

HD-Physiology Project

**A Japanese Flagship
Physiological Modeling Project**

Hiroaki Kitano

Okinawa Institute of Science and Technology
The Systems Biology Institute

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HD-PHYSIOLOGY

HIGH

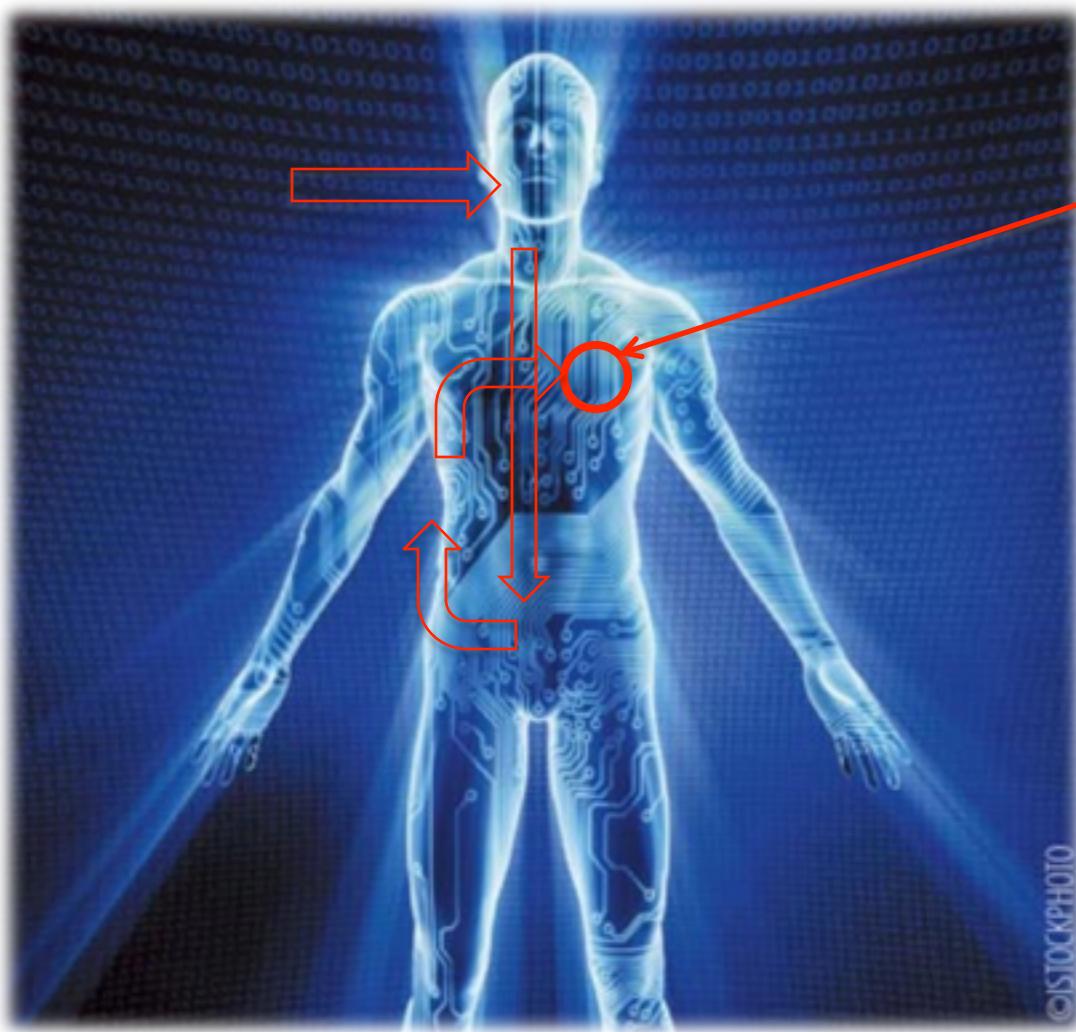
DEFINITION

HUMAN

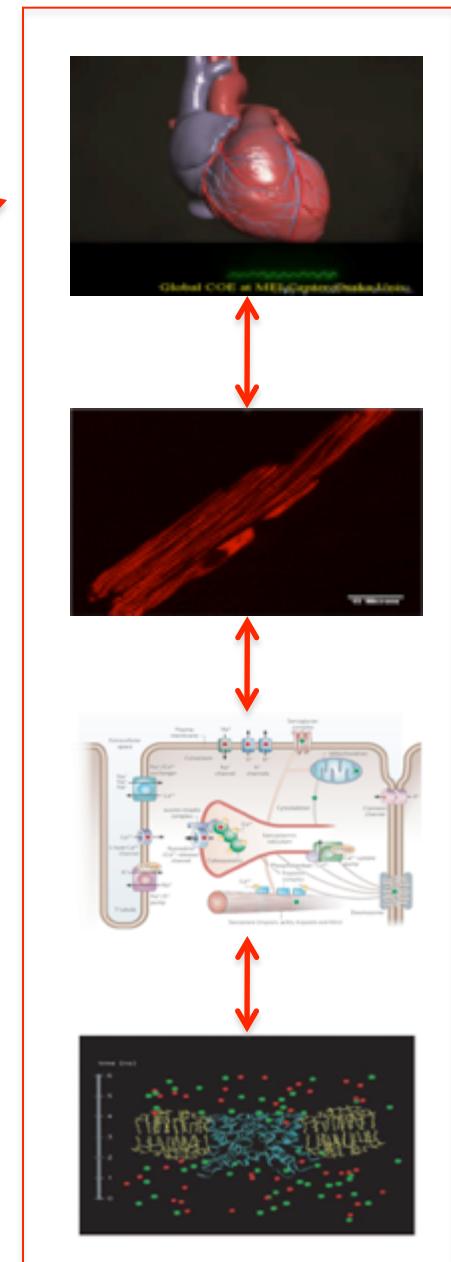
DISEASE

HIERARCHICALLY DESIGNED

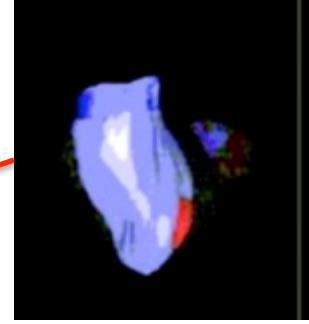
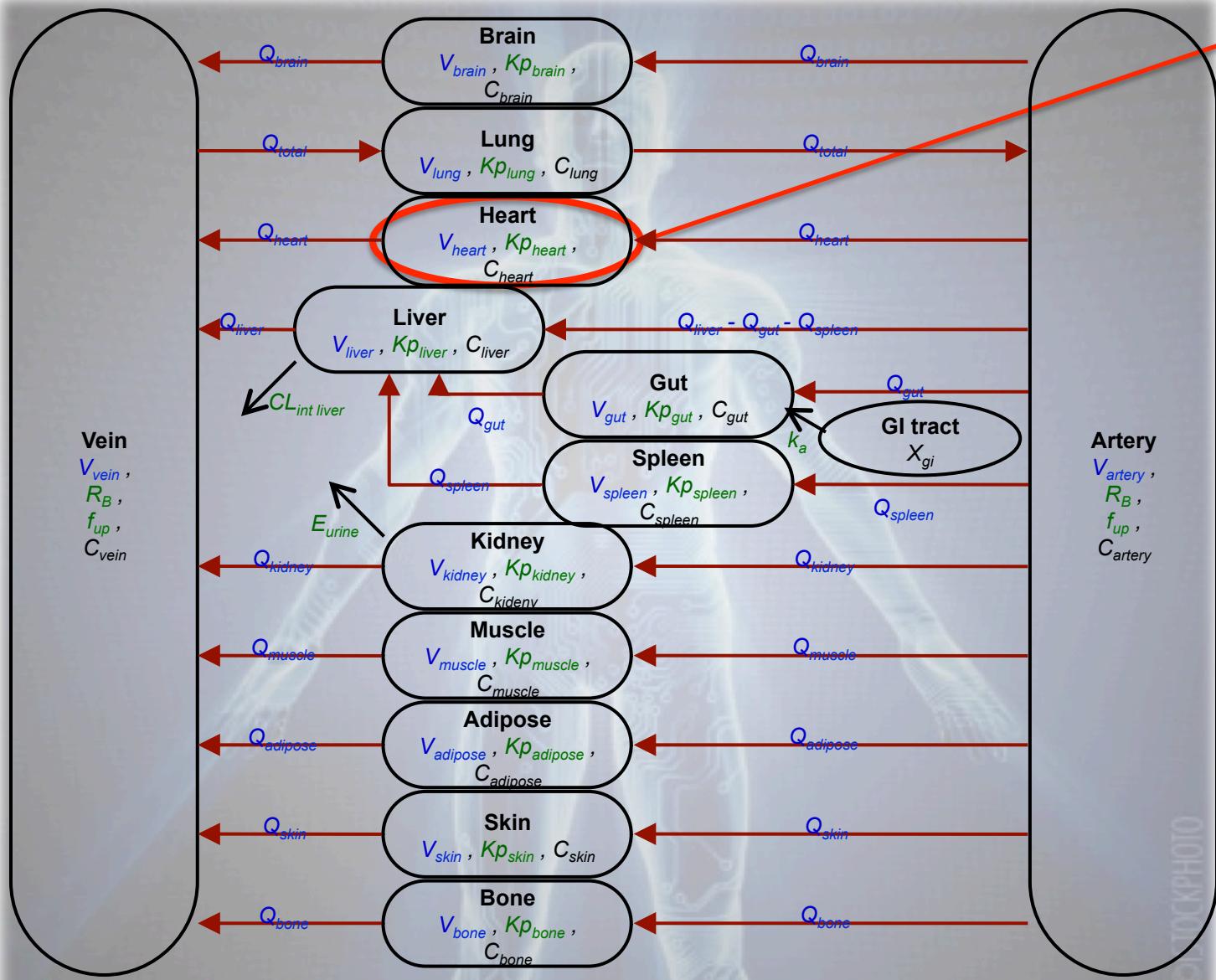
HD-Physiology Project



