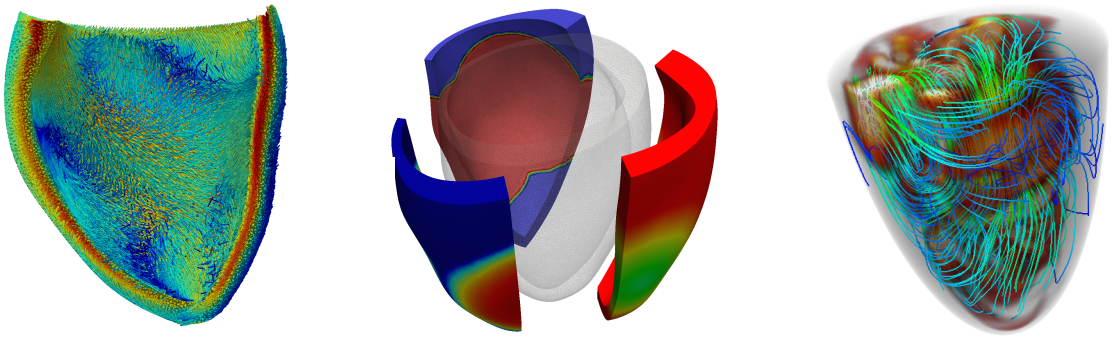

2019 RISM Congress
iHEART - Modelling the Cardiac Function

July 22-24, 2019

Riemann International School of Mathematics
Varese, Villa Toeplitz, ITALY

Conference organized by
RISM - Riemann International School of Mathematics
MOX - Politecnico di Milano

Support
EU ERC-ADG - Advanced Grant iHEART Project ID: 740132

iHEART - MCF2019
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Multiscale description of chemical-mechanical coupling in cardiac modeling – Thermodynamics and numerics

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The Frank-Starling mechanism is a crucial regulation mechanism in cardiac physiology, by which the cardiac output can be adjusted by varying the passive inflation of the ventricles. At the fiber level, this relies on the length-dependence of the active force developed in sarcomeres. At the microscopic level, it can be explained by a length-dependence of the activation of both actin and myosin filaments – also called thin and thick filaments, respectively – that chemically interact to create so-called cross-bridges in which active forces are generated. Various descriptions have already been proposed to explain the length-dependent activation of actin filaments by calcium. In this work, we consider the activation of actin as given – i.e. separately modeled – and we focus on the modeling of the length-dependence in the activation of myosin and the impact thereof on the creation-destruction and behavior of cross-bridges, which is represented in the form of an extension of the classical Huxley'57 "sliding filament" model. We show that our coupled chemical-mechanical model satisfies the principles of thermodynamics, and we propose a consistent numerical scheme. Finally, we show how this model of active force generation can be integrated in a complete cardiac model – still consistent with thermodynamics – and provide some illustrations of heartbeat simulations, exemplifying the Frank-Starling mechanism, in particular.

Potential Implications of the Helical Heart in Congenital Heart Defects

Antonio F. Corno

East Midlands Congenital Heart Center - Leicester (UK)

The anatomic and functional observations made by the late Francisco Torrent-Guasp, in particular his discovery of the helical ventricular myocardial band (HVMB), have challenged what has been taught to cardiologists and cardiac surgeons over centuries.

Adequate understanding of the heart structure and function is obviously indispensable for the decision-making process in congenital heart defects.

The HVMB described by Torrent-Guasp and the potential impact on the understanding and treatment of congenital heart defects has been analyzed in the following settings:

- embryology
- ventriculo-arterial discordance (= transposition of great arteries)
- Ebstein's anomaly
- pulmonary valve regurgitation after repair of tetralogy of Fallot
- Ross operation for aortic valve disease.

The common structural spiral feature is only one of the elements responsible for the functional interaction of right and left ventricles; and understanding the form/function relationship in congenital heart defects is more difficult than for acquired heart disease because of the variety and complexity of congenital heart defects.

Collaborations between surgeons and mathematicians allow investigating structure and function of the heart with mathematical and computational fluid dynamic models to evaluate the efficiency of the currently available surgical strategies and potential surgical alternatives.

Cardiac hemodynamics simulations for implantable devices assessment

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Mitral valve regurgitation (MR), also known as mitral insufficiency, is one of the most important cardiac valve diseases. Surgery is the gold-standard treatment for severe MR, but the choice of the best repair technique remains debated and patient outcomes are mainly driven by the surgeon's expertise. Alternative surgical options based on new minimally invasive implantable devices could potentially benefit many patients. In this talk, we will discuss how numerical simulation can play a fundamental role in the assesment of such devices. To this purpose, we will focus on some fundamental aspects related to the modeling and simulation of cardiac hemodynamics, using reduced and fluid-structure interaction models. This work has been carried out in the framework of an industrial collaboration funded by the Kephalios and Epygon companies.

New horizons in Electrophysiology. Math, simulation and prediction of arrhythmias

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Coupled Scales and Coupled Physics in Cardiac Simulation

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In this talk we present and discuss discretization and solution methods in space, time, and space-time for cardiac simulation. Starting from pure electrophysiology, we discuss the coupling of electrophysiology and mechanics, and eventually comment on fluid structure interaction and contact in the heart valves. As it turns out, either on the side of the solution method (multigrid) or on the side of the coupling of different discretizations (mortar methods), discrete L^2 projections turn out to be a versatile ingredient - may it be for the construction of multi-level approximation spaces, for the discretization of contact constraints, or for the transfer of discrete quantities. We will describe our discretization and solution methods and will comment on how to handle efficiently the arising discrete constrained and coupled systems.

Viscoelastic Model of Human Myocardium

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Introduction

Across species, myocardial tissue has been shown to exhibit viscoelastic behaviour [1,2]. Significant hysteresis at low shear rates, stress relaxation, and frequency dependent stiffness have all been observed experimentally. Despite this long history of experimental evidence, the myocardium is typically modelled as a hyperelastic material [3]. New viscoelastic models have been proposed [4], but these lack the capacity to account for these varying viscoelastic factors that are encountered experimentally.

