31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Modelling Heart Beat Initiation and Propagation using the MML Framework

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***Abstract*—The Modeling Markup Language (MML) framework provides a temporo-spatial level modeling tool, consisting of two representation languages with tools which utilize CellML, a mathematical biological model representational language. The purpose of MML is to encourage reuse, sharing and efficiency. In this study, we utilize MML to investigate the role of the hyperpolarizing activated (i_f) current of the sinoatrial node (SAN), the natural pacemaker of the heart. The i_f is believed to play an important role in heart automaticity and pacing rate. By using the MML framework and CellML specification, we construct a range of models to examine the role of i_f in the SAN as well as aspects of wavefront propagation from the SAN into the atria.**

I. Introduction

The Physiome project [1] was developed to provide a framework to represent and share integrative biological models at all scales of biology. The aims of part of this project were to provide standardized representational languages for different scales of biological models. The Modeling Markup Language (MML) framework is intended to partially fulfill this aim[2] by providing a set of tools and languages to specify and construct an organ level temporo-spatial biological model.

The MML framework consists of two representation languages. The first is the ModelML specification which is primarily responsible for importing geometric and mathematical models, storing the relational information, overall mathematical system information and attaching field information to the governing mathematical models. Secondly, the FML (a field representational language) representation language is responsible for storing field data. Field data may include geometric representation or attributes related to a region of space, such as temperature, voltage, etc. The MML framework also provides a basic set of tools to aid in the authoring and exporting of MML models into solvers.

In this paper, we present an investigation of the effect of the hyperpolarizing-activated (i_f) current of cardiac sinoatrial node (SAN) cells on the propagation of the electrical impulse into the atria using the MML framework.

The SAN forms the natural pacemaker of the heart. It consists of central and peripheral cells with electrical characteristics driven by underlying membrane currents. One of these is the hyperpolarizing-activated (i_f) current, widely accepted to play a role in the activity of the pacemaker, however the precise role remaining unclear [3]. It has been suggested that i_f plays a predominant role in cardiac automaticity[4], In this study we explore the role of i_f in SAN-atrial interaction.

The MML framework allows us to reconstruct temporo-spatial computational models quickly and efficiently by allowing geometries and cellular mathematical models to be inserted, swapped or adjusted at the ModelML level. Using this tool, we can create a SAN-atrial model and modify underlying currents to examine the effect of these on heartbeat initiation and propagation.

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II. MML Overview

The MML framework consists of the ModelML and FML representational languages with application toolset consisting of authoring tools and utility applications including the capability to convert the MML models into a solvable format for import into a commercially available finite element solver. The representation language is based on the XML and HDF5 data formats, with the main goal of the specification being to provide a modular and simple approach that utilizes existing CellML[5] technology to develop biological models.

The MML framework is targeted towards the organ level modeling scope [6] where the governing factors are the physical conservation laws. In this level of modeling, the main functionality can be described without necessarily implementing the finer components which underlie the overall functionality. For example, a model of cardiac electrophysiological cardiac cell models can be represented without modelling the complex underlying configuration of membrane-spanning proteins which govern ion channel flow.

A. ModelML

ModelML serves three main purposes: 1) to describe the relationship between different information domains, 2) to attach spatial information to ordinary differential equations and 3) to provide an interface that will allow different documents to interact with each other. ModelML is also tasked with providing a mechanism to override certain parameter values of the imported CellML models and to provide metadata and other mathematical declaration support.

With multiple imported CellML models, there is a need to

provide an interface to connect these models in a meaningful way. ModelML provides a general mechanism that can be used to declare mathematical or physical systems that maps variables from different model under a common identifier. These include ODE mathematical systems or spatial variables such as those of equation (1) and (2).

$$e_a \frac{\partial^2 v}{\partial t^2} + d_a \frac{\partial v}{\partial t} = F \quad (1)$$

$$e_a \frac{\partial^2 v}{\partial t^2} + d_a \frac{\partial v}{\partial t} + \nabla.\Gamma = F_1 \quad (2)$$

Currently, ModelML is primarily used to relate spatial domains such as geometric subdomains, boundaries or point objects to relevant mathematical information such as the governing equations from CellML or boundary conditions from the ModelML document. In general, ModelML references ordinary differential equations from CellML models as seen in equation (1) and attaches field information to create a partial differential equation system as seen in equation (2) by adding the $\nabla.\Gamma$. This overriding mechanism allows minor changes to parameter values of the imported models from the ModelML scope; this includes adjusting the F_1 term from equation (2) (i.e. adding stimulus terms), providing new parameter values, or substituting equations or variables.

