Si-PEAC: A Simulation Platform for Electrical Activities of Cardiac Cells

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Abstract

With development of cardiac electrophysiology and computing power, various biophysically detailed computer models of cardiac electrical activity have been developed to simulate the electrical activities of cardiac systems at cellular, tissue and organ levels. In this study, we developed a modelling and simulation platform for electrical activities of cardiac cells (Si-PEAC) with aims to provide a user-friendly interface to study the ionic mechanisms underlying the genesis of cardiac electrical action potentials under various physiological and pathological conditions. The effectiveness of system is validated by editing and testing several popular cell models.

1. Introduction

Advances in cell biology and experimental technology have improved the understanding of underlying life behavior of cells and generated massive amounts of biophysical data. As an effective approach, a number of computational cell models based on different animal experimental data have been constructed and employed by cell biologists, bioengineer and other researchers to help them simulate, analyze and explain these data. However, the fact that there is no unified architecture or software system for these cell models, which were built by different groups with programming languages, obstructed profound applications of these models. So, developing a unified infrastructure or system for these cell models is pretty plausible, interesting and useful. In this study, we use object-oriented design patterns to reconstruct the architecture of these models, provide a XML description and editor to specify computational cell models and develop a modeling and simulation platform for electrical activities of cardiac cells (Si-PEAC) with aims to provide a user-friendly interface to study the electrical activities of cells under various physiological and pathological conditions. Several popular cell simulation software systems have been developed such as E-cell [1] and Virtual Cell [2]. Compared with them, our platform is designed for simulation of electrical activities of cardiac cells and provides some particular functions for analyzing electrical activities of cardiac cells such as automatically plotting the current – voltage relationship curve (I-V curve) and action potential duration (APD) restitution curve. A few cardiac cell models have been employed for testing and validating the Si-PEAC system including the Luo-Rudy model [3] for guinea-pig ventricular cell, the Nygren et al. model for human atrial cells [4] and the Zhang et al. model for rabbit sinoatrial node cells [5]. As a result, the Si-PEAC system conveniently and easily helps both cell biologist and mathematical modelers to build, validate, analyze and share their models.

2. Framework of Si-PEAC

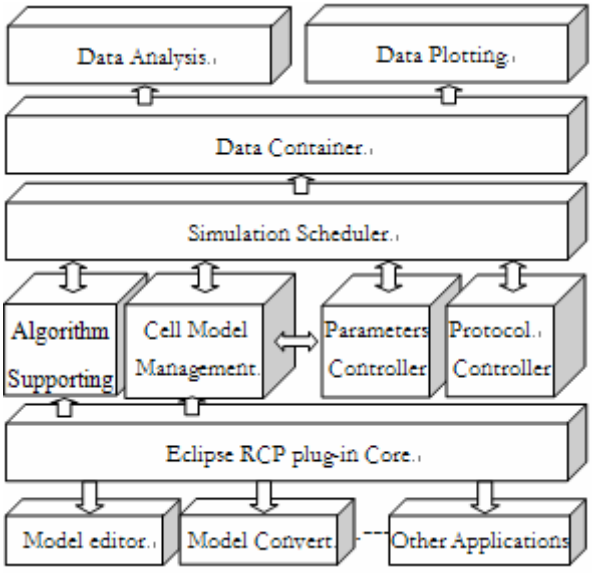

Figure 1. The framework of Si-PEAC. The platform is made of six layers from bottom to top. They are Extensible Applications Layer, Plug-in Layer, Simulation Computing Layer, Simulation Scheduler Layer, Data Container Layer and Data Expression Layer.

The framework of Si-PEAC consists of six layers (as

shown in Figure 1). Every layer is briefly illustrated from bottom to top as below.

1) Extensible Applications Layer

The layer is composed of some interfaces and programs for the larger scope or scale of the system. For example, the model editor is a program for defining cell models with XML language and the module of Model Convertor is developed for translating models depicted by XML language into executed Java code automatically.

2) Plug-in Layer

The rich client platform (RCP) plug-in Core, which is offered by the Eclipse project, is a powerful tool for developing pluggable and dynamically extensible systems. With the tool, all expandable applications can be built into our system easily and conveniently.

3) Simulation Computing Layer

The simulation computing layer is the core of the whole system. It consists of some important functional modules, which support simulation system, such as numerical computation, cell model management, parameters controlling and protocol controlling.

4) Simulation Scheduler Layer

The layer is responsible for interacting with customers, calling each simulation functional module and controlling the whole simulation process.

5) Data Container Layer

In order to satisfy requirements of post-processing of simulation data, the layer is designed for cataloging, organizing and managing these simulated data.

6) Data Expression Layer

The layer includes two parts data analysis and data plotting. Data analysis component has some basic statistic functions. Data plotting takes charge of plotting data and compares simulation data with experimental data.

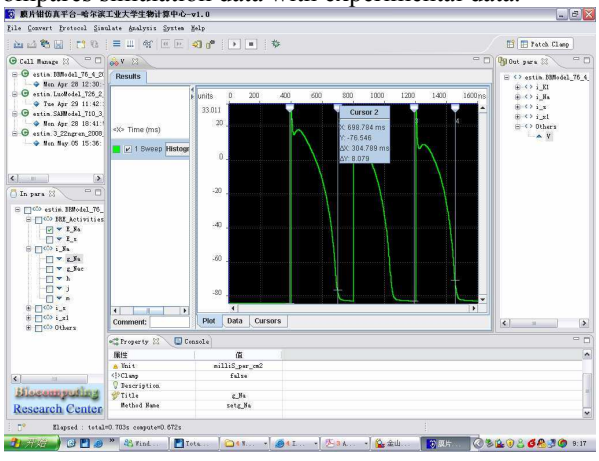

Figure 2. The graphical interface of Si-PEAC.The cell manager view (upper left) is the field to select one cell model to simulate. The input view (bottom left) is the area to select which parameters of current cell model need to be set or updated before simulation. The plotting view (middle) shows the graphs or tables of simulation results. The output view (right) is the field to select one or two output parameters to be ploted. The console view (bottom) is the field to set input parameters of cell models and show some messages during the simulation process.

3. Features of Si-PEAC

Si-PEAC platform distinguishes itself with the following significant features.

• User-friendly interface (UI)

It provides a user-friendly interface (as shown in Figure 2). The UI shows all input and output properties of a cell model such as gated variables, individual ion current, and membrane action potentials, which can be computed by the platform automatically. Simulation results can be outputted as graphs and tables in the middle of the window. Customers can define the outputted content by themselves on their interested parameters, directly get the value of a point or the distance between two interested points with cursors and draw their interested field through mouse to resize and repaint the graphs.

• Virtual voltage-clamp experiments

It performs virtual voltage-clamp experiments (as seen in Figure 3). The voltage-clamp is very important technique to investigate ion channel properties of cells. It measures the ion currents cross cell membrane with various voltage steps and plots activate or inactivate curves of ion channels. The system permits that users freely define their voltage clamp protocol with square, sine/cosine or stochastic signals. When the protocol is implemented, changes of individual ion current under voltage clamp protocol and the I-V curve can be generated automatically through the platform.

• APD restitution curve plotting

It is known that the steepness of APD restitution has played a critical role in stability of cell models. Therefore, there is a built-in algorithm to compute APD restitution curve (as depicted in Figure 4). Standard protocols including the s1-s2 protocol and the dynamic protocol have been programmed in the software to investigate the relationship between APD and a variety of stimulus time intervals. Customers need manipulate a couple of cursors to define scope of each APD, and the APD restitution curve can be characterized automatically.

• Simulation of drug actions or diseases

It performs simulations of drug actions or diseased conditions. The reason of changes of electrical activities of cells is generally known as unusual kinetics mechanism of ion channel. The system can easily model and simulate the hypothesis of complicated physiological

and pathological conditions by blocking ion channels thoroughly or partially, changing of intercellular or extracellular ion concentrations and redefining properties of activation or inactivation of ion channels.

• Edition or updating of cell models

It provides a useful function of editing or updating cell models by an extensible application program myocardiacal cell modeling language (MCML) editor, which comes from another project held by our group [6]. Cell biologists and computational modelers do not need write any code and just need some simple operations of mouse and keyboard to build their cell models through the MCML editor (as illustrated in Figure 5). There is another extensible application program the Model Convertor modules, which automatically translates cell models into executed Java codes.

• Models and data importing or exporting

It is easy to perform model updating based on newly available experiment data. Experimental data can be imported into this system with .txt files or .jpg files. The users can modify parameters or variables of cell models based on the experimental data, or validate their simulations against the data.

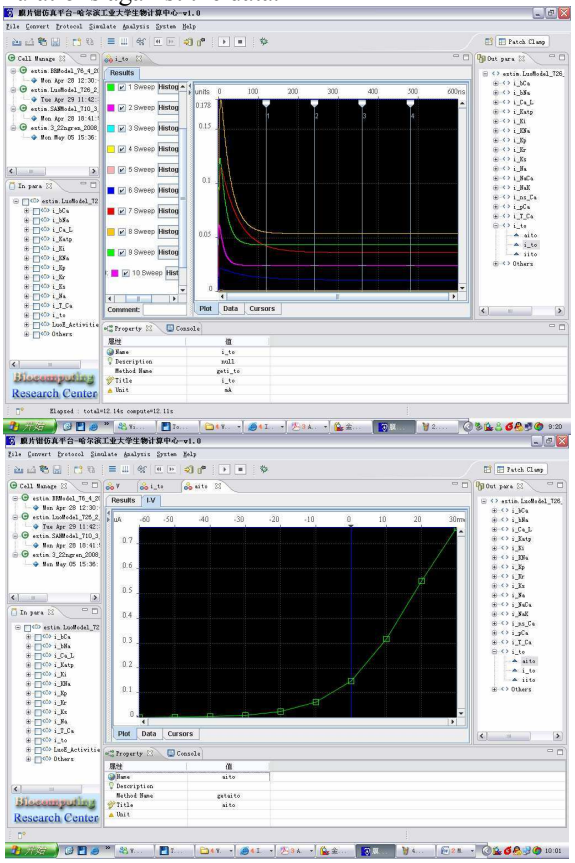

Figure 3. I-V curve Simulation. It separately shows the simulation results of ion currents (top) and active curve of the ion channel (bottom) computed by the Luo-Rudy cell model under 10 various voltage steps from -60V to +40V.

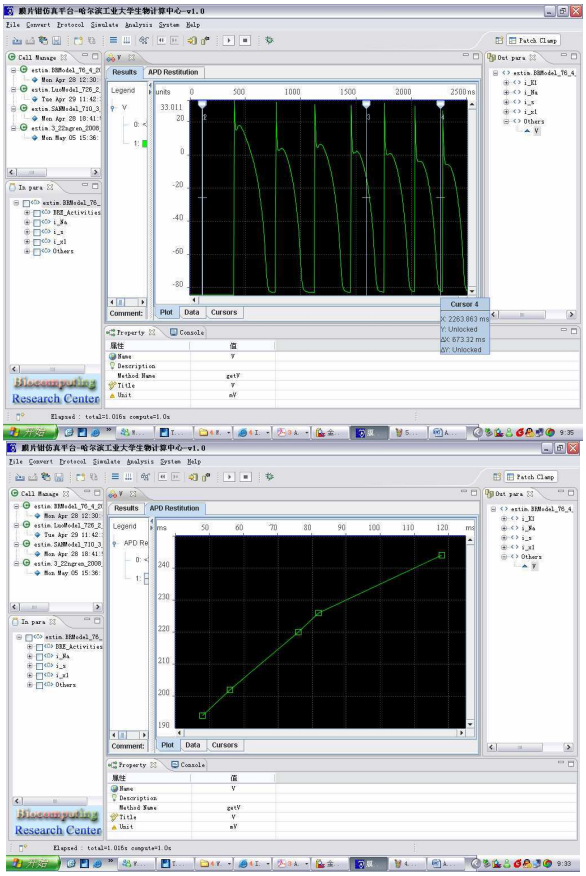

Figure 4. APD restitution curve simulation. It separately shows the simulation results of APs (top) and APD restitution curve (bottom) computed by the BR model under S1-S2 stimulus protocol.

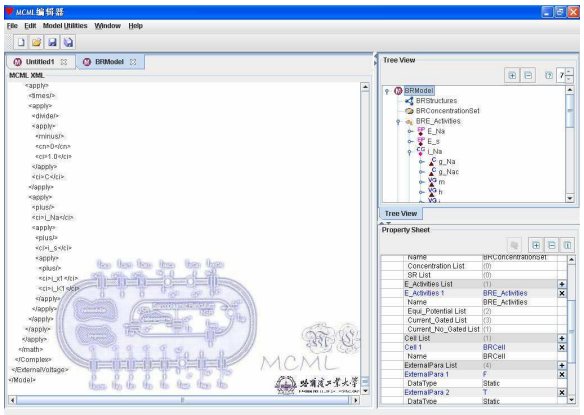

Figure 5. A snapshot of MCML editor. The code view (left) shows the XML code automatically generated with user's cell model description. The node view (top right) is the field to append or to delete different type nodes of

cell models with definition of MCML. The properties view is the field to set properties of currently edited node. All operations to define a cell model are complete by some simple mouse or keyboard input.

4. Discussion and conclusions

The Si-PEAC platform is designed for cell biologist and mathematical modelers in that it enables the construction of computational cell models in a user-friendly manner and validating their models with simulation or experimental data. The system is developed by Java programming and is compatible to Windows and Linux systems. So far, Si-PEAC has been tested for different cell type models that include the Luo-Rudy model for ventricular cell, the Nygren et al. model for human atrial cells and the Zhang et al. model for rabbit sinoatrial node cells. In conclusion, Si-PEAC provides a powerful tool to study the electrical activities of cardiac cells and the ionic mechanism(s) underlying the genesis of cardiac action potentials.

Acknowledgements

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