IN PARTNERSHIP WITH:
Université de Bordeaux

Activity Report 2017

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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Creation of the Team: 2011 October 01, updated into Project-Team: 2016 June 01

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2. Overall Objectives

2.1. Overall Objectives

The Carmen team develops and uses models and numerical methods 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 (http://ihu-liryc.fr), 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 being developed in the Carmen team, based on previous work [49] and on the data available at IHU LIRYC:

- Enrichment of the current monodomain and bidomain models [49], [59] 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 [51] and sudden-cardiac-death (SCD) syndromes [7], [6] [54]. 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], [8], [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

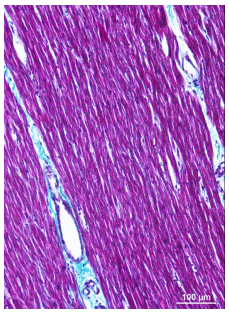
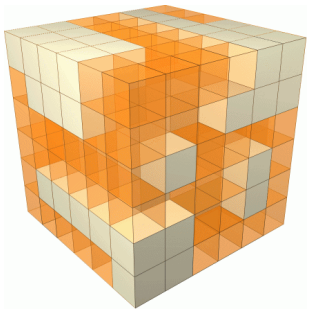
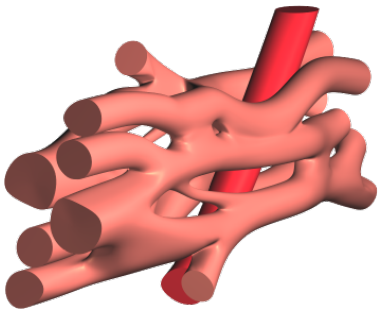
Numerical models of whole-heart physiology are based on the approximation of a perfect muscle using homogenisation methods. However, due to aging and cardiomyopathies, the cellular structure of the tissue changes. These modifications can give rise to life-threatening arrhythmias. For our research on 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 [63]. Existing models are two-dimensional [55] 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 (figure 1), 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) [28] [48], [47].

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 [53], [52], [45]. 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.

A ***B*** ***C***

Figure 1. ***A:*** *The cardiac muscle consists of a branching network of elongated muscle cells, interspersed with other structures. Sheets of connective tissue (blue) can grow between the muscle cells and become pathogenic.* ***B:*** *Current models can only represent such alterations in a coarse way by replacing model elements with different types; each cube in this illustration would represent hundreds of cells.* ***C:*** *This hand-crafted example illustrates the type of geometric model we are experimenting with. Each cell is here represented by hundreds of elements.*

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 bring applied mathematics and scientific computing closer to experimental and clinical cardiac electrophysiology. In collaboration with experimental and clinical researchers at Liry we work to enhance fundamental knowledge of the normal and abnormal cardiac electrical activity and of the patterns of the electrocardiogram, and we 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 help to write new concepts concerning the multiscale organisation of the cardiac action potentials that will serve our understanding in many electrical pathologies. For example, we model the structural heterogeneities at the cellular scale [28], 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 [51]. These heterogeneities ar thought 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 [25].

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.

5. Highlights of the Year

5.1. Highlights of the Year

5.1.1. Awards

Michał Kania received a Gary and Bill Sanders poster award for his contribution “Prediction of the Exit Site of Ventricular Tachycardia Based on Different ECG Lead Systems” to the Computing in Cardiology meeting in Rennes, September 2017 .

5.1.2. Inria domain evaluation

In October the Carmen team participated in the evaluation of the Inria domain Life sciences, theme *Modeling and Control for Life Sciences*, during a 3-day seminar in Paris. The report was very positive about our work in general. The jury, composed of high-profile international scientists, noted especially the development of a bilayer model of the atria [56], [50] [15], the modified monodomain model which can reproduce much of the much more expensive bidomain model [49], and our contributions to electrocardiographic imaging [24], [17], [23], [27].

