Preface

The international workshop series on Latest Advances in Cardiac Modeling (LACM) was started in 2013 to congregate top-level researchers working mainly on methodological aspects in mathematical and computational cardiac modeling. As cardiac function depends on several, coupled biophysical phenomena, we intend to stimulate the discussion across all aspects currently being investigated.

Presented topics include:
- Novel mathematical models for cardiac tissue (e.g. electrophysiology, active/passive mechanics, metabolic activity) and their analysis
- Efficient, mathematically well founded numerical algorithms for the solution of partial differential equations used for modeling of the cardiac behavior (e.g. bidomain equations, nonlinear fluid-structure interaction, poromechanics)
- New data acquisition techniques relevant for modeling (in particular advanced magnetic resonance imaging)
- Validation of models and simulation tools with experimental data
- Biophysical personalization of models through data assimilation
- Computational simulations addressing relevant clinical problems

In this version, we are hosted at the German Heart Center Munich, which is the main clinical center for cardiovascular diseases in Germany and one of the biggest in Europe. This confirms the increasing interest of clinical partners to collaborate with modelers, which we want to use to strengthen the research efforts into clinically meaningful questions, of course including serious methodological advancements.

Munich, March 2015

Cristóbal Bertoglio, Isabel Deisenhofer, Markus Schwaiger and Wolfgang A. Wall
International scientific committee

Dominique Chapelle, INRIA Saclay Ile-de-France, France
Yves Coudière, INRIA Bordeaux, France
Olaf Dössel, Karlsruhe Institute of Technology, Germany
Jean-Frédéric Gerbeau, INRIA Paris-Rocquencourt, France
Serdar Göktepe, Middle East Technical University, Turkey
Daniel Hurtado, Pontificia Universidad Católica, Chile
William Klug, University of California Los Angeles, USA
Sebastian Kozerke, ETH Zurich, Switzerland
David Nordsletten, King’s College London, UK
Sasha Panfilov, Ghent University, Belgium
Alfio Quarteroni, EPFL, Switzerland
Alessandro Veneziani, Emory University, USA
Martin Weiser, Zuse Institute Berlin, Germany

Organizing committee

Cristóbal Bertoglio, Center for Mathematical Modeling, Chile
Isabel Deisenhofer, German Heart Center Munich
Markus Schwaiger, Institute for Nuclear Medicine, TUM
Wolfgang A. Wall, Institute for Computational Mechanics, TUM

Conference secretary

Renata Nagl, Institute for Computational Mechanics, TUM
General information

Conference venue
The workshop (together with the coffee and lunch breaks) will be held in the main auditorium of the German Heart Center Munich (Deutsches Herzzentrum München), Lazarettstr. 36, 80636 München. The closest metro station is "U1 Maillingerstraße".

Instructions for presenters
Please do not exceed 15 minutes for the presentation of your work, such that around 5 minutes remain for discussion.
Please bring your own laptop computer to project your presentation or arrange with other presenters or organizers to share a laptop.
We kindly ask you to test the compatibility of your laptop with the LCD projector in the lecture room before the scheduled time of your presentation (e.g. during the break before your talk).
Please consider for the preparation of your talk that, although attending scientists have a broad knowledge about cardiovascular physiology and modeling, not everyone will be an expert in your field.

Workshop dinner
The workshop dinner will be held on Thursday evening (March 12th) starting at 7:00 pm at the “Löwenbräukeller” (Nymphenburger Str. 2, 80335 München), which is located in walking distance (approx. 15 min.) of the Heart Center. The conference fee includes the meal (soup, main dish, dessert) plus drinks until 9:30 pm.
Thursday, March 12th

08:30 – 09:00 Registration
09:00 – 09:05 Welcome

09:05 – 09:50 Jean-Frédéric Gerbeau, INRIA Paris-Rocquencourt
  Forward, inverse and reduced order modeling in cardiac electrophysiology

09:50 – 10:10 Nagaiah Chamaruki, Johann Radon Institute Linz
  Multiscale modeling and simulation of calcium cycling in cardiac myocytes

10:10 – 10:30 Emanuela Abbate, INRIA Bordeaux
  In silico assessment of drugs effects on human embryonic stem cells cardiomyocytes electrical activity

10:30 – 10:50 Sehun Chun, Stellenbosch University
  An electrodynamic model of the cardiac electric signal propagation: Electromagnetic vector fields for the propagation of charged ions and the membrane current

10:50 – 11:20 Coffee Break

11:20 – 11:40 Hans Diercx, Ghent University
  Drift of scroll waves in thin layers caused by thickness features

11:40 – 12:00 William Klug, University of California at Los Angeles
  Modeling the electrophysiology of heart failure

12:00 – 12:20 Christian Vergara, Politecnico di Milano
  Inclusion of the Purkinje network in computational cardiology with applications to pathological cases

12:20 – 12:40 Marco Favino, University of Lugano
  Parallel methods for cardiac simulation:
  From light weight adaptivity to coupled models
12:40 – 13:00 Matthias Lange, University of Sheffield
Hybrid CPU/GPU numerical methods for electrophysiology equations over cardiac Purkinje networks: Algorithms and verification

13:00 – 14:30 Lunch

14:30 – 14:50 Alessio Gizzi, University of Rome
Non-ohmic propagation of action potential in cardiac tissue: A porous-medium approach

14:50 – 15:10 Serdar Goktepe, Middle East Technical University
In silico modeling of electrical and mechanical disorders in cardiac tissue

15:10 – 15:30 Nele Vandersickel, Ghent University
The role of heterogeneities in the development of Torsade de Pointes: a computational study

15:30 – 15:50 Liia Asner, King’s College London
Modelling full-cycle left-ventricular mechanics with parameter estimation based on 3D tagged MRI data

15:50 – 16:10 Thomas Fritz, Karlsruhe Institute for Technology
Reconstruction of ventricular active tension distribution from wall motion for three different infarction settings

16:10 – 16:40 Coffee Break

16:40 – 17:00 Radomír Chabiniok, INRIA Saclay & KCL
Contractility estimation in dobutamine stress patients

17:00 – 17:20 Dominique Chapelle, INRIA Saclay Ile-de-France
Thermodynamical framework for modeling chemical-mechanical coupling in muscle contraction - Formulation and validation

17:20 – 17:40 Alfonso Santiago, Barcelona Supercomputing Center
A 3D-1D cardiovascular computational model: In the pursue of physiological feedback
17:40 – 18:00 **Marc Hirschvogel**, Technische Universität München
Towards reliability in patient-specific cardiac dynamics simulation and predictive modeling for cardiac assist device engineering

18:00 – 18:20 **Sander Land**, King’s College London
Modeling a broken heart: Investigating the mechanisms of Takotsubo cardiomyopathy

19:00 – 21:30 Conference Dinner
Löwenbräukeller (Runde Stube)
Nymphenburger Str. 2, 80335 München

Friday, March 13th

09:00 – 09:25 **Isabel Deisenhofer**, German Heart Center Munich
Current challenges in clinical electrophysiology

09:25 – 10:10 **Sebastian Kozerke**, ETH Zurich & KCL
Advanced cardiovascular magnetic resonance

10:10 – 10:30 **Constantin von Deuster**, ETH Zurich
A reference dataset of in-vivo human left-ventricular fiber architecture in systole and diastole

10:30 – 10:50 **Andreas Nagler**, Technische Universität München
Cardiac fiber estimation from arbitrarily spaced diffusion weighted MRI

10:50 – 11:20 Coffee Break

11:20 – 10:40 **Martin Genet**, ETH Zurich
Is ventricular deformation affine?

11:40 – 12:00 **Alessandro Veneziani**, Emory University
Variational estimation of cardiac conductivities: Numerical issues, sensitivity analysis, computational cost reduction

12:00 – 12:20 **Stefano Pagani**, Politecnico di Milano
Inverse uncertainty quantification problems in cardiac electrophysiology: Reduced order models for state and error reduction
12:20 – 12:40 **Simone Pezzuto**, Simula & Lugano University  
*Space-discretization error analysis and stabilization schemes for conduction velocity in cardiac electrophysiology*

12:40 – 13:00 **Julia Hörmann**, Technische Universität München  
*Discontinuous Galerkin approximation for cardiac electrophysiology*

**13:00 – 14:30 Lunch**

14:30 – 14:50 **Luca Dede**, EPFL  
*Modeling the fluid dynamics of the heart: From blood flows in idealized left ventricles to patient-specific aortic valve simulations*

14:50 – 15:10 **Helena Švihlová**, Charles University in Prague  
*Modeling of flow in stenotic valves and arteries*

15:10 – 15:30 **Jack Lee**, King’s College of London  
*A model-based investigation of coronary wave intensity and perfusion*

15:30 – 15:50 **Andrew Coockson**, King’s College of London  
*A Poroelastic scalar transport formulation for modelling magnetic resonance perfusion imaging in the beating heart*

15:50 – 16:10 **Kristin Tøndel**, Simula Laboratory  
*Insight into model mechanisms and more efficient model development and validation by multivariate metamodelling*

**16:10 – 16:15 Closing**
Book of Abstracts
(in order of presentation)
Multiscale modeling and simulation of calcium cycling in cardiac myocytes

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Abstract

In this talk we present a detailed model of the intracellular calcium dynamics in a cardiac myocyte and their efficient numerical treatment is discussed in the present work. The set of reaction diffusion equations describe the behavior of the intracellular calcium concentrations in cytoplasm as well as in the sarcoplasmic reticulum (SR) domain. We adopted a detailed highly stochastic calcium release unit (CRU) model [2] to describe the source functions in the PDE model. The bidirectional coupling of deterministic model and membrane potential model is investigated in our adaptive numerical simulations and the dynamics of the membrane potential is based on the rabbit ventricle model of Mahajan et.al [1]. We developed a efficient adaptive finite element simulator interface for the numerical simulation of such multiphysics and multiscale model of the cardiac myocyte. To save the computational time and computer memory we considered a highly unstructured grid where the fine spatial resolution is placed at the CRUs and coarse resolution far from the CRUs location. The numerical convergence of solutions and parallel results are demonstrated.

