

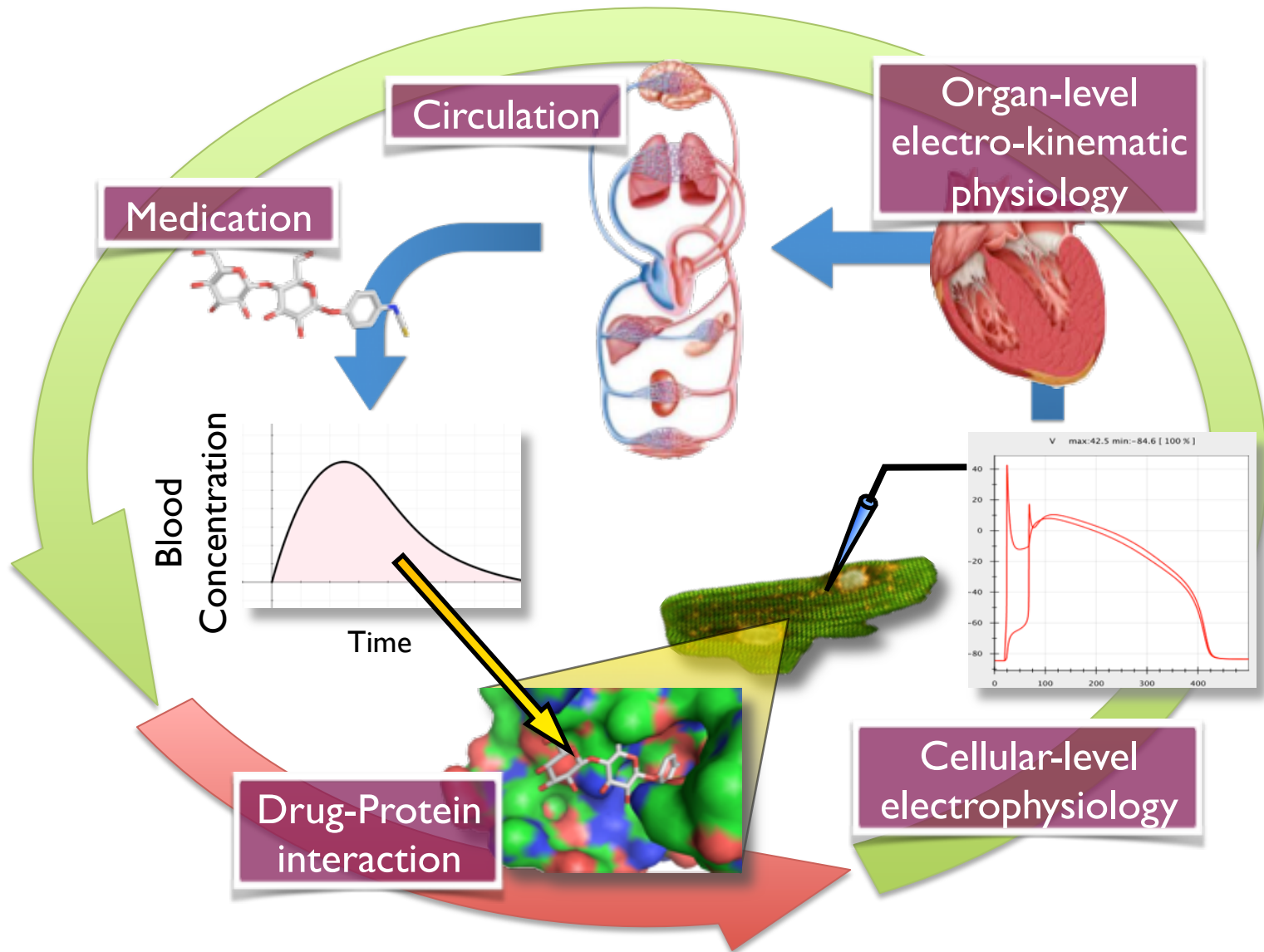
# PhysioDesigner: A versatile platform for multilevel modeling of physiological systems network

Yoshiyuki Asai, Takeshi Abe, Li Li, Hiroaki Kitano



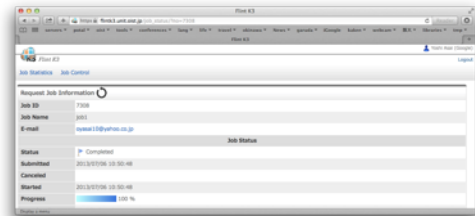
Okinawa Institute of Science and Technology  
Integrated Open Systems Unit

# Multilevel Physiological Systems

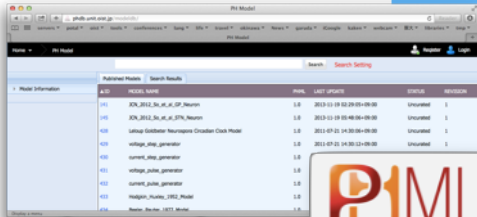


# PhysioDesigner and relevant tools

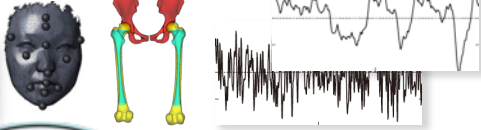
 Flint K3



PH Database



**Physiome.jp**



**PIML**



**PL** PH Plotter

**PD** PhysioDesigner

**DB** PHDB Client

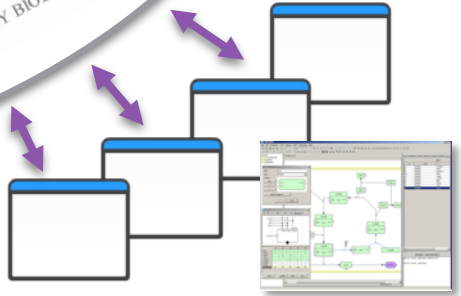
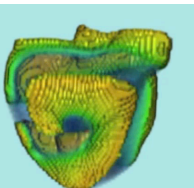
**Im** ImageViewer

**Mo** MorphoSpace

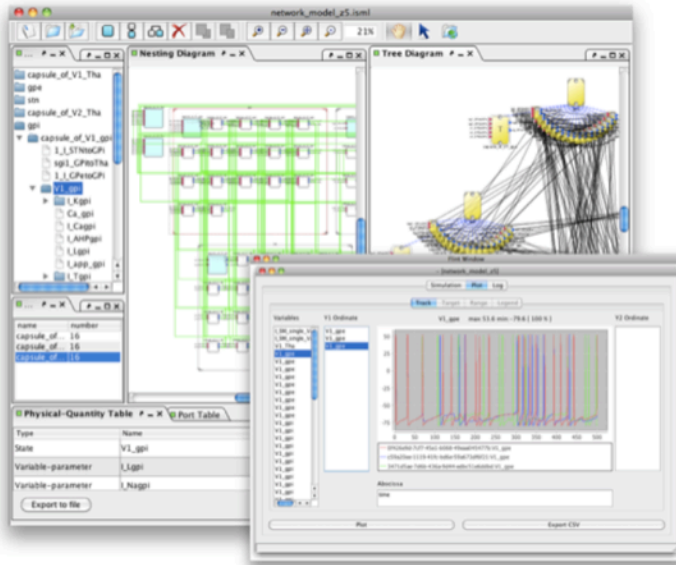
**FLINT**



**PV** PhysioVisualizer



## PhysioDesigner



### An open platform for multilevel modeling

PhysioDesigner is an open platform that supports multilevel modeling of physiological systems in the field of integrated life sciences and systems biology, including physiology and neuroscience. Users can combine and build mathematical models of biological and physiological functions on PhysioDesigner. Users can also integrate morphometric data on a model, which is used, for example, to define a domain in which partial differential equations are solved.

The models developed by PhysioDesigner are stored in PHML (Physiological Hierarchy Markup Language) format, which is an XML-based specification, to describe a wide variety of models of biological and physiological functions with a hierarchical structure. PHML fully inherits the specifications from [insilicoML](#) (ISML). PhysioDesigner can act as an editor and browser of the models written in PHML and ISML. It is also possible to import models written in [CellML](#) format and export models to CellML (some model expressions in PHML cannot be exported to CellML).

Another distinguishing feature of PhysioDesigner is that it provides a user function to create SBML-PHML hybrid models, which is a novel way to create multilevel physiological systems. In addition, morphological data can be integrated into the model.

### What's new

2015.7.24

- Flint 1.3.1 has been released!

2015.7.14

- PhysioDesigner 1.3 has been released!
- Flint 1.3 has been released!

2015.3.31

- PhysioDesigner 1.2 has been released.
- Flint 1.2 has been released.

2015.1.23

- PhysioDesigner 1.1.1 has been

### Related project

[CellDesigner](#)

A modeling tool of biochemical networks

### Former project

[insilicoPlatform](#)

[Development History](#)

### Database

[ModelDB in Physiome.jp](#)

[Sitemap](#)

### Supported by:



### Collaborating with:



physiome.jp

1:gmail 2:gDict 3:AlcPro 4:baidu 5:OWA 6:gmap potal oist tools conf life sci lang travel okinawa News >> +

# Physiome.jp


Home PH Database Tools About us Links Sitemap

## PH Database

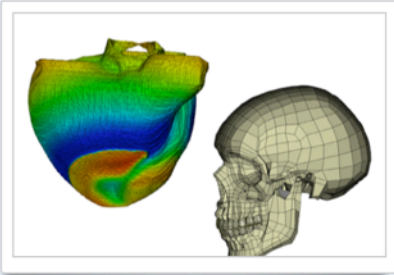
The PH database (PHDB) at [www.physiome.jp](http://www.physiome.jp) currently includes three databases, i.e. a database for PHML models, and databases for morphological and time series data. In the PHML framework, it is possible to integrate morphological and time series data in a PHML model. These three databases can interoperate to each other to support such models including morphological and time series data.

(Updated, 16 June 2015)

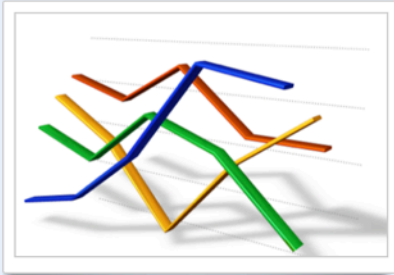
PHML Model Database



Morphology Database



Timeseries Database



[Terms of Use](#)

Display a menu

Physiome.jp

Home PH Database Tools

## PhysioVisu

#	Layer Name	Type
<input checked="" type="checkbox"/>	1 Wavefront	condition
<input checked="" type="checkbox"/>	2 Cardio	data

Physiome.jp - to

Physiome.jp is a part of the Wo  
Physiome and Systems Biolo  
physiological data) representing  
elements in the catalogue of h  
of human physiology, eventua  
predictive medicine.

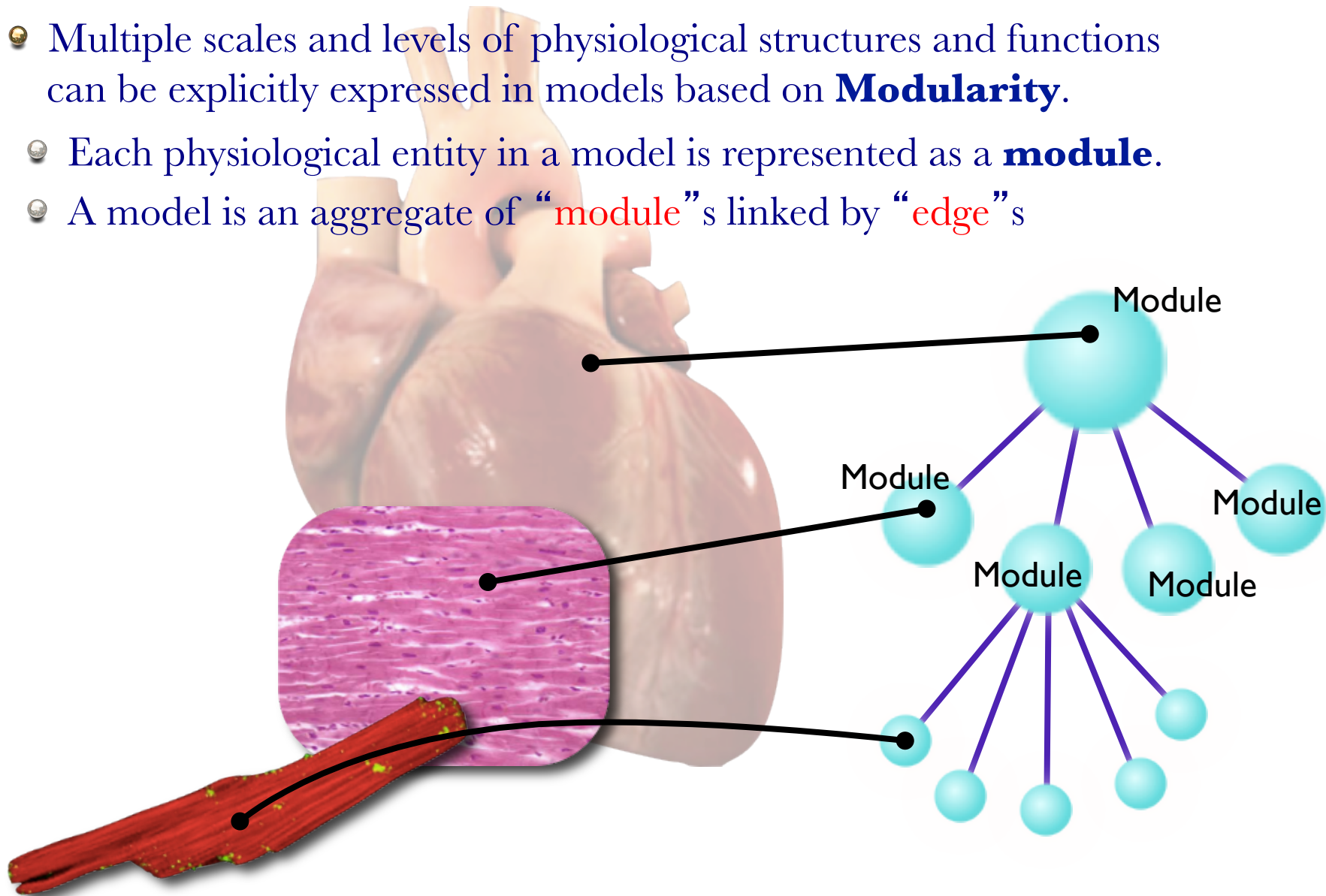
### Platform Overview

Our platform is composed of  
application to support modeling  
Flint. Also tools for medical im  
development.