BEST PAPER AWARD:

[25]
M. KANIA, Y. COUDIÈRE, H. COCHET, M. HAÏSSAGUERRE, P. JAÏS, M. POTSE. *Prediction of the Exit Site of Ventricular Tachycardia Based on Different ECG Lead Systems*, in "Computing in Cardiology", Rennes, France, September 2017, https://hal.inria.fr/hal-01567961

6. New Software and Platforms

6.1. CEPS

Cardiac ElectroPhysiology Simulation
KEYWORDS: 3D - Cardiac - Mesh - Health - Simulation - Cardiac Electrophysiology
SCIENTIFIC DESCRIPTION: As compared to other existing softwares, 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. CEPS also includes software engineering and and validation tools.
FUNCTIONAL DESCRIPTION: CEPS is a numerical simulation tool focused on the modeling of cardiac electrophysiology. The goal of CEPS is to easily allow the development of new numerical methods and new physical models.

- Participants: Mehdi Juhoor and Nejib Zemzemi
- Partners: Université de Bordeaux - CNRS - INP Bordeaux - IHU - LIRYC
- Contact: Yves Coudière
- URL: https://gforge.inria.fr/projects/ceps/

6.2. Platforms

6.2.1. CEMPACK

CEMPACK is a new collection of software that was previously archived in different places. It includes the high-performance simulation code Propag and a suite of software for the creation of geometric models, preparing inputs for Propag, and analysing its outputs. In the course of 2017 the code was colleced in an archive on Inria's GitLab platform, and a public website was created where documentation will be placed (http://cempack.gforge.inria.fr).

The main components of CEMPACK are the following.

Propag-5.1 Applied modeling studies performed by the Carmen team, especially M. Potse and M. Kania, in collaboration with IHU Liryc and foreign partners [17] [7] [61], [51] [43] rely to a great extent on high-performance computations on the national supercomputers Curie, Occigen, and Turing. The Propag-5 code is optimized for these systems. It 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. Since 2016 most of the development on Propag has been done by M. Potse at the Carmen team. 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.

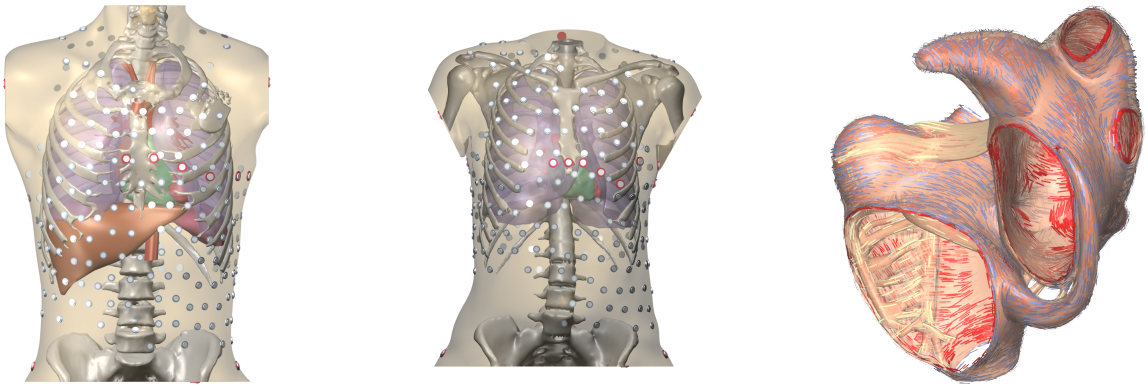
The code has been stable and reliable for several years, and only minor changes are being made currently. It can be considered the workhorse for our HPC work until CEPS takes over.

Gepetto The Gepetto suite, named after a famous model maker, 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 [60]. 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.

Blender plugins Blender (https://www.blender.org) is a free software package for the production of 3-D models, renderings, and animations, comparable to commercial software such as Cinema4D. CEMPACK includes a set of plugins for Blender that facilitate the production of anatomical models and the visualization of data. It uses the MMG remeshing library, which is developed by the CARDAMOM team at Inria Bordeaux.

6.2.2. 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.



A ***B*** ***C***

Figure 2. ***A and B:*** *Complete heart-torso geometries created with CEMPACK tools.* ***C:*** *Bundle structures and different layers of fiber orientation created by the Gepetto software.*

Several members of the Carmen team use MUSIC for their work, and the team contributes to the sfotware through the IDAM project.

7. New Results

7.1. A parameter optimization method to solve the ECG inverse problem

Existing electrocardiographic inverse models express their results either in terms of potentials on the heart surface or in terms of activation times in the heart. G. Ravon developed a new method which gives a potentially more useful answer in terms of three parameters of the underlying action potentials in the heart [27]. Since there are more parameters, care had to be taken to avoid overfitting. Tests on in-silico and ex-vivo data showed good results: the method gave better activation maps than the method of fundamental solutions to which it was compared, and fitted the repolarization phase of the ECG accurately. Figure shows an example of an inversely estimated repolarization map.

