IN PARTNERSHIP WITH:
Université de Bordeaux

Activity Report 2019

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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Project-Team CARMEN

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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Yves Bourgault [University of Ottawa, Jun 2019]
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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 [56] and on the data available at IHU LIRYC:

- Enrichment of the current monodomain and bidomain models [56], [67] 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 [60] and sudden-cardiac-death (SCD) syndromes [7], [6] [64]. 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

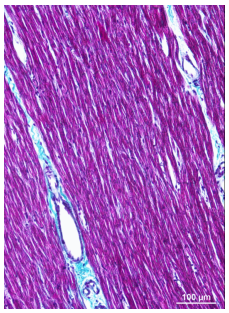
Numerical models of whole-heart physiology are based on the approximation of a perfect muscle using homogenisation methods. However, due to aging and cardiomyopathies, the cellular structure of the tissue changes. These modifications can give rise to life-threatening arrhythmias. For our research on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

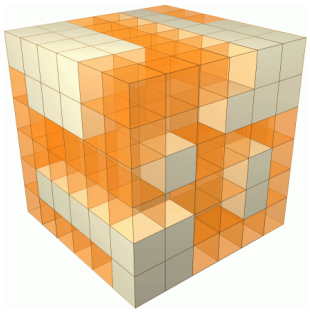
The literature on this type of model is still very limited [74]. Existing models are two-dimensional [65] or limited to idealized geometries, and use a linear (purely resistive) behaviour of the gap-juction channels that connect the cells. We propose a three-dimensional approach using realistic cellular 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], [49]. P-E. Bécue defended his PhD thesis on this topic in December 2018.

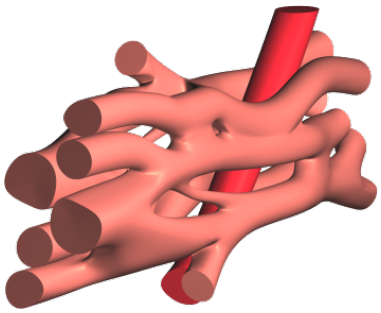
4. Application Domains

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 [63], [61], [48]. 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 [50], 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 [69] [60]. 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 [66].

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

Mark Potse has been recruited on a permanent position researcher at Bordeaux University.

The team has been involved in the organization of the 10th international conference on Functional Imaging and Modeling of the Heart (FIMH), that was held at Bordeaux in July 2019.

The Direction Generale de l'offre de soins (DGOS) has accepted to found the clinical project of phase III Parkeo2 In this project 11 hospitals in France will use the software OptimDBS for the planification of deep cerebral surgery. The project will start in October 2020 and will last three years.

6. New Software and Platforms

6.1. 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 modular high-performance computing software for performing numerical simulations in cardiac electrophysiology. It is based on modules : - management of geometries represented by meshes in 3D, 2D or 1D (volumes, surfaces, trees), - model simulation of cellular electrophysiology, - calculating the tissue propagation of the action potentials in the cardiac geometries, - calculation of extracardiac potentials, - time approximation methods in order 2, 3 and 4 specific to electrocardiography.

- Participants: Mehdi Juhoor, Nejib Zemzemi, Antoine Gerard, Charlie Douanla Lontsi, Pierre-Elliott Bécue, Marc Fuentes, Yves Coudière, Michael Leguebe, Andjela Davidovic, Pauline Migerditichan and Florian Caro
- Partners: Université de Bordeaux - Fondation Bordeaux Université - CHU de Bordeaux - Inria
- Contact: Michael Leguebe
- URL: https://gforge.inria.fr/projects/ceps/

6.2. OptimDBS

Optimizing the Deep Brain Stimulation

KEYWORDS: Image analysis - Deep brain stimulation - Statistical learning

FUNCTIONAL DESCRIPTION: Targeting software for deep brain stimulation

- Participants: Nejib Zemzemi, Louise-Amelie Schmitt, Emmanuel Cuny and Julien Engelhardt
- Partner: CHU de Bordeaux
- Contact: Nejib Zemzemi
- URL: https://gitlab.inria.fr/optimdbs/optimdbs-medinria/-/wikis/home

6.3. Platforms

6.3.1. 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.