ADME/PK model

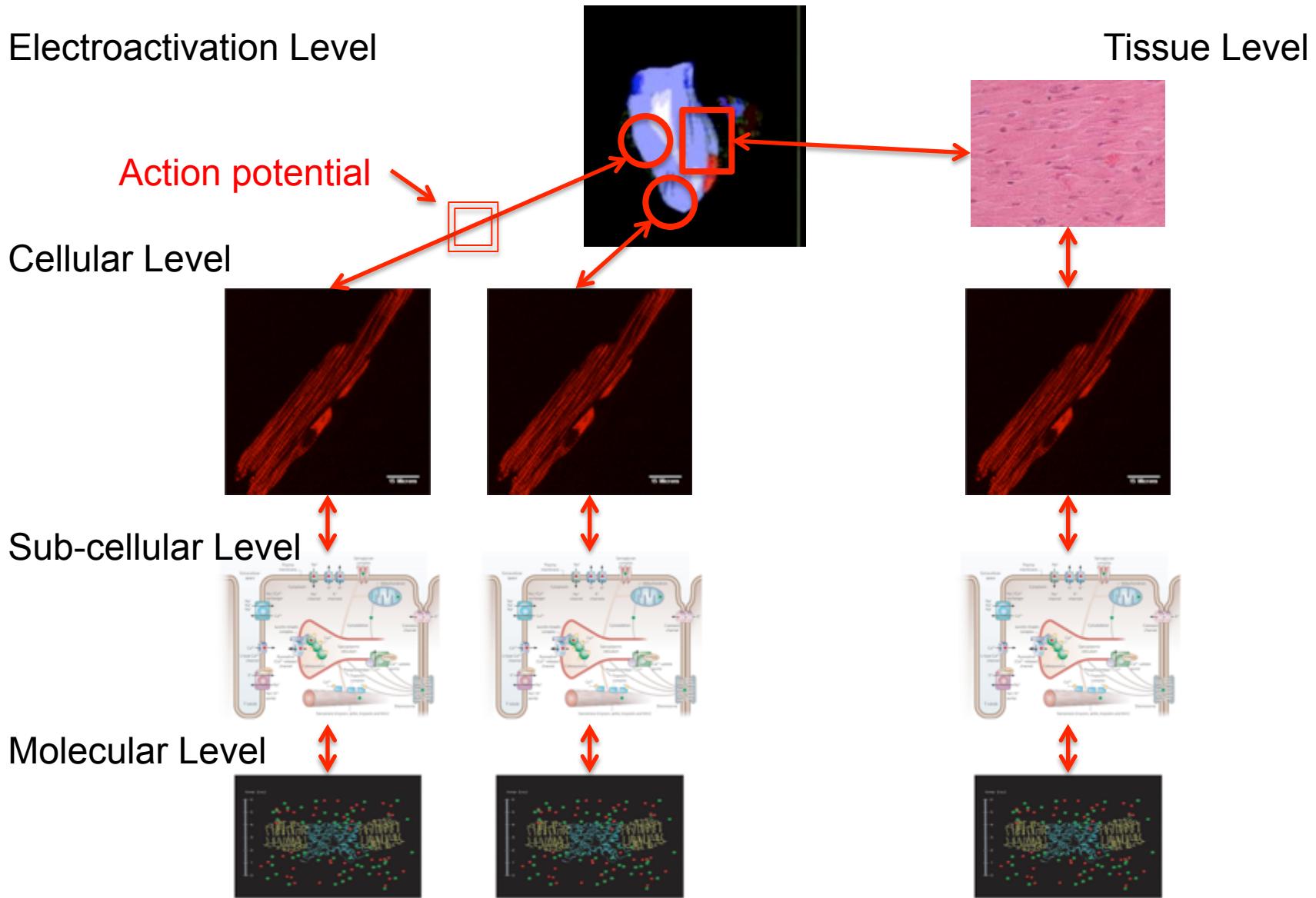


Horizontal Integration

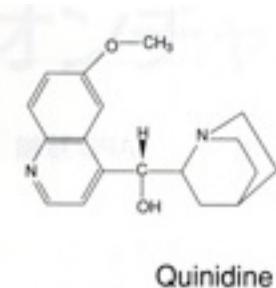


Vertically Integrated Heart Model

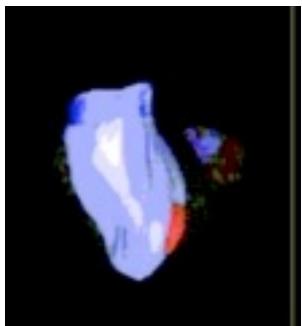
Vertical Integration



Inter-layer interactions

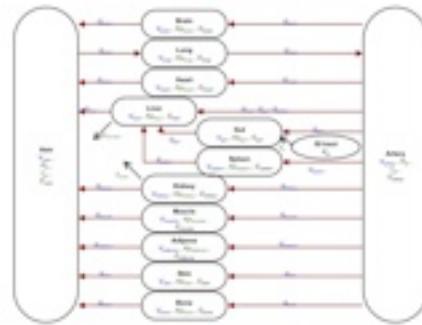


Drug

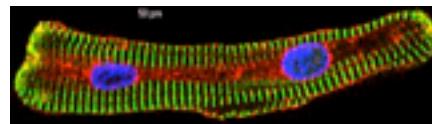


Electrophysiology

Doze, patterns, etc.

