S17. Mathematical and numerical modeling of the cardiac electro-mechanical coupling

Organizers:

- Luca Gerardo-Giorda (BCAM - Basque Center for Applied Mathematics, Spain)
- Simone Scacchi (University of Milan, Italy)

Speakers:

1. Jazmín Aguado (Barcelona Supercomputing Center, Spain)
   An in-silico framework for cardiac safety drug testing: Effect of Wenxin Keli and quinidine to suppress arrhythmogenesis on a Brugada syndrome tissue model
2. Lara Charawi (University of Milan, Italy)
   Isogeometric analysis for the Bidomain model of electrocardiology
3. Piero Colli-Franzone (University of Pavia, Italy)
   Parallel solvers for cardiac electromechanics
4. Andjela Davidović (INRIA-Bordeaux and University Bordeaux 1, France)
   Role and modelling of some heterogeneities for cardiac electrophysiology
5. Adelaide de Vecchi (King's College London, UK)
   Multi-scale modelling of ventricular dynamics in patients with congenital heart defects
6. Simone Palamara (MOX, Politecnico di Milano, Italy)
   An effective algorithm for the generation of patient-specific Purkinje networks in computational electrocardiology

Alya Red: An HPC framework for mechano-electric simulations of the heart

Jazmín Aguado-Sierra

Computer Applications in Science and Engineering, Barcelona Supercomputing Center, C/Gran Capit 2-4, Barcelona, Spain
jazmin.aguado@bsc.es

Describing the heart in a quantitative manner can be used to evaluate our understanding of key biological processes that interact in complex manners, thus predicting or explaining some of the clinical physiology or pathology that might not been evident otherwise. Detailed, accurate, mathematical, computational models are a useful tool to study in a controlled, analytic fashion the human biventricular heart anatomies to understand the heart in health and disease and predict the outcomes of treatment. Alya Red is the Barcelona Supercomputing Center, in-house, HPC-based multi-physics simulation code that is used for the electro-mechanic heart simulations presented in this work. It has been designed from scratch to be able to run efficiently in parallel supercomputers solving coupled multi-physics problems. Up to date, the code has shown a good scalability behavior and performance up to 100,000 cores in Blue Waters supercomputer [1]. HPC-based simulations are required to solve highly detailed simulations to understand cardiac physiology and pathology from the macromolecular to the organ scale. For this purpose, Alya Red is used to compute the solution of ordinary (ODEs) and partial differential equations (PDEs) on a highly refined domain. The scales are strongly coupled, in a single high resolution mesh, covering different orders of magnitude from descriptions of protein concentrations and cellular ion channels [2, 3], cell compartments and myofiber orientation; excitation-contraction coupling and passive material properties; and up to the geometry of the cardiac chambers. In this talk, I will provide examples of the kind of problems solved using the described framework.

[1] Vazquez, M., Houzeaux, G., Koric, S., Artigues, A., Aguado-Sierra, J., Aris, R., Mira, D., Calmet, H., Cucchietti, F., Owen, H., Taha, A., Cela, J.M., Alya, Towards Exascale for Engineering Simulation Codes, 2014; http://arxiv.org/abs/1404.4881.

[2] Ten Tusscher K H W J, Noble D, Noble P J, Panfilov A V, A model for human ventricular tissue *Am J Physiol Heart Circ Physiol* **286** (2004), H1573–H1589.

[3] O'Hara T, Virg L, Varr A, Rudy Y, Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation, *PLoS Comput Biol.* **7(5)** (2011), e1002061.

