IN PARTNERSHIP WITH:
Université de Bordeaux

Activity Report 2018

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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1. Team, Visitors, External Collaborators

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Nejib Zemzemi [Inria, Researcher]
Mark Potse [Inria, Advanced Research Position]

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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 [54] and on the data available at IHU LIRYC:

- Enrichment of the current monodomain and bidomain models [54], [63] 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 [56] and sudden-cardiac-death (SCD) syndromes [7], [6] [59]. 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.

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 our numerical simulations to be efficient, accurate, and reliable with respect to the needs of the medical community. 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 Krylov solvers. New developments include high-order explicit integration methods and task-based dynamic parallelism.

3.4. Cardiac Electrophysiology at the Microscopic Scale

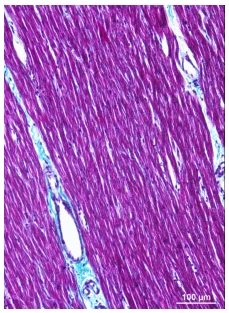
Numerical models of whole-heart physiology are based on the approximation of a perfect muscle using homogenisation methods. However, due to aging and cardiomyopathies, the cellular structure of the tissue changes. These modifications can give rise to life-threatening arrhythmias. For our research on 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.

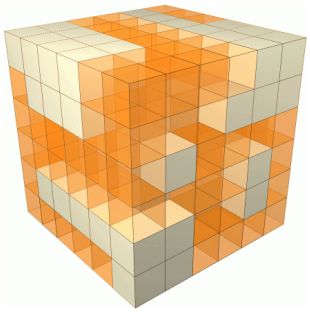
The literature on this type of model is still very limited [67]. Existing models are two-dimensional [60] or limited to idealized geometries, and use a linear (purely resistive) behaviour of the gap-juction channels that connect the cells. We propose a three-dimensional approach using realistic cellular 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) [52], [51], [50]. P-E. Bécue defended his PhD thesis on this topic in December 2018.

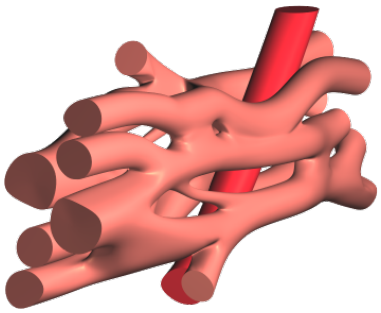
4. Application Domains

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 [58], [57], [47]. 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 [31], 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 [34] [56]. These heterogeneities ara 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, which is supposed to play a major role in sudden cardiac death, and (2) modeling the heteogeneities related to the complex organization and disorganization of the myocytes and fibroblasts, which 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 arrhythmia 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 [40].

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. New Software and Platforms

5.1. CEPS

Cardiac ElectroPhysiology Simulation
KEYWORDS: Simulation - Health - Mesh - Cardiac - 3D - 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 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, Nejib Zemzemi, Antoine Gerard, Charlie Douanla Lontsi, Pierre-Elliott Bécue, Marc Fuentes and Yves Coudière
- Partners: Université de Bordeaux - Fondation Bordeaux Université - CHU de Bordeaux - Inria
- Contact: Yves Coudière
- URL: https://gforge.inria.fr/projects/ceps/

5.2. Platforms

5.2.1. 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 2017 the code was collected in an archive on Inria's GitLab platform, and a public website was created for documentation (http://cempack.gforge.inria.fr). The main components of CEMPACK are the following.

