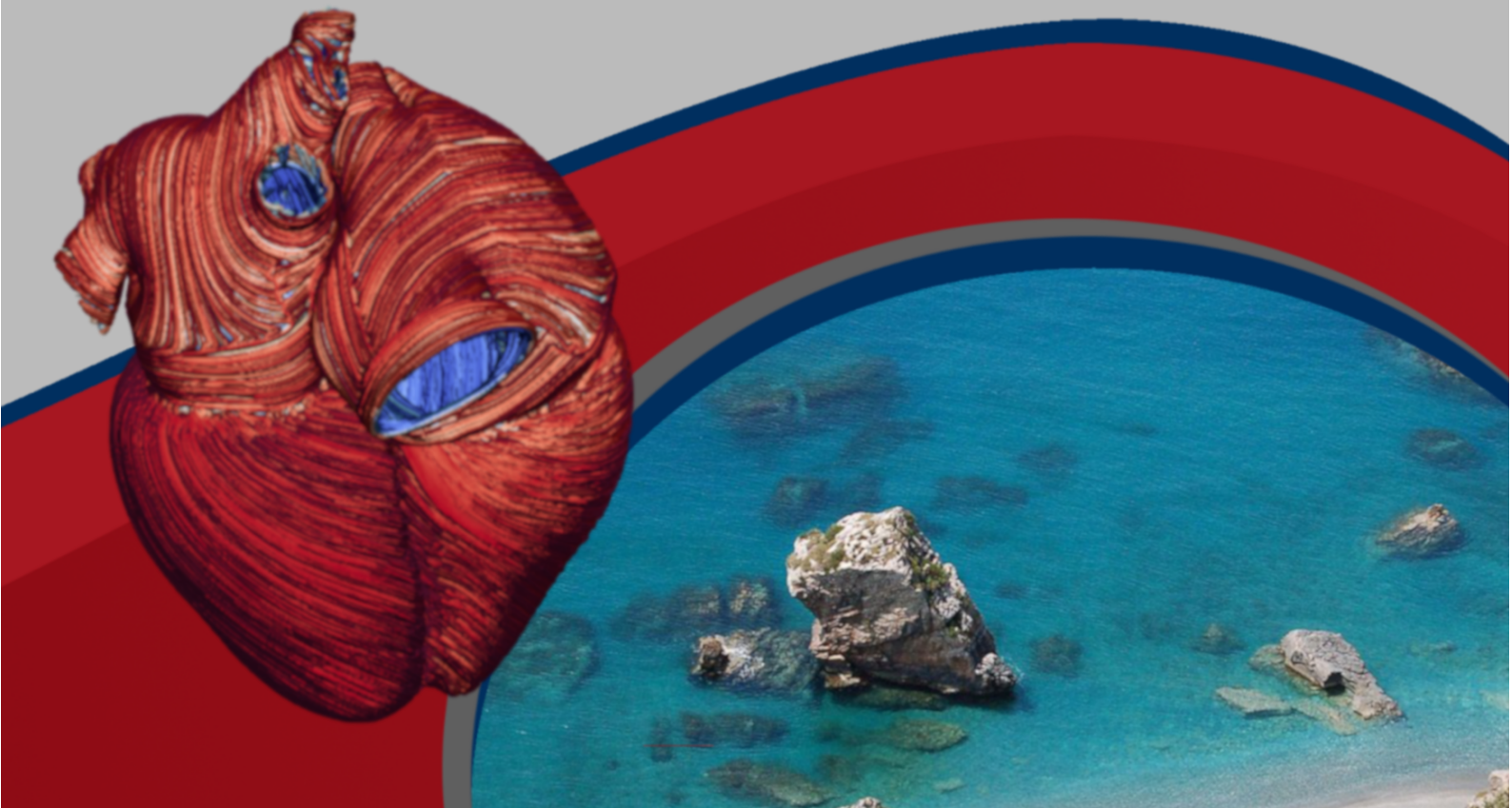
Modelling the Cardiac Function

Theory, Numerical Methods, Clinical Applications

Cetraro, Italy

30th September - 2nd October, 2022



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This conference is supported by the ERC Advanced Grant iHEART, "An Integrated Heart Model for the simulation of the cardiac function", 2017–2022, P.I. A. Quarteroni (ERC–2016– ADG, project ID: 740132).

Timetable

Friday, 30th September 2022

8:30-9:00 Registration

Legend - PL: Plenary Lecture, PS: talk in Parallel Session

	SALA CRATI (GROUND FLOOR)		
9:00–9:05	**Opening by Alfio Quarteroni**		
9:05–9:50	PL	**Alison Marsden** Stanford University	Patient specific modeling of flow and cardiac function in single ventricle physiology
9:50–10:35	PL	**Michael S. Sacks** University of Texas	High-speed cardiac mechanics simulations using a neural network finite element approach
10:35–11:05	**Coffee break**		
11:05–11:25	PS	**Martin Pfaller** Stanford University	A Computational Model for Cardiovascular Fluid-Solid-Growth Interaction
11:25–11:45	PS	**Lorenzo Bennati** Università di Verona	From cardiac cine-MRI to image-based computational blood simulations in presence of mitral regurgitation
11:45–12:05	PS	**Sara Bridio** Politecnico di Milano	A kernel optimization-based classification model for predictions of stroke treatment outcomes
12:05–12:25	PS	**Pasquale Claudio Africa** Politecnico di Milano	`life`^{x}: a friendly, high-performance framework for complex cardiac simulations
12:25–16:00	**Lunch break**		
16:00–16:20	PS	**Alireza Jafarinia** Graz University of Technology	Dominant morphological parameters impacting the false lumen thrombosis in type B aortic dissection
16:20–16:40	PS	**Francesca Renzi** Università di Verona	Patient Specific Image-Based Computational Fluid Dynamic Model of the Right Heart
16:40–17:00	PS	**Jochen Brenneisen** Karlsruhe Institute of Technology	Influence of pressure boundary condition definition on flow patterns in cardiac simulations
17:00–17:30	**Coffee break**		
17:30–18:15	PL	**Gerhard Holzapfel** Graz University of Technology	Viscoelastic modeling for the myocardium
18:15–19:00	**Poster blitz session**		

Friday, 30th September 2022

	SALA PUGLIESE (FIRST FLOOR)		
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11:45–12:05	PS	**Andrea Tonini** Politecnico di Milano	A mathematical model to assess the effects of COVID-19 on the cardiocirculatory system
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16:00–16:20	PS	**Mathias Peirlinck** Delft University of Technology	Towards precision medicine through multiscale and multiphysics human heart modeling
16:20–16:40	PS	**Christian Bilas** Technical University of Munich	Image Based Patient-Specific Pediatric Heart Growth
16:40–17:00	PS	**Tahar Arjoune** Technical University of Munich	Patient Specific Cardiovascular Modeling to Inform Pulmonary Valve Replacement in Tetralogy of Fallot Patients

Saturday, 1st October 2022

	SALA CRATI (GROUND FLOOR)		
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11:00–11:20	PS	**Simone Pezzuto** Università della Svizzera italiana	Physics-informed neural networks to learn cardiac fiber orientation from multiple electroanatomical maps
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Saturday, 1st October 2022

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11:40–12:00	PS	**Marco Fedele** Politecnico di Milano	Modeling the electromechanics of the entire human heart
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Sunday, 2nd October 2022

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9:20–9:40	PS	**Chi Zhang** Technical University of Munich	Unified meshfree algorithm for modeling cardiac function with the Purkinje network
9:40–10:00	PS	**Michele Bucelli** Politecnico di Milano	Coupling electrophysiology, mechanics and hemodynamics in integrated multiphysics simulations of the human heart
10:00–10:20	PS	**Silvia Caligari** Università degli studi di Pavia	An electro fluid structure model based on an embedded strategy with application to cardiac simulations
10:20–10:50	**Coffee break**		
10:50-11:35	PL	**Roberto Verzicco** Università di Roma Tor Vergata	A high-fidelity computational model of the human heart
11:35–12:20	PL	**Natalia Trayanova** Johns Hopkins University	AI-Powered Personalized Computational Cardiology
12:20–12:40	**Poster award & closure**		
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Sunday, 2nd October 2022

	SALA PUGLIESE (FIRST FLOOR)		
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9:40–10:00	PS	**Pierfrancesco Siena** SISSA	Machine learning-based reduced order method for cardiovascular flows with physical and geometrical parameters: application to coronary bypass graft
10:00–10:20	PS	**Caterina Balzotti** SISSA	Optimal control of hemodynamics in coronary artery bypass grafts through reduced order models based on neural networks

Plenary Speakers

Gerhard Holzapfel

Graz University of Technology, Austria; Norwegian University of Science and Technology, Norway

Viscoelastic modeling for the myocardium

Alison Marsden

Stanford University, CA, United States of America

Patient specific modeling of flow and cardiac function in single ventricle physiology

Gernot Plank

Medical University of Graz, Austria

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

Alfio Quarteroni

Politecnico di Milano, Italy; École Polytechnique Fédérale de Lausanne, Switzerland

An integrated mathematical model for the simulation of the complete cardiac function

Michael S. Sacks

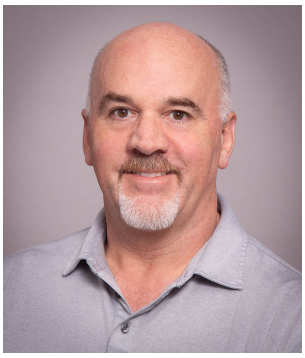
University of Texas, TX, United States of America

High-speed cardiac mechanics simulations using a neural network finite element approach

Charles Taylor

Heartflow Inc., United States of America

Patient-specific Modeling of Blood Flow in the Coronary Arteries



Natalia Trayanova

Johns Hopkins University, MD, United States of America

AI-powered personalized computational cardiology

Roberto Verzicco

Università di Roma "Tor Vergata", Italy

A high-fidelity computational model of the human heart

Viscoelastic modeling for the myocardium

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Current state-of-the art constitutive equations account for the nonlinear anisotropic stress-strain response of cardiac muscle using the theory of hyperelasticity. While providing a solid foundation for understanding myocardial structure and mechanics, most current laws neglect experimentally observed viscoelastic phenomena. This lecture deals with viscoelastic constitutive modeling and the corresponding computational analysis of viscoelasticity in the human myocardium. In accordance with recent experimental findings, ventricular myocardial tissue is assumed to be incompressible, thick-walled, orthotropic and viscoelastic. We model the mechanical response by invariants and structure tensors associated with three orthonormal basis vectors. In particular, a spring element coupled in parallel with Maxwell elements imparts viscoelastic features to the model, such that four dashpots describe the viscous response due to matrix, fiber, sheet and fiber-sheet fragments [1]. Furthermore, we present a more recent fractional nonlinear anisotropic viscoelastic constitutive model [2]. In the sequel, we cover some numerical aspects of the constitutive model by applying it to elastic, cyclic and relaxation test data obtained from biaxial extension and triaxial shear tests. Both models are shown to replicate biaxial stretch, triaxial cyclic shear and triaxial stress relaxation experiments. Model sensitivity, accuracy and uniqueness of parameters are demonstrated.

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Patient specific modeling of flow and cardiac function in single ventricle physiology

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Congenital heart disease affects 1 in 100 infants and is the leading cause of infant mortality in the US. Among the most severe forms of congenital heart disease is single ventricle physiology, in which the heart forms with only one functional pumping chamber. These patients typically undergo three open chest surgeries, culminating in the Fontan procedure at three years of age. Prior work has extensively explored the use of multiscale models, combining hemodynamics with lumped parameter models of single ventricle physiology to assess surgical methods for all three stages of single ventricle palliation. Here, we present our recent work, which extends traditional models of Fontan hemodynamics to include multiple physical processes and cardiac function. We will discuss our recent progress towards: 1) growth and remodeling of tissue engineered vascular grafts in the Fontan circulation, 2) design of a 3D printed pulsatile conduit to provide a power source for Fontan physiology, and 3) modeling the effect of growth on electrophysiology and ventricular dyssynchrony in Fontan patients. Finally, we discuss progress and challenges of developing whole heart models incorporating machine learning for image segmentation, fluid mechanics, active contraction, electrophysiology and valves.

