
Enjoy Biophysical Simulation on *insilico*IDE

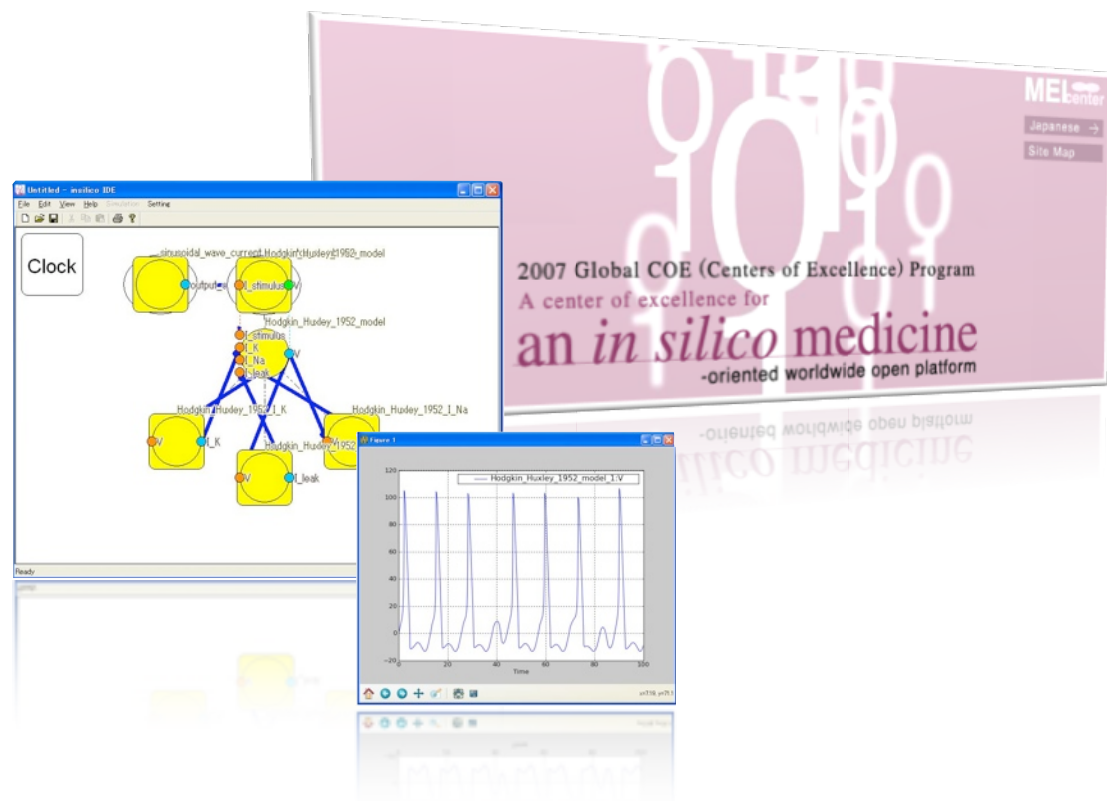
“in silico Medicine” Spring School 2009

Course on Computational Biology and Biomedical Engineering

Yoshiyuki Asai, Yasuyuki Suzuki, Taishin Nomura

The Center for Advanced Medical Engineering and Informatics, Osaka University

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INTRODUCTION

The *insilicoIDE* (ISIDE) has been developed by “*in silico* Medicine” project at Osaka university aiming at supporting to construct multi-level and multi-scale models of biophysical functions. The models are written in the *insilicoML* (ISML) which is a descriptive language based on XML (eXtensible Markup Language). Details of these technologies are available on the website <http://www.physiome.jp>. In this site, one can find also the Model database and Morphology database.

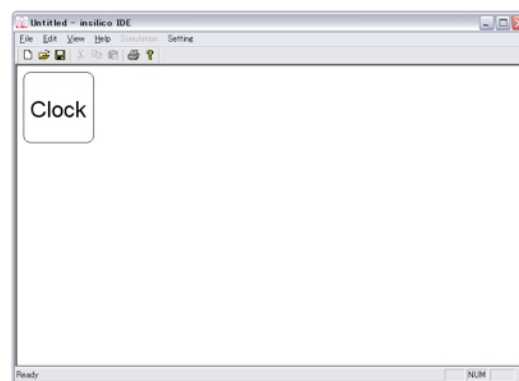


Figure 1. A main window of the ISIDE.

Open *insilicoML* file

This tutorial shows how to enjoy sample models which are included in the archive of the ISIDE which is available on the web site

<http://www.physiome.jp/downloads/index.html>.

At first, launch the ISIDE by double clicking the file *insilicoIDE.exe*. You can see a white canvas as shown in Fig. 1.

Select [File]-[Open New File] in the Menu-bar (Fig. 2) at left upper side of the window to open an ISML model. If there is already a model on the canvas, this operation clears the currently edited model at first.

