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organized by
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PROGRAM

Monday, April 16, 2018

14:00-14:15 Opening and Welcome

Chair: L. F. Pavarino

14:15-15:00 P. Colli Franzone (Università degli Studi di Pavia, Italy), L. F. Pavarino, S. Scacchi: *Stability of re-entrant cardiac dynamics: influences of mechano-electric feedbacks and of infarct scar geometric properties*

15:00-15:45 R. Krause (Università della Svizzera Italiana, Switzerland), M. Favino, M. Nestola, S. Pozzi, P. Zulian, A. Auricchio: *Fast Solution Methods for Coupled Problems in Cardiac Simulation*

15:45-16:10 Coffee break

16:10-16:30 C. Cherubini (Università Campus Bio-Medico di Roma, Italy), S. Filippi, A. Gizzi, A. Loppini, R. Ruiz-Baier: *On Stress-driven Anisotropic Electrical Diffusion in Cardiac Electro-Mechanics*

16:30-16:50 C. Pierre (Université de Pau, France), C. Douanla-Lontsi: *Efficiency of high order schemes for the monodomain model*

16:50-17:10 L. Gerardo Giorda (Basque Center for Applied Mathematics, Spain), N. Cusimano: *Combining tissue anisotropy and heterogeneity in cardiac electrophysiology: a space-fractional Monodomain model*

17:10-17:30 M. K. Gobbert (University of Maryland, USA), C. Barajas, S. Khuvis: *Challenges and Opportunities for the Simulations of Calcium Waves on Modern Multi-Core and Many-Core Parallel Computing Platforms*

17:30-17:50 R. Spiteri (University of Saskatchewan, Canada), J. Cervi: *High-Order Operator-Splitting Methods for the Bidomain and Monodomain Models*

17:50-18:10 M. Landajuela (Politecnico di Milano, Italy), C. Vergara, A. Gerbi, L. Dedè, L. Formaggia, A. Quarteroni: *Numerical approximation of the electromechanical coupling in the left ventricle with inclusion of the Purkinje network*

Tuesday, April 17, 2018

Chair: G. Plank

09:00-09:45 A. F. Frangi (University of Sheffield, UK), R. Attar, M. Pereanez, J. M. Pozo, A. Sarrami-Foroushani, L. Zhang, A. Gooya, T. Lassila, Z. A. Taylor: *Towards computational imaging phenomics and in silico clinical trials in cardiovascular science: vision and progress so far*

09:45-10:30 K.-A. Mardal (University of Oslo & Simula, Norway): *Mathematical modeling of the glymphatic system*

10:30-10:50 Coffee break

10:50-11:10 C. Corsi (Università degli Studi di Bologna, Italy), A. Masci: *Medical imaging for cardiac simulation studies*

11:10-11:30 E. Votta (Politecnico di Milano, Italy), F. Piatti, O. Pappalardo, A. Caimi, M. Selmi, G. Rossini, F. Sturla, A. Redaelli: *Clinically driven numerical models in cardiovascular surgery*

11:30-11:50 T. Weber (Otto von Guericke University Magdeburg, Germany), E. Scholz, F. Langkamp, H. A. Katus, S. Sager: *Applicability of the PREMAP algorithm to accelerate activation mapping of scar-related ventricular reentry tachycardia*

11:50-12:10 F. Caforio (INRIA & Université Paris-Saclay, France), S. Imperiale, D. Chapelle: *Modelling of impulsive source in a prestressed soft tissue*

12:10-12:30 S. Pozzi (Politecnico di Milano, Italy), F. Piatti, A. Camporeale, N. Cobo Gomez, G. Di Giovine, S. Castelvecchio, L. Menicanti, A. Greiser, E. Votta, A. Redaelli, M. Lombardi: *Towards the exhaustive analysis of left ventricle dysfunctions in ischemic cardiomiopathy: integrating wall kinetics, scar transmurality and wall shear stress*

12:30-14:00 Lunch break

Chair: R. Krause

14:15-14:45 W. A. Wall (Technische Universitaet Muenchen, Germany): *TBA*

14:45-15:30 M. Behr (RWTH Aachen University, Germany), S. Hassler, L. Pauli: *Towards Predictive Simulation of Artificial Blood Pumps*

15:30-15:45 Coffee break

Wednesday, April 18, 2018

Chair: Y. Coudiere

09:00-09:45 D. Chapelle (INRIA & Université Paris-Saclay, France): *Multi-scale modeling of chemo-mechanical coupling in muscle contraction and applications to cardiac modeling*

09:45-10:30 L. Dedè (Politecnico di Milano, Italy), A. Gerbi, A. Quarteroni: *Mathematical and Numerical Modeling of Cardiac Electromechanics: Numerical Coupling and Large-Scale Simulation*

10:30-10:50 Coffee break

10:50-11:10 C. Cavaterra (Università degli Studi di Milano, Italy), E. Beretta, M. C. Cerutti, A. Manzoni, L. Ratti: *An inverse problem arising from cardiac electrophysiology*

11:10-11:30 A. Quaglino (Università della Svizzera Italiana, Switzerland), S. Pezzuto, R. Krause: *Enabling uncertainty quantification for the monodomain equation via multifidelity techniques*

11:30-11:50 A. Manzoni (Politecnico di Milano, Italy), S. Pagani, A. Quarteroni: *Reduced Order Modeling for Uncertainty Quantification of the cardiac function*

11:50-12:10 Z. Zainib (SISSA, Italy), F. Ballarin, G. Rozza: *Reduced order modelling for cardiovascular haemodynamics: optimal flow control, data assimilation and geometrical reconstruction*

12:10-12:30 F. Regazzoni (Politecnico di Milano, Italy), L. Dedè, A. Quarteroni: *Active contraction of cardiac cells: a reduced model of force generation*

12:30-12:50 L. Fassina (Università degli Studi di Pavia, Italy), M. Cornacchione, M. E. Mognaschi, G. Magenes, F. Naro: *Ergotropic effect in cardiac tissue after electromagnetic and β-adrenergic stimulus*

12:50-14:15 Lunch break

Chair: C. Vergara

14:15-14:45 M. Domanin (Università degli Studi di Milano, Italy), C. Vergara: *Computational fluid dynamic modeling for the choice of the closure technique in carotid surgery*

14:45-15:15 E. Macchi (Università degli Studi di Parma, Italy), L. Magnani, M. Miragoli, E. Musso, S. Rossi: *Arrhythmia vulnerability by single premature stimulation in normal ventricular myocardium*

15:15-15:45 D. Catanzariti (Ospedale S. Maria del Carmine, Rovereto, Italy): *Learning by doing (pacing, burning and mapping)*

15:45-16:15 M. Miragoli (Università degli Studi di Parma, Italy), G. Rozzi, F. P. Lo Muzio, S. Rossi, L. Fassina, S. Strozzi, G. Faggian, G. B. Luciani: *Real-time video evaluation of the right ventricle kinematics during cardiac surgery: novelties, implications and future perspectives*

16:15-16:40 Coffee break

16:40-17:10 R. Scrofani (Ospedale L. Sacco, Milano, Italy), F. Nicolò, G. Cagnoni, C. Antona: *Cardiac Surgery and Biomedical Engineering*

17:10-17:40 N. Salvarani (Humanitas Clinical and Research Center, Milano, Italy), P. Carullo, M. Miragoli: *Anode Break Excitation in Hypertrophic Cardiomyocytes: An Investigative Tool for Predicting Modulation of Cardiac Excitability*

17:40-18:00 C. Contarino (Università degli Studi di Trento, Italy), E. F. Toro, A. Louveau, S. Da Mesquita, D. Raper, I. Smirnov, N. Agarwal, J. Kipnis: *A global, multi-scale mathematical model of the murine fluid systems: application to idiopathic intracranial hypertension*

18:00-18:20 F. Scardulla (Università degli Studi di Palermo, Italy), S. Hu, L. D'Acquisto, S. Pasta, L. Barrett, P. Blanos, L. Yan: *Systolic blood pressure detection using a multi-wavelength Opto-Electronic patch sensor at peripheral circulation*

20:00: Social Dinner

Thursday, April 19, 2018

Chair: G. Rozza

09:00-09:45 A. V. Panfilov (Ghent University, Belgium), M. P. Nash, L. D. Weise: *Mechano-electric feedback and initiation of cardiac arrhythmias*

09:45-10:30 Y. Coudiere (Université de Bordeaux & IHU Lyric, France), A. Davidovic, C. Poignard: *Modeling the propagation of cardiac action potential in hearts with structural heterogeneities*

10:30-10:50 Coffee break

10:50-11:10 L. Gastaldi (Università degli Studi di Brescia, Italy), D. Boffi, L. Heltai, M. Annese: *A distributed Lagrange multiplier formulation for the finite element discretization of FSI*

11:10-11:30 S. Pasta (Fondazione Ri.MED, Palermo, Italy), G. Gentile, G. M. Raffa, D. Bellavia, M. Pilato: *In Silico Shear and Intramural Stresses are Linked to Aortic Valve Morphology in Dilated Ascending Aorta*

11:30-11:50 A. This (INRIA Paris, France), L. Boilevin-Kayl, H. G. Morales, O. Bonnefous, M. A. Fernández, J.-F. Gerbeau: *Modeling isovolumic phases using a pressure corrected RIS model*

11:50-12:10 M. Fedele (Politecnico di Milano, Italy), E. Faggiano, L. Dedè[1], A. Quarteroni: *Patient-specific simulations of the hemodynamics through a moving aortic valve with the resistive immersed implicit surfaces method*

12:10-12:30 S. Zonca (Politecnico di Milano, Italy), L. Formaggia, C. Vergara: *Fluid-Structure Interaction via an XFEM/DG Approach for Valve Dynamics*

12:30-12:50 V. Meschini (SISSA, Italy), R. Mittal, R. Verzicco: *Flow-Induced Mitral Leaflet Motion in Hypertrophic Cardiomyopathy*

12:50-14:15 Lunch break

Chair: L. Dedè

14:15-15:00 G. Plank (Medical University of Graz, Austria): *Personalizing models of total heart function*

15:00-15:45 L. Teresi (Università degli Studi Roma Tre, Italy), V. Varano, P. Piras, S. Gabriele, I. Dryden, P. Nardinocchi, P. E. Puddu: *Shape Analysis for 3D Cardiac Imaging*

15:45-16:10 Coffee break

16:10-16:30 S. Severi (Università degli Studi di Bologna, Italy), A. Fabbri, M. Paci, R. Wilders, Y. Lutz, A. Loewe: *Computational Modeling of the Cardiac Pacemaking in Humans*

16:30-16:50 A. Gizzi (Università Campus Bio-Medico di Roma, Italy), D. Bianchi, M. Marino, G. Vairo, S. Filippi: *Multi-Scale Computational Modeling of FSI in Aorta Physiopathology: A Quantitative Risk Assessment Study*

