage for lumbar interbody fusion through a fully-parametric spine model generator

Davide Ninarello[1], Giacomo Morozzi[2], Alberto Ballardini[2], Luigi La Barbera[1,3]
[1]Politecnico di Milano, Italy; [2]Greenbone Ortho S.p.A., Italy; [3]IRCCS Istituto Ortopedico Galeazzi, Italy

Introduction: Lumbar disc degeneration is typically treated via lumbar interbody fusion (LIF), involving the stabilization of the affected level by implanting a rigid cage and an external fixation system [1]. However, commercially available cages lack degradability. The present study aims to assess the effectiveness and safety of a ceramic bio-degradable cage for LIF exploiting a validated fully-parametric spine model generator [2].

Material & Methods: A biphasic ceramic scaffold (b.BONE™ - GreenBone Ortho S.p.A.) was selected as LIF cage material. Exploiting prior mechanical characterization, a transversely isotropic material model was calibrated. Three main LIF techniques were simulated, differentiated by the cage access point: PLIF (posterior), TLIF (transforaminal) and XLIF (lateral). Different lumbar functional unit configurations were considered, varying lordotic angles and morphometric dimensions. Following clinical indications, rigid fixation through titanium pedicle screws and spinal rods (5.5 mm in diameter) was simulated. Complex loading conditions (Follower load + Pure moment) were applied for each technique assuming short-term contact conditions at the bone-cage interface. Range of motion (ROM), principal strains distribution at the implant-bone interface and on the cage were evaluated.

Results and Discussion: All techniques stabilized the affected area, reducing ROM by 85%-99%. Principal strains at the bone-cage interface varied among techniques and morphologies. Smaller cage footprints (PLIF and TLIF) induced higher strains, increasing the risk of cage subsidence. Larger XLIF cages yielded lower strains, preserving vertebral trabecular bone. Finally, higher strains on the cage were observed for PLIF, due to reduced cage dimensions, while the most conservative condition was observed in XLIF. In all cases, no critical strains were registered on the implant.

Conclusion: This study exploited digital-twin technology to speed-up the development of an innovative bio-degradable LIF cage, proving its effectiveness and safety across various spine morphologies.

References:

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Modelling percutaneous vertebroplasty (and other processes) using the theory of porous media

Jan-Sören Lennart Völter, Tim Ricken, Oliver Röhrle
University of Stuttgart, Germany

Percutaneous vertebroplasty (PV) is a medical procedure in which bone cement is injected into an osteoporotic or otherwise mechanically unstable vertebral body. During and after the injection, the bone cement undergoes curing, stabilising the vertebral body from within. This stabilisation requires an adequate distribution of cement inside the vertebral body. At first glance, increasing the amount of cement seems favourable. However, the employment of an excessive amount of cement increases the risk of cement leakage considerably. This is the most common complication during PV.

The PV procedure is irreversible and thus also not repeatable for a given vertebral body. In the future, numerical simulations will be able to aid in the prediction and prevention of unfavourable outcomes. In this regard, the Theory of Porous Media (TPM) has been employed to mathematically model the cement injection and involved mechanisms. The TPM poses an appropriate modelling framework for the macroscopic description of processes within porous media, based on fundamental balance laws and thermodynamic principles.

Since various processes may be taken into consideration when modelling PV, we have devised multiple models expanding upon each other. As first model, we consider the purely mechanical problem, which is the displacement of bone and bone marrow due to the forced injection of cement. Expanding upon this model, we consider the thermal problem, accounting for the difference in temperature of the cement and biological tissue. Further, we incorporate the chemical reaction which drives the cement curing process, influencing material properties of the cement.

As such, our mathematical model already covers the processes most relevant for the prediction of cement leakage. However, the capabilities of the TPM are not exhausted. We may further consider the vertebral vasculature as an embedded porous medium itself. This enables the description of blood perfusion and, thus, the transfer of heat and dissolvable cement components into the bloodstream. Naturally, the individual parts of our models as well as the concepts of the TPM are applicable and extendable to other biomedical applications.

5.A: Heart Modelling - Applications II

Thursday, September 5

3:30am – 5:00pm

05.019

Instantaneous biomechanical model of the heart to characterize ventricular remodeling in complex congenital heart disease

Maria Gusseva[1], Nikhil Thatte[2], Daniel A. Castellanos[2], Peter E. Hammer[3], Sunil J. Ghelani[2], Ryan Callahan[4], Tarique Hussain[1], Radomir Chabiniok[1]

[1]UT Southwestern Medical Center, United States of America; [2]Department of Cardiology, Boston Children's Hospital, Boston, MA, USA; [3]Department of Cardiac Surgery, Boston Children's Hospital, Boston, MA, USA; [4]Division of Cardiology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA

In patients with congenitally corrected transposition of great arteries ccTGA, the left ventricle (LV) is connected to the pulmonary circulation, and the right ventricle (RV) to the aorta and systemic circulation. Such an anatomy deconditions LV over time making it vulnerable to failure after the double switch operation (DSO). Post-DSO LV failure rates are ~15%. Surgical pulmonary artery band tightening (PABt) can be introduced (usually for ~6 months) to retrain the LV, and a subsequent follow-up exam establishes LV preparedness for DSO. This work aims to use a biomechanical model of the heart on one patient with ccTGA (like [Gusseva et al., FIMH 2023]) to evaluate LV remodeling accrued between two subsequent PABt events and to predict LV preparedness for DSO.

Clinical data of a patient with ccTGA collected during the PABt-1 and PABt-2 (performed 6 months apart) included cardiac magnetic resonance imaging (MRI), LV and RV catheterization, and LV conductance measurements. Biomechanical models of the RV ejecting into the aorta (RV-to-AO), and LV ejecting into the pulmonary artery (LV-to-PA) were built corresponding to the PABt-1 and PABt-2 datasets. *In silico* DSO was performed at both PABt-1 and PABt-2. The model of AO was connected to the model of LV cavity – i.e. *in silico* LV-to-AO scenario. Each calibrated model provides a value of myocardial contractility that characterizes an inotropic state of a given ventricle.

Measured LV mass, end-diastolic volume, and end-systolic volume were [24; 34] g, [64; 101] ml, and [28; 61] ml, respectively, at [PABt-1; PABt-2]. Measured LV peak systolic pressure (PSP) was [52; 85] mmHg, PA PSP was [21; 20] mmHg, and AO PSP was [80; 70] mmHg at [PABt-1; PABt-2]. In the LV-to-PA model, LV contractility was [29; 39] kPa at [PABt-1; PABt-2]. *In silico* LV-to-AO model predicted LV contractility [53; 34] kPa at [PABt-1; PABt-2].

The results show that if the DSO was performed at PABt-1 time point LV would need an 80% increase in contractility, and at PABt-2 contractility would decrease by 13%. The PABt-2 *in silico* model suggests the LV remodeling accrued since PABt-1 is likely to be sufficient for LV to sustain its function after DSO.

Construction and manufacturing of an MRI-ready experimental left heart phantom model

Moritz Wiegand[1], Tim Bierewirtz[1], Leonid Goubergrits[1,2], Katharina Vellguth[1]
[1]ICM, Deutsches Herzzentrum der Charité, Germany; [2]Einstein Center Digital Future

CFD simulations using patient-specific geometries are a promising tool for diagnostics and treatment planning of left ventricular (LV) and mitral valve diseases. To validate these simulations, extensive data on flow characteristics is necessary. This data can be obtained from patients/probands with time-resolved 3D phase contrast imaging using three-directional velocity encoding. However, image quality may be impaired by movements, irregular heart frequency and low dwell times in the MRI. To obtain data without these disturbances, we developed an MRI-ready experimental left heart phantom model with a flexible LV made of PVA based hydrogel (10% PVA, 10% glycerol, 80% water).

The parts of the experimental setup which are inside or close to the MRI scanner need to be metal free to exclude interference with its magnetic field. A backup tank around the phantom model ensures leakage free operating.
The flexible LV is made in the end-systolic shape and planted into a fluid filled, 3D printed end-diastolic geometry of the LV which is connected to an MRI-compatible pump. Therewith the pressure around the flexible phantom can be changed to achieve physiological movement and therewith flow profiles in the ventricle.

The heart geometry of the phantom model was taken from proband MRI-data and adapted using CAD software such that all experiment requirements are met. The flexible LV was cast into 3D-printed molds and hardened through several freezing/thawing cycles. The PVA based hydrogel was chosen due to its elastic and robust behavior to ensure a changing ventricular volume during the heart cycle. As it is made of similar substances as the blood mimicking fluid (glycerol/water), the frequency shift inside the MRI can be kept to a minimum.

Both aortic and mitral valve were thermoformed from a 1 mm thick polyurethane film. They were manufactured in an almost closed state to ensure a correct shape and proper closing. Threads, acting as chordae tendineae were added and anchored in the ventricular tissue to avoid severe regurgitation.

Next, we will conduct detailed measurements in a 3T MRI and then perform CFD simulations based on the obtained geometries to comprehensively compare them.

Predicting cardiac conduction disturbances during balloon aortic valvuloplasty from patient-specific computational models

Benjamin Ayo Matheson[1,2], Haoran Dou[1,2], Cristina Teleanu[1,2], George Hyde-Linaker[3], Rebecca Bryan[3], David Flynn[4], Daniel Blackman[5], Toni Lassila[1,2], Nishant Ravikumar[1,2], Alejandro F. Frangi[1,6,7], Zeike A. Taylor[1,2]

[1]Centre for Computational Imaging and Simulation Technologies in Biomedicine (CISTIB); [2]University of Leeds, United Kingdom; [3]Synopsys, Inc.; [4]Boston Scientific Corporation; [5]Leeds Teaching Hospitals NHS Foundation Trust; [6]Christabel Pankhurst Institute; [7]University of Manchester, United Kingdom

The objective of this study is to utilize patient-specific computational models to predict conduction disturbances (CDs) in balloon aortic valvuloplasty (BAV), with a focus on the predictive value of localized strains and contact pressures in the conduction region. BAV, often implemented as a pre-step to transcatheter aortic valve implantation (TAVI), is associated with the development of CDs, highlighting the necessity of investigating BAV independently to TAVI. The study includes 30 patients from the REPRISE III clinical trial undergoing BAV pre-TAVI with a maximum balloon diameter of 20 mm. Patient models are created from computed tomography angiography images using a fully automated workflow. Synopsys' Simpleware™ software was used for anatomical segmentation and meshing, and an in-house Python script for generating patient-specific LS-Dyna input files. Aortic and valve tissues are modelled as linear elastic materials. Hard contact interactions are defined between the balloon and surrounding tissues. Models of the balloon inflation are solved using explicit time integration. Strains and contact pressures in conduction regions are subsequently assessed and related to known CD outcomes for each patient.

The findings aim to identify specific strain thresholds that significantly correlate with the likelihood of CDs during BAV, offering biomechanical insights into the procedure's impact. This crucial observation will involve comparing simulated strain values with clinical observations of CDs, highlighting the significance of biomechanical strain analysis in pre-procedural assessments. By concentrating on BAV, the methodology is expected to provide a critical predictive tool that could enable more informed clinical decisions and personalized patient care. The study's focused approach seeks to enhance understanding of the impact of BAV on the heart's conduction system, potentially marking a significant advancement in cardiac care.

Hierarchical VVUQ strategy for the development and credibility assessment of a pulmonary heart valve model

Nils Götzen[1], Tahir Turgut[1], Omar Zahalka[1], Vincent Bouwman[1], Mikel Isasi[2], Malte Rolf-Pissarczyk[3], Rick van Tunen[4], Mathias Peirlinck[4], Mohammad Mirzaali[4]

[1]4RealSim Services BV, Netherlands, The; [2]Leartiker, Spain; [3]TU-Graz, Austria; [4]TU-Delft, Netherlands, The

Within the EU-funded SimInSitu project (GA No. 101017523), we implemented a hierarchical VVUQ approach to develop a credible patient-specific in-silico FEM model for biodegradable heart valves. This approach encompasses seven levels of complexity, beginning with material modelling and concluding in the actual in-silico patient-specific platform. We hereby report on the development progress of a Pulmonary Heart Valve, which is made from a biodegradable scaffold. This scaffold gradually dissolves in the human body, simultaneously promoting the formation of new native tissue.

The modelling process thus far encompasses three levels: Material Characterization and Constitutive Modelling, Device Component, and Complete Device. For each of the levels, we systematically carried out verification, validation, and uncertainty quantification activities. At the material level, we also engaged in calibration efforts to account for various sources of uncertainty related to material behaviour and experimental characterization.

The hierarchical approach allowed us to propagate the uncertainty from the lower complexity levels to the higher one, while also identifying the significant factors and parameters.

All modelling activities and simulations were executed with Abaqus Standard/Explicit including V/UMAT programming. All automation and UQ tasks including meta-modelling were conducted with Isight.

Experimental validation tests were designed and conducted to specifically evaluate the functions of the device's conduit and leaflets independently. While the model realistically captured the behaviour of the leaflets, the structural response of the conduit exhibited significant discrepancies when compared to the experimental data. A subsequent, detailed root-cause-analysis identified a mismatch in the mechanical behaviour between the test coupons of the conduit and the actual conduit itself. After making adjustments, conducting additional characterization, and recalibration, the validation was successfully repeated with positive results.

The hierarchal approach requires substantial work at all levels of development and complexity but is particularly useful in establishing model credibility.

Predictive model for the assessment of the TEVAR procedure

Sara Barati[1], Giulia Luraghi[1], Anna Ramella[1], Benedetta Grossi[2], Francesco Migliavacca[1], Josè Felix Rodriguez Matas[1]
[1]Politecnico di Milano, Italy; [2]Humanitas University, IT

Utilizing prostheses in minimally invasive cardiovascular treatments has improved the patient prognoses. However, optimizing device performance necessitates costly evaluations. Leveraging advancements in the in-silico modeling and the artificial intelligence, we present a framework for assessing Transcatheter Endovascular Aortic Repair (TEVAR) procedures. Our methodology integrates simplified structural simulations, synthetic population generation, and machine learning (ML) models.

The framework includes the use of non-parametric registration, statistical shape modelling (SSM) and principal component analysis (PCA) to generate a population of synthetic aorta geometries from a set of patient images with post-operative information. A template thoracic aorta geometry is deformed into clinically valid geometries with aortic aneurysm. The prosthesis deployment is simulated through a simplified model reducing the cost of simulations needed for the predictive model. The results are compared with the previously validated standard simulation of the TEVAR. The initial real patient-specific geometries are partitioned into training, validation, and test sets. ML algorithms are trained on a combination of synthetic and real models to predict TEVAR placement, evaluated against post-operative data.

The clinical and data driven assessments show that the synthetic geometries represent the properties of the initial patient-specific geometries ensuring the compactness, specificity and generalization of the population. Simplified simulations yield results comparable to previously established models, with a 60% reduction in simulation time and stent ring placement differences under 10%. The trained model effectively predicts TEVAR outcomes.

A framework for predicting the TEVAR procedure outcomes has been developed that can reduce the cost of the prosthesis evaluations. This tool can speed up the process of evaluating different prostheses in the clinical applications, aiding surgeons in selecting optimal treatment options for individual patients.

Alterations of the in vivo myocardium mechanical properties in aortic stenosis: Finite element analysis in a rat model

Mohammad Javad Sadeghinia[1], Henrik Nicolay Finsberg[1], Emil Espe[2,3], Ida Marie Hauge-Iversen[2,3], Lili Zhang[2,3], Einar S. Nordén[2,3], Ivar Sjaastad[2,3], Samuel Wall[1], Joakim Sundnes[1]

[1]Simula Research Laboratory, Oslo, Norway; [2]Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, Oslo, Norway; [3]K.G. Jebsen Center for Cardiac Research, University of Oslo, Oslo, Norway

Aortic stenosis (AS) is characterized by the narrowing of the aortic valve and increased cardiac afterload. AS is also a common cause of heart failure with preserved ejection fraction (HFpEF), a condition in which heart failure symptoms occur despite normal ejection fraction (EF) [1], possibly due to the drastic remodeling of the myocardium. In this study, we use a finite element (FE) model to investigate the changes in the mechanical properties of the myocardium due to induced aortic stenosis in rats.

We utilized datasets from a model of increased afterload via aortic banding. Rats underwent aortic constriction using o-rings with three different levels of inner diameter, ensuring precise aortic constriction [2]. This simulates aortic stenosis, leading to ventricular hypertrophy and myocardial remodeling. A sham procedure was also performed for a control group. MRI scans were done longitudinally at two, four, eight, and twenty weeks post-operation for each group. MR images were then used to create subject-specific geometries, and employing the measured pressure-volume curves from the experiment, FE models were created and tuned to estimate the passive and active material behavior of the myocardium throughout the development of induced AS.

FE models provide insights into the time-dependent mechanical remodeling of myocardial tissue due to increased afterload. Importantly, the estimated mechanical properties of the myocardium can be utilized to assess the performance of the novel diagnostic markers in HFpEF, e.g., myocardial work (MW). While MW has been previously utilized based on echocardiography, these methods do not account for thickness or curvature, both of which can be altered in the presence of abnormal afterload [3].

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5.B: Aneurysms & Appendages

Thursday, September 5

3:30am – 5:00pm

02.017

In silico pre-operative TEVAR planning: Application to a patient-specific case

Anna Ramella[1], Giulia Luraghi[1], Sara Barati[1], Maurizio Domanin[2,3], Santi Trimarchi[2,3], Francesco Migliavacca[1]
[1]Politecnico di Milano, Milan, Italy; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Università degli Studi di Milano, Milan, Italy

Introduction. Thoracic endovascular aortic repair (TEVAR) has become the preferred approach for treating thoracic aortic pathology and involves the insertion of a self-expandable stent-graft (SG) into the pathological region to repair the lesion. Pre-procedural planning is essential for limiting complication risks and requires a precise anatomical evaluation to identify the ideal treatment. This study shows the potentiality of a validated finite element (FE) simulation in the pre-TEVAR planning for a patient-specific case.

Materials and methods. The involved patient suffered from descending thoracic aortic aneurysm. The aortic lumen, thrombus and calcifications were segmented from anonym pre-operative CT images. Each component was discretised with shell elements using ANSA (BETA CAE) and modeled with linear elastic materials from the literature. The model also incorporates vessel wall prestress due to blood pressure. FE explicit simulations were done in LsDyna (ANSYS) to perform the SG implantation in three different landing zones, following indications from clinicians. Three different SG sizes were recreated and discretised with beam (S) and shell (G) elements. The stent was modelled with a nitinol shape memory alloy, while the graft with a PET fabric material.

Results. The analysis of simulation results focused on SGs final configurations, cross-sections, SG-to-aorta distances and stress distributions on the aorta. Outcomes were shared with clinicians before the intervention, and one of the simulated cases significantly aided clinicians in determining the optimal treatment. After the intervention, 1-week post-operative CT images were segmented to compare simulation results directly with the actual scenario for validation purposes. The opening area errors between the simulated and segmented stent struts aligned with other studies (below 10%).

Conclusions. The FE methodology adopted was previously validated following the V&V40 framework. The patient-specific simulation paved the way for a broader integration of this approach in clinical practice helping clinicians in the decision-making process to select the best treatment for the patient.

The role of secondary flow activities in the emergence of sidewall intracranial aneurysms

Benjamin Csippa, Péter Friedrich, György Paál
Budapest University of Technology and Economics, Faculty of Mechanical Engineering, Department of Hydrodynamics Systems,Hungary

Intracranial aneurysm initiation is still an open scientific problem. The debate on whether high wall shear stress (WSS) or low WSS and oscillatory behavior governs the hemodynamic condition leading to aneurysm formation is not settled. On the one hand, the WSS field is the hemodynamic signal that activates complex biochemical pathways through mechanotransduction; its calculation relies heavily on the local geometrical features, inherently on the creation of the geometry from medical images. On the other hand, the velocity field – the underlying force triggering shear stresses – is significantly less sensitive to local surface features and is mainly affected by the overall shape of the vessel section. In this study, we analyzed the secondary flow field along the abscissa of the pre-aneurysmal state of the vessel to find local flow features that correspond to the later site of the aneurysm.

30 patients with intracranial aneurysms near the posterior communicating artery of the internal carotid artery (ICA) were included in the study. Pre-aneurysmal state geometries were created with an objective algorithm for the hemodynamic simulations. Walls were assumed to be rigid and blood to be Newtonian. Heart-beat waveforms for the inlet boundary conditions were scaled patient-specifically, and outlet conditions were proposed according to Murray's law. An evaluation framework was developed to calculate the cycle-averaged secondary flows along the centerline of the vessel to compare the flow field with the geometrical features of the vessel in the same reference coordinate system.

For a given case, the ICA leading toward the circle of Willis consists of several bends. According to our results, the occurrence of an aneurysm is more probable statistically in the bend with a higher relative curvature. In the presence of higher relative curvature, higher secondary flows emerge. Elevated secondary flows could initiate focally high WSS gradients or a fluctuating load due to the time-varying emergence of the phenomenon. Therefore, mechanotransduction could trigger parts of the biochemical pathways in the cascade process of vessel-wall remodeling.

Use of shape analysis and computational fluid dynamics for identification of factors relevant for aneurysm rupture

Ivan Benemerito[1], Luca Gherardini[2], Maria-Cruz Villa-Uriol[1], Andrew Narracott[1], Alberto Marzo[1], Jose Sousa[2]
[1]Insigneo Institute for in silico medicine, University of Sheffield, United Kingdom; [2]Sano Centre for Computational Medicine, Krakow, Poland

Introduction

The decision of how to treat unruptured intracranial aneurysms (UIAs) is based on the evaluation of its risk of rupture, which is estimated through the PHASES score [1]. This is based on clinical measurements and disregards haemodynamics and shape factors, known to influence the evolution of UIAs [2]. In this study we evaluate the ability of data derived from shape analysis and computational fluid dynamics (CFD) simulations to help discriminate between patients with ruptured and unruptured aneurysms.

Material and methods

We collected PHASES data (P) and 3D Rotational Angiographies from 190 patients, and extracted shape parameters (S) and haemodynamic variables (C) from CFD simulations. We grouped the features in five different groups (P, PC, PS, CS, PCS) and used feature abstraction and knowledge graphs [3] on each group to stratify patients and compute the most relevant features. This approach produced, for each feature, a cut-off threshold that optimally separates between the two target classes, and that was then used to partition the original values into "high" and "low" values. Group's performances were evaluated through balanced accuracy.