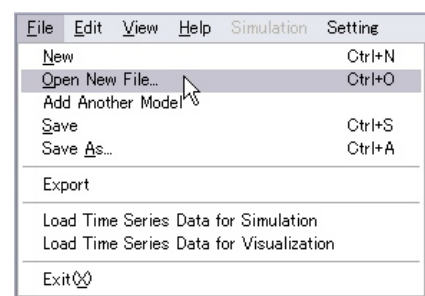


Figure 2. A context menu

Add ISML file

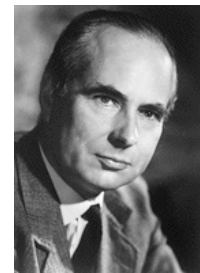
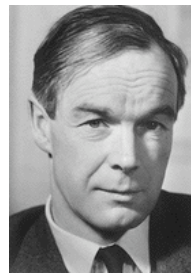
If users select [File]-[Add Another Model] from the menu (Fig. 2), the specified model is added into the currently edited model as one component.

Then a dialog for setting simulation environment appears in which users can set the time unit and so on. Click [OK] button for continuing to edit the model.

HODGKIN HUXLEY MODEL

What is Hodgkin-Huxley model?

A. L. Hodgkin and A. F. Huxley formulated an excitation of neuron membrane by four coupled differential equations in 1952. Later they received a Nobel prize in physiology for their research in 1961.



Alan L. Hodgkin Andrew. F. Huxley

They investigated the membrane potential and currents through the membrane of the squid giant axon, which runs from the head to the tail



Giant axon of squid

(yellow one in the left figure). The axon can approach 1mm diameter (typically 0.5 mm) and controls part of the water jet propulsion system which is used to very fast movements, like escape from predators.

On the axon electrical pulses propagates (so called *spikes*), which are main carriers of the information in the nervous system.

A. L. Hodgkin and A. F. Huxley determined that the membrane potential can be calculated by an integration of three major currents, i.e. voltage-dependent persistent Potassium ion (K^+) current, voltage-dependent transient Sodium ion (Na^+), and a leak current which is considered to be mainly carried by Chloride ion (Cl^-), but at the same time to represent other channels which are not described explicitly.

Let's begin

Load `Hodgkin_Huxley_1952_model.xml` file into ISIDE. Then, one object composed of circle and yellow square appears on the canvas of ISIDE, which represents a graphical notation of the model, referred to as a Module (Fig. 3).

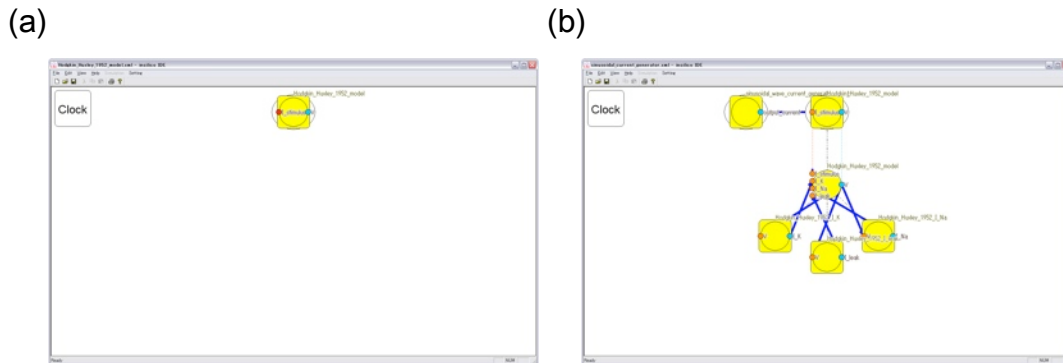


Figure 3. (a) A module representing a hodgkin-huxley model imported into the canvas. (b) Modules in under layers of the Hodgkin-Huxley model. Three modules at the lowest level correspond to, respectively, K^+ , Leak, and Na^+ channel currents.

Usually a model is composed of an aggregation of modules. By considering a group of modules as like one module, a hierarchical structure of a model is represented. ISIDE can show users the under layers of the model by double clicking the module as shown in Fig. 4. Relationships between modules are indicated by lines called Edges with several types.

This model needs an external stimulus current for performing simulation. Add a new model which provides a sinusoidal stimulus current. The file name of the stimulator is `sinusoidal_current_generator.xml`. (Note: do not use [Open New File] instead of [Add Another Model]. Otherwise the Hodgkin-Huxley model is replaced by the stimulus model). Then as shown in Fig. 3(b), a new module labeled as `sinusoidal_wave_current_generator_membrane` appears beside the module of the Hodgkin-Huxley model. The stimulus module outputs a current via an output port graphically represented as a small blue ball at the right-hand-side of the module.

