Intermediate Activity Report on the CardioSense3D Research Action

Contents

1 Introduction

This document briefly summarizes the activity of the CardioSense3D research action during the period between May 2005 and January 2008.

1.1 Overview

CardioSense3D is a 4-year large initiative action ("Action d'Envergure Nationale" in French acronymed as AEN) funded by INRIA in May 2005 dedicated to the simulation of the cardiac function. Although others AEN are planned to be launched in 2008, CardioSense3D is the unique AEN funded by INRIA so far.

The partners of CardioSense3D are structured in two circles. The first (or main) circle contains researchers of 4 INRIA research teams (Asclepios , Macs , Reo , Sisyphe) belonging to two different INRIA research centers (Asclepios is located in Sophia-Antipolis while the other teams are located in Rocquencourt, near Paris). Asclepios team focuses on cardiac image analysis, Macs on bi-solid simulation and estimation, Reo on bio-fluid and electrophysiology simulation, and Sisyphe on cardiac

control and modeling. The second circle of partners is summarized in the Table 1, where a distinction is made between clinical, industrial and academic partners.

Clinical Partners	Industrial Partners	Academic Partners
Guy Šs Hospital London	PHILIPS Medical Systems Paris	The CAIMAN research team:
and KingŠs College: R. Razavi, K. Rhode	O. Gérard	S. Lanteri, S. Piperno
Laboratory of Cardiac Energetics,	ELA Medical	The GAMMA research team:
National Institutes of Health: E. McVeigh	A. Ripart	P-L. George
Hopital Européen Georges Pompidou		The GEOMETRICA research team:
and INSERM unit 494: B. Diebold		J-D. Boissonnat, M. Yvinec
InParys, Clinique Georges Bizet		The CREATIS Laboratory :
S. Cazeau		P. Clarysse, I. Magnin
Hôpital de Bicêtre and Paris 11 University		The New Technologies Research Centre
D. Chemla		in Plzen (Czech Republic): R Cimrman
Hopital Henri Mondor Créteil :		The Medical Imaging Group at
J. Garot		University College London : D. Hawkes
		The laboratory of Mathematics Jean Leray
		Nantes University: Yves Coudière
		The robotics department of LIRMM
		in Montpellier: P. Poignet

Table 1: Second circle of partners involved in CardioSense3D

CardioSense3D has followed a 4 year multidisciplinary research projects called ICEMA and ICEMA2 that gathered most of the first circle partners of CardioSense3D (see figure 1). The creation was decided in May 2005 by the president of INRIA, Gilles Kahn, after a review of the proposal (available here) by INRIA direction committee and a specific committee of the Scientific and Technological Orientation Council researchers (acronymed as COST). This latter committee composed of researchers from different INRIA research centers with various background in computer science met on February 19th 2005 and audited the CardioSense3D proposal.

1.2 CardioSense3D Organization

The action is managed by the project leader, Hervé Delingette (Asclepios team), with the assistance of Miguel A. Fernández (Reo team), project coordinator. The executive committee of Cardiosense3D is composed of H. Delingette, M.A. Fernández and the 4 scientific leaders of the 4 INRIA teams of the first circle of partners, namely, Nicholas Ayache, Dominique Chapelle, Jean-Frédéric Gerbeau and Michel Sorine. Its role is to perform a scientific supervision of the research done and to discuss and solve managements issues between the different partners.

The partners meet in a plenary meeting twice a year, with additional meetings organized upon request. To exchange information, the web site http://www-sop.inria.fr/CardioSense3D/ has been setup by Philippe Moireau (Macs team). This web site relies on a content management system (here SPIP) in order to allow a decentralized management of the content of the site. The site has a private section and a public one. A set of mailing-lists (*e.g.* `cardiosense3d.membres at sophia.inria.fr`) have been created for email exchange within the first circle of

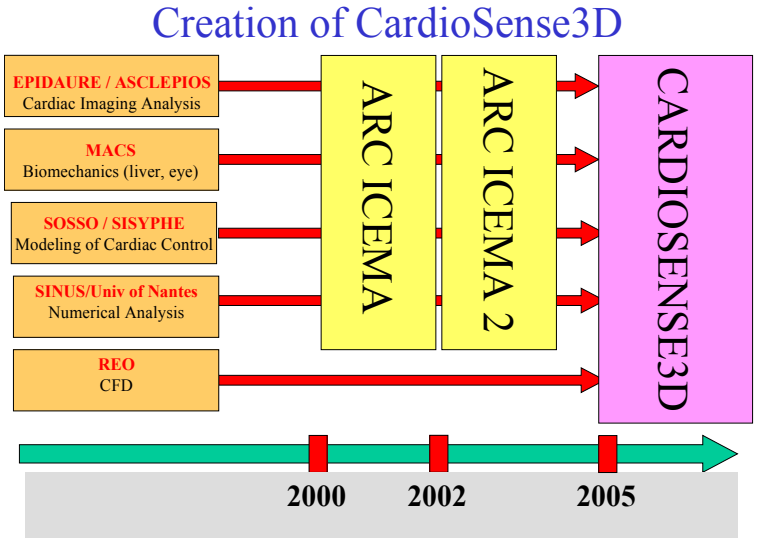

Figure 1: This diagram pictures the different research actions that lead to the creation of CardioSense3D.

partners and within all partners.

1.3 CardioSense3D Financial Support

The four INRIA teams of the first circle have received direct funding from INRIA scientific direction to partially sustain the research activity and develop collaborations with partners of the second circle. Figure 2 summarizes the funding and its split between the following categories : salary, travel and hardware. In terms of personnel, three PhD students have been recruited either through direct funding (for Asclepios team) or through Cordi scholarships (for Reo and Macs teams):

- Florence Billet in the Asclepios team started her PhD in october 2006 on the problem of estimating mechanical parameters from cardiac image sequences.
- Radomir Chabiniok in the Macs team started his PhD in septermber 2007 on the study of remodeling. Radomir is a MD from the Charles University of Prague.
- Matteo Astorino in the Reo team started his PhD in januray 2007 on the numerical simulation of the heart valves.

In addition, funding was used to hire trainees at the Master level or to complement the salary PhD students. In terms of hardware, the funding was used to acquire computers but also a digital holter monitor by the Sisyphe team.

It is important to note that the bulk of the funding and recruitment has started in the third quarter of 2006, more than one year later than the official start (may 2005) of the research action. This has been mainly caused by administrative constraints related to the fact that CardioSense3D was (and still is) the first INRIA large initiative research action.

Teams		Asclepios	Sisyphe	MACS	REO	Total
Salary	Year 2005	15 427 €				15 427 €
	Year 2006	30 000 €	30 000 €	10 000 €	10 000 €	80 000 €
	Year 2007	50 000 €	40 000 €	10 000 €	0 €	100 000 €
	Total	95 427 €	70 000 €	20 000 €	10 000 €	195 427 €
Travel expenses + Software	Year 2005	7 970 €	6 300 €		1 500 €	15 770 €
	Year 2006	18 000 €	15 000 €	16 000 €	3 000 €	52 000 €
	Year 2007	20 000 €	15 000 €	16 000 €	9 000 €	60 000 €
	Total	45 970 €	36 300 €	32 000 €	13 500 €	127 770 €
Hardware	Year 2005				2 500 €	2 500 €
	Year 2006	6 000 €	3 000 €	6 000 €	3 000 €	18 000 €
	Year 2007	2 000 €	3 000 €	3 000 €	3 000 €	11 000 €
	Total	8 000 €	6 000 €	9 000 €	8 500 €	31 500 €
	Total 2005					33 697 €
	Total 2006					150 000 €
	Total 2007					171 000 €
Grand Total	2005-2007	149 397 €	112 300 €	61 000 €	32 000 €	354 697 €
CORDI scholarship				1 Scholarship	1 Scholarship	2 Scholarships

Figure 2: Financial support received by the CardioSense3D teams during the period 2005-2007.

Finally, the Macs, Reo and Asclepios teams have hired two junior software engineers, Elsie Phè and Nicolas Toussaint, with the support of INRIA scientific direction and the direction of the Paris-Rocquencourt and Sophia-Antipolis research centers.

1.4 Personnel and Extra funding

The personnel involved in CardioSense3D includes permanent researchers of each teams but also students and staff that are funded through other means (industrial contracts, national and european projects,...).

The main permanent researchers involved are:

- **Asclepios team**: Nicholas Ayache, Hervé Delingette, Maxime Sermesant
- **Macs team**: Dominique Chapelle, Philippe Moireau, Jacques Sainte-Marie, Marina Vidrascu
- **Reo team**: Miguel A. Fernández, Jean-Frédéric Gerbeau, Irène Vignon-Clémentel, Marc Thiriet
- **Sisyphe team**: Michel Sorine, Qinghua Zhang

The students and staff involved (full time or part time) in the CardioSense3D but not funded through CardioSense3D include (non exchaustive list) :

- **Asclepios team**
  - Since 2005: PhD of J.M. Peyrat (contract with Siemens Corporate Research)
  - since 2007: PhD of D. Lepiller (contract with Philips Medical Systems Paris)

  - since 2007: PhD of T. Mansi (Eureopean project Health-e-Child)

- **Reo team**
  - 2003 - 2007: PhD of Nuno M. Diniz Dos Santos (EU RTN project HaeMOdel)
  - 2005: Post-doc of Muriel Boulakia (contract ELA medical)
  - Since 2006: PhD of Najib Zemzemi (National scholarship)
  - 2006-2007: Post-doc of Linda El Alaoui (Pôle de compétitivité Systematic)
  - Since 2007: Post-doc of Géraldine Ebrard (contract ELA Medical)

- **Sisyphe team**
  - Since 2005: PhD of M. Laleg (industrial contract)
  - Since 2005: PhD of K. Djabella (industrial contract)

- **Macs and Sisyphe teams**
  - 2005-2007: junior software engineer Mathieu Alba (Inria internal funding)

1.5 CardioSense3D Software

The current software development for cardiac modeling is based on three platforms :

1. LifeV co-developped by the Reo team for computational fluid dynamics and electrophysiology
2. HeartLab developed by the Macs team for cardiac solid mechanics simulations and data assimilation, developped in the framework of Matalab and the OpenFEM software for finite element computations.
3. Mips and MedInria used by the Asclepios team for medical image analysis and soft tissue modeling.

An informal group has been created to discuss issues related to software and data sharing. It has been decided to develop a common platform, CardioViz3D, that would have three objectives (see Figure 3) : providing common tools for post-processing the cardiac simulations, providing tools for building models from images, developing tools to launch simulations. Furthermore, CardioViz3D should be used to display the simulation results towards the medical community in order to obtain multiple feedbacks.