References


In silico assessment of drugs effects on human embryonic stem cells cardiomyocytes electrical activity

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† Reo team, Inria Paris-Rocquencourt, Le Chesnay, France
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Abstract

Computational modeling and simulation is extensively used to investigate diseases in cardiac electrophysiological activity and also drug effects, side effects and interactions [1]. Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) have been recently considered as a promising tool in regenerative medicine: their major role in repairing damaged tissue is due to pluripotency and ability to differentiate [2]. These pluripotent cells are also used in early stages of drugs development. Pharmaceutical companies use the MultiElectrode Array (MEA) device in order to perform many in vitro experiments on hESC-CMs. The goal of our study is to model and simulate these in vitro experiments.

Since we work under the hypothesis that the cells constitute a monocellular layer, the mathematical domain $\Omega$ is bidimensional (see Fig. 1(a)). We use the bidomain model in order to compute the transmembrane potential $V_M$ and the extracellular potential $u_e$:

$$
\begin{cases}
\frac{dw}{dt} - g(V_M, w) = 0 & \text{in } \Omega \\
A_M \left( C_M \frac{\partial V_M}{\partial t} + I_{ion} \right) - \text{div} (\sigma I \nabla V_M) - \text{div} (\sigma E \nabla u_e) = A_M I_{stim} & \text{in } \Omega \\
-\text{div} ((\sigma I + \sigma E) \nabla u_e) - \text{div} (\sigma I \nabla V_M) = \frac{1}{z_{thick}} \sum_{e_k} \frac{I_{el}^k}{|e_k|} & \text{in } \Omega.
\end{cases}
$$

In system (1), the bidomain model has been modified to take into account the presence of the MEA electrodes by adding the source term in the third equation. The electric current $I_{el}^k$ is measured by electrode $k$ and computed using the electric model of Fig. 1(a). The measured field potential is then $U_{mes}^k = R_i I_{el}^k$, where $R_i$ stands for the inner resistance. $I_{ion}$ is computed with an “hybrid ventricular-like” ionic model, which is obtained by modifying the model proposed in [3] to avoid auto-excitability.

As concerns the drug action, we have compared two different categories of drug models [4]: a simple-pore block description and the guarded receptor theory. For the first one, the conductance of the targeted channel is reduced by a factor depending on the drug dose. The second model requires the introduction of a Markov model (MM) for the considered channel $s$ in order to characterize $N$ different states (including blocked states) and the transitions between them. The probability $P_i$ of being in state $i$ is computed by solving

$$
\begin{cases}
\frac{dP_i}{dt} = \sum_{j=1}^{N-1} k_{ji} P_j - \sum_{j=1}^{N-1} k_{ij} P_i & \text{for } i = 1, \ldots, N - 1 \text{ and } i \neq j \\
\sum_{i=1}^{N} P_i = 1,
\end{cases}
$$

(2)
where $k_{ij}$ are the transition rates between states $i$ and $j$. The current of channel $s$ is then $I_s = g_s P_O (V_M - E_s)$, where $O \in [1, N]$ is a fixed state and $P_O$ is the probability of the channel to be at the open state $O$. In Fig. 1(b) we show a MM for the action of mexiletine on the sodium channel: the action and the field potential obtained with this model in control conditions and for two different drug doses are shown in Fig. 1(c).

In all our numerical experiments, both the proposed drug models reproduce qualitatively the expected physical behaviour. The main limitation of this description is that we still do not take into account the heterogeneity of the hESC-CMs.

Figure 1: (a). Domain $\Omega$ and circuit for the electrodes. (b). Markov model for mexiletine binding with the sodium channel: blocked state in red. (c) Action potential (left) and field potential (right) over the 9 electrodes for different doses of mexiletine.

References


An electrodynamic model of the cardiac electric signal propagation: Electromagnetic vector fields for the propagation of charged ions and the membrane current

SEHUN CHUN∗

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Abstract

Since the pioneering work of Hodgkin and Huxley, the diffusion-reaction type equation in the bidomain has been the most popular and successful method of modelling the cardiac electric signal propagation. But, at the same time, this kind of equation has revealed its limitations in providing helpful tools on some critical electrophysiological phenomena. For example, the changes of the conductivity of the myocardial tissue or the changes of the 2D or 3D shape of the heart are known to be related to reentry and fibrillations, but little can be known until the computational simulation is performed on an artificial heart being constructed from the experimentally-obtained data. To be briefly stated, the main reason is that the diffusion-reaction type equation describes the phenomenological contour of the action potential, not the more fundamental flow of charged ions and the membrane current [1].

The main goal of this research is thus to express the mechanisms of the cardiac electric signal propagation as the flow of charged ions and the membrane current. In the perspective of kinematics, this means that the cardiac dynamics is described as trajectory, not wavefront or contour. To achieve this, a set of Maxwell’s equations is constructed such that the dynamics of the scalar potential represents the Bonhoeffer van der Pol (BvP) mechanism of the cardiac electric signal propagation same as the FitzHugh-Nagumo model in the macroscopic bidomain. Then it represents the following dynamics: Depending on the magnitude of the electric field, the membrane current responding to the BvP oscillator is activated for the generation of the electric polarization of the displacement field.

This set of Maxwell’s equations represents the new signal propagation in the new media, which is fundamentally different from the classical electromagnetic wave propagation in the space. Consequently, the maximum propagational velocity can be assigned to be the same as that of the cardiac action potential, not the speed of light. This new approach not only provides new insights on the unique properties of the cardiac electric signal propagation that were not explained in classical dynamics, but also paves the most efficient mathematical and computational analysis on the behaviour of the propagation on complex anisotropic structure of the heart, especially on fibrillation and defibrillation [2].

References


Drift of scroll waves in thin layers caused by thickness features

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Abstract

During several types of arrhythmia, electrical activation in the heart is believed to take the shape of a rotating spiral wave in 2 dimensions or a so-called scroll wave in 3 dimensions. Some parts of the heart such as the atrial wall and, to a lesser extent, the right ventricular wall, are very thin compared to the spiral wave core. Therefore, the scroll waves behave similar to a spiral wave but are affected by the layer geometry.

We identify the effect of sharp variations of the layer thickness, which is separate from filament tension and curvature-induced drifts described earlier. By averaging over the layer thickness, we show analytically and numerically that scroll waves in thin portions of the cardiac wall may anchor and drift along thickness steps, ridges, ditches, and disk-shape thickness variations [1]. Asymptotic predictions agree with numerical simulations.

References

Modeling the electrophysiology of heart failure

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Abstract

Ventricular fibrillation (VF) is a life-threatening condition in which the heart ventricles activate chaotically and are unable to pump blood to the rest of the body. VF is one of the leading causes of sudden death and computational models offer the unique capability to isolate single factors, study their arrhythmogenic potential, and evaluate in silico new interventional and pharmacological therapies.

We have constructed verified and validated a multiscale finite element model of the heart ventricles [1]. Our model includes an anatomically accurate heart geometry obtained from MRI, fiber directions obtained from DT MRI, a Purkinje activation network, and experimentally based ionic cellular models divided in nine transmural and apex-to-base regions to guarantee repolarization dispersion. We were able to reproduce a normal electrocardiogram (ECG), which met all the necessary validation criteria expected by our collaborators in cardiology, including the correct QRS and T wave progression and morphology with no fractionation or slurring.

In this work we use our validated model to evaluate cardiac electrophysiology (EP) in hearts with failing myocardial cells. Our goal is to understand the inducibility of VF in presence of failing cell EP. We model the changes in the failing cell to achieve a model of congestive heart failure [2]. These changes can be categorized in membrane type changes, calcium handling changes, and microstructural changes. In regard to the membrane currents in the failing myocardial cell, we decrease the peak slow and fast potassium inward currents, decrease the peak potassium delayed rectifier current, and introduce a late sodium inactivation current. In order to modify the calcium dynamics, we decrease the peak sodium calcium exchange flux and modify the calcium release from the JSR to myoplasm. Finally, we consider changes in the myocardial microstructure by decreasing tissue conductance and its anisotropy. The change in the description of the tissue microstructure is due downregulation of Cx43, which leads to increased conduction lateralization and gap junction remodeling.

Modeling the aforementioned changes to ion channel physiology, we were able to obtain all the expected characteristic of a failing cell EP, i.e., longer action potential, elevated sodium transient, lower and slower calcium transient, and earlier alternans as detected in the dynamic restitution curve. With a validated single failing cell model, we have studied the dynamics of heterogeneous 1D cell cables, observing spatial APD alternans (beat-to-beat variations, see
Figure 1: Left: space time plot obtained by pacing at 250 ms a 1D cable of failing myocardial cells. The cable consists of approximately 200 cells divided equally in apex, mid, and base cells. Discordant alternans are clearly visible. Right: ECG measured in full heart simulations using a failing cell model and pacing cycle length equal to 250 ms. T-wave alternans are clearly visible in V4 through V6.

Figure 1, left) at pacing cycle lengths equal to 250ms. In a full biventricular heart geometry, at a pacing cycle length of 250ms, the failing cell model produces T-wave alternans (Figure 1, right), which is a known risk factor and potential precursor to VF.

Of immediate interest is the progression from T-wave alternans to VF. We consider the question, is QRS alternans visible in the ECG before wave break and VF occur? Moreover, we want to isolate the changes at the cellular level responsible for T-wave and QRS alternans because they can be targeted by pharmacological therapies. Are classic pharmacological therapies (e.g., calcium blockers) effective also in the presence of failing cells?

References


Inclusion of the Purkinje network in computational cardiology with applications to pathological cases

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Abstract

In the first part of the talk we discuss a method to generate a patient-specific Purkinje network starting from clinical data of the activation times acquired in real patients [1]. In particular, we considered the Eikonal problem to describe the electrical activity both in the network and in the left ventricle and we applied the proposed methodology to three different pathological cases, namely the presence of scar tissue due to an old myocardial infarction, the Wolff–Parkinson–White syndrome, and the left bundle branch block. For the last two cases, we also discussed how to treat intra-myocardial sources generated by the pathology. A cross-validation test performed over the results obtained in real geometries and with real data showed the accuracy of our method in comparison with a non-patient-specific network [2, 3].

