Activity Report 2013

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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Team CARMEN

Keywords: Multiscale Models, Numerical Methods, Scientific Computation, High Performance Computing, Biomedical Engineering

Creation of the Team: 2011 October 01.

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- Yves Bourgault [Univ. Ottawa, Professor, from Sep 2013 until Dec 2013]
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- Mohamed Jebalia [Assistant Professor, ENIT (Tunisie), from May 2013 until Jul 2013]
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2. Overall Objectives

2.1. Overall Objectives

The team Carmen plans to develop 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:

- our knowledge and the treatment of electrical cardiac pathologies;
- the 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.

A cooperation with physiology, physiopathology and medicine is being developed. the team will build 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.

2.2. Highlights of the Year

- Simon Labarthe was awarded the « prix de THESAQT », during the « Forum NOVAQT » on innovation organized by the region Aquitaine. The price was awarded for his scientific achievements during his PhD.

3. Research Program

3.1. Complex models for the propagation of cardiac action potentials

Cardiac arrythmias originates from the multiscale organisation of the cardiac action potential from the cellular scale up to the scale of the body. It relates the molecular processes from the cell membranes to the electrocardiogram, an electrical signal on the torso. The spatio-temporal patterns of this propagation is related both to the function of the cellular membrane and of the structural organisation of the cells into tissues, into the organ and final within the body.

Several improvements of current models of the propagation of the action potential will be developped, based on previous work [10], [2], [11] 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 will use high-performance computing techniques in order to explore numerically 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 developped. 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 plan 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 cours 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 some electrical sources;
- construct some families of reduced order models, using e.g. statistical learning techniques, which would accurately represent some families of well-identified pathologies;
- construct some 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.

Additionnaly, we will need to develop numerical techniques dedicated to our simplified eikonal/levl-sets 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 need of the medical community. It needs to 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 [12], [13] and [15] 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.

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.

4.3. Cardiac electrical signals

The LIRYC use, on a daily basis and in the clinical context, complex electrical imaging systems, like intracardiac catheters and the CardioInsight vest with 252 body syrface electrodes.

The numerical models can guide the analysis of these signals and conversely, the models can be guided by the signals.

Other applied questions can be addressed by modeling, like the nature of the various electrical signals measured by catheters, that heavily depends on the nature and spatial localisation of the electrodes.

5. Software and Platforms

5.1. 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. Thanks to an ADT, actual developments started at the end of 2012 and still continue.

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 [30]. We use the platform GForge (gforge.inria.fr/projects/ceps) based on Subversion. 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 Université de Pau et des Pays de l'Adour;
- R. Turpault, LMA Université de Nantes;
- L. Gerardo-Giorda, BCAM Bilbao.

5.2. PROPAG

The workhorse for our applied simulation studies of the whole human heart is PROPAG, a code that has its origins at the Université de Montréal in Canada, and has been further developed by the Institute of Computational Science in Lugano, Switzerland. PROPAG is highly configurable, runs with complex model geometries, and runs efficiently on high-performance computing systems with many thousands of cores. It is particularly useful for whole-heart studies, which typically rely on very large model sizes (in the order of 10^8 elements), several different membrane models and cell types in a single simulation run, and several regionally varying parameters.

PROPAG is presently used in our group to study the relation between the substrate, complexity, and electrocardiographic features of atrial fibrillation and of cardiomyopathy-related ventricular arrhythmia, providing the efficiency and flexibility that is required to handle the complex anatomical structures that are involved.

5.3. Model construction – A new project

Many of our projects rely on realistic or even patient-tailored meshes to represent the anatomy of the human heart and torso. The construction of such meshes provides challenges on many levels, from the delineation of the anatomical structures in medical images to the construction of high-quality meshes. The construction of such meshes provides challenges on many levels, from the delineation of the anatomical structures in medical images to the construction of high-quality meshes. We presently use a variety of in-house and public software packages to perform this work and are able to produce meshes of sufficient quality, but we strive for an important streamlining of this work. We have initiated a discussion with several groups inside and outside Inria who have similar needs or can offer solutions. We specifically investigate the possibility to build a common software which combines and complements our present solutions. The new code should make various methods easily accessible and automate the work as much as possible. Because accuracy and mesh quality are important requirements, the new code should also provide convenient options for human intervention where algorithms fall short. For example, manual segmentation and mesh editing should be as easy and efficient as they are in medical-imaging tools and 3D-editing software, respectively, but well integrated into the workflow.

