Incorporating Local Ca^{2+} Dynamics into Single Cell Ventricular Models

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Abstract. Understanding physiological mechanisms underlying the activity of the heart is of great medical importance. Mathematical modeling and numerical simulation have become a widely accepted method of unraveling the underlying mechanism of the heart. Calcium (Ca^{2+}) dynamics regulate the excitation-contraction coupling in heart muscle cells and hence are among the key players in maintaining normal activity of the heart. Many existing ventricular single cell models lack the biophysically detailed description of the Ca^{2+} dynamics. In this paper we examine how we can improve existing ventricular cell models by replacing their description of Ca^{2+} dynamics with the local Ca^{2+} control models. When replacing the existing Ca^{2+} dynamics in a given cell model with a different Ca^{2+} description, the parameters of the Ca^{2+} subsystem need to be re-fitted. Moreover, the search through the plausible parameter space is computationally very intensive. Thus, the Grid enabled Nimrod/O software tools are used for optimizing the cell parameters. Nimrod/O provides a convenient, user-friendly framework for this as exemplified by the incorporation of local Ca^{2+} dynamics into the ventricular single cell Noble 1998 model.

Keywords: Cardiac Cells, Mathematical modeling, Parameter optimization, Grid Computing.

1 Introduction

Researchers have been developing complex models of cardiac cells for many years, in an attempt to explore the detailed physiology and operation of the heart. Ultimately, the goal is to produce better treatment strategies and to develop novel drugs for treating heart disease. This case study concerns the detailed modeling of particular ion channels in heart muscle cells.

The key physiological function of the heart is to pump blood around the living organism. This function is enabled by the spread of electrical excitation through the

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cardiac tissue and contraction of the cardiac muscles. On the single-cell level (a myocyte), the mechanisms of excitation-contraction coupling are closely regulated by calcium ion (Ca^{2+}) dynamics. Ca^{2+} entering the cell triggers the release of Ca^{2+} from the sarcoplasmic reticulum (SR) which is the organelle that stores calcium. The resulting rise of intracellular Ca^{2+} (Ca_i) activates the contraction of the cell. This phenomenon is known as Ca^{2+}-induced Ca^{2+} release (CICR). Local Ca^{2+} dynamics are characterized by the interactions within localized microdomains (known as dyadic spaces) between L-type Ca^{2+} channels (LCCs) located on the Transverse–tubules (T–tubules), which are deep invaginations of the membrane into the cell, and closely opposed Ca^{2+} release channels (known as ryanodine receptors, RyRs) located on the sarcoplasmic reticulum (Fig. 1). The sarcoplasmic reticulum is an extensive and well organized network, that repeatedly comes in contact with each T-tubule, so that the number of dyadic spaces throughout the cell has been estimated to be of the order 50,000 – 300,000.

