iHEART - MCF2021
Modelling the Cardiac Function
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Reidmen **Aróstica** - Bernoulli Institute, University of Groningen (NL)

Nicolas A. **Barnafi** - Dipartimento di Matematica "F. Enriques", Universitià degli Studi di Milano (IT)

Jochen **Brenneisen** - Institute of Biomedical Engineering, Karlsruhe Institute of Technology (DE)

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Numerical simulation of cardiac electromechanics: towards multiscale and multiphysics modeling of the whole heart

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We present recent advancements in the framework of the *iHEART* project on the integration of mathematical and numerical models for the simulation of the whole cardiac function. After an overview of coupled models for the numerical simulation of the human heart, we detail our contributions to the electromechanics of the ventricles. Specifically, we couple state–of–the art models for the electrophysiology of the tissue, mechanical activation at the cellular level, and the passive mechanical response of the muscle, thus yielding a coupled electromechanical problem within the active stress paradigm. Our multiscale model for cardiac electromechanics accounts for miscroscopic active force generation at the cellular level by exploiting model order reduction techniques based on Machine Learning algorithms. In addition, our 3D electromechanical model is coupled with a 0D, closed-loop model of the systemic and pulmonary blood circulations, other than of the remaining cardiac chambers. We consider the space approximation of the Partial Differential Equations therein involved by means of the Finite Element method and the time discretization by using Backward Differentiation Formulas. We numerically solve the coupled electromechanics problem by exploiting intergrid transfer operators, as well as staggered approaches for realizing the numerical coupling. We present and discuss several numerical results of the cardiac electromechanics problem in the human heart, both in phsyiological and pathological conditions, obtained in the high performance computing framework.

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Analysis of functional and structural abnormalities in arrhythmias based on high-density electro-anatomical maps

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Ultra high-density mapping systems are currently used worldwide to guide electrophysiologists in the definition of the ablation strategy. The acquired data are post-processed to describe, with high resolution, the wavefront propagation pattern (activation map) and some electrophysiological properties of the tissue (such as low voltage and high-fractionation areas). Their interpretation is subject to an ongoing discussion, as is the development of new ablation protocols.

In this talk we present our strategy for the analysis and interpretation of electroanatomical maps aimed at quantitatively characterizing the electrophysiological substrate in patients suffering from atrial fibrillation. Specifically, we process EA maps to identify slow conduction (SC) corridors, wavefront collision, and pivot points by numerically approximating conduction velocities from activation time data. From the analysis of these electrophysiological properties, we show that the progression of the disease is directly linked with the distribution and severity of slow conducting areas and pivot points. Moreover, this analysis supported by numerical simulations, also shows that substrate characteristics strongly influence the shape of reentry circuits and their sustainment. The presence of multiple slow conduction areas offers anchoring to reentry circuits. Their dynamics strongly depend on functional phenomena, such as head-to-tail interactions, affecting directly their stability and sustainment.

Cardiac Fluid-Structure Interaction

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Fluid-structure interaction is a fundamental aspect of cardiac dynamics, and it is critically involved in both the normal function of the cardiac valves and also disorders of native and prosthetic heart valves. This talk will describe ongoing work to develop effective numerical methods for simulating cardiac fluid-structure interaction via extensions of the immersed boundary method. It also will detail work that aims to apply these methods to create a validated platform for modeling the performance of both natural and prosthetic heart valves. Results will be presented from simulation studies of natural and prosthetic aortic valves, with a focus on in vitro models that can be directly compared to experimental studies, and from a fluid-structure interaction model of the human heart that accounts for interactions among the heart, its valves, the great vessels, and the blood. This whole-heart model, which includes detailed descriptions of all four valves, uses constitutive models parameterized using tensile test data from human tissue specimens.

Precision Medicine in Human Heart Modeling

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Precision medicine is a new frontier in healthcare that uses scientific methods to customize medical treatment to the individual genes, anatomy, physiology and lifestyle of each person. In cardiovascular health, precision medicine has emerged as a promising paradigm to enable cost-effective solutions that improve quality of life and reduce mortality rates. However, the exact role in precision medicine for human heart modeling has not been fully explored. Digital twins, virtual patients based on computational modeling and simulation, have advanced as an important technology to improve the efficiency of clinical trials for new device designs. In the context of cardiac device design, efforts are underway to explore the potential of human heart simulators as a digital evidence for new cardiovascular device approvals. The objectives of these in-silico clinical trials are to reduce animal testing and minimize the number of required patients while still ensuring safety and efficacy of the novel device.
The ENRICHMENT trial, a new in-silico clinical trial for cardiac device design, combines digital evidence from simulations with physical evidence from real patients and assesses model credibility in accordance with engineering standards. The trial focuses on functional mitral regurgitation and its treatment using edge-to-edge repair. To accurately simulate the clinical endpoints of these functional mitral regurgitation patients, their computational models include their annulus, their mitral valve, their papillary muscles, their chordae, and their left ventricle. This "left ventricle-mitral valve in-silico model" will be presented. Additionally, three other studies of cardiac function modeling will be presented. These include: (1) a novel treatment for heart failure that significantly reduces adverse left ventricular remodeling; (2) simulations coupling the aorta and left ventricle that provide meaningful insight into myocardial biomechanical derangements that accompany aortic stenosis; and (3) a novel approach to left atrial appendage closure that leaves no device behind.

Cardiac imaging: what are the clinical needs and what are the gaps to be filled

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Advanced cardiovascular imaging has emerged in recent years as a key junction in the diagnosis and therapeutic management of patients with heart disease. In fact, the multimodality approach that includes echocardiography, cardiac CT and cardiac MRI provides an integration of fundamental data to choose the most appropriate and personalized procedure for the patient. This has been made possible thanks to the technological implementation of diagnostic equipment. Among the main fields of application emerges the non-invasive study of the coronary arteries, the non-invasive evaluation of coronary flow and myocardial perfusion, the study of myocardial texture, the study of 4Dflow. If on the one hand this abundance of data represents an important diagnostic resource, on the other hand the management of these datasets with the standard approach based on physician interpretation has limitations. The aim of this report is to summarize the state of the art in cardiovascular imaging, which are the clinical needs that imaging currently covers and which are the missing gaps that need artificial intelligence or mathematical modeling approaches to be developed.

Space–Time Flow Computation with Contact Between the Heart Valve Leaflets

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In computation of flow problems with moving boundaries and interfaces (MBI), including fluid–structure interaction (FSI), high-resolution boundary-layer representation near fluid–solid interfaces requires mesh-resolution control near the interface. Moving-mesh methods, such as the Space–Time Variational Multiscale (ST-VMS) method [1], meet that requirement. In an FSI or MBI problem with contact between solid surfaces, until recently, one had to either give up on representing the actual contact and leave a small gap or give up on using a moving-mesh method and thus give up on having high-fidelity flow solution near the solid surfaces. The ST Topology Change (ST-TC) method [2] changed all that. Now we can both represent the actual contact and have high-fidelity flow solution near the solid surfaces.

With the ST-TC and two other special ST methods around the core method ST-VMS, we have created a powerful computational framework, the "ST-SI-TC-IGA" [3]. The two other methods are the ST Slip Interface (ST-SI) method [4] and the ST Isogeometric Analysis (ST-IGA) [1, 5, 6]. The ST-SI-TC-IGA is enabling high-fidelity flow analysis in some of the most complex problems.

In this talk, we will describe the ST-SI-TC-IGA and present examples of heart valve computations [2, 7, 3, 8, 9].

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Personalized Simulations + AI: Could it be a Recipe for Success?

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In this overview presentation, we summarize a number of translational studies aimed at addressing important questions in clinical cardiology and electrophysiology. The goal here is to demonstrate the synergy between mechanistic personalized computational modeling and machine learning in predictions of disease progression and sudden death for a number of conditions. We will focus on several studies.

In the first study, we developed and evaluated a methodology that combines machine learning (ML) and personalized computational modeling to predict, before pulmonary vein isolation (PVI), which patients are most likely to experience atrial fibrillation (AF) AF recurrence after PVI. This retrospective study included 32 patients with paroxysmal AF and MRI. For each patient, a personalized computational model of the left atrium simulated AF induction via rapid pacing. Features were derived from pre-PVI MRI images and from results of simulations of AF induction. The most predictive features were used as input to an ML classifier, which was trained, optimized, and evaluated with 10-fold nested cross-validation to predict the probability of AF recurrence post-PVI. In our cohort, the ML classifier predicted probability of AF recurrence with a validation area under the curve of 0.82, indicating that ML and personalized computational modeling can be used together to accurately predict, using only pre-PVI MRI scans as input, whether a patient is likely to experience AF recurrence following PVI, even when the patient cohort is small.

Another study focused on cardiac sarcoidosis (CS) - an inflammatory disease characterized by formation of non-caseating granulomas in the heart, which is associated with high risk of sudden cardiac death (SCD). Current "one-size-fits-all" guidelines for SCD risk assessment in CS result in a low rate of appropriate primary prevention. Here, we present a two-step precision risk prediction technology for CS patients. First, a patient's arrhythmogenic propensity arising from heterogeneous CS-induced ventricular remodeling is non-invasively assessed using a novel personalized MRI and PET fusion mechanistic model. The resulting simulations of arrhythmogenesis are fed, together with a set of imaging and clinical biomarkers, into a supervised multi-variable classifier. In a proof-of-concept retrospective study of 45 patients, the technology achieved AUROC of 0.754 [95%CI:0.710-0.797]. It significantly outperformed three common clinical metrics, highlighting its potential to transform risk stratification of CS patients.

