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Activity Report 2016

Project-Team CARMEN

Modélisation et calculs pour l'électrophysiologie cardiaque

RESEARCH CENTER
Bordeaux - Sud-Ouest

THEME
Modeling and Control for Life Sciences

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2. Overall Objectives

2.1. Overall Objectives

The Carmen team develops and uses models and numerical methods in order to simulate the electrophysiology of the heart from the molecular to the whole-organ scale, and its relation to measurable signals inside the heart and on the body surface. It aims at

- improving understanding of normal and pathological cardiac electrophysiology,
- improving the efficiency and accuracy of numerical models, and
- exploitation of all available electrical signals for diagnosis, in particular for prediction of life-threatening cardiac arrhythmias.

The numerical models used and developed by the team incorporate the gating dynamics of the ion channels in the cardiac cell membranes and the heterogeneities and coupling processes on the cellular scale into macroscopic reaction-diffusion models. At the same time we use reduced models to solve the inverse problems related to non-invasive electrical imaging of the heart.

The fields involved in our research are: ordinary and partial differential equations (PDE), inverse problems, numerical analysis, high-performance computing, image segmentation, and mesh construction.

A main goal of the team is to contribute to the work packages defined in the IHU LIRYC, an institute founded in 2011 that focuses on cardiac arrhythmia.

We cooperate with physiologists and cardiologists on several projects. The team is building new models and powerful simulation tools that will help to understand the mechanisms behind cardiac arrhythmias and to establish personalized and optimized treatments. A particular challenge consists in making the simulations reliable and accessible to the medical community.

3. Research Program

3.1. Complex models for the propagation of cardiac action potentials

The contraction of the heart is coordinated by a complex electrical activation process which relies on about a million ion channels, pumps, and exchangers of various kinds in the membrane of each cardiac cell. Their interaction results in a periodic change in transmembrane potential called an action potential. Action potentials in the cardiac muscle propagate rapidly from cell to cell, synchronizing the contraction of the entire muscle to achieve an efficient pump function. The spatio-temporal pattern of this propagation is related both to the function of the cellular membrane and to the structural organization of the cells into tissues. Cardiac arrythmias originate from malfunctions in this process. The field of cardiac electrophysiology studies the multiscale organization of the cardiac activation process from the subcellular scale up to the scale of the body. It relates the molecular processes in the cell membranes to the propagation process and to measurable signals in the heart and to the electrocardiogram, an electrical signal on the torso surface.

Several improvements of current models of the propagation of the action potential are developed, based on previous work [44] and on the data available at IHU LIRYC:

- Enrichment of the current monodomain and bidomain models [44] [8] by accounting for structural heterogeneities of the tissue at an intermediate scale. Here we focus on multiscale analysis techniques applied to the various high-resolution structural data available at the LIRYC.
- Coupling of the tissues from the different cardiac compartments and conduction systems. Here, we develop models that couple 1D, 2D and 3D phenomena described by reaction-diffusion PDEs.

These models are essential to improve our in-depth understanding of cardiac electrical dysfunction. To this aim, we use high-performance computing techniques in order to numerically explore the complexity of these models.

We use these model codes for applied studies in two important areas of cardiac electrophysiology: atrial fibrillation [20] [46] and sudden-cardiac-death (SCD) syndromes [14], [51], [48]. This work is performed in collaboration with several physiologists and clinicians both at IHU Liryc and abroad.

3.2. Simplified models and inverse problems

The medical and clinical exploration of the cardiac electric signals is based on accurate reconstruction of the patterns of propagation of the action potential. The correct detection of these complex patterns by non-invasive electrical imaging techniques has to be developed. This problem involves solving inverse problems that cannot be addressed with the more compex models. We want both to develop simple and fast models of the propagation of cardiac action potentials and improve the solutions to the inverse problems found in cardiac electrical imaging techniques.

The cardiac inverse problem consists in finding the cardiac activation maps or, more generally, the whole cardiac electrical activity, from high-density body surface electrocardiograms. It is a new and a powerful diagnosis technique, which success would be considered as a breakthrough. Although widely studied recently, it remains a challenge for the scientific community. In many cases the quality of reconstructed electrical potential is not adequate. The methods used consist in solving the Laplace equation on the volume delimited by the body surface and the epicardial surface. Our aim is to

- study in depth the dependance of this inverse problem on inhomogeneities in the torso, conductivity values, the geometry, electrode positions, etc., and
- improve the solution to the inverse problem by using new regularization strategies, factorization of boundary value problems, and the theory of optimal control, both in the quasistatic and in the dynamic contexts.

Of course we will use our models as a basis to regularize these inverse problems. We will consider the following strategies:

- using complete propagation models in the inverse problem, like the bidomain equations, for instance in order to localize electrical sources;
- constructing families of reduced-order models using e.g. statistical learning techniques, which would accurately represent some families of well-identified pathologies; and
- constructing simple models of the propagation of the activation front, based on eikonal or level-set equations, but which would incorporate the representation of complex activation patterns.

Additionaly, we will need to develop numerical techniques dedicated to our simplified eikonal/level-set equations.

3.3. Numerical techniques

We want the numerical simulations of the previous direct or inverse models to be efficient and reliable with respect to the needs of the medical community. They should qualify and guarantee the accuracy and robustness of the numerical techniques and the efficiency of the resolution algorithms.

