BIOPHYSICS-BASED MODELING AND DATA ASSIMILATION IN MEDICAL IMAGING

Workshop Booklet

Edited by
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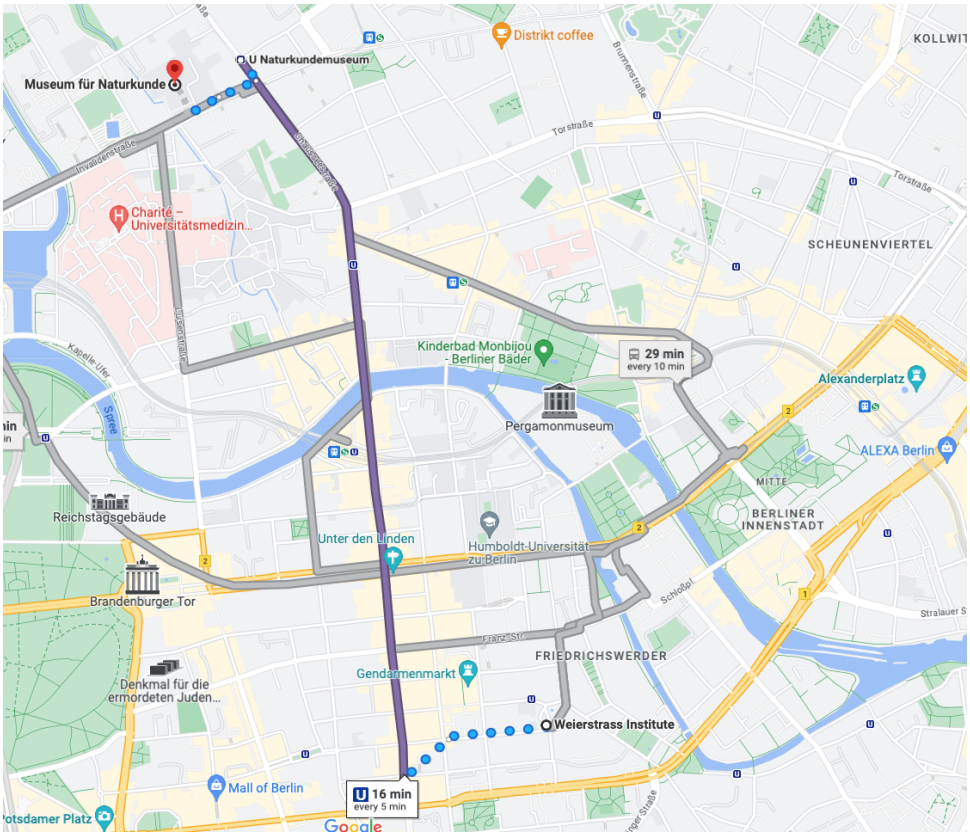
General information

Visit to Natural History Museum

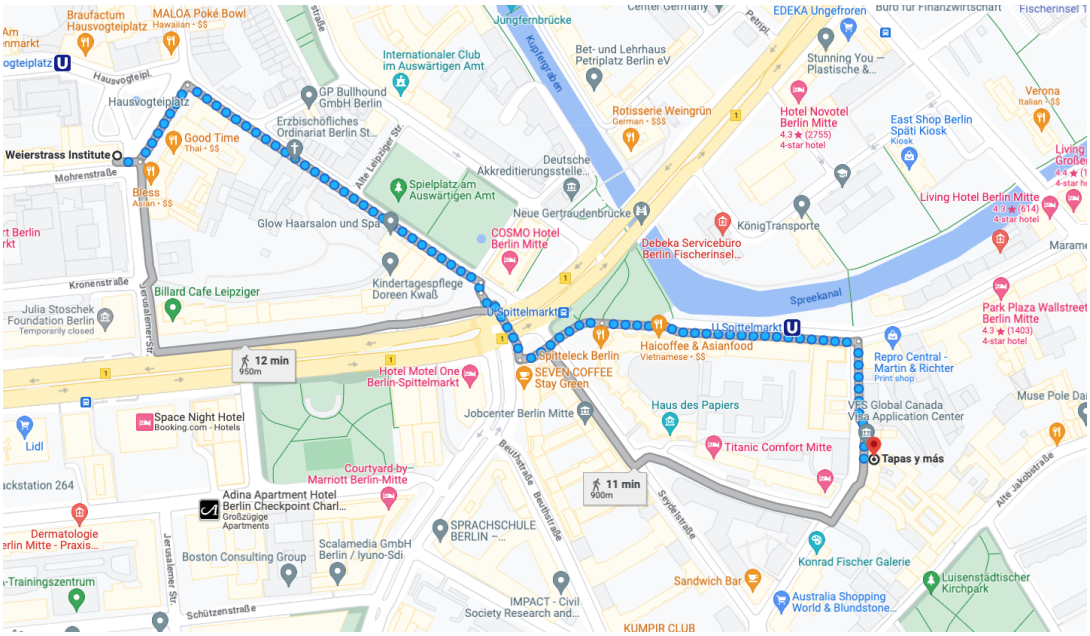


On Wednesday, August 30, workshop participants are invited to a guided tour of the archives of the Museum für Naturkunde (Natural History Museum). The archives are not part of the standard collection and can only be visited on request.

The tour will start at 18 and last about one hour. Participation is free of charge, but we require participant to register (via email or at the WIAS desk on Wednesday).

We will leave after the last session on Wednesday around 17:30 to the Museum. Please note that you need a valid BVG ticket to travel to the Museum with the subway.