Display a menu

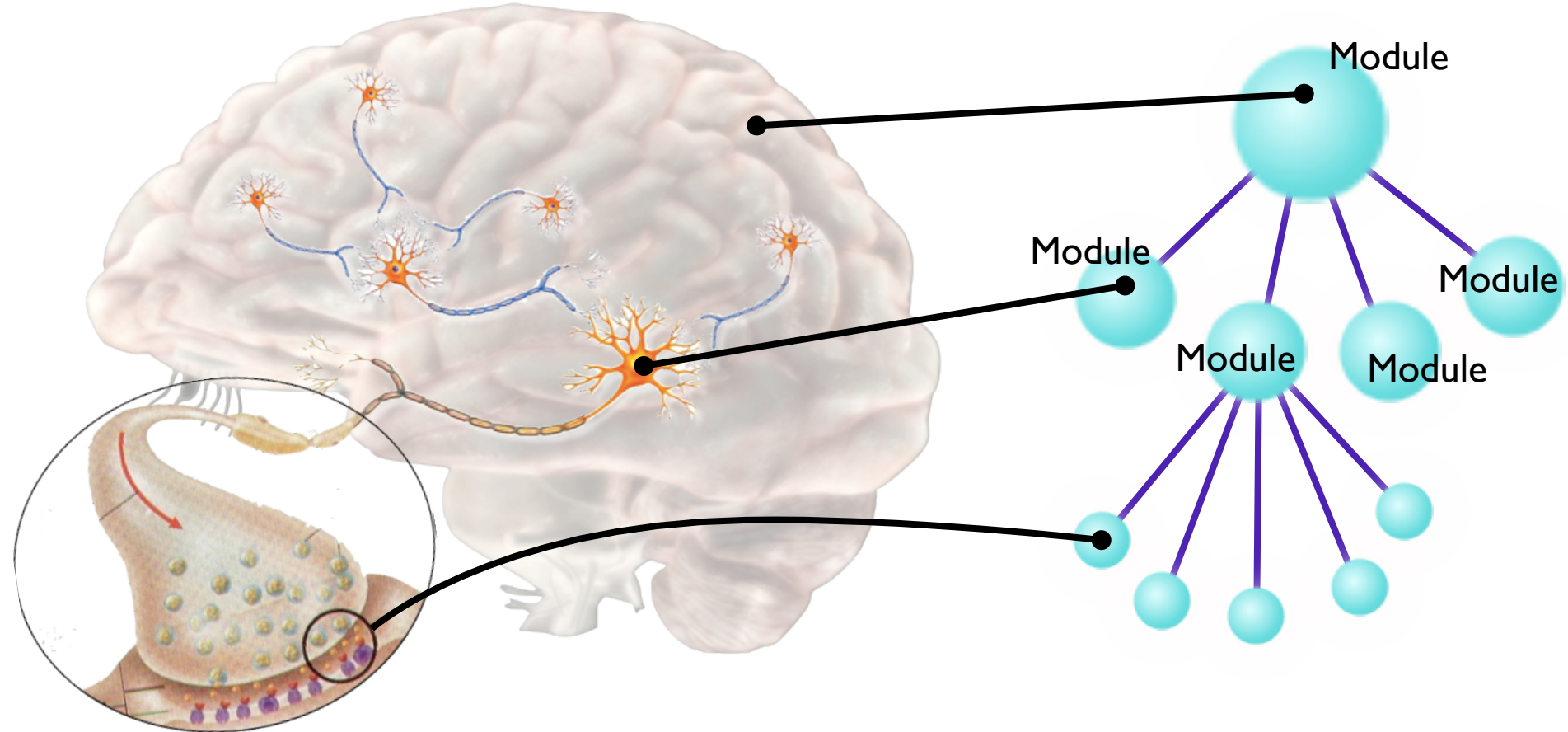
# Principle Idea of PhysioDesigner

- Multiple scales and levels of physiological structures and functions can be explicitly expressed in models based on **Modularity**.
- Each physiological entity in a model is represented as a **module**.
- A model is an aggregate of “**module**”s linked by “**edge**”s



# Principle Idea of PhysioDesigner

- Multiple scales and levels of physiological structures and functions can be explicitly expressed in models based on **Modularity**.
- Each physiological entity in a model is represented as a **module**.
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# Structure of Mathematical Expressions in a Model

Simple example) Hodgkin-Huxley model in ODEs

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

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

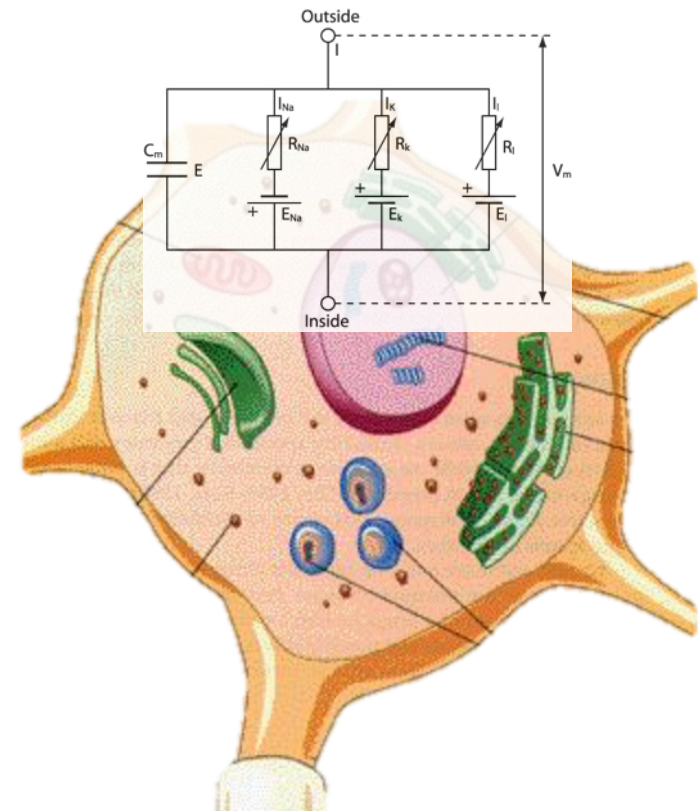
$$I_L = g_L (V_m - E_L)$$

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

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

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

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



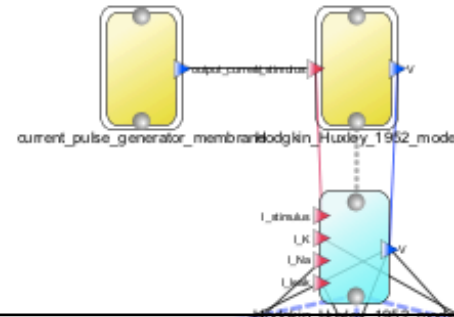


# Structure of Mathematical Expressions in a Model

## Hodgkin Huxley Model

Membrane

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

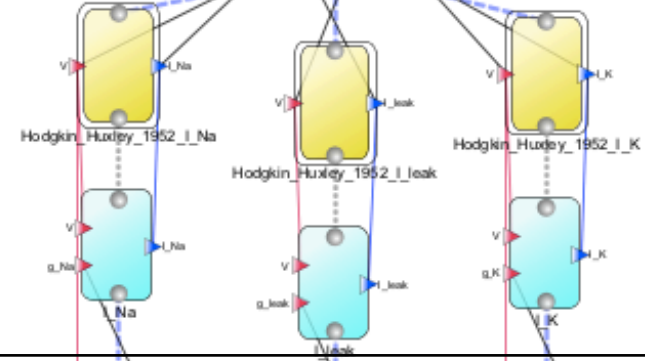


Ionic Currents

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

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

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



Conductance

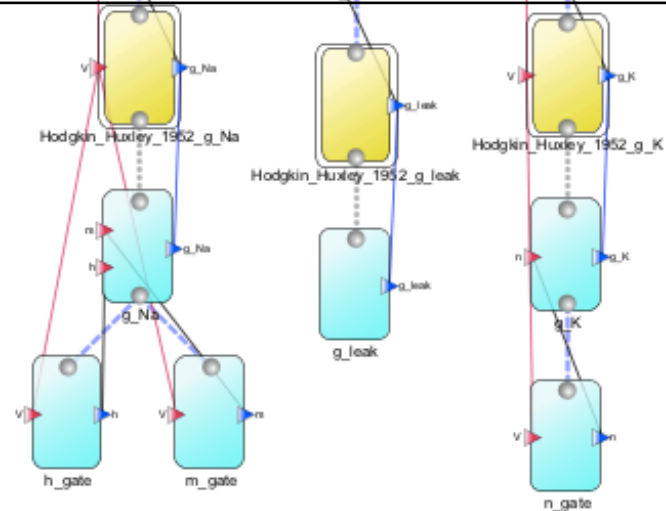
$$g_{ion} = \bar{g}_{ion} r$$

Channel Gate Variables

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

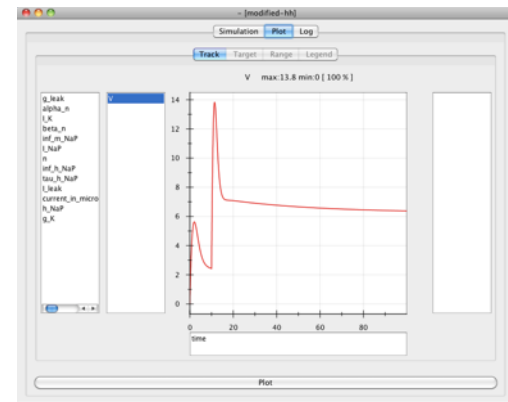
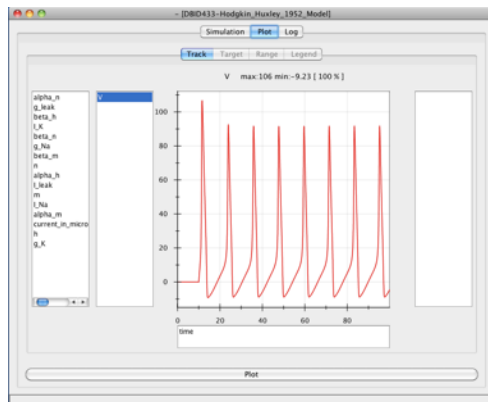
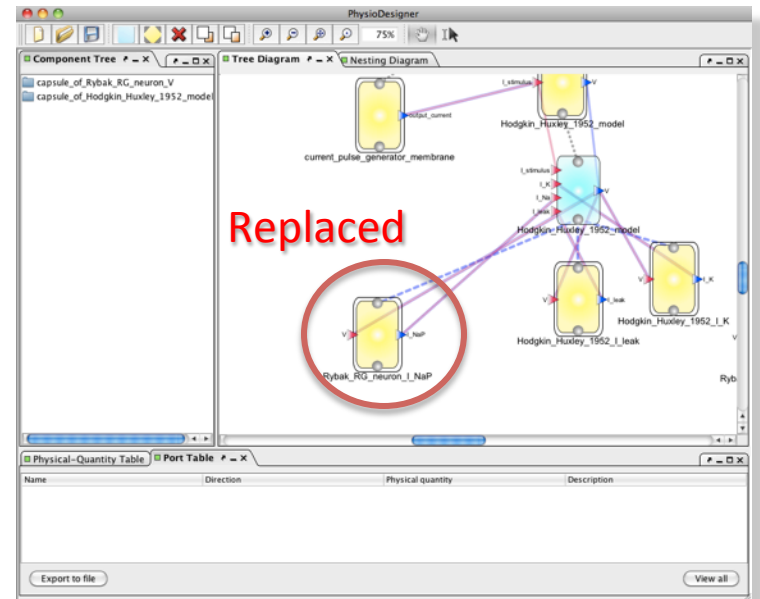
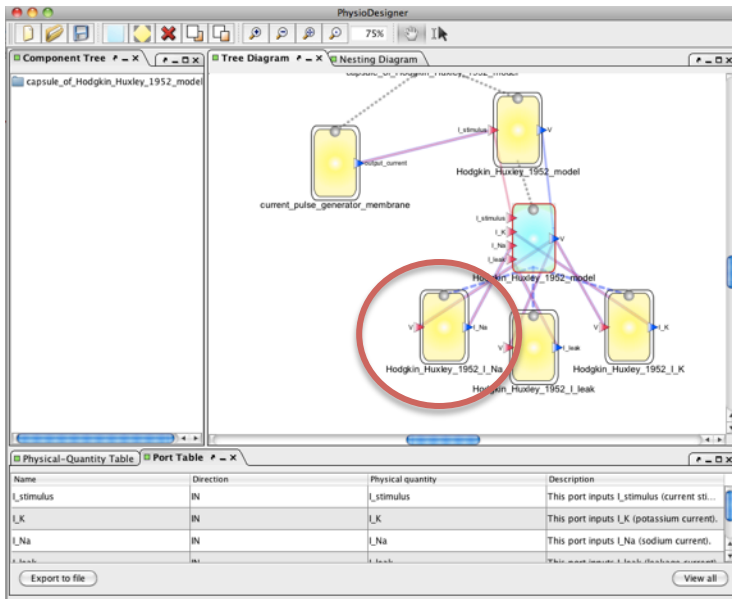
$$\frac{dn}{dt} = \alpha_n(V_m)(1 - n) - \beta_n(V_m)n$$