In the second part of the talk we discuss the coupling between Purkinje network and myocardium where monodomain subproblems are considered [4]. The inclusion of monodomain model is of great interest, in particular in view of the electro-mechanical coupling in presence of Purkinje network. In particular, we discuss the well-posedness of the coupled problem and we compare for an idealized geometry the results obtained with this strategy with the ones given by the coupling between Eikonal problems.

References


Parallel Methods for Cardiac Simulation: from Lightweight Adaptivity to Coupled Models

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†Institute for Advanced Simulation, Jülich Supercomputing Centre, Germany

Abstract

In this talk, we discuss novel parallel simulation approaches and methods for the massively parallel simulation of electrophysiology and electro-mechanical models for the human heart.

We start our talk with a novel lightweight adaptive algorithm which aims at combining the plainness of structured meshes with the resolving capabilities of unstructured adaptive meshes. Our patch-wise adaptive approach is based on locally structured mesh hierarchies which are glued along their interfaces by a non-conforming mortar element discretization. To further increase the overall efficiency, we keep the spatial meshes constant over suitable time windows in which error indicators are accumulated. This approach facilitates strongly varying mesh sizes in neighboring patches as well as in consecutive time steps. For stability reasons, for the transfer of the dynamic variables between different spatial approximation spaces, a discrete $L^2$-projection is used. Finally, we derive a spatial preconditioner for elliptic problems, which is tailored to the special structure of the patch-wise adaptive meshes.

We analyze the (parallel) performance and scalability of the resulting method by several realistic examples from computational electrocardiology of different sizes and furthermore compare our method to a standard adaptive refinement strategy using unstructured meshes. As it turns out, our novel adaptive scheme provides a very good balance between reduction in degrees of freedom and overall parallel efficiency.

In the second part of the contribution we present ongoing efforts on the development of a coupled electro-mechanical heart model. As part of work of the Center for Computational Medicine in Cardiology in Lugano, we implemented EWE, a novel front-end for the open source general purpose C++ finite element framework MOOSE, see [2]. This library allowed for major acceleration of the software development process. Although only a few months old, coupled simulations of electrocardiology and cardiomechanics are now possible with EWE.

Currently the code offers the implementation of three passive cardiac models: the pole-zero Nash-Hunter [4], Holzapfel constitutive law [5] and Fung-type exponential approach [6]. These allow to include anisotropic properties of the cardiac muscle. The mono-domain equation is coupled with a Bernus type ion channel model. Coupling between electrical and mechanical parts is realized by means of an active stress strategy which allows to include the active forces obtained from cellular models into the mechanical one.

Making use of the very modular formulation of MOOSE, EWE is easily extendible to incorporate additional material laws and cell membrane models. For parallelization, the code relies on the widely used and well developed solver library PETSc [3]. We will present and discuss scaling benchmarks for the coupled problem on both a Linux cluster and a state-of-the-art Cray supercomputer. Finally, further directions of development for EWE will be outlined.
References


Hybrid CPU/GPU Numerical Methods for Electrophysiology Equations over Cardiac Purkinje Networks: Algorithms and Verification

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Abstract

We present a verification study of numerical solvers for the fast conduction system in the heart. To this end, the $L^2$-error between the numerical and analytical solution is calculated, followed by a performance test of different implementations on CPUs and GPUs. Thus, we present a first step towards a benchmark for the numerical solution of the one dimensional monodomain equation with branching points.

The coordinated contraction of the heart is controlled by the fast conduction system consisting of Purkinje cells. The Purkinje network covers large proportions of the sub-endocardium. It is an extensively branching and rejoining network, which is important for the reliability and fault-tolerance of the conduction [1]. Purkinje cells are excitable and ion channels on the cell membrane open when a threshold potential difference between the intra- and extracellular compartments is reached. This mechanism is responsible for the conduction of action potentials over large distances.

Currently, the simulation of the action potential propagation in a Purkinje network is based on the bidomain equation [2], or the cable equation with a reaction term [3]. The latter approach by Vigmond et al. [3] treats the Purkinje network as a branching tree of 1-D line segments, however current loops and the important effect of multiple connection pathways in the Purkinje network are neglected. Therefore, we extended the former approach such that loops in the network are now allowed.

We compare three different implementations; the first distributes the solving of the ionic models over different CPUs, while the second does this work with the GPU, but both solve the linear system with a single CPU. Thus only the computationally most expensive part is solved in parallel. The third solves the problem completely on the GPU, which reduces the time spent on communication, and the linear system is solved in parallel.

Whenever numerical approximations are widely used, their error compared to the true solution should be estimated. The difference between the exact and numerical solutions depends on many factors like the algorithm chosen, the numerical precision used for calculation, the time step, the spatial resolution etc. Therefore, it is important to verify the solver for the
Figure 1: Problem domains for the equilibrium solutions, where the dashed area are unstable unstable cells. (a) for a line segment and (b) for symmetric bifurcation.

cable equation including branching [4], which to the best of our knowledge has not been done. Two ways of verification are used the first is the difference between the analytical and the numerical solutions [4] and the second is a comparison of the performance of different solvers on the same complex problem [5].

For the comparison with the exact solution, we use two categories of experiments; the first are equilibrium solutions and the second travelling pulse solutions. The equilibrium solution gives the possibility to study solutions of branching systems. Therefore, we construct two problem domains (shown in Fig. 1). The solution in the domain (a) is well known [6], while for (b) it follows from the first solution. We obtained the numerical solution of the same problem with our solvers. For all solvers and both meshes, a convergence test of the the $L^2$-error with respect to the spatial step size $h$ is performed. For the travelling pulse, an analytical solution in one line segment is used [7].

For a parallel efficiency benchmark, all three implementations are used with a realistic Purkinje system [8] and the time for solving the linear system, the ionic cells, the intermediate task associated with the Hermite basis, and the preconditioning are measured.

In summary, we present an algorithm for solving the cable equation on a branching network with loops, using CPU, CPU/GPU hybrid, and GPU-only solvers, and developed a verification process to judge the accuracy and the speed of the solver. It shows, that the accuracy is in the same range, but the GPU implementations are more than five times faster.

References

Non-ohmic propagation of action potential in cardiac tissue: a porous-medium approach

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Abstract

The electrophysiological behavior of the heart has been traditionally modeled using the monodomain or bidomain model descriptions. To account for the propagating nature of electrical waves in cardiac tissue, virtually all cardiac electrophysiology formulations consider a linear diffusion flux term typically resulting from an ohmic-material assumption. Only recently [1], fractional diffusion formulations have been proposed to model the propagation of action potentials through a medium with structural inhomogeneities in 1D domains. Myocardium, in fact, is characterized by intracellular and extracellular spaces mainly composed of blood vessels, collagen, fibroblasts, and fat, among others. Ionic currents, moreover, have long been recognized as a continuous-discontinuous process and, at a submicron scale, intercalated discs can be considered as a porous membrane where ions can only pass through gap junctions. The gap-junctional conductance, in particular, is strongly nonlinear with the voltage resulting in ionic flow saturation effects. Therefore, the non-smooth nature of ion conduction at the sub-cellular level is in contrast with the standard linear-diffusion flux and such a lack of proper mathematical representation calls for novel approaches in the modeling of the intra- and extra-cellular ionic flow resembling similar approaches in stochastic dynamics [2].

In this work, we propose an alternative formulation of the cardiac electrophysiology model using a nonlinear diffusion term of the porous-medium-equation (PME) kind [3], which accounts for the non-ohmic nature of cardiomyocytes and resulting in a nonlinear parabolic equation well suited for structurally heterogeneous active media. The system of non-linear partial differential equations is solved using an efficient non-linear implicit finite-element scheme that is suitable for simulations in complex domains with arbitrary boundary conditions. We show that this new approach recovers steeper wave fronts than classical models, while affecting the time scales related to activation and repolarization timing.

We compare and contrast our PME approach with respect to the dispersion of repolarization analysis conducted in [1]. We finally demonstrate the capabilities of our method by simulating the activation and repolarization sequences in a three-dimensional MRI-based bi-ventricular human heart model, where microstructural features like cardiomyocyte fiber orientation and the His-Purkinje activation network are considered. We quantify the differences in the activation/repolarization time scales, conduction velocity, propagating fronts and pseudo-electrocardiograms between the proposed model and the classical cable equation using existing phenomenological cardiac models [4].
References


In Silico Modeling of Electrical and Mechanical Disorders in Cardiac Tissue

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Abstract

Cardiovascular disease remains to be the leading cause of death worldwide. Recent advances in the field of mathematical modeling and physics enhance the existing diagnostic and therapeutic techniques through the realistic computer models of the heart. The main motivation to develop these models is to improve our understanding of the basic underlying mechanisms within the cardiovascular system for both healthy and dysfunctional cases. This will allow the researchers to create more advanced and efficient diagnostic and therapeutic techniques.

In this contribution, we develop computational heart models to investigate electrical and mechanical disorders related to myocardial infarction and maladaptive cardiac growth. For these cases, the direction and magnitude of the heart vector changes considerably and results in a distortion in the EKG, obtained for the healthy heart. Moreover, a reduced cardiac efficiency is observed by simulating the ventricular pressure-volume relationship through the PV curves. To model the electromechanical coupling, we use the recently proposed generalized Hill model [1]. This new approach combines the advantageous features of the active-stress and active-strain models. To this end, the total deformation gradient and the free energy function are decomposed into their active and passive parts. The electrical excitation is modeled by using the two-parameter Aliev-Panfilov model [2]. In our computer models, the infarction is accounted for by changing the material parameters to make the infarcted cardiac tissue electrically inert and non-contractile. The hypertrophied heart models are generated in our recent work [3] for the simulation of the PV curves. The predictive capacity of the proposed approach for the simulation of the above-mentioned electrical and mechanical disorders is demonstrated by comparing the clinical data with the computationally obtained results.

