Cardiosense3D:
Patient-Specific Cardiac Simulation
INRIA Large Wingspan Project

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The **objectives** of the **CardioSense3D** project are threefold :

1. To **build a cardiac simulator**, with identifiable parameters, that couples 4 different physiological phenomena: electrophysiology, mechanical contraction and relaxation, myocardium perfusion and cardiac metabolism,
2. To **build data assimilation software** that can estimate patient specific parameters and state variables from given observations of the cardiac activity,
3. To **build several application softwares** based on this simulator and data assimilation techniques to solve clinical problems related to the diagnosis or therapy of cardiac pathologies.

in order to :

- **significantly improve medical practice** in terms of better prevention, diagnosis, quantitative follow-up, simulation and guidance of therapy,
- **support biomedical research** in the preparation and evaluation of new diagnostic and therapeutic tools,
- **advance** the **fundamental knowledge** of the integrative *physiology* of the **heart**.

Contents

1 Motivations

1.1 On the importance of patient-specific cardiac simulators

Toward quantitative and personalized medicine

There is an irreversible evolution of medical practice toward more quantitative and personalized decision procedures for prevention, diagnosis and therapy, based on ever larger and more complex sets of measurements. This deep trend induces a crucial need for producing a new type of so-called computational models of the anatomy and the physiology of the human body [5], able to explain the observations, detect abnormalities, predict evolutions, as well as to simulate and evaluate therapies.

The simulation of the heart has received a growing attention due to the importance of cardiovascular diseases in industrialized nations[1] and to the high complexity of the cardiac function. Indeed, formulating a computational model of the cardiac function of a specific patient represents a great challenge due to :

- i) the intrinsic physiological complexity of the underlying phenomena which combine tissue mechanics, fluid dynamics, electro-physiology, energetic metabolism and cardiovascular regulation;
- ii) the partial information available for a specific patient and the variety of the objectives of data processing ranging from global detection of pathological situations to local diagnosis and personalized therapy planning.

Cardiac models and cardiac data

Cardiac models are useful to represent in an unified manner the various and complex physiological mechanisms mentioned in i). The associated simulators can be used for testing hypotheses on new mechanisms (the "Sliding filament hypothesis" of Huxley (1957) is a famous example, the associated model being the basis of most modern excitation-contraction models for cardiac muscles). During these tests the model parameters have in general nominal values identified from various experiments.

A desirable property when coupling models and data – in situations mentioned in ii) – is the identifiability of the relevant parameters for the model considered (and the observability of its state for a dynamical model) using the available data. Of course this property relies on a good balance between the accuracy of the model and the quantity (and type) of information contained in the data. In particular the most complete model will not be the best in the case of partial information. When a good match is found, model-based data processing will allow to extract relevant information from the available data in a more sensitive way, and discrimination of physiological and pathological situations will be easier. This information extraction (parameter identification, state estimation) is the inverse problem associated with the model and the data.

[1] With 180 000 deaths per year, cardiovascular diseases represent the leading cause of death in France before cancer. In the United States more than 1 million deaths occur every year caused by cardio-vascular diseases.

Assessing the cardiac performance : the main approaches

In this project we aim at formulating :

1. identifiable predictive models, and
2. methods for solving the corresponding inverse problems in order to assess the cardiac function.

Such models can be the basis of patient-specific cardiac simulators, useful for diagnosis and therapy planning.

Methods for performing a model-based assessment of the cardiac function are very dependent upon the type of the available information and they are the object of different research approaches. To illustrate this, we can consider the cardiac output (CO) – namely, the amount of blood ejected by the left ventricle every minute – as an indicator of the cardiac function. A very elementary model is $CO = SV.HR$ where the heart rate (HR) and the stroke volume (SV, the amount of blood ejected by the ventricle at every beat) can be viewed as macroscopic descriptions of the "space-time" behavior of the heart. Depending upon the information available for a specific patient, data processing will have different objectives and will be based on models adapted to the available information.

For example without any spatial information (in particular without information on SV, e.g. without images of the heart), analysing sequences of physiological signals (electrocardiogram (ECG), aortic pressure...) is useful for the detection and the diagnosis of pathologies that impact the cardiac function CO: the joint analysis of the Heart Rate Variability (HRV, the beat-to-beat fluctuations in the cardiac period) and pressure is used to detect troubles of the cardiovascular regulation by the autonomous nervous system (ANS) ; more surprisingly, recent results seem to show that the detection of ischaemia is possible by monitoring ST segments[2] of long sequences of ECG. These methods based on ECG (and pressure) rely more or less explicitely on models of the electrical activity in the heart and of the balance in sympathetic and vagus nervous activity (the baroreflex external control of the heart by the ANS).

Integrative Physiology projects and the heart

Understanding the cardiac electrical activity was the main objective of early works that focused on modeling cardiac cells resulting in highly sophisticated models [40]. These "ionic current" models, originating in the Hodgkin-Huxley model (1952) have benefited from four decades of iterative interactions between experimental and simulation work on the cell scale [48]. Recent developments of those cellular models have led to the simulation of the effects of particular genetic mutations characterized by changes in protein function [13]. To foster the exchange of knowledge, data and modeling on these topics, an ambitious international collaborative project called the Physiome Project [6] started four years ago by a worldwide group of physiologists and bioengineers including the universities of Auckland (New-Zealand), Oxford (UK), Johns Hopkins (USA), MIT (USA) and Washington University (USA). Nevertheless, we point out that simpler models originating in the FitzHugh-Nagumo

[2]The sequence PQRST designates different typical temporal events of the ECG signal.

model (1961) are sufficient to represent the propagation of action potential in the heart, as seen through ECGs.

The role of 3D imagery

In the present project we are mainly concerned with the opportunity for improved clinical and diagnosis performance via new 3D cardiac acquisition techniques (including sequences of images, the so-called 4D data). In this case the available information allows to obtain heart volumes in time, and in particular SV, so that the cardiac output CO – or the ejection fraction (EF) – can now be estimated on a beat per beat basis. Details seen in images lead to considering the estimation of the local contribution of tissue to the cardiac function. In this situation, in a first step, short sequences of images are considered (beat per beat analysis) and the focus is on EF on the organ scale and its local equivalent, the strain field on the tissue scale. For short sequences (a few heart beats), the external control by the ANS is in open loop. The corresponding information then consists of short sequences of 3D images, ECG and aortic pressure if simultaneously measured. It concerns the electromechanical activity of the heart. Models matching these data have to represent electrical as well as mechanical phenomena on various scales (at least organ and tissue).

With the constant progress of medical imaging, it has been possible in the late nineties to obtain anatomically detailed models of the ventricles from MR images. Whole heart models have then been built by coupling these anatomical models with various types of multiscale models of the electromechanical cardiac activity. However, inverse problems associated with this type of heart models are still largely unsolved.

Models for today inverse problems and tomorrow extensions

In the ICEMA-X [3] actions, such a multiscale model has been proposed based on an excitation-contraction model on the cell and tissue scales compatible with present descriptions of actin-myosin molecular motors [12]. The explicit averaging from cell to tissue performed in this model allows to consider only the organ and tissue scales when building a whole heart model. With its reduced number of averaged tissue parameters, this model is a good candidate for solving inverse problems associated with the data described above. This is one of the challenges of the present project. Remark that even if the model is in some sense reduced, an important computing power is nevertheless necessary: this is an obstacle for clinical applications and intensive computing techniques must be specifically developed.

As already mentioned the models have to be matched to the available data in order to obtain tractable inverse problems, and their development requires considerable efforts. In the same time there is a constantly increasing number of biomedical devices providing in vivo measurements of structures and processes inside the human body, at scales varying from the organ to the cellular and even molecular level. Hence, special care must be exercised to keep these models open for further extensions. In our project the modeling principle followed to that purpose is to preserve

[3] We use the acronym ICEMA-X to designate the two INRIA collaborative actions ICEMA and ICEMA-2

the thermodynamic consistency of models and to consider living systems as open thermodynamic systems far from equilibrium. This principle will be followed to enhance and couple the ICEMA-X models with perfusion models and oxygen consumption with heart work: this extension will allow to consider ischaemia. The thermodynamic approach is natural here due to the mechano-energetic meaning of oxygen supply. Finding the above-mentioned good balance between the accuracy of the model and the quantity of information contained in the data is a true challenge for this extension. Quantitative assessment of the impact of ischaemia on the cardiac function and local diagnosis will be possible using such models, as well as therapy planning based on their predictive value.

Cardiac simulation for diagnosis and prediction

Global cardiac simulators or patient-specific cardiac simulators – provided a good match is found between model and data – will also allow a more profound understanding of the cardiac anatomy and physiology, and of the correlation between anatomical or physiological anomalies and the development of certain pathologies. Indeed, the models underlying such simulators and their extensions will be helpful to better exploit the huge amount of available biomedical signals (from in vivo molecular and cellular imaging to macroscopic cardiac imaging) as well as the genetic information potentially available for each patient. A major objective is to increase the potential for pre-symptomatic diagnosis and early treatment for maximum efficiency. These simulators will also allow the quantitative evaluation and optimization of various therapies (including gene or cell therapies), and the development of image guided therapies. The pharmaceutical domain is also an application area, as computational models will have inputs that can be exploited to better predict and quantify the effect of new drugs.

1.2 From ICEMA-X to CardioSense3D : an INRIA continuing effort

The INRIA collaborative action ICEMA-2 (2002-2004) that followed the ICEMA action (2000-2002) has focused on the building of an electro-mechanical model of the heart. The CEA-EDF-INRIA school on cardiac modeling (Rocquencourt, April 26th- April 30th 2004) has served to expose the outcome of the ICEMA-X research as well as to benchmark this research against other state-of-the-art research groups. The very positive feedback obtained during this meeting has strengthen our belief that the scientific and technological developments of the ICEMA-X projects were both relevant and original. A detailed positioning of the CardioSense3D project with respect to major research groups is described in appendix A but can be summarized as follows:

- We aim at formulating identifiable predictive models having an accuracy matched to the information content of 3D images, ECG and pressure. In consequence, all constitutive equations underlying physiological models are designed with the objectives of minimizing their number of parameters and state variables which is beneficial for solving inverse problems and for speeding-up computation of direct problems.