Based on previous work on solving the monodomain and bidomain equations [4], [5], [7], [1], we will focus on

- High-order numerical techniques with respect to the variables with physiological meaning, like velocity, AP duration and restitution properties.
- Efficient, dedicated preconditioning techniques coupled with parallel computing.

Existing simulation tools used in our team rely, among others, on mixtures of explicit and implicit integration methods for ODEs, hybrid MPI-OpenMP parallellization, algebraic multigrid preconditioning, and a BiCGStab algorithm with adaptations to retain numerical accuracy while handling large underdetermined systems.

3.4. Cardiac Electrophysiology at the Microscopic Scale

Numerical models of whole-heart physiology are based on the approximation of a perfect muscle using homogenisation methods. However, due to aging and cardiomyopathies, the cellular structure of the tissue changes. These modifications can give rise to life-threatening arrhythmias. For our research on this subject and with cardiologists of the IHU LIRYC Bordeaux, we aim to design and implement models that describe the strong heterogeneity of the tissue at the cellular level and to numerically explore the mechanisms of these diseases.

The literature on this type of model is still very limited. Existing models are two-dimensional or limited to idealized geometries, and use a linear (purely resistive) behaviour of the gap-juction channels that connect the cells. We propose a three-dimensional approach using realistic cellular geometry, nonlinear gap-junction behaviour, and a numerical approach that can scale to hundreds of cells while maintaining a sub-micrometer spatial resolution (10 to 100 times smaller than the size of a cardiomyocyte).

4. Application Domains

4.1. Scientific context: the LIRYC

The University Hospital of Bordeaux (*CHU de Bordeaux*) is equipped with a specialized cardiology hospital, the *Hôpital Cardiologique du Haut-Lévêque*, where the group of Professor Michel Haïssaguerre has established itself as a global leader in the field of cardiac electrophysiology. Their discoveries in the area of atrial fibrillation and sudden cardiac death syndromes are widely acclaimed, and the group is a national and international referral center for treatment of cardiac arrhythmia. Thus the group also sees large numbers of patients with rare cardiac diseases.

In 2011 the group has won the competition for a 40 million euro *Investissements d'Avenir* grant for the establishment of IHU Liryc, an institute that combines clinical, experimental, and numerical research in the area of cardiac arrhythmia (http://ihu-liryc.fr). The institute works in all areas of modern cardiac electrophysiology: atrial arrhythmias, sudden death due to ventricular fibrillation, heart failure related to ventricular dyssynchrony, and metabolic disorders. It is recognized as one of the most important centers worldwide in this area.

The Carmen team was founded to partner with IHU Liryc. We aim at bringing applied mathematics and scientific computing closer to experimental and clinical cardiac electrophysiology. In collaboration with experimental and clinical researchers at Liry we aim at enhancing fundamental knowledge of the normal and abnormal cardiac electrical activity and of the patterns of the electrocardiogram, and we will develop new simulation tools for training, biological, and clinical applications.

4.2. Basic experimental electrophysiology

Our modeling is carried out in coordination with the experimental teams from IHU Liryc. It will help to write new concepts concerning the multiscale organisation of the cardiac action potentials and will serve our understanding in many electrical pathologies. For example, we will be modeling the structural heterogeneities at the cellular scale, and at an intermediate scale between the cellular and tissue scales.

At the atrial level, we apply our models to understand the mechanisms of complex arrythmias and the relation with the heterogeneities at the insertion of the pulmonary veins. We will model the heterogeneities specific to the atria, like fibrosis or fatty infiltration. They are supposed to play a major role in the development of atrial fibrillation.

At the ventricular level, we focus on (1) modeling the complex coupling between the Purkinje network and the ventricles and (2) modeling the heteogeneities related to the complex organization and disorganization of the myocytes and fibroblasts. Point (1) is supposed to play a major role in sudden cardiac death and point (2) is important in the study of infarct scars for instance.

4.3. Clinical electrophysiology

Treatment of cardiac arrhythmia is possible by pharmacological means, by implantation of pacemakers and defibrillators, and by curative ablation of diseased tissue by local heating or freezing. In particular the ablative therapies create challenges that can be addressed by numerical means. Cardiologists would like to know, preferably by noninvasive means, where an arrhythima originates and by what mechanism it is sustained.

We address this issue in the first place using inverse models, which attempt to estimate the cardiac activity from a (high-density) electrocardiogram. A new project aims at performing this estimation on-site in the catheterization laboratory and presenting the results, together with the cardiac anatomy, on the screen that the cardiologist uses to monitor the catheter positions.

An important prerequisite for this kind of interventions and for inverse modeling is the creation of anatomical models from imaging data. The Carmen team contributes to better and more efficient segmentation and meshing through the IDAM project (section 6.2).

5. Highlights of the Year

5.1. Highlights of the Year

5.1.1. Events

On 4 November 2016 the new building of the IHU Liryc was officially opened in the presence of representatives from the municipal, departmental, regional, and national authorities.

On 9 December 2016 A. Davidović defended her thesis Multiscale Mathematical Modeling of Structural Heterogeneities in Cardiac Electrophysiology.

5.1.2. Recruitments

M. Potse, whose work had been funded by IHU Liryc since 2013, has become a full-time member of the Carmen team and has won an Inria Advanced Research Position in June 2016. He will continue his numerical studies on cardiac sudden-death syndromes and atrial fibrillation and is developing a new project on the application of electrocardiographic inverse methods in the catheterization laboratory.