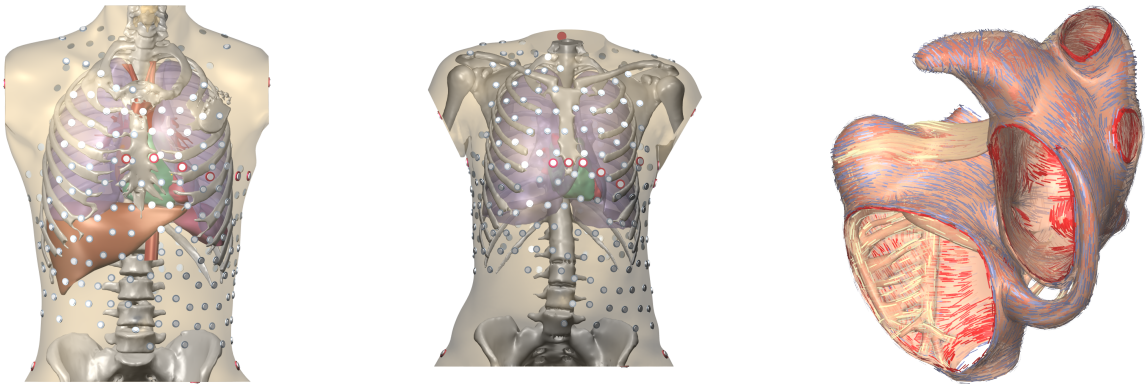
Propag-5.1 Applied modeling studies performed by the Carmen team in collaboration with IHU Liryc and foreign partners [7] [71], [60], [57], [53] rely on high-performance computations on the national supercomputers Irene, Occigen, and Turing. The Propag-5 code is optimized for these systems. It is the 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 [72]. 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 [68]. 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.*

6.3.2. 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.

7. New Results

7.1. Modelling, direct simulation and prediction of cardiac phenomena

Using high-performance simulations on a detailed model of the human atria [58] we investigated several aspects of atrial fibrillation (AF). We showed that AF initiation by rapid pacing is sensitive to very small changes in parameter values [70] [32], [38] , and investigated effects of antiarrhythmic drugs and interventions [59] [34] and pathologies [35]. An example movie is available online at https://www.potse.nl/papers/potse/potse-fimh19.html.

High-performance simulations of human ventricular activity have contributed to the testing of new electrocardiographic mapping methods (“inverse models”) [73], [36].

We are also developing new methods to help with the treatment of these patients by rapidly guiding an ablation catheter to the origin (strictly speaking: the exit site) of an arrhythmia. These methods are also being tested with simulated data. [33].

We contributed to work by Prof. Michel Haissaguerre and his team in which it is argued that many patients who are now believed to suffer from abnormalities in the genes for specific cardiac ion channels are in reality affected by structural diseases of the heart muscle [62] [26], [41]. These influential publications represent an important change in thinking about these patients and their treatment.

Simple mitochondrial model based on thermodynamic fluxes (PhD work of B. Tarraf): Mitochondria are involved in the regulation of calcium which plays a crucial role in the propagation of cardiac action potentials. However, they are not taken into account in the ionic models that are used to perform simulations at the tissue level. In the framework of the ANR MITOCARD project, we wrote a simple model of mitochondrial calcium regulation based on an extensive review of models of the litterature, which are not suited for further calibration due to their excessive complexity [39]. Now that the equations are written down, we are performing a parameter analysis on the whole model before including other key biological mechanisms.

In a collaboration with Jeremy Darde (IMT Toulouse), we have developed a numerical method on a cartesian grid to solve the direct problem of Electrical Impedance Tomography (EIT) in complex geometries, with first-order convergence. The objective is to solve then the inverse problem of EIT to identify heterogeneities of conductivities on the torso volume.

7.2. Inverse problems: parameter estimation, data assimilation and ECGi

- Data assimilation: In A. Gérard PhD thesis, it is showed that accounting for the anisotropy in the atria is crucial to reconstruct correctly activation maps compatible with a mono-domain model from sparse punctuals activation times. To this purpose, we have developed a new data assimilation method for the mono-domain model, using a Luenberger filter and a Kalman-type filter (ROUKF), based on the dissimilarity measure introduced in A. Collin PhD thesis.
- Parameter estimation: We have been working on the following theoretical question: What are the condition under which the parameters, in the mathematical codomain and bidomain models, are identifiables. Then we proposed an algorithm capable of estimating different ion-channels conductance parameters. mettre ref?
- ECGI: Several approaches have been investigated to improve the resolution of ECGi.
  - development of a new algorithm to choose the regularization coefficient for the resolution of ECGi with the Method of Fondamental Solutions (MFS).
  - a study using a parametrized model of action potentials, showing that accounting for the endocardium can improve the resolution of ECGi.
  - in joint work with Laura Bear (IHU Liryc), development of a new method for improving the resolution of ECGI by combining several solutions obtained with various numerical methods (FEM and MFS). The method is based on the selection of the smallest residuals on the torso surface.
  - Development of new methods for the ECGI problem, based on machine learning methods. The idea is to learn activation maps from body surface signals.
  - collaborative work on the set up of an experimental platform for the experimental non-invasive validation of the reconstruction of cardiac signals

