Multi-formalism modelling and simulation: application to cardiac modelling.

Antoine Defontaine, Alfredo Hernández, Guy Carrault

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Defontaine Antoine , Hernández Alfredo * , Carrault Guy

LTSI, Laboratoire Traitement du Signal et de l'Image INSERM : U642, Université Rennes I, FR

* Correspondence should be adressed to: Alfredo Hernández <alfredo.hernandez@univ-rennes1.fr>

Abstract

Cardiovascular modelling has been a major research subject for the last decades. Different cardiac models have been developed at a cellular level as well as at the whole organ level. Most of these models are defined by a comprehensive cellular modelling using continuous formalisms or by a tissue-level modelling often based on discrete formalisms. Nevertheless, both views still suffer from difficulties that reduce their clinical applications: the first approach requires heavy computational resources while the second one is not able to reproduce certain pathologies.

This paper presents an original methodology trying to gather advantages from both approaches, by means of an hybrid model mixing discrete and continuous formalisms. This method has been applied to define a hybrid model of cardiac action potential propagation on a 2D grid of endocardial cells, combining cellular automata and a set of cells defined by the Beeler Reuter model. For simulations under physiologic and ischemic conditions, results show that the action potential propagation as well as electrogram reconstructions are consistent with clinical diagnosis. Finally, the interest of the proposed approach is discussed within the frame of cardiac modelling and simulation.

MESH Keywords Action Potentials ; Cardiovascular System ; anatomy & histology ; Humans ; Models, Anatomic

Introduction

Although cardiac pathologies are the first cause of mortality worldwide, mechanisms involved on some common pathologies are still not all known, limiting the design of new therapies or preventive actions. One of the most common cardiac pathologies is myocardial infarction and the subsequent alterations of the cardiac rhythm (cardiac arrhythmia). These pathologies are frequently caused by a compromised balance between oxygen consumption and blood irrigation on the cardiac muscle, known as ischemia.

Different types of computational models have been widely used as a means of representing, in a compact manner, the complex physiopathological knowledge of the cardiac activity. They can be useful to better understand the basic mechanisms of the cardiac function, in normal or pathologic conditions, as well as to assist in the definition of new therapies [Noble, 2002]. Modelling and simulation take a particular importance in this precise context, allowing to reproduce processes ad infinitum for different configurations.

However, existent models are not adapted to the simulation of the entire heart behaviour in an acceptable time, nor to the simulation of pathologies defined at different scales. These aspects seriously limit the clinical application of a modelling-simulation approach.

This paper presents a global consideration of the cardiac modelling issue in a first part. In a second part, it sets the problems that lead to a multi-formalism approach as well as a brief review of adapted modelling tools. After presenting the difficulties of this approach, the next parts of this paper will focus on an original methodological development based on an multi-formalism consideration of the system which shows good promises.

Problem Statement

Being able to reproduce cardiac arrhythmia using numerical tools presents great advantages compared to real human or animal experiments. Examples of such approach are reproducibility of the experiments and results, the possibility to access a wide range of data and the full control on all the parameters affecting the simulation. However, compared to models achieved in traditional engineering fields (automatics, electronics, industrial processes, …), models of the electrical propagation in the heart still suffer from precise limitations [Blanc, 2002]:

- The biological processes involved are still only partly understood, mainly because of the invasive nature of in-vitro or in-vivo experiments which leads to a massive use of only estimated behaviour based on theoretical considerations;

- The mechanisms involved present wide ranges for spatial and temporal scales. Studies go from the molecular level, to centimetres, for the whole organ, and from milliseconds, for molecular processes, to several seconds when dealing with heartbeats;

- The biological processes underneath cardiac mechanisms are mainly non-linear with regulations spread over wide time scales;

- Modelling such complex phenomena requires high needs in terms of computational resources.

Moreover, all these limitations affect a proper validation of these tools and in this sense, caution has to be made when using these models for in silico experimentation.

Modelling the global cardiac electrophysiologic activity implies to reconstruct an electrogram - or the electrocardiogram (ECG) if the interest is to reproduce the thoracic potential -, for different pathologic cases from a set of individual action potentials. In order to do so, two approaches currently exist: whole cardiac models at a cellular level and complete heart models developed at the tissue or organ level.

Cellular level

A number of cardiac models have been proposed at a cellular level. Two representative examples of this kind of models are Cardiowave and the Cardiome project. Developed at Duke University, Cardiowave [Pormann, 1999] is a cardiac model defined by standard bidomain equations. Based on systematic modelling of ionic exchanges at a cellular level, main research work is focused on computing and calculation issues with extensive use of supercalculators. The Cardiome project [McCulloch et al., 1998, Noble, 2002], which is part of the larger Physiome project, has been initiated by Noble's work. It aims at modelling different characteristics of the heart (e.g. biomechanics, bioelectrics) with all the characteristics modelled at a systematic cellular scale.

In this type of approach, systems are defined by a network of many ‘atomic’ cells whose description is usually implemented by means of models representing different physiological aspects:

- Aliev Panfilov [Aliev and Panfilov, 1996] which is only a morphological description of the action potential;

- Beeler Reuter [Beeler and Reuter, 1977] which reproduces action potential of ventricular cells based of physiological parameters;

- Luo Rudy [Luo and Rudy, 1991] which is an exhaustive model of ventricular cardiac action potential.

In general, these atomic cellular models can be represented as follows:

$$\frac{dV}{dt} = G(P)$$

where V is the membrane potential and G is a function of several parameters P. The coupling between cells can be modelled by an electrical analogy with a resistive network (fig. 1) and the conduction through this network depends on the Laplacian of neighbouring cells. The obtained equation, called 'cable equation' [Keener and Sneyd, 1998, Joyner et al., 1975], is defined by:

$$\frac{dV}{dt} = G(P) + K \cdot \nabla^2 V$$

where K is a diffusion coefficient depending on physiological values and ∇2 V the Laplacian of the membrane voltages of the neighbouring cells.