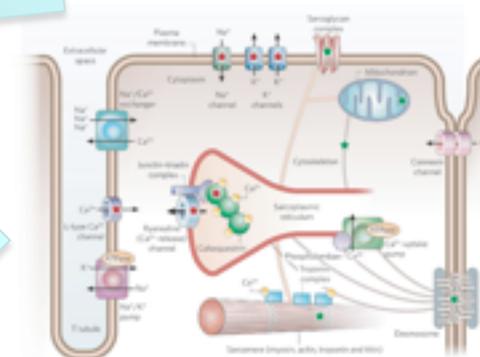


Genetic Polymorphism

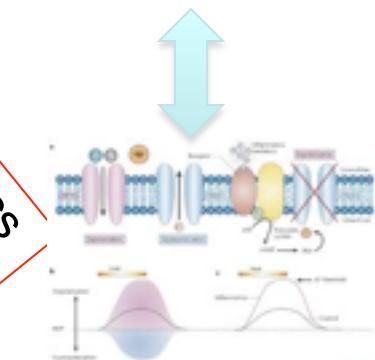


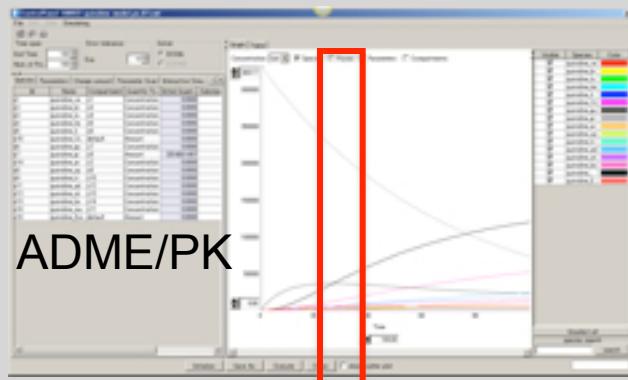
Action potential

Concentration at cellular level

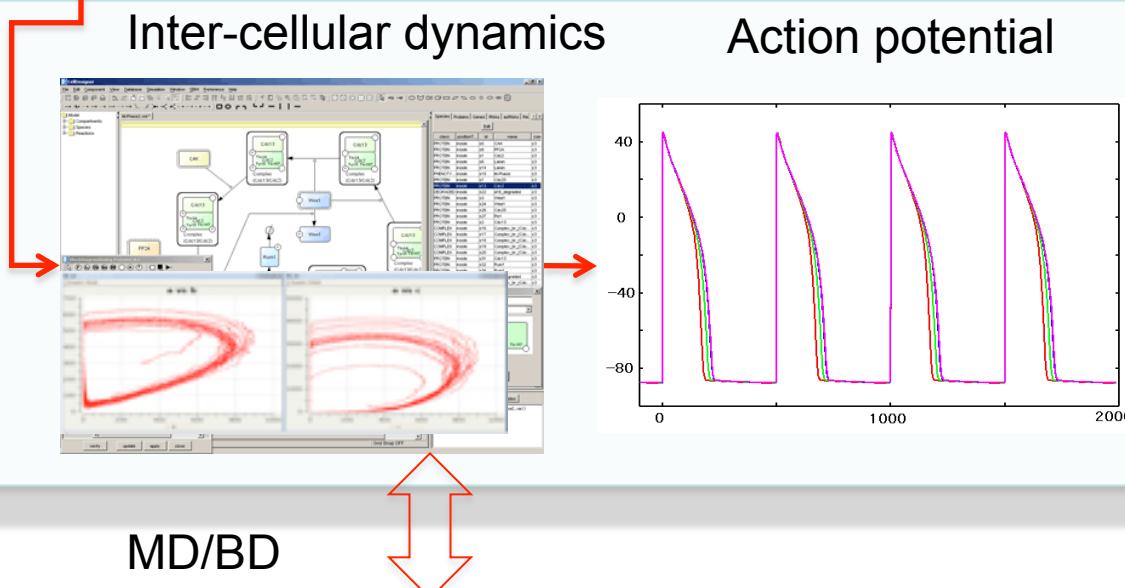


Intra-cellular dynamics

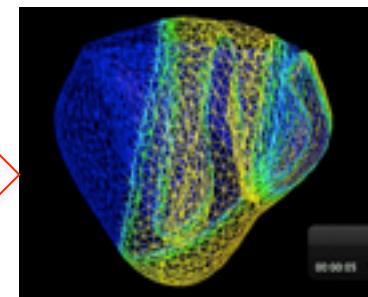




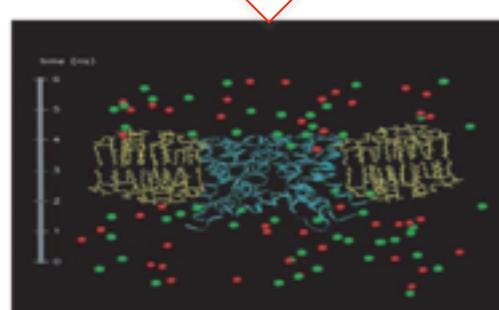
Loosely coupled real-time computing



Electrophysiology



Off-line computing
and visualization

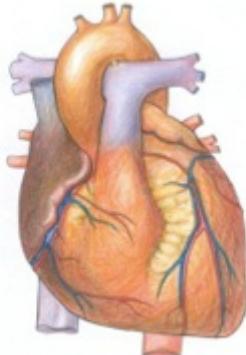


Off-line computing and
parameter integration

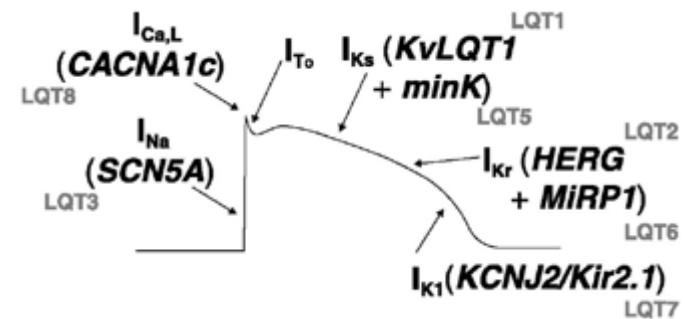


Possible application of cell based toxicology

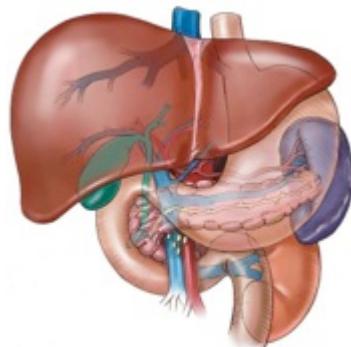
Prediction of QT elongation



QT elongation is one of the major cause of drug withdrawal. HERG channel is the main target of QT elongation.