7.2. Optimal control to Bidomain-Bath model

This project is concerned with the study of the convergence analysis for an optimal control of a bidomain-bath model. The bidomain-bath model equations describe the cardiac bioelectric activity at the tissue bath volumes where the control acts at the boundary of the tissue domain. In recent work [13] [44], we established the well-posedeness of the direct bidomain-bath model by a discrete Galerkin approach. The convergence proof is based on deriving a series of a priori estimates and using a general $L2$-compactness criterion. Moreover, the well-posedeness of the adjoint problem and the first order necessary optimality conditions are shown. Comparing to the direct problem, the convergence proof of the adjoint problem is based on using a general L^1-compactness criterion. The numerical tests are demonstrated which achieve the successful cardiac defibrillation by utilizing less total current. Finally, the robustness of the Newton optimization algorithm is presented for different finer mesh geometries.

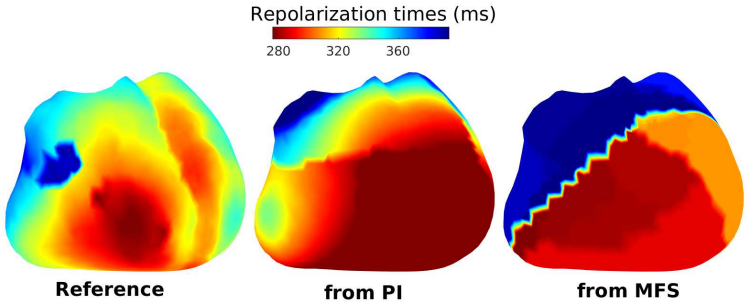


Figure 3. Reference repolarization map and inversely estimated maps, using the newly developed method (middle) and the method of fundamental solutions to which it was compared (right). The new method results in more realistic patterns.

7.3. Bidomain Calcium Dynamics in Cardiac Cell

In our project [35], we are interested in modeling the interaction of Calcium dynamics in a bidomain medium including Sarcolemma and Sarcoplasmic reticulum. The governing equations consist of a nonlinear reaction-diffusion system representing the various calcium fuxes and theirs buffers in the two medias. A priori stability bounds and the solvability of the system is analyzed using a fixed-point approach. We introduce a finite element method to numerically solve our model equations. Moreover, we establish existence of discrete solutions and show convergence to a weak solution of the original problem. Finally, we report several 2D and 3D numerical experiments illustrating the behavior of the proposed scheme.

7.4. Cardiac electromechanics with physiological ionic model

This project [37] is concerned with the mathematical analysis of a coupled elliptic-parabolic system modeling the interaction between the propagation of electric potential coupled with general physiological ionic models and subsequent deformation of the cardiac tissue. A prototype system belonging to this class is provided by the electromechanical bidomain model, which is frequently used to study and simulate electrophysiological waves in cardiac tissue. The coupling between muscle contraction, biochemical reactions and electric activity is introduced with a so-called active strain decomposition framework, where the material gradient of deformation is split into an active (electrophysiology-dependent) part and an elastic (passive) one. We prove existence of weak solutions to the underlying coupled electromechanical bidomain model under the assumption of linearized elastic behavior of the updated nonlinear diffusivities. The proof of the existence result is proved by means of a non-degenerate approximation system, the Faedo-Galerkin method, and the compactness method.

7.5. Electrocardiographic lead fields

Currently a monodomain reaction-diffusion model is a well-established method to simulate the electrical activity of the heart [58], [59], even more so because it can be adapted to approximate a bidomain model very closely [46], [49]. Computing the electrocardiogram (ECG) from the results of such models is harder because it requires large linear systems to be solved, and does not scale well to large numbers of processors. A possible solution is to use so-called lead fields, the electrocardiographic term for a linear combination of Green's functions that express the ECG potential as an integral over a field of electric current dipoles. M. Potse has implemented and tested methods to compute and use lead fields for ECG simulation with the Propag code. It turned out that this classical method is practical and sufficiently accurate, and gives a huge scaling advantage on modern highly parallel computers. This result is of practical importance for our applied work, and a journal manuscript on this topic will be submitted in January 2018.