6. New Results

6.1. Mathematical models

- *Mathematical derivation of a bilayer surface model of the atria using asymptotic analysis methods [28], [16]*

  We derived rigorously, by using asymptotic analysis tools, a bilayer model of atrial electrophysiology. Starting with a 3D model of atrial tissue that includes two layers with distinct electrophysiological characteristics and with an aspect ratio of ϵ, we obtained an asymptotic equivalent model when $\epsilon \longrightarrow 0$ made up of two surface models coupled by a coupling term. The bilayer model discribes the evolution of the mean in the thickness of the 3D potential in each layer. This approach is an improvement of the classical surface model of cardiac electrophysiology, because it guaranties a higher convergence speed, and allows to take into account transmural heterogeneities. We numerically implemented the 3D and bilayer models and compared it to the classical surface model. We observed a second order accuracy of the bilayer model and drastically reduced computational times respectively to the 3D model.

- *Formal derivation of a macroscopic model of propagation that includes the non linear behavior of gap junctions [16]*

  A macroscopic model of electrical propagation that take into account the non linear conductivity of the gap junction is obtained by a formal homogenization method. We derived a one dimensional macroscopic model which diffusive tensor varies in time. We compared this macroscopic model

with a cell-to-cell propagation. This is an very important improvement of existing models that only consider a linear cell-to-cell coupling. The introduction of this non linear phenomenon in homogenized models gives a simulation tool to investigate the impact of the microscopic nonlinear mechanisms on the macroscopic propagation.

- *Influence of periodic diffusive inclusions on the bidomain model [29]*

  We present a new mathematical model of the electric activity of the heart. In the standard bidomain model we can distinguish the intra- and the extracellular space with different conductivities for excitable cells and the fibrotic tissue around them. The main drawback is that it assumes the existence of excitable cells everywhere in the heart, while it is known that there exist non small regions where fibroblasts take place. The fibroblasts are equally distributed and since they are non excitable cells, they can be considered as a diffusive part. Hence we extend the standard bidomain model as follows: we assume that we have periodic alternation of the healthy tissue (linear bidomain model) and fibrotic extracellular space (diffusive part). We use homogenisation techniques to derive our macroscopic partial differential equations. Interestingly, we obtain again a bidomain type model with modified conductivities that involve the volume fraction of the diffusive domain. Preliminary numerical experiments will conclude on the influence of these diffusive inclusions.

6.2. Construction of numerical models

- *Implementation of an accurate bilayer model of human atria, including realistic geometry and qualitative fibre direction [19], [21], [16]*

  We introduce a bilayer model of the human atria. We set a specific mathematical model based on two surface monodomain problems coupled by a coupling term. We recalled convergence results of the bilayer model towards a 3D model for thin tissues, we formalized an optimization method to set the coupling coefficient and we present two different asymptotically equivalent numerical implementation of the model. We then present a geometrically and electrophysiologically accurate model of the atrial heterogeneities, including two layers of fibre directions and ionic function heterogeneities based on histological and modelling works. We assess the physiological relevance of the model during a sinus wave and we check the occurrence of three-dimensional electrical behaviour such as slight electrical dissociation. This bilayer model is able to take into account transmural heterogeneities only accessible since then with full 3D models, while keeping the low computational load associated with surface models. It is then a light and relevant tool for long-lasting simulations designed to investigate atrial arrhythmia.

- *Personalization method of the bilayer model to registrate the geometry to a patient dependant geometry [16]*

  If the generic atrial bilayer model developed in [21] allows to conduct general experiments, greater customization of the model is necessary to carry out more specific studies on a given patient. We present a methodology to obtain a patient-dependant model containing the geometry of the patient, a generic fibrous organization and an image of the patient's fibrosis obtained by late-enhancement MRI. This is a common work with the clinical team of the CHU du Haut-Lévêque (H. Cochet and P. Jaïs) and the Asclepios Inria team.