References


The role of heterogeneities in the development of Torsade de Pointes: a computational study

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Abstract

Torsade de Pointes is a polymorphic ventricular tachycardia, which can potentially degenerate in ventricular fibrillation and sudden cardiac death. The underlying mechanism of this arrhythmia are under debate. Two mechanism were put forward for the continuation of TdP, reentry and ectopic activity. However in the dog model of Vos et al., it was shown that in most cases of self-terminating TdP ectopic activity is responsible for the perpetuation of the TdP (> 90 % of the cases) [1]. It was described that the origin of the first activation varies from beat to beat, whereby for certain beats a competition between 2 foci was recorded. However, the question remains why and how these ectopic beats continuously emerge.

One possibility, is the existence of heterogeneities as a possible source of ectopic activity. A possible type of heterogeneities might be the existence of M-cells. It has been shown that M-cells are much more susceptible to the existence of EADs than epic- or endocardial cells. However, any type of heterogeneity which has a reduced repolarization reserve in comparison with the surrounding tissue can be used for this study.

We have investigated the effect of M-cell heterogeneity in tissue with reduced repolarization reserve in a patch of cardiac tissue and in an in a silico model of human ventricles. All our models contained layers of epicardial and endocardial cells with one or several regions of M-cells. We have studied whether this heterogeneity can generate ectopic beats and if the ectopic beat origitation cite can shift in space as in Vos et al., experiments.

We have found that these heterogeneities can indeed generate ectopic beats in a wide range of parameters and the frequency of these beats can give rise to a tachycardia. Moreover, in case of multiple heterogeneities we observed complex excitation patterns with ectopic beats emerging from various locations which gave rise to TdP like behaviour and ECG.

Therefore, we conclude that several ionic heterogeneities or several regions with M-cells can produce excitation patterns similar to those recorded during TdP.

References

Modelling full-cycle left-ventricular mechanics with parameter estimation based on 3D tagged MRI data

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Abstract

The mechanical function of the myocardium is an important indicator of cardiac health and disease. While direct in vivo examination of cardiac tissue properties remains a challenge, personalised mechanics modelling can bridge the gap by providing a useful non-invasive tool for patient assessment. A wide application in the clinic would require reliable and robust models, where patient-specific characteristics – such as passive and active model parameters – are easily determined from the available data.

We propose a complete workflow for personalised full-cycle left-ventricular (LV) mechanics simulation. The process is based on a purely non-invasive data acquisition protocol currently applied in a study of dilated cardiomyopathy. Patient-specific geometry and parameters are derived from a dataset including a short-axis CINE MRI stack, a time-resolved 3D tagged sequence [6] and a peak systolic LV pressure estimated from cuff readings [2].

The formulation of the solid mechanics problem, as described in [1], incorporates constitutive laws with passive stress parametrised by two constant scalings, and active stress by a single time-dependent scaling. The model is sufficiently complex to represent the main features of myocardial behaviour through the cycle (physiological pressure-volume loops, twist and shortening in systole, inflation in diastole). Its personalisation relies on a rich dataset of LV deformations through most of the cycle, which is obtained by motion tracking in 3D tagged images [3]. Importantly both passive [4] and active parameters are uniquely identifiable in this setup. As a result, these parameters as well as the computed myocardial strains and stresses can be used to assess the state of the myocardium with the aim of informing diagnosis.

The efficiency of the computational steps is ensured by the use of the reduced-order unscented Kalman filter [5] for data assimilation. Due to the low number of parameters in the model the method is able to find their optimal values at the computational cost of the order of two simulation runs.

Estimation results are validated in silico using an idealised human LV model, where the data are reproducible by the model and the correct parameters are known. The workflow is then applied to data acquired in vivo from a human volunteer. We show that the workflow is well-suited for reliable and robust model personalisation.
References


Reconstruction of Ventricular Active Tension Distribution from Wall Motion for three Different Infarction Settings

Simulation Study of the Inverse Problem of Cardiac Mechanics

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Abstract

Modern cardiac MRI techniques like Tagging, PCMRI and SENC provide quantitative measurements. These help the cardiologist to assess the cardiac function. Most measurable parameters like cardiac strain or the trajectory of tagging points are determined by underlying mechanisms like the active tension development. If for instance, an area of the ventricle does not contract actively anymore e.g. as result of a myocardial infarction, then this area will still be deformed by the contracting adjoining tissue while the deformation will differ from that of the healthy case. These internal parameters like the active tension development are usually not directly measurable but could be of great diagnostic value. The estimation of these internal values from measurable values is referred to as an inverse problem. In this work, we present a new method to estimate the active tension distribution of the ventricles from the motion of its surfaces based on spatial and temporal Tikhonov regularization [1]. This method was evaluated using synthetic data of the motion of the endocardial surface obtained from electromechanical simulations of the ventricular contraction.

An electromechanical simulation framework [2] was used to simulate the ventricular contraction (forward simulation) in a whole heart model for three different settings: One for a healthy heart, and three with different infarction scars in the left ventricle (anterior, posterior, septal). The framework included an electrophysiological cell model in combination with an active tension development model of the human heart. For the infarction areas, the cells were defined to be not excitable. The resulting active tension distribution over time provided the input for a biomechanical model which was used to calculate the deformation of the heart (forward solution). From the results, the motion of the endocardial surface of the ventricles was extracted. This data was then used as input for the inverse solving algorithm (inverse solution). This algorithm optimized the active tension development in the ventricles for each time step in such a way, that the resulting deformation matched best to the input data.
The reconstructed active tension of the inverse solution showed a good match to the active tension of the forward simulation in terms of spatial distribution and time course during the contraction. Apart from that, the deformation of the heart obtained from the inverse solution matched almost perfectly to that, obtained from the forward simulation. In the simulation settings with infarction scars, this respective area was clearly identifiable. Here, the reconstructed active tension was significantly reduced and almost zero near the center.

The presented algorithm allowed to reconstruct the active tension development distribution of the ventricles from the motion of the endocardial surfaces. However, it has to be considered that in this simulation study, other parameters like fiber orientation, passive mechanical properties and boundary conditions were identical for the forward and inverse simulation. The next step is a sensitivity analysis in order to evaluate how uncertainties of these parameters affect the reconstruction.

References


Contractility estimation in dobutamine stress patients

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Abstract

Regional wall motion abnormalities can occur prior to the onset of symptoms in patients with flow-limiting stenoses of coronary arteries or abnormalities of the microcirculation, where an increased demand due to a higher contractility cannot be matched by increased blood supply. A dobutamine stress test is used routinely to identify regional wall motion abnormalities to guide management on therapeutic options, such as revascularisation. It is performed at increasing doses of dobutamine, an inotropic drug, with simultaneous imaging at each dosage level. Significant risks such as arrhythmia and cardiac arrest at higher doses requires a rapid data acquisition which should not exceed two minutes at each dobutamine dosage. This limits the spatio-temporal resolution of the acquired image data. The estimation of regional myocardial contractility by using a biomechanical model [1] represents a way for obtaining quantitative contractility values which directly target regional mechanical properties of the tissue. This may provide a higher reproducibility of the exam and lower inter-observer variability, and additionally can also allow to use a lower dose of dobutamine.

In this talk we will present our current experience with the contractility estimation in such patients from cardiac cine MRI by using the modeling and data assimilation frameworks [2, 1], with applying the image processing pipeline [3] beforehand. First, we will demonstrate a possibility how to address the decreased spatio-temporal resolution of the stress image data. In this part, we will present non-invasive experimental data of a healthy volunteer by using a negatively inotropic beta-blocker stimulation1, which allows a safe data acquisition of the pharmacologically modulated heart function. Such carefully designed experimental datasets may provide an important insight into the data assimilation problem, for instance the level of discretization of the myocardium in order to get a reliable contractility estimate from a given type of clinical dataset.

The quality of data acquired in the special experiment presented in the first part allows employing the automated image processing tools based on Image Registration Toolkit 2 for the spatial registration (to compensate the non-reproducibility of breath-holding) and to track the cardiac motion [3]. However, the datasets of patients obtained during the dobutamine stress may not be as suitable for automated image processing using the pipeline [3]. Therefore, in the second part of the talk we will review some issues affecting the image quality and possible ways to increase the efficiency of motion tracking.

Finally, we will apply the experience gathered in our trials to perform the contractility estimation in a dobutamine-stress patient (Fig. 1) and will discuss the possible outcomes of the current image acquisition-processing and modeling setup, and the perspectives of the work.

1The dataset was acquired within British Heart Foundation grant NH/11/5/29058 in collaboration with M. Hadjicharalambous, L. Asner and D. Nordsletten (King’s College London).
2http://www.doc.ic.ac.uk/~dr/software
Figure 1: Contractility estimation for increasing dose of dobutamine in a patient: absolute values (top) and relative increase with respect to the baseline dose 0 (bottom).

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**References**


Thermodynamical framework for modeling chemical-mechanical coupling in muscle contraction - Formulation and validation

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Abstract

Muscle contraction occurs at the nanoscale of a hierarchical multi-scale structure with the attachment of so-called cross-bridges within sarcomeres, namely, the creation of chemical bonds between myosin heads and specific sites on actin filaments. A cross-bridge in itself can be seen as a special chemical entity having internal mechanical variables - or degrees of freedom - pertaining to the actual geometric configuration, which implies that the free energy of the cross-bridge - whether in an attached or unattached state - must be made dependent on these internal variables (T.L. Hill, Free Energy Transduction And Biochemical Cycle Kinetics, Dover, 2004). This provides a thermodynamical basis for modeling the complex interplay of chemical and mechanical phenomena at the sarcomere level. Within this framework we propose a muscle model with two mechanical variables associated with a cross-bridge. For the action of individual cross-bridges occurring at the nanometer scale, the energy provided by the Langevin thermostat cannot be neglected, and we therefore propose to endow the internal mechanical variables with stochastic dynamics.