In this study, we develop a viscoelastic model for human myocardium. The model - based on a nonlinear viscoelastic anisotropic generalized power law - is demonstrated to capture the viscoelastic features of myocardial tissue across shear relaxation, cyclic shear and biaxial experiments. The model is also shown to exhibit behaviours observed in animal studies, including frequency dependent stiffness and transitional nonlinearity.

Integrating the new model into a patient-specific heart model, the behaviors of the hyperelastic and viscoelastic models are compared within the myocardium, focusing specifically on passive inflation and active contraction. Quasi-static and transient cardiac models are considered, demonstrating the impact of these assumptions on the behaviour of biventricular heart models.

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Personalizing models of total heart function

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Advances in numerical techniques and the ever increasing computational power have rendered the execution of forward models of total heart function feasible. Using such models based on clinical images and parameterized to reflect a given patient's physiology, are a highly promising approach to comprehensively and quantitatively characterize cardiovascular function in a given patient. Such models are anticipated to play a pivotal role in future precision medicine as a method to stratify diseases, optimize therapeutic procedures, predict outcomes and thus better inform clinical decision making.

However, to translate modeling into a clinically applicable modality a number of key challenges have to be addressed. In particular, expensive computational models must be made efficient enough to be compatible with clinical time frames. This can be addressed either with hierarchical models of varying complexity which are cheaper to evaluate, by using computational efficient techniques such as spatio-temporal adaptivity, or by exploiting the power of new HPC hardware through massive parallelization or the use of accelerators. Further, the etiology of most cardiac pathologies comprises Multiphysics aspects, requiring the coupling of various physics, which may be characterized by very different space and time scales, rendering their coupling a challenging endeavor. Finally and most importantly, to be of clinical utility generic models must be specialized based on clinical data, which requires complex parameterization and data assimilation procedures to match model behavior with clinical observations.

Multi-scale Computational Modelling of Coronary Blood Flow

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The complexities associated with understanding coronary blood flow are in many cases produced by the number of determinants that control its function including network anatomy, systemic afterload and mechanical interaction with the myocardium throughout the cardiac cycle. Furthermore, the location of coronary artery disease is often distributed heterogeneously. In large epicardial vessels, coronary disease status can often be determined directly from anatomically based angiograms. However, in contrast, small vessel and microcirculatory dysfunction must be inferred indirectly from morphological imaging and/or functional measurements including experimental quantification using microspheres or in the clinic MR first pass perfusion and imaging of myocardial motion. This range of spatial scales combined with the requirement to integrate multiple data types to analyse coronary perfusion highlights the need for a validated and, where possible, anatomically based multi-scale framework that captures the relevant details at each level of the network. To address this need in this study we present our integrated coronary blood flow model with the capacity to span detailed coronary anatomical and flow modelling integrated with frameworks which represent microvascular perfusion and cardiac contraction.

Blending Engineering and Medicine

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Sudden cardiac death (SCD) from arrhythmias is a leading cause of mortality. For patients at high SCD risk, prophylactic insertion of implantable cardioverter-defibrillators (ICDs) reduces mortality. Current approaches to identify patients at risk for arrhythmia are, however, of low sensitivity and specificity, which results in a low rate of appropriate ICD therapy. There is a critical clinical need to develop risk metrics that directly assess the interplay between abnormal myocardial structure and electrical instability in the heart, that together predispose to SCD. Here we present a novel non-invasive personalized approach to assess SCD risk in patients with ischemic cardiomyopathy, myocarditis, repaired Tetralogy of Fallot, hypertrophic cardiomyopathy and sarcoidosis, based on a number of cardiac imaging modalities and on computational modeling. This is an example of the emerging field of computational cardiology.

In computational cardiology, we construct personalized 3D computer models of heart function in disease. Each heart model incorporates detailed myocardial structure and electrophysiological functions from the sub-cellular to the organ, allowing for representation of electrical instability. Thus the interplay between abnormal myocardial structure and electrical instability in the heart that predisposes to SCD can be directly assessed. In each heart model, we conduct a virtual multi-site delivery of electrical stimuli so that the patients heart propensity to develop ventricular arrhythmias can be comprehensively evaluated. Simulations are conducted for each virtual heart, probing its propensity to develop ventricular arrhythmia. The robust and non-invasive multiscale virtual-heart arrhythmia risk prediction approach has the potential to prevent SCD and eliminate unnecessary ICD implantations in patients with a number of heart diseases.

Here, we also show that personalized virtual-heart technology based on cardiac imaging and computational modelling can be used to guide patient treatment by identifying optimal ablation targets for both atrial and ventricular arrhythmias. In a number of studies, we assessed, using first retrospective analysis, the capability of the technology to determine the minimum-size ablation targets for eradicating all ventricular and atrial tachycardias. We also demonstrate that using CT scans to determine the distribution of intramyocardial fat and incorporating the electrophysiological and paracrine effects of adipose tissue in the surrounding myocardium can be used to assess the arrhythmogenic substrate in patients. The approach could improve the arrhythmias ablation guidance, where accurate identification of patient-specific optimal targets could be achieved on a personalized virtual heart before the clinical procedure.

Mathematical and numerical analysis of a general linearized poro-hyperelastic formulation

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In this work we present the well-posedness analysis at both discrete-in-space and continuous levels of a recent linear poromechanics model [1], which is derived as the linearization by small deformations of a novel thermodynamically consistent poromechanics model [2]. The theory of Differential Algebraic Equations allows us to reformulate the existence of the discrete-in-space solutions as a saddle point problem, where we analysed a generalized divergence form that weights the fluid and solid contributions according to the porosity. We show that finite element spaces of Taylor-Hood type are inf-sup stable, where higher order approximation is required in both fluid and solid spaces. In practice it has been observed that the fluid dominates the inf-sup stability, so we present a procedure to estimate the inf-sup constant which allows to explain this kind of asymmetric behavior. Finally, the well-posedness of the continuous problem is obtained by a standard Faedo-Galerkin argument.

We present three numerical experiments. The first one is a swelling test, which is a classic benchmark in poromechanics. The second one is similar but the porosity presents spatial dependence, so as to show that inf-sup stable and unstable regimes can coexist. The last one is a real-case simulation, in which we replace the linear solid stress term with the nonlinear Guccione law plus an active stress term, which shows promising results for further applications regarding myocardium perfusion.