Results

The use of PHASES variables reached a balanced accuracy of 66.5%, with the most important feature being the depth of the aneurysm (cut off: 3.4 mm). PC reached 71%, while PS and PCS reached 67.2% and 70.4% respectively. Using exclusively derived data yielded 70.8% balanced accuracy. Most discriminating features were the non sphericity index (shape variable, cut off: 0.15) and the maximum oscillatory shear index (CFD variable, cut off: 0.44 Pa), for both of whom high values were associated with rupture.

Discussion

Models that included derived data consistently outperformed the use of clinical variables alone, showing the potential for integrating in silico analysis within currently established clinical protocols. Identified risk factors and their values were coherent with literature findings [2].

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Virtual particle tracking in geometries with cerebral aneurysms

Dániel Gyürki, György Paál
Department of Hydrodynamic Systems, Faculty of Mechanical Engineering, Budapest University of Technology and Economics, Műegyetem rkp. 3., H-1111 Budapest, Hungary

Particles placed inside 3D flow fields can behave chaotically, even in the case of simple flows. The numerous bends of a healthy internal carotid artery can amplify this chaotic behaviour. After the growth of a cerebral aneurysm, the presence of the sac may complicate the chaoticity further.

A workflow is introduced to evaluate the chaotic nature of virtual particles placed inside the flow of an artery with an aneurysm. First, the medical images are preprocessed into stereolithography files. Next, the flow field is calculated using the software hemoFlow, which is built around the open-source lattice-Boltzmann solver, Palabos. The resulting flow field is numerically integrated to calculate the paths of one million massless, passive virtual particles released into the domain near the inlet. The outlets through which the particles leave the domain are recorded and processed to assess the chaotic nature of the particles.

The study aims at investigating two aspects. The first aspect is the effect of the presence of the aneurysm sac. Every geometry is prepared twice, one with the aneurysm sac present and one with the aneurysm sac objectively removed. The second aspect is the time instance of the particle release. Ten equidistant time instances are defined in the heart cycle, and the particles are released into the flow at those instances. 15 cases are investigated using this workflow.

The results show that the particle release time is essential and has to be taken into account when particle paths are calculated. Based on the investigated cases, if the particles are still inside the domain during the decelerating phase of the heart cycle, the chaoticity of the resulting paths is increased. The particles projected back to the release plane show a more complex filamentary structure if the outlets they take are considered. The presence of the aneurysm sac can further increase the effect of the deceleration.

This fundamental research contributes to the topic of particle paths in blood flows. Mathematical modelling of physiological processes, where the residence time and paths of small particles are essential, like coagulation or drug delivery can benefit from these results.

Left atrial appendage occlusion: A virtual model to simulate the implant procedure in patient-specific scenarios

Francesca Danielli[1,2], Francesca Berti[1], Benigno Marco Fanni[3], Emanuele Gasparotti[3], Andrea Colella[1], Alessandro Vitozzi[1], Simona Celi[3], Giancarlo Pennati[1], Lorenza Petrini[2]

[1]Department of Chemistry, Materials and Chemical Engineering, Politecnico di Milano, Italy; [2]Department of Civil and Environmental Engineering, Politecnico di Milano, Italy; [3]BioCardioLab, Bioengineering Unit, Fondazione Monasterio, Italy

Left Atrial Appendage Occlusion (LAAO) is a percutaneous procedure to prevent thromboembolism in atrial-fibrillated patients by implanting a self-expandable device. Despite its demonstrated efficacy, LAA morphological complexity hinders the implant procedure, resulting in post-procedural drawbacks (e.g., peridevice leaks or device-related thrombosis).

The use of virtual models to simulate percutaneous interventions has demonstrated significant potential in guiding clinical decisions, leading to a more patient-centric treatment, and enabling the prediction and improvement of the implant outcomes. The majority of the existing literature focused on LAAO virtual modeling deals with Computational Fluid Dynamics (CFD) simulations before and after the intervention. Differently, Finite Element (FE) simulations of the device's implantation are performed by very few works, that either lack important details on the adopted numerical approaches or are characterized by a reduced degree of realism, which is fundamental to ensure the simulation credibility.

In this context, the current study proposes a structured pipeline to simulate patient-specific implant scenarios, paying special attention to an accurate description of the crucial steps that distinguish the implant procedure.

The pipeline involves the following steps: (i) development of the validated digital twin of a widely employed occlusion device (Watchman FLX) along with its delivery system (catheter and guidewire); (ii) reconstruction of patient-specific anatomies (left atrium and LAA) starting from pre-operative CT images; (iii) FE simulation of the device's implant, mimicking the real procedure performed by the clinician; (iv) post-procedural CFD simulation.

The outcomes of the simulated clinical scenarios were assessed by looking at essential indicators used by the clinician to evaluate the implant success: (i) peri-device leaks, and (ii) excessive device protrusion beyond the LAA and/or excessive implantation depth that may cause device-related flow disturbances.

Finally, the authors are currently working on validating the proposed pipeline by exploiting post-operative CT images of the simulated implant scenarios.

Left atrial wall dynamics in in-silico fluid simulations of atrial fibrillation patients

Carlos Albors[1], Nerea Arrarte Terreros[2,3,4], Josquin Harrison[5], Xabier Morales[1], Marta Saiz Vivó[1], Nils Planken[3], Joris R. de Groot[4], Maxime Sermesant[5], Oscar Camara[1]

[1]Universitat Pompeu Fabra, Barcelona, Spain; [2]Biomedical Engineering and Physics, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [3]Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [4]Cardiology, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [5]Inria, France

Introduction: The left atrial appendage (LAA) is a major site of thrombus formation in atrial fibrillation (AF) patients. Left atrial (LA) wall dynamics, together with LAA morphology, play a role in LAA thrombus formation in AF patients. In-silico cardiac models can help elucidate the complex LA(A) hemodynamics and identify pro-thrombotic regions. The limited data acquired in standard AF protocols challenges the inclusion of LA wall motion in computational models. In our study, we conducted a sensitivity analysis comparing four LA wall boundary conditions, showing their potential in identifying pro-thrombotic areas in an AF patient undergoing LAA-excision.

Methods: For the sensitivity analysis, we selected 4 AF patients with available dynamic computed tomography (dCT) scans. For each patient, we compared 4 different LA wall motions: rigid wall condition; dynamic mesh method with a spring-based mitral valve displacement; patient-specific dCT wall motion; and atrial wall motion by using parallel transport (PT) methodology. As use-case, we applied these boundary conditions to an AF patient undergoing LAA excision, with available pre- and post-excision CT scans. For each condition, blood flow patterns, velocities, and endothelial cell activation potentials (ECAP) were calculated. In-silico flow simulations were performed using Ansys Fluent 2021 R2.

Results: The dCT and PT methods showed a better LAA washout. The thrombus formation risk was higher for the rigid wall method, as shown by higher ECAPs. For the post-excision case, all wall conditions exhibited high velocities and lower ECAPs, even for rigid walls, indicating a successful procedure.

Conclusion: Although PT approximated blood flow results to dCT motion, differences in simulated patterns were observed. For PT to better resemble patient LA dynamics, relevant patient's demographical, hemodynamical, and morphological characteristics should be matched. LA dynamics are key for in-silico predictions of thrombus formation, which cannot always be resembled by over-simplified simulations. PT has the potential to assist such simulations, especially given that most patient undergo static imaging in clinical practice.

5.C: Good Simulation Practice in Healthcare

Thursday, September 5

3:30am – 5:00pm

07.017

Saving lives today while building the personal digital avatar: An ambitious yet pragmatic digital transformation of healthcare

Thierry Marchal[1,2]
[1]ANSYS, Wavre, Belgium; [2]Avicenna Alliance, Brussels, Belgium

Collaboration between different healthcare stakeholders (industries, academic researchers, clinicians, regulators and policy makers) gives us confidence that we are all successfully collaborating towards personalized, predictive and preventive medicine with the perspective of creating personal digital avatars in a not-too-distant future. However, it remains crucial to harness current advances in digital healthcare to improve the lives of patients today and build more trust with regulators.

PyAnsys-heart: A python library for LS-DYNA multi-physics heart simulations

Martijn Hoeijmakers[1], Wenfeng Ye[2], Karim El Houari[2], Clémentine Shao[2], Michel Rochette[2], Mark Palmer[3]
[1]Ansys, Netherlands; [2]Ansys, France; [3]Ansys, USA

Physics-based computer simulations of the heart have huge potential in the medical device industry and clinical practice, for instance to accelerate and improve device designs, assist clinical decision making, or guide treatment planning. The importance of modeling choices with respect to electrophysiology, mechanics and fluid dynamics, and their respective coupling strongly depends on the application of interest. LS-DYNA is a finite element solver that offers the necessary multi-physics capabilities and features for heart modeling. However, setting up these models and obtaining physiological results is still a highly manual process and requires expertise in LS-DYNA usage, heart physiology, and scripting. In this paper we propose a python-based high-level interface to LS-DYNA, that is free-to-use and dedicated to heart modeling. We introduce the relevant heart modeling features that are available and introduce the modular python library to set up and drive these simulations. Two example models are presented: a bi-ventricular mechanical model and a full heart electro-mechanical coupled model.

Toward good simulation practice: Best practices for the use of computational modelling and simulation in the regulatory process of biomedical products

Vincenzo Carbone[1], Thierry Marchal[2,3], Liesbet Geris[4,5,6], Luca Emili[1], Marco Viceconti[7]

[1]InSilicoTrials Technologies, Trieste, Italy; [2]Avicenna Alliance, Brussels, Belgium; [3]ANSYS, Wavre, Belgium; [4]VPH Institute, Leuven, Belgium; [5]University of Liège, Belgium; [6]KU Leuven, Belgium; [7]Alma Mater Studiorum – University of Bologna, Italy

In 2021, the Avicenna Alliance (AA) created a Good Simulation Practice (GSP) Task Force within its Policy Development Working Group to drive a consensus process for the collection and drafting of best practices for the use of M&S in the regulatory process of medical products.

The consensus process was hosted by the In Silico World community of practice, supported by VPH Institute (VPHi) and AA, as a public grass-root initiative, involving hundreds of in silico trials experts worldwide working in academia, healthcare, industry, and regulatory bodies. Moreover, a team of 13 FDA M&S experts, covering all three medical product centres (CDRH, CDER, and CBER), provided feedback on the whole draft document.

The resulting position report has been published as an open access book titled "Toward Good Simulation Practice". This book represents the first attempt to define GSP on how to develop, evaluate, and use *in silico* trials, aiming to play a role similar to Good Clinical Practice (GCP), Good Laboratory Practice (GLP), or Good Manufacturing Practice (GMP).

Topics of the book include: Theoretical foundations of GSP, Model development and credibility, Possible qualification and health technology assessment pathways, Ethical review, Roles of sponsor and investigator. The book also contains an updated review of the existing regulatory guidance on the use of M&S.

"Toward Good Simulation Practice" is a public non-binding document, representing the consensus among the most representative authorities in the field of in silico trials, and providing an expert opinion to orient policies or standards. It is hoped that this book will stimulate further conversations amongst all stakeholders, ultimately contributing to the development of community accepted GSP, bringing M&S and *in silico* methodologies for medical products to maturity.

Acknowledgements

The publication of this book was financially supported by VPHi and AA.

The authors received fundings from the EU Horizon 2020 R&I programme under grant agreements No 101016503 [In Silico World], No. 101016496 [SimCardioTest], No 101017578 [SIMCor], and from the EC Digital Europe Programme under grant agreement No 101083771 [EDITH].

AlmaHealthDB: A digital infrastructure for secure management, interoperability and reuse of health research data

Antonino A. La Mattina[1], Sabato Mellone[1,2], Marco Viceconti[1,3]
[1]Medical Technology Lab, IRCCS Istituto Ortopedico Rizzoli, Bologna (IT); [2]Department of Information Engineering, Alma Mater Studiorum – University of Bologna (IT); [3]Department of Industrial Engineering, Alma Mater Studiorum – University of Bologna (IT)

Abstract

Balancing the contrasting demands of FAIR research [1] and GDPR requirements [2] is a complex task, especially for collaborative research projects. The university and the three research hospitals of Bologna joined forces to create AlmaHealthDB, a secure digital environment to collect, process, and standardise data in compliance with legal, organizational, and regulatory requirements.

Data controllers appoint AlmaHealthDB as data processor for their specific research project. Input data origin, consents and conditions for use are stored as metadata linked to the dataset. The variables collected in the studies are minimised and (if needed) pseudonymised before entering AlmaHealthDB infrastructure.

AlmaHealthDB operates as a subnet of the regional healthcare service system network, accessible only by system administrators via nominal VPN connections. Disks are encrypted, and the entire infrastructure is backed up daily.

A server is exposed on the Internet to allow uploading of data and files by researchers, after two-factors authentication. In the data ingestion phase, constraints on data type and completeness, file format and associated metadata are enforced to minimise data imputation errors.

Basic data manipulations are performed inside the protected AlmaHealthDB subnet, while complex simulations and models are run on GDPR-compliant HPC and Cloud infrastructures of Italian research network. In any case, researchers are asked to provide their processing software in a replicable and possibly portable fashion.

Input and derived data are mapped early in the study design phase, thus enabling a prompt reuse and sharing of the dataset in HL7 FHIR and/or OMOP CDM standards, if allowed by the collected consent.

References

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Acknowledgments

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An in silico medicine info kit for effective stakeholder engagement

Martina Contin[1], Davide Montesarchio[1], Zita Van Horenbeeck[1,2], Raphaelle Lesage[1], Artem Platonov[1], Goran Stanic[1], Roberta De Michele[1], Janaki Raman Rangarajan[1], Liesbet Geris[1,3,4]

[1]Virtual Physiological Human Institute (VPHi), Belgium; [2]Centre for Sociological Research, KU Leuven, Belgium; [3]GIGA Research Institute, , University of Liège, Belgium; [4]Division of Biomechanics, KU Leuven, Belgium

INTRODUCTION: *In silico* medicine includes all the practices of computer modelling & simulations (CM&S) for prevention, diagnosis, and treatment of a disease, as well as the development and de-risking of biomedical products. Bringing together all the relevant stakeholders of *in silico* medicine, be it policymakers, clinicians, patients, etc. requires a community effort. As the International Society for *in silico* medicine, we have developed a variety of stakeholder engagement tools to rally the community, through an ***In Silico* Medicine Info Kit specifically designed for the modelling community to engage with key stakeholders in the realm of *in silico* medicine**.

MATERIALS & METHODS: The **strategies for stakeholder engagement** have been developed through direct experience gained from our involvement in EU-funded projects, focused on *in silico* medicine. Here, we briefly outline some of the key strategies and accompanying tools that we developed:

- Guidelines on **'How-to'** conduct **'Delphi study'** and **'surveys'**, in the context of *in silico medicine*, for instance to capture the needs and barriers, or awareness and perceptions.
- A step-by-step handbook to organize **focus groups**, featuring pre-designed templates tailored for the field of *in silico* medicine.
- **Focus cards** containing fictive scenarios crafted by *in silico* experts, to foster dynamic discussions and engagement.

Collectively, they provide guidelines, tools and resources, including multimedia examples, for effective stakeholder interaction.

OUTLOOK: *In silico* medicine represents the future of healthcare and has entered into a transformational phase of becoming part of real-life applications. Within this landscape, active engagement with diverse stakeholders such as patients, clinicians, policymakers, and industry leaders is imperative. The **"*In silico* medicine infokit"** would foster such endeavours, by addressing the unique challenges and needs of *in silico* medicine. We welcome the community to take advantage of the tools, as well as join us to co-create further.

Acknowledgment: We thank the EU-funded projects, SimCardioTest (GN.101016496), InSilicoWorld (GN.101016503), SIMCor (GN.101017578) and EDITH-CSA (GN. 101083771).

5.D: Cellular & Systems Biology II

Thursday, September 5

3:30am – 5:00pm

02.005

Physiome: Encouraging the publication and reuse of reproducible models

David Phillip Nickerson[1], Weiwei Ai[1], Shelley Fong[1], Karin Lundengård[1], Anand Rampadarath[1,2], Tommy Yu[1], Poul Nielsen[1], Peter Hunter[1]
[1]Auckland Bioengineering Insitute, University of Auckland, New Zealand; [2]Plant and Food Research, New Zealand

Reproducibility and confirmation of results is crucial for useful science and should be one of the supporting pillars of good research. However, only one third of computational physiological models published in scientific journals provide sufficient information to even attempt reproduction let alone demonstrate reproducibility.

Physiome is a journal committed to reproducibility and reusability of mathematical models of physiological processes. Every model published in *Physiome* is connected to a curated and permanent version of the model implementation with a persistent identifier. The code necessary to run the model is easily accessible, to be reused as it is or as a module in a novel model. Model validation and scientific value is ensured by being connected to a primary paper published in a domain-specific journal. We have collaborated with supporters of open science Digital Science (figshare and Overleaf) and Curvenote to build an open-source curation and publication system, with all journal articles published open access on a Curvenote powered website and archived in figshare.

Using these systems, *Physiome* publications are a complement to your primary article that ensures reproducibility, reusability and discoverability of you model. The format encourages modularity that facilitates combination of different models to develop the next level of systems understanding. And all the models are in one place, easy to find and accessible.

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For more information visit: https://journal.physiomeproject.org

Development of a computational inflammation model of osteoarthritis including obesity

Juntong Lai, Damien Lacroix
Insigneo Institute, Department of Mechanical Engineering, University of Sheffield, United Kingdom

Introduction: During obesity adipokines are released from local adipose tissue to prompt a chronic inflammation leading to osteoarthritis (OA). However, the understanding of inflammation regulation through obesity, physical activity level (PAL) and nutrition is still limited. Thus, this study aims to develop a general computational model of inflammation and obesity in OA in order to unravel the sensitivity of adipokines in the OA inflammatory process.

Methods: A 5D model was developed based on a previous model of cartilage inflammation (Baker et al., 2017). The model is based on ordinary differential equations to simulate the interactions of pro- and anti-inflammatory cytokines (PICs and AICs), matrix metalloproteinases (MMPs), fibronectin fragments (Fn-fs) and adipokines. The production of adipokines is measured by Body Mass Index (BMI) and regulated by PAL. Hill functions are used to describe the enzyme kinetics and the nonlinear regulation of PAL on the adipokine level. The variation of the system dynamics was analysed through bifurcations and local sensitivity analysis (LSA) of the nondimensionalised parameters.

Results: LSA shows that parameters from adipokines are relatively not sensitive in both the inflamed state and healthy state, whereas the bifurcations of BMI suggest that a threshold that can be altered by PAL exists to lead the persistent inflammation by reducing the system bistability. In addition, the bifurcation of the parameter inhibiting MMPs by AICs indicates that the system tends to stable inflammation when decreasing the weight of MMPs inhibition compared to PICs.

Discussion and Conclusion: Obesity does not directly result in a high level of cytokines but increases the risk of inflammation by regulating the dynamics of its process. Proper PAL can reduce adiposity when the inflammation is persistent so that the stability of a healthy state is returned. In addition to that, the sensitivity of two inhibiting inflammation pathways reflects the greater significance of MMPs on inflammatory progress. Overall, parameter sensitivity analysis and bifurcations provide insights into the dynamics of inflammation with obesity.

Modeling the interplay among TIMP, proteases and proinflammatory cytokines within the human intervertebral disc

Laura Baumgartner, Sandra Witta, Jérôme Noailly
Pompeu Fabra University, Spain

Intervertebral disc degeneration (IDD) contributes largely to low back pain. Within the Nucleus Pulposus (NP), the central tissue of the disc, IDD correlates with increased levels of proinflammatory cytokines, especially IL1B and TNF-α, and proteases, primarily MMP3 and ADAMTS4. Proteases are mainly inhibited by TIMP, potential therapeutical targets for IDD. Yet, the dynamics of TIMP regulation in the multifactorial NP environment remains underexplored. Hence, we aim to leverage a novel network modeling approach to integrate cell nutrition and mechanical loads to anticipate dynamics among proteases, TIMP and proinflammatory cytokines to predict protein expression and relative levels of protease inhibition by TIMP.

The Parallel Network Methodology was used to estimate relative mRNA expression (exp) of TIMP subgroups 1, 2 and 3, MMP3, ADAMTS4, IL1B and TNF-α. Intradiscal pressure and frequency was varied to simulate walking, sitting, jogging, hiking with 20 kg extra weight and exposure to vibration (15 Hz). The nutritional cell environment was optimal; 5 mM glucose, pH 7.1. mRNA exp results were coupled to directed networks to predict corresponding protein levels to eventually calculate inhibition of proteases through TIMP under the presence and absence of proinflammatory cytokines.

TIMP1 and TIMP2 mRNA exp were typically found to be lower compared to the one of TIMP3. In absence of proinflammatory cytokines, TIMP strongly downregulated MMP3 and ADAMTS4 in all conditions but vibration. Proinflammatory cytokine exposure generally led to an impaired inhibition of MMP3.

A higher TIMP3 exp agrees with experimental measurements of lower percentages of TIMP1,2- compared to TIMP3 immunopositive cells. The presence of proinflammatory cytokines caused higher protease but stagnant TIMP mRNA exp, which was experimentally verified by stagnant percentage of TIMP3 and rising ADAMTS4 immunopositive cells with increasing grades of IDD.

The proposed network model combination successfully provided insights into inhibitory regulations of TIMP, highlighting a need for further investigation of the therapeutic potential of TIMP3 in IDD.

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Building a digital twin for rheumatoid arthritis, one cell at a time

Anna Niarakis[1], Naouel Zerrouk[2], Sahar Aghakhani[3], Vidisha Singh[4], Oceane Saibou[4], Sylvain Soliman[5], Franck Augé[6]

[1]University of Toulouse III - Paul Sabatier & INRIA Saclay; [2]University of Evry, Paris Saclay & Sanofi Aventis R&D; [3]University of Evry, Paris Saclay & INRIA Saclay; [4]University of Evry, Paris Saclay; [5]INRIA Saclay; [6]Sanofi Aventis R&D

Rheumatoid arthritis is an autoimmune disorder that triggers a multifaceted joint inflammation. Conventional antibody treatments prove ineffective in approximately 40% of cases. Our work focuses on constructing a dynamic 'digital joint,' aiming at simulating the disease's progression, diverse treatment responses, and the potential risks associated with novel pharmaceutical therapies. We have constructed a multicellular joint representation by leveraging bulk and single-cell omics data and logic-based and data-driven modeling techniques, intricately capturing the interactions between immune and resident cells, inflammation processes, and cartilage integrity. Through collaboration with Sanofi R&D, we have successfully built one of the most comprehensive multicellular models (>1000 biomolecules), currently undergoing peer review. The multicellular model for the RA joint comes after many years of work on modeling RA, which includes the unveiling of metabolic reprogramming within affected cells and even identifying promising therapeutic targets and combinations in RA fibroblasts and macrophages. Ongoing efforts aim to enrich the RA model with more cell types by developing an agent-based model and methods to correlate in silico data with actual patient imaging, providing a critical bridge between simulated models and real-world clinical observations.