Important motivations for this modeling choice include the ability to represent (i) the so-called power-stroke phenomenon and (ii) short-time responses of a muscle, e.g. to load steps. Our approach allows for systematic treatment of the model energetics, and in particular one goal of the proposed description is to investigate the potential benefit in mechanical efficiency with systems including - in addition to chemically-induced transformations - thermally-induced conformational changes such as the power-stroke.
A 3D-1D cardiovascular computational model: in the pursuit of physiological feedback

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Abstract

In this work, a first version of an HPC-optimized cardiovascular coupled model is presented. To achieve this goal two already developed models are used: Alya, the BSC* in-house tool for biomechanical simulations; and ADAN55, the LNCC† model for the arterial blood flow circulation.

Alya is a 3D, multiscale, multiphysics, HPC code, that allows modelling and solving the heartbeat electromechanic problem using the Finite Element Method (FEM) [1, 2]. This tool solves three sets physics problems: the electrophysiology model, which governs the propagation of the action potential in the domain of interest; the solid model, that predicts the deformation of the solid geometry; and the fluid dynamics equations for the blood, which are solved in a region contained and deformed by the solid domain. The ADAN55 is a reduced 55-artery version of the Anatomically Detailed Arterial Network (ADAN) model, which takes into account more than 1500 arteries from an average human body. This model employs one dimensional mesh where the fluid is solved by the condensed 1D Navier-Stokes equations in compliant vessels, featuring a physiologically consistent systemic impedance at the aortic root, among other characteristics [3]. Both codes are coupled by a black-box decomposition approach previously proposed in [4, 5]. This technique enhances the inclusion of a third coupling software that, by a Jacobian free solver, allows strong iterative coupling between the models. At each time step the Fluid Structure Interaction (FSI) problem is solved in the ventricle, computing the output flow through the aorta. This flow is passed to the arterial network model that solves the equations in the ADAN55 and, after that, the pressure response is given back to Alya. In this way convergence is reached in each time step with an implicit coupling scheme.

In previous generations of the involved projects, each model had predefined boundary conditions: for Alya a pressure value was imposed on the endocardium to simulate the resistance of the arterial network to the bloodflow, and an experimentally measured flow contour was imposed in the aortic root of the ADAN55 model to mimic the pumping action of the heart. Attaching an arterial network model to the Alya computational heart allows having a more physiological response to the blood ejection, as the systemic impedance is a complex result of the entire 1D arterial model which changes with the flow generated by the heart model. In the same way, using the heart model output flow connected to the ADAN55 input, offers the possibility to obtain a physiological and feedbacked stimuli that varies with changes in the arterial system. Thus, all kind of fully cardiac-systemic interactions can be accounted for.

In this work we show preliminary results of a coupled simulation tool that widens the possibilities in cardiovascular modelling. A complete simulator of the cardiovascular system will allow bioengineers and medical researchers to study the response of the full model to
changes in any of the components, extending the predictive and descriptive capabilities of
the standalone versions of the models, and providing further insight in the cardiac-systemic
interactions.

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2013.
Towards reliability in patient-specific cardiac dynamics simulation and predictive modeling for cardiac assist device engineering

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Abstract

The adequate predictive modeling of cardiac mechanics, that is capable of accurately reproducing the heart’s functionality and response to external disturbances, remains a challenging task. Especially the different physical domains involved, i.e. structural and fluid mechanics as well as electrophysiology, pose high demands on the numerical solution strategies. We present a high-resolution 3D nonlinear finite element model of patient-specific heart geometries, which includes an active material law prescribing the ventricular contraction along a generic muscle fiber orientation [1]. In addition, a passive material model captures the highly anisotropic nonlinear behavior of the myocardium [2].

Furthermore, the structural model is strongly coupled with the ventricular blood compartments, addressed by so-called windkessel models [3] serving as 0D fluid representations of the cardiovascular system. We use a closed-loop lumped-parameter model which is able of modeling venous return by assuring conservation of volume within the loop, similar to [4] and [5].

This leads to a monolithic windkessel-structural system of equations being solved within an iterative Newton-Raphson scheme with adequate block preconditioners at hand and allows for the physiologically meaningful solution of the heart contraction mechanics without considering a full fluid-structure interaction problem.

We demonstrate efficient strategies for calibrating the model to real-life experimental data, starting from low-fidelity models serving as initial guess for high-fidelity large-scale discretizations.

Given a calibrated patient-specific heart model that reproduces a specific situation of heart failure, we demonstrate the model’s predictability for cardiac assist device engineering and optimization.

References


Modelling a Broken Heart: Investigating the Mechanisms of Takotsubo Cardiomyopathy

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Abstract

Takotsubo cardiomyopathy is a severe form of heart failure in which the shape of the left ventricle resembles the Japanese fisherman’s octopus pot (tako-tsubo) during systole: the apex of the heart balloons while the base is hypercontractile. This condition is associated with sudden emotional or physical stress, and the potential for a romantic breakup to trigger the disease has given it the nickname ‘broken heart syndrome’. Triggers mentioned in the literature span a broad range, including illnesses ranging from sepsis to a common cold, death of pets and family members, and even public speaking [2].

While the majority of patients recover without intervention, there are currently limited treatment options available and serious complications may occur, with associated 2% mortality rate. Improved understanding of the mechanisms underpinning this disease is required to improve early diagnosis and treatment of these patients. The disease is especially common in post-menopausal women (90% of patients), while sudden cardiac death related to similar high stress situations has an approximately 80% male bias. This makes the syndrome potentially important for understanding gender differences in heart failure and sudden cardiac death.

The goal of our recent research was to investigate what the biophysical requirements are for generating the typical ‘takotsubo’ morphology. We investigated both the potential dominant change in protein regulation as well as the spatial gradient required to produce an apical ballooning phenotype [1]. For this purpose we have developed a quantitative measure of apical ballooning and a series of biophysically based computational models of the left ventricle. A common factor in most current hypotheses is the high level of beta-adrenergic stimulation which have been measured in patients, and reproduced in recent animal studies. Thus, in our models we investigate three hypotheses related to beta-adrenergic overload on their ability to result in apical ballooning. Firstly, a dominant mechanism of apical-basal differences in the calcium transients. Secondly, we test apical-basal differences in calcium sensitivity as a dominant mechanism. Finally, we test apical-basal differences in maximal active tension due based on recent research into crossbridge inhibition after beta-adrenergic overload.

For the study we developed a finite element model of the rat left ventricle. The model is driven by a new biophysical contraction model of the rat and new experimental data on the effects of beta-adrenergic stimulation on rat calcium transients. In total we performed and analysed a over 1000 biophysically detailed whole cycle cardiac simulations. To ensure stability of the wide range of unusual shapes and high strain encountered in simulations of left ventricular ballooning, we also developed new techniques for stabilizing finite element simulations of the heart [3]. Furthermore, to help in the analysis of these results we introduced a new metric for apical ballooning which effectively captures the degree the heart corresponds to a typical ‘takotsubo’ morphology.

Results show that spatial variations in all three mechanisms investigated can lead to the typical ‘takotsubo’ shape. A gradual linear change in contractility is completely ineffective
in producing apical ballooning, whereas more sharper transitions are more effective but less physiologically plausible. On balance, changes in the calcium transients are most effective in producing a ‘takotsubo’ shape when considering physiological constraints on the smoothness of spatial gradients. At very high and low ejection fractions we also see significantly less apical ballooning in our results. This gives a potential explanation of why researchers have found difficulty applying the rat as an animal model in Takotsubo cardiomyopathy, as for human patients a healthy ejection fraction is approximately 60%, versus 75–80% in rats.

Detailed analysis of the model results revealed that apical ballooning at end ejection is significantly less than earlier in ejection, as shown in Figure 1 (A). This contrasts with clinical observations, where apical ballooning is still significant at end ejection. As a follow-up study we investigated the role of the length-dependence of tension in producing takotsubo cardiomyopathy, by rerunning all simulations with a 50% and 100% reduction in length-dependence of tension. Results showed a clear pattern of increase in apical ballooning, with many cases of extreme ballooning at end ejection in simulations that showed no apical ballooning before the reduction in length-dependence of tension. Figure 1 (B) shows a selected example. Thus, a decrease in length-dependent activation may be an important factor underlying apical ballooning after a beta-adrenergic overload, or may be a factor in pre-existing conditions.

In conclusion, our models have shown the quantitative gradients in tension generation required to produce apical ballooning consistent with Takotsubo cardiomyopathy. Based on this we suggest that an experimental study measuring the spatial gradients in changes in calcium transients and calcium sensitivity in the heart would benefit from 4–5 measurements along the long axis of the ventricle, instead of assuming a smooth gradient. Furthermore, a small reduction in ejection fraction is likely to improve results in murine animal models.

References

A reference dataset of in-vivo human left-ventricular fiber architecture in systole and diastole

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Abstract

Introduction: Realistic computational cardiac models require a detailed description of left-ventricular cardiac fiber architecture. So far, information on the architecture of myofiber aggregates has been obtained from histology or from diffusion tensor imaging (DTI) of excised post-mortem hearts. However, ex-vivo physiological conditions including ventricular pressure and residual contractile forces deviate significantly from in-vivo conditions, hence potentially impacting measured fiber metrics. The objective of this work was to obtain and make available cardiac DTI data of the in-vivo human heart with full cardiac coverage in both peak systole and mid diastole including correction for myocardial strain.