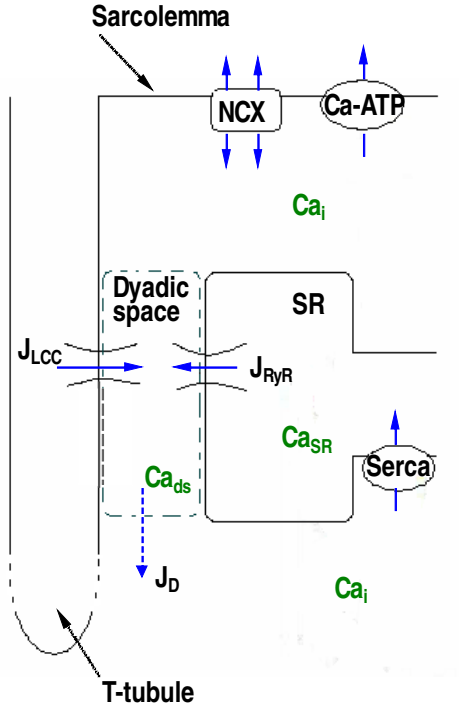

Fig. 1. Local Ca^{2+} dynamics of Greenstein et al. 2006 [1] model. Arrows represent the direction in which Ca^{2+} flows. Ca_i, Ca_{ds} and Ca_{SR} denote intracellular, dyadic and SR Ca^{2+} respectively. The diagram illustrates the local control theory: LCCs and RyRs contribute to local J_{LCC} and J_{RyR} fluxes respectively within the dyadic space, J_D represents the diffusion of Ca^{2+} out of the dyad into the bulk myoplasm, SERCA re-uptakes Ca^{2+} back into the SR, Ca^{2+}-ATPases and NCXs pump Ca^{2+} out of the cell.

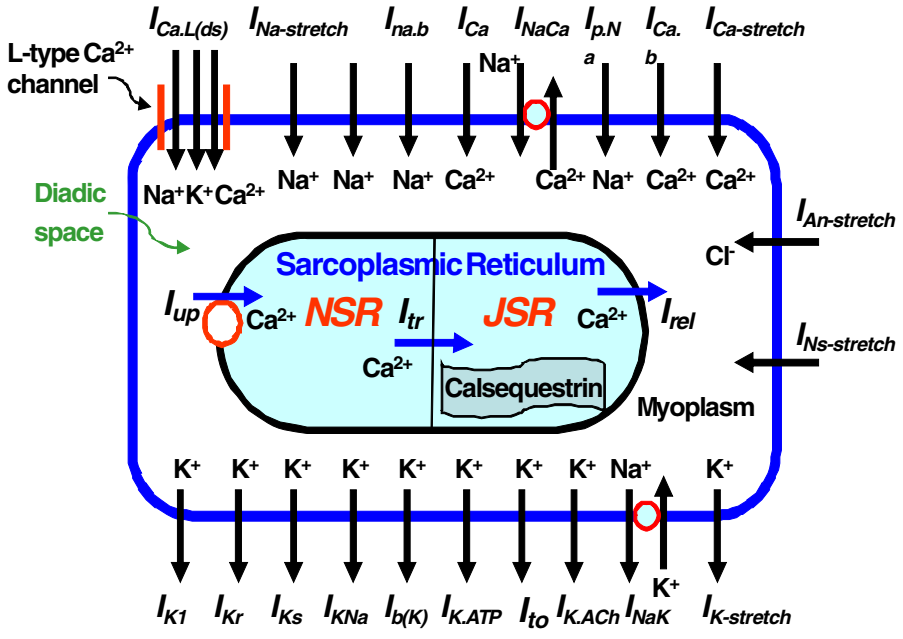

Fig. 2. Schematic representation of the single cell Noble et al. 1998 [3] model (adapted from a diagram at `www.cellml.org` model repository). Arrows represent the direction in which the ions flow and the label of the corresponding ionic current is located above or bellow the arrow. The model includes four Ca^{2+} compartments which are the intracellular, dyadic, network SR (NSR) and junctional SR (JSR). This model is an example of the deterministic non-common pool ventricular model that uses phenomenological description of Ca^{2+} in the dyadic space and Ca^{2+} related currents. While such a model succeeds in producing graded SR Ca^{2+} release, it lacks the mechanistic description of local SR Ca^{2+} release, i.e. the stochastic interaction between LCCs and RyRs within the dyadic spaces.

The local Ca^{2+} release mechanisms are essential to reproduce the characteristic properties of the excitation-contraction coupling such as high gain and graded Ca^{2+} release. However, most existing single cell models lack the description of the biophysical nature of local Ca^{2+} dynamics. In this paper we present a methodology of how local Ca^{2+} dynamics can be efficiently incorporated into a single cell model of ventricular myocyte in order to produce a biophysically accurate cell model. The two stages involved are (i) development of the Ca^{2+} subsystem and (ii) its incorporation into a single cell model. The first stage is the generation of the local control CICR models (also known as the coupled LCC-RyR models) such as, for instance, the ones that have been developed by Hinch et al. [2] and Greenstein et al. [1]. The second stage, which is the focus of this paper, involves the incorporation of the coupled LCC-RyR models into a single cell model. Specifically, the steps are as follows:

- The equations that describe Ca^{2+} dynamics in the original single cell model (e.g. Noble 1998 model[1] [4] (Fig. 2)) are substituted by equations of the biophysically detailed Ca^{2+} subsystem (e.g. baseline 40-state coupled LCC-RyR Greenstein 2006 model [1] (Fig. 1)), provided that units are modified accordingly;
- The parameters of the newly obtained single cell model are refitted. This is done to ensure that the newly obtained single cell model, which contains the replaced Ca^{2+} subsystem, is capable of reproducing the data of the original model. In particular, the specific aim is to fit the dynamics of the Ca^{2+} of the newly developed whole-cell model either to the dynamics of the Ca^{2+} of the original model (e.g. Noble 1998) and/or to the available experimental data (e.g. Ca_i transient, IV curves, tail currents recorded from the voltage-clamp experiments, etc.). To achieve this, we need to optimize the parameters of the Ca^{2+} subsystem, or, in other words, to solve an inverse problem.

In this paper we demonstrate how the novel Grid computing tools allows the incorporation of local Ca^{2+} dynamics into the existing cellular models at a low computational cost. The optimization methods that are used require repeated evaluation of the models, and thus the time required to compute the optimal model parameters can be very long. The computational Grid can be exploited to speed the execution by delivering a large number of processors. The Grid enabled Nimrod/O tool that we use in this experiment incorporates a range of non-linear optimization methods, and these can be used to optimize the cell parameters accordingly. Section 2 briefly introduces the Grid and the Nimrod tools. Section 3 discusses challenges and results of incorporating local calcium dynamics on the example of the ventricular single cell Noble 1998 model.

2 Grid Computing

The Grid provides a general platform for integrating computation, data and instruments [8]. It serves as the infrastructure for implementing novel applications, particular in science and engineering.

In particular, “computational” Grids have emerged as a viable platform for delivering on-demand access to a range of very high performance machines. Whilst it may not be possible to gain access to sufficient resources at any single site, computational Grids can aggregate a number of otherwise separate resources into a single large super-computer. Such a virtual machine, or testbed, is an ideal base for simulating complex systems using computational models because the resources can be assembled at a period of peak demand and then released for use when not required. Such platforms have the potential to offer very cost effective solutions, leveraging everything from spare cycles on high end machines through to large pools of inexpensive desktops that are idle.

[1] The Noble 1998 model is extensively used by various researchers and, thus, it is important to assess the effect of replacing the existing phenomenological description of Ca^{2+} in the dyadic space and Ca^{2+} related currents with the local, biophysically sound Ca^{2+} dynamics. Therefore, the Noble 1998 model is chosen as the case study.

In spite of the enormous progress in building operation Grids, and the significant effort in developing middleware, assembling such a testbed on demand is difficult. Most Grids are built from different components, and this resource heterogeneity is a fact of life. Likewise, Grids are built across multiple administrative and security domains, posing problems for aggregating them into a single virtual machine. Lack of a single owning organization also means that resource scheduling becomes complex – no single job scheduler can guarantee access to sufficient computational power, making it difficult to deliver the guaranteed levels of service. Importantly, Grid application users don't want to know about the complexity of the underlying fabric, and wish to concentrate on their domain science.

Difficulty in using the Grid is not a hypothetical concern. Currently, very few scientists use the Grid routinely, and instead rely on local resources, which are under their control. This means that the scale and nature of the work is limited. Until we can make it easier to use, the Grid will never be adopted by more than the most hardy or desperate users!

Over the years we have developed a strategy for delivering the high levels of performance, and have built software tools that make it easy for scientists to leverage the computational power of the Grid. Specifically, the Nimrod family of tools allows a non-expert to specify large computational experiments using legacy software, and execute these over a range of Grid resources. Nimrod is not a single tool: it incorporates a component that distributes computations to the resources (Nimrod/G) [5], [7]; a component that searches for "good" solutions using non-linear optimization algorithms (Nimrod/O) [4], [6]; and a component that helps evaluate which parameter settings are important using experimental design (Nimrod/E). Most aspects of Nimrod have been written about extensively over the years, so we will only provide a cursory overview in Section 2.1 of the paper.