Workshop Dinner



The dinner will take place at the restaurant Tapas y más, Neue Grünstraße 17-18, 10179 Berlin, starting from 19. The restaurant is about 10 minutes by foot from WIAS, a group will walk starting from the institute around 18:30. The dinner and one drink per person are covered within the conference fees. Additional drinks can be purchased at own expenses.

Places to have lunch

- Lunch Time - pizza, pasta, and salads
- Chupenga - burritos, tacos
- Little Green Rabbit - fresh salads, hearty soups and baked potatoes
- MALOA Poké Bowl - Hawaiian bowls
- Nanoosh - falafel wraps, Mediterranean salads, and hummus
- Frittenwerk - french fries meet diverse street food creations
- Q Burger - creative burgers (10 minutes to walk)
- Fontana di Trevi - antipasti, pasta, pizza, main dishes, business lunch
- Thu My Marie Concept - Asian fusion cuisine
- Spätzle Club - schnitzel, goulash, Swabian “spätzle” and “maultaschen”
- Spitteleck Berlin - savory German regional cuisine
- Bakery Steinecke - snacks, cakes, and coffee
- Huong Sen - Vietnamese cuisine (10 minutes to walk)

On Wednesdays and Fridays (12-2pm) there is also the possibility to have lunch at different food trucks on Spittelmarkt.

Program

Wednesday, 30.08

13:30 - 15:10 Opening Session	
13:30 - 13:50	Welcome and Opening Remarks
13:50 - 14:30	Luca Heltai
14:30 - 15:10	Jing Guo
15:10 - 15:30 Coffee Break	
15:30 - 17:10 Multiscale modeling in biomechanics	
15:30 - 16:10	Silvia Budday
16:10 - 16:30	Felipe Galarce
16:30 - 16:50	Yasmine Safraou
16:50 - 17:10	Camilla Belponer
17:10 - 17:30 Free time	
17:30	Transfer to Museum
18:00 - 19:00	Visit to Museum

Thursday, 31.08 (morning)

9:00 - 10:30 Data assimilation and ML/1	
9:00 - 9:40	Damiano Lombardi
9:40 - 10:00	Vikram Sunkara
10:00 - 10:20	Jia-Jie Zhu
10:20 - 10:40	Franziska Gaidzik
10:40 - 11:00 Coffee Break	
11:00 - 12:20 Data assimilation and ML/2	
11:00 -11:40	Stefania Fresca
11:40 - 12:00	Stefan Klemmer-Chandia
12:00 - 12:20	Joaquin Mura
12:20 - 14:00 Lunch Break	

Thursday, 31.08 (afternoon)

14:00 - 15:20 Biomechanics & MRE	
14:00 - 14:40	Tim Ricken
14:40 - 15:20	Elijah Van Houten
15:20 - 15:50 Coffee Break	
15:50 - 16:50 Biomechanics & MRE	
15:50 - 16:10	Christos P. Papanikas
16:10 - 16:30	Tom Meyer
16:30 - 16:50	Jakob Schattenfroh
16:50 - 17:30 Research Data Management	
16:50 - 17:10	Karsten Tabelow
17:10 - 17:30	Discussion (research data)
17:30 - 19:00 Free time	
19:00	Workshop dinner

Friday, 01.09

9:20 - 10:40 Mathematical modeling	
9:20 - 10:00	Paolo Zunino
10:00 - 10:40	Claudia Schillings
10:40 - 11:00 Coffee Break	
11:00 - 13:00 Applications in cardiovascular imaging	
11:00 - 11:40	Cristobal Bertoglio
11:40 - 12:00	Alena Jarolímová
12:00 - 12:20	Jana Brunátová
12:30 - 13:00	Closing remarks

Abstracts

Multiscale immersed modelling of vascular tissues

Belponer, Camilla
Universität Augsburg, Germany

We present a multiscale computational approach for the efficient simulation of vascularized tissues. The work is motivated by the solution of inverse problems in the context of tissue imaging, where available medical data (such as those obtained via Magnetic Resonance Elastography) have a limited resolution, typically at the scale of an effective - macro scale - tissue, and cannot resolve the microscale of quantities of interests related, for instance, to the tissue vasculature. Our model is based on a geometrical multiscale 3D (elastic) -1D (fluid) formulation combined with an immersed method.

At the tissue-fluid interface we impose a trace-averaged boundary condition whose goal is to impose only a local Dirichlet boundary condition – driven by vessel deformation – allowing the enforcement of a pure normal displacement at the fictional vessel boundary. In order to decouple the discretization of the elastic tissue from the vessel boundary, the boundary condition on is imposed via a Lagrange multiplier, modelling the fluid vessels as immersed singular sources for the elasticity equation (see, e.g., [1,2]).

Next, to efficiently handle the multiscale nature of the problem, the problem is formulated as a mixed-dimensional PDE using the recently proposed framework of reduced Lagrange multipliers on a space of co-dimension 2. In this talk, we present the numerical analysis of the obtained formulation and we discuss accuracy properties and convergences of the method, validating it in several numerical examples. Finally, we present perspectives for the coupling with a one-dimensional flow model defined on the vascular network and for the numerical upscaling of the tissue model.

References

1 L. Heltai, A. Caiazzo. Multiscale modeling of vascularized tissues via non-matching immersed methods. *International Journal for Numerical Methods in Biomedical Engineering*, 35.12: e3264, 2019.