Isogeometric solvers for reaction-diffusion systems in electrocardiology

Lara Charawi

Dipartimento di Matematica, Università degli Studi di Milano, Via Saldini 50, 20133, Milano, Italia
lara.charawi@unimi.it

We present and study overlapping additive Schwarz preconditioner for the isogeometric discretization of reaction-diffusion systems modeling the heart bioelectrical activity, known as the Bidomain and Monodomain models. The cardiac Bidomain model consists of a degenerate system of parabolic and elliptic PDE, whereas the simplified Monodomain model consists of a single parabolic equation. These models include intramural fiber rotation, anisotropic conductivity coefficients and are coupled through the reaction term with a system of ODEs, which models the ionic currents of the cellular membrane. The overlapping Schwarz preconditioner is applied with a PCG accelerator to solve the linear system arising at each time step from the isogeometric discretization in space and a semi-implicit adaptive method in time. A theoretical convergence rate analysis shows that the resulting solver is scalable, optimal in the ratio of subdomain/element size and the convergence rate improves with increasing overlap size. Numerical tests in three-dimensional ellipsoidal domains confirm the theoretical estimates and additionally show the robustness with respect to jump discontinuities of the orthotropic conductivity coefficients.

Parallel solvers for cardiac electromechanics

Piero Colli Franzone*, Luca F. Pavarino, Simone Scacch

Department of Mathematics, University of Pavia, via Ferrata 1, 27100 Pavia, Italy
colli@imati.cnr.it, piero.collifranzone@unipv.it

The anisotropic Bidomain model describes the bioelectrical activity of the cardiac tissue, see [1]. It consists of a system of a parabolic non-linear partial differential equation (PDE) and an elliptic linear PDE coupled with a system of ordinary differential equations (ODEs), modeling the cellular membrane ionic currents and the cellular tension development in response to electric excitation. In order to take into account the contraction of the cardiac muscle, the bioelectric model is coupled with a non-linear elastic model based on the active-stress approach and considering the myocardium as a quasi-static nearly-incompressible anisotropic hyperelastic material, see [3]. The simulation of the electromechanical system is a difficult multiscale problem. The discretization of the whole electro-mechanical model is performed by finite elements in space and a semi- implicit finite difference scheme in time. This approximation strategy yields at each time step the solution of a large scale ill-conditioned linear system deriving from the Bidomain model and a non-linear system deriving from the finite elasticity equations and requires the development of a 3D parallel solver. The electro-mechanical solver is used to study the relationship between pacing rate and cardiac contraction force development in both cardiac tissue and myocytes culture models. Extracellular cardiac cathodal or anodal stimulation by a unipolar electrode generates a characteristic transmembrane potential pattern called virtual electrodes response (see [2]) and a similar pattern is also observed in the intracellular calcium concentration. We present some simulations in 3D block of cardiac tissue of the four different excitation mechanisms of the myocardium with and without tissue contraction.

[1] Pennacchio M., Savaré G. and Colli Franzone P., Multiscale modeling for the bioelectric activity of the heart, *SIAM J. Math. Anal.* **37** (2006), 1333–1370.

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Role and modelling of some heterogeneities for cardiac electrophysiology

Andjela Davidović

INRIA, University of Bordeaux, IMB, LYRIC, France
andjela.davidovic@inria.fr

Introduction: The most used model in the electrophysiology of the heart, known as *the bidomain model*, is the system of degenerate parabolic PDEs coupled with the non-linear ODE. Even though these equations provide quite accurate results, they are based on the fact that active cardiomyocytes are present everywhere in the heart, while it is known that non-small regions exist where fibroblasts and other non-excitable cells or additional extracellular media take place. These regions, which play an important role in diseased hearts, are often taken into account through ad-hoc rough tuning of the tissue conductivities. In this work, we introduce a rigorous way to derive these conductivities from a microscopic description of the heterogeneities in the tissue.

Method: We assume a periodic alternation of the healthy tissue (bidomain model) and the fibrotic tissue (diffusive part). In order to reduce the computational cost, we derive a homogenized model at the macroscopic scale, following a two-scale convergence method. There are two problems rising here. First one has to deal with the degeneracy of parabolic equations and second one comes from the non-linearity of the ionic model of the cardiac cells.

Results: Interestingly, we recover a bidomain type model, but with modified conductivities, that depend on the volume fraction of the diffusive inclusions but also on their geometries. The numerical results confirm the convergence of the microscopic model to the homogenized equations in the linear case. We are currently working on the numerical simulations for the non-linear case, where we expect to observe the influence of the diffusive inclusions on the propagation of action potentials.