B. FML

FML refers to field representation format. Its main purpose is to provide a mechanism to describe field data and to provide relevant geometric representation schemes if applicable. Field data may include geometric objects or regions or user defined interpolating functions. These field data can then be used to construct a geometric model or used within a spatial region to define field attributes. Field attributes are generally scalars, vectors or tensors which can be used to describe physical variables such as temperature, voltage or stress, etc.

The basic component of a FML model is the frame of reference: this container defines gross spatial properties such as dimensions and all field data resides in this container. FML provides basic support for primitive geometric objects such as lines, triangles or tetrahedra as well as interpolating functions such as BSpline or Bezier curves and surfaces. It also provides a mechanism to describe user defined interpolating functions.

FML supports two types of geometric modeling methods: mesh modeling (1D-3D) and boundary representation methods (1D-2D).

C. Area of Application

The main area of focus for the MML specification is to provide a temporo-spatial modeling toolkit. Its modular setup allows field and mathematical models to be interchanged more rapidly and efficiently. Furthermore, the CellML repository[7] provides a number of usable curated[8] models that can be used. ModelML provides a mechanism to adjust the information of imported CellML models; this allows parameters of the models to be adjusted to observe effects that may have clinical or physiological implications.

III. SINOATRIAL SIMULATION

The SAN is composed of central and peripheral cells and surrounded by atrial myocytes. It has been proposed that the hyperpolarizing activated current (i_f) plays an important role in cardiac automaticity underlying pacemaker depolarization and influencing the cardiac pacing rate[9]. For impulse propagation to occur from the SAN, the SAN must be electrically well-coupled to the atria and also well protected from its hyperpolarized atrial load[10]. The i_f current density is higher in the peripheral cells than the central cells, possibly to protect the SAN from the hyperpolarizing influence of the surrounding atrial tissue. This is because hyperpolarization leads to further activation of the i_f current which will oppose the effect of the hyperpolarization[3].

Arrhythmia is defined as the abnormal propagation of electrical activity in the heart, which may lead to deficient contraction of the heart muscle, impairing its blood pumping function. In this study, we simulate the effect of mutual entrainment central and peripheral SAN cells and observe the role that i_f plays, in its ability to alter the pacing rate and protect the SAN from the atrial electrical load.

A. Model Setup

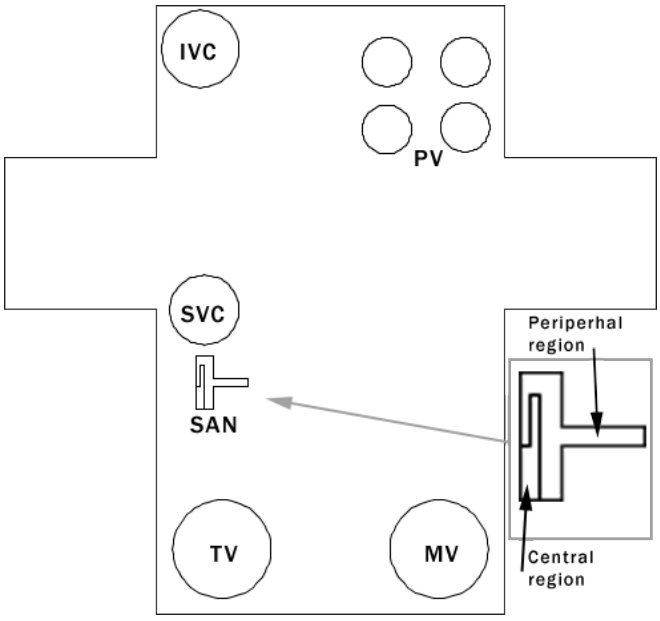

Fig. 1. A simplified atrial geometric model representing spatial features of spatial features of the atrial including superior vena cava (SVC), inferior vena cava (IVC), tricuspid valve (TV), pulmonary veins (PV) and mitral valve (MV) and Sinoatrial Node (SAN, central and peripheral domain).

