Software challenges in the new field of integrated cardiac models

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Abstract— **With cardiac research spanning the whole range from molecular mechanisms to whole organ preparations and computational capabilities expanding dramatically, it is becoming more tractable to create realistic models and simulations that integrate physiological behavior at these different scales. Large-scale integration generates new challenges that include linking the different model components developed over the years into one framework and developing the sophisticated visualization schemes that are needed to obtain useful insights from these models. Here we outline the specific nature of these challenges and describe one approach to developing integrated software systems for bioelectric field modeling, simulation and visualization.**

Keywords— **multi-scale modeling, bidomain model, tridomain model, cellular model, simulation software**

I. Introduction

One of the goals in cardiac modeling that has always received great attention is the quest to understand the mechanisms behind a variety of cardiac diseases. In recent years, the scope of studies of the heart has increased to include a wide range of levels, reaching from genetics to full heart preparations. It has become increasingly clear that all these different levels are interlinked and that expression of certain genes are the underlying basis of cardiac diseases at the macroscopic level. However genetic defects are only one factor of many in determining the behavior of systems at the macroscopic level. For instance, a blood clot in one of the coronary arteries can have devastating effects on the heart, even though genetic predisposition plays a role in creating the required substrate for occlusion. Ultimately, there is a wide variety of causes that determine one's susceptibility to disease.

Modeling and simulation can play a useful role in studying the interactions of multiple levels of influence on macroscopic behavior. Modeling also addresses a fundamental limitation of experimental approaches in that they are not capable of measuring all variables of interest and certainly not all variable simultaneously.

Moreover, the challenge in designing tools for these mechanistic investigations in the heart consists of various layers. First of all, with a lot of parameters involved the visualization becomes more challenging, as one has to display multiple modalities at the same time, coupled in time and space. One can think for example of the distribution between gap-junctions and electrical potentials. Overlaying both modalities in the same visualization may reveal new information. Such visualizations require a large set of tools for dissecting the model and displaying parameters at every level of the heart to reveal mechanistic bridges.

Another challenge is to link the various modeling modalities that exist. Over the last decades many tools for simulating cardiac events have been developed, however most of them do not communicate with each other. The challenge to gain a more comprehensive understanding of the heart is now to integrate the existing tools into one comprehensive framework. It will be the framework's task to ensure that the different simulation tools are able to communicate with each other. The communication protocol between the different applications is not always a matter of writing a converter algorithm to translate one data structure into the data structure of another program, several other steps may be needed. For example, consider a cardiac simulation at a cellular scale resulting a heterogeneous distribution of properties on this cellular scale, before this data can be used in a full heart simulation it needs to be spatial averaged to comply with the scales of a model at an organ level. These spatial averaged properties often stem from different simulations of different tissue types and all need to be combined into one whole heart scale model. Often one wants this process of filling out properties into a model to be stochastic. Since a lot of tools have been designed to function on only one scale, these kinds of conversion steps do not usually exist in the simulations packages currently available. Hence the framework that couples all these simulations together, needs to supply the necessary tools to accomplish this "in between" processing.

II. Methods

At the Scientific Computing and Imaging (SCI) Institute, we have designed and implemented an integrated software environment called SCIRun/BioPSE for scientists wishing to carry out modeling, simulation, and visualization of bioelectric field problems. This system is based on a dataflow structure and a visual programming environment in which individual modules carry out sequential steps required for a complete simulation and analysis [1]. Figure 1 contains an example screenshot of a network in SCIRun/BioPSE,

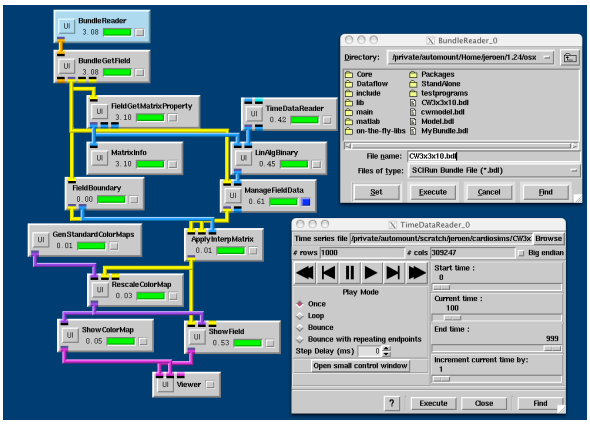

Fig. 1. SCIRun/BioPSE Problem solving environment. This figure shows a screenshot of the visual programming paradigm used in by the SCIRun/BioPSE software platform. The different boxes on the left represent different functional components linking by data streams. The interface windows on the right represent some of the settings used by these components.