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Dealing with wraps in phase-contrast images: from postprocessing to data assimilation

Bertoglio, Cristóbal
University of Groningen, Netherlands

In this talk, we will present the challenges of acquiring and assimilating phase-contrast MRI data into fluid flow models. First, we will discuss the importance of flow velocity data and its potential applications in cardiovascular modeling. Next, we will provide background information on the acquisition of phase-contrast data and explain the occurrence of the aliasing artefact. We will then introduce methods for correcting the aliasing and demonstrate how to directly assimilate aliased velocity images into fluid flow models.

Computational modeling of blood flow from medical images

Brunátová, Jana
University of Groningen, The Netherlands

Medical imaging techniques play a crucial role in acquiring non-invasive information about physiological processes within the human body. One such technique is 4D phase-contrast magnetic resonance imaging (4D PC-MRI), which enables the measurement of blood flow velocity fields. However, the accuracy of velocity field estimation is often limited due to the presence of noise in the acquired images. In this presentation, we introduce an improved technique tailored for situations involving significant variability of flow velocities in 4D PC-MRI images. Our approach is based on the Optimal Multiple Motion Encoding (OMME) method, which requires a minimum of two measurements using different velocity encoding parameters (vencs). By performing a single measurement using a large venc, phase wraps in the results can be eliminated, but the noise level remains high as it is proportional to the venc. Conversely, selecting a lower venc reduces the noise level but increases the number of wrapped voxels. By carefully selecting appropriate vencs, the OMME method effectively combines both measurements, resulting in phase wrap-free images with low noise levels. However, using a ratio of low venc over high venc that is too small introduces another type of noise in the resulting image. To address this, we propose an improvement by incorporating a wavelet transform in the time domain, which exploits the temporal characteristics of the artifacts present in the noisy image. Using this method, we were able to obtain better reconstruction of the velocity field both on synthetic data and on in-vivo data.

Biomechanical modeling of the human brain

Budday, Silvia
Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

The brain is not only one of the most important but also the arguably most complex and compliant organ in the human body. While long underestimated, increasing evidence confirms that mechanics plays a critical role in modulating 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. By closely integrating biomechanical experiments on human brain tissue, microstructural analyses, continuum mechanics modeling, and finite element simulations, we develop computational models that capture both biological processes at the cellular scale and macroscopic loading and pathologies. We introduce the cell density as an additional field controlling the local tissue stiffness and brain growth during development. 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. In the future, those models can provide deeper insights into the behavior of the human brain under physiological and pathological conditions, and simulate progression of injury and disease.

Deep learning-based reduced order models for parametrized PDEs: application to cardiac electrophysiology

Fresca, Stefania
Politecnico di Milano, Italy

Conventional reduced order models (ROMs) anchored to the assumption of modal linear superimposition, such as proper orthogonal decomposition (POD), may reveal inefficient when dealing with nonlinear time-dependent parametrized PDEs, especially for problems featuring coherent structures propagating over time, such as cardiac electrophysiology (EP). To enhance ROM efficiency, we propose a nonlinear approach to set ROMs by exploiting deep learning (DL) algorithms as convolutional neural networks. In the resulting DL-ROM, both the nonlinear trial manifold and the nonlinear reduced dynamics are learned in a non-intrusive way by relying on DL algorithms trained on a set of full order model (FOM) snapshots, obtained for different parameter values. Performing then a former dimensionality reduction on FOM snapshots through POD and using a suitable multi-fidelity pretraining enable, when dealing with large-scale FOMs, to speed-up training times, and decrease the network complexity, substantially. Accuracy and efficiency of the DL-ROM technique are assessed on different parametrized PDE problems in cardiac EP, representing both physiological and pathological scenarios, computational mechanics and fluid dynamics, where new queries to the DL-ROM can be computed in real-time. In particular, DL-ROMs are shown to be able to solve, after the training stage, cardiac EP problems on realistic geometries, for any new scenario in real-time, even in extremely challenging contexts such as re-entry and re-entry break-up problems, modeling the triggering phenomena related with cardiac arrhythmias.

Experiment-based super-resolution in intracranial aneurysms using direct data assimilation and gradient inhomogeneity correction

Gaidzik, Franziska
Otto-von-Guericke-Universität Magdeburg, Germany

Hemodynamics play a central role in various cardiovascular diseases, such as intracranial aneurysms (IAs). The blood flow in arteries can currently be estimated using different methods. Phase-Contrast Magnetic Resonance Imaging (PC-MRI) measurements can provide 4D flow information (time-resolved 3D spatial flow velocities), albeit with limited temporal and spatial resolution. Computational Fluid Dynamics (CFD) simulations can capture the blood flow in IAs but are strongly influenced by the boundary and initial conditions. Data assimilation (DA) combines sparse experimental data and numerical methods in such a way that it is used to steer the simulations in an optimal manner. This study introduces a direct data assimilation approach that enhances measured intracranial velocity values in such a way that low-resolution 3T-MRI values appear in the high-resolution of simulations, without the need for improved experimental methods. Specifically, the raw grey value data from the MRI scanner itself are directly mapped with the simulated velocity values. Direct assimilation makes the use of additional processing steps (or non-intuitive post-processing software), as currently needed, on the raw PC-MRI data redundant and will later improve the practical applicability of DA in routine clinical examinations for the assessment of intra-aneurysmal flow. The potential of such a data assimilation approach is to provide detailed information on vascular flow based on measurement data and physical principles, as well as to reduce the uncertainty in related estimates while giving a prediction of the actual flow field. Furthermore, DA is promising because it directly estimates non-measurable quantities (e.g. pressure or wall shear stress (WSS)) through the observation operator. By including patient-specific measurement data, data assimilation provides a reliable alternative of intracranial flow assessment in contrast to purely numerical methods, which often face limited acceptance among neuroradiologists.