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

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Computational models of cardiac function are increasingly being adopted in the medical device industry for design and optimization of device therapies, and, are considered a promising approach for diagnosis, stratification and therapy planning in the clinic to achieve tailored patient-specific precision 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 the physical reality and the predictive capabilities of mechanistic models. This remains a significant challenge as measurements are limited and afflicted with significant uncertainties, and biophysically detailed models are characterized by a high dimensional parameter vector that must be identified from low dimensional, noisy and uncertain data. Further, even for carefully calibrated models, the ability of models to predict the cardiac response to therapies based on their mechanistic nature is assumed, but supporting evidence is limited. A final concern are the significant computational costs which render many industrial and clinical applications economically unviable.

In this talk I report on our latest advances addressing these issues. Specifically, real-time enabled whole heart electrophysiology simulations as well as computationally efficient whole heart multiphysics models of cardiac electromechanics will be discussed. Techniques for automated patient-specific parameterization will be presented with examples of both industrial and clinical applications related to the modeling of cardiac device therapies.

An integrated mathematical model for the simulation of the complete cardiac function

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In this presentation, I will report on some recent advances in the iHEART project by covering the mathematical, numerical, algorithmic, and application aspects. Our model encompasses all the basic physiological cardiac processes, including electrophysiology, passive and active mechanics, valve dynamics, fluid dynamics, myocardial perfusion, and their mutual interactions. It is based on state-of-the-art numerical techniques of variable orders for both space and time discretizations, and it is implemented in a high-performance computing platform achieving extreme parallel performances. It takes advantage of parameter calibration, reduced order models, scientific machine learning and numerical tools for uncertainty quantification. Our integrated heart model is verified and validated on several benchmark problems of clinical relevance. We believe that, in its current form, our model is very likely the most comprehensive, integrated, and mathematically grounded cardiac model available today.

Acknowledgment: This work has been funded by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 740132, IHEART 2017-2022, P.I. A. Quarteroni).

High-speed cardiac mechanics simulations using a neural network finite element approach

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The full characterization and modelling of three-dimensional (3D) mechanical behaviour the heart is essential in understanding its function in health and disease. Our group has extensively utilized traditional finite element-based approaches for cardiac simulations, which have demonstrated high fidelity and excellent predictive capabilities. While novel and insightful, the length of time to perform such simulations continue to preclude their use in real-time clinical decision making. In this talk I will present some recent results to address this problem using a form of machine learning to solve the hyper-elasticity equations directly. Our first step was to address the highly anisotropic heterogeneous mechanical behaviour of the myocardium. We have developed a novel numerical-experimental approach to determine the optimal parameters for 3D constitutive models of the myocardium using an inverse model. Due to the natural variations in structures, the mechanical behaviors of myocardium can vary dramatically within the heart. Thus, to obtain the responses of the myocardium with different realizations of structures, the resulting hyperelastic problem needs to be solved with spatially varying parameters and in certain cases different boundary conditions. To alleviate the associated computational costs at the time of simulation, we have developed a neural network-based direct PDE solution method. The resulting neural network was then trained by minimizing the potential energy of the hyperelastic problem on a training dataset generated by sampling over the entire physiological range. The neural network model was trained with satisfactory convergence, resulting ultrafast predictions of complex 3D deformations in full kinematic space with population-based fiber structures by forward passes in the neural network. I will also recent work on scaled up for complete organ-level cardiac and heart valve models to provide efficient and robust computational models for to improve patient outcomes in clinically relevant timeframes.

Patient-specific Modeling of Blood Flow in the Coronary Arteries

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Patient-specific models of blood flow constructed from coronary CT angiography (cCTA) images and using computational fluid dynamics are transforming the diagnosis of heart disease by providing a safer, less expensive and more efficient procedure as compared to the standard of care that often involves nuclear imaging and invasive diagnostic cardiac catheterizations. Such image-based computations require an accurate segmentation of the coronary artery lumen from cCTA images and employ biologic principles relating form (anatomy) to function (physiology). Leveraging research originally performed at Stanford University, HeartFlow has developed a non-invasive test, FFRCT, based on computing flow and pressure in the coronary arteries. FFRCT has been validated against invasive pressure measurements in more than 1000 patients and demonstrated to improve care in numerous clinical studies including more than 10,000 patients. At present, FFRCT has been used for clinical decision making in more than 250,000 patients in routine practice in the United States, Europe, and Japan. In the United States, the American College of Cardiology and the American Heart Association guidelines include FFRCT in the recommended diagnostic pathway for heart disease. Medicare and the vast majority of U.S. private insurance companies reimburse physicians for using FFRCT. In England, National Health Services hospitals are mandated to offer this technology to patients. Patient data is uploaded to the HeartFlow application running on Amazon Web Services and then image analysis methods leveraging deep learning are used to create an initial patient-specific geometric model, which is inspected and corrected by a trained analyst. Next fully-automated mesh generation techniques are used to discretize the model. Computational fluid dynamic analysis is performed on AWS to compute the blood flow solution. Results are returned to the physicians through a web interface or mobile application. New developments including software for predicting changes in blood flow arising from alternate treatment plans and methods to assess the risk of a heart attack will be discussed

AI-powered personalized computational cardiology

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Precision medicine is envisioned to provide therapy tailored to each patient. The rapidly increasing ability to capture extensive patient data, coupled with machine learning, a powerful tool for processing massive amounts of data and identifying correlations in it, 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. 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. An application of mechanistic computational modeling is illustrated by the development of a precise treatment for patients suffering from atrial fibrillation, in a prospective clinical trial. 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.

A high-fidelity computational model of the human heart

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Clinical trials are key for advancing cardiovascular research although they entail long and costly processes for the recruitment of representative cohorts of volunteers. The problems are exacerbated for rare pathologies or if multiple concurrent requirements have to be met; in fact, uneven sampling and missing data might result in biased cohorts which, in turn, yield incomplete or misleading results. On the other hand, a digital twin of the heart (or a virtual physical model), once fed by appropriate input parameters, can be resorted to surrogate real patients provided its outcome is reliable and cost effective. Building a virtual model of the whole heart, however, is a formidable task since it involves the complex deforming biological tissues, the transitional and turbulent hemodynamics, the myocardium electrophysiology the strong multi-way interaction of all these systems. Furthermore, in order for the digital twin to be predictive, hundreds of million degrees of freedom are necessary and, even on supercomputers, they require simulation times of weeks or months, thus preventing the clinical use of these models: overcoming such limitations has huge cardiovascular potential and this motivates the present work. In this study we present a high-fidelity computational model of the whole human heart, relying on the latest GPU-acceleration technologies, fully replicating the cardiac dynamics within a few hours. The predictive capability of the model combined with the unprecedented computational speed-up open the way to simulation campaigns to study the response of synthetic cohorts to pathologies. This study is a major step towards in-silico clinical trials in the era of digital medicine.

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life^x: a friendly, high-performance framework for complex cardiac simulations

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As the cardiac function involves several complex physical, chemical and biological processes interacting at a tyranny of space and time scales, whole-heart fully-coupled simulations are highly computationally demanding and call for simple yet accurate, high-performance computational tools.

In this work we introduce life^x [1], a parallel C++ library for the simulation of multi-physics, multi-scale and multi-domain problems arising in cardiac modeling. From the one side, life^x aims at providing a robust and friendly interface enabling the wider public to easily access and reproduce *in silico* experiments, yet without any compromise on computational efficiency and numerical accuracy. On the other hand, being conceived as a research library, life^x can be exploited by scientific computing experts to address new modeling and numerical challenges within an easily approachable development framework.

life^x incorporates solvers for the simulation of state-of-the-art numerical models of cardiac electrophysiology, mechanics, blood fluid dynamics and circulation, either as standalone or coupled, for instance, into electromechanics, fluid-structure interaction and electro-mechano-fluid models.

We showcase life^x capabilities of reproducing physically sound results and prove its low computational footprint enhanced by advanced numerical solvers in a high-performance computing framework (see, *e.g.*, [2]).

The first module of life^x has been recently made publicly available [3] and will be followed by more core models in the near future.

Acknowledgments This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement ID: 740132).

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Patient-Specific Cardiovascular Modeling to Inform Pulmonary Valve Replacement in Tetralogy of Fallot Patients

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One of the most common late consequences after repair of Tetralogy of Fallot (ToF) is pulmonary valve regurgitation. Significant pulmonary valve regurgitation progressively induces right ventricular enlargement, dysfunction and is an important factor of late morbidity and mortality. While it has been shown that pulmonary valve replacement improves symptoms and functional status in these patients, the optimal timing and indications for the replacement intervention after repaired ToF are still debated [4, 5]. Therefore, a patient-specific computational model of the cardiovascular mechanics supports the physicians in their decision-making by assessing the preoperative function of the right ventricle and estimating its postoperative performance.

The 3D-0D coupled closed-loop model of the heart and the vascular system delivers valuable quantities of interest for the physicians, such as blood pressure, blood flow and the contraction of the myocardium [1, 2]. The heart muscle is modeled as a 3-dimensional nonlinear anisotropic elastic solid with an active material component, which simulates the cardiac contraction. The patient-specific geometry of the ventricular myocardium is extracted from medical imaging data such as computed tomography (CT) or cardiovascular magnetic resonance (CMR) through a segmentation process. The entire vascular system is modeled with a 0-dimensional lumped-parameter model, where each of the arterial and venous compartments of the systemic and the pulmonary circulation is described with a specific multi-element windkessel model [3]. The modeling of the valves is also 0-dimensional and is based on the Bernoulli formulation proposed in [9], which is able to describe the regurgitation of leaky valves and is parametrized in a physically interpretable way.

Since the ToF patients undergo a catheter examination, pressure measurements in the four heart chambers as well as in the pulmonary artery and aorta are available. In addition, CMR enables non-invasive phase contrast measurements of flow through planes transecting large vessels such as the main pulmonary artery and the aorta [6]. The patient-specific parameters of the windkessel and valve models are calibrated using these measurements [7].

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Cardiac Blood Flow Simulations and Stasis Assessment in Patients with Atrial Fibrillation

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In patients with atrial fibrillation (AF), the risk for stroke is increased. It is believed that this could be caused by reduced cardiac function and in particular reduced mechanical atrial contraction leading to increased blood stasis resulting in thrombus formation. The aim of this study was to investigate atrial blood flow and function in AF patients to better understand the correlation between blood residence time and atrial contraction. Time-resolved computed tomography (CT) data, covering the whole heart in 20 timeframes, were acquired in 21 AF patients with paroxysmal AF in sinus rhythm. For each of the 21 patients, the atrial and ventricular blood pool were segmented and tracked over the cardiac cycle. These were imposed as a boundary condition for the computational fluid dynamics (CFD) simulation conducted using Ansys Fluent. The mesh contained approximately 8 million cells and the simulation time step was 0.5 ms. To quantify the risk of stasis, the blood residence time, an indicator for the time the blood has spent in the left heart, was computed together with functional data such as ejection fraction and atrial volume.

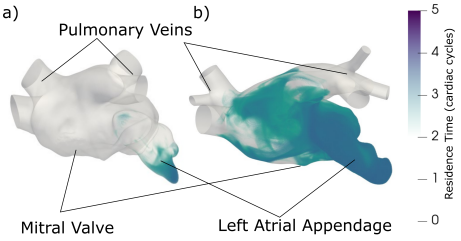

Figure 1: Residence time in the left atrium in a) patient with low average residence time and b) patient with high average residence time

We found large differences in average atrial blood residence time between patients and an association between increased left atrial volume and increased left atrial residence time. Furthermore, there was a strong correlation (R^2=0.69, $p<0.001$) between reduced left atrial ejection fraction and increased average residence time in the left atrium.

In conclusion, atrial wall motion is coupled to cardiac flow dynamics and plays an important role when investigating stasis in the left atrium. Biomarkers based on the cardiac motion and blood residence time could support thrombus risk assessment in AF patients.

From automized geometry segmentation to the FEM simulation of thoracic impedance cardiography.

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Impedance cardiography (ICG) is a non-invasive method for diagnosing several cardiac diseases. ICG measures thoracic impedance changes mainly originating from the blood flow pulsation into the aorta. This is because of blood's higher electrical conductivity than the surrounding tissue types. Realistic simulation models for evaluating cardiac-synchronous impedance changes are necessary to show the feasibility of ICG in the clinical setting. The challenge is how to generate tissue geometries for the simulation model. In this work, we use semi-automatic segmentation methods to segment the aorta with 3D slicer software. First, specific areas of interest with a digital brush are selected. Then, the algorithm automatically generates the remaining regions of the aorta. Next, we extract centerlines containing information about the positioning of various points and the radius of the segmented aorta at the respective position. Finally, we use the Python interface of Cubit software to create vertices for the points. Each vertex is the center of a circle, which gets the radius assigned by it. The circle is then generated as a surface, and an interpolation of the generated surfaces leads to the aortic model in Cubit, which then can be meshed.
We have set up a 3D FEM simulation model in openCFS software to evaluate the thoracic impedance. The Laplace's equation for the electric potential given proper boundary conditions and respective material properties is solved.
Fig. 1 shows the meshed geometry of the aorta and the electric potential values in the thorax domain by applying ICG. In the next step, more thorax tissues will be segmented and added to the geometry to improve the simulation model.