Usually, as in Cardiowave for instance, thousands of cells are coupled in a predefined geometry to represent both ventricles. Due to this extensive definition, models defined at the cellular level require massive computing resources. Moreover, their coupling with other models remains tricky and even with high performance calculating resources, computational time limits their clinical application.

Organ level

Models developed at the organ level are based on a coupled network of macrostructures, defined at a tissue level, which represent specific anatomical structures of the heart. Due to their low computational costs, this kind of models has been used in different clinical setups [Malik et al., 1987, Ahlfeldt et al., 1988, Virag et al., 1998].

CARMEM is an organ-level cardiac model developed in our laboratory [Hernández, 2000, Hernández et al., 2002]. Its aim is to reproduce cardiac behaviour at a global scale using a set of cellular automata, representing nodal or myocardial tissues. The state behaviour of each automaton of such an event-based approach can be defined by [Hernández et al., 2000]:

$$E = H(P)$$

where E is the state of the cellular automaton and H is the function governing internal state transitions, depending on parameters P. When a given macrostructure reaches the depolarisation state, neighbouring tissues are activated by the transmission of a flag (external state transition).

Although major cardiac rhythms can be reproduced and explained by these models, some difficulties remain when dealing with complex rhythms and when simulating pathologies implying modifications at a cellular or molecular level such as myocardial ischemia [Hernández et al., 2002]. These difficulties are inherent to the definition of the models at a macroscopic scale and, consequently, to the inability of considering a physiopathological process at a cellular level.

From a mono-formalism description to a hybrid approach

When dealing with these two approaches of cardiac modelling (cellular-level and organ-level), one can naturally think that a way to take advantage from the benefits of each approach would be to selectively define different regions of the modelled heart at different scale levels, depending on its physiological or pathological state.

In our mind, the CARMEM model represents a basis adapted to this kind of multi-scale approach to the problem of cardiac modelling. We aim at refining pathologic regions (modelled by a cellular approach) keeping a global view on healthy parts (modelled by cellular automata at a tissue scale), the same manner an expert would do during a clinical examination. Validation is a problem in such a complex model and requires key criteria to be defined such as a realistic physiologic behaviour in accordance with real ECGs.

This approach parallels recent works presented by Holden, which are based on a multi-model definition of the cardiac problem [Poole et al., 2002, Holden et al., 1995], considering a model description based on different formalisms rather than an exhaustive use of supercalculation.

Formalisation of different descriptions

As mentioned before, different types of description can be used to model cardiac electrical behaviour. These formalisms (the ‘description toolkit') range from one or more mathematical equations (numerical models) to, why not, literal description of the behaviour (literary models). If it seems obvious that the later cannot be directly used in standardised computed modelling, many other approaches can have their interest. The selection among candidate model formalisms will depend on the properties of the system to be modelled, if it is [Dawant, 1995]: (1) static or dynamic; (2) linear or nonlinear; (3) stationary or nonstationary; (4) deterministic or stochastic; (5) single or multiple inputs and/or outputs, (6) lumped or distributed, and on the level of detail in which the model will be described.

Nevertheless, two main views result from the different standard approaches. Basically, the system can either be defined by a continuous model or by a discrete model, be it discrete-time or discrete-event. In this way, three main types of generic model specifications have been defined by Zeigler [Zeigler et al., 2000]:

- Differential Equation System Specification (DESS): The definition of the system is based on a time and event continuous model whose behaviour is ruled by a system of one or more differential equations;
- Discrete Time System Specification (DTSS): The variations of the system states only occur at regular time intervals;
- Discrete EVent system Specification (DEVS): Each system state is characterised by an activity period leading to two types of possible transition: internal transition, when no external event has occurred during activity period of the current state, or external transition during activity period when an external event occurs.

These formalisms present great similarities which can reveal useful when implementing a modelling architecture. In a way, they only differ by the simulators (the ‘visualisation toolkit') associated. Zeigler's work has been centred on defining a unique model entity grouping all the common characteristics as well as common methods, the type of formalism used will just remain a parameter [Zeigler et al., 2000].

Existing modelling tools

Different modelling and simulation tools are currently available. Generic tools and well known environments, such as Matlab/Simulink, Stella/Berkeley Madonna, Scilab or Mathematica, are widely represented. Even if these systems seem to be rather ease of use, they suffer from a lack of multi-formalism or multi-scale modelling capabilities.

Nevertheless, in a multi-formalism approach, gathering different models requires dealing with their proper characteristics (i.e. type of description formalism, time scale, etc). This implies to design ad-hoc an interface between models presenting different formalisms and some techniques have been recently proposed in this sense.

Vangheluwe [Vangheluwe, 2001, de Lara and Vangheluwe, 2002] has set a formalism transformation graph (fig. 2) presenting the existing links between numerous formalisms. Three main approaches are usually retained [Vangheluwe, 2000, de Lara and Vangheluwe, 2002]:

- Common model representation: It consists in transforming all models into a unique formalism, or meta-formalism, integrating all the other descriptions. It is also possible to transform all the initial models to a common representation thanks to the 'closing under coupling' property, which states that, replacing several coupled sub-models defined by the same formalism F by a single model using the same type F, is possible. Most of the time, the common formalism retained is DEVS. The advantage of this approach lies in the fact that only one simulation, and therefore one simulator, is necessary. Moreover, it is not necessary to define a particular coupling interface between the models components. Nevertheless, the difficulty of this method stands in the practical application of the theorem that states that any formalism can be transformed into DEVS formalism [de Lara and Vangheluwe, 2002];

- Co-simulation: It is based on the individual simulation of each one of the different formalisms. The synthesis is then performed in the observation frame (where all behaviours are visualised - fig. 2) once each sub-model has been simulated. This implies the definition of a temporal interface between the models components as also pointed out in [Zeigler et al., 2000]. This approach eases the simulation of each sub-model but much care has to be taken when doing the synthesis by a fine analysis of the links between the models;

- The third approach consists in a mix of the two previous ones.