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

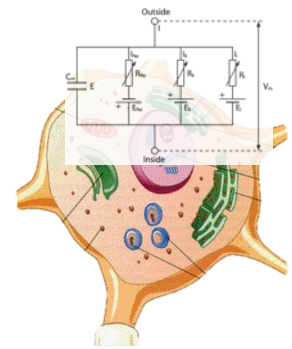


# Reuse of Modules

## Replacement of a channel module



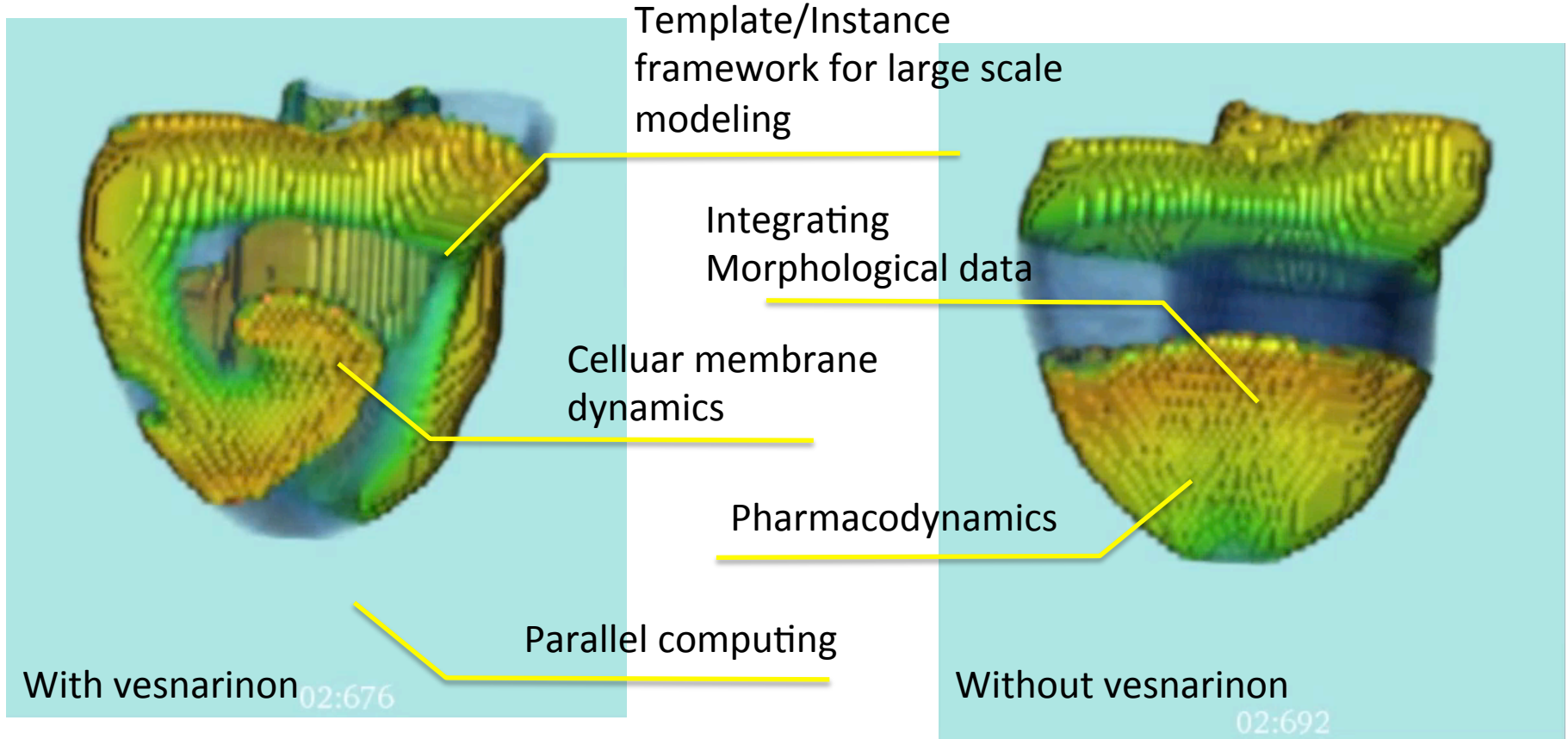
# Example of Simulations



Model

Name: **FSK 2008 Endocardial Ventricular Myocyte with Vesnarinon**

MID: 632 in Model DB @ Physiome.jp




Ventricular morphological model

Name: **human\_ventricles\_shape\_data**

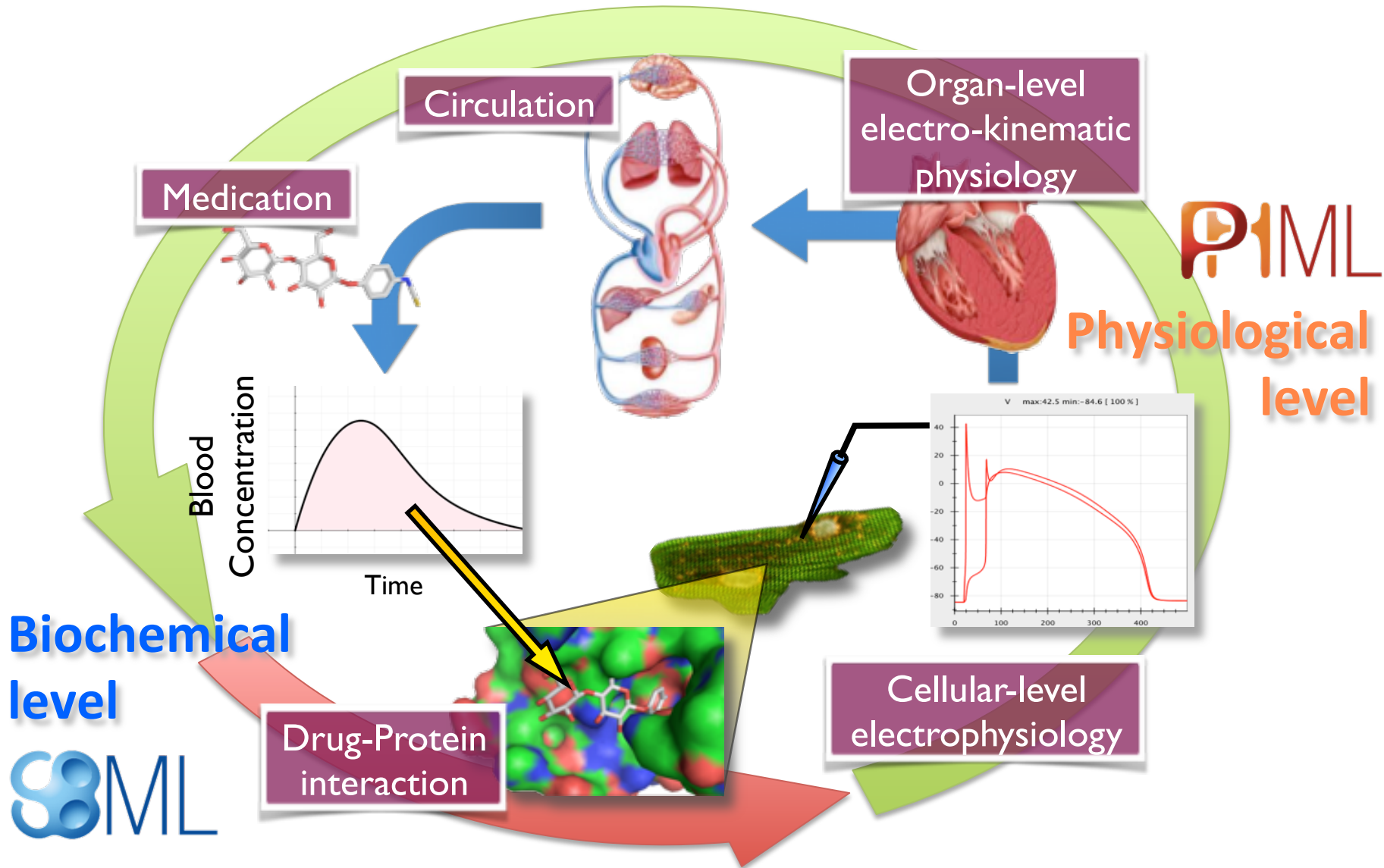
MID: 7 in Morphology DB @ Physiome.jp



The background features several flowing, wavy lines in shades of light blue and teal, creating a sense of movement and depth. These lines curve across the top and right side of the slide.