A sympathetic neuron computational model for hypertension treatment

Finbar John Argus[1,2,5], Ni Li[2], Jakub Tomek[2], Jenny Wang[3], Harvey Davis[4], Chenchen Zhang[2], Gonzalo Maso Talou[1], Dan Li[2], Blanca Rodriguez[3], Filipa Simões[5], David Paterson[2]

[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Department of Physiology, Anatomy, and Genetics, University of Oxford, UK; [3]Department of Computer Science, University of Oxford, UK; [4]Department of Neuro, Physiology, and Pharmacology, University College London, UK; [5]Institute of Developmental and Regenerative Medicine, University of Oxford, UK

Hypertension affects over 1 billion people, increases the risk of cardiovascular disease, and strains healthcare systems globally. Currently, treatment follows a one-size-fits-all approach that does not optimise for individual patients. The sympathetic nervous system has a critical regulatory role in hypertension, with many treatments attempting to directly modify the sensitivity to, and the activity of, sympathetic firing (beta-blockers, renal denervation).

We have developed a computational model of the postganglionic sympathetic neuron to optimise treatment choice for hypertensive patients. This computational model was calibrated to data from stellate ganglia neurons excised from spontaneous hypertensive rats, a good experimental model for hypertensive patients. Model parameters were further calibrated with human iPSC-derived sympathetic neuron action potentials to better represent a human sympathetic neuron. Bayesian calibration techniques were used to provide uncertainties in the prediction response that account for experimental error, model error, and calibration uncertainty.

We validated the simulated response to sodium channel blockers, calcium channel blockers, and m-type potassium channel up-regulators to demonstrate the accurate response to drug effects. We effectively showed the neuron changing between tonic firing phenotype and phasic firing with the increase of drug concentration. The effects of combining drugs on firing rate and rheobase were also accurately predicted, demonstrating that this model could have utility for optimising drug combinations and predicting treatment outcomes.

The model predicts norepinephrine release at the pre-synaptic synapse and, in future work, will be coupled to i) cardiomyocyte models for predicting cardiac electrophysiological response and to ii) vascular smooth muscle models for predicting constriction response in arterioles, venules, veins, and the renal system. This baseline sympathetic neuron model forms the foundation for creating digital twin models of circulatory system sympathetic control, aiming to predict individual patient responses to hypertension treatment, ultimately advancing personalised medicine.

Computational modelling for mechanistic explorations of biomarkers and biomechanical cues in atherosclerosis

Mané Sarkissian[1], Jérôme Noailly[1], Vicenta Llorente Cortes[2]
[1]Pompeu Fabra University, Spain; [2]Consejo Superior de Investigación Científica (CSIC), Spain

Most cardiovascular diseases are driven by atherosclerosis (AS). AS is influenced by inflammation and mechanics and characterized by lipid accumulation and formation of foam cells (FC). Healthy lifestyle and drug treatments can reduce the disease burden, but AS has usually no cure if diagnosed beyond a very early stage. Hence, new approaches are necessary to characterize subclinical AS. Accordingly, we aimed to create a model of early AS dynamics, which incorporates LRP1 signalling and the effects of wall shear stress (WSS), for mechanistic risk stratification and biomarker candidate identification of subclinical AS.

Conceptual regulatory network models of the biological regulation of AS for both high (>1.2 Pa) and low (<0.5 Pa) WSS were created, based on a corpus of 33 journal articles. They were coupled with an agent-based model (ABM) that represented endothelial cells (EC), macrophages, T cells, FC, and vascular smooth muscle cells (VSMC). Agent regulation involved key molecules shared with the regulatory network, which were solved iteratively as a dynamic system of ODEs withing the ABM solver, to predict ABM cell activation, migration, differentiation, and death.

The normal-case model, with optimal LDL, HDL and WSS, could simulate the non-pathological evolution of the intima as far as AS is concerned. Low shear stress (LSS) alone was sufficient to induce inflammation of the endothelium and drive macrophage infiltration. NO production was strongly undermined by low HDL levels under optimal LDL and WSS. FC tended to appear at 7-8 months of simulated time in hypercholesterolemia cases. LRP1 activation positively correlated with LDL.

LSS was sufficient to cause vascular inflammation by inducing the EC expression of VCAM1, and of the inflammatory cytokines MIF and IL-6, which are biomarkers of endothelial dysfunction. Similar results were reported by other studies. This unique mechanosensitive systems biology model replicated key aspects of AS by incorporating WSS. In conclusion, LSS might be proposed as an independent biomarker of AS. The model shall include the proliferation of EC and VSMC in the future.

Acknowledgements: ERC-2021-CoG-O-Health-101044828

5.E: Lung Modelling II

Thursday, September 5

3:30am – 5:00pm

02.011

The use of rapid expiratory occlusion (REO) to simultaneously identify lung elastance, airway resistance, and muscular effort

Ella F. S. Guy, Jaimey A. Clifton, Trudy Caljé-van der Klei, Jennifer L. Knopp, Lui R. Holder-Pearson, J. Geoffrey Chase
University of, New Zealand

Background: Respiratory testing currently requires significant clinical resources and interpretation, consequently limiting access and frequency of assessment, and thus limiting the ability to optimise care. Model-based monitoring methods have the potential to improve automation in respiratory care, and to reduce the clinical time and specialist equipment required. However, parameter trade-off in the identification of pulmonary physiological variables is a limiting factor, particularly in spontaneously breathing (un-sedated) patients. The interrupter method has previously been used to identify passive mechanics (elastance and resistance). However, the required 100ms occlusions have previously introduced significant resistance and accompanying patient effort dynamics.

Methods: Data from 20 subjects spontaneously breathing for 60s without non-invasive mechanical ventilation (NIMV) was used in this analysis. Passive mechanics were identified by implementing rapid expiratory occlusion (REO), with ~10x faster occlusions than the interrupter method (theoretically) requires. Thus, allowing active mechanics to be fit to the un-interrupted breath segments, as work of breathing (WOB), without trade off.

Results/Discussion: Identified median subject elastances (E) and resistances (R) (median [min max]), of E = 5.95 [2.08 11.3] $cmH2OL^{-1}$ and R = 1.05 [0.484 1.80] $cmH2OL^{-1}s$, correlated well with expected normal ranges from literature of E » 2 to 10 cmH_2O $cmH2OL^{-1}$ and R » 0.6 to 2.4 $cmH2OL^{-1}s$. Identified WOB components matched expected profiles across both inspiration and expiration. Expiratory WOB values were significantly lower than inspiratory WOB values, indicative of the expected near-passive expiration in healthy spontaneously breathing.

Conclusions: REO methods effectively estimated passive mechanics, allowing active mechanics to be identified without trade-off due to common assumptions of passive expiration or constant elastance or due to patient response to slower occlusions. Future work will validate these methods against gold-standard tests in cases of known disease to assess robustness in the face of respiratory dysfunction.

Pulmonary elastance identification and predictive methodology for PCV in a digital twin

Trudy L. Caljé-van der Klei[1], Ella F. S. Guy[1], Qianhui Sun[2], Jaimey A. Clifton[1], Cong Zhou[1], J. Geoffrey Chase[1]
[1]University of Canterbury, New Zealand; [2]University of Liege, Belgium

Background: In invasive mechanical ventilation (IMV), protective manoeuvres have proven effective in improving the efficacy of ventilator therapy. Protective manoeuvres have prevented ventilator overloading and in turn, overdistension of the lungs and ventilator induced lung injury (VILI). However, few patient-specific methods exist or are actively in practice in the control of IMV. Patient specific analysis and feedback control of ventilator settings and monitoring can be expected to increase efficacy of IMV across wider demographics and over treatment duration, with the ability to rapidly assess and respond to changes in patient state, without clinical intervention. Thus, providing a foundation for continuous monitoring and feedback during weaning, where patients are transitioned from IMV to non-invasive mechanical ventilation (NIMV), which is currently highly reliant on clinical judgement.

Methods: A non-linear hysteresis loop model (HLM) establishes patient specific identifiable lung dynamics, from measured ventilator data. A virtual patient model, fully automated using hysteresis loop analysis (HLA), was used to identify lung elastances from clinical data. Data provided from the Maastricht trial of 15 patients at 4 different baseline positive end-expiratory pressures (PEEPs), ranging from 6 cmH_2O through 12 cmH_2O, was used in this analysis. Predictions from each baseline PEEP were conducted, up to 6 increasing 2cmH_2O increments of PEEP, yielding 293 cases. From these prediction steps a maximum ΔPEEP of 12 cmH_2O was analysed with a maximum PEEP of 24 cmH_2O.

Results/Discussion: From previous studies, the exponential basis function for prediction was the most viable option for predicting lung elastance in PCV. A single breath was split into 5 elastance parameters, with a primary focus on , which defines the primary inspiratory recruitment elastance. This models prediction of in this dataset observes higher accuracy with higher PEEP levels. This is preferable as these higher PEEP levels are more clinically relevant for IMV.

Bridging micro to macro in pulmonary mechanics: Interpretable neural networks for surrogate modelling

Katerina Skardova[1,2], Alexandre Daby-Seesaram[1,2], Martin Genet[1,2]
[1]Laboratoire de Mécanique des Solides, École Polytechnique/ CNRS/IPP, France; [2]Inria, France

Idiopathic Pulmonary Fibrosis (IPF) is a disease characterized by the progressive formation of scar tissue in the lungs, leading to locally increased tissue stiffness and impaired respiratory function. Despite its significant impact on patient health, IPF remains poorly understood and poorly diagnosed. Our focus on IPF is motivated by the complex impact the fibrosis has not only on the lung tissue structure but also on the lung kinematics, and mechanics. The coupling between the disease progress and mechanical environment, as well as the multiscale nature of the disease, calls for a multiscale modeling approach to connect phenomena arising on various spatial scales. In order to integrate the existing micromechanical and organ-level models, the micro-model needs to undergo reduction. In our work, we propose to address this challenge by using a machine learning-based surrogate modeling framework.

In the presented framework, we use structured neural networks designed to be able to produce standard FEM shape functions. Similarly, to classical Physics-informed neural networks, this framework also has the capability to incorporate mechanistic knowledge through appropriate definition of the loss function. Due to the specific structure of the neural network, the number of trained parameters is significantly lower compared to a fully connected neural network and the individual weights and biases have a clear interpretation. In addition to higher reliability, the interpretability also allows us to strongly impose Dirichlet boundary conditions and thus avoid some of the changes caused by including additional terms in the loss function.

In this contribution, we present the capabilities of the model on several 1D and 2D test cases. The architecture of the neural network is defined by the discretization of the domain on which the governing equations are solved. There are however other choices, that effect the results, including the definition of the loss function and selection of optimizer and training strategy. We discuss the benefits and limitation of the tested variants and show how they affect the results obtained by the model.

Integrating macro-vascular and micro-vascular models to elucidate wall shear stress dynamics in pulmonary hypertension: A novel approach to understanding CTEPH development

Behdad Shaarbaf Ebrahimi, Haribalan Kumar, Alys Clark, Merryn Tawhai
The University of Auckland, New Zealand

Network models have been instrumental in understanding the impact of arterial occlusion on pulmonary vascular resistance and gas exchange function in pulmonary hypertension, particularly in acute cases such as pulmonary embolism. Chronic Thromboembolic Pulmonary Hypertension (CTEPH) poses unique challenges, where network models can mimic remodeling but fall short in predicting changes in flow dynamics and shear stress due to a lack of precise coupling with macro-vascular models. A significant gap in the literature is the absence of models capable of predicting multi-scale function across the complex pulmonary vasculature network, spanning different spatial scales.

To address this gap, we present a novel pulmonary circulation model that integrates a 3D representation of the main pulmonary arteries with a detailed 1D network model of the entire downstream circulation. This model accounts for key factors influencing lung perfusion distribution, such as anatomical structure variations across scales and the effects of gravity. It also features the capability to accurately predict Wall Shear Stress (WSS) in the major pulmonary arteries. The focus on WSS in various phenotypes underscores the innovative approach of this study.

Our comprehensive analysis reveals that while vascular remodeling seems to exert a negligible influence on flow distribution, occlusions—depending on their strategic locations—significantly disrupt lung flow dynamics. This study challenges prevailing narratives in the literature by demonstrating only moderate reductions in WSS within PH contexts, as opposed to previously reported substantial decrements. It posits that the reduction in WSS observed in PH patients is primarily attributable to a decrease in pulmonary flow, thus indicating that the vasculopathy associated with PH indirectly leads to WSS decline. The findings suggest that diminished cardiac output is the main contributor to WSS reduction, underscoring a secondary effect of PH on vascular shear stress, which shifts the focus towards systemic rather than local vascular alterations in PH progression.

A virtual asthma patient successfully predicts patient-specific impact of bronchial thermoplasty

Mahesh Ola, Richard Russell, Chris Brightling, Himanshu Kaul
University of Leicester, United Kingdom

Asthma is an airway disease that is characterised by heterogeneity in clinical forms and severity. Globally, it is repsonsible for >1000 deaths/day. Precision medicine is a powerful approach to treating asthma. However, we lack the capability to stratify *a priory* patient-specific response to therapy due to lack of 1) multiscale models that can integrate activity between networks of genes and cells, 2) standardised clinical data that can serve as reliable patient initial conditions, and 3) effective validation strategies. This represents a key barrier to precision medicine.

We overcame this barrier by developing and extending our virtual asthma patient to predict the impact of Bronchial Thermoplasty (BT) on asthma patients across 4 international cohorts (n=60 patients). BT is a minimally invasive procedure that delivers targeted radiofrequency energy to airway walls. We constructed virtual patients by using pre-procedure patient biopsy information and simulated the impact of BT. The model predicted changes in virtual muscle mass, mucous, and inflammatory cells. We used these results to predict i) *patient biopsy response* defined as reduction in muscle mass and ii) *clinical outocome* defined as improvement in patient symptoms.

Our model stratified patients based on their *biopsy response* highly accurately: non-responders were predicted with >94% accuracy and responders with >81% accuracy. The model stratified both *clinical* non-responders and responders with >75% accuracy. Our data revealed that BT is more efficacious for patients with T2-high asthma. Our work also highlighted lack of standardisation in clinical data gathering as a barrier to accurate patient stratification. Specifically, biopsy features were not consistently captured, which made stratifying *clinical response* more challenging. Still, our results demonstrate that we can stratify patients with unprecedented acuracy. Our next step entails converting this logic into a pipeline the clinicians can use for clinical decision-making. We anticipate our virtual patient strategy will remove impediments to making available at clinical scale precision medicine strategies to treat/manage asthma.

5.F: Population-based Modelling

Thursday, September 5

3:30am – 5:00pm

09.019

Classification of glenoid bone loss patterns using statistical shape modelling

Harnoor Saini[1], Julie Kim[1], Marc Hirner[2], Sumit Raniga[3], Desmond Bokor[3], Thor Besier[1]

[1]Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand; [2]Northland Orthopaedic Clinic, Whangarei, New Zealand; [3]Shoulder and Elbow Clinic, Macquarie University, Sydney, NSW, Australia

Glenoid bone loss classifications are important to assess shoulder joint status and planning glenohumeral reconstructions. Classifications help assess the degree and pattern of bone loss but current methods are prone to low inter-observer reliability, neglect the 3D surface of the glenoid, and struggle to distinguish normal anatomical variation from pathologic bone loss. We propose an automated method to classify glenoid bone loss using dual statistical shape models.

A normative scapula shape model (NSM) quantified bone loss, similar to [1], and a pathologic shape model (PSM) quantified the uniqueness of the bone loss pattern. The NSM was created using 76 healthy scapulae and the PSM using 45 glenoids with bone loss. We classified each patient's glenoid bone loss according to two metrics: degree of bone loss and uniqueness of bone loss. Degree of bone loss was computed by predicting the pre-morbid glenoid using the NSM and computing distances between the predicted and original glenoid. Uniqueness was computed by reconstructing the patient's glenoid via the PSM and analysing the principal components required for the reconstruction. All pathologic glenoids were classified using these metrics.

Shape models were validated using leave-one-out analysis and both achieved sub-millimeter accuracy. The principal components of the PSM revealed glenoid bone-loss regions (in order of descending frequency): posterior-inferior, anterior and posterior-superior. The degree of bone loss was related to the bone loss pattern, where less frequent patterns typically showed more pronounced bone loss. For example, the highest degree of bone loss was seen in a posterior-superior pattern. An automated and objective method to quantify glenoid bone loss may aid clinical decisions regarding shoulder pathologies such as glenohumeral osteoarthritis.

[1] Plessers K, et al. *J Shoulder Elbow Surg.* **29**(5):1050-1058, 2020

Strain analysis in the right ventricular outflow tract using non-parametric deformable shape modelling

Liam David Swanson[1,2], Raphael Sivera[1,2], Nicholas M. Jacobson[3], Claudio Capelli[1,2], Catalina Vargas-Acevedo[4,5], Gareth J. Morgan[5,6,7], Silvia Schievano[1,2]
[1]Institute of Cardiovascular Sciences, University College London, London, United Kingdom; [2]Great Ormond Street Children's Hospital, London, United Kingdom; [3]College of Engineering, Design and Computing, University of Colorado, Aurora, CO, United States of America; [4]Department of Pediatric Cardiology, University of Colorado, Aurora, CO, United States of America; [5]The Heart Institute, Children's Hospital Colorado, Aurora, CO, United States of America; [6]School of Medicine, Anschutz Medical Campus, University of Colorado, Aurora, CO, United States of America; [7]Department of Cardiology, University of Colorado Hospital, Aurora, CO, United States of America

The surgically repaired right ventricular outflow tract (RVOT)/pulmonary artery in congenital heart disease is a highly dynamic cardiac region undergoing large deformations during the cardiac cycle [1]. In systole, these structures dilate to accommodate the ejected blood volume while also elongating due to the contraction of the ventricle. These co-occurring deformations in orthogonal directions suggest a negative Poisson's ratio. In this study we use non-parametric, deformable shape modelling to estimate the characteristic axial and circumferential strains and compute the regional Poisson's ratio of the RVOT/pulmonary artery in a population of patients assessed for percutaneous pulmonary valve implantation (PPVI).

3D RVOT geometries were reconstructed at the time of maximum and minimum right ventricular volume, corresponding to end diastole and end systole, respectively, from 4D computed tomography images of 20 patients (34 ± 15 years-old, 50% pulmonary stenosis; 40% tetralogy of Fallot; 10% other diagnosis, 35% female). A large deformation metric mapping framework was used to estimate the RVOT deformation of each subject and establish point-correspondence with a resulting template shape. The axial and circumferential components of the linear elastic strain for each patient was computed from the deformations and used to calculate the Poisson's ratio at each point. The population average of each strain component and Poisson's ratio was computed for the RVOT, pulmonary valve and pulmonary trunk.

Axial and circumferential strain both showed compressive deformation in the RVOT and expansion elsewhere. 91% of the template surface area had a negative median Poisson's ratio. The estimated average Poisson's ratio was -0.35 in the RVOT, -0.20 in the pulmonary valve and -0.91 in the pulmonary trunk.

The computed shape model quantified axial and circumferential strain in the RVOT/pulmonary artery which confirmed the macroscopic negative Poisson's ratio observed during the cardiac cycle. This may have implications for clinic and future PPVI device designs that better accommodate RVOT/pulmonary artery dynamics.

[1] S. Schievano et al., Eur. Radiol., 2011.

Hexahedral mesh fitting using scaffolds and statistical shape modelling to reproduce the cortical bone morphology of the femur

Ted Yeung, Thor Besier, Peter Hunter, Vickie Shim
Auckland Bioengineering Institute, University of Auckland, New Zealand

Accurately capturing cortical bone morphology (size + shape) is essential to understanding the mechanical strength of bone and modelling orthopaedic implants, which interface with the inner cortical surface. Finite element modelling enables virtual assessment of implant designs and prediction of load sharing to the surrounding bone tissue (i.e. stress shielding). However, generating patient-specific meshes of the cortical bone is time-consuming and, in most cases, the inner cortical bone surface is not explicitly modelled. We present a new approach that uses higher-order elements to accurately fit both the outer bone morphology and inner cortical surface. We applied statistical shape modelling across a population of 307 femurs using principal component analysis [1] on the higher-order elements to constrain the optimisation and produce volumetric hexahedral meshes of the cortical bone. The higher-order mesh fit produced an average max error of 3.17 mm when fitted to the testing data set. Our approach resulted in a more compact shape model (i.e. reduced number of principal components) compared to a linear mesh of the same morphology. For example, the first principal component of the higher-order shape model explained 90% of the variance, compared to 70% with the linear model. The combination of shape modelling with higher-order elements enables the inner cortical surface to be modelled independent to the trabecular bone, providing a useful tool to investigate implant broaching, subsidence, and stress-shielding, which are clinically relevant applications. Subsequent hexahedral meshes can be input to commercial or open-access finite element modelling packages, such as FEBio or OpenCMISS, for structural analysis.

[1] Zhang, J., Malcolm, D., Hislop-Jambrich, J., Thomas, C.D.L. and Nielsen, P.M., 2014. An anatomical region-based statistical shape model of the human femur. *Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization*, *2*(3), pp.176-185.