Finally we present a project on COVID-19 and its cardiovascular (CV) manifestations. Current risk prediction for CV complications in COVID-19 is limited and existing approaches fail to account for the dynamic course of the dis-

ease. Here, we develop and validate the COVID-HEART predictor, a novel continuously-updating risk prediction technology to forecast CV complications in hospitalized patients with COVID-19. The risk predictor is trained and tested with retrospective registry data from 2178 patients to predict two outcomes: cardiac arrest and imaging-confirmed thromboembolic events. In validating the model, we show that it predicts cardiac arrest with a median early warning time of 14 hours and an AUROC of 0.93, and thromboembolic events with a median early warning time of 168 hours and an AUROC of 0.85. The COVID-HEART predictor is anticipated to provide tangible clinical decision support in triaging patients and optimizing resource utilization, with its clinical utility potentially extending well beyond COVID-19.

Cardiovascular Mathematics in the Era of Data: Developing and Reducing Models for the Clinics

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Working in Cardiovascular Mathematics is a rewarding experience, as one has the opportunity to bridge theory and practice with the ultimate purpose of improving healthcare. The reliability and efficiency required by the clinical timelines naturally triggered the development of data assimilation, uncertainty quantification, and reduced-order modeling techniques. The integration of Data-driven and Model-driven approaches is crucial in this field, where each patient may represent a different and unique challenging problem. The talk will cover some applications with the common denominator of bringing state-of-art numerical methodologies to clinical problems with a sophisticated combination of data and models. In particular, we will address the *fast estimation of the cardiac conductivity with reduced order models.*

We will also address applications of coronary stenting and pediatric surgical planning (Total CavoPulmonary Connection).

The underlying rationale to all these applications is that *a collaborative attitude of Model- and Data-driven approaches should be preferred to any competitive vision, as they have complementary advantages that will consolidate the role of cardiovascular mathematics in clinics.*

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Introducing life^{x}, a New High-Performance Library for Integrated Heart Simulations

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In recent years computational cardiology has assumed a key role to investigate and better understand the cardiac function and to provide answers to related clinical questions.

However, modeling the whole heart function involves several challenges related to its intrinsic complexity: a satisfactory model must be able to describe a wide range of different processes, such as the evolution of action potentials and ionic currents in myocardial cells, the mechanical deformation caused by the muscle contraction, the anisotropy due to the spatial orientation of myocardial fibers, the dynamics of the blood flowing inside the heart chambers and through valves, the influence of the pulmonary and systemic circulatory loops and the myocardial perfusion itself. All such processes feature terribly different temporal and spatial scales, thus hampering the development of an effective and efficient integrated computational model.

To our knowledge, despite different attempts have emerged to propose community standard software addressing some subsets of the aforementioned models, no library is currently available for fully integrated cardiac simulations.

Here, we present life^{x}[1], a new scientific library focused on mathematical models and numerical methods for high-performance cardiac simulations. life^{x} implements different *core models* describing all the physical phenomena involved (electrophysiology, passive and active mechanics, fluid dynamics, circulation, perfusion, ...). On the one hand, multi-scale and multi-physics coupling schemes are targeted for integrating such models together on a single domain. On the other hand, multi-domain approaches are also addressed for solving each of the core models and their couplings on multiple cardiac chambers simultaneously.

life^{x} exploits the most modern programming techniques available in the C++17 standard and is based on the deal.II[2] core, providing effective data structures for a variety of finite element problems exposing high-level interfaces to Trilinos[3], PETSc[4] and to built-in linear algebra backends. In this regard, life^{x} provides a flexible framework for simulating complex cardiac models without sacrificing the numerical accuracy, the usability and the performance. Accurate and efficient solvers, preconditioners, partitioning schemes for (non-)linear, time-evolving problems are integrated. The whole library exploits parallel computing paradigms and is shown to be scalable.

[1]https://lifex.gitlab.io/lifex/
[2]https://www.dealii.org/
[3]https://trilinos.github.io/
[4]https://www.mcs.anl.gov/petsc/

`life`[x] also welcomes input from clinical data for personalizing the mathematical models within patient-specific and pathological contexts, such as in the presence of ischemia, ventricular tachycardia (VT), atrial fibrillation (AF), left bundle branch block (LBBB), systolic anterior motion (SAM) of the mitral valve, and so forth.

Its current and future development will be released open-source to the general public, thus providing the scientific community with an invaluable tool with the two-fold goal of improving the current understanding of the complex heart function and of supporting clinical decisions with non-invasive *in-silico* experiments.

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

A physiological benchmark for cardiac mechanics

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In cardiovascular mechanics, reaching consensus in simulation results under a specific range of physical parameters allows to obtain comparable results when estimating those parameters from clinical data and to make the results from different studies reproducible by other groups. Moreover, an analysis and comparison among groups on how the numerical setup (e.g. polynomial degree of basis functions, numerical quadratures, time integrators) affects the results is also crucial for reproducibility purposes.

Land et al. [3] proposed a first benchmark containing some of the features that cardiac mechanics models typically include. However, some important aspects were lacking, like inclusion of physiological passive and active modeling, as well as realistic geometrical dimensions, boundary conditions, and time dependent effects (i.e. inertia and viscosity).

Here we aim to propose a new set of cardiac benchmark problems and solutions for assessing passive and active material behavior under the well-stablished model proposed in Hotzapfel & Ogden [2], viscous effects, and pericardial boundary as proposed in Pfaller et al. [4]. The problems proposed include simplified analytical fiber definition and a simplified active stress model by Bestel et al. [1], allowing straightforward testing and validation with already developed solvers.

We will detail the partial-differential equation to be solved, and show results for different set of physical parameters and numerical setups to encourage the participation and discussion with other research groups. A first comparison of the solvers of Groningen and Munich has been successfully performed. We warmly welcome more groups interested to participate.

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Scalable domain decomposition preconditioners for cardiac mechanics

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Nonlinear elasticity is at the core of all cardiac modeling software, and its numerical approximation is very challenging. The most widely used method for this is the Newton-Raphson method, which consists in an iterative linearization scheme performed at the level of the momentum conservation equation. The solution of the linear system of equations arising from such procedure is very computationally expensive, and improving its efficiency is the main goal of our work. We focus on the preconditioning of such problem by means of the Balancing Domain Decomposition by Constraints (BDDC) preconditioner, which belongs to the family of non-overlapping domain decomposition methods. These methods have been proved to exhibit quasi-optimal conditioning for the linear elasticity problem, which makes them specially well-suited for high-performance environments.

To obtain the best possible performance of the preconditioner, we execute tests to obtain i) the degrees of freedom to be used for strong continuity across processors and ii) the best available direct solver (SuperLU, MKL, PETSc, Mumps). After this, we compare the performance of the BDDC and AMG preconditioners for first and second order conforming finite elements, where our experiments show that the BDDC preconditioner outperforms AMG when using a large number processors. This is further observed when using second order elements, where multigrid methods are known to be less performant, and instead BDDC presents very similar performance to the first order case.

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A sequential coupling approach for fluid-structure interaction in a patient specific whole heart geometry

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In order to be used in a clinical context, numerical simulation tools have to strike a balance between accuracy and low computational effort. For reproducing the pumping function of the human heart numerically, the physical domains of cardiac continuum mechanics and fluid dynamics have a significant relevance. In this context, fluid-structure interaction between the heart muscle and the blood flow is particularly important: Myocardial tension development and wall deformation drive the blood flow. However, the degree to which the blood flow has a retrograde effect on the cardiac mechanics in this multi-physics problem remains unclear up to now.

To address this question, we implemented a cycle-to-cycle coupling based on a finite element model of a patient-specific whole heart geometry. The deformation of the cardiac wall over one heart cycle was computed using our mechanical simulation framework. A closed loop circulatory system model as part of the simulation delivered the chamber pressures. The displacement of the endocardial surfaces and the pressure courses of one cycle were used as boundary conditions for the fluid solver. After solving the Navier-Stokes equations, the relative pressure was extracted for all endocardial wall elements from the three dimensional pressure field. These local pressure deviations were subsequently returned to the next iteration of the continuum mechanical simulation, thus closing the loop of the iterative coupling procedure.

Following this sequential coupling approach, we simulated three iterations of mechanic and fluid simulations. To characterize the convergence, we evaluated the time course of the normalized pressure field as well as the euclidean distance between nodes of the mechanic simulation in subsequent iterations. For the left ventricle (LV), the maximal euclidean distance of all endocardial wall nodes was smaller than 2 mm between the first and second iteration. The maximal distance between the second and third iteration was 70 μm, thus the limit of necessary cycles was already reached after two iterations.

In future work, this iterative coupling approach will have to prove its ability to deliver physiologically accurate results also for diseased heart models. Altogether, the sequential coupling approach with its low computational effort delivered promising results for modeling fluid-structure interaction in cardiac simulations.

