Activity Report 2015

Team CARMEN

Modélisation et calculs pour l'électrophysiologie cardiaque

Inria teams are typically groups of researchers working on the definition of a common project, and objectives, with the goal to arrive at the creation of a project-team. Such project-teams may include other partners (universities or research institutions).

RESEARCH CENTER
Bordeaux - Sud-Ouest

THEME
Modeling and Control for Life Sciences

Table of contents

Team CARMEN

Creation of the Team: 2011 October 01

Keywords:

Computer Science and Digital Science:

6.1.2. - Stochastic Modeling (SPDE, SDE)
6.1.4. - Multiscale modeling
6.2.1. - Numerical analysis of PDE and ODE
6.2.6. - Optimization
6.2.7. - High performance computing
6.3.1. - Inverse problems
6.3.2. - Data assimilation
6.3.4. - Model reduction

Other Research Topics and Application Domains:

2.2.1. - Cardiovascular and respiratory diseases
2.6.2. - Cardiac imaging

1. Members

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2. Overall Objectives

2.1. Overall Objectives

The team Carmen develops and uses models and numerical methods in order to simulate the propagation of the cardiac action potential, from the cellular scale to the scale of the body. It aims at improving:

- Knowledge and the treatment of electrical cardiac pathologies.
- Exploitation of all available electrical signals.

Therefore, we want to incorporate the heterogeneities and coupling processes from the intermediate scales into the macroscopic PDE models. They play a primary role in the cardiac electrical arrhythmias. Meanwhile, we want to use the models to solve the inverse problems related to non-invasive electrical imaging of the heart.

The mathematical fields involved in our research are: PDE modeling and in particular reaction-diffusion equations, inverse problems, numerical analysis, and scientific computing.

A main goal of the team is to contribute to the work-packages defined in the IHU LIRYC, which focuses on electrical arrhythmias and how heart failure relates to electrical asynchrony.

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 an activation wave that rapidly propagates through the tissue. The spatio-temporal pattern of this propagation is related both to the function of the cellular membrane and to the structural organisation of the cells into tissues. Cardiac arrythmias originate from malfunctions in this process. The field of cardiac electrophysiology studies the multiscale organisation 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.

Several improvements of current models of the propagation of the action potential will be developped, based on previous work and on the data available at the LIRYC:

- Enrichment of the current monodomain and bidomain models 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 want to develop model that couples 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 and check that they are reliable experimental tools.

3.2. Simplified models and inverse problems

The medical and clinical exploration of the electrical signals is based on accurate reconstruction of the typical patterns of propagation of the action potential. The correct detection of these complex patterns by non-invasive electrical imaging techniques has to be developed. Both problems involve 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 in the cardiac diagnosis. Although widely studied during the last years, it remains a challenge for the scientific community. In many cases the quality of reconstructed electrical potential is not sufficiently accurate. The methods used consist in solving the Laplace equation on the volume delimited by the body surface and the epicardial surface. We want to

- Study in depth the dependance of this inverse problem inhomogeneities in the torso, conductivity values, the geometry, electrode placements...
- Improve the solution to the inverse problem be using new regularization strategies 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 conside the follwong strategies:

- using complete propagation models in the inverse problem, like the bidomain equations; for instance in order to localize electrical sources;
- construct families of reduced-order models, using e.g. statistical learning techniques, which would accurately represent some families of well-identified pathologies; and
- construct simple models of the propagation of the activation front, based on eikonal or level-sets 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] and [6] and [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 preconditionning 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 cardiac physiology are based on the approximation of a perfect muscle using homogenisation method. However, due to the age and due to some cardiomyopathies, the cellular structure of the tissue changes. These modifications 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 numerically explore the mechanisms of these diseases.

The problem is that literature on this type of model is still very poor and existing models are bidimensionels or limited to idealised geometries. We propose an approach in opposition with the usual homogenisation way. We want to describe the muscle as a system of three-dimensional cells, whose dynamics is given by the modeling of ion fluxes across cell membranes in equilibrium with the electrostatic potentials in the intracellular and extracellular environments.

The goals are to design, analyse, and explore numerically a model of cardiac electrophysiology at a level of discretisation of about $1\mu m$ (that means 10 to 100 times smaller than the size of cardiomyocytes), develop model and its numerical discretisation, define realistic geometries or actual cells.

Issues are scale simulations for thousands of cores to take into account thousands or tens of thousands cells. For this, a hybrid parallelism approach OpenMP and MPI will be considered.