16:50-17:10 D. E. Hurtado (Pontificia Universidad Católica de Chile, Chile), J. Jilberto: *Non-conforming finite-element schemes for cardiac electrophysiology*

17:10-17:30 I. van Herck (Simula, Norway), B. H. Bentzen, V. Seutin, J. T. Koivumaki, M. M. Maleckar, N. V. Marrion, A. G. Edwards: *Development* in silico *model of SK channel gating, calcium sensitivity and drug interaction*

17:30-17:50 E. M. Wuelfers (University of Freiburg, Germany), G. Seemann: *Estimating ion current fractions in mathematical models of non-selective channels*

17:50-18:10 C. Mahapatra (IIT Bombay, India), R. Manchanda: *A computational model of action potential in the mouse detrusor smooth muscle cell*

18:10-18:20 Closing

ABSTRACTS

Towards Predictive Simulation of Artificial Blood Pumps

Marek Behr[1], **Stefan Hassler**[1], **Lutz Pauli**[1]
[1] Chair for Computational Analysis of Technical Systems, RWTH Aachen University, Aachen, Germany

Modeling and computational analysis play an increasingly important role in bioengineering, particularly in the design of implantable ventricular assist devices (VAD) and other blood-handling devices. Numerical simulation of blood flow and associated physiological phenomena has the potential to shorten the design cycle and give the designers important insights into causes of blood damage and suboptimal performance. A set of modeling techniques is presented which are based on stabilized space-time finite element formulation of the Navier-Stokes equations. Alternate methods that represent the rotating components in an averaged sense using a rotating frame of reference will be discussed [1]. In order to obtain quantitative hemolysis prediction, cumulative tensor-based measures of strain experienced by individual blood cells must be developed; red blood cells under shear can be modeled as deforming droplets, and their deformation tracked throughout the flow volume [2]. The methods are applied to a simplified rotary blood pump, which is currently a subject of an inter-laboratory round-robin study.

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Modelling of impulsive source in a prestressed soft tissue

Federica Caforio[1,2], **Sébastien Imperiale**[1,2], **Dominique Chapelle**[1,2]
[1] Inria, Université Paris-Saclay, France
[2] LMS, Ecole Polytechnique, CNRS, Université Paris-Saclay, France

Shear acoustic waves remotely induced by the acoustic radiation force (ARF) of a focused ultrasound beam generated by piezoelectric probes have been increasingly used in biomedical applications, e.g. in transient elastography techniques [Bercoff et al., 2004; Sarvazyan et al., 1998]. By measuring the velocity of propagation of generated shear waves in biological tissues and fluids, it is possible to locally assess biomechanical properties which 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 [Correia et al., 2017; Pernot et al., 2011]. In this context, the wave propagation induced by the ARF is superposed with the nonlinear mechanics associated with the heart deformation during the cardiac cycle.

The aim of this work is to mathematically justify an original expression of the excitation induced by the ARF in nonlinear solids, based on energy considerations and asymptotic analysis. In soft media, such as biological tissues, the propagation velocity of shear waves (110 ms^{-1}) is much smaller than the velocity of pressure waves (1500 ms^{-1}). The approach we propose consists in consid- ering a family of problems, parametrised by a small parameter ϵ related to the velocity ratio between the two wave propagation phenomena, the high frequency of the piezoelectric source term and the viscosity. In order to derive a simplified model for the expression of ARF, we investigate the limit behaviour of the solution for $\epsilon \to 0$.

By formal asymptotic analysis – an asymptotic expansion of the solution is used – we show that the leading order term of the expansion is the underlying nonlinear cardiac mechanics, the electrical activation of the heart being the corresponding source term. Then, two corrector terms are computed. The first consists in a fast-oscillating pressure wave excited by the probes, and we show that it is the solution of a scalar quasi-static Helmholtz equation at every time step. Additionally, its existence and properties are rigorously analysed in the linearised case. On the other hand, the second corrector term is an elastic field with prescribed divergence, having as source term a function of the first corrector. This field corresponds to the shear acoustic wave induced by the ARF. As a by-product of our analysis we prove that, in prestressed media, the presence of viscosity is essential to produce shear waves with ARF, and that they are related to the nonlinear form of the expression of volume deformation.

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[3] M. Pernot, M. Couade, P. Mateo, B. Crozatier, R. Fischmeister and M. Tanter. Real-time assessment of myocardial contractility using shear wave imaging. J. Am. Coll. Cardiol., (2011) 58 (1): 65–72.
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Learning by doing (pacing, burning and mapping)

Domenico Catanzariti[1]

[1] Electrophysiology Laboratory, S. Maria del Carmine Hospital, Division of Cardiology, Rovereto, Italy

Aim of my talk is to expose our electrophysiological laboratory results in some of our fields of interest and theoretical problems encountered in our daily work. This can serve the purpose of collecting different experiences and promoting dialogue between mathematical science and "cardiological world".

Tipically, during ventricular ablation we mapped global endocardial activation of left ventricle in order to obtain a detailed sequence of electrical activation also considering the rapid endocardial network of the so-called Purkinje fibers.

In our clinical experience, we evaluated intraprocedural Coronary sinus activation patterns in patients with and without left bundle branch block undergoing electroanatomic mapping system-guided cardiac resynchronization therapy device implantation. Indeed, the implantation of the left ventricular (LV) lead in segments with delayed electrical activation may improve response to cardiac resynchronization therapy (CRT). To this purpose, we examined the amount and regional distribution of LV electrical delay (LVED) in patients with or without left bundle branch block (LBBB) in 60 patients who underwent electroanatomic mapping system-guided CRT device implantation. Activation mapping of the coronary sinus (CS) branches was performed using an insulated guidewire. LVED was defined as the interval between the beginning of the QRS complex on the surface electrocardiogram (ECG) and the local electrogram and expressed in milliseconds or as percentage of the total QRS duration (LVED%). Patients with LBBB showed higher maximum LVED when compared to patients without LBBB. The maximum LVED was usually recorded in mid-basal anterolateral or inferolateral LV segments (traditional CRT targets), significantly more often in patients with LBBB than in patients without LBBB (85% vs 59%; P = .02). The number of CS branches showing LVED >50% of the total QRS duration, >75% of the total QRS duration, and >85 ms was significantly higher in patients with LBBB than in patients without LBBB. Thus patients without LBBB showed lower LVED and more heterogeneous electrical activation of the CS than did patients with LBBB. This finding may contribute to a lower rate of response to CRT of patients without LBBB and suggests the use of activation mapping to guide LV lead placement.

In order to reduce pacing-induced intra- and inter-ventricular desynchronization and its detrimental effects, we performed his bundle pacing in 30 patients. During conventional right ventricular apical pacing (RVAP), LV ejection fraction decreased (50.1 ± 8.8% vs. 57.3 ± 8.5%, P < 0.001), mitral regurgitation increased (22.5 ± 10.9% vs. 16.3 ± 12.4%; P = 0.018), and inter-ventricular delay worsened (33.4 ± 19.5 ms vs. 7.1 ± 4.7 ms, P = 0.003) in comparison with HBP. No asynchrony was revealed during His Bundle Pacing, while during RVAP the asynchrony index was significantly higher. Thus His-bundle pacing has long-term positive effects on inter- and intra-ventricular synchrony and ventricular contractile performance in comparison with RVAP. It prevents asynchronous pacing-induced LV ejection fraction depression and mitral regurgitation.

Intuitive analysis of low voltage fractionated signals with a close spatial clustering at the border zone between dense scar and normal voltage, during electrical mapping of left atrium and ablation procedures, appear to be effective in terminating some episodes of persistent and long-duration atrial fibrillation. Complex and in-depth studies of chaotic signals aimed at analyzing these signals and at discriminating different form of noises are desirable where there is theoretical difficulty in extrapolating low amplitude and long duration signals incorporated in complex electrograms with just a single repetitive characteristic of building up in

specific sites. Closer co-peration between mathematicians and interventional electrophysiologists may result in the creation of sophysticated mathematical models with formalization and forecasting capabilities.

An inverse problem arising from cardiac electrophysiology

Cecilia Cavaterra[1], **Elena Beretta**[2], **Maria Cristina Cerutti**[2], **Andrea Manzoni**[2], **Luca Ratti**[2]

[1] Dipartimento di Matematica, Università degli Studi di Milano, Milan, Italy

[2] Dipartimento di Matematica, Politecnico di Milano, Milan, Italy

We consided a model describingtheevolution ofthe electric potential in the heart tissue. The goal is the determination of a small inhomogeneity inside the domain occupied by the heart from observations of the potential on the boundary. Such a problem is related to the detection of myocardial ischemic regions, characterized by severely reduced blood perfusion and consequent lack of electric conductivity. Both theoretical analysis and numerical reconstruction techniques are developed.

Multi-scale modeling of chemo-mechanical coupling in muscle contraction and applications to cardiac modeling

Dominique Chapelle[1]

[1] Inria & LMS, Ecole Polytechnique, CNRS, Université Paris-Saclay, France

We propose a chemo-mechanical model of muscle contraction by which myosin heads - that can chemically bind to actin, thus creating so-called cross-bridges producing contraction forces in sarcomeres at the subcellular level - are considered as special chemical entities having internal mechanical variables pertaining to the actual geometric configuration. This provides a thermodynamical basis for modeling the complex interplay of chemical and mechanical phenomena at the sarcomere level. The resulting model is in the form of stochastic equations governing the dynamics of these microscopic mechanical variables in a Langevin framework. Equivalently, Fokker-Planck equations can be derived to describe the evolution of the associated probability densities. Under certain assumptions, the corresponding moment equations can be closed, thus directly providing access to macroscopic quantities that can be incorporated in the overall constitutive equations of the muscle tissue. The underlying thermodynamical framework also enables the derivation of compatible numerical schemes, in particular in terms of energy balances. These modeling and discretization ingredients can be integrated in a global model of the cardiac system, to represent physiological and pathological phenomena in various medical applications.

On Stress-driven Anisotropic Electrical Diffusion in Cardiac Electro-Mechanics

Christian Cherubini[1,2], **Simonetta Filippi**[1,2], **Alessio Gizzi**[1], **Alessandro Loppini**[1], **Ricardo Ruiz-Baier**[3]

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[2] International Center for Relativistic Astrophysics Network, Pescara, Italy

[3] Mathematical Institute, University of Oxford, Oxford, UK

We discuss a novel generalized theoretical framework aimed to describe reaction-diffusion processes within the cardiac tissue in the context of active deformable media, i.e. mechano-electric feedback (MEF). In detail, we couple the electrical diffusivity tensor to the mechanical stress, taking inspiration from the physics of classical deformable dielectrics. The models analysis reveals that initially isotropic and homogeneous diffusivity tensors turn into inhomogeneous and anisotropic ones upon deformations. More in detail, numerical results obtained using a mixed-primal finite element method clearly support relevant evidences of stress-driven diffusion effects on anisotropy patterns, drifting, and conduction velocity of the resulting excitation waves. Possible extensions of the model are finally discussed.