- We aim at building patient-specific heart models (i.e. models with their data-driven inverse problem solvers) in cooperation with specialists of the biomedical field by combining three expertises:

    1. Modeling: creating a compact but realistic model of the heart at the electrical, mechanical (including perfusion) and metabolic levels,
    2. Image analysis: analysing medical images and signals to obtain relevant observations of the geometry and physics of a given patient heart,
    3. Scientific computing: solving inverse problems to estimate parameters and state variables from those observations.

The CardioSense3D project will benefit from the scientific and technological momentum created by the ICEMA-X actions, but it will also extend its objectives in several ways:

- The CardioSense3D project will address new modeling issues (perfusion) and new technical issues (data assimilation and associated inverses problems) that we consider as being scientifically challenging. Those hard points justify the duration of the project (4 years) and the involvement of several Phd students.
- We want to demonstrate during the course of this project, the clinical relevance of our cardiac simulator. We have included three workpackages dedicated to clinical objectives, including clinical and/or industrial partners.

We believe that the CardioSense3D project fits well into the scientific objectives of INRIA[4] and that the involved INRIA teams and their partners have the proper structure (small and reactive teams) and expertise (multi-disciplinary) to achieve both theoretical and applicative breakthroughs in this field.

2 Objectives

The objectives of the CardioSense3D project are threefold :

1. To build a cardiac simulator, with identifiable parameters, that couples 4 different physiological phenomena: electrophysiology, mechanical contraction and relaxation, myocardium perfusion and cardiac metabolism,
2. To build data assimilation software that can estimate patient specific parameters and state variables from given observations of the cardiac activity,
3. To build several software applications based on this simulator and data assimilation techniques to solve clinical problems related to the diagnosis or therapy of cardiac pathologies.

[4]We consider the CardioSense3D project is in agreement with the following three strategic objectives of INRIA: Coupling models and data to simulate and control complex systems, Modeling living beings, Fully integrating ICST into medical technology.

To reach each of those three objectives will require new scientific developments :

1. The introduction of models and related numerical procedures to represent some important physiological phenomena still not considered, in particular: cardiac metabolism, perfusion and tissue remodeling. The extended models must remain identifiable with the available data and computationally tractable. This will set the limits of the otherwise endless quest for model fidelity and simulation accuracy.

2. The formulation of effective data assimilation methodologies associated with those models, that can estimate patient-specific indicators from actual measurements of the cardiac activity. Major shortcomings of existing methods include robustness and computational cost (the "curse of dimensionality").

3. The adaptation and optimization of the cardiac simulator (including both direct and inverse approaches) to some targeted clinical applications. For each application, specific problems connected with clinical science will be considered.

We provide additional comments regarding those three objectives in 2.1, 2.2 and 2.3 before describing how those three objectives are articulated.

2.1 Building a Cardiac Simulator

In the CardioSense3D project, we want to maintain and even develop the modeling choices that underlied the ICEMA-X projects. Indeed, following the proposal of the SOSSO team, the current ICEMA electro-mechanical modeling is based on a compact set of equations involving only 5 state variables, which is significantly less than other existing simulators of the cardiac function (see appendix A). The low number of variables is beneficial for two aspects: efficiency for computing the direct problem (simulating cardiac activity) and possibility to address inverse problems (estimating model parameters and states from observations). However, unlike other existing models, this compact description is not obtained by heuristic approaches or experimental testing based on the fitting of macroscopic experimental data[28] or the identification of attachment and detachment rates of the bridges[57].

Instead, we have designed a chemically-controlled constitutive law which is consistent with general thermodynamics and with the behavior of myosin molecular motors[37], the Huxley sliding filament hypothesis[35] and with the Hill force-velocity relation. Thus, the nature of the ICEMA models can be interpreted at the microscopic, mesoscopic and macroscopic levels. Such physical interpretations are important for managing the possibility of future extensions of the model.

In the CardioSense3D project, we want to follow the same approach for expanding the current model with the incorporation of additional physiological phenomena such as energetic metabolism. Indeed, the current model describes the contraction or relaxation of cardiac fibers under the control of the action potential (chemical control). In the CardioSense3D project, we want to add in the electro-mechanical coupling equations, two state variables that are involved in the energetic balance of the contraction and relaxation of myocardium fibers.

In addition, the coronary flow which originates from the aorta and which supplies the oxygen to cardiac tissue will also be modeled, thus closing the loop between the electro-mechanical model and the energetic metabolism model (see figure 1). The fluid dynamics within the coronary network will be based on a hierarchical approach: from a 3D-fluid structure interaction model at the level of the aortic valves to a poroelastic model at the level of the myorcardium.

Finally, some clinical applications listed in section 3.2 will include additional efforts in modeling or optimization. Some of them are listed below:

- **Cardiac resynchronisation.** Asynchronous ventricular contraction yields ventricular dysfunction. For example, a left bundle branch block yields an asynchronous ventricular contraction and a decreased left ventricular contractility. Cardiac Resynchronisation by means of simultaneous biventricular or multisite leftventricular pacing is used for improving left ventricular systolic performance in patients with heart failure and conduction abnormalities. In biventricular pacing, it seems that the improvement of contractility is optimal when pacing the mid lateral epicardial sites of the left ventricle. Nevertheless, the questions of the leads optimal locations and of the choice of the timing delay between RV and LV stimulation are largely open. A preliminary study has shown that using the electromechanical model developed during ICEMA-X actions, it is possible to assess the effectiveness of the electrical stimulation. This preliminary study deserves to be extended in two directions: i) modeling of the stimulation leads has to be refined and validation procedures of the electrical simulations have to be settled and ii) optimization algorithms for the automatic positioning of the leads have to be designed. See WP5.

- **Remodeling of the myocardium tissue.** The heart responds to abnormal conditions such as high blood pressure or overload with a structural change of cardiac cells. This structural damage called remodeling has several anatomical (enlargement of the myocardium), physical (decrease in contraction) and physiological (mitral valve regurgitation) effects which can lead to heart failure. Remodeling will be considered in WP1 and WP6.

2.2 Building data assimilation software

Data assimilation aims at estimating the state variables and parameters of the cardiac simulator from a set of observations of the cardiac activity. In other words, it consists in solving an inverse problem associated with the model described in the previous section.

We do not see data assimilation has being a by-product of a cardiac simulator. It is instead a pivotal task in this project at least for two reasons. First, it allows us to create a patient specific simulator, *i.e.* to use a set of parameters that matches the cardiac physical and physiological performance of a given patient. Second, the set of parameters extracted from the observations of a given patient heart is a compact description of the heart physical and physiological function. As such, it is ideal to use those parameters to establish a diagnosis (through the use of a classifier in the parameter space) or to find unknown correlations on a large database of patients (through data-mining).

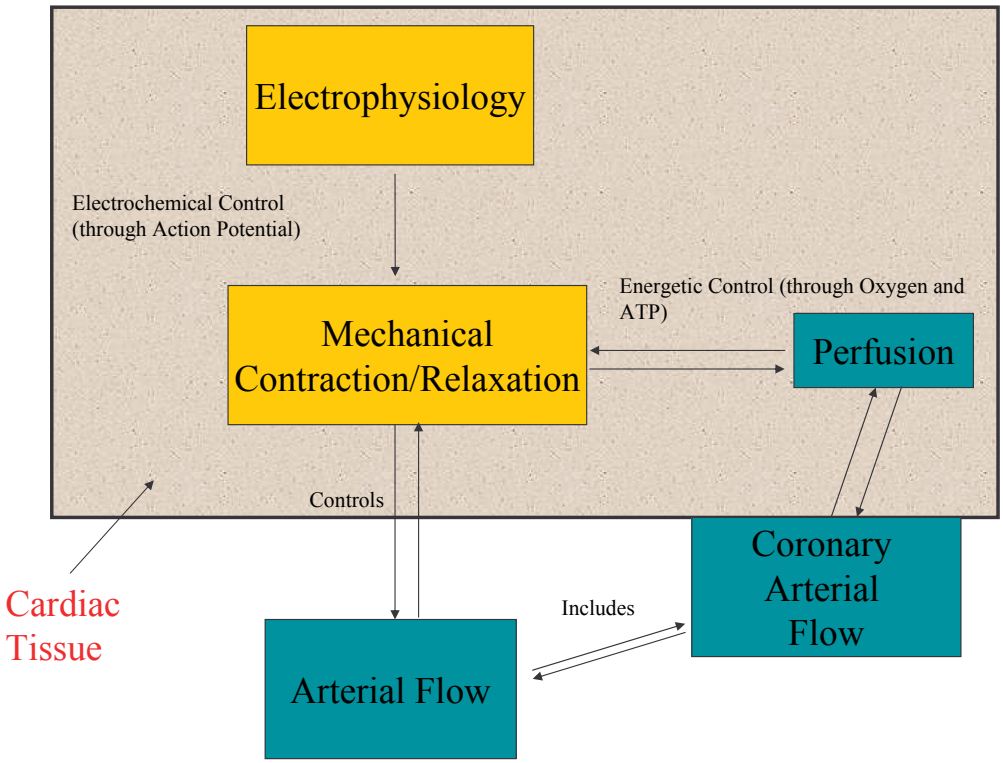

Figure 1: Relationships between the 5 physiological components. The yellow boxes correspond to components whose modeling have already been addressed in the ICEMA-X projects while the green ones indicates modeling components added in the CardioSense3D project. The cardio-vascular flow component will serve both as input (through the coronary arteries) and the output (flow after the aortic valve) of the current model. The energetic metabolism component interacts both with the coronary arterial flow model (through blood flow and pressure) and with the mechanical model of the heart (through energetic balance).