4. Application Domains

4.1. Scientific context: the LIRYC

Our fields of application are naturally: electrophysiology and cardiac physiopathology at the tissue scale on one side; medical and clinical cardiology on the other side.

The team's research project is part of the IHU LIRYC project, initiated by Pr. M. Haissaguerre. It is concerned by the major issues of modern electrocardiology: atrial arrhythmias, sudden death due to ventricular fibrillation and heart failure related to ventricular dyssynchrony.

We aim at bringing applied mathematics and scientific computing closer to biomedical research applied to cardiac rhythmology and clinical cardiology. It aims at enhancing our fundamental knowledge of the normal and abnormal cardiac electrical activity, of the patterns of the electrocardiogram; and we will develop new simulation tools for training, biological and clinical applications.

4.2. Basic experimental electrophysiology

Our modeling is carried out in coordination with the experimental teams from the LIRYC. It will help to write new concepts concerning the multiscale organisation of the cardiac action potentials and will serve our understanding in many electrical pathologies:

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 vein.

At the ventricula level, we focus on (1) modeling the complex coupling between the Purkinje network and the ventricles and (2) modeling the structural heterogeneities at the cellular scale, taking into account the complex organisation and disorganisation 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.

5. Highlights of the Year

5.1. Highlights of the Year

A large part of the newly-constructed LIRYC building, hosting researchers' offices, has been taken in use. The extra space greatly facilitates collaboration between Carmen and LIRYC researchers.

The *service de cardiologie-électrophysiologie et stimulation cardiaque* of the CHU Haut-Leveque, the clinical partner in LIRYC, was ranked first in the classification 2015–2016 of Hospitals and Clinics published by the news magazine *L'Express*, while its director, professor M. Haissaguerre, has been awarded the Gold Medal of the European Society of Cardiology.

M. Potse published a high-profile paper with a group of internationally renowned researchers on terminology and criteria for the diagnosis of a rare but potentially fatal ECG abnormality named Early repolarisation syndrome [37].

In silico assessment of drugs effects on human embryonic stem cells derived cardiomyocytes electrical activity Computational modeling and simulation is extensively used to investigate diseases in cardiac electrophysiological activity and also drug effects, side effects and interactions. Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) have been recently considered as a promising tool in regenerative medicine: their major role in repairing damaged tissue is due to pluripotency and ability to differentiate. These pluripotent cells are also used in early stages of drugs development. Pharmaceutical companies use the MultiElectrode Array (MEA) device in order to perform many in vitro experiments on hESC-CMs. The goal of our study is to derive a mathematical model and to simulate these in vitro experiments. Sensitivity of the Electrocardiography Inverse Solution to the Torso Conductivity Uncertainties Electrocardiography imaging (ECGI) is a new non invasive technology used for heart diagnosis. It allows to construct the electrical potential on the heart surface only from measurement on the body surface and some geometrical informations of the torso. The purpose of this work is twofold: First, we propose a new formulation to calculate the distribution of the electric potential on the heart, from measurements on the torso surface. Second, we study the influence of the errors and uncertainties on the conductivity parameters, on the ECGI solution. We use an optimal control formulation for the mathematical formulation of the problem with a stochastic diffusion equation as a constraint. The descretization is done using stochastic Galerkin method allowing to separate random and de-terministic variables. The optimal control problem is solved using a conjugate gradient method where the gradient of the cost function is computed with an ad-joint technique. The efficiency of this approach to solve the inverse problem and the usability to quantify the effect of conductivity uncertainties in the torso are demonstrated through a number of numerical simulations on a 2D geometrical model. Our results show that adding $\pm$50alter the inverse solution, whereas adding $\pm$50lung conductivity affects the reconstructed heart potential by almost 50

Inverse Localization of Ischemia in a 3D Realistic Geometry: A Level Set Approach The reconstruction of cardiac ischemic regions from body surface potential measurements (BSPMs) is usually performed at a single time instant which corresponds to the plateau or resting phase of the cardiac action potential. Using a different approach, we previously proposed a level set formulation that incorporates the knowledge of the cardiac excitation process in the inverse procedure, thus exploiting the spatio-temporal correlations contained in the BSPMs. In this study, we extend our inverse level-set formulation for the reconstruction of ischemic regions to 3D realistic geometries, and analyze its performance in different noisy scenarios. Our method is benchmarked against zero-order Tikhonov regularization. The inverse reconstruction of the ischemic region is

evaluated using the correlation coefficient (CC), the sensitive error ratio (SN), and the specificity error ratio (SP). Our algorithm outperforms zero-order Tikhonov regularization, specially in highly noisy scenarios.

