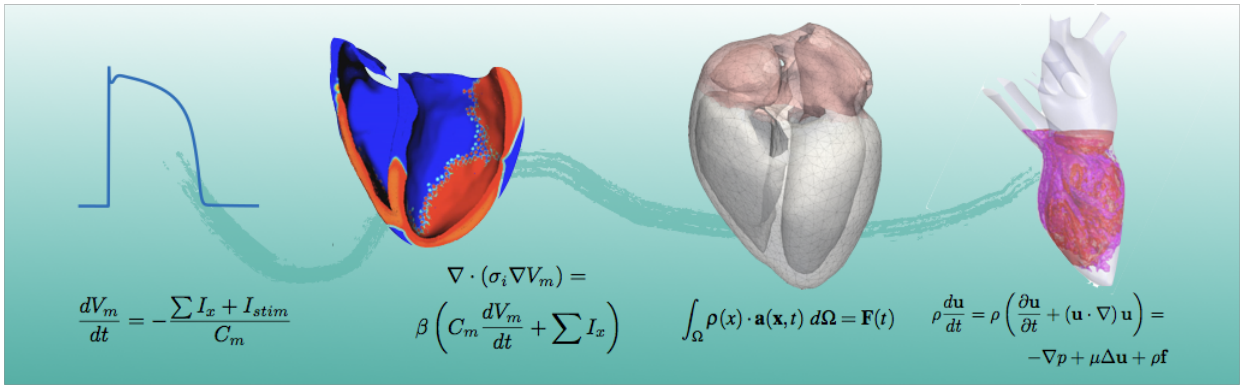
Workshop on Cardiac Modeling

Towards an integrated numerical heart model, Coupling the relevant physics the right way

April 15-17 2019, Bad Herrenalb



Organizers:
Prof. Dr. Christian Wieners
Prof. Dr. Olaf Dössel, Dr. Axel Loewe
Prof. Dr. Bettina Frohnapfel
Prof. Dr. Vincent Heuveline

Bundesministerium für Bildung und Forschung

Karlsruhe Institute of Technology

EMCL

Workshop Schedule

Monday		Tuesday		Wednesday
15.04.19		16.04.19		17.04.19
		9:00-10:00	Peter Kohl	Rolf Krause
10:00-10:15	Welcoming / Opening	10:00-10:30	Coffee break	Coffee break
10:15-11:15	Luca Dedè	10:30-11:30	Steven Niederer	Stefan Frei
				Henry Sutanto
11:15-12:15	Gernot Plank	11:30-12:30	The integrated heart model	Alfonso Santiago
12:15-13:30	Lunch break	12:30-13:30	Lunch break	Lunch
13:30-14:00	Jan Christoph	13:30-16:00	Social program	
14:00-14:30	Stefano Pagani			
14:30-15:00	Ekaterina Kovacheva			
15:00-15:30	Coffee break			
15:30-16:30	Poster session	16:00-16:30	Coffee break	
16:30-17:00	Nagaiah Chamakuri	16:30-17:30	Electro-Mechanical benchmark	
17:00-17:30	Simone Pezzuto			
17:30-18:30	Gary Mirams	17:30-18:30	Maxime Sermesant	
		20:00-21:30	Poster session / get-together	

Abstracts

Monday, April 15

Cardiac Electromechanics: Multiscale Modeling, Coupling Schemes, and Numerical Simulation

Invited speaker

Luca Dedè[a], A. Gerbi, F. Regazzoni[a], A. Quarteroni[a]
[a]MOX, Politecnico di Milano, Milano, Italy

We consider the mathematical and numerical modeling of cardiac electromechanics with application to the left ventricle of the human heart. We proceed 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 within the active strain paradigm. We consider the spatial approximation of the Partial Differential Equations therein involved by means of the Finite Element method and the time discretization by Backward Differentiation Formulas. We numerically solve the coupled electromechanics problem by exploiting both monolithic and staggered approaches, for which we verify, compare, and critically discuss their accuracy properties and computational efficiency in simulating the whole cardiac cycle. In addition, we develop a multiscale model for cardiac electromechanics that accounts for miscroscopic active force generation at the cellular level within the active stress paradigm; with this aim, we exploit model order reduction techniques based on Machine Learning algorithms to enable efficient numerical simulations of multiscale electromechanics. Finally, we present several numerical results of the electromechanics problem in the human left ventricle obtained in the high performance computing framework.

This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme: grant agreement No 740132, iHEART - "An integrated Heart Model tor the Simulation of the Cardiac Function", 2017–2022.

Multiphysics modeling of total heart function

Invited speaker

Gernot Plank
Medical University Graz, Graz, Austria

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 cardiac anatomy and physiology, is considered a highly promising approach to comprehensively and quantitatively characterize cardiovascular function in a given patient. Assuming that models correctly capture all fundamental mechanisms relevant to a given clinical problem, it is anticipated that modeling and simulation of cardiovascular function will play a pivotal role in future precision medicine as a

method for stratifying diseases, optimizing therapeutic procedures, predicting outcomes and thus for better informing clinical decision making.