7.3. Numerical schemes

- Very-high order Finite Volume methods: We have showed the very good behavior of a specifically devised domain decomposition technique: the communications are minimized without impacting the accuracy or the order of convergence of the scheme. The total amount of communications dos not increase significantly between the second and the 6th order. The 6th-order Finite-Volume scheme is thus the most performing scheme.
- Numerical analysis of a cartesian method for elliptic problems with immersed interfaces: We have studied the convergence of a cartesian method for elliptic problems with immersed interfaces previously published [54]. The convergence is proved for the original second-order method in one-dimension and for a first-order version in two dimensions. The proof uses a discrete maximum principle to obtain estimates of the coefficients of the inverse matrix.

7.4. Miscellanous

- Refactoring of the CEPS software. Our CEPS software underwent an important refactoring phase so that future students spend less time getting hands on the code. Also, several features developped by previous PhD students were merged into the version that we intend to distribute : high order numerical schemes suited for ionic models, volume fraction due to tissue heterogeneities. We are currently in the process of licensing with Inria and University of Bordeaux.
- Deep brain stimulation procedure: We have been working on three different learning methods for the prediction of the optimal pacing sites in the Deep brain stimulation procedure. We also compared the found position to the position of the stimulation sites to the anatomical geometries in the Ewert brain atlas. Results show the robustness of the methods in founding the stimulation regions.
- Generation of boundary conditions for the Boussinesq system: In a collaboration with David Lannes (IMB, Bordeaux) we have developed a new method for the numerical implementation of generating boundary conditions for a one dimensional Boussinesq system. The method is based on a reformulation of the equations and a resolution of the dispersive boundary layer that is created at the boundary.
- Simulation of solid suspensions in incompressible fluids: In a collaboration with B. Lambert and M. Bergmann (IMB, Bordeaux) we have extended a previously published local lubrication model to non-Brownian suspensions of ellipsoidal solid particles in incompressible flows. This lubrication model used virtual spheres to evaluate local lubrication corrections instead of the global corrections found in the classical lubrication theory.

8. Partnerships and Cooperations

8.1. Regional Initiatives

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.

8.2. National Initiatives

8.2.1. 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.

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 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] [71], and for new HPC developments [72].

8.2.4. PHRCN Multi-centric project

This project has been accepted for funding in December 2019. N Zemzemi is partner of the project and Prof. Emmanuel Cuny (PU-PH CHU de Bordeaux) is the Principal investigator. It is entitled "Deep brain stimulation for Parkinson disease: Probabilistic STN Targeting under general anaesthesia without micro-electrode recordings (MER) vs current surgical procedure." It will start in 2020 and end in 2023.

8.2.5. BOUM project on ECGi

This project is coordinated by 2 PhD students (A. Karoui and O. Bouhamama) and 1 postdoc (M. Diallo), and is funded by the French applied and industrial math society (SMAI). It consists in organizing a national workshop on ECGI.

8.2.6. Inria Ciescard project

This project entitled "Combiner des Information Electriques et Structurelles pour aider les cardiologues à mieux Cibler la thérApie caRDiaque" funds an engineer for 2 years to develop some plugins in the software platform Music. The PI is N. Zemzemi.

8.2.7. Inria project OptimDBS

This project is designed to develop a software for the prediction of the optimal Deep stimulation targets based on machine learning techniques. It is funded by Inria as part of the ATT program. The PI is N. Zemzemi

8.3. Transfert

Together with Prof. Emmanuel Cuny and the help of AST (Aquitaine Science Transfert) and Inria Startup Studio, we are working on the creation of a startup company based on the software OptimDBS, and an associated the submitted patent. We follow the Founders 101 program of Inria to help us with the business, marketing, and management parts. The associated patent entitled Méthode de détermination d'une cible cérébrale stéréotaxique has been submitted to INPI by N. Zemzemi, J. Engelhardt, and E. Cuny under the number 71959FR. Our Software is currently used for the treatment of Essential Trauma in a Phase I clinical study at the CHU de Bordeaux and CHU de Lyon. A new PHRC-National multi-centric project has been accepted in December 2019 (see above, funded projects). This project is led by Emmanuel Cuny and aims at assessing the efficiency of our solution in the treatment of Parkinson Disease. The OptimDBS software will be used by 11 medical centers in France.