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Stability of re-entrant cardiac dynamics: influences of mechano-electric feedbacks and of infarct scar geometric properties

Piero Colli Franzone[1], **Luca F. Pavarino**[1], **Simone Scacchi**[2]
[1] Department of Mathematics, University of Pavia, Pavia, Italy
[2] Department of Mathematics, University of Milan, Milan, Italy

In this work, we investigate the influence of cardiac tissue deformation on re-entrant wave dynamics. We have developed a 3D strongly coupled electro-mechanical Bidomain model posed on an ideal monoventricular geometry, including fiber direction anisotropy and stretch-activated currents. The cardiac mechanical deformation influences the bioelectrical activity with two main mechanical feedbacks: a) the geometric feedback (GEF) due to the deformation gradient and deformation rate, and b) the mechano-electric feedback (MEF) due to stretch-activated currents (SAC). We investigate the relative contribution of these two factors to the scroll wave stability by considering the full electro-mechanical model with both selective and non-selective components of the stretch activated currents. Finally, by means of the Bidomain simulations we investigate also the role of repolarization properties and thickness of the border zones (BZs) superimposed on a necrotic scar volume in the genesis of sustained re-entry pathways mimicking ventricular tachycardia.

A global, multi-scale mathematical model of the murine fluid systems: application to idiopathic intracranial hypertension

Christian Contarino[1], Eleuterio F. Toro[2], Antoine Louveau[3], Sandro Da Mesquita[3], Daniel Raper[3], Igor Smirnov[3], Nivedita Agarwal[4], Jonathan Kipnis[3]

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[4] Section of Radiology Ospedale Santa Maria del Carmine, Rovereto, Italy

Building upon the recent discovery of a meningeal lymphatics system for the mouse [1] and mathematical modelling capabilities developed for extracellular fluids in humans [2-5], here we propose a holistic, multi-scale and closed-loop mathematical model for the murine circulatory system coupled to the cerebrospinal fluid (CSF), and the CSF-draining lymphatic system. A validation of the mathematical model for the circulatory system is provided by comparing the theoretical model results with in-vivo pressure and MRI flow measurements. The mathematical model shows how the intracranial venous and CSF fluid compartments respond to the high pressure arterial cerebral blood inflow, in particular, by displacing CSF into the spinal subarachnoid space. We will show how the dynamics of the cerebral fluid is influenced by impairments of the venous system through the computational model and measurements on a mouse model of Idiopathic Intracranial Hypertension, a neurological disorder characterized by an abnormal intracranial pressure increase. Preliminary theoretical results show that under ligation of the major intracranial-blood draining vessels, the intracranial pressure increases by more than 100%, and this is broadly in agreement with experimental measurements.

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Medical imaging for cardiac simulation studies

Cristiana Corsi[1], **Alessandro Masci**[1]
[1] Department of Electrical, Electronic and Information Engineering "Guglielmo Marconi", University of Bologna, Bologna, Italy

In medical imaging, a large number of applications are moving towards the use of 3D geometrical models, including surgical planning, patient risk assessment and stratification. 3D anatomical models are increasingly being used in the precision medicine field, including simulations of biological processes and functions. For simulations of cardiac function in a personalized setting, a volumetric mesh defining the computational domain of the problem is required. Many subsequent steps, including imaging, segmentation and meshing must be taken into account to achieve accurate geometric representations from cardiac imaging. In this talk we will briefly discuss on the generation of patient-specific 3D geometries which serve as domain definitions in simulation studies.

Modeling the propagation of cardiac action potential in hearts with structural heterogeneities

Yves Coudiere[1,2,3], **Andjela Davidovic**[2,3], **Clair Poignard**[4]
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The bidomain or monodomain equations model the propagation of the cardiac action potential (AP) at the tissue scale. They rely on the tissue being described as a regular, homogeneous, network of cardiomyocytes. Though, several pathologies can affect the organisation of cells at various scales, e.g. in fibrosis (remodeling), fatty infiltrations, border zone of an infarct scar, myostructural diseases in general. Such regions with structural defects are hypothesized to play a role in arrhythmias. I will present an adaptation of the bidomain model to these situations. It is obtained by multiscale analysis, assuming periodic alterations in the tissue. I'll show how the propagation velocity is modified by these structural defects, and how we used the model to build a computational heart model accounting for structural heterogeneities from high-resolution MR images of a rat heart.

Mathematical and Numerical Modeling of Cardiac Electromechanics: Numerical Coupling and Large-Scale Simulation

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The simulation of the whole cardiac function is a challenging task from several standpoints: mathematical, numerical and computational. This is the main consequence of the multiphysics nature of the cardiac function, which is the result of the concerted action of several core models, namely electrophysiology, cellular activity, passive and active mechanics of the tissue, valves dynamics, and blood flow dynamics. In addition, each of these models is intrinsically complex and feature wide ranges of spatial and temporal scales along the heartbeat. Such scales need to be suitably captured to correctly represent the mutual interactions of the heart components and meaningfully characterize its multiscale nature.

In this talk, we consider the mathematical and numerical modeling of the left ventricle by integrating 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. We consider the spatial approximation of the Partial Differential Equations therein involved by means of the Finite Element method and the time discretization by means of Backward Differentiation Formulas. We solve the coupled electromechanical problem by exploiting both monolithic and staggered approaches in combination with either implicit of semi-implicit schemes. For the monolithic approach, we solve the large-scale discrete problem by means of the GMRES method with a newly proposed, physics-based preconditioner exploiting the coupling of core models through the block structure of the linear system. We numerically verify, compare, and critically discuss the accuracy of the monolithic and staggered schemes, as well as their computational efficiency and feasibility for simulating the whole cardiac cycle.

Finally, we present several numerical results of the electromechanics problem in the human left ventricle obtained in the high performance computing framework.

Computational fluid dynamic modeling for the choice of the closure technique in carotid surgery

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Hemodynamic is essential to acquire a thorough knowledge in vascular surgery, besides depth studies of the arterial anatomy, the pathophysiology of vascular atherosclerotic disease and surgical skilfulness. In fact, hemodynamic knowledge is basilar to fully understand the development and growth of the abdominal aortic aneurysm, the clinical relevance of steno-occlusive lesion of peripheral arterial disease of the lower limbs to diagnose severe carotid stenosis in cerebrovascular insufficiency.Moreover, at the end of vascular intervention in our daily practice the surgeon must always evaluate the hemodynamic results, to correct in advance eventual technical defects or to forecast immediate and long term outcome of the revascularization procedure.

Thanks to the advancement of Computational Fluid-Dynamic (CFD) models we have now the opportunity to control complex physiopathological issues, to explore alternative solutions and to forecast the results of vascular surgery.

Our research effort in these years has been, with the help of various collaborators, to transfer this knowledge from the bench to the bedside, starting from the field of the pure basic research and landing on the analysis of more practical aspects.

In this field, a typical case study research design is constituted by our work about the use of different closure techniques, i.e. primary closure vs patch graft, after carotid surgery.

By means of CFD, we have analysed WSS related quantities (OSI and RRT) in the two different closure techniques configurations in patients with severe carotid stenosis ($> 70\%$) submitted to carotid endarterectomy. At the end of the study we have discovered that both OSI and RRT values resulted higher when PG was preferred to DS and also areas with disturbed flow resulted wider. The absolute higher values computed by means of CFD were observed when PG was used indiscriminately regardless of carotid diameters. DS does not seem to create negative hemodynamic conditions with potential adverse effects on long-term outcomes, in particular when CEA is performed at the CCA and/or the bulb or when ICA diameter is greater than 5.0 mm.

Then, performing the opposite intervention i.e. virtually removing/adding the patch graft, we have analysed with CFD the results of the switched closure technique of the arteriotomy. OSI and RRT values resulted generally higher in PG cases with respect to PC, especially for high carotids and/or when the arteriotomy is mainly at the bulb region. Thus, an elective use of patch should be considered in order to prevent disturbed flows.

At least we have analysed, various geometric quantities of the carotid bifurcations with the hemodynamic results and matching those values respect of the localization and the severity of new atherosclerotic lesions, responsible for restenosis and potentially influencing the long-term outcomes of the surgical interventions.

In conclusion, we can argue that CFD analysis has now exceeded the limit of the past decade, where it was considered just a powerful research tool not amenable for routine clinical use, and currently can help the surgeon to improve and optimise the results of vascular surgery.

Ergotropic effect in cardiac tissue after electromagnetic and β-adrenergic stimulus

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A core idea of Tissue Engineering is to understand the relationships between structures and functions in mammalian cells. This information is important during the growth of tissue substitutes *in vitro*; in other words, Tissue Engineering constructs are based not only on the use of growth factors, but also on the stimuli provided by the structural context (e.g., the biomaterials with their biocompatibility and mechanical properties) and provided by the biophysical context (e.g., the forces acting onto the plasma membrane, transmitted to the cytoskeleton, and biochemically transduced). In particular, a modulation of the cellular function is well attested by the cardiomyocytes subjected to the mechanical forces induced by an electromagnetic field [1,2]. In addition, in the heart, the β-adrenergic receptors, associated to G proteins, play a fundamental role in regulating the cardiac function. In this work, we have studied the contraction movement of murine cardiomyocytes under electromagnetic stimulation (magnetic induction field, 3 mT; frequency, 75 Hz) and/or β-adrenergic stimulation (isoproterenol, 10 μM), addressing, in particular, the ergotropic effect (contraction energy). Via an image processing analysis, we have found that the electromagnetic stimulation is able to counteract the β-adrenergic action of isoproterenol.

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Patient-specific simulations of the hemodynamics through a moving aortic valve with the resistive immersed implicit surfaces method

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We present a full framework to simulate the hemodynamics in the aorta including the valve. The open and the closed position of the aortic valve and the lumen aorta are reconstructed directly from medical images allowing patient-specific simulations. In the fluid dynamics problem, the aortic valve is modeled with a resistive penalization term based on level set functions, enforcing the blood to adhere to the valve leaflets. A reduced geometric 0D model is adopted to represent the dynamics of the valve between its closed and open position. The global problem results in a new 3D-0D fluid-structure interaction model. At a discrete level, we adopt a stabilized finite element formulation for the fluid problem and a staggered approach for the coupling between the 3D fluid and 0D valve models. This computational framework, applied to a patient-specific geometry and data, allows to simulate the sharp pressure jump across the leaflets and the blood flow inside the aorta influenced by the movement of the valve. Possible applications of the method to other cardiovascular districts are briefly discussed.