	States to be estimated	Parameters to be estimated	Observations from which is based the estimation
Electrical Level	extra-cellular and action potential	electrical conductivity, fiber direction	ECG, 3D Mapping from endocardial catheters, ECG Imaging
Mechanical Level	displacement, stress, strain rate	contractility, compliance	Tagged or Cine MR Images, 3D echocardiographics images
Perfusion level	coronary pressure, coronary flow, oxygen pressure	porosity and permeability	CT angiography, MR angiography, cardiac CT, SPECT

Figure 2: Description of parameters to be extracted from data assimilation at three different levels

From the beginning of the ICEMA-X projects, the choice of the modeling equations has been governed by their ability to alleviate the data assimilation task. This has led us to design equations with a compact and observable set of parameters and states. However, because it assumes the availability of the direct model, data assimilation has not been largely investigated in the past ICEMA-X projects. More precisely, two preliminary attempts concerning the data assimilation of the mechanical model [51] and the electrical model [46] were performed at the end of the ICEMA-2 project.

In the CardioSense3D project, we want to pursue this grand challenge of performing the data assimilation at the electrical, mechanical and cardio-vascular levels. We provide in figure 2 the expected parameters and observations related to each level.

The methodology to achieve this grand challenge will be based on a range of techniques. For the estimation of electrical parameters such as the electrical conductivity, the causality of the phenomenon (propagation from the apex to the base) can be exploited to drastically reduce the complexity of the signal. Preliminary results suggest that variational approaches based on a local analysis of isochrones may be sufficient to achieve the identification of electrical conductivity parameter. For the mechanical behavior, however, existing procedures – either variational or sequential (e.g. Kalman filtering and variants) – feature major shortcomings (as regards computational cost and robustness with respect to perturbations, in particular) that motivate a methodological approach aimed at formulating more effective and adapted data assimilation procedures.

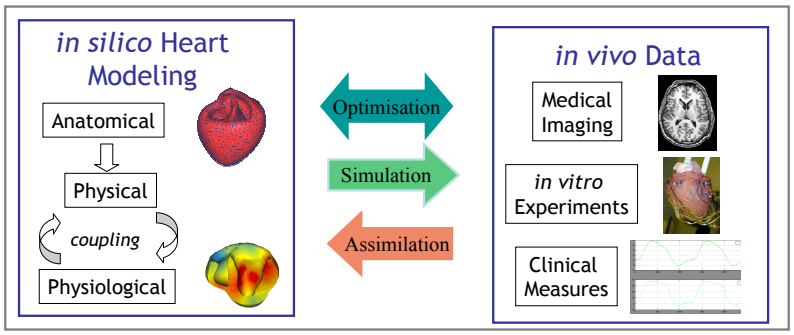

Figure 3: Three different tasks linking a cardiac model and cardiac observations : simulation, data assimilation and optimisation.

2.3 Building clinical applications

With the expertise and software already developed during the ICEMA-X projects, we believe it is feasible to build applications based on the previous two components that will impact clinical practice within the duration of the CardioSense3D project. The choice of clinical applications is driven by its clinical importance, the relevance of our cardiac simulator in solving that particular clinical problem but also by practical considerations (such as the acquaintance with the clinician leading the application, the geographical proximity and the availability of datasets).

We propose to distinguish between computer-aided diagnosis applications and therapy planning applications. In a computer-aided diagnosis study, model parameters are extracted from the dataset of a given patient through data assimilation. Given that this extraction is performed on a sufficiently large population, a database including the model parameters and other clinical information can be used to find a limited number of parameters that correlate well with the occurrence of some pathologies. In such a case, a quantitative and reproducible computer-aided system can be designed to help the medical expert in the diagnosis of those pathologies.

In a therapy planning application, a patient specific model is first built by adapting a general model to the observations of that patient heart (data assimilation). Then the clinician can play different "what-if" scenarios to plan a given therapy and, when appropriate, he can optimize some aspects of the therapy (like the placement of pace-makers) in an automated way.

The different applications are detailed in the list of workpackages in section 3.2.

We classify below the applications depending of their physiological targets :

- **Electrical parameters** : multi-site stimulation planning (WP5), Simulation of electrical conductivity pathologies (WP4), Right Ventricle dysplasia (WP6)
- **Mechanical parameters** : Surgery Planning of akinetic plaques (WP6), Diagnosis of infarcted/ischemic tissue (WP3), Myocardial contractility (WP7)

The ambition of the CardioSense3D project, is to reach medical objectives on top of scientific ones. This is what justifies, in our view, the wingspan of this project both in terms of duration (4 years) and size. Impacting the medical field is especially difficult and is a long term objective. We wish to impact this field in three ways :

- **Publications in medical methodological journals** such as *Medical Image Analysis* and *IEEE Transaction in Medical Imaging* with an impact factor close to 4 and that are read by medical imaging experts both in the medical and scientific fields.
- **Publications in medical clinical journals and conferences** that are mostly read by medical experts (cardiologists, radiologists) and biologists. Our experience is that we can produce those publications only if there is a close and fruitful collaboration with clinicians that are well established in their fields. Since building successful clinical applications requires building successful methodological tools, we can hope to publish in those journals only in the second term of the project.
- **Building clinically useful applications**.

To reach those three goals, we rely on a pool of first class clinical partners. Those partners are listed in section 3.1.2 and allow us to get two expertises :

1. **Expertise in acquiring advanced datasets**. To validate and improve our models, we will rely on sophisticated datasets originating from a laboratory of the NIH (directed by Pr. E. McVeigh) and a clinical team of the Guy's Hospital (directed by Pr. R. Razavi). The former provides motion and electrical data on dogs heart (with the ability to control the location of pathologies) while the latter provides motion and electrical data on pathological human hearts. Both of them have developped sophisticated experimental setups that have no equivalent elsewhere.
2. **Clinical expertise in specific therapies**. Pr. S. Cazeau, Pr. B. Diebold and Pr. R. Razavi are world class experts for their respective fields of pacemaker positionning, akinetic plaque resection and ventricular radiofrequency ablation.

2.4 Software Integration

Figure 4 pictures how we plan to integrate the three main objectives of the CardioSense3D project : simulating cardiac activity, recovering model parameters from observations and building applications. As shown below, there will not be a single

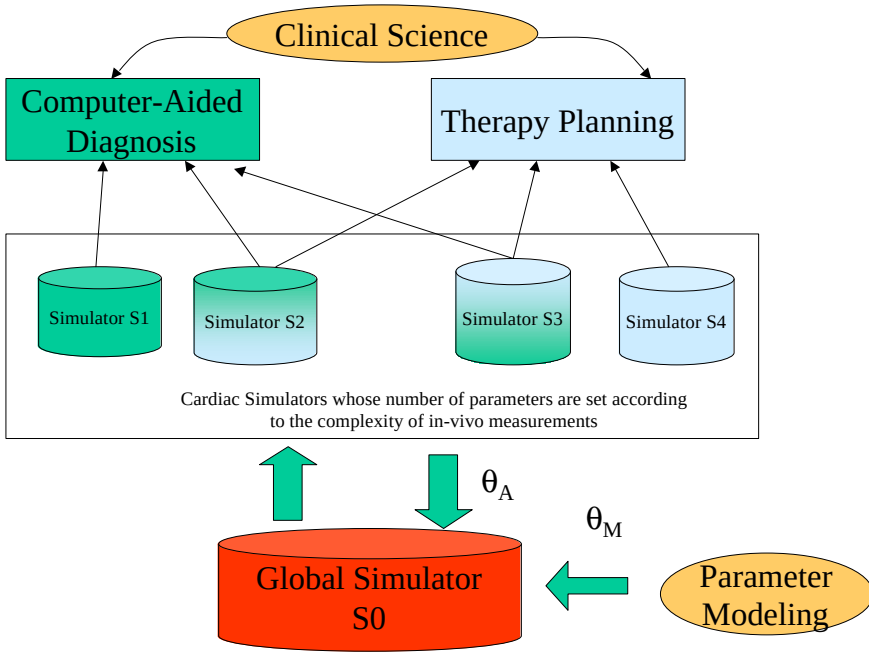

Figure 4: Interaction between the different simulators built for each application.

simulator but several of them. A global simulator S_0 which will integrate all components described in section 2.1. Note that the integration may be loose (through shell scripts) since efficiency and user operability is not an issue at this level and since pieces of software may come from different research groups. This simulator will serve as the basis for all validation studies.

Each application will require a specific simulator that will be tailored to the datasets and the computation time and accuracy requirements of that particular application. Thus, dedicated modeling and data assimilation techniques may be developed to cope with the specificity of that application.

The set of parameters $\{\theta\}$ needed to run the simulation must first be determined based on the scientific literature and possibly from heuristics. Those parameters which are first roughly estimated are written as $\{\theta_M\}$ in Figure 4. Then, once data assimilation techniques have been applied, a better estimate of some parameters $\{\theta_A\}$ (those that are observable) will be computed, finally replacing the initial estimate. For patient-specific simulations, the estimated values of $\{\theta_A\}$ parameters will be employed while for a generic simulation, the user could choose a value of those parameters within a valid range.

3 Project Description

3.1 List of Partners

We have chosen to describe two circles of partners. The first circle of partners include INRIA research teams mainly involve in the course of the project. Financial

responsibility will only be granted to partners within the first circle. Partners in the second circle will receive support only through collaborative action with a first circle partner.

For each partner we provide below some relevant information related to its expertise in the field.