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

Electromechanical Vortex Filaments and Vortex-Substrate Interactions during Cardiac Fibrillation

talk

Jan Christoph

University Medical Center Göttingen, Department of Cardiology and Pneumology, Göttingen, Germany

The visualization of the highly dynamic electrical wave phenomena evolving within the heart muscle during cardiac fibrillation is a major scientific challenge. In recent work, we demonstrated that simultaneous imaging of both electrical and mechanical dynamics of the heart can provide novel insights into the spatio-temporal organization of cardiac fibrillation within the heart muscle. Using high-resolution 4D ultrasound, we showed that it is possible to identify mechanical filament-like phase singularities within the contracting, fibrillating heart wall. The mechanical filaments appear to evolve like fingerprints of electrical vortex filaments through the ventricular muscle, indicating the core regions of three-dimensional electrical scroll waves. On the deforming ventricular surface, it can be observed that electrical spiral vortices create vortex-like mechanical deformation patterns, which similarly rotate and whose core regions co-exist and co-localize with the core regions or phase singularities of the electrical vortices. Furthermore, it is possible to observe interactions of electrical and mechanical vortices with heterogeneities such as scar tissue, as both electrical and mechanical phase singularities equally attach to or co-localize with the heterogeneities. Lastly, the integration of the data into computer models could be used to infer in 3D the electrical wave patterns that had caused the deformations, but can not be measured yet directly.

Uncertainty quantification in cardiac electrophysiology disease modeling

talk

Stefano Pagani[a], Andrea Manzoni[a], Alfio Quarteroni[a,b]
[a]MOX, Politecnico di Milano, Milano, Italy
[b]EPFL, Lausanne, Switzerland

We develop a computationally efficient framework to perform uncertainty quantification (UQ) in cardiac electrophysiology in order to improve the ability of cardiac models to reproduce both physiological and pathological patient-specific behaviors. Electrophysiology numerical models, obtained from the discretization of nonlinear parametrized coupled system of ordinary and partial differential equations (PDEs), are inevitably affected by uncertainty, e.g., in (i) the computational domain, (ii) physical coefficients and (iii) boundary conditions.

We address a complete UQ pipeline, including: (i) a variance-based sensitivity analysis for the selection of the most relevant input parameters; (ii) forward UQ (or uncertainty propagation) to investigate the impact of intra-subject variability on clinically relevant outputs related to the cardiac action potential; (iii) backward UQ (or parameter and state estimation and data assimilation) in view of both model calibration and personalization.

In this context, numerical strategies involve the approximation of PDEs for several (usually, order of thousands) input parameter values, thus making high-fidelity, or full-order, techniques (e.g. the finite element method) ill-suited.

To mitigate this computational burden, we replace the high-fidelity model with computationally less expensive projection-based local reduced-order models aimed at reducing the state-space dimensionality. Numerical experiments dealing with both physiological and pathological cases illustrate the ability of the UQ pipeline based on reduced-order models to realize a cost-effective-but still accurate-methodology.

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

A Bidirectionally Coupled Model of Electrophysiology and Elastomechanics of the Human Heart

talk

Tobias Gerach[a], Ekaterina Kovacheva[a], Larissa Hütter[a], Olaf Dössel[a], Axel Loewe[a]
[a]Institute of Biomedical Engineering, Karlsruhe Institute for Technology (KIT), Karlsruhe, Germany

The contraction of the heart is a complex process involving the interaction of different mechanisms. On the one hand, electrical activation propagates through the tissue and leads to tension development and thus to mechanical contraction of the myocytes. On the other hand, the deformation of the myocardium and stretch activated channels (SAC) influence the electrical excitation. Each of these mechanisms is modelled by a different mathematical description and can be reproduced in-silico. Nevertheless, to estimate how these mechanisms influence each other, a coupling method is needed to interconnect the electrical propagation in the tissue and the heart mechanical contraction. In this study we investigate whether a bidirectional coupling of the electrophysiology and the elastomechanics is necessary during normal sinus rhythm. The electromechanical propagation was simulated on an idealized left ventricle geometry for three different scenarios: first, we simulated the elastomechanics self-contained, second the elastomechanics strongly coupled with the electrophysiology, and finally we added SACs to the electrophysiology model. We compared the global indicator ejection fraction as

well as measurements on a local scale such as the action potential and tension development for a single cell. This will help us to decide which complexity of the coupled model is necessary to simulate certain scenarios with sufficient accuracy. In the future this study will be extended to include a cardiomyopathy case, where the mutual influence of both electrophysiology and the elastomechanics will also be evaluated and compared to the healthy heart beat. This will provide important insights in terms of developing new diagnostic tools and therapeutic options for the treatment of a cardiomyopathy.