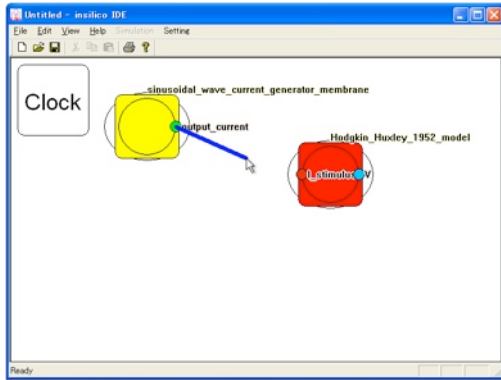


Figure 4. Spanning an edge between two ports.

Now we want to make a connection between these two modules. More precisely we will input the current generated by the secondly added stimulator module to the Hodgkin-Huxley module. To make a functional (input-output) relationship between the stimulus module and the Hodgkin-Huxley model module, drag a mouse pointer with pressing left button from a blue small circle on the stimulus module to a orange small ball (input port) at the left-hand-side of the Hodgkin-Huxley model module, which is named I_stimulus. Then these two ports (blue and orange) are connected by a line called a functional edge, meaning that sinusoidal stimulus from the stimulus module is given to the Hodgkin-Huxley model via the input port.

Finally we draw a graph of the dynamics of the membrane potential. At first select an output port of the Hodgkin_Huxley_1952_model module labeled as V by a single click on the port. Then select [Show Simulated Waveforms] in the context menu that appears by right clicking on the Module (Fig. 5). Then, the model is simulated in background and the new dialog appears in which a graph of time-series of the membrane potential is displayed as shown in Fig. 6.

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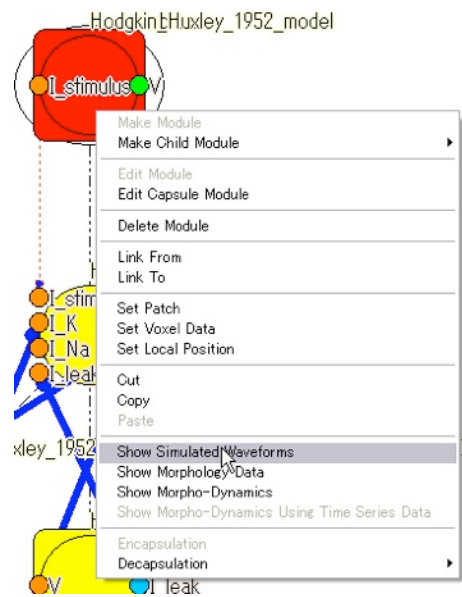


Figure 5. Performing a numerical calculation on ISIDE

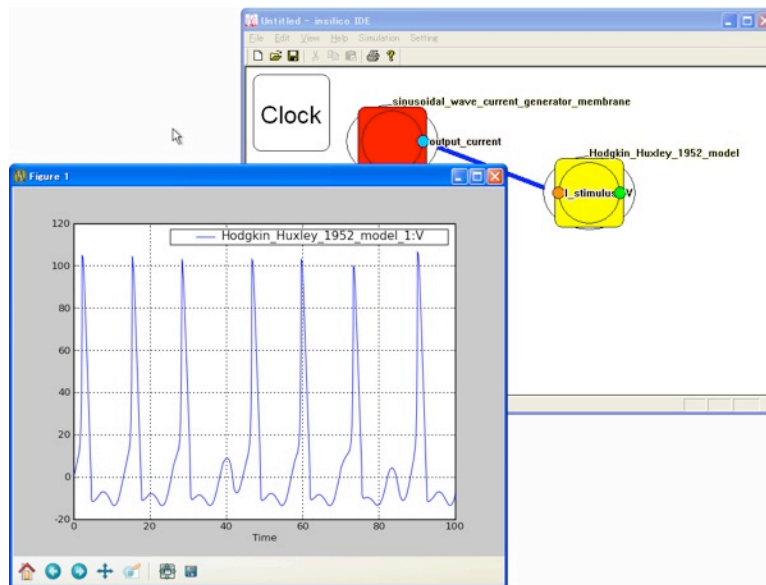


Figure 6. Simulated waveform. Numerical computation is done background.

Play more

Physiome.jp has been established to provide building blocks useful to develop *in silico* human. The blocks will include mathematical models and experimental data representing physiological functions. Physiome.jp is a part of the Worldwide Integrative Biomedical Research Cooperation to promote Physiome and Systems Biology. The building blocks (modules, models, biological data) representing biological functions and structure are databased and served as elements in the catalogue of human knowledge.