Data assimilation of medical noisy images

Galarce, Felipe
Pontificia Universidad Católica de Valparaíso, Chile

Corrupted and noisy data are common across several fields. This is particularly true for ultrasound data, where artifacts and a complex noise structure make the implementation of state estimation algorithms challenging. We propose a variational approach for assimilating medical data while considering the inherent noise in the data. This approach allows for the inclusion of a noise model either analytically or by sampling simulations of the observation process. The method incorporates a key physically informed component, and we demonstrate its potential through numerical experiments where the underlying phenomena exhibit a slow decay in the Kolmogorov n-width.

Updates and Outlooks in Elastic and Anisotropic Tissue Imaging

Guo, Jing
Charité - Universitätsmedizin Berlin, Germany

The biomechanical properties of soft tissue quantified by magnetic resonance elastography (MRE), a non-invasive imaging technique based on magnetic resonance imaging (MRI), have been shown over the past 20 years to reflect the composition and structure of the tissue. Tomoelastography is an advanced MRE technique that includes multiple actuators, multifrequency mechanical vibrations, and noise-robust data processing. Tomoelastography provides elastograms that depict anatomical features and small lesions with high resolution and precision. Additionally, tomoelastography delivers independent parameters such as stiffness, viscosity, fluidity, anisotropy, solid stress which reveal the deep connection between tissue biology and biomechanics. The current focus of tomoelastography is to tackle these issues with novel pulse sequences, advanced inversion algorithm, and realistic rheological models that best describes the biomechanical properties over an extended range of times and frequencies, thereby offering quantitative imaging biomarkers that are sensitive and reflective of different aspects of the collective mechanical tissue behavior in vivo.

An overview on non-matching approximation methods for coupled problems across heterogeneous dimensions

Heltai, Luca
Scuola Internazionale Superiore di Studi Avanzati, Italy

Many physical problems involving heterogeneous spatial scales, such as the flow-through fractured porous media, the study of fiber-reinforced materials, or the modeling of blood circulation in living tissues – just to mention a few examples – can be described as coupled partial differential equations defined in domains of heterogeneous dimensions that are embedded into each other. The definition and the approximation of coupling operators that are suitable for such problems remain challenging, both theoretically and computationally. In this presentation, I will introduce a comprehensive mathematical framework for analyzing and approximating partial differential equations coupled with non-matching constraints across different scales, with a focus on using Lagrange multipliers for the enforcement. I will discuss the well-posedness, stability, and robustness of the problem with respect to the small scale, as well as its numerical approximation based on non-matching and immersed finite element methods, which provide a natural way to perform geometric dimensionality reduction.

Assimilation of 4D PC-MRI data into a blood flow model

Jarolímová, Alena
Charles University, Czech Republic

Patient-specific blood flow simulations have great potential to provide useful information in clinical practice. In order to make the simulation accurate, the model has to be provided with sufficiently precise estimates of material parameters, boundary conditions, and segmentation of the computational geometry. However, some of the necessary parameters are hard to measure directly. Therefore, we use a variational data assimilation technique on 4D phase-contrast magnetic resonance images instead. We created a model of blood flow in descending aorta containing patient-specific parameters which are a priori unknown, one of them being the amount of Navier slip along the aortic wall. The implementation was done in the FEniCS framework using the dolfin-adjoint library to deal with the PDE-constrained optimization which arises from the formulation of the problem. We tested the implementation on artificially generated data in 3D and then proceeded to perform experiments with real patient data from several volunteers. Our results suggest that the introduction of the Navier slip boundary condition can improve the fit to the 4D PC-MRI data compared to the standard no-slip boundary condition.

Kalman filtered based frequency decomposition for time resolved time harmonic elastography

Klemmer Chandía, Stefan
Charité - Universitätsmedizin Berlin, Germany

Background Elastography is a non-invasive imaging method for the quantification of stiffness in soft tissue. Usually, elastography only provides a time-averaged estimate of stiffness over the acquisition period. However, in moving organs with dynamic stiffness changes such as the heart or aorta (1) time-averaged measurements may not be sufficient for tissue characterization. Time-harmonic elastography (THE) (2) provides quantitative shear wave speed maps as surrogate for stiffness over the full field of view. THE was recently developed towards a time-resolved method which utilizes standard ultrasound imaging in synchrony to externally excited multi-frequency harmonic vibrations. To obtain the shear wave speed maps, tissue displacement was estimated from the acquired ultrasound frames (3). A crucial step in THE processing is the frequency decomposition of the displacement induced by multi-frequency harmonic vibration, which is usually done in Fourier space. However, especially in cardiac applications, anatomical displacement and noise make it challenging to recover harmonic vibration components with sufficient temporal resolution. Therefore, we propose a recursive Kalman filter model (4,5) for time-resolved frequency decomposition in cardiac THE. Our hypothesis is that our Kalman filter model provides a better signal-to-noise ratio (SNR) and better temporal resolution than classical Fourier decomposition in cardiac applications of THE.