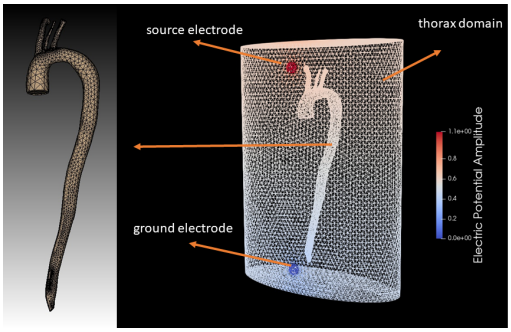

Figure 1: 3D FEM simulation of human thorax with ICG.

Optimal control of hemodynamics in coronary artery bypass grafts through reduced order models based on neural networks

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Coronary artery diseases are one of the most common heart diseases in the world. They consist in the narrowing or blockage of one or more coronary arteries, which are therefore unable to supply the heart with oxygen-rich blood. Typical treatment for damaged arteries is coronary artery bypass (CABG) surgery, an invasive procedure that circumvents the blockage by diverting blood flow. In recent years the medical community has shown a growing interest in the development of fast and accurate numerical models for the hemodynamics of CABGs as a support to surgical planning.

In this talk, we focus on a bypass performed with the right internal thoracic artery on the left anterior descending artery, using a patient-specific geometry obtained by processing clinical images from computed tomography scan. We set up an optimal control problem on the outlet boundary conditions to match measured clinical data with numerical simulations, which are parametrized by the Reynolds number. During the offline phase, we solve incompressible Navier-Stokes equations with finite elements method to collect the set of snapshots that feed the reduced order model. This stage is very expensive in terms of computational time. The construction of the reduced basis space relies on the Proper Orthogonal Decomposition, while the modal coefficients are estimated through feedforward neural networks. Finally, in the online phase we reconstruct the dynamics in the parameter space in a considerably reduced time. We show that this methodology provides a significantly higher computational speed-up than the one obtained from classical projection-based approaches [1, 2].

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Scalable, efficient and robust parallel solvers for cardiac mechanics

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The deformation of the heart is fundamental in the correct functioning of the human body, and it is typically modeled using the framework of continuum mechanics. The numerical approximation of these equations using FEM results in a large and complex system of nonlinear PDEs. Its solution involves several steps, which can be thought as being composed of i) a nonlinear solver, typically a Newton-Krylov; ii) a linear solver, typically GMRES, and iii) a preconditioner, typically an Algebraic Multigrid method (AMG). In this talk we will study the overall solution process in a top-down fashion, and focus in improving points i) and iii) to obtain an efficient and robust solver that is scalable for its use in HPC infrastructures.

For the nonlinear solver, we focus on inexact- and quasi-Newton methods, i.e. L-BFGS and Eisenstat-Walker. We consider two variants of the BFGS method, which are defined according to the inexactness of the initial Hessian approximation. We show the results for both compressible and incompressible mechanics in standard benchmarks in mechanics, and conclude with a test on a simplified heartbeat. The scalability of the solvers was tested up to 32 cores, and no significant difference was observed among the different solvers in terms of scalability.

For the preconditioners, we provide a comparative study between the Balanced Domain Decomposition by Constraints (BDDC) and AMG. The latter has been much more studied, so we perform a thorough tuning of the BDDC to have a fair comparison. In particular, we focus on the software used in each direct solve and on the primal degrees of freedom used to define the continuity of solutions between subdomain interfaces. We further improve the performance of both preconditioners by setting the minimum energy modes of the problem (rigid motions) and by informing the preconditioners of the strided structure of the degrees of freedom, given by the spatial components of the displacement. This ensures that both preconditioners are compared in a peak performance setting. Tuning tests are performed in standard benchmarks for cardiac mechanics, and we conclude with an electromechanics simulation on a realistic geometry. Scalability of the preconditioners was verified up to a thousand CPU cores on a large problem with almost 10 million degrees of freedom.

From cardiac cine-MRI to image-based computational blood simulations in presence of mitral regurgitation

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Mitral Valve Regurgitation (MVR) is the formation of a regurgitant flow in the left atrium due to an incomplete closure of the leaflets during the systole. Haemodynamic quantities such as velocity and Wall Shear Stresses (WSS) can help the surgeons to better understand the pathology and can be computed through imaging techniques or by means computational methods. The advantage of these latter is the higher space-time resolution. We focused on Computational Fluid Dynamics (CFD) with imposed motion, where the displacement of the heart walls and the valves is provided by medical images. In particular, starting from cine-MRI, we reconstructed the geometry and the systolic motion of the left ventricle and atrium, the shape of the mitral valve, and then we completed the domain by adding a template of the aortic root and the aortic valve. After, we created three different virtual scenarios: i) a healthy case (H) with a physiological mitral valve; ii) a regurgitant case (R1) with an insufficient mitral valve and increased heart rate and iii) a regurgitant case (R2) with the same valve of R1 and dilation of the domain [1]. We performed image-based systolic CFD simulations in a moving domain with a resistive immersed method [2] to handle the mitral valve and a turbulence model [3]. Our results highlighted that the regurgitant jets lead to high WSS and to transition to turbulence in the atrium.

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Image Based Patient-Specific Pediatric Heart Growth

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Pediatric growth and remodeling G&R of the heart is driven by a combination of mechanical and hormonal signals which can lead to different growth patterns. Predictive models of cardiac growth could be an important tool to help us understand these growth patterns and to design new treatment methods in case of cardiovascular diseases in children. In this presentation, we introduce a model for patient-specific pediatric cardiac mechanics simulation, which couples a heartbeat and cardiac growth simulation. The heartbeat simulation consists of 3D finite element model of the heart, which is coupled to a reduced order 0D closed-loop vascular system, whereas the cardiac growth and remodeling (G&R) simulation couples the 3D finite element model of the heart with a 0D cell-level hormonal and mechanical stimuli system. A multiscale-in-time approach is presented to couple the different time scales multi-physics problem of cardiac muscle growth in the magnitude of days to month and the cardiovascular dynamics of the heart at the scale of seconds. Based on patient-specific data from experiments, we put emphasis on calibrating the model to obtain experimentally measured data using an inverse analysis framework. We examine our G&R framework for a patient-specific case and show first results.

Keywords: **growth and remodeling, cardiovascular mechanics, 3D-0D coupling, parameter estimation**

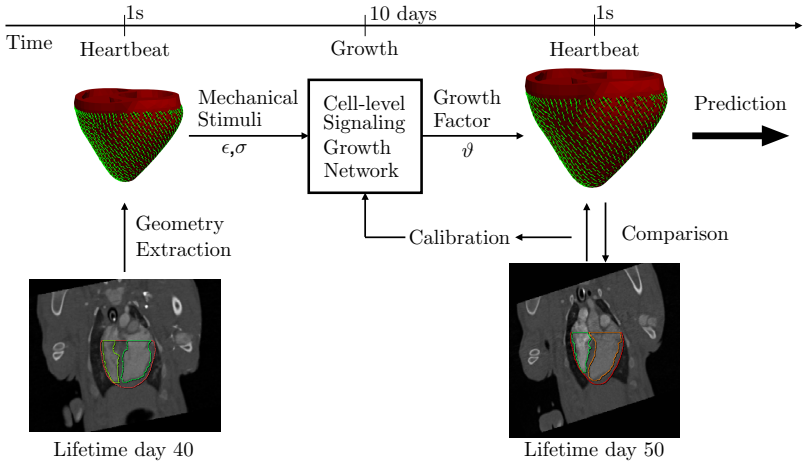

Figure 1: Multiscale-in-time approach for the growth and remodeling process.

Influence of pressure boundary condition definition on flow patterns in cardiac simulations

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Blood flow dynamics in the human heart can be impaired by diverse disease effects. To distinguish between various influences and also quantify the impact of e.g. disease severity, computer simulations based on mathematical models that reproduce the cardiac function in silico are a powerful method: by varying geometry and parameters, different conditions can be simulated, analyzed and compared. However, a main challenge in this context remains the high level of accuracy of the heart models that is necessary to faithfully resemble reality. In particular, the influence of boundary conditions on the fluid dynamics in whole heart simulations is of interest and thus investigated in this computational study.

While fluid simulations are carried out in a 3D finite element model, the systemic and pulmonary circulation state variables are commonly, and also in this study, computed based on a 0D lumped element parameter model. Thus, information has to be transferred between the two models at every instant of the cardiac cycle, like the pressure or flow at defined inlet and outlet interfaces. Secondly, to compute spatially resolved pressure and velocity fields in the heart chambers, the inlet and outlet pressures are commonly described at the orifices: in case of the left heart side at the pulmonary veins and the aorta. The veins and arteries are often not segmented from the medical images. For this reason and to allow for a straight tube vessel approximation that minimizes the influence of dynamic processes, the inlet and outlet trunks are commonly prolonged by straight tubes. At the end of these trunks, pressure boundary conditions provided by the circulatory system model are prescribed.

In this study, we systematically investigated the influence of a variation of the trunk length on the blood flow in the heart chambers.

First results for a trunk shortened by ≈25% of the standard length (≈95 mm, 6-fold diameter of a pulmonary vein) show a drop in the averaged chamber pressure of up to ±2 mmHg in the left atrium and ±6 mmHg in the left ventricle. This deviation can be explained by the shorter distance in the Hagen–Poiseuille equation for a straight tube. However, as the difference between inlet orifice pressure and mean left atrial pressure is determined by the circulatory system model beforehand, the length of the trunks is interrelated to the circulatory system model parameters. Besides the pressure deviations, a moderate variation in the blood flow patterns can be observed visually. Quantitatively, the washout fraction of the left atrium is reduced by up to 1%.

Our results highlight the importance of accurate boundary conditions as well as an accurate interaction of circulatory system and fluid dynamics model. It also indicates that the optimal length of the trunk has to be computed individually for each geometry and most notably in accordance with the circulatory system parameters to obtain accurate flow results.

A kernel optimization-based classification model for predictions of stroke treatment outcomes

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Cardiac pathologies can cause problems in other body districts: atrial fibrillation is one of the causes of acute ischemic stroke, pathology occurring when a thrombus obstructs a cerebral artery. Endovascular thrombectomy (EVT) is a mechanical stroke treatment, aiming at removing the thrombus with a stent-retriever. The treatment must be performed in the first few hours from symptoms onset, allowing a short time window for preoperative planning. In this work, a classification model is proposed, trained on high-fidelity EVT simulations, for providing fast estimates on the success of the procedure.

To create the training dataset, 94 high-fidelity finite-element simulations of the EVT procedure are run, with patient-specific cerebrovascular anatomies and thrombi. 81 out of 94 simulations have a positive outcome, i.e. thrombus is removed from the vasculature, and 13 have a negative outcome. The classification model is intended to cluster samples with positive and negative outcome based on vascular anatomy and thrombus characteristics, and to predict the class where new test samples lie. The method used for classification relies on two successive kernel Principal Component Analyses (kPCA). The first is applied to the anatomic description. The second, including the thrombus characteristics, uses a kernel optimized with a Semidefinite Programming (SDP) kernel optimization algorithm[1] such that, in the principal components space, the distance between samples belonging to different clusters is maximized. The same kernel function is used to project new test cases (defined by vascular anatomy and thrombus characteristics) to the principal components space and to assign the test sample to either the positive EVT outcome cluster, or the negative one. The classification model is evaluated with 20 bootstraps, randomly selecting 15% of the samples for testing. In all the bootstraps, the two clusters are successfully described. The classification of the test samples provides an average of 77% correct predictions. Despite the performance of the model is limited by the small number of samples belonging to the negative outcome class, the proposed method is promising and it is seen as a valuable tool for performing a fast pre-operative evaluation of the chances of success of an EVT procedure.