together two user interface (UI) elements. The UI for each module provides user control of the parameters relevant to that module. Currently, SCIRun has extensive support for visualization of many different datasets within the same framework and an infrastructure that supports computational steering, *i.e.*, the user can direct or steer a simulation when it executes. The current software development at the SCI institute is focused on extending this software package to include more simulation and computational tools to accomplish a synergy of modeling tools.

The software development focuses on several means to accomplish this goal. Firstly, with some good cardiac simulators out there we are incorporating existing tools by building a bridging mechanism between tools. This bridging mechanism will allow for other simulation packages to be run within SCIRun. An example of such a bridge being created is the integration of CardioWave, a simulation tool developed at Duke University, into the SCIRun platform. CardioWave is a software package that solves the bidomain equations and can be used for various whole heart and tissue level simulations of cardiac propagation. Building a bridge to this package will allow for editing and creating models within SCIRun in a visual manner and use CardioWave as a dedicated solver to the propagation of cardiac activation. Likewise, a bridging interface has been created to Matlab, a programming environment that is used by many scientists to a wide variety of simulation tools.

The bridging mechanism has been set up in such a way, that the different applications controlled by SCIRun can run on different platforms and still communicate with each other. For example when running a simulation using CardioWave a lot of computational power is needed, hence one wants to run these kinds of simulations on a powerful multi-processor computer or computer(s), taking advance of the advancements in parallel computing. Whereas for the visualization part, one wants to take full advantage of the new generation of graphics cards, hence here it is not important to run the visualization a machine with multiple processors, but rather a powerful graphics card. Within the bridging software communication protocols and server programs are available to set up the simulation chain disturbed over several computers, with the simulation being controlled from one computer using the SCIRun software.

The visual tools for editing and data organization require a solution that is far more closely integrated with the system controlling the system than for instance the software for solving the linear system. Since the data organization part is the glue that merges the different applications together, it is something that needs to be an integral part of problem solving environment, in this case SCIRun. One of the difficulties facing the design of this integrated system is that one does not want to use all the different conventions used by the different underlying applications. For instance physicals units should be harmonized within the problem-solving environment, similarly naming conventions of parameters should be equal and the way geometrical data is represented. Hence, the bridging mechanism is designed to do a translation to the local nomenclature and data structure conventions whenever an external simulation packages is invoked.

As a mechanism for this kind of data organization did not exist in SCIRun, a new data representation has been designed and implemented, which acts as a database and catalogs the different pieces of a model under an alphanumeric name. These databases represent a cardiac model and every component within the database is forwarded to the converters to be translated to for a specific simulation package. Examples of these different components are for instance the geometrical mesh used for the simulation, a table with different electrical conductivities, a table with local fiber orientation, the parameters of various membrane models. The current design allows for extracting several components out of the model database and to visual adjust them or do computations with the different components within the SCIRun environment. Currently, we are exploring the most convenient ways of organizing the data for the different simulations packages, in order to reduce amount of conversions that the user has to do when linking different simulations together.

III. Results

In order to explore visualization needs and ways to communicate to other programs, several cardiac simulations and visualizations were performed to better structure the software and to further analyze the tasks ahead. In the sections below, short descriptions of simulations and the software development to accommodate these are described:

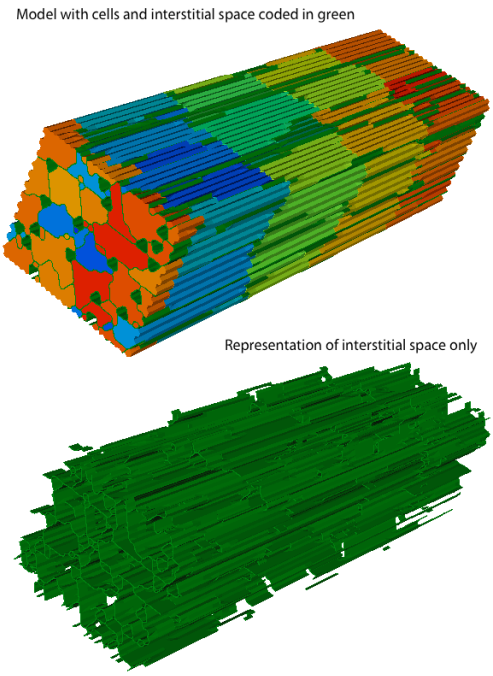

Fig. 2. Representation of the geometrical model used for computing passive conductivities. The upper panel shows the different cells color-coded and the interstitial space shown in green. This model consists of cells, interstitial space and capillaries (not shown). The lower panel shows the interstitial space only.