Inverse problem in electrocardography via the factorization method of boundary value problems We present a new mathematical approach for solving the inverse problem in electrocardiography. This approach is based on the factorization of boundary value problems method. In this paper we derive the mathematical equations and test this method on synthetical data generated on realistic heart and torso geometries using the state-of-the-art bidomain model in the heart coupled to the Laplace equation in the torso. We measure the accuracy of the inverse solution using spatial Relative Error (RE) and Correlation Coefficient (CC).

It is now possible for all Carmen members to go to the IHU LIRYC since the construction of the new building. This aims for the Carmen teams to follow doctors and researchers at Xavier Arnozan hospital.

6. New Software and Platforms

6.1. CEPS: a Cardiac ElectroPhysiology Simulator

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

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. We use the platform GForge (ceps) based on Git. This allows to keep a history of developments for developers and users.

Some of our collaborators actively participate to the testing and discussion for the development of CEPS, namely:

- C. Pierre, LMA University of Pau et des Pays de l'Adour;
- R. Turpault, IMB University of Bordeaux;

Several people work and make and an usefull code for researchers and users.

- Development of an external procedure to compile depandancies for CEPS. This allows a very simple way to install CEPS for partners or students.
- Improve continious integration test cases in order to have a best coverage of the code as possible.
- Overwrite C++ class for ionic models and adding new models in collaboration with A. Gérard.
- Integration of the partionneur PTSchotch in order to realise a partitionning on the nodes.
- Turorials for beginers on the code (linear algebra, installation, compilation...).
- New implementation of the bilayer model developped by L. Simon during his PhD thesis. The most important part will provide by M. Fuentes works. Difficulties are currently the specification of two layers in CEPS and how connect them.
- The strategy remains at this time is to have two meshes in entry (on global mesh for the auricles and an other *under-mesh* corresponding to the twolayers domain). This means, that we have to create a connectivity table between the global mesh and the *under-mesh*.
- Development of an interface for users in order to specify data in a text file for the code such physical values for ionic models or numerical values for numerical methods (especially in time) used.

6.2. IDAM

The goal of IDAM project is to defined a conceptual module in MUSIC in order to create realistic meshes for the CEPS code. Informations come from IRM done by doctors. Furthermore, objectives are the continuation of used methods in the team and the visualisation of numerical results obtained by CEPS (https://bil.inria.fr/fr/software/view/2630/tab.

This project started on 1st december 2015 for two years. M. Juhoor is in charge of this project in collaboration with the MedInria team and the IHU LIRYC.

7. New Results

7.1. Inverse Problem

Electrocardiograms simulated by our group with a highly realistic and detailed forward model were used for several inverse-modeling studies [34], [33], [38], [35].

- Stability analysis of the POD reduced order method for solving the bidomain model in cardiac electrophysiology: In this work we show the numerical stability of the Proper Orthogonal Decomposition (POD) reduced order method used in cardiac electrophysiology applications. The difficulty of proving the stability comes from the fact that we are interested in the bidomain model, which is a system of degenerate parabolic equations coupled to a system of ODEs representing the cell membrane electrical activity. The proof of the stability of this method is based an a priori estimate controlling the gap between the reduced order solution and the Galerkin finite element one. We present some numerical simulations confirming the theoretical results. We also combine the POD method with a time splitting scheme allowing a faster solution of the bidomain problem and show numerical results. Finally, we conduct numerical simulation in 2D illustrating the stability of the POD method in its sensitivity to the ionic model parameters. We also perform 3D simulation using a massively parallel code. We show the computational gain using the POD reduced order model. We also show that this method has a better scalability than the full finite element method.
- In silico assessment of drugs effects on human embryonic stem cells derived cardiomyocytes electrical activity: Computational modeling and simulation is extensively used to investigate diseases in cardiac electrophysiological activity and also drug effects, side effects and interactions. Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) have been recently considered as a promising tool in regenerative medicine: their major role in repairing damaged tissue is due to pluripotency and ability to differentiate. These pluripotent cells are also used in early stages of drugs development. Pharmaceutical companies use the MultiElectrode Array (MEA) device in order to perform many in vitro experiments on hESC-CMs. The goal of our study is to derive a mathematical model and to simulate these in vitro experiments.
- Sensitivity of the Electrocardiography Inverse Solution to the Torso Conductivity Uncertainties: Electrocardiography imaging (ECGI) is a new non invasive technology used for heart diagnosis. It allows to construct the electrical potential on the heart surface only from measurement on the body surface and some geometrical informations of the torso. The purpose of this work is twofold: First, we propose a new formulation to calculate the distribution of the electric potential on the heart, from measurements on the torso surface. Second, we study the influence of the errors and uncertainties on the conductivity parameters, on the ECGI solution. We use an optimal control formulation for the mathematical formulation of the problem with a stochastic diffusion equation as a constraint. The descretization is done using stochastic Galerkin method allowing to separate random and deterministic variables. The optimal control problem is solved using a conjugate gradient method where the gradient of the cost function is computed with an ad-joint technique. The efficiency of this approach to solve the inverse problem and the usability to quantify the effect of conductivity uncertainties in the torso are demonstrated through a number of numerical simulations on a 2D