Towards computational imaging phenomics and in silico clinical trials in cardiovascular science: vision and progress so far

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These are exciting times for medicine and engineering. Big data meets in silico medicine. Phenomenological and mechanistic models converge in new ways. New approaches and tools to disease understanding promise to improve healthcare dramatically in the years to come. This talk overviews our vision and progress towards two exciting avenues of in silico medicine in cardiovascular science, namely, computational imaging phenomics and in silico clinical trials. First, we discuss the challenges and opportunities in scaling up image analytics and image-based modelling at population scale to undertake deep in vivo and in silico phenotyping. Computational imaging phenomics harnesses image phenotypes and links it to multiple omics (imaging phenomics). We illustrate these concepts with our recent work on cardiac MR analytics on population imaging coming from the UK Biobank and work on cardiac imaging genetics by other groups. Second, we discuss some challenges and opportunities in in silico clinical trials introducing modelling and simulation with increase explanatory and predictive capabilities. These concepts are illustrated with past/recent work in virtual endovascular embolisation of cerebral aneurysms. Finally, we introduce MULTI-X (www.multi-x.org) and some of its underlying architectural design concepts and abstractions. MULTI-X is a cloud-based software platform streamlining and distributing computational analytics and simulation workflows scaling up and addressing the massive computational problems arising from the previous exemplars.

A distributed Lagrange multiplier formulation for the finite element discretization of FSI

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We provide a general variational framework for the finite element discretization of fluid-structure interaction problems. This formulation originates from the so called Finite Element Immersed Boundary Method (FE-IBM) and is suited to deal with immersed structures which can be of codimension 0 or 1. The main idea consists in using the Navier-Stokes equations all over the domain occupied by both the fluid and the structure and considering the effect of the presence of the structure as additional forces acting on the fluid. In the case of thick structure, the FE-IBM can be interpretd as a fictitious domain approach and a new formulation based on the introduction of a Lagrange multiplier has been studied. The main constraint of such formulation consists in requiring that the velocity of the structure equals that of the fluid, and, consequently, only incompressible structures can be easily considered. Recently, a new formulation has been introduced which can take into account also compressible structures. The mathematical formulation of the problem fits into the framework of saddle point systems, thus requiring an accurate analysis in order to obtain the solvability of the problem at each time step. Some results on the accuracy of the method are also avalaible in a simplified situation.

Combining tissue anisotropy and heterogeneity in cardiac electrophysiology: a space-fractional Monodomain model

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Classical models of electrophysiology often feature extremely accurate descriptions of the underlying cardiac fiber structure but do not typically account for the effects that high tissue heterogeneity has on electrical pulse propagation. In particular, experimental data point at peculiar features of the electrophysiological dynamics, such as wide action potential foot [1] and a marked dispersion of action potential duration (APD) away from the stimulus source [2].

We combine structural anisotropy and tissue heterogeneity via a nonlocal modification of the classical Monodomain model, obtained by considering a fractional power (of exponent $0 < s < 1$) of its diffusive term: as the power s decreases, nonlocal effects are enhanced and increasing levels of heterogeneity are represented. Differently from available examples of space-fractional models for cardiac electrophysiology [2, 3] that are limited to 1D intervals or cartesian domains, we use an integral representation of the nonlocal operator on bounded domains that does not rely on direct knowledge of its spectrum [4]. This formulation allows to handle both simple, cartesian domains, and irregular geometries within the same framework.

In this talk, we will describe the fractional Monodomain model, and discuss its numerical approximation. We will also present some simulations, on cartesian and realistic geometries, capturing the characteristic features of both anisotropy and heterogeneity. Fibers direction triggers anisotropic propagation patterns, as in the case of classical models, while fractional powers of the diffusion term in Monodomain yield the physical behaviour expected in the presence of structural micro-heterogeneities.

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Multi-Scale Computational Modeling of FSI in Aorta Physiopathology: A Quantitative Risk Assessment Study

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Preventive diagnostic and therapeutic strategies associated with cardiovascular diseases are still limited due to the lack of knowledge concerning the key mechanisms influencing and governing hemodynamic physio-pathological behaviors. In this framework, modeling approaches able to describe the mechanisms associated with blood-vessel interaction in vascular segments can furnish useful clinical indications on dominant mechanical features affecting the onset and evolution of vascular diseases.

In this contribution we discuss a flow-tissue multiscale modeling strategy for analyzing aorta physiopathology. In particular, we account for the influence of histological and biochemical environment explicitly and perform a quantitative assessment of the risk indices based on the recent Three-Band Decomposition analysis, associated to the dynamics of the wall shear stress and to the vessel wall mechanical strains.

We assume blood as an incompressible Newtonian fluid, described via Navier-Stokes equations and formulated in a Eulerian framework. Boundary conditions are defined by considering a Dirichlet-type inflow and a Neumann-type outflow determined via 0-D Windkessel model. Accordingly, we obtain a realistic description of the downstream vasculature and outflow proximal pressure. The arterial tissue is modeled via a structurally-motivated nonlinear multiscale constitutive rationale accounting for collagen hierarchical organization. The numerical scheme used for the solution of the nonlinear fluid-structure-interaction problem is based on a staggered explicit time-marching technique enforcing compatibility and equilibrium relationships via an incremental multiphysics approach.

We discuss a number of computational analyses associated to patient-specific aneurysmatic geometries highlighting soundness and consistency of the adopted modeling approach in accurately describing tissue nonlinearities and blood dynamics. In addition, we provide useful insights into the etiology of mechano-driven tissue remodeling mechanisms opening towards the definition of quantitative and reliable synthetic clinical risk indices.

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Challenges and Opportunities for the Simulations of Calcium Waves on Modern Multi-Core and Many-Core Parallel Computing Platforms

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State-of-the-art distributed-memory computer clusters contain multi-core CPUs with 16 and more cores. The second-generation of the Intel Xeon Phi many-core processor has more than 60 cores with 16 GB of high-performance on-chip memory. These processors are ideally suited for many applications, for instance in particular for parameter studies of long-time simulations of calcium waves in a heart cell.

We contrast the performance of the second-generation Intel Xeon Phi, code-named Knights Landing (KNL), with 68 computational cores to the latest multi-core CPU Intel Skylake with 24 cores.

A special-purpose code solving a system of non-linear reaction-diffusion partial differential equations with several thousands of point sources modeled mathematically by Dirac delta distributions serves as realistic test bed. The system is discretized in space by the finite volume method and advanced by fully implicit time-stepping, with a matrix-free implementation that allows the complex model to have an extremely small memory footprint. The method is implemented in C with MPI and OpenMP for distributed- and shared-memory parallelism. The sample application is a seven-variable model of calcium induced calcium release (CICR) that models the interplay between electrical excitation, calcium signaling, and mechanical contraction in a heart cell.

The results demonstrate the scale and speed of simulations possible on both platforms, but particularly with CPUs that are accessible also for individual research labs. Additionally, we demonstrate the use of the VTune performance analyzer to identify bottlenecks in a parallel code.

Non-conforming finite-element schemes for cardiac electrophysiology

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The study of cardiac disease in the human heart has greatly benefitted from computational tools in the last decade. Computational models of the electrical activity of the heart have enabled in-silico studies of arrhythmogenesis, cardiac failure and therapy design that are otherwise impossible to perform in-vivo. Despites these advances, the computational effort associated to whole heart simulations remains costly, as accuracy of such simulations impose strict discretization demands both in space and time. For example, in order to recover accurate conduction velocities and wavefront shapes in cardiac simulations, the mesh size in Q1 finite-element formulations cannot exceed 0.1 mm [1]. In this contribution, we present a novel non-conforming finite-element formulation for solving the cardiac electrophysiology equations, suitable for arbitrary cardiac domains [2], which we integrate with implicit and semi-implicit time integration schemes. We show that the proposed spatial interpolation scheme results in more accurate wavefront shapes and lower mesh-dependence in the conduction velocity than traditional Q1 formulations, while retaining the same number of global degrees of freedom. Our formulation enables coarser discretizations of cardiac domains, that can be employed in simulations without significant loss of accuracy, at the same time they reduce the overall computational effort. We demonstrate the applicability of the proposed scheme in simple and biventricular geometries, and study the effect of non-conforming schemes in improving the accuracy-efficiency trade-off of cardiac simulations.

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Fast Solution Methods for Coupled Problems in Cardiac Simulation

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For numerical simulation of electrical and biomechnical processes in the human heart, large scale systems arising from the discretization of coupled and non-linear differential equations have to be solved. This includes electrophysiology, electro-mechanical activation, and fluid-structure interaction in hert valves. In this talk, we present different coupling and solution strategies for the arising non-linear and discrete large-scale systems. Our approaches are based on ideas from multilevel and domain decomposition methods. Particular emphasis will be put on transfer opertors betweeen different scales and between different discretizations, which are crucial for the construction of efficient solution methods. We will discuss efficiency and parallel scalability of our methods using different examples, including contact problems, the electro-mechanical activation of the human heart, and fluid-structure interaction in heart valves.

We will moreover shortly comment on personalization, e.g. parameter fitting and uncertainty quantification.

Numerical approximation of the electromechanical coupling in the left ventricle with inclusion of the Purkinje network

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In this talk, we consider the numerical approximation of the electromechanical coupling in the leftventricle with inclusion of the Purkinje network. The mathematical model couples the 3D elastodynamicsand bidomain equations for the electrophysiology in the myocardium with the 1D monodomain equation in the Purkinje network.For the numerical solution of the coupled problem, we consider a fixed-point iterative algorithm that enables a partitioned solution of the myocardium and Purkinje network problems. Different levels of myocardium-network splitting are considered and analyzed. The results are compared with those obtained using standard strategies proposed in the literature to trigger the electrical activation. Finally, we present a physiological cardiac simulation,including the initiation of the signal in the Purkinje network, and the systolic and diastolic phases.

Arrhythmia vulnerability by single premature stimulation in normal ventricular myocardium

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Background. Single high-intensity premature stimuli when applied to the ventricles during ventricular drive of an ectopic site, as in Winfrees pinwheel experiment, usually induce reentry arrhythmias in the normal heart, while single low-intensity stimuli barely do.

Objective. With a view to identify ventricular vulnerability to unidirectional conduction block and reentry, we revisited the pinwheel experiment with reduced constraints in the in situ rat heart.

Methods. New features included single premature stimulation during normal sinus rhythm, stimulation and unipolar potential mapping from the same high-resolution epicardial electrode array, and progressive increase in stimulus strength and prematurity from diastolic threshold until arrhythmia induction. Measurements were performed with 1-ms cathodal stimuli at multiple test sites in seven rats.

Results and discussion. Stimulus induced virtual electrode polarization during sinus beat recovery phase influenced premature ventricular responses. Specifically, gradual increase in stimulus strength and prematurity progressively induced make, break, and graded-response stimulation mechanisms.

Lower intensity premature stimuli induced one or more ventricular complexes termed repetitive ventricular response (RVR). This type of reentry was independent on stimulation strength, occurred in the absence of an apparent conduction block, and very rarely induced ventricular tachycardia.