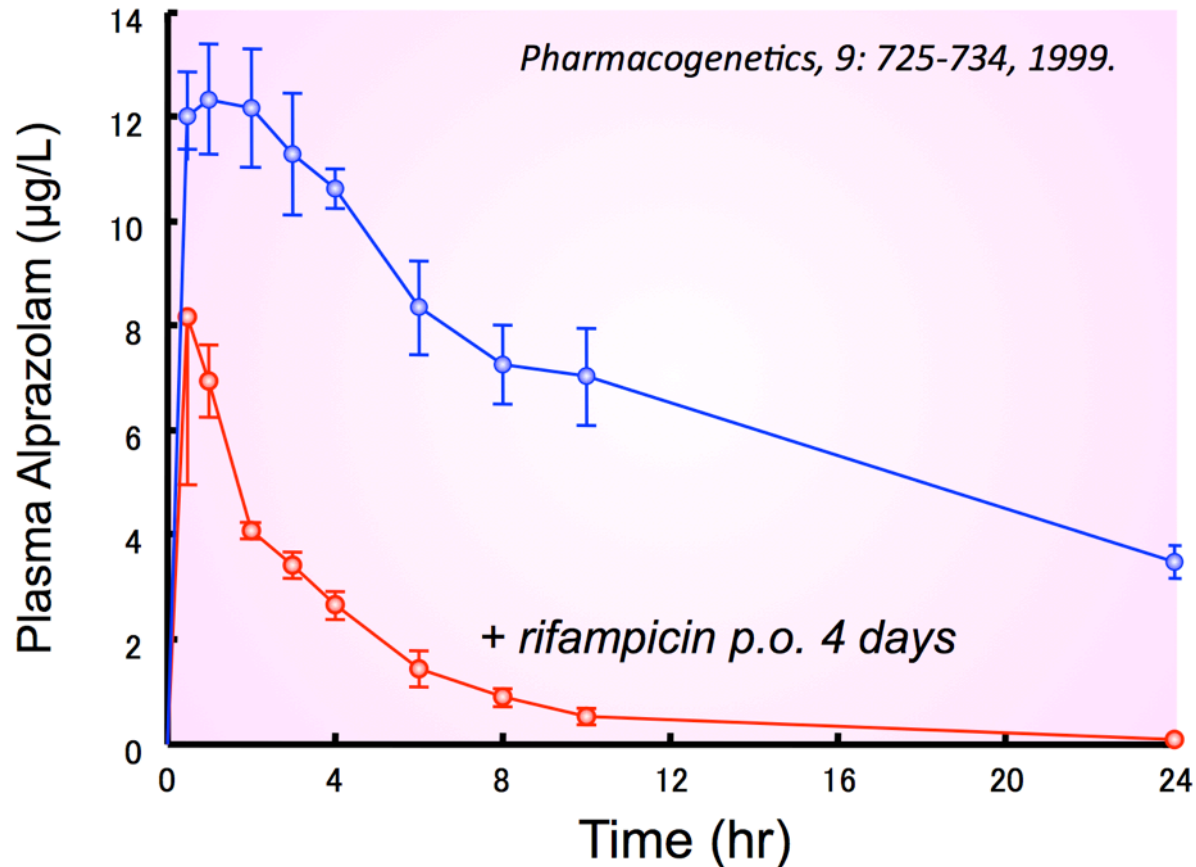
# SBML-PHML Hybridization

# Modeling target

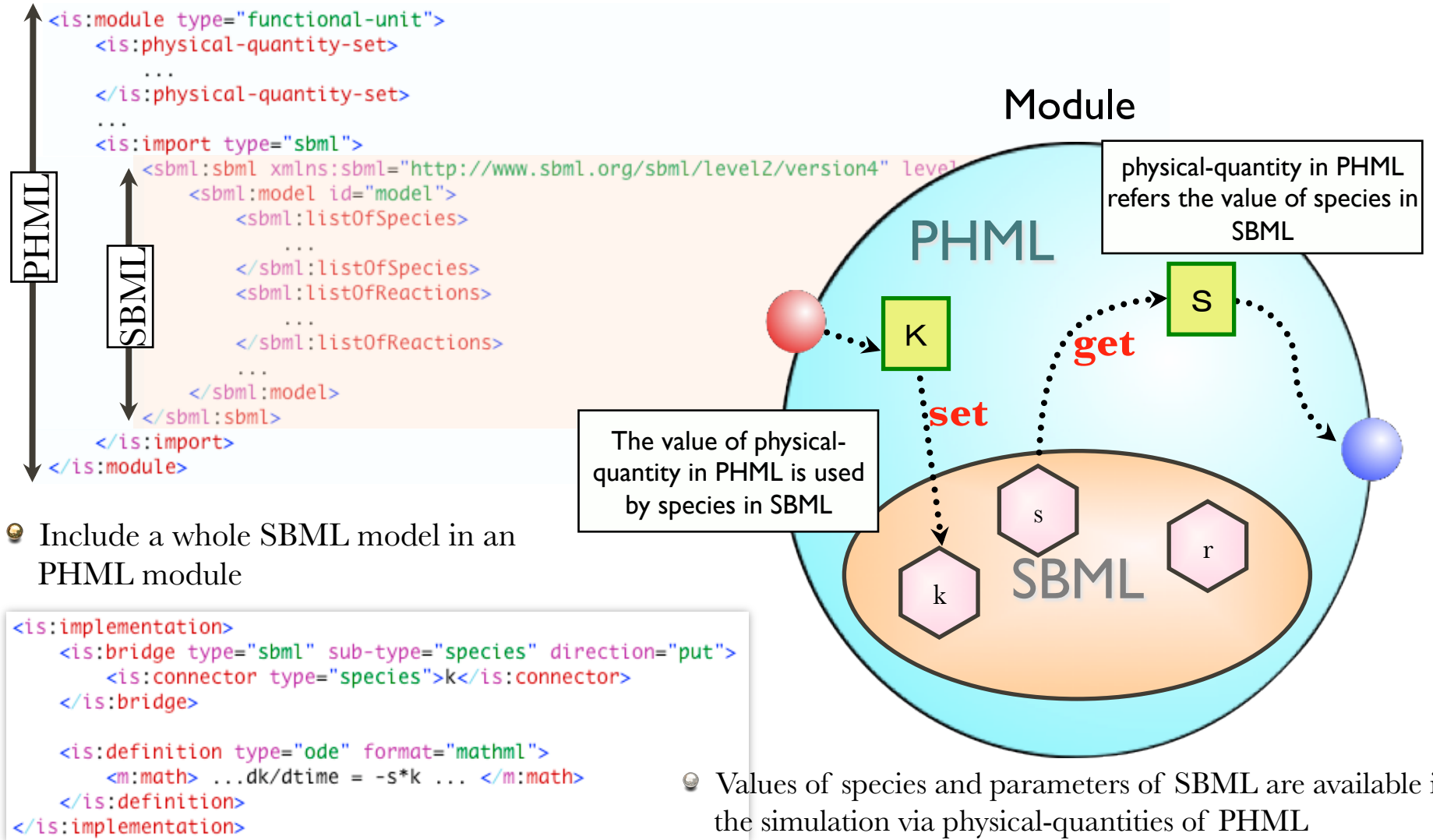


# Drug-Drug Interaction

**Rifampicin**  $\longrightarrow$  **Alprazolam**  
CYP3A4 induction

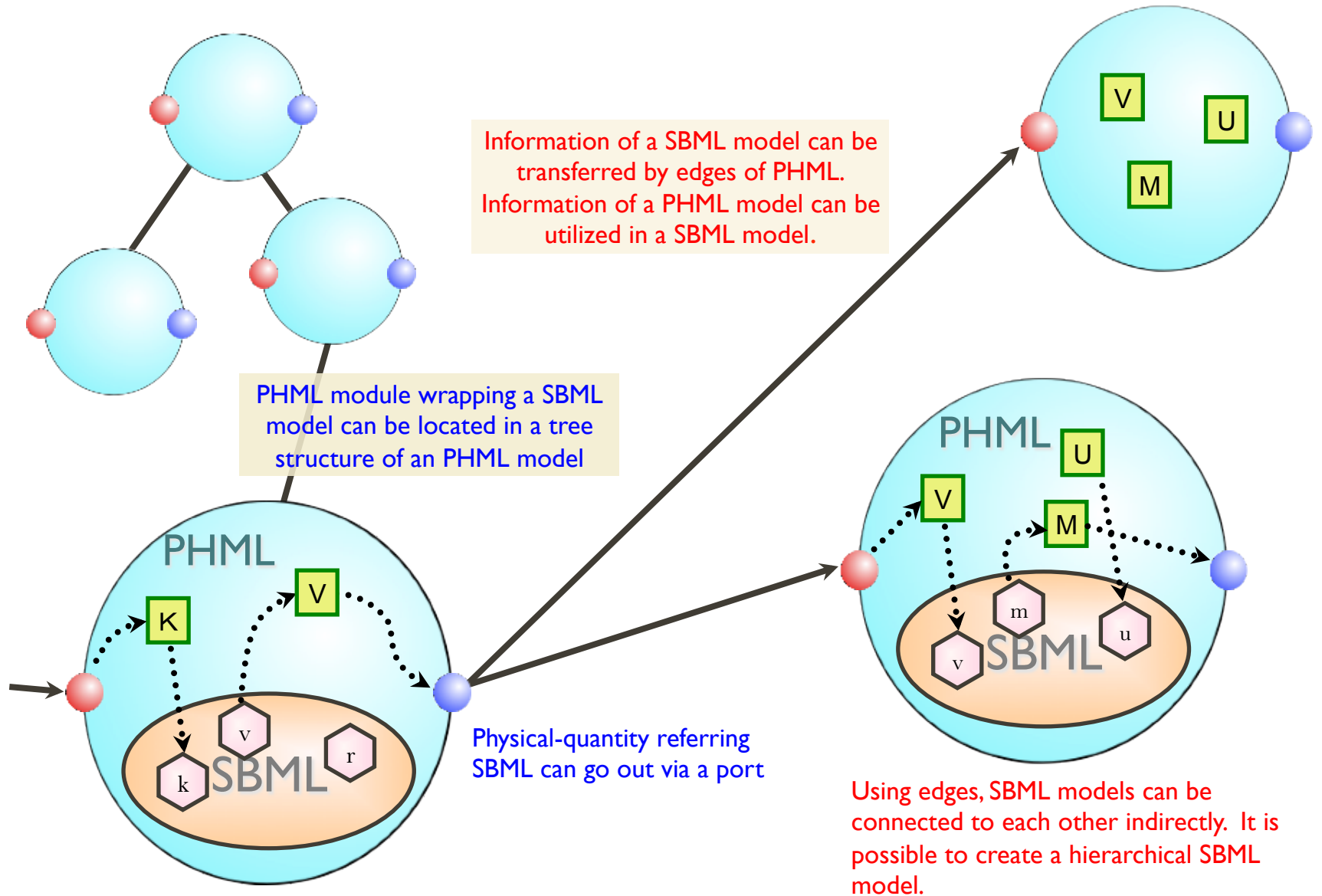


# SBML-PHML Hybridization



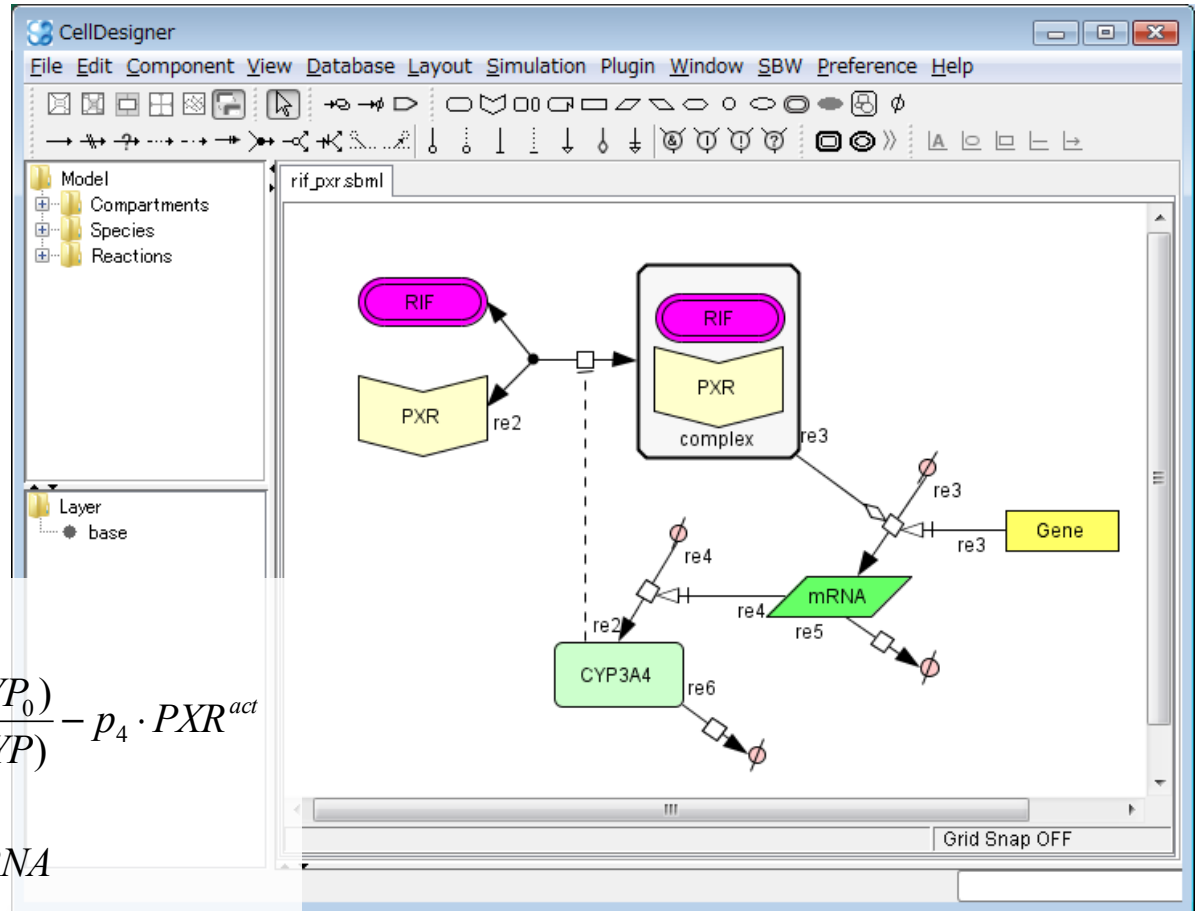


# SBML Connections in PHML



# Model of CYP3A4 Induction by Rifampicin

Yamashita, F., et al. (2013). Modeling of rifampicin-induced CYP3A4 activation dynamics for the prediction of clinical drug-drug interactions from in vitro data. *PLoS One*, 8(9), e70330. doi:journal.pone.0070330