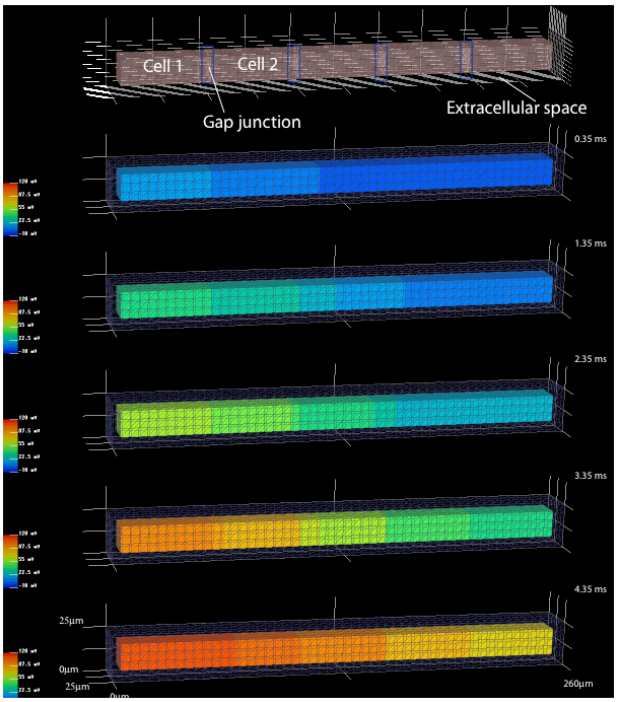

Fig. 3. Results of a simulation using a single strand of regular cells. In the top row, the layout of the model is shown. The model consisted of five cells connected by gap junctions, modeled as a resistive plane that connects both cells. In the lower five panels the progression of the potential is shown in the first 5msec after stimulating the first cell. As one can see there is a propagating wave going from left to right.

A. Modeling passive conductivity

One of the important parameters in cardiac models is the passive electrical conductivity of tissue. Although conductivities can be measured, most models rely on a subdivision of the conductivity tensor into an intracellular and extracellular conductivity with both being anisotropic. The latter subdivision is far more difficult to measure accurately, especially under pathological circumstances such as ischemia. Hence, we set out to create a model that describes the structure of cardiac tissue at a cellular level [2,3]. This model was used to estimate the passive conductivity of cardiac tissue. Due to the specific mesh-generation requirements, the mesh generation and solving phase were accomplished in Matlab using a dedicated linear system solver and a mesh generation toolkit that was developed with this purpose in mind. The only thing that was hard to accomplish in Matlab was the visualization of the solutions and meshes. Since the goal of the project was to create a model of cardiac tissue as realistic as possible, a mesh generator was created that mimicked the small clefts of extracellular space that is found in real tissue. The main problem was to visualize the results on such an intricate mesh. In order to make use of the visualization modules that are available in SCIRun, we improved the bridge between SCIRun and Matlab, so that it sends objects, such as geometrical meshes and datasets, from Matlab's programming environment to SCIRun's visual Problem Solving Environment and vice versa. In this process, Matlab is controlled from SCIRun and can be programmed to do tasks such as mesh generation.