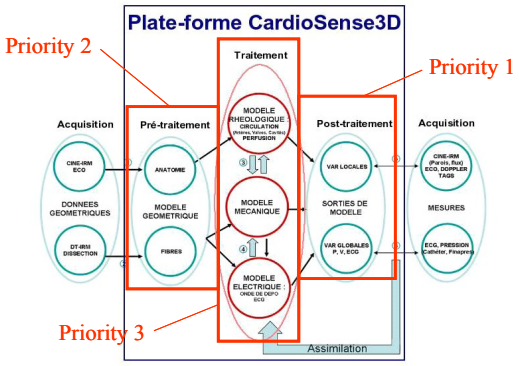

Figure 3: Overview of the software pipeline (in french) and the 3 priorities of CardioViz3D.

1.5.1 CardioViz3D

Participants: N. Toussaint, T. Mansi

CardioViz3D has been mainly developed by Nicolas Toussaint (junior software engineer) on top of the KwWidget, VTK, ITK and MIPS library. The current version includes tools for visualizing image and mesh sequences as well as a complete image processing pipeline to segment ventricles from cine MR images (see Figure 4). Some interactive demonstrations for cardiologists are being built to showcase the CardioSense3D research on the reconstruction of fiber and sheet architecture and on cardiac simulation. A public but limited version of Cardioviz3D is available here.

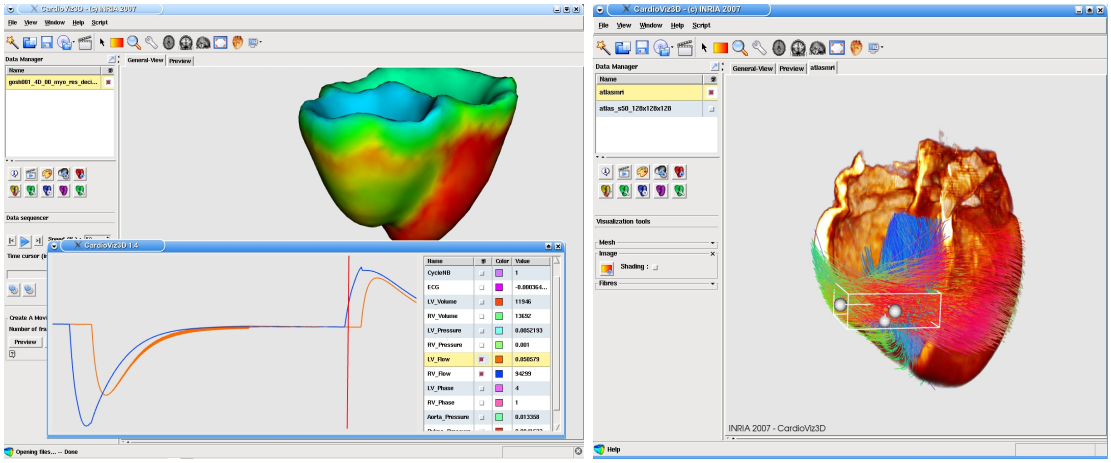

Figure 4: (Left) Visualization of global indices (volume, pressure) of the cardiac motion from a time series of simulated cardiac meshes(Right) View of volume rendered canine myocardium from a T1-weighted MR image overlaid with cardiac fibers extracted from DT-MRI.

1.5.2 HeartLab

Participants: D. Chapelle, E. Phé, P. Moireau

The Matlab procedures of the heart simulator now include both modeling and estimation modules. The implementation was performed with a particular concern for the modularity of the code, since modeling and estimation use the same finite element operators. This modularity also allows to couple the code with other FEM solvers, such as LifeV developed in the REO team-project. In particular, we are now able to include perfusion and electrical coupling with LifeV, using PVM and on the way to update this coupler with MPI which is more actively maintained. We also included geometric data and tools in the code to define heart anatomical models compatible with the simulation requirements in terms of mesh quality, fiber data defined within each element, and referencing necessary for boundary conditions and estimation, in particular. These geometries are analytical or come from CT scans of humans or pigs. The mesh operations performed to obtain computational meshes were carried out using the 3Matic package from Materialise, and the Yams and GHS3D software developed in the Gamma team-project.

2 Summary of Scientific Activity

In this section we briefly summarize the research tackled in CardioSense3D from May 2005 to January 2008. The summary is structured around the 3 main bio-physical phenomena involved in the activity of the heart (see Figure 5): electrophysiology, cardiac mechanics and physiological flows. We also summarize the CardioSense3D activity on cardiac anatomy modeling, data assimilation techniques and clinical applications.

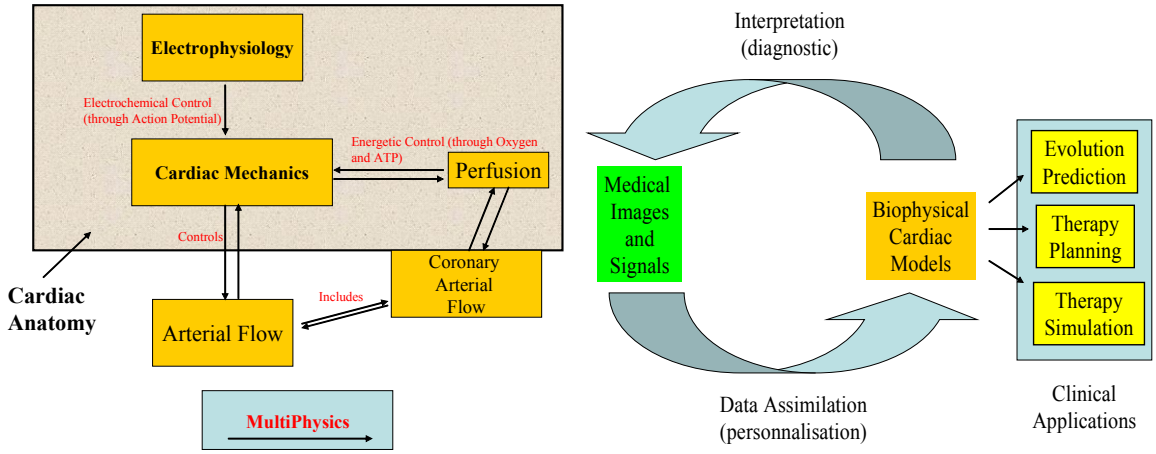

Figure 5: (Left) Block diagram that displays the different biophysical phenomena that are are under investigation in Cardiosense3D; (Right) Description of the link between data assimilation and clinical applications.

2.1 Cardiac Anatomy

This section tackles the issue of constructing computational meshes from various sources (anatomical images, DT images or generic commercial meshes). In addition to building image segmentation tools (§2.1.1), a key aspect for the realism of the simulation is the definition of the fiber architecture. Paragraphs §2.1.2 and §2.1.3 focus

on the generation of (anatomically consistent) approximations of the myocardium fibers directions.

2.1.1 Image segmentation Pipeline

Participants: T. Mansi, M. Sermesant, H. Delingette, N. Ayache

A segmentation pipeline has been developed to reconstruct the right and left ventricles from 3D+t short-axis cine-MRI sequences. First the RV endocardium is interactively segmented on two or more frames by fitting a statistical shape model. Dynamic 3D segmentation is obtained through optical flow. Then the Left ventricle (LV) endocardium is manually delineated utilizing variational implicit surfaces and recursively deformed to get dynamic surfaces. The RV and LV myocardium thickness was estimated using manual delineation of epicardium on the first frame. Dynamic meshes of myocardium are built from endocardia meshes and morphological operations.

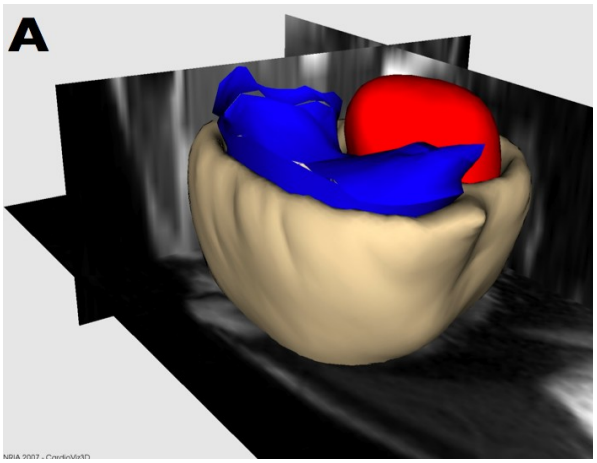

Figure 6: (Visualization of the reconstructed right (blue) and left (red) as well as the biventricular volumetric mesh (beige).

2.1.2 Computational Framework for the Statistical Analysis of Cardiac Diffusion Tensors

Participants: J.M. Peyrat, M. Sermesant, X. Pennec, H. Delingette, N. Ayache

A unified computational framework has been proposed [47, 48] to build a statistical atlas of the cardiac fiber architecture from diffusion tensor magnetic resonance images (DT-MRIs). An interactive groupwise registration of the anatomical MRIs is performed to align the different geometries to an average geometry (see Fig. 15). Coacquired with the anatomical MRIs, the DT-MRIs need to be properly transformed into the average geometry. Once DT-MRIs are transformed into the average geometry, we proceed to a statistical analysis of a population of diffusion tensors at each voxel. Then, an average cardiac fiber architecture and a measure of its variability are computed using novel diffusion tensor statistical tools.

This framework was applied to a small database of nine ex vivo canine hearts (see Fig. 15). The resulting statistical analysis confirmed the already established good stability of the fiber orientations and a higher variability of the laminar sheet orientations within a given species. The statistical comparison between the canine atlas and a standard human cardiac DT-MRI showed a better stability of the fiber orientations than their laminar sheet orientations between the two species[49].

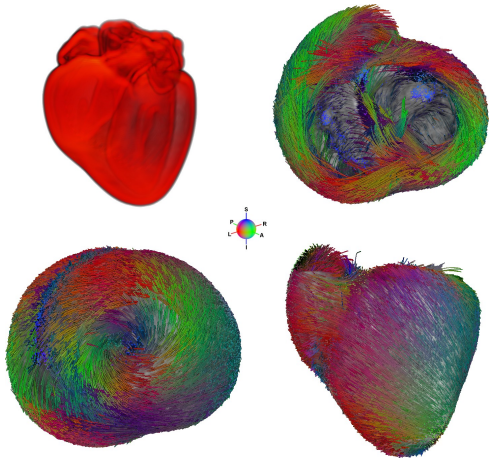

Figure 7: Average geometry and fiber tracking on the DT-MRI atlas

2.1.3 Fiber interpolation

Participants: P. Moireau, E. Phè

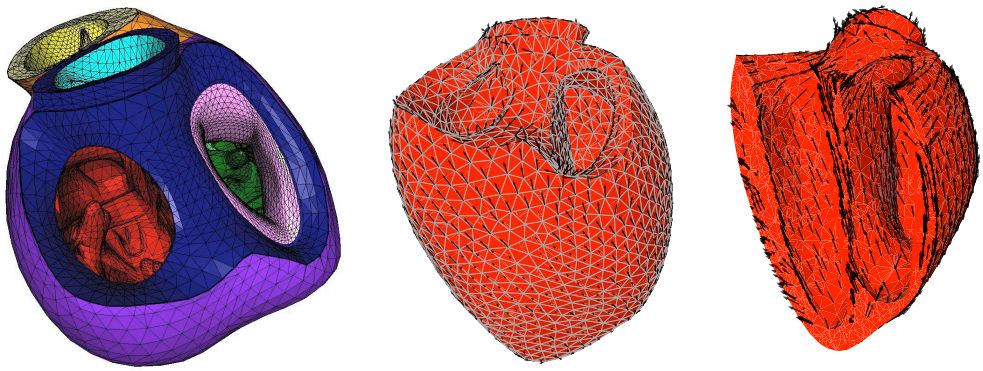

Figure 8: Original mesh without fibers (left), simplified mesh with interpolated fibers (center), half-cut (right)

We derived an intuitive method to prescribe fiber orientation on any heart geometry using different physiological knowledge and constraints. We start from an analytical description of the fiber orientation consistent with physiological considerations and interpolate it on the whole geometry, using additional physiological knowledge around the valves. This interpolation is performed on the surface using a geodesic interpolator, and in the volume using a distance-to-mesh algorithm or

harmonic lifting.