Methods: Data from one healthy volunteer without history of cardiac disease (heart rate 85 ± 2 bpm, weight 65 kg, age 26) were acquired using a dual-phase dual-slice stimulated echo acquisition mode (STEAM) method [1] on a 1.5T Philips Achieva system (Philips Healthcare, Best, The Netherlands) equipped with a 5- channel cardiac receiver array. Written informed consent according to institutional guidelines was obtained from the subject prior to imaging. The acquisition (ECG trigger delays: 260ms and 560ms) was separated into 22 navigator-gated (gating window 5mm) breath holds and data along ten diffusion encoding directions [2] with a b-value of 450s/mm\textsuperscript{2} and nine signal averages were obtained. The entire left ventricle was covered in both systole and diastole with a total of 12 slices with the following imaging parameters: field-of-view (FOV): 224x100mm\textsuperscript{2}, in-plane resolution: 2.2x2.2mm\textsuperscript{2}, slice thickness: 6mm, TE/TR 18ms/2R-R intervals, partial Fourier factor 0.62. To correct diffusion tensors for material strain, additional 3D tagging data were acquired and incorporated into the diffusion tensor calculation [1]. Cardiac motion data were obtained using complementary spatial modulation of magnetization tagging (CSPAMM) [3] with spatial and temporal resolution of 3.5x7.7x7.7mm\textsuperscript{3} (FOV: 108x108x108mm\textsuperscript{3}) and 18ms, respectively. Tagging data acquisition was navigator gated (acceptance window 15mm) within three consecutive breath holds, each spanning over 18 heartbeats. Upon affine image registration [4] of the diffusion-weighted images, data were filtered using a lowrank model and edge constraints according to [5] (rank order L: 8, regularization parameter \lambda: 50). Diastolic and systolic diffusion tensors were mapped into a prolate spheroidal coordinate system [6] for 3D diffusion tensor field reconstruction. Data analysis was performed on the local helix elevation (helix angle α) and the deviation of the helix from circumferential structure (transverse angle β). Sheet angles γ were defined as the angle between the third eigenvector and the surface parallel to the endo- and epicardium.
**Results:** Data across the entire left ventricle were successfully acquired in both systole and diastole. The linear relation of helix angles as a function of transmural position can be seen in Figure 1A. The slope of a linear fit for all segments was found to be steeper in systole \(-1.10\pm0.08^\circ/\%\) transmural depth than in diastole \(-0.86\pm0.03^\circ/\%\) transmural depth with a mean helix angle range of \((95.4\pm12.1)^\circ\) in systole and \((68.1\pm5.9)^\circ\) in diastole (Figure 1B,C). Transverse angles \(\beta\) were distributed around zero degrees in both systole \((-3.1\pm26.1)^\circ\) and diastole \((1.2\pm21.5)^\circ\) (Figure 1D). Sheet angles in diastole show a high population for very high and low values \(\pm90^\circ\), whereas the sheet angle distribution in systole has more counts of small angulations (Figure 1E,F). Figure 1G shows the helix angle maps in long axis and short axis views (basal, mid, apical) upon dense tensor field interpolation [6].

![Figure 1](image_url)

**Conclusion:** The data presented here provides a comprehensive set of information on cardiac fiber architecture. In combination with available motion data it has the potential to improve the general understanding of cardiac mechanics and may serve as realistic input for computational heart modeling projects. The data are available at:

[www.biomed.ee.ethz.ch/cardiacdtiatlas](http://www.biomed.ee.ethz.ch/cardiacdtiatlas)

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Cardiac fibres estimation from arbitrarily spaced diffusion weighted MRI

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Abstract

Diffusion Tensor Magnetic Resonance Imaging (DTMRI) allows observing the fibre structure non-invasively [1, 2]. Unfortunately, a full three-dimensional, high-resolution acquisition of the fibre data through DTMRI requires extremely long scan times, and therefore it has been applied only to ex-vivo heart samples e.g. [3] and references therein. Recently, in-vivo DTMRI acquisitions for a limited number of slices along the heart were reported [4, 5, 6]. Hence, a three-dimensional fibre reconstruction across the heart is needed, which has to deal not only with high noise levels (arising from eddy current effects), but also with the spatial mismatch of the single diffusion weighted images (DWIs) due to inconsistent breath holds during acquisition.

To the authors best knowledge all tensor reconstruction schemes from a set of DWIs rely on the co-existence of the images in the same spatial location, see e.g. [7] and references therein. In this work, we propose a tensor estimation scheme, which can handle arbitrarily located DWIs. The method is based on a parametric representation of the diffusion tensor across the left ventricular volume utilizing a constructed orthogonal system within the ventricular wall and the helix angle as degree of freedom (DOF), inspired from [8]. This allows to relate sparsely located diffusion weighted information by estimating the cardiac fibre orientations solving a nonlinear least squares problem.

Ongoing work consists in the extension of the current transverse isotropic approach for the diffusion tensor to a orthotropic respresentation, including additional degrees of freedoms for the sheet angle. Furthermore the method is compared with the curvilinear tensor interpolation method [9] in real geometries, with both synthetic and real data. Moreover the framework would enable to adjust the DOFs resolution and amount of data required (i.e. the number of slices and diffusion encoding directions) in order to estimate the fibre architecture up to a certain precision. Another relevant aspect is that the flexibility of the choice of the diffusion encoding directions and slices may allow in the future to speed-up the acquisition of diffusion MR sequences.
References


Is ventricular deformation affine?

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Abstract

Introduction. Recent advances in cardiac diffusion tensor imaging (DTI) have enabled robust imaging of the in vivo heart [1]. This allows to non-invasively assess myofiber and myosheet orientations, which has been a long-standing bottleneck of patient-specific cardiac modeling [2]. Thanks to efficient sequence design, in vivo DTI has even been performed in patients [3] and at multiple cardiac phases [4]. In this study, we analyze dual phase cardiac DTI data of normal humans to investigate the affinity of ventricular deformation. The angulation data is compared to predictions based on myofiber transportation by macroscopic deformation, to quantify the potential relative sliding between myofibers.

Methods. In vivo DTI data was obtained on a healthy human volunteer, using a slice interleaved dual heart phase stimulated echo acquisition mode (STEAM) imaging method [4]. Ten short-axis slices were acquired with diffusion weighting along ten directions [4]. In addition, three dimensional tagged magnetic resonance images were acquired using a complementary spatial modulation of magnetization (3D CSPAMM) method, and post-processed using the SinMod algorithm to obtain the displacement field throughout the ventricle during the cardiac cycle [5]. They were used (i) to account for myocardial strain during diffusion tensor reconstruction [4]; and (ii) to map the tensor points acquired at end-diastole and end-systole (see next paragraph).

The analysis consists in comparing the angulation of the myocardial microstructure from end-diastole to end-systole (or vice versa), (i) measured using in vivo DTI; and (ii) associated to the macroscopic deformation measured using 3D CSPAMM. First of all, the end-systolic position of the end-diastolic tensor points was computed, and the closest end-systolic tensor point of each transported end-diastolic tensor point was found. Then, to compute the former, i.e., the measured rotation between end-diastole and end-systole, the angles between the myofiber vectors of each couple of tensors was assessed. Finally, to compute the later, i.e., the rotation induced by the macroscopic deformation, the rotation part of the deformation gradient was extracted.

Results. Figure 1(a-b) shows the tensor points at end-diastole & end-systole, while Figure 1(c-d) compares the transmural variation of measured & transported helix & transverse angle change. The data suggests that there is an average additional rotation of 10° of the myofibers from end-diastole to end-systole, in addition the rotation induced by the macroscopic transformation. Measured & transported transverse angles are more similar.
Figure 1: Analysis of a high-resolution in vivo DTI & tagged MRI dataset.

**Discussion.** The present analysis provides an element of response to the long-standing question of the affinity of the ventricular deformation; our findings are however limited by the use of a single in vivo dataset. We are now working toward performing the analysis on a dataset of ten human volunteers, in order to confirm the finding. The non-affinity foreseen here could have a significant impact in cardiac modeling, where mostly first order continuum models are currently used, as well as in cardiology, where it could help to better explain the complex cardiac deformation and potentially represent a valuable biomarker for diagnosis.

**References**


Variational Estimation of Cardiac Conductivities: Numerical Issues, Sensitivity Analysis, Computational Cost Reduction

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Abstract

One possible strategy for estimating the cardiac conductivities is through a variational data assimilation procedure. This consists of a classical constrained minimization of a functional measuring the mismatch between available measures and numerical computations. The constraint is represented by the equations of electrocardiology that establish a link between conductivities and potential propagation. These are given by the Bidomain system for transmembrane and extracellular potential. Preliminary results presented at the first edition of this Workshop pointed out that the method may provide good estimates of conductivities even in real geometries [2]. Results are of interest also in view of possible extensions to multivariable assimilation, including the fiber orientation. However several theoretical and numerical issues were raised. In this talk, we will address some of them.

1. Uniqueness of the solution. While existence of the minimizer is proved with classical arguments, uniqueness requires some additional assumptions that we will investigate.

2. Sensitivity to the ionic model. The selection of the ionic model is clearly important for the quality of the data assimilation procedure. We present results to assess the sensitivity of the results on this choice and on the associated parameters.

3. Numerical issues related to the ionic model. The minimal model proposed by Flavio Fenton and his co-workers features discontinuous functions that requires special numerical treatment. Classical regularization procedures actually prevent the convergence of iterative procedures for solving the inverse problem and more ad hoc numerical procedures carefully capturing the discontinuity are required.

4. Reduction of the computational costs. This approach has a solid mathematical foundation. However it features high computational costs, in particular in presence of regions with different conductivities like scars. This motivates the investigation of specific methods for reducing the computational costs. We address pitfalls and success of different possible approaches. Model reduction techniques based on an appropriate replacement of the Bidomain equations with the simplified Monodomain system do not provide reliable results. Solution reduction techniques based on a surrogate representation of the numerical solution built up on the online-offline paradigm are problematic too. As a matter of fact, classical Proper Orthogonal Decomposition (POD) approaches do not give good results. In fact, the decay of the singular values obtained after the SVD of the snapshot matrix is not fast enough to grant a significant reduction of the solution size. Inspired by the work of Boulakia, Schenone and Gerbeau [1] we present preliminary results of two Reduced Basis methods based on POD that provide promising results in view of real test cases and experimental validation [3].
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References


Inverse uncertainty quantification problems in cardiac electrophysiology: reduced order models for state and error reduction

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Abstract

The design of efficient solvers for inverse problems governed by PDEs is an important step in cardiac electrophysiology. In this context, the forward problem is typically modeled by a nonlinear unsteady PDE problem, e.g. the monodomain or the bidomain equations for the propagation of the electric potential in the cardiac muscle. Inverse identification problems, and more generally uncertainty quantification (UQ) problems, require a huge amount of forward solutions – e.g. in the context of Bayesian inversion, through Monte Carlo Markov Chain (MCMC) algorithms or Bayesian Kalman filters – thus entailing an often prohibitive computational cost.