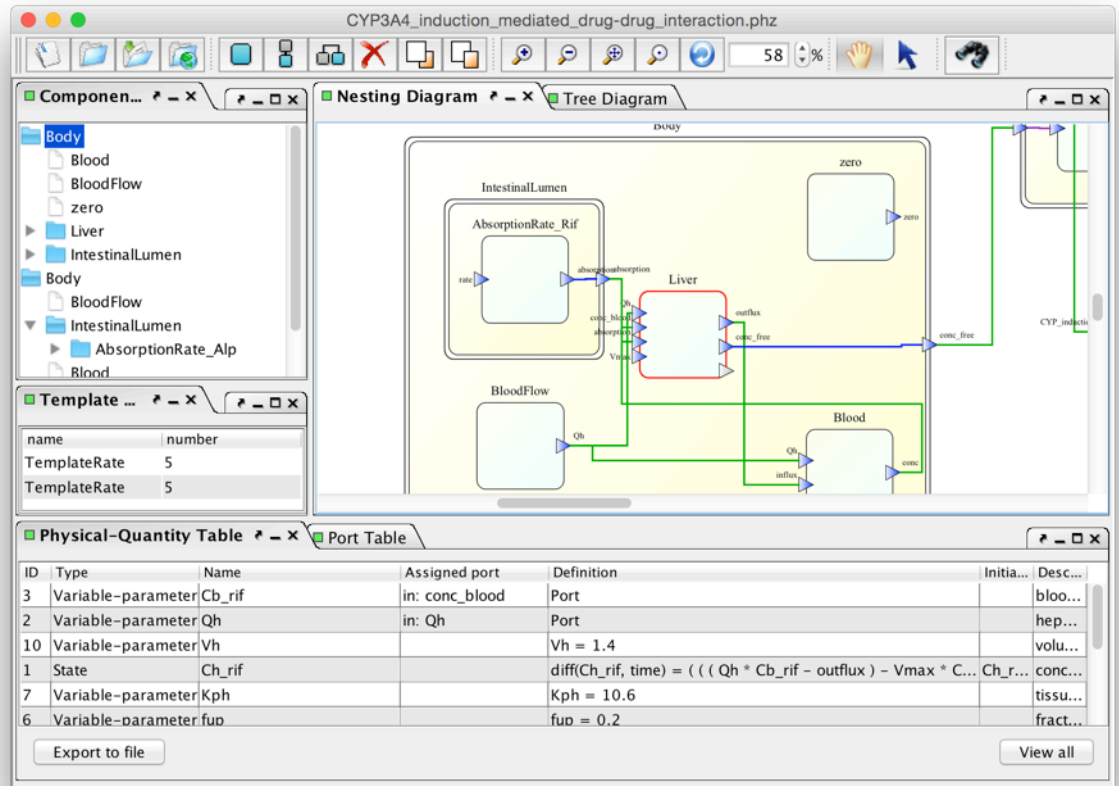
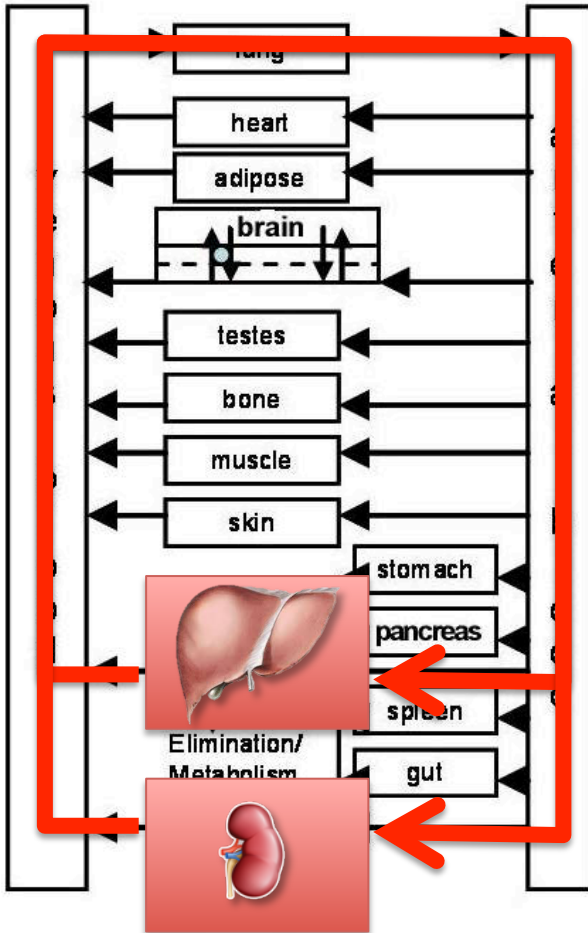
$$\frac{dPXR^{act}}{dt} = \frac{p_1 \cdot Rif}{p_2 + Rif} \cdot \frac{(1 + p_3 \cdot CYP_0)}{(1 + p_3 \cdot CYP)} - p_4 \cdot PXR^{act}$$

$$\frac{dRNA}{dt} = p_4 \cdot PXR^{act} + q_1 - q_2 \cdot RNA$$

$$\frac{dCYP}{dt} = r_1 \cdot RNA - r_2 \cdot CYP$$

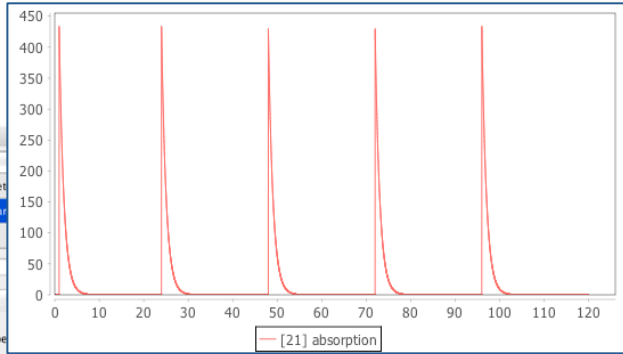
# Pharmacokinetics

## Physiologically Based Pharmacokinetics (PBPK) model



# Pharmacokinetics of Rifampicin

## Absorption



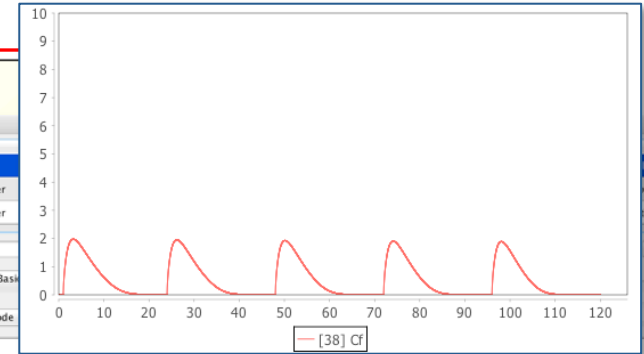
Definition-type: ode

$$\text{rate\_in\_rif} = ka \cdot FaFg \cdot \text{dose} \cdot e^{((-ka) \cdot (time - timeDosing))}$$

Equation:  $\text{rate\_in\_rif} = ka \cdot FaFg \cdot \text{dose} \cdot \exp((-ka) \cdot (time - timeDosing))$

Body

## Concentration in Hepatocyte



Definition-type: ode

$$\frac{d}{dt} Ch_{rif} = \frac{Qh \cdot Cb_{rif} - \text{outflux} - \frac{vmax \cdot Cf}{Km + Cf} + \text{absorption}}{Vh}$$

Equation:  $\text{diff}(Ch_{rif}, time) = (((Qh \cdot Cb_{rif} - \text{outflux}) - Vmax \cdot Cf / (Km + Cf)) + \text{absorption}) / Vh$

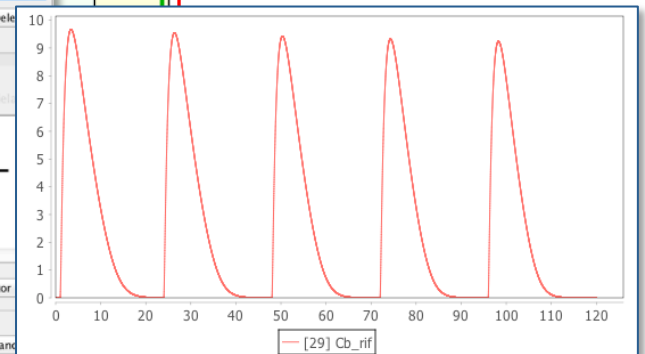
## Concentration in blood

P...	Type	Name	Assigned port	Definition	Initial-value	Description
1	Static-parameter	V1		V1 = 17.2		volume of distribution
2	Static-parameter	CLr		CLr = 1.8		renal clearance
3	State	Cb_rif	out: conc	$\text{diff}(Cb_{rif}, time) = ((-Qh_{rif}) \cdot Cb_{rif} - CLr \cdot Cb_{rif} + \text{influx}) / V1$	Cb_rif = 0	blood concentration

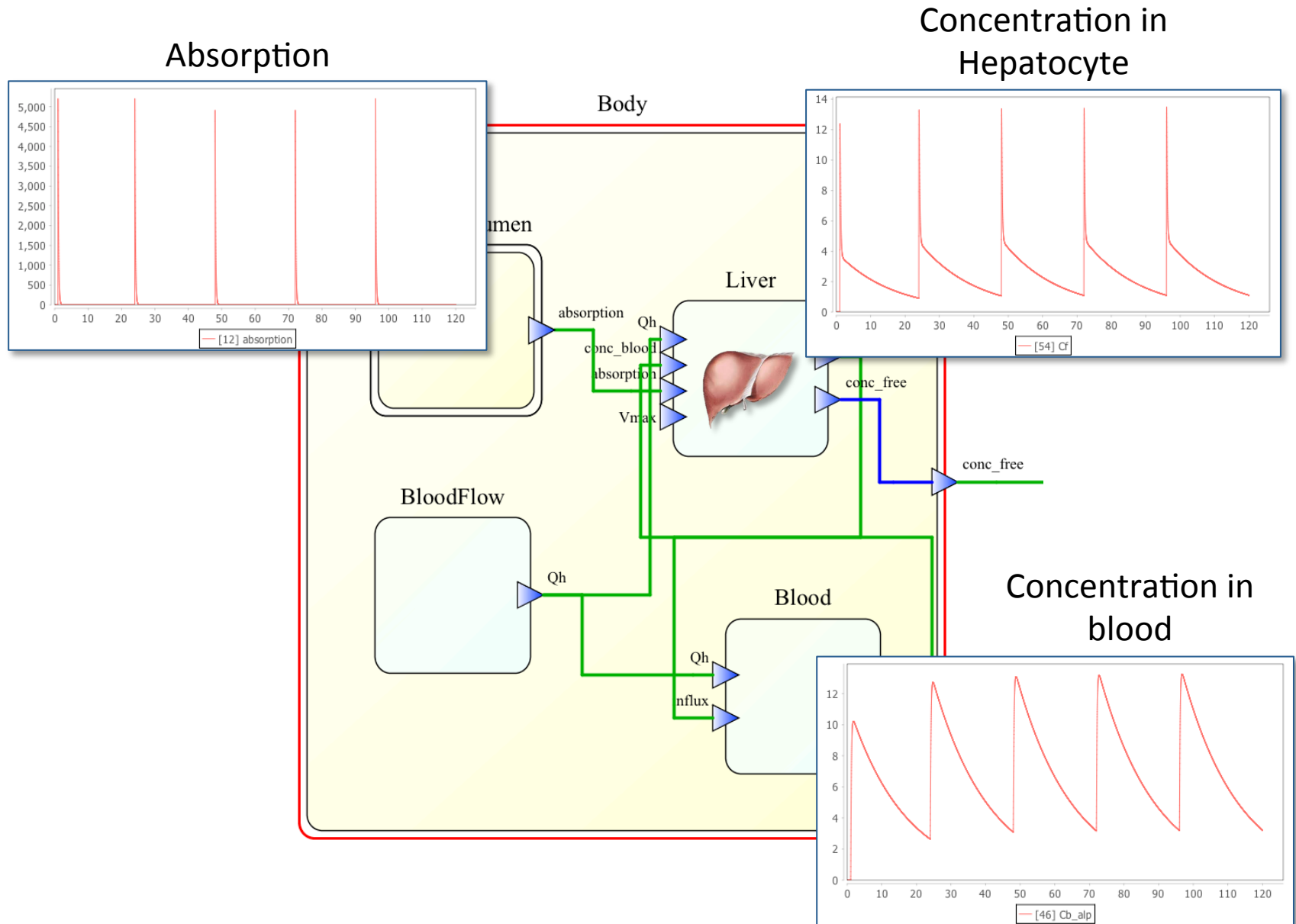
Definition-type: ode

$$\frac{d}{dt} Cb_{rif} = \frac{(-Qh_{rif}) \cdot Cb_{rif} - CLr \cdot Cb_{rif} + \text{influx}}{V1}$$