We recruited the engineer P. Migerditichan; she started working in November 2016 on a project named EPICARDial electrical signals VIZualisation (EPICARD-VIZ). The aim of this project is to build a software solution for the electrocardiographic inverse problem, coded in the MUSIC platform. The goal of the project is twofold: First, we aim at building a semi-automatic functionality that allows to obtain meshes of the epicardium, torso, lungs, liver, and skeletal muscle with minimal human interaction. Second, our aim is to include a dense linear algebra library and to construct a computational framework in which we will be able to compare different methods of solving the inverse problem.

After the completion of her PhD thesis A. Davidović was hired as an Engineer, granted by the ANR HR-CEM project. She continues her work on multiscale modelling of heterogeneities in cardiac tissue. She is going to use the experimental high-resolution MRI data on animal and human hearts that are provided by the imaging team of IHU Liryc. By means of image analysis and numerical simulations she is going to study the effects of fibrotic, fatty, and other kinds of tissue on AP propagation.

6. New Software and Platforms

6.1. CEPS: a Cardiac ElectroPhysiology Simulator

The Carmen team develops a software library to perform high-performance numerical simulations in cardiac electrophysiology using unstructured three-dimensional grids. The software, called CEPS (*Cardiac Electrophysiology Simulation*) is developed as a common tool for researchers in the Carmen team and for our partners and colleagues in scientific computing and biomedical engineering. The goal of CEPS is to facilitate the development of new numerical methods and new physical models.

Compared to other existing software, CEPS aims at providing a more general framework of integration for new methods or models and a better efficiency in parallel. CEPS is designed to run on massively parallel architectures, and to make use of state-of-the-art and well-known computing libraries to achieve realistic and complex heart simulations. The largest part of CEPS was developed by the Junior Engineer M. Juhoor, supervised by N. Zemzemi, during the CEPS ADT (*Action de Développement Technologique*).

To enforce a sound development process, some engineering and validation tools are used:

- Git hosted at the Inria GForge (ceps) to manage versions;
- Cmake for the building process
- Jenkins, hosted at the Inria continuous integration service, which runs a test suite of about 200 tests after every commit.

Main users and developers of CEPS are the PhD students of Carmen, i.e.

- A. Gérard, who uses CEPS for patient-specific modeling, has implemented a bilayer model using coupled nodes.
- Charlie Douanla-Lountsi currently works on high-order temporal integration methods, for later integration in CEPS.
- P. E. Bécue is developing a code to run microscopic-scale models (section 3.4) and wrote a coupled node assembler to support this work.

Since January 2015, M. Fuentes from the *Service d'Experimentation et de Développement* (SED), is responsible for developing new features in CEPS, improve robustness, efficiency, and documentation. M. Juhoor, who has previously worked on CEPS, and works on the IDAM project, brings us from time to time his expertise. Actions done in 2016 include:

- support for P2 Lagrange finite Elements
- node partitioning using the PTScotch partitioner
- input files and VtkReader (M. Juhoor)
- code refactoring
- documentation writing

6.2. IDAM

The goal of the IDAM project is to define a collection of plugins in the MUSIC software in order to create realistic meshes for the CEPS code. MUSIC is a multimodal platform for cardiac imaging developed by the imaging team at IHU LIRYC (https://bil.inria.fr/fr/software/view/1885/tab). Information comes from magnetic resonance imaging and cardiac tomography performed in the clinic and in the LIRYC laboratories. Building complete cardiac models directly from imaging data requires expert knowledge and is time-consuming and error-prone: specific expertise and multiple software tools are often needed to process data stemming from medical imaging into realistic meshes and parameter distributions.

IDAM aims to streamline the workflow of a complete cardiac simulation: anatomical mesh generation from patient-specific data, description of simulation parameters, and eventually analysis of simulation results obtained by simulation packages like CEPS (https://bil.inria.fr/fr/software/view/2630/tab). IDAM integrates tools from other Inria teams by using specialized libraries, for example MMG (https://bil.inria.fr/fr/software/view/2824/tab) for high-quality mesh generation.

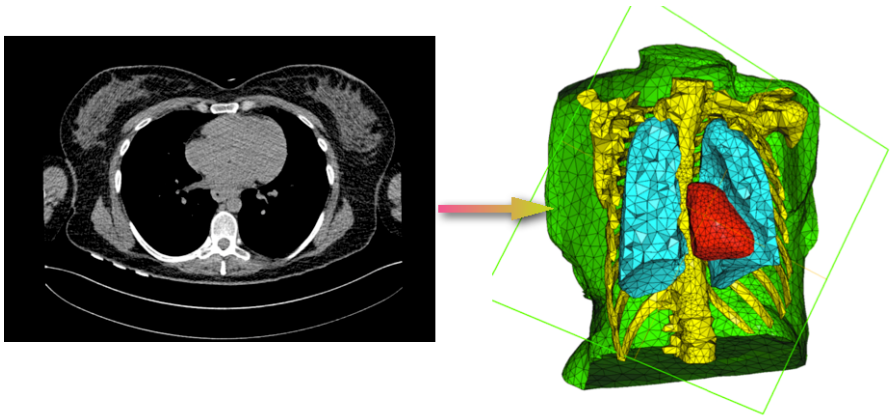

Figure 1. Mesh of a human torso and one of the X-ray computed-tomography slices on which it was based.