2.2 Cardiac dynamics: electrophysiology

In this section we describe the activity of CardioSense3D related to the modeling of the electrical activity of the heart. Paragraph §2.2.1 focuses on the modeling at the cell scale, we here deal with ordinary differential equations (ODE), the so-called 0D models. On the contrary, in Paragraph §2.2.2 the level of description is that of the organ, so we make use of partial differential equations (PDE), the so-called 3D models. Paragraph §2.2.3 refers to an application of the 3D modes in the framework of the cardiac resynchronization.

2.2.1 Reduced order differential models of cardiac cells

Participants: K. Djabella, M. Landau, M. Sorine.

There exists already many models of cardiac cells. In Cardiosense3D we are concerned by both direct and inverse modeling (data assimilation, see paragraph §2.5) so that a particular attention has to be paid to well-posedness of the associated problems. Our objective is then to contribute by proposing thermodynamically consistent identifiable 0D models of cells (e.g. ordinary differential equations) to be used on the organ scale as constitutive laws in 3D computations or as "averaged cell models" in 0D computations. We have already obtained a chemically-controlled constitutive law of cardiac myofibre mechanics [2] currently embedded into the Cardiosense3D models [55]. We focus our current efforts on electrical models (e.g. regularized versions of the Mitchell-Schaeffer model) and energetics (metabolism, coupling with perfusion models...).

Excitation–contraction coupling in a cardiac cell for multi-cycles simulations We have developed [17] a differential model of excitation - contraction coupling in a cardiac cell intended to be used in simulations of one or many heart cycles on the cell or the heart scales. It takes into account the dynamics of the main ionic currents flowing through the membrane channels (fast sodium, L-type calcium and outward potassium) and Na+/Ca2+ exchangers and Na+/K+ pumps. The model includes also a description of the dynamics of the main calcium buffers in the bulk cytosol and in the sarcoplasmic reticulum. With thirteen state variables, its complexity is between that of FitzHugh-Nagumo type models of the action potential (two state variables) and that of the more complex ionic channels models (up to sixty state variables for some of them). It allows realistic modelling of action potential, total ionic current, current gating, intracellular calcium transients, in particular for calcium bound on troponin C, and multicycle effects, like restitution curves for the action potential duration, CICR dependence on intracellular calcium concentration, positive staircase effect for the heart rate. Due to its sound asymptotic behavior without drifts of the state and its medium complexity, this model can be used in multi-beat simulations from the cell to the heart scales. The model has been also reduced and extended to represent pacemaker or Purkinje cells [18, 22].

A two-variable model of cardiac action potential with controlled pacemaker activity and ionic current interpretation Since the introduction of the historical Fitzhugh-Nagumo model (1961) with its two state-variables used to describe the excitability phenomena of cell membranes and action potential generation, more complex models have been proposed to better capture the physiology of cardiac cells. However in some model-based signal or image processing applications, two-state-variable models are still useful and there is a need to improve both their qualitative behaviors (shape of action potential, pacemaker activity, ...) and the interpretation of their parameters. Several models have then been derived from the Fitzhugh-Nagumo model, e.g. the van Capelle-Durrer (1980) or Aliev-Panfilov (1996) models, or from simplifications of more complex ionic models, like the Mitchell-Schaeffer model (2003). In this work, we introduce a two state-variable model of cardiac action potentials from which the above mentioned models can be derived for particular values of its parameters. Like the Mitchell-Schaeffer model, it has an ionic current interpretation relevant for inverse problems and it improves that model, being capable of pacemaker activity as we show using the phase plane representation and a bifurcation analysis. This work has been reported in [15]

Reduction of a cardiac pacemaker cell model using singular perturbation theory Cardiac-cell models are now frequently used on the heart scale in model-based signal or image processing applications for understanding cardiac diseases. For these applications, it is necessary to design models representing a good trade-off between detailed description of the complex physiological phenomena on the cardiac-cell scale and available data on the heart scale. In order to contribute to this issue, a detailed cardiac cell model has been developed and is briefly presented. However, the computational burden associated with such a detailed model, the number of parameters and state variables used to describe the behavior of the cardiac electrical activity may render its practical application very difficult. To overcome this problem, singular perturbation theory has been applied to reduce the order of the detailed cardiac pacemaker cell model, while retaining the relevant dynamics with respect to the real system. The model exhibits three time scales (Tikhonov generalized form). Validation results show the ability of the reduced order model to match some of the behavioral features of the detailed model, such as the excitability, but fails to reproduce other features, such as the shape of pacemaker action potential. This drawback is the consequence that our cardiac pacemaker cell model has a non-Tikhonov asymptotic structure. This work has been reported in [21].

2.2.2 3D simulation of the ECG

Participants: M. Boulakia, M.A. Fernández, J.-F. Gerbeau, N. Zemzemi

We have addressed here the three-dimensional numerical simulation of the electrocardiogram (ECG), namely, the so-called direct problem of cardiac electrophysiology. Our 3D model of the ECG is based on the coupling of:

- the three-dimensional bidomain equations [7, 32] and a distributed membrane (or ionic) model (see Paragraph §2.2.1), describing the electrical activity of the heart,

- a diffusion equation, describing the conducting behavior of the surrounding torso tissue.

The resulting ECG solver was implemented in the framework of the LifeV library. Quite realistic electrocardiograms have been obtained, see *e.g.* Figure 9. Is is worth noticing that, although a lot of works have been devoted to the numerical simulation of the electrical activity of the heart (both a the cell and organ scale), only a very few are able to provide realistic numerical ECG's.

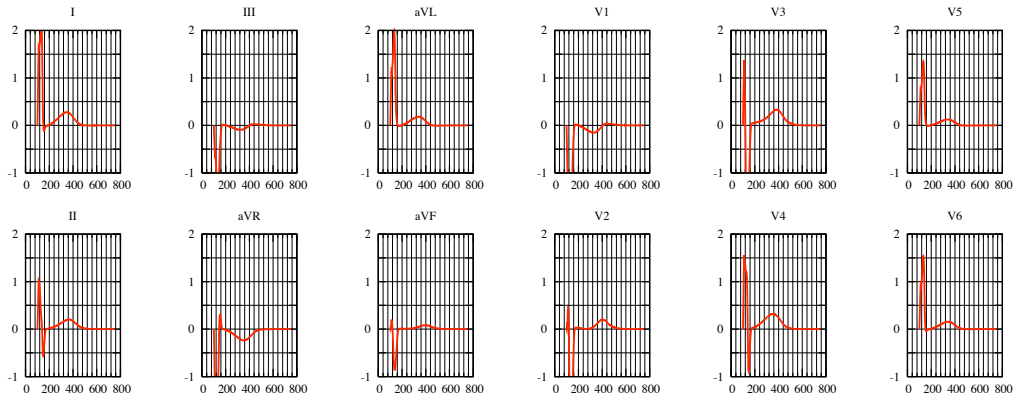

Figure 9: A numerical electrocardiogram obtained by coupling the electrical activity of the heart (bidomain equations and the Mitchell-Schaeffer's ionic model) and the torso

Our numerical ECG solver has then been used in order to assess what could be the "minimum requirements" to numerically simulate the ECG. Some modelling assumptions have been also tested in order to asses their impact on the quality of the simulated electrocardiogram. For instance, cardiac tissue anisotropy and cell heterogeneity (in terms of action potential duration) are crucial. Moreover, different interface coupling conditions (isolated heart, presence of pericardium) and a few ionic models have also been compared. As pointed out by Figure 9, the simple Mitchell-Shaeffer membrane model seems to be enough to provide realistic ECG's. A preliminary version of this study has been reported in [3]. We have also performed a mathematical analysis (*i.e.* study of the existence and uniqueness of solution) of the equations involved in the modelling of the ECG. We have proved that the model admits a global weak solution. The result holds for a wide class of ionic models (including the Mitchell-Shaeffer model) and uniqueness is proved for FitzHugh-Nagumo type ionic models. This work has been reported in [4].

2.2.3 Multisite resynchronization: a first application of 3D models

Participants: L. Dumas, L. El Alaoui, M.A. Fernández, J.-F. Gerbeau

Some dysfunctions of the electrical activity of the heart lead to a heartbeat which is too fast, too slow or irregular. Such pathologies can be treated by using an artificial pacemaker: a small device containing a battery and electrode(s) transmitting an electrical impulse.

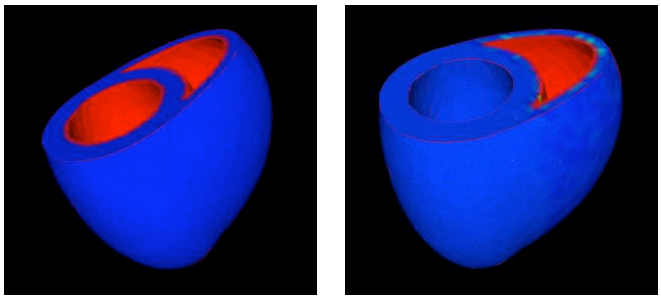

Figure 10: Healthy (left) and pathological (right) stimulations

Using the numerical 3D model described in Paragraph 2.2.2, we have addressed the problem of determining the optimal position of the pacemaker electrodes. This problem can be formulated as an inverse optimization problem. The optimal position of the electrodes has been evaluated in terms of two different cost functions: one related to the delay of the depolarization phase, and the other based of the shape of the ECG. The resulting optimization problem was solved using a genetic algorithm, which is suitable for obtaining global minima.

Figure 10 shows the healthy and pathological stimulations. The latter simulates a left bundle branch block. In figure 11 we have reported the optimal electrode positions, for each cost function.