Prediction of Hepatotoxicity



Liver takes central role in the clearance and transformation of chemicals

Step 1 oxidation, reduction, hydrolysis, hydration

Step 2 transferase

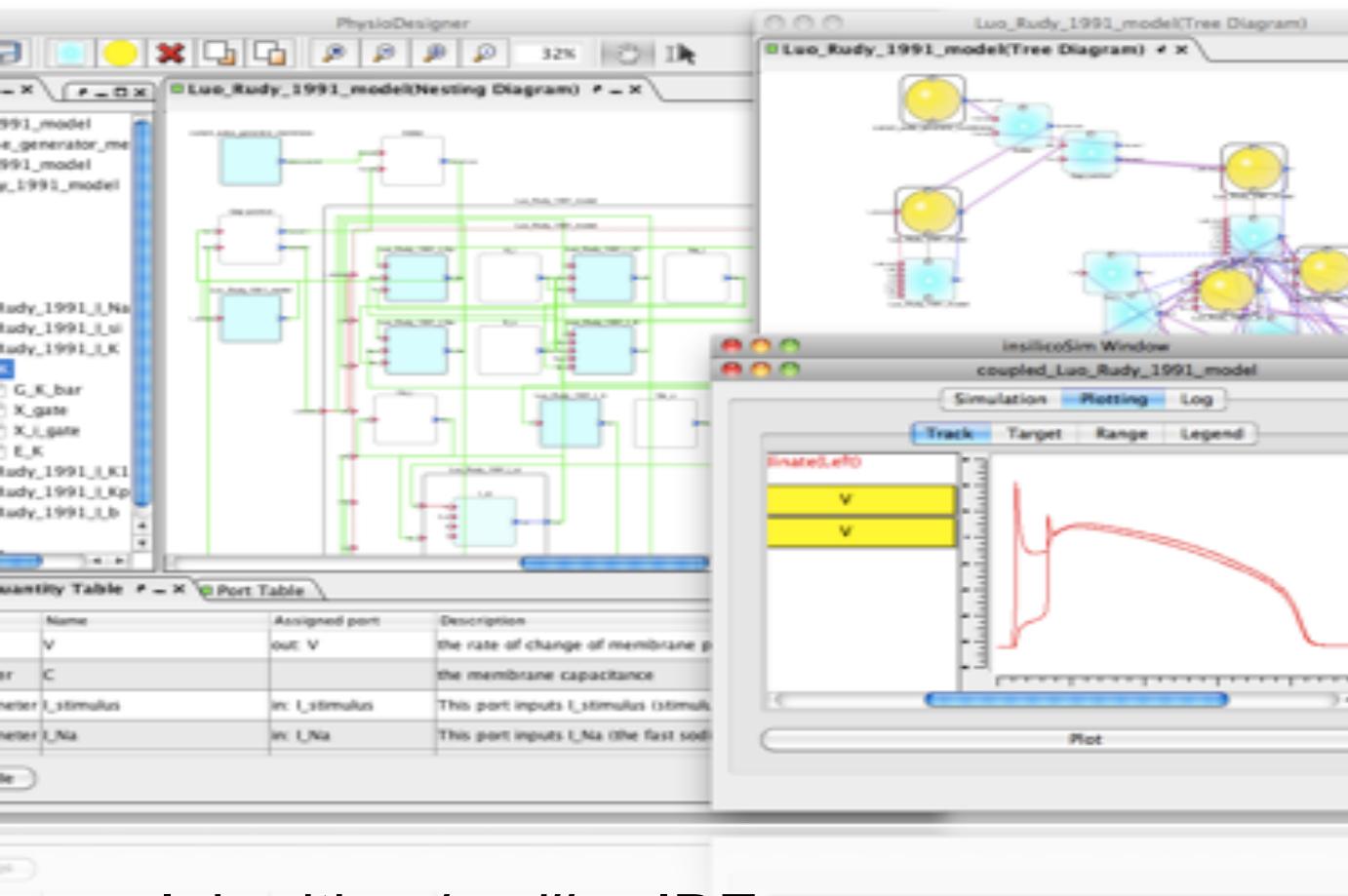
Hepatotoxicity means the liver damage induced by chemicals.