For a generic approach to multi-formalism, specific libraries (independent pieces of code focused on precise points to be included in one's development) have been developed, most of the time by international research groups or consortia. DEVS++1 has been developed after Zeigler' s work and the DEVS formalism. It deals with an object oriented implementation of the formalism and co-simulation but suffer from a lack of development. AToM3 (A Tool for Multi-formalism and Meta-Modeling)2 [Vangheluwe and de Lara, 2002, de Lara and Vangheluwe, 2002] is a modelling project lead by Vangheluwe at MacGill University. Contributions fall in the field of meta-modelling which focus mainly on formalism modelling and on transitions between formalisms. Main works are centred around the use of DEVS as a common formalism and, in particular, on a method of transforming continuous formalisms onto DEVS formalism. The multi-formalism approach and the resulting distributed and modular architecture of this system make it interesting from an object oriented point of view. However their 'common formalism' approach would be difficult to apply to our project, as it would require the definition of a specific graph grammar for combining DEVS and DESS models.

Modelica3 results from what is probably the most important international research group on multi-formalism and multi-scale modelling and simulation. It is an object oriented language allowing the simulation of massive heterogeneous and complex systems using co-simulation. Particularly developed for multi-domain systems defined by several types of heterogeneous formalisms, its efficiency is acquired and especially the problems of synchronisation solved. This language presents numerous libraries that allow to simulate easily various complex systems but mainly axed on simulation of industrial or artificial processes and seldom on natural processes (physical or biological).

Most of these approaches have been developed for usual modelling fields (automatics, electronics, industrial processes), and, although they reveal efficient in those traditional fields, their adaptation for modelling natural processes will require an additional effort. Nevertheless, methods and architectures presented could be useful to our project.

Proposed methodology

The proposed approach tries to take into account the previous considerations in order to set an original means of dealing with cardiac modelling. The main steps of a generic modelling methodology will be adapted to the multi-formalism case, and presented in the following sections, namely:

- Model description: Although the model description level is not directly addressed in this work, our goal is to be able to read, simulate and couple different kinds of models represented in a standardised description language, even if they are based on different formalisms. The major standards will be presented;

- Formalism: Choice of the appropriate set of model formalisms and, in particular, how to couple them;

- Simulator/Simulation library: Here, we aim at developing a generic library of classes allowing coupling different formalisms together based on Zeigler's work. Retained method for coupling is co-simulation. By its definition and architecture, we want a tool as generic as possible with ease of use in other fields than cardiology and ease of implementing new types of models or new simulation algorithms.

Model description level

Several projects have been proposed for model description in biophysiology. E-Cell4 [Takahashi et al., 2002] and VirtualCell5 [Schaff et al., 1997] are centred on modelling at a cellular level but focusing on genomics or cellular reproduction. SBML (System Biology Markup Language) and SBW (System Biology Workbench)6 aim at grouping many biological systems under a wrapper interface using a UML (Unified Modeling Language)/XML (Extensible Markup Language) description language. Each system is defined its own way and the standardisation only occurs at the interface level. CellML7 is also an open standard based on XML with the purpose of storing and exchanging computer-based biological models. It includes information about model structure as well as mathematics or additional information about the model.

Coupling multi-formalism cellular models

We have seen previously that cellular models can either be continuous (eq. 1) or discrete (eq. 3) - cellular automata representing tissues can easily be adapted to model cells. Both approaches allow to model the coupling between neighbouring cells but in different ways. Indeed, the coupling parameter between continuous defined cells correspond to a Laplacian with a multiplicative coefficient depending on cells physiology, as shown on eq. 2, whereas the coupling between discrete defined cells is done by a flag transmission. Consequently, a big issue raises when trying to couple multi-formalism defined cells. We have identified three ways of approaching these coupling difficulties in a hybrid tissue:

- Using a transmission flag as processed for discrete models, applying appropriate thresholds for continuous models;

- Using a function of the neighbouring potential as processed for continuous models, which implies the definition of an internal variable into the event-based models, allowing to define a method behaving the same way as for continuous models;

- Each homogeneous region can be modelled its own way and a coupling method has to be defined at the interfaces of heterogeneous regions.

In our work, we have chosen to use the second approach. Many points seem to legitimate this option. In our concern for developing as generic as possible a system, using the same manner of coupling (same method in the tissue model) for all the types of tissues will allow to define a unique standard coupling procedure. Adaptations of the methods will be done in each model definition.

The retained idea in our simulation process is consequently to keep each cell defined on its own. For each time step, each cell state is computed and then the coupling is done and added to the parameters for the next time step computation. The formalisation of this approach is presented hereafter.

Let $C^{F}_{i,j,k}$ be an atomic cell component of a cardiac tissue, defined by a formalism F (where F equals Fc for a DESS or Fd for a DEVS model). The generic coupling behaviour can be extended from eq. 2 and modelled as follows:

$$C^{F}_{i,j,k} = G_F(P) + Coup_F(K \cdot \nabla^2 V)$$

where G_F is the function of parameters P, $Coup_F$ he coupling method and K as defined in eq. 2. The coupling method is defined as follows:

$$Coup_F = \begin{cases} thres & \text{if the cell model is discrete} (F = Fd) \\ id & \text{if the cell model is continuous} (F = Fc) \end{cases}$$

where id is the identity function and thres a threshold function setting external activation for the cellular automata if the input is greater than the limit value necessary for depolarisation of an equivalent continuous model (fig. 3).

The main difficulty here is to define a coupling method, adapted to both formalisms, which permits to keep an appropriate diffusion at the interface between neighbouring components of different formalisms. In order to do so, our choice of retaining the continuous approach for the component coupling, has been implemented by means of a piece-wise linear fitting of the Beeler Reuter action potential calculated for each cellular automaton (fig. 4).

With this type of approach, the coupling between a set of cells of a tissue will always be defined by the generic definition (eq. 4) whatever their description formalisms are and allows to keep into account the influence of the neighbouring cells during the whole activation.