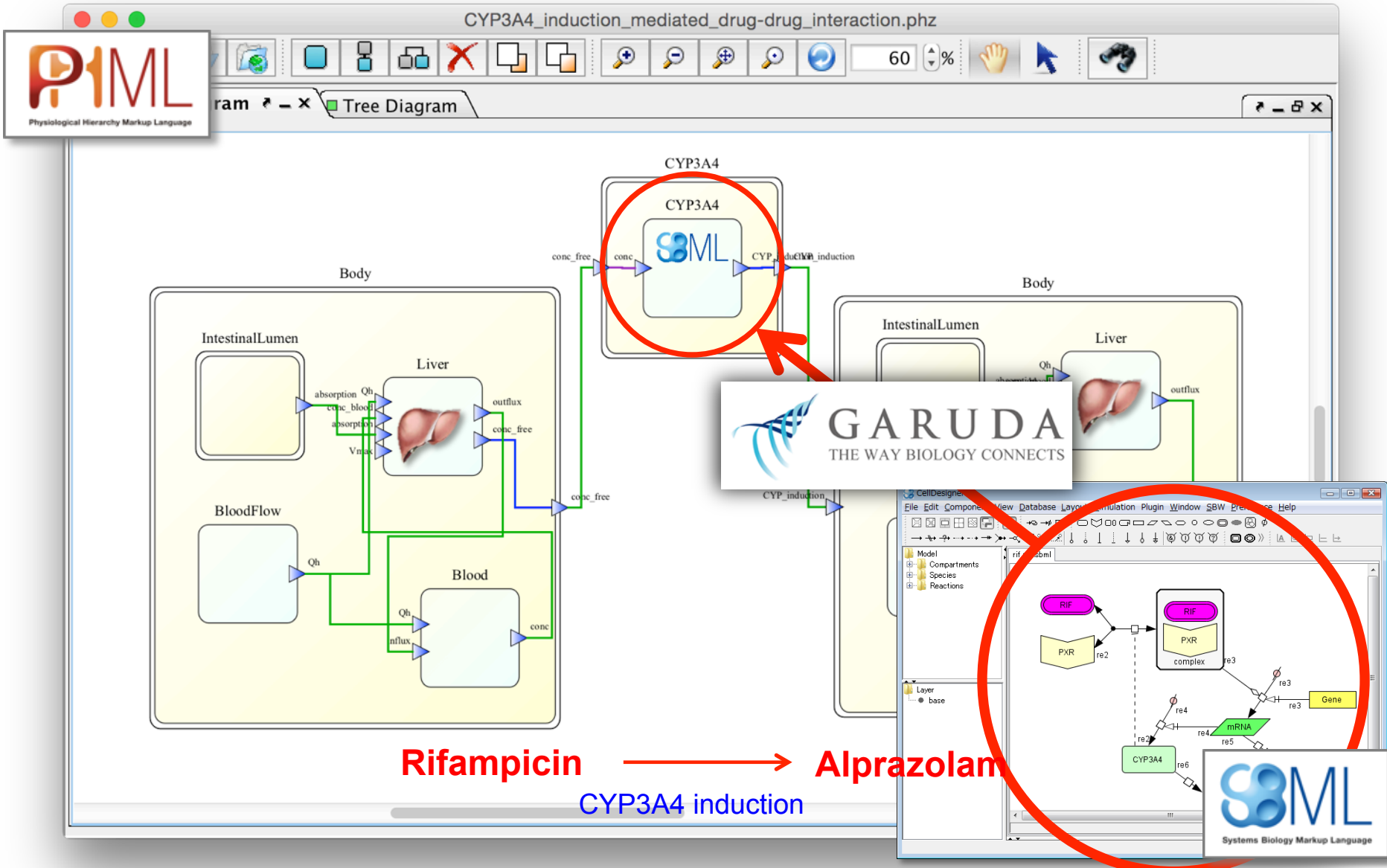
Equation:  $\text{diff}(Cb_{rif}, time) = (((-Qh_{rif}) \cdot Cb_{rif} - CLr \cdot Cb_{rif} + \text{influx}) / V1)$



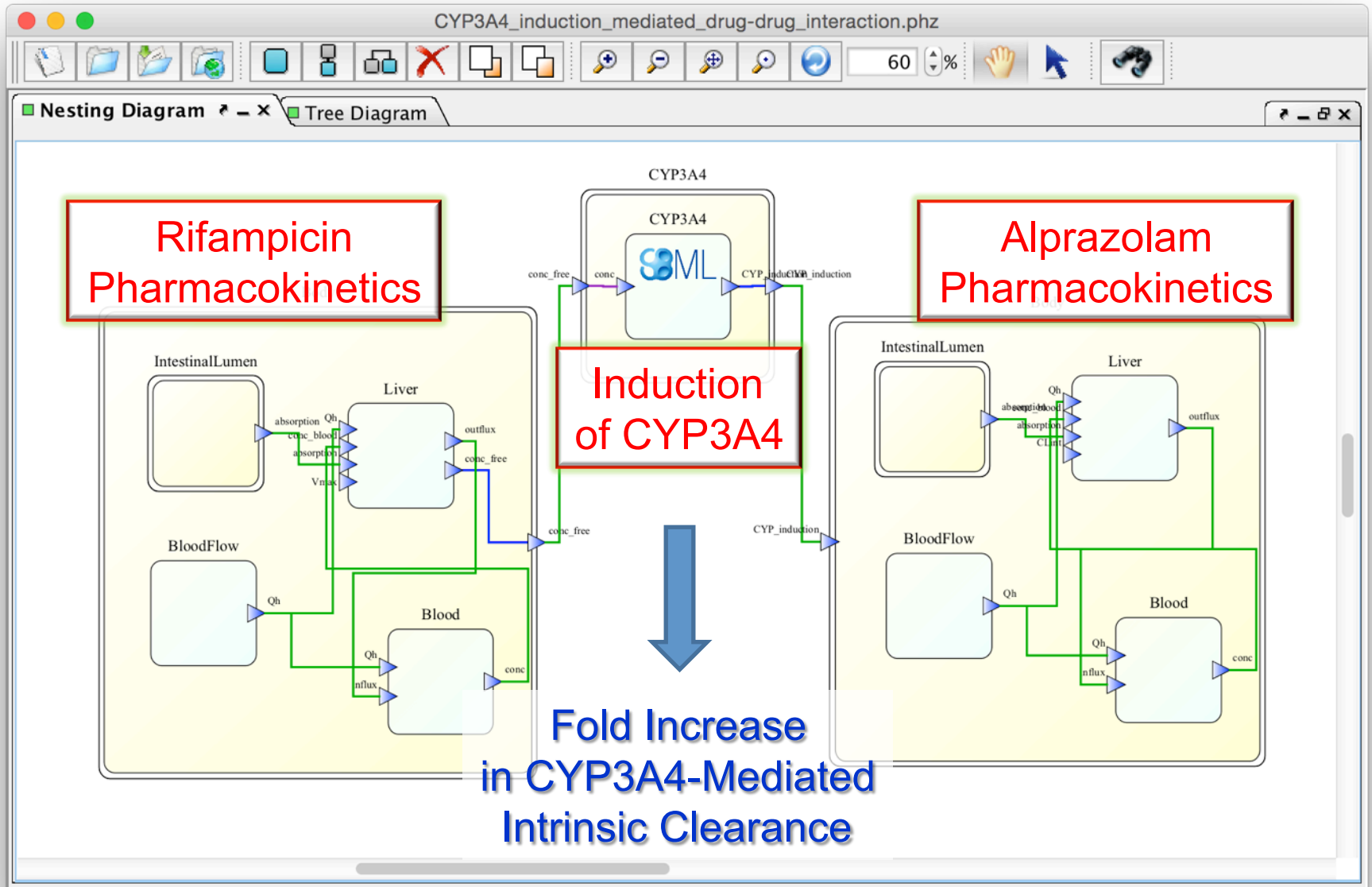
# Pharmacokinetics of Alprazolam



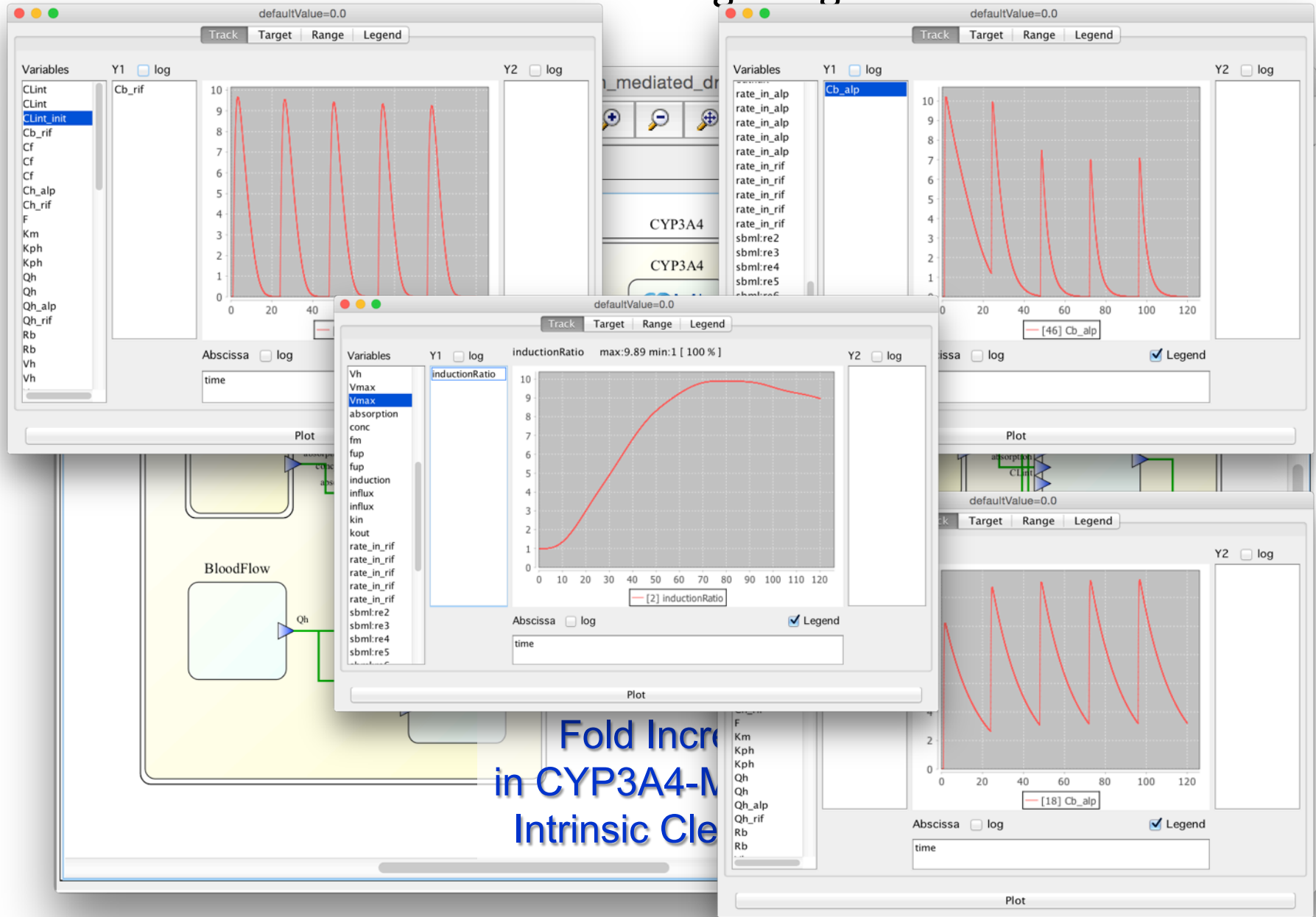
# PHML-SBML Hybrid Simulation for Dynamics of In Vivo Pharmacokinetic Drug-Drug Interaction



# Implementation of Pharmacokinetic Interaction of Alprazolam with Rifampicin



# PHML-SBML Hybrid Simulation for Dynamics of In Vivo Pharmacokinetic Drug-Drug Interaction





# Simpler Model -- One Compartment Model --

The image displays a software interface for modeling a one-compartment model. The main window shows a component tree on the left with 'Body', 'Body', and 'CYP3A4' components. The central area contains nesting diagrams showing the relationship between 'IntestinalLumen', 'CYP3A4', and 'one\_compartment\_alp' compartments. A detailed view of the 'one\_compartment\_alp' compartment is shown on the right, illustrating the flow of 'absorption' and 'CypInduction' into the compartment, and 'concentration' as an output.