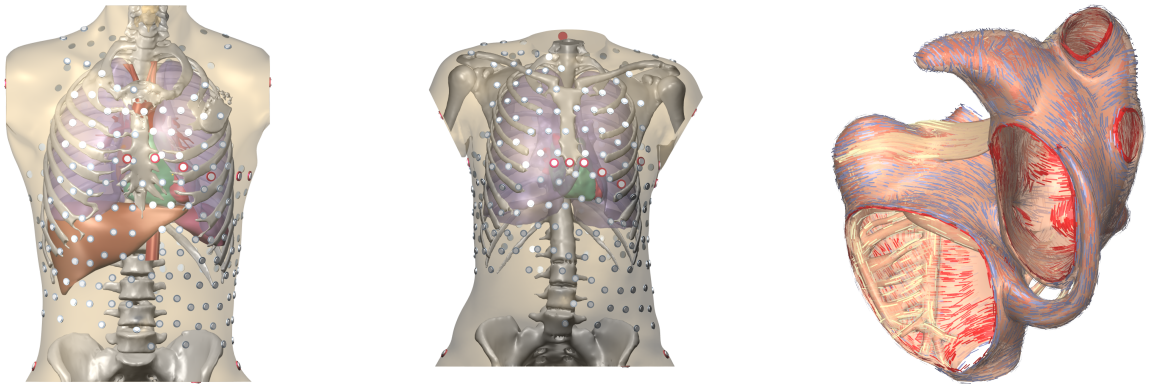
Propag-5.1 Applied modeling studies performed by the Carmen team in collaboration with IHU Liryc and foreign partners [7] [65], [56], [55], [53] rely on high-performance computations on the national supercomputers Irene, Occigen, and Turing. The Propag-5 code is optimized for these systems. It is the 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 [27]. 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. 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 [64]. 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 measured and simulated data. It uses the MMG remeshing library, which is developed by the CARDAMOM team at Inria Bordeaux.



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.*

5.2.2. 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.

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

6. New Results

6.1. Exponential Adams Bashforth integrators for cardiac electrophysiology simulations

Models in cardiac electrophysiology are coupled systems of reaction-diffusion PDEs and ODEs. The ODE system displays a very stiff behavior. It is nonlinear and its upgrade at each time step has a high computational cost. A solution that we propose is to develop high-order explicit and stable integration methods. In an article published in 2018 [17] we investigated the use of exponential Adams Bashforth (EAB) integrators in cardiac electrophysiology. The paper demonstrates stability under perturbation (or 0-stability) and provides a new approach for the convergence analysis of the method. The Dahlquist stability properties of the method were also tested in a new framework that incorporates the discrepancy between the stabilizer and the system Jacobian matrix. Provided this discrepancy is small enough, the method was shown to be A(alpha)-stable. This result is interesting for an explicit time-stepping method. Numerical experiments were performed for two classes of stiff models in cardiac electrophysiology. The EAB method was observed to be as stable as implicit solvers and cheaper at the same level of accuracy.

6.2. Inverse models for identification of cellular ionic parameters from macroscopic signals

Traditional inverse models in cardiac electrophysiology have aimed at identifying the activation (and relaxation) order of the cardiac muscle from body surface potentials. However, many cardiac anomalies cannot be reduced to such simple parameters. Underlying the activation and “repolarization” of the cells is a complex interplay of different ion channels, each with its own dynamics. Genetic and other abnormalities express themselves in one or more of these channels. We have therefore taken several initiatives to identify the properties of the channels themselves.

Measurements with micro-electrodes can capture currents generated by a handful of cultured cells. Together with the REO team at the Inria center in Paris we have developed methods to identify properties of individual ionic currents from such measurements [28], [10].

On the level of the whole heart, two studies have attempted to identify cellular properties from surface electrocardiogram (ECG) signals [29], [11]. Ravon et al. have previously developed a method that identifies activation times as well as repolarization properties of a simplified ionic model (the Mitchell-Schaeffer model) [66], but considering only the outer surface of the heart muscle. We now evaluated the capability of this method to distinguish properties of the inner and outer surfaces, which are expected to differ importantly [29]. This turned out to be extremely challenging. Abidi et al. [11], on the other hand, demonstrated that the solution to such problems is unique even for intermediately complex ionic models such as the Beeler-Reuter [46] and Luo-Rudy I [61] models.

Thus, we found that a unique solution exists but is very hard to find in practical situations. This result suggests that further work should aim at removing confounding factors such as limitations in the volume conductor models.