  The methodology is based on a registration method developed by Durrleman et al. [34] that allows to register surfaces : the generic model is registrated towards a patient-specific geometry (work by M. Sermseant and R. Cabrera-Lozoya, Asclepios Team). The fibre organisation is transported by the same linear local transformations. The late-enhancement is projected on the model to take into account the complex patient-specific fibrotic repartition. A similar methodology was presented by McDowell et al. [37]. However, the authors took as a starting point a three-dimensional geometry and a different methodology to registrate the geometry. The work presented here is therefore innovative.

- *Faster solvers for cardiac electro-physiology problems [27]*

There are many applications in cardiac electro-physiology where computational time is the main requirement to fulfill, even by sacrificing accuracy. Some techniques were investigated in this direction, in order to obtain a break-even point between accuracy and speed. The complete problem involves solving some ODEs on each mesh node and inverting large sparse matrices, often ill-conditionned.

We first designed a method based on the Proper Orthogonal Decomposition (POD) technique: we project the linear system onto a well-chosen orthogonal basis of smaller dimension while still solving the ODES. We tried the method on both the bidomain and monodomain equations, and extended the tests on an HPC machine, in order to observe scalability performances. There is no improvment for the monodomain equations because its linear systems are well-conditionned. For the bidomain equations, the CPU time decreases by a factor of 10 between the full and reduced models, and better scalability performances.

We secondly developped an eikonal model, in view of serious games applications for the Medic Activ project. The Dijkstra algorithm is used to solve the eikonal equation and the transmembrane potential is determined by the solution of a Mitchell-Schaeffer model on each mesh node. Some modifications where introduced to take into account re-excitability and allox re-entrant waves. Compared by the algorithm proposed by [38], the transmembrane potential comes from the solution of an underlying model, not through an approximation. This represent an innovation, to our knowledge not present in literature.

6.3. Medical applications of numerical models

- *Influence of Transmural Slow-Conduction Zones on the Long-Time Behaviour Of Atrial Arrhythmia. A Numerical Study with a Human Bilayer Atrial Model. [20], [31], [16]*

  Atrial fibrosis is known to be a factor in the perpetuation of atrial arrhythmia. Despite the thinness of atrial tissue, the fibrosis distribution may not be homogeneous through the entire thickness of the atria. The aim of this study is twofold. 1) We want to elucidate the respective influences of a transmural and a non-transmural distribution of fibrosis, described as a slow conduction zone, on the perpetuation of a rotor-like arrhythmic episode, compared to a control situation. 2) We aim to assess which is the more efficient ablation protocol between a) a lesion-box ablation, b) an ablation line connecting the fibrotic zone to the closest anatomical obstacle, c) ablation spots.

  We used a bilayer monodomain representation of the atria that included transmural heterogeneities of fibre organisation, and an arrhythmic scenario composed of a rotor initiated near the pulmonary veins. This model allowed long simulations for a sustainable computational load. We observed that when the fibrosis was transmural, the centre of the rotor was anchored in the slow conduction zone and was stable during a 10 seconds simulation, whereas the other simulations showed meandering rotors that disappeared after a few seconds. In our model framework, only a transmural fibrosis distribution had a stabilizing effect on reentrant circuits. Furthermore, the lesion-box ablation and the line ablation were able to stop the arrhythmia, unlike the spot lesions. The bilayer model proved to be a good trade-off between accuracy and speed for observing the influence of transmural heterogeneities on atrial arrhythmia over long periods.

- *Effects of L-type Calcium channel and hERG blockers on the electrical activity of the human heart: A simulation study.*

  Class III and IV drugs affect cardiac hERG (IKr) and L-type calcium (ICaL) channels, resulting in complex alterations in repolarization with both anti and pro-arrhythmic consequences. Interpretation of their effects on cellular and ECG-based biomarkers for risk stratification is challenging. As pharmaceutical compounds often exhibit multiple ion channel effects, our goal is to investigate the simultaneous effect of ICaL and IKr block on human ventricular electrophysiology from ionic to ECG level. ECG simulations show that ICaL block results in shortening of the QT interval, ST elevation and reduced T wave amplitude, caused by reduction in APD and AP amplitude during

the plateau phase, and in repolarization times. In contrast, IKr block results in QT prolongation and reduced T wave amplitude. Combined ICaL and IKr block are combined, the degree of ICaL block strongly determines QT interval whereas the effect of IKr block is more pronounced on the T wave amplitude.