3.1.1 First Circle

1. The **Epidaure Team** is dedicated to the analysis of medical and biological images as well as the study of computational anatomy and physiology. In the course of the ICEMA-X projects, it has acquired the expertise of building geometric meshes of the heart ventricles from medical images, of extracting motion information from time series of cardiac images, of extracting fiber directions from Diffusion tensor images, of building a dedicated electro-mechanical model of the heart and of solving inverse problems from electrophysiological data. Persons to be involved in this CardioSense3D project include : N. Ayache, H. Delingette, T. Picart, V. Moreau, M. Sermesant.

2. The **SOSSO2 Team** The SOSSO2 team is involved in modeling, observation and control of natural or engineered feedback-controlled systems. The main emphasis, since the ICEMA project, is on controlled multi-scale systems, in particular for energy conversion.
   Some topics related to physiological systems are considered with applications to diagnosis and therapy:

   - Modeling of the controlled chemomechanical conversion in the heart on the cell, the tissue and the organ scales ;
   - Non-invasive assessment of the function of the cardiac pump on the cardiovascular system scale ;
   - Multi-scale modeling of the selection of ovulatory follicles.

   Control of energy conversion is also considered in low emission automobiles:

   - Reduced-order multi-scale modeling and control of auto-ignition in internal combustion engines ;
   - Modeling, control and monitoring of fuel-cell systems.

   Participants to CardioSense3D: Q. Zhang, A. Manriquez, E. Crépeau, Y. Papelier, M. Sorine, PhD A, Post-Doc A (also with REO).

3. The **MACS Team** The MACS project is specialized in the modeling and numerical simulation of problems arising in solid and structural mechanics, with a particular emphasis on biomechanics and medical applications. As part of the ICEMA-X projects, the role of the team was to formulate the 3D continuum mechanics model and corresponding simulation procedures, and also to study and implement some related data assimilation tools. The staff involved in this new project will include: D. Chapelle, G. Derveaux, Ph. Moireau (conditional on granting of "détachement X-Telecom"), M. Vidrascu.

4. The **REO Team** REO is a joint project of the INRIA Research Unit of Rocquencourt and the Jacques-Louis Lions Laboratory (LJLL) of the Pierre and Marie Curie (Paris 6) University. Its research activities are aimed at :

   - modeling the flow of biological fluids, more especially blood in large vessels and air in the respiratory tracts (mainly in conduits which are sufficient large to be visible using common medical imaging techniques), both in normal and pathological states;
   - developing and analyzing efficient, robust and reliable numerical methods for the simulation of such flows;
   - developing effective simulation software to guide medical decision and to design more efficient medical devices.

   The staff involved in CardioSense3D will include Miguel Fernández, Jean-Frédéric Gerbeau, Marc Thiriet, PhD C, Post-doc A.

We provide below the approximative involvement of permanent researchers in the CARDIOSENSE3D project :

- **MACS** : D. Chapelle 30% (team scientific leader), M. Vidrascu 30%
- **EPIDAURE** : N. Ayache 20 % (team scientific leader), H. Delingette 40 %
- **SOSSO2** : M. Sorine 30 % (team scientific leader), Q. Zhang 40 %
- **REO** : J.-F. Gerbeau 30% (team scientific leader), M. Thiriet 30%, M. Fernandez 40 %

3.1.2 Second Circle

Collaboration between partners of the first circle and those of the second circle may have different format ranging from informal sharing of knowledge, software or data to a co-supervision of a Master, Phd or Post-doc student. In many cases, the co-supervision of a master student could be the format of choice for many such collaborations. We have therefore planned a budget for financing 2 to 3 Master students per year (starting in 2006).

We distinguish between four types of collaborations : collaborations with INRIA, academic, industrial and clinical partners.

INRIA Partners

- The **CAIMAN Team** based in Sophia-Antipolis. The CAIMAN team, a joint team between the "Ecole des Ponts et Chaussées" and INRIA located in Sophia-Antipolis, is focused on designing efficient solutions for the numerical simulation of physical phenomena related to wave propagation and complex flows in interaction. The team was involved in the ICEMA-2 project where its expertise in parallel computing and numerical analysis has allowed to significantly speed-up the computation of the mechanical model implemented by the Epidaure team. In the CardioSense3D project, it is planned to keep this parallel computing expertise but also to expand its involvement in two

directions (both in Workpackage WP4). The first direction is the simulation of the twelve electrocardiogram (ECG) derivations from the propagation of the action potential. A Master student (T. Picart) co-supervised with the EPIDAURE and CAIMAN teams has recently been working on that topic. The second direction includes the modelling of the thermal effects induced by the deposition of electrical energy in tissues using radio-frequency electrodes (involved in radio-frequency ablation). In a previous project (Headexp), the CAIMAN team has indeed acquired a good expertise on the bioheat equation that governs this phenomenon.

- The **GAMMA Team** based in Rocquencourt. The team expertise is in automatic generation and refinement of meshes needed in scientific computations. This expertise will be particularly valuable for the numerical simulation of action potential propagation. Indeed, the numerical analysis results obtained during the ICEMA projects have shown that mesh sizes near the wave front must be very small in order to correctly capture the phenomenon, which is incompatible with homogeneous mesh sizes. Hence, time-dependent mesh refinement/generation is a promising path to handle this difficulty. In addition, the pre- and post-processing tools developed in the team are of primary interest and could serve as the basis of software components designed to manipulate geometrical models.

- The **GEOMETRICA Team** based in Sophia-Antipolis. The GEOMETRICA team expertise is in computational geometry and has recently proposed efficient algorithms for generating high quality triangulations from scalar fields [14]. A collaboration is currently running between the GEOMETRICA and EPIDAURE team to apply this technique to the meshing of isosurfaces extracted from medical volumetric images. Other developments are aiming at generating non-homogeneous high quality tetrahedral meshes from triangular shells and scalar fields. In the course of the CardioSense3D project, those tools will be tested and utilized by the EPIDAURE team to produce surface and volumetric meshes from medical images that are suitable for scientific computing.

Other Academic Partners

- **The CREATIS laboratory** is a joint Research Unit between CNRS (UMR 5515), INSERM U630, INSA of Lyon and Claude Bernard University of Lyon focused on medical imaging with a strong activity on cardio-vascular imaging and analysis. In particular, they have developed an expertise for the registration of PET/MR images which allows to fuse cardiac anatomical and functional information [56] on the same temporal and spatial reference frames. A long term experience has been also acquired in the analysis of vascular images. Methods and software for vessels tracking from 3D angiographic imaging have been developed that can be applied for the analysis of the coronary network. We plan to collaborate in the course of the CardioSense3D project to build patient specific maps of perfusion, metabolism and contraction activities of the heart through the acquisition, registration and processing of anatomical and functional images (MRI, PET, SPECT,...) and to produce realistic

geometrical models of the coronary network. Functional maps and vascular geometrical models should be very helpful to qualitatively evaluate the energetics and coronary flow models developed in workpackages 1 and 2.

- The **New Technology Research Center (NTC) in Plzen(Czech Republic)** Within this laboratory, we are planning to collaborate with the group of E. Rohan on the modeling and simulation of perfusion. This group contains in particular R. Cimrman who was a post-doc at INRIA-Rocquencourt (Macs) during ICEMA-2.

- The **University College London**. The Medical Imaging group at UCL lead by Pr. D. Hawkes and Pr D. Hill was formely established at King's College where they worked closely with Pr R. Razavi (see below). As such, they have built image registration software to register MR images with X-ray images of the XMR system (described below) to merge motion and electrophysiology data in the same temporal and geometric reference frame. Despite the recent move of this group at University College London the connection with Pr Razavi and the Guy's Hospital prevails and the existing collaboration with the EPIDAURE and MACS teams will be extented around the acquisition of motion and electrophysiological data for creating patient specific models (Workpackage 3 and 4).

- The **Mathematical Laboratory Jean Leray, Nantes University**. Yves Coudière, assistant Professor, was involved in the ICEMA-X projects where he was involved in the mathematical and numerical study of the modeling equations of electrophysiology. More precisely, he studied the FitzHugh-Nagumo and Aliev-Panfilov equations and he is now studying the mathematical and numerical properties of the *bidomain model* equations governing the propagation of extra-cellular and action potentials. He will be involved in Workpackage 4.

Industrial Partners

- **Philips Medical System Research Paris.** The Paris research laboratory of Philips Medical System has a strong expertise in medical image analysis and was already involved in the ICEMA-X projects. Philips Medical System has recently launched a suite of 3D echocardiographic probes that can provide 3D echographic images of the heart cavity around 25 Hz. To our opinion, this represents a plausable alternative to MR Imaging for the observation of the mechanical contraction and blood flow (through Doppler imaging) of the heart. Indeed, this modality bears several advantages compared to MR including its relatively low cost and its high frame rate. In the CardioSense3D project, we plan to collaborate with Philips Medical System Research Paris to have access to collection of 3D-echocardiographic images of healthy and non-healthy subjects and extract motion fields suitable for the validation of the mechanical model (Workpackage 3).

- **ELA Medical** ELA Medical, a Sorin Group company, is an innovative leader in research, development, manufacturing and marketing of cardiac rhythm management implantable and diagnostic systems. ELA Research is actively

engaged in developing innovative therapeutic solutions to treat CHF. Close collaboration between ELA's engineers and world-renowned cardiologists led in 1994 to the world's first implant of a cardiac stimulator with a four-chamber configuration carried out by Dr. Philippe Ritter and Dr. Serge Cazeau from InParys Clinical Research Associates, using an ELA pacemaker and to the initiation of the MUSTIC study in 1996 [5].