Methods A Kalman filter is an algorithm that recursively finds the optimal tradeoff between a prior input model and the actual observation. In particular, it compares the output of the state-space model of a system with the system's noisy output signal. In this way, the Kalman filter isolates each frequency component and suppresses noise. In the case of THE, the state-space model describes the phase and amplitude of each excitation frequency component as a complex, analytical signal. Additionally, phase offsets between the acquired ultrasound scan lines are integrated into the model. We evaluated the algorithm on cardiac THE datasets of healthy volunteers, acquired with multi-frequency harmonic vibration at 60, 70 and 80 Hz. The differences to the Fourier-based decomposition was evaluated based on the SNR, which we defined as the ratio between the signal in the Fourier bin of each excitation frequency and the signal in 5 Hz distance to the signal bins.

Results and Discussion Using the Kalman filter-based frequency decomposition the SNR improved by 123% [47%, 183%] for 60 Hz, 127% [27%, 193%] for 70 Hz and 51% [34%, 87%] for 80 Hz compared to the Fourier-based method. This also resulted in wave fields with visually improved delineation of anatomical features, in particular, better contrast between myocardium and blood pool. Our findings suggest that the use of a Kalman filter for multi-frequency decomposition of time resolve THE displacement data, could provide wavefields with better SNR. This is important in the context of data robustness and stability, but also for reliably estimating the viscoelastic dispersion as a quantitative biomarker for tissue viscosity. Furthermore, the recursive architecture of the Kalman filter allows it to react rapidly to changes in stiffness, without over-smoothing the time resolved signal. As a results, elastograms with higher temporal resolution than classical Fourier-based approaches can be obtained.

References

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Enabling data assimilation in haemodynamics

Lombardi, Damiano

Inria, CNRS and Sorbonne Université (Laboratoire Jacques-Louis Lions), National Institute for Research in Digital Science and Technology, France

Numerous biomedical applications are related to the solution of data assimilation tasks. These are usually demanding from a computational point of view. To alleviate the computational burden, several numerical methods are currently investigated. The application we are focusing on is the ability to estimate haemodynamics quantities (such as velocity, vorticity, pressure drop, wall shear stress) by exploiting non-invasive measurements. In this talk few contributions will be presented.

First, state estimation problems will be discussed. An optimal recovery method will be detailed, which makes it possible to efficiently solve inverse problems. Two methodological issues will be briefly discussed. The first one is related to the ability of taking into account the geometric variability and uncertainty, the second one is related to the extension of optimal recovery methods to dynamical applications.

Second, we will focus on parameter estimation, which often involves non-linear non-convex optimisation problems. A method to perform a sequential bayesian parameter estimation will be presented. This takes advantage of adaptive low-rank tensor methods to efficiently solve parametric systems of Partial Differential Equations.

Several numerical applications will be presented.

Functional Time Harmonic Elastography of the Liver: Stiffness Pulsatility as a Novel Marker of Tissue Compliance

Meyer, Tom
Charité - Universitätsmedizin Berlin, Germany

Background Elastography quantifies tissue stiffness and is used in the liver for detecting fibrosis. Doppler ultrasound measures blood velocity and can reveal functional information such as pulsatility of hepatic vessels. The relationship between blood perfusion and hepatic stiffness varies across liver diseases including fibrosis and portal hypertension. Therefore, blood-flow driven pulsatility of liver stiffness could provide important diagnostic information about tissue pressure and hepatic compliance.(1) We here investigate whether hepatic stiffness varies in correlation with portal vein pulsation using novel time-harmonic elastography (THE) (2) with real-time feedback of tissue pulsation.

Methods In a group of healthy volunteers (n = 13, 5 women, age range 26 - 51 years) shear wave speed (SWS) as surrogate marker of liver stiffness was quantified based on multifrequency vibrations (30, 40, 50 Hz) induced by a vibration bed (GAMPT, Merseburg, Germany). Data were acquired in a single-angle plane-wave imaging mode using a Verasonics Vantage 64 LE system (Washington, USA) with a 2.75-MHz convex transducer. The image slice was positioned within the right liver lobe, covering the portal vein for Doppler imaging. A burst of 10 ultrafast Doppler frames at 2.75 kHz framerate and one frame for elastography was acquired over 7.5 s in an interleaved fashion resulting in an effective framerate of 200 Hz for elastography and Doppler imaging. Time-resolved SWS maps were generated using k-MDEV inversion (3). To account for potential spatial heterogeneity in the temporal variation of hepatic stiffness, the spatially dominating temporal SWS pattern was automatically selected by hierarchical clustering of SWS time curves. The time curves in each voxel were grouped into clusters using correlation as a measure of similarity. The average SWS time curve within the largest Cluster was obtained as the dominating SWS pattern.

Results/Discussion The spatially dominating SWS pattern varied in synchrony with portal venous blood velocity v. SWS-pulsatility of 5?nd v-pulsatility of 28?as observed in all subjects (mean SWS = 1.39 ± 0.12 m/s; ?SWS = 0.064 ± 0.017 m/s, mean v = 15 ± 4 cm/s; ?v: 3.9 ± 1.7 cm/s). The SWS time curve was negatively correlated with blood velocity ($R = -0.45$ $p < 0.01$, Fig. 1) indicating softening of the liver during passage of the venous blood wave. Following this technical feasibility study, we plan to recruit patients with liver fibrosis in order to assess stiffness pulsatility in situations where tissue compliance is impaired.

