Activity Report 2012

Team CARMEN

Modélisation et calculs pour l'électrophysiologie cardiaque

RESEARCH CENTER
Bordeaux - Sud-Ouest

THEME
Observation, Modeling, and Control for Life Sciences

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Team CARMEN

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

The team Carmen is part the the Liryc Institute (http://www.ihu-liryc.fr). It belongs to the modelling group of the institute and its research participates to the realisation of the WP of the Liryc project.

Creation of the Team: October 01, 2011 .

1. Members

Research Scientist
Nejib Zemzemi [Junior research scientist]

Faculty Members
Mostafa Bendahmane [Maître de conférence, Université Bordeaux Segalen, HdR]
Yves Coudière [Team Leader, professeur, Université Bordeaux 1, HdR]

External Collaborators
Ed Vigmond [Research Fellow on a Liryc funding, Université Bordeaux 1]
Charles Pierre [Research Engineer CNRS, Laboratoire de Mathématiques de Pau]

Engineer
Mehdi Juhoor [Young engineer working on the ADT Cep-Liryc, arrived on November 2012]

PhD Students
Andjela Davidovic [Arrived in October 2012]
Simon Labarthe [Université Bordeaux 2, funding from Hopital du Haut-Lévêque]
Gwladys Ravon [Funding from Liryc and CRA, arrived in October 2012]

Post-Doctoral Fellow
Myriam Rioux [Fellowship from FQRNT (Fond Québecois pour la Recherche – Nature et Technologie) – Maternity leave from July to December 2012]

Administrative Assistant
Chrystel Plumejeau [Shared with other teams]

2. Overall Objectives

2.1. Overall Objectives

The team Carmen plans to develop some 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

- S. Labarthe was awarded the poster price for the theoretical and applied aspects of his work on atrial modeling by to distinct communities:
  - poster award by the medical community after at the « printemps de la cardiologie 2012 »;
  - poster award by the applied mathematics community at the CANUM 2012.
- N. Zemzemi: best poster presentation award at the international conference Computing in Cardiology 2012 (CINC'2012), [25].

3. Scientific Foundations

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 [11], [3], [12] 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 [13], [14] and [19] and [2], 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. New Results

5.1. Models

- [12]: we explain the links between the solutions of the bidomain and monodomain models using some analytical arguments. The result is partially based on the theory of the bidomain operator explained in [11].
- [23]: Fibre structure and anisotropy is a determinant issue to provide accurate simulations of the electrical activity of atrial tissue. Though, atrial fibre architecture remains unreachable to standard imagery techniques on patients. A method to construct models of the fibre architecture on patient-specific geometries is then a key for numerical simulations of atrial tissues. Such a method is proposed. Pathological and non pathological patient specific surface models of the left atria (LA) are defined. Hence, a pathological scenario is explored : a mechanism of micro- reentry in the left superior pulmonary vein (LSPV) and its interaction with the sinus rhythm (SR).

5.2. Numerical techniques

- [19]: In this paper we propose a preconditioning for the bidomain model either for an isolated heart or in an extended framework including a coupling with the surrounding tissues (the torso). The preconditioning is based on a formulation of the discrete problem that is shown to be symmetric positive semi-definite. A block LU decomposition of the system together with a heuristic approximation (referred to as the monodomain approximation) are the key ingredients for the preconditioning definition. Numerical results are provided for two test cases: a 2D test case on a realistic slice of the thorax based on a segmented heart medical image geometry, a 3D test case involving a small cubic slab of tissue with orthotropic anisotropy. The analysis of the resulting computational cost (both in terms of CPU time and of iteration number) shows an almost linear complexity with the problem size, i.e. of type nlogα(n) (for some constant α) which is optimal complexity for such problems.

5.3. Medical applications of numerical models

- [26]: We computed some bidomain solutions for use by M. Pop and M. Sermesant in the STACOM'11 challenge from the MICCAI 2011 conference and derived collaborative article [26].
- [18]: The aim of this study was to describe a new familial cardiac phenotype and to elucidate the electrophysiological mechanism responsible for the disease. Mutations in several genes encoding ion channels, especially SCN5A, have emerged as the basis for a variety of inherited cardiac arrhythmias. Three unrelated families comprising 21 individuals affected by multifocal ectopic purkinje-related premature contractions (MEPPC) characterized by narrow junctional and rare sinus beats competing with numerous premature ventricular contractions with right and/or left bundle branch block patterns were identified. All the affected subjects carried the same transition in the SCN5A gene. Patch-clamp studies revealed a net gain of function of the sodium channel, leading, in silico, to incomplete repolarization in Purkinje cells responsible for premature ventricular action potentials. In vitro and in silico studies recapitulated the normalization of the ventricular action potentials in the presence of quinidine.