Clinical Partners

- **Hopital Européen Georges Pompidou and INSERM unit 494** Pr Benoit Diebold is a Professor and Cardiologist (Praticien Hospitalier (PU-PH)) in the cardiology department of Hôpital Européen Georges Pompidou. He is also member of the INSERM unit UMR-S 678 (ex U494) and author of many publications (around 19 publications in peer-reviewed journals [6] and several keynote speeches) many of them related to quantification of the cardiac function through the analysis of echocardiography. Pr. Diebold will be strongly involved in the Workpackage 6 where the electro-mechanical heart model will be used to plan the resection of akynetic plaques caused by ventricular aneurysms.

- The **Guy's Hospital and King's College** in London. Pr R. Razavi is a Professor of Paediatric Cardiovascular Science, a director of Cardiac MRI and is an honorary consultant paediatric cardiologist for the NHS. He is appointed by the King's College for his research and teaching but he has strong connections with the research group at University College London (formerly at King's College London). He has a strong expertise in the MRI-guided catherization of the heart to cure congenital diseases on children. He is the author and co-author of many publications including a recent article in the prestigious journal "The Lancet" [50]. In the past two years, Pr Razavi has collaborated with the EPIDAURE and MACS teams through M. Sermesant, a former EPIDAURE Phd student, who is working in his team for his postdoctoral study. The Guy's Hospital is equipped with a unique imaging system called XMR that allows to acquire MRI and X-ray images few minutes apart and with a simple translation of the patient bed. This system is the key device for providing both mechanical (through MR) and electrical (through X-ray) information of the heart function for a given patient. M. Sermesant has recently published several papers [52] where he shows the first encouraging attempts to create patient specific models of the heart from the data acquired by the XMR system. In the course of the CardioSense3D project, we plan to collaborate with Pr Razavi to assess the accuracy of automatically estimated patient specific models (Workpackages 3 and 4), to assess the predictive behavior of those models and to evaluate the feasibility of building a radio-frequency ablation planning software.

[5] MUSTIC (Multi-site Stimulation in Cardiomyopathy) is a European multi-center trial supported by a financial grant and technical assistance from ELA and Medtronic (MDT) and conducted under the auspices of the European Society of Cardiology.

[6] See the following page for his publications : $e2.imed.jussieu.fr/afficherMembre.php?pers_id = 17$

- The **Inserm Unit 446 in Chatenay-Malabry**
- The **Medical Imaging Section of the Laboratory of Cardiac Energetics, National Institues of Health**. This laboratory directed by Pr E. McVeigh gathers computer programmers, magnetic resonance physicists, chemists and biologists working together on issues such as bio-compatibility, magnetic resonance physics, patient monitoring, image analysis, computer visualization, and interventional procedures. In particular, this team has the expertise to perform complex experiments on dog hearts combining MR imaging and epicardial electrical mapping. This dataset is very valuable for validating the CardioSense3D electro-mechanical model of the heart since pathologies (ischemic or infarted tissue) can be artifically created as known locations. A collaboration is running between the Laboratory of Cardiac Energetics and the EPIDAURE team for estimating appearent electrical conductivity from epicardial mapping [46]. This research will be pursued and extended in the CardioSense3D project (Workpackage 4) to estimate electrical parameters on a volumetric heart model (instead of a surface model).
- **InParys**, Clinique Georges Bizet, Paris and Centre Chirurgical du Val d'Or, Saint-Cloud, France.

3.2 List of Workpackages

To clarify the involvement of the different partners and their relationships, we propose to describe the work to be performed in this CardioSense3D project as a set of workpackages. The team responsible for each workpackage is printed in bold face.

3.2.1 WP1. Modeling issue I: Cardiac mechanoenergetics on the cell and tissue scales

Main partners : **SOSSO2**, REO, MACS

This workpackage considers cardiac mechanoenergetic models on different scales: very short term models on a subcellular scale, short term (one heart beat) models on the cellular and tissue scales and a very preliminary issue, cardiac remodeling on the long term. The short term models of the cell will be our pivot models, the main issue of this WP.

WP 1.1 The balance between ATP demand and supply on the cell scale We plan to extend the excitation-contraction model (E-C model) used in the ICEMA-X projects to take into account some bioenergetic aspects, in particular the oxygen consumption. The main objective of this extension is to couple this E-C model with a model of oxygen supply through the coronary microcirculation (see WP 2) so that it will be possible to consider ischemic heart disease. For this short-term model (typically the horizon is one heart beat) we will consider the memory effect of ischemia on tissues, an "aging effect" due to oxidative damage (this effect is at the origin of ischemic preconditioning: brief periods of hypoxia followed by reperfusion protect the heart against ischemia for some time).

The basis of this E-C model extension will be:
a) The experimentally observed linear dependence between oxygen consumption and mechanical workload on different scales (pressure-volume area on the organ scale, stress-strain area on the tissue and cell scales). In this first step we will consider a perfect regulation of the ATP (adenosine triphosphate) supplied to the actine-myosin motors. This will lead to a first model, rapidly available to test a complete electromechanical model with oxygen supply.
b) The recent descriptions of the mitochondrial oxidative phosphorilation and the relations between Calcium, ATP and ROS (reactive oxygen species) (see e.g. the review paper by P.S. Brookes et al, AJP Cell Physio 287: C817-C833, 2004).
c) The utilization of Nonequilibrium Thermodynamics (NET) techniques. The E-C model is already thermodynamically consistent: it can be derived from thermodynamic potentials (defined by a small number of parameters) that satisfy a Clausius-Duhem inequality. It will be extended by refining the descriptions of the input and output chemical potentials respectively associated with ATP and ADP, P. The NET approach will also be used to describe the (linear) relation between the inflow oxygen consumption and the outflow ATP production on one side and, on the other side, the redox input potential of oxidizable substrates and the output force of the phosphate potential (here, we will follow Cairns et al AJP-Reg. Integr. Comp. Physiol. 1998, 433, R1376).

The cell scale will be the starting point of our model. A scaling approach will be used to derive a model on the tissue scale. This will be tightly coupled with WP2.

WP 1.2 Subcellular mechanisms of regulation of cardiac contractility The linearity mentioned above (point a) is a rather strong (and convenient) property that we will try to understand in cooperation with the Inserm unit "Cellular and Molecular Cardiology" (U446) of Châtenay-Malabry (92). It is still valid for very high heart rates (800 bpm for rats) and in the same manner the ATP level near the sarcomere is remarquably constant. The regulation mechanisms behind these properties are poorly understood.

WP 1.3 Chemomechanical conversion efficiency, contractility and cardiac remodeling During the transition from left ventricular hypertrophy (LVH) to left ventricular failure (LVF), decreases in myocardial contractility and cardiac remodeling (CR) have been observed in animal models of heart failure, together with nearly unchanged high values of the chemomechanical conversion efficiency. The following interpretation of these observations will be the main hypothese underlying our CR modeling tentative: the response to persistent stresses (oxydative and mechanical) is a cardiac remodeling (biochemical modifications of the ventricular wall and then changes in the orientation of the cardiac muscle fibers and ventricular chamber geometry) in order to maintain high (optimal ?) chemomechanical conversion efficiencies. The consequence of the decrease of oxygen will then be a decrease of the contractility (not of the ATP production efficiency).
On the whole heart scale, this hypotheses will be used to determine the CR parameters sensitivity to changes in chemomechanical conditions (e.g. perfusion or afterload changes). In particular, coupling a LV model to a simple model of the aorta (windkessel like model) seems to be interesting in order to estimate the con-

tribution of CR to hypertension.
Remark: remodeling on the cell scale is also a topic of interest (not only for the heart) and will be considered by the MACS project.

3.2.2 WP2 : Modeling issue II : CFD for a hierarchies of arteries (from 3D fluid-structure models to porous media models)

Main partners : **REO**, SOSSO2, EPIDAURE

The modeling of metabolism described in WP1 is strongly dependent on the modeling of the coronary network which supplies the oxygen to the cardiac tissue. We plan to described this network with a three level hierarchical model :

- 3D fluid-structure interaction model: the right and left coronary arteries originate behind the aortic valves. When the valves are opened, the lumen in the coronary arteries is reduced by the contraction of the ventricles. The blood enter these arteries when the valves close. This mechanism involves complex three-dimensional fluid-structure interaction phenomena which are in the front of the research in this field.

- 1D fluid-structure interaction model: the larger coronary arteries divide to form a network that can be described by one-dimensional hyperbolic systems (typically for about 6 generations of bifurcations [54, 55]). This network could be based on "real geometries" obtained by recent works in the EPIDAURE project. The effect of the surrounding tissues is taken into account by an external pressure coming from the electromechanical model.

- Poroelastic model: in the ultimate level, we will use a mixture theory resulting from an homogenization of the blood and the myocardium. In such theories [20, 36], the permeability of the porous media depends on the deformation of the surrounding tissues. This level is therefore still coupled to the electromechanical model.

This hierarchical description of the flow will be completed by a transport equation for the oxygen. The resulting global system will make possible the simulation of pathological situations (occlusion of an artery, ischemic area, ...).

Some ingredients of this research program will be based on previous studies: 3D fluid-structure interaction models [22, 27, 26], 1D models [24], reactive transport in porous media [9, 8].

3.2.3 WP3 : Assimilation of Mechanical Data

Main partners : **MACS**, EPIDAURE, SOSSO2, Guy's Hospital

The issue that we plan to address in this work-package is the formulation of *robust and computationally-effective* data assimilation procedures tailored to the specific type of mechanical system considered. During the ICEMA-1 and ICEMA-2 projects we have used and assessed "off-the-shelf" methodologies of the main two categories, namely variational and sequential (such as Kalman filtering and

its extensions), and found that these existing methodologies are computationally prohibitive, while their robustness (with respect to various perturbations) is highly uncertain.