6.4. Inverse problems

- *A Steklov-Poincaré approch to solve the inverse problem in electrocardiography [23]*

  In the cardiac electrophysiology imaging commu- nity the most widely used approach to solve the inverse prob- lem is the least square formulation with different Thikhonov regularizations. Clinicians are not yet fully satisfied by the technology that solves the inverse problem. Reformulating the inverse problem could bring new techniques to solve it. In this paper we use the Steklov-Poincare ´ formulation of the Cauchy problem in order to solve the inverse problem in electrocardiography imaging. We present in this work the technique and an algorithm of gradient descent. We also show numerical results based on simulated synthetical data.

- *A machine learning regularization of the inverse problem in electrocardiography imaging [22]*

  Radio-frequency ablation is one of the most ef- ficient treatments of atrial fibrillation. The idea behind it is to stop the propagation of ectopic beats coming from the pulmonary vein and the abnormal conduction pathways. Medical doctors need to use invasive catheters to localize the position of the triggers and they have to decide where to ablate during the intervention. ElectroCardioGraphy Imaging (ECGI) provides the opportunity to reconstruct the electrical potential and activation maps on the heart surface and analyze data prior to the intervention. The mathematical problem behind the reconstruction of heart potential is known to be ill posed. In this study we propose to regularize the inverse problem with a statistically reconstructed heart potential, and we test the method on synthetically data produced using an ECG simulator.

- *Inverse problem in electrocardiography via factorization method of boundary value problems : How to reconstruct epicardial potential maps from measurements on the torso ? [26]*

  We are working on a new approach for solving the inverse problem of electrocardiography. This approach is based on an invariant embedding method: the factorization method of boundary values problems [35]. The idea is to embed the initial problem into a family of similar problems on subdomains bounded by a moving boundary from the torso skin to the epicardium surface. For the direct problem this method provides an equivalent formulation with two Cauchy problems evolving on this moving boundary and which have to be solved successively in opposite directions. This method calculates Neumman-Dirichlet and Dirichlet-Neumann operators on this moving boundary that satisfy Riccati equations. Regarding the inverse problem, mathematical analysis allows to write an optimal estimation of the epicardial potential based on a quadratic criterion. Then, the ill-posed behaviour of the inverse problem can be analyzed and a better regularization and discretization of the problem can be proposed. One of the advantages of this method is the computation of the potential at different times during cardial cycle: it is not necessary to repeat the resolution of all the equations at every time. In a first time the simplar case of a cylinder is considered. In a second time the method is applied to the 3D model of concentric spheres. The next step will be to use 3D deformed surfaces.

- *Reconstruction of 3D depolarization wavefronts from surface optical mapping images [33]*

  Starting from the diffusion-absorption equation of light in a tissue we solved the forward problem for excitation light using the `FreeFem++` software (www.freefem.org/ff++). We first considered a spherical wave front expanding in time: the tissue is depolarized inside the sphere. This choice allowed us to locate the position of the excitation. Using this representation of the wavefront, we obtained in silico data. We defined a functional to minimize and implemented the BFGS method to solve the inverse problem. We tested our method on in silico data and obtained good results. We next compared our results with an approach developed by Khait [36] and found that our method is more accurate and that we have less restrictions for the convergence of the method. We modified the wave front into ellipsoid in order to start working on experimental data.

7. Bilateral Contracts and Grants with Industry

7.1. Contract Medic Activ between Inria and Interaction Healthcare (Groupe Interaction)

The contract between Interaction Healthcare and Inria was signed on April, 13th, 2013.

Aiming to develop a numerical platform for simulation in medicine called « Medic Activ », the society Interaction Healthcare requested the help of the team Carmen, within a call for project entitled « serious games » from the Région Aquitaine.

The team Carmen will provide its expertise in numerical simulation of cardiac electrophysiology and the ECG (ElectroCardioGram), based on realistic human datasets. The society Interaction Healthcare is specialized in the design and creation of digital services and e-health. The complementarity between both partners is mandatory for the project to start on a coherent scientific basis.