Our geometric model is based on the Blanc[11] simplified atrial topology. The geometric model comprises a simplified atrial rectangular prism. The 2D model is obtained by

unfolding the surface of that prism into a two dimensional topological representation. The holes in the geometry are anatomical features of the atria including superior vena cava (SVC), inferior vena cava (IVC), tricuspid valve (TV), pulmonary veins (PV) and mitral valve (MV). Two extra domains were inserted which represent the central and peripheral SAN regions as described in figure 1.

For the SAN, we used the Lovell et al.[12] (LCCD) and Garny et al.[13] (GY) models. The atria will be modeled using the Roger Modified Fitzhugh Nagumo [14] (RM) equations.

The ModelML document imports the FML and CellML documents and creates a relational mapping between the field and mathematical domains. ModelML is used to alter the CellML parameters to adjust the i_f current density for the peripheral SAN region using the i_f current conductance variable. In the LCCD model, this conductance variable is the "g_f_Na" variable while in the GY model, these variables are "g_f_Na_Periphery_1DCapable" and "g_f_K_Periphery_1DCapable". ModelML is also used to supply the field conductivity values for the spatial domains. By altering the i_f current density and conductivity values, we can observe the role of the i_f current and central and peripheral cell interaction as well as their effect on atrial propagation.

B. Simulation Results

1) SAN Conductivity

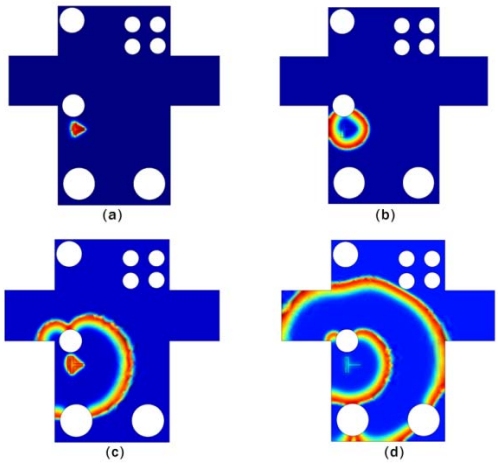

Fig. 2. SAN entrainment (conductivity set at 9e-5 S/m for both SAN and the atria) and propagation into the atria at time a) 0.3s, b) 0.4s, c) 0.6s and d) 0.8s.

The first scenario is the effect of a mutually entrained central and peripheral SAN domain to serve as a base model for atrial excitation. In a well-entrained setup, we can see that the action potential propagates outward in a uniform manner in all directions as seen in figure 2.

When the conductivity values in the sinoatrial region were adjusted for non-entrainment, more complex activation patterns occur in the atria as seen in figure 3. This includes propagation from the peripheral SAN domain only, creating an irregular spiral pattern that re-enters the SAN as it propagates outward into the atria.

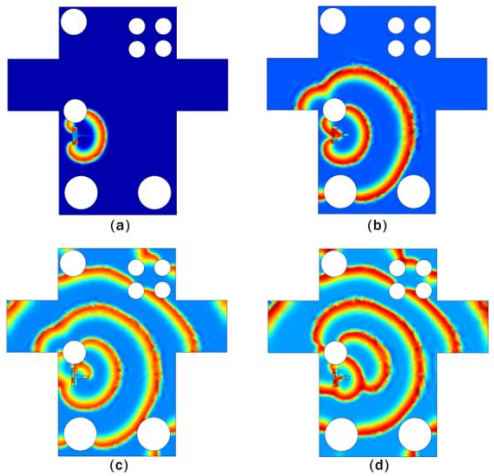

Fig. 3. SAN Non-entrainment (conductivity set at 1e-6 S/m for SAN and 9e-5 S/m for Atria) and propagation into the atria at time a) 0.3s, b) 0.55s, c) 1s and d) 1.4s.