One of our ideas is to use an observer approach inspired – in the sense of the duality between control and observation – from robust control strategies, such as collocated control. The major advantages of these strategies are that they enjoy "built-in" robustness with negligible computational costs (they are – indeed – designed for real-time command and stabilization of mechanical systems). Hence, the main difficulty in formulating such sequential procedures would be to analyze – and optimize, in some sense – their effectiveness, namely, their ability to provide an accurate estimation of the parameters and state variables as needed in the medical indicators of interest. In this respect, we emphasize that for the "reference" sequential methodologies, namely, Kalman filtering and such, effectiveness is also an issue as their so-called "optimality" does not hold for the actual systems considered.

Of course, in order to achieve the above objectives we need to address specific issues related to observation. In particular, we need to define the observation operator to be used in conjunction with actual measurements, taking into account both the nature of these measurements (in particular the imaging modality being used) and observability considerations. An interesting observability issue, for example, is whether localized electrical activation can be estimated using only the mechanical model with electrical input (i.e. without a PDE model of action potential propagation), images of cardiac deformations and "standard" external electrical measurements (namely, ECG or VCG).

The objective of constructing a specific data assimilation procedure based on the observer approach is intended to be the topic of the PhD of Ph. Moireau (X-Telecom), already present for an extended DEA internship in the MACS project [45, 52]. This PhD would be co-supervised by D. Chapelle and P. Le Tallec (Ecole Polytechnique), also in collaboration with M. Sorine. This topic will also be tackled by a PhD student (PhD D) in the Epidaure team, that will focus on the processing on input data (4D cardiac sequence of images) but also on the identification of mechanical parameters of a simplified cardiac model. This work will be done in collaboration with University College London and Guy's hospital (D. Hill, M. Sermesant) to take advantage of their state-of-the-art XMR datasets.

3.2.4 WP4 : Assimilation of Epicardial and Endocardial electrical measurements

Main partners : **Epidaure**, REO, MACS, NIH, Guy's Hospital

In the course of the ICEMA-X actions, the depolarization and repolarization of the action potential from the Purkinje fibers to the base has been simulated by on the macroscopic model proposed by Aliev and Panfilov [2]. This model includes two states variables, the action potential and the repolarization variable and a set of parameters among which two parameters control the electrical conductivity and the duration of the depolarisation plateau.

First, we plan to improve the accuracy and computational efficiency of the current implementation of this model by locally refining the tetrahedral mesh upon

the arrival of the depolarization wave. Indeed, during this phase, a rapid change of potential occurs thus requiring a mesh with greater spatial resolution. Also the use of models relying on bidomain electrophysiology will be investigated.

But the main objective of this workpackage will be to estimate the two parameters of the Aliev and Panfilov electro-physiological models from relevant observations. Since extracellular potentials rather than action potentials can be measured experimentally, we plan to rely on isochrones maps of the depolarization and repolarization waves in order to estimate those parameters. A preliminary study on the epicardial surface [46] based on data obtained from a a multi-electrode epicardial sock placed on a dog heart, has shown that electrical conductivity can be estimated on a limited number of regions.

Solving this type of inverse problems with classical optimal control approaches is difficult because the observation (depolarization time) is not simply related with the state variables. Instead, the causality of the reaction-diffusion equations can be used to perform the estimation locally as the electrophysiological waves progress from the apex to the base. Ultimately, we want to produce volumetric regional maps of the electrical conductivity that are suitable for diagnosis by cardiologists.

The input isochrone maps could originate from different electrophysiological devices, from the most invasive (sock of electrodes [43]) to the least invasive (like ECG Imaging [15]). Collaborations with the laboratory of cardiac energetics at the National Institutes of Heath (Bethesda, USA) and the Guy's hospital in London will be essential to obtain the most relevant input data and to analyse the conductivity maps.

This work will be performed by a post-doctoral student Sylvain Jaume from October 2004 til October 2005 (Post Doc B) and by a Phd student (PhD D).

3.2.5 WP5 : Therapy Planning Simulator I : planning of pace-maker positioning for biventricular stimulation

Main partners : **REO**, MACS, InParys, Sosso2,ELA Medical

Asynchronous ventricular contraction yield ventricular dysfunction. For example, the left bundle branch block is correlated with a decreased left ventricular function (reduced peak dp/dt) and with an asynchronous ventricular contraction.

The notion of cardiac resynchronisation therapy appeared less than 10 years ago [18, 16]. In the early nineties, clinical studies claimed that the health of patient with severe heart failure was improved by a short atrioventricular delay imposed by a dual-chamber pacemaker pacing at right atrium and right ventricle. But this has not been confirmed by the following studies. The focus has now shifted to left ventricular or biventricular pacing whose benefits have been shown in various clinical studies ([17, 4, 1]). In biventricular pacing, it seems that the improvement of $(dp/dt)_{max}$ is optimal when pacing the mid lateral epicardial sites of the left ventricle [53]. Nevertheless, the questions of the leads optimal location and of the choice of the timing delay between RV and LV stimulation are mainly open.

A preliminary study – based on a simple trial-error procedure – has shown that the effectiveness of the electrical stimulation could be assessed by numerical simulations, using the electromechanical model developed during ICEMA-X actions. This

work has been done during the summer school CEMRACS 2004, with the financial support of ELA Medical and in collaboration with Dr. Serge Cazeau (InParys, Clinique Georges Bizet, Paris) who is one of the pioneers of the resynchronisation therapy. This preliminary study deserves to be extended in two directions, in the PhD C for example. First, the modeling of the stimulation leads has to be refined and sound validation procedures of the electrical simulations have to be settled (by computing numerical ECG or VCG for example). Second, optimization algorithms for the automatic positioning of the leads have to be designed.

3.2.6 WP6 : Therapy Planning Simulator II : planning for acute left ventricular aneurysm pathology

Main partners : **MACS**, Sosso2, HEGP

The objective of this work package will be targeted on the modeling and simulation of:

- the pathological behavior and functional deficiencies of an infarcted heart;
- some corresponding therapeutic strategies.

The basic symptom in an infarcted organ is that the ability of the impacted area to contract under action potential activation is decreased or sometimes even lost. This is what is called a hypokinetic – or akinetic, depending on the seriousness of the symptom – area in clinical terminology. As a result, this area undergoes some stretching (due to the surrounding tissue contracting) during systole, which in itself is detrimental to mechanical efficiency as regards the pressure increase rate and the ejected fraction. In addition, this periodic stretching can lead to pathological remodeling of the tissue in the form of an acute aneurysm, which in turn aggravates the symptoms. In order to prevent the occurrence of this phenomenon and to improve the mechanical indicators, surgery can be resorted to perform a "resection", namely, an extraction of part or the whole of the infarcted area. However, balancing the surgery-related risks with the expected benefits is a key difficulty for clinicians, which is why we aim at providing simulation tools which can be used as an assistance in clinical decision-making.

The immediate impact of an infarct can be represented by the activation / contraction model and simulator that we have already formulated and implemented. However, these simulation tools need some heavy adaptation and reformatting in the perspective of being used in a clinical environment to simulate the specific effects of resection of infarcted tissue on the relevant indicators (to be specified by clinicians themselves). This will be the main task of a junior engineer just hired at INRIA-Rocquencourt (in the "Ingénieur-associé" framework for a 2 years period), and will involve regular interactions with our clinical partners (HEGP, in particular).

As regards tissue remodeling and its application to aneurysm forming, we propose to undertake a longer-term research action with a multiscale approach based on the modeling of the phenomenon at the cellular level. Hence this approach would be based on the modeling of how a cell (or population of cells) behaves – namely, in particular deforms and multiply – when submitted to mechanical stresses. A key object of study in this respect would be the plasma membrane that surrounds cells.

3.2.7 WP7 : Therapy Planning Simulator III : planning for stem cells therapy

Main partners : **Epidaure**

Stem cell therapy appears today as a promising research track for improving the cardiac function of patients suffering from post-ischemic heart failure[7] (patients that suffered from a heart attack). Indeed, preliminary clinical studies show that the injection of adult autologous cardiac stem cells (to be distinguished from embryonic stem cells) leads to an improvement of the cardiac function and in particular of the myocardium contractility. This represents a potential breakthrough for thousands of patients who are waiting in despair for a heart transplant for survival.

In this workpackage, we plan to use our cardiac simulator to quantitatively and regionally assess the change of contractility of the myocardium caused by cellular therapy and to estimate the optimal location of stem cells injection in order to maximize the cardiac function (measured for instance through the ejection fraction).

Because stem cells therapy is still in its infancy, we need to gain more knowledge and to establish more intense clinical contacts before building a clear work program concerning this workpackage. Our current plan is to set up this work program in 2005 and to have a master student working on this topic in 2006 in order to make a first proof-of-concept by the end of 2006.

Potential clinical sites for collaboration include the Hopital Bichat in Paris (Pr Philippe Menasché) and the INSERM Unit 582 at the La Pitié Salpétrière Hospital (Pr Ketty Schwartz).

4 Project Management

We propose to structure the project management in the following way : one project leader, one project coordinator, an executive committee and an advisory medical committee. The project leader will embody the CardioSense3D project and will be responsible of its financial and reporting aspects in front of INRIA scientific direction. As such he will be entitled to speak in the name of the partners whenever presenting the project developpement to a third party.

The project coordination will be shared between the project leader and the project coordinator, both of them being located at different INRIA research unit (the former at Sophia-Antipolis, the latter at Rocquencourt). The coordination will include organizing bi-annual plenary meetings, checking the proper course of Phds and trainees financed by the project, supervising the proper allocation of financial ressource. The project coordinator can replace the project leader for presenting the project whenever necessary.

It is expected that the project leader and coordinator will allocate 40 % of their time to the management of this project. In total, with the active involvement of the steering committee (4 project-team directors, 15% of their time), more than 1 full man-year per year will be dedicated to the project management. The objective is to have a collegial direction in practice more efficient and responsive than a single full time person.

[7] There are 60 000 of such patients per year in France.