geometrical model. Our results show that adding $\pm 50\%$ uncertainties in the fat conductivity does not alter the inverse solution, whereas adding $\pm 50\%$ uncertainties in the lung conductivity affects the reconstructed heart potential by almost 50%.

- Inverse Localization of Ischemia in a 3D Realistic Geometry: A Level Set Approach: The reconstruction of cardiac ischemic regions from body surface potential measurements (BSPMs) is usually performed at a single time instant which corresponds to the plateau or resting phase of the cardiac action potential. Using a different approach, we previously proposed a level set formulation that incorporates the knowledge of the cardiac excitation process in the inverse procedure, thus exploiting the spatio-temporal correlations contained in the BSPMs. In this study, we extend our inverse level-set formulation for the reconstruction of ischemic regions to 3D realistic geometries, and analyze its performance in different noisy scenarios. Our method is benchmarked against zero-order Tikhonov regularization. The inverse reconstruction of the ischemic region is evaluated using the correlation coefficient (CC), the sensitive error ratio (SN), and the specificity error ratio (SP). Our algorithm outperforms zero-order Tikhonov regularization, specially in highly noisy scenarios.
- Inverse problem in electrocardography via the factorization method of boundary value problems: We present a new mathematical approach for solving the inverse problem in electrocardiography. This approach is based on the factorization of boundary value problems method. In this paper we derive the mathematical equations and test this method on synthetical data generated on realistic heart and torso geometries using the state-of-the-art bidomain model in the heart coupled to the Laplace equation in the torso. We measure the accuracy of the inverse solution using spatial Relative Error (RE) and Correlation Coefficient (CC).
- In the inverse problem en electrocardiology, the goal is to recover electrophysiological activity in the heart without measuring directly on its surface (without using catheter in- terventions). Note that today the inverse computation is frequently used by solving the quasi-static model. This model doesn't take into account the heart dynamic in time and may result in considerable errors in the reconstruction of the solution on the heart. In [1] we study a 3D numerical inverse problem constrained by the bidomain equations in electro- cardiology. The state equations consisting in a coupled reaction-diusion system modelling the propagation of the intracelullar and extracellular electrical potentials, and ionic cur- rents, are extended to further consider the eect of an external bathing medium. Thus, we demonstrate that the novel concept of applying electrophysiological data might be useful to improve noninvasive reconstruction of electrical heart activity. Finally, we present numerical experiments representing the eect of the heart dynamic on the inverse solutions. Moreover in [2], we study the stability result for the conductivities of the approximate bidomain model. The proof is based on the combination of a Carleman estimate obtained in [3] and certain weight energy estimates for parabolic systems.
- The static inverse ECG problem needs to solve the well known ill posed Cauchy problem for the Laplace equation. A new approach investigated in the team uses the method of factorization of bounadary value problems. This method, studied for itself, provides in this context the computation of Dirichlet-Neumann operators as solution of a Riccati equation. Results have been presented at IEEE international symposium on biomedical imaging, New York april 16-19, 2015. Further investigations will be lead using more precise numerical methods to solve the Riccati equation. The non-linearity and time dependence of the coupling resistance between cardiac cells (gap junctions) is stdied in the Liryc institute and thought to be of importance in the unerstanding of cardiac arrhythmias. The internship of Nhan Le Thanh was a first step to investigate their numerical simulation.