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Coupling electrophysiology, mechanics and hemodynamics in integrated multiphysics simulations of the human heart

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We propose a computational model of the human heart, aiming at capturing the complex interplay between the physical processes characterizing its function. The model features three-dimensional descriptions of electrophysiology, muscular mechanics and blood dynamics, with reduced models of valves and of the circulatory system. We include interaction effects such as electro-mechanical and mechano-electrical feedbacks [3], feedbacks between contractile force generation and fiber stretch [2], fluid-structure interaction [1] and the interplay between heart and circulation [4]. We use a discretization scheme that is staggered in time for flexibility and efficiency. Coupling terms are treated explicitly, except for the fluid-structure interaction coupling, solved implicitly with a monolithic solver. We run simulations on a realistic model of the human heart, obtaining results that are in agreement with physiology, in terms of major biomarkers as well as muscular displacement and blood flow patterns.

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An electro fluid structure model based on an embedded strategy with application to cardiac simulations

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Numerical models of cardiac activities require to simulate electrophysiology, mechanics and fluid-dynamics. For this aim, one has to couple three different physics and mathematical models whose discertization involves different time and space scale lengths.

In this contribution we first focus on an electrophysiology finite-element framework which solves the Monodomain equation, describing the propagation of the electrical signal in the heart, coupled with an ionic membrane model. In particular we present a novel high-order time integrator scheme based on operator splitting, a technique capable of splitting complex system equations into smaller parts easier to solve, which allows for the use of an explicit second order predictor corrector scheme for the time integration of the non linear subproblem and the Crank-Nicolson time integration of the linear subproblem, in order to obtain the over-all second-order accuracy. We test the proposed approach on a modified FitzHugh-Nagumo model [Aliev and Panfilov, 1995] characterized by an action potential wave similar to the cardiac one.

We also present a fluid-structure interaction framework coupled with an *active stress term* to represent muscle contraction. This represent the first step toward a fully coupled electrophysiology fluid structure interaction framework. The proposed method is inspired by the Immersed Boundary technique. The dynamic behavior of the solid structure is simulated in a finite element framework, while the Navier-Stokes equations for the incompressible flow are discretized with high-order finite difference. The coupling strategy is based on an L2-projection to transfer the discrete field between the two fluid and the solid subdmain.

This work has been supervised by Prof. Rolf Krause (USI, Lugano - Switzerland), Dr. Maria Giuseppina Chiara Nestola (USI, Lugano - Switzerland) and Dr. Marco Favino (UNIL, Lausanne - Switzerland)

Physics-based and data-driven reduced order models for parameterized PDEs in structural mechanics

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Full order models (FOMs) are commonly employed to compute high-fidelity solutions to cardiac mechanics problems. Nonetheless, they may demand several hours of CPU time to simulate just a few heartbeats, making the investigation of a broad range of virtual scenarios – obtained by changing the parameters that characterize the biophysical model – unfeasible as soon as a huge number of degrees of freedom is required. To allow the translation of patient-specific simulations into clinical practice is thus of paramount importance to reduced the computational time required by the FOMs.

Physics-based reduced order models and statistical emulators have been extensively developed to compute accurate and inexpensive approximations of high-fidelity solutions. To the former class of models belongs the reduced basis (RB) methods, which consists of a Galerkin projection of the FOM onto a linear low-dimensional subspace. The latter class, instead, comprehends data-driven models that directly learn the underlying relationship between input parameters and corresponding outputs.

Recently, semi-intrusive strategies exploiting surrogate models to achieve different tasks have been extensively developed. In [1] Gaussian process (GP) regression is employed to learn, in a supervised framework, the map between parameters and coefficients of the RB expansion, whereas in [2] a deep learning-enhanced reduction technique, combining a Galerkin-RB method with deep neural networks, is proposed. In this presentation, we compare different semi-intrusive approaches to speed-up the solution to benchmark problems of nonlinear structural mechanics with respect to the widely used finite element method, addressing both accuracy and efficiency issues.

This is a joint work with Stefania Fresca, Andrea Manzoni, Alfio Quarteroni and Paolo Zunino.

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Hemodynamics in the left atrial appendage in atrial fibrillation patients: does its occlusion affect stroke risk?

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Introduction. The morphological and functional remodelling of the left atrium (LA) caused by atrial fibrillation (AF) favours blood stasis and, consequently, stroke risk. Because of its hooked morphology, left atrial appendage (LAA) is the LA site of the highest blood stasis risk, increasing the incidence of thrombus formation. Oral anticoagulation therapy was the only option available until recently when different strategies have been developed such as the LAA percutaneous closure, which seems to better reduce risk of thromboembolism compared to anticoagulation therapy. Unfortunately, these treatments are restricted to small subgroups of patients, due to the procedural risks and costs which may overcome the preventive antiembolic efficacy. The aim of this study was to simulate the fluid dynamics effects of the LAA occlusion (LAAO) in AF patients to predict patient-specific hemodynamic changes caused by the occlusion, by mimicking the two most popular and used devices.
Methods. LAAO was reproduced on 3D LA anatomical models obtained from real clinical data of five AF patients. For each patient, CFD simulations in AF condition were performed on the entire LA model and on the models with the two LAAOs. Significant fluid dynamics indices (blood velocity, vortex structures and residence time analysis) were determined to evaluate the changes in the flow patterns after the occlusion in relation to the thrombogenic risk.
Results. After the occlusion, blood velocities at the PVs were slightly lower with respect to the model with the LAA (30-40 cm/sec vs 15-20 cm/s). At the mitral valve (MV) we observed higher values of the velocities with respect to the simulation with the LAA (mean peak velocities – 60 cm/s vs 70 cm/s). Importantly, in LAAO simulations the direction of all the vectors seemed to converge towards the MV and the distal parts of the atrial chamber were reached slowly. Vortex structures minimally decreased in number in the LA after the occlusion, but they increased their size. Blood velocities at the LAA ostium significantly increased after the occlusion (mean peak velocity – 15 cm/s vs 49 cm/s). These characteristics could favor a better washout of a larger quantity of the blood flow with respect to the complete model of the atrium with the LAA. Blood stasis in the LA significantly decreased after the occlusion with a slightly improved washout effect with one of the two implanted devices (mean number of particles after 5 cardiac cycles – 221 vs 136 and 151).
Conclusions. A workflow for simulating the fluid dynamics effects of LAAO in AF was tested. The results of this study contribute to understand the fluid dynamics conditions leading to thrombogenesis and to identify the most effective devices in reducing the stroke risk for patient-specific LA morphologies.

Modeling the electromechanics of the entire human heart

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While ventricular electromechanics is extensively studied in both physiological and pathological conditions, four-chamber models have only been addressed in recent years, most of which however neglecting atrial contraction. Since atria are characterized by a complex anatomy and a physiology that is strongly influenced by the ventricular function, developing computational models capable of capturing the physiological atrial function and atrioventricular interaction is very challenging. In this work, we propose a biophysically detailed electromechanical models of the whole human heart that considers both atrial and ventricular contraction. Our model includes: i) an anatomically accurate whole-heart geometry; ii) a comprehensive myocardial fiber architecture; iii) a biophysically detailed microscale model for the active force generation; iv) a 0D closed-loop model of the circulatory system, fully-coupled with the mechanical model of the heart; v) the fundamental interactions among the different *core models*, such as the mechano-electric feedback or the fibers-stretch and fibers-stretch-rate feedbacks; vi) specific constitutive laws and model parameters for each cardiac region. Concerning the numerical discretization, we use an efficient segregated-intergrid-staggered scheme and we employ recently developed stabilization techniques – regarding the circulation and the fibers-stretch-rate feedback – that are crucial to obtain a stable formulation in a four-chamber scenario. We are able to reproduce the healthy cardiac function for all the heart chambers, in terms of pressure-volume loops, time evolution of pressures, volumes and fluxes, and three-dimensional cardiac deformation, with unprecedented matching (to the best of our knowledge) with the expected physiology. We also demonstrate the importance of considering atrial contraction, fibers-stretch-rate feedback and suitable stabilization techniques, by comparing the results obtained with and without these features in the model. The proposed model represents the state-of-the-art electromechanical model of the iHEART ERC project – an Integrated Heart Model for the Simulation of the Cardiac Function – and is a fundamental step toward the building of physics-based digital twins of the human heart.

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Deep learning-based reduced order models for the efficient solution of parametrized PDEs

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Traditional reduced order models (ROMs) anchored to the assumption of linear superimposition of modes, 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. To enhance ROM efficiency, we propose a nonlinear approach to set ROMs by exploiting deep learning (DL) algorithms, such as feedforward, convolutional and autoencoder 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. Accuracy and efficiency of the DL-ROM technique are assessed on different parametrized PDE problems where new queries to the DL-ROM can be computed in real-time.

Finally, preliminary results on the mathematical interpretation of the hyperparameters defining a neural network architecture will be shown.

This is a joint work with Andrea Manzoni, Luca Dede' and Alfio Quarteroni.

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Computational hemodynamics and fluid-structure interaction of pathological and prosthetic valves

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In the framework of cardiac hemodynamics, the patient-specific displacement of the myocardium can be reconstructed from diagnostic acquisitions (e.g. cine MRI), whereas, due to limited time and/or space resolution of imaging data, the description of the motion of the valve leaflets and other components of prosthetic valves often require the use of computational models. Different approaches have been proposed in the literature, ranging from prescribed-displacement Computational Fluid Dynamics (CFD) to Fluid-Structure Interaction (FSI) simulations. The choice of a suitable model is mainly dictated by the clinical question of interest, the available computational resources, and the required response time.

In this talk, we present the application of computational methods to answer specific clinical questions concerning prosthetic valves: the identification of prediction factors for TAVI degeneration by 3D FSI [1]; the hemodynamics assessment of a prosthetic pulmonary valve by a 3D-0D geometric multiscale approach; an investigation on aortic stenosis by means of a lumped-parameter model for the elastic response of the aortic valve leaflets [2]. We discuss the clinical relevance of each application and compare the different methods employed, in terms of level of detail and computational efficiency.

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Generation of Cardiac Digital Twins of Whole Heart Electrophysiology

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Introduction: Computer models of cardiac electrophysiology (EP), personalised to match both the anatomy and electrical activity of an individual patient, are termed Cardiac Digital Twins (CDTs). CDTs show high potential to aid in clinical diagnostics, treatment planning, prognostics, and device development. Challenges during anatomical and functional personalization, however, have limited clinical applicability. We aimed to overcome many of these challenges and report on a clinically-viable CDT of a single subject capable of simulating sinus rhythm and ventricular-based diseases with high fidelity.
Materials and Methods: Using an automated framework for the generation of the CDT from non-invasive clinical data, a whole heart model was built, personalised based on the 12-lead electrocardiogram (ECG) during sinus rhythm, and retrofit with a physiologically-detailed His-Purkinje system (HPS). Whole heart EP was accounted for by including atrial and atrio-ventricular (AV) conduction. The predictive capabilities of the CDT were tested under a variety of clinical disorders. EP simulations were carried out with real-time performance. Computed pathological ECGs were evaluated with clinical diagnostics.
Results: Goodness of fit was assessed for sinus rhythm. Predictive capabilities of the mechanistic model were probed by interrupting conduction in the left and right bundle branches (LBBB, RBBB), by creating accessory paths, and by pacing at the RV apex. ECGs associated with these pathological activation sequences showed good agreement, as assessed by diagnostic criteria.
Discussion and Conclusions: The personalised 12-lead ECG under normal sinus rhythm showed close correspondence with the measured 12-lead ECG. Most expected morphological ECG features manifested, in agreement with diagnostic criteria. Minor discrepancies were also observed. These are attributed to additional pathological factors that were not taken into account, such as dilation or slower cell-to-cell conduction, as it is the case with a clinical LBBB aetiology. While the CDT shows promise for patient care in a single subject, broader validation with clinical data is needed to demonstrate agreement between models and physical reality.

Dominant morphological parameters impacting the false lumen thrombosis in type B aortic dissection

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Treatment and management of type B aortic dissection (TBAD) are associated with high risks of complications, especially under the presence of a partially thrombosed or a patent false lumen (FL). Therefore, it is crucial to reveal the conditions required to develop FL thrombosis to identify high-risk patients. Although clinical studies have shown that some morphological parameters are associated with FL thrombosis, sometimes conflicting results are reported. Hence, we aim to identify the most significant morphological parameters influencing FL thrombosis. We showcase that recent models of thrombus formation combined with methods from sensitivity analysis may yield valuable insights as to how combinations of morphological parameters influence the FL thrombosis.