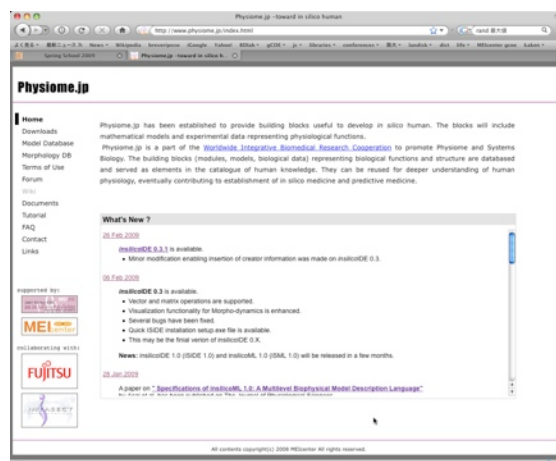


Figure 7. <http://www.physiome.jp>

Visit <http://www.physiome.jp> by any internet browser. Users can download the latest ISDIE from Downloads in this site. Now we visit Model Database instead, and search a current pulse generator which will be used as a stimulus

generator to the Hodgkin-Huxley model. Use “pulse” as a keyword to search in “description” category. You will find several items as search results in the model database. Here we download a model named `current_pulse_generator_membrane`, which will appear as a file named “inSilicoML-RMID164.xml” after downloading. You can drag & drop the downloaded file onto the canvas. The ISIDE asks about the setting of clock for numerical calculation. Default is fine for the moment.

At first, let us remove the edge between sinusoidal wave current stimulus generator and the Hodgkin-Huxley model. Right click on the edge, and select Delete Link. Then make a new edge from the output port of the current pulse generator to

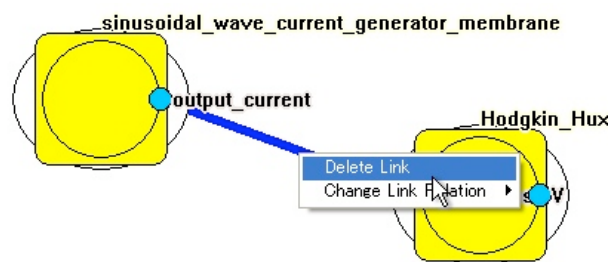


Figure 8. Delete an edge

the input port on the Hodgkin-Huxley model. Select the output port V on the Hodgkin-Huxley model. At the same time, this time, select the output port of the stimulus generator with pressing CTRL key. Users can select multiple ports simultaneously to view their dynamics. Select [Show Simulated Waveforms] again in the context menu as above (Fig. 5). Figure 9 shows the results of the simulation with a pulse current stimulus.

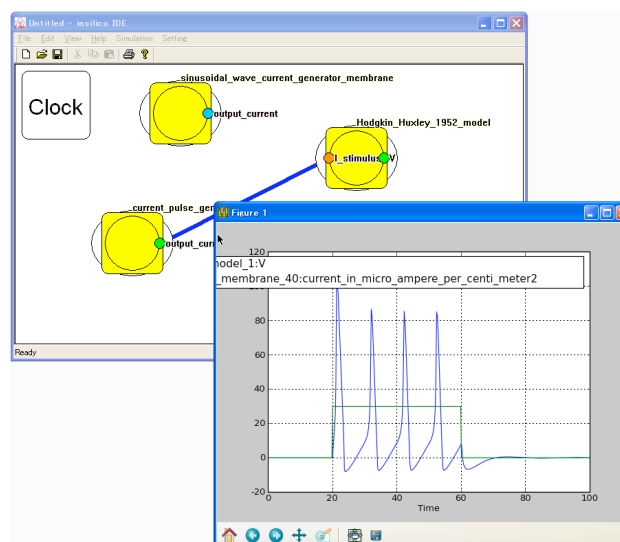


Figure 9. The dynamics of the Hodgkin-Huxley model receiving a pulse current. Blue and green graphs show the membrane dynamics of the Hodgkin-Huxley model and the pulse stimulus current, respectively.

What we do in the above operation is building up experimental environments as like building lego blocks. At first we stimulate the Hodgkin-Huxley neuron model by a sinusoidally oscillating current. This is the first experiment to observe the reaction of the membrane potential to such a stimulus. In the second experiment, we used a pulse current as stimulus to the neuron model.

As the last example with Hodgkin-Huxley model, let us construct a coupled two Hodgkin-Huxley model which is the very simple caricature of a neural network, but still can be the first step to investigate the complicated neural network. Let us start with the Hodgkin-Huxley model receiving a stimulus from the current pulse generator (delete the sinusoidal current generator).

In this coupled model, two Hodgkin-Huxley models are connected by a gap junction (Fig. 10), which is a mechanical and electrical intercellular connection. At gap junctions, the intracellular space is very narrow (25 nm to 3 nm), and two membranes are penetrated by channel proteins like tunnels. According to the difference in the membrane potentials of the cells attached to each other, a current flows through the gap junction. This electrical connections (called electrical synapses) by gap junctions are found in certain locations in the brain where require the fast response, such as defensive reflexes, and are particularly important in cardiac muscles.

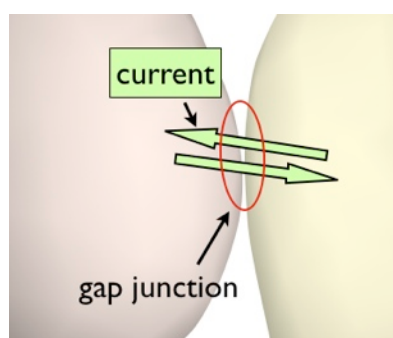


Figure 10. A schema of a gap junction. Currents flow bidirectionally according to the difference of the membrane potentials of both cells.