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

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Effect of valve tissue anisotropy on turbulent systolic blood flow past bioprosthetic heart valves

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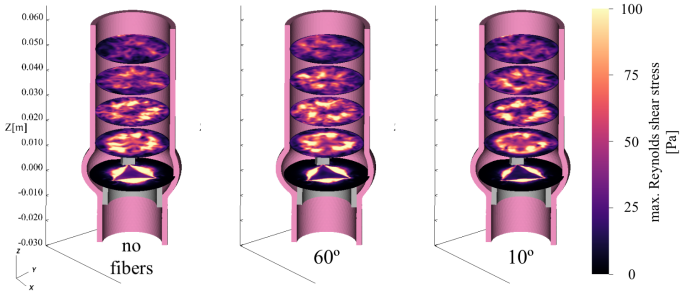
Bioprosthetic heart valves (BHV) are used to replace diseased native heart valves. Despite the clinical success of this treatment, the longterm outcome is limited by several factors such as mechanical failure of the BHV, bioprosthetic leaflet thrombosis and adverse aortic events. These factors can be related to turbulent flow structures in the flow field past the BHV. Therefore, it is of high interest to better understand the mechanisms which lead to these blood flow structures, including elevated and chaotic (wall) shear stresses past BHV. This may help design better BHV with a more benign wake.

Here, we investigate the effect of the mechanical properties of the valve tissue on the flow field past the BHV. In particular, we study the effect of the mechanical anisotropy which is a well-known property of native valve tissue.

We have developed a novel computational model for fluid-structure interaction which uses finite elements to discretize the full elastodynamics equations and high-order finite differences for the Navier–Stokes equations. The physics models are coupled via the immersed boundary method where we use an L^2-projection for the variational transfer of velocities and forces between the fluid grid and solid mesh.

We performed numerical simulations with an anatomically correct model of the aortic root and a BHV consisting of a stiffer ring supporting the three valve cusps made from soft tissue. We used a linear elastic law for the walls of the aortic root and the valve ring. We use three different descriptions for the soft tissue of the cusps: 1. neo-Hookean, 2. Holzapfel–Ogden model with two fiber families with 60° relative angle, 3. Holzapfel–Ogden model with the same fibers with 10° relative angle.



The resulting systolic flows at Reynolds numbers around 3500 (see figure) were analyzed for mean flow, turbulent fluctuations, Reynolds shear stresses and turbulent kinetic energy. We found that higher anisotropy generally yields a lower turbulent intensity and reduced leaflet motion (fluttering) during systole.

Mathematical modelling and numerical simulation of transient shear wave elastography in the heart

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Transient elastography techniques, based on remote generation of shear waves by the acoustic radiation force (ARF) of a focused ultrasound beam, have raised a growing interest in clinical applications [1]. In fact, by characterising the propagation of the induced shear waves, it is possible to locally assess biomechanical properties that are highly sensitive to structural changes corresponding to physiological and pathological processes. Recent experimental studies show the applicability of transient elastography in the cardiac setting [2].
The aim of this work is to provide a mathematical model and a numerical simulation framework of impulsive Acoustic Radiation Force (ARF)-driven Shear Wave Elastography (SWE) imaging in a prestressed soft tissue, with a specific reference to the cardiac setting.
First, the talk will breafly deal with the derivation of an original mathematical model of the ARF. In particular, starting from an accurate biomechanical model of the heart, and based on asymptotic analysis, we infer the governing equation of the pressure and the shear wave field remotely induced by the ARF, and we compute an analytical expression of the source term responsible for the generation of shear waves from an acoustic pressure pulse.
Furthermore, we propose efficient numerical tools for a realistic numerical simulation of an SWE experiment. The spatial discretisation is based on high-order Spectral Finite Elements. Concerning time discretisation, we propose a novel method adapted to incompressible elasticity [3]. In fact, it is well known that the numerical treatment of the incompressibility constraint is a difficult task, and fully implicit or explicit methods can give rise to major issues in terms of efficiency. In the approach we propose, only the terms travelling at infinite velocity, associated with the incompressibility constraint, are treated implicitly by solving a scalar Poisson problem at each time step of the algorithm. In addition, we adopt a novel matrix-free, high-order, fast method to solve the Poisson problem, based on the use of the Discrete Fourier Transform.
A three-dimensional numerical test case will conclude the talk, to illustrate a realistic application to elastography imaging.

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An efficient and accurate numerical methods for the solution of bidomain equations

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The most complete description of cardiac bioelectrical activity at the cardiac tissue is given by the bidomain model which consists of a system of a non-linear partial differential equations (PDEs). The evolution equation is coupled through the non-linear reaction term with a stiff system of ordinary differential equations (ODEs) describing the ionic currents through the cellular membrane. Many attempts to made to increase the bidomain solver efficiency by using decoupled strategies and operator splitting schemes. More importantly, the monodomain equations are often decoupled into one parabolic equation that is computationally cheap to solve and other set of ODEs which are even very cheap to solve by using implicit-explicit (IMEX) time stepping schemes. Thus, it is not clear if commonly used splitting methods can outperform a coupled approach by maintaining the good accuracy. Moreover, the splitting methods constrain the maximum time step that may be used for stability as well as accuracy considerations. In this talk, we present the numerical results for the coupled solver approach as compared with commonly used splitting methods by considering more sophisticated physiological models, like Ten tusscher 2006 and O'Hara-Rudy 2011 models. Our numerical results demonstrate that the coupled method is computationally slower than the conventional uncoupled methods but it produces more accurate results in pathological simulations. To accelerate the coupled solver, a novel computational technique will be demonstrated which is memory efficient and speed up the computations.

Computing Riemannian curvature tensor for stopping conditions of cardiac electric flow in multidimensional anisotropic cardiac tissue

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One of the most important matters in tracing the propagation of the cardiac electric signal, or also called the cardiac action potential propagation, is to know when the propagation stops, which provides important indications on the initiation of various heart diseases such as fibrillation. The stopping conditions can be viewed as a *sink-source* mismatch in a cell level, and can be indicated by a threshold value of *front curvature* of the wavefront. Challenges in verifying these stopping conditions lies in the fact that the real heart tissue is both multidimensionally curved and strongly anisotropic where the curvature of wavefront is not informative any more. One way to overcome this problem is to re-interpret the understanding of wavefront curvature into the Riemannian curvature tensor of the *trajectory* that can easily incorporate the multidimensionality and anisotropy of geometry in sense of Riemannian geometry [1].