References

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Fast in-plane flow acquisitions using radial angle velocity encoding

Mura, Joaquín
Universidad Tecnica Federico Santa Maria, Chile

One way to measure biological flows non-invasively is to use Magnetic Resonance Imaging (MRI). This technique compares a reference image with another one that has been encoded to show the movement in a specific direction. We usually need three MRI scans to get the complete picture of two-dimensional flows. However, in this presentation, we will show a new method, Radial-Angle Velocity Encoding (RAVE), that can do it with only two scans. This method uses a polar encoding and the Fourier-slice theorem to match the MRI data with the image model. We will present two ways to solve this problem: one that is nonlinear and non-convex and another that is composed of two convex subproblems. Our numerical results demonstrate that our method is accurate and efficient.

Brain cancer development simulation using an implicit, mesh-adaptive finite element methodology

Papanikas, Christos Panagiotis
University of Cyprus, Cyprus

Glioblastoma is the most aggressive and infiltrative form of glioma - the most common primary tumour type in brain cancer patients who have poor survival rates. To understand glioblastoma development, we present here a continuum-based, finite element methodology to simulate the 3D growth of glioblastomas in the brain. The proposed work builds upon the established PIHNA model that accounts for cancer cell proliferation, invasion, hypoxia, necrosis, and tumour-induced angiogenesis. Model sensitivity analysis is performed to test our model with respect to the dynamics of angiogenesis, the aggressiveness and invasiveness of neoplastic cells, the phenotypic changes of cancer cells in the glioblastoma's evolution.

Individualized multiscale and multiphase simulation of functional perfusion processes in the liver

Ricken, Tim
Universität Stuttgart, Germany

Introduction As the key organ for metabolic processes in the human body, 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 [1].

Materials and Methods To better 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, cf. [2,3], using a multicomponent mixture theory based on the Theory of Porous Media (TPM, see [4]). 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 peripportal 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. The phases consist of a carrier phase, called solvent, and solutes, representing microscopic components, e.g. nutrients, dissolved in the solvent. 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.

Results In order to represent realistic condtextbftextbfitions 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.

Discussion and Conclusions A workflow is designed that directly prepares the model for clinical application by (semi-) automatically processing the data, considering uncertainties, and reducing computation time.

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The influence of static portal pressure on compression modulus, shear modulus and water diffusion in ex-vivo liver specimens

Safraou, Yasmine
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Introduction We investigated the effect of portal pressure on liver shear stiffness, water diffusion, bulk modulus and tissue-vascular structures in rat liver specimens. Therefore, volumetric 3D MRI, MR elastography (MRE), and diffusion-weighted imaging (DWI) were performed while applying excess portal pressures of 0, 0.99, 1.23, 1.47, and 1.72 kPa [1,2]. Three scenarios were investigated based on different organ confinements, vessel compliances, and inflow solution viscosities[1-3]. We hypothesize that liver stiffness increases with increasing portal pressure[4].

Methods Liver preparation: Fifteen rat lives were cannulated from the portal vein (PV) and perfused with heparinized phosphate buffer saline (PBS) solution to prevent blood coagulation. A subgroup of 5 livers was subsequently perfused with 4?araformaldehyde solution. After perfusion, hepatic venous outflow vessels were sealed. Inflow scenarios: Three scenarios were designed with $n = 5$ livers each: Unconfined: native livers were embedded in soft matrix gel (0.5 agar-agar) and infused with a fluid of low viscosity (PBS) Confined-fixed: formaldehyde fixed livers (crosslinked) were embedded in rigid matrix (1:1 WiroGel®/water) gel and infused with a fluid of low viscosity (PBS) Confined-viscous: native livers were embedded in rigid matrix gel 1:1 (WiroGel®/water) and infused with a fluid of higher molecular weight 250 kDa and higher viscosity (Arabic gum) [1,3]. Image acquisition: 3T MRI (Lumina, Siemens, Germany) with an 18-channels knee coil was used. Acquisition parameters were: $T2w$ with 0.5×0.5× $1\,mm^3$ resolution, coronal slices with full liver coverage; MRE and DWI with 1.5mm isotropic resolution, four mechanical frequencies (130, 140, 150, 160 Hz) for MRE and four b-values (0, 50, 400, 800 s/mm²) for DWI. Image post-processing: Liver and vessels were segmented based on T2 images. Vessel-tissue volume fraction (VTVF) was defined as the ratio between the vessel and tissue volumes. MRE data were post-processed with the k-MDEV method which provided shear wave speed (SWS) maps [4]. MRE magnitude images, SWS, and apparent diffusion coefficient (ADC) maps were all registered to T2w images. Bulk modulus estimation: K was determined by linear regression of total volumetric strain (difference in tissue volume $\hat{V}$ over baseline volume V, denoted as $\hat{V}/V$) over excess portal pressure P. Bulk modulus K was obtained from the regression function $P = K\hat{V}/V$ in each liver.

Results The stiffness of the agar matrix was 2.25±0.25 m/s, while the stiffness of the WiroGel/water matrix for both confined scenarios was 8.46±0.27 m/s. The induced increase in the portal pressure resulted in: Unconfined: increase in VTVF (223%, p<0.05) and ADC (77%, p<0.01), decrease in SWS (12%, p<0.05) Confined-fixed: increase in VTVF (49%, p < 0.001) and ADC (11%, p<0.01), decrease in SWS (12%, p<0.01). Confined-viscous: increase in VTVF (162%, p<0.01) and ADC (26%, p<0.001), increase in SWS (12%, p<0.001) Estimated mean bulk modulus K values were: 4.2±1.2 kPa (unconfined), 50.85±38 kPa (confined-fixed); 41.30±20 kPa (confined-viscous).