An efficient and accurate numerical methods for the solution of bidomain model.

talk

Nagaiah Chamakuri

University of Hohenheim, Stuttgart, Germany

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

Enabling high-dimensional uncertainty quantification for cardiac electrophysiology via multifidelity techniques

talk

Simone Pezzuto[a], Alessio Quaglino[a], Rolf Krause[a]

[a]Università della Svizzera italiana, Lugano, Switzerland

Mathematical modeling of the heart, as many other models in biomedical sciences, involves a large number of parameters and simplifying approximations. Uncertainties for cardiac models are ubiquitous, including anatomy, fiber direction, and electric and mechanical properties of the tissue. Hence, both UQ and parameter sensitivity naturally arise during modeling, and they shall become fundamental in view of clinical applications. Despite the relevance of UQ for cardiac models has been acknowledged multiple times in the last 5 years [1], the literature on this topic is still very limited.

For high-dimensional input uncertainties, e.g., substrate heterogeneity or cardiac fibers orientation, the method of choice for UQ is the classic Monte Carlo (MC) method. MC convergence rate does not suffer from the curse of dimensionality, but it is notoriously slow. While

sampling a random field can be done very efficiently via the pivoted Cholesky decomposition, computing the cardiac activation from the bidomain 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]. A key ingredient of the multifidelity approach is the choice of low-fidelity models. Typical strategies are projection-based or data-fit surrogates, which however need to be trained anew for each patient and may become inefficient for a large dimensionality of the input, 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, 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, which provide confidence intervals and full probability distributions at selected points, thus augmenting the information provided by standard frequentist approaches.

References:

[1] Pathmanathan, P. & Gray, R. A. (2018). Validation and trustworthiness of multiscale models of cardiac electrophysiology. Frontiers in Physiology, vol. 9, no. FEB, pp. 1-19.
[2] Peherstorfer, B., Willcox, K., & Gunzburger, M. (2018). Survey of multifidelity methods in uncertainty propagation, inference, and optimization. SIAM Review, 60(3), 550-591.
[3] Quaglino, A., Pezzuto, S., Koutsourelakis, P.S., Auricchio, A., Krause, R. (2018). Fast uncertainty quantification of activation sequences in patient-specific cardiac electrophysiology meeting clinical time constraints. Int J Numer Meth Biomed Engng, e2985.

Uncertainty Quantification in Cardiac Electrophysiology Modelling

invited speaker

Gary Mirams

Centre for Mathematical Medicine & Biology, School of Mathematical Sciences, University of Nottingham, Nottingham, England

The Uncertainty Quantification (UQ) field typically focusses on the challenging process of propagating uncertainties in model inputs and parameter values through to model predictions. But perhaps more important in cardiac electrophysiology modelling is our uncertainty in model structure - the right set of equations to use. Unpicking whether variability in experimental data is biologically-relevant or due to experimental artefacts is also a challenge. Here, I'll discuss sources of uncertainty that are important to consider when doing cardiac electrophysiology modelling. We will examine a case study selecting and parameterising models for the hERG/IKr potassium current. There are over seven different structures and thirty parameterisations in the literature for this one current. I'll show how designing more information-rich experiments helps us to minimise uncertainty in parameter values with short training experiments, whilst leaving time to do independent validation experiments which help with model selection. The project raises questions about how best to deal with discrepancy between the models and reality when using model predictions to make real world decisions that are increasingly safety-critical.

Tuesday, April 16

The Non-Textbook Heart: Structure, Electrics, Mechanics

invited speaker

Peter Kohl

Institute for Experimental Cardiovascular Medicine, University Heart Centre Freiburg / Bad Krozingen, Faculty of Medicine, University of Freiburg, Germany

The heart is an amazing organ. It beats once per second, about 2 billion times by the time we retire, and if it stops – so does life. The volume it pumps in a year is equivalent to that of an Olympic-sized swimming pool. Pumping itself involves intra-cardiac volume redistribution between atria and ventricles, without a discernible change in the overall external volume occupied by the blood-filled heart. This mechanical activity results from electrically-orchestrated contractions of billions of individual heart muscle cells. Each of them displays slightly different stress-strain behaviour, depending on the local mechanical environment which differs as a function of basico-apical and transmural position. The mechanical environment furthermore changes differentially with any alteration in pre- (volume) or after- (pressure) load, such as on every breath we take, when we change posture, or during exercise. The matching of local mechanical activity to global demand requires finely tuned auto-regulatory abilities, and all that in the absence of the kind of neuro-muscular junctions that tune skeletal myofibre activity. In addition, the cross-talk between electrics and mechanics is far from uni-directional, as electrical excitation and conduction, as well as the mechanisms underlying electro-mechanical coupling, are exquisitely mechano-sensitive. Add to this the observation that the heart contains more non-myocytes than muscle cells, combined with recent insight into electrical coupling between those different cell populations, and it becomes clear that we need to take a fresh look at the intriguing aspects of cardiac structure and function that extend beyond current textbook knowledge. This lecture will address some of those aspects that may be of relevance on the path towards an integrated numerical heart model.