To implement this approach, a new computational scheme is proposed using moving frames to effectively demonstrate the propagation and its Riemannian curvature tensor of the cardiac electric flow from the the popular diffusion-reaction type equations on anisotropic media. Firstly, an orthonormal frame, or called *moving frame*, is constructed at every grid points. Secondly, the diffusion-reaction type equations simulating the cardiac electric signal propagation is computational solved to align the frames. Then, *connection* is successfully constructed for the given alignment of moving frames, and Riemannian curvature tensor in the direction of the *separation vector* immediately is related to the possibility of the stopping of the propagation [2]. Advantages of this approaches are (1) to quantify the propagational pattern of the cardiac electric flow, (2) to implicitly measure the strength of the underlying cardiac fiber, and (3) to easily incorporate the real propagational data into the *curvature map* from computational simulation. For clinical purpose, this scheme may provides efficient *trace maps* to visualize and quantify the propagation of the cardiac electric flow in the real heart.

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A computational multiscale approach for modeling myocardial perfusion

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Myocardial perfusion is the delivery of blood to the heart muscle, supplied by the coronary circulation. A proper heart function strongly relies on this phenomenon, since reduced coronary flow rate, due for example to atherosclerosis, can lead to ischaemic cardiopathy and, possibly, to an infarct of the myocardium. In this talk, we present a mathematical and numerical model of myocardial perfusion which accounts for the different length scales of the vessels in the coronary tree. Precisely, we observe a clear scale separation between the coronaries laying on the epicardium and the smaller vessels penetrating into the tissue. We adopt a multiscale approach in which the epicardial vessels are represented with a fully three-dimensional fluid-dynamics description while all the intramural vessels are modeled by means of a multi-compartment porous medium. These two models are coupled using interface conditions based on the continuity of mass and momentum.
Since we aim at modeling *in-vivo* human geometries, for which detailed intravascular networks can not be reconstructed from medical images, we propose a strategy to generate a network in a non-convex domain which will be used to estimate the multi-compartment Darcy model parameters.
The proposed model is applied to a realistic biventricular human geometry and shows promising results for future clinical application.

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

Image processing and mesh generation tools for the integrated heart project

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The mathematical and numerical modeling of the cardiac function is a very complex problem characterized by multi-physics models and multi-scale phenomena. In practice, in order to simulate the cardiac function in a realistic or patient-specific geometry, the generation of the computational meshes is a challenging and crucial aspect. In this talk we discuss the general pipeline to generate cardiac computational mesh starting either from a medical image or from a template realistic geometry.

The talk is divided into two different parts: the former gives a panorama of all the aspects related to the cardiac medical image processing; the latter is focused on the mesh generation. Concerning the medical image processing, we show a complete example of a cardiac magnetic resonance image processing involving both image segmentation and image registration. Concerning the mesh generation, we propose a set of flexible tools for polygonal surface processing, intended to make easier all the necessary steps in a cardiac mesh generation pipeline. In particular, these tools are focused on the following actions:

- tagging precisely a mesh to define the different regions for the boundary conditions;
- defining a mesh-size depending on relevant quantities like curvature or thickness;
- connecting two different disconnected surfaces;
- defining conforming meshes between different physics of the cardiac function.

We present the tools using examples of cardiac mesh generation and we conclude showing some related simulations.

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

Deep learning based model order reduction for cardiac electrophysiology

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In multi-query applications, the solution of a full-order model (FOM) entails prohibitive computational costs when its dimension is large. A classical approach to model order reduction (MOR) consists in approximating the solution manifold through a linear trial manifold. Linear MOR however is not well-suited to problems featuring travelling wave behaviours, e.g. cardiac electrophysiology, due to the fact that the dimension of the linear trial manifold could be excessively large to ensure an acceptable accuracy on the approximated solution. To overcome this deficiency, we adopt a nonlinear approach to MOR in which the function defining the nonlinear trial manifold as well as the reduced dynamics are learned, by means of deep learning models, from FOM solutions.

In particular, we report some preliminary results and highlight accuracy and efficiency by the technique here developed in comparison with linear MOR on some significant test cases in cardiac electrophysiology.

Acknowledgment. This project has received funding from the European Re-search Council (ERC) under the European Unions Horizon 2020 research and innovation programme (grant agreement No 740132).

A numerical study of fully coupled cardiac simulations on the human heart

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Simulating the cardiac function of a human heart involves the consideration of a multitude of systems. The propagation of electric charge in the cardiac tissue, the resulting mechanical contraction of the muscle and the blood pressure within the heart chambers all take into account a variety of physiological models, both on a macroscopic tissue level as well as on a microscopic cellular scale.

Using the models of ten Tusscher et al. and Courtemanche et al. to account for action potential generation in the ventricles and atria, respectively, as well as the model by Land et al. for cellular tension development, we consider a coupled electromechanical system on a full heart geometry. On the tissue level, a monodomain model for the electrophysiology and the passive materials of Guccione and Holzapfel are implemented. The boundary condition given by the blood pressure within the chambers is calculated through a closed-loop circulatory model. While the physiology of the individual models is well understood and documented, their interaction on a coupled system is not.

We present the aforementioned fully coupled system and illustrate the implementation of the coupling strategies. Additionally, we discuss the behaviour of this system regarding modifications of selected ways of coupling and model parameters.

Hemodynamics in a pathological left ventricle: from clinical data to numerical results

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The work presented in this talk is motivated by a pathological condition known as Systolic Anterior Motion (SAM) of the mitral valve. This pathology can arise due to different and possibly concurrent causes – among which hypertrophic cardiomyopathy of the interventricular septum – and results in a partial obstruction of the left ventricle outflow tract. In order to assess the severity of this condition, a computational fluid dynamics (CFD) study was performed, in patient-specific geometries.