2.1 The Nimrod Tool Family

Figure 3 shows the architecture of the Nimrod tool family and the interaction between the major components. Typically, users interact through a Web browser using the Nimrod portal. This single point of presence then directs traffic to one of three different components – Nimrod/G which support parameter studies and distributes the computations to the Grid, Nimrod/O which performs optimization and Nimrod/E which uses experimental design techniques to scope parameter studies. Importantly, each of these components acts either as a user level tool, or as middleware, depending on the client use. For example, Nimrod/G can interact directly with users using a Web enabled interface, or can provide services to other software (such as Nimrod/E, Nimrod/O) via an API. Each of the applications discussed here leverages different aspects of the tools. In many cases, they used Nimrod/G to perform a crude sweep of the overall parameter space, and then launched Nimrod/O to refine the solutions. Nimrod/E is a fairly new development, and whilst it has been used in the cardiac modeling work, we do not have results at this stage.

An important aspect of the tool family is that they share a common specification language – which is written in a text document called a "plan" file. This file contains details of the parameters and how to invoke the application, and is typically quite small. Over the years, we have expanded the plan file to allow more complex

workflows to be specified [9], however, in the simplest form a single application is run many times. Nimrod/O plan files contain some additional information about which heuristics to use This specifies the optimization algorithm, or algorithms, and associated settings. For example, the file may specify simulated annealing and the associated cooling regime. Starting points for iterative algorithms are also specified as Nimrod/O can perform multiple concurrent searches. The Nimrod/E plan file contains information about which parameter combinations are to be estimated, and which are assumed negligible.

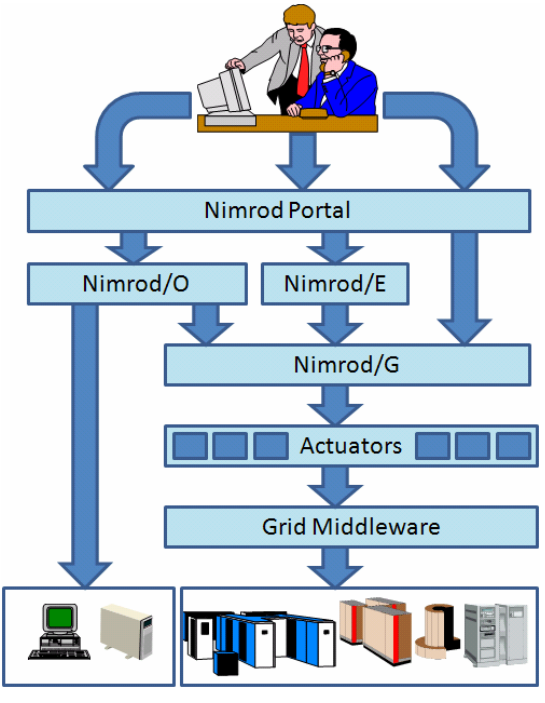

Fig. 3. The Nimrod tool chain

2.2 Nimrod Methodology

Each of the case studies discussed in the next section adopted the same overall methodology – regardless of which Nimrod tool was used. The following steps summarize this process:

1. Testbed construction. The use must decide which resources will be included in the grid testbed, and configure Nimrod to use these. The Nimrod portal provides a number of high level interfaces for making this fairly easy. Nimrod assumes that users already have accounts (and the necessary authentication) on each of the testbed resources.
2. Software preparation. Here the applications are compiled and tested on each of the Grid resources. This can either be performed manually by logging into each

of the different remote resources, or by using a tool like Distant [9] which manages the process through a single user oriented client. Even when configured manually, it is possible to prepare the application binary on one machine, and use Nimrod to distribute it to similar resources before execution.