A staggered scheme for the numerical simulation of the heart: towards full coupling of 3D electrophysiology, mechanics and fluid dynamics

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The mathematical modeling and numerical simulation of cardiac physiology is challenging due to the different spatio-temporal scales and physical phenomena involved in heart function. We propose a mathematical model that couples electrophysiology at the cellular and tissue scale, a detailed model of active muscular contraction, myocardium solid mechanics and 3D blood fluid dynamics, resulting in a fully coupled model of the heart function that incorporates the fluid-structure interaction (FSI) between the cardiac muscle and the blood. We introduce a staggered approach for the numerical solution of the integrated model, segregating the solution of electrophysiology from that of the FSI equations, while retaining implicit coupling of fluid and structure to preserve stability. Numerical simulation results for a realistic left ventricle are presented, showcasing the ability of the model and solver to recover the major characteristics of a physiological heartbeat.

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Image-based modelling of left ventricular function using physics informed neural networks

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We present a framework for the simulation of left ventricular cardiac function from medical images. We first derive a computational mesh from cardiac Magnetic Resonance exams using a rendering approach based on a left ventricular shape model [1]. For this task, left ventricular masks are obtained on all images using a segmentation network and are then positioned relative to one-another in 3D space. Then, the parameters of the shape model are fit to obtain a volumetric mesh for the best match with the 2D masks. The proposed method does not require any ground-truth mesh training data. Additionally, it corrects for slice misalignment and can propagate these corrections back to the original image data. The method is expressive enough to capture diverse morphology, and is also differentiable, allowing for direct inclusion in deep-learning pipelines and, thanks to its modular structure, it can be applied to any cardiac image modality upon selection of an appropriate segmentation network. Also, this approach performs automatic parametrization of the anatomy and definition of a local physiological coordinate system, suitable for simulation. Fitting a mesh to the selected cardiac phase of an exam containing 12 slices takes less than one minute on a TitanX GPU (including all segmentations and pre-processing).

After the generation of the anatomy, left-ventricular biomechanics is simulated using a physics informed neural network [2]. It is trained to predict the weights of a set of radial basis functions capturing characteristic deformations of left ventricles using a cost function representing the energy potential functional specifically tailored for hyperelastic, anisotropic, nearly-incompressible active materials. The neural network is coupled with a simplified circulation model and can efficiently generate computationally inexpensive estimations of cardiac mechanics. Our model is 30 times faster than our reference Finite Element model, including training time, and provides satisfactory average errors in the predictions of ejection fraction (-3%) and myocardial strains (14%). The model can be used to estimate cardiac function for multiple operative conditions at a very low computational cost, and to investigate the impact of the uncertainty on physiological parameters on metrics of interest.

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Studying the effects of pulse wave propagation on cardiac function with a 3D model of cardiac electromechanics coupled to a 1D model of the cardiovascular system

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The influence of increased vessel wall stiffness and pulsatile load on the circulation and the heart function is documented not only for cardiovascular events but also for ventricular dysfunctions. Thus, computer models of cardiac electromechanics (EM) shall integrate effects of the circulatory system on heart performance for clinical applications. In order to ensure a satisfactory trade-off between accuracy and computational cost, simplified representations of the circulation are adopted. In this talk, we describe a novel strategy for a coupled model based on a 3D EM model of the heart function [1, 2], together with a 1D model of blood flow in the arterial system [3]. The coupling approach is based on the resolution of a saddle-point problem for the volume and pressure in the cavity. As a first illustration, we show the effects of vessel stiffening in a configuration composed by a 3D model of the left ventricle (LV) coupled to an arterial outflow consisting of a 1D viscoelastic tube with stenosis [5] and lumped terminal boundary conditions. As a second example, we analyse the results for a coupled system consisting of the LV and an aortic vessel network with 116 vessels [4] in two physiological configurations, corresponding to a healthy younger and a healthy older individual, in order to explore the effects of ageing on cardiac function. Finally, from the perspective of model personalisation, we show the results of a preliminary sensitivity analysis on the model. The use of 1D arterial models enables to efficiently capture the effects of vascular changes and distributed properties, since they allow for a more accurate representation of the impact of pulse wave propagation on the circulation and cardiac function. Therefore, the use of our 3D-1D coupled model has great potential in understanding the impact of haemodynamic mechanisms in a broad spectrum of cardiovascular pathologies.

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Electrophysiology of the Zebrafish Heart: A Computational Model

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Aims: Recent studies suggest that the physiology of the zebrafish heart resembles that of the human in many aspects, namely: spontaneous heart rates are found to be similar, its cardiac action potential much more closely resembles that of the human, and QT-interval in electrocardiograms is heart rate dependent. Thus, zebrafish has been proposed as a potential model for genetic and pharmacological screening of factors affecting heart function. However, despite this rising interest, very few studies concern the development of computational models.

Methods: This work develops a full electrophysiology model of the heart + body of a zebrafish 3 days post fertilization. The model is composed of three main parts: body, heart chambers, and heart myocardium[1]. The latter is, in turn, divided into four regions: ventricular wall, atrio-ventricular band (AV band), atrial wall, and sinoatrial region (SAR), where the stimulus is delivered. The heart tissue is considered isotropic. The action potential (AP) of the different heart regions has been simulated using the four-variables minimal model (BV4)[2]. The BV4 model has been adjusted to fit experimentally reported AP of the zebrafish together with AP-duration restitution curve data. The bidomain model has been used to solve the coupled problem. The complete set of equations have been solved in the software LS-DYNA (ANSYS, Canonsburg, PA, USA) using a semi-implicit numerical scheme with a fixed time step of 0.02 ms. The model has been stimulated at a BCL of 500 ms.

Results: The activation times and sequence were found to be in line with experimental data. Namely, the results showed an activation time of 34 ms for the atrium starting from the SAR region where the stimulus has been delivered, followed by a delay of 25 ms in the AV band, and an activation time of 26 ms for the ventricle that show an apex-to-base depolarization pattern. Furthermore, the main characteristics of the AP morphology i.e., APD_{90}, AP amplitude, and maximum and minimum AP derivative, have been evaluated and compared with values reported in literature. In addition, with this model, a dipolar ECG can be obtained to be compared to in vivo recordings found in literature.

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In Silico Investigation of SARS-CoV-2 Inhibitor Hydroxychloroquine towards Sinoatrial Arrhythmogenesis

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The outbreak of coronavirus disease 2019 (COVID-19) poses a serious threat to global public health and local economies. The combination of antimalarials hydroxychloroquine (HCQ) with azithromycin has confirmed the anti-viral treatment on an urgent basis in limited clinical studies. With the growing interest in the potential use of HCQ for the treatment of COVID-19, it is essential to reflect on the risks of treatment, particularly for cardiac toxicity. The purpose of this in-silico study was to investigate the propensity of HCQ on various ionic mechanisms to cause diverse effects on the sinoatrial action potential (AP). The sinoatrial node cell (SAN) was described as an equivalent electrical circuit with a number of variable conductances representing voltage-gated Na+ channels (INa), voltage-gated Ca2+ channels (ICa), voltage-gated K+ channels (IK), Ca2+-dependent K+ channels (IKCa) and hyperpolarization-activated current (funny current, If). A HCQ drug model for the multiple ion channels was simulated after mining data from experimental studies. The biophysically altered ionic currents (ICa, IK, and If) were integrated into the single one-dimensional SA node electrophysiological model. The resting membrane potential was set at 80mV. The modulating effects of ICa, IK, and If are simulated after applying 1 micro Molar HQN. The steady-state values for activation and inactivation parameters are altered. The If current was substantially reduced with comparison to other currents. As a consequence, the model evoked SAN AP prolongation, and the frequency was reduced. The results show that the modified funny current plays an important role in reducing the frequency of the spontaneous APs at SA node. The model successfully reproduces both ionic currents and APs observed in intracellular recordings from individual SAN cell. As Hydroxychloroquin reduces the frequency rate of the spontaneous AP firing, we should prevent it as a potential drug against COVID-19. It also supports the FDA guideline against using HCQ for COVID-19.

A deep learning-based operator approximation for model order reduction in cardiac mechanics

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Simulating cardiac mechanics with high-fidelity full-order models (FOMs) is a very demanding task from a computational standpoint, especially when aiming at spanning a broad range of virtual (e.g., pathological) scenarios. Reduced-order models (ROMs) have been developed in order to replace the FOM solution by a problem of much smaller dimension. Classical projection-based ROMs, built, e.g., through the Reduced Basis (RB) method, have been successfully applied to cardiac mechanics, so far under a quasi-static assumption, requiring an intrusive hyper-reduction stage to make the assembling of the ROM independent of the FOM dimension [1].

To deal with nonlinear elastodynamics problems and overcome the hyper-reduction bottleneck, we propose a novel strategy for learning nonlinear ROM operators using deep neural networks [2]. The resulting Deep-HyROMnet is a physics-based model, still relying on a POD-Galerkin strategy, but employing a deep neural network architecture to approximate reduced residual vectors and Jacobian matrices once a Galerkin projection has been performed.

The proposed approach has been assessed in several scenarios dealing with the myocardial displacement of a patient-specific left ventricle, suitably coupled with a 0D lumped-parameter windkessel model for external blood circulation and a surrogate active tension model, yielding extremely good approximation properties in terms of both accuracy and computational speed up.