An Example of calculus on a torso is shown in figure 1

7.2. Cardiac Electromechanics

In [1] we study a coupled elliptic-parabolic system modeling the interaction between the propagation of electric potential and subsequent deformation of the cardiac tissue. The problem consists in a reaction-diusion system governing the dynamics of ionic quantities, intra and extra-cellular potentials, and the

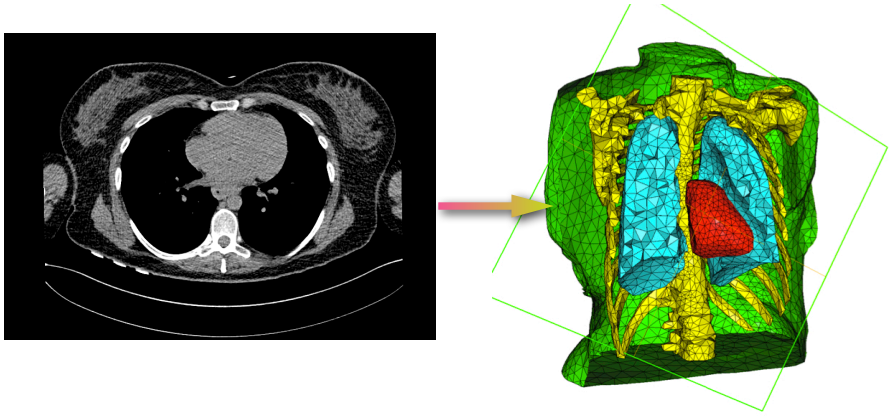

Figure 1. Mesh of the torso obtained with an IRM picture; this problem is link with the IDAM project

linearized elasticity equations are adopted to describe the motion of an incompressible material. The coupling between muscle contrac- tion, 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. In this paper we prove exis- tence of weak solutions to the underlying coupled reaction-diusion system and uniqueness of regular solutions. We close with a numerical example illustrating the convergence of the method and some features of the model.

7.3. Cardiac Electrophysiology at the Microscopic Scale

We focused on establishing a microscopic model for cardiac electrophysiology simulations and proving the existence of a solution. We started with writing a mathematical proof allowing from well known physical equations and properties of the cardiac tissue to establish the model. Then, we worked on a variational formulation of the problem, and describing a weak solution of it. The idea is to compute energy estimates and to bound them so that we can extract a convergent sequence of functions in the appropriate Sobolev space. With my PhD advisor, we started to write an article about these two proofs. We also worked on CEPS code to implement some functionalities that will fit my requirements in a near future regarding the simulations we have to design. The main difficulty we identified is, provided we get a well defined geometry and mesh of cardiac cells, to implement the ionic flux between cells. First simulation of a simple "two-cells communication" problem will probably, if the results meet experimental observations, lead to another article. We also attended Imaged Based Biomedical Modelling 2015, a summer course organized by SCI institute (University of Utah), which was designed to give attendees guidelines about vizualisation and modelling, especially on cardio electrophysiology.

7.4. High order numerical scheme for ionic models

C. Douanla lonti worked on time numerical schemes like Admas-Bashforth in order to have a high degree of convergence between an exact solution and the approximated solution. This method is a generalisation of Rush-Larshen scheme adapted for electrophysiology cardiac.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. IHU LIRYC

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

- For 2015: the salary of M. Potse, member of Carmen, is paid by LIRYC..
- For 2012-2015: 1/2 PhD thesis associated to the project *Modélisation pour les données multimodales* (see section Regional Initiaves).

8.1.2. ANR HR-CEM

In 2014, we are supported for the project "High Resolution Cardiac Electrophysiology Models: HR-CEM" within the call for project « Modèles Numériques » of the ANR.

The scientific start of the project was on November 4th, 2013.

It is an international project that involves three partners: Inria (coordinator), IHU LIRYC, and UMI-CRM at Montréal (Canada). The project has some 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.

8.1.3. AMIES – Medic Activ

We were granted by the Agency AMIES a financial support to complete the one obtained from the Région Aquitaine for the Medic Activ project (see above). The objective of this support is to developp reduced order models of cardiac electrophysiology that might enter the MedicActiv framework. The difficulty is to define qualitatively realistic but fast numerical simulations of the ECG and cardiac function, for educational purpose.

8.1.4. ANR Labcom CardioXcomp

We are participant in the ANR Labcom project between Inria and the society Notocord (www.notocord.com). At Inria, the proejct is leaded by J.-F. Gerbeau from the Reo team and we participate to the study and developpment of cardiac electrophysiology models suited to the context of the proejct.