List of Workpackages	Epidaure	Sosso2	Reo	Macs
WP1 : Modeling Perfusion		PhdA + Post-DocA	Post-DocA	
WP2 : Modeling Coronaries			Post-Doc A	
WP3 : Assimilation of Mechanical Data	PhD D			PhD B
WP4 : Assimilation of Electrical Data	Post-Doc B + Phd D			
WP5 : Planning of Pacemaker Placement			PhD C	
WP6 : Planning of Ventricular Aneurysm		Engineer A		Post-Doc C + Engineer A

Figure 5: Allocation of human ressources in the CardioSense3D project

The executive committee will be composed of the project leader, the project coordinator and the groups leaders of all INRIA partners in the first circle. The objective of this committee is to discuss and solve management problems that may arise during the coarse of the project. In the absence of the project leader and coordinator, a member of the executive committee will be entitled to present the content of the CardioSense3D project.

The scientific management will be done collectively without any specific structure. This has proven to be very successful during the ICEMA-X projects.

The advisory medical committee provides advices and thoughts on the medical objectives of the CardioSense3D project. It is expected that the committee provides a written report on those objectives in the first three months of the project and to communicate this report to an evaluation committee.

5 Financial Requirements

5.1 Dedicated Staff

We first detail the allocation of additional research staff according to the different partners and workpackages (see table 5).

Two PhDs students will be fully supported by the CardioSense3D project : PhD A, PhD C. Regarding PhD B, an outstanding candidate (Ph. Moireau, see also

WP3) with perfectly adapted background and very strong motivation is already present as an intern (X-Télécom/DEA) and has undergone intensive preparation for these specific PhD objectives, hence we ask INRIA to recruit him as part of the 2005 X-Télécom secondment ("détachement") procedure. PhD D will be partially supported by the Région Provence Alpes Côte d'Azur.

Two post-docs (A and B) are already supported through a european grant (RTN Haemodel) and INRIA Post-doc program. Post-doc C can also be funded by other ressources of the MACS project. The junior engineer, Engineer A, will be funded by the Research Unit of Rocquencourt.

Furthermore, we have added the funding for three Master students per year starting in 2006. Those students could work on collaborative topics with other INRIA teams or academic partners.

5.2 Travel and Hardware expenses

The travel budget will cover the travel expenses of two bi-annual meeting, one additional informal meeting per year, one international conference for four members of each team, thus reaching 15 Keuros per team per year. Additional travel expenses will be allocated to PhD E to support his periodic travel to the Guy's Hospital in London.

Similarly, the budget for replacing 4 PC machines for each team during the course of the project has been estimated at 12 keuros per team.

5.3 Summary of Financial Needs

The financial support from INRIA required to achieve the CardioSense3D project is summarized in figure 6.

A Positioning of the CardioSense3D project with the state of the art

The web site http://www.cardiacsimulation.org/ResearchGroups.html provides some links towards research groups involved in cardiac simulation. Among those, the list of groups having a long experience in the design of an electro-mechanical model of the heart includes (but is not restricted to) :

- The group of Peter Hunter at the Auckland University Bioengineering Institute[8]
- The Cardiac Mechanics research group[9] lead by A. McCulloch at the University of California in San Diego
- The Cardiac Electrophysiology Group lead by D. Noble[10] at Oxford University

[8] www.bioeng.auckland.ac.nz
[9] cmrg.ucsd.edu/lab_info/info.html
[10] noble.physiol.ox.ac.uk/People/DNoble/

Category	Team	Item	Année1	Année2	Année3	Année4
Salaries	SOSSO2	PhD A	10 000 €	30 000 €	30 000 €	20 000 €
	MACS	PhD B	Détachement X-Telecom			
	REO	PhD C	10 000 €	30 000 €	30 000 €	20 000 €
	EPIDAURE	PhD D	20 000 €	20 000 €	20 000 €	0 €
	MACS	Post-Doc C	0 €	0 €	9 000 €	9 000 €
	All	Trainees	0 €	15 000 €	15 000 €	15 000 €
Equipement	EPIDAURE	Machines	3 000 €	3 000 €	3 000 €	3 000 €
	MACS	Machines	3 000 €	3 000 €	3 000 €	3 000 €
	SOSSO2	Machines	3 000 €	3 000 €	3 000 €	3 000 €
	REO	Machines	3 000 €	3 000 €	3 000 €	3 000 €
Travel Expenses	EPIDAURE	PhD D	6 000 €	6 000 €	6 000 €	6 000 €
	EPIDAURE		15 000 €	15 000 €	15 000 €	15 000 €
	MACS		15 000 €	15 000 €	15 000 €	15 000 €
	SOSSO2		15 000 €	15 000 €	15 000 €	15 000 €
	REO		15 000 €	15 000 €	15 000 €	15 000 €
Total			118 000 €	173 000 €	182 000 €	142 000 €
Grand Total	615 000 €					
Ventilation par projet	Epidaure		44 000 €	47 750 €	47 750 €	27 750 €
	MACS		18 000 €	21 750 €	30 750 €	30 750 €
	SOSSO2		28 000 €	55 500 €	55 500 €	45 500 €
	REO		28 000 €	51 750 €	51 750 €	41 750 €

Figure 6: Financial breakdown of the CardioSense3D project

- The group on Modelling of Biological Structures lead by T. Arts[11] at the Maastricht University

To position our scientific approach with respect to the state-of-the-art, we propose to distinguish between the following three levels of modeling : electrical, mechanical and perfusion.

A.1 Electrical Modeling

There exists a large number of electro-physiogical models that have been developped for the past 4 decades [49, 10, 47, 39]. Most complex ones, like the Luo-Rudy [41, 42] models, tend to describe all different ionic current mechanisms underlying the initiation and modulation of repolarization of the cardiac action potential. Due to their high computational complexity, several other models have proposed a trade-off between complexity and accuracy. Those include the Beeler-Reuter model [7], taking into account the specific ionic channels of the ventricular cells with eight

[11] www.bf.unimaas.nl/theo.htm

variables or more recently [21, 11] models which are computationally efficient but which do not retain all the details of each ionic current.

During the ICEMA-X actions, we have chosen to base our electro-physiogical simulation on the FitzHugh-Nagumo model [23] that can be considered as one of the more simple model, since it is solely based on 2 state variables : action potential and the repolarization variables. To be more precise, we use the Aliev and Panfilov model [3], which is a modified version of FitzHugh-Nagumo equations to cope with the changes in pacing frequency.

Indeed, to adjust parameters of the model from macroscopic measures, a global model with only two variables is sufficient since the subtle phenomena modeled in accurate cellular models like Luo and Rudy models [41, 42] are not available from macroscopic measures. Moreover, with a more complex model, we would have too many parameters to estimate given the number of measures available (namely isochrones of depolarization and repolarization phenomena).

A.2 Mechanical Modeling

Models used to represent the mechanical behavior of the heart (see e.g. [34, 19]) have a common structure. Following A.V. Hill's rheological scheme for striated muscles [31, 30] (see also [25]), the constitutive law of the fiber is chosen as follow: an active contractile element, in series with a linear elastic passive element, modelizes the transformation of biochemical energy into mechanical work during activation and a passive, nonlinear elastic element is added in parallel to represent the relaxed muscle.

The contractile element model considered here has been proposed in [12]. As most other models of the cardiac muscle contraction, it is based on the "sliding filament hypothesis" introduced by A.F. Huxley in [35] and extended in [32, 33]. In these models, the tension between actin and myosin filaments in the sarcomeres of striated muscles is the sum of the tensions in the cross-bridges, the chemical links between actin and myosin. It is a function of the cross-bridge deformation distribution that depends on the rates at which cross-bridges fasten and unfasten. Huxley-like models are first-order hyperbolic equations describing the evolution of this distribution. They differ by their rate functions, chosen to recover experimental sarcomere force-length relations. These rates are usually chosen as functions of the cross-bridge deformations (see e.g. [38]).

More recently, observed history-dependent force-length relations have led to consider attachment and detachment rates as functions of the cross-bridge deformations and deformation velocities [57]. The model in [12] has a similar structure coming from considering attachment and detachment rates allowing to recover the Hill force-velocity relation during isotonic contraction [29] and the force-length relation during passive relaxation [44]. They are furthermore functions of an input representing the action of the electrical potential on the fiber scale and of the intracellular calcium potential on the cell scale. Positive values of the input correspond to increasing cross-bridge density (activation) and negative values to a decreasing density (active relaxation). This model is consistent with the collective behaviour of myosin molecular motors [37]. The sarcomere tension being well approximated by a combination of the first two moments of the cross-bridge deformation distribution, the

force-length relation can be reduced to a simple set of two ordinary differential equations by scaling, using the method of moments. This sarcomere constitutive law is embedded in the fiber rheological model used in [19] for whole heart simulations.

References

[1] W.T. Abraham, W.G. Fisher, A.L. Smith, and et al. Cardiac resynchronization in chronic heart failure. *The New England Journal of Medicine*, 346:1845–1853, 2002.

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

[3] R.R. Aliev and A.V. Panfilov. A simple two-variables model of cardiac exictation. *Chaos, Soliton and Fractals*, 7(3):293–301, 1996.

[4] A. Auricchio, C Stellbrink, S. Sack, and et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J. Am. Coll. Cariol.*, 39:1895–1898, 2002.

[5] N. Ayache, editor. *Computational Models for the Human Body*. Handbook of Numerical Analysis (Ph. Ciarlet series editor). Elsevier, 2004.

[6] J. B. Bassingthwaighte. Strategies for the physiome project. *Annals of Biomedical Engineering*, 28:1043–1058, 2000.

[7] G.W. Beeler and H. Reuter. Reconstruction of the action potential of ventricular myocardial fibres. *Journal of Physiology*, 268(1):177–210, 1977.