Development of a statistical shape and density model of the paediatric femur for personalised FE models in children

Yidan Xu, Laura Carman, Thor Besier, Julie Choisne
Auckland Bioengineering Institute, The University of Auckland, New Zealand

Children are not small adults and therefore computational models using adult generic bone geometry and material properties are not representing children's bone shape and bone mineral density (BMD) appropriately [1]. Therefore, this study aimed to create and validate a paediatric statistical shape and density model (SSDM) of the femur for a paediatric population aged from 4 to 18 years old. CT scans of 330 children (136 F, 12 ± 5 y.o., 148 ± 24cm tall, 49 ± 22kg) were acquired from the Victorian Institute of Forensic Medicine (Melbourne, Australia). After manually segmenting 660 femora, a template volumetric mesh was morphed to each femur surface mesh. BMD was extracted from each scan through the HU/BMD relationship from a calibration phantom using Bonemat. Principal Component Analysis was performed on nodal coordinate and density in each femur. The resulting principal component (PC) weights were used to train a Partial Least Square Regression along with participants demographics in a leave one out analysis. The first PC was characterized by changes in bone length, width and distinct morphological variation of the femur. Cross sectional area showed a distinct shape change in cortical bone shape in the anterior-posterior axis. Cortical thickness variation was represented on the 3rd PC and cortical bone density variation was highlighted in the 4th PC. In the leave-one-out (LOO) analysis, the average RMS distance error between the predicted and segmented surface mesh was 1.77 ± 0.46 mm. The average RMSE for BMD prediction across elements was 0.10109 g/cm^3, with a nRMSE of 27.4%. When looking at BMD prediction by region, the nRMSE dropped to less than 13%. This study represents the first to develop a comprehensive SSDM that captures both geometry and BMD variations of the femur in a paediatric population aged 4 to 18 years. A crucial next step will be to analyse how these differences affect strain and stress prediction in a FE analysis to accurately assess the precision of the SSDM for FE analysis.

[1] Haider. Bone. 2018, 110, pp..295:303

Generation of digital genetic twins satisfying utility and privacy metrics for robust post-hoc analyses

Igor Faddeenkov[1], Olivia Rousseau[1], Sonia Bourguiba-Hachemi[1], Sophie Limou[1,2], Nicolas Vince[1], Pierre-Antoine Gourraud[1,3]

[1]Nantes Université, CHU Nantes, INSERM, Center for Research in Transplantation and Translational Immunology, UMR 1064, F-44000 Nantes, France; [2]Ecole Centrale de Nantes, F-44300 Nantes, France; [3]Nantes Université, CHU Nantes, PHU11Santé Publique, Clinique des données, INSERM CIC 1413, F-44000 Nantes, France

With the growing amount of health data and the emerging execution of secondary analyses thereof, ethical considerations concerning data protection arose leading in the European Union notably to the General Data Protection Regulation. Anonymization using digital twins of real data, that maintain the informativity as well as the privacy, may serve as the solution to let loose post-hoc analyses. Under the lens of Big Data, genetic data such as Human leukocyte antigen (HLA) is of particular interest given its great implication in autoimmune diseases and transplantation. Hence, there is a need to extend the anonymized digital twin generation to individual HLA genotypes.

From the US National Marrow Donor Program, restricted on European Caucasian (N=1.242.890), we estimated haplotype frequencies by the expectation-maximization algorithm, implemented in Hapl-o-mat, as a ground for sampling in silico HLA digital twins reproducing the distributions of real patients' HLA genotype data. In total, we developed 4 methods with increasing complexity: 1) a naive weighted sampling of 2 haplotypes; 2) a prior statistical phasing of haplotypes to sample phased diplotypes; 3) a hybrid of both methods to fortify reidentification metrics; 4) similar as 3), save for a correction algorithm to maintain a more precise haplotypes distribution in the virtual HLA population. For each of the 4 methods, we ran simulations with 10000 in silico patients, verifying both the consistency of and calculating the fraction of re-identified patients in the data. We obtain a good match between the haplotype frequency distributions of the real and digital genetic twin population (modified Hellinger distance <0.2). The 1st, 2nd, 3rd and 4th methods have a re-identification percentage of 12%, 7%, 10% and 5%, respectively.

We proved that the generated digital HLA twins are suited for informed secondary analyses while preserving the privacy of sensitive patient data – especially for the 4th method. This work accelerates the reuse of data via equally valuable in silico data without breaching privacy in patients' genetic data in the era of open research.

Domain adaptation methods for emotion and pain recognition via synthetic data

Jonas Nasimzada[1], Constantin Seibold[2], Alina Roitberg[1]
[1]University of Stuttgart, Germany; [2]University Medicine Essen, Germany

Recognizing a patient's emotional and physical state is essential for the design of patient-computer interaction systems, but collecting large datasets in compromising scenarios (i.e. filming a person in pain) is a difficult and ethically problematic task.

The main goal of this work is to investigate the feasibility of exploiting the enormous potential of synthetic data as a surrogate data source for the development of models capable of accurately recognizing and capturing patients' pain and classifying it. First of all a collection of synthetic data was created that will serve as the basis for model development. To ensure the relevance of the diversity of the synthetically generated data set, a 3D model of real people is first created. For this, we extract facial landmarks of a source dataset to generate 3D-Meshes using Emotion Driven Monocular Face Capture And Animation (EMOCA). Simultaneously, we extract a variety of facial textures from publicly available datasets such as CelebA via FFHQ-UV. This allows us, based on the extracted 3D models as well as the extracted textures, new characters are then created that have the same facial expressions but different facial textures which allows us to increase not only gender and ethnical diversity but also enables the visualization of unseen viewpoints.

Through the application of domain adaptation methods, this research aims to bridge the gap between the virtual world of synthetic data and the real-world context of medicine, eliminating the need for human participants and addressing the ethical concerns associated with traditional data collection methods. Afterwards a model is trained to recognize emotions and pain states of real people. Through the help of domain adaptation techniques, like feature-level adaptation, as well as transfer learning we could adapt the characteristics of synthetic data to the target healthcare domain.

[1] Daněček, Radek et al. "Emoca: Emotion driven monocular face capture and animation." CVPR. 2022.

[2] Bai, Haoran, et al. "Ffhq-uv: Normalized facial uv-texture dataset for 3d face reconstruction." CVPR. 2023.

5.G: In-silico Orthopedics I

Thursday, September 5

3:30am – 5:00pm

01.005

In-silico analysis of physiological joint mechanics within a complex musculoskeletal leg-system and its application to biomechanical evaluation of implants

Okan Avci[1], Animesh Ranjan[2], Armagan Can Yildiz[3]
[1]Fraunhofer IPA, Germany; [2]Fraunhofer IPA, Germany; [3]Fraunhofer IPA, Germany

There is a lack of physics-based tools available for surgeons to quantify their decision-making measures towards resolving their patients' orthopaedic disorders. Such decisions rely on static medical imaging and surgical experience. There is consensus about the lack of understanding the consequences of performed surgical interventions on the resulting patients' biomechanics. Such problems are prevalent across orthopaedics, esp. with implants, where the influence of implantation on individual biomechanics is unknown. Hence, the subject-specific interaction of the implant with the patient's locomotor system cannot be determined. Our motivation is to overcome these issues using in-silico analysis with models representing accurate tissue physiology and pathology of a given biomechanical joint, thereby enabling implant testing for an individual patient or a cohort of virtual patients in the future. In this regard, I will be present our developments on Fraunhofer IPA's In-Silico Human Modelling (ISHM) platform, ranging from medical imaging to complex 3D biomechanical simulations of the musculoskeletal system using finite element method (FEM).

A practical application of our current research work with an industrial partner will be also presented. In this in-silico study of a total knee tumour implant, the functional and biomechanical performance of the implant has been evaluated. The novel analysis uncovers the differences in knee kinematics between an implanted knee and a physiological knee joint. Aspects related to surgical misalignment of the implant and its impact on knee joint motion have also been analysed. The results of the ongoing study will be incorporated into implant navigation strategies for surgeons and into the conception of next generation of patient-specific implant designs.

Development of a validated software framework for in-silico clinical trials of orthopedic devices

Lukas Connolly, Christine Mueri, Adam Henderson
Zimmer Biomet, Switzerland

Introduction

In silico clinical trials (ISCT) have the potential to enrich clinical trials. However, for regulatory bodies to approve such methods, ISCT must be built on a thoroughly validated software framework. The purpose of this study is to present how regulatory grade finite-element (FE) simulations of CT-based bones and orthopedic implants automated across multiple commercial and internal software can be built, adhering to industry's best practices in terms of consistency, reproducibility, and traceability.

Approach

Requirements of the framework were identified early in the development cycle. To achieve credibility for later validation, automated tests were developed together with new features to ensure each requirement was satisfied. Git was used to track each step of the development and develop in parallel on branches. After completion of a feature, a pull request was created and peer reviewed to ensure that new code satisfied all internal guidelines (feature functionality, documentation, code style and automated tests). The pull request also triggered an automated build of the entire test suite and documentation page. This ensured the code was always functional and documented.

Interfacing various programs based on different Python API versions required the creation of both cross-compatible and specific Python modules to accommodate the various environments. A configuration file was introduced to orchestrate the modules without requiring code changes and allowing for versatility. It specified the required steps and associated options for virtual surgery, meshing, boundary conditions, material mapping, FE analysis, post-processing, and for comparing results across surgical or anatomical parameters via plotting. Aside from versatility, incorporating traceability through logging was paramount for review and debugging purposes.

Conclusion

The framework has been validated according to internal software validation guidelines and ensures credibility in the eye of regulatory bodies which is largely overlooked in literature. An initial version of the framework has already been successfully used in a published biomechanical analysis [doi: 10.1007/s10439-024-03452-w].

In silico clinical trial to predict the efficacy of alendronate for preventing hip fractures

Sara Oliviero[1,2], Giacomo Savelli[1,2], Antonino Amedeo La Mattina[2], Sophie Nguyen[1,3], Marco Viceconti[1,2]
[1]Department of Industrial Engineering, Alma Mater Studiorum, University of Bologna, Italy; [2]Medical Technology Lab, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; [3]Department of Mechanical Engineering, Biomechanics Section, KU Leuven, Belgium

Osteoporosis (OP) is associated with an increased risk of hip fracture, mainly due to the progressive loss of bone mineral density (BMD). Current treatments (e.g. alendronate) have limited efficacy in preventing fractures. *In Silico* Trials could be used to improve the development and assessment of new treatments.

The aim of this work was to apply an *In Silico* Trial methodology to predict the efficacy of alendronate and validate it against clinical data.

A cohort of 1325 virtual patients was generated using an anatomical atlas based on CT scans of proximal femurs [1]. OP progression and alendronate treatment were simulated by updating the femur BMD over time. A Markov chain process was used to predict hip fracture incidence over 3 years of follow-up. A Negative Binomial distribution was sampled to simulate the occurrence of fall events for each patient, and the impact load associated with each fall was estimated with a multiscale stochastic model [2]. Finite Element models were used to predict femur strength [2]. A patient was considered fractured when the impact force exceeded the femur strength.

Preliminary results (N=493) show that the model was able to predict a reduction in hip fracture incidence in the alendronate arm (RR=0.76), although effectiveness was partially overestimated compared to clinical data (RR=0.83) [3].

Current developments are focused on introducing the effect of ageing and frailty on the frequency and dynamics of falls, and replicating the equivalent of a phase III clinical trial (N>1000). The potential of this technology includes the possibility of testing different interventions or their combination to improve clinical trial design and the time- and cost-effectiveness of drug development.

[1] La Mattina et al, Ann Biomed Eng, 51:117-124, 2023.

[2] Bhattacharya et al, Biomech Model Mechanobiol, 18:301-318, 2019.

[3] Cummings et al, JAMA, 280:2077-2082, 1998.

Acknowledgements

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Assessing hip implant stability: A parametric surrogate modelling approach

Marlis Reiber[1,2], Fynn Bensel[1,3], Udo Nackenhorst[1,2,3]
[1]Leibniz University Hannover, Institute of Mechanics and Computational Mechanics, Appelstraße 9a, Hannover, 30167, Germany; [2]Hannover Medical School, TRR [298]Safety Integrated and Infection Reactive Implants (SIIRI), Carl-Neuberg-Straße 1, Hannover, 30625, Germany; [3]Leibniz University Hannover, International Research Training Group (IRTG) 2657, Appelstraße 11/11a, Hannover, 30167, Germany

In clinical practice, X-Ray images are commonly employed to monitor the patient's condition before and after implantation. High-fidelity computational simulations play a crucial role in aiding physicians in therapeutic decision-making by predicting hip implant stability, taking into account individual patient conditions. Long-term stability can be assessed by simulating the bone remodelling process, the adaption of the bone to altered loading conditions, which is reflected in changes to the bone mass density (BMD). However, the high computational effort of these computational models are preventing their clinical application.

In this work, a surrogate model with a reduced complexity is presented to facilitate real-time evaluation of BMD changes in the femur after the implantation. To account for varying implant positions, isotopological Finite Element Meshes (FEM) meshes are generated using the Laplace equation. Subsequently, bone remodelling simulations are conducted for the different implant positions. For the reduced model, the Proper Orthogonal Decomposition (POD) is combined with Radial Basis Functions (RBFs) interpolation [1, 2]. Here, the POD modes reflect the spatial variation in the BMD distribution and the RBFs incorporate the parameter dependency, in this case the change in implant position. The presented model reduces the computation time for a new set of parameters from hours to milliseconds while maintaining a certain level of accuracy, paving the way for real-time application in daily clinical practice.

References

[1] Dang V. T., Labergere C. and Lafon P., "POD surrogate models using adaptive sampling space parameters for springback optimization in sheet metal forming", *Procedia Engineering*, 207, 1588-1593 (2017)

[2] Dutta S., Farthing M. W., Perracchione E., Savant G. and Putti M., "A greedy non-intrusive reduced order model for shallow water equations", *Journal of Computational Physics*, 439, 110378 (2021)

Digital orthopedic methods for total knee arthroplasty: Insights from comparative analysis and validation studies

Kevser Banu Köse, Mohammad Hussein, Ramadan Abu Rabia, Zekra Hajer, Mustafa Yusuf Saatci
Istanbul Medipol University, Turkiye

Total knee arthroplasty (TKA) stands as an effective treatment for knee osteoarthritis, yet prosthetic longevity remains a concern necessitating further innovation. This study aims to explore digital orthopedic methods and their application in TKA procedures.

Digital orthopedic methods leverage software and algorithms to analyze numerical mechanical outputs derived from mathematical modeling of medical image data (DICOM). Herein, pre- and post-operative image data of five TKA patients were segmented in 3D, with virtual simulations replicating surgical steps. Results were compared against actual post-operative outcomes for consistency assessment.

Comparative analysis of various datasets and utilization of a novel intermediate design proposal yielded critical insights into virtual knee replacement efficacy. Findings reveal promising outcomes, demonstrating high consistency between virtual simulations and real-world post-operative situations. These insights contribute to enhanced surgical planning and decision-making in TKA procedures.

Furthermore, validation procedures underscore the importance of accurately evaluating proposed virtual knee replacement techniques. The project's iterative approach, involving multiple research articles and further optimization of parameters and implant designs, promises more realistic outcomes for comparison with actual implants. This endeavor marks a pivotal step towards innovative medical solutions and validation in knee joint treatment, particularly for osteoarthritis and related conditions.

5.H: Movement Biomechanics and Activity Tracking

Thursday, September 5

3:30am – 5:00pm

08.019

Estimating daily dynamic skeletal loading from ankle-worn activity monitors after menopause

Emma Fortune[1], Omid Jahanian[1], Melissa M. Morrow[2], Michelle M. Mielke[3]
[1]Mayo Clinic, Minnesota, United States of America; [2]The University Medical Branch Texas, Texas, United States of America; [3]Wake Forest University School of Medicine, North Carolina, United States of America

Introduction: One in eight women have their ovaries removed before reaching natural menopause (premenopausal bilateral oophorectomy; PBO), resulting in accelerated aging and increased risk for low bone mineral density (BMD). While accurate tracking of habitual physical activity (PA) is improving, the ability to translate this into bone health evaluations has been limited. We validated the use of ankle accelerometers to estimate bone loading during gait and showed it was a significant predictor of hip areal BMD (aBMD) in women after natural menopause [1,2]. This ongoing study investigates the relationships of daily skeletal loading estimates with aBMD in women with PBO history.

Methods: Fift**y** women with PBO history and 50 age-matched referent women had full-body DEXA scans to measure spine, pelvic, and leg aBMD, and wore ankle accelerometers for 7 days. Each participant's daily loading index (cumulative sum of each step's skeletal loading normalized to body weight) was calculated from acceleration data. Between group differences were assessed using paired t-tests. Associations of loading index with aBMD were assessed using linear regression. Covariates were age, BMI, menopause type (PBO or natural), and hormone replacement therapy use (HRT; ever vs never used).

Results & Discussion: There were no between group differences in mean daily loading index or aBMD ($p>0.11$). BMI and HRT use were higher in PBO vs referent women ($p<0.01$). Daily loading index was a predictor of pelvic aBMD ($p<0.005$), accounting for 28% variance and with pelvic aBMD increasing with increasing daily loading index. BMI was a predictor of spine, and right and left leg aBMD ($p<0.006$), accounting for 47, 29 and 34% variance, respectively, with aBMD measures increasing with increasing BMI.

Significance: Larger sample sizes are needed to determine if PBO history results in lower daily loading indices. Given the elevated risk of low BMD for women with PBO history and the relationship of daily loading index with pelvic aBMD, loading index monitoring could be used to guide PA-based interventions for osteoporosis prevention.

1. Madansingh et al., Gait Posture, 2019, 2. Madansingh et al., Menopause, 2020.

Validating the Fitbit Charge 6 wearable activity monitor for use in physical activity interventions in lung cancer: Study protocol

Roberto Benzo[1,2,3], Rujul Singh[3], Carolyn Presley[1,2], Zach Chaplow[4], Brian Focht[4], Chloe Hery[3], Macy Tetrick[3], Allison Cleveland[3], Jane Yu[5], Emma Fortune[6]
[1]Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio, USA.; [2]Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, Ohio, USA.; [3]Division of Cancer Prevention and Control, Department of Internal Medicine, College of Medicine, The Ohio State University, Columbus, Ohio, USA.; [4]Kinesiology, Department of Human Sciences, The Ohio State University, USA.; [5]College of Medicine, The Ohio State University Columbus Ohio USA.; [6]Division of Health Care Delivery Research, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota, USA.

Background. Commercial wearable activity monitors (WAM) provide information on individual physical activity (PA) levels and are increasingly used in behavioral interventions as well as cancer survivorship research. While the accuracy of these commercial monitors has been well-validated in healthy adults with typical movement patterns, little research has been conducted on their accuracy in survivors, and none in lung cancer (LC). Therefore, the aim of this study is to evaluate the validity of the Fitbit Charge 6's PA measurements in laboratory conditions and its agreement in free-living conditions against two research-grade WAM in LC survivors.

Methods: We will recruit 15 adults diagnosed with LC (stage I-IV) to participate in an in-lab and a free-living environment protocol between April and July, 2024. Participants will wear the Fitbit Charge 6, activPAL 3 micro, and ActiGraph LEAP WAM. During the two-hour in-lab visit, participants will complete various bouts of activities (i.e., walking, sitting, standing, and lying down) and several functional tests (i.e., 5X Sit-to-Stand and the Short Physical Performance Battery). In the free-living environment portion, participants will wear the three devices 24 hours a day for seven consecutive days, except for bathing/swimming activities. Lab-based validity of each WAM to classify step count, intensity level, and sedentary behavior per second will be compared to direct observation (video recorded, gold standard) and assessed using sensitivity, specificity, positive predictive values, bland-altman plots, percentage of mean absolute difference (MAD), and equivalence tests. Performance of the WAMs in the free-living environment will be compared using bland-altman plots to determine agreement, MAD, and regression models to determine correlations.

Impact: Conducting validation studies are essential to composing and interpreting clinical studies using WAMs, given the strong evidence showing a beneficial relationship between PA and patient-reported outcomes (e.g. fatigue, physical function, quality of life). The results from this analysis will help inform the accuracy and reliability of WAMs to measure PA in LC survivors.

Accelerating clinical decision making: Tailoring generic MSK models with subject-specific information is a good approximation to the personalized models

Pratik Nag[1,2], Alessandra Aldieri[1,2,3], Xinshan Li[4,5], Giorgio Davico[1,2], Marco Viceconti[1,2]

[1]Department of Industrial Engineering, Alma Mater Studiorum - University of Bologna, Bologna, Italy; [2]Laboratorio di Tecnologia Medica, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; [3]PolitoBIOMed Lab, Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy; [4]Department of Mechanical Engineering, University of Sheffield, Sheffield, UK; [5]INSIGNEO Institute for in silico Medicine, University of Sheffield, Sheffield, UK

Musculoskeletal (MSK) modeling has become increasingly popular in understanding human movement, improving clinical decision-making, and enhancing patient care. Typically, MSK models derived from literature data or healthy adults, also known as generic models, are employed and scaled to the subject's anthropometry. However, this procedure neglects crucial subject-specific geometric variations such as femoral neck angle (FNA), anteversion angle (AVA), tibial torsions, etc.

The present study compares three different MSK models- Model 1: scaled generic model, Model 2: scaled generic model with personalized FNA and AVA angles, and Model 3: MR (image)-based model, to evaluate an effective way for clinically relevant outcomes. Moreover, the study also aims to combine the MSK-FE (finite element) framework to understand how such differences in the MSK model generation affect the load distributions. The hypothesis is that overall geometry agreement with the personalized model would improve the accuracy of musculoskeletal simulations.

A static standing trial data of a subject (height 164 cm, age 70.5, FNA= 128.50°, AVA= 11.60°) was considered for the present study. The generated MSK models were made of 7 segments (pelvis, thigh, patella, shank, talus, calcaneus, and toes) and 29 muscles per leg. Model 2 was a modified version of Model 1 generated with the Torsion Tool [1]. All the analyses were conducted using OpenSim v4.4 [2].

The HJR forces were found to be higher for Model 1 (35%BW (R), 64% BW (L)) and similar to almost identical for Models 2 and 3 (~32%BW (R), ~61% BW (L)). The KJR forces in Model 1 (47%BW (R), 78% BW (L)) and Model 2 (44%BW (R), 73% BW (L)) were found to be higher than Model 3 (40%BW (R), 71% BW (L)). Model 2 has improved the moment arms for most of the muscles, with values closer to the MR-based model as compared to Model 1. Thus, the overall personalization of the generic femur could be an effective alternative to the resource-intensive MR-based MSK models.