- [22]: In some cases, the standard methods to construct activation maps based on the derivatives of the signals may lead to inaccurate results. In this paper, we evaluated a novel Directional Activation Algorithm (DAA) based on EGM analysis. The DAA calculates the time delays between adjacent EGMs and assigns to each a localized propagation vector. The accuracy of the proposed methodology is compared with known activities obtained from a monodomain, isotrope, Beeler-Reuter model of the atria.
- [20]: Although the ECG is a widely used tool, the ionic basis underlying its changes caused by drugs and diseases are often unclear. In this work we present a computational model of the human ECG capable of representing drug-induced effects from the ionic to the surface potential level. We use the state-of-the-art bidomain model coupled to a membrane kinetics model in the heart and the Laplace equation in the torso. The membrane kinetics are represented by a detailed physiological human action potential model. We modified the potassium (respectively sodium) representation in the model in order to introduce the ion channel/drug interactions representing classIII (respectively class I) drugs. The drug model is represented by an ion channel conduction block depending on the IC50 value and the drug dose. We conduct numerical simulation of the ECGs measured on the surface of the thorax and could assess each of the potassium and sodium block effects (for class I and class III drugs).

5.4. Inverse problems

- [24]: The treatment of atrial fibrillation has greatly changed in the past decade. Ablation therapy, in particular pul- monary vein ablation, has quickly evolved. However, the sites of the trigger remain very difficult to localize. In this study we propose a machine-learning method able to non-invasively estimate a single site trigger. The machine learning technique is based on a kernel ridge regression algorithm. In this study the method is tested on a simulated data. We use the monodomain model in order to simulate the electrical activation in the atria. The ECGs are computed on the body surface by solving the Laplace equation in the torso.
- [16]: In the present paper, an optimal control problem constrained by the tridomain equations in electrocardiology is investigated. The state equations consisting in a coupled reaction–diffusion system modeling the propagation of the intracellular and extracellular electrical potentials, and ionic currents, are extended to further consider the effect of an external bathing medium. The existence and uniqueness of solution for the tridomain problem and the related control problem is assessed, and the primal and dual problems are discretized using a finite volume method which is proved to converge to the corresponding weak solution. In order to illustrate the control of the electrophysiological dynamics, we present some preliminary numerical experiments using an efficient implementation of the proposed scheme.
- [17]: This note is devoted to the analysis of the null controllability of a nonlinear reaction–diffusion system, approximating a parabolic–elliptic system, modeling electrical activity in the heart. The uniform, with respect to the degenerating parameter, null controllability of the approximating system by a single control force acting on a subdomain is shown. The proof needs a precise estimate with respect to the degenerating parameter and it is done combining Carleman estimates and energy inequalities.

6. Partnerships and Cooperations

6.1. 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.

6.2. National Initiatives

6.2.1. IHU Liryc

Our work is partially funded by the Liryc project.

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

6.3. European Initiatives

6.3.1. Collaborations with Major European Organizations

Partner 1: CNR, IMATI (Italie) – G. Manzini.

Finite volume discretization on general, distorted meshes, for second order operators with anisotropy and discontinuities. Applications to the simulation of ECG.

Partner 2: Computational Biology Group, University of Oxford. Department of Computer Science (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.

6.4. International Initiatives

6.4.1. Inria 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:* for the last years the collaboration was 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
- Equipe Problèmes Inverses et Contrôle (EPIC), University Tunis Al Manar. 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.

6.5. International Research Visitors

6.5.1. Visits of International Scientists

- Y. Bourgault, Pr. Univeristy of Ottawa, Department of mathematics and statistics. 22/10/2012 to 26/10/2012.

  Comparison between the monodomain and bidomain models for cardiac electrophysiology.
- Moncef Mahjoub, Teaching assistant at University of Tunis Al Manar (ENIT-LAMSIN), Tunisia. 01/10/2012 to 06/10/2012.

  Inverse problems.
- Fadhel Jeday. Teaching assistant at University of Sousse, Tunisia. 03/12/2012 to 07/12/2012.

  Inverse problems.