The human resources engaged on the Inria side includes a engineer deveoted to the transfert side of the project, while a postdoc will be recruited to work on the research of the project (additional funding from *Agence AMIES*, see below).

8. Partnerships and Cooperations

8.1. Regional Initiatives

- Project Modélisation pour les données multimodales (2012-2015) funded by the Conseil Regional Aquitaine. Coordinator J.-F. Aujol (Pr University Bordeaux 1). The PhD of G. ravon is funded within this project: 3D reconstruction by inverse problem in cardiac optical mapping.

8.2. National Initiatives

8.2.1. IHU LIRYC

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

- For 2013: the salary of M. Potse, member of Carmen, is payed by the LIRYC.
- The LIRYC gives us a partial financial support. In 2013: support to go to the conference IEEE EMBC in Osaka, Japan (http://embc2013.embs.org), and partial support for a PhD jury.
- For 2012-2015: 1/2 PhD thesis associated to the project *Modélisation pour les données multimodales* (see section Regional Initiaves).

8.2.2. ANR HR-CEM

In 2013, we obtained a financial support 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. Nantes, Univ. Pau and BCAM (Basque Center for Applied Math) at Bilbao (Spain).

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 that take advantage of in-silico cardiac simulation and, hopefully, become references. In particular we shall provide the first exhaustive model of an animal heart including the four chambers coupled through the special conduction network, with highly detailed microstructure of both the atria and the ventricles. Such a model embedded in high-performance computational software will provide stronger medical foundations for in-silico experimentation, and elucidate mechanisms of cardiac arrhythmias.

8.2.3. 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.

8.2.4. 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 JF. 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 project is in its starting phase in 2013: the objective of the first 6 months is to define precisely the nature and objectives of the common laboratory between Inria and Notocord. A contract is planned to be signed after these 6 months, and the ANR financial support to be granted at that time.

8.3. European Initiatives

8.3.1. Collaborations with Major European Organizations

Partner 1: Computational Biology Group, Department of Computer Science, Oxford University (United Kingdom).

Our work with the computational biology group concerns the development of multi-scale models of the drugs and their effect on the electrical activity of the heart. The main goal is to assess the drug-induced effects on the electrocardiogram, using a computational model describing the physiology from ion channel to body surface potentials.

Partner 2: BCAM (Basque Center for Applied Mathematics), Bilbao (Spain).

We collaborate with L. Gerardo Giorda, research fellow at the BCAM on: the development of our new sopftware CEPS, the design and study of new domain decomposition methods suited to our cardiac electrophysiology models, the evaluation of some sensitivity analysis issues in cardiac electrophysiology.

Partner 3: Department of Experimental Cardiology, Academic Medical Center, University of Amsterdam (Netherland).

With the groups of Pr J. de Bakker and of Dr R. Coronel, we work on the arythmias related to degradations of the tissues (due to aging or cardiomyopathies), combined with diseases of the ionic channels, qsuch as the Brugada syndrome.

8.4. International Initiatives

8.4.1. Inria International Partners

8.4.1.1. Informal International Partners

- Collaboration with the Pr. Y. Bourgault (http://aix1.uottawa.ca/ ybourg/personal.html) from the department of Mathematics and statistics of the University of Ottawa (Canada).

  Subject: models and numerical methods for cardiac electrophysiology.

  Support: This collaboration has been supported by the ANR project Momme (ANR-JCJC-07-0141), the Region des Pays de la Loire and the Natural Sciences and Engineering of Research council of Canada (NSERC). From 2013, it is supported by the ANR project HR-CEM. Y. Bourgault had an "invited researcher" position at Inria for two months for October and November, 2013.

8.4.2. Inria International Labs

- LIRIMA: Equipe Problèmes Inverses et Contrôle (EPIC), University Tunis Al Manar et Laboratoire de Modélisation Mathématique et Numérique dans les Sciences de l'Ingénieur (LAMSIN), Tunisia.

  The EPIC team has an important experience in dealing with ill-posed inverse problems for static and evolution problems. The goal of this collaboration is to apply the methods developed in this team to inverse problems in electrocardiography.

  This collaboration is mainly supported by the international laboratory LIRIMA.

8.5. International Research Visitors

8.5.1. Visits of International Scientists

- Y. Bourgault, Pr. University of Ottawa, Department of mathematics and statistics. Invited researcher for 2 months, 1/10/2013 to 30/11/2013.