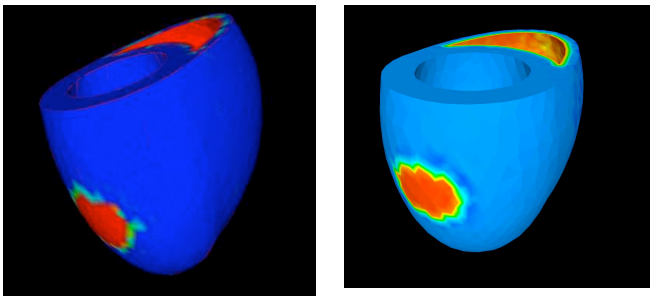

Figure 11: Optimal electrode positions: with respect to the delay of depolarization (left) and the ECG (right)

This results have been reported in [27] and the *Second European Conference on Computational Optimization (EUCCO 2007).*

2.2.4 Towards a real-time model of cardiac electrophysiology

Participants: M. Sermesant, H. Delingette, N. Ayache

As mentioned in Paragraph §2.2.1, a critical point in integrating models within clinical application is to design models which parameters are observable in clinical data and which computational time is compatible with clinical constraints. In order to achieve fast enough simulations of cardiac electrophysiology, and thus be clinically applicable, we worked on a fast model of cardiac electrophysiology, based on the fast marching method. A particular Eikonal equation has been shown to be an

approximation of reaction-diffusion electrophysiology models. But in order to simulate realistically cardiac electrophysiology, in a normal and pathological behaviour, we had to introduce anisotropy and multi-front capabilities into this model. The current implementation is almost real-time, which opens up possibilities for cardiac intervention simulation. Future work includes quantitative comparison with PDE based models.

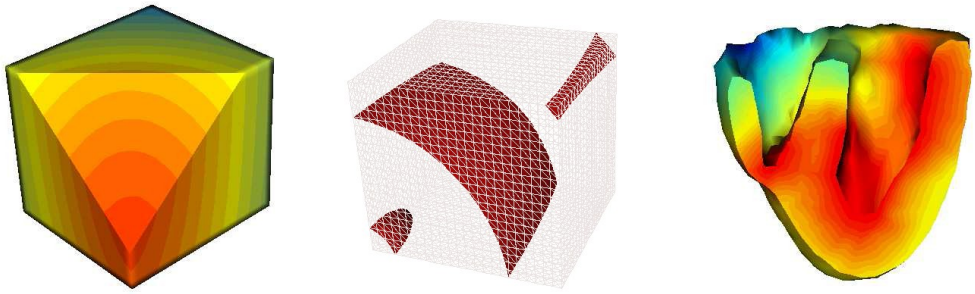

Figure 12: Fast Model of Cardiac Electrophysiology. (Left) anisotropic fast marching; (Middle) multi-front propagation; (Right) resulting isochrones in the myocardium.

2.3 Cardiac dynamics: solid mechanics

The 3D heart mechanical model used in CardionSense3D, developed within the framework of the multidisciplinary research projects ICEMA (see Paragraph §1.1), is based on the chemically controlled constitutive law of cardiac myofiber mechanics introduced in [2]. We refer to [55] for a detailed description of the model, and to [34, 33] for its mathematical analysis.

With the aim of developing valuable tools for some clinical applications, we have considered the problem of reducing the complexity of the 3D mechanical model. In the next paragraph the model reduction is based on POD techniques, whereas in Paragraph §2.3.2 the reduction relies on a simplified constitutive law.

2.3.1 POD based reduced models on the heart scale

Participants: D. Chapelle, P. Moireau, K. Pham, J. Sainte-Maire

As mentioned in Paragraph 2.2.4, an important aspect in the development of valuable tools for clinical applications is to reduce the computational cost. This motivates the analysis and simulation of the heart behavior with techniques leading to reduced size models, and in particular the proper orthogonal decomposition (POD) method. For the mechanical heart model used in CardioSense3D (see [55]), we have studied the size of the POD basis necessary to accurately recover the reference simulation. It seems this can be achieved with approximatively 10 POD modes. Furthermore, the stability of this POD basis with respect to variations of the main mechanical parameters has been demonstrated. The results have been reported in [50]. This activity will be further developed in 2008. More specifically, the stability of the POD basis with respect to the variations of the electrical activity will be

studied. The objective is also to derive some error estimates between the complete and reduced simulations.

2.3.2 Reduced electro-mechanical coupling

Participants: F. Billet, M. Sermesant, H. Delingette, N. Ayache

The aim of this work is to propose a simplified electro-mechanical model of the heart in order to decrease the computation time while still providing realistic deformations compared to those observed from medical images. Indeed our overall objective is to estimate mechanical and electrical parameters whose computational complexity is (at best) proportional to the number of parameters times the computation time for each cardiac cycle.

This simplified model is based on the multi-scale approach of Bestel-Clement-Sorine [2] where the dependence of the active stress on the strain rate has been removed and where the myocardium material is an anisotropic linear elastic material. Linear tetrahedral finite elements are used and Lagrange multipliers are introduced in the isovolumetric phases to compute the forces associated to the isovolumetric constraint. Typical computational time is on the order of 7mn for a cardiac cycle on a regular PC. Different outputs of the simulation of heart cycles are presented in Figure.

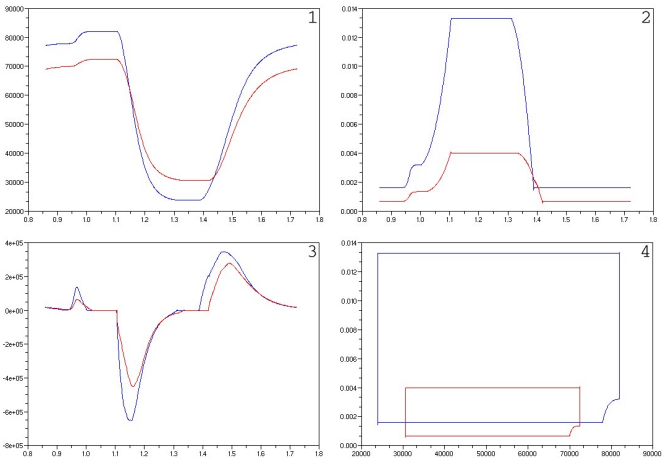

Figure 13: Different outputs of the simulation of a heart cycle from a simplified model. In Red: the right ventricles curves. In Blue: the left ventricles curves. (1) volumes (in mm3). (2) pressures (in MP a). (3) flow curves (in mm^3/s). (4) PV diagram. Time scale is in seconds.

2.4 Cardiac dynamics: fluid-solid interaction

The role of the heart is to pump oxygen-rich blood throughout the arteries and vessels to every living cell in the body. Still, in order for the heart to function properly, it must receive itself a continuous supply of fresh oxygen-enriched blood. The coronary arteries surrounding the heart carry the blood which nourishes the heart muscle.

In this section we consider the simulation of the fluid-solid interaction involved in the blood flow within the heart ventricles and the surrounding vessels (aorta,

pulmonary artery, coronary vessels). The next paragraph addresses the simulation of blood flow in large arteries (*e.g.* aorta). Paragraph §2.4.2 focus on the simulation of the heart valves and Paragraph §2.4.3 on the simulation of the myocardium perfusion through the coronary vessels.

2.4.1 Blood flows in arteries

Participants: M. Astorino, M.A. Fernández, J.-F. Gerbeau, C. Grandmont

Blood velocity and pressure fields in (large) arteries are greatly influenced by the deformability of the vessel. Moreover, wave propagation phenomena in the cardiovascular system can only be described considering wall compliance, since blood is usually described as an incompressible fluid. The modeling and numerical simulation of the interaction between blood flow and the vessel wall raises many issues:

1. the displacement of the wall cannot be supposed to be small, geometrical non-linearities are therefore present in the structure (non-linear elastodynamics)

2. as a result, the fluid equations have to be solved on a moving domain (ALE formalism)

3. the densities of the vessel wall and blood being close, the coupling between fluid ans solid is strong and has to be tackled very carefully to avoid numerical instabilities.

The numerical properties of the fluid-structure coupling in blood flows are rather different from other classical fluid-structure problems (from aeroelasticity, for instance). In particular, due to the above mentioned numerical instabilities, it seems impossible to successfully apply the standard explicit coupling schemes, which only involve one (or a few) fluid and solid resolution per time step.

Figure 14: Simulated blood flow in a compliant vessel (half a cut)

Up to now, these numerical instabilities have been overcome through the use of implicit coupling schemes. Such an approach leads to a monolithic (i.e. fully coupled) problem at each time step, the solution of which often requires a huge computational effort (several days of computation per cardiac beat).

In [28] we have proposed and analyzed a semi-implicit coupling scheme which is not fully implicit but it exhibits very good stability properties. It basically relies upon two ideas. The first one is to couple implicitly the pressure stress with the structure to ensure stability. The rest of terms (fluid domain motion, viscosity and convective effects) are explicitly treated. The second idea, relies upon the fact that this kind of implicit-explicit splitting can be conveniently performed using a Chorin-Temam's projection scheme. Numerical experiments (see Figure 14) showed that this new scheme is up to 10 times faster than the best implicit coupling schemes.

Recently, in collaboration with E. Burman (Univeristy of Sussex, UK), we have proposed a (stabilized) explicit coupling scheme, based on Nitsche's method, whose stability properties are independent of the fluid and structure density ratio. Stability is obtained thanks to the dissipative structure of the Nitsche coupling and a

stabilization term giving control of the time fluctuations of the interface fluid load. A preliminary version of this work has been reported in [5].

2.4.2 Heart valves simulation

Participants: M. Astorino, N.M. Diniz Dos Santos, J.-F. Gerbeau

Simulation of valves, either at the outflow of the cardiac chambers or in veins, is another example of difficult fluid-structure problem arising in blood flows. In addition to above mentioned difficulties, here we have to deal with very large displacements and changes of topology (contact problems when valves close).

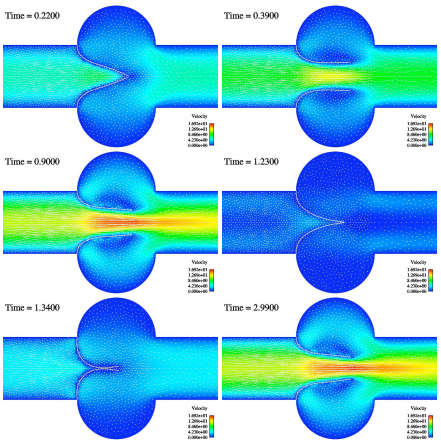

Figure 15: Valve simulation with multi-body contact (from [13])

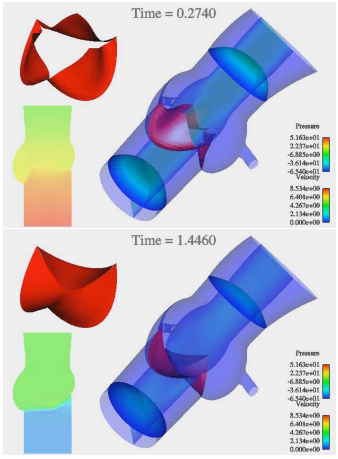

Figure 16: Simulation of fluid-solid interaction in the aortic valve without contact (from [13])

Within the framework of the PhD thesis of Nuno M. Diniz (started in September 2003) [13], we have proposed a numerical method to simulate the motion of a thin valve immersed in an incompressible viscous fluid. The fluid and structure meshes

are not matching: the kinematic continuity is imposed using Lagrange multipliers. The method therefore belongs to the "Fictitious Domain" family. This approach allows very large displacements. A partitioned fluid-structure algorithm has also been proposed: it keeps the fluid and structure solvers independent. Moreover, the proposed algorithm is able to manage contact without assuming that the structure solvers include contact capabilities, see [12]. The proposed approach has also been combined with the ALE formalism, in order to tackle problems involving both an elastic valve and an elastic wall. The methodology has recently been adapted to manage contacts between several structures immersed in a fluid in 2D, see Figure 15. One of the topics of the PhD thesis of Matteo Astorino (started in January 2007) concerns the extension of this results two the 3D case, see Figure 16.