Moreover, activation patterns during RVR were characterized by the surfacing within the paced ventricle of breakthrough points as during sinus rhythm. Accordingly, results of the present study suggest that a myocardial impulse, even initiated by a low-intensity premature stimulus, can eventually encounter an appropriate substrate for unidirectional conduction block and reentrant excitation within the specialized conducting system (macro-reentry).

Higher intensity stimuli induced unidirectional conduction block at the pacing site that eventually initiated figure-eight or spiral wave reentry and tachycardia. A novel finding of this study was that ventricular tachycardia is sustained by episodes of recurring scroll-like wave and focal activation couplets.

A computational model of action potential in the mouse detrusor smooth muscle cell

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Urinary incontinence (UI) is defined as the involuntary loss of urine that can be demonstrated objectively and which constitutes a social or hygienic problem. Overactive Bladder is a type of UI, which is an associated with a strong premature desire to urinate and correlates with an overactive detrusor smooth muscle (DSM) cell. Spontaneous contractile activity is recorded in DSM strips of mouse, rat, pig, guinea pig and humans. Membrane electrical activity in the form of action potentials (AP) play an important role in initiating the DSM contraction by mediating influx of Ca^{2+} through voltage-gated Ca^{2+} channels. It is suggested that the spontaneously evoked action potentials (sAPs) in DSM cells initiate and modulate the contractions. Computational models can quantitatively analysis the interactions among various ion channels and allow the user to investigate the contribution of each ion channel to the overall observed cellular electrical behavior. In order to further our understanding of the underlying ionic mechanisms in sAP generation, we present here a biophysically detailed computational model of a single DSM cell. We constructed mathematical models for nine ion channels found in DSM cells based on published experimental data. After incorporating all ion channels, our DSM model is capable of reproducing experimentally recorded spike-type sAPs of varying configurations. Our model, constrained heavily by physiological data, provides a powerful tool to investigate the ionic mechanisms underlying the genesis of DSM electrical activity, which can further shed light on urinary bladder function and dysfunction.

Reduced Order Modeling for Uncertainty Quantification of the cardiac function

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The mathematical and numerical modeling of the cardiovascular system requires a huge amount of data when trying to reproduce both physiological and pathological behaviors. Often partially missing, these data are inevitably hampered by uncertainty, e.g., in (i) the computational domain, (ii) physical parameters (e.g. vascular material properties) and (iii) boundary conditions, among others. These are the main reasons behind the very rapid growth of applications of uncertainty quantification (UQ) methods to cardiovascular problems in the past decade, in view of both model calibration and personalization - that is, the adaptation of model inputs to subject-specific conditions.

Reduced-order models (ROMs) such as the reduced basis (RB) method, are emerging methodologies in the UQ framework since they are aimed at reducing the computational complexity entailed by the repeated solution of PDEs without affecting their accuracy. In this talk we show how to take advantage of ROM techniques to treat forward and backward propagation of uncertainty, for the latter case focusing on statistical inversion methods within a Bayesian framework, in relevant problems dealing with cardiac electrophysiology and electromechanics.

Mathematical modeling of the glymphatic system

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The newly proposed glymphatic system offers a potential explanation for how the brain (which mostly lack a lymphatic system) clears waste. As malfunctioning waste clearance seems to be a main problem in diseases such as Alzheimer, where accumulation of amyloid-beta plaques is one of the hallmark features, an understanding of this process may have huge potential. The glymphatic system remains controversial. It is a biomechanical theory that links the transport between the cerebrospinal fluid, the peri- and paravascular spaces that surrounds the blood vessels and the extracellular matrix and has as such been the subject of subject of many recent modeling efforts. In this talk we present an overview of mathematical models for the glymphatic system and include our own results in this type of modeling.

Flow-Induced Mitral Leaflet Motion in Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is considered the cause of sudden cardiac death in developed countries. Clinically it is found to be related to the thickening of the intra-ventricular septum combined with elongated mitral leaflets [1]. During systole the low pressure, induced by the abnormal velocities in the narrowed aortic channel, can attract one or both the mitral leaflets causing the aortic obstruction and sometimes instantaneous death. In this paper a fluid structure interaction model for the flow in the left ventricle with a native mitral valve, essentially the one presented in [2], is employed to investigate the physio-pathology of HCM. The problem is studied using direct numerical simulations of the Navier-Stokes equations with a two-way coupled structural solver based on interaction potential approach for the structure dynamics. Simulations are performed for two different degrees of hypertrophy, and two values of pumping efficiency. The leaflets dynamics and the ventricle deformation resulting from the echocardiography of patients affected by HCM are well captured by the simulations. Moreover, the procedures of leaflets plication and septum myectomy are simulated in order to get insights into the efficiency and reliability of such surgery.

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Real-time video evaluation of the right ventricle kinematics during cardiac surgery: novelties, implications and future perspectives

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Survival after repair of congenital heart disease (CHD) in infancy incidence has dramatically improved, with over 90% of children surviving into adulthood nowadays. It is estimated that the population of adults with CHD has since overcome the one of children in Western World countries. Amongst the complex congenital heart lesions associated with the best survival into late adulthood is repaired Tetralogy of Fallot (TOF). Unfortunately, a growing proportion of adult with operated TOF show the long-term sequelae chronic pulmonary regurgitation, which follows the relief of right ventricular outflow tract in infancy, namely right ventricular volume overload and dysfunction. The ideal timing to recommend surgical reintervention to insert a pulmonary valve for pulmonary regurgitation after TOF repair are controversial, due to intrinsic limitations in estimating RV dysfunction and its recovery. Nowadays, evaluation of RV function is limited to pre and post-operative imaging analysis using MRI, but the gold-standard technique to assess cardiac function during surgery (transesophageal echocardiography) is inadequate for RV assessment.

Here proposed is an innovative method for intraoperative RV function monitoring using video-kinematic evaluation of the beating heart. This method has been previously shown to describe global RV parameters such as kinetic energy, force, contractility and displacement (Fassina L, Rozzi G et al. Sci Rep. 2017 Apr 11;7:46143) before and after the cardiac operations. Furthermore, the contraction/relaxation trajectories on RV can be monitored as index of preserved cardiac cycle before and after surgical interventions. In six TOF patients with chronic pulmonary regurgitation undergoing surgical pulmonary valve implantation the average kinetic energy, contraction velocity and force decreased significantly. The trajectories were preserved before and after pulmonary valve implantation. Echocardiographic follow-up evaluation of patients after surgery confirmed the data displayed in the operating room. A case study is also here reported whereby an intra-operative tachycardia after pulmonary valve implantation for TOF drastically modified RV kinematic parameters. Similar conditions have been simulated in in-vivo female heart rats at the open chest, showing that cardiac kinematics following the triggered heart rate is frequency dependent.

The results herein suggest that acute reduction of chronic RV volume overload in TOF patients allows recovery requires of normal RV mechanics with less force and energy expenditure. Real-time evaluation in the cardiac theater offers laboratory information which might guide physicians in pharmacological intervention. Moreover, real-time evaluation of the RV during cardiac surgery in TOF patients may provide for laboratory indices, which may display prognostic relevance in terms of functional recovery.

Mechano-electric feedback and initiation of cardiac arrhythmias

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The heart beat is controlled by electrical excitation waves which propagate through the heart and initiate cardiac contraction. Contraction of the heart also affects the process of wave propagation resulting in a complex global feedback phenomenon known as mechano-electrical feedback (MEF). MEF has been studied in electrophysiology for well over a century and may have both pro-arrhythmic and arrhythmogenic consequences. Some time ago we have developed an approach to study the phenomenon of MEF as coupled reaction-diffusion-mechanics system, which combines the parabolic reaction-diffusion equations with the elliptic equations of finite elasticity. For electrophysiological tissue properties we use models of cardiac tissue either low dimensional of the FitzHugh-Nagumo type, or detailed ionic model for human ventricular cells developed in our group. For representation of mechanics we either use a finite element approach, or a discrete mass-lattice framework.

We report the results of our studies on the various mechanisms of initiation of cardiac arrhythmias due to MEF caused by stretch activated channels, discuss other MEF mechanisms and unsolved questions.

In Silico Shear and Intramural Stresses are Linked to Aortic Valve Morphology in Dilated Ascending Aorta

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The reported prevalence of dilatation of the ascending aorta among individuals with bicuspid aortic valve (namely "BAV aortopathy") ranges from 20 to 84%. Fatal complications related to the presence of an ATAA are aortic rupture and acute dissection, which are both considered cardiovascular emergencies with high morbidity and mortality. To improve the clinical-decision making process related to the interventions of patients with dilatation of ascending aorta, we adopted extensively fluid-solid interaction analysis to assess both the intramural and wall shear stresses on a cohort of n.150 patients with BAV aortopathy. Correlation between clinical data (ie, age and aortic diameter) revealed that wall shear stress and intramurals stress are linked to the aortic valve morphology (ie, tricuspid vs bicuspid aortic valve) and the pattern of aortic dilatation (ie, aortic root vs ascending aortic dilatation). We conclude that valve-mediated haemodynamic and structural parameters may be used to identify which regions of aortic wall are at greater stress and enable the development of a personalized approach for the diagnosis and management of aortic dilatation beyond traditional guidelines.

Efficiency of high order schemes for the monodomain model

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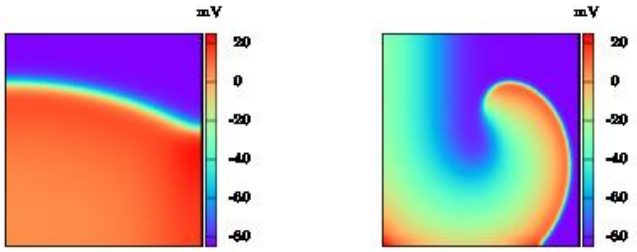
Simulations in cardiac-electrophysiology are associated to sharp changes in space and in time. This is related to the stiffness of the transmembrane potential wavefront and to the stiffness of the depolarization of the cardiac action potential. Therefore computations in cardiac-electrophysiology are performed using very fine grids in space and in time inducing high computational costs.



To avoid that situation, we propose to go towards high order schemes. Following [1], we recently developed and analyzed in [2] new time-stepping methods of exponential type. We called these methods high order Rush-Larsen. They allow an explicit integration of the reaction terms in the monodomain model (the ionic model). Meanwhile they have strong stability properties allowing accurate computations at large time step. In the present communication, we use the high order Rush Larsen schemes in conjunc- tion with P^k Lagrange finite element up to order 3 ($1 \leq k \leq 3$). We assess the question of the accuracy for that computational setting. The accuracy is thought from a physiological point of view. We will consider relative errors on the activation times and on the potential wavefront velocity. Two test cases will be investigated. Both involve the Beeler and Reuter ionic model together with physiologically set parameters (anisotropic conductivities and cell membrane surface to volume ratio) on the square. The first one represents a normal propagation of excitation following a one site stimulation. The second one displays a more complex pattern of excitation with a spiral potential wave. They are illustrated in the figure above. The scheme numerically displays a convergence up to order 4 for the activation times and up to order 3 for the wavefront velocity. For a relative error of 5%, the P^3 finite elements allow to use 8 times coarser meshes than at order 1. We show that, on the considered test cases, a 5% of relative error can be reached with a mesh size of almost $h = 0.1\,cm$ and with a time step of $\Delta t = 0.2\,ms$. The gain in CPU time consumption is evaluated.