An abstracted 2D geometry of a TBAD is generated and parameterized based on the clinical data. After implementing the rheological and thrombus growth model into computational fluid dynamics simulations, a global sensitivity analysis is performed on chosen morphological parameters. In addition, we introduce non-dimensional parameters to make the results transferable between patients.

The sensitivity analysis results show that the most sensitive parameters impacting FL thrombosis are the diameter of FL and the size and location of the intimal tear. A higher risk of partial thrombosis is observed when the FL diameter is larger than the true lumen (TL) diameter. Decreasing the ratio of the distal to the proximal tear size increases the risk of FL patency. To conclude, these parameters play a dominant role in classifying morphologies into a patent, a partially thrombosed, and a completely thrombosed FL. In this study, we indicate the predictive role of morphological parameters for FL thrombosis in TBAD and show that the results are in good agreement with available clinical studies.

*Co-first author: Alireza Jafarinia and Gian Marco Melito contributed equally to this work.

Impact of false lumen thrombosis on blood flow dynamics and electrical conductivity in type B aortic dissection

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A rupture of the innermost layer of the aortic wall, namely the intima layer, leads to aortic dissection pathology. The blood flow will reach the media layers and propagate between them to create a cavity where blood stagnates. A false lumen develops besides the original aorta, i.e., the true lumen. The hemodynamics alterations generate flow disturbances and recirculations, hence low wall shear stress values, leading to the formation of a blood thrombus. Thrombus formation prediction and monitoring affect aortic dissection prognosis and influence the selection of possible treatment, such as medication or surgery.

The electrical properties of blood depend on its hemodynamic conditions like flow velocity and shear stress, but also red blood cells orientation and deformation. Since the blood is much more conductive than other tissues in the body, it is possible to identify the dynamic changes in blood flow by analyzing its electrical conductivity. The presented study focuses on analyzing hemodynamic changes due to the presence of false lumen and thrombus.

The computational model is composed of a 3D computational fluid dynamics simulation set up to model thrombosis growth in the false lumen and its impact on the conductivity changes of blood. A new method is introduced to model the electrical conductivity of the blood in the many hemodynamics conditions to account for the anisotropic property of the blood, which derives from the orientation and deformation of red blood cells.

The study shows that the presence of the thrombus alters the hemodynamics and, consequently, the electrical property of the entire domain. From this, it is possible to conclude that the electrical properties of blood can be employed to analyze and monitor a patient affected by aortic dissection.

Computational tools for the analysis and prediction of cardiac arrhythmias

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Arrhythmias are alterations in the normal heart rhythm that might compromise the heart's pumping activity. They result from the concomitance of several predisposing factors: structural defects of the myocardium, like scars or fibrosis, and functional defects, altering the electrical properties of myocardiocytes. Their identification from patients' clinical data is a continuous challenge addressed by clinicians and researchers to improve diagnostic and therapeutic tools.

In this talk, we present some computational tools that enable extracting relevant information from electro-anatomical data. Specifically, we develop machine and deep learning (M-DL) techniques for identifying novel indicators of arrhythmic propensity that provide stratification of patients and support the definition of tailored intervention strategies. We adopt DL techniques that flexibly integrate multiscale mathematical models describing the underlying electrophysiological processes. This approach balances the possible lack of information generated by uncertain or biased measurements. We incorporate physical knowledge directly in neural networks (NNs) training procedures by employing dimensionality reduction techniques (physics-aware NN) or penalizing partial differential equations in strong form within the NN cost function (physics-informed NN).

Clinical data analysis also supports the construction of patient-specific numerical models of cardiac electrophysiology. These models, equipped with new parameterizations based on calculated biomarkers, can predict arrhythmia initiation and maintenance. Simulation thus provides an additional tool that improves etiopathogenic mechanisms' understanding and clinical biomarkers' interpretation, confirming their role in characterizing the arrhythmic risk.

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Towards precision medicine through multiscale and multiphysics human heart modeling

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We have come to a point where human heart modeling can really start to benefit the patient, for improved diagnosis, prognosis, treatment planning, and medical device design. The development of multiscale patient-specific heart models equipped with realistic Purkinje networks provides accurate predictions of the heart's electrophysiological behavior under both physiological and pathological conditions. Moreover, it allows us to characterize the effects of drugs in cardiac electrophysiology and develop novel population-specific in silico drug risk stratification. Similarly, we can now confidently and robustly model the physiology and mechanical behavior of the healthy beating human heart. Such a simulation tool provides inexhaustible opportunities to probe pathological conditions and guide device design and treatment planning in health and disease. We can now predict the long-term response of the heart to various forms of pressure and volume overloading and show that our predictions qualitatively match pathophysiological remodeling at the cell, tissue and organ scale. Additionally, we use these tools to simulate the consequences of myocardial infarction and compute how the non-contracting scar region leads to mitral regurgitation. The resulting diseased digital twin of the patient-specific heart forms an interesting in silico bench test to quantify the potential success of various treatment strategies. Particularly, we have used these models to optimize novel mitral annuloplasty rings, predict the coaptation of the mitral valve following edge-to-edge repair, quantify the mechanical loads on pacing leads and the effects of left ventricular assist devices on myocardial dynamics. With a view toward translational medicine, our models also provide a clinical perspective on virtual imaging trials and a regulatory perspective on medical device innovation.

Physics-informed neural networks to learn cardiac fiber orientation from multiple electroanatomical maps

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We propose a method to estimate *in vivo* the cardiac fiber architecture of the human atria from multiple catheter recordings of the electrical activation. Cardiac fibers play a central role in the electromechanical function of the heart, yet they are difficult to determine *in vivo* and hence rarely truly patient-specific in existing cardiac models.

In this work, the fibers arrangement is obtained by solving an inverse problem through the physics-informed neural network formulation. The inverse problem amounts of identifying the conduction velocity tensor of a cardiac propagation model from a set of sparse activation maps. The use of multiple maps enables the simultaneous identification of all the components of the conduction velocity tensor, including the fiber angle.

We extensively test the method on synthetic 2-D and 3-D examples, also with realistic atrial geometry. We show that 3 maps are sufficient to accurately capture the fibers also in the presence of noise. With fewer maps, the role of regularization becomes prominent. Moreover, we show that the fitted model can robustly reproduce unseen activation maps. Finally, we apply the methodology to a publicly available atrial atlas and to clinical data obtained at our center, with very convincing results.

A Computational Model for Cardiovascular Fluid–Solid-Growth Interaction

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Local hemodynamics play a crucial role in blood vessels adapting to changes in loading conditions through growth and remodeling (G&R), i.e., the continuous deposition and degradation of tissue constituents. This work presents a new open-source framework that enables three-dimensional fluid-solid-growth interaction simulations using a fast, rate-independent mechanobiologically equilibrated model [1].

In cardiovascular problems, G&R is commonly triggered mechanically through fluid-structure interaction by pressure-induced intramural stress and flow-induced wall shear stress [2]. Previous implementations of the equilibrated constrained mixture model relied on an assumed form for intramural stress and flow-induced wall shear stress. We propose combining fluid-structure interaction and G&R in a novel fluid-solid-growth (FSG) framework to predict disease progression, using the mechanobiologically equilibrated constrained mixture theory, enabling efficient three-dimensional FSG simulations for patient-specific geometries.

Our FSG model is implemented in our open-source multiphysics finite element solver svFSI (`github.com/SimVascular/svFSI`). We explore three coupling methods to inform the G&R model with fluid pressure and wall shear stress. First, we utilize a semi-analytical approach, assuming fully-developed laminar Poiseuille flow through a long cylinder. This approximation yields good results in simple tube-like geometries, with pressure assumed uniform axially, but is inaccurate for more complex flow fields. In our second approach, we propose partitioned coupling, where we consecutively solve steady-state fluid flow, solid G&R, and mesh displacement. Finally, we simultaneously solve for fluid velocity, pressure, and solid displacements in a monolithic coupling approach.

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Modelling a detailed whole heart myofiber architecture in cardiac electromechanical simulations

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Abstract

A major issue for accurate numerical simulations of cardiac electromechanics (EM), consists in modeling the complex arrangement of the muscular fiber architecture that characterizes the cardiac tissue. Aggregations of myofibers, namely the results of cardiomyocytes orientation, play a key role in the electric potential propagation within the muscle and also in the myocardial contraction. This motivates the need to accurately include fiber orientations, in EM computational models, in order to obtain physically meaningful results. Due to the difficulties of reconstructing cardiac muscle fibers from medical imaging, a widely used strategy, for generating myofiber orientations in EM models, relies on the so called Rule-Based Methods (RBMs). Among them, Laplace-Dirichlet-Rule-Based Methods (LDRBMs), which rely on the solution of Laplace boundary-value problems, are the most used RBMs for prescribing ventricular fibers. The ventricular LDRBMs have been recently reviewed under a communal mathematical description in [1]. Concerning the atria, several RBMs have been developed, using mainly semi-automatic rule-based approaches or atlas-based methods. These require a huge manual intervention and often are designed for specific morphologies. Only in the last years, a LDRBM have been proposed for the atria [1]. Prescribing the myofibers architecture is significantly more challenging in full heart geometries. Consequently, many of the existing four-chambers EM models embed only the ventricular fibers or include simplified architecture for the atria. In this work we present a LDRBM for the generation of full heart myofibers architecture, that is able to reproduce all the important characteristic features of the four-chambers, particularly those of the right ventricle and the bi-atrial bundles. The newly whole heart LDRBM is built upon the combination of the ventricular and atrial LDRBMs presented in [1] and on a novel definition of several inter-heart distances. The validity of the model is demonstrated through EM simulations on a realistic biventricular, biatrial and also whole heart geometries.

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Patient Specific Image-Based Computational Fluid Dynamic Model of the Right Heart

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Clinical interest in the right side of the hart (RH) has seen a significant increase in the last decades, due to the key role it plays in many congenital heart diseases, and the close relationship it has with the left counterpart. Therefore, it is essential to characterize this anatomical region as deeply as possible.

Starting from cardiac magnetic resonance images, in this work we aim to develop a pipeline for the reconstruction of the patient RH, together with its motion during the cardiac cycle, so to generate a model suitable for image-based computational fluid dynamic (CFD) analysis, in the wake of the CFD study performed by Bennati et al.[1] of the left heart. In particular, we put forward a new technique for the reconstruction of anatomical geometries from cine-MRI images. This consists of contouring the endocardium on all the slices of the available images and of generating the endocardial surface at each instant of the cardiac cycle by means of the gradual deformation of a generic surface. Then the endocardial displacement field is derived registering the surface of each time instant on the end-diastolic configuration. We accounted of the tricuspid and pulmonary valve leafltes as immersed in the moving domain according to a resistive method and, finally, CFD simulations were performed over the systolic phase of the cardiac cycle using the C++ library `life`$^{\mathtt{x}}$. The reconstruction and CFD results were analyzed in order to compare the new reconstruction technique we propose with the already present and widely used procedure developed in the context of the left ventricle by Fumagalli et al. [2].

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Stabilization of staggered schemes for 3D cardiac mechanics coupled with 0D blood dynamics

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The numerical simulation of the cardiac electromechanical function requires a closure relationship that links the pressure acting on the endocardium with the blood fluxes occurring among the cardiac chambers. With this aim, 3D models of one or more cardiac chambers are typically coupled with 0D (i.e. lumped-parameter) models of blood circulation. However, this coupling can lead to numerical instabilities when using staggered schemes. These issues are still not well understood, and, to the best of our knowledge, to date there is no mathematical explanation for the onset of oscillations and no estimates that can predict for which parameter values and time step sizes they occur. Moreover, the only known cure to date is to use monolithic schemes (that is, solving the coupled problem in one shot) instead of staggered ones. In this talk we analyze the numerical oscillations affecting time-staggered schemes for 0D-3D fluid-structure interaction (FSI) problems and we propose a novel stabilized scheme that cures this issue [1]. We study two staggered schemes. In the first one, the 0D fluid model prescribes the pressure to the 3D structural mechanics model and receives the flow. In the second one, on the contrary, the fluid model receives the pressure and prescribes the flow. These schemes are respectively known, in the FSI literature, as Dirichlet-Neumann and Neumann-Dirichlet schemes, borrowing these terms from domain decomposition methods, although here a single iteration is performed before moving on to the next time step. Should the fluid be enclosed in a cavity, the Dirichlet-Neumann scheme is affected by non-physical oscillations whose origin lies in the balloon dilemma, for which we provide an algebraic interpretation. Moreover, we show that also the Neumann-Dirichlet scheme can be unstable for a range of parameter choices. Surprisingly, increasing either the viscous dissipation or the inertia of the structure favours the onset of oscillations. Our analysis provides an explanation for this fact and yields sharp stability bounds on the time step size. Inspired by physical considerations on the onset of oscillations, we propose a numerically consistent stabilization term for the Neumann-Dirichlet scheme. We prove that our proposed stabilized scheme is absolutely stable for any choice of time step size. These results are verified by several numerical tests, including the coupling between a multiscale 3D model of cardiac electromechanics and a closed-loop 0D model of blood circulation. We show that our proposed scheme successfully removes the non-physical oscillations that would otherwise affect the numerical solution.