6.3. Platforms

6.3.1. Propag-5

Applied modeling studies performed by the Carmen team, especially M. Potse and M. Kania, in collaboration with IHU Liryc and foreign partners [39], [43], [18], [20], [14] [45], rely to a great extent on high-performance

computations on the national supercomputers Curie, Occigen, and Turing. While the newly developed CEPS code is not ready to run efficiently on these systems we rely on an older code named Propag-5. This code is the result of a decades-long development first at the *Université de Montréal* in Canada, then at Maastricht University in the Netherlands, and finally at the Institute of Computational Science of the *Università della Svizzera italiana* in Lugano, Switzerland. Relatively small contributions to this code have been made by the Carmen team.

The predecessor of Propag-5, named Propag-4, was developed by M. Potse at the *Université de Montréal* [8]. It was based on earlier model code developed there by the team of Prof. R. Gulrajani [50], [53], and was parallellized with OpenMP to utilize the shared-memory SGI supercomputers available there at the time. Propag-4 was the first code ever able to run a bidomain reaction-diffusion model of the entire human ventricles; a problem 30 times larger than what had been reported before [8].

In order to utilize the more recent distributed-memory architectures Propag-4 was transformed into the hybrid MPI-OpenMP code Propag-5 at the Institute of Computational Science in Lugano by D. Krause and M. Potse [49]. The resulting code has been used for numerous applied studies. An important limitation of the Propag code is that it relies on a semi-structured mesh with a uniform resolution. On the other hand, the code scales excellently to large core counts and, as it is controlled completely with command-line flags and configuration files, it can be used by non-programmers. It also features

- a plugin system for membrane models,
- a completely parallel workflow, including the initial anatomy input and mesh partitioning, which allows it to work with meshes of more than 10^9 nodes,
- a flexible output scheme allowing hundreds of different state variables and transient variables to be output to file, when desired, using any spatial and temporal subsampling,
- a configurable, LUSTRE-aware parallel output system in which groups of processes write HDF5/netCDF files, and
- CWEB documentation of the entire code base.

The code has been stable and reliable for several years, and only minor changes are being made currently. It can be considered the workhorse for our HPC work until CEPS takes over.

6.3.2. Gepetto

Gepetto, named after a famous model maker, is a sofware suite that transforms a surface mesh of the heart into a set of (semi-)structured meshes for use by the Propag software or others. It creates the different fiber orientations in the model, including the transmurally rotating ventricular fibers and the various bundle structures in the atria (figure 2), and creates layers with possibly different electrophysiological properties across the wall. A practically important function is that it automatically builds the matching heart and torso meshes that Propag uses to simulate potentials in the torso (at a resolution of 1 mm) after projecting simulation results from the heart model (at 0.1 to 0.2 mm) on the coarser torso mesh [52]. Like Propag, the Gepetto software results from a long-term development that started in Montreal, Canada, around 2002. The code for atrial fiber structure was developed by our team.

6.3.3. MUSIC

MUSIC is a multimodal platform for cardiac imaging developed by the imaging team at IHU LIRYC in collaboration with the Inria team Asclepios (https://bil.inria.fr/fr/software/view/1885/tab). It is based on the medInria software also developed by the Asclepios team. MUSIC is a cross-platform software for segmentation of medical imaging data, meshing, and ultimately also visualization of functional imaging data and model results.

Several members of the Carmen team use MUSIC for their work. The team also contributes a series of plugins for MUSIC through the IDAM project (section 6.2).

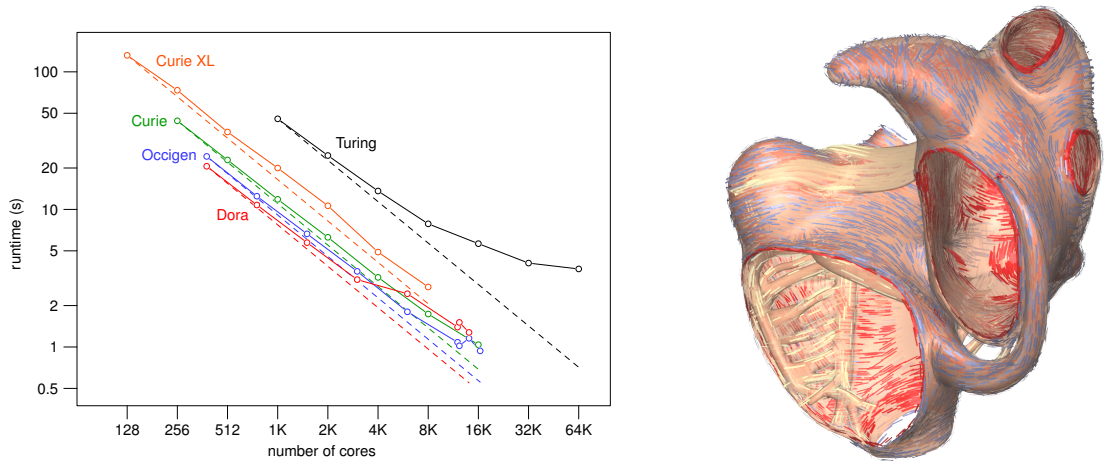

Figure 2. ***Left:*** *Strong scaling of the Propag-5 code on a monodomain reaction-diffusion equation for four systems: The Bull clusters Curie (small nodes and large nodes, XL) and Occigen, The Cray XC30 "Piz Dora" at the Swiss supercomputing center CSCS and the IBM BlueGene/Q "Turing". The graph shows the runtime needed for 10 ms of propagated activity using an explicit (forward) Euler integration. Dashed lines indicate the ideal scaling line with respect to the lowest number of cores measured.* ***Right:*** *Bundle structures and different layers of fiber orientation created by the Gepetto software.*