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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 the comprehensive quantitative characterization of 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. Key challenges to be addressed are two-fold. Expensive computational models must be made efficient enough to be compatible with clinical time frames and generic models must be specialized based on clinical data, which requires complex parameterization and data assimilation procedures.

Towards the exhaustive analysis of left ventricle dysfunctions in ischemic cardiomiopathy: integrating wall kinetics, scar transmurality and wall shear stress

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Post-ischemic dilated cardiomyopathy (DCM) is a complex clinical condition characterized by adverse left ventricular (LV) remodeling, with impairment of LV systolic and diastolic function. Different features of DCM, like LV function and location and extension of the ischemic scar, can be assessed through different cardiac magnetic resonance modalities. Recently, it was proposed to characterize in vivo intraventricular flow patterns through 4D Flow MRI sequences. However, the information yielded by these modalities is typically not integrated, thus limiting the potential for comprehensive understanding of DCM pathophysiology. The purpose of this work was to integrate standard MRI and 4D Flow analysis. In particular, LV hemodynamics were described from 4D Flow in terms of wall shear stress and diastolic vortices. Study population included 19 patients (all males, age $= 66 \pm 10$ years) with post-ischemic DCM and severe LV dysfunction (EF$< 35\%$). Preliminary results confirmed the potential of 4D Flow in describing LV impairments, aiming at elucidating the fluid-dynamic determinants of post-ischemic DCM.

Enabling uncertainty quantification for the monodomain equation via multifidelity techniques

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In cardiac electrophysiology, there are numerous sources of uncertainty, both in the parameters and in the modeling aspects. For instance, the *de facto* standard monodomain model has several parameters with large uncertainties: location and timing of source currents, microstructure organization (fibers and sheets), anatomy, electrodes location, etc. In particular, the conductivities are not known exactly. This motivates modeling them as spatially-correlated random fields via, e.g., a truncated Karhunen-Love expansion, yielding a solution that is also a random field.

While sampling a random field can be done very efficiently via the pivoted Cholesky decomposition [1], computing the activation map from the monodomain equation is a computational demanding task. A single patient-tailored simulation can take several CPU hours even on a large cluster. This makes uncertainty quantification (UQ) unfeasible, unless modeling reduction strategies are employed. One such strategy is represented by multifidelity methods [2]. The central idea of this approach is to build a hierarchy of increasingly faster low-fidelity models, which might be inaccurate but exhibit some degree of correlation with the high-fidelity one. It is the control of the correlation, rather than of the error estimates, that ensures that low-fidelity models provide useful information on the statistics of the high-fidelity quantity-of-interest.

A key ingredient of the multifidelity approach is the choice of low-fidelity models. Typical strategies are projection-based or data-fit surrogates [2], which however need to be trained anew for each patient and may become inefficient for a large dimensionality (> 10) of the input [3], as in the case under consideration. Instead, a more physics-based approach is to take advantage of the natural hierarchy of available models. These include different cellular models for the monodomain equation, the time-independent eikonal equation [4], and the 1D geodesic point activation [3]. By exploiting the statistical correlations in this hierarchy, we observed a reduction of the computational cost by at least two orders of magnitude, enabling to perform a full analysis within a reasonable time frame. Moreover, we incorporate Bayesian techniques [5], which provide confidence intervals and full probability distributions at selected points, thus augmenting the information provided by standard frequentist approaches [2].

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Active contraction of cardiac cells: a reduced model of force generation

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The primary role of the heart as a pump is made possible by the ability of cardiac cells to contract. The mathematical modelling of the complex phenomena behind the active contraction of cardiomyocytes is crucial for understanding heart functionality, since it represents the natural bridge between electrophysiology and mechanics [1, 2]. The most detailed models of muscle contraction, based on the Huxleys model of crossbridge cycling [3], are Markov Chain models describing the attachment-detachment of actin and myosin filaments. The centrality of the phenomenon of cooperativity between adjacent binding sites prevents applying the mean-field hypothesis in order to reduce the complexity of the model [4]; therefore, the time-consuming Monte Carlo method is typically employed in simulations, hindering the applicability of such models to the simulation of the full organ [5]. In our work we propose a reduced ODE model for the mechanical activation of cardiac myofilaments, which is based on explicit spatial representation of nearest-neighbour interactions. Our reduced model is derived, by combining different techniques, starting from the cooperative Markov Chain model presented in [6] and later modified in [7], under the assumption of conditional independence of specific sets of events. This physically motivated assumption allows to drastically reduce the number of degrees of freedom, thus reducing the computational cost by more than 10 000 times [8]. Thanks to its computational efficiency, our reduced model is suitable for multiscale full organ simulations. We show through numerical tests that our model is able to reproduce physiological behaviours observed under various experimental settings, including the steady-state relationships between calcium, length and force, isosarcometric and shortening twitches, and force redevelopment after a sudden active force drop.

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Anode Break Excitation in Hypertrophic Cardiomyocytes: An Investigative Tool for Predicting Modulation of Cardiac Excitability

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Excitation at the closure of the anode is one of the two ways by which action potentials in single cells can be electrically elicit. Despite the fact that "anode break" excitation has long been observed in cardiac myocytes (the phenomenon of anodal excitation of cardiac muscle has been described by Cranefield et al., in the late-1950s), very little is known about its mechanism and implications. Anodal stimulation of cardiac tissue has been explained for long time using bidomain models of cardiac tissue (Henriquez et. al. "A planar slab bidomain model for cardiac tissue". Ann. Biomed. Eng. 1990) until Ranjan et al. demonstrated that anode break excitation has an active cellular basis ("Mechanism of anode break stimulation in the heart". Biophys. J. 1998). Indeed, they described that the activation of a hyperpolarization-activated inward current (If) provides the current necessary to drive the potential to more depolarized levels, and the time-dependent block of inwardly rectifying K+ current (IK1) aids the process by increasing membrane resistance. Furthermore, a very important property of anode excitation, first described by Dekker et al. in 1970 ("Direct current make and break thresholds for pacemaker electrodes on the canine ventricle". Circ. Res. 1970), is represent by "supernormal excitability" and consists in an increase of the excitability in the refractory heart due to anode break excitation as compared with its diastolic values. Consequently, if a stimulus falls in the vulnerable period of a spontaneous cycle, the risk of triggering an arrhythmic event is higher with anodal than cathodal stimulations (Merx et al. "Effects of unipolar cathodal and bipolar stimulation on vulnerability of ischemic ventricles to fibrillation". 1975). Even supernormal excitability has been explained using bidomain models of cardiac tissue relying solely on passive cardiac tissue properties. The characterization of the fundamental basis of anodal stimulation at cellular level will advance the understanding of either the excitability in the heart and the mechanism of potential clinically important properties (e.g. "supernormal excitability") of anodal excitation in the ventricular myocardium.

In this work, we tested the hypothesis that anode break excitation might unmask in hypertrophic heart alterations in cardiac electrical excitability in both the diastolic and refractory period. Experiments were performed on single ventricular cardiomyocytes from healthy and hypertrophic mice derived from transverse aortic constriction (TAC). Cathodal and anodal excitability in diastole and during refractory period were recorded using dedicated whole cell patch clamp protocols in order to obtain strength-duration and strength-interval curves. The comparison of strength-duration curves, as a global index of excitability, showed that the ratio between anodal and cathodal rheobase was much higher in healthy than TAC cardiomyocytes. We finally measured strength-interval curves to investigate anodal excitability during refractory period and found not only that supernormal excitability was present in both healthy and hypertrophic cardiomyocytes but it was significantly decreased in TAC cardiomyocytes.

These findings demonstrate an increased excitability in pathologic mice following anodal stimulations both in the diastole and refractory period. Of interest, cathodal strength-duration and strength interval curves did not show significant differences among hypertrophic and healthy cardiomyocytes. Furthermore, we have proved that the phenomenon of "supernormal excitability", which was observed only in the tissue, is intrinsic to the mechanism of cellular excitability (the anodal "strength-interval" curve in single mice ventricular myocytes was measured for the first time in this research). These findings taken together open the intriguing possibility of making anode break a tool both to unmask potential arrhythmogenic ionic mechanisms in pathological hearts and study, for the first time, action potentials in the refractory period.

Systolic blood pressure detection using a multi-wavelength Opto-Electronic patch sensor at peripheral circulation

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Through the use of a multi-wavelength opto-electronic patch sensor (MOEPS) (1) based on PPG technology, we sought to determine the systolic blood pressure (SBP), detecting the changes in the morphology of the MOEPS signal. The pressure acquisitions were performed both with gold standard, using an electronic sphygmomanometer, and the MOEPS sensor (experimental procedure), on subjects from a multiethnic cohort (aged 29 ± 6). More specifically, the MOEPS sensor was applied together with a manual inflatable cuff placed around the left upper arm, that was inflated going slightly above the level of the systolic pressure with increases of +10 mmHg and subsequently deflated, by 10 mmHg until reaching full deflation. MOEPS signals were captured using four wavelength illumination sources (i.e., green 525 nm, orange 595 nm, red 650 nm and IR 870 nm) on three different measuring sites, which are forefinger, radial artery and wrist. The MatLab algorithm analyzed each wavelength of every sensor position taking into account different parameters. It provided approximations on the instant at which the SBP was reached and therefore the loss of the signal occurred since the vessel was completely blocked, as well as the instant in which it came back again below the systolic pressure and therefore there was a resumption of the signal. It also provided a correlation between diastolic pressure as the starting point in which the signal starts reducing. The general pattern described by green light recorded the best performance for every site. Capillary site has provided the most accurate values for all wavelengths. In addition, better results were achieved in the inflation phase than with the deflating of the cuff, since some delay was observed in the recovery of the bloodstream in the artery and therefore in regeneration of the signal. Further studies will improve the clinical relevance on patients cohort diagnosed with hyper- or hypotension.

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Cardiac Surgery and Biomedical Engineering

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Nowadays, even if the role of mathematical consultant in medical team is discussed, we must be aware that the potential benefit of this collaboration will allow to tackle the large and complex medical problems. Cardiothoracic surgeons have been inventors, developers and modifiers of a wide range of technologies from medical devices, such as heart mechanical or biological valves, bypass machines, blood vessel substitutes and novel imaging techniques. But it is not just the individual pratictioner or researcher who can contribute to the process of bringing new technology to the clinic. In the deep evolution obtained in cardiac surgery, mathematics has been the link between the measured data and the primary structured information on which the realization of an idea was possible.