Applying Cardiac Modelling to Study Drugs, Devices and Diagnosis

invited speaker

Steven Niederer

King's College London, London, England

The ability to measure the heart, its shape, its structure and its function across multiple spatial and temporal scales continues to grow. Interpreting this data remains challenging. Computational biophysical models of the heart allow us to quantitatively link and interpret these large disparate data sets within the context of known cardiac physiology and invariable physical constraints. Within these models, we can infer unobservable states, propose and test new hypothesis and predict how systems will respond to challenges increasing our ability to interrogate and understand biological systems. We are increasingly applying this approach to modelling human hearts to investigate clinical applications.

In this presentation, I will give an overview on our modelling work simulating anthracycline-induced heart failure, how we are using models of individual patients to study cardiac resynchronisation therapy and how we are using simulations to characterise the anatomy and pathophysiology of atrial fibrillation patients. Finally, I will present some of our preliminary results on simulating the four-chamber heart to begin simulating the interactions between atrial and ventricular function.

Biophysics & AI for Computational Cardiology: Learning by Heart

invited speaker

Maxime Sermesant
Inria, Sophia Antipolis, France

Electromechanical models of the heart have made important progress over the last decades, and personalised models can now be envisaged for clinical applications. However there are still challenges in translating such models to the clinics. The recent progress in computing power and available data makes it possible to develop accurate data-driven approaches for healthcare but such artificial intelligence approaches often lack of robustness. Machine learning and biophysical modelling are very complementary approaches, with biophysical models offering a principled way to introduce physiological constraints. In this talk I will present results on personalised electromechanical models of the heart and research where we combined biophysics and AI in different ways in order to leverage their strengths. Different clinical applications in computational cardiology will be presented.

Wednesday, April 17

Coupling Scales, Coupling Physics - Multi-physics in Cardiac Simulation

invited speaker

Rolf Krause[a], P. Zulian, S. Pozzi, M. Favino, M. Nestola, P. Benedusi
[a]Università della Svizzera italiana, Lugano, Switzerland

In this talk we present and discuss discretization and solution methods in space, time, and space-time for cardiac simulation. Starting from pure electrophysiology, we discuss the coupling of electrophysiology and mechanics, and eventually comment on fluid structure interaction and contact in the heart valves.

As it turns out, either on the side of the solution method (multigrid) or on the side of the coupling of different discretizations (mortar methods), discrete L^2 projections turn out to be a versatile ingredient - may it be for the construction of multi-level approximation spaces (electrophysiology) , for the discretization of contact constraints (heart valves) , or for the transfer of discrete quantities (FSI). We will describe our discretization and solution methods and will comment on how to handle efficiently the arising discrete constrained and coupled systems, with particular focus on their parallel solution.

Eventually, we will comment on how to deal with uncertain data and in which way the created multi-level hierarchies can be exploited for uncertainty quantification.

Modelling and simulation of mechano-chemical fluid-structure interaction with application to atherosclerotic plaque growth

talk

Stefan Frei[a], Thomas Richter[b], Thomas Wick[c]

[a]University College London, England
[b]University of Magdeburg, Gerrmany
[c]University of Hannover, Germany

In this talk, we present a numerical framework for mechano-chemical fluid-structure interactions with long-term effects. In particular, we investigate a model for atherosclerotic plaque growth in arteries including the interaction of the growing solid with the flow in the vessel. The mechano-chemical interaction is modelled by a multiplicative splitting of the deformation gradient.

This application includes two particular difficulties: First, growth may lead to very large deformations, up to full clogging of the fluid domain. Therefore, we use a Fully Eulerian approach, that is able to handle very large deformations up to contact. The second difficulty stems from the different time scales: while the dynamics of the fluid demand to resolve a scale of milliseconds to seconds, growth typically takes place in a range of months. To include both long-scale and short-scale effects in an efficient and accurate way, we derive a temporal two-scale approach.

The numerical methodology is substantiated with several numerical tests that include comparisons of the Eulerian approach to an ALE method, the performance of the temporal two-scale algorithm as well as numerical convergence studies.

Understanding species-, atrial-, disease- and rate-specific effects of clinically used antiarrhythmic drugs using computational models

talk

Henry Sutanto[a], Lian Laudy[a], Michael Clerx[b], Dobromir Dobrev[c], Harry J.G.M. Crijns[a], Jordi Heijman[a]

[a]Department of Cardiology, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands
[b]Department of Computer Science, University of Oxford, Oxford, United Kingdom
[c]Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Essen, Germany

Background: Cardiac arrhythmias remain a major cause of death and disability. Despite the improved understanding of arrhythmia mechanisms, progress in the development of new antiarrhythmic drugs (AADs) has been limited and clinical application of currently available AADs often remains suboptimal, likely in large part due to the incomplete understanding of the complex mechanisms-of-action of AADs. Here, we present a novel user-friendly computational tool designed to facilitate a better understanding of AADs (the Maastricht Antiarrhythmic Drug Evaluator; MANTA).

Methods: MANTA integrates published computational cardiomyocyte models of different species (mouse, guinea-pig, rabbit, dog, human), regions (atrial, ventricular, purkinje) and disease conditions (atrial fibrillation- and heart failure-related remodeling). It enables simulations of the effects of clinically available AADs (Vaughan-William Classes I, III, IV and multi-channel blockers) on action potential (AP) properties and the occurrence of proarrhythmic effects such as early-afterdepolarizations. AAD effects were simulated based on published IC_{50} values for each cardiac ion channel and by integrating state-dependent block of I_{Na} by

Class I AADs using a Markov-model approach in all cardiomyocyte models.