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Fibonacci sequence in the universe, nature and heart

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Leonardo Bonacci from Pisa (son of Bonacci = fi' Bonacci), in his "Liber Abaci" (Book of Calculus, 1202) introduced the so-called *"Modus Indorum"* (method of the Indians), today known as the Hindu-Arabic numeral system. *"Liber Abaci* posed and solved a problem involving the growth of a population of rabbits based on idealized assumptions. The solution, generation by generation, was a sequence of numbers later known as "Fibonacci numbers". The resulting "Fibonacci spiral", created by drawing circular arcs connecting the opposite corners of squares in the Fibonacci tiling, approximates the spiral obtained with the "Golden Ratio", introduced by Pythagoras (500 B.C.) and Euclid (300 B.C.), but never quoted by Fibonacci.

The harmony and the complexity of the "Fibonacci spiral" have attracted the attention of researchers since the 15th century, including Leonardo da Vinci.

After since, the presence of spiral shape entities has been documented in the universe, nature and heart.

In the universe, the spiral appears in the shapes of gargantuan relatives, from the feature of the cosmic galaxies, to the hurricanes, with right or left direction of their rotation accordingly with the Northern or Southern hemisphere, to the microscopic dimensions of the ionic channels, such as the Calcium ions, the actin/myosin complex, and the helix of DNA.

In nature, the spiral is easily recognizable in the animal world, including the shape of horns in muttons, snails, shells. In the plant world, the trees have a spiral distribution of their branches, such as in oaks, elms, cherry and pear trees, and spiral features are present as well as in flowers and in pine cones.

As architecture copies nature, architects have used the "Fibonacci spiral" to create design constraints, from the Renaissance to the contemporary design of modern architecture. The spiral was used even before the publication of the *"Liber Abaci"*, as it has been found in the pillars of the ancient Greek temples, and before in the bas-reliefs of the Neolithic tombs.

The "Fibonacci Sequence" also plays a big part in harmony and musical scales. Composers and instrument makers have been using the "Fibonacci Sequence" and the Golden Ratio for hundreds of years to compose and create music. The notes produced by the white and black keys of a piano follow the "Fibonacci Sequence", as well as the structure of the violin follows the "Golden Ratio".

The first known representation of the spiral in the heart was on the sketch of the leaflets of the aortic valve by Leonardo da Vinci, who also recognized the asymmetrical feature of the heart.

The human body, although bilaterally symmetrical in appearance, shows a considerable left-right asymmetry involving many internal organs in their position and shape, and this is particularly valid for the heart.

The external aspect of the cardiac outflow tracts is complex and harmonic, as

all spirals in nature. The right ventricular infundibulum is anterior and right-sided, whereas the pulmonary artery runs to the left and posteriorly. The left ventricular outflow tract arises posteriorly and left-sided, whereas the aorta, crossing posteriorly to the pulmonary artery, becomes anterior and right-sided. The comprehensive aspect of the cardiac outflow tracts results in a right-handed spiral pattern with a clockwise rotation seen from the apex. The spectacular morphology of the complex geometry of the cardiac outflow tracts represent admirable examples of anatomical and functional equilibrium within the heart, with a spiral shape.

Randomization or inversion of such spiral asymmetry results in severe congenital heart defects, with effects ranging from prenatal death in 20% and 10% of stillbirths, to a very defective postnatal life, requiring multiple and complex surgical procedures. Many of these congenital heart defects are caused by the initial breaking of the spiral symmetry and the early control of lateralization.

Recent embryology studies have documented the origin of these complex defects in abnormal laterality genes, similar to the genes present in animals and trees.

A 3D Nitsche-XFEM method for immersed FSI with thin-walled solids

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The mechanical interaction of an incompressible viscous fluid with an immersed thin-walled structure appears in a wide variety of engineering fields (from micro-encapsulation to aeroelasticity) and is particularly ubiquitous in nature (from heart valves to the wings of a bird). Nitsche-XFEM based unfitted mesh approximations (see, e.g., [2, 1, 4]) are very appealing from a mathematical and computational point of view since they allow for weak and strong discontinuities (which guarantees optimal accuracy) and are Lagrange multiplier free (no additional unknowns are introduced). This superior accuracy comes at a price: these methods demand a much more involved computer implementation and require a specific track of the interface intersections, with respect to traditional fictitious domain methods(see [5, 6, 7]), particularly in the 3D case with unstructured meshes (see [1, 4, 3]). Indeed, besides the evaluation of the intersection between the fluid mesh and the evolving deformed solid mesh, the methods require (for consitency) the evaluation of (volume and surface) integrals on the resulting cut elements (arbitrary polygons), which is generally handled via local mesh generation (see, e.g., [1, 4, 3]). In this work, we present and extension to the 3D case of the Nitsche-XFEM method introduced in [1]. The main contributions are:

- a simple approach to treat the case of interfaces with boundaries inside the fluid mesh (so called tip interfaces);
- an efficient and robust intersection algorithm, which avoids to resort to blackbox mesh generators.

Numerical results in 3D, motivated by bio-medical applications and involving dynamic interfaces, illustrate the capabilities of the proposed approach.

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Terminating Spiral Waves with a Single Designed Stimulus: Teleportation as the Mechanism for Defibrillation

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Rotating spiral waves are a striking driver of complexity in many excitable systems. In the heart, spiral waves of electrical activity induce deadly arrhythmias and must be eliminated to restore a healthy rhythm. A significant topological constraint of excitable systems is that spirals can only be destroyed in oppositely rotating pairs. In this talk, I will first show how to automatically design a minimal shock stimulus capable of eliminating every spiral wave simultaneously. In practice, applying such a stimulus is feasible only for extremely artificial setups. Nevertheless, the underlying topological mechanism is responsible for all successful defibrillation, including traditional high-energy single-shock therapies.

Mathematical description of linear-core rotors in terms of phase defect lines.

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During cardiac arrhythmias, electrical activation can organize itself into dynamically moving vortices called rotors. However, the precise nature of the rotor core is still under discussion, and such knowledge is imperative in order to further unravel the fundamental dynamics of rotors, as well as to detect and control them in real tissue.

Both early pioneering work and recent observations report conduction block lines at the core of cardiac rotors, which is confirmed in many ionic cell models. We demonstrate that if the rotor core exhibits a region where newly excited tissue meets unrecovered tissue, this region cannot be a classical phase singularity. Rather, in this situation an extended line of conduction block is present, which is in the phase space picture equivalent to a mathematical branch cut from complex analysis.

We discuss the implications of this viewpoint in terms of further theory development, rotor detection in numerical models and experiments, comparing different cardiac models with each other, and potential clinical use in the long term.

Tuning parameters across the monodomain, bidomain, and EMI models in cardiac electrophysiology

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Much research has been performed in the last decades to study the electrical activity in cardiac muscle. Numerical simulations are particularly important to obtain valuable conclusions without the need of in-person laboratory tests. In this talk, we focus on the parametrization of the well-known monodomain and bidomain models as well as the newly developed EMI model in cardiac electrophysiology. Specifically, we investigate the values of the parameters in each model that can provide us with a similar behaviour of the electric potential in cardiac muscle. The results presented here are a joint work with R. Spiteri (USask), K. Green (USask), and J. Reimer (USask).

A novel pipeline from cardiac cine-MRI to patient-specific image-based hemodynamics simulations

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Among the possible medical image techniques, Magnetic Resonance Imaging (MRI) can be considered nowadays the gold-standard procedure to assess the cardiac function and, in particular, the left ventricle function. A cardiac MRI data includes the cine-MRI series that allows to capture the motion of the ventricle with a very accurate time resolution. On the contrary, concerning the spatial resolution, the usually sole 3D data available is the so-called cine short-axis (SA) view, that lacks accuracy along the left ventricle long-axis. Conversely, long-axis (LA) views are usually acquired only for few 2D slices. In this context, if the interest is in an accurate reconstruction of the 3D left ventricle shape and motion, information of the various views should be mixed in some way.

In this work, we first propose a way to create artificial cine-MRI series with higher spatial resolution, by mixing information from all the cine-MRI views. Then, we propose a pipeline to accurately reconstruct the 3D left ventricle shape and motion. In this context, we pay particular attention to polygonal surface processing and mesh generation algorithms. Finally, we exploit these geometric and functional data to perform patient-specific computational hemodynamics simulations, driven by the motion reconstructed from the images.

The hemodynamics indicators measurable from numerical simulations are of promising interest to study pathological scenarios. Indeed, the proposed methods are applied to some patients enrolled by "Ospedale L. Sacco" in Milan affected by hypertrophic cardiomyopathy of different severity. The results show the importance of using all available cine-MRI views to improve the accuracy of the reconstruction and, consequently, to enrich classic clinical outputs with information from an image-based hemodynamics simulation.