Hepatotoxicity is one of the major cause of drug withdrawal.

supported by:



collaborating with:

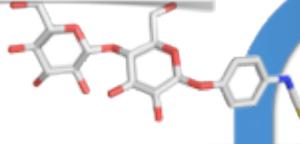


Inheriting *in silico* IDE
Tight integration with CellDesigner
Supports ISML, SBML, etc.
Garuda compliant

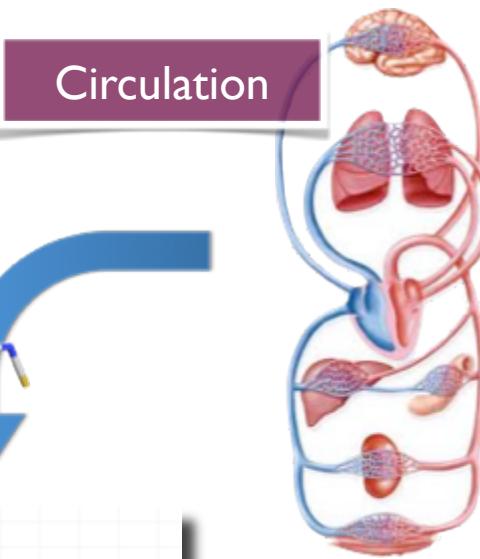
Modeling of Multi-level Physiological System