Results: Markov model parameters were optimized to replicate published INa characteristics (voltage-dependent activation, inactivation, recovery from inactivation) and AP upstroke velocity in all cardiomyocyte models and reproduced experimental use-dependent onset and recovery of I_{Na} inhibition by flecainide and lidocaine. MANTA provides a graphical user interface allowing users to select different AADs, concentrations, and experimental conditions (rate, electrolyte concentrations). Using MANTA, we demonstrated and characterized important species-, rate-, cell-type-, and disease-state-specific AAD effects, including 1) a stronger effect of Class III AADs in large mammals than in rodents; 2) a frequency-dependent decrease in upstroke velocity with Class I AADs and reverse use-dependence of Class III AADs; 3) ventricular-predominant effects of pure I_{Kr} blockers and preferential reduction in atrial AP upstroke velocity with vernakalant; and 4) excessive AP prolongation with Class III AADs other than amiodarone in heart failure.

Conclusion: The effects of AADs are complex and highly dependent on the experimental or clinical conditions. MANTA is a powerful, freely available tool able to reproduce a wide range of AAD characteristics that enables analyses of the underlying ionic mechanisms. Use of MANTA is expected to improve understanding of AAD effects on cellular electrophysiology under a wide range of conditions, which may provide clinically-relevant information on the safety and efficacy of AAD treatment, thereby potentially improving cardiac arrhythmia management.

A tightly coupled three-physics model of the human heart

invited speaker

Alfonso Santiago[a], Jazmin Aguado-Sierra[a], Federica Sacco[b], Constantine Butakoff[b], Mariano Vázquez[a]

[a]BSC, ELEM Biotech, Barcelona, Spain
[b]BSC, Universitat Pompeu Fabra, Barcelona, Spain

The heart is a complex system. From the engineer's standpoint, it gathers electrical depolarization, mechanical deformation and fluid dynamics, tightly coupled in a very intricate geometry. Although simplified and reduced order models are crucial nowadays to transfer science to industry and clinic, comprehensive and integrative models of the heart are also required to understand the complex connections between the different physics. This detailed modelling strategy leads to an expensive computational cost, requiring an efficient use of the resources following a clear parallel programming strategy, from the algorithms down to the implementation issues. In this talk we see the heartbeat from an engineer's point of view, decomposing it in each one of the independent physical problems. After, the way the problems are tightly coupled is explained. On the one hand, the Land model is used for the excitation-contraction coupling and the mechano-electric feedback. On the other hand the bidirectional fluid-structure Interaction problem is tackled with a staggered quasi-Newton approach, with a specific focus on the parallel implementation. The FSI problem in the heart is particularly complex due to the similar densities of both domains, a fact that makes the system prone to added mass instability in a partitioned scheme. Together with this challenge, two FSI interfaces should be simultaneously coupled and converged: the right and left ventricles. Finally, we show two use cases for this three-physics model.

Poster session

Development of a simulation environment to understand the charge-based mapping of cardiac physiology from single measurement points

M. E. Hesar[a], R. Vitushinsky[b] and S. Ingebrandt[a]

[a]Institute for Materials in Electrical Engineering 1, RWTH Aachen University, Aachen, Germany
[b]RAM Group DE GmbH, Zweibrücken, Germany

In many research projects as well as in clinical tests the cardiac physiology has been investigated noninvasively. To date, the differential measurement of the body surface potential (BSP) is well-known and state-of-the-art in clinical routine (Electrocardiography – ECG). Only after differential BSP measurements, solving the ill-posed inverse problem [1] of the heart is possible. Typically, numerical or analytical modeling of the heart as an electronic signal generator (e.g. 2D or 3D dipole [3], mono-domain [2], bi-domain [3] etc.) is utilized to understand and simulate the signal propagation from the heart as a signal source towards the micro- and nanoelectrodes used for low ohmic skin-electrode contacts.

In our project, in contrast to ECG, we are utilizing an ultra-low noise, charge based sensing technique from single measurement points on the skin to acquire cardiac signals representing mechanical and electrical features of the heart activity. We coin this technique single point cardiography (SPC) as a complementary technique to routine ECG. Our signals contain periodic features, which show signal components of standard ECG overlaid by components, which we attribute to the mechanical action of the heart. We are aiming to develop a simulation environment and solve the inverse problem of the heart action including electrical activity and mechanical movement of the tissue using the classical simulation techniques.

Moreover, similar to other biological signal recordings, noise reduction and signal averaging techniques are required to extract the prominent signal features of the SPC recordings. Here, the sensor front ends, which are highly sensitive to the tiny skin charge changes, are posing high demands for electromagnetic shielding.