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Deep learning-based reduced order models for the real-time approximation of nonlinear time-dependent parametrized PDEs

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Conventional reduced order models (ROMs) anchored to the assumption of modal linear superimposition, such as proper orthogonal decomposition (POD), may reveal inefficient when dealing with nonlinear time-dependent parametrized PDEs, especially for problems featuring coherent structures propagating over time. To enhance ROM efficiency, we propose a nonlinear approach to set ROMs by exploiting deep learning (DL) algorithms, such as convolutional neural networks. In the resulting DL-ROM, both the nonlinear trial manifold and the nonlinear reduced dynamics are learned in a non-intrusive way by relying on DL algorithms trained on a set of full order model (FOM) snapshots, obtained for different parameter values. Performing then a former dimensionality reduction on FOM snapshots through POD enables, when dealing with large-scale FOMs, to speedup training times, and decrease the network complexity, substantially. Accuracy and efficiency of the DL-ROM technique are assessed on different parametrized PDE problems in cardiac electrophysiology, computational mechanics and fluid dynamics, possibly accounting for fluid-structure interaction (FSI) effects, where new queries to the DL-ROM can be computed in real-time.

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A reduced 3D-0D FSI model of the aortic valve considering bending forces

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We propose a novel lumped-parameter model for the dynamics of the aortic valve, including elastic effects depending on the curvature of the leaflets [1]. This model is derived from a momentum balance and is thus characterized by parameters with direct physical meaning, and a simpler calibration with respect to phenomenological models, e.g. [2]. The valve equation is coupled with a 3D description of the blood flow by Navier-Stokes equations, with the valve surface immersed in the domain by the Resistive Immersed Implicit Surface (RIIS) method [3, 4], resulting in a reduced 3D-0D fluid-structure interaction (FSI) system. For this coupling, we developed an inexpensive reconstruction of the leaflets' normal, curvature and velocity in the RIIS context, as well as of the stress exchanged with the flow. A SUPG-PSPG stabilized finite element space discretization is adopted, with a first-order time discretization for the 3D flow and a fourth-order Runge-Kutta scheme for the valve equation. The numerical method is implemented in `life`$^{\mathtt{x}}$ [`lifex.gitlab.io/lifex`], a high-performance C++ library based on the `deal.II` [`https://www.dealii.org`] finite element core. By computational results, we show the suitability of the 3D-0D FSI system in representing the leaflets motion, the blood flow in a realistic ascending aorta, and the pressure jump across the leaflets, both in physiological conditions and in the case of aortic stenosis.

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Fast characterization of inducible regions of atrial fibrillation models with multi-fidelity Gaussian process

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Computational models of atrial fibrillation have successfully been used to predict optimal ablation sites. A critical step to assess the effect of an ablation pattern is to pace the model from different, potentially random, locations to determine whether arrhythmias can be induced in the atria. In this work, we propose to use multi-fidelity Gaussian process classification to efficiently determine the regions in the atria where arrhythmias are inducible. We will build a probabilistic classifier that operates directly in the atrial surface. To reduce the computational cost, we will use active learning to determine the optimal locations to pace the model and reduce the classification error. We will take advantage of lower resolution models to explore the atrial surface and combine seamlessly with high resolution models to identify region of inducibility. We hope this new technique will allow faster and more precise clinical applications of computational models for atrial fibrillation.

Homogenized Constrained Mixture Model for Prediciting Cardiac Growth and Remodeling

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Cardiac hypertension and myocardial injury can induce pathologic tissue growth, increasing the risk of heart failure and malignant arrhythmia [1]. Computational models of growth and remodeling (G&R) show great promise to help understand pathological tissue adaption. The majority of the models of cardiac G&R proposed so far base upon the kinematic growth theory [2] that captures the consequences of growth only phenomenologically. In contrast, constrained mixture models [3] describe the mechanobiological fundamentals of G&R, i.e., continuous deposition and degradation of constituents (turnover). To the best of the authors knowledge, constrained mixture type models have not been applied to cardiac G&R yet [4]. In this talk, we propose a novel model of cardiac G&R based on the homogenized constrained mixture model [5, 6, 7]. The model describes G&R individually for cardiomyocytes and the extracellular matrix. We apply the model to a truncated ellipsoid and demonstrate that the model can inherently predict stable and unstable growth. In contrast to many phenomenological models, *a priori* limiting growth to yield stable growth is not necessary. The model also captures fibrosis which plays a key role in pathogenesis [1].

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Pulmonary vein isolation increases efficacy of antiarrhythmic drugs in a 3D computer model for atrial fibrillation

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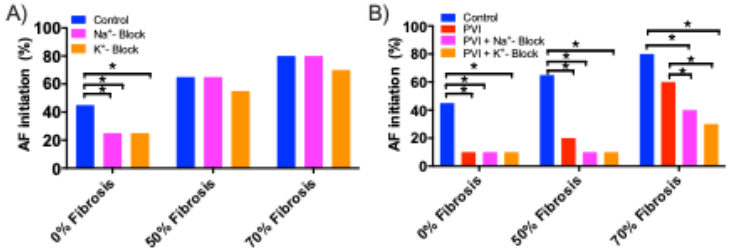
Background: The success rate of antiarrhythmic drugs (AADs) and pulmonary vein isolation (PVI) in atrial fibrillation (AF) termination or recurrence significantly depends on the degrees of structural remodelling, fibrosis, induced by AF. Not all triggers initiating AF are located within the PVs as evidenced by AF recurrences in patients with proven PV isolation. Recent clinical study showed that the AADs and PVI have a synergy to reduce AF recurrences. However, the underlying mechanisms are not well understood. We hypothesized that the presence of AADs can suppress induction of AF by residual non-PV triggers.

Methods: We simulated the effect of fibrosis on AF initiation likelihood in the presence of AADs, PVI, and the combination of AAD and PVI in a highly detailed 3-dimensional model of the human atria with realistic electrophysiology and fibre orientations. The model geometry was based on MR images and histo-anatomical studies. AF was initiated in each simulation by a train of stimuli that lasted 2 seconds with progressive reduction in pacing intervals applied to 20 different pacing locations, outside of ablated area, in both atria. Two different AADs were simulated by either 60% reduction in I_{Na} conductivity (Na^+-Block) or 30% reduction in I_{K1} conductivity (K^+-Block).

Results: In simulations without PVI, an increase in the degree of fibrosis led to a significant efficacy loss of both Na^+- Block and K^+-Block in AF recurrence prevention. PVI, only reduced significantly AF recurrences in simulation with 0% and 50% of fibrosis but not in simulations with 70% of fibrosis. The combination of AAD and PVI showed a significantly higher efficacy compare to PVI or AAD only simulations in simulations with 50% and 70% fibrosis.



Conclusions: In this simulation study, we showed that AADs, despite being ineffective before ablation, effectively suppress induction of AF after ablation.

GEASI: Geodesic-based Earliest Activation Sites Identification in cardiac models

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The identification of the initial ventricular activation sequence is a critical step for the correct personalization of patient-specific cardiac models. In heathly conditions, the Purkinje network is the main driver of the electrical activation, but under pathological conditions the so-called Earliest Activation Sites (EASs) are possibly sparser and more localized. Yet, their number, location and timing may not easily be inferred from remote recordings, such as the epicardiac potential or the 12-lead electrocardiogram (ECG), due to the underlying complexity of the model.

We introduce a Geodesic-based EAS Identification (GEASI) method as a novel approach to simultaneously identify all EASs. To this end, we start from the anisotropic eikonal equation computing cardiac electrical activation times ϕ for given initiation sites Γ, g and conduction velocities $\mathbf{D}$. It can be solved efficiently in its standard partial differential equation (PDE) formulation (left), but can also be expressed in terms of ordinary differential equations (ODEs), describing the geodesic distances δ on the domain (right):

$$\begin{cases} \sqrt{\langle \mathbf{D}\nabla\phi, \nabla\phi\rangle} &= 1, \quad \text{in } \Omega \setminus \Gamma, \\ \phi &= g, \quad \text{on } \Gamma, \end{cases} \quad \Leftrightarrow \phi(\mathbf{x}) = \min_{\mathbf{y}\in\Gamma}\{g(\mathbf{y}) + \delta(\mathbf{x},\mathbf{y})\}$$

In the latter formulation, we are able to explicitly formulate an optimization problem w.r.t. a discrete set of EASs $\mathbf{y} \in \Gamma$ and their associated timings $g(\mathbf{y})$. Moreover, this versatile approach can be extended for computing topological gradients to estimate the number of sites (i.e. adaptively increasing the size of Γ), or fitting a given ECG.

We conducted various experiments in 2D and 3D for in-silico models and an in-vivo intracardiac recording collected from a patient undergoing cardiac resynchronization therapy. The results demonstrate the clinical applicability of GEASI for potential future personalized models and clinical intervention.

BDDC and FETI-DP preconditioners for Newton-Krylov solvers for the cardiac Bidomain model

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We present here an overview of Newton-Krylov solvers for implicit time discretizations of the cardiac Bidomain equations, preconditioned by dual-primal Domain Decomposition algorithms.

The Bidomain model describes the propagation of the electric signal in the cardiac tissue by means of two parabolic partial differential equations; it is coupled through the non-linear reaction term to a system of ordinary differential equations, modeling the ionic currents through the cell membrane and the associated opening and closing process of ionic channel gates.

One of the main issues to face when computing these systems is the choice of an appropriate solver, which can combine computational efficiency and accuracy in representing the solution. As a matter of fact, the need of accurately representing phenomena both at macroscopic and at microscopic level leads to time and space discretizations with millions of degrees of freedom (dofs). The associated large systems represent a very tough challenge for modern computation: in this sense, it is very important to design efficient solvers.