Consequently no information will be lost during the global ECG reconstruction. Each specification of the methods will be done for each model definitions in the sense of an object oriented approach.

For a practical application, in the case of an isotropic tissue, discrete development of the Laplacian of eq. 4 gives, considering cell $C_{i,j}$ of a two-dimensional tissue:

$$\nabla^2 V_{C^F_{i,j}} = V_{C^F_{i+1,j}} + V_{C^F_{i-1,j}} + V_{C^F_{i,j+1}} + V_{C^F_{i,j-1}} - 4 \cdot V_{C^F_{i,j}}$$

Equation 6 can also be viewed as the processing of a 3 × 3 filter over the two-dimensional tissue, defined as follows:

$$\begin{bmatrix} 0 & 1 & 0 \\ 1 & -4 & 1 \\ 0 & 1 & 0 \end{bmatrix}$$

This coupling presents a complete isotropic definition. To cope with anisotropy of propagation, as in reality, coefficients have to be changed in a same row - or column, the sum of all the coefficients still needing to be equal to 0. The following filter is an example of anisotropic coupling:

$$\begin{bmatrix} 0 & 1 & 0 \\ 3 & -8 & 3 \\ 0 & 1 & 0 \end{bmatrix}$$

This procedure can be easily extended to the three-dimensional case.

Simulator/Simulation library

Traditional processing of the 'cable equation' (eq. 2) is usually done using a lumped approach (fig. 5.a) where the whole simulation is done at a unique level.

In our approach, the behaviour of the simulator is based on a parallelism between the model and the simulator (fig. 5.b). This distributed approach has been proposed by Zeigler [Zeigler et al., 2000] and, especially, the introduction of coordinator objects grouping sub-models. It eases the use of a multi-formalism approach and could facilitate a parallelisation of the calculation tools.

Results

The proposed generic method has been implemented on a two-dimensional tissue for different types of configuration with the aim to reproduce the propagation of the action potential along the tissue.

A 16 × 16 endocardial cells square tissue8 has been defined, corresponding to an average size of 0.62 × 0.62 mm. The coupling coefficient K has been adapted from [Keener and Sneyd, 1998] and set to 1.90 S.mm2 in order to maintain a propagation speed from the upper left cell (pacemaker) to the lower right cell of 8 cm.s¯ 1 in the case of healthy tissues. The isotropic mask (7) has been used. Triggering of the pacemaker cell occurs after 50 ms.

For healthy tissues, simulations have been done for three types of models:

- CA model: All the cells defined by cellular automata (fig. 6.a);
- BR model: All the cells defined by Beeler Reuter model (fig. 6.b);
- hybrid model: Central cells defined by Beeler Reuter model and peripheral cells by cellular automata (fig. 6.c).

Depolarisation fronts (repolarisation fronts are too slow to be visualised statically) are represented in figs. 7–8–9 for each configuration. We also present dipolar projections (fig. 10) over the tissue's main axis, corresponding to a rough ventricular electrogram reconstruction (or the global contribution of the tissue to the ECG).

Differences in depolarisation fronts between cellular automata (fig. 7) and Beeler Reuter (fig. 8) tissues are caused by the atomic behaviour of each model and especially by the shape of depolarisation slopes. It is an affine line in cellular automata model while it has a more complex shape with an inflection point (could be assimilated to a sigmoid) for Beeler Reuter model (fig. 4). Border effects can be observed for the

Beeler Reuter tissue (fig. 8) while they do not affect propagation in cellular automata tissue (fig. 7). Those effects are inherent to the use of modified filter mask at the borders and would be relatively insignificant for wide tissues.

As for dipolar projections (fig. 10), they are in accordance with what expected for two-dimensional cardiac tissues at this resolution. The first negative inflections (followed in the case of Beeler Reuter tissue by a positive inflection) appear during depolarisation of the cells and reveal the QRS complex of the surface ECG. As for repolarisation, the second positive inflections are characteristic of the T wave. Moreover, durations of the electrograms, appearance instants of each wave, as well as polarity are consistent with real electrograms. Nevertheless, despite the morphological differences, and especially artifacts in cellular automata or hybrid tissues, the important point is that clinical interpretation is the same for all the electrograms.

These previous results are interesting for validation purposes but present a limited clinical interest. Ischemic tissues, presenting higher clinical interest, have consequently been modelled, based on the previous models:

- continuous model: healthy cells modelled by Beeler Reuter model;
- hybrid model: healthy cells modelled by cellular automata.

Ischemic cells are reduced to the set of 4 × 4 central cells and to simulate this pathologic behaviour, a set of membrane current modifications proposed by Sahakian [Sahakian et al., 1992] have been adapted to the Beeler Reuter defined cells (fig. 11). Basically, an ischemic cell presents a higher resting potential, calcic current plays a stronger role on the cell's depolarisation and the action potential length is reduced from normal. Depolarisation fronts are presented (figs. 12–13) as well as dipolar projection (fig. 14). Differences between healthy electrograms (fig. 10) and ischemic electrograms (fig. 14) have been quantified using a quadratic distance (fig. 15).

Activation fronts (fig. 12–13) show clearly the differences of the membrane potential behaviour between healthy and ischemic cells. Higher resting potential for ischemic cells is visible in figs. 12.a–13.a compared to figs. 8.a–9.a. Quicker repolarisation is also visible in figs. 12.c–13.c compared to figs. 8.c–9.c.

As for the electrograms (fig. 14), the influence of ischemic cells is clearly identified with the quadratic distance (fig. 15) between normal and pathologic tissues. The first peak shows a prolongation of the QRS complex. The second one, mainly visible in Beeler Reuter model, corresponds to the quicker repolarisation of ischemic cells and consequently to a modification of the ST segment which is one of the most important clinical markers of cardiac ischemia on the surface ECG. The third peak shows an alteration of the end of the repolarisation (alteration of the T wave of the ECG). As previously, differences between Beeler Reuter tissue and hybrid tissue, the clinical interpretation of both electrograms would be the same and characterised as ischemic.