3. Determine which Nimrod tool to use. As discussed, Nimrod has a number of different components. The user must select the most appropriate component, depending on whether a complete, partial or guided search is required.
4. Describe how to execute the application, and which files are required for input and output. These steps are described in the Nimrod plan file, using a simple declarative language. Nimrod can be instructed to copy input files to each resource, and return output files. Large output files can be left on remote resources for later analysis. Nimrod also managed parameter substitution via command line options or special control files.
5. Determine the parameters and their ranges. This will vary depending on the application requirements, These are then described in the Nimrod plan file using the 'parameter' keyword. Most parameters are independent, however, it is also possible to specify sequences of parameters that create complex workflows [9]. In this paper we use Nimrod/O to compute optimal parameter settings.
6. Execute the experiment. This is usually performed through the Nimrod portal, but it is also possible to use the Nimrod command line tools. Long running experiments can be left unattended, and monitored using the Nimrod monitoring tools.
7. Analyze the results, possibly returning to step 5 to refine the parameter ranges.

3 Incorporating Local Ca^{2+} Dynamics

The models of the local Ca^{2+} dynamics is a system of ODEs of approximately 30-70 variables with up to 100 parameters. These ODEs do not exhibit stiffness, thus, time integrators such as the forward Euler integrator or a Runge-Kutta 4^{th} order method are appropriate to simulate these Markov models. The results presented below are simulated in Matlab 6.5 using an inbuilt `ode45' solver - a one-step solver based on an explicit Runge-Kutta of 4^{th} and 5^{th} order, that is appropriate for non-stiff problems and has medium accuracy.

Each simulation on a personal laptop (e.g. Toshiba 512 MB RAM, 2 GHz, 60 GB Hard Drive, Windows XP) takes under five minutes, thus the computational resources required to perform one simulation are minimal. However, to optimize the set of parameters in the newly developed Ca^{2+} subsystem, the software tools which perform optimization algorithms within the framework of the distributive computing are essential. In particular, Nimrod/O provides a computationally effective manner of tuning the parameters and examining their effects within the newly developed models. Interestingly, in the case of running the simulations discussed above, the limiting factor is the number of Matlab licenses available rather than the number of processors. This is an issue that requires consideration by both the community and independent software vendors if the true power of the Grid is to be realized for this class of software. Nimrod/O offers a variety of optimization methods, such as "subdivision search" and downhill type search methods, etc. The simulation results

presented below are obtained using the downhill simplex method of Nelder and Mead. The optimal set of parameters, calculated using the simplex method, is obtained by fitting the action potential (AP), Ca_i transient and I_{CaL} current, with the objective function calculated using the least-square approximations.

The direct incorporation of the canine 40-state Greenstein 2006 coupled LCC-RyR model 1 into Noble 1998 guinea pig model (Fig. 2) results in a distorted electrical behaviour of the cell such as a significant second peak in Ca_i transient and a pronounced plateau phase in an action potential (compare dashed and dotted curves in Fig. 4). An optimized set of parameters obtained using Nimrod/O significantly improves the dynamical behaviour of the modified Noble 1998 model (solid curve).