2.4.3 Coronary perfusion

Participants: J.-F. Gerbeau, I. Vignon-Clementel, G. Rossi, J. Sainte-Maire.

Coronary perfusion (i.e. the delivery of blood flow to the coronary arteries) is an essential component of the hearts performance. Our goal is to develop a numerical model that reproduces its main behavior in terms of its physiologic coupling with the beating myocardium, which is still poorly understood. At each heart beat, the myocardium propels blood into the vascular circulation. As a consequence, it also compresses most coronary arteries, since they are embedded in it, producing a high resistance to flow until the myocardium relaxes. For our purpose, it is thus important to take into account blood flow, pressure together with the displacement of the myocardium. A strategy has been developed to couple the 3D mechanical model of the heart to an (ALE) Darcy solver. The coupling was then successfully verified on simple test cases. Some physiological aspects can be already represented by these simulations: both ventricular contraction and perfusion pressure affect coronary blood flow (see Figure 17). Further developments are however necessary to improve the physiological relevance of the results.

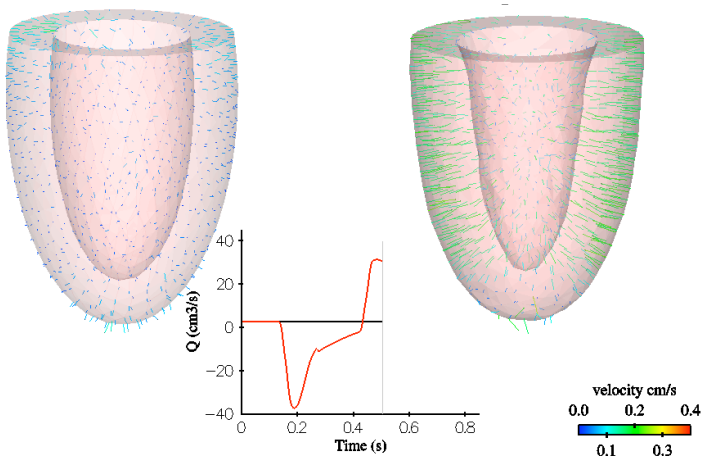

Figure 17: Coronary perfusion simulation in a simplified heart geometry: perfusion alone (left) and perfusion coupled to myocardium contraction/relaxation (right). The increase in coronary flow velocity is clearly visible during relaxation.

2.5 Model-based estimation of cardiac state and parameters

This section is devoted to the description of the CardioSense3D activity in the field of inverse problems. More precisely, the aim here is to estimate the state variables and parameters, of some of the models mentioned in the previous sections, from observations (*i.e.* measurements) of the cardiac activity.

The parameters estimation of 3D models is considered in Paragraphs §2.5.1, §2.5.2 and §2.5.3, whereas in Paragraphs §2.5.4, §2.5.5 and §2.5.6 the inverse problem involves reduced models.

2.5.1 Intracardiac electrogram-based parameter estimation

Participants: D. Lepiller, M. Sermesant, H. Delingette, N. Ayache

This work is in collaboration with two clinical sites : electrical measures on canine hearts have been provided by the Laboratory of Cardiac Energetics, NIH (E. McVeigh) while those on human hearts are provided by the Cardiac MR Research Group at Kings College London, Guys Hospital (R. Razavi). We study the problem of estimating the electrical conductivity of cardiac tissue from a set of temporal in vivo recordings of extracellular potentials. The underlying electrical model is the reaction-diffusion model on the action potential proposed by Aliev and Panfilov [1]. After a global adjustment, we propose a minimization of the quadratic error between the model isochrones and those measured on canine or human data. The parameter to be locally adjusted is the diffusion coefficient of the model that we call apparent conductivity. By taking into account the causality of the propagation of the electrical wave, the minimization problem becomes a succession of one dimensional minimization problems solved using BrentŠs method. We apply this approach to canine measures in normal and infarcted hearts. In the latter, we observe a strong correlation between the regions where a low apparent conductivity is estimated and the infarcted regions (Figure 18).

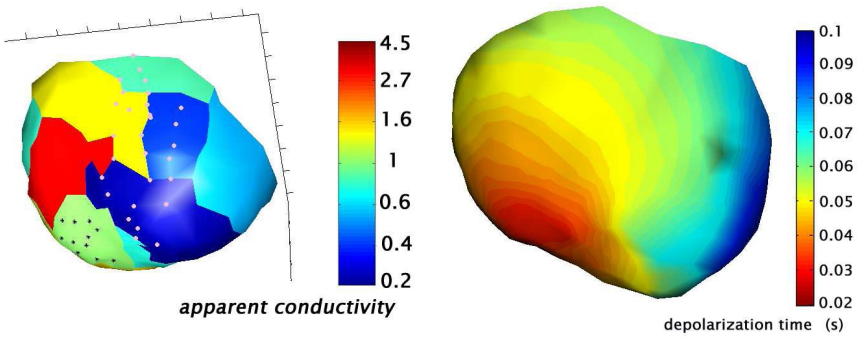

Figure 18: Estimation of apparent conductivity for a myocardium with an anterior infarct. (a) Apparent conductivity estimated. The bright circles indicate the location of the infarct while the points marked with a dark star indicate the pacing sites. The depolarization time distribution computed with these apparent conductivity values is displayed in (b).

The estimation of electrical parameters has been extended from 2D isotropic surfaces (as shown in Figure 18) to anisotropic volumetric meshes, thus taking into

account the fiber orientation. Furthermore by taking into account depolarisation and repolarisation isochrones, it is possible to estimate additional parameters that control the action potential duration of the simulated propagation. Experiments on calcium imaging and intracardial electrophysiological mappings data are in progress.

2.5.2 Joint state and parameter estimation for distributed heart mechanical models

Participants: D. Chapelle, P. Moireau, P. Le Tallec

Using the electro-mechanical heart model, our objective is to develop robust "data-model coupling algorithms". This approach aims at achieving good estimation of the behavior and physiological parameters of a patient-specific heart, using measurements from medical imaging in combination with simulations of the mechanical model. This inverse problem, called data assimilation, remains very challenging because the current state of the art in the domain is unadapted to our problem. In fact, the heart model is too sensitive and too large to be well inverted by classical Kalman filters or variational assimilation techniques. Hence, the PhD thesis of Philippe Moireau (started in August 2005) is dedicated to the research on robust effective state filters inspired from engineering, and their extensions to combined state-parameter estimation procedures.

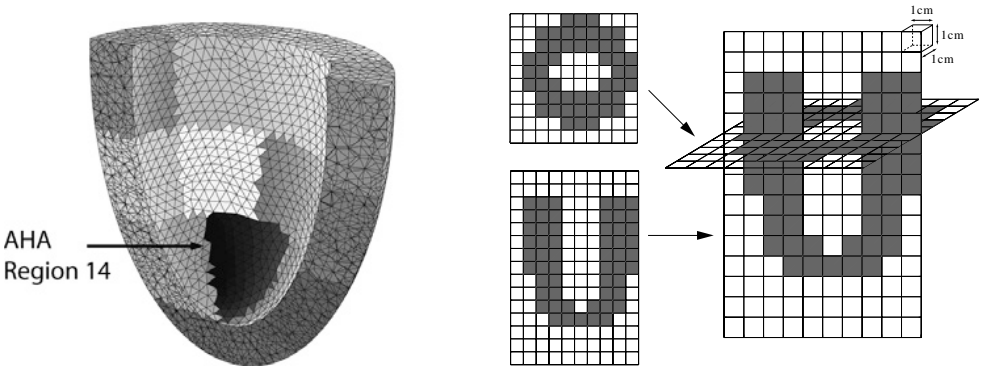

Figure 19: Simplified left ventricule geometry (left) and measurements cells (right)

In the estimation of loading parameters (fully linear for the whole state-parameter observer system) and stiffness parameters (bilinear observer problem) with volume-distributed measurements of the velocity, the complete analysis is now published in [43], see figure 19 for the problem description, and figure 20 for numerical results. In the case of surface measurements, typically concentrated on the epicardium, the challenge is mostly mathematical, since the classical measurement white noise used in Kalman filtering is not compatible with the physical energy space. Therefore, in order to deal with such measurement errors we have reformulated our state-parameter estimation approach within an H^∞ robust estimation framework. In other words, we are now able to couple our robust state filter with an H^∞ filter on parameters, with a complete analysis of the estimation (including detailed numerical assessments).

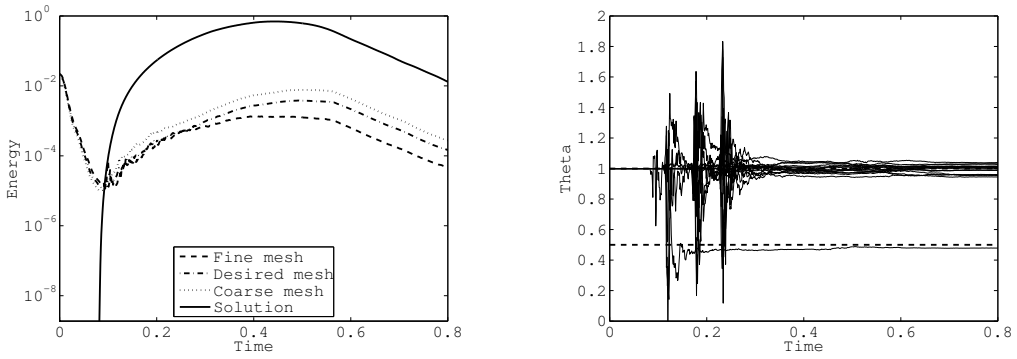

Figure 20: State an parameter convergence in the linear case

2.5.3 Ultrasound image simulations for the assessment of optical flow tracking

Participants: E. Angelini, D. Chapelle, P. Moireau, O. Talcoth

This was the topic of O. Talcoth's Master's thesis [61], co-supervised by E. Angelini (ENST), D. Chapelle and P. Moireau, see also [26]. In order to evaluate the possibilities of using an optical flow (OF) algorithm in a cardiac data assimilation context, three-dimensional cardiac ultrasound images were simulated using an electro-mechanical model of the human heart and a signal processing simulation framework. Several extensions to an existing ultra sound simulation method were proposed and implemented:

1. The acquisition geometry was changed from Cartesian to spherical.
2. The spatial resolution was improved by performing local convolutions.
3. The echoegeneity parameters were optimised using the Kolmogorov-Smirnov test.
4. Specular reflections were modeled.