Discussion Increasing portal pressure led to a significant elevation of VTVF and ADC in all scenarios due to the increased fluid content in the liver. The unconfined scenario with the softest embedding matrix had the highest changes in ADC and VTVF, accompanied by liver softening. Confined-viscous livers exhibited the greatest increase in VTVF, potentially due to the hydrophilic Arabic gum used as an inflow solution, which limited water accumulation in vessels. Liver softening was observed in both unconfined and confined-fixed livers, while confined-viscous livers stiffened under increased pressure. Livers in the confined-fixed scenario exhibited the lowest compressibility and yielded the largest bulk modulus K: This could be attributed to the duality of the rigidly crosslinked liver tissue being unable to expand and the strong confinement of the liver. Meanwhile, livers in the unconfined scenario experiencing minimal confinement were the most compressible and yielded the lowest bulk modulus. Livers in the confined-viscous scenario appeared to be less compressible compared to unconfined livers, possibly due to the strong confinement degree they underwent. However, they exhibited higher compressibility than formaldehyde-fixed livers, which could be explained by the ability of the

portal vascular tree to expand and exert pressure onto the surrounding native tissue despite confinement, allowing compression stiffening of the liver.

Conclusion Our findings provide a deeper understanding of the relationship between the fluid pressure and the hepatic biophysical properties. Our study design allowed us to manipulate the amount and distribution of fluid content in the liver, which was manifested in imaging parameters such as tissue-vascular structure, stiffness, and water diffusivity. In summary, liver stiffness increases with increasing portal pressure only if fluid remains in the vessels to effectively compress the surrounding ECM, whereas fluid leaking into the tissues increases the total fluid content, decreasing shear stiffness. These findings suggest that MRE combined with DWI can be used as a noninvasive biomarker for the detection of pressure abnormalities in patients.

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Brain tissue stiffness and imaging sensitivity: insights from functional MR elastography

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Increased oxygen metabolism resulting from neural activity triggers a complex neurovascular response. Changes in blood perfusion pressure and vascular dilation allow for an increased supply of oxygen and occur within seconds after the stimulus onset (slow response: neurovascular coupling). This effect is the basis of the blood oxygen level-dependent (BOLD) contrast used as a marker for neural activity in standard fMRI experiments. However, the neural activity itself occurs within milliseconds (fast response: underlying neural activity) and includes changes in action potentials and electrochemical gradients. The aim of this study is to use magnetic resonance elastography (MRE) to investigate dynamic changes in the viscoelasticity of brain tissue resulting from local neural activity on both time scales. The assessment of local stiffness changes due to neural activity may provide valuable insights into the associated neurovascular and other physiological mechanisms. However, motion or physiological and thermal noise can significantly degrade the data quality and may result in the inability to accurately detect functional activation.

To assess data quality and reliably detect small changes in stiffness, minimal detectable signal (MDS) change is introduced as a quality measure for fMRI time series. MDS provides voxel-wise estimates of the lower detection threshold based on the number of acquisition time points, the temporal signal-to-noise ratio (tSNR), and a statistical significance parameter. MDS maps can be used to assess the impact of MR sequence settings such as voxel dimensions or fat suppression on the quality of the fMRI dataset. Using the whole-brain MDS as an optimization target, 3D spin-echo MRE and 2D real-time MRE were optimized to simultaneously measure BOLD activation and viscoelastic changes of cerebral tissue in response to visual stimulation.

Two stimulation paradigms were designed to each target the slow and fast response with the two functional MRE (fMRE) sequences. Robust viscoelastic activation patterns were observed, including distinct regions of

tissue stiffening within the visual cortex and regions of softening in proximity to the visual cortex. These effects occurred on the timescale of the neurovascular response (slow response) whereas no significant viscoelastic changes were observed on the timescale related to neural activity (fast response). These results suggest a strong relationship between neurovascular coupling and tissue stiffness as measured by 3D MRE, whereas real-time MRE was not sensitive to rapid changes in mechanical parameters that may be related to neural activity.

Subsampling in Emsemble Kalman Inversion

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We consider the ensemble Kalman inversion which has been recently introduced as an efficient, gradient-free optimisation method to estimate unknown parameters in an inverse setting. In the case of large data sets, the ensemble Kalman inversion becomes computationally infeasible as the data misfit needs to be evaluated for each particle in each iteration. Here, randomised algorithms like stochastic gradient descent have been demonstrated to successfully overcome this issue by using only a random subset of the data in each iteration, so-called subsampling techniques. Based on a recent analysis of a continuous-time representation of stochastic gradient methods, we propose, analyse, and apply subsampling-techniques within ensemble Kalman inversion. Indeed, we propose two different subsampling techniques: either every particle observes the same data subset (single subsampling) or every particle observes a different data subset (batch subsampling).

Class DisEntanglement through XAI for medical imaging semantic segmentation tasks

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Healthcare guided by semantic segmentation has the potential to improve our quality of life through early and accurate disease detection. Convolutional Neural Networks, especially the U-Net-based architectures, are currently the state-of-the-art learning-based segmentation methods and have given unprecedented performances. However, their decision-making processes are still an active field of research. In order to reliably utilize such methods in healthcare, explainability of how the segmentation was performed is mandated. To date, explainability is studied and applied heavily in classification tasks. Recently, we propose the Chimeric U-Net a U-Net architecture with an invertible decoder unit, that inherently brings explainability into semantic segmentation tasks. We found that the invertible decoder helps to disentangle the class information in the latent space embedding and to construct meaningful saliency maps. The most surprising result was that, we could predict the Intersection over Union scores of unseen data, demonstrating that the latent space, constructed by the Chimeric U-Net , encodes an interpretable representation of the segmentation quality. We demonstrate the class disentanglement and prediction IoU of unseen data on two publicly available Magnetic Resonance Imaging (MRI) datasets: The Multimodal Brain Tumor Segmentation Challenge 2017 (BraTS), and the Zuse Insitute Berlin?s curated Osteoartheritis Initiative dataset 2018 (OAI ZIB). In conclusion, the Chimeric U-Net arises from the principle of enforcing explainability into the architecture, rather than studying explainability of a general architecture. Through the invertibility of the decoder we could inherently produce both global- and local explainability through class embeddings and saliency maps, respectively. We believe that the Chimeric U-Net architecture is a step in the right direction towards growing confidence, reliability, and trust in Deep Learning approaches in healthcare.