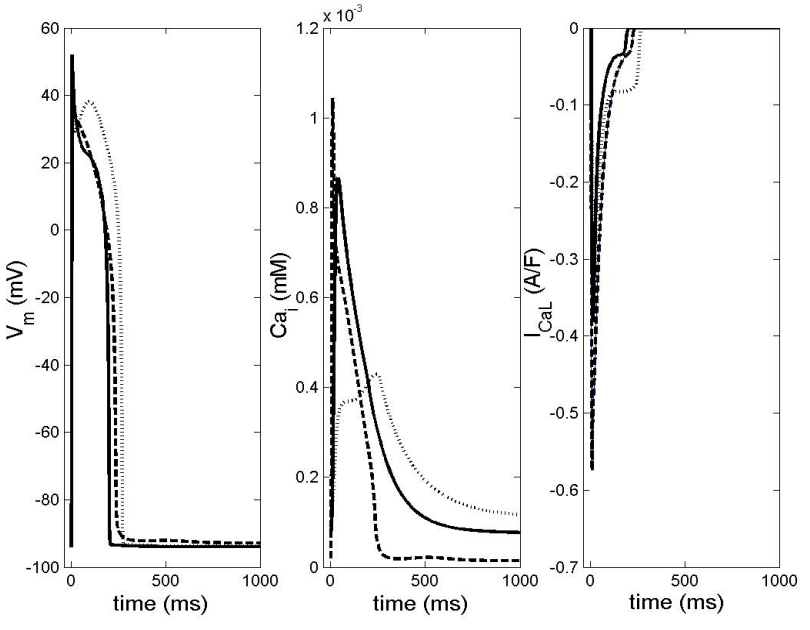

Fig. 4. Cardiac model output: The guinea pig Noble 1998 [4] ventricular model modified to include local Ca^{2+} dynamics. Dashed curve represents the Noble 1998 model. Dotted curve shows the modified Noble 1998 model that incorporates the 40-state coupled LCC-RyR Greenstein et al. 2006 model. Solid curve denotes Noble 1998 model modified to include Greenstein et al. 2006 Ca^{2+} dynamics with an optimized set of parameters[2].

[2] The optimal set of parameters (corresponding to the solid curve) is as follows: an increase in the maximum rate of the SERCA pump (1.4-fold), an increase in the conductance of RyR (3.5-fold) and LCC (1.5-fold) channels, modified constants of the 10-state LCC Markov model (the transition rate to the Ca^{2+}-dependent inactivation (CDI) state by 1.33-fold; the transition rate out of the CDI-state constant by 0.34-fold; the transition rate out of the closed state by 2.2-fold; the transition state out of the open state by 0.59-fold) and of the 4-state RyR Markov model (the transition rate into the open state from CDI-state 2 by 4.58-fold; the transition rate out of open state into CDI-state 2 by 0.79-fold; the transition rate into the open state from CDI-state 4 by 2.4-fold; the transition rate out of the closed state by 2.1-fold).

Importantly, the new set of parameters, which falls within the physiologically acceptable ranges, results in an elimination of the second peak in Ca_i transient (middle panel in Fig. 4). Further, the results demonstrate that Nimrod/O provides a convenient, user-friendly framework for tuning the parameters in the cardiac cell models in an efficient computional manner by taking advantage of parallel batches of evaluations**.** This study provides a valuable platform for future incorporation of the biophysically detailed Ca^{2+} subsystems into whole-cell models of various species.

It is important to note that the use of Nimrod/O highlighted the issues of the parameter sensitivity and over-parameterizations of cardiac ionic models (data not shown). Specifically, the challenges involved in analyzing and characterizing the significance of a given set of parameters in ionic models include (1) potentially fewer-than-necessary constraints being imposed when calculating the objective function, (2) the cardiac ionic models being complex nonlinear systems which have many local minima as opposed to global minima, etc. Parameter estimation in cardiac systems is an ongoing area of research. Thus, while Nimrod/O is a valuable tool in parameter optimization with low computational cost, further studies need to be performed in order to improve the method of finding the optimal set of parameters in a given ventricular single cell model.

4 Conclusions

In this paper we have outlined the steps necessary for updating the ventricular myocytes models with the local Ca^{2+} dynamics. Nimrod/O was used as the tool to incorporate the coupled LCC-RyR models in the place of the existing Ca^{2+} dynamics. To conclude, the incorporation of the local Ca^{2+} dynamics into the Noble 1998 model shows that Nimrod/O is a convenient, user-friendly framework for tuning the parameters in the cardiac cell models in an efficient computational manner by taking advantage of parallel batches of evaluations. Thus, Nimrod/O, provides a valuable, low-computational tool for the incorporation of the biophysically detailed Ca^{2+} subsystems into whole-cell models of various species.

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