Differences on computation time also appear in those results. On a Pentium4 2.4 GHz, 1GB of RAM, Linux machine, computing the CA tissue takes 1 minute and 30 seconds, while it takes 1 minute and 35 seconds to compute the hybrid tissue and 2 minutes and 57 seconds to compute BR tissue. Regarding to these considerations, the addition of few continuous cells to the CA tissue does not length the calculation time a lot while a whole continuous tissue takes twice as much time. Moreover the results will be amplified after code optimisation and on considering wider tissues, since the complexity is not linear. The computing advantage of the hybrid approach allows to consider a complete modelling of the cardiac tissue. Moreover, this hybrid approach is the only way of explaining such pathologies, since ischemia can not be modelled only by cellular automata.

Discussion, perspectives

Previous results show good promises in the multi-formalism field with physiologically interesting results. Polarisation fronts do not really suffer from multi-formalism description and electrogram reconstructions are relevant.

Nevertheless, we had to tackle difficulties to cope with multi-formalism approach. As the coupling is done using the Laplacian between neighbouring cells, disparities occurred in the coupling coefficient at the interface between cells defined by cellular automata and those defined by the Beeler Reuter model. These disparities have great influences in the resulting action potentials and that wrong 'behaviour' of the input Laplacian of a continuous cells leads to abnormal electrograms. To cope with this problem, we have calculated a fitted action potential for each cellular automata to the Beeler Reuter shape, in order to have as homogeneous as possible atomic activations.

One great advantage of the proposed method is the possibility of simulating pathologies such as ischemia, based on a hybrid model composed by cellular automata and adapted Beeler Reuter cells (figs. 11–13–14). Indeed, compared to other projects in the same field [Poole et al., 2002], we benefit from the use of the Beeler Reuter model, which has physiological sense, instead of Aliev Panfilov model, which is only a

morphological description of the action potential. The planned use of Luo Rudy model [Luo and Rudy, 1991] is going in that idea of having increasing physiologically explained systems.

Immediate developments will be based on the use of wider tissues to be able to simulate larger ischemic regions. The replacement of the piece-wise linear action potential shape used in cellular automata by a more adapted action potential template will also upgrade the results thanks to a closer fit to the continuous used models. We will then focus on a classic three dimensional approach, based on realistic geometry, but included the proposed multi-formalism approach.

Besides, many arguments seem to legitimate not only a multi-formalism, but also a multi-scale approach for cardiovascular system modelling. One such approach can allow to manage and to optimise computing resources with no systematic use of extensive simulation in regions of lower interest. Using CARMEM as a starting point we possess a simulator at a global level. Refining certain regions up to cellular level would allow to simulate, understand and explain complex rhythms and conduction disorders. As mentioned before, one such approach is relevant regarding the clinical approach used by clinicians to set a diagnosis. We can consequently imagine a coupling of low resolution healthy regions modelled by cellular automata and high resolution pathologic regions modelled by a continuous formalism (Beeler Reuter model). In this multi-scale approach of the problem, main issues concern the way of passing from a micro-system to a macro-system. Two main difficulties appear in this context: defining ad hoc state variables adapted for the coupling and determining inter-level association functions (i.e. multi-formalism and multi-level). To deal with these issues, variable aggregation theory [Auger and de la Parra, 2000] will be looked at as well as homogenisation theory [Zeigler et al., 2000].

Footnotes:

1

http://www.acims.arizona.edu (Accessed November 1, 2003)

2

http://atom3.cs.mcgill.ca (Accessed November 1, 2003)

3

http://www.modelica.org (Accessed November 1, 2003)

4

http://www.e-cell.org (Accessed November 1, 2003)

5

http://www.nrcam.uchc.edu (Accessed November 1, 2003)

6

http://www.sbw-sbml.org (Accessed November 1, 2003)

7

http://www.cellml.org (Accessed November 1, 2003)

8

Due to computing and memory limitations, especially for the Beeler Reuter case, we chose to do our developments on relatively small tissues.

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Figure 1

Resistive network corresponding to electrical analogy of the coupling process.

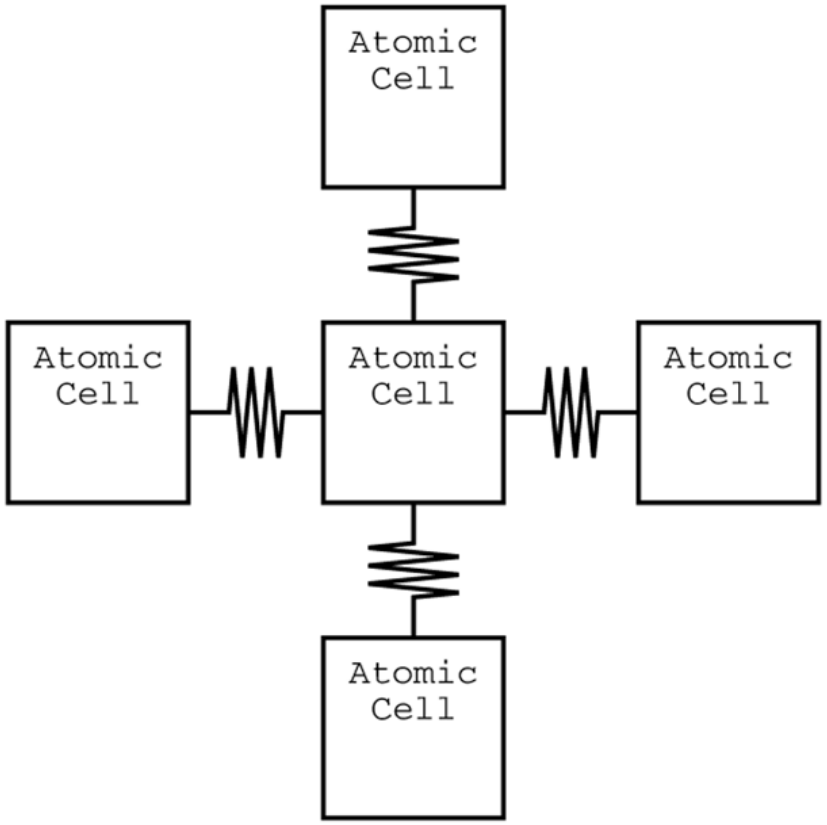


Figure 2

Formalism Transformation Graph (published with authorisation of the author [de Lara and Vangheluwe, 2002]). Filled arrows correspond to the existence of conservative transformation between two formalism, dotted arrows corresponds to existence of simulator allowing visualisation in the trajectory state.