7.6. Rapid localization of arrhythmia

Our pilot studies using model data [25] have shown promising results for a proposed simple and rapid localization method to be used in the catheterization laboratory. We have found that even with only a few ECG electrodes accuracies in the order of millimeters can be achieved for the position of an arrhythmia origin with respect to a catheter position. A journal manuscript on this topic is expected to be complete in February 2018.

7.7. Bilayer model

The rigorous proof that mathematically found the bilayer model from S. Labarthe PhD thesis [56] was actually published in SIAM Journal of Applied Math [15]. Based on sophisticated energy estimates, it proves that the bilayer model is the rigorous limit of the underlying three-dimensional model.

7.8. multi-electrode array measurement

In the context of the CardioXComp project, in collaboration with the REO team and the company Notocord, we proposed a strategy to analyze the signals acquired by multi-electrode array (MEA) on cultures of hiPSC-CMs cells with drug compounds, and to automatically deduce the channels affected by the drug. First, in [10], we study how MEA meausrement can be modeled in such a way that the produced in-silico signals are comparable to real ones. The main problems concern the heterogenities of cell cultures. Then, in [20] a method based on parameter identification, by comparing the in-silico and real signals, was used on signals acquired with commercial systems on cell culture with various drugs. The IC-50 and dose-response of several drugs could be assessed. This kind of techniques could contribute to promote the technology based on MEA and hiPSC-CMs.

7.9. High-order integration methods for ion channel models

On November 15, 2017, C. Douanla Lontsi defended his PhD thesis [9] on the numerical analysis of time-stepping methods for the cardiac monodomain equations. A huge amount of work was carried out in the thesis. The thesis builds on the seminal Rush-Larsen technique [62], [57], and the recent novel computational interest in exponential integrator methods. Two new exponential methods of arbitrarily high order are proposed (EABk and RLk). Most notably, Rush-Larsen techniques of order $k = 2, 3, 4$ were entirely explicited. The theory was adapted to analyse these methods and convergence proofs were derived. The complete Dahlquist stability region of these methods was documented. Finally, the methods were integrated into an IMEX strategy to solve the monodomain equation in 1D to 3D problems, with two ionic models (BR and TNNP). The results essentially show that order at least 3 is required to leas to reasonably accurate simulations. Three journal papers were submitted in 2017, [39], [41], [40].

7.10. High-order finite-volume discretizations

Y. Coudière and R. Turpault proposed new simple and efficient high-order finite volume discretizations to be applied to the monodomain equation. They showed how the method can be easily implemented up to the order 6, with very good results, also for simulation of complex propagation patterns. The results were published in [16].

7.11. Identification of multiple space dependent ionic parameters in cardiac electrophysiology modelling

In this paper, we consider the inverse problem of space dependent multiple ionic parameters identification in cardiac electrophysiology modelling from a set of observations. We use the monodomain system known as a state-of-the-art model in cardiac electrophysiology and we consider a general Hodgkin-Huxley formalism to describe the ionic exchanges at the microscopic level. This formalism covers many physiological trans-membrane potential models including those in cardiac electrophysiology. Our main result is the proof of the uniqueness and a Lipschitz stability estimate of ion channels conductance parameters based on some observations on an arbitrary subdomain.

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. CALM

The project "Cardiac Arrhythmia Localization Methods" has been granted by the Région Nouvelle-Aquitaine, with matching from funds held by our clinical collaboraters Dr. Hubert Cochet and Dr. Pierre Jaïs, and from Inria. The purpose of this project is to develop a tool that can predict the exit site of an arrhythmia with moderate accuracy (1 cm) in an absolute sense, with respect to the anatomy of the heart in situ, and with a resolution of about 2 mm in a relative sense, with respect to a nearby pacing site. This tool must fulfill the following criteria:

- it uses only data that are already recorded in the cathlab by other systems: ECG data and electroanatomical mapping data;
- it must work in nearly real-time; catheter displacement advice must be available within 5 seconds after a paced beat;
- it must work automatically, requiring the operator only to indicate which ECG data correspond to the target arrhythmia; and
- it must be safe and easy to operate.