Below the diagrams, two tables provide details for the physical quantities:

P...	Type	Name	Assigned port	Definition	Initial-value	Description
1	Variable-parameter	absorption_rif	in: absorption	Port		
2	State	conc_rif	out: concentration	diff(conc_rif, time) ...	conc_rif = 0	
5	Static-parameter					

P...	Type	Name	Assigned port	Definition	Initial-value	Description
1	Variable-parameter	absorption_alp	in: absorption	Port		
2	State	conc_alp	out: concentration	diff(conc_alp, time) = ( absorption...	conc_alp = 0	
3	Static-parameter	ko		ko = 0.04		

The detailed view also shows the definition type set to 'ode' and the following differential equation:

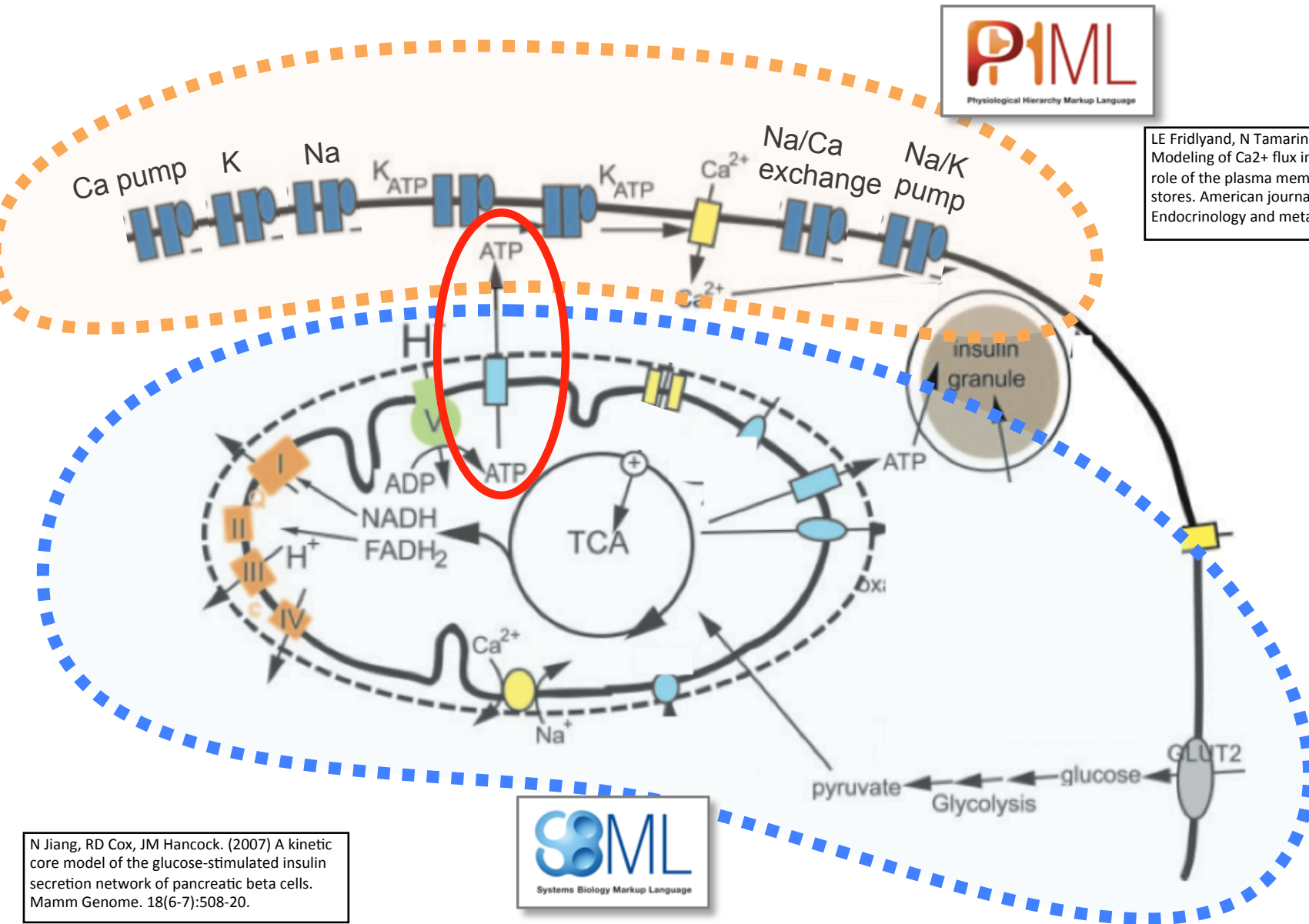
$$\frac{d}{d \text{ time}} \text{conc\_alp} = \frac{\text{absorption\_alp} - (CLr + (1 - fm + \text{CypInduction} \cdot fm) \cdot CLh) \cdot \text{conc\_alp}}{V\_alp}$$

Below the equation, the software provides the implementation code: `diff(conc_alp, time) = ( absorption_alp - ( CLr + (( 1 - fm ) + CypInduction * fm ) * CLh ) * conc_alp )/V_alp`

# Example: Pancreatic Beta Cell



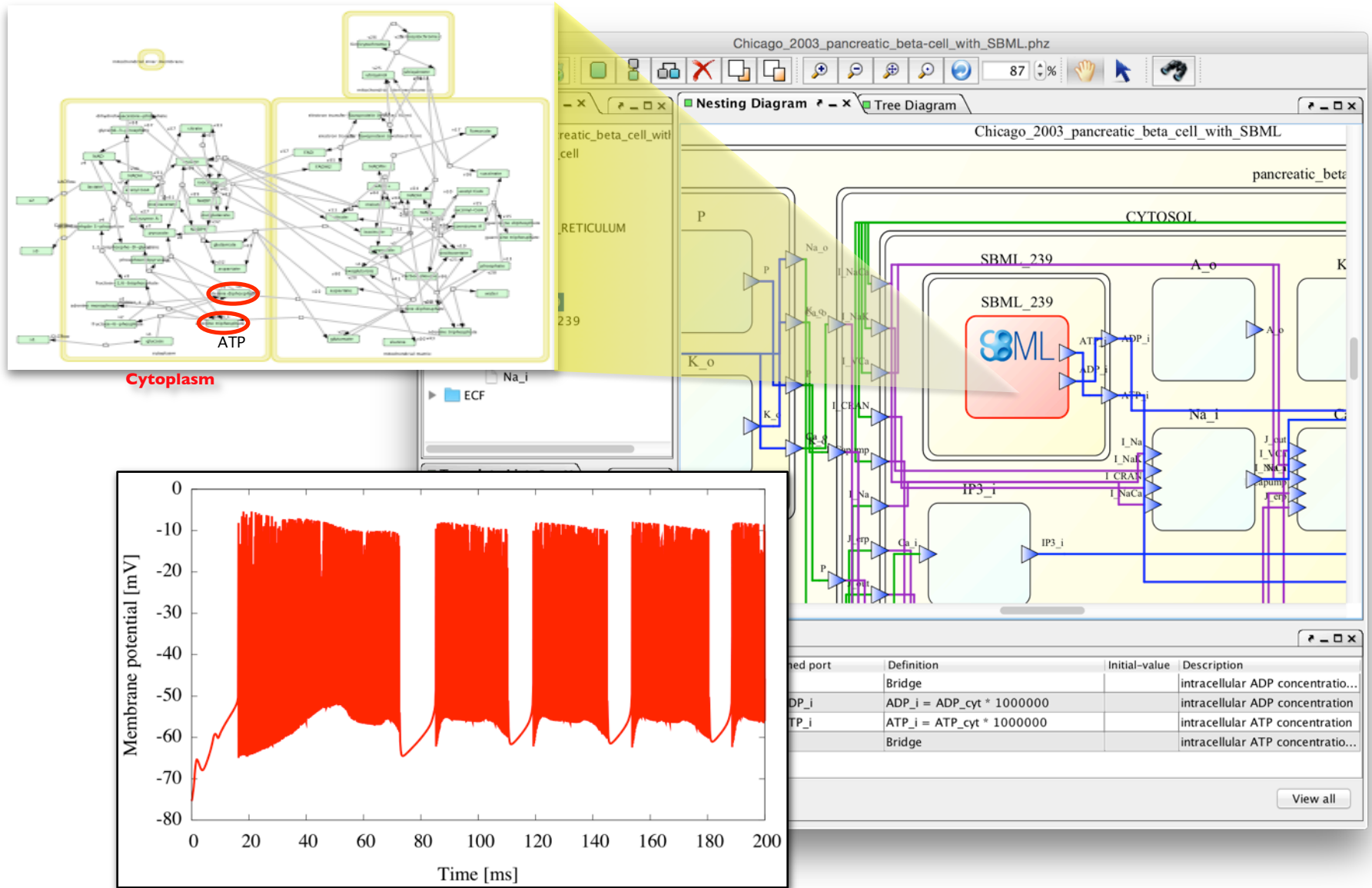
LE Fridlyand, N Tamarina, LH Philipson (2003) Modeling of Ca<sup>2+</sup> flux in pancreatic beta-cells: role of the plasma membrane and intracellular stores. American journal of physiology. Endocrinology and metabolism. vol. 285




N Jiang, RD Cox, JM Hancock. (2007) A kinetic core model of the glucose-stimulated insulin secretion network of pancreatic beta cells. Mamm Genome. 18(6-7):508-20.



# Example: Pancreatic Beta Cell





# Simulation Flint

# Simulation

Simulator *Flint*

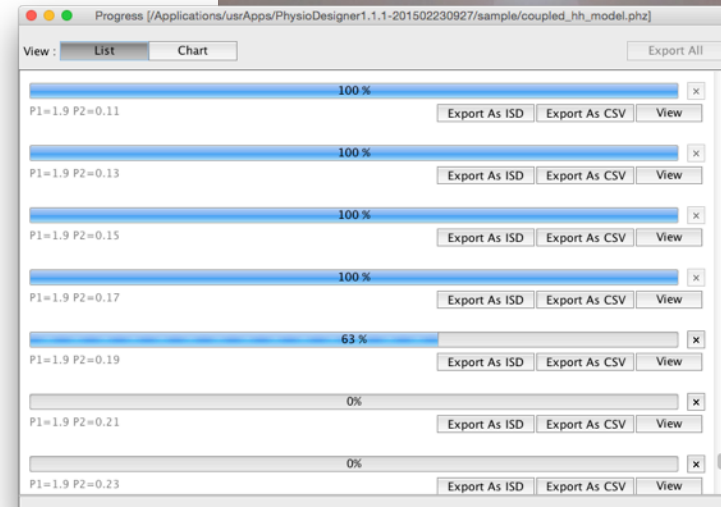
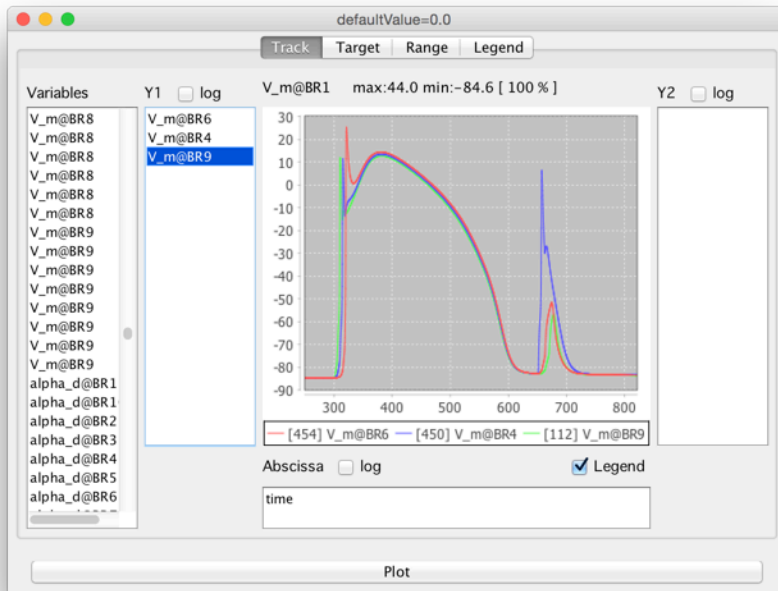