7. New Results

7.1. Convergence analysis of a bidomain-bath model

M. Bendahmane and N. Chamakuri performed a convergence analysis for optimal control of a bidomain-bath model by using a finite-element scheme. The bidomain-bath model represents a commonly used experimental setup where a small piece of cardiac tissue is kept alive and studied for some time in a nutrient bath. The bidomain-bath model equations describe the cardiac bioelectric activity in the tissue and bath volumes where the control acts at the boundary of the tissue. The existence of the finite element scheme and convergence to a unique weak solution of the direct problem were established. The convergence proof was based on deriving a series of a-priori estimates and using a general L2-compactness criterion. Moreover, the well-posedness of the adjoint problem and the first order necessary optimality conditions were shown. Comparing to the direct problem, the convergence proof of the adjoint problem is based on using a general L1-compactness criterion. The model was used for a simulation of low-energy defibrillation.

7.2. An exponential Adams–Bashforth ODE solver for stiff problems

C. Douanla Lontsi, together with Y. Coudière and C. Pierre, obtained an important result on time integration of stiff differential problems. They considered Adams exponential integrators with general varying stabilizers. General stabilization brings flexibility and facilitates the integration of ODE systems and semilinear evolution PDEs coupled with ODE systems. They were able to prove the stability and convergence of this type of integrator by introducing a new framework that extends multistep linear methods. Dahlquist stability was numerically investigated. A(α)-stability was observed under a condition on the stabilizer, which is a singular property for explicit schemes. The method was numerically studied for two stiff models in electrophysiology. Its performance was compared with several classical methods. The authors concluded that for stiff ODE systems, it provides a cheaper way to compute accurate solutions at large time steps than implicit solvers.

7.3. Homogeneous Neumann condition on the torso for solving inverse problems

The electrical activity of the heart creates an electrical field in the body. This phenomenon is classically modelled in a quasistatic manner by Laplace's equation. The non-invasive electrocardiographic imaging (ECGI) problem consists in retrieving the best electrical map on the heart from given torso measurements. Classically, the solution is found as the best fit between data generated by a forward problem and the actual torso measurements, and it needs a regularization. Hence the inverse solution depends on the matrix of the forward problem, called the transfer matrix, and the choice of the regularization procedure. In 2006, a meshless method based on the method of fundamental solutions (MFS) was adapted by Y. Wang and Y. Rudy [54] to directly solve the inverse problem, combined with a 0-th order Tikhonov regularization. The MFS method is notably more robust than previous methods (e.g. BEM) to the uncertainties introduced by the segmentation of the geometries. In the MFS, the potential is expressed as summation of the fundamental solution of the Laplace equation over a discrete set of virtual point sources placed outside of the domain of interest. The inverse solution is searched as the set of sources that best fit the boundary conditions on the torso, up to the regularization term. This formulation yields a linear system, which matrix depends on the torso and heart geometries, and the boundary conditions at the torso surface. The regularization parameter also heavily depends on the properties of the transfer matrix. The boundary conditions considered in [54] are: i) the Dirichlet conditions, meaning that the potentials at the torso surface are fitted to the recorded ones, ii) homogeneous Neumann conditions (HNC) meaning that the normal flux of current is minimized.

Numerically, the HNC requires to build accurate directions at each measurement location of the body surface, which is a first difficulty. In addition, the body is cut at the top and the bottom where no-flux conditions are probably not relevant. Lastly, the matrix coefficients related to the HNC appears to be much smaller than the ones from the Dirichlet condition, due to the distance between the torso and the actual electrical source (the heart).

J. Chamorro-Servent, Y. Coudière and R. Dubois studied the effect of the HNC on the matrix. They showed that enforcing the Neumann condition has a negligible effect on the solution of the inverse problem. Reconstructed potentials and activation time maps were built for in-silico data. No major differences were found between the standard MFS and the MFS removing the HNC in terms of potentials and activation times. In addition, removing the HNC reduces the ill-conditioning of the problem and the computational burden: the normal at the torso surface is not required anymore, and the problem size is divided by 2. The results of this work were presented as a poster in CinC 2016, and collected in a proceeding for the same conference by J. Chamorro-Servent et al. [18].

7.4. Adaptive placement of the pseudo-boundaries improves the conditioning of the inverse problem

In order to complete the investigaton concerning the MFS technique from [54], J. Chamorro-Servent, Y. Coudière and R. Dubois also studied the effect of the location of the virtual sources of the MFS method on the solutions of the inverse problem. Specifically, the regularization term spoils the biophysical content of the solution, and the regularization parameter must be chosen as small as possible. But the problem must be regularized enough to overcome its sensitivity to: i) noise on the measured potentials, ii) uncertainty in the location of measurement sites with respect to the surface on which the sources are distributed, iii) errors of segmentation of the geometries, iv) influence of cardiac motion, etc.