We will in the first place test a number of proposed methods using synthetic data, produced with our realistic models of cardiac electrophysiology and accurate geometric models of different patients. This in-silico testing phase will answer a number of important practical questions. Subsequently we will use offline clinical data, and within 2 years we aim to build a clinical prototype that can be tested (without interfering in the procedure) in the cathlab. In order to work real-time we will initially use very simple methods. However, the clinical prototype and the collectoin of synthetic data that we created will later serve also as a platform to test also more sophisticated inverse methods.

8.1.2. EXACARD

We started a collaboration with the STORM team at Inria Bordeaux Sud-Ouest to work on further scaling of the Propag code, to push the limit from about 10^4 to 10^6 parallel processors. A pre-proposal has been submitted to the ANR, and we are doing preparatory work.

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 lasted until November 2017.

This international project involved 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 MITOCARD

The MITOCARD project (Electrophysiology of Cardiac Mitochondria), coordinated by S. Arbault (Université de Bordeaux, ISM), was granted by the ANR in July 2017. The objective of MITOCARD is to improve understanding of cardiac physiology by integrating the mitochondrial properties of cell signaling in the comprehensive view of cardiac energetics and rhythm pathologies. It was recently demonstrated that in the heart, in striking contrast with skeletal muscle, a parallel activation by calcium of mitochondria and myofibrils occurs during contraction, which indicates that mitochondria actively participate in Ca2+ signaling in the cardiomyocyte. We hypothesize that the mitochondrial permeability transition pore (mPTP), by rhythmically depolarizing inner mitochondrial membrane, plays a crucial role in mitochondrial Ca2+ regulation and, as a result, of cardiomyocyte Ca2+ homeostasis. Moreover, mitochondrial reactive oxygen species (ROS) may play a key role in the regulation of the mPTP by sensing mitochondrial energetics balance. Consequently, a deeper understanding of mitochondrial electrophysiology is mandatory to decipher their exact role in the heart's excitation-contraction coupling processes. However, this is currently prevented by the absence of adequate methodological tools (lack of sensitivity or selectivity, time resolution, averaged responses of numerous biological entities). The MITOCARD project will solve that issue by developing analytical tools and biophysical approaches to monitor kinetically and quantitatively the Ca2+ handling by isolated mitochondria in the cardiomyocyte.

MITOCARD is a multi-disciplinary project involving 4 partners of different scientific fields: the CARMEN team as well as

ISM, the largest chemistry laboratory of the Université de Bordeaux, where the necessary measurement methods will be developed;

Liryc, where mitochondria are studied at all levels of integration from the isolated mitochondrion to the intact heart; and

LAAS, the MiCrosystèmes d'Analyse (MICA) group at the Laboratory of Analysis and Architecture of Systems, which develops the biological microsensors for this project.

The project will

- develop chips integrating 4 different electrochemical microsensors to monitor in real-time key mitochondrial signaling parameters: Ca2+, membrane potential, quinone reduction status, O2 consumption, and ROS production;
- develop microwell arrays integrating ring nanoelectrodes to trap single mitochondria within micrometric chambers and measure locally by combined fluorescence microscopy and electrochemical techniques intra- (by fluorescence) and extra-mitochondrial (electrochemistry) metabolites; and
- develop a mathematical model of mitochondrial Ca2+ and ROS handling built on existing knowledge, new hypotheses, and the measured data.

The model may serve both to assess biological assumptions on the role of mitochondria in Ca2+ signaling and to integrate pathological data and provide clues for their global understanding.

8.2.3. 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 September 2017, has been granted 9 million core-hours on the three major systems Curie, Occigen, and Turing. This compute time is primarily destined for our research into the interaction between ionic and structural heart disease in atrial fibrillation, Brugada syndrome, and early repolarisation syndrome [7] [61].

8.3. European Initiatives

8.3.1. FP7 & H2020 Projects

We participated in two H2020 Research and Innovation Action proposals.

8.3.2. Collaborations in European Programs, Except FP7 & H2020

We coordinated a proposal with 5 European partners. The proposal could not be submitted due to administrative problems related to one of the partners, but we will benefit from the existing consortium to submit a new proposal in April 2018.

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 in Bordeaux headed by Professor Michel Haïssaguerre. We would like to non-invasively construct the electrical potential on the heart surface only from measurements of the electrical potential on the the chest of the patient.

