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# A Platform for in silico Modeling of Physiological Systems III.

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*Abstract*— **Physiome and systems biology have been recognized as emerging and important research areas that can integrate quantitatively growing knowledge about biological structure and physiological functions at multiple scales of time and space. For the integration, it is important to build physiologically plausible and sharable mathematical models that can be used for dynamic simulations of functions at multi-scale and multi-level. Here we describe new features of our open platform *insilico*ML (ISML) and *insilico*IDE (ISIDE) that have been presented previously. The platform can support reuse existing mathematical models of physiological functions in the model databases, to construct brand new models, and to simulate models. The major new features of the platform include improvement of the capabilities to incorporate experimentally obtained data such as time-series and morphological data with dynamic simulation of models that may be driven by the data, and extension of variety of model types that can be described by ISML and simulated on ISIDE, such as multi agent systems and models described by partial differential equations that are solved by the finite element method.**

## I. Introduction

PHYSIOME project in its early stage aims at establishing a framework of describing, databasing, and sharing the human knowledge about biological structure and physiological functions at multiple scales of time and space for integrating every piece of knowledge quantitatively [1, 2]. Systems biology markup language (SBML) [3] and CellML [4, 5] have promoted pioneering efforts to establish the framework. Models written in SBML and CellML formats are registered on their model repositories, and can be downloaded from there. In parallel with these efforts, we have proposed *insilico*ML (ISML) [6] which is a XML-based description language for mathematical models of physiological functions, and developed the integrated development environment: *insilico*IDE (ISIDE) that can be used as a composer, viewer and simulator of models, and a database called *insilico*DB (ISDB) to store ISML models [7]. Our open platform directing towards the physiome project is composed of these three pieces, *i.e.* ISML, ISIDE, and ISDB.

Ordinary differential equations (ODEs) are often used for describing dynamics of physiological functions. Membrane potential dynamics of cellular membranes, compartment model of pharmacokinetics, and mechanical dynamics of human body are such examples. So far, our open platform provides a user friendly graphical interface to built and simulate ODE models and those models have been registered in the ISDB. However, there are varieties of physiological phenomena which can be modeled by mathematical expressions other than ODEs, such as partial differential equations, rule-based system. In order to deal with and perform simulations on those models, we are developing novel new features on the platform.

This paper is an extension of our previous report [7]. Here we illustrate the open platform focusing only on our recent progresses that include:

- A framework for Multi Agent Simulation
- A framework for time-series data driven simulation
- A framework for Finite Element Method simulation

## II. Platform Outline

### *insilico*ML / *insilico*IDE / *insilico*DB

ISML is a XML based description language, in which each of elements constructing a model is called a *module*, and relationships between *modules* are defined as *edges* which are categorized into two types, *i.e.* structural and functional relationships. Each *module* is quantitatively characterized by several constant or variable parameters and morphology data which are defined as *physical-quantities* in the ISML format. During a simulation, variable *physical-quantities* change their values according to mathematically defined dynamics. *Modules* can affect each other quantitatively by transmitting values of *physical-quantities*. A value of a *physical-quantity* goes out through an *output port* which is placed on a *module*, and is received by other *modules* via their *input ports*. These ports are connected by the functional relationship of the *edges*.