An image segmentation and registration pipeline was developed and applied to cineMRI clinical data, in order to provide the geometry and motion of the left ventricle and of the mitral valve. Missing information was recovered using a third-party template geometry. The motion of the ventricle drives the CFD analysis, in an arbitrary Lagrangian-Eulerian finite element framework. A resistive term [1, 2, 3] is employed to immerse the moving mitral valve in the fluid domain. Numerical experiments show the suitability of this pipeline to feed CFD simulation with patient-specific, time-dependent geometrical data, and thus get insight on pathological hemodynamics such as in the case of SAM.

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

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Non-linear Scalable Solvers for Cardiac Reaction-Diffusion Models

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The development of effective solvers for the solution of mathematical models of the cardiac electro-mechanical activity has increasingly grown in the last decade. In particular, the need to handle the multiscale systems arising from the discretization of such models has required the development of specific techniques to both accurately represent physiological data and reduce the computational costs of the resulting large-scale simulations.

In this work, we study a new class of non-linear Domain Decomposition (DD) methods, called non-linear Dual-Primal Finite Element Tearing and Interconnecting (FETI-DP) methods, recently proposed in [1], for finite element discretizations of the non-linear parabolic reaction-diffusion Partial Differential Equations describing the propagation of the electric impulse in the cardiac tissue, coupled with a simple phenomenological ionic membrane model. The main idea of the non-linear FETI-DP method consists in decomposing the global non-linear problem into weakly coupled local non-linear problems, each solved independently.

We investigate numerically the quasi-optimality and scalability of the new method, and we evaluate its efficiency by comparing it with a more standard Newton-Krylov FETI-DP method, where the decomposition of the problem is made after the Newton linearization. The obtained preliminary results provide a basis for an extension of this study to the inclusion of more complex realistic membrane models and to monolithic discretizations of cardiac electro-mechanical models.

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

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Abnormal heart rhythm: a numerical study of the electrophysiological substrate

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In this work we present a new personalized computational model to numerically simulate re-entrant arrhythmias from patients' high-resolution catheter mapping data. We investigate ventricular tachycardia (VT) induction and sustainment on varying the pacing protocol and the ectopic stimuli location. The ability of the method in reproducing patients' re-entrant circuits is verified by comparing the numerical results with complete VT activation maps obtained from high-resolution mapping.

We also present a computationally efficient framework to perform uncertainty quantification and sensitivity analysis in cardiac electrophysiology, aimed at better understanding the mechanisms behind cardiac rhythm disorders. To this goal, we develop a data-model integration strategy based on reduced-order numerical solvers combined with machine learning and uncertainty quantification techniques. Numerical experiments dealing with pathological cases, such as tachycardia, illustrate the ability of the pipeline in estimating which parameters and which interactions among them generate a pathological condition.

This project has received funding from the European Research Council under the European Unions Horizon 2020 research and innovation programme (grant n. 740132).

Multiscale numerical simulation of the cardiac function: exploiting machine learning for modeling active force generation

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High-fidelity mathematical models of cardiac active force generation typically feature a large number of state variables in order to capture the intrinsically complex underlying subcellular mechanisms. With the aim of drastically reducing the computational burden associated with the numerical solution of these models, we propose a machine learning technique that builds a reduced order model (ROM) from a collection of input-output pairs generated with a high-fidelity (HF) model. The ROM is the best-approximation of the HF model within a class of candidate models represented by means of Artificial Neural Networks (ANNs), that are trained to learn the dynamics of the HF model in a non-intrusive way. A drastic reduction in both computational cost and memory storage is achieved, with accurate results with respect to the HF model. We show that our ROM for active force generation is crucial when performing numerical simulations of the whole heart function, that is when active force models are exploited in the problem of cardiac electromechanics. Specifically, a speedup of about one order of magnitude, while preserving almost the same accuracy of the HF solution, is achieved.

This project was founded from the European Research Council under the EU's Horizon 2020 research and innovation program: grant agreement No.740132, iHEART, 2017-2022.

Electromechanical modeling of the left ventricle in physiological and pathological conditions

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In the framework of efficient partitioned numerical schemes for the simulation of coupled problems described by PDEs, we propose using intergrid transfer operators based on radial basis functions to exchange accurately information between models defined in the same computational domain. Different (potentially non-conforming) meshes can be used for the space discretization of the PDEs. The projection of the variables that are needed for the coupling is made by means of Rescaled Localized Radial Basis Functions (RL-RBF). We apply our approach to the coupled electromechanical model for the human heart function, simulating in the High Performance Computing context heartbeats of both idealized and patient-specific left ventricles in physiological and pathological conditions.

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

Parameter estimation and uncertainty quantification in patient-specific models of cardiac mechanics.

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Detailed knowledge of the stress state of the cardiac muscle is potentially of huge value for cardiac research and clinical practice. Stress is directly linked to the work and energy usage of the muscle, and is also believed to be tightly coupled to growth and remodeling of the tissue. Precise quantification of tissue stress may therefore lead to better prediction of pathological remodeling, and thereby improved diagnosis and treatment of heart failure. Detailed strain analysis is readily available to clinicians by modern medical image modalities such as cardiac ultrasound and tagged magnetic resonance imaging. However, tissue stress is not possible to measure directly, and must be computed based on the estimated strain and on knowledge of tissue material properties. Estimating the material properties of soft muscle tissue is challenging even in laboratory experiments, and any in vivo, patient specific estimate of cardiac tissue material properties will contain a large degree of uncertainty. In this study we evaluate and compare alternative approaches for parameter estimation and uncertainty quantification in cardiac mechanics.

First, parameters are fitted using a classical deterministic optimization approach, where the material parameters are chosen to minimize the misfit of model results and measured data. Robust and efficient data fitting is obtained with a gradient-based optimization algorithm, where the gradients are computed by solving an automatically derived adjoint problem. The approach has been shown to give an excellent fit of model strains and volumes to the dynamic measured data, but gives little insight into the potential impact of uncertainty in measurements and fitted parameters. To gain insight into these questions, we applied a a forward-model uncertainty quantification (UQ) based on polynomial chaos expansion. This approach makes assumptions on model parameter uncertainties in the form of probability distributions, and computes how these uncertainties are propagated through the forward model and impact output quantities of interest. Although this is a powerful approach for forward UQ and sensitivity analysis, a potential limitation is that one needs to make assumptions about the probability distributions of input parameters. These assumptions are difficult to relate to actual uncertainties and noise in measurements, since the parameter values are solutions of an inverse problem and not measured directly. Finally, in an attempt to better quantify model parameter uncertainty, we have adopted a Bayesian approach for the parameter estimation problem. This approach computes probability distributions of material parameters by combining prior assumptions on parameter uncertainty with the actual uncertainty in measured quantities such as volumes, pressures and strains.