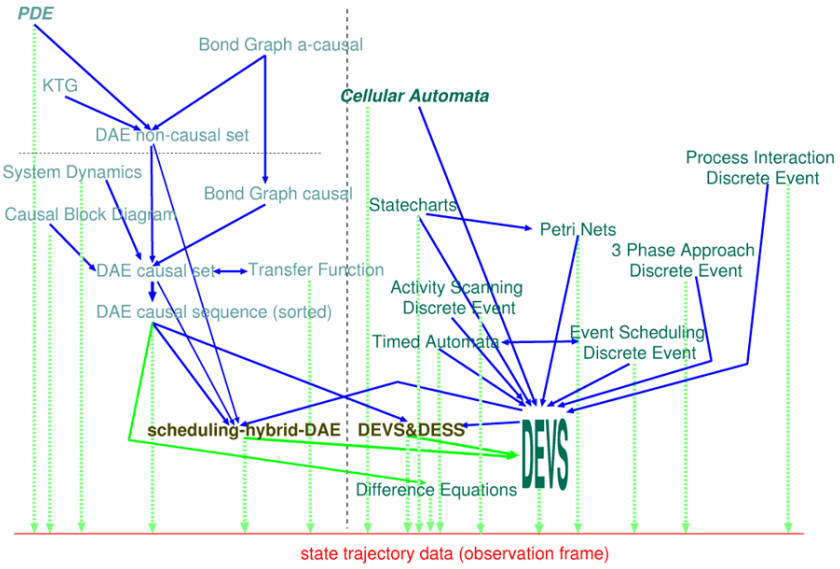


Figure 3

Peak membrane voltages for a Beeler Reuter model, as a function of a variable input current. Retained value for the activation threshold of cellular automata is 3.5mA.

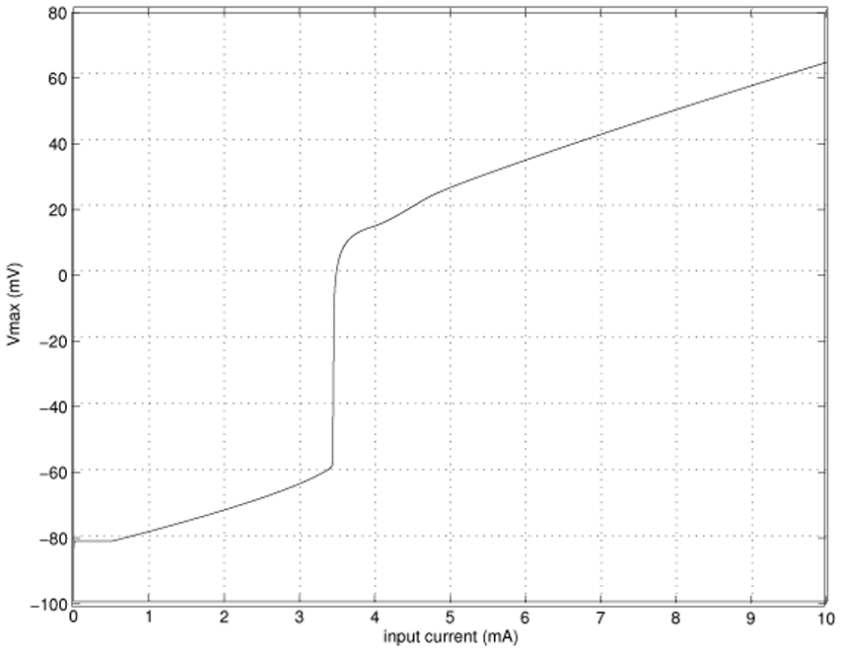


Figure 4

Atomic action potentials of the models used. Piece-wise linear cellular automaton model has been fitted to continuous Beeler Reuter model. The vertices of the cellular automaton model shape correspond to the state transitions of this event-based model.

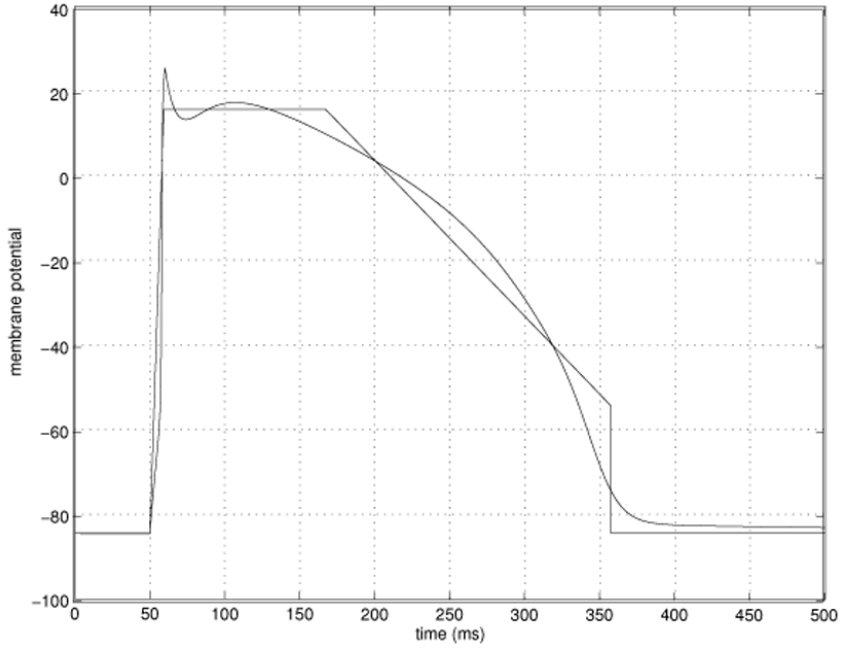
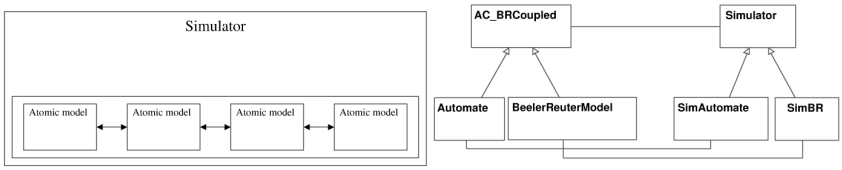