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Cellular Heterogeneity in the Atria: Effect on arrhythmic vulnerability and pharmacological cardioversion

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In silico modelling is increasingly relied upon to gain new insights into the underlying mechanisms of atrial fibrillation. Due to the complex nature of the atria, in silico models typically exclude cellular heterogeneity. One question that remains unanswered is how cellular heterogeneity affect the arrhythmic vulnerability. This study aims to present the impact of cellular heterogeneity on the susceptibility to reentry behaviour and its effect on pharmacological cardioversion.

Cellular heterogeneity was introduced using the population of models approach and calibrated on a regional basis based on 5 biomarkers: action potential amplitude (APA), resting membrane potential (RMP), and action potential duration (APD) at 20, 50, 90 percentage repolarization. A comparable regionally homogeneous atrial model was created as a control. The atrial model was preconditioned with a sinoatrial stimulation at a basic cyclic length of 800ms. Nine rapid-paced ectopic beats were applied in 2 locations in the LA to induce a re-entry. The re-entrant path, frequency, and vulnerable window were compared between the two models at these two ectopic beat locations. SA stimulation was continued at EB onset to evaluate the sustainability of the reentry.

Results showed a slight increase in frequency of re-entry due to cellular heterogeneity (5.66Hz versus 5.73Hz for the homogeneous and variable models respectively). In both cases, the re-entrant pattern was stablished through the coronary sinus corresponding with a pattern of atrial tachycardia. In the Homogeneous model, ectopic beats applied to the centre of the LA resulted in re-entrant activity with a vulnerable window of 700 ms, whereas cellular heterogeneity increased the VW to 800 ms. In the second EB location, sustained re-entry the vulnerable window was of 800 ms for both models.

To further study the effect of electrophysiological variability, pharmacological cardioversion with amiodarone and flecainide was simulated using 1x and 10x the effective therapeutic concentrations (EFTC) resulting in effective removal of the arrhythmia for flecainide at 10x concentration for the electrophysiological variable model.

Physics-informed neural networks for image registration: computing cardiac strain

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Heart disease is one of the leading causes of death in the world. Disturbances in the mechanical performance of the heart can lead to many, sometimes catastrophic, conditions. Traditionally, cardiac function is assessed with simple metrics, such as the left ventricular ejection fraction. This quantity only reflects the global function of the heart, leaving out important information. For example, it is well documented that patients with ejection fraction in normal ranges can still experience what is called heart failure with preserved ejection fraction. For this reason, more sophisticated metrics that give regional information have appeared, such as cardiac strain. Here, the deformation of cardiac tissue is characterized locally, resulting in much richer information. However, determining cardiac strain from medical images is a challenging and open problem. In this work, we focus on the computation of cardiac strain from cine magnetic resonance images, which contain a sequence of snapshots of the heart motion. These images are ubiquitous and considered the gold standard to assess cardiac function with metrics such as ejection fraction. Nevertheless, cardiac strain cannot be derived directly from these images, as they do not contain motion information. For this reason, we use physics-informed neural networks to solve an image registration problem and estimate cardiac strain from cine magnetic resonance images. Physics-informed neural networks are a promising new tool to solve inverse problems, such as this one, that will allow us to infer the displacement field that transforms images between different stages of the cardiac cycle. This method allows to include the knowledge about cardiac mechanics into the learned displacement field. Here, we enforce the near cardiac tissue incompressibility to improve the accuracy of cardiac strains. We also use a space-time continuous neural network, to reflect the different motion states of the cardiac cycle. We demonstrate the feasibility of this method in a synthetic example, and we show that our method performs favorably to other registration techniques using a cardiac strain benchmark. We expect that our methodology will improve the accuracy and robustness of cardiac strain measures from cine magnetic resonance images. This will pave the way to more sophisticated diagnostic tools for a range of cardiac diseases.

High-order methods for cardiac electrophysiology

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Developing mathematical methods to perform accurate and efficient numerical simulations of cardiac electrophysiology encompasses several challenges, ranging from the definition of the computational domain to the steep gradients that characterize this wave propagation problem. High-order methods tackle these specific issues. Multipatch NURBS-based Isogeometric analysis (IGA) eases encapsulating the exact representation of complex computational geometries by means of high-order continuity basis functions. Moreover, as in the Spectral Element Method (SEM), IGA results in very small numerical dissipation and dispersion with respect to linear Finite Elements while also allowing for a faster convergence rate with respect to the number of Degrees of Freedom. We employ the Monodomain equation coupled with physiologically-based ionic models for atrial and ventricular chemical species in several test cases, ranging from a slab of cardiac tissue to realistic four chamber hearts. We perform the numerical discretization by means of IGA and SEM to show the potential of these methods. In the IGA framework, we propose different preprocessing algorithms for surface and volumetric CAD geometries with complex features and multiple holes, such as atria and ventricles. These algorithms allow to obtain geometrically and parametrically conforming NURBS multipatch domains on which electrophysiological simulations may be effectively performed. On the other hand, for SEM, we implement a massively parallel matrix-free solver that enables a very efficient use of high-order polynomials by combining sum factorization and vectorization. As a matter of fact, the matrix-free SEM solver endowed with a suitable matrix-free Geometric Multigrid preconditioner entails up to 50x speed-up if compared to a conventional matrix-based solver.

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Machine learning-based reduced order method for cardiovascular flows with physical and geometrical parameters: application to coronary bypass graft

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Coronary artery diseases represent one of the leading cause of death worldwide. When they occur, some vessels are partially or totally occluded, causing a decreasing blood flow around the heart. Nowadays, coronary artery bypass graft (CABG) is still one of the most effective surgical technique to restore a proper blood supply. However, due to the specific features of each patient, a virtual platform to predict meaningful quantities can help the clinical staff to choose the most suitable configuration. Therefore, the need of quantitative and patient-specific investigations provide a strong motivation in recent times to develop fast and accurate numerical methods.

In this work, a data-driven reduced order method based on machine learning techniques is proposed for a patient-specific geometry of CABG. The domain is provided by Sacco Hospital in Milan and it is composed by the left main coronary artery (LMCA), which divides into the left anterior descending artery (LAD) and the left circumflex artery. A single bypass is performed with the left internal thoracic artery (LITA) on the LAD, due to the presence of a stenosis in the LMCA. The blood flow is modeled by unsteady Navier-Stokes equations and high fidelity solutions are extracted with the finite volume method for primary (velocity and pressure) and derived quantities (wall shear stress). Once the snapshot matrix is assembled, the proper orthogonal decomposition extracts the reduced basis (RB), then the modal coefficients are interpolated using feed-forward neural networks [1, 2]. The reduced solution is the linear combination of RB and modal coefficients. The physical parameter introduced in the reduced framework is the inlet flow rate in the LITA and in the LMCA. In addition, different degrees of stenosis in the LMCA are considered as geometrical parameter. The free form deformation strategy is employed to warp the computational mesh, preserving the number of cells.

A speed-up of about 10^5 shows the powerful capability of our data-driven approach in a complex and patient-specific geometry with respect to more classic projection-based strategies [3, 4].

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A mathematical model to assess the effects of COVID-19 on the cardiocirculatory system

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The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory coronavirus 2 (SARSCoV-2) primarily affects the respiratory system, although other organ systems are involved, like the cardiovascular one [1]. The impairments of the heart deriving from the infection occur mainly in the right ventricle, while consequences on the left ventricle are rarer. Indirect effects on the right cardiac function can stem from an impairment in the pulmonary vascular circulation due to a higher pulmonary arterial pressure and a lower oxygen supply. The interplay of COVID-19 with cardiovascular complications is still far from being fully understood.

We introduced measured data coming from COVID-19 patients in an improvement of the 0D cardiocirculatiory model previously proposed in [2] in order to calibrate the lumped parameter model and to make patient-specific predictions. In particular, this allowed us to study the consequences of the infection of COVID-19 on the cardiocirculatory system representing real patients, retrieving clinical quantities not provided by the measured data and performing a statistical analysis on these quantities.

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An electromechanical heart-torso coupled model for the simulation of ECG

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The electrocardiogram (ECG) is one of the most commonly-used non-invasive diagnostic technique to gain insights into the electrical behavior of the heart. Most importantly, it is used to detect a broad range of cardiovascular diseases. Being able to compute realistic ECGs, however, is not an easy task due to their high sensitivity on physical, numerical and geometrical parameters. Moreover, the electrical sources within the heart move due to myocardial contraction, thus altering the ECG signal.

We present an electromechanical *in-silico* heart-torso (EMT) coupled model. This EMT model is comprised of a 3D-0D closed-loop model for cardiac electromechanics (EM) [1] and a generalized Laplace equation to simulate the torso electrophysiology. To take into account the movement of the torso induced by the EM simulation, we extend the heart displacement to the torso by means of a lifting technique and we incorporate mechano-electric feedbacks in the generalized Laplace equation. Differently from previous work [2], we solve the EMT model on a *reference configuration* to avoid online remeshing at each time step of the numerical simulation. Moreover, we implement a suitable segregated-intergrid-staggered numerical scheme to handle the different space-time scales required by the different core models involved [1].

We perform numerical simulations with the EMT model on a realistic in-silico biventricular geometry and we compare the ECG obtained with different level of byophysical detail in sinus rhythm and under arrhythmia.

Acknowledgment This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 740132).

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Unified meshfree algorithm for modeling cardiac function with the Purkinje network

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Cardiac diseases due to complex mechanisms represent one of the most important category of problems in public health, effecting millions of people each year according to the reports of World Health Organization (WHO). Computational study of cardiac function has received tremendous efforts and is recognized as the community's *next microscope, only better*. Since the heart's physiology involves multiple physics systems, e.g. electrophysiology, (passive and active) mechanics and hemodynamics, an effective integrated computational model is very challenging and requires accurate coupling of all these biophysical systems and asks for advanced numerical techniques. Despite of substantial efforts on integrated cardiac modeling, including fluid-structure interaction (FSI) and fluid-structure-electrophysiology interaction (FSEI), by applying the finite-element method (FEM) and the immersed-boundary method (IBM). An integrative model capable of simulating the fully coupled cardiac function is still in its infancy due to the meshing bottlenecks of the FEM and the Lagrangian-Eulerian mismatches on the kinematics of the IBM.

As an alternative, the meshless, fully Lagrangian smoothed particle hydrodynamics (SPH) method has shown peculiar advantages in handling multi-physics problems thanks to its very feature of representing each sub-system by an ensemble of particles. Since its original inception for astrophysical applications, the SPH method has been successfully applied in a broad variety of applications ranging from fluid mechanics and solid dynamics to multi-phase flows and FSI. As the first attempt towards an integrative meshless model for cardiac modeling, an unified meshless algorithm is first developed for cardiac function in dealing with the following aspects : (i) correct capturing of the stiff dynamics of the transmembrane potential and the gating variables, (ii) robust predicting of the large deformations and the strongly anisotropic behavior of the myocardium, (iii) proper coupling of the electrical excitation and the tissue mechanics for electromechanical feedback. Then, a multi-order scheme is presented to handle the electrical propagation through the Purkinje system and in the myocardium with monodomain/monodomain coupling strategy. To that end, an efficient algorithm is proposed for network generation on arbitrarily complex surface by exploiting level-set geometry representation and cell-linked list neighbor search algorithm. Then, a reduced-order meshless method is developed to solve the one-dimensional monodomain equation to characterize the fast electrical activation through the Purkinje network. Finally, a multi-order coupling paradigm is introduced to capture the coupled nature of potential propagation arising from the interaction between the network and the myocardium.