In this talk we present some reduced order modelling (ROM) techniques for the efficient and accurate solution of (Bayesian) inverse UQ problems in cardiac electrophysiology, for the identification of myocardial ischemias from surface potential measurements [5, 3, 2]. For the reduction of the state equation, we rely on a reduced basis (RB) method built by combining few snapshots of the high-fidelity (finite element) problem, computed for properly selected parameter values [6, 7]. The RB approximation of the problem can thus be obtained by projecting the original problem onto the low-dimensional space spanned by this small set of snapshots. To tackle the computational difficulties caused by the nonlinear nature of the problem, we consider suitable empirical interpolation techniques [1, 8].

For the sake of error reduction, we consider suitable reduction error models (REM), developed in [4] and based on computable a posteriori error bounds, to quantify the error between the high fidelity and the reduced-order model, in order to gauge the effect of the state reduction on the posterior distribution of the identifiable parameters.

Our numerical results show that this combined approach makes it possible (i) to speedup the solution of each forward query, and (ii) to quantify the propagation of reduction errors along the whole inversion process. Some preliminary results exploiting a monodomain model for the description of the electrical potential in presence of ischemic areas, described through some unknown or uncertain parameters/fields, will be presented.
References


Space–discretization error analysis and stabilization schemes for conduction velocity in cardiac electrophysiology

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Abstract

The bidomain equation is the most commonly used model to describe in detail the spatial and temporal electric activity of the heart [1]. It couples the macroscale behaviour of the tissue with the cellular membrane ionic dynamic, giving rise to a traveling action potential that orchestrates the muscular contraction and relaxation. It is well known that the action potential is characterised by a very steep front, about 200 μm thick. This yields a considerable computational effort on patient–specific human geometries, where the numerical domain scales as cm but the required mesh resolution is of the order of 0.1 mm [2].

A vast literature on the topic has been produced over the last decades. For instance, a common solution to the problem is to use with relatively simple numerical algorithms to achieve good scalability on HPC architectures [3]. Otherwise, adaptivity in space and time provides a viable way to significantly reduce the computational cost, although some aspects of the approach, such as the error estimation and the effective implementation of the algorithm, require substantial efforts [5].

In mathematical terms, the bidomain model is a reaction–diffusion system of equations whose solutions we are interested in are travelling waves, i.e. solutions of the form \( \phi(x \cdot k - ct) \), where \( c \) is the speed and \( k \) the direction of the propagation. The same concept can be applied to any numerical discretisation of the equation, defining a so–called discrete traveling wave solutions. As it might be expected, these solutions, which should be close to their continuous counterpart, strongly depend on the numerical scheme adopted, either being finite element or finite difference, low order or high order, with or without operator splitting, and so forth.

The first aim of this work is to analyse in detail the effect of specific discretisations in space on traveling wave solutions of the bistable (or Nagumo) equation, which is a simple but mathematically reasonable approximation of the dynamics at the front of the wave. We show how specific discretisation schemes (finite difference, continuous and discontinuous finite element, etc.), and the choice of a coarse grid, can affect the solution, leading so to possibly erroneous physiological conclusions.

We provide and analytically prove several error estimates of the conduction velocity for different numerical schemes, by performing a perturbation analysis of the discrete problem associated to the discrete traveling wave. For instance, we show that the speed of the wave is always over–estimated by finite element discretisation with exact integration of the non–linear term, and that a quadrature approximation can have a significant effect on the conduction velocity. We also analyse the impact of mass lumping, adopted by several authors in relation with operator splitting schemes. While the approximate quadrature always tends to reduce the conduction velocity, the mass lumping can either reduce or increase the speed depending on the so–called detuning parameter, which encodes the specifications of the ionic model.
The second aim of the paper is to exploit the error estimates to design a robust numerical scheme for the problem of interest. We propose and analyse two different schemes: the first one is a forth–order (in space) scheme obtained by a weighed average of the finite difference and the finite element method. The second one is a “stabilised” finite element scheme, where we introduce a numerical conductivity to consistently adjust the conduction velocity, as it has been done for decades in other contexts of numerical analysis. The latter idea is not new in electrophysiology either: it is indeed quite common to manually or semi–automatically “tweak” the conductivities, uniformly in space, to match a target conduction velocity. Unfortunately this methodology is neither robust when the mesh is not uniform nor consistent when the numerical grid is refined or coarsened.

These novel schemes show very good approximation properties of the conduction velocity. Moreover, the additional implementation and computational efforts for these two schemes is practically zero, since in the former case it is enough to use a “half-lumped” mass matrix, while in the latter it is only required to adjust the conductivity field with respect to a characteristic mesh size.

The last part is devoted to test the methodology on realistic ionic models and geometries. The results are in excellent agreement with our analytical results based on the bistable model, thus showing the validity of the approach.

References

Discontinuous Galerkin approximations for cardiac electrophysiology

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Abstract

Introduction Cardiac electrophysiology simulations are numerically extremely challenging, due to the steep wave front during depolarization. Hence, to obtain physiological depolarization and propagation velocities the usage of very small time steps and fine spatial discretisations is required. This is a bottleneck when moving towards patient-specific simulations in clinically relevant times.

In contrast to standard continuous Galerkin approaches (CG), spatial discretisations based on discontinuous methods have received very little attention for cardiac electrophysiology simulations. Only finite volume methods have been reported (see [1] and references therein), however, no detailed comparison against other methods have been performed, to the authors best knowledge. In this work we provide a detailed comparison among CG, local discontinuous Galerkin (LDG) and hybridizable discontinuous Galerkin (HDG) methods for the electrophysiology equations at hand of the 1D monodomain model.

Methods We investigate the behavior of different combinations of the different spatial discretisations in combination with different treatments of the ionic current term for the monodomain equations. For this purpose, we use the following setup: \( \Omega = [0, 14] \text{mm} \), and the so called “minimal cell model” introduced in [2], which is able to reproduce physiological action potential with only four gating variables.

The investigation of different spatial discretisations includes the standard continuous Galerkin, the local discontinuous Galerkin, derived from [3] (with central and upwind flux), and the hybridized discontinuous Galerkin, derived from [4]. The integration of the ionic current term was approximated either from evaluation the current at the degrees of freedom of the finite element nodes, with and without mass lumping, or at the Gauss points of the quadrature rule (see [5, 6, 7]).

Results The results are calculated in terms of the conduction velocity (CV), for a physiological range of diffusivities (\( \sigma = 0.001 - 2.0 \text{mm}^2/\text{ms} \)). All methods, CG, LDG and HDG, with every approximation of the ionic current, converged to the same reference solution for small time steps and mesh sizes.

The choice of an upwind flux for the LDG method for the calculated range of diffusivities resulted, independent of the treatment of the ionic current, in a higher CV compared to the central flux. For a fixed mesh size the LDG with upwind flux gives a higher accuracy in terms of the CV than HDG and standard CG method. The HDG method results more accurate in a lower CV range compared to the CG method.
Conclusion  The LDG method gives a considerable improvement in the accuracy with respect to classical CG methods. However, the improvement in the results obtained with the HDG method is relatively small in a one dimensional setup. The HDG method provides however the possibility of postprocessing the solution to gain better convergence rates and since the standard postprocessing technique does not result in higher convergence rate, further development is required. The same applies to to better choices of the stabilization parameter in HDG. Future work would be also to test the convergence and accuracy of CG, LDG HDG methods with higher order elements in a higher dimensional setup since the advantages of HDG are more visible on higher order elements as the degrees of freedom increase with a smaller factor.

References


Modeling the fluid dynamics of the heart: from blood flows in idealized left ventricles to patient–specific aortic valve simulations

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Abstract

The computational fluid dynamics of the heart represents a challenging task both in terms of mathematical and numerical modeling; this is mainly due to the pulsatile nature of the blood flow, to its complex interaction with the valves, and, more in general, to the reciprocal action of the components responsible for the heart functioning. Even if one focuses on the study of the left ventricle, the blood flow patterns ([3, 5]) result to be significantly dependent on the mechanical contraction and relaxation of the muscle, on the conformation of the chamber, and on the interaction with the valves, which define a complex fluid–structure interaction problem ([2]). In this respect, also the blood flow in the aorta, and hence in the downstream circulation, is strongly affected by the aortic valve, whose behavior should be suitably mathematically and numerically modeled.

In this work, we firstly focus on the study of the fluid dynamics inside the left ventricle in idealized configurations, for which we propose a mathematical model based on the Navier–Stokes equations endowed with mixed, time–dependent boundary conditions, which allow a simplified treatment of the aortic and mitral valves’ behavior. In this idealized setting, we perform numerical simulations which highlight the role and influence of modeling the valves to study and characterize the blood flow patterns inside the ventricle, as well as other parameters of clinical relevance.

In addition, we consider a reduced, patient–specific fluid–structure–interaction model for the simulation of the blood flow through the aortic valve. Specifically, we propose an efficient coupled model which represents the valve dynamics by means of a zero–dimensional (0D) equation with the opening angle as primitive variable ([4]), while the blood flow by means of the full 3D Navier–Stokes equations. In this coupled model, the valve’s leaflets, which are reconstructed from MRI data of the open and closed configurations for a specific patient, influence the Navier–Stokes equations by means of resistive immersed surfaces, whose position depends on the opening angle of the valve ([1]). Moreover, the dynamics of the valve described by the 0D model is dependent on the velocity and pressure variables, specifically on the pressure jump and the flow rate through the valve itself. We perform patient–specific numerical simulations of the aortic valve based on this reduced 3D–0D model, for which we highlight its ability to correctly capture the fluid dynamics indicators expected for the patient.
References


Modeling of flow in stenotic valves and arteries

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Abstract

A stenosis in the cardiovascular system is a reduction in cross-sectional area of a structure across which blood flows due to the plack or other incapabilities. Interventional and surgical treatments have provided improvements in survival, cardiac function, and functional capacity. Still, accurate and precise assessment of stenosis severity is required in order to appropriately decide whether and what type of treatment is warranted for a given lesion.