8.4. European Initiatives

8.4.1. Collaborations in European Programs, Except FP7 & H2020

Program:MSCA-ITN

Project title: "Personalized Therapies for Atrial Fibrillation. A Translational Approach."

Start Feb 2020 - End 2024

Coordinator: for UB/Liyrc: N. Zemzemi, PI: M. Guillem (University of Valencia, Spain)

8.4.2. 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).

8.5. International Initiatives

8.5.1. Inria International Labs

International Laboratory for Research in Computer Science and Applied Mathematics

Associate Team involved in the International Lab:

8.5.1.1. EPICARD

Title: inversE Problems In CARDiac electrophysiology

International Partner (Institution - Laboratory - Researcher):

ENIT (Tunisia) - Department of Intelligence Science and Technology - Mourad Bellassoued

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.

8.5.1.2. 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 [60]. The Maastricht group was partially funded by the FP7 project EUTRAF and our simulations were supported by GENCI (section 8.2.3).

N. Zemzemi works with Cesare Corrado at King's College London on the development of new eikonal models allowing conduction velocity adaptation [55].

Mostafa Bendahmane works with Kenneth H. Karlsen at university of Oslo (Norway) on the stochastic bidomain model in electrocardiology [46].

8.6. International Research Visitors

8.6.1. Visits of International Scientists

- Yassine Abidi, Ecole Nationale d'Ingénieurs de Tunis, Jun 2019,
- Abir Amri, Tunis El Manar University, from May 2019 until Jun 2019,
- Veronica Anaya, Universidad Nacional Autonoma de Mexico, from Jun 2019 until Jul 2019
- Yves Bourgault, University of Ottawa, Jun 2019
- Elmahdi Erraji, Cadi Ayyad University, Jun 2019
- Moncef Mahjoub, Tunis El Manar University, from Oct 2019 until Nov 2019

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Member of the Organizing Committees

Several members of the team were involved in the organization of the 10th international conference on Functional Imaging and Modeling of the Heart (FIMH), that was held at Bordeaux in July 2019.

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

Lisl Weynans co-organizes with Edward Vigmond (IHU Liryc) the bi-monthly journal club of the modelling group at Liryc, and organizes a monthly workgroup about applied numerical methods, within the Scientific Computing and Modelling team at IMB (Institut de Mathématique de Bordeaux)

9.1.2. Journal

9.1.2.1. Member of the Editorial Boards

Mostafa Bendahmane is member of the editorial board of the "Moroccan Journal of Pure and Applied Mathematics", Mark Potse is an associate editor for "Frontiers in Cardiac Electrophysiology" and an Associate editor for "Journal of Electrocardiology".

9.1.3. Invited Talks

- Lisl Weynans: Mini-symposium on "Numerical methods for interfacial dynamics", ICIAM 2019, Valence, Spain.
- Nejib Zemzemi: Maghrebian Meeting of Young Researchers in Pure and Applied Mathematics, MYRPAM. Hammamet, Tunisia 9-12 December, 2019.
- Mostafa Bendahmane: "Recent progress in inverse problems in electrocardiology", at CAMS, American university of Beirut, Libanon.
- Mark Potse: "Atrial fibrillation dynamics", invited talk at the 2019 International Congress on Electrocardiology, Belgrade, Serbia, 2019.
- Mark Potse: "ECG imaging without imaging", invited talk at the 2019 International Congress on Electrocardiology, Belgrade, Serbia, 2019.
- Lisl Weynans: invited talk on "Hywec 2 : The Hydrodynamics of Wave Energy Convertors", Talence, 2019.
- Lisl Weynans: invited talk at the Seminar of "Institut de Mathematiques de Toulouse", 2019.
- Lisl Weynans: invited talk at the Workshop of ANR RheoSuNN, Ecole Polytechnique, Palaiseau, March 2019.
- Yves Coudière: invited plenary talk at the "9e biennale des mathématiques appliquées et industrielles de la SMAI", Guidel, 2019.
- Nejib Zemzemi: invited talk on "Mathematical Modelling of the electrical activity of the heart from ion-channels to the body surface: Forward and Inverse problems", at Institut de recherche mathématique de Rennes, March 14, 2019.

9.1.4. Research Administration

Yves Coudière is a deputy director of Directeur IMB (Institut de Mathématiques de Bordeaux, UMR 5251 CNRS, Ub, Bdx-INP). Gathering around 160 permanent members, it organizes the research in mathematics and applications of mathematics in Bordeaux.