6.3. Cellular and sub-cellular models

The electrical activation of the heart relies on rapid propagation of activation impulses through intercellular connections. Cardiac arrhythmia are often due to damage to these intercellular connections. In various pathologies, loss of individual connections can lead to the formation of a complicated maze in which very slow propagation is possible, leading to reentrant arrhythmias. To investigate such phenomena, the PhD thesis work of P.-E. Bécue was dedicated to the development of a three-dimensional model of the cardiac tissue with sub-cellular resolution [31], [50], [51], [52], [49]. This work builds on our CEPS software, which was specifically extended for this purpose.

Aouadi et al. have specifically developed a model for the connections between the network of cardiac Purkinje fibers and the working myocardium [13] [45]. It handles the myocardium with a standard bidomain model and the Purkinje network, which consists of discrete bundles, with a one-dimensional monodomain model.

On an even smaller scale, the team also worked on a three-dimensional model of calcium release from intracellular organelles and its diffusion inside the cell [42].

6.4. Highly scalable ECG simulation with electrocardiographic lead fields

Currently a monodomain reaction-diffusion model is a well-established method to simulate the electrical activity of the heart [62], [63], even more so because it can be adapted to approximate a bidomain model very closely [48], [54]. 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 fundamental solutions that express the ECG potential as an integral over a field of electric current dipoles. A paper published in 2018 has shown that this method gives a huge scaling advantage on highly parallel computers [27]. This result is also of practical importance for our applied work.

7. Partnerships and Cooperations

7.1. Regional Initiatives

7.1.1. PhD thesis O. Bouhamama

L. Weynans and L. Bear (Liryc) obtained funding for a PhD thesis from the Université de Bordeaux, for a project titled "Méthodes numériques pour la résolution du problème inverse en électrocardiographie dans le cas d'anomalies structurelles du tissu cardiaque." Candidate O. Bouhamama started in October 2018.

7.1.2. CALM

The project "Cardiac Arrhythmia Localization Methods," granted by the Région Nouvelle-Aquitaine, with matching from funds held by our clinical collaboraters H. Cochet and P. Jaïs, has started. 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.

7.2. National Initiatives

7.2.1. ANR 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 proposal for this project was funded this year by ANR. It allows a postdoc to be employed for 2 years.

7.2.2. 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.

7.2.3. 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 2018, has been granted 8 million core-hours on the three major systems Irene, 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] [65], and for new HPC developments [27].

7.3. European Initiatives

7.3.1. Collaborations with Major European Organizations

BCAM (Basque Center for Applied Mathematics), Bilbao, Spain: L. Gerardo-Giorda.

We develop surrogate models of Radiofrequency Catheter Ablation for machine learning purposes, with the ambition to provide real-time estimations of lesion depths to clinicians (M. Leguèbe, Y. Coudière).

7.4. International Initiatives

7.4.1. Inria International Labs

International Laboratory for Research in Computer Science and Applied Mathematics

Associate Team involved in the International Lab:

7.4.1.1. EPICARD

Title: inversE Problems In CARDiac electrophysiology

International Partner (Institution - Laboratory - Researcher):

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

Start year: 2018

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

Model personalization is a very challenging question in the numerical modeling community, especially for medical applications like cardiac electrophysiology. Our main idea is to adapt the input data like model parameters and boundary conditions of the electrophysiological measurements. There are two mathematical problems raising from this challenge. The first issue is the identifiability of the parameters and the sensitivity of the identification problem to the measured data. The question is: For given measurements, could we prove that there exist a set of parameters that allows to fit these measurements? The second issue is, how can we estimate parameters, when they are identifiable,? Our idea is to provide a theoretical analysis for the identification of each of the parameters and to construct suitable numerical methods to estimate them.

7.4.2. Inria International Partners

7.4.2.1. 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 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 [56]. The Maastricht group was partially funded by the FP7 project EUTRAF and our simulations were supported by GENCI (section 7.2.3).

N. Zemzemi works with Cesare Corrado at King's College London on the development of new eikonal models allowing conduction velocity adaptation [16].

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific Events Selection

8.1.1.1. Chair of Conference Program Committees

N. Zemzemi organized a mini-symposium "inverse problems in cardiac electrophysiology" at the PICOF conference (Inverse Problems, Control and Shape Optimization conference), which was held at the American University of Beirut, Lebanon, June 18–20, 2018.