Supports SBML as well as PHML

Supports SBML + PHML hybrid

Export to C++, JAVA

Export to FreeFEM format





# Flint K3

**Interface Server** is at somewhere in the internet.

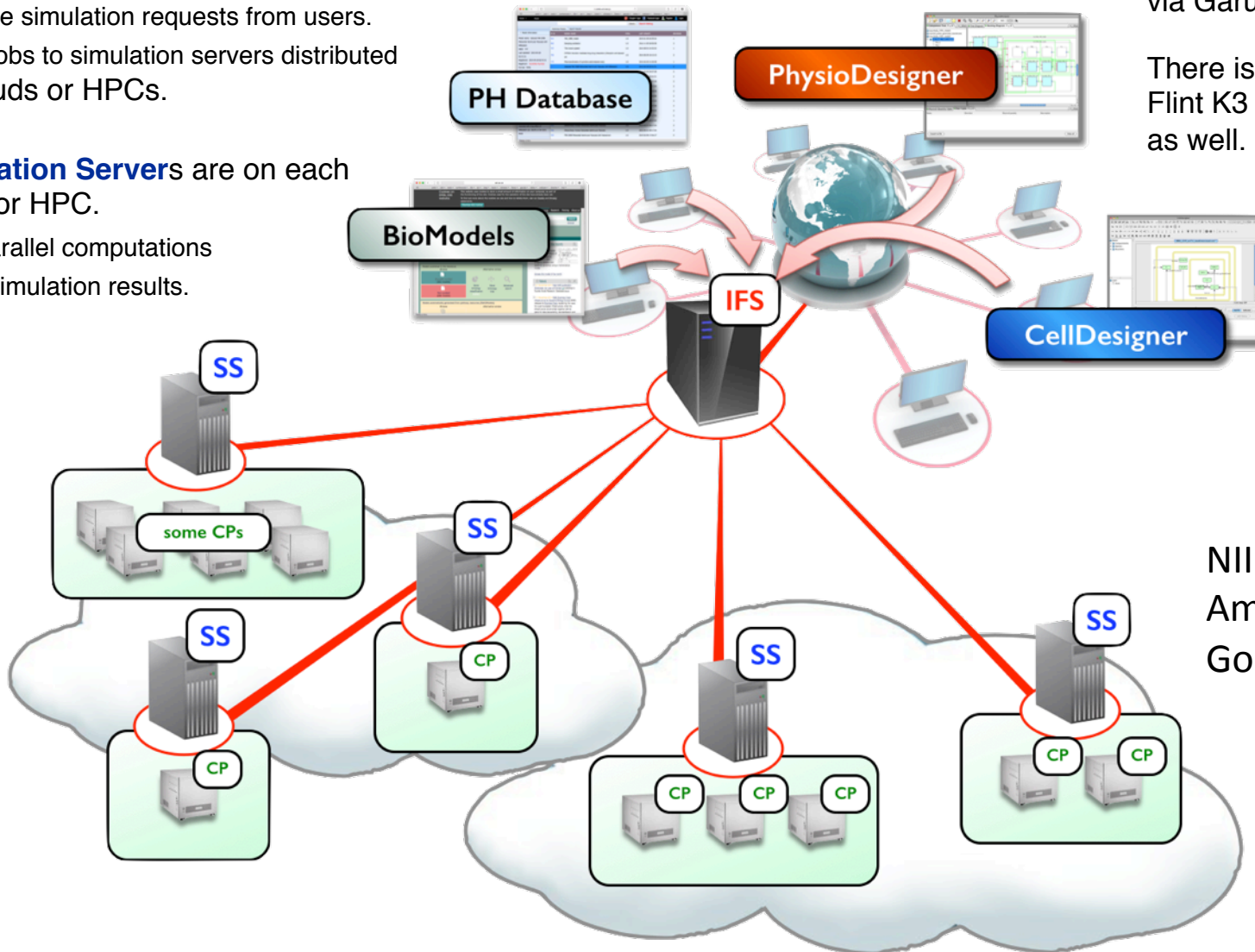
- Receive simulation requests from users.
- Send jobs to simulation servers distributed on clouds or HPCs.

**Simulation Servers** are on each cloud or HPC.

- Run parallel computations
- Store simulation results.

Garuda alliance member applications can send simulation jobs to Flint K3 via Garuda APIs.

There is a web interface of Flint K3 to submit requests as well.



NII cloud  
Amazon cloud  
Google cloud  
etc...

# Flint K3

<http://flintk3.org>

OIST Biological model simul x

servers potal oist iGoogle tools conferences lang

Flint K3

Login with your Social Account

DropBox Facebook Google+ Twitter Evernote

If you do not have any SNS accounts, click <here> to login with a temporary

Copyright c 2012 - OIST

Pad 2:06 PM 100%

Job Status

Status Completed

Submitted 2015/01/30 14:40:12

Canceled

Started 2015/01/30 14:40:12

Progress 100 %

Completed 2015/01/30 14:40:21

Request Job Information - Progress report settings

SNS Last Update Control

Progress report settings

Graph Image

Download Simulation Data (3.79 MB)

Transfer to Your Storage Directory

DropBox Facebook Google+ Twitter Evernote

SmartBank 14:28 73% 100%

Graph Image

Download Simulation Data (3.79 MB)

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OIST Biological model simul x

https://flint.unit.oist.jp/job\_status/?no=7195

servers iGoogle potal oist tools conferences Other Bookmarks

Login : asai yoshiyuki (DropBox)

Biological model simulation

Top Job Control

Last login:2012/07/17 12:36:24

Request Job Information

Job ID	7195
Job Name	instances
e-mail	yoshiyuki.asai@oist.jp

Job Direction Information

Direction	Submit
Request Day	2012/07/17 12:39:54
Canceled Day	
LastUpdate Day	2012/07/17 12:39:54

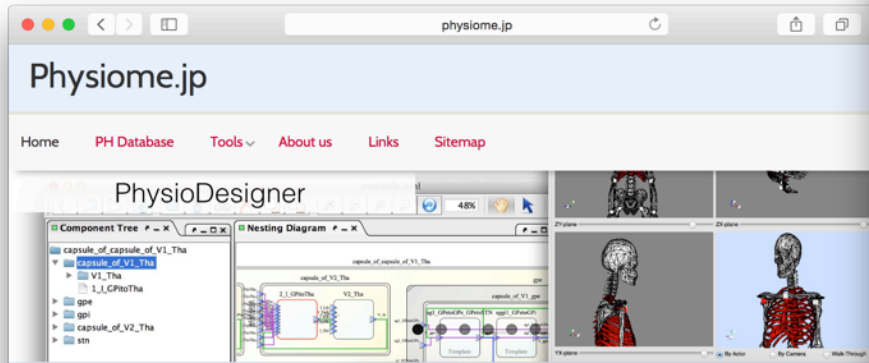
Job Status Information

Status	Completed
Started Day	2012/07/17 12:39:55
Progress	100 %
Finished Day	2012/07/17 12:40:29

BACK

Result Graph

# Physiome.jp and PH Database



phdb.unit.oist.jp

Home Model

Search Search Setting

Published Models Search Results

ID	MODEL NAME	PHML	LAST UPDATE	REVISION
829	Pribe-Beuckelmann human ventricular epicardial cell model	1.0	2015-02-22 01:54:39	1
828	Pribe-Beuckelmann human ventricular midcardial cell model	1.0	2015-02-23 18:10:26	1
827	Pribe-Beuckelmann human ventricular endocardial cell model	1.0	2015-02-22 21:16:20	1
826	Pribe-Beuckelmann human ventricular myocyte model (heart failure condition)	1.0	2015-02-23 18:10:26	1
825	Pribe-Beuckelmann human ventricular myocyte model	1.0	2015-02-22 01:54:39	1
824	Kurata 2005 Human Ventricular Myocyte Model (Midcardial cell) EAD generation condition	1.0	2015-02-23 01:35:03	1
821	Kurata 2005 Human Ventricular Myocyte Model (Midcardial cell)	1.0	2015-02-22 00:10:37	1
820	Kurata 2005 Human Ventricular Myocyte Model (Epicardial cell)	1.0	2015-02-22 21:17:57	2
819	Kurata 2005 Human Ventricular Myocyte Model (Endocardial cell)	1.0	2015-02-23 03:32:30	2
818	Ohara-Rudy Human Midcardial Ventricular Myocyte (modified Ina)	1.0	2015-02-22 21:16:20	1
817	Ohara-Rudy Human Epicardial Ventricular Myocyte (modified Ina)	1.0	2015-02-23 02:26:42	1
816	Ohara-Rudy Human Endocardial Ventricular Myocyte (modified Ina)	1.0	2015-02-23 02:09:36	1

Model Information

Model name: Pribe-Beuckelmann human ventricular endocardial cell model

DBID: 827

Last Updated: 2015-02-22 21:16:20

Registered: 2015-02-22 21:16:20

Registrant: Kunichika Tsunoto

Format: PHML

State: Uncurated

Revision: 1

Description: Leo Pribe, Dirk J. Beuckelmann. Simulation study of cellular electric properties in heart failure. Circulation Research. 1998;82:1206-1223.

## Physiome.jp - toward in silico

Physiome.jp is a part of the Worldwide Integrative promote Physiome and Systems Biology. The building and physiological data) representing biological function served as elements in the catalogue of human knowledge understanding of human physiology, eventually contribute to medicine and predictive medicine.

## Platform Overview

Our platform is composed of several applications and application to support modeling of physiological systems simulator Flint. Also tools for medical image processing.

## Physiome.jp

Home PH Database Tools About us Links Sitemap

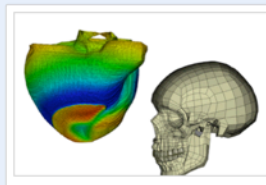
## PH Database

The PH database (PHDB) at www.physiome.jp currently includes three databases, and time series data. In the PHML framework, it is possible to integrate morphological and time series data. (Updated, 1st January 2015)

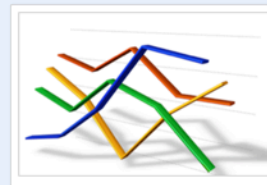
PHML Model Database



Morphology Database



Timeseries Database

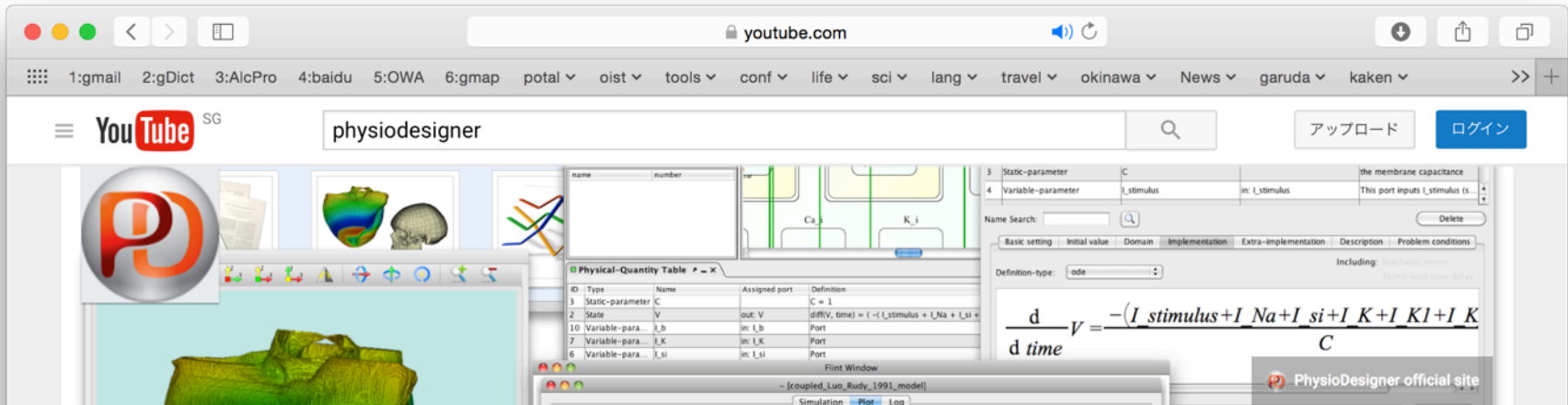


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<http://physiome.jp>



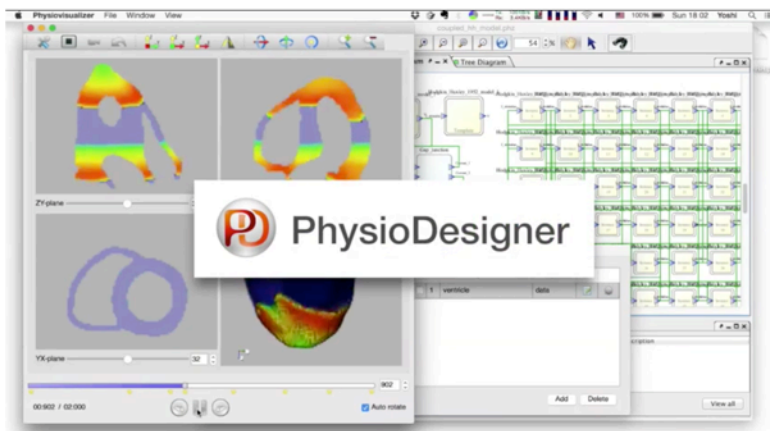
# On-line Tutorials @ YouTube



## PhysioDesigner

チャンネル登録 14

ホーム 動画 再生リスト チャンネル フリートーク 概要



### Channel Trailer

視聴回数 96 回 1 か月前

PhysioDesigner is software to assist you to develop multi-level models of physiological functions with graphical user interface. A simulator Flint can perform simulations of those models. More information is available at <http://physiodesigner.org>. Relevant tools are available at <http://physiome.jp>.

BGM: "I Can't Imagine Where I'd Be Without It" in Thoughtless by Chris Zabriskie. <http://freemusicarchive.org...> under a Creative Commons Attribution 4.0 (<http://creativecommons.org/...>) もっと読む

### Tutorials



# People behind

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