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Gait analysis of patients with spinal cord injury: Influence of postoperative rehabilitation

Sanyam Phutela[1], Mahshida Hamid[1], Rounak Bhattacharyya[1], Manish Gupta[2], Bhavuk Garg[2], Rajesh Malhotra[2,3], Madhusudan Pal[4,5], Anoop Chawla[1], Sudipto Mukherjee[1], Kaushik Mukherjee[1]

[1]Indian Institute of Technology Delhi, India; [2]All Indian Institute of Medical Sciences, New Delhi, India; [3]Indraprastha Apollo Hospital, New Delhi, India; [4]Defense Institute of Physiology & Allied Science, Defence Research & Development Organisation, Delhi, India; [5]Center of Excellence, Footwear Design & Development Institute, Noida, India

Introduction

Motion Capture (MoCap) systems have made a significant impact on the gait evaluation of patients suffering from various musculoskeletal injuries. A general approach of evaluating the performance of a spinal cord injury (SCI) patient is to check the improvement in independent walking speed [1]. This study is aimed at gaining further insight into the use of MoCap with musculoskeletal (Msk) modelling to understand how rehabilitation improves the walking cycle of patients with SCI.

Methods

A 27-year-old SCI patient (Male) operated at All India Institute of Medical Sciences, New Delhi was recruited along with one age-matched male healthy subject. The patient needed walker assistance during the first visit (1.5 months post-op), but the patient could walk independently during the second visit (four months post-op). The motion data were captured using 12 BTS Smart DX-700 infrared cameras, and eight BTS force plates at 500 Hz and 1000 Hz, respectively. A full-body marker protocol using thirty three markers was used. A generic OpenSim model [2] was scaled to develop subject-specific musculoskeletal models. Lower-limb joint angles during walking were then estimated through inverse kinematics for both participants.

Results and Discussion:

The gait cycle of the SCI patient improved with rehabilitation. The stance phase of the SCI patient reduced from 80% to 65% with rehabilitation. Simultaneously, the mean stride length also improved from 0.62 m to 1.14 m. The healthy participant exhibited a stance phase of 61% and a stride length of 1.3 m. Four-month post-op lower-limb joint angles (hip, knee, and ankle) of SCI patient during normal walking were also found to match better with those of the healthy subject. In this way, this study establishes a MoCap-based protocol to evaluate the efficacy of rehabilitation for SCI patients.

References

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Acknowledgements

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Cloud-enabled online gait analysis

Hakan İlikçi[1], Sanaz Maghsoudi[1], Fatma Turan[2], Bora Ayvaz[3], Ali Fuat Ergenç[3], Fuat Bilgili[4]

[1]Department of Orthopedic and Biomedical Neurotechnology, Institute of Graduate Studies in Health Sciences, Istanbul University, Istanbul, Turkey; [2]Department of Biomechanics, Institute of Biomedical Engineering, Bogazici University, Istanbul, Turkey; [3]Department of Control and Automation Engineering, Faculty of Electrical and Electronics Engineering, Istanbul Technical University, Istanbul, Turkey; [4]Department of Orthopaedics and Traumatology, Istanbul Faculty of Medicine, Istanbul, Turkey

3D gait analysis system plays a crucial role in clinical and basic research, however, it is expensive and cumbersome. We aimed to find a more accessible and cost-effective system to obtain kinematic data for gait analysis.Four subjects(mean age: 26.76, SD: 0.71) with 8 limbs were included in the study. Two cameras (Basler, 50 Hz) and a custom-developed Inertial Measurement Unit (IMU) system were used to obtain gait data from the subjects during gait. The IMU system is integrated with internet of things architecture which was builded on a server infrastructure that enables the utilization of live sensor data alongside with online image processing data, leads to the creation of a system that can offer immediate visualization and fast analysis of gait. This architecture embodies the convergence of IoT, sensor technology, and advanced data processing, with profound implications for biomechanical analysis and healthcare innovation. The developed IMU system was placed on the subjects and operated simultaneously with cameras and the gold standard 3-dimensional gait analysis systems (Vicon (Oxford, U.K.)) The data obtained from the cameras were processed using MATLAB and TRACKER applications. Synchronized data was collected and compared with the 3D gait analysis system.Correlation analyzes were performed to examine whether the data obtained from the 2D gait analysis system we developed, and the gold standard 3D gait analysis system display changes in the gait cycle. According to the results, there is a high correlation for the hip and knee joints, but this is not the case for the ankle. According to the non-parametric Mann Whitney U test after the Shapiro-Wilk normality test, the results were not significant in the hip (p=0.726), while the results were significant in the knee (p=0.00001) and ankle (p=0.00036).This pilot study demonstrated the potential of using industrial cameras and IMU systems for gait analysis practically. We can obtain reliable data swiftly with the implementation of this method. Also, we anticipate that further research in this area will enable clinicians to assess individuals who require gait analysis in a more practical and time-efficient manner.

6.A: Heart Modelling - Perfusion and Blood Flow

Friday, September 6

9:00am - 10:30am

05.019

Data-driven analysis of modelling approaches for distal vessel trees in coronary blood flow

Jack Lee, Mohammed Salim Ibrahim
King's College London, United Kingdom

In the era of FFR_{CT}, modelling of coronary blood flow has continued to make forward strides with recent work encompassing multiscale (including porous myocardial flow), whole heart function coupled physics, and efforts to incorporate emerging imaging technology such as CT perfusion. But amidst this progress a basic question remains unanswered, pertaining to the treatment of the vessels that cannot be seen in via imaging. The characterisation of the distal circulation underpins the estimation of resistance distribution as well as myocardial parcellation i.e. the attribution of the myocardium to their feeding segments. The extent of the coronary circulation visible from CTA is limited by imaging resolution, motion, and contrast dynamics, and even in the optimal case little beyond the epicardial segments are captured. This has driven modellers to synthesise the branching sub-structures below the resolvable scale using approaches that are principally theoretical and heuristic, with key consequence being that the microcirculation becomes an under-constrained member of the multiscale model that introduces or hides error. Though novel generative methods continue to be developed, direct validation has been elusive due to a lack of hard data.

We outline our work to address the unsettled issues through a data-driven approach. Specifically, we set out to perform a high-resolution imaging of whole heart porcine coronary network. Using a custom modality biventricular vessel network was resolved to 56.5um, revealing detailed intramural as well as epicardial segments. The network was then segmented using an in-house AI implementation and reconstructed to a centreline-radius graph format for further analysis. The measurement of radii is well-documented to show dependence on the specific method used, and represents a major source of uncertainty increasingly at the smaller scale vessels. We used several different kernels to quantify a representative variation. The reconstructed network was then used to reexamine the typical assumptions embedded in the allometric scaling and heuristics powering the subtree generation, across vascular scales and myocardial sub-territories.

An integrated computational model for coronary and myocardial blood flow applied in a clinical diagnostic setting

Giovanni Montino Pelagi[1], Andrea Baggiano[2], Francesco Regazzoni[3], Jacques Huyghe[4], Marco Alì[5], Silvia Bertoluzza[6], Gianluca Pontone[2], Giovanni Valbusa[5], Christian Vergara[1]

[1]LABS, DCMC, Politecnico di Milano, Italy; [2]Cardiovascular Imaging Department, Centro Cardiologico Monzino, Italy; [3]MOX, DMAT, Politecnico di Milano, Italy; [4]School of Engineering, University of Limerick, Ireland; [5]Bracco Imaging S.p.A., Italy; [6]IMATI, CNR, Italy

Introduction - quantification of coronary flow and Myocardial Blood Flow (MBF) is critical for diagnosing coronary artery disease. The *in silico* replica of invasive exams with computational analyses needs to address specific issues: capturing the contraction - coronary flow interplay, predicting the regional MBF distribution and including personalized inputs for model calibration. We propose a new integrated model to simulate hyperemic coronary flow up to the tissue level and we apply it to patients from Monzino Cardiology Centre to virtually predict the outcome of late-stage diagnostic tests, e.g. Fractional Flow Reserve (FFR) and stress CT perfusion.

Methods - Patients anatomy is segmented from cCTA images. The perfusion model features 3D hemodynamics in the epicardial arteries and a multi-compartment Darcy formulation for the microvasculature, including vessels compliance and the effect of ventricular contraction. The model is calibrated integrating anatomical features with literature data. Perfusion simulations are run for a mixed population of patients using the Finite Element library **life^x**, developed at MOX (DMAT), in cooperation with LaBS (DCMC), both at Politecnico di Milano. Simulations accuracy is assessed by direct comparison of the results with the outcome of the clinical exams.

Results and Discussion - characteristic phasic flow patterns with high arterial inflow in diastole and venous outflow in systole are recovered. Significant epicardial lesions (i.e. FFR < 0.8) are correctly spotted with sensitivity and specificity of 97% and 100%. MBF maps show much higher values in patients without significant stenoses compared to patients with at least one lesion with FFR < 0.8. MBF distribution after anatomy-driven calibration of the model shows very good accordance with the clinical maps in the healthy subjects. In pathological patients, culprit lesions and perfusion defects are also spotted, although the accuracy of MBF distribution is lower than in the healthy case. Precise localization of perfusion defects and association with a specific epicardial branch are key features that will be investigated for a robust predictive application in a clinical setting.

Computational modeling of myocardial perfusion and oxygen transport in coronary venous retroperfusion treatments

Haifeng Wang[1], Lei Fan[2], Jenny Choy[3], Ghassan Kassab[3], Lik-Chuan Lee[1]
[1]Michigan State University, USA; [2]Marquette University and Medical College of Wisconsin, USA; [3]California Medical Innovations Institute, USA

Coronary venous retroperfusion treatments are emerging as a clinical approach for treating myocardial ischemia, particularly, with the introduction of a coronary sinus reducer (CSR) device for treating refractory angina linked to myocardial ischemia. The exact mechanisms of action of these treatments, however, are not well understood. Motivated by this issue, we have developed a novel computational model to predict hemodynamics and oxygen (O_2) transport in a realistic coronary arterial-capillary-venous system and their interactions with the beating heart to investigate retroperfusion treatments. A novel approach to compute capillary transit time (CTT) directly using a particle-tracking approach was also developed. We use the model to predict the impact of coronary artery stenosis on CTT and hemodynamics. It shows that arterial occlusion elevates CTT, with moderate stenosis (FFR > 0.6) increasing CTT from 1.21s to 2.23s primarily due to a reduction in capillary flow rates. In severe stenosis (FFR = 0.1), CTT further increases to 14.2s as a result of both diminished flow rates and elongated particle-path lengths in the capillary network. We have also found that CSR's effectiveness varies with the severity of coronary stenosis. With moderate stenosis, CSR enhances tissue oxygenation by increasing CTT whereas in severe stenosis, CSR also redistributes blood from non-ischemic to ischemic regions and reduces capillary flow heterogeneity. Besides investigating retroperfusion treatments, we also applied the model to investigate how O_2 delivery in the coronary microcirculation is affected in cardiovascular pathologies (e.g., microvascular rarefaction, hypertrophy). The proposed computational modeling framework can not only help advance our understanding of cardiovascular diseases but also aids in the development of targeted therapeutic interventions.

Integrating time-varying resistance in a lumped parameter model of the coronary circulation

Enhui Yong[1,2], Vivek Muthurangu[1], Ryo Torii[2]
[1]Institute of Cardiovascular Science, University College London, London, UK;
[2]Department of Mechanical Engineering, University College London, London, UK

Introduction

Modelling the coronary circulation presents distinct challenges due to its passage through the beating heart. Conventional lumped parameter models (LPMs) successfully simulate diastolic dominant coronary flow using intramyocardial pressure (IMP) and vascular compliance, often assuming constant resistance despite the intuitive understanding of dynamic resistance due to myocardial contraction. This study aims to develop a coronary LPM integrating time-varying resistance, intramyocardial pressure and vascular compliance to simulate phasic flow, and critically evaluate each of those influencing factors.

Methods

A closed-loop LPM was constructed. The coronary vascular tree consists of coronary arterial resistance R_a, coronary arterial compliance C_a, time-varying coronary arterial microvascular resistance $R_{micro}(t)$, myocardial compliance C_m, coronary venous resistance R_v and time-varying intramyocardial pressure $P_{im}(t)$. A mathematical relationship between coronary microvascular resistance and myocardial elastance was derived. Separate left and right coronary $R_{micro}(t)$ functions were prescribed. The model was implemented in Simulink and numerically solved with the backward Euler method. Scenarios of normal physiology and raised RV afterload from pulmonary hypertension were studied. Model output was assessed against in-vivo literature to examine its validity.

Results and discussion

The model replicated phasic coronary flow, consistent with literature. Varying resistance caused systolic impediment and diastolic augmentation. Mean diastolic-systolic flow ratio (mDSFR) exceeded 1 for both LAD and RCA, contrasting only the LAD conventionally. In pulmonary hypertension mDSFR rose 2.8 versus 2.1-fold accentuating the altered RCA flow observed clinically. The IMP component was crucial for realistic systolic flow waveforms in coronary veins.

The study introduced a simple to implement methodology exhibiting increased accuracy to conventional, notably in the RCA and in resilience to ventricular afterload change. The inclusion of time-varying resistance into coronary LPMs warrants thoughtful consideration given its physiological relevance and impact on model accuracy.

Biventricular modelling of human heart with right ventricular outflow tract

Debao Guan[1], Mark Danton[2], Xiaoyu Luo[1], Hao Gao[1]
[1]University of Glasgow, United Kingdom; [2]Golden Jubilee National Hospital, Glasgow, United Kingdom

Computational cardiac models have provided a unique approach to improving our understanding of cardiac physiology and pathology. While most existing studies focus on acquired cardiovascular diseases often in the left ventricle (LV), little attention has been paid to the right ventricle (RV) despite its great importance.

In this study, we have developed a pipeline of patient-specific biventricular models with right ventricular outflow tract (RVOT) using routinely available clinical data. Myocardial wall boundaries were first manually segmented from in vivo cardiac magnetic resonance scans at early diastole when the filling pressure was lowest. Segmented LV and RV boundaries were further aligned according to long-axis views. Then the LV and RV endocardial boundaries and the epicardial boundary were fitted with b-spline surfaces and finally stitched together to generate the biventricular geometry. A rule-based myocardial fibre generation method was used to generate a layered myofibre architecture by solving a series of Laplace-Dirichlet problems. The passive response of the myocardium is derived from an invariant-based strain energy function with 8 unknown parameters, and the active stress is determined by a well-established length-tension model. Similar to a previously developed multiple-step optimization procedure, we first estimated passive properties by matching measured LV and RV end-diastolic volumes by parametrizing passive parameters in two groups. Subsequently, myofibre stiffness was refined by using the Klotz curve. The passive property of RV was scaled based on LV stiffness. In the second stage, myocardial contractility was inferred by matching the ejection fraction of each ventricle.

We have successfully applied this pipeline to five health volunteers, and our results show that each bi-ventricular model can match in vivo measured pump function very well. The inclusion of RVOT in this biventricular model will further enable in silico modelling of pathologies where it is relevant, such as Tetralogy of Fallot.

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Examining flow dynamics after left atrial appendage occlusion using CFD simulations: Influence of device implant depth

Jordi Mill[1], Carlos Albors[1], Pedro Cepas-Guillen[2], Manal Barrouhou[1], Íñigo Anduaga[2], Laura Sanchis[2], Ana Laffond[3], Ignacio Cruz-Gonzalez[3], Xavier Freixa[2], Oscar Camara[1]
[1]Universitat Pompeu Fabra, Spain; [2]Department of Cardiology, Hospital Clinic Barcelona, Spain; [3]Department of Cardiology, Hospital Universitario de Salamanca, Spain

Left atrial appendage occlusion (LAAO) is a minimally invasive procedure that involves sealing the left atrial appendage (LAA) with a device. It represents an effective therapeutic approach for reducing the risk of strokes in patients with atrial fibrillation, particularly those with counterindication to anticoagulants. However, a notable proportion of individuals treated with LAAO experience device-related thrombosis (DRT) following device implantation.This study presents preliminary findings from the analysis of 14 patients who underwent LAAO utilizing two devices positioned at different depths within the LAA: the Watchman (Boston Scientific, United States) and the Amplatzer Amulet (St. Jude Medical-Abbott, United States). Among the participants, eight received Amulet devices placed proximally to the left atrial ostium, while six were fitted with Watchman devices, with five positioned proximally and one situated deeper. Computational fluid dynamics (CFD) simulations were run to assess the influence of device placement on hemodynamic parameters relevant to DRT. A Carreau model, incorporating a non-Newtonian approach, was employed. Patient-specific boundary conditions, derived from Doppler ultrasound velocity curves at the mitral valve, were imposed as outlets of the system. An artificial pressure wave from a patient with atrial fibrillation at the pulmonary vein level was defined as the system's inlet. Discrete phase modeling (DPM) was integrated with the continuous phase, whereby platelet clusters, representing particles, were introduced through the pulmonary veins during initial cardiac cycles. The simulations spanned five cardiac cycles, with a time step of 0.01s, synchronized with the patient's ECG. Additionally, a half-scaled function simulating mitral valve annulus displacement (4 mm peak) was applied. Hemodynamic indices, encompassing velocities, endothelial cell activation potential (ECAP), flow patterns, and particle attachment, were investigated. Our findings underscore that deeper device placement was related with lower velocities, heightened recirculation phenomena, compromised washing effects, and consequently, an increased predisposition to DRT formation.

6.B: Stent Modelling

Friday, September 6

9:00am - 10:30am

02.017

Multiscale computational model of blood flow of deployed vascular stents

Gabor Zavodszky, Christian Spieker, Alfons Hoekstra
University of Amsterdamm, The Netherlands

Vascular stents are cylindrical support devices engineered from biocompatible materials such as metalic alloys or polymers. They are instrumental in interventional cardiology and radiology for addressing vascular lumen narrowing or obstruction across multiple vessels, including the coronary, carotid, and peripheral arteries. Due to their wide-spread use and diverse application they are manufactured in various designs, including lazer-cut balloon-expandable, and woven self-expanding variants. In this study we apply a multiscale computational method to investigate the flow profile of deployed stents from the macroscopic flow to the cellular trafficking around the struts. Three different stent designs are considered: woven single layer, woven dual layer, and lazer cut. The stents are deployed in a straight tube. The macro-scale flows of these stented geometries are computed using COMSOL Multiphysics (Inc., Burlington). The resulting flow fields then provide the boundary information for the cell-scale flows, computed using HemoCell [1]. The cellular flows are simulated under stationary conditions, using a small repeating element from each deployed stent geometry. We demonstrate significant flow pattern differences between these three designs including recirculation zones, stagnation zones, cell accumulation, and shear rate distribution. The presented method establishes a new approach to evaluate blood contact micromedical devices in flow, including their influence on cell accumulation. In the future such method could be useful to assist the design and optimisation process of stents in order to minimize adverse reactions like thrombogenesis and inflammation, and promote positive outcomes such as rapid endothelialization and reduced in-stent restenosis.

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Optimizing surgical outcomes in infants with ductal-dependent pulmonary blood flow conditions

Kevser Banu Köse, Wael Shamsi Basha, Mohamad Humam Alzaeim, Selma Mulla
Istanbul Medipol University, Turkiye

Infants with ductal-dependent pulmonary blood flow conditions present unique challenges in surgical management. This study investigates personalized treatment modalities, including computer-aided anatomical modeling and hemodynamic analysis, to optimize surgical planning and predict postoperative outcomes.

The primary objective is to assess personalized treatment approaches' impact on surgical outcomes for these infants, particularly evaluating stent insertion or shunt deployment efficacy.

We utilize computational fluid dynamics (CFD) modeling and digital twin simulations, analyzing seven preoperative patient datasets for parameters like wall shear stress and velocity profiles across stented and shunted configurations.

Results depict differences in velocity profiles, with stent models exhibiting lower velocities. Wall shear stress analysis favors PDA stent insertion over shunts, while pressure drop varies across configurations.

These findings highlight PDA stent insertion's potential in mitigating hemodynamic complications and improving surgical outcomes, emphasizing tailored approaches' importance.

In conclusion, this study underscores the promising role of stenting in enhancing flow dynamics for infants with ductal-dependent pulmonary blood flow conditions, emphasizing the need for further investigation into personalized treatment modalities' efficacy in pediatric cardiac interventions.

Optimization of braided stent deployment techniques

Reza Abdollahi[1,2], Simon Lessard[2,3], Rosaire Mongrain[4], Gilles Soulez[1,2]
[1]Université de Montréal, H3T 1J4 Montreal, Canada; [2]Centre de Recherche du CHUM, H2X 0A9 Montréal, Canada; [3]École de Technologie Supérieure, H3C 1K3 Montreal, Canada; [4]Mechanical Engineering Department, McGill University, H3A 0C3 Montreal, Canada

Braided stents (BSs) are pivotal medical devices in vascular interventions due to their flexibility and maneuverability features. However, optimizing decision-making for device sizing and deployment techniques is crucial to mitigate complications. This study introduces an innovative method for selecting BS deployment techniques for enhancing preoperative planning and operational readiness. The BS is a crisscrossed cylindrical device manufactured by braiding strands in a helical shape. The morphological behavior of BS is predictable by a better understanding of the geometrical function of the lumen. We dissect the deployment procedure into an initial snapback phase and a subsequent dynamic push-pull technique (DPPT). Snapback occurs when the stent's distal end detachs from the microwire and snapback in the first stage of retracting the microcatheter. This significantly influences the landing zone, making its prediction vital. The DPPT, combining microwire pushing and microcatheter pulling, adjusts the metal coverage ratio and prevents incomplete stent apposition. Our methodology first focuses on predicting the deployed BS diameter by understanding its morphological behavior in relation to the lumen's geometrical factors, identifying lumen cross-section diameter, perimeter, curvature, tortuosity, and bulge as influential factors. Notably, a 2% scale-up in lumen diameter effectively supersedes the impact of other geometrical considerations. We demonstrate our method's applicability through a case study, dividing the lumen into five continuous zones for targeted snapback prediction and DPPT ratio adjustment. The snapback length of 2.97 mm was found for the first zone, and the remaining zones could be anticipated with the push-pull ratios of 1.05, 2.23, 2.21, and 1.15, from distal to proximal zones. This information can aid physicians in the navigation of endovascular devices through the lumen. By increasing the validity and precision of the method it can also be applicable for programming in the automation of endovascular robotic-assisted surgery.