6.5.1.1. Internships

Nicolas Claude (from July 2012 until September 2012)

Subject: Real-time simulation of ECGs based on the finite element Sofa library developed at Inria Lille.

Institution: ENSEIRB-MATMECA, Bordeaux (Master 1 student).

Jamila Lassoued (from August 2012 until November 2012)

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

Institution: Ecole Nationale d'Ingénieurs de Tunis (Tunisia – Master 2 student)

Sinda Ben Khalfalla (from 04/12/2012 to 21/12/2012)

Subject: Inverse problems for the quasistatic inverse problem in electrocardiology.

Institution: Ecole Nationale d'Ingénieurs de Tunis (Tunisia – PhD student)

Mohammed Addouche (from 08/12/2012 to 05/01/2013)

Subject: On using factorisation methods for the quasistatic inverse problems of electrocardiology.

Institution: University of Tlemcen (Algeria – PhD student)

7. Dissemination

7.1. Scientific Animation

- reviewing for (many) applied mathematics journals
- N. Zemzemi was an Invited speaker in *Workshop on Efficient Solvers in Biomedical Applications*. July 2-5, 2012 Graz, Austria.
- Leading the cardiac challenge group in *the 3rd VPH NoE Study Group*. Plenary session on Cardiac modeling challenges (1h) + 4 hours course (cardiac modeling, mathematical methods in cardiac elecrtphysiology, drug modeling and computational tools in cardiac electrophysiology). May 7-11, 2012. Barcelona, Spain.
- Invitation to give a presentation at the *Inria-Bcam workshop*, Bilbao, 2012.
- LAMSIN Seminar: 6 hours course on cardiac modeling for the EPIC groupe (*Équipe Proble`mes Inverses et Contrôle*), Forward and inverse problem in cardiac electrophysiology. June 18-21, 2012, Tunis, Tunisia.

Partial list of presentations given by the team members (besides the invitations above).

- *Printemps de la cardiologie*, March 2012.
- *Congrès d'Analyse Numérique* (CANUM), May 2012.
- *21st International Conference on Domain Decomposition Methods*. June 25-29 2012, Inria Rennes, Bretagne-Atlantique, France.
- *Computing in Cardiology 2012* conference. September 9-12 2012, Krakow, Poland.

7.2. Teaching - Supervision - Juries

7.2.1. Teaching

Licence : Y. Coudière, Calcul scientifique : résolution des grands systèmes creux, 34.66 h eq. TD, L3, Université Bordeaux 1.

Master : Y. Coudière, Analyse numérique avancée, 36 h eq. TD, M2 Enseignant, titre du cours, nombre d'heures en équivalent TD, niveau (M1, M2), Université Bordeaux 1.

Licence : Simon Labarthe, probabilité et statistique, 22 h eq. TD, première année IUT, IUT HSE, Université Bordeaux 1.

Licence : Simon Labarthe, introduction aux bases de données, 24h eq. TD, première année IUT, IUT HSE, Université Bordeaux 1.

Licence : Enseignant, titre du cours, nombre d'heures en équivalent TD, niveau (L1, L2, L3), université, pays

Master : Enseignant, titre du cours, nombre d'heures en équivalent TD, niveau (M1, M2), université, pays

Doctorat : Enseignant, titre du cours, nombre d'heures en équivalent TD, université, pays

7.2.2. Supervision

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

PhD in progress : S. Labarthe, *Modélisation de l'activité électrique cardiaque dans les oreillettes et les veines pulmonaires*, started on October 2010, supervised by Y. Coudière and J. Henry.

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

7.2.3. Juries

- Y. Coudière Reviewer and member of the jury for defense of the PhD of J. Relan, *Personalised Electrophysiological Models of Ventricular Tachycardia for Radio Frequency Ablation Therapy Planning*, June 2012.
- Y. Coudière, supervisor and member of the jury for defense of the PhD of A. Uzureau, *Modélisations et calculs de la cicatrisation osseuse. Application à la modélisation d'un bioréacteur*, December 2012.
- Recruitment commitee for an associate professor position, University of Nice, June 2012.

7.3. Popularization

- Reception of the students from *Ecole Nationale des Ponts et Chaussées*, September 2012.
- Exposé *Unithé ou café*, June 12, 2012. Inria Bordeaux Sud-Ouest. France.

8. Bibliography

Major publications by the team in recent years

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Publications of the year

Articles in International Peer-Reviewed Journals

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International Conferences with Proceedings

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