Michael Leguebe is the secretary of the CLHSCT (Comité Local Hygiène et Sécurité au travail) of the Inria BSO research center.

Lisl Weynans is a member of the "conseil UFR maths et interactions", a member of the "conseil scientifique IMB" and a member of the "BCP" of the Inria BSO research center.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

The 2 assistant professors and 1 professor of the team teach at several levels of the Bordeaux University programs in Mathematics and Neurosciences (respectively, 192, 192 and 96 h/year on average). The researchers also have a regular teaching activity, contributing to several courses in the Applied Mathematics at the Bachelor and Master levels (usually between 16 and 32 h/year).

The PhD student are used to teach between 32 and 64 h/year, usually courses of general mathematics in L1 or mathematics for biologists in L1 or L2.

Teaching responsibilities at the University of Bordeaux:

- Yves Coudière: Master MAS (Mathématiques Appliquées, Statistiques), parcours MNCHP (Modélisation Numérique Calcul Haute Performance),
- Yves Coudière: Licence Mathématique parcours ingénierie mathématique,
- Lisl Weynans: Mineure Mathématiques du parcours International de la Licence
- Mostafa Bendahmane: Responsable de la mobilité internationale des étudiants de Licence MIASHS.

Courses (L for Bachelor level, M for Master level):

- Numerical analysis (L2)
- Programming for scientific computing with C++ (L3)
- Programming projects with Python (M1)
- Numerical approximation of PDEs: Finite Differences, Finite Elements, Finite Volumes (M1, M2)
- Supervision of programming projects (L3, M1)
- Mathematical modelling in L2 parcours medicine and physics
- Linear Algebra, Optimization under constraints (L2 and Essca school)
- Analysis, L2
- Computational Neurosciences, M2
- Neuropsychology and Psychophysiology, L3
- Graduate program EUR Digital Public Health, Bordeaux University, March 2019. Philosophy of science and the role of numerical models: introductory course in the module Modeling in life science

Courses at doctoral level:

- Liryc summer school, July 2019: Computer modeling of cardiac electrophysiology, 3 hours
- Course of mathematics for medicine students: March 2019, course organized by the Ecole Doctorales EDMI and SVS of Bordeaux University Introductory course of mathematical modelling and parameter estimation techniques in complex models (4h30)

9.2.2. Supervision

PhD : Antoine Gérard, Modèles numériques personnalisés de la fibrillation auriculaire , Univ. Bordeaux, July 12th 2019, encadrant: Yves Coudière
PhD in progress : Andony Arrieula, Oct. 2018, encadrant: Mark Potse
PhD in progress: Oumayma Bouhamama, Oct. 2018 , encadrante: Lisl Weynans
PhD in progress : Syed Hassaan Ahmed Bukhari, Oct. 2018, encadrant: Mark Potse
PhD in progress : Amel Karoui, Oct 2017, encadrants: Mostafa Bendahmane and Nejib Zemzemi
PhD in progress : Bachar Tarraf, Oct. 2018, encadrant: Yves Coudière and Michael Leguebe

9.2.3. Juries

- Lisl Weynans: member of the Jury for the recruitment of CR Inria, BSO research center.
- Lisl Weynans : member of the jury for the PhD of Umberto Bosi in applied mathematics (Univ. Bordeaux)
- Yves Coudière: chairman of the jury for the PhD of J. Engelhardt in neurology (Univ. Bordeaux)
- Yves Coudière: member of the jury for the PhD of A. Gérard in applied mathematics (Univ. Bordeaux)
- Nejib Zemzemi : member of the jury for the PhD of Rabeb Chamekh in applied mathematics
- Mostafa Bendahmane: member of the jury for the PhD of Mohamed Zagour in applied mathematics.

9.3. Popularization

9.3.1. Internal or external Inria responsibilities

Coordination of a workgroup entitled "CultureMATH Bordeaux", working on writing dissemination articles for the website https://culturemath.ens.fr.

9.3.2. Education

Organization of "Moi informaticienne, moi mathématicienne (MIMM)": one week internship at the University for young girls (15-16 year old) interested in maths and informatics.

9.3.3. Interventions

- National events: Fête de la Science, Semaine des maths,
- In educational institutions: several talks in high-schools about scientific computing and applied mathematics
- Presentation stand for "Simric" at the 10 years anniversary of the Inria Bordeaux Sud-Ouest centre.
- Modeling stand at the "Journée portes ouvertes de Liryc", 2019.
- Reception of 5 high-school pupils (élèves de 3e, 15 years old).

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