To approach this problem from a fundamental science aspect, we develop a 3D upper body geometrical model similar to the human anatomy to verify the numerical and mathematical models for signal generation and propagation. This will allow us to verify our simulation results with standard signal sources.

References:

[1] Nejib Zemzemi. Theoretical and Numerical study of the electric activity of the heart. Modeling and Numerical simulation of electrocardiograms. Mathematics [math]. Université Paris Sud - Paris XI, 2009. English.

[2] Coudière, Y., Rioux, M.: Virtual electrodes mechanisms predictions with a current-lifted monodomain model. Comput. Cardiol. 39, 837–840 , 2012.

[3] Gerardo-Giorda, L. An Introduction to Mathematical and Numerical Modeling of Heart Electrophysiology. In Nonlinear Dynamics in Biological Systems (pp. 83-111). Springer, Cham. , (2016).

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Initiation and maintenance of re-entrant cardiac propagation: a computational vulnerability study

Luca Azzolin

Institute of Biomedical Engineering, Karlsruhe Institute for Technology (KIT), Karlsruhe, Germany

Nowadays, a large share of the global population is affected by heart rhythm disorders. Computational modelling is a useful tool for understanding the dynamics of cardiac arrhythmias. Several recent clinical and experimental studies suggest that atrial fibrillation is maintained by re-entrant drivers (e.g. rotors). As a consequence, numerous works have addressed atrial arrhythmogenicity of a given electrophysiological model using different methods to simulate the perpetuation of re-entrant activity. However, no common procedure to test atrial fibrillation vulnerability has yet been defined. Here, we systematically evaluate and compare two state-of-the-art methods. The first one is rapid extra-stimulus pacing from rim of the four pulmonary veins. The second consists of placing phase singularities in the atria, estimating an activation time map by solving the Eikonal equation and finally using this as initial condition for the electrical cardiac propagation simulation. In this way, we are forcing the wavefronts to follow re-entrant circuits with low computational cost thus less simulation time. We aim to identify a methodology to quantify arrhythmia vulnerability on patient-specific atrial geometries and substrates. We will proceed with in-silico experiments, comparing the results of these two methods to initiate re-entrant activity, checking the influence of the different parameters on the dynamics on the re-entrant drivers and finally extracting a valid set of parameters allowing to reliably assess re-entry vulnerability. The final objective is to come up with an easily reproducible minimal set of simulations to assess vulnerability of a particular atrial substrate (cellular and tissue model) or of distinct anatomical atrial geometries to arrhythmic episodes. Given the great need of exploring susceptibility to atrial arrhythmias, i.e. after a first ablation procedure, this study can provide a useful tool to test new treatment strategies and to learn how to prevent the onset and progression of atrial fibrillation.

Optimization of Cardiac Resynchronization Therapy in 3D Electrophysiological Ventricular Models

Edison Carpio[a], Juan F. Gomez[a], Rafael Sebastian[b], Alejandro Lopez-Perez[a], Eduardo Castellanos[c], Jesus Almenral[c], Jose M. Ferrero[a], Beatriz Trénor[a]

[a]Universitat Politècnica de València, València, Spain
[b]Universitat de València, València, Spain
[c]HM Hospitales, Universidad CEU-San Pablo

Cardiac Resynchronization therapy (CRT) is an assigned treatment for cardiac diseases, such as heart failure (HF) with left bundle branch block (LBBB), which reduces electrical ventricular dyssynchrony. In CRT, an electrical stimulus is usually applied to both the right ventricle (RV) and the left ventricle (LV). An optimal location of the LV pacing lead is fundamental to an effective CRT. The LV posterior-lateral wall is the usual location recommended for CRT application. Nevertheless, several optimization criteria such as the latest electrical activated region in the LV or the LV site leading to the shortest QRS have also been proposed to guide the location for the LV pacing lead.

The aim of the present study was to systematically analyze the optimal location LV pacing lead based on these three different optimization criteria during CRT procedure, using computer simulations. A human ventricular anatomical model including cardiac conduction system was used to reproduce the electrical behavior of a tissue under non-pathological and HF and

LBBB conditions. Precordial leads signals were computed upon human torso geometry. Computational simulations were performed using a modified version of the O'Hara et al. action potential model.

Simulation results showed that the greatest reduction in electrical ventricular dyssynchrony during CRT application, measured as the shortest total ventricular activation time (TAT), was reached when the LV lead was located in the mid-posterior wall. This LV site is in accordance with the region leading to the shortest QRS. On the other hand, the latest electrically activated area of the LV did not lead to the shortest TAT.

In conclusion, an optimal location of the LV lead is important to achieve a higher degree of electrical synchrony in a heart with HF and LBBB. A criterion based on the shortest QRS could be used to determine the optimal location of the LV lead.

ASIC - a hybrid modeling system for a prediction of critical states in the ICU

Konstantin Sharafutdinov[a], Richard Polzin[a], Andreas Schuppert[a]

[a]Joint Research Center for Computation Biomedicine RWTH Aachen, Aachen, Germany

The demand for intensive care medicine will strongly increase over the next years facing unmet medical needs, such as early diagnosis of the acute respiratory distress syndrome (ARDS). Within the ASIC project we are developing a system for continuous analysis of data obtained from the hospital patient data management system (PDMS) in order to enable model-based 'algorithmic surveillance' of the state of critically ill patients. We are developing and integrating a hybrid modeling system which consists of two components: the Virtual Patient (VP) and the Diagnostic Expert Advisor (DEA).