In medical engineering and in heart surgery in particular it is of increasing importance to recognize the essentials out of a huge amount of information about a very complex situations and to draw the right conclusions. Mathematical models of the heart and circulation offers many interesting options both in diagnosis and therapy planning of heart surgery:

- **Electophysiological models** allow to
  - optimize radio-frequency (RF) ablation for atrial fibrillation;
  - adapt stimulation sequences for heart pacemaker and cardiac resynchronization.
- **Elastomechanical models** allow to
  - optimize preoperative surgical cuts in open heart surgery for treatment of aneurysms and for reconstruction of ventricle in endoventricoloplasty;
  - optimize preoperative surgical techniques in valvuloplasty therapy;
  - predict the trans-catheter percutaneous valve implantation preoperative results;
  - test new surgical techniques;
  - self-education in young training surgeons.
- **Computational Fluid dynamical models** allows to
  - better planning the behavior of stenoses of the coronary arteries;
  - understand the behavior of stenoses and/or the insufficiency of the heart valves;
  - optimize the behavior of different kind of anastomoses between coronary arteries and arterial or vein grafts in bypass surgery.
- **Circulation models** allows to
  - control extracorporeal circulation during heart surgery;
  - study the fluid structure interaction in the artificial heart and ventricular assisted devices;
  - optimize the fluid dynamic effect of the vascular graft thoracic aortic aneurysm surgery.

Today the process of bringing technological advances to our patients has become complex and more structured. What seems to be most needed is to extend the areas of collaboration among different specialty. Knowledge transfer and "team work" for multidisciplinary approach could give us new ways to treat some of the most daily diseases.

Computational Modeling of the Cardiac Pacemaking in Humans

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The sinoatrial node (SAN) is the normal pacemaker of the mammalian heart. Over several decades, a large amount of data on the ionic mechanisms underlying the spontaneous electrical activity of SAN pacemaker cells has been obtained, mostly in experiments on single cells isolated from rabbit SAN. This wealth of data has allowed the development of mathematical models of the electrical activity of rabbit SAN pacemaker cells. However, the translation of animal data/models to humans is not straightforward. Even less so for SAN pacemaker cells than working myocardial cells given the big difference in their main output (i.e. pacing rate) between human and laboratory animals. The development of a comprehensive model of the electrical activity of a human SAN pacemaker cell strictly based on and constrained by the available electrophysiological data will be presented. We started from the Severi-DiFrancesco rabbit SAN model, which integrates the two principal mechanisms that determine the beating rate: the "membrane clock" and "calcium clock". Several current formulations were updated based on available measurements. A set of parameters, for which no specific data were available, were automatically optimized to reproduce the measured AP and calcium transient data. The model was then validated by assessing the effects of several mutations affecting heart rate and rate modulation. Moreover, two recent applications of the model will be presented: i) We used our SAN AP computational model to assess the effects of the inclusion of the small conductance K+ current (ISK) on the biomarkers that describe the AP waveform and calcium transient; ii) We analysed the effect of altered electrolyte levels (as systematically occurring in hemodialysis patients) on pacemaking to investigate the possible mechanisms of the bradycardic sudden cardiac deaths pointed out by two recent human studies using implantable loop recorders.

High-Order Operator-Splitting Methods for the Bidomain and Monodomain Models

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The bidomain and monodomain models are among the most widely used mathematical models to describe cardiac electrophysiology. They take the form of multi-scale reaction-diffusion partial differential equations that couple the dynamic behaviour on the cellular scale with that on the tissue scale. The systems of differential equations associated with these models are large and strongly non-linear, but they also have a distinct structure due to their multi-scale nature. Operator-splitting methods attempt to take advantage of this structure to efficiently produce numerical solutions.

The focus of this presentation is on operator-splitting methods with order higher than two. Such methods require backward time integration and historically have been considered unstable for solving deterministic parabolic systems. The stability and performance of operator-splitting methods of up to order four to solve the bidomain and monodomain models are demonstrated on several examples arising in the field of cardiovascular modeling.

Shape Analysis for 3D Cardiac Imaging

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Keywords: shape analysis, heart function, differential geometry, parallel transport.

Shape analysis encompasses many powerful tools used to compare shapes and to quantify their differences. Here we present a biological application aimed at comparing the motion of the cardiac revolution of different subjects, using raw data from 3D Speckle-Tracking Echocardiography; our goal is comparing the motion of the same organ, the human heart, from different individuals, and to assess the differences in the cardiac revolution by filtering out inter-individual shape differences. This method is under scrutiny, and is being applied to a database of 200 echocardiographic data acquired at the University Hospital Umberto I, at Sapienza University of Rome.

The use of the shape analysis to compare both the deformation and the shape of motion itself (and not merely shapes) requires advanced tools from differential geometry and statistics. In particular, we present an appropriate definition of parallel transport along the geodesics of the Size-and-Shape Space that enables shape analysis with the possibility of comparing not only different shapes but also different motions.

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Modeling isovolumic phases using a pressure corrected RIS model

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Introduction. Modeling often trade computational complexity against phys- ical accuracy. In the case of the heart modeling, the physics involves a complex mix between chemical activity, electri- cal activity, mechanics and fluid dynamics. However, multi- physics simulations are computationally expensive. Alternative to fully coupled multi-physics simulation is to only solve a subset of the physical mechanism. For instance, Image-driven CFD is a way to model the blood flow inside the heart by using patient-specific images as boundary conditions of the fluid problem.

Although very attractive, those methods introduce artificial difficulties when trying to resolve multi-physics phenomenon. For example, modeling the LV isovolumic phases turns into a challenging task due to two main reasons. Generally speaking, when an incompressible fluid is enclosed in a cavity under Dirichlet boundary conditions, the pressure inside the cavity can only be determined up to a constant. Secondly, the Dirichlet boundary condition imposed on the cavity surface may violate the incompressibility constraint. This issue arises for example when the image framerate is too low to properly recover all the cardiac phases([3], [2]).

The contribution of this work is to propose a strategy that builds upon a simplified valve model (RIS, [1], [4]) in order to properly resolve isovolumic phases.

Material and Methods. A fluid cavity enclosed by a solid surface and two valves is considered. Valves are modeled using RIS (i.e. a penalization method on an immersed surface with duplicate degrees of freedom to correctly capture the pressure jump, [1], [4]) and no-slip boundary condition is applied on the other solid surfaces. When both valves are closed and thanks to the incompressibility of the fluid, one can derive a simplified expression of the cavity pressure which relates the inside of the cavity with the cavity wall velocity, the penalization term and the exterior pressure. This explains why realistic isovolumic phases cannot be obtained in the given setting. A pressure correction term is designed in order to counteract those contributions and allows the cavity pressure to reach a given pressure value, which we assume to be either given by measurements or by an electro-mechanical simulation.

The method is validated on an academic toy problem for various boundary conditions and domain motions. Additionally, the method was also experimented on a 3D heart simulation where the motion of the ventricle was given by an electro-mechanical simulation ([4]) for which atrium, ventricular and aortic pressure time series were also provided. The goal was to allow modeling of isovolumic phases even if the given ventricular motion was subject to the issues described in the introduction (i.e the ventricular volume was changing even during what should have been isovolumic phase).

Results. A reasonable agreement between the theoretical pressure and the average cavity pressure for the tested boundary condition on the toy model. In particular, it was possible to correct the cavity pressure in complex situations involving important gaps with exterior pressures and a changing cavity volume induced by inhomogeneous valve and wall motion for example. The correction term was applied and cavity pressures could be set to arbitrary values.

Similar results were obtained on the complex 3D LV simulation where the theoretical ventricular pressure was reasonably close to the average ventricular pressure. It has therefore been possible to obtain physiological ventricular pressures for a complete cardiac cycle even during isovolumic phases.

Discussion. he presented correction term benefits from the fact that the RIS model is penalizing the fluid on the valve surface and not strictly enforcing Dirichlet boundary condition. First, this means that, unlike a cavity enclosed under full Dirichlet BC, the inner pressure is defined by the outer pressure. Additionally, this means that the incompressibility constraint of the fluid can be satisfied even when the enclosed cavity undergoes volume change by allowing small leaks through the valve.

However, as the penalization factor goes to infinity, the RIS model leads to a singular problem equivalent to imposing Dirichlet BC everywhere. This means that the intraventricular pressure cannot be computed nor corrected properly anymore in this case. Therefore a trade-of on the penalization factor has to be chosen.

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Development *in silico* model of SK channel gating, calcium sensitivity and drug interaction

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Computational models are increasingly used in clinical and pharmaceutical settings, for example in guiding surgery and arrhythmia drug testing initiative such as CiPa. Biological targets linked to disease and treatments are often not included in available computational models, or lack important mechanistic detail. One such example is the small conductance calcium-activated potassium (SK) channel, which is active in the late repolarization phase of the atrial action potential and thought to contribute to arrhythmogenic substrate in atrial fibrillation (AF). *In vitro* and *in vivo* experiments support involvement of the SK current in AF arrhythmogenesis, specifically in initiation and disease progression.

An initial Markov state model of the SK2 channel [Hirschberg et al. 1998], based on single-channel patch clamp data, utilized 4 closed and 2 open states to capture SK channel gating dynamics. We extend this model to reflect new inside-out patch clamp data in which we have observed a strong temperature sensitivity of calcium-dependent SK activation, with a shift in EC50 towards the diastolic calcium range. New patch clamp experiments at the single channel level are also included in the presence of known inhibitor apamin and novel SK modulator, AP14145. These data have allowed us to develop a model of channel gating that more closely replicates in vivo behavior and incorporates two modes of drug interaction. We anticipate this will pave the way for further work investigating myocyte- and tissue-level simulations assessing the impact of SK channels and pharmacological modulation on human atrial arrhythmogenesis.

Clinically driven numerical models in cardiovascular surgery

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Current imaging technologies allow or accessing extensive patient-specific anatomical and functional information. In clinical practice, this information is often only partially exploited when performing diagnoses, prognoses or when planning clinical solutions.

In principle, this information can be further exploited by feeding state-of-the-art numerical models to quantify the physical behaviour of tissues and organs on a patient-specific basis. Such analysis may provide insight into pathological conditions and highlight physics-based reasons for the changes in the clinical scenario as well as for the effects of different therapies.

However, despite this great potential, the application of this approach in the real clinical setting is limited because the most advanced and detailed modelling approaches, i.e., the most realistic and reliable ones, typically are not user-friendly nor sufficiently time-efficient.

On this basis, the search for an effective trade-off between models sophistication and clinical applicability becomes crucial. This aspect will be discussed in light of some of the most recent computational modelling activities carried out by the Biomechanics Research Group at Politecnico di Milano in collaboration with several clinical centres.

Applicability of the PREMAP algorithm to accelerate activation mapping of scar-related ventricular reentry tachycardia

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Background. We published a mapping algorithm (PREMAP) that based on linear regression analysis and mathematical optimization significantly speeds up the localization of focal cardiac arrhythmias (Heart Rhythm 2017;14:875-882). When integrated into 3D electroanatomical mapping systems this algorithm could guide the operator to the source of focal activity by continuously optimizing the search path. In the current study we extend the algorithm to scar related ventricular tachycardia (VT).