We propose here two solution approaches: given the finite element semi-discrete problem, monolithic and staggered fully implicit time discretizations lead to two different solution strategies, both yielding a non-linear algebraic system to be solved at each time step. The non-linear problem is solved with the Newton method, where the Jacobian linear system is solved with a Krylov method: the Generalized Minimal Residual method, if the Jacobian problem is non-symmetric (monolithic case), or the Conjugate Gradient method otherwise (staggered case). Fast convergence is ensured by preconditioning with non-overlapping Domain Decomposition techniques, such as BDDC and FETI-DP preconditioners.

In this talk we will briefly present theoretical convergence analysis results for both approaches and their validation through parallel numerical tests, which show scalability, robustness and efficiency of the proposed solvers, thus enlarging the class of dual-primal preconditioners for Newton-Krylov solvers of the Bidomain model.

This is a joint work with Simone Scacchi (Univ. of Milan) and Luca F. Pavarino (Univ. of Pavia).

Data-Driven Variational Multiscale Reduced Order Models

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In this talk, we put forth the data-driven variational multiscale reduced order model (DD-VMS-ROM) framework, which is an extension to reduced order modeling of the VMS methodology pioneered by Hughes and his collaborators in computational mechanics. We construct the DD-VMS-ROMs by leveraging the intrinsic hierarchical structure of the ROM basis within the VMS framework, and by using data-driven modeling. First, we decompose the ROM space into a large scale space (which approximates the dominant dynamics of the underlying system) and a small scale space. Next, we use a Galerkin projection to obtain the equations for the large scale variables, which include a term representing the interaction between the large scales and the small scales. To model this term, we first postulate an ansatz (model form), and then we solve a least squares problem to find the ansatz parameters that ensure the best fit between the ansatz and the numerical or experimental data. The DD-VMS-ROM framework is very simple, yet extremely powerful: Our numerical results show that it can dramatically increase the ROM accuracy in challenging applications in computational fluid dynamics and soft tissue mechanics.

Incorporating Heart Valves Using a Varying Permeability Approach

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Simulating the total heart function includes computational fluid dynamics (CFD) blood flow models which serve as the hydrodynamic load imposed on cardiac mechanics. Heart valves play a pivotal role in filling and ejection of cardiac chambers. Thus, their functional representation in CFD simulations of hemodynamics in the human heart and the attached vessels is vital. Usually this task is achieved using fluid-structure-interaction (FSI) where valves are modeled as thin structures. We investigate the suitability of an alternative approach: A fictitious domain method is realized by extending the Navier-Stokes equation with a linear permeability term, which results in the Navier-Stokes-Brinkman equation. In this setting the permeability parameter is used to model a valve as a fictitious solid domain. The (fast) opening and closing of the valve is realized by changing the permeability within the finite elements which are covered by the moving valve in its current configuration. The underlying mesh representing the blood pool remains unchanged but the equations contain a volume fraction parameter denoting the degree of partial coverage of finite elements in the blood pool by the valve. To deal with turbulence occurring at higher Reynolds numbers the residual based variational multiscale (RBVMS) turbulence model [1] was employed. The RBVMS formulation has the additional property of stabilizing our method, which allowed the use of lowest equal order finite elements reducing also the implementation work in the cardiac modeling framework CARPentry. In this talk we will present ongoing validation work, sensitivity analysis using probabilistic surrogate models and applications stemming from clinical datasets.

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Insights into FSI models of the thoracic endovascular aortic repair procedure

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Thoracic Endovascular Aortic Repair (TEVAR) is a minimally invasive technique to treat thoracic aortic pathologies, as aneurysms and dissections. This work develops a numerical workflow to virtually implant a stent-graft and to reproduce the pre- and post-TEVAR hemodynamics in an idealized aorta through FSI simulations.
Firstly, the explicit Finite Element solver LS-DYNA (ANSYS) is employed to carry out the stent-graft deployment into an idealized aorta with physiological anatomy. The stent and the graft materials are Nitinol and PET. The aorta is modeled with an isotropic hyperelastic material. Then, weakly coupled, 2-way, and boundary-fitted FSI simulations are performed using the ICFD solver of LS-DYNA (ANSYS). A physiological velocity waveform is imposed as inlet boundary condition, while 3-elements Windkessel circuits are assigned to each outlet (supra-aortic branches and descending aorta) to model the downstream resistances. Blood is modelled as incompressible and Newtonian. The pre-TEVAR fluid domain corresponds to the aorta domain. In the post- TEVAR, the aorta and device configurations and stress distributions are imported from the structural simulation to model both the implantation and the following post-implantation scenario. The device is embedded in the fluid domain thus allowing some local movements (tipically not considered in CFD post-TEVAR hemodynamic analyses).
Comparing the results, in the post-TEVAR systolic pressure is higher in the proximal regions because the device increases the downstream resistance. Also, the presence of the stent-graft reduces the compliance of the system. The compliance mismatch phenomenon occurs at the interface device-arterial wall where there is a difference in compliance due to the mechanical coupling.
This comprehensive numerical tool can be used for both procedural planning and stent-grafts design optimization to minimize the complications. Moreover, the presence of Windkessel boundary conditions makes the model customizable for patient-specific analyses.

Identification of circulatory system properties from parameters in heart failure with a preserved ejection fraction (HFpEF) patients using a mathematical model and parameter estimation

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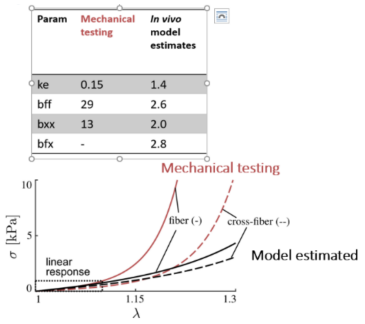
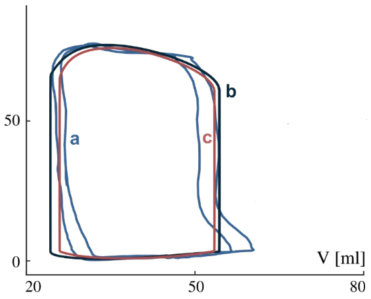
Introduction: HFpEF is an enigmatic disease affecting millions worldwide but with no effective therapeutic agent identified in over 25 randomized clinical trials. Using a low order mathematical model, echocardiographic and hemodynamic data we utilized parameter estimation to determine several parameters reflecting left ventricular (LV), right ventricular (RV), right atrial (RA) and left atrial (LA) stiffness and contractile force. We also estimated aortic impedance, systemic vascular resistance and pulmonary vascular resistance properties. A set of validation experiments were performed with a **porcine** HFpEF model and a pilot study of ten HFpEF **patients** were compared to controls. IAUAC (animal studies) and IRB (human) approval was obtained.



(a) Figure 1.



(b) Figure 2.

Methods: HFpEF **pigs** were banded (n=2) with an inflatable cuff 3 cm distal to the aortic valve or underwent downsize (9 mm) stent placement in the descending aorta (n=2). 4 control animals were included. Animals were studied with echocardiograms (TTE and TEE) monthly. At four months a terminal study was performed. Invasive hemodynamics (INCA PV loops, Millar pressure catheters), stress-strain testing of isolated LV muscle were obtained. **Patients** received full clinical echocardiograms and had non-invasive BP measured. Mathematical models were constructed using echo-derived dimensions for each pig and human. Using Levenberg-Marquardt parameter estimation, model-predicted valvular flow velocities, strains, volumes and dimensions were

optimized to those measured using echo. Systolic and diastolic BP were optimized to those measured in each animal or patient. Twelve parameters were determined reflecting the properties listed above.

Circulatory Properties	**Properties: HFpEF / Control**	Parameters	Parameter Values HFpEF patients n=10	Parameter Values Controls n=11
LV force	**1.8**	$k_m k_{av}$	502,142	354,148
LV stiffness	**2.5**	c_1	1.84	0.75
RV force	**2.6**	$k_{m\ rv}$	78	29.5
RV stiffness	**6.2**	$c_{1\ rv}$	3.74	0.6
RA force	**1.3**	$k_{m\ ra}$	13.9	10.6
RA stiffness	**1.5**	$c_{1\ ra}$	2.15	1.33
LA force	**1.2**	$k_{m\ la}$	13.1	10.7
LA stiffness	**2.5**	$c_{1\ la}$	1.9	0.75
Aortic Impedance	**1.4**	A_{01}, G	0.03,0.000006	0.03,0.000001
Systemic Vascular Resistance	**1.3**	$R_{sp}R_{sa}R_{sv}$	0.18,0.02,0.03	0.14,0.02,0.03
Pulmonary Vascular Resistance	**5.2**	$R_{pa}R_{pp}R_{pv}$	0.026,0.001,0.001	0.005,0.001,0.001

Figure 2: Table 1: Estimated parameters for HFpEF patients and controls using Levenberg-Marquardt Algorithm. Properties are derived from the parameters. Force and stiffness units are kPa. SVR/PVR are $kPa\,s/cm^3$ and G is in $(dynes/cm^2)^{-1}$ and A_{01} in cm.