Optimization based estimation of activation sites in the heart

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This talk is concerned with an inverse problem in cardiac electrophysiology. In particular, the locations of the activation sites in the heart are estimated from the arrival times of the excitation wave on the epicardium of the heart. The electrophysiologic activity of the heart is often modeled using the Bidomain equations, whose numerical solution is very expensive. If one is only interested in the activation times T of the tissue, the Bidomain model can be reduced to the simpler viscous Eikonal equation

$$\begin{cases} -\varepsilon \operatorname{div}(M\nabla T) + M\nabla T \cdot \nabla T = 1 & \text{in } \Omega, \\ T = g_a & \text{on } \Gamma, \\ \varepsilon \nabla T \cdot n = 0 & \text{on } \Gamma_N. \end{cases} \tag{1}$$

The domain Ω models the geometry of the heart. The epicardium of the heart is denoted by Γ_N and the boundaries of the activation region (activation sites) by Γ. The matrix M describes the fiber orientation of the heart tissue and the function g_a the activation times in the activation regions. On the basis of this model we formulate the inverse problem in the following form

$$\min_{\Gamma} J(\Gamma) := \frac{1}{2} \int_{\Gamma_N} (T(\Gamma) - z)^2 \, \mathrm{d}x \quad \text{subject to (1)}, \tag{2}$$

where z is the measured data on the epicardium. Problem (2) constitutes a shape optimization problem. We approach problem (2) using a gradient descent method. Thus we calculate the shape derivative DJ of J with respect to Γ on the continuous level. The numerical calculation of a perturbation field for Γ based on DF involves the numerical solution of (1), the adjoint equation of the linearized version of (1) and a vector-valued elliptic equation. These equations are discretized using linear finite elements and the non-linearity is treated using a quasi Newton method. The talk is concluded with the presentation of numerical experiments on a three-dimensional heart geometry with synthetic data.

Numerical approximation of a fluid-structure interaction model for the aortic valve dynamics

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The aortic valve is a biological structure that regulates the blood flow between the left ventricle of the heart and the aorta. In normal conditions, the anatomy of the aortic valve presents three leaflets that open during the systole thanks to the higher pressure in the ventricle than in the aorta, and close during the diastole as a consequence of the pressure drop in the ventricle. In physiological conditions, the opening and the closure phases of the valve are very fast, the leaflets exhibit a large displacement, they have to sustain high pressure drops and the fluid-dynamics in the aortic root is very complex. The aim of this work is to numerically approximate the dynamics of the aortic valve through a fluid-structure interaction model in order to study its healthy function. A three-dimensional model is employed for describing the geometry of the leaflets and an unfitted numerical method is used to deal with their large displacement. This unfitted approach is based on the Extended Finite Element method which is able to track the moving geometry by maintaining the fluid mesh fixed in time, avoiding stretched elements and without the aid of a remeshing procedure. Moreover, a discontinuous Galerkin approach is used to couple the fluid and structure problems at their unfitted interface. Numerical tests show the effectiveness of the proposed method which is applied to obtain a preliminary result on a realistic geometry of an aortic valve in physiological conditions.

Local reduced order modeling for parameterized problems in cardiac mechanics

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The numerical solution of the cardiac mechanical problem is a very demanding task in cardiovascular simulations, especially in view of the electromechanical coupling. For accuracy purposes, numerical discretization must be carried out on fine computational meshes, hence high-fidelity full-order models (such as the finite element method) feature a huge computational complexity. In this context, reduced-order models (ROMs) have been developed aiming at approximating the full-order model by a problem of much smaller dimension. Starting from the Reduced Basis method, we have developed a strategy that allows to reduce the dimensionality and, as a matter of fact, the computational effort of parameter-dependent mechanical problems. We have tested our approach on the mechanical solution of the myocardial displacement in a patient-specific left ventricle configuration, when varying the intensity of the pressure exerted on the endocardium and the material parameters that characterize the myocardium. Our aim is to apply the developed strategy in order to deal quickly and efficiently with the repeated solution of coupled electromechanical problems, as well as to address uncertainty quantification problems relevant to cardiovascular modeling.

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

Effect of MRI frequency-space undersampling in inverse problems in hemodynamics

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The goal of this work is to study how physical flow parameters can be reconstructed from raw data sets in the context of 4D flow MRI. Specifically, we will analize how standard MRI undersampling protocols, such as Compressed Sensing and kt-BLAST can enhance the total scan time at the expense of some noise/artefacts in the reconstruction.

The study will consist in two parts. First, how does the undersampling affect the reconstruction of pressure maps from 4D flow [1]? And second, how do the undersampling artefacts affect the estimation of boundary condition parameters when using a PDE-constrained data assimilation approach [2]?

In particular, what are the reasonable acceleration factors in the data acquisition that allow reliable estimations?

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A compositional model of the Heart- Pacemaker system in CospanSpan(Graph)

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The compositional CospanSpan(Graph) model, introduced in [5, 6], has been shown to model cleanly a variety of phenomena from asynchronous circuits to hierarchy, mobility and coordination [3]. The elements of the model are cospans and spans of graphs which here we shall call simply *Automata with interfaces*. These automata are an extension of the "classical" finite state automata introduced in the seminal paper of McCulloch and Pitts, as a *discrete* model for threshold neurons and neural networks. Automata, since then, have become the standard model for the specification and verification of *sequential* discrete dynamical systems, and have been extended in order to represent probability (Rabin) and time. In recent years we have been assisting to a paradigmatic shift from sequential systems (exemplified by Turing Machines) to *networks* of interacting components. Hence, various models of automata with product (of states) have been proposed to represent *interactions* (Zielonka, Petri). These models are rather natural, but unfortunately are not compositional, that is they lack an algebra. On the contrary, *compositionality*, i.e. an algebraic calculus, is an essential feature of CospanSpan(Graph). Basic elements of the model are automata with states and transitions, as well as interfaces and conditions. There are two classes of operations on these automata - parallel (or product) and sequential (or sum) operations - hence yielding a categorical algebra of automata. An expression (or even a recursive equation) in this algebra represents a hierarchical, reconfigurable network of interacting components.