First of all, we create a module of the gap junction, which takes membrane potentials of both neuron models as inputs and calculates the currents according to the difference of the potentials. The module outputs two currents to input to both of cells separately.

Select [Make Module] from the context menu appeared by a right click on the white canvas. In the pop-upped window, select "Function" for module type, set name such as "gap_junction". Go to the "Parameter" tab and create a new parameter as shown in Fig. 11(a), i.e. Name: G, Data Type: double, Unit: milli_siemens_per_centimeter2, Parameter Value: 0.1. Press Add button.

Next, go to “Input Port” tab to create two input ports to receive membrane potentials of cells. In Fig. 11(b), input ports V_1 and V_2 are created.

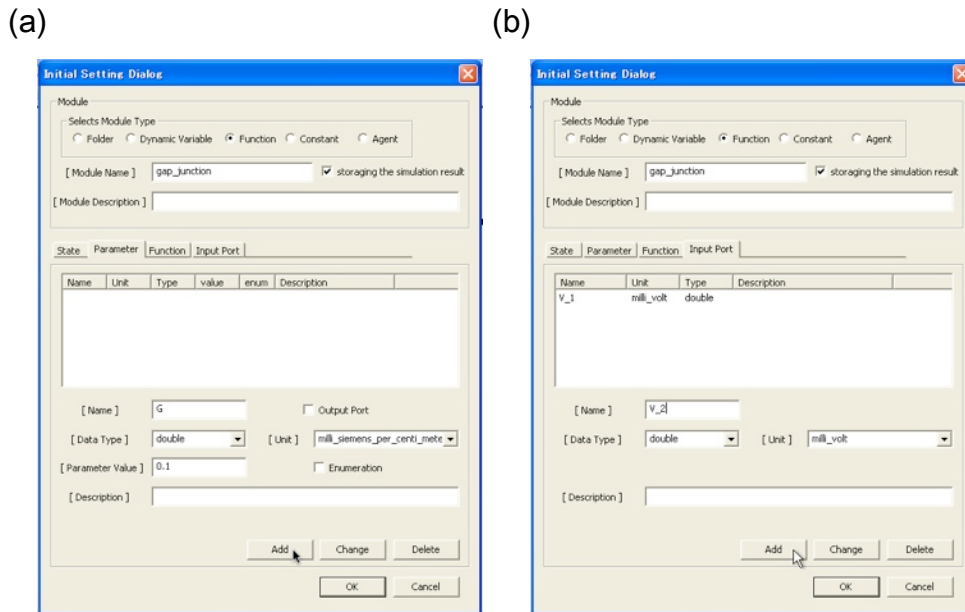


Figure 11. (a) Create a new module and a Parameter. (b) Create two Input Ports.

Finally, create two functions in “Function” tab representing currents flow the gap junction. Set name as I_1, and unit as “micro_ampere_per_centimeter2”. Put a check in the check box “Output Port” to create an output port which is associated to this value. And press Add button. After creating functions, select one of functions you created and press “Edit Function Rule”. In a window for edit function, click the right mouse button on the “ROOT” (Fig. 12(a)) then a window shown in Fig.12(b) appears, in which the definition of the function is described. In this case, $I_1 = G * (V_2 - V_1)$ and $I_2 = G * (V_1 - V_2)$.

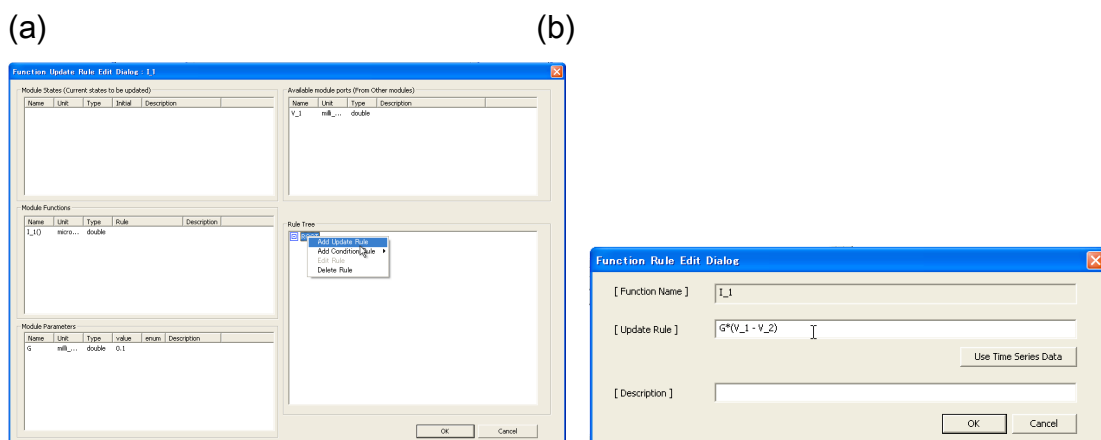


Figure 12. (a) Edit function. Right click on “ROOT” and “Add Update Rule”. Then a window in the panel (b) appears in which the definition of the function is described.