The regularization parameter can be studied in view of the singular values of the matrix, or for given measurments, the discrete Picart condition as defined by Hansen [47].

In the MFS problem, explained in section 7.3, the virtual sources are placed by inflating and deflating the heart and torso surfaces with respect to the heart's geometric center. However, for some heart-torso geometries, this geometrical center is a poor reference. Furthermore, it has been proved in other fields that the placement of the virtual sources influences the ill-posedness of the MFS problem. However, this has not been tested for the ECGI problem.

J. Chamorro-Servent, R. Dubois and Y. Coudière proposed a new method of placement of these virtual sources based on the minimal distance of each point considered on the heart surface to the torso electrodes. The singular value analysis and the discrete Picard condition were used to optimize the location of these sources. The new distribution of sources was compared with the standard one for a set of experimental data. These data consist of simultaneous acquisition of the cardiac (on a Langendorff perfusion of the heart) and body surface potentials, in a controlled experimental environment.

The results presented by J. Chamorro-Servent et al. at CinC2016 [24] showed that the new distribution of sources made the inverse problem less ill-posed and therefore, less sensitive to the regularization parameter chosen. This improved the reconstructed potentials on the heart surface, especially when artefact (as for example the baseline) or noise were present.

Further results from the combination of the works described here and in section 7.3 were presented in a poster in the Liryc workshop of October 2016 [33] by J. Chamorro-Servent et al. A journal manuscript is currently under preparation (to submit in 2017).

7.5. Reduced sodium current in the lateral ventricular wall induces J waves in the ECG

"J waves," a particular abnormal waveform in electrocardiogram (ECG) leads, are associated with a higher risk for ventricular fibrillation. M. Potse has performed a series of simulations to investigate three possible mechanisms that could explain such waves and the associated arrhythmia risk. Out of these, a reduced sodium current in the lateral area of the left ventricular wall turned out to be the most powerful to cause J waves. The lateral area is particular because it is normally late activated, and a further delay due to regionally reduced sodium current can lead to J waves in the ECG. If the same occurs elsewhere in the heart, the resulting J waves would be masked by other ECG peaks. The simulations were supported, as far as possible, by experiments performed at the University of Amsterdam. The results have been published in the journal Frontiers in Physiology, and further refinements have recently been shown in a poster at the Annual workshop of IHU Liryc [14], [43].

7.6. Atrial fibrillation due to complex geometry

Atrial fibrillation (AF), a situation in which the electrical activation of the atria proceeds chaotically, is believed to be due to abnormal tissue structure (for example fibrosis), which slows propagation, and abnormalities in ionic currents, which make the action potential shorter. In collaboration with the Center for Computational Medicine in Cardiology in Lugano, Switzerland, we performed series of simulations in which we tried to reproduce these effects [20]. Rapid stimulation of the atria caused AF in some of the simulations, with a likelihood related to the severity of fibrosis. However, we also observed a 30 % likelihood of AF initiation in a model with no fibrosis at all. In these cases, the complex structure of our highly realistic models alone in combination with the rapid-pacing protocol sufficed to create situations of conditional propagation block, which led to a reentrant arrhythmia. These results may shed a new light on the course of new-onset AF. A manuscript on this topic is under preparation.

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. IHU LIRYC

Our work is partially funded by the LIRYC project (ANR 10-IAHU 04).

- Until November 2016 the salary of M. Potse was funded by LIRYC.

8.2. National Initiatives

8.2.1. ANR HR-CEM

The project "High Resolution Cardiac Electrophysiology Models: HR-CEM" within the ANR call *Modèles Numériques* started in November 2013 and will last until November 2017.

It is an international project that involves three partners: Inria (coordinator), IHU LIRYC, and UMI-CRM in Montréal (Canada). The project has external collaborators in Univ. Bordeaux and Univ. Pau.

Based on these collaborations and new developments in structural and functional imaging of the heart available at LIRYC, we plan to reconsider the concepts behind the models in order to improve the accuracy and efficiency of simulations. Cardiac simulation software and high-resolution numerical models will be derived from experimental data from animal models. Validation will be performed by comparing of simulation output with experimentally recorded functional data. The validated numerical models will be made available to the community of researchers who take advantage of in-silico cardiac simulation and, hopefully, become references. In particular we shall provide the first exhaustive model of an animal heart including the four chambers coupled through the special conduction network, with highly detailed microstructure of both the atria and the ventricles. Such a model embedded in high-performance computational software will provide stronger medical foundations for in-silico experimentation, and elucidate mechanisms of cardiac arrhythmias.

