Activity Report 2014

Team CARMEN

Modélisation et calculs pour l'électrophysiologie cardiaque

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

Creation of the Team: 2011 October 01.

1. Members

Research Scientists

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    Mark Potse [Inria]

    Nejib Zemzemi [Inria]

Faculty Member

    Yves Coudiere [Team leader, Univ. Bordeaux, Professor, HdR]

Engineers

    Emanuela Abbate [Inria, from Nov 2014]

    Dragan Amenga Mbengoue [Inria]

    Mehdi Juhoor [Inria, until Nov 2014]

PhD Students

    Pierre-Elliott Bécue [Inria and Maison de la Simulation, from Oct 2014]

    Andjela Davidovic [Inria]

    Charlie Douanla Lontsi [Inria, from Nov 2014]

    Gwladys Ravon [Inria]

Post-Doctoral Fellows

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    Jason Bayer [Univ. Bordeaux]

    Myriam Rioux [until Aug 2014]

Visiting Scientists

    Najib Fikal [PhD, Inria]

    Mohammed Addouche [PhD, Inria, until Jun 2014]

    Carlos Chavez Borges [PhD, from May 2014 to Sep 2014]

    El Mahdi El Guarmah [Prof. of Univ., Jun 2014]

    Ali Gharaviri [PhD, from Apr 2014 to May 2014]

    Wajih Mbarki [PhD, until Aug 2014]

    Jamila Lassoued [PhD Univ Tunis, until Aug 2014]

Administrative Assistant

    Chrystel Plumejeau [Inria]

Others

    Thomas Roy [Master student, from Nov 2014 to january 2015]

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    Colin Larrue [Inria, Master MIMSE, Univ.Bordeaux, from May 2014 to Aug 2014]

    Paul Picq [Inria, Master MIMSE, Univ. Boreaux, from May 2014 to Aug 2014]

    Cesare Corrado [until Apr 2014]

    Simon Labarthe [Inria, until Aug 2014]

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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.

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 [8] 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 [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.

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. New 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 Electro-physiology 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 the ADT, we are now able to use CEPS for the benchmark named *Second N-version Cardiac Electrophysiology Benchmark Specification actual developments*, see (benchmarck) for more details.

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

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 and works with arbitrary model geometries. It runs efficiently on high-performance computing systems with many thousands of cores, including a "difficult" system such as the BlueGene/Q "Turing" at IDRIS. 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 electro-cardiographic 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. YAPI: A new project for the development of a platform for the simulation of the electrophysiology cardiac with CEPS

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. Highlights of the Year

- New associated team EPICARD (principal investigator N. zemzemi, Y. Coudière and J. Henry). The aim of of this associated team for the first year is to overcome the technical difficulties that we pointed out during the year 2014 in inverse problem for the heart.

- June 2014: Based on a peer-reviewed proposal, the Grand équipement national de calcul intensif (GENCI) has attributed us 3 million core-hours on the national high-performance computing system Turing, to be used in the year 2014.

- December 2014: Based on a peer-reviewed proposal, the Grand équipement national de calcul intensif (GENCI) has attributed us 3.5 million core-hours on the national high-performance computing machines Turing, Curie, and Occigen, to be used in the year 2015.

- LIRYC will fund a 2-year postdoctoral position on simulation of Brugada syndrome, a rare ECG anomaly predictive of sudden cardiac death in young, apparently healthy subjects. This work will be performed in tight collaboration with clinicians at the Haut-Lévèque hospital

6.2. Inverse problem

We tested our method using synthetic data generated with a highly realistic forward model. Propagating action potentials were generated using a monodomain reaction-diffusion model with a Ten Tusscher 2006 membrane model. An anisotropic human heart model at 0.2-mm resolution was used for this purpose. Torso potentials were then computed from the simulated transmembrane currents using a finite-difference torso model at 1-mm resolution with intracavitary blood, anisotropic myocardium, lungs, and an anisotropic skeletal muscle layer. We simulated 20 cases: 5 single stimuli, 1 dual stimulus and 14 re-entry simulations. From the simulated torso potentials a 200-channel body surface map recording was extracted and used to test the inverse methods. Inverse solutions in terms of epicardial potentials were computed both with MFS and with our .new optimal control approach. With our algorithms, we were able to construct the electrical potential on the heart surface with a very good accuracy in terms of correlation coefficient. Thus, we could accurately reconstruct the activation pattern.

6.3. CEPS

- Integration of some ionic models into CEPS (N. Zemzemi and F. Caro). Those developments will allow us now to use CEPS for the benchmark named *Second N-version Cardiac Electrophysiology Benchmark Specification actual developments*, see (benchmarck) for more details.

- Development of usefull tools for the code (compilation in order to check the depandancies, validation and coverage of the code). 16 test cases are now implementated in CEPS. Those test cases concern unit test case as test for small resolution of linear system (for the FE P1 implemented into the code) and validatation test case as the heat PDE problem. Tests verify also the parallel implementation.