Now you have a gap junction module in the ISIDE as shown in Fig. 13.

Since we consider coupled two Hodgkin-Huxley models, we need to prepare two of them. You can duplicate the first one by just copy and paste. Right click on the Hodgkin-Huxley model, and select `copy` in the menu. Then at white canvas, again Right click and select `paste`.

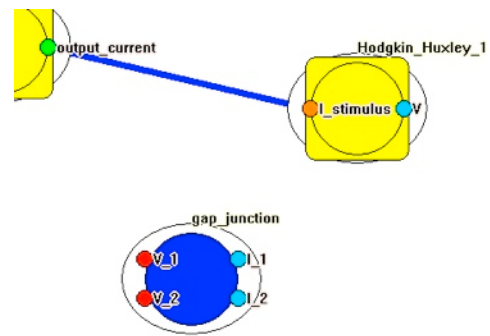


Figure 13. The module of the gap junction.

Now we connect two Hodgkin-Huxley models via the gap junction (Fig. 14). Link modules by edges from the output port on Hodgkin-Huxley module (named V) to the input port of the gap junction (V_1 or V_2), and from the output port of the gap junction (I_1 or I_2) to the input port of the Hodgkin-Huxley module (I_stimulus).

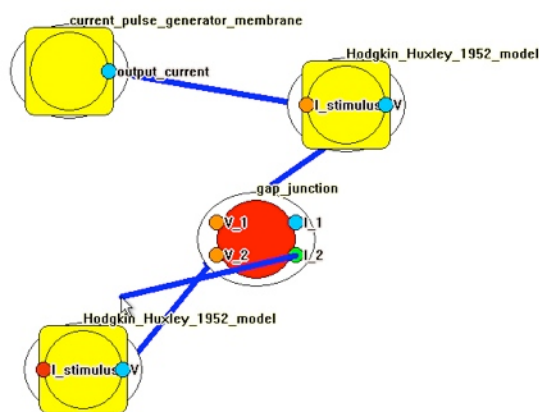


Figure 14. Links two Hodgkin-Huxley modules via the gap junction.

An input port can have only one access. The first Hodgkin-Huxley module cannot accept the input from the gap junction since it is already occupied by input from the stimulator. We need to prepare a summation calculator of the currents, which receives two current inputs and outputs one current (Fig. 15).

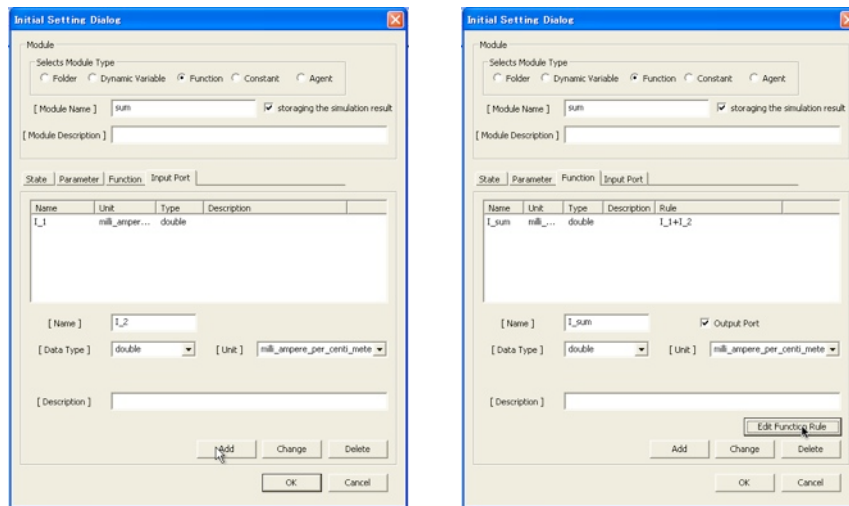


Figure 15. A module to sum up two currents.

Input the currents from the gap junction and stimulator to the current adder and lead the output of the summation to the first Hodgkin-Huxley module. Finally we have the two coupled Hodgkin-Huxley model as shown in Fig. 16.

Now we can perform a simulation. What will happen? Let us investigate the dynamics of the membrane potentials of both Hodgkin-Huxley modules. You will see the dynamics as shown in Fig. 17.

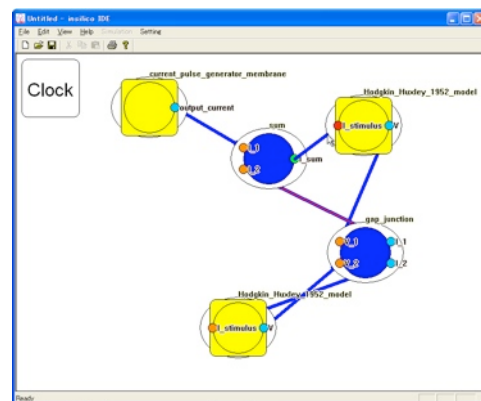


Figure 16. Overall diagram of the two coupled Hodgkin-Huxley model.