  Comparison between the monodomain and bidomain models for cardiac electrophysiology, and design of an optimalmonodomain aprroximation of the nidomain equations.
- In July, 2013, B. Smaill, Professor at the Auckland Bioengineering Institute (ABI) and leader of the Cardiac Electrophysiology group, and M. Nash, Professor and Associate Director of the ABI, visited the LIRYC Institute, including a visit to our team Carmen and rich exchanges about our approaches of modelling and the role of experimental data.
- Mohamed Jebalia, Assistant professor, ENIT (Tunisia), researcher from the LAMSIN, May toJuly 2013.

8.5.1.1. Internships – Visiting PhD Students

- Mohammed Addouche, March 2013.

  Institution: University of Tlemcen (Algeria)

  Subject: On using factorisation methods for the quasistatic inverse problems of electrocardiology.
- Najib Fiakl, PhD student, December 2013.

  Institution: University of Rabat (Morroco)

  Subject: Study of the uncertainties on the thoracic electrical conductivities on the resolution of the direct problem of electrocardiology.
- Wajih Mbarki, November to December 2013.

  Institution: Université El Manar of Tunis, Tunisia

  Subject: Theoretical and numerical study of the Purkinje-muscle coupling in cardiac electrophysiology.
- Jamila Lassoued, September 2013.

  Institution: ENIT of Tunis, Tunisia

  Subject: application of model reduction techniques to the inverse problems in cardiac electrophysiology.

- Laura Bear, October to December 2013, was co-localized between the LIRYC and Inria.

  Institution: University of Auckland (New Zealand), Auckland Bioengineering Institute

  Subject: Laura started to work on our inverse solutions for the cardiac electrical imaging problem using the datasets obtained during the first two years of her PhD at the Auckland Bioengineering Institute. The objective is to investigate the possibility and limitations of cardiac non-invasive electrical imaging.

8.5.1.2. Internships

- Hamed Bourenane, July to August 2013

  Institution: Student in medicine at the University Bordeaux Segalen

  Subject: Segmentations of CT-scan images from the CardioInsight system including fat, bones, lungs, etc.

- Valentin heisel, June to September 2013

  Institution: ENSEIRB-MATMECA

  Subject: Developped a fortran module to account for 2nd order solvers in cardiac electrophysiology and compared various solvers for cellular electrophysiology.

- Nina Le Devehat, June to July 2013

  Institution: First year of University Bordeaux I, supported by the programme “stages d’excellence” from the University

  Subject: She studied the modelling of cellulat electrophysiology by the Vanderpol equations.

- Abdessamad Sobhi, July to September 2013

  Institution: ENSEIRB-MATMECA

  Subject: Inverse problem of cardiac electrophysiology.

- Thibaut Vandromme, June to September 2013

  Institution: ENSEIRB-MATMECA

  Subject: Fast solvers for cardiac electrophysiology, continued the work in SOFA of a previous trainee (N. Claude in 2012).

- Bastien Verot, June to September 2013

  Institution: ENSEIRB-MATMECA

  Subject: Numerical approximation of the microscopic bidomain equations of cardiac electrophysiology in a simplified linear context.

- Mathias Cassonnet, January 2013

  Institution: secondary school pupil

  Subject: Trainee for observation only

- Alexandre Lourenco Peirera, January 2013

  Institution: secondary school pupil

  Subject: Trainee for observation only

8.5.2. Visits to International Teams

- Y. Coudière visited the GIREF (« Groupe Interdisciplinaire de Recherche en Éléments Finis »), June, 2013.