Th esimulated images were processed by the OF and thee stimated movements were compared to the true ones from the heartmodel. Different norms used to measure the OF errors were discussed. Although simple movements yielded good results, the OF did not perform well when more complicated movements were examined. A probabilistic model for the OF results was proposed permitting an improvement of the OF method to be suggested.

2.5.4 QT interval detection and ECG-based restitution curve estimation

Participants: A. Illanes Manriquez, C. Médigue, Y. Papelier, M. Sorine, Q. Zhang.
For isolated and electrically excited cardiac cells, there is a well known relationship between each action potential duration (APD) and the preceding diastolic interval (DI) under the name of *restitution curve*. A similar relationship has been recently revealed between the QT interval and the preceding TQ interval computed from

electrocardiogram (ECG) signals measured at the body surface[30]. By analogy to the cellular restitution curve, we call this relationship *ECG-based restitution curve*. To successfully build this curve, the ECG signals must be recorded under some particular conditions. The isometric Handgrip test has proved to be a good choice for this purpose. It is also important to delimit the QT interval with a sufficient accuracy. In our previous work, the QT interval was obtained by adding a constant to the RT interval which is easier to delimit [30], [62]. More recently, in order to improve the delimitation of the QT interval, an algorithm for QRS onset detection has been developed. It is based on the computation of the envelop signal of the QRS defined with the Hilbert transform, and also on the application of a statistical detection algorithm. This new algorithm is now used for building ECG-based restitution curves and has been reported in [29].

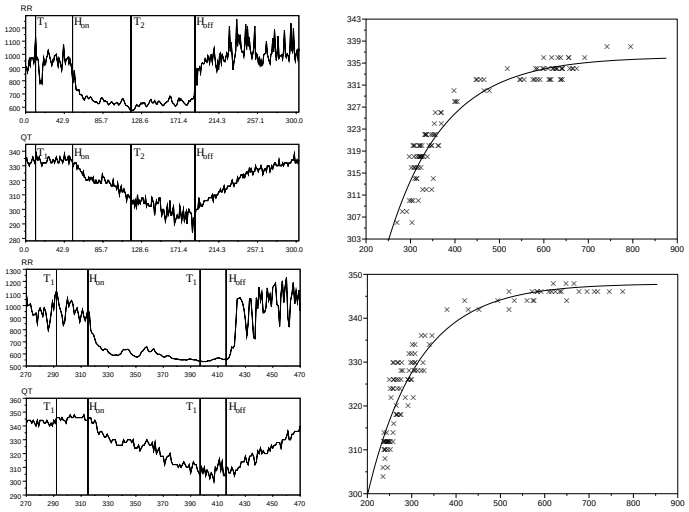

Figure 21: At the left are shown the RR and QT variation, the time instant of onset and offset of the handgrip (H_{on} and H_{off}), and the time intervals taken to plot the ECG-based restitution curve (T_1 and T_2) during acceleration of heart rate for two ECG records. At the right are shown the respectively ECG based restitution curves (crosses) and the parametric restitution curve of the identified Mitchell & Schaeffer model.

2.5.5 Scattering based analysis of pulse-shaped signals

Participants: E. Crépeau-Jaisson, T.-M. Laleg, M. Sorine, Q. Zhang

In this work we develop a new signal processing technique based on scattering theory [39, 36]. This inverse scattering technique consists on solving the spectral problem associated to a one-dimensional Schrödinger operator perturbed by a potential depending upon the signal to analyze, and optimized in order to approximate this signal. Some functions associated with the Schrödinger equation (the squared Jost solutions) play an analogous role to sinus and cosinus in the Fourier analysis of signals. In the proposed analysis, by using an interpretation in term of traveling

waves (the N-solitons), low and high frequency components of the standard Fourier analysis, are replaced by low and high velocity components. Applications of the method to physiological signals, in particular the ABP are currently studied (see section 2.5.6 and Fig. 22 and Fig. 23).

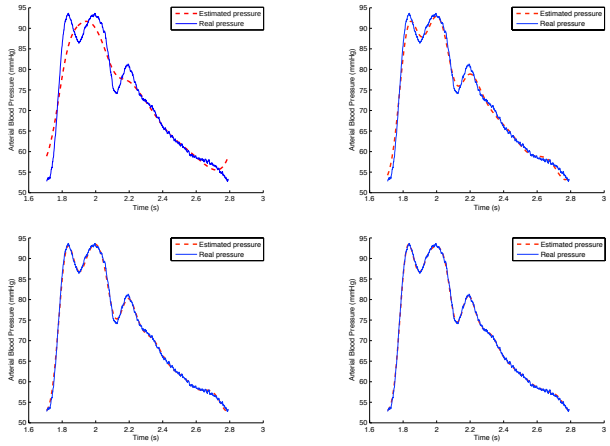

Figure 22: Measured and reconstructed pressures at the aorta with N solitons. From left to right: $N = 3$, $N = 5$ (Up). $N = 7$, $N = 9$ (Down)

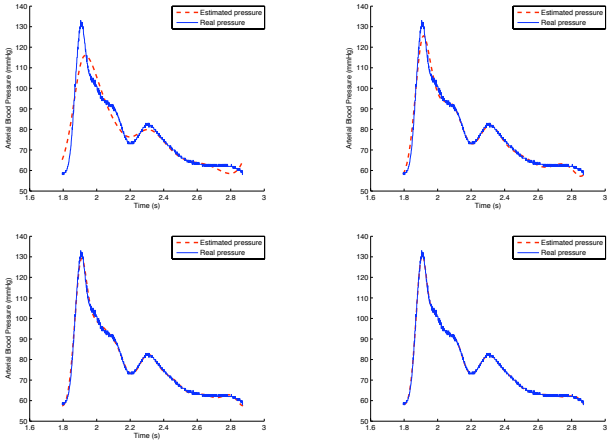

Figure 23: Measured and reconstructed pressures at the finger with N solitons. From left to right: $N = 3$, $N = 5$ (Up). $N = 7$, $N = 9$ (Down)

2.5.6 Nonlinear spectral analysis of arterial blood pressure waveforms: estimation of averaged cardiac indices

Participants: F. Cottin, T.-M. Laleg, C. Médigue, Y. Papelier, M. Sorine

We have proposed [8] a reduced model of the input-output behaviour of an arterial compartment, including the short systolic phase where wave phenomena are predominant. A more detailed analysis is now available [9], [37]. The objective is to provide basis for model-based signal processing methods for the estimation from non-invasive measurements and the interpretation of the characteristics of these waves. We develop now the corresponding signal processing method (see 2.5.5) and some applications.

This method, based on scattering transform for a one dimensional Schrödinger equation, provides new parameters, related to the systolic and diastolic parts of the pressure. They are compared to the classical blood pressure indexes in four conditions: moderate chronic heart failure, exercise before and after training in high fit triathlets [40], handgrip isometric exercise and orthostatic tilt test. [41]. In each case these parameters are more significant than the classical ones. Moreover, they bring up new indexes, difficult to measure routinely: we think that the two first invariants might give information about the variation of the stroke volume and the ventricular contractility. At last, the first eigenvalue seems to reflect the baroreflex sensitivity in a certain way. We are now working on the validation of these hypotheses. Fig. 24 illustrates a significant statistical difference of the VHF amplitude for diastolic and systolic invariants before and after training.

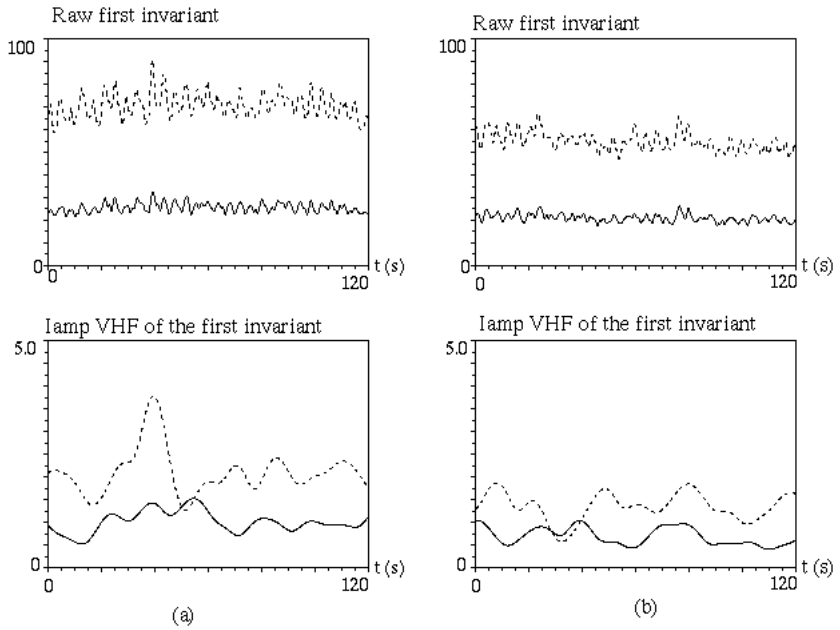

Figure 24: First invariants of the ABP (top) and their VHF instantaneous amplitude (bottom) for a subject before (a) and after (b) training. Dotted lines stand for diastolic parameters, continuous lines stand for systolic ones. The decrease in VHF amplitude for diastolic and systolic invariants after training for this subject is representative of the significant statistical difference over the 8 subjects of the study.

2.6 Imaging and Clinical Applications

2.6.1 Optical Imaging of the Myocardium Transmembrane Potential

Participants: M Pop, M. Sermesant, D. Lepiller H. Delingette, N. Ayache

In collaboration with the Sunnybrook Health Sciences Center in Toronto, Canada, we are working on validating electrophysiology models using optical recordings of electrical waves on pig hearts. A fluorescent dye is injected in extracted hearts, and it reacts to the depolarisation of the membrane. Two cameras record the scene, making it possible to reconstruct the heart surface with stereoscopy.

We defined the filtering and analysis methods of the recordings which allow the automatic extraction of the depolarisation and repolarisation times. We then rectify and project them on the stereo surface. A 3D MR image is also acquired of the same heart, making it possible to create a volumetric mesh of the myocardium. Diffusion tensor images are used to measure the heart fibres orientations. Using markers, we register this mesh with the stereo surface and project the recorded times.

We can then simulate electrophysiology models on this mesh and adjust the conductivity parameters, which is work in progress. This work will allow to quantify the model error and test its suitability for prediction of inducibility of arrhythmias [52, 53, 51].

