Grid Computing Simulations of Ion Channel Block Effects on the ECG Using 3D Anatomically-Based Models

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Abstract

In this study, a computational framework combining state-of-the-art cardiac simulation software and Grid computing is used to investigate the impact of the block of the HERG current on the ECG waveform using state-of-the-art 3D ventricular models of electrophysiology. The technology developed enables (i) automated parameter sweeping using multiscale models (from ion channel to ECG) and (ii) reduced execution time of the simulations performed.

1. Introduction

Sudden cardiac death is the major cause of mortality in industrialised societies, and thus understanding cardiac activity in health and disease is a crucial research topic. For the last 40 years, multiscale computational modelling in cardiac electrophysiology has evolved into a mature discipline, which has played a crucial role in the understanding of the physiology and pathology of the heart. Continuous advances in computational techniques and resources allow tackling modelling and simulation research problems of increasing complexity and interest.

In this work, Grid computing technology is combined with state-of-the-art cardiac simulation software and 3D ventricular models to provide the computational framework required to investigate changes in the electrocardiogram (ECG) caused by ion channel block. The technological challenges addressed through this work are highly interdisciplinary including numerical, computational, modelling and electrophysiological aspects. The first application of this work is to enable the investigation of the impact of different degrees of ion channel block on the ventricular electrophysiology and the ECG using state-of-the-art 3D computational models.

2. Methods

2.1. From ion-channels to ECG

The forward problem of electrocardiography in complex cardiac geometries is challenging in terms of biological complexity and computational tractability. Here we employ a multi-scale modelling approach to the problem, which includes representation from the ion channel to the ECG level. The cardiac simulation framework Chaste was used to simulate propagation of the AP throughout the ventricles using the bidomain model. This set of two partial differential equations (PDEs) consists of a reaction-diffusion system, modeling the intra and extracellular potentials coupled through a nonlinear reaction term described by a system of ODEs representing membrane kinetics. In this case, the Faber and Rudy model, a set of 25 ordinary differential equations (ODEs) [1], was used to describe ion channel kinetics and intracellular ionic concentration changes, characterising the cellular action potential (AP) at each node. Cardiac electrical activity was simulated over a computational finite element mesh describing ventricular anatomy (Figure 1). Transmural differences in ionic currents were also incorporated into the model.

Outside the heart region, the space was modelled as a passive resistive network where electrical propagation obeys the Laplace equation. The ECG was extrapolated by plotting the potential over time at the surface of the control volume at a node located in proximity of the heart. The control volume representing the body was a regular cuboid within which the heart is immersed.

The main advantage of this multi-scale approach is the ability to bridge the gap between micro-scale (ion channel kinetics) and macro-scale (ECG). By using a detailed and biophysically-based cell model ([1]), it is possible to evaluate the impact of a variety of cellular parameters on the shape of the ECG. Here we present simulation results

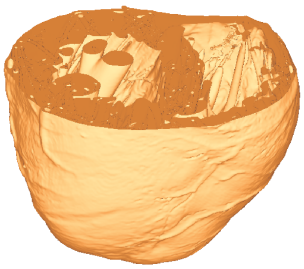

Figure 1. Anatomically-based ventricular model geometry.

showing changes in the ECG caused by alterations in the conductance of the delayed rectrifier K^+ current (I_{Kr}), due to its importance in drug-induced arrhythmogenesis (see for instance [2]). In the next sections, we describe the different components of the computational framework developed to conduct these simulations.

2.2. Chaste

Chaste is an open source cancer, heart and soft tissue parallel simulation environment developed using professional software engineering techniques and state-of-the-art computational tools [3]. Its C++ source code (and binaries) can be downloaded from `www.comlab.ox.ac.uk/chaste`.

Chaste is currently able to simulate monodomain and bidomain electrical activity in any cardiac model provided by the user or automatically generated based on a geometric description. Several ionic models are available for the description of the membrane kinetics. Additionally, any model implemented in CellML can be easily imported into Chaste by means of PyCML [4]. Chaste is able to generate fibre orientation data for any cardiac model based on the mathematical formulation of Streeter [5]. Different stimulation and pacing protocols are available. As well as the possibility of specifying different tissue parameters such as electrical conductivities and numerical techniques and parameters. All the simulation parameters are supplied to the Chaste executable through its XML configuration file.

2.3. The Nimrod Toolset

Exploration of the parameter space is usually required in studies of computational cardiac electrophysiology, and with 3D ventricular models, this becomes a challenging problem. The Nimrod suite of tools aim at addressing this issue and have been widely used for a variety of scientific applications [6] Nimrod/G [7] generates combinations of jobs, executing them on appropriate resources and coordinating the associated file transfers. Specification of the experiment is done via a simple text file that defines the parameters to vary, the values for these parameters and the commands needed to run the model and transfer files required or produced. Importantly, the user is shielded from the technicalities of the grid. Other items in the toolset are Nimrod/E, which selects a subset of a full sweep for a more parsimonious experiment, and Nimrod/O, which will optimise selected outputs of the computational model.

	Number nodes	Number cores	Total RAM	Network Technology
EG East	20	160	160GB	Infiniband
MSG	90	310	1272GB	Infiniband

Table 1. Computational resources used in this work.

2.4. Integration

The equations that arise in modelling the problem described in Section 2.1 are solved using Chaste. Refer to [3] for a complete description of the numerical techniques used. In order to investigate the impact of variation of I_{Kr} on the ECG profile, six values are evaluated from a control situation to a 50% inhibition of the ionic current. Traditionally, this would have required the investigator to (1) identify the computational resources available at his/her organisation, (2) set up six different simulations and (3) schedule them appropriately according to the resources available. Moreover, step (3) often can not be performed optimally since the investigator does not have a global view of the system and of its available resources at any given time.

In this work, the Chaste cardiac simulator was coupled to the Nimrod toolkit, in order to automate the three tasks described before and facilitate further investigations (Figure 2). The optimisation of resources allocation as well as the scheduling of the simulations is transparent to the user. In addition, Nimrod provides its own language for the definition of parameter sweeping studies.

Two clusters located at Monash University in Melbourne (Australia) were used to run the simulations presented in Section 2.1. Table 1 summarises their characteristics. Figure 3 shows our experiments described as a Nimrod execution plan. It should be noted that this execution plan is platform-agnostic and Nimrod is able to translate it into requests to the job scheduler of both clusters.

Chaste and its dependencies were installed in both clusters. This includes a certain number of libraries (i.e. MPI, BLAS, LAPACK, PETSc, HDF5, etc.) that were installed and tested separately. This process proved to be challenging due to the heterogeneity of the systems. Future improvements of this process could include moving to a dif-

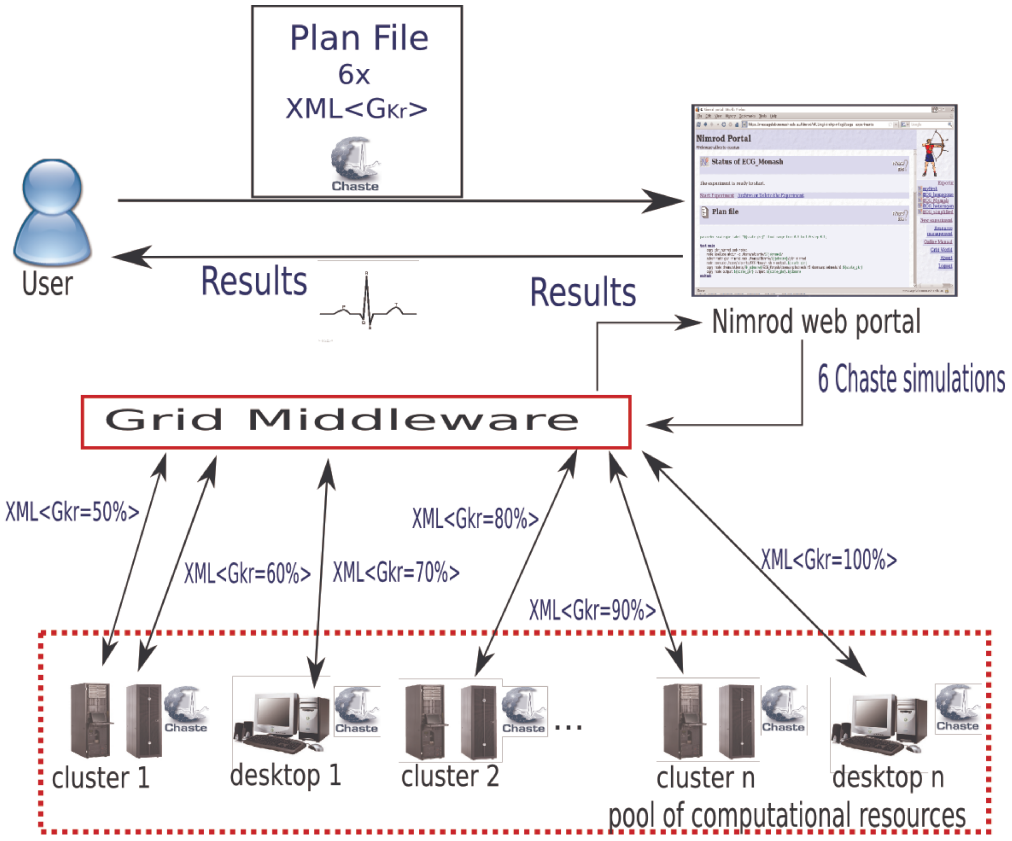

Figure 2. System interaction diagram.

```
parameter scale_gkr label "${scale_gkr}" float range from 0.5 to 1.0 step 0.1;

task main
   copy gkr_nimrod.sub node:.
   substitute gkr_nimrod.sub /home/alberto/${jobname}/gkr_nimrod

   node:execute /home/alberto/Chaste ${jobname}/gkr_nimrod > output.${scale_gkr}
   copy node:/home/alberto/${jobname}/ECG_simplified/EllipsoidInCube.h5 EllipsoidInCube.h5.${scale_gkr}
endtask
```

Figure 3. Nimrod execution plan.

ferent execution model, where Nimrod will have statically-linked versions of Chaste ready to run in most common architectures. Every time a job is sent to a new computational resource, an appropriate binary will be deployed. In a dynamic environment as the Grid, this will avoid installing Chaste and all its dependencies every time a new computational resource is added.

3. Results

Figure 4 presents the results of the experiment described in Section 2.1. The top panel shows different profiles for APs measured in an arbitrary cardiac cell located within the cardiac wall for different values of the I_{Kr} conductance (G_{Kr}). In the bottom panel we can see how the ECG signal recorded at a node in the medium surrounding the heart varies as the K^+ current is gradually blocked. Both results are consistent and show that the APD prolongation caused by the block of I_{Kr} directly translates in QT interval prolongation that can be appreciated from the ECG trace.

4. Conclusions

In this work we have successfully integrated a cardiac simulator with a Grid toolkit, and we have applied the newly created software pipeline for the simulation of multiscale processes in cardiac electrophysiology. As a proof

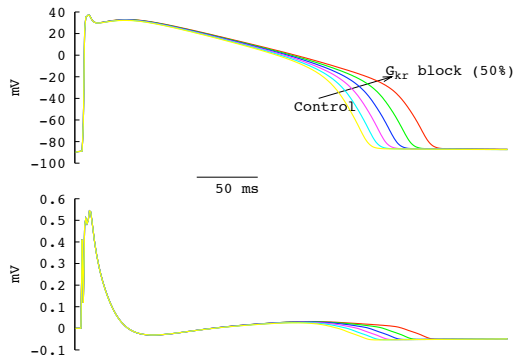

Figure 4. Simulation results. The top panel shows six cellular APs obtained with six different levels of I_{Kr} block (from control case to 50% block). Corresponding surface ECG traces are shown in the bottom panel.

of concept, we have shown that the application of such tools allows direct assessment of the impact of G_{Kr} on the shape of the ECG waveform. We believe this work will set the path for future highly computing-demanding studies on how cellular processes affect the overall cardiac mechanism.

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