Figure 5

Simulation approaches a. Classical lumped approach: the link between the different components and the whole simulation are done in a unique level; b. Parallelism between model and simulator: the coupled model represents the coordinator with an associated simulator. The simulation of the global system is performed at the coordinator level whereas each component is simulated at the model level.

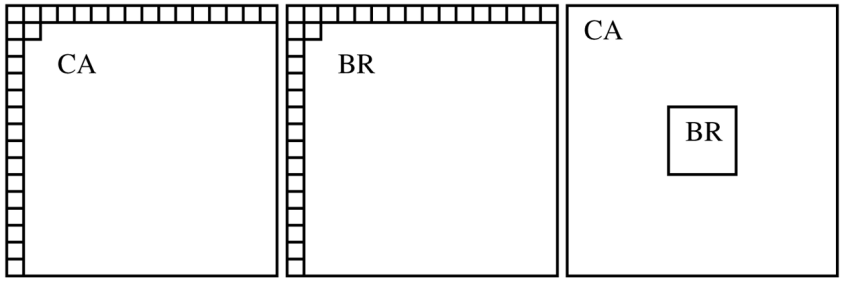


(a) classical mono-formalism lumped approach

(b) distributed multi-formalism approach

Figure 6

Different types of healthy simulated tissues.

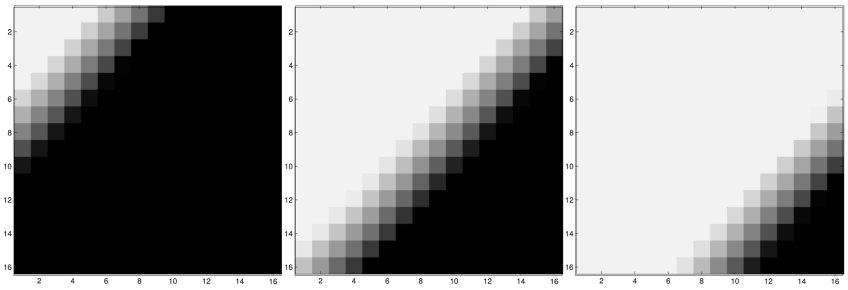


(a) CA model

(b) BR model

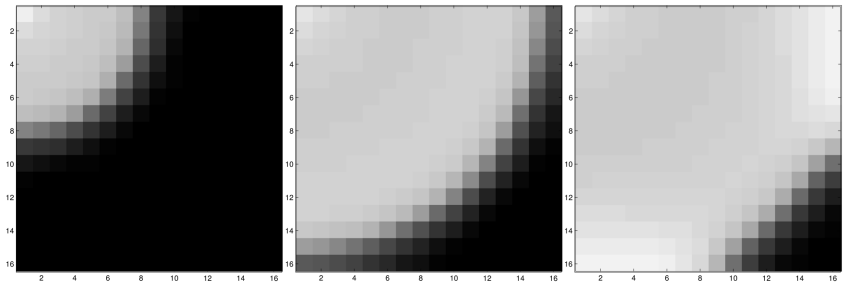
(c) hybrid model

Figure 7
Depolarisation front for CA model.



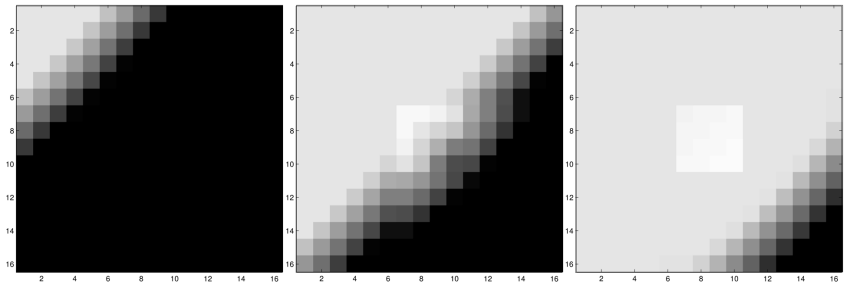
(a) t1 = 53.5 ms (b) t2 = 57.0 ms (c) t3 = 59.5 ms

Figure 8
Depolarisation front for BR model.



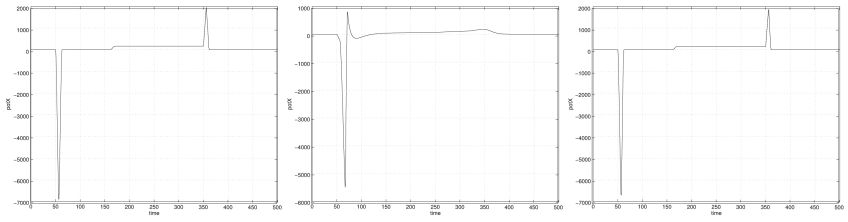
(a) t1 = 53.5 ms (b) t2 = 57.0 ms (c) t3 = 59.5 ms

Figure 9
Depolarisation front for hybrid model.