The purpose of this talk is to investigate further the expressivity of the Cospan-Span model, in particular for the modeling of biological discrete real-time systems. In [2], we gave a rather simple but compositional description of the heart. Here we show that it is possible to extend this simple model by considering time and probability (to change its "regular" behavior). Furthermore, a complete description of a Dual Chamber Pacemaker was provided, following [1,4], but again in a compositional way [7]. Finally, here, we compose the heart model and the pacemaker model, so obtaining a complete specification of the Heart-Pacemaker system.

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A Method for Pressure-Volume-Based Parameter Identification for a Passive Constitutive Model of Myocardium

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The contraction of the heart is a complex process involving the interaction of active stress development, which is elicited by the electrical activation of the cells, and the passive material properties of the tissue. In computer simulations of cardiac mechanics, the latter can be mathematically described by a constitutive model and can be integrated in a non-linear finite element solver. Once the input parameters are defined, the deformation of a discretized geometry can be calculated. Nevertheless, selecting the set of input parameters is a challenge, as there is no clear consensus in the literature on how to chose the parameters for an in silico simulation.

In this study, we present a simple and robust method to identify the passive parameters of a predefined model applied on the ventricles of a whole heart geometry. Here, the constitutive model, which defines the passive stress resulting from tissue deformation is the one presented in Guccione et al. 1991. It describes a transversely isotropic material with respect to the fiber coordinate system. To enforce incompressibility, a penalty term is added to the strain-energy function.

The proposed method is based on measured end-diastolic pressure-volume relations as described in Klotz et al. 2006. There, the measurements were normalized in the volume dimension and were approximated by an exponential analytical expression. We extended it by adding a linear term, which allows a better fit to the measured data, which we refer to as the "adapted Klotz curve".

The identification method consists of sampling the parameter space of the constitutive model (C, b_f) and minimizing a cost function. For each set of parameters, the left ventricle is inflated with pressure increasing from 0 to 30 mmHg. The relation between pressure and normalized volume is established and the squared error $e(C, b_f)$ to the adapted Klotz curve is calculated. Minimizing the error is not sufficient to uniquely identify the constitutive parameters. Therefore, the cost function is extended: $F_c(C, b_f) = (1 + e(C, b_f)) \cdot (1 + |vol_{min}/vol_{max} - 0.42|)$. Here, vol_{min} and vol_{max} are the left ventricle volumes at 0 and 30 mmHg respectively. The target volume ratio 0.42 results from eq. (8) in Klotz et al. 2006. The parameters for the stiffness in the plane perpendicular to the fiber direction and under shearing deformation are coupled to b_f: $b_t = 0.4 b_f$ and $b_{ft} = 0.7 b_t$ (Genet at al. 2014). For our particular geometry, we obtained the parameters: $C = 556$Pa and $b_f = 12$.

In future, we will include an unloading procedure to avoid overestimation of loaded ventricular volume. Altogether, the optimized parameters of the constitutive model are expected to deliver more physiological simulation results in terms of the passive behaviour of the ventricles.

Energy-consistent discretisation for one-dimensional blood flow models

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Reduced-order (RO) models are very widespread in clinical applications, since they enable to perform simulations at an acceptable computational cost and are more adequate to the resolution of inverse problems (IP), enabling patient-specific predictions. However, IP strategies may fail if the forward problem lacks of appropriate stability properties. In this regard, energy-preserving schemes are ideal to discretise the forward problems, since they are stable and flexible with respect to a variation of parameters and they ensure a reliable control on the behaviour of the solution. Among numerous cardiovascular RO models, the reduced-dimensional multi-physics beating heart model [1] that has been developed in the Inria research team MΞDISIM relies on a strategy introduced in [2] to perform an energy-preserving time discretisation. However, this model currently takes into account simple outflow boundary conditions, based on 0D Windkessel models.
The objective of this work is to derive a novel, energy-consistent discretisation for blood flow in the ascending aorta that is suitable to the coupling to the nonlinear mechanical model of [1]. In more detail, the proposed model corresponds to a time discretisation of the nonlinear 1D equations of haemodynamics in a generic arterial segment that preserves, at the discrete level, the energy relation provided in [3, Lemma 2.1] at the continuous framework. In more detail, our formulation is based on an adequate change of variables such that the energy density of the system becomes quadratic with respect to the new unknowns. Then, we derive a compatible space discretisation by an appropriate choice of quadrature rule and we recover a semi-discrete energy relation. Finally, we adopt an implicit mid-point time discretisation and perform an appropriate treatment of the boundary terms to guarantee the unconditional stability of the scheme and preserve an energy relation at the fully discrete level.
The end-goal is to obtain a stable and accurate framework for the modelling of the heart and the ventriculo-vascular coupling, in order to investigate stable IP strategies and obtain patient-specific simulations, and accurately estimate some physiological markers, e.g. the dicrotic notch. The model output will be compared with in vivo measurements that we have at our disposal.

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Influence of cardiac muscle fibers on the heart electrophysiology.

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A critical issue in simulating cardiac electrophysiology is the arrangement of the myocardial fibers feeding the heart model. Aggregations of myofibers, namely the cardiomyocytes orientation, determine how the electric wave propagate within the cardiac muscle. Hence, fiber orientations should be accurately modelled in the whole heart muscle to obtain physically meaningful results. Rule-Based-Methods (RBM) are one of the most used strategies to prescribe fiber orientation for computational cardiac models. In this work, we review existing RBM for fiber generation in the heart ventricles, making a comparison with some biomarkers (e.g. activation time) in different fiber scenarios. We also propose a novel RBM to be used for generating atria fiber based on an extensions of RBMs for the ventricles that are able to reproduce main atria fiber bundles. Finally, we show numerical results including the discussed fiber generation and phisiological activation sites in a four chamber realistic computational domain of the heart.

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

An effective numerical model for fluid-structure interaction in carotid arteries based on CINE MRI images

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Hemodynamics play an important role in the development, growth and risk of rupture of atherosclerotic plaques. In this work, we present an effective numerical model for fluid-structure interaction (FSI) simulations to study the fluid-dynamics in carotid arteries in presence of plaque, performed using subject-specific geometries and boundary conditions based on clinical imaging.