[8] M. Belhadj, E. Cancès, J.F. Gerbeau, and A. Mikelic. Homogenization approach to filtration through a fibrous medium. INRIA Research Report No 5277, 2004.

[9] M. Belhadj, J.-F. Gerbeau, and B. Perthame. A multiscale colloid transport model with anistropic degenerate diffusion. *Asymptotic Analysis*, 34(1):41–54, 2003.

[10] M.E. Belik and A.D. McCulloch. *Computational Models for the Human Body*, chapter Computational methods for cardiac electrophysiology. Handbook of Numerical Analysis. Elsevier, 2004.

[11] O. Bernus, R. Wilders, C.W. Zemlin, H. Verschelde, and A.V. Panfilov. A computationnally efficient electrophysiological model of human ventricle cells. *Am J Physiol HeartCirc Physiol*, 282(6):2296–2308, 2002.

[12] 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.

[13] M. Bober, K. Wiehe, C. Yung, T. O. Suzek, M. Lin, W. Baumgartner Jr., and R. L. Winslow. Cage: Cardiac gene expression knowledgebase. *Bioinformatics*, 7(18):1013–1014, 2002.

[14] Jean-Daniel Boissonnat and Steve Oudot. An effective condition for sampling surfaces with guarantees. In *Proc. ACM Symposium on Solid Modeling and Applications*, 2004.

[15] John Burnes, Bruno Taccardi, and Yoram Rudy. A noninvasive imaging modality for cardiac arrhythmias. *Circulation*, 102:2152–2158, 2000.

[16] S. Cazeau, C. Alonso, G. Jauvert, A. Lazarus, and P. Ritter. Cardiac resynchronization therapy. *Europace*, 5:S42–S48, 2004.

[17] S. Cazeau, C. Leclercq, T. Lavergne, and et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *The New England Journal of Medicine*, 344(12), 2001.

[18] S. Cazeau, P. Ritter, H. Bakdach, and et al. Four chamber pacing in dilated cardiomyopathy. *Pacing Clin. Electrophysiol*, 17:1974–1979, 1994.

[19] D. Chapelle, F. Clément, F. Génot, P. Le Tallec, M. Sorine, and J.M. Urquiza. A physiologically-based model for the active cardiac muscle. In *Lectures Notes in Computer Science*, volume 2230, pages 128–133. Eds T. Katila, I.E. Magnin, P. Clarysse, J. Montagnat, J. Nenonen, Springer-Verlag, 2001.

[20] R. Cimrman and E. Rohan. Modelling heart tissue using a composite muscle model with blood perfusion. In K.J. Bathe, editor, *Computational Fluid and Solid Mechanics*. Elsevier, 2003.

[21] F. Fenton and A. Karma. Vortex dynamics in three-dimensional continuous myocardium with fiber rotation-filament instability and fibrillation. *Chaos*, 8:20–47, 1998.

[22] M.A. Fernández and M. Moubachir. An exact block-newton algorithm for the solution of implicit time discretized coupled systems involved in fluid-structure interaction problems. In K.J. Bathe, editor, *Second M.I.T. Conference on Computational Fluid and Solid Mechanics*. Elsevier, 2003.

[23] R.A. FitzHugh. Impulses and physiological states in theoretical models of nerve membrane. *Biophysical Journal*, 1:445–466, 1961.

[24] L. Formaggia, J.-F. Gerbeau, F. Nobile, and A. Quarteroni. On the coupling of 3D and 1D Navier-Stokes equations for flow problems in compliant vessels. *Comp. Meth. Appl. Mech. Engrg.*, 191(6-7):561–582, 2001.

[25] Y.C. Fung. Comparison of different models of the heart muscle. *J. Biomechanics*, 4:289–295, 1971.

[26] J.-F. Gerbeau, M. Vidrascu, and P. Frey. Fluid-structure interaction in blood flows on geometries coming from medical imaging. Technical report, INRIA No 5052, 2003. to appear in *Comp. & Struct.*

[27] J.F. Gerbeau and M. Vidrascu. A quasi-newton algorithm based on a reduced model for fluid-structure interactions problems in blood flows. *Math. Model. Num. Anal.*, 37(4):631–648, 2003.

[28] J. Guccione and A. McCulloch. *Theory of Heart: biomechanics, biophysics, and nonlinear dynamics of cardiac function*, chapter Finite element modeling of ventricular mechanics, pages 121–144. Springer-Verlag, 1991.

[29] A.V. Hill. The heat of shortening and the dynamic constants in muscle. *Proc. Roy. Soc. London (B)*, 126:136–195, 1938.

[30] A.V. Hill. Mechanics of the contractile element of muscle. *Nature*, 166:415–419, 1950.

[31] A.V. Hill. The series elastic component of muscle. *Proc. Roy. Soc. London (B)*, 137:272–280, 1950.

[32] T.L. Hill. Theoretical formalism for the sliding filament model of contraction of striated muscle. part I. *Prog Biophys Mol Biol.*, 28:267–340, 1974.

[33] T.L. Hill. Theoretical formalism for the sliding filament model of contraction of striated muscle. part II. *Prog Biophys Mol Biol.*, 29:105–159, 1975.

[34] P.J. Hunter, M.P. Nash, and G.B. Sands. Computational electromechanics of the heart. In *Computational biology of the heart*, pages 345–407. A.V. Panfilov and A.V. Holden Eds, John Wiley & Sons, 1997.

[35] A.F. Huxley. Muscle structure and theories of contraction. *Progress in Biophysics & Biological Chemistry*, 7:255–318, 1957.

[36] J.M. Huyghe, T. Arts, and D.H. van Campen. Porous medium finite element model of the beating left ventricle. *Am. J. Physiol.*, 262, 1992.

[37] F. Jülicher, A. Ajdari, and J. Prost. Modeling molecular motors. *Reviews of Modern Physics*, 69(4), October 1997.

[38] J. Keener and J Sneyd. *Mathematical Physiology*. Springer, 1998.

[39] V. Krinski, A. Pumir, and I. Efimov. *Encyclopedia of nonlinear science*, chapter Cardiac muscle models. Routledge, September 2004.

[40] C.H. Luo and Y. Rudy. A model of the ventricular cardiac action potential: depolarization, repolarization, and their interaction. *Circ. Res.*, 68:1501–1526, 1991.

[41] C.H. Luo and Y. Rudy. A model of the ventricular cardiac action potential. Depolarization, repolarization and their interaction. *Circulation Research*, 68(6):1501–1526, 1991.

[42] C.H. Luo and Y. Rudy. A dynamic model of the cardiac ventricular action potential - simulations of ionic currents and concentration changes. *Circulation Research*, 74(6):1071–1097, 1994.

[43] E. McVeigh, O. Faris, D. Ennis, P. Helm, and F. Evans. Measurement of ventricular wall motion, epicardial electrical mapping, and myocardial fiber angles in the same heart. In T. Katila, I. Magnin, P. Clarysse, J. Montagnat, and J. Nenonen, editors, *Functional Imaging and Modeling of the Heart (FIMH'01)*, number 2230 in Lecture Notes in Computer Science (LNCS), pages 76–82. Springer, 2001.

[44] I. Mirsky and W.W. Parmley. Assessment of passive elastic stiffness for isolated heart muscle and the intact heart. *Circul. Research*, 33:233–243, 1973.

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

[46] V. Moreau-Villéger, H. Delingette, M. Sermesant, O. Faris, E. McVeigh, and N. Ayache. Global and local parameter estimation of a model of the electrical activity of the heart. Technical report, INRIA No 5269, 2004.

[47] D. Noble. Modeling the heart from genes to cells to the whole organ. *Science*, 295:1678–1682, march 2002.

[48] D. Noble and Y. Rudy. Models of cardiac ventricular action potentials: iterative interaction between experiment and simulation. *Phil Trans Roy Soc*, 359:1127–1142, 2001.

[49] D. Noble and Y. Rudy. Models of cardiac ventricular action potentials: iterative interaction between experiment and simulation. *Phil. Trans. R. Soc. Lond. A*, pages 1127–1142, 2001.

[50] R. Razavi, D. L. Hill, S. Keevil, M. Miquel, V. Muthurangu, S. Hegde, K. Rhode, M. Barnett, J. van Vaals, D. Hawkes, and E. Baker. Cardiac catheterisation guided by MRI in children and adults with congenital heart disease. *Lancet*, 362(9399):1877–1882, 2003.

[51] J. Sainte-Marie, R. Cirmrman, M. Sorine, and D. Chapelle. Modelling and estimation of the cardiac electromechanical activity. In *Proceedings of the CEA-EDF-INRIA school on Electromechanical behaviour of the heart : confronting models with data towards medical applications*. INRIA, 2004.

[52] 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.

[53] Balbir Singh. Biventricular pacing in congestive heart failure. *Indian Pacing Electrophysioly Journal*, 2, 2002.

[54] N.P. Smith, P.J. Mulquiney, M.P. Nash, C.P. Bradley, D.P. Nickerson, and P.J. Hunter. Mathematical modelling of the heart: cell to organ. *Chaos, Solitons and Fractals*, 13:1613–1621, 2002.

[55] N.P. Smith, A.J. Pullan, and P.J. Hunter. An anatomically based model of transient coronary blood flow in the heart. *SIAM J. Appl. Math.*, 62(3):990–1018, 2002.

[56] P. Clarysse J. Lotjonen O. Sipila H. Hanninen K. Lauerma J. Knutti T. Makela, Q.C. Pham and T. Katila. A 3d model-based registration approach for he pet, mr and mcg cardiac data fusion. *Medical. Image. Analysis*, 7(3):377–389, 2003.

[57] J.Z. Wu and W. Herzog. Modelling concentric contraction of muscle using an improved cross-bridge model. *Journal of Biomechanics*, 32:837–848, 1999.