8.2.2. ANR Labcom CardioXcomp

We are participant in the ANR Labcom project between Inria and the company Notocord (www.notocord.com). In this project, we propose a mathematical approach for the analysis of drug effects on the electrical activity of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) based on multi-electrode array (MEA) experiments. Our goal is to produce an *in-silico* tool able to simulate drug actions in MEA/hiPSC-CM assays. The mathematical model takes into account the geometry of the MEA and the electrode properties. The electrical activity of the stem cells at the ion-channel level is governed by a system of ordinary differential equations (ODEs). The ODEs are coupled to the bidomain equations, describing the propagation of the electrical wave in the stem cells preparation. The field potential (FP) measured by the MEA is modeled by the extra-cellular potential of the bidomain equations. First, we propose a strategy allowing us to generate a field potential in good agreement with the experimental data. We show that we are able to reproduce realistic field potentials by introducing different scenarios of heterogeneity in the action potential. This heterogeneity reflects the differentiation atria/ventricles and the age of the cells. Second, we introduce a drug/ion channels interaction based on a pore block model. We conduct different simulations for five drugs (mexiletine, dofetilide, bepridil, ivabradine and BayK). We compare the simulation results with the field potential collected from experimental measurements. Different biomarkers computed on the FP are considered, including depolarization amplitude, repolarization delay, repolarization amplitude and depolarization-repolarization segment. The simulation results show that the model reflect properly the main effects of these drugs on the FP.

8.2.3. REO

The CARMEN team is a partner with the REO team at Inria Paris Rocquencourt and the Notocord company in the CardioXcomp project.

8.2.4. MedicActiv

The CARMEN team cooperates in interaction with the MedicActiV project.

8.2.5. GENCI

GENCI (*grand équipement national de calcul intensif*) is the agency that grants access to all national high-performance resources for scientific purposes in France. GENCI projects have to be renewed yearly. Our project renewal *Interaction between tissue structure and ion-channel function in cardiac arrhythmia*, submitted in October 2015, has been granted 9.4 million core-hours on the three major systems Curie, Occigen, and Turing. This compute time, to be used in the calendar year 2016, is primarily destined for our research into the interaction between ionic and structural heart disease in atrial fibrillation, Brugada syndrome, and early

repolarisation syndrome [51]. A renewal request has been submitted in October 2016 and was granted with 9.8 million core-hours.

8.3. European Initiatives

8.3.1. FP7 & H2020 Projects

The Carmen team is a core member of two H2020 proposals that are to be submitted in March 2017.

8.4. International Initiatives

8.4.1. Inria International Labs

8.4.1.1. EPICARD

Title: inversE Problems In CARDiac electrophysiology

International Partner (Institution - Laboratory - Researcher):

ENIT (Tunisia) – Department of Intelligence Science and Technology - Nabil Gmati

Start year: 2015

See also: https://team.inria.fr/carmen/epicard/

Improving the information that we can extract from electrical signals measured on patients with heart diseases is a major priority for the IHU LIRYC. We would like to non-invasively construct the electrical potential on the heart surface only from measurements of the potential on the the chest of the patient. It is known that algorithms that have been used in the literature for solving this electrocardiography imaging (ECGI) problem, including those used in commercial medical devices, have several limitations. This problem could be mathematically seen as a boundary data completion problem for elliptic equations. Many studies have been carried out in order to solve this Cauchy problem, but have never been used for solving the ECGI problem. The goal of this Inria International Lab (IIL) is to develop an experimental platform allowing to test various methods and compare their performance on real life experimental data.

We describe here two projects that have been performed in the context of this IIL.

8.4.1.1.1. Mathematical analysis of the parameter estimation problem

N. Zemzemi, J. Lassoued, and M. Mahjoub worked on the mathematical analysis of a parameter identification problem in cardiac electrophysiology modeling. The work was based on a monodomain reaction-diffusion model of the heart. The purpose was to prove the stability of the identification of the parameter τ_{in}, which is the parameter that multiplies the cubic term in the reaction term. The proof of the result is based on a new Carleman-type estimate for both the PDE and ODE problems. As a consequence of the stability result they proved the uniqueness of the parameter τ_{in} giving some observations of both state variables at a given time t_0 in the whole domain and the PDE variable in a non empty open subset w_0 of the domain.

8.4.1.1.2. Uncertainty quantification in the electrocardiography problem

N. Zemzemi worked with N. Fikal, R. Aboulaich and EL.M. El Guarmah on uncertainty quantification in electrocardiography imaging. The purpose of this work was to study the influence of errors and uncertainties of the imput data, like the conductivity, on the electrocardiographic imaging (ECGI) solution. They propose a new stochastic optimal control formulation to calculate the distribution of the electric potentiel on the heart from the measurement on the body surface. The discretization was done using a stochastic Galerkin method allowing to separate random and deterministic variables. The problem was discretized, in spatial part, using the finite element method and the polynomial chaos expansion in the stochastic part of the problem. The problem was solved using a conjugate gradient method where the gradient of the cost function was computed with an adjoint technique. The efficiency of this approach to solve the inverse problem and the usability to quantify the effect of conductivity uncertainties in the torso were demonstrated through numerical simulations on a 2D analytical geometry and on a 2D cross section of a real torso.

8.4.1.2. Informal International Partners

M. Potse works with the group of Prof. U. Schotten at Maastricht University (The Netherlands) and the Center for Computational Medicine in Cardiology at the *Università della Svizzera italiana* (Lugano, Switzerland) on simulation studies of atrial fibrillation [20]. The Maastricht group was partially funded by the FP7 project EUTRAF and our simulations were supported by GENCI (section 8.2.5).

8.5. International Research Visitors

8.5.1. Visits of International Scientists

Professor Y. Bourgault (University of Ottawa) visited the team from 12 to 26 March.

Professor A. Fraguela Collar, from the *Benemerita Universidad Autonoma de Puebla-Mexico* visited us in July 2016.