The VP is a model-based system which relies on the physiological models of respiratory and cardiac system and allows personalized modeling of a patient physiology. In contrast to the VP the DEA is a data-driven component which utilizes ML tools and will support the VP model in stratification of patients and parameters estimation for individual patients. These two components together build up a hybrid modeling system which will enable individual prognosis for a particular patient.

The importance of the atrial heterogeneous wall thickness and fibre orientation transmurality in fibrillatory patterns

Sara Rocher[a], Alejandro Lopez[a], Ana Ferrer[a], Laura Martinez[a], Damián Sanchez-Quintana[b], Javier Saiz[a]

[a]Centro de Investigación e Innovación en Bioingeniería, Universitat Politècnica de València, Valencia, Spain

[b]Departamento de Anatomía, Universidad de Extremadura, Badajoz, Spain

Atrial fibrillation (AF) is the most prevalent cardiac arrythmia and is considered a major cause of morbidity and mortality. However, despite the progress in health technology, AF treatment is still suboptimal because the physiopathology of the disease remains incompletely understood. Multiscale cardiac modelling has been increasingly used since it provides a promising framework to advance in AF diagnosis and treatment. Atrial wall thickness and fibre orientation have been suggested to have a significant role in arrhythmogenic dynamics. Thus, in this study we have developed a highly detailed 3D model of the human atria.

We improved our previous atrial model by adding an anatomical and heterogeneous description of the wall thickness (from 0,5 to 7 mm; mean value of 3 mm) and realistic and transmural fibre orientation. The new 3D model has a spatial resolution of 300 μm and is comprised of 1.945.101 hexahedral elements and 2.174.034 nodes. The Courtemanche model was used to solve the electrical activity and tissue propagation was described by the monodomain formalism. To reproduce the heterogeneity in action potential morphology and in tissue conduction of the different atrial regions, nine cellular models and ten tissue materials were defined. Additionally, we added the electrical remodelling characteristic of a chronic AF substrate.

The electrical behaviour of the new model in control conditions was validated by comparing the propagation sequence in sinus rhythm with respect to the experimental local activation times. Then, we compared the fibrillatory activity of the new model with two models with the same electrophysiological properties but less anatomically detailed: i) a model with homogeneous wall thickness of 600-900 μm and ii) a model with genuine heterogeneous wall thickness, both including detailed fibre orientation without transmurality. We observed how the three models reproduced different fibrillatory patterns with the appearance of rotors at different areas. Therefore, our results suggest that the anatomical and functional definition of the model affects atrial activation, especially in abnormal heart rhythms, highlighting the importance of using realistic models to obtain reliable outcomes.

In conclusion, our new highly detailed model is an excellent tool for gaining insight into AF, allowing to consider new variables of study like effects of transmurality in fibrosis or ablation.

Impact of ventricular deformation on the body surface potential map during repolarization

Robin Moss[a,b], Eike M. Wülfers[a,b], Gunnar Seemann[a,b]

[a]Faculty of Medicine, University of Freiburg, Freiburg, Germany,
[b]Institute for Experimental Cardiovascular Medicine, University Heart Center Freiburg Bad Krozingen, Germany

Computational cardiac modelling of electrophysiology is frequently used to understand how and where signals measured on the body surface originate. Yet, one aspect impacting cardiac signals is rarely considered or stated as negligible – the effect of deformation. As deformation of the heart occurs mainly during ventricular contraction, this simplification might be valid when looking at the P-wave or QRS complex. But when considering the movement of the heart one has to consider how this shift of field origins might affect the surface signal.

To asses these effects, we combined two previous existent frameworks of mechanics (CardioMechanics) and electrophysiology (acCELLerate). We calculated excitation propagation using the monodomain equation and the resulting electrical field within the torso using the Poisson equation. The consequential deformation of the heart was then determined by the governing equation for balance of linear momentum. Therefore, we considered the active stress originating from cellular contraction, the passive elastic properties of the tissue, stress resulting from interaction with the blood within the heart, as well as the interaction with the surrounding tissue.

The overall differences between simulated signals (deforming vs. non-deforming heart) on the body surface map decrease with distance from the originating sources. Thus, when looking at the Einthoven I-III leads which are measured relatively far away from the heart, the change

in T-wave amplitude is rather small (∼8-25%). When looking at the Wilson I-VI leads, which are located towards the apex of the heart, this change increases to up to 35%. Overall, our results show that there is a distinct impact of deformation on the repolarization signals on the body surface. It has yet to be determined how this change compares to the overall naturally occurring variability in measured signals.