This helps the medical doctor to visualise an image of the electrical potential of the heart of the patient. It is known 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 works in the literature have been carried out in order to solve this Cauchy problem, but have never been used for solving the ECGI problem. Our goal from the associate team is to develop an experimental platform allowing to test various methods and compare their performance on real life experimental data.

8.4.2. Inria International Partners

8.4.2.1. Informal International Partners

Y. Coudière works with the group of Prof. Y. Bourgault from the Department of Mathematics and Statistics of the University of Ottawa (Canada). Some results on the numerical analysis of time-stepping methods from C. Douanla's PhD were carried out together, as well as some theoretical results on parameter identification in the PhD of A. Gérard.

M. Potse and O. Bernus (Liryc) work with the group of Prof. A. Panfilov in Ghent, Belgium, on simulation and analysis of complex reentrant arrhythmia.

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 [51]. The Maastricht group was partially funded by the FP7 project EUTRAF and our simulations were supported by GENCI (section 8.2.3).

M. Potse set up a project and recruited a PhD student to co-direct with Dr. Esther Pueyo of the University of Zaragoza, within the context of the H2020 International Training Network "Personalised In-silico Cardiology" (PIC), coordinated by Dr. Pablo Lamata of King's College London.

N. Zemzemi works with Cesare Corrado at King's College London on the development of new eikonal models allowing conduction velocity adaptation [14].

N. Zemzemi collaborated with Jesús Requena-Carrión from the Queen Mary University of London to study the effects of the spatial resolution of electrode systems on the spectrum of cardiac signals in cardiac electrocardiography [12].

N. Zemzemi worked with R. Aboulaich group from Mohamed V university in Morocco on sensitivity of the electrocardiographic problem to multiple independent sources of uncertainty including noise in the measurements and the heterogenity in the torso [34].

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Organisation

9.1.1.1. General Chair, Scientific Chair

Y. Coudière co-organised the Workshop on Mathematical Methods in Cardiac Electrophysiology, November 4–6, 2017, at the University of Ottawa in Canada. Approximately 30 scientists from the US, Canada, and several European countries participated in this workshop.

9.1.2. Scientific Events Selection

9.1.2.1. Member of the Conference Program Committees

Y. Coudière was a program committee member for the Functional Imaging and Modeling of the Heart (FIMH) meeting 2017 in Toronto, Canada.

M. Potse is a track chair for the International Congress of Cardiology 2018 in Chiba, Japan.

9.1.2.2. Reviewer

Y. Coudière and M. Potse reviewed abstracts for the Computing in Cardiology meeting in Rennes, September 2017.

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

L. Weynans: Computers and Fluids, Multiscale Modeling and Simulation

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, Mathematical Modelling of Natural phenomena.

9.1.4. Invited Talks

N. Zemzemi: Problèmes directs et inverses en electrophysiologie cardiaque. Séminaire du Laboratoire de mathématiques à Université de Technologie de Compiègne. November 14th 2017.

P.-E. Bécue: A Three-Dimensional Computational Model of Action Potential Propagation Through a Network of Individual Cells. *Workshop on Mathematical Methods in Cardiac Electrophysiology*. University of Ottawa, Ottawa, Canada, November 2017. http://www.fields.utoronto.ca/activities/17-18/electrophysiology

A. Davidovic: Modified bidomain model addressing structural heterogeneities. Application to the rat heart ventricles using HR MRI. *Workshop on Mathematical Methods in Cardiac Electrophysiology*. University of Ottawa, Ottawa, Canada, November 2017.

A. Gérard: Data assimilation applied to electroanatomical mapping in a bilayer atrial model. *Workshop on Mathematical Methods in Cardiac Electrophysiology*. University of Ottawa, Ottawa, Canada, November 2017.

M. Potse: Chaos, order, and numerical errors in a large-scale atrial fibrillation model. *Workshop on Mathematical Methods in Cardiac Electrophysiology*. University of Ottawa, Ottawa, Canada, November 2017.

M. Potse: Patient-specific modeling to understand cardiac disease. *BCAM Workshop Quantitative Biomedicine for Health and Disease*. Basque Center for Applied Mathematics, Bilbao, Spain, 21 February 2017.