- At this time, the development of the bi-domain model in CEPS is in progress in CEPS with N. Zemzemi.

- First integration of the new model of S. Labarthe initiated during his PhD with L. Colin. This task needs improvment for validation in terms of development.

6.4. Numerical Scheme

Y. Coudière, C. Pierre and R. Turpault wrote some new high order FV schemes. The goal of this study is a future implementation in CEPS.

6.5. Mathematical Model

M. Potse, P.E. Becue and F. Caro wrote a new model for numerical simulations for cardiac electrophysiology at the microscopic scale. We interfer with the LIRYC in order to describe, as much as possible, the interactions between the extra-cellular medium and the intra-cellular medium.

7. Partnerships and Cooperations

7.1. Regional Initiatives

Modélisation of the multinodal date (years 2012–2015) funded by the Conseil Regional Aquitaine. Coordinator J.-F. Aujol (Pr University Bordeaux). The PhD of G. ravon is funded within this project: 3D reconstruction by inverse problem in cardiac optical mapping.

7.2. National Initiatives

7.2.1. IHU LIRYC

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

- For 2014: the salary of M. Potse, member of Carmen, is payed by the LIRYC..

- For 2012-2015: 1/2 PhD thesis associated to the project *Modélisation pour les données multimodales* (see section Regional Initiaves).

7.2.2. 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 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.

7.2.3. *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.

7.2.4. *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.

7.2.5. *REO*

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

7.2.6. *MedicActiv*

The CARMEN team cooperate in interaction with the MedicActiV project.

7.3. International Initiatives

7.3.1. *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.

- Cooperation with Laboratoire de Modélisation Mathématique et Numérique dans les Sciences de l'Ingénieur (LAMSIN in Tunisia.

7.4. International Research Visitors

7.4.1. *Visits of International Scientists*

In the framework of the EPIC project in the LIRIMA lab, N. Zemzemi has invited:
- Mohamed Jebalia assistant professor from LAMSIN Tunisia
- Moncef Mahjoub assistant professor from LAMSIN Tunisia
- Jamila Lassoued. Phd student from LAMSIN Tunisia
- Najib Fikal PHD student from University MohamedV, Moroco
- El Mahid El Guarmah assitant professor from University of Marrakech. Moroco.

7.4.2. Internships – Visiting PhD Students

- Carlos Chavez Borgesn, from may 2014 to Sep 2014,*Inverse Problem of Electrocardiography: estimating the location of cardiac isquemia in a 3D geometry*
- Ali Gharaviri, from Apr 2014 to May 2014
- Wajih Mbarki, until Aug 2014, *Analysis of an interaction problem in biomathematics: purkinje/myocardium coupling in the heart*
- Jamila Lassoued, until Aug 2014, *Construction of reduced order methods for optimization problems in cardiac electrophysiology*

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific events selection

- Y. Coudiére member of the Scientific Commity for the international conference FCVA "Finite Volumes for Complex Applications", Berlin, juin 2014.".
- From the 1st january 2014, Y. Coudière is in charge of the team CSM at the IMB.
- From september 2014, Y. Coudière is in charge of the Licence "Ingénérie Mathématiques" at the university of Bordeaux.

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

License : S. Labarthe, *pre-BAC Analysis and Geometry*, 24 h eqTD.

License : S. Labarthe, *Introduction to analysis*, 48 h eqTD.

License : S. Labarthe, *Help for the redaction of a resume*, 21 h eqTD.

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)*, 28 h eqTD

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.

8.2.2. Supervision

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, strted on october 2013, co-supervized by N. Zemzemi with Moncef Mahjoub, École Nationale d'Ingénieur de Tunis (Tunisia).

PhD in progress: W. Mbarki, Études thérique et numérique du couplage purkinje-myocarde en electrophysiologie cardiaque, started on october 2013, co-supervised by N. Zemzemi with Saloua Aouadi, Faculté des sciences de Tunis (Tunisia).

PhD in progress: P.E. Bécue, Numerical simulations for cardiac electrophysiology at the microscopic scale, started on october 2014, co-supervised by M. Potse with F. Caro, U. Bordeaux and Maison de la Simulation at Saclay.

8.2.3. *Juries*

- Y. Coudière, reviewer, PhD of Elisa Schenone, 26 Nov. 2014
- M. Potse, member, D Carlos Sánchez Tapia, Universidad de Zaragoza, Zaragoza, Spain, 23 June 2014.
- M. Potse, member, PhD Annabelle Collin, Univ. Pierre et Marie Curie, Paris VI; France, 6 Oct. 2014

8.3. 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.
- S. Labarthe presented the work of the team at the June session of the Inria Bordeaux-Sud Ouest "Unithé ou café" scientific diffusion presentation.

9. Bibliography

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