Virtual coronary stenting simulations: On the use of data from patient-specific imaging for validation and clinical interpretation

Luca Antonini[1,2], Gianluca Poletti[1], Georgia S. Karanasiou[3,4], Antonis Sakellarios[3,4], Michail I. Papafaklis[4], Lampros K. Michalis[5], Dimitrios I. Fotiadis[3,4], Lorenza Petrini[6], Giancarlo Pennati[1], Francesca Berti[1]

[1]LaBS - Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133 Milano, Italy; [2]Parametric Design, Gessate (MI), Italy; [3]Department of Biomedical Research Institute–FORTH, University Campus of Ioannina, 45110 Ioannina, Greece; [4]2nd Department of Cardiology, University Hospital of Ioannina, 45110 Ioannina, Greece; [5]Faculty of Medicine, School of Health Sciences, University of Ioannina, 45110 Ioannina, Greece; [6]Department of Civil and Environmental Engineering, Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133 Milano, Italy

The exploitation of a digital twin of coronary stenting that can reliably mimic the clinical reality could lead to improvements in individual treatments, reducing the reliance on animal and clinical trials during device development. Consequently, in silico studies have become integral to medical research, prompting the need to establish the reliability of both the stent and coronary artery models used in simulations. In this work, we aim to discuss the use of patient-specific images (i.e. OCT) acquired at different timepoints, namely pre-, post-operatively and at after 12 months, for preparing and validating the model used for simulating the acute phase, then exploited for correlating local quantities, such as vessel overstretch, with the clinical outcome at follow up. Pre- and post-operative image data from six patients and the associated procedural indications are used to prepare and validate the virtual patient-specific finite element models of the stenting procedure. Specifically, the model is tested and proved accurate in replicating the acute clinical outcomes, such as postoperative vessel lumen area and the presence of any stent malapposition. When available, follow-up data at 12 months are used to correlate the potential vessel wall weakening due to overstretch at deployment with the intima hyperplasia. In a few cases, it is possible to establish a link between the vessel area that are subjected to high strains at the stent deployment with those experiencing the greatest intima proliferation, although 12 months can be not a sufficient interval for appreciating a severe vessel reocclusion.

Effect of oversize stenting using a measurement-driven numerical approach for sidewall aneurysms

Levente Sándor, Benjamin Csippa, György Paál
Department of Hydrodynamic Systems, Faculty of Mechanical Engineering, Budapest University of Technology and Economics

Predicting the efficacy of Flow Diverter (FD) treatment of intracranial aneurysms is challenging due to the complex nature of the device deployment, the underlying biochemical processes and the patient-specific vessel section geometry. While such complex simulations become more feasible day by day, a quick assessment of treatment scenarios is needed to aid in the decision-making process. Our objective is to provide hemodynamic analysis for intracranial sidewall aneurysms using nominal and oversized scenarios. The hydraulic Darcy-Forcheimer resistance coefficients of the deployed stents are based on our previous in-vitro study.

More than 20 patient-specific vessel sections were virtually treated for nominal and oversized scenarios, using two stent designs (Phenox - P64, Medtronic - PED). Several computational fluid dynamic simulations were performed per patient beyond the pre-treatment case. The hydrodynamic resistance effect of the stent was modelled with a homogenous porous layer with linear and quadratic resistance parameters obtained from our measurements. Time and space-averaged hemodynamic quantities were analysed in the aneurysm sac volume.

Scenarios using nominal stent deployment showed better velocity reduction efficiency, from which P64 performed better than the PED design, due to the higher wire number. However, in oversized cases, no significant difference was detectable between the two devices.

Our study was currently limited by the homogenous porous properties of the braided stent. For future studies, the results of the in-vitro study can be utilised for an non-homogeneous approach through the metallic surface area and pore density properties of the deployed device.

6.C: Experimental Surgery, Animal Models, and Model Transfer

Friday, September 6

9:00am - 10:30am

07.017

Exploring hepatic vascular dynamics and function in metabolic syndrome and steatotic liver disease: Insights from human and rat models

Sandra Nickel[1], Laura Bütow[2], Rebecca Sternkopf[1], Anton Schnurpel[1], Hans-Michael Tautenhahn[1]
[1]University Hospital Leipzig, Germany; [2]Jena University Hospital, Germany

In modern affluent societies, lifestyle-induced diseases are burgeoning, notably metabolic syndrome featuring type 2 diabetes, obesity, and hypertension. This constellation not only elevates cardiovascular risks but also leads to metabolic dysfunction-associated fatty liver disease (MASLD), considered a hepatic manifestation of the syndrome. Steatotic liver disease (SLD) incidence is mounting in recent decades, complicating surgical interventions for liver tumors like hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Extensive liver resection, often necessary for treatment, poses significant risks, particularly with MASLD, resulting in morbidity rates of 20-30%. The hepatic arterial buffer response (HABR) is pivotal in maintaining liver perfusion and function during surgery, yet its interaction with metabolic syndrome and SLD remains poorly understood. The lack of correlation between hepatic artery flow and portal venous pressure/flow in such patients hampers accurate liver function assessment. The existence of the HABR in humans post-liver resection and its interaction with hepatosteatosis remain unanswered questions. Additionally, clarifying the relationship between arterial malperfusion and impaired liver function is imperative. Understanding these dynamics could inform pharmacological interventions targeting arterial spasm in steatotic livers. Our hypothesis posits that hepatosteatosis compromises hepatic vascular function and post-resection liver function in experimental and clinical settings. Investigating these aspects may pave the way for tailored interventions to ameliorate surgical outcomes in patients with SLD and metabolic syndrome.

In-silico enhanced animal experiments for evaluation of cardiovascular implantable devices

Jan Brüning[1,2], Adriano Schlief[1,2], Pavlo Yevtushenko[1,2], Jan Romberg[3], Andreas Arndt[3,4,5], Leonid Goubergrits[1,2]

[1]Institute of Computer-assisted Cardiovascular Medicine, Charité – Universitätsmedizin Berlin; [2]Deutsches Herzzentrum der Charité; [3]Biotronik SE & Co. KG; [4]Technische Universität Dresden, Germany; [5]Kurt-Schwabe-Institut für Mess- und Sensortechnik Meinsberg e.V., Meinsberg, Germany

In-silico modelling of performance of high-risk medical devices holds the promise to reduce or even replace in-vitro and in-vivo methods, such as animal experiments. Nonetheless, animal experiments are still relevant and often even mandatory for medical device evaluation. This study presents an approach on how to use those two methodologies to simultaneously refine the animal experiment and validate the in-silico assessment of medical devices.

This study leveraged data obtained from a chronic animal experiment investigating a pulmonary artery pressure sensor (PAPS) in 10 pigs over a duration of approx. 3 months. The animal experiment focused on assessing the risk of different adverse events, such as device thrombosis and resulting lung embolism. Two sensors have been implanted into each animal in favorable as well as non-favorable positions, aiming to increase the risk of occurrence of these adverse events. CT scans have been performed before and after the device implantation.

An in-silico representation of the animal experiment was conducted. Here, the pulmonary artery was reconstructed from the pre-interventional CT. Virtual device implantation was performed, ensuring that its position mimics the post-interventional CT data. Transient computational fluid dynamics simulations have been carried out to calculate hemodynamic parameters associated with thrombosis, such as oscillating shear indices (OSI) and wall shear stresses (WSS). Changes in pre-interventional hemodynamics due to the implanted device, as well as hemodynamic differences between optimally and non-optimally implanted devices have been assessed. In addition, results of histopathologic examinations regarding occurrence of thrombosis were mapped against hemodynamic results.

The device caused no changes in OSI or WSS and the average pressure drop across the device was below 1 mmHg. Non-optimally positioned devices did not result in relevant changes and no hemodynamic differences to optimally positioned devices was observed. No lung embolism was observed and only small thrombi in the vicinity of the PAPS were found. Pulmonary arteries in which a thrombus was found featured slightly elevated WSS.

Computer modelling of cortical pathophysiology in parkinsonism

William Lytton[1], Donald Doherty[1], Adam Newton[1], Thomas Wichmann[2], Yoland Smith[2], Liqiang Chen[3], Hong-yuan Chu[3]
[1]DHSU, United States of America; [2]Emory University, USA; [3]Georgetown University, USA

Clinicians always hope to find a single site of damage which will then provide a single target for repair by one drug -- the magic-bullet doctrine of medicine. This desire is often frustrated: organs alter other organs in cascades of pathophysiological compensation, decompensation and further damage. A good example of this is Parkinson's disease (PD). PD motor features start to develop with damage to the dopamine-producing neurons in substantia nigra. Basal ganglia is hit the hardest, but neocortex is also subject to damage, both from loss of dopaminergic input, and from changes due to changed neural activation patterns from damaged basal ganglia.

Motor cortex provides the final common motor output to the body. Our studies have therefore focused on activity changes in cortical neurons and networks seen in PD. We used an established model of mouse motor cortex, implemented in the NEURON/NetPyNE simulation system. We assessed the effects of the 64% reduction in corticospinal neuron excitability that has been identified as an independent pathophysiological feature in parkinsonian mice. We found that this experimentally identified 64% *decrease* in corticospinal neuron excitability led to a paradoxical 25% *increase* in corticospinal neuron firing in the context of the simulated network, due to the effects of feedforward and feedback loops within this single cortical area. We also found an overall network change with a 2.2-fold strengthening of beta-band spectral power of local field potential signals (LFP). In addition, the dominant beta-band LFP frequency slowed from 19 Hz to 14 Hz, its duty cycle (i.e., duration of oscillation peaks/oscillation period) decreased from 46% to 36%, and synchronous pyramidal tract (PT) neuron firing increased 2.6-fold. These oscillatory changes could contribute to the beta-oscillation changes seen in PD. Abnormal signals from PT neurons to the spinal cord could then create motor coordination deficits or outright failure. More generally, our studies provide further insights into the role of cortical circuit changes in the manifestations of PD.

Induction of steatohepatitis in large animals – An example of successful collaboration between medical doctors, veterinarians, and basic scientists to establish a model for translational research

Philipp Felgendreff[1], Silvana Wilken[2], Bruce Amiot[2], Moritz Schmelzle[1], Scott Nyberg[2]
[1]Hannover Medical School, Germany; [2]Mayo Clinic, USA

Large animal models are increasingly crucial in the highly complex, individualized medicine era. Due to the increasing number of patients with steatohepatitis, the need for large animal models to investigate innovative approaches in a human-like disease model is immense. However, these models also face significant challenges, like the efficient feasibility in a laboratory setting, achieving a high degree of comparability with human disease, and considerations of animal care regulations, calling for a joint effort of multiple science disciplines. Particularly for models of liver regeneration in systemic treatment approaches, these challenges have confined the progress in translational research.

Establishing steatohepatitis in large animals is a case where these challenges were successfully solved. In cooperation with medical doctors, veterinarians, and basic researchers, feeding a methionine-choline-deficient high-fat diet to pigs for eight weeks induced severe steatohepatitis. Besides demonstrating the practical feasibility of the model by implementing a specific study protocol, a systematic histological assessment showed the comparability to the human disease. The reproducible increase in macrovesicular steatosis in the liver, up to 60% during the study period, was remarkable and offered innovative preclinical study options. However, the specific diet was also associated with side effects that raised potential animal welfare concerns. Next to diet-associated dermatitis, also weight loss and signs of anemia were seen. In close cooperation with the veterinaries, these side effects were characterized, and treatment strategies were developed to keep the animal burden as low as possible. However, the missing increase of extracellular matrix in the liver or histological signs of cirrhosis is the current limitation of this model. Upcoming studies combining the steatohepatitis approach with genetically engineered pigs with Fumarylacetoacetate hydrolase deficiency or Gal-KO can further close this gap. Therefore, establishing steatohepatitis in pigs is a remarkable example of interdisciplinary cooperation in establishing a large animal model for translational research.

Reduced lifespan in rats with low intrinsic exercise capacity is associated with reduced complex I threshold in females in aging

Alena Spagnolo[1], Estelle Heyne[2], Michael Schwarzer[2], Torsten Doenst[2]
[1]Universitätsklinikum Leipzig, Germany; [2]Universitätsklinikum Jena, Germany

High exercise capacity is associated with high mitochondrial function and extended life expectancy. In a rat model of high (HCR) and low intrinsic (LCR) running capacity mitochondrial respiration and complex activities of HCR were higher compared to LCR in skeletal muscle. Aging is known to decrease mitochondrial function in heart and skeletal muscle and complexes I and IV have been described impaired. It has been suggested that the coupling between complex function and respiration may change with aging. Thus, it is not clear how a decrease in complex I and IV activity affects respiratory capacity.

We aimed to investigate the effect of complex I and IV inhibition on respiratory capacity dependent on intrinsic exercise capacity, age and sex. Therefore, respiratory capacity and enzyme activities of complex I and IV were measured using different concentrations of specific inhibitors. We determined complex I and IV specific threshold effect in isolated interfibrillar mitochondria from heart and gastrocnemius muscle from adult and old HCR and LCR.

In heart complex I specific threshold was comparable between adult HCR and LCR but was higher in old HCR compared to old LCR. Complex IV specific threshold was comparable between HCR and LCR and decreased with age. In gastrocnemius muscle, complex I specific threshold was not affected by phenotype or age. Complex IV specific threshold was comparable between HCR and LCR and decreased with age especially in HCR. Separated for sex, in heart in males complex I specific threshold was not affected by phenotype or age. In females, complex I specific threshold decreased with age just in LCR and was lower in old LCR compared to old HCR. Complex IV specific threshold decreased in males with age tendentially in LCR and was lower in old LCR compared to old HCR. In females, complex IV specific threshold was comparable between HCR and LCR decreased with age.

Inhibition of complex I in heart muscle from females had a greater effect on respiratory capacity in old LCR compared to old HCR. In contrast inhibition of complex IV in heart muscle had a greater effect on old LCR compared to old HCR just in males.

6.D: Clinical Decision Support for Cardiovascular Applications

Friday, September 6

9:00am - 10:30am

09.019

Improved patient classification from 2D cardiac ultrasound using multi-modal transfer learning

Debbie Zhao[1], Joshua R. Dillon[1], Gina M. Quill[1], Bram W. M. Geven[1,2], Stephen A. Creamer[1], Edward Ferdian[1], Vicky Y. Wang[1], Thiranja P. Babarenda Gamage[1], Timothy M. Sutton[3], Boris S. Lowe[4], Malcolm E. Legget[5], Nicola C. Edwards[4,5], Robert N. Doughty[4,5], Alistair A. Young[6], Martyn P. Nash[7]

[1]Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand; [2]Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands; [3]Counties Manukau Health Cardiology, Middlemore Hospital, Auckland, New Zealand; [4]Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand; [5]Department of Medicine, University of Auckland, Auckland, New Zealand; [6]School of Biomedical Engineering and Imaging Sciences, King's College London, London, United Kingdom; [7]Department of Engineering Science and Biomedical Engineering, University of Auckland, Auckland, New Zealand

Background—Cardiac ultrasound is widely applied for the classification of patients into normal and diseased groups, which is used to guide clinical decision-making. However, the manual analysis of ultrasound images is a subjective and time-consuming task, which can lead to substantial variability and poor diagnostic agreement with gold-standard cardiac magnetic resonance imaging (MRI). We present a novel transfer learning-based model for the automated analysis of 2D cardiac ultrasound images by leveraging subject-specific labels from MRI, and show how this approach outperforms manual expert analysis in a clinical context.

Methods—More than 100 human subjects were prospectively recruited for multi-modal imaging consisting of routine cardiac ultrasound and MRI examinations, <1 hour apart. Labels were generated by automated segmentation of standard long-axis MRI slices and manually registered to corresponding ultrasound images belonging to the same subject. A deep learning model was trained to segment the left heart from standard apical 2- and 4-chamber images using knowledge transferred from MRI. This enabled the calculation of routine indices for left heart assessment, providing a basis for patient classification with respect to LV ejection fraction (LVEF), LV mass index (LVMi), and LA volume index (LAVi).

Results—We found a high correlation in left heart indices between automated 2D cardiac ultrasound measurements and those derived from MRI as the reference modality. Our workflow for automated analysis improved patient classification with respect to reduced LVEF, increased LVMi, and increased LAVi, compared to manual analysis. Furthermore, our approach outperformed a similar model trained using manual segmentations from the public CAMUS dataset with respect to agreement with MRI.

Conclusions—We have developed a novel workflow for automated quantification of left heart structure and function from 2D cardiac ultrasound images that outperformed expert manual analysis. Knowledge transfer from cardiac MRI can enhance the analysis of routine cardiac ultrasound examinations to enable rapid and accurate patient classification for improved clinical decision-making.

Bayesian inversion enables personalised septic shock treatment guided by noisy arterial pressure waveforms

Finneas JR Catling[1,2], Kim H Parker[1], Alun D Hughes[2], Steve Harris[2], Rebecca J Shipley[2], Anthony C Gordon[1]
[1]Imperial College London, London, United Kingdom; [2]University College London, London, United Kingdom

Background

Septic shock produces heterogeneous cardiovascular changes which have different effects on the arterial pressure waveform, motivating personalised treatment guided by waveform shape. Waveform interpretation 'by eye' is challenging, however, especially as fluid-filled pressure measurement catheters introduce noise. We present a system that uses Bayesian inversion to infer patients' cardiovascular status from their noisy pressure waveforms.

Methods

Our system combines an empirical heart model and a one-dimensional human arterial tree model emulated using a neural network, plus a measurement error model. We simulate 219 noisy radial and femoral pressure waveforms and arterial catheter fast-flush tests (FFTs) from virtual patients by sampling from the prior predictive distribution. We attempt to recover the ground-truth parameter values from the waveforms by Bayesian inversion, based on two strategies: 1) a one-stage approach which jointly infers the measurement noise and cardiovascular parameters from the pressure waveform, 2) a two-stage approach which first infers the measurement noise from the FFT, then infers the cardiovascular parameters from the pressure waveform using an informed prior over the measurement noise parameters.

Results

Measurement noise was accurately inferred from the FFTs. The two-stage approach reduced posterior multimodality (4% of two-stage experiments had R-hats > 1.3 versus 8% with one-stage) due to erroneous modes in the posterior over catheter natural frequency, but global performance of the two approaches was similar. Inference was most informative about left ventricular ejection time (13 [5, 23] ms*), stroke volume (12 [6, 19] ml*), large artery stiffness (18 [8, 33] %†*) and dilation (10 [5, 17] %†*), reducing uncertainty over brain, renal, splanchnic and pelvic blood flow (20 [10, 31] %†*).

* Two-stage posterior median [q25, q75] absolute error

† Percent of ground truth

Conclusions

Bayesian inference in our realistic cardiovascular model is made more reliable by the two-stage approach. Our system provides novel cardiovascular insights that could be used to personalise IV fluid, vasopressor and inotrope therapy in septic shock.

Enhancing ECMO device development through machine-learned virtual patient data

Micha Landoll[1,2,3], Yifei Huang[1], Ulrich Steinseifer[1], Stephan Strassmann[2], Christian Karagiannidis[2], Michael Neidlin[1]
[1]Department of Cardiovascular Engineering, Institute of Applied Medical Engineering, Helmholtz Institute, RWTH Aachen University, Aachen, Germany; [2]ARDS and ECMO Centre Cologne-Merheim, Dept. of Pneumology and Critical Care Medicine, Kliniken der Stadt Köln gGmbH, Witten/Herdecke University, Cologne, Germany; [3]Institute for Computational Biomedicine II, University Hospital Aachen, RWTH Aachen University, Aachen, Germany

The integration of clinical data into the modelling of Extracorporeal Membrane Oxygenation (ECMO) therapies marks a significant advancement in patient outcomes and the development of medical devices. This study aims to overcome current limitations such as patient privacy concerns and inadequate dataset sizes by generating high-quality synthetic patient data.

This study employs a Conditional Tabular Generative Adversarial Network (CTGAN) to generate synthetic data from the Electronic Health Records (EHR) of 767 patients undergoing ECMO. It focuses on 59 selected therapy parameters, such as vital signs, blood gases, and organ function indicators. The methodology involves structured data preprocessing, missing value imputation, and CTGAN hyperparameter tuning. This systematic process ensures the generation of synthetic data that closely mirrors the complex characteristics of actual patient records.

The CTGAN's effectiveness is shown by synthetic data achieving an average coverage score of 95% (min. 58%) against the original dataset, alongside achieving boundary and synthesis scores of 100%. The mean absolute differences in correlation coefficients between the synthetic and original data were minimal, averaging 5.9% with a maximum deviation of 44.7%.

Such precision in data generation underscores synthetic data's potential for in silico clinical trials. The study acknowledges scaling limitations to complex, larger datasets. Alongside future explorations in synthetic data benchmarking and patient trajectory modelling, the development of an online platform for virtual patient data generation based on EHR could enhance accessibility to patient data and catalyse innovation towards in silico clinical trials in ECMO research.

Towards an in silico clinical trial on the use of fractional flow reserve based on a data-driven modeling approach

Pjotr Hilhorst[1], Sabine Verstraeten[1], Frans van de Vosse[1], Marcel van 't Veer[1,2], Pim Tonino[2], Wouter Huberts[1]
[1]Eindhoven University of Technology, The Netherlands; [2]Catharina Hospital Eindhoven, The Netherlands

In Silico clinical trials have the potential for reducing the amount of real clinical trials. This study focuses on reproducing the FAME study, in which the clinical benefit of fractional flow reserve (FFR) measurements for decision support was demonstrated for patients suffering from multivessel coronary artery disease. We present our strategy to reproduce the outcomes of the FAME study using an *in Silico* trial only. Our focus here is on the generation of virtual patients to compute their patient-specific FFR.

Virtual patients were generated using a multi-scale model. It comprises a one-dimensional pulse wave propagation model (PWPM) to compute the coronary hemodynamics within the arterial tree and lumped models to mimic patient-specific stenotic lesions and boundary conditions (a one-fiber heart model as driving force and windkessel models to represent outflow conditions). Sensitivity analysis and uncertainty quantification are used for model input prioritization and quantifying uncertainty in model output predictions, respectively. The lumped stenosis model is optimized and made patient-specific through a data-driven approach, using geometric parameters resulting from a statistical shape model, patient demographics, and 3D CFD simulations, allowing it to efficiently describe the pressure drop of geometrically complex stenotic lesions. To validate the optimized stenosis model, the resulting pressure drop is compared to a 1D-3D coupled model, assuming the latter serves as a golden standard for considering radial velocities.

The PWPM model can accurately simulate coronary hemodynamics (*e.g.* diastolic dominant flow) and pathophysiology (*e.g.* pressure drop across a stenotic lesion). Additionally, by providing patient-specific information, the model is representative of lesions in the FAME study and makes a reasonably accurate estimation of the pressure drop. Sensitivity analysis helps to assess the inputs that have the biggest contribution to the variance of the FFR value, easing the generation of patient-specific cohorts. Overall, the proposed framework exhibits significant potential to serve as a virtual cohort generator to recreate the FAME study *in Silico*.