9. Dissemination

9.1. Scientific Animation

- The members of the team are regular reviewers for international journals and conferences in applied mathematics, biomedical engineering, cardiac electrophysiology, and electrocardiography.
- N. Zemzemi was a member of the Inria delegation at the India-France technology summit, New delhi, October 23-24th, 2013.
- Y. Coudière did participate to the organization of the First Scientific Workshop of the LIRYC, October, 24-25th, 2014.
- Y. Coudière is a member of the Scientific Committee of the international conference on « Finite Volume for Complex Application », to be held in Berlin, June, 2014, www.wias-berlin.de/workshops/fvca7.
- Y. Coudière is a member of CAIMS, The Canadian Applied and Industrial Mathematics Society, and presented the work of Carmen during the CAIMS conference in Québec, June, 2013.
- Y. Coudière is the scientific coordinator of the ANR research project HR-CEM.
- S. Labarthe presented the work of Carmen based on HPC solvers at the PlaRim day, April, 2014, LABRI, Bordeaux.
- S. Labarthe presented his work at the « Printemps de la Cardiologie », the national conference of the French Cardioolgist Society, held in April 2013 in Marseille, and was invited to the symposium "AF: Clinical challenges for biophysical modelling" in London, June, 2013.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Licence : S. Labarthe, *Probabilities and statistics, introduction to databases*, 64 h eqTD, IUT HSE U Bordeaux 1.

Engineering school: S. Labarthe, *Scientific computing with Fortran 90*, 96h eqTD, ENSEIRB-MATMECA, IPB.

Engineering school: N. Zemzemi, *Scientific computing project: finite elements method application to cardiac electrophysiology*, 2nd year, 28h eqTD, ENSEIRB-MATMECA, IPB.

Engineering school: F. Caro, *TER* 2nd year, 6h eqTD, ENSEIRB-MATMECA, IPB.

Engineering school: F. Caro, *Finite elements, variational formulation and Sobolev spaces*, 36h eqTD, Institut Galilée, Univ. Paris 13.

Engineering school: Y. Coudière, *TER* 2nd year, 6h eqTD, ENSEIRB-MATMECA, IPB.

Cursus Ingénieur: Y. Coudière, *project in scientific computing, F90* 1st year, 16h eqTD, ENSEIRB-MATMECA, IPB.

Master : Y. Coudière, « *Analyse numérique approfondie* », 36h eqTD, M2, Univ. Bordeaux 1.

9.2.2. Supervision

PhD : S. Labarthe, « Modélisation de l'activité électrique des oreillettes et des veines pulmonaires », Université Bordeaux Segalen, December, 13th, 2013, supervised by Y. Coudière and J. Henry.

PhD in progress : A. Davidovic, Modelling the cardiac ventricular structural heterogeneities, started on October 2012, supervised by Y. Coudière and C. Poignard.

PhD in progress : G. Ravon, An inverse problem for cardiac optical mapping, started on October 2012, supervised by Y. Coudière and A. Iollo.

PhD in progress : J. Lassoued, « Construction de methodes de reduction de modèle pour le problème d'estimation de parametres en electrophysiologie cardiaque », co-supervized by N. Zemzemi with Moncef Mahjoub, École Nationale d'Ingénieur de Tunis (Tunisia).

PhD in progress : W. Mbarki, « Etudes thérique et numérique du couplage purkinje-myocarde en electrophysiologie cardiaque », co-supervised by N. Zemzemi with Saloua Aouadi, Faculté des sciences de Tunis (Tunisia).

9.2.3. Juries

- Y. Coudière was a member of the jury for defense of the PhD of V. Desveaux, « Contribution à l'approximation numérique des systèmes hyperboliques », Université de Nantes, November 26th, 2013.
- Y. Coudière was a member of the jury for defense of the PhD of S. Labarthe, « Modélisation de l'activité électrique des oreillettes et des veines pulmonaires », Université Bordeaux Segalen, December, 13th, 2013

9.3. Popularization

- S. Labarthe, Forum Emploi Maths 2013, invited for an intervention to the round table « Témoignages : métiers du secteur santé », 01/2013, Paris.
- S. Labarthe and G. Ravon welcomed two secondary school pupils for a week dedicated to the observation of research work in our team and the Inria research center.
- N. Zemzemi, recieved 4 groups of pupils in final year of high school, that were following a special option on computer, numerical sciences. He animated a workshop on modelling for health sciences.
- The team was represented by N. Zemzemi at the « Rencontre Inria-Industrie » (meeting Inria – Industry) on: Modelling, simulation, and high-performance computing, Paris, June 11th, 2013.
- A. Davidovic presented herself and her work during a meeting with the public called « Visages de sciences », organized at « Cap Sciences », Bordeaux, Spring 2013.

10. Bibliography

Major publications by the team in recent years

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