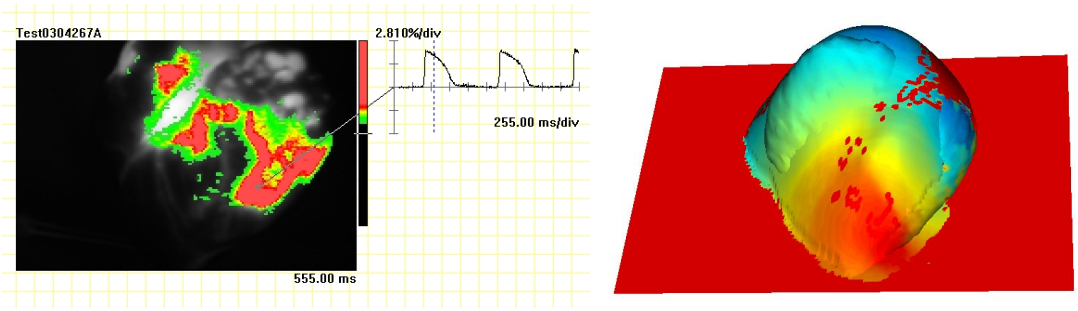

Figure 25: (Left) Electrophysiology signals extracted from calcium imaging; (Right) The isochrones are registered on a 3D volumetric mesh of the myocardium reconstructed from stereoscopic images.

2.6.2 Simulation of paediatric cardiac pathologies using an electromechanical model of the heart

Participants: T. Mansi, M. Sermesant, H. Delingette, N. Ayache

Within the framework of the European project Health-e-Child, we are adapting the electromechanical model of the heart to simulate three groups of paediatric cardiac pathologies: right-ventricle overload, dilated cardiomyopathies and hypertrophied cardiomyopathies. As a first stage, we expressed biomedical observations (clinical, cellular, etc.) as macroscopic geometrical and electromechanical parameters to simulate those pathologies. Once this calibration process was performed, the three diseases were simulated by modifying the internal parameters according to the medical observations.

To simulate right-ventricle overload due to atrial defects, right-atrial pressure was augmented and the geometry of the right ventricle was slightly stretched to take into account the increased pre-load. Similarly, dilated cardiomyopathies were simulated by dilating the 3D geometry of the normal heart and decreasing the contractility parameters of the biomechanical model (to account for the observed impaired contractility of the myocardium). Finally, hypertrophied cardiomyopathies were simulated by increasing the thickness and the stiffness of the myocardium while decreasing the electrical conductivity. The results were discussed and evaluated with the help of the cardiologists involved in the project. The results of the simulations have been published in a web site as a deliverable of the Health-e-Child project.

3 Dissemination Activity

"The Digital Heart" Movie The partners of CardioSense3D have released in December 2006 a 20mn movie presenting some of the research results and perspectives obtained within Cardiosense3D. The movie is dedicated to the memory of G. Kahn.

The movie is available online but also in DVD format in french and english.

Data and Software Releases Version 1.3 of the public version of the CardioViz3D software is available here. The Statistical Atlas of Cardiac Muscle Fibre Architecture described in 2.1.2 is available as a description (images, tensors, fibers and meshes) on the mean canine heart over a database of 9 DT-MRI images.

Invited presentations at conferences or workshops Several researchers have given invited talks about the work done within CardioSense3D at several conferences or workshops : ISBI'07, FIMH'06, CMBBE'06, Euro-Bio 2006, First European Cardiac simulation group meeting, ... An exhaustive list can be found here.

Elements of National and International Visibility CardioSense3D was presented in following exhibitions or seminars : Euro-Bio'06 (October 2006), European research & Innovation exhibition (June 2007), EuroBio'07 (September 2007), seminar INRIA-industry (January 2006), First NIH-INRIA seminar (April 2007), French academy of Science (May 2006).

Cardiosense3D was also presented for general audience in two short articles published in ERCIM News (April 2007) and La Recherche (February 2008).

The Reo team organized the CEA-EDF-INRIA school on Numerical Simulations of Blood Flows in December 2005, and the Asclepios will organize the 2009 issue of the FIMH conference in Nice.

CardioSense3D is also mentioned in the white paper of the European commission on the Virtual Physiological Human initiative and was presented in 2006 in Brussels at the ICT-Bio conference preparing the 7^{th} framework program of the European union.

Awards The ARTS program is funded by Apple Corp. and aims at supporting leading European research institutes in the ICST field and help young scientists

through their projects by giving them access to Apple technology. Cardiosense3D research group received the ARTS awards in 2007 with a 30 000$ prize worth of Apple hardware, software and assistance.

4 Future Research Activity

In this section, we first describe the European project EuHeart, starting in June 2008, that strongly involve the partners of CardioSense3D. We then provide a brief description of the future research activities of CardioSense3D in the next 2 years for the topics listed in section 2. Finally we list some important milestones that we wish to reach within the next 2 years.

4.1 European project EuHeart

A project proposal involving several leading partners in cardiac modeling (University of Oxford, Auckland University, University of Karlsruhe, Philips Medical Systems, ...) has been accepted by the European Commission in January 2008. This Integrated project entitled *EuHeart* will start in June 2008 for a duration of 4 years. This project aims at building personalized models of the heart and to demonstrate their impact in providing better therapies or diagnosis. The researchers of CardioSense3D are heavily involved in this project since INRIA has the responsibility of two workpackages : WP4 on the personalization of cardiac models and WP6 on the improvement of cardiac radiofrequency ablation planning for atrial and ventricular fibrillation based on biophysical models.

4.2 Main Research Activities

4.2.1 Cardiac Anatomy

Future research activities will include :

- Segmentation and tracking cardiac motion from tagged MRI and cine-MR
- Construction of cardiac fiber architecture on patient data
- Study of variability of laminar sheets.

4.2.2 Cardiac Dynamics : Electrophysiology

4.2.3 Cardiac Dynamics : solid Mechanics

4.2.4 Cardiac Dynamics : fluid-solid interaction

4.2.5 Model-based estimation of cardiac state and parameters

4.2.6 Imaging and Clinical Applications

4.3 Expected Milestones

5 Bibliography

We list below the papers that have been published on the topic of cardiac modeling and simulation since 2005.

References

[1] R. Aliev and A. Panfilov. A simple two-variable model of cardiac excitation. *Chaos, Solitons & Fractals*, 7(3):293–301, 1996.

[2] J. Bestel, F. Clément, and M. Sorine. A biomechanical model of muscle contraction. In W.J. Niessen and M.A. Viergever, editors, *Medical Image Computing and Computer-Assisted intervention (MICCAI'01)*, volume 2208 of *Lecture Notes in Computer Science (LNCS)*, pages 1159–1161. Springer, 2001.

[3] M. Boulakia, M.A. Fernández, J.-F. Gerbeau, and N. Zemzemi. Towards the numerical simulation of electrocardiograms. In F. Sachse and G. Seemann, editors, *Functional Imaging and Modeling of the Heart*, number 4466 in Lecture Notes in Computer Science, pages 240–249. Springer, 2007.

[4] M. Boulakia, M.A. Fernández, J.-F. Gerbeau, and N. Zemzemi. A coupled system of PDEs and ODEs arising in electrocardiograms modelling. *Applied Mathematics Research eXpress*, 2008. To appear.

[5] E. Burman and M.A. Fernández. Stabilized explicit coupling for fluid-structure interaction using Nitsche's method. *C. R. Math. Acad. Sci. Paris*, 345(8):467–472, 2007.

[6] Desmond Chung, Mihaela Pop, Maxime Sermesant, and Graham Wright. Stereo reconstruction of the epicardium for optical fluorescence imaging. In *MICCAI Workshop on Biophotonics Imaging for Diagnostics and Treatment*, pages 33–40, 2006.

[7] P. Colli Franzone and G. Savaré. Degenerate evolution systems modeling the cardiac electric field at micro- and macroscopic level. evolution equations, semigroups and functional analysis. *Progr. Nonlin. Diff. Eq. Appl.*, 1(50):49–78, 2002.

[8] E. Crépeau and M. Sorine. Identifiability of a reduced model of pulsatile flow in an arterial compartment. In *Proceedings of 44th IEEE CDC and ECC 2005*, Sevilla, december 12-15 2005.

[9] E. Crépeau and M. Sorine. A reduced model of pulsatile flow in an arterial compartment. *Chaos, Solitons & Fractals*, 34(2):594–605, October 2007.

[10] H. Delingette, M. Sermesant, J.-M. Peyrat, N. Ayache, K. Rhode, R. Razavi, E. McVeigh, D. Chapelle, J. Sainte-Marie, P. Moireau, M. Fernandez, J.-F. Gerbeau, K. Djabella, Q. Zhang, and M. Sorine. Cardiossense3d: Patient-specific cardiac simulation. In *Proceedings of IEEE International Conference on Biomedical Imaging: From Nano to Macro (ISBI'07)*, pages 628–631, Metro Washington DC, USA, 12-15 April 2007.

[11] Hervé Delingette, Xavier Pennec, Luc Soler, Jacques Marescaux, and Nicholas Ayache. Computational models for image guided, robot-assisted and simulated medical interventions. *Proceedings of the IEEE*, 94(9):1678– 1688, September 2006.

[12] N. Diniz dos Santos, J.-F. Gerbeau, and J.-F. Bourgat. A partitioned fluid-structure algorithm for elastic thin valves with contact. *Computer Methods in Applied Mechanics and Engineering*, 2008. In press.

[13] N.M. Diniz Dos Santos. *Numerical methods for fluid-structure interaction problems with valves.* PhD thesis, Univerisity of Paris VI, 2007.

[14] K. Djabella, M. Landau, and M. Sorine. Bifurcation analysis of the control mechanism of pacemaker activity in a mathematical cardiac cell model. In *7th IFAC Symposium on Nonlinear Control Systems - NOLCOS'07*, Pretoria, South Africa, 22-24 August 2007.

[15] K. Djabella, M. Landau, and M. Sorine. A two-variable model of cardiac action potential with controlled pacemaker activity and ionic current interpretation. In *Proceedings of 46th IEEE Conference on Decision and Control*, December 2007.

[16] K. Djabella, M. Landau, and M. Sorine. A two-variable model of cardiac action potential with controlled pacemaker activity and ionic current interpretation. In *Proceedings of 46th IEEE Conference on Decision and Control*, December 2007.

[17] K. Djabella and M. Sorine. A differential model of excitation-contraction coupling in a cardiac cell for multicycle simulations. In *Proceedings of the 3rd European Medical and Biological Engineering Conference*, November 20–25 2005.

[18] K. Djabella and M. Sorine. A differential model of controlled cardiac pacemaker cell. In *Modelling and Control in Biomedical Systems (MCBMS)*, Reims, France, 2006. IFAC.

[19] K. Djabella and M. Sorine. A reduced differential model for cardiac action potentials. In *SIAM Conference on the Life Sciences*, Raleigh, USA, July 31-August 4 2006.

[20] K. Djabella and M. Sorine. Cardiac cell modelling: Bifurcation analysis of a reduced differential model. In *5ème Conférence sur le Génie Électrique*, Alger, 16-17 Avril 2007. Ecole polytechnique d'Alger.

