Developing Cardiac Cell Models (Kyoto Model) on simBio

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1 Introduction

Computers have become the necessities of life science with improvements of information technologies. Thus, Systems Biology, whose aim is to describe the whole biological interactions as a mathematical model and understand the whole mechanisms by simulation, has been emerged. We, Cell/Biodynamics simulation project of Kyoto University [1], have started developing a comprehensive cardiac model (Kyoto model) for medicine and pharmacy.

2 simBio

We have been improving mathematical models using our hand-made tool, simBio [2]. Biological systems are simulated on simBio using Java classes, which describe mathematical representation of biological functional units, and XML files, which define interaction and initial values of functional units. Every animal experiment is designed to apply some interventions and analyze reactions. In silico experiments, it can be replaced by applying variable parameter set and analyzing model behaviors. So, it will be needed to visualize the model behaviors in the parameter space.

3 Cardiac Cell Model (Kyoto Model)

3.1 Excitation-Contraction Coupling Model

We have reported the excitation-contraction coupling model of guinea-pig ventricular myocytes in 2003 [3]. The functional components, of which the Matsuoka 2003 model consists, are displayed on the tree table of graphical user interface of simBio, when open the model xml file. Under the model tree, ion concentrations in the external solution, the stimulus, and the cell are defined. The cell consists of the ATP synthesis, the Ca buffer, the contraction model, 18 types of membrane currents, Sarcoplasmic Reticulumn (SR), 4 types of SR currents.

3.2 Pacemaker Model

One of the features of Kyoto model is that the ventricular cell [3] and the pacemaker cell model [4] are described with the common set of equations. It reflects the idea that the common functional proteins with different expression will result in the different phenotype of a cell. In the xml file of the pacemaker model, functional units are presented as followings;

<compartment name="model" initial_value="0.0" className="org.simBio.bio.matsuoka_et_al_2003.Compartment">
Each component has a name, an initial value, a units, and a class name, which points to the mathematical equations written in the Java class. So the common Java classes, thus equations, are used in different contexts.

3.3 Excitation-Contraction-Metabolism Coupling Model

Next, we included the mitochondria model, and develop the excitation-contraction-metabolism coupling model [5] to study energy homeostasis in working heart. It is apparent in the xml files that the ATP related substrates and the mitochondria model are added to the Matsuoka 2003 model [3] to compose the Matsuoka 2004 model [5].

3.4 Volume Regulation Model

Next, we proposed the volume regulation model [6], which is pivotal function for all kind of cell. After creating a model with the minimum set of functional units for volume regulation, a comprehensive cardiac cell model was composed and tested. Then, the simplified model or single functional units were refined at every cycle of improvements.

4 Discussion

In our Cell/Biodynamics simulation project of Kyoto University, biological systems are modeled on computers from enormous amounts of medical and biological knowledge. To develop a mathematical model by evaluating experimental data and composing equations is the same thing as to understand biological mechanisms. In modeling process, hypothesis will be derived from a model and new experiments will be conducted. It will also be possible that a model will digest striking experimental results and enable us to understand the mechanisms instead of conventional mental discussions. Furthermore, we may prospect biological behaviors to interventions by the model. A model may able to represent one aspect of complex biological systems, but it will help mental models and lead a comprehensive understanding with adding multiple aspects.

References