Results: Porcine validation studies: Substantial variability is demonstrated in model-estimated LV stiffness parameters compared with those measured using ex vivo stress-strain testing (Fig 1). However, both parameter sets predict similar PV loops (Fig 2). **Human studies:** Parameters and properties for the HFpEF and control group are given in Table 1.

Conclusion: The **porcine validation** studies show that substantial variability in parameter estimates is consistent with similar properties (for LV stiffness). For **human studies**: RV stiffness and PVR are elevated in HFpEF patients out of proportion to LV, RA and RV stiffness properties although both stiffness and contractile force are elevated in the LV, RA and LA in HFpEF patients. Impedance and SVR are mildly increased in this group of HFpEF patients.

Comparison of source models and forward calculation methods for atrial electrophysiology regarding activation times and electrocardiograms

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In computational cardiac electrophysiology, bidomain source models and finite element forward calculation methods are considered the most detailed and accurate approaches to simulate electrical activation propagation in the heart and obtain body surface potentials or electrocardiograms. However, both methods are computationally demanding and unsuitable for the generation of large scale datasets of in-silico signals. Simplified models with reduced computational cost are thus needed.

To assess the accuracy of computationally more efficient approaches in an atrial simulation setup, we first conducted electrophysiological simulations on an atrial geometry in sinus rhythm with different excitation propagation models (bidomain, monodomain, reaction-eikonal, and eikonal solved by the fast iterative method). P waves of the 12-lead electrocardiogram were then computed with different forward projection techniques (finite element, boundary element with spatial downsampling, and infinite volume conductor) from a transmembrane voltage distribution simulated with the bidomain source model.

For an anisotropic and spatially heterogeneous conductivity setup in the atria, the mean and standard deviation of the absolute local activation time differences to the bidomain results were 1.01 ± 0.77 ms, 1.40 ± 1.50 ms and 1.43 ± 1.19 ms for the monodomain, reaction-eikonal and fast iterative method simulations, respectively. For the forward projection comparison, the correlation coefficient between the P waves computed with the finite element and each of the boundary element and the infinite volume conductor method resulted to 0.94 and 0.79, respectively. The correlation coefficient between P waves of the full bidomain simulation and a combination of the reaction-eikonal source model with the boundary element forward calculation method quantified to 0.92.

Our results demonstrate that the monodomain, the reaction-eikonal and the eikonal excitation progagation models yield local activation times of a similar accuracy compared to the bidomain results for a heterogeneous and anisotropic sinus rhythm simulation setup in the atria. With the boundary element forward calculation method, sinus rhythm P waves with a high correlation coefficient compared to the finite element approach can be obtained.

A computational study of the electrophysiological substrate triggering arrhythmias

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We present a new computational pipeline to study the electrophysiological substrate of patients affected by electrical disorder phenomena, such as post-ischemic ventricular tachycardia and atrial fibrillation, obtained by integrating high-density electroanatomical (EA) data within suitably parameterized mathematical models.

We first process EA maps to identify slow conduction (SC) corridors by numerically approximating conduction velocities from activation time data using a least-squares approach. This allows a first stratification of the patients based on the severity and distribution of these corridors.

Then, we numerically simulate the formation and sustainment of reentrant circuits using a new parametrization of the mathematical model for cardiac electrophysiology based on conduction velocities. We specifically consider a parametrized version of the monodomain model with a heterogeneous conductivity tensor, coupled with a parametrized ionic model describing the dynamics of ionic species at the cellular level.

Numerical results show the substrate characteristics' contributions to the initiation and progression of the pathology. In particular, they highlight the link between conduction heterogeneity and functional phenomena, such as head-tail interactions, and the role of SC corridors in sustaining reentrant circuits.

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3D-0D closed-loop numerical modeling of cardiac biventricular electromechanics

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Abstract

Over the years, cardiac computational electromechanical (EM) models have been developed with increasingly biophysical details, by taking into account the interacting physical phenomena contributing to the heart electromechanics - electrophysiology, active contraction, mechanics. Two crucial issues to be accounted for in EM modeling are i) the interaction between the heart and the circulatory system that determines pressures and volumes loads in the heart chambers; ii) the muscular fiber architecture that plays a key role in the electric signal propagation and in the myocardial contraction. In this work, we present a 3D biventricular EM model coupled with a 0D closed-loop model of the whole cardiovascular system. We introduce a boundary condition for the mechanical problem that accounts for the neglected part of the domain located above the biventricular basal plane and that is consistent with the principles of momentum and energy conservation. We provide the numerical framework by fully detailing our approach to couple the 3D and the 0D models. We perform electromechanical simulations in physiological conditions using the 3D-0D model. Our results match the experimental data of relevant mechanical biomarkers available in literature. Furthermore, we investigate different arrangements in cross-fibers active contraction, that surrogate the myofibers dispersion. We prove that an active tension along the sheet direction counteracts the myofiber contraction, while the one along the normal direction enhances the cardiac work. Finally, several myofiber architectures are analysed. We show that a different fiber field in the septal area and in the transmural wall influence the ventricular pump work, in particular the left ventricle one.

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An oscillation-free segregated algorithm for the numerical simulation of cardiac active mechanics

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In this work we address an unresolved problem in the numerical modeling of cardiac electromechanics, that is the onset of numerical oscillations due to the dependence of force generation models on the fibers shortening velocity. A way to avoid numerical oscillations is to use monolithic schemes for the solution of the coupled problem of active-passive mechanics. However, staggered strategies, which foresee the sequential solution of the models of force generation and of tissue mechanics, are preferable, due to their reduced computational cost and low implementation effort. In light of this motivation, in this work we propose a new numerical scheme, that is numerically stable and accurate, yet within a fully partitioned (i.e. segregated) framework.

To derive our stabilized scheme, we move from energetic considerations on the coupling, at the microscale, between active and passive mechanics models. We show that instabilities are linked to the mismatch between macroscopic and microscopic strains, inconsistently expressed in Lagrangian and Eulerian coordinates, respectively. Hence, we formulate a novel scheme, in which all the variables are framed in a coherent fully Lagrangian reference system. By considering a model problem of active mechanics we prove that the proposed scheme is unconditionally absolutely stable (i.e. it is stable for any time step size), yet within a fully staggered framework.

We apply the proposed method to several force generation models available in the literature, namely the Niederer-Hunter-Smith model, the model of Land and coworkers and a biophysically detailed model that we have recently proposed. We show, by means of several numerical tests, that the proposed stabilization term successfully removes the nonphysical numerical oscillations characterizing the non-stabilized segregated scheme solution. This is verified in two different test cases, namely an isotonic twitch and a test case where a contracted fiber shortens as a consequence of a gradual decrease of the external load, similarly to what happens in the ejection phase of the heart cycle. We show that the new scheme preserves the first order convergence with respect to Δt of the non-stabilized staggered scheme. The numerical error is only slightly larger than the error obtained with the monolithic scheme and it tends to zero with the same rate. Finally, we successfully apply the proposed scheme in the context of a three-dimensional multiscale electromechanical simulation of the left ventricle.

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Numerical Simulation of Long QT Syndrome Symptoms, Triggers, and Treatments

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Computational cardiac models are powerful tools used for research by scientists and engineers; however, their role in clinical settings is limited. This presentation discusses potential clinical applications of cardiac electrophysiological models. Two channelopathies, Long QT Syndromes 1 and 2, are numerically characterized based on data for specific genetic variants of the diseases and are then simulated using established action potential models. Triggering events including exercise and a startle response are then applied to the model, and arrhythmogenic electrical activity is observed at the cellular level. Finally, treatment options are explored using the parametrized models. The work presented here demonstrates the capacity for digital cardiac models to advance the field of clinical cardiology, particularly in the implementation of personalized approaches in the treatment of arrhythmias.

Learning atrial fiber orientations from intracardiac maps using physics-informed neural networks

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Electroanatomical maps are a key tool in the diagnosis and treatment of atrial fibrillation. Current approaches focus on the activation times recorded. However, more information can be extracted from the available data. The fibers in cardiac tissue conduct the electrical wave faster, and their direction could be inferred from activation times. In this work, we employ a recently developed approach, called physics informed neural networks, to learn the fiber orientations from electroanatomical maps, taking into account the physics of the electrical wave propagation. In particular, we train the neural network to weakly satisfy the anisotropic eikonal equation and to predict the measured activation times. We use a local basis for the anisotropic conductivity tensor, which encodes the fiber orientation. The methodology is tested both in a synthetic example and for patient data. Our approach shows good agreement in both cases, with an RMSE of 2.2ms on the in-silico data and outperforming a state of the art method on the patient data. The results show a first step towards learning the fiber orientations from electroanatomical maps with physics-informed neural networks.

Electromechanical modeling of human ventricles with ischemic cardiomyopathy: numerical simulations in sinus rhythm and under arrhythmia

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We developed a novel patient-specific computational model for the numerical simulation of ventricular electromechanics in patients with ischemic cardiomyopathy (ICM). This model reproduces the activity both in sinus rhythm (SR) and in ventricular tachycardia (VT). The presence of scars, grey zones and non-remodeled regions of the myocardium is accounted for by the introduction of a spatially heterogeneous coefficient in the 3D electromechanics model. This 3D electromechanics model is firstly coupled with a 2-element Windkessel afterload model to fit the pressure-volume loop of a patient-specific left ventricle (LV) with ICM in SR. Then, we employ the coupling with a 0D closed-loop circulation model to analyze a VT circuit over multiple heartbeats on the same LV. We highlight similarities and differences on the solutions obtained by the electrophysiology model and those of the electromechanics model, while considering different scenarios for the circulatory system. We observe that very different parametrizations of the circulation model induce the same hemodynamical considerations for the patient at hand. Specifically, we classify this VT as unstable. We conclude by stressing the importance of combining electrophysiological, mechanical and hemodynamical models to provide relevant clinical indicators in how arrhythmias evolve and can potentially lead to sudden cardiac death. 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).