[21] K. Djabella and M. Sorine. Reduction of a cardiac pacemaker cell model using singular perturbation theory. In *European Control Conference (ECC)*, Kos, Greece, July 2007.

[22] K. Djabella and M. Sorine. A reduced differential model for cardiac action potentials. In *SIAM Conference on the Life Sciences*, Raleigh, USA, July 31–August 4, 2006.

[23] Karima Djabella and Michel Sorine. A differential model of controlled cardiac pacemaker cell. In *Proc. of the 6th IFAC Symposium on Modelling and Control in Biomedical Systems*, 20 September 2006.

[24] Karima Djabella and Michel Sorine. Reduction of a cardiac pacemaker cell model using singular perturbation theory. In *European Control Conference (ECC)*, Kos, Greece, July 2007.

[25] Q. Duan, P. Moireau, E.D. Angelini, D. Chapelle, and Laine A.F. Simulation of 3d ultrasound with a realistic electro-mechanical model of the heart. In *Proceedings of FIMH'07 Conference*, pages 463–470, Salt Lake City, USA, June 2007.

[26] Q. Duan, P. Moireau, E.D. Angelini, D. Chapelle, and A.F. Laine. Simulation of 3D ultrasound with a realistic electro-mechanical model of the heart. In F. Sachse and G. Seemann, editors, *Functional Imaging and Modeling of the Heart*, number 4466 in Lecture Notes in Computer Science, pages 463–473. Springer, 2007.

[27] L. El Alaoui and L. Dumas. How genetic algorithms can improve a pacemaker efficiency. In *Genetic and Evolutionary Computation Conference: GECCO 2007*, pages 2681–2686, 2007.

[28] M.A. Fernández, J.F. Gerbeau, and C. Grandmont. A projection semi-implicit scheme for the coupling of an elastic structure with an incompressible fluid. *Int. J. Num. Meth. Engrg.*, 69(4):794–821, 2007.

[29] A. Illanes Manriquez and Q. Zhang. An algorithm for qrs onset and offset detection in single lead electrocardiogram records. In *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Lyon, France, August 2007.

[30] A. Illanes Manriquez, Q. Zhang, C. Médigue, Y. Papelier, and M. Sorine. Electrocardiogram-based restitution curve. In *Computers in cardiology*, Valencia, Spain, 2006.

[31] Alfredo Illanes Manriquez. *Segmentation de l'électrocardiogramme pour la modélisation de la dynamique du QT lors de l'exercice du handgrip.* PhD thesis, Université de Rennes 1, January 2008.

[32] W. Krassowska and J.C. Neu. Homogenization of syncitial tissues. *CRC Crit. Rev. Biomed. Eng.*, 2(21):137–199, 1993.

[33] P. Krejci, J. Sainte-Marie, M. Sorine, and J.M. Urquiza. Modelling and simulation of an active fibre for cardiac muscle. Submitted to Biomechanics and Modelling in Mechanobiology, 2006.

[34] P. Krejci, J. Sainte-Marie, M. Sorine, and J.M. Urquiza. Solutions to muscle fiber equations and their long time behaviour. *Nonlinear Analysis: Real World Applications*, 7(4):535–558, 2006.

[35] P. Krejci, J. Sainte-Marie, M. Sorine, and J.M. Urquiza. Solutions to muscle fiber equations and their long time behaviour. *Nonlinear Analysis: Real World Applications*, 7(4), September 2006.

[36] T.-M. Laleg, E. Crépeau, Y. Papelier, and M. Sorine. Arterial blood pressure analysis based on scattering transform I. In *29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, IEEE EMBC, Lyon, France, August 23-26 2007.

[37] T.-M. Laleg, E. Crépeau, and M. Sorine. Separation of arterial pressure into a nonlinear superposition of solitary waves. *Biomedical Signal Processing and Control*, 2(3):163–170, 2007.

[38] T.-M. Laleg, E. Crépeau, and M. Sorine. A soliton-based signal analysis method. In *5ème Conférence sur le Génie Électrique*, Alger, 16-17 Avril 2007. Ecole polytechnique d'Alger.

[39] T-M. Laleg, E. Crépeau, and M. Sorine. Travelling-wave analysis and identification: A scattering theory framework. In *European Control Conference*, Kos, Greece, July 2-5 2007.

[40] T.-M. Laleg, C. Médigue, F. Cottin, and M. Sorine. Arterial blood pressure analysis based on scattering transform II. In *29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, IEEE EMBC, Lyon, France, August 23-26 2007.

[41] T.M. Laleg, C. Médigue, Y. Papelier, E. Crépeau, and M. Sorine. New cardiovascular indices based on nonlinear spectral analysis of arterial blood pressure waveforms. Research report 6312, INRIA, Rocquencourt, 2007.

[42] P. Moireau and D. Chapelle. Effective estimation in cardiac modelling. In *Proceedings of FIMH'07 Conference*, pages 361–372, Salt Lake City, USA, June 2007.

[43] P. Moireau, D. Chapelle, and Le Tallec P. Joint state and parameter estimation for distributed mechanical systems. *Computer Methods in Applied Mechanics and Engineering*, 197:659–677, 2008.

[44] Ph. Moireau. Assimilation de données en modélisation cardiaque. Master's thesis, Ecole Polytechnique, 2005. `http://www.enst.fr/~moireau/documents/HeartModel.pdf`.

[45] V. Moreau-Villéger, H. Delingette, M. Sermesant, H. Ashikaga, O. Faris, E. McVeigh, and N. Ayache. Building maps of local apparent conductivity of the epicardium with a 2D electrophysiological model of the heart. *IEEE Transactions on Biomedical Engineering*, 53(8):1457–1466, August 2006.

[46] Valérie Moreau-Villéger, Hervé Delingette, Maxime Sermesant, Hiroshi Ashikaga, Owen Faris, Elliot McVeigh, and Nicholas Ayache. Estimating local apparent conductivity with a 2-D electrophysiological model of the heart. In *Proc. of Functional Imaging and Modeling of the Heart 2005 (FIMH'O5)*, volume 3504 of *LNCS*, pages 256–266. Springer, June 2005.

[47] J-M. Peyrat, M. Sermesant, H. Delingette, X. Pennec, C. Xu, E. McVeigh, and N. Ayache. Towards a statistical atlas of cardiac fiber structure. In *Proc. of MICCAI'06, Part I*, number 4190 in LNCS, pages 297–304, 2-4 October 2006.

[48] Jean-Marc Peyrat, Maxime Sermesant, Hervé Delingette, Xavier Pennec, Chenyang Xu, Elliot McVeigh, and Nicholas Ayache. Statistical comparison of cardiac fibre architectures. In *Proceedings of Functional Imaging and Modeling of the Heart 2007 (FIMH'07)*, volume 4466 of *LNCS*, pages 413–423, 7-9 June 2007.

[49] Jean-Marc Peyrat, Maxime Sermesant, Xavier Pennec, Hervé Delingette, ChenYang Xu, Eliot R. McVeigh, and Nicholas Ayache. A computational framework for the statistical analysis of cardiac diffusion tensors: Application to a small database of canine hearts. *IEEE Transactions on Medical Imaging*, 26(11):1500–1514, November 2007.

[50] K. Pham. Réduction de modèle pour la simulation cardiaque (in french). Master's thesis, École Normale Supérieur, Cachan, 2007.

[51] Mihaela Pop, Maxime Sermesant, Yves Coudière, J. Graham, M. Bronskill, A. Dick, and Graham Wright. A theoretical model of ventricular reentry and its radiofrequency ablation therapy. In *3rd IEEE International Symposium on Biomedical Imaging: Macro to Nano (ISBI'06)*, pages 33–36, 2006.

[52] Mihaela Pop, Maxime Sermesant, Alexander Dick, John Graham, Yves Coudière, and Graham Wright. Aid of computer modelling to identify ventricular reentries due to infarct scars. In *15th World Congress in Cardiac Electrophysiology and Cardiac Techniques (Cardiostim'06)*, 2006.

[53] Mihaela Pop, Maxime Sermesant, Alexander Dick, John Graham, Yves Coudière, and Graham Wright. Assessment of radio-frequency ablation of ventricular arrhythmias via magnetic resonance imaging and computer modelling. In *15th World Congress in Cardiac Electrophysiology and Cardiac Techniques (Cardiostim'06)*, 2006.

[54] K. Rhode, M. Sermesant, D. Brogan, S. Hegde, J. Hipwell, P. Lambiase, E. Rosenthal, C. Bucknall, S. Qureshi, J. Gill, R. Razavi, and D. Hill. A system for real-time XMR guided cardiovascular intervention. *IEEE Transactions on Medical Imaging*, 24(11):1428–1440, 2005.

[55] J. Sainte-Marie, D. Chapelle, R. Cimrman, and M. Sorine. Modeling and estimation of the cardiac electromechanical activity. *Computers & Structures*, 84:1743–1759, 2006.

[56] M. Sermesant, Y. Coudière, V. Moreau-Villéger, K.S. Rhode, D.L.G Hill, and R. Ravazi. A fast-marching approach to cardiac electrophysiology simulation for XMR interventional imaging. In *Proceedings of MICCAI'05*, volume 3750 of *LNCS*, pages 607–615, Palm Springs, California, 2005. Springer Verlag.

[57] M. Sermesant, H. Delingette, and N. Ayache. An electromechanical model of the heart for image analysis and simulation. *IEEE Transactions in Medical Imaging*, 25(5):612–625, 2006.

[58] M. Sermesant, Ph. Moireau, O. Camara, J. Sainte-Marie, R. Andriantsimiavona, R. Cimrman, D. Hill, D. Chapelle, and R. Razavi. Cardiac function estimation from MRI using a heart model and data assimilation: Advances and difficulties. *Medical Image Analysis*, 10(4):642–656, 2006.

[59] M. Sermesant, Ph. Moireau, O. Camara, J. Sainte-Marie, R. Andriantsimiavona, R. Cimrman, D.L.G. Hill, D. Chapelle, and R. Razavi. Cardiac function estimation from MRI using a heart model and data assimilation: advances and difficulties. In *Proceedings of FIMH Conference*, 2005.

[60] M. Sermesant, K. Rhode, G. Sanchez-Ortiz, O. Camara, R. Andriantsimiavona, S. Hegde, D. Rueckert, P. Lambiase, C. Bucknall, E. Rosenthal, H. Delingette, D. Hill, N. Ayache, and R. Razavi. Simulation of cardiac pathologies using an electromechanical biventricular model and XMR interventional imaging. *Medical Image Analysis*, 9(5):467–480, 2005.

[61] O. Talcoth. Movement estimation in simulated 3D ultrasound images. Master's thesis, Chalmers University, 2007.

[62] Q. Zhang, A. Illanes Manriquez, C. Médigue, Y. Papelier, and M. Sorine. An algorithm for robust and efficient location of t-wave ends in electrocardiograms. *IEEE Trans Biomed Eng.*, 53:2544–52, 2006.