The SuLMaSS project: Development of a sustainable open source software package for cardiac electrophysiology

Gunnar Seemann[a], Gernot Plank[b], Edward Vigmond[c], Yung-Lin Huang[a], Eike M. Wülfers[a], Jorge Sánchez[d], Mark Nothstein[d], Felix Bach[d], Robert Ulrich[d], Michael Selzer[d], Axel Loewe[d]

[a]University of Freiburg, Freiburg, Germany,
[b]Medical University of Graz, Graz, Austria,
[c]LIRYC and University Bordeaux, Bordeaux, France,
[d]Karlsruhe Institute of Technology, Karlsruhe, Germany

In the SuLMaSS project, we will advance, develop, build, evaluate, and test infrastructure for sustainable lifecycle management of scientific software. The infrastructure will be tested and evaluated by the successor of the cardiac electrophysiology simulator CARPentry which will be advanced towards optimal usability and a large and active user community. First, we are going to provide a high quality, user-friendly cardiac electrophysiology simulation software package that accommodates attestable needs of the scientific community. Second, we will deliver infrastructure components for testing, safe-keeping, referencing, and versioning, which has been advanced, evaluated, and thoroughly tested during SuLMaSS. Third, the way software lifecycle management will be performed will be documented and disseminated and will serve as a best practice example for sustainable scientific software also for other communities. Scientific software development in Germany and beyond will benefit through the best practice role model and the advanced infrastructure that will, in part, also be available for external projects.

Particularly, we are going to advance the cardiac simulator based on a detailed user needs analysis and a target performance comparison. We will extend the unique proposition of the software and add value for the wider scientific cardiac electrophysiology community. By providing the user-friendly software under an open source license, we will offer the optimal solution for a large share of research groups potentially leveraging computational cardiac modeling methods. SuLMaSS will drive and showcase the infrastructure formation, thus serving as a lighthouse project.

SuLMaSS aims to support the full research lifecycle from exploration through conclusive analysis and publication, to archival, and sharing of data and source code, thus increasing the quality of research results. Moreover, we will support the full lifecycle of research software from requirements management and architecture design through community-based collaborative development and advancement, to testing, archival, change management, continuous integration, dissemination, and user documentation, thus improving sustainability of research software.

Influence of the fibrotic tissue arrangement during persistent atrial fibrillation

Jorge Sánchez[a,b], Luca Azzolin[a], Axel Loewe[a], Olaf Dössel[a], Javier Saiz[b], Beatriz Trénor[b]

[a]Institute of Biomedical Engineering, Karlsruhe Institute for Technology (KIT), Karlsruhe, Germany,

[b]Centro de Investigación e Innovación en Bioingeniería (Ci2B), Universitat Politècnica de València, Valencia, Spain.

The mechanisms that initiate, maintain and terminate atrial fibrillation (AF) are still unclear. Inflammation is associated with structural remodeling of the atrial substrate and recent studies also suggest that cytokines like the transforming growth factor $\beta 1$ (TGF-$\beta 1$) may alter the myocyte's electrophysiology. The aim of this work is to analyze the contribution of AF myocyte's electrical remodeling, coupling of myofibroblasts and myocytes, collagen deposition and inflammatory cytokines during persistent atrial fibrillation (peAF).

Human atrial myocyte and myofibroblast electrophysiology was simulated using mathematical models proposed by Koivumäki et al. under persistent atrial fibrillation remodeled myocytes of 3 different regions of the atria: right atrium posterior wall (RA), left atrium posterior wall (LA) and pulmonary vein (PV). We simulated 2D patches of 5×5cm with a spatial discretization of 100μm and created a circular fibrotic region of 2cm diameter. In this region, we introduced random uniformly distributed fibrosis with three different densities: 10%, 20% and 40%. Additionally, we considered different ratios of elements that represent collagen deposition (non-conductive elements) and myofibroblast coupling (0%-100%, 25%-75%, 50%-50%, 75%-25% and 100%-0% correspondingly). Furthermore, myocytes within this region were electrically remodeled due to peAF and the TGF-$\beta 1$.

The results of our simulations show that reentry dynamics change depending on the characteristics of the fibrotic region. Different ratios of myofibroblasts – collagen changes the dynamic of the reentry with low fibrosis density (10%). For high fibrosis density (20% and 40%) due to a block of conduction the reentry meanders around the fibrotic region.

Our results suggest that structural remodeling and the presence of cytokines like TGF-$\beta 1$ due to an inflammatory process may alter the dynamics of the arrhythmia.

Stretching Strands of Neonatal Murine Cardiac Myocytes Co-Cultured with Myofibroblasts Causes Prominent but only Transient Conduction Slowing

Andrea Buccarello[a], Frédéric Michoud[b], Stéphanie P. Lacour[b], Jan P. Kucera[a]

[a]Institut für Physiologie, Universität Bern, Bern, Switzerland

[b]Bertarelli Foundation Chair in Neuroprosthetic Technology, Laboratory for Soft Bioelectronic Interfaces, Institute of Microengineering, Institute of Bioengineering, Centre for Neuroprosthetics, École Polytechnique Fédérale de Lausanne (EPFL), Geneva, Switzerland

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