The aim of CarioXcomp is to code human induced pluripotent cardiomyocyte cells and drug/hiPS-CMs interaction. N. Zemzemi works on this project with E. Abbate (PhD thesis until october 2015) for th coupling between human induced pluripotent cardiomyocyte cells and the measurement tool multi-electrode array (MEA). In this project, some different tests on drug models and selection of the most suitable for the hiPS-CMs. In the same time, N. Zemzemi with collaborators N. Fikal, R. Aboulaich and EL.M. El Guarmah worked on the quantification of the effect of uncertainty in the conductivity values on the Electrocardiography imaging (ECGI) inverse solution. N. Zemzemi and J. Lassoued C. Corrado and M. Mahjoub worked on the stability analyssis of the reduced order model for the bidomain equation using proper orthogonal decomposition and on the estimation of the location of cardiac isquemia in a 3D geometry with inverse problem tools with C. Chavez F. Alonso-Atienz, D. Alvarez and Y. Coudière.

8.1.5. REO

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

8.1.6. MedicActiv

The CARMEN team cooperates in interaction with the MedicActiV project.

8.1.7. GENCI

GENCI – grand équipement national de calcul intensif – is the agency that grants access to national high-performance resources for scientific purposes in France. GENCI projects have to be renewed yearly. Our project renewal *Interaction between tissue structure and ion-channel function in cardiac arrhythmia*, submitted in October 2015, has been granted 9.4 million core-hours on the three major systems Curie, Occigen, and Turing. This compute time, to be used in the calendar year 2016, is primarily destined for our research into the interaction between ionic and structural heart disease in atrial fibrillation, Brugada syndrome, and early repolarisation syndrome [37].

8.2. International Initiatives

8.2.1. Inria International Labs

LIRIMA: Associate Team involved in the International Lab:

8.2.1.1. EPICARD (https://team.inria.fr/carmen/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 Haissaguerre. 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.

8.2.2. Inria International Partners

8.2.2.1. Informal International Partners

Applied work on atrial fibrillation is performed in collaboration with the experimental and clinical groups of professors U. Schotten and H. Crijns at Maastricht University [36].

M. Potse collaborates on several projects with the Institute of Computational Science at the *Università della Svizzera italiana* in Lugano, Switzerland, and the Department of electronics, informatics, and bioengineering of the *Politecnico di Milano*, Milan, Italy.

8.3. International Research Visitors

8.3.1. Visits of International Scientists

8.3.1.1. Internships

- B. Mostafa
  - The Faculty of Mathematics and Natural Sciences, University of Oslo, Norway
  - Johann Radon Institute for Computational and Applied Mathematics (RICAM) Austrian Academy of Sciences, Linz, Austria.
  - CI^{2}MA y Departamento de Ingenieria Matemática, Universidad de Concepcion, Concepcion, Chile.
  - Departamento de Matemática Aplicada e Estatistica, Instituto de Ciências Matemáticas e de Computação – USP, São Carlos, Brazil

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Journal

9.1.1.1. Member of the editorial boards

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

9.1.1.2. Reviewer - Reviewing activities

- M. Potse: Heart Rhythm, IEEE Transactions on Biomedical Engineering, Medical & Biological Engineering & Computing, Journal of Electrocardiology.
- M. Potse is council member of the International Society of Electrocardiology.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

IUT Orsay : P.E. Bécue - Discrete Mathematics, 64h.
IUT Orsay : P.E. Bécue - Introduction to modelling and Principal Component Analysis, 64h.
Engineering school: N. Zemzemi, (How to switch from a mathematical model to a numerical solution (examples with the cardiac activity of the heart in 2D)

9.2.2. Juries

- Y. Coudière, PhD advertiser for the PhD thesis of G. Ravon obtained on 17 december 2015
- Y. Coudière, PhD advertiser for the PhD thesis of A. Davidlovic expected on the first quarter of 2016.
- Y. Coudière, Rapporteur for the PhD thesis of Rocio Cabrera Lozoya

9.3. Popularization

- G. Ravon and Y. Coudière obtained a financial support from Cap'Math for the game: "Heart Attack". It is destinated to middle and high school students to introduce mathematical modelling.
- Poster price at the CNIC 2015 for A. Djokovic.

10. Bibliography

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Articles in International Peer-Reviewed Journals

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