Multiscale Modeling of LV Growth under Autonomic Regulation of Baroreflex Feedback Loop

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Cardiac hypertrophy initiates as an adaptive response to altered ventricular loading or mutations in sarcomeric proteins. Prolonged hypertrophy is associated with increased risk of atrial fibrillation, heart failure, or even sudden death. Computational models have been developed to investigate the adverse growth and remodeling that are related to cardiac hypertrophy. This study introduces a new cardiac growth model, incorporated with a multiscale model of cardiovascular function, which can predict cardiac hypertrophy in response to valvular disorders like aortic stenosis and mitral regurgitation while the arterial pressure is preserved via the baroreflex feedback loop.

A previously published multiscale model of cardiovascular function, named PyMyoVent, was extended by implementing a unified stress-driven growth module. The growth law for concentric hypertrophy (wall thickening) was driven by the total stress in the half-sarcomeres, whereas the passive stress drove the eccentric growth law (chamber dilation). The contractile behavior of the left ventricular myocardium was simulated via a model of half-sarcomere mechanics, which accounts for the cross-bridge cycling of myosin heads on the thick filament. The hemodynamics in the multiscale model were regulated with a baroreflex feedback module to maintain the arterial pressure at a set-point level via continuous regulation of heart rate, myofilament contractility, Ca^{2+} transient inside the cell, and the vascular tone.

The growth module predicted concentric growth and eccentric growth for simulated aortic stenosis (pressure overloading) and mitral valve regurgitation (volume overloading), respectively. In comparison to clinical data found in the literature, the model could appropriately predict both the trend and magnitude of change in the ventricular dimensions for both types of valvular disorder. Furthermore, as a simulation of clinical interventions in alleviating the ventricular overloading, such as mitral valve surgery, the growth module could reverse/ undo the predicted cardiac hypertrophy when the overloading condition was removed.

In conclusion, the multiscale model of cardiovascular function, presented in this study, can predict different types of cardiac hypertrophy in response to alterations in the ventricular loading while the arterial pressure was preserved with the baroreflex feedback model.

Keywords: Multiscale Model, Cardiac Mechanics, Cardiac Growth, Concentric Hypertrophy, Eccentric Hypertrophy, Baroreceptor

A fast cardiac electro-mechanics model with blood circulation using the Eikonal equation

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In this work we present a cardiac electro-mechanics (EM) model coupled with blood circulation with the aim of reducing the computational costs to evaluate significant mechanical outputs in view of clinical practice. For the electrophysiology (EP) part, we started from the strategy of the reaction-eikonal model [1], proposing an efficient way to solve the reaction problem. We couple EP with a physics-based active force model [2] to better characterize the coupling with respect to a phenomenological model. We finally couple the 3D EM model with a windkessel model for blood circulation. We show the capability of the model to accurately reproduce physiological PV loops. We also analyze numerical results to show the validity of the method in reproducing significant mechanical outputs (PV loops, ejection fraction) comparing them with the ones obtained with the full EM model with blood circulation using the monodomain model for EP.

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PDE-aware Deep Learning for Inverse Problems in Cardiac Electrophysiology

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In this work, we present a PDE-aware deep learning (DL) model, named Space-Time Reduced Basis Deep Neural Network (ST-RB-DNN), for the numerical solution to the Inverse Problem of Electrocardiography. The main feature of the proposed neural network (NN) is that it both leverages data availability and exploits the knowledge of a physically-based mathematical model, expressed by means of partial differential equations (PDEs), to carry out the task at hand. The goal is to estimate the epicardial potential field from measurements of the electric potential at a discrete set of points on the body surface. Such a problem has become central in biomedical research, providing the theoretical basis for Electrocardiographic Imaging (ECGI), but it is extremely hard to solve because of its ill-posedness. The employment of deep learning techniques in this context is made difficult by the low amount of clinical data at disposal (*small data regime*), as measuring cardiac potentials requires invasive procedures. Suitably exploiting the underlying physically-based mathematical model allowed to circumvent the data availability issue and led to the development of fast-training and low-complexity PDE-aware DL models. In particular, physical-awareness has been pursued by means of two elements: the projection of the epicardial potential onto a Space-Time Reduced subspace, spanned by the numerical solutions of the governing PDEs, and the inclusion of a tensorial Reduced Basis (RB) solver of the Forward Problem in the network architecture. Numerical tests have been conducted only on synthetic data, obtained via a Full Order Model (FOM) approximation of the problem at hand, and two variants of the model have been addressed. Both proved to be accurate, up to an average ℓ^1-norm relative error on epicardial activation maps of $\approx 3.5\%$, and both could be trained in $\approx 10\ min$. Nevertheless, some improvements, mostly concerning data generation, are necessary in order to bridge the gap with clinical applications.

Keywords: Cardiac Electrophysiology, Deep Learning, ECGI, Inverse Problem of Electrocardiography, Partial Differential Equations, PDE-aware Deep Learning

Stable numerical schemes for modelling hemodynamic flows in time-dependent domains

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We present a unified numerical approach to finite-element modelling of incompressible flows in time-dependent domains. The approach features relatively large (independent of mesh size) time steps, solution of one linear system per time step, and relatively coarse computational meshes in space. The approach is monolithic and allows standard $P_2 - P_1$ (Taylor–Hood) finite element spaces. It is applicable to the Navier-Stokes equations in time-dependent domains, the fluid-structure interaction (FSI) problems, and the fluid-porous structure interaction (FPSI) problems. The properties of the schemes are shown on several benchmarks and hemodynamic applications.

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Efficient solution of coupled problems through DEIM-based data projection across non-conforming interfaces

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The study of the electrical behavior of the heart, considering different instances of relevant geometrical and physical parameters, is nowadays of key importance to predict and monitor cardiac diseases. Computing electrical outputs of interest, such as electrocardiograms (ECGs) or body surface potential maps, requires the approximation of large coupled nonlinear dynamical systems on different domains. Enhancing the computational efficiency of such expensive problems poses one of the major challenges, especially when considering realistic heart and torso geometries, characterized by non conforming interfaces.

In this talk, we propose a parametric reduced order model (ROM) for one-way coupled models, combining efficient ROMs applied on each subproblem with the discrete empirical interpolation method (DEIM) to efficiently interpolate or project parameter dependent data across conforming and non-conforming meshes at the interface of the coupled-model domains. In particular, we investigate the possibility to reconstruct parametric Dirichlet data through a set of basis functions spanning a suitable low dimensional space.

The presented technique can be regarded as an alternative to the numerical schemes such as those relying on domain-decomposition methods, improving the computational performances and reducing the costs of multi-query computations of one way coupled models such as electrophysiological segregated heart-torso problems. Preliminary numerical results obtained in several test cases involving parametric steady and unsteady problems highlight the efficiency of the proposed reduced order modeling technique compared with high fidelity, full order models built through the finite element method.

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Accurate multiscale numerical simulation of blood flow in the human heart

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Blood flows in the heart are usually studied and analysed through experimental techniques and imaging processes. However, these approaches often suffer from a lack of resolution into the spatio-temporal scales. Computational fluid dynamics (CFD) stands as a tool to complement such techniques to provide a detailed description of blood flows in both physiological and pathological conditions. Nevertheless, CFD modeling of heart's flows faces several challenges: i) the fluid domain is geometrically complex and undergoes large deformations; ii) the dynamic of valves leads to topological changes of the domain over the heart-cycle; iii) flows are driven by complex electro-mechanical-fluid interactions; and, iv) the blood flow regime is neither laminar, nor fully turbulent, but rather transitional [1]. In our CFD model, we adopt the Navier-Stokes equations in Arbitrary Lagrangian Eulerian (ALE) framework to account for the endocardium displacement. We use a Variational Multiscale - Large Eddy Simulation (VMS-LES) method [2–4] to get a stable formulation of the Navier-Stokes equations discretized by means of Finite Element Method and, then, to account for turbulence modeling within the framework of LES. We model the cardiac valves by means of the Resistive Immersed Implicit Surface (RIIS) model [5, 6]. We then present a multiscale computational model for the simulation of the whole left heart, using a realistic geometry and a realistic displacement. The motion of the walls is driven by electromechanics simulation on the left ventricle [7] and a novel preprocessing procedure to extend the displacement to the whole boundary of the domain and modeling the left atrium motion with a volume-based displacement definition. Our 3D-CFD model is coupled to a lumped-parameter circulation model of the whole cardiovascular system [7, 8], to account for realistic and physiological boundary conditions that are respectful of the closed-loop circulation model of the whole cardiovascular system. Finally, advances regarding a CFD multiscale model of the whole human heart coupled with the circulation model will be introduced and discussed.

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