CellML

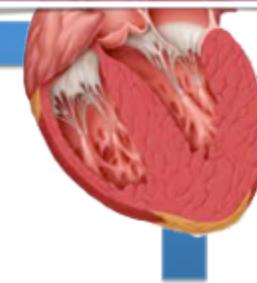
Medication



Circulation

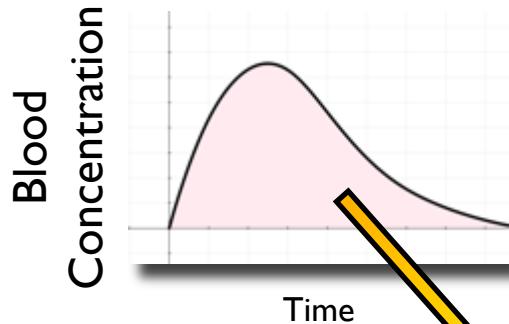


Organ-level
electro-kinematic
physiology



PHML

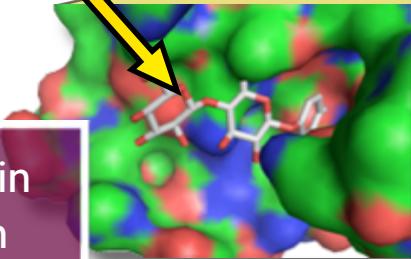
Blood
Concentration



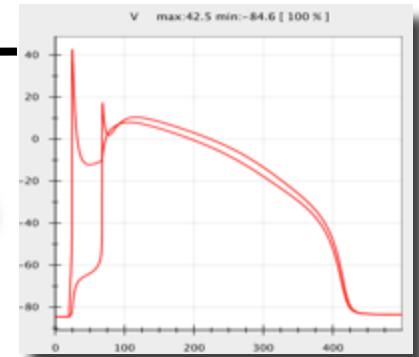
Time

SBML

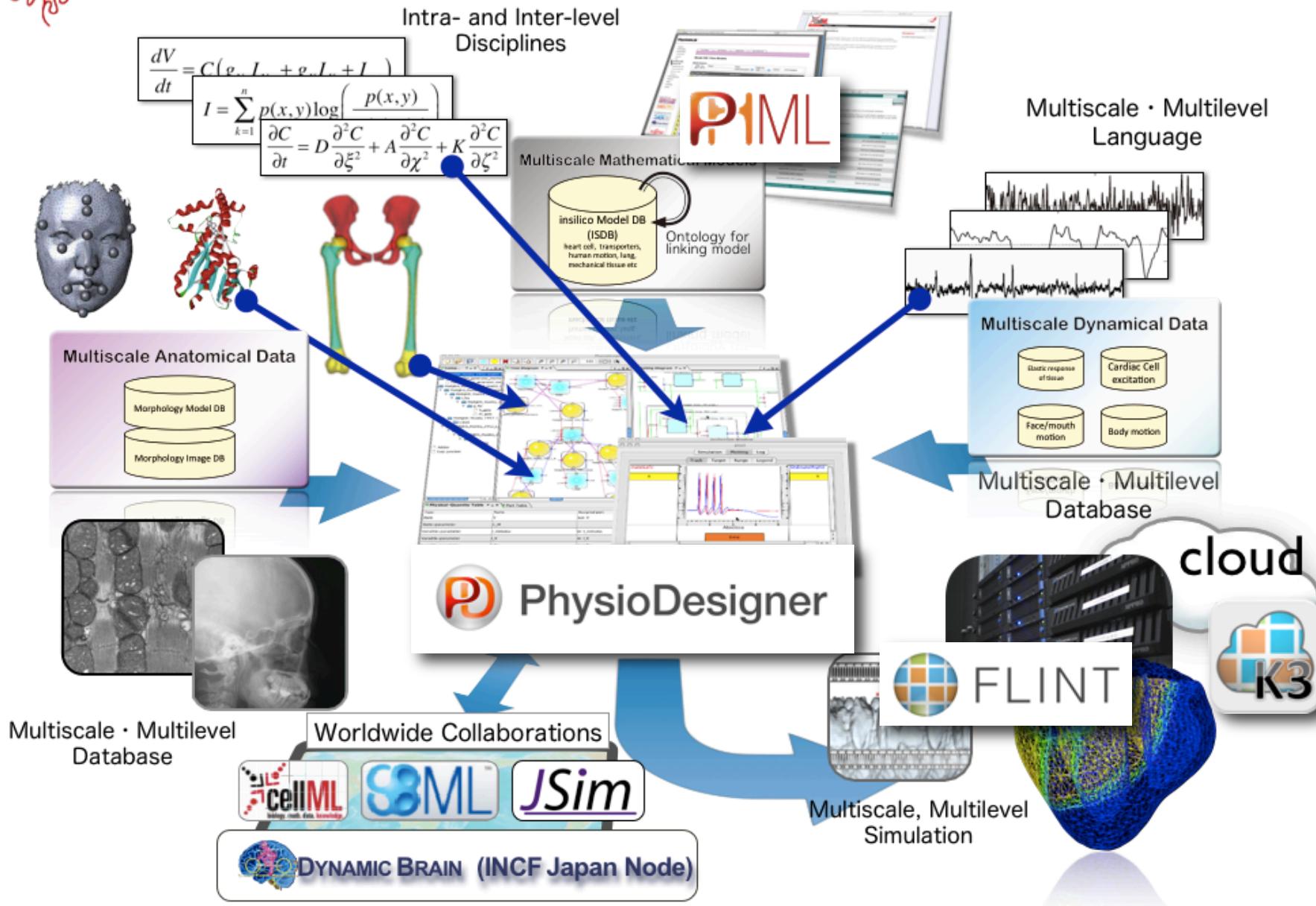
Drug-Protein
interaction



Cellular-level
electrophysiology

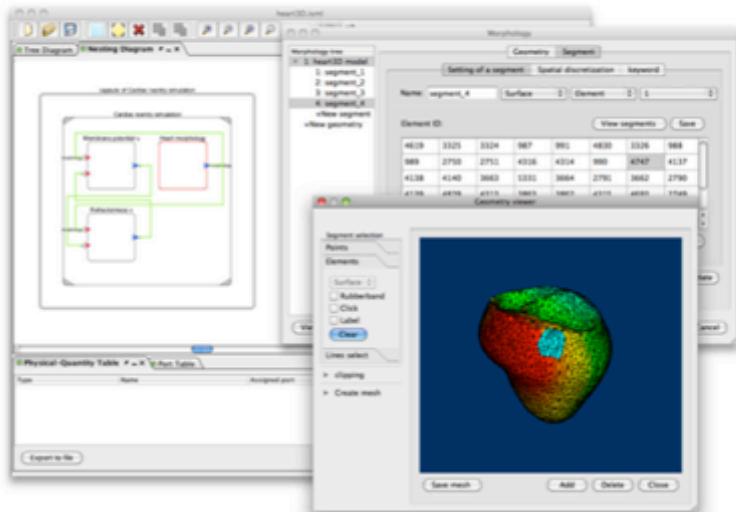


PhysioDesigner, PHML and Databases





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).

What's new

2013.04.24

- PhysioDesigner 1.0beta4 has been released.

2013.01.05

- PhysioDesigner 1.0beta3 has been released.

2012.09.18

- PhysioDesigner 1.0beta2 has been released.
- PhysioDesigner now complies Garuda alliance (see [here](#) for Garuda alliance)

2012.04.24

Former project

[InsilicoPlatform](#)

[Development History](#)

Model database

[ModelDB in Physiome.jp](#)

[Sitemap](#)

PhysioDesigne

r Supported by:

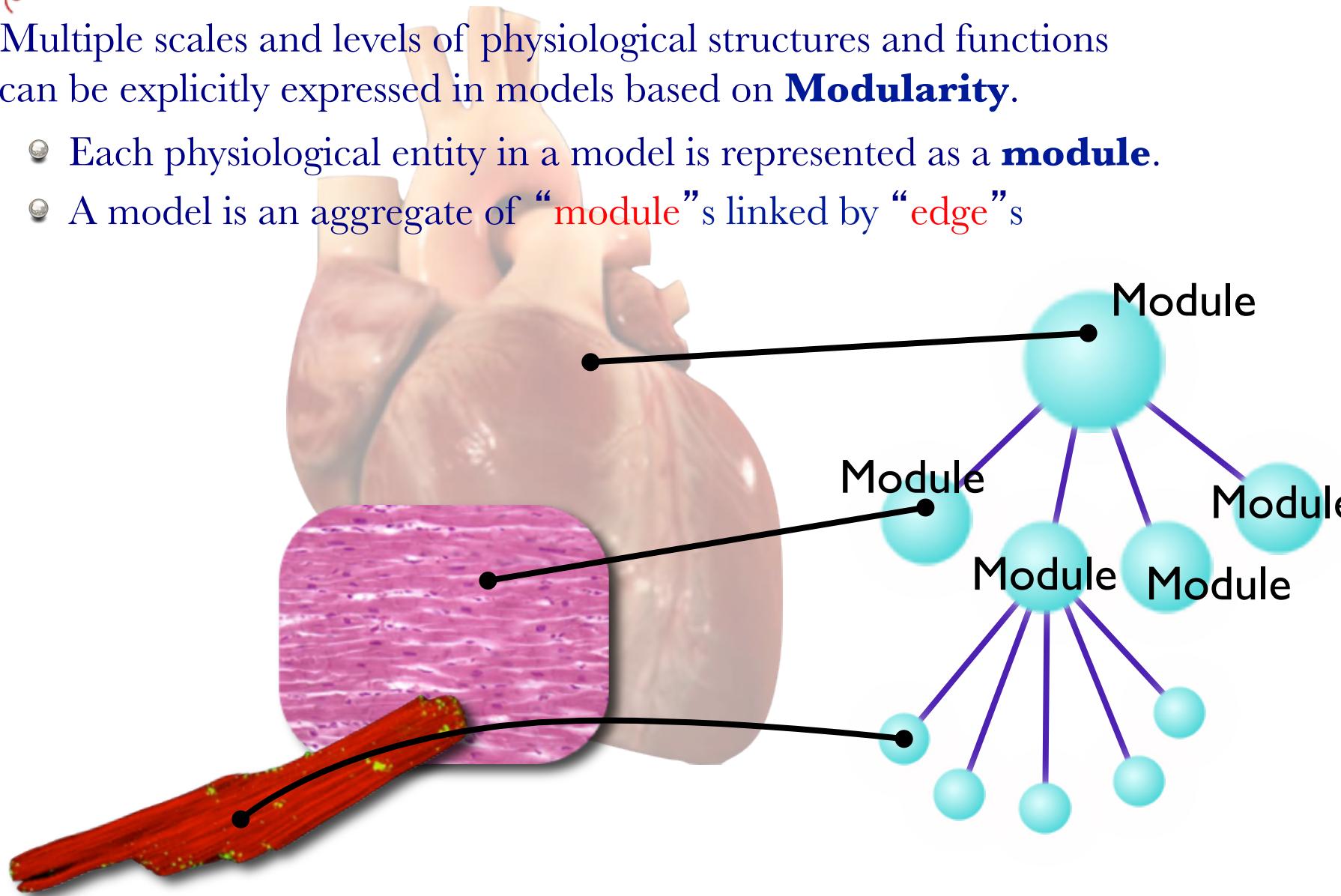


Collaborating with:



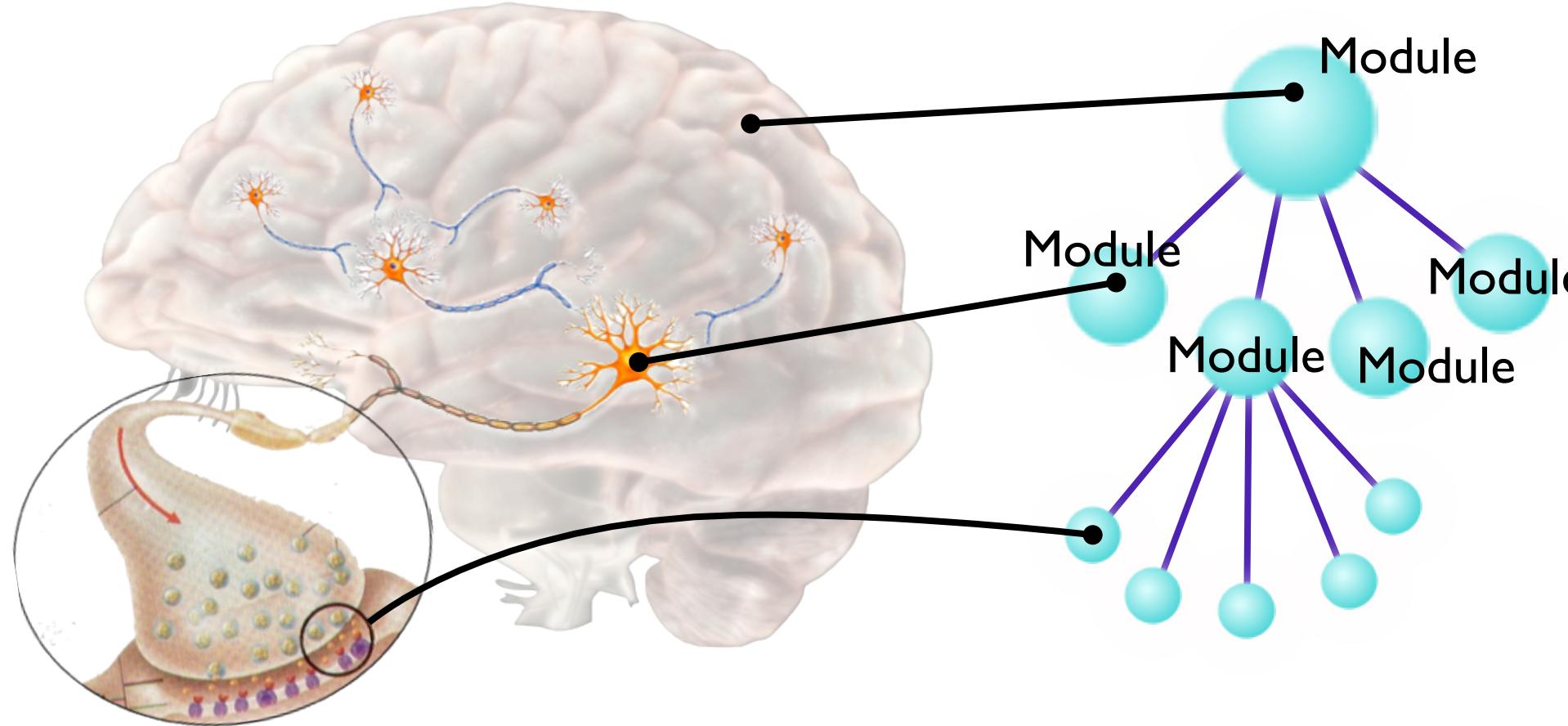
Principle Idea of PhysioDesigner

- 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

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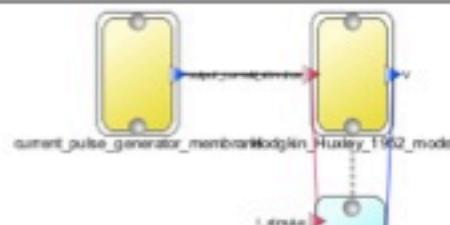


Structure of Mathematical Expressions in a Model

Hodgkin Huxley Model

Membrane

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