Conclusion: With the final non-linear model, we shall provide cheap modeling tools to account for tissue heterogeneities at intermediate scales, as can be observed, e.g., in the fibrotic tissue.

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Multi-scale modelling of ventricular dynamics in patients with congential heart defects

Adelaide de Vecchi*, David A. Nordsletten, Nicolas P. Smith

Division of Imaging Sciences and Biomedical Engineering, Kings College London, St Thomas Hospital, SE1 7EH, London, UK
adelaide.de vecchi@kcl.ac.uk

Recently developed imaging techniques supply detailed data to fit computer models to each patients anatomy and functioning, providing the foundations for a more effective, personalised clinical planning. This study focuses on the application of patient-specific fluid-structure interaction (FSI) simulations to a congenital heart patient with hypoplastic left heart syndrome.

This method, relies on an Arbitrary Eulerian-Lagrangian (ALE) approach with Lagrange multipliers for the fluid problem, and on the quasi-static incompressible finite elasticity equations for the solid problem [1]. The system of equations is discretized and solved using a classic Galerkin finite element method. The present model is based on a continuum approach where an additional coordinate system aligned with the fibre, sheet and sheet normal directions is defined throughout the myocardium. An anisotropic constitutive model based on a modified version of the Costa Law is embedded in the myocardium using this coordinate system [2]. An isotropic stress component is also used to approximate the stress distribution near the singularity in the apex, where the tissue is expected to behave in a more isotropic fashion due to variations in the collagen density.

In the patient-specific approach, the material parameters must be estimated for each case. An iterative procedure is proposed based on the inflation and deflation of the uncoupled solid model, from end-diastole to a zero-pressure reference state and then to the final end-sytolic state. The resulting cavity shape is validated against MRI data. Finally, FSI simulations are performed and the tissue behaviour is validated by comparing the myocardial velocity and displacement predictions against MRI data.

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Generation of patient-specific Purkinje networks driven by clinical measurements: normal and abnormal electrical activations in the left ventricle

S. Palamara*, D. Catanzariti, M. Centonze, E. Faggiano, F. Nobile, A. Quarteroni and C. Vergara

MOX, Dipartimento di Matematica, Politecnico di Milano, Piazza Leonardo da Vinci 32, I-20133, Milano, Italy
simone.palamara@polimi.it

A key aspect of the heart modeling is the study of electrical activation, that triggers the heart contraction. The electrical activation is regulated by the cardiac conduction system (CCS), responsible for the fast and coordinated distribution of the electrical impulse in the heart. In particular, the ventricular activation is regulated by the peripheral part of the CCS, the Purkinje fibers (PF). The electrical signal spreads rapidly in the PF and it enters the ventricular wall only at certain insertion sites located at their endpoints, called Purkinje muscle junctions (PMJ). Since the electrical activation of the ventricle depends strongly on the PF, it is necessary to model its presence to obtain a realistic activation model. The focus of our work is to provide a computational algorithm for the generation of a patient-specific Purkinje network, driven by clinical measures of the electrical activation in the ventricle. These measures consist of the activation times acquired on the endocardium of the left ventricle, for example before an ablation procedure to burn anomalous propagation sites. The proposed algorithm for the generation of the patient-specific Purkinje network is based on searching the optimal locations of the PMJ to best fit the clinical measures, computing the activation times in the PF and in the ventricles by solving Eikonal problems. We tested the accuracy and robustness of our method considering both an ideal geometry with synthetically generated data and five patient-specific geometries, with real clinical measures, considering both normal and pathological activations. As pathological activations, we considered data from four patients, two of them had a case of Wolff-Parkinson-White syndrome, one had a case of heart failure and the last one suffered from Left Bundle Branch Block. The numerical results proved the essential role of a patient-specific Purkinje network, both in modeling the healthy and the pathological activations of the patients under consideration.