Due to difficulties in 3D plaque reconstruction and modelling from the available radiological data, a reduced model was introduced to surrogate the presence of the atherosclerotic plaque. The support of surrounding tissues, modelled by enforcing Robin boundary conditions on the external wall of the artery, was spatially differentiated to take into account the presence of different tissues, such as the atherosclerotic plaque.

As a first application of the method, we considered three subjects with a degree of stenosis greater than 70%. For each subject, velocity signals were acquired from Echo-Color Doppler (ECD) measurements, which were used as inflow Dirichlet boundary conditions. MR images were segmented to obtain subject-specific 3D geometries.

The resulting FSI simulations were quantitatively assessed by comparing the results with dynamic image sequences. ECD measurements taken at the internal branch (2 cm downstream from the site of maximum stenosis) were used as reference data to assess the flow division. Reference displacements on the lumen-wall interface were obtained throughout the cardiac cycle by segmenting CINE MRI images acquired in the axial plane at several positions along the vessel. The comparison between computed and imaging wall displacements shows a very good agreement, confirming the validity of the proposed approach.

A realistic detailed 3D model of the human atria and torso for studying supraventricular arrhythmias

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Introduction: Atrial arrhythmias are the most common sustained cardiac arrhythmias in human. Atrial arrhythmias, mainly atrial fibrillation (AF), are considered major causes of morbidity and mortality. In recent years, computational modelling has provided a framework of multi-scale integrated models for the study of cardiac arrhythmias.
Aim: The main objective of this work is to present a complete realistic three-dimensional (3D) model of the human atria and torso that our group has developed in the last years. These models have integrated in a multi-scale platform that has proved to be a powerful tool in understanding complex mechanisms underlying atrial arrhythmias as well as to predict the effect of different therapies.
Results: The realistic 3D model of the human atria includes the main structures of the atria: sinoatrial node (SAN), Crista Terminalis (CT), Bachmann bundle (right and left part, BBR, BBL), intercaval bundle (IB), septum (RAS), lateral wall (RLW), right and left appendage (RAA, LAA), pectinate muscles (PM), isthmus (IST), superior (SCV) and inferior (ICV) cava veins, ring of the tricuspid (TV)and mitral valve (MV), left superior wall (LSW), left septum (LAS), left posterior wall (LPW), right (RPV) and left pulmonary veins (LPV) and the coronary sinus (CS). In addition, the fossa ovalis (FO) and its limb (LFO), which connects the right atrium (RA) and left atrium (LA), were considered as one independent structure.
The model presents a heterogeneous wall thickness (from 0,5 to 7 mm, mean value of 3mm) and a realistic transmural fiber orientation based on experimental observations. The 3D atrial model has a spatial resolution of 300 μm and is comprised of 1.945.101 hexahedral elements and 2.174.034 nodes. To reproduce the heterogeneity in action potential morphology and in tissue conduction of the different atrial regions, nine cellular models and ten tissue materials were defined.
The torso dataset was obtained from University of Utah and comprises of the principal organs: lungs, bones, liver, ventricle, blood pools and flesh. The torso was segmented (Seg3D) and meshed (TetGen) resulting in 190.804 nodes and 1.149.531 tetrahedral elements with a spatial resolution of 0.6 mm.
Conclusion: Our realistic 3D multi-scale model of human atria and torso has proved to be a powerful platform for the study of atrial arrhythmias and for the advancement of improved therapies by predicting their effects without irreversible damage to the patients.

Computational cardiac electrophysiology based on septal and epicardial mapping

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In this work we present the first steps towards the validation of the electrophysiological bidomain ionic model on patient-specific left ventricles, using septal and epicardial mapping of activation times.

The preprocessing of the data starts with the acquisition of the cineMRI and the corresponding left ventricle epicardial activation map, acquired using the NavX system. The map consists in the local activation times in different points on the septum and on the epicardial coronary tree of the left ventricle. After the reconstruction of the patient-specific geometry and the computational mesh generation, we need to transform and project the activation map onto such surfaces. This procedure turns out to be necessary because the activation map is acquired in a different moment with respect to the cineMRI, and with a different clinical machine.

Numerical simulations were performed in the Finite Elements library lifev using the bidomain equations coupled with the Bueno-Orovio ionic model. Electrophysiological patient-specific parameters were chosen in order to obtain physiological results. In particular, the septum data were used as applied current, whereas the coronary data were used to quantify the discrepancy with the numerical solution.

We present some results obtained by applying the procedure described above on different patients.

An smoothed particle hydrodynamics approach for electrophysiolgy

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Smoothed particle hydrodynamics (SPH) has been successfully exploited in a broad variety of problems ranging from solid mechanics to fluid mechanics and fluid-structure interactions (FSI) due to its fully Lagrangian feature. However, the implementation of SPH method in modeling cardiac electrophysiolgoy has not been explored. In this paper, we present an SPH approach for electrophysiolgoy where a monodomain model, a system of a parabolic semilinear reaction-diffusion equation coupled with a nonlinear ordinary differential equation, is considered. An operator splitting and adaptive time step is adopted for solving the reaction-diffusion equation. The diffusion problem is solved by an anisotropic SPH approximation, and the reaction term is solved by using quasi-steady-state (QSS) method to obtain the approximate exact solution. Numerical experiments assess the validity of the proposed SPH approach.

Computational Fluid Dynamics of Blood Flows in the Left Heart

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Blood flows in the heart are usually studied and analysed through experimental techniques and imaging processes. However, these approaches suffer from a lack of resolution into the spatial and temporal scales of the blood flow. Computational fluid dynamics stands as a tool to complement such techniques to provide a detailed description of the physiological condition, as well as for an in-depth analysis of pathological scenarios. In this work, we investigate the blood flow dynamics of the left human heart, with special focus on the left atrium. In particular, the incompressible Navier-Stokes equations are considered in Arbitrary Lagrangian Eulerian (ALE) framework with a Variational Multiscale-Large Eddy Simulation (VMS-LES) model in order to mimic the transitional and nearly turbulent regime of blood flow.

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