Current approaches to interpreting non-invasive data are still incapable of ascertaining hemo-dynamic stenosis severity. Various methods have been used to evaluate stenoses by either anatomic or physiologic criteria. In this work, we use full solution of the incompressible Navier-Stokes equation for determination of the blood energy dissipation and the pressure differences across cardiovascular stenoses, which can be applied to non-invasive diagnostic modalities.

We will start with the flow in different simplified geometries of the stenotic vessels to obtain the reference velocity field and pressure drop across the stenosis and compute corresponding dissipation. Finally, we discuss two approaches to obtain the pressure directly from a measured velocity field.
A Model-based Investigation of Coronary Wave Intensity and Perfusion

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Abstract

Clinical diagnosis of coronary artery disease continues to be a subject of intense investigation. On one hand, questions remain regarding newer imaging technologies such as perfusion MRI due to the difficulties in relating the acquired data to the underlying physiological state. Meanwhile, enhanced invasive indices such as wave intensity analysis (WIA), which has the potential to offer broader diagnostic information on combined coronary and cardiac function, remains poorly understood. A common obstacle in these pursuits is the difficulty of addressing the physiological complexity in a quantitative manner. In this work, we present new methodological advances based on integrative computational modeling which aims to address these conventional limitations [1].

Our framework comprises a multi-scale model of cardiac perfusion encompassing both macro and microcirculation. The varying flow regimes over these scales are addressed by heterogeneous mathematical models (one-dimensional elastic tube flow and poromechanics) that are coupled together. The regional influence of cardiac motion on coronary flow is captured through actively contracting myocardium. Coronary anatomy and the compartment-averaged microvascular properties are derived from high-resolution imaging. The complete numerical model including systemic hemodynamics is solved via finite element method.

The utility of the model is demonstrated through an in silico wave WIA, which is sensitive to both myocardial and coronary function. In particular the effects of QRS duration and aortic valve dynamics on major coronary waves are quantified. Furthermore, the calculated flow field forms the basis for simulation of transport phenomena, allowing in silico perfusion imaging based on the passage of contrast agent through the myocardium.

References

A Poroelastic Scalar Transport Formulation for Modelling Magnetic Resonance Perfusion Imaging in the Beating Heart

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Abstract

Contrast agent enhanced magnetic resonance (MR) perfusion imaging provides a direct, non-invasive, early indication of defects in the coronary circulation. The standard clinical procedure is to inject a dye or contrast agent (CA) into the circulation and take multiple image slices as the CA passes throughout the myocardium. Darker regions in these image slices indicate a lack of CA accumulation, insufficient perfusion and thus significant vascular disease.

The CAs currently used are freely-diffusive, which means that they can permeate the capillary wall and diffuse into and through the extra-vascular space. This behaviour - creating false-negative readings - combined with variation in CA transport properties and magnetic response parameters, imaging sequences and spatio-temporal sampling tradeoffs, means that optimising protocols is difficult to achieve through clinical trials alone.

Computational modelling can therefore play an important role in accelerating this optimisation of protocols and thereby optimise the application of MR perfusion imaging in clinical practice. Previously the authors used a 2D static finite element model of contrast agent transport in the capillaries [1] to reveal the sensitivity of perfusion image characteristics to contrast agent parameters. In this paper we extend our model to a 3D dynamic formulation for use in the beating heart, producing the first such model of its kind.

Specifically, building on a poroelastic model of perfusion flow and mechanics in the beating heart [2], we present a poroelastic formulation of contrast agent transport in the beating heart. Using a consistent, systematic framework provided by the Arbitrary Lagrangian Eulerian (ALE) formulation, a generic scalar conservation law is first derived within a deforming poroelastic medium. This enables a natural derivation of the equations for both fluid mass and scalar transport in a poroelastic medium.

The complete model presented also includes active contraction mechanics, 1D Navier-Stokes vessel models for large epicardial arteries, and transient Darcy flow in the capillaries. The transport of a freely-diffusive CA is described by a coupled system of reaction-advection-diffusion equations. These latter equations are discretised using a Petrov-Galerkin scheme and the resultant linear system solved using a monolithic-coupling scheme within our in-house, parallelised, multi-physics modelling code, Cheart [3].

Results will be presented that show the effect of varying contrast agent transport parameters, focusing on extra-vascular diffusivity, and how this manifests in the image for models of both normal and diseased physiology. Figure 1(a) shows simulation data for a contrast agent with moderate extra-vascular diffusivity, and illustrates the fat-tail that typically appears in perfusion imaging signals due to the storage and subsequent slow release of contrast agent in the extravascular space. This simulated result shows good qualitative agreement with measurements reported in the medical literature. Further, for the diseased model, it is observed that
(a) Simulated signal for fluid, solid and total concentration in a normally-perfused region, for a freely-diffusive CA.

(b) Data from Fig. 1(a) down sampled to once per heart beat.

Figure 1: Both signals show qualitative agreement with those reported in the clinical literature, however the effect of downsampling Fig. 1(a) to once per heart beat as in clinical imaging, blunts both the peak value and gradients of the true underlying signal. Sampling at a different point in the cardiac cycle or with a different frequency can significantly effect the observed signal.

as extra-vascular diffusivity is increased, a greater quantity of CA diffuses into the diseased myocardium, which again accords well with clinical experience.

Figure 1(b) demonstrates that a temporal sampling of once per heart beat - currently used in clinical imaging - causes an underestimation of the peak concentration and affects the measurement of signal gradients. It is also clear that altering the point in the cardiac cycle at which the signal is sampled will affect the degree of attenuation, and therefore results will be presented that quantify the impact these sampling protocols have on the measured signal, and the interaction with contrast agent transport parameters.

References


Insight into model mechanisms and more efficient model development and validation by multivariate metamodelling

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Abstract

Modelling in biology and physiology is increasingly realising its potential to provide a deeper understanding of biological function, guide the development of new intervention strategies and inform treatment optimisation in personalised medicine. However, the development and validation of large, multi-scale models remain hampered by several significant challenges that limit the clinical applicability of models and their adaptation to fit new contexts. The complexity of the models needed in order to account for our rapidly increasing knowledge of physiological mechanisms [1], poses considerable challenges for uniquely linking model parameters to experimental and clinical data. Additionally, including a high level of biophysical detail in large multi-physics models leads to computationally demanding simulations, the results of which are hard to validate sufficiently since they can not be run under sufficiently diverse conditions within a reasonable computational time. To ensure robust parameter fitting to measured experimental or clinical data requires models which can be solved rapidly to allow a comprehensive exploration of the parameter space.

In many cases the model structure is such that the inverse problem of parameter fitting is ill-posed due to multiple parameter values producing the same model output (model sloppiness) [2], leading to low identifiability of many parameters from available data. This situation is exacerbated by the lack of consensus on the optimal method for fitting model parameters to data, taking into account the, often, poor signal to noise ratio in the measurements, as well as ill-defined cost functions. Including an excessive complexity increases the risk of parameters being fitted to noise, limiting the applicability of the models to new cases. The high complexity of the models also makes it challenging to foresee the relationships between the variables in the system, and select the most informative metrics to measure in order to fit individual or groups of parameters. However, including too little detail limits the flexibility of models to provide the necessary level of insight into the biological phenomena they are intended to represent. It is therefore important to have a balanced level of detail in computational models.

Multivariate metamodelling, i.e. statistical modelling of the relationships between model inputs and outputs, has the potential to allow us to overcome a number of these challenges by reducing computational demand, efficiently extracting the most relevant features describing the system functionality, facilitating model reduction and transparent integration of modelling results with experimental data. The regression coefficients from classical metamodels - predicting the model outputs as functions of the inputs - are direct measures of the model sensitivity, i.e. the impact of variations in the various inputs on the model outputs. Analysis of these regression coefficients thus allows identification of the most important features determining system behaviour [3]. Reduction in model complexity through identification of redundant model components is important in that it typically increases the sensitivity of model outputs to the various parameters and hence the consequences of introducing changes to the model become more transparent. It also improves the likelihood that the models will
be predictive outside the regime of the parameterising data. Specifically, if the identifiability of model parameters can be increased, this will enhance the ability to find the most relevant experimental measurements in order to constrain parameters within a given model framework, decreasing the uncertainty in parameter estimates.

**Inverse metamodells**, where the input parameters are predicted as functions of the model outputs, can aid parameterisation of models in relation to experimental data [4,5]. However, inverse metamodelling is often not able to predict all the input parameters with sufficient accuracy due to model sloppiness. To overcome this problem, we have developed a parameter fitting pipeline based on a combination of inverse metamodelling and iterative generation of new experimental designs zooming into the biologically relevant input space regions [6]. This pipeline has been applied to fit the parameters of cardiac contraction models to measured data for mouse, rat and human, and to quantify inter-species differences in cardiac contraction [7]. We show in the present study that our parameter fitting methodology gives more reliable parameter estimates than the more traditional Simplex optimisation, both for two different cardiac contraction models, and for a model of the electrical activity of the heart.

Our results indicate that a combination of classical and inverse metamodells can provide more efficient and accurate fitting of nonlinear mathematical models to measured data by first identifying the most important input parameters affecting the various model outputs by classical metamodelling, and subsequently inverse metamodelling can aid the fitting of model parameters from measured data. Moreover, different models may also be compared through their metamodel surrogates, allowing selection of the most suitable model alternative for a given context, as well as effective identification of the similarities and differences between models. We therefore believe that multivariate metamodelling will be of significant value for future model development.

**References**