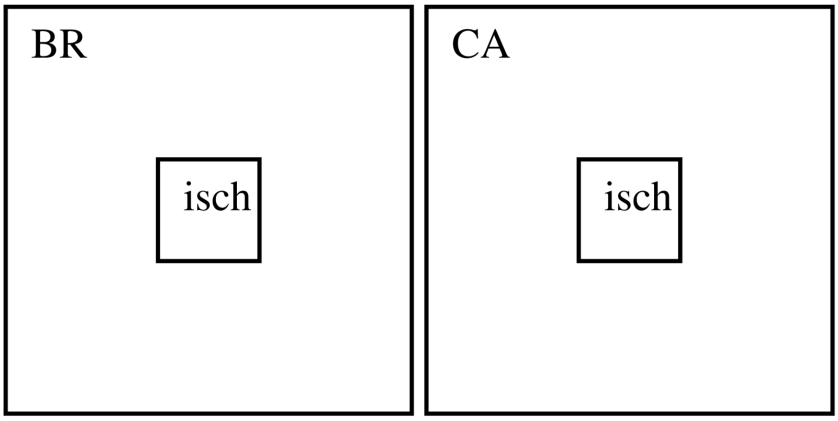
(a) t1 = 53.5 ms (b) t2 = 57.0 ms (c) t3 = 59.5 ms

Figure 10
Dipolar projections for healthy tissues (due to isotropy in propagation, projections for both axis are the same). The first negative inflections (followed by a positive one on the case of BR model) correspond to the QRS complex while the second positive inflections are characteristic of the T wave of the surface ECG.



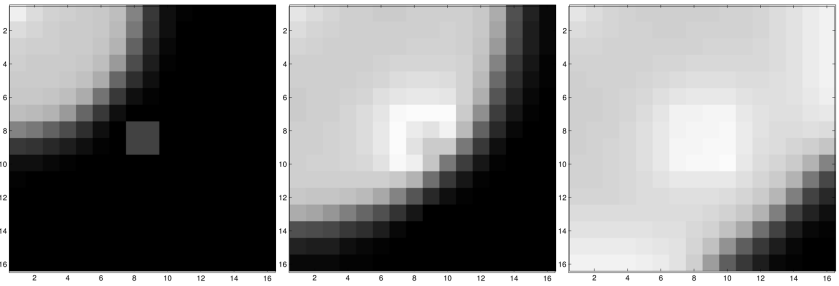
(a) CA model (b) BR model (c) hybrid model

Figure 11
Ischemia simulated tissues.



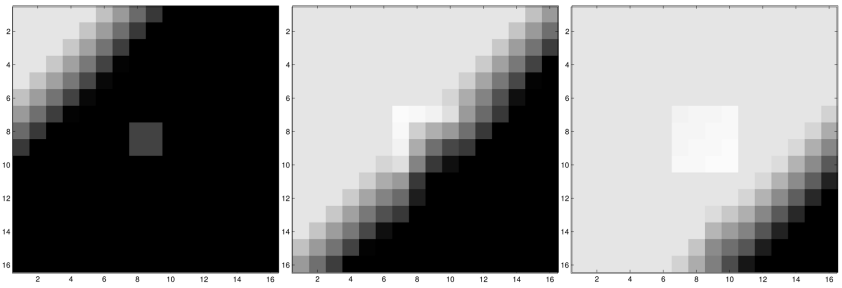
(a) Continuous model (b) Hybrid model

Figure 12
Depolarisation front for continuous ischemic model.



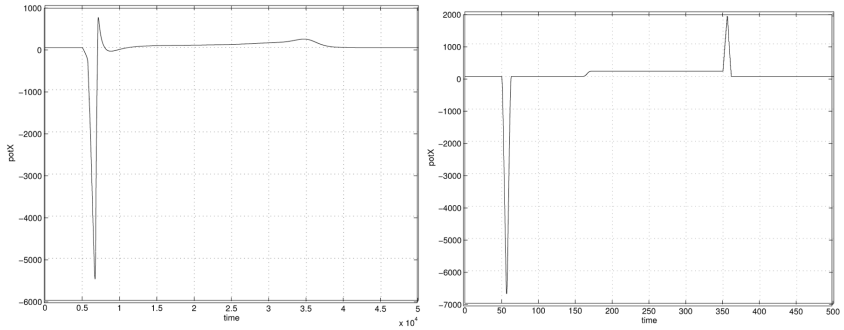
(a) t1 = 53.5 ms (b) t2 = 57.0 ms (c) t3 = 59.5 ms

Figure 13
Depolarisation front for hybrid ischemic model.



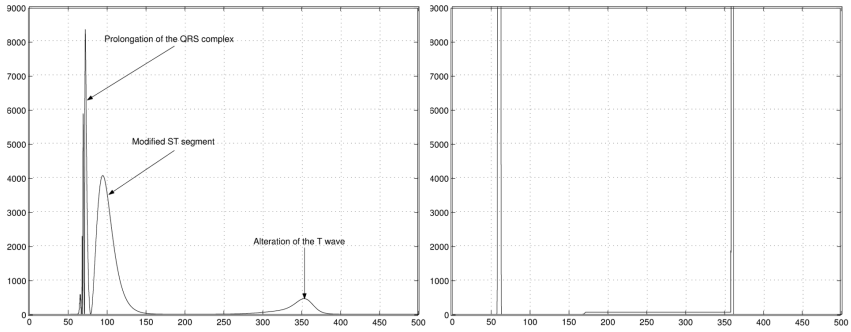
(a) t1 = 53.5 ms (b) t2 = 57.0 ms (c) t3 = 59.5 ms

Figure 14
Dipolar projection for ischemic simulated tissues.



(a) Continuous model (b) Hybrid model

Figure 15
Quadratic distance between 'ECG' reconstruction of healthy and ischemic tissues. In the case of ischemic tissues, the QRS complex is prolonged and beginning as well as ending of repolarisation are affected.



(a) Continuous ischemic model vs BR model (b) Hybrid ischemic model vs hybrid healthy model