Research Data Management - the MaRDI Project

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Research Data Management has become a central issue in current science to address the growing amount of data at the one hand and the reproducibility crisis at the other. This includes also mathematics as discipline where MaRDI is the Mathematical Research Data Initiative to tackle related tasks. Its goal is to contribute services and infrastructure for mathematical research data to the German National Research Data Infrastructure. Having started in 2021 now first services emerge that are supposed to easy the management of research data for mathematicians and scientists that use math. As mathematics is also important in many other scientific disciplines Mathematical Research Data Management is important for those as well. In this talk, we will introduce MaRDI and some of its services and how Research Data Management benefits research in general.

Intrinsic Activation Elastography: characterizing biophysics-based models via their response to the cardiac pressure pulse.

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Historically, Magnetic Resonance Elastography (MRE) has used extrinsically induced vibration sources to activate the mechanical responses used to reconstruct the biomechanical model parameters (typically the viscoelastic properties) that form the elastograph itself, i.e., the image of the distributed mechanical properties of the tissue. These methods have developed to the point where multifrequency vibration response can be used to characterize complex dispersive properties of tissue that represent homogenizations of the underlying tissue microstructure. More recently, so-called intrinsic activation elastography methods have been developed, where motions induced by the cardiac pressure pulse (or direct contact with the heart itself) are used for biophysical characterization. Such methods provide an alternative approach to explore tissue biomechanics, based on the functional characteristics of the microstructure rather than its dispersive effects. While these approaches have certain practical advantages over traditional elastography, such as removing the experimental variable of poor actuator placement or actuator malfunction, they pose additional challenges for the inverse elastography problem given the quasi-static nature of the mechanical response and the complex physiological signals present in the detected motion fields. This talk will explore some of these challenges and present a biophysical-model based elastography approach to this complex inverse problem. Specifically, recent MRE results in clinical liver imaging based on intrinsic activation will be presented, exploring the choice of data processing methods appropriate to achieve diagnostic results in liver carcinoma and non-alcoholic steatohepatitis. In addition, a newly developed MRE atlas of the viscoelastic properties of the brain characterized by intrinsic activation elastography will be presented. This atlas provides a novel opportunity to explore the use of more complex biophysical models of brain tissue (namely poroelasticity) to allow more detailed characterization of the complex micro-vascular and intercellular flow components of the brain. Such methods have exciting potential to investigate both brain structure and function, and these, importantly, in the natural physiological operating conditions of the brain.

Distributional Uncertainty Quantification for Data-driven Nonlinear Dynamics Models

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To robustly control and optimize systems with uncertainties components, this work studies the multiple-step propagation of the ambiguity sets – the uncertainty over the underlying probability distributions themselves. Different from previous works that use either static ambiguity sets, e.g., fixed Wasserstein balls, or ambiguity sets under known piece-wise linear (or affine) dynamics, we show an algorithm that exactly propagates ambiguity sets through nonlinear data-driven models using kernel conditional mean embedding, which is also applicable to the data-driven approximation to the Koopman operator. The takeaway message is that our kernel ambiguity set is a natural geometric structure for the learned data-driven dynamical system models.

Multiscale models for microcirculation empowered by model order reduction

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The microcirculation exemplifies the multiscale scenario in physiological systems, bridging larger and smaller scale phenomena. Multiscale and multiphysics mathematical models represent a valuable tool to investigate and understand such phenomena, where a brute force computational approach is not viable yet. However, to exploit such tools in the context of precision medicine, it is essential to integrate physics-based models with personalized diagnostics, such as clinical and imaging data. The starting point for data assimilation for pathologies related to microcirculation is the ability to combine the interpretative power of advanced multi-physics model of the vascular microenvironment with state of the art, robust sensitivity analysis and uncertainty quantification methods, with the aim to highlight what factors affect the most some quantity of interest, related to the disease diagnosis, prognosis and treatment. This is an ambitious task in the context of many-query applications, where model order reduction is a necessary enabling technology. Starting from a sophisticated multiscale and multiphysics mathematical model of microcirculation, representing the full order model (FOM), we discuss different strategies to develop a non-intrusive reduced order model (ROM) particularly suited for representing problems with microstructure. We work in the framework of projection-based ROM, exploiting the approximation properties of artificial neural networks for extreme computational efficiency. We use this approach for studying the sensitivity of the oxygenation with respect to the physiological parameters of microvasculature and for the estimation of statistics of oxygen-related quantities of interest. Further developments of this work will aim at applying these tools to the simulation of microcirculation in very complex scenarios, such as whole vascularized tumors.

This is a collaboration with : N.R. Franco, A. Manzoni, P. Vitullo, MOX, Department of Mathematics, Politecnico di Milano

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