High Throughput Cardiac Science on the Grid

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Cardiac electrophysiology, a mature discipline with the first model of a cardiac cell action potential developed in 1962 [14]. Current models of cardiac electrophysiology span the range from models of single ion channels (for instance, those of Capener [5]), through to very complex models of individual cardiac cells (see [17] for a review), to geometrically and anatomically detailed models of the electrical activity in whole ventricles (see review by Kerckhoffs [13]).

Software that simulates cardiac electrical activity varies in scale and complexity. Initially, codes were developed as stand alone applications, coded in traditional scientific languages such as Fortran and C. More recently, languages such as Matlab have been used extensively because of the higher level, and more mathematically oriented expressive power. Moreover, the Matlab runtime contains a number of powerful “tool boxes” which accelerate coding by providing mature and efficient solvers for, for example, differential equations. Whilst earlier research has made significant progress with these stand-alone codes, recent activity has focussed on building specific software packages for modelling the heart. These packages include CARP [6], CMISS [10], CONTINUITY [11], and Chaste [9], among others.

As with many other simulation endeavours, there is no single model that can reproduce the behaviour of a complete organ such as a heart. The enormous differences in scale of the physical processes (10⁹ spatially and 10¹⁵ temporally) means that individual models can only represent a subset of the processes, and higher level simulations need to incorporate parameterisations of lower level processes. When done this way, it is common to develop a high-resolution model of some low level process, and use this to calibrate a coarser grain model with parameters controlling key processes. This multi-scale simulation can then be used to investigate particular research questions related to behaviour of the organ under specific conditions – for example, to understand the effect of an infarct on cardiac propagation or external defibrillation on the heart. A critical issue then, is how to choose parameters that allow the model to faithfully reproduce observed physiological effects without over-fitting.

Over the past 15 years we have developed a family of software tools, called Nimrod, that perform parameter exploration on computationally expensive applications [3][8]. Nimrod allows a user to describe an “experiment” in which a model is run repeatedly across different parameter combinations. Because we expect models to be time consuming, they run on Grid enabled resources; exploiting internal parallelism in the application (if it is available), and also external parallelism of many independent simulations. This means that we can achieve very high throughput given sufficient Grid resources, allowing us to explore many different parameter combinations.

The Nimrod tool family consists of 4 main variants: G, E, O and K. Nimrod/G, supports complete parameter sweeps. A user provides details of the parameters and computational tasks to be performed, and the system generates and runs all combinations of the parameter values. Nimrod/E, on the other hand, automates the design of fractional factorial experiments [15]. Here, the user specifies the factors and which interactions can be ignored. Nimrod/E produces an efficient design, and generates the parameter values for the resulting jobs in a form suitable for Nimrod/G. The outcome is a Nimrod/G style sweep that explores only those parameter combinations likely to influence the experiment results, reducing the number of runs required to achieve useful scientific outcomes. Nimrod/O supports design optimization rather than complete enumeration [2]. Computation models are treated as functions that accept input parameters and return an objective cost value. Nimrod/O incorporates a number of different search heuristics ranging from gradient descent to genetic algorithms. Nimrod/O leverages Nimrod/G as a lower middleware layer, allowing jobs to be executed on the Grid. Finally, Nimrod/K allows users to express experiments as complex scientific workflows [1]. This means that multiple steps can be incorporated into a pipeline of activities rather than only using a single computational model. Nimrod/K is built on the Kepler workflow engine, and incorporates novel dataflow mechanisms for orchestrating the workflow.

We have applied different members of the Nimrod family to a range of cardiac modelling projects over the past few years. In this paper, we will discuss a few case studies, as outlined below:

• On the single-cell level, the mechanisms of excitation-contraction coupling are closely regulated by calcium ion (Ca²⁺) dynamics. Ca²⁺ entering the cell triggers the release of Ca²⁺ from the sarcoplasmic
reticulum, which is the organelle that stores calcium. Most existing single cell models lack the description of the biophysical nature of local Ca\(^{2+}\) dynamics. In this work we incorporated local Ca\(^{2+}\) dynamics into a model (written in Matlab) of a single ventricular myocyte, and the parameters of the newly obtained single cell model were refitted [18]. The specific aim was 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 and/or to the available experimental data. This was setup as an inverse problem, and Nimrod/O was used to automatically find parameters that minimized the error between the new model, the old model and real experimental data. The resulting plots of voltage, Ca\(^{2+}\) transient and current against time, are shown in Figure 1. The dashed curve represents the original Noble 1998 model. The dotted curve shows the modified Noble 1998 model that incorporates the 40-state coupled LCC-RyR Greenstein et al. 2006 model. The solid curve denotes Noble 1998 model modified to include Greenstein et al. 2006 Ca\(^{2+}\) dynamics with an optimized set of parameters.

- At tissue level, we used a 3D ventricular model which includes multiscale representation of ventricular electrophysiology from the ion channel to the ECG level [4]. Simulations of bidomain electrical propagation were conducted with Chaste to investigate changes in the electrocardiogram (ECG) caused by ion channel block. Specifically, we wanted to conduct a number of simulations with conductance of the rapid component of the delayed rectifier K\(^{+}\) current (I\(_{Kr}\)), varying from a control situation through to a 50% inhibition of the ionic current. The simulations, presented in Figure 2A, show that the APD prolongation caused by the block of I\(_{Kr}\) directly translates in QT interval prolongation, a result of physiological significance. The top panel shows six cellular APs obtained with six different levels of I\(_{Kr}\) block (from control case to 50% block). Corresponding surface ECG traces are shown in the bottom panel. In addition, similar simulations were run incorporating a stochastic model of the slow component of the delayed rectifier K\(^{+}\) current (I\(_{Ks}\)) which includes representation of ion channel fluctuations [16]. Figure 2B shows spatial dispersion in action potential duration due to ion channel fluctuations. Figure 2C and 2D show propagation in the whole ventricular model. Because we varied I\(_{Ks}\) over a fixed range, and were not concerned with optimizing the model output, we used Nimrod/G to perform the simulations.

These examplars made use of a variety of Grid resource from the PRAGMA testbed [7] and also the NGS [12]. In the paper we will present details of the performance gains and show that it is possible to solve some very large modeling experiments this way.

References


Figure 1 – Single myocyte parameter optimization

Figure 2 – Results of whole ventricular simulations using the cardiac solver Chaste and Nimrod for parameter sweeping. A. Effect of IKr block on the action potential and the ECG. B. Spatial variability in action potential duration due to ion channel fluctuations. C, D. Propagation of electrical excitation in an anatomically based rabbit whole ventricular model.