Methods and Results. 3D electroanatomical maps of 20 patients that had undergone mapping and ablation of scar related left ventricular tachycardia were used for analysis. To increase the quality of our models, anatomical obstacles such as the mitral anulus and scarred area were defined as non- or slowly-conducting zones. Reentry tachycardia was simulated by randomly defining exit sites along the border of the scar. Within this simulation environment, the algorithm was given the task to reconstruct the VT and locate the exit site with a minimal number of local activation time measurements (LAT). For this purpose, the PREMAP algorithm performs linear regression analyses thereby (1) predicting the exit site of the tachycardia (2) and positioning the next measurement at the position with maximum additive value. Within 400 simulated VTs, the algorithm reconstructed the VT circuit including the exit site with a mean number of 10.0 ± 5.6 LAT measurements.

Conclusion. Taken together we show that an algorithm based on regression analysis and mathematical optimization is able to efficiently reconstruct activation and estimate the exit site of scar-related ventricular tachycardia. The mapping performance was not attenuated by the increased complexity of the geometries. This algorithm might significantly accelerate the mapping procedure by guiding the operator to the optimallocation for the next LAT measurement, reducing the number of points with redundant information and predicting the exit site with high accuracy from an early stage of the mapping procedure.

Estimating ion current fractions in mathematical models of non-selective channels

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In many mathematical models of non-selective channels, the total channel current is formulated using Ohm's law in the form $I_{Ch,Ohm} = g_{Ch} \cdot G_{Ch} \cdot (V_m - E_{Ch})$, depending on the transmembrane voltage V_m and the channel's equilibrium potential E_{Ch}. The channel conductivity g_{Ch} combines single-channel conductivity, channel density, optionally modulated by a gating mechanism G_{Ch} modeled based on patch-clamp data.

However, the formulation based on Ohm's law can only describe the total electric current, the sum of all ion currents passing through the channel. In some electrophsiological models, however, intracellular ion concentrations are not constant but part of the model state. Then, state trajectories could become inaccurate when not accounting for the ions passing through non-selective channels. Here we suggest an approach to transform a model formulation based on Ohm's law such that partial ion currents can be accounted for.

The Goldman-Hodgkin-Katz (GHK) current equation states that the ion current of species X through a membrane pore is

$$I_X = \frac{V_m F^2}{RT} P_X z_X^2 \frac{[X]_i - [X]_e \exp(-z_X V_m F/RT)}{1 - \exp(-z_X V_m F/RT)},$$

with $[X]_i$ and $[X]_e$ intra- and extracellular concentrations, and P_X and z_X permeability and valence of X, respectively [1]. With $I_{Ch,GHK} = \sum_X I_X$ for all ions X that can pass through the channel, we can then choose unknown parameters in $I_{Ch,GHK}$, such that $I_{Ch,GHK} \approx I_{Ch,Ohm}$, meaning the total current through the channel would follow a similar trajectory as predicted by Ohm's law, but we would also have formulations for the partial ion currents of every species.

In the instance of Channelrhodopsin-2 (ChR2), a light-gated non-selective cation channel, P_K and P_{Ca} have been measured relative to P_{Na}, and the ratio P_H/P_{Na} has been calculated based on the equilibrium potential using the GHK voltage equation (e.g., [2]). Considering those four cations only, we are left with one unknown, P_{Na}. Solving $g_{ChR2} = \lim_{V_m \to 0\,mV} \frac{\mathrm{dI_{Ch,GHK}}}{\mathrm{dV_m}}$ in order to match the Ohmic relationship in slope at 0 mV, we find

$$P_{Na} = 2 g_{ChR2} \frac{RT}{F^2} \left([Na^+]_i + [Na^+]_e + \frac{P_H}{P_{Na}}([H^+]_i + [H^+]_e) + \frac{P_K}{P_{Na}}([K^+]_i + [K^+]_e) + 4\frac{P_{Ca}}{P_{Na}}([Ca^{2+}]_i + [Ca^{2+}]_e) \right)^{-1}.$$

We integrated the ChR2 model by Williams et al. [4] into the human ventricular AP model by ten Tusscher & Panfilov [5] Fig. 1 shows the resulting ion currents compared to the Ohmic relationship. The contribution ratio of the different cations to the total current in our model also correlates well with measured data at multiple ion concentrations [3].

Using both variants, we further investigated two scenarios: Pacing by optical stimulation, and long-term illumination, a case particularly interesting in light of recent investigations of using ChR2 to terminate atrial fibrillation [6]. Fig. 2 shows ion concentration trajectories for those scenarios using the unaltered formulation from Williams et al. (bulk current, no direct influence on ion concentrations, $g_{ChR2} = 0.12_1, mS/cm^2$) and our GHK-based modification. When optically pacing,

the bulk model leads to a linearly declining intracellular potassium concentration, counteracting the charge imbalance caused by the unspecific ChR2 current. For continuous illumination, our model suggests an increase in intracellular sodium that is not predicted by the bulk model.

First results show that considering ion species for non-specific channels can have an effect on intracellular ion concentrations in models. In the concrete example of ChR2, pacing using an unspecific bulk current model would only in a long term lead to unphysiological concentrations that could affect the cellular electrophysiology in a significant way. However, for continuous illumination the bulk current results could be misleading (e.g., in our optical defibrillation model, not predicting a sodium overload). Our method can be applied to any non-selective channel given sufficient experimental data.

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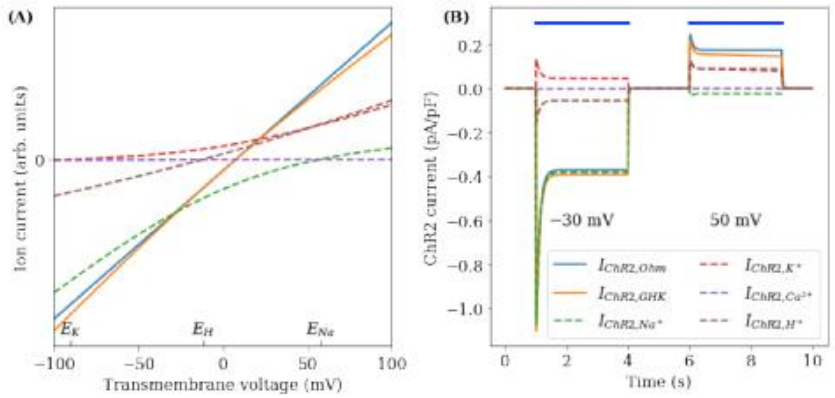

Fig. 1: **(A)** Current-voltage relationship for ChR2 at physiological concentrations for the Ohmic model ($g_{ChR2} = 0.12$ mS/cm^2, no gating), as well as the adapted GHK model, based on permeabilities from [2]. **(B)** Patch-clamp simulation at -30 mV and $+50$ mV showing both models' behaviors in the presence of a gating mechanism. Blue bar indicates illumination (0.5 mW/mm^2, 470 nm, $g_{ChR2} = 0.12$ mS/cm^2).

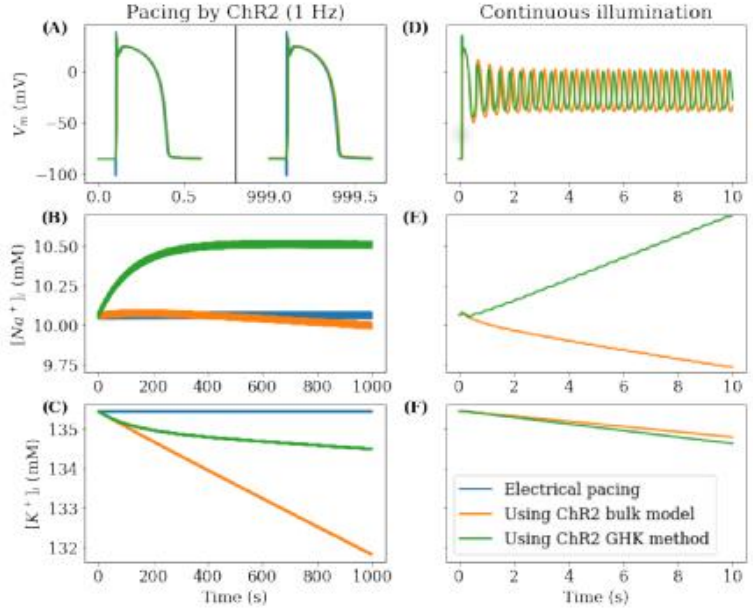

Fig. 2: **Left column:** Results from pacing simulations (1 Hz; ChR2: $g_{ChR2} = 0.12$ mS/cm^2, 5.5 mW/mm^2, 470 nm, 5 ms; electrical: biphasic, 4 nA, 3 ms). **(A)** Overlay of first and last action potentials from all stimulation modi. **(B), (C)** Intracellular sodium and potassium concentration trajectories, respectively. **Right column:** Results from 10 s continuous illumination (5.5 mW/mm^2, 470 nm). **(D)** Transmembrane voltages. **(E), (F)** Intracellular sodium and potassium concentration trajectories, respectively.

Reduced order modelling for cardiovascular haemodynamics: optimal flow control, data assimilation and geometrical reconstruction

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Bypass grafting is a commonly used procedure to restore blood flow in obstructed cardiovascular system, caused by diseases such as arterial stenosis or aortic coarctation [2, 4, 3]. We present a complete pipeline incorporating real-patient geometries (reconstructed from clinical images), numerical simulations [8], and optimal control [5] on physical parameters while investigating the haemodynamics in grafts, and their corresponding arteries [7]. Furthermore, by exploiting reduced-order methods [1, 6] in our framework, we not only lessen the computational cost but also proficiently bridge the gap between numerical simulations and medical measurements, thanks to flow control. In the end, some examples illustrating the application on real-patient geometries for coronary artery bypass graft (CABG) will be discussed.

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Fluid-Structure Interaction via an XFEM/DG Approach for Valve Dynamics

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We present a numerical method that relies on unfitted and overlapping meshes to simulate a three-dimensional (3D) immersed elastic structure that undergoes large displacements interacting with an incompressible fluid. The idea is to discretize independently the fluid and solid domains so that the solid mesh overlaps the fluid one. The fluid mesh is kept fixed, while the solid one is free to move, resulting in unfitted meshes at the fluid structure interface. The proposed method is based on the Extended Finite Element Method (XFEM), that is able to treat discontinuities of the numerical solution within the same element, coupled with a Discontinuous Galerkin (DG) mortaring, in order to couple the numerical solution at the fluid-structure interface. Due to the unfitted nature of the meshes, this method avoids adaptation or remeshing procedures of the fluid mesh when the structure moves. This framework is applied in the study of the interaction arising between blood and leaflets of the aortic valve.