2) The Role of i_f

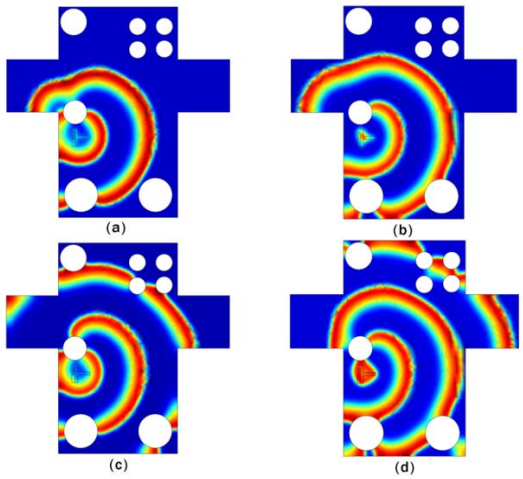

Fig. 4. This image shows the effect of an increase in SAN I_f current density in terms of SAN propagation into the atria at time a) 0.3s, b) 0.35s, c) 0.45s and d) 0.55s. for conductivity value of 2.24e-4 S/m for both SAN and the atria for GY-RM model.

We wish to explore the role of i_f in protecting the SAN rhythm from the hyperpolarized atria and its ability to control the basal rate of SAN firing. For the GY–RM setup, we were able to observe an increased i_f in the peripheral SAN region protected the SAN rhythm from the atrial load. The SAN conductivity was set such that the atrium suppressed the SAN (2.24e-4 S/m). The membrane conductance variable of i_f in the peripheral SAN region was increased, causing the SAN to regain its beat.

For the GY model, we were able to control the frequency of SAN rhythm by altering i_f membrane conductance. For a decreased SAN rate, the propagation pattern remained the same as the base model, however as the SAN rate was increased, certain pathways in the atria were affected and the propagation would dissipate within the narrow geometric

features between the SVC and the boundary, creating more complex activation patterns as seen in figure 4.

For the LCCD-RM setup, we were unable to find a SAN conductivity value which causes the atria to suppress the SAN; an explanation may be the lack of difference between the LCCD and RM initial membrane potential values are not wide enough for the RM model to suppress the LCCD model. The RM atrial model was than swapped with the Earm[15] atrial model where it is able to suppress the LCCD SAN model. However, interfering the i_f membrane conductance does not affect its ability to entrain and propagate. Further investigation revealed that although a decrease in i_f causes a decrease in the basal SAN, any increase of the i_f current density does not significantly increase the basal rate of the LCCD model suggesting that this model is limited in its capacity to reproduce the effect of greater i_f current as seen in figure 5.

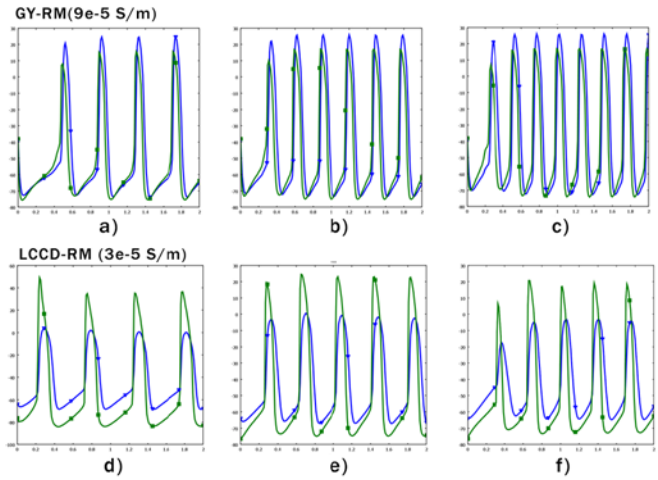

Fig. 5. This graph illustrates the effect of altering the i_f on SAN rhythm. The top row illustrates the GY-RM model where a) i_f is decreased b) i_f is normal c) i_f increased. The bottom row illustrates the LCCD-RM models where d) i_f is decreased e) i_f is normal f) i_f is increased.

IV. Conclusion

The MML framework provides a modular approach to rapidly construct temporo-spatial biological models to simulate physiological systems. In this study, MML was used to examine the role of the hyperpolarizing-activated membrane current in cardiac cells in the initiation and propagation of the heart beat. The i_f was altered to observe its role in protecting the SAN from the atria. Furthermore non-entraining SAN propagation of irregular waveform patterns into the atria was observed. This was achieved by altering the conductivity values of the SAN. This setup facilitates the use of more complex cardiac models in combination with realistic geometric models. The development of the MML framework is an ongoing process. Future work includes expanding beyond electrophysiological cardiac models, multi-physics implementations, and FML mapping between multiple FML models and a more robust support application toolset.

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