A fluid dynamics model for the simulation of the whole human heart

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In this talk, we introduce a Computational Fluid Dynamics (CFD) model for the numerical simulation of the whole heart hemodynamics, by accounting for all the physical processes that influence cardiac flows: moving domain and interaction with electromechanics, transitional-turbulent flows, cardiac valves and coupling with the external circulation. We employ the Navier-Stokes (NS) equations in Arbitrary Lagrangian Eulerian (ALE) framework and the Resistive Immersed Implicit Surface (RIIS) method [1] to model the presence of valves in the fluid. To impose a physiological displacement of the domain boundary, we employ the iHEART cardiac electromechanical model of the whole heart (based on [2]). Thus, we obtain a multiphysics one-way coupled electromechanics-fluid dynamics model [3]. To better match the 3D CFD with blood circulation, we also couple the 3D CFD model to a 0D closed-loop circulation model. We obtain a multiphysics and geometric multiscale coupled 3D-0D fluid dynamics model that we solve via a segregated numerical scheme [3]. We carry out numerical simulations for a healthy whole heart geometry and we validate our model by showing that meaningful hemodynamic indicators are correctly reproduced.

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List of Posters

Atrial Digital Twins to Assess Arrhythmia Vulnerability and Guide Ablation Therapy

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The long-term success rate of ablation therapy is still sub-optimal in patients with persistent atrial fibrillation (AF), mostly due to arrhythmia recurrence originating from arrhythmogenic atrial sites outside the pulmonary veins. Computational modeling provides a framework to integrate and augment clinical data, potentially enabling the patient-specific identification of AF mechanisms and the identification of optimal ablation sites. We developed a technology to tailor ablations in anatomical and functional digital atrial twins of patients with persistent AF aiming to identify the most successful ablation strategy [1]. Twenty-nine patient-specific computational models integrating clinical information from tomographic imaging and electro-anatomical activation time and voltage maps were generated [2]. Areas sustaining AF were identified by a personalized induction protocol [3]. State-of-the-art anatomical and substrate ablation strategies were compared to our proposed Personalized Ablation Lines (PersonAL) plan, which consists of iteratively targeting emergent high dominant frequency (HDF) regions, to identify the optimal ablation strategy. Localized ablations were connected to the closest non-conductive barrier to prevent recurrence of AF or atrial tachycardia. The first application of the HDF strategy had a success of >98% and isolated only 5-6% of the left atrial myocardium. In contrast, conventional ablation strategies targeting anatomical or structural substrate resulted in isolation of up to 20% of left atrial myocardium. After a second iteration of the HDF strategy, no further arrhythmia episode could be induced in any of the patient-specific models. The novel PersonAL technology allows to unveil all AF-perpetuating areas and personalize ablation by leveraging atrial digital twins.

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SIMULATION OF VALSALVA MANOEUVRE USING PULSATILE LUMPED MODEL OF CARDIOVASCULAR SYSTEM

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The Valsalva Manoeuvre (VM) is a simple and convenient clinical test that results in sequence of blood pressure variations in the cardiovascular system. It is an important tool to diagnose problems in cardiac as well as autonomic functions since the response to the manoeuvre is associated with the cardiovascular physiology as well as the baroreflex mechanism. A mathematical model for simulating this response can aid in medical education by facilitating analyses of the haemodynamics during and after the manoeuvre.

In previous literature, only non-pulsatile models have been formulated that have been able to simulate the VM response waveform. However, pulsatile lumped parameter models have failed to simulate this response as, the heart rate varies but the blood pressure recovery as expected in later half of phase 2 of the VM are not seen due to the blood pooling in the veins.

In the current study, a pulsatile lumped parameter model of the cardiovascular system is designed and developed, which consists of the four chambers of the heart, the heart valves, the pulmonary circulation, the vena cavae, the aorta and the systemic circulation along with the aortic baroreceptor. A linear Pressure-Volume relation is used for modelling the elastance of the blood vessels. A volume dependent non-linear external pressure has been applied to systemic veins instead of a non-linear elastance. The Frank-Starling mechanism has been simulated using a piecewise linear function of Left Ventricular End Diastolic Volume. The baroreflex system in this model consists of parasympathetic control of the heart rate and the sympathetic control of the heart rate, the peripheral resistance, the contraction of the heart and the venous capacity.

The four phases of the VM as seen in clinical practice are correctly simulated. A fall of aortic pressure from the normal 120/80 mm-Hg to 85/60 mm-Hg in phase 2 is observed before the recovery back to the normal occurs with a Valsalva Ratio of 1.8. The baroreflex sensitivity is varied to visualise insufficient or non existent baroreflex response marked by lack of phase 2 recovery and phase 4 overcompensation.

In the future, the correlation between the various measurements of the autonomic function and the baroreflex sensitivity in the model will be studied.

Intracardiac hemodynamics: a parametric study

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A numerical framework to compute the blood flow within patient-specific human hearts was developed by Chnafa et al. [1, 2]. The geometry of the heart cavities and their wall dynamics were extracted from medical images, and the simulations were made using the in-house YALES2BIO [3] solver in order to obtain a well-resolved description of the turbulent fluctuations within the intra-cardiac flow.

With some improvements, this model will be used in order to validate a methodology named 4D-iVFM [4] for data reconstruction from color Doppler imaging. Namely, 4D-iVFM extends the single component velocity field measured by echocardiography into a 3-components field. The aim of this still on-going research effort is to develop an efficient and accurate tool which can be easily used by cardiologists to determine if a flow is abnormal or not, and prevent certain heart diseases.

In this context, variations of the heart models developped by Chnafa at al. [1, 2] are generated by varying some key features of the flow (frequency of the heartbeat, volume of the heart, shape of the mitral valve) in order to better understand their influence on the cardiac hemodynamics and challenge the 4D-iVFM algorithm in a variety of situations.

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Thermoelectric model to study the cardiac action potential and Arrhythmias

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We propose a new thermoelectric model of the left ventricle to examine the behavior of the heart in cooling situations. A modified Karma model with temperature-dependence is exploited to describe the ion exchange dynamics at the mesoscopic scale while the propagation of the action potential is governed by a mono-domain equation at the macroscopic scale. In addition to perfusion and heat metabolism, we call the Penne equation coupled to the mono-domain equation by using the Joule effect to depict the temperature behavior in the system. Galerkin's finite element method is utilized to start solving the partial differential equations governing the action potential and temperature propagations. The incomplete Lower-Upper decomposition and generalized minimal residual methods are solicited to solve the resulting nonlinear system. The cases of zero temperature and potential gradients are integrated through the scheme of Runge Kutta and the results obtained corroborate well with those of the literature. We analyze the contributions of the nonlinear coupling tensor and arterial temperature on the thermal and electrical responses of the system. The established results reveal that when the temperature in the medium augments, the duration of the action potential decreases and the Joule coupling tensor plays a crucial role in the propagation of the action potential. Moreover, we show that the temperature and the potential are in phase and that the propagation of this potential generates thermal energy. Furthermore, we establish the existence of spiral waves in the heart cell and show that the effect of global cooling helps to modulate or completely dampen these spiral waves, leading to control of the cardiac arrhythmia. In addition, this work puts forward a technique to resolve conduction disorders and cancel them completely. It exhibits increased added value to the use of hypothermia as therapy during cardiac arrest and makes it possible to anticipate and perhaps avoid this pathology.

Keywords: Bioheat equation; mono-domain equation ; hypothermia ; nonlinear tensor ; global cooling ; cardiac arrhythmia.

Stroke risk increase in atrial fibrillation patients: contribution of hemodynamic simulations

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Introduction. Atrial fibrillation (AF) is a major risk factor for ischaemic stroke, associated with a five-fold increase in risk. In clinical practice, the risk of stroke in AF is qualitatively evaluated by the CHA_2DS_2-VASc score. Information on blood flows within the left atrium (LA) and left atrial appendage (LAA) might contribute towards a quantitative ad more objective assessment of stroke risk. To test this hypothesis, we applied a previously developed computational fluid dynamics (CFD) model to enhance the differences in blood flow in normal subjects (NL), patients affected by paroxysmal AF (PAR-AF) and patients affected by persistent AF (PER-AF).
Methods. Patient-specific 3D LA geometry and displacement model throughout the cardiac cycle were derived from dynamic CT imaging. The series of dynamic 3D anatomical models represented the computational domain for the CFD simulations in which inflow initial conditions at the mitral valve and pulmonary veins were derived from PW Doppler measurements. Blood velocity field, vortex structures and blood stasis were assessed for both LA and LAA in 10 NL, 5 PAR-AF and 4 PER-AF.
Results. LA and LAA velocities had different amplitude and distribution in the 3 groups (peak velocity – NL: 50÷60cm/s, PAR-AF: 40÷50cm/s, PER-AF: 15÷25cm/s). The mean velocity at the ostium and inside the LAA was also decreasing from PAR-AF to PERS-AF (mean velocity – PAR-AF: 25÷35cm/s, PER-AF: 8÷20cm/s) showing a wash-out effect strongly reduced (see Figure and Table). A higher number of vortex structures was observed in NL with respect to the AF patients, thus favouring a better washout of the atrial chamber and the LAA.

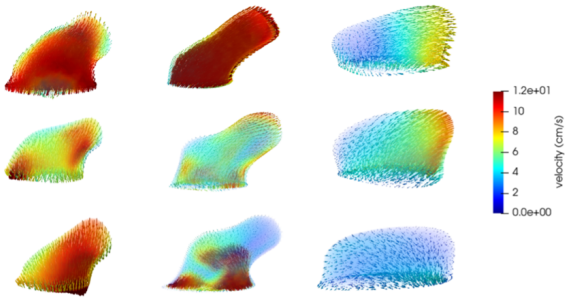

Figure: Velocity fields in 3 representative subjects (NL, PAR-AF and PER-AF in the 1^{st}, 2^{nd} and 3^{rd} column respectively), in three phases of the cardiac cycle (1^{st} row: beginning of ventricular systole, 2^{nd} row: beginning of ventricular diastole, 3^{rd} row: atrial systole).

Cardiac cycle	NL	PAR-AF	PER-AF
Beginning (1° cycle)	500	500	500
End (5° cycle)	5±2	18±3	41±10

Table: Number of particles still present after five cardiac cycles in the LAA populated with 500 particles at the beginning of the simulation.

Conclusions. Results demonstrated the capabilities of the CFD model to reproduce the expected physiological behavior of the blood flow dynamics inside the LA and the LAA, allowing a stratification of the disease progression in terms of changes in the blood velocity, organization of blood flow and quantification of blood stasis. Simulations on a larger population are required to confirm these results.

Correlating electrical dysfunctions and structural remodeling in arrhythmogenic mouse hearts by advanced optical methods

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Severe remodeling processes may occur in the heart due to both genetic and non-genetic diseases. Structural remodeling, such as collagen deposition (fibrosis) and cellular misalignment, can affect electrical conduction at different orders of magnitude and, eventually, lead to arrhythmias. In this scenario, arrhythmogenic cardiomyopathy (ACM) is an inherited heart disease that involves ventricular dysfunction, arrhythmias, and localized replacement of contractile fibers with scar tissue. Unfortunately predicting the impact of fine structural alterations on the electrical dysfunction in entire organs is challenging, due to the inefficacy of standard imaging methods in performing high-resolution three-dimensional reconstructions in massive tissues. In this work, we developed a new full-optical correlative approach to quantify and integrate the electrical dysfunctions with three-dimensional structural reconstructions of entire hearts, both in controls and in a mouse model of ACM. We combined optical mapping of the action potential propagation (APP) in Langendorff-perfused hearts with advances in tissue clearing and light-sheet microscopy techniques. We converted the previously electrically characterized organs into well-preserved and fully-transparent specimens with the SHIELD procedure. A high-throughput light-sheet microscope has been developed following the *MesoSPIM Initiative* to reconstruct the whole mouse hearts with a micrometric resolution, allowing fine quantification of myocytes alignment and fibrosis deposition across the organ. We co-registered APP maps with the 3D high-resolution anatomy, including the fibrosis deposition on each heart, and we are combining this morpho-functional data in a new integrated computational model of the electrical activity. We believe that this promising methodological framework will allow clarifying the involvement of fine structural alterations in the electrical dysfunctions, thus enabling a unified investigation of the structural causes that lead to electrical and mechanical alterations after the tissue remodeling.