Predicting ventricular tachycardia, taking time into the equations

Carlijn Buck[1], Marloes de Winter[1], Anouk de Lepper[2], Marcel van 't Veer[2], Wouter Huberts[1], Frans van de Vosse[1], Lukas Dekker[2]
[1]Eindhoven University of Technology, the Netherlands; [2]Catharina Hospital Eindhoven, the Netherlands

Post-myocardial infarction (MI) patients have a risk of developing ventricular tachycardia (VT) years later. Primary risk stratification, based on left ventricular ejection fraction and symptoms, proves to be insufficient in identifying high risk patients. We postulate that Digital Twins (DTs) which integrate time-evolving pathophysiology through hybrid models possibly lead to better VT prediction.

A hybrid approach of interest is the fast-scale-slow-scale model of Regazonni *et al*. (Int. j. numer. method. biomed. eng., 2021, 37(7)). Here, physics based models are used to predict diseases in the next seconds (fast time scale). However, over months or years (slow time scale), patient change, and thus the physics based models parameters remodel. This remodeling is unknown but could be learned by data-driven models. While fast-scale physics-based VT prediction models are established, understanding the slow-scale dynamics remains underexplored.

In this retrospective study (1997-2023), laboratory data, vital functions and echocardiogram reports from 160 VT and 2789 control MI patients without VT were collected to explore the time-evolving trends. This resulted in 459 laboratory, 289 vital functions and 362 echocardiogram parameters with 1.33 million, 866950 and 270643 values respectively.

Exploratory data analysis focused on control-VT differences at four time points: one day, three months and one year after MI, and one year before VT or last available parameter. Utilizing clinical data proved challenging due to its inherent sparsity, heterogeneity and occurrences of missing data, resulting in a steep decline in available parameters and patients over time. Despite these challenges, insightful trends showed in expected parameters (left ventricular volume-related parameters) and unexpected parameters (cholesterol-related parameters).

This exploration into time-evolving trends demonstrates potential for identifying patients at risk for VT. Furthermore, it emphasizes the need to take time into account in DTs. Future steps include using linear mixed models and AI to potentially identify patients at risk for VT.

6.E: Human Brain Modelling

Friday, September 6

9:00am - 10:30am

02.011

Multiscale modelling in deep brain stimulation

Ursula van Rienen, Revathi Appali
University of Rostock, Germany

Deep brain stimulation (DBS) is an important treatment for several brain disorders, but its mechanisms remain elusive. Computational modelling is crucial to elucidate the effects of DBS, refine therapies and explore new stimulation methods [1], [2]. Multiscale modelling is essential due to the hierarchical structure of brain tissue. Our open-source toolbox OSS-DBS v2.0 facilitates macroscopic modelling by generating volume conductor models (VCM) [2]. Our approach extends from macroscopic VCM to mesoscopic network modelling, facilitating patient-specific therapy planning [3]. We integrate the different scales using the Multiscale Modeling and Simulation Framework (MMSF) [4]. MMSF facilitates the exchange of information between models and scales, which is crucial for the simulation of DBS effects. The MMSF formalism consists of four steps: modelling, architecture, implementation and execution. The creation of the Scale Separation Map (SSM) of the problem is essential for the modelling step. Briefly, the SSM is a 2D map with temporal and spatial axes separating the scales of the problem. The second step is to define the coupling between the models, the inputs and outputs, and the coupling topology. Both steps are crucial for the development of an efficient computational framework for the multiscale problem, which consists of the implementation of single scale models, scale bridging techniques and their execution.

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Holography-assisted simulation of brain function

Wieslaw Nowinski[1], Agnieszka Pluta[2], Pawel Holas[2], Anastazja Kozlyk[3], Katarzyna Bochenska[3], Witold Janczynski[3]
[1]Sano Center for Computational Personalised Medicine, Poland; [2]University of Warsaw; [3]Ledholo Sp. z o.o

The human brain is the most complex and yet not fully uncovered organ and many large-scale and long-term projects aim to study its structure and function. Our goal is to develop a holography-assisted simulator for the visualization of brain function.

Brain modeling requires an enormous amount of data. As a brain model, we used a three-dimensional (3D) brain atlas (Nowinski et al, *The Human Brain, Head and Neck in 2953 Pieces,* Thieme New York, 2015). This model was constructed from multiple 3 and 7 Tesla magnetic resonance imaging and high-resolution computed tomography scans. It contains about 3,000 3D components and several systems that are parcellated by color, labeled, and placed in a stereotactic coordinate system. The model is composable and any 3D scene can be composed or decomposed like from the Lego blocks. This model provides the underlying structure upon which brain function is simulated.

Brain function simulation applies modeling and video editing methods and tools. Brain at work is visualized dynamically by employing holographic displays ranging from 30 cm to 180 cm that use 2/4/6 fast-moving rotors producing 3D images of full HD resolution floating in the air (www.ledholo.com). Simulations depict the information flow via cortical regions, deep nuclei, white matter tracts, and cranial nerves for various cerebral systems. The simulated functions so far include language production and understanding, movement generation, somatosensory sensation, vision with extraocular muscle control, hearing, and emotions as well as some disorder-related processes.

This simulator is applicable in neurosurgical training, medical education (including classrooms and auditoria using large-size holographic displays), and layman instruction and presentations. Replacing the brain atlas with patient-specific data makes it also potentially useful for neurosurgery planning and intra-operative support in the operating room.

Multiscale model of spreading depolarization in neocortical microcircuits

Adam John Hunter Newton[1], Craig Kelley[2], Siyan Guo[3], Joy Wang[3], Sydney Zink[4], Marcello DiStasio[4], Robert A McDougal[5,6,7], William W Lytton[1,8,9,10]

[1]Department of Physiology and Pharmacology, SUNY Downstate Health Sciences University; [2]Department of Biomedical Engineering Doctor of Philosophy, Columbia University; [3]Health Informatics Program, Yale School of Public Health; [4]Department of Pathology, Yale School of Medicine; [5]Department of Biostatistics, Yale University; [6]Program in Computational Biology and Bioinformatics, Yale University,; [7]Wu Tsai Institute, Yale University; [8]Department of Neurology, SUNY Downstate Health Sciences University; [9]Department of Neurology, Kings County Hospital Center; [10]The Robert F. Furchgott Center for Neural and Behavioral Science

Spreading depolarization (SD) is characterized by a wave of depolarization preceded by a brief period of hyperexcitability that propagates through grey matter at 2-7 mm/min. SD is accompanied by spreading depression, a prolonged neuronal silence caused by depolarization block, and disruption of ion homeostasis. SD is observed in neurological disorders, including migraine aura, epilepsy, traumatic brain injury, and ischemic stroke. Blood vessels contribute to SD as a source of oxygen and nutrient supply to the affected tissue. Understanding these mechanisms is essential for targeted interventions in conditions like ischemic stroke.

We used the NEURON and NetPyNE simulation platforms to investigate ion homeostasis at the tissue scale. We based this in vivo network model on an established cortical microcircuit, equipping neurons with additional homeostatic mechanisms (Na^+/K^+-ATPase, KCC1, NKCC2) and adding energy-dependent clearance of extracellular K^+ by glia. We used NEURON RxD to track the intracellular and extracellular concentration dynamics of Na^+, K^+, Cl^-, and O_2. Histologic images of a 2.0 x 2.3cm cross-section of the human cortical plate in V1 with immunostaining for CD34, we determined the locations of 918 capillaries (mean capillary density: 199.6/cm^2; mean±SD capillary cross-sectional area: 16.7±11.9μm^2). These loci provided the sources of oxygen for this in vivo model. SD was reliability triggered in this model by a bolus of extracellular K^+ applied to layer 4. Neuronal depolarization occurred in all cortical layers, with pathological activity spreading both through connectivity and ECS diffusion. Neuronal proximity to an oxygen source was a good predictor of its ability to maintain physiological firing rates.

Investigation of intracranial dynamics using a personalised computational model

Alireza Sharifzadeh-Kermani, Samantha Holdsworth, Soroush Safaei, Gonzalo Maso Talou
The University of Auckland, New Zealand

Intracranial hypertension is a serious neurological condition where build-up in CSF levels is related to an anomalous increase of pressure. Current proposed methods to measure intracranial pressure (ICP) non-invasively are still not translatable to clinical practice due to a need for more data to reduce the estimation confounders. To this end, having a detailed in-silico computational model of a specific subject can help to increase the understanding of this complex system, especially the sensitivity of ICP estimation with respect to different factors, and modify/develop an existing/new method to estimate ICP accordingly.
In this study, we created a personalised computational model of intracranial dynamics containing a coupled 0D bond graph hemodynamic (blood) and 3D fluid (CSF)-structure (brain) interaction (FSI) model. The CSF and brain are represented as a time-dependent Stokes flow and a linear poroelastic material, respectively, and spinal compliance is taken into account. ICP is defined as the mean pressure in the CSF compartment. The model is constructed based on multiple MR modalities, depicting structure, perfusion, flow, vasculature, and brain motion.
Here, we explore how different levels of anatomical and functional information incorporated in the model --such as having different perfusion regions for driving brain pulsation or anatomical details for the brain surface and CSF space-- affect the ICP estimation. The results can pave the road to developing a reduced order model of the system by disregarding the unnecessary modelling contributions towards an efficient mechanistic approach to estimate ICP non-invasively.

Challenges and perspectives in human brain tissue modeling

Silvia Budday
Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

The brain is arguably our most important and complex, but also most compliant organ. Increasing evidence confirms that mechanics plays a critical role for brain function and dysfunction. Computational models based on nonlinear continuum mechanics can help understand the basic processes in the brain, e.g., during development, injury, and disease, and facilitate early diagnosis and treatment of neurological disorders. They can provide access to data such as the stress and strain distributions within the brain that would otherwise not be accessible with the current medical technology. Still, important challenges need to be overcome, before such models can be translated into daily clinical practice. By closely integrating biomechanical experiments on human brain tissue, microstructural analyses, continuum mechanics modeling, and finite element simulations, we aim to develop computational tools that capture both biological processes at the cellular scale and macroscopic loading and pathologies at the tissue and organ scales. We demonstrate that our models are capable of capturing the evolution of cell density and cortical folding in the developing brain as well as regional variations in tissue properties in the adult brain. We show how important it is to account for regional and temporal variations in properties for simulations of the human brain. We highlight the potential but also the challenges of using computational models to assist the diagnosis and treatment of neurological disorders, e.g., through surgical procedures. The presented studies and results have important implications for choosing appropriate region-dependent material parameters for human brain simulations in the future to ensure reliable predictions that can eventually become relevant for clinicians.

6.F: Pathway to Digital Twins

Friday, September 6

9:00am - 10:30am

02.005

From clinical research to digital twins: How personalised computational modelling can add value in clinical care

Robyn Walker May[1,2], Tom Gentles[3], Frank Bloomfield[2], Finbar Argus[1], Gonzalo Maso Talou[1], Soroush Safaei[1]

[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Liggins Institute, University of Auckland, Auckland, New Zealand; [3]Starship Hospital, Te Toka Tumai Auckland, Auckland, New Zealand

Background

Babies born preterm may suffer from cardiovascular instability and also have an increased lifetime cardiovascular risk, yet mechanisms of cardiovascular remodelling are poorly understood. Our aim was two-fold: to collect ultrasound data on the structure and function of the developing cardiovascular system in healthy late preterm newborns and term controls, and to develop newborn digital twins, i.e., personalisable computational models of the neonatal cardiovascular system.

Methods

Our single-centre, prospective, observational cohort study collected ultrasound data on the cardiovascular system of 15 term (≥ 37+0 weeks' gestation) and 10 late preterm (34+0-36+6 weeks' gestation) babies at two time points. These data inform personalised 0D closed-loop bond graph models that simulate blood pressures and flows in the newborn cardiovascular system.

Results

There were no differences in ultrasound measures of cardiovascular structure (heart size or arterial diameters) or function (Doppler flows) between the term and preterm groups. However, there were differences between the term and preterm digital twin models. Lower body resistance was similar at birth (term median 5.9x109 Js/m6 (IQR 3.8x109, 8.7x109) vs preterm 4.9x109 Js/m6 (3.2x109, 8.3x109), p=0.5), but by three to six weeks of age, the preterm group showed evidence of greater vascular resistance (term median 3.8x109 Js/m6 (2.6x109, 5.0x109) vs preterm 2.6x1010 Js/m6 (1.0x1010, 4.7x1010), p=0.043), suggesting a possible mechanism of cardiovascular remodelling.

Conclusions

We have created the first newborn cardiovascular digital twin, computationally modelling the cardiovascular system in early life. This model extends our understanding of the complex physiology of cardiovascular remodelling related to preterm birth.

A demonstrator of the EDITH virtual human twin platform

Marian Bubak, Marek Kasztelnik, Maciej Malawski, Jan Meizner, Piotr Nowakowski, Piotr Połeć
ACC Cyfronet AGH and Sano Centre for Computational Medicine, Krakow, Poland, Poland

To realize the idea of personalized medicine, we need good mathematical models of human physiology implemented as computer simulation modules and availability of medical data. The way to such innovation leads through elaboration of so called virtual human twin (VHT), which is an integrated, multi-scale, multi-temporal and multi-disciplinary representation of quantitative human physiology and pathology. To put it in practice, we require an appropriate software environment on top of modern compute and storage resources. We have analyzed internal structure and functional requirements of seven typical applications simulating human physiology related to osteoporosis, cardiovascular, cancer, brain, glycemic control. This formed a basis for elaboration of a demonstrator of the execution subsystem of the VHT ecosystem. The demonstrator is a software system agnostic to the supported classes and formats of data items, easy to support a comprehensive data repository where various data items may be queried, retrieved, and fed into the computational models which constitute the simulation workflow, to run on classical HPC resources for scale-out studies which involve processing large amounts of data and "parameter study" types of computations. It enables model versioning: previous versions of the model are stored and may be referred to if needed, as well as reproducibility of computer simulations. The demonstrator enables execution of computational models controlled by a set of scripts with a versioning system enabling collaborative editing and tagging specific versions that may be later selected to suit the researchers' need. It provides a straightforward way to display, download and analyze simulation results. The functionality of the demonstrator was successfully validated with a set of available typical VHT modules on the ACC Cyfronet HPC resources. In future work we plan to enhance the demonstration functionality using AI solutions.

We acknowledge the support of EU grants EDITH No 101083771 (Digital Europe) and Teaming Sano No 857533, as well as computational grant no. PLG/2023/016723.

12 Labours DigitalTWINS platform: Enabling development and clinical translation of virtual human twins

Thiranja P Babarenda Gamage[1], Chinchien Lin[1], Linkun Gao[1], Jiali Xu[1], Ayah Elsayed[1,2], Alan Wu[1], Mathilde Verlyck[1], Gregory Sands[1], Koray Atalag[3], Martyn P Nash[1,4], Peter J Hunter[1], David P Nickerson[1]

[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Auckland University of Technology, New Zealand; [3]GALATA-Digital; [4]Department of Engineering Science and Biomedical Engineering, University of Auckland, New Zealand

Personalised physics-driven digital twins of human anatomy and physiology have the potential to significantly advance healthcare. This requires integrating international developments in computational modelling of cells, tissues, organs, and organ system levels to create a "Virtual Human Twin" (VHT) that can improve our understanding of human physiology and pathophysiology. One such initiative is the Auckland Bioengineering Institute (ABI) 12 Labours (12L) project, which aims to develop VHTs and demonstrate their application in exemplar projects related to pulmonary hypertension, upper limb disorders, breast cancer, and pregnancy.

We present our latest efforts towards delivering an open-source prototype collaborative platform called 12L "DigitalTWINS" (Digital Translational Workflows for INtegrating Systems). This aims to provide common infrastructure and services to support the assembly of computational physiology workflows for creating personalised VHTs, while also supporting collaborative clinical studies to demonstrate their efficacy. These include standardisation of data objects within a harmonised and FAIR data management system for storing measurements, models, tools, workflows, and workflow processes. We also present a novel unified ethics application framework that will initially be adopted across studies conducted at ABI to support contribution of data to the platform while maximising potential secondary use and linking of the data, which is essential for creating multi-organ integrated virtual human twins. This is paired with a novel approach to organise, link, search, and access all available primary measurements and workflows outputs collected across different studies for a specific individual using the FHIR healthcare standard. An API and a web portal containing data catalogues and dashboards are also presented to enable interaction with end-users including researchers and clinicians.

We envision that the adoption and support of this platform has significant potential to foster an ecosystem that enables FAIR and reproducible research outcomes, while also providing a foundation for integrating international research to create VHTs.

AI-CARE: Digital twin for cancer research

Daniele Tartarini[1,2]
[1]Department of Computer Science, University of Sheffield, United Kingdom; [2]Insigneo Institute for in Silico Medicine, University of Sheffield, Sheffield, United Kingdom

Digital Twin in Healthcare is the virtual replica of a human being where computational models are used to understand the physiology and pathology, improve diagnostic accuracy and deliver personalised treatments [1]. The AI revolution has enhanced the predictive capability of mechanistic models with the power of modelling phenomena by learning from data. The accuracy and reliability of these models depends on the quality, availability and representativity of datasets. In our digital twin platform we implemented the federate learning approach to improve the limited representativity of sub populations and to be able to train the digital twin on the patient data at the clinical premise without exporting them. This allows better personalisation of diagnosis and treatments to those cancer types whose occurrence depends on specific characterisics of subpopulations (often under represented). In our digital twin platform we follow the FAIR principles [2], the ASME V&V40 [3] to achieve the highest model credibility to achieve the Software as Medical Device standards. Our platform currently develops digital twins in the cancer domain with the goal to allow early diagnosis, personalised treatment but also to mitigate the diagnostic variability among clinical operators [4]. To support the constant improvements for AI and mechanistic models (due to advancement in knowledge and data availability), our platform supports traceability and dynamic diagnosis so allow the clinician to revise them when more accurate models are available.

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OSS-DBS v2.0: Adaptive meshing for deep brain stimulation modeling

Jan Philipp Payonk[1], Konstantin Butenko[2], Ursula van Rienen[1,3,4], Julius Zimmermann[1,5]
[1]Institute of General Electrical Engineering, University of Rostock, Germany; [2]Department of Neurology Brigham & Women's Hospital, Harvard Medical School, USA; [3]Department Life, Light & Matter, University of Rostock, Germany; [4]Department of Ageing of Individuals and Society, University of Rostock, Germany; [5]Now with: Synthetic Physiology Lab, University of Pavia, Italy

Computational modeling plays a crucial role in the advancement of deep brain stimulation (DBS). However, biophysically accurate modeling within a reasonable time is challenging. Therefore, we present the second release of OSS-DBS [1], an open-source software framework for advanced DBS modeling. One key to its effectiveness is the mesh generation and refinement techniques, which balance accuracy and computational efficiency. This work focuses on the methods used to optimize the meshing in DBS simulations to bring patient-specific modeling closer to clinical practice. OSS-DBS utilizes medical imaging data to generate a comprehensive Volume Conductor Model (VCM). Further, the open-source finite element library NGSolve [2] is used to solve the electro-quasistatic approximation of Maxwell's equations. Solving this problem enables the evaluation of essential quantities, such as electric potential and electric field within the brain. To obtain accurate results within a reasonable computational time, we tested various mesh refinement techniques for different scenarios and compared their results with those obtained from an ultra-fine mesh. Our findings emphasize the crucial impact of mesh refinement strategy on both accuracy and computational time in DBS modeling. Global refinements can achieve reasonable accuracy but increase computational requirements. Prioritizing initial refinement at active contacts yields superior accuracy with fewer unknowns, reducing the computational burden. In addition, we employed h-refinement and hp-refinement to improve model fidelity while maintaining computational efficiency. This study underscores the significance of selecting the appropriate meshing strategy in DBS modeling. Exploring alternative approaches and their combinations may lead to further improvements, providing flexibility tailored to specific scenarios and advancing both clinical applications and research in DBS.

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6.G: In-silico Orthopedics II

Friday, September 6

9:00am - 10:30am

01.005

Experimental validation of in silico models of orthopaedic implants

Luca Cristofolini
Alma Mater Studiorum - University of Bologna, Italy

The credibility of in-silico models must be proven, especially when they are used to drive clinically relevant decisions. One of the most challenging tasks is the validation of the in-silico model against a ground truth. This is a demanding process, that requires painstaking methodological rigor, and cannot be bypassed. Experimental testing allows imposing controlled conditions and performing a number of measurements that are not possible in living subjects. Comparison of a generic models against data from the literature can be a first step to assess the relevance of the model, but should not be called "validation". To provide a true validation, dedicated experiments must be designed, where an adequate of specimens are tested in the lab, and simulated in-silico, so as to validate the modeling pipeline. The model must be "challenged" in a number of different configurations (e.g. changing the type of loading and/or the boundary conditions) that are representative of the intended use of the model and can be replicated experimentally. The experiment must enable measuring different physical magnitudes (e.g. displacements, rotations, relative motions between implant and host tissue, strains, failure load) that must be compared with the in-silico model. One of the most challenging steps is when it comes to providing an accurate registration of the model, of the point of application of the loads, and of the points where magnitudes are measured experimentally. Inaccurate registration unavoidably results in poor match between the experiment and the in-silico model. Finally, metrics must be defined to quantify the agreement between the in-silico model and the experiment. This talk will provide an overview of the steps to achieve a quantitative validation of in-silico models in the field of orthopaedics. Success stories will be presented to exemplify the procedure.

In silico clinical trial for a regulatory submission of a total shoulder arthroplasty system

Christine Mueri[1], Ghislain Maquer[1], Henderson Adam[1], Connolly Lukas[1], Maged Awadalla[2], Jeff Bischoff[2], Philippe Favre[1]
[1]Zimmer Biomet, Switzerland; [2]Zimmer Biomet, USA

Introduction

Enriching trials with simulations in *in silico clinical trials* (ISCT) is an innovative way for addressing the need for clinical data in an effective manner. This study showcases an ISCT application comparing a new humeral stem (device A) to an established stem (device B) on a virtual cohort. Although similar, device A features a widened proximal design, which might reduce the risk of humeral loosening (HL) with a potential impact on stress shielding (SS).

Materials and Methods

More than 300 finite element models from 45 CT scans were generated for each risk (HL &SS). Various surgical conditions were simulated for each device by varying implant tilting, sizing (nominal, under-, oversized) and stem length variant (long/short). Loading conditions consisted of physiological joint reaction and muscle forces scaled to body weight. Interface conditions were modelled to simulate short (HL) or long (SS) term fixation. Bone-implant interface micromotion (HL) and change in cortical strain energy density between the intact and implanted states (SS) were compared between the two devices.