B. Modeling propagation at cellular level

A second example of a model currently being explored is a model of propagation of the action potential at a cellular scale in cardiac tissue. The main question here is how the propagation of the action potentials relates to the underlying tissue structure. For instance, what is the impact of changes in interstitial fluid distributions in ischemic regions, what is the influence of different distributions of gap-junctions, and what are the implications of cell deaths on propagation? In order to answer these kinds of questions, the SCI group is collaborating with Duke University to build a framework in which these kinds of experiments can be done. In order to accomplish this we are currently bridging the SCIRun environment towards the CardioWave package developed at Duke University. The idea of this bridge is that we can reuse the meshing algorithms we developed for the passive conductivity models (see section A), use the finite element stiffness matrix generation in SCIRun, use CardioWave as a dedicated bidomain solver and finally use SCIRun to do the visualization. The advantage is that most of the components are present and they are well tested and hence, we can quickly devise a new modeling tool. A first visualization of

a propagating wave front in a small set of five cells is depicted in figure 3, showing the possibility of doing these kinds of simulations. This model is a small-scale model that is used to evaluate the propagation simulations and to test all the software design issues involving the integration of the different programs. This simulation was accomplished using a finite element scheme for the intra- and extracellular spaces to solve the electrical potentials. In this model, both spaces were coupled by an active membrane model (Lou-Rudy membrane model) to simulate the propagation of the action potential. Currently the development in this field is to enhance the visual editing of the model, to better control the simulated tissue morphology and distribution of membrane models.

C. Modeling ischemia in a full anisotropic heart model

Since one of the goals of the tissue level models is to provide parameters for a cardiac model of an entire heart, we have been investigating the construction of models as well. In figure 4, an example of such a model is given. The simulation shown was based on a full anisotropic model of the left and right ventricle, in which the epicardial potentials were computed using a finite element model [4,5]. The model was constructed in Matlab and the results were visualized using SCIRun/BioPSE. This model had been created to simulate the effect of ischemia on the ST segment observed at the epicardium. The advantage of a visualization such as the one shown in figure 4, is that the epicardial potential distribution, the ischemic region and the fiber orientation can all be shown in one framework. In this framework the visual displays are coupled; if one rotates or zooms in on one of the figures, the same operation is performed on the other two figures, which makes it easier to interpret the results from the simulation.

The science that led to this investigation was to describe the effect of fiber orientation on the potentials observed at the epicardium. If one looks closely at the fiber orientation then the two minima observed at the epicardial surface are aligned along the axis as the local fiber orientation is at the depth of the simulated ischemia. When growing the ischemic region transmurally, a rotation of the epicardial potentials can be observed, which coincides with the fiber orientation more closely to the epicardial surface [5].

IV. Discussion

Currently the simulations at these different levels are still done independently, but having most of the tools now integrated into one framework, we can start the explore the synergy between these modeling tools. An example of the synergy we used in the model studies described above is the use the conductivity tensors derived using cellular model (A) in the model of the ischemic heart (C). Another synergy we hope to be using soon is to couple the mesh generators developed for the passive conductivity model to the cellular propagation model and to implement the resulting propagation speeds into the anisotropic heart model.

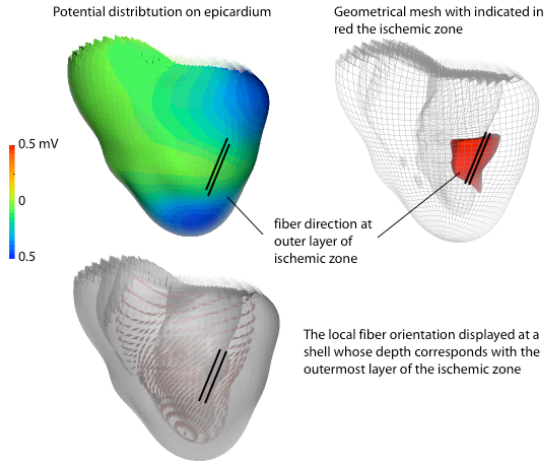

Fig. 4. Simulation using a full anisotropic heart model in order to study the effects of ischemia on epicardial potentials (ST-segment). In the upper left corner the potential distribution is show, the ischemic zone is displayed on the right and the fiber orientation is displayed below. Note that the fiber orientation locally in the ischemic zone matches the line connecting the two minima on the epicardial surface.

Although the synergy between the modeling in Matlab and the computational steering and visualization in SCIRun is starting to prove useful, more tools are needed to really benefit from the synergy between the modeling modalities. One of the drawbacks of using Matlab is its inability to do parallel computing. Hence in the future we like to do common operations, like the generation of stiffness matrices in parallel in SCIRun. Another field that needs more attention is the creation of visual editing tools, to make it easier to simulate a variety of different scenarios.

Acknowledgment

This research would not have been possible without generous support of the National Institutes of Health Grant P20 HL68566-01, Grant 04-SC-NIH-1061, and the Whitaker Foundation.

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