8.5.2. Visits to International Teams

8.5.2.1. Other international activities

N. Zemzemi gave a course in the CIMPA research school: "Modelling and simulating the electrical activity of the heart Direct and Inverse problems."

N. Zemzemi organized a mini-symposium intitled "Imaging and inverse modeling" in PICOF 2016: https://picof.sciencesconf.org/resource/page/id/4#. From 01/06/2016 to 03/06/2016. Autrans, France.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Organisation

9.1.1.1. Member of the Organizing Committees

- 6th international conference on "Computational Surgery," Bordeaux, May 2016 (Y. Coudière).
- The annual workshop of IHU Liryc, Bordeaux, October 2016 (Y. Coudière).

N. Zemzemi organized a mini-symposium intitled "Imaging and inverse modeling" in PICOF 2016, from 01/06/2016 to 03/06/2016. Autrans, France.

9.1.2. Scientific Events Selection

9.1.2.1. Member of the Conference Program Committees

- 6th international conference on "Computational Surgery," Bordeaux, May 2016 (Y. Coudière).
- CARI 2016 (N. Zemzemi)

9.1.3. Journal

9.1.3.1. Member of the Editorial Boards

M. Potse: associate editor of Frontiers in Cardiac Electrophysiology.

9.1.3.2. Reviewer - Reviewing activities

M. Potse: Heart Rhythm, IEEE Transactions on Biomedical Engineering, Medical & Biological Engineering & Computing, Journal of Electrocardiology.

Y. Coudière: Journal of computational and applied mathematics, PLOS ONE, SMAI Journal of Computational Mathematics

N. Zemzemi: Inverse Problems, Europace, Inverse Problems in Science and Engineering

9.1.4. Invited Talks

M. Bendahmane: Université Qadi Ayyad, IST d'Essaouira (Morocco), April 2016

M. Bendahmane: University of Oslo (Norway), October 2016.

Y. Coudière: University of Ottawa (Canada), February 2016.

N. Zemzemi gave a course in the CIMPA research school: "Modelling and simulating the electrical activity of the heart Direct and Inverse problems". From 04/10 to 10/10 2016. Tunis, Tunisia.

N. Zemzemi: Course on the electrophysiology modelling: Forward and Inverse problems.Ecole doctorale de mathématique. Faculté des sciences de Tunis. From 10/01/2016 to 15/01/2016. Tunis, Tunisia.

M. Potse gave an invited presentation titled "Visualization of 3D Lead Fields" at the 43rd International Congress on Electrocardiology.

9.1.5. Leadership within the Scientific Community

M. Potse is council member of the International Society of Electrocardiology.

9.1.6. Scientific Expertise

Y. Coudière:

- ATER committee for Université de Bordeaux
- Reviewer PhD Thesis of P.-L. Colin, Université Lille 1, 27/06/2016
- Reviewer HDR Thesis of M. Sermesant, Université de Nice Sophia-Antipolis, 09/06/2016
- SNF (Swiss National Science foundation)

9.1.7. Research Administration

Y. Coudière:

- Scientific responsability of the IMB (CNRS UMR 5251) team "Calcul Scientifique et Modélisation," 60 persons.
- Responsible for the scientific communication (*Chargé de mission à l'animation scientifique*) of the IMB

N. Zemzemi: Administration of the Inria associated team Epicard (section 8.4.1.1).

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

DUT : P. E. Bécue, Introduction to modelling and Principal Component Analysis, 43 hours, level N/A, IUT Orsay, France

DUT : P. E. Bécue, Object Oriented Programming with java, 9 hours, level N/A, IUT Orsay, France

9.2.2. Supervision

PhD : A. Davidović, "Multiscale Mathematical Modeling of Structural Heterogeneities in Cardiac Electrophysiology," Université de Bordeaux, 9 December 2016, supervised by Y. Coudière.

PhD in progress: P. E. Bécue, "Modélisation et simulation numérique de l'électrophysiologie cardiaque à l'échelle microscopique," started 1 October 2014, supervised by F. Caro, M. Potse, and Y. Coudière.

PhD in progress: C. Douanla Lontsi, "Schémas d'ordre élevé pour des simulations réalistes en électrophysiologie cardiaque," started 1 November 2014, supervised by Y. Coudière.

PhD in progress: A. Gérard, "Modèles numériques personnalisés de la fibrillation auriculaire," started 1 September 2015, supervised by Y. Coudière.

9.2.3. Juries

M. Bendahmane was a jury member (*rapporteur*) for the PhD thesis of Jamila Lassoued (*Université de Tunis*).

9.3. Popularization

The Carmen team has responded to a call of Cap'Maths in 2014 on dissemination and popularization of mathematics destined for young pupils, the general public, and (future) mathematical professionals. For this project, G. Ravon and Y. Coudière developed a *serious game* called Heart Attack. The game is destined for middle and high school students as an introduction to mathematical modeling. The principal goal of the game is to illustrate the notion of numerical modeling in medical research, and in particular in cardiac rhythmology. The player takes the role of a scientist having developed a numerical model for the electrical activity of the heart and tries to learn how to prevent an arrhythmia. A secondary goal is to teach about the electrical activation mechanism of the heart.

Integrating scientific simulations in an interactive website is challenging because of the constraints imposed by a web-based framework. As a result of this project we have learned a great deal about such developement and about the collaboration with professional web developers.

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