Results

HL - Micromotion was consistently lower with device A, independent of surgical and loading conditions. For both devices, increased micromotion was observed with undersized stems. Due to the metaphyseal fixation of both devices, the stem length did not significantly influence micromotion.

SS – No difference in average SS potential was found between devices A and B, independent of the implant tilting, sizing, or regions around the stem. Resorption was more likely in the calcar region for both devices and found in 1/3 of cases.

Discussion and Conclusions

A concern when altering implant design is a potential for opposite effects on identified patient harms. This ISCT showed that the altered proximal profile of device A may improve primary stability (HL), without significantly impacting the risk for SS. In addition to allowing a direct comparison of two devices on the same cohort (which is not possible *in vivo*), ISCT allows a comprehensive virtual safety assessment before the first surgery. Such virtual data can also be used to enrich clinical trials for regulatory submissions.

InSole: An in-silico workflow towards personalized prescription of corrective insoles during walking

Bryce Adrian Killen[1], Sam Van Rossom[2], Fien Burg[2], Jos Vander Sloten[3], Ilse Jonkers[1]

[1]Human Movement Biomechanics Research Group, Department of Movement Sciences, KU Leuven; [2]Materialise Motion, Materalise NV; [3]Biomechanics Section, Department of Mechanical Engineering, KU Leuven

Corrective insoles are prescribed to correct foot deformities by providing additional support to control unwanted movement during gait e.g. excess pronation or sunken medial arch. Insole design, prescription, and personalization is often informed by subjective qualitative assessment and rarely static quantitative measures. This leads to limited personalization and as a result, potentially suboptimal patient outcomes. Although highly detailed quantitative methods (i.e. motion capture) exist to capture foot motion during dynamic activities, they are not able to predict how a patient will respond to an insole without first manufacturing and measuring the response, creating a highly inefficient time, and cost burdened approach. An alternative to a pure measurement-based approach is to create computational models which can not only measure motion, but also include a virtual insole model capable of *predicting* a patient's kinematic response. Such an approach would allow for the testing of multiple *virtual* candidate insole and design optimization to achieve a desired kinematic response.

In this abstract, we combine measurements of foot-ankle motion from gold standard motion capture performed on healthy participants and patients with flatfoot deformity. Participants (n=27) walked in minimalist footwear with and without an insole. Measured gait kinematics were used to calibrate a spring-based insole model whereby stiffness parameters were optimized to produce, using a predictive forward simulation, the measured insole response from a single trial (i.e. one "with insole" trial). Insole parameters were then combined with the remaining "without insole" conditions to determine the accuracy of our predictive model. Average prediction errors were 4.7±3.1, 4.5±3.1, 2.3±2.3, and 2.3±2.7 degrees for the chopart obliquity, chopart anterior-posterior axis, tarsometatarsal 1st ray, and tarsometatarsal 5th ray (mid-/fore-foot joints) respectively. The developed workflow offers distinct advantages to previous modeling workflows and provides a solid basis for future work on improving predictive accuracy by adapting the currently implemented insole model and incorporating additional data.

In-silico analysis of dropfoot disease and biomechanical evaluation of ankle-foot orthoses

Armagan Can Yildiz, Okan Avci, Animesh Ranjan
Fraunhofer IPA, Germany

Ankle Foot Orthoses (AFOs) play a crucial role in orthopedics and rehabilitation, providing support and stability for individuals with neuromuscular and musculoskeletal diseases. Traditionally, AFO design has relied on empirical methods and the experience of orthopedic technicians. However, the current approach to adapting AFOs often falls short in addressing the specific functional needs of each patient, such as foot support, ankle stabilization, and muscle-driven movement, with traceable and objective decision-making criteria.

To understand the biomechanics of ankle-foot joint motion in both healthy individuals and those with neuromuscular disorders, we have developed a detailed musculoskeletal lower limb finite-element model, encompassing all relevant leg muscles, bones, tendons, ligaments, as well as surrounding fat and skin tissue, using Magnetic Resonance Imaging (MRI) dataset for segmentation. The ankle joint motion is facilitated through articulated surfaces provided by bones, with ligaments contributing to joint stiffness. Therefore, the ankle joint is modeled in detail without employing artificial, unphysiological joint constraints. The physiological mechanical behavior, both passive and active, of the muscle tissue is described by a non-linear, hyperelastic, transversely isotropic constitutive law.

The forward simulation of the musculoskeletal ankle joint system provides significant insights, including the fibre stretches, the forces exerted by muscles, and the deformations of soft tissues during the desired foot movements. Moreover, the characteristics of drop foot disease were replicated in our simulation model by adjusting material parameters of selected muscle tissues and we could examine their effects on the complex ankle joint kinematics. Subsequently, the impact of a polypropylene AFO on joint kinematics and tissue deformations has numerically investigated for a muscular imbalanced ankle joint by variation of design and stiffness of the AFO.

This traceable, physics-based forward simulation method of the ankle joint motion holds the potential to improve the current subjective decision-making process for determining functional AFO designs.

Verification of finite element wear models of a total ankle replacement

Cristina Curreli[1], Melissa Taliani[2], Emma Spilla[1], Francesca Di Puccio[3,4], Marco Viceconti[2]

[1]IRCCS Istituto Ortopedico Rizzoli, Bologna (Italy); [2]Department of Industrial Engineering, Alma Mater Studiorum - University of Bologna (Italy); [3]Department of Civil and Industrial Engineering, University of Pisa (Italy); [4]Center for Rehabilitative Medicine "Sport and Anatomy", University of Pisa (Italy)

Total Ankle Replacement (TAR) still exhibits lower performance compared to more common hip and knee replacements, with polyethylene insert wear considered one of the main causes of early revision surgery. Finite Element (FE) modelling has demonstrated its potential in supporting the safety and effectiveness of new devices, reducing time and costs of traditional experimental tests. However, before computational models can be used for in silico device testing, credibility tests including verification, validation, and uncertainty quantification analyses are necessary.

This study aims to develop an FE model to predict wear in the polyethylene insert of the commercial FAR Total Ankle prosthesis (Adler Ortho) and perform initial verification tests. The wear model was built in Ansys using the PyAnsys programming language and the Archard-based wear routine. The ISO 22622-2019 standard was considered for defining boundary conditions, and quasi-static non-linear contact analysis simulated 10 wear cycles to extract critical quantities on both tibial and talar insert surfaces. Verification tests were conducted following ASME V&V 40 standard guidelines.

The simulation results align with existing studies on ankle prosthesis insert wear, showing maximum contact pressure ranging from 3 to 28 MPa with a peak at about 50% of the gait cycle on the talar side. Extrapolated volumetric wear results fell within a range of 50-60 mm^3 after 5 million cycles. Verification analyses indicated that the total worn volume of the polyethylene insert reached mesh convergence faster compared to other wear quantities extracted, dropping below 1% error for both the talar and tibial sides with a 1 mm mesh. Sensitivity analyses on key solver parameters highlighted the significant impact of contact formulation on wear results.

This study proposes a first FE wear model of the FAR ankle implant and defines the verification activities to identify and quantify possible numerical errors, emphasizing the importance of defining acceptable criteria for adopting the modelling techniques in regulatory processes of new TAR design.

6.H: In-silico Toxicology

Friday, September 6

9:00am - 10:30am

08.019

Prediction of higher airway particle deposition in children compared with adults: A modelling study

Ge Jin, Megan Soo, Kelly Burrowes, Ho-Fung Chan, Merryn Tawhai
Auckland Bioengineering Institute, New Zealand

Background: Children's smaller airways may cause higher deposition fractions (DF) of inhaled particles than adults. We test this hypothesis by simulating drug particle deposition in MRI-derived paediatric airway models and compare with adults.

Methods: MRI data was acquired during free breathing from a cohort of 10 healthy children. Lung surface shape was segmented from MRI, and pseudo-fissure surfaces were placed by scaling adult fissure location. A finite element mesh of the lung lobes was fit for each subject. Airways were modelled using subject-specific central airways (generations 0-3) extracted from imaging. Additional airways were generated using a volume-filling branching algorithm to fill the lobe volumes. 12 healthy adult airway models derived from end-inspiratory CT imaging in a previous study were scaled to FRC volume.

Single breath particle inhalation was simulated assuming a 2 s inhalation, with tidal volumes (VT) and inhalation flow rates (Q) set to 200 ml and 100 ml/s, respectively, for children and 500 ml, 250 ml/s, respectively, for adults. Particle concentration was governed by a 1D advection-diffusion equation and mechanisms for airway and alveolar deposition. A Lagrange-Galerkin method solves the conducting airways, and a finite difference method handles acinar transport where diffusion dominates. Simulations were conducted for particle sizes from 0.01-10 μm, and DF was compared between children and adults.

Results: The paediatric airway models had an average tracheal radius of 4.77±0.794 mm, a Horsfield ratio of 1.12±0.012, and an L/D Ratio of 2.98±0.17. The VT/FRC Ratio averaged 0.14±0.02 for children and 0.17±0.05 for adults. Analysis of intra-pulmonary, bronchial, and alveolar DF (DF_t, DF_b, DF_a) across particle sizes revealed significantly higher values for children (all $p<0.05$ for DF_t and DF_b). DF_a was lower in children for dp = 0.01 μm ($p<1e-05$) and higher for larger particle, though difference was not significant for dp = 0.05, 5, and 10 μm ($p = 0.38$, 0.94, and 0.11),

Conclusion: Children show significantly higher DF in the conducting airways than adults. Similar trend in alveolar region except for very small or large particles.

Towards a virtual embryo: Computational modeling of neural tube closure defects

Job H. Berkhout[1,2], James A. Glazier[3], Aldert Piersma[1,2], Julio M. Belmonte[4], Juliette Legler[2], Richard M. Spencer[5], Thomas B. Knudsen[5], Harm J. Heusinkveld[1]

[1]Utrecht University, The Netherlands; [2]IRAS, Utrecht University, The Netherlands; [3]Biocomplexity Institute, Indiana University, Bloomington, United States; [4]Department of Physics, NC State University, Raleigh, North Carolina, United States; [5]U.S. EPA/ORD, Research Triangle Park, North Carolina, United States

Human embryonic development of the brain and spinal cord begins with the folding of neural tissue into a tube. This process, neural tube closure, is a critical event that occurs early in development, between day 23 and day 30 of human gestation. Its failure underlies neural tube defects (NTD) such as spina bifida. With an estimated global incidence of two cases per 1000 births, NTDs are among the most severe and prevalent human birth defects. To understand how neural tube defects may occur and which genes are most important for successful neural tube closure, we developed a complex multicellular agent-based model (ABM) in the CompuCell3D modeling environment. This model recapitulates the dynamics of normal neural tube closure, such as tissue bending, fusion, proliferation, differentiation and cell delamination. These dynamics are driven by a gene regulatory network of neural tube closure, based on a previously created physiological map (Heusinkveld et al. 2021). This regulatory network allows us to introduce perturbations by varying the expression level of genes in the model. These perturbations lead to a wide variety of dynamic and structural phenotypes seen in both human and mice. Analyzing the phenotypes predicted by our ABM revealed mechanistic insights that are challenging to detect in animal models. Our ABM helps clarify these processes, providing a clearer understanding of how perturbations might disrupt neural tube closure at a cellular and molecular level. Future applications of our model include studying the effect of chemical related perturbations on neural tube closure. Changes in gene expression observed in vitro will be replicated as adjusted parameters in our ABM. Agent-based modeling provides a useful tool to mimic complex biological processes and demonstrates their potential to contribute to the prediction of chemical-induced disruptions of notoriously hard-to-study developmental processes.

Disclaimer: This abstract does not necessarily reflect USEPA policy.

Development of a multiscale data-driven lung model to understand the health effects of vaping

Marzieh Aghababaie[1], Peter Hunter[1], Sue McGlashan[2], Vinod Suresh[1], Merryn Tawhai[1], Kelly Burrowes[1]
[1]Auckland Bioengineering Institute, University of Auckland, New Zealand; [2]Department of Anatomy & Medical Imaging, University of Auckland, New Zealand

The unprecedented uptake of electronic cigarettes (ECs or 'vapes') has been termed an epidemic. Significant gaps remain in our understanding of their short- and long-term health effects. ECs use heat to aerosolise a liquid ('e-liquid') that the user inhales. Aerosolised e-liquid has been found to contain toxicants that are transported throughout the airway network. Studies addressing our understanding of the health effects of vaping have been disjointed, either measuring the chemicals within EC aerosol, its impact on cell function, or the impact on lung function – in human or animal studies. We are developing a multiscale biophysical *in silico* toxicology testing framework centred on the integration of experimental and imaging data to enable a holistic understanding of EC harm. We are aiming to determine where inhaled aerosols go, how they interact with lung cells, and how any changes impact organ-level lung function.

Our modelling framework consists of organ-level lung models that can represent subject-based airway, pulmonary vessel, and lung anatomy from imaging data. Within these models, we have applied existing mathematical models to predict organ function, including ventilation, blood flow, and particle transport and deposition. Our particle transport model uses 1D advection-diffusion to represent particle transport in the conducting and respiratory airways and includes the impact of sedimentation, impaction, and Brownian diffusion to determine deposition. Predicted values of particle deposition throughout the airway network were used to inform a custom-made EC aerosol-cell exposure device.

Alveolar epithelial cells were cultured at the air-liquid interface and exposed to EC aerosol. Cell viability, barrier permeability, and the expression of key genes related to cell membrane transporters and ion channel proteins were measured 24 hours after exposure. *In vitro* measurements will be used to parameterise a Bond Graph model representing epithelial cell function, which will be linked to the organ-level models. The resulting multiscale model will be used to provide an increased understanding of the holistic effect of vaping on the lung from cell to organ level.

Building disease ontology maps: In silico tools for applications in toxicology

Bernard Staumont[1], Luiz Ladeira[1], Alessio Gamba[1], Anouk Verhoeven[2], Julen Sanz Serrano[2], Eliška Kuchovská[3], Job Berkhout[4], Devon A. Barnes[5], Marc Teunis[6], Thomas H. Luechtefeld[7], Thomas Hartung[8], Ramiro Jover[9], Tamara Vanhaecke[2], Ellen Fritsche[3,10], Harm J. Heusinkveld[4], Aldert Piersma[4,11], Rosalinde Masereeuw[5], Mathieu Vinken[2], Liesbet Geris[1,12]

[1]Biomechanics Research Unit, GIGA In Silico Medicine, University of Liège, Liège, Belgium; [2]Department of In Vitro Toxicology and Dermato-cosmetology, Vrije Universiteit Brussel, Brussels, Belgium; [3]IUF - Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany; [4]Centre for Health Protection, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; [5]Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [6]Innovative Testing in Life Sciences & Chemistry, University of Applied Sciences Utrecht, The Netherlands; [7]ToxTrack, Baltimore, MD, USA; [8]Center for Alternatives to Animal Testing (CAAT) - Europe, University of Konstanz, Germany; CAAT, Johns Hopkins University, Baltimore, MD, USA; Johns Hopkins University, Doerenkamp-Zbinden Chair for Evidence-based Toxicology, Baltimore, MD, USA; [9]Departamento de Bioquímica y Biología Molecular, Universidad de Valencia, Valencia, Spain; Experimental Hepatology and Liver Transplant Unit, Health Research Institute La Fe, Valencia, Spain; Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain; [10]Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany; [11]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands; [12]Skeletal Biology and Engineering Research Center, Department of Development and Regeneration, KU Leuven, Leuven, Belgium; Biomechanics Section, Department of Mechanical Engineering, KU Leuven, Leuven, Belgium

Developed within the H2020 ONTOX project, ontology maps are computational tools that allow integration, organization and visualization of biological, toxicological, chemical and kinetic data coming from various sources. Organ-specific ontology maps are designed for 6 adverse outcomes: cholestasis & steatosis (liver), tubular necrosis & crystallopathy (kidney), neural tube closure & cognitive function defects (developing brain).

The foundation of each ontology map is a biological layer of information, i.e. a physiological map (PM) which graphically represents biological mechanisms. For all case studies, we designed organ-specific PMs, standardized with the Systems Biology Graphical Notation (SBGN) using the CellDesigner software and visualized and annotated using the MINERVA platform. These computational tools are able to integrate and annotate data from a variety of sources, allow for an easy-to-interpret visual representation and for machine readability and compatibility with other platforms. On top of the biological layers, ontology maps will integrate standardized AOP networks and tables with structural and physico-chemical properties of chemicals and kinetic data (e.g. absorption, distribution). Beyond structuring diverse concepts and data and showing their properties and relations between them, ontology maps aim to serve as a basis for setting up in vitro test batteries and in silico models (e.g. Boolean modeling) to evaluate specific toxicity endpoints. They also allow querying other formal ontologies (e.g. ChEMBL, DrugBank, CTD) whose data can be overlaid on biological interactions, facilitating mechanistic risk assessment. The maps will also be interoperable with other tools and platforms (e.g. Biobricks, WikiPathways). Ontology maps are tools that should be updated when new data becomes available and are the result of a collaborative effort by domain experts and biocurators, using guidelines for comprehensive annotation and documentation. Their development is expected to support and accelerate the generation of new approach methodologies for next-generation risk assessment, through collaboration between the toxicology and systems biology communities.

Modelling toxicity after prostate cancer radiotherapy using genetically guided pixel-wise analysis

Tiziana Rancati[1], Eliana Gioscio[1], Michela Carlotta Massi[2], Nicola Rares Franco[2], Petra Seibold[3], Barbara Avuzzi[1], Alessandro Cicchetti[1], Barry Rosenstein[4], David Azria[5], Ananya Choudhury[6], Dirk De Ruysscher[7], Maarten Lambrecht[8], Elena Sperk[9], Christopher J. Talbot[10], Ana Vega[11], Liv Veldeman[12], Adam Webb[11], Paolo Zunino[2], Anna Maria Paganoni[2], Francesca Ieva[2], Andrea Manzoni[2], Sarah L. Kerns[13], Alison Dunning[14], Sara Gutierrez-Enriquez[15], Jenny Chang-Claude[3], Catharine M. L. West[6]

[1]Fondazione IRCCS - Istituto Nazionale dei Tumori, Italy; [2]Politecnico di Milano, Italy; [3]German Cancer Research Center (DKFZ), Germany; [4]Icahn School of Medicine at Mount Sinai, US; [5]Université de Montpellier, France; [6]University of Manchester, UK; [7]Maastricht University Medical Centre, The Netherland; [8]University Hospitals Leuven, Belgium; [9]University Medical Centre Mannheim, Germany; [10]University of Leicester, UK; [11]Fundaciòn Pùblica Galega Medicina Xenòmica, Spain; [12]Ghent University Hospital, Belgium; [13]Medical College of Wisconsin, US; [14]University of Cambridge, UK; [15]Vall d'Hebron Institute of Oncology, Spain

Radiotherapy (RT) sterilises cancer cells by delivering radiation to tumors. The RT dose safely delivered to the tumor is limited by the presence of the surrounding healthy organs. Developing predictive models for toxicity is crucial to optimise RT at the patient level. State-of-the-art models are currently based on dose-volume histograms (DVHs) of organs. DVHs reduce the 3D dose distribution in the organ to 1D representation, disregarding any spatial aspect (intra-organ dose variability, variation in intra-organ radio-sensitivity, organisation in organ functioning). Some initial studies proposed analysis of dose-surface maps (DSMs) using pixel-wise analysis (PWA) to improve limitations. DSMs could effectively describe the hollow organs (bladder/rectum) involved in prostate cancer (PC) RT. PWA is an established method, but fragmented and not powerful enough for predictive modelling due to lacking (a) automation of creation of DSMs, (b) analysis of large prospectively collected population, (c) inclusion of patient-specific risk factors.

We developed a tool for the automated creation of DSMs and allowing the inclusion of patient-specific information by coupling PWA with a polygenic risk score (PRS).

We exploited the REQUITE PC dataset (prospective study, follow-up up to 8 years, 674 patients available) to develop a population-based model and use DSMs to identify bladder subregions associated with late urinary symptoms (urinary frequency and haematuria) after PC RT.

We incorporated the PRSi in DSMs via proportional adjustment of the single voxel doses. On the resulting PRS-modulated DSMs, we performed Cox PWA with Benjamini-Hochberg correction and identified the bladder subregions to be spared within personalised RT optimisation.

Specifically, we identified a caudal-posterior region covering 30% of the bladder wall and a cranio-caudal extension of 54% for urinary frequency and a region covering the whole bladder wall, except for two cranio-caudal areas, for haematuria.

Modulation by the PRS increases the size of significant areas, further supporting the value of personalized PWA.

Virtual Cornea: A computational approach for predicting corneal injury and recovery from chemical exposures

Joel Vanin[1], Michael Getz[1], James A. Glazier[1], Thomas B. Knudsen[2], Catherine Mahony[3]

[1]Department of Intelligent Systems Engineering and Biocomplexity Institute, Indiana University, Bloomington, IN;; [2]Center for Computational Toxicology and Exposure, Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, NC;; [3]Procter & Gamble, Technical Centre, Reading, United Kingdom

Introduction: Virtual Cornea is an innovative agent-based model designed to simulate corneal homeostasis, injury, and recovery processes. This Virtual Tissue (VT) modeling approach offers a novel methodology for predicting corneal injury risk, addressing the limitations of traditional Draize rabbit eye tests and improving accuracy in human response predictions.

Methods: Developed in CompuCell3D and Tissue Forge, Virtual Cornea is a two-dimensional model that mimics the cornea's complex structure, including its various cell types and layers. It integrates cellular behaviors such as proliferation, differentiation, migration, and signaling in response to injuries, aiming to replicate the dynamic healing process.

Results: Virtual Cornea has successfully simulated the organization of the corneal epithelium and stroma under normal conditions and post-injury scenarios. The model emphasizes differentiating mild from moderate injuries by examining factors like myofibroblast persistence and basement membrane recovery. It offers insights into the mechanisms of corneal damage and healing, providing a basis for further computational toxicology studies.

Conclusion: Virtual Cornea represents a significant advancement in predicting corneal injury and recovery. By incorporating comprehensive biological data, it aims to refine injury severity classifications, estimate recovery timelines, and evaluate potential complications. This tool is poised to enhance chemical risk assessments and regulatory evaluations, offering a more ethical and accurate alternative to animal testing.

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