Y. Coudière: Modélisation d'hétérogénéités de la structure myocardique. GRD Mamovi. Lyon, 27 September 2017.

Y. Coudière: High-order finite volume scheme for cardiac electrophysiology, invited talk for the workshop *Schémas volumes finis*, Nice, 30-31 March 2017, http://math.unice.fr/~krell/Colloque/index.php

9.1.5. Leadership within the Scientific Community

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

9.1.6. Research Administration

L. Weynans: member of the "Conseil du département Sciences et Technologies" of Bordeaux University.

Y. Coudière:

- Scientific responsibility 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.

M. Leguèbe: co-organization of team "Calcul Scientifique et Modélisation" seminar.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Licence : Y. Coudière, Groupe de Travail Applicatif, 33h,L2, Université de Bordeaux, France

Master : Y. Coudière, Méthodes d'éléments finis pour la mécanique des fluides incompressibles, 33h, M2, Université de Bordeaux, France.

Licence : Y. Coudière, Projet multidisciplinaire Matmeca, 33h, L2, Université de Bordeaux, France.

Licence : M. Bendahmane, Mathématiques générales, 36h, L1, Université de Bordeaux, France

Licence : M. Bendahmane, Algèbre Linéaire, 46h, L2, Université de Bordeaux, France

Licence : M. Bendahmane, Fonctions de plusieurs variables et optimisation, 33h, L2, Université de Bordeaux, France

Licence : M. Bendahmane, Analyse appliquée, 33h, L1, Université de Bordeaux, France

Licence : M. Bendahmane, Séries et intégrales multiples, 33h, L1, Université de Bordeaux, France

Master : M. Bendahmane, Analyse appliquée, 33h, M2, Université de Bordeaux, France

Licence : L. Weynans, Fortran MMk, 20h, L1, Université de Bordeaux, France

Master : L. Weynans, Fortran MMk, 28h, M1, Université de Bordeaux, France

Licence : L. Weynans, Introduction Analyse Numérique, 24h, L3, Université de Bordeaux, France

Licence : L. Weynans, Cours Programmation avancée pour le calcul scientifique, 24h, L3, Université de Bordeaux, France

Licence : L. Weynans, TP Programmation avancée pour le calcul scientifique, 34h, L3, Université de Bordeaux, France

Licence : L. Weynans, encadrement de projets 1ère année Matmeca, 25h, L1, Université de Bordeaux, France

Y. Coudière is responsible for the program "Ingénierie mathématique" in the Mathematics Bachelor, and responsible for the program "Modélisation Numérique et Calcul Haute Performance" in the Master program Applied Mathematics and Statistics, at the Université de Bordeaux.

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: 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: 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: A. Gérard, “Modèles numériques personnalisés de la fibrillation auriculaire,” started 1 September 2015, supervised by Y. Coudière.

PhD in progress: B. Lambert, “Modélisation et simulation numérique de suspensions de particules dans un fluide,” started 1 October 2015, supervised by M. Bergmann and L. Weynans.

PhD : N. Fikal, “Quantification d’incertitudes en électrocardiographie par la méthode éléments finis stochastique,” Université de Mohamed V au Maroc, 21 July 2017, supervised by R. Aboulaich and N. Zemzemi.

PhD : W. Mbarki, “Modélisation et analyse d’un problème d’interaction en biomathématiques : couplage en électrophysiologie cardiaque,” Université de Tunis El Manar, 28 July 2017, supervised by S. Aouadi and N. Zemzemi.

PhD in progress : Y. Abidi, “Etude théorique et numérique de problème d’identification de paramètres en électrophysiologie cardiaque”. Université de Tunis El Manar, started in October 2015, supervised by M. Bellassoued and M. Mahjoub in Tunis and N. Zemzemi in Bordeaux.

9.2.3. Juries

L. Weynans: PhD comittee of Isabelle Lagrange (Onera, Toulouse), “comité de sélection” at Pau University

Y. Coudière: reviewer for the HDR Thesis of C. Le Potier (Construction et développement de nouveaux schémas pour des problèmes elliptiques et paraboliques), defended 15 november 2017.

Y. Coudière: reviewer for the HDR Thesis of E. Vigmond, defended January 10, 2017.

Y. Coudière: jury member for the PhD defense of Rémi Tesson, Université Marseille-Provence, defended December 12th, 2017.

9.3. Popularization

L. Weynans:

- Responsible for the communication (*Chargé de communication*) of the IMB
- Organization of the day “Filles et Maths, une équation lumineuse”
- Several presentations for high-school students about scientific computing

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Major publications by the team in recent years

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