An optimization based 3D-1D coupling for the simulation of perfusion and substance delivery in evolving vascular networks

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A new numerical approach is proposed for the simulation of the exchanges between a capillary network and the surrounding tissue. In particular the interplay between blood perfusion and substance delivery is taken into account. Thanks to proper modeling assumptions the capillaries are reduced to their centerline: a well posed mathematical model is hence worked out, based on the coupling between a three-dimensional and a one-dimensional equation (3D-1D coupled problem). Such reduction is known to be extremely convenient, since it avoids the generation of a 3D mesh inside the small inclusions and lowers the computational cost of solving the discrete problem. The actual novelty of our approach lies in the solving strategy, which resorts to the recasting of the problems into a PDE-constrained optimization form. This is achieved by the introduction of two auxiliary variables approximating the value of the unknowns on the vessel wall and of a properly designed cost functional, which is minimized constrained by the 3D-1D set of equations. The resulting strategy appears to be highly robust and flexible in handling geometrical complexities. Thanks to the structure of the functional, the method does not require the 3D mesh and the 1D partition of the centerlines to be conforming, thus making the mesh generation an easy task. This is a great advantage especially in the modeling of evolving microvascular structures, i.e. of the angiogenesis process. Indeed, the 3D mesh does not need to be adapted to newly generated capillary sprouts and the blood perfusion and substance exchange problems can be easily solved at any stage of the network growth. In addition to these phenomena, the angiogenesis model accounts also for the diffusion of a chemotactic growth factor, modeled by a 3D equation with a singular sink term.

Fluid Dynamic Tool for the Analysis of Medical Images

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Higher Order Dynamic Mode Decomposition [1] is an extension of the well-known fluid dynamic tool dynamic mode decomposition. Higher Order Dynamic Mode Decomposition (HODMD) is a fully data-driven method widely used in fluid dynamics applications and in the analysis of complex non-linear dynamical systems. This technique has shown a remarkable performance in numerous applications (turbulent flows, aeroelasticity, bio-inspired marine propulsion...). In our work, we investigate its performance one more time in a new field, which is the medical field. Where HODMD is applied for the first time, to the best of our knowledge, for the analysis of cardiac images. Two different datassets were analyzed in this research, echocardiography datasets and magnetic resonance imaging (MRI) datasets. The echocardiography datasets consists of video loops taken with respect to two view, a long axis view (LAX) and a short axis view (SAX), where each video loop does not surpass 300 frames (snapshots). Meanwhile, the MRI datasets consists of 10 MRI sequences, representing 10 slices of the heart, each sequence has 20 snapshots, covering one full heartbeat. We leverage the HODMD method to accomplish two different tasks:

- Pattern recognition and feature extraction: where echocardiography datasets, taken from mice in both healthy conditions and afflicted by different cardiac diseases, were analyzes and the DMD modes retrieved for each dataset represent the dominant features and patterns for each cardiac disease (more details can be found in our published paper [2]).
- Generate new data: where the HODMD method was able to reconstruct extra snapshots for each slice, extending the number from 20 to 100 snapshots per MRI sequence (further details can be found in [3]).

These applications highlight the utility of the HODMD algorithm in different fields alongside the field of fluid mechanics.

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An automatic approach for left atrium regional segmentation in atrial fibrillation patients by including anatomical variations in pulmonary veins and appendage

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Background: The study of the left atrium (LA) is increasingly attracting the interest of the scientific community. Unlike the left ventricle, a standardized approach for regional segmentation of the LA is not available, and this topic is still a matter of investigation, in particular for arrhythmias characterization. This study sought to define an automatic technique to divide LA into well define standard regions by considering anatomical variations in pulmonary veins (PVs).
Methods and Results: 3D patient-specific anatomical models were derived from CT through an active contour segmentation algorithm. The first detected region was the left atrial appendage (LAA) by applying a thresholding approach based on shape diameter function values. Then the algorithm automatically calculated the barycenter of each PV and excluded the extra PVs by considering their area and position. Furthermore, these points were used to detect the roof and the posterior wall. The line connecting the weighted barycenter of the PVs and the center of the mitral valve (MV) was defined as the long axis of the LA. The annulus of the MV was divided into four equal parts allowing to extract four points. The boundaries of the anterior, inferior, lateral, septal regions were detected considering the position of these four points on the MV and of the centers of the PVs. To validate the results of the proposed approach, an expert electrophysiologist graded the result of segmented regions as: unacceptable, poor, fair, and good. We considered 10 LA models from atrial fibrillation (AF) patients having a varied number of PVs, size, and location and different LAA shapes; the algorithm ran on all cases and successfully divided the LA into seven regions. The grading of the expert was fair and good in 3 and 7 patients, respectively.
Conclusions: This proposed approach was effective in dividing the LA into seven standard regions irrespective of the variation in number, size, and location of pulmonary veins. It represents a first step towards the quantification of regional LA function and contraction. Further testing is required to confirm these results by including a greater number of atrial fibrillation patients.

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Triple decomposition of the velocity gradient tensor in fluid-structure interaction simulations of blood flow through the left ventricle and aortic valve

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Ischemic heart disease is the number one cause of death worldwide. It is caused by atherosclerotic plaque forming a narrowing of blood vessels, where blood clots may get stuck and block the vessel. Such blood clots are formed when platelets in the blood are activated and start aggregating. Platelet activation has been linked to high shear levels in the blood, so to simulate and evaluate the risk for blood clot formation in the blood, models have been designed to extract and evaluate the shear component of the blood flow. However, such models often fail to accurately distinguish the shear component from strain.

Here we demonstrate how the triple decomposition of the velocity gradient tensor successfully distinguishes three separate components of the blood flow: irrotational straining flow, rigid body rotation, and shear flow. The triple decomposition is done by initially performing a similarity transformation of the velocity gradient, effectively aligning the rotation axis of the flow with one of the axes of the coordinate space. We use a real Schur decomposition to perform this coordinate transformation. In the transformed space, the three components may be subtracted simply as a symmetric part (strain), a skew-symmetric part (rotation), and a non-normal part (shear).

To demonstrate the usefulness of the triple decomposition in blood flow, we here show it applied to blood flow in a patient-specific left ventricle (LV) of a human heart, and an idealized model of an aortic valve (AV). In the LV model, the valves are modeled as in- and outflow conditions. The mitral valve opening is a time-dependent projection of the leaflets onto the ventricle wall, whereas the outflow in the LV model is fully open in systole and closed in diastole.

In the idealized AV model, the three valve leaflets are modeled using a fluid-structure interaction (FSI) approach, with the leaflets and walls constructed as elastic solids encompassing a fluid domain. The mesh is monolithic, with the fluid and solid subdomains marked in a single mesh. To capture the deformations of the domains, an arbitrary Lagrangian-Eulerian (ALE) method is used. This lets the mesh deform following the motions of the fluid and solid domains, with the Lagrangian movement of the mesh vertices handled by subtracting a mesh velocity in the Navier-Stokes equations, letting the fluid motion be tracked as Eulerian on the deforming domain. To keep a satisfactory mesh quality throughout the simulations, two mesh smoothing algorithms are used: a Laplacian, and an elastic. To eliminate the need for remeshing mid-simulation, contact between the leaflets is simulated by letting fluid cells between the leaflets switch state from fluid to solid when the distance between the leaflets is small. Thus mesh cells between the leaflets are never at risk of completely collapsing as they get squeezed between the leaflets.

Experimental Characterization of Myocardial Infarction Impact on Porcine Cardiac Tissue Mechanical Response

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Cardiac tissue has been widely analysed due to its complex electromechanic behaviour. From the mechanical point of view, it undergoes very specific conditions during the cardiac cycle including biaxial extension as well as significant compression and shear stresses[1]. It is widely accepted that the this tissue presents an orthotropic or transversely isotropic behaviour[2]. Furthermore, this study is focused on the myocardium infarction, which has a great impact into the mechanical behaviour of the tissue. All this events suggest that it is necessary considering different loading scenarios in order to accomplish a complete three-dimensional characterization. Following this line, several mechanical tests were performed into porcine specimens, including healthy and infarcted hearts.

Porcine left ventricular transmural biopsy specimens were obtained from 12 white pigs. 7 animals were used for control purposes, and 5 animals were infarcted in the anteroapical region by temporal occlusion of the left anterior descending coronary artery. Following the experimental procedures at the literature[3], cyclic biaxial extension tests and triaxial shear tests were performed at samples from different locations across the left ventricle free wall. For future simulations, Costa material model parameters were obtained considering individual mean animal results and global mean results[4].

Results proved a transversely isotropic behaviour for healthy cardiac tissue, obtaining a stiffer response at muscular fibers direction. A stiffer, more isotropic and more exponential-like behaviour was obtained for infarcted tissue, confirming its great impact on the mechanical response of the tissue. Costa parameters were obtained showing great fitting of the experimental behaviour. The presented procedure allowed us to fully characterise the complex nature of the tissue, obtaining consistent results according to literature in every test.

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A novel service for benchmarking myocardial mechanics

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As biomechanical models of the heart have reached maturity, and in anticipation of their wider use bedside, more and more "in-house" software is being developed in the cardiac modelling community to test novel computational techniques for mechanical simulations and image analysis. There is thus a growing need for tools that can be used for standardisation, code testing and error analysis. In this contribution, we present an openly available service for generating benchmarking data sets for myocardial mechanics, which can address these needs.

Our service provides analytical solutions of baseline problems in cardiac mechanics, based on the homogeneous deformations of simple geometries within the hyperelastic material description framework. Specifically, solutions for two axisymmetric geometries, which have been traditionally used to model the left ventricle, are provided: the thick walled cylindrical and spherical shells, under inflation, stretch & torsion (Fig. 1) [1]. Additionally, we also provide solutions for homogeneous deformations of rectangular geometries. The user can select the geometry/size of the data set, the material description and specify the deformed state; and our service provides the continuous kinematics & dynamics, the corresponding boundary conditions, as well as estimates of work and energy. An additional functionality can provide meshes of the reference and deformed geometries with user specified resolution and interpolation schemes. The solutions are implemented in MATLAB R2021b (MathWorks, Natick, MA, USA), and the code is openly available to allow its wide implementation by the community.

The benchmarking data sets generated by our service, despite their simplicity, can represent significant aspects of myocardial mechanics and provide an improved benchmarking test compared to popular alternatives based on rectangular shapes that ignore axisymmetry.

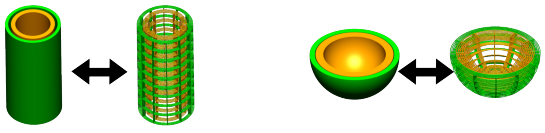

Figure 1: Examples of two benchmarking data sets: inflation of cylindrical and spherical thick-walled shells, visualised with cmGUI (www.cmiss.org/cmgui).

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Calibration of cohorts of virtual patient heart models using Bayesian history matching

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Model calibration (MC) is the process of adjusting the parameters of a model to maximise the agreement between observed data and simulations. Most MC techniques treat each patient independently, making the methods too expensive for clinical timelines. Surrogate models offer a low-cost alternative to full model evaluation and can be used for MC. In this work, we use Gaussian Process Emulators (GPEs) and Bayesian History Matching (BHM) to calibrate cardiac models and show how we can reuse simulations from one subject into another in a pipeline compatible with clinical timelines.

To represent the anatomy, we use a Statistical Shape Model. We ran electrophysiological (EP) simulations using the reaction-eikonal model. As a result, the model can be represented as a vector of scalars (shape coefficients and EP parameters). We study the use of 14 biomarkers (anatomical and functional measurements) to calibrate the model. Thus, we train 14 GPEs, one per biomarker. To fit the models, we followed a BHM strategy. BHM is an iterative method in which in each iteration a region of the parameter space is ruled out if emulation with that set of parameter values produces an "implausible" result. If a set of parameters is unlikely to give a good match, it has a high value of implausibility.

We tested the pipeline using previously reported simulation results as ground truth. We evaluated the initial 14 emulators, training with 280 simulations. The minimum R^2 scores achieved was of 0.99. We also monitored the uncertainty of the emulators that obtain variance quotients (emulator over ground truth) of 1.08, suggesting that the uncertainties of the emulators are comparable to the uncertainties of the ground truth data.

If we compare the GPEs trained using data from previous cases with the GPEs trained using data from a new case, we found that 83.61% of the implausible points in the first scenario were also implausible in the second. This could imply that if we already had simulations for one patient, there is no need to run more simulations for the second patient.

We conclude then that it is possible to reuse results from previous simulations on unseen subjects to save resources on model calibration. This innovation allows for a reference GPE that could be used in a BHM pipeline for any case, without the need of running more simulations.

The open-source LaTeX template, AMCOS_booklet, used to generate this booklet is available at `https://github.com/maximelucas/AMCOS_booklet`