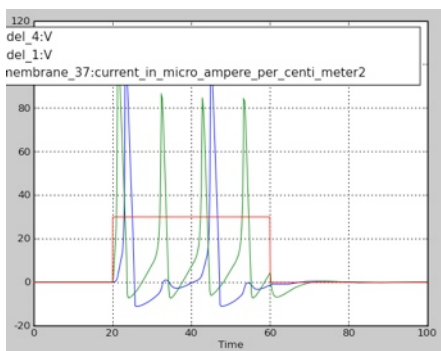


Figure 17. The dynamics of the membrane potentials of the coupled two Hodgkin-Huxley modules via a gap junction. Green: the first. Blue: the second. Red: input stimulus current.

Then try making several simulations with different configuration of parameters, such as duration of the stimulus, conductance of the gap junction, etc. Duration of simulation can be changed from “Clock” at the left upper of the canvas. Right click it and change parameters. You might find the dynamics shown in Fig. 18, for example.

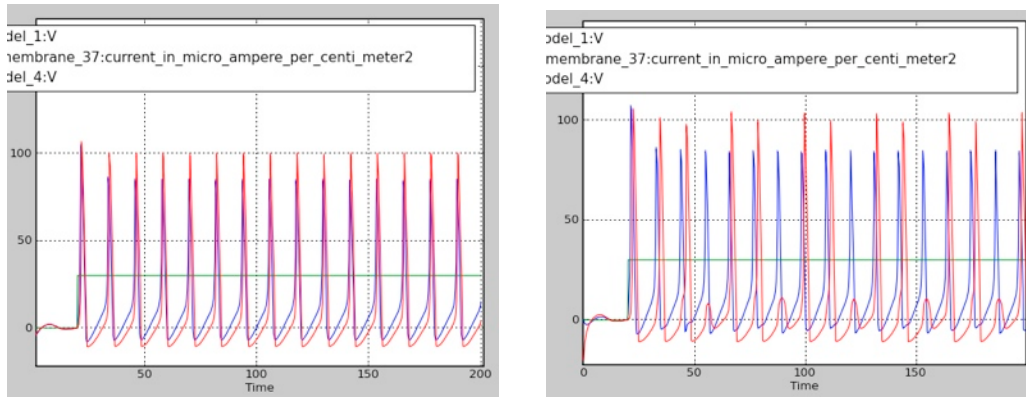


Figure 18. Some other examples of simulations.

A little bit details of the Hodgkin-Huxley model

The Hodgkin-Huxley model describes the dynamics of the membrane potential. The derivative of the membrane potential V_m is represented by a summation of aforementioned currents;

$$C \frac{dV_m}{dt} = -I_K - I_{Na} - I_L + I_{ext}$$

where C , I_K , I_{Na} , I_L and I_{ext} represent, respectively, membrane capacitance, K^+ current, Na^+ current, leak current and current additionally given externally. Each ion current is described by the potential difference between the cell membrane V_m and the equilibrium potential of the ion (E_{ion}) multiplied by a conductance (g_{ion}) where $ion = K^+, Na^+$ or L .

$$I_{ion} = g_{ion} (V_m - E_{ion})$$

The conductance for the leak current is a constant while the conductance for K^+ and Na^+ is modeled as a time dependent variable in Hodgkin-Huxley model. By denoting the maximum conductance (all gates are open) as \bar{g}_{ion} , the conductance g_{ion} can be written with its activation ratio r which is called a gating variable.

$$g_{ion} = \bar{g}_{ion} r$$

The gating variable evolves according to the following equation

$$\frac{dr}{dt} = \alpha_r(1-r) - \beta_r r$$

where α and β are the transition rates which are non-linear functions of membrane potential V_m . K^+ current is controlled by four same type activation gate n , similarly Na^+ current by three activation gate m and one inactivation gate h . The ion currents in the Hodgkin-Huxley model are described as follows:

$$I_K = \bar{g}_K n^4 (V_m - E_K)$$

$$I_{Na} = \bar{g}_{Na} m^3 h (V_m - E_{Na})$$

$$I_L = g_L (V_m - E_L)$$

Transition rates have the following dynamics:

$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$

$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n$$

$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$

STROEVE MODEL

Stroeve model is a neuro-musculoskeletal system model (Stroeve in 1999). This model consists of 2 limbs (upper arm and forearm), 6 muscles, neural input and external force. External force is added into forefront of forearm, and the angle of shoulder and elbow are calculated.

Open `Stroeve_1999_neuromusculoskeletalSystem.xml` by ISIDE.