8.1.1.2. Member of the Conference Program Committees

M. Potse: track chair (modeling) for *International Congress of Electrocardiology*, Chiba, Japan, June 2018.

8.1.1.3. Reviewer

M. Potse, Y. Coudière: reviewers for *Computing in Cardiology*, Maastricht, The Netherlands, September 2018.

8.1.2. Journal

8.1.2.1. Member of the Editorial Boards

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

M. Potse: section editor (Electrocardiology and Computing), *Journal of Electrocardiology*.

8.1.2.2. Reviewer - Reviewing Activities

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

M. Potse: Heart Rhythm, Medical & Biological Engineering & Computing, Journal of Electrocardiology, Frontiers in Computational Physiology and Medicine, Mathematical Biosciences, American Journal of Physiology.

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.

M. Bendahmane: Afrika Matematika, Journal of Computational and Applied Mathematics, Journal of Theoretical Biology.

8.1.3. Invited Talks

L. Weynans. “Local Lubrication Model for Ellipsoidal Particles within an Incompressible Navier-Stokes Flow.” Pre-meeting of the Fifth International Workshop on Modeling, Analysis, Simulations, and Applications of Inter-Facial Dynamics and FSI Problems (IMA-FSI), Chinese Academy of Sciences, Bejing.

L. Weynans. “Super-convergence of the gradient for the Shortley-Weller method.” Fifth International Workshop on Modeling, Analysis, Simulations, and Applications of Inter-Facial Dynamics and FSI Problems (IMA-FSI), Chinese Academy of Sciences, Sanya, China, June 2018

M. Bendahmane, “Mathematical analysis and numerical simulation of optimal control in cardiac models.” ENSA d’Essaouira, Université Cadi Ayyad, Morocco, April 2018.

M. Bendahmane, “Recent progress on Inverse problems in Electrocardiology.” Université Cadi Ayyad, Morocco, December 2018.

M. Potse, “The lead field: modern applications of a classic.” International Congress of Electrocardiology, Chiba, Japan, june 2018.

Y. Coudière, “Modeling the propagation of cardiac action potential in hearts with structural heterogeneities.” 18ème Journée “Calcul scientifique et modélisation mathématique” aux journées scientifiques de l’Université d’Amiens, https://www.u-picardie.fr/recherche/presentation/actualites/18eme-journee-calcul-scientifique-et-modelisation-mathematique–514070.kjsp

Y. Coudière, “Modeling the propagation of cardiac action potential in hearts with structural heterogeneities.” INdAM Workshop “Mathematical and Numerical Modeling of the Cardiovascular System,” Roma, April 16–19, 2018 Istituto Nazionale di Alta Matematica (INdAM) http://www-dimat.unipv.it/workshoproma/

Y. Coudière, “Modeling the propagation of cardiac action potential in hearts with structural heterogeneities.” QBIO2018 – Quantitative Biomedicine in Health and Disease, Bilbao, February 28th-March 1st, 2018. https://wp.bcamath.org/qbio/

Y. Coudière, “Simulation numérique en électrocardiologie.” 2ième Edition “Rencontre Santé Civilo-Militaire du Sud-Ouest,” 27 March 2018. https://sante.u-bordeaux.fr/Actualites/2eme-Edition-Rencontre-Sante-Civilo-Militaire-du-Sud-Ouest

N. Zemzemi gave a talk "Inverse problems in cardiac electrophysiology" at the LIRIMA evaluation seminar 18 and 19 september 2018,

8.1.4. Leadership within the Scientific Community

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

Y. Coudière: committee member HCERES for the evaluation of the UMMISCO lab (http://www.ummisco.fr/) 27–28 February, 2018.

Y. Coudière: recruitment committee ATER, IUT de Bordeaux, May 2018

Y. Coudière: special recruitment committee for a permanent contract (LRU) for J. Bayer.

L. Weynans: local correspondent for SMAI.

N. Zemzemi: recruitment committee of permanent research scientists at Inria Bordeaux Sud-Ouest 2018.

8.1.5. 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.

N. Zemzemi: Administration of the Inria associated team Epicard.

M. Leguèbe: co-organization of team “Calcul Scientifique et Modélisation” seminar (IMB, Université de Bordeaux).

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

A. Karaoui, Initiation à l’informatique, 34h, L1 Université de Bordeaux, France

A. Gérard, TD Analyse Numérique, 48h, ENSEIRB-Matmeca, Bordeaux, France

A. Gérard, Équations différentielles, 20h, ENSEIRB-Matmeca, Bordeaux, France

A. Gérard, TP Programming in C++, 48h, ENSEIRB-Matmeca, Bordeaux, France

M. Leguèbe, Utilisation de plateforme industrielle pour le calcul intensif, 16h, M1, Université de Bordeaux, France

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

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

L. Weynans, Linear Algebra, L1, Université de Bordeaux, France

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

L. Weynans, TD approximation of partial differential equations, M1, Université de Bordeaux, France

L. Weynans, integration and rational fractions, 1st year prepa INP

N. Zemzemi, Optimisation et statistiques, 80h, ESSCA Bordeaux, France

N. Zemzemi, Computational modeling in medicine, 8h, PhD, Université de Bordeaux, France

N. Zemzemi, Modelling and numerical methods in cardiac electrophysiology, 14h, doctoral school, department of mathematics Puebla, Mexico,

M. Bendahmane, Algèbre Linéaire, CM/TD 36h, L2, Université de Bordeaux, France

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

M. Bendahmane, Neurosciences computationnelles applications à l'ingénierie, CM/TD 30h, M2, Université de Bordeaux, France

M. Bendahmane, Séries et intégrales multiples, CM 27h, L2, Université de Bordeaux, France

M. Bendahmane, Séries et intégrales multiples, TD 25h, L2, Université de Bordeaux, France

M. Bendahmane, Mise à niveau L2, TD, 12h L2, Université de Bordeaux, France

M. Bendahmane, Neuropsychologie et Psychophysiologie, CM 7h L3, Université de Bordeaux, France

M. Bendahmane, Neuropsychologie et Psychophysiologie, TD 8h L3, Université de Bordeaux, France

Y. Coudière, GTA, 12h, L3, Université de Bordeaux, France

Y. Coudière, utilisation de plateforme de calcul intensif, 28h, M1, Université de Bordeaux, France

Y. Coudière, Éléments finis avancés, 36h, M2, Université de Bordeaux, France

Y. Coudière, Projets longs, 20h, INP-MATH

Y. Coudière, Enseignement scientifique Médecine, 4h, L2, Université de Bordeaux, France

Y. Coudière, responsible for Licence and Masters teaching at the Mathematics department, Université de Bordeaux, France

8.2.2. Supervision

PhD thesis, P-E. Bécue, "Modélisation et simulation de l'électrophysiologie cardiaque à l'échelle microscopique." Université de Bordeaux, 5 December 2018, supervised by Y. Coudière.

8.2.3. Juries

Y. Coudière: jury member for HDR, L. Weynans, "Prise en compte précise de géométries complexes pour l'approximation d'EDP sur grilles cartésiennes et leur simulation en calcul parallèle," Université de Bordeaux, 4 December 2018.

L. Weynans, M. Potse: jury members for PhD thesis of P-E. Bécue, "Modélisation et simulation de l'électrophysiologie cardiaque à l'échelle microscopique." Université de Bordeaux, 5 December 2018, supervised by Y. Coudière.

Y. Coudière, jury member (rapporteur) for the PhD thesis of S. Corre, Insa de Rennes, 19 October 2018.

8.3. Popularization

8.3.1. Internal or external Inria responsibilities

- L. Weynans is responsible for the communication (*Chargé de communication*) of the IMB
- Exhibit at the open days on the occasion of the 10-years anniversary of the Inria center Bordeaux Sud-Ouest.

8.3.2. Interventions

L. Weynans:

- Organization of the day "Filles et Maths, une équation lumineuse"
- Several presentations for high-school students about scientific computing

9. Bibliography

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