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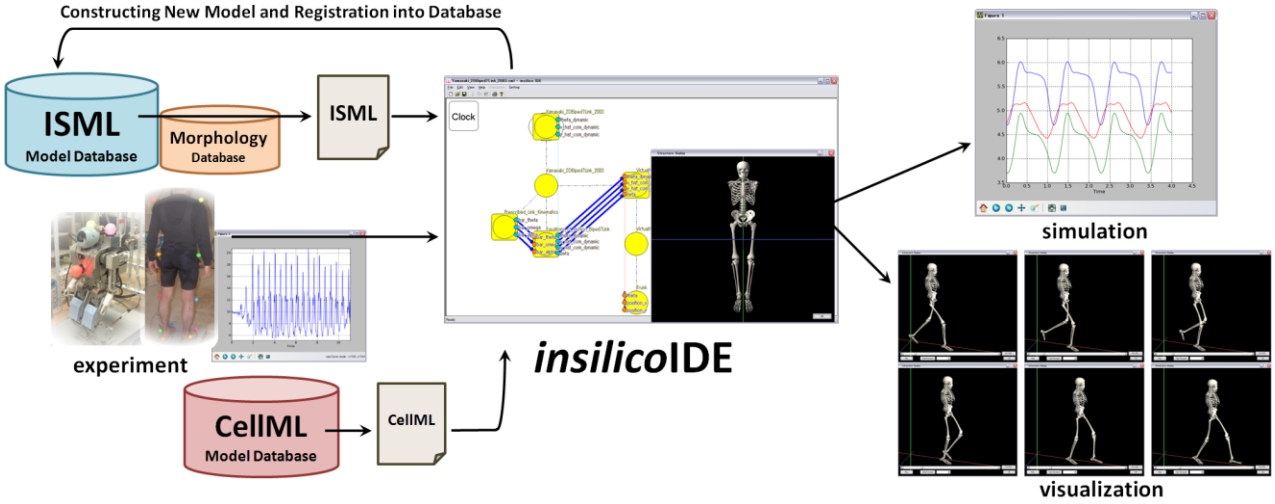


Fig. 1. Overview of the platform
Models written in the *insilico*ML (ISML) format are registered into *insilico*DB (ISDB) with morphology data. *insilico*IDE (ISIDE) is a model composer, model viewer, and simulator. ISIDE can import and export mathematical model which is described in the CellML format too. Additionally, ISIDE can deal with the time-series data for not only visualization but also simulation. ISML, ISIDE and ISDB are main actors of our open platform.

ISIDE provides a graphical user interface which allows the users to construct models intuitively. Models written in the ISML format are registered into ISDB. Anyone can download models from ISDB (http://physiome.jp), and reuse them on ISIDE to construct their own models (Fig.1). To perform simulations, ISIDE converts ISML models into C++ source codes including solver algorithms such as Euler, Runge-Kutta methods for solving ODEs.

## III. Extended Features

### A. Multi Agent System

Multi agent system (MAS), which is referred also to as self-organized system, is a system composed of multiple interacting agents whose behaviors are defined individually. Each agent has autonomy and agent-agent and agent-environment interactions. MAS is suitable and useful for modeling motion of individual elements in a system that include appearance and disappearance of the elements.

For example MAS is used for modeling dynamics of calcium ions in the dyadic space which is very tiny space between T-tubule and sarcoplasmic reticulum (SR) in the cardiac cell [8]. Figure 2 shows an example of MAS simulation similar to [8] on our platform. In this case, ions and ion channels are modeled as different type of agents, and the cell membrane is considered as the environment. The number of ions during the simulation needs to vary according to the circumstances (such as influx and efflux through the ion channels), although the description of ISML is static and thus number of *modules* representing ions written in the ISML model is constant. ISML can define conditions for event occurrence for each *module*, by which every module (*i.e.* ion in this case) can detect the proper timing to evoke a signal for a certain action during the simulation. ISML can also define a *controller* which receives signals from modules and makes actions such as construction and destruction of agents dynamically during the simulation. A sample ISML description defining a *controller* is as follows:

```
<is:event event-id="..." type="...">
  <is:call controller-id="..." operation-id="..." />
  <is:situation>
    <is:definition>
      situation expression (such as membrane potential reaches the threshold)
    </is:definition>
  </is:situation>
</is:event>

<is:controller controller-id="...">
  <is:template module-id="..." />
  <is:operation-set>
    <is:operation operation-id="..." type="...">
      <is:situation> called </is:situation>
      <is:count> count of agents </is:count>
      <is:initialization>
        initial state information (such as position, initial velocity)
      </is:initialization>
    </is:operation>
  </is:operation-set>
</is:controller>
```

In the MAS simulation shown in Fig. 2 (a) the channels are modeled by a Markov model. When the channel is at an 'open' state, there is stochastic influx of ions through the channel, more precisely, the channel evokes a signal corresponding to creation of instances of ion objects during the simulation. Every state in the Markov model and transition rules can be defined in a *physical-quantity* in a module in the ISML format. Figure 2 (b) shows the number of ions in the dyadic space as a function of time. We can calculate the ionic concentration in the space at every time step which can be used for bridging between different types of models such as the one described by ordinary differential equations.

### B. Simulation Using Time-Series Data

Incorporating experimentally recorded time-series data into dynamic simulations of models is a useful and powerful method to investigate dynamics of target physiological functions, and plays a significant role for combining theoretical models and experimental studies.

In the ISML format, time-series data can be assigned to a physical-quantity. This means that, if a data is kept in a separate file, a reference to the data file is described as a definition of a *physical-quantity* of a module. During a

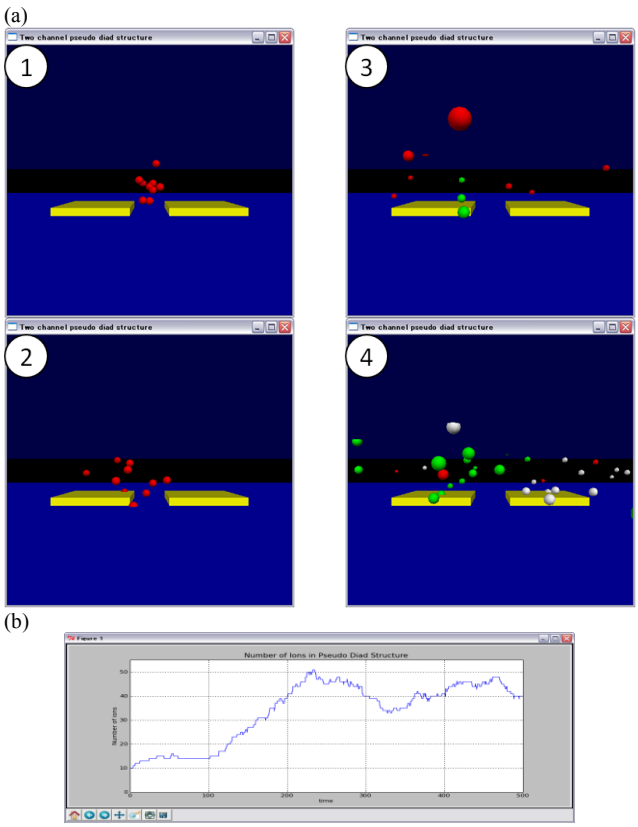


Fig. 2. Multi agent simulation
(a) Snapshots of animation of ion diffusion simulation in a dyadic space. Ions are generated from channels when the state of channels is "open", and diffuse in the tiny space. When ions flow out from the area for the simulation, they are removed. If ions hit to walls, they bounce back. (b) The number of ions presenting in the dyadic space.

simulation, the value of the *physical-quantity* associated with time-series data is updated from the data file at a proper timing that is determined according to the time step of the time evolution and sampling interval of the time-series data. Once a value in the time-series data is assigned to a *physical-quantity* of the module, it can be available even for other modules that are linked to the *module* by functional *edges*. A sample ISML description to include a data file is a follows.

```
<is:physical-quantity type="variable-parameter" physical-quantity-id="•••">
  <is:implementation>
    <is:definition type="assign" sub-type="timeseries">
      <is:reference timeseries-id ="•••" record-id ="•••" />
    </is:definition>
  </is:implementation>
</is:physical-quantity>
</is:physical-quantity>

<is:timeseries-set>
  <is:timeseries timeseries-id="•••" type="external">
    <is:insilico-attribute iref ="../../•••.xml" />
  </is:timeseries>
</is:timeseries-set>
```

Figure 3 shows a schema of an action potential clamp experiment of a cardiac cell *in vitro* and *in silico* with ISIDE. The membrane potential of the cell is clamped to the experimentally recorded time-series data of an action potential. In Fig. 3, there are two *modules* representing a stimulator and a cardiac cell modeled by a modified Faber Rudy model [9]. The time-series data of an action potential time course is assigned to a *physical-quantity* in the stimulator *module*. The calcium ion current through an L-Type calcium channel over a single action potential was observed. The most right panel in Fig. 3 shows the calcium current time profile in response to the time-varying clamped voltage.

### C. *Finite Element Method Simulation with Morphology data*

Morphology of a biological entity provides a basis of physiological functions. In models of physiological functions morphology data define boundaries of a space for agent-based simulations, a shape of a medium on which electrical excitation propagates, a domain on which partial differential equations (PDEs) are solved, and so on. Morphology data can be defined as a *physical-quantity* in a *module* in ISML, and be shared between *modules* linked by functional *edges* similarly

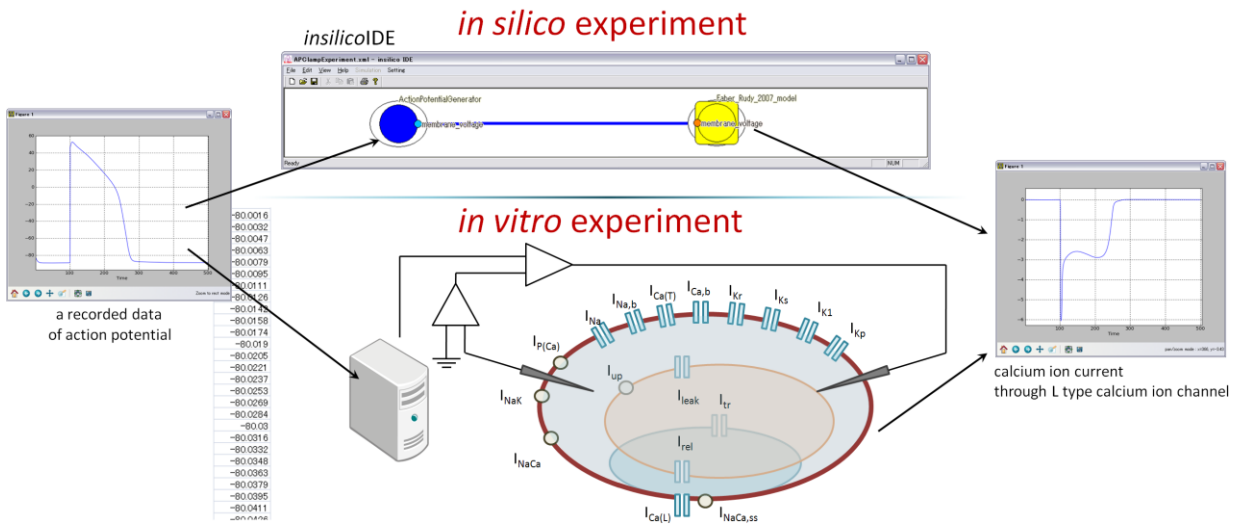


Fig. 3. Utilization of time-series data in modeling and simulation
The time-series data can be assigned in a module and used in simulation. The figure shows a model of action potential clamp experiment, as an example, which is a technique to investigate the cell activity. Membrane voltage is clamped to values given by time-series data. An ionic current through a channel is measured. ISIDE can simulate this experiment. A module which is associated to time-series data updates its state according to the data, and sends the value to the other module representing a cell membrane.

to any other *physical-quantities*. The morphology data can be described either by mathematical equations, such as $0 \le x \le 1$ and $0 \le y \le 1$ representing a square field or by an aggregation of spatially-discredited vertexes in a finite element method mesh format. The data can be written either in the ISML model or in a separate file. In the latter case, the reference to the data file is written in the ISML model. Governing equations are written in the MathML format at *physical-quantities* in *modules* connected by structural *edges* to the *module* having the morphological data.

To solve the PDE we used the finite element method (FEM)

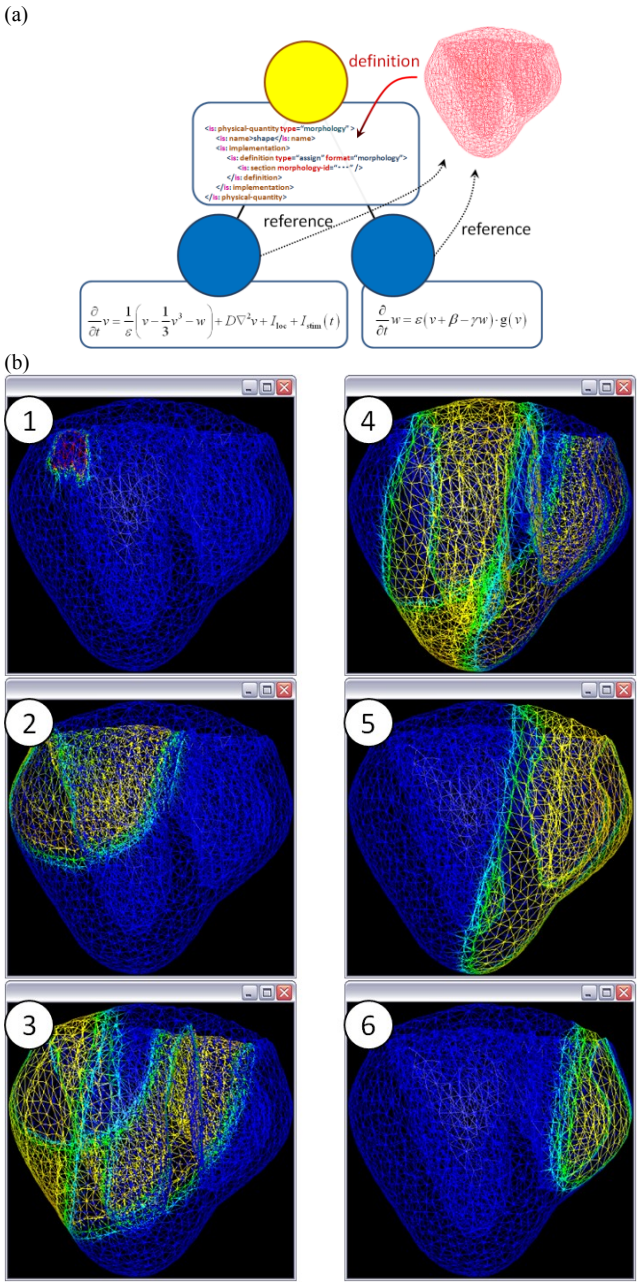


Fig. 4. Action potential propagation on the 3-dimensional heart model (a) Morphology data can be assigned to physical quantities in ISML, and used as domain in which PDEs are solved, constraint conditions and so on. (b) ISIDE can export the model including mathematical expressions and morphological data into a solver format of finite element method.

which requires morphology data for defining the domain, PDEs as governing equations, initial conditions and boundary conditions. ISIDE can export a model including mathematical expressions and morphology data into the freeFEM format, which is a free FEM solver developed at Pierre et Marie Curie University [11]. PDEs are transformed into the weak form in the conversion process.

Figure 4 exemplifies a simulation of excitation propagation on a heart. The morphology data is given as an object with triangulated mesh. Each node of the heart represents an excitable medium modeled by FitzHugh Nagumo model [10] with its PDE formulation. The ISML model was converted into the freeFEM format and was numerically integrated by freeFEM.

## IV. Conclusion

Our project has been proposing the open platform composed of a model descriptive language "*insilico*ML", integrated development environment "*insilico*IDE" and model database "*insilico*DB" for developing the multi-scale and multi-level models of physiological functions. Through recent progress, we augmented the capability of this platform.

Our platform is still under development and improvement. Nevertheless, it can be used by the users as a tool for understanding the physiological phenomenon through multi-scale modeling and simulations. The platform and models are freely available at the project's official website [12] http://www.physiome.jp/.

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