Stroeve model uses morphology data which is located in the folder named `VisualModel` at the same folder with ISML file. Select menu [Show Morphology Data] which is appeared by right click on a module to view the morphology data. A window pops up in which an object is displayed in 3D space.

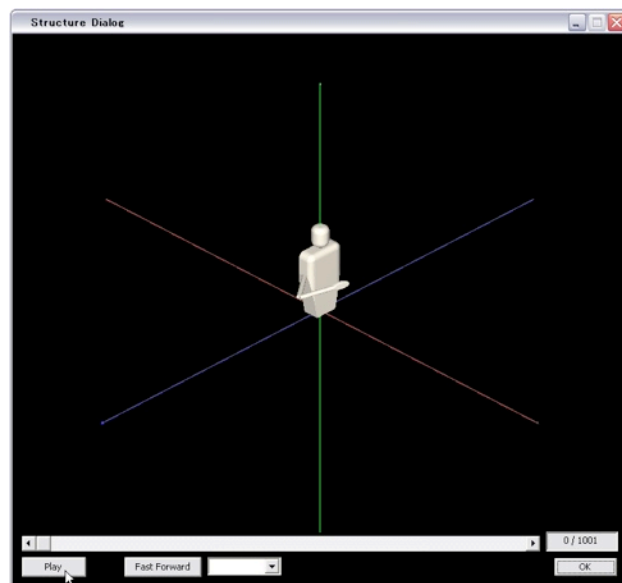
You can see the morpho-dynamics by a [Show Morpho-Dynamics]. This command executes simulation according to the equations of motion and neural dynamics described in this model, and generates time-series data of joint angles. Then it loads the time-series data for making animation using the toy model of human skeletal system. Press the [Play] button in the OpenGL dialog.

You can adjust the size of the object in the window by arrow keys and page up and down keys as follows.

↑ and ↓ : rotate around x-axis (red axis).

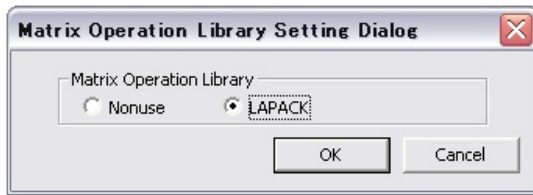
← and → : rotate around y-axis (green axis).

Page Up and Page Down : zoom in or zoom out.



DOUBLE PENDULUM MODEL

Open a DoublePendulum model (DoublePendulum.xml) by ISIDE.



DoublePendulum model calculates motion dynamics using vectors and matrices. The Lapack library, which provides routines to deal with linear algebra, is used for the numerical computation done in simulation of

this model. If users want to use this library on the ISIDE, users need to put a check on a check box on the dialog which appears by selecting menu [Setting]-[Matrix Operation Library] on menu bar.

Double pendulum model includes the morphology data. This data file is in the folder VisualModel, which is in the same Folder with ISML file. To view the morphology data, select a menu [Show Morphology Data]. ISIDE show the morphology data in 3D space.

You can see the Morpho-dynamics as animation by [Show Morpho-Dynamics] in the context menu appearing by right clicking on the module. In this example model, it reads a time series data which was generated by another simulation beforehand, and according to this data, morphology data moves. After appearing the OpenGL dialog, please press the [Play] button.

ACTION-POTENTIAL-CLAMP MODEL

The voltage clamp is a technique used to control the voltage of the membrane of a nerve cell by an electronic feedback circuit. Usually the voltage is stepped to a several levels, and currents flow across the membrane are observed. Instead of the step voltage, any other voltage as a function of time can be used for voltage clamp. Action potential clamp is one of such voltage clamp experiments in which the experimentally recorded action potential is used for the guide voltage to clamp.

We try to reconstruct the action potential clamp experiment using ISIDE. Open Hodgkin-Huxley model (Hodgkin_Huxley_1952_model_forAPClamp.xml). In this example, users can simulate an action potential clamp experiment using a

Hodgkin-Huxley neuron model and time series data of a membrane potential which is generated by other simulation. However in principle the source of the time series data can be anything, e.g. experimentally obtained data is available in this purpose.

This Hodgkin-Huxley model needs external input to the membrane from other module. Users need to add another model (`ActionPotentialGenerator.xml`) which generates data of voltage.

This module loads a external time series data and output the data from the output port. The time series data file is in a folder named `TimeSeriesData` at the same folder with ISML file in this example. Connect the output port of the action potential generator model to the input port of the Hodgkin-Huxley model by dragging the mouse cursor with pressing left button. Now the Hodgkin-Huxley neuron is receiving the time series data with which the membrane potential is clamped.

At last, select [`Show Simulated Waveforms`] which in a right click context menu, after selecting the `I_K` output port on `Hodgkin_Huxley_1952_model`. Then, the model is simulated and you can view a new dialog which shows a graph of time-series data of the potassium ion current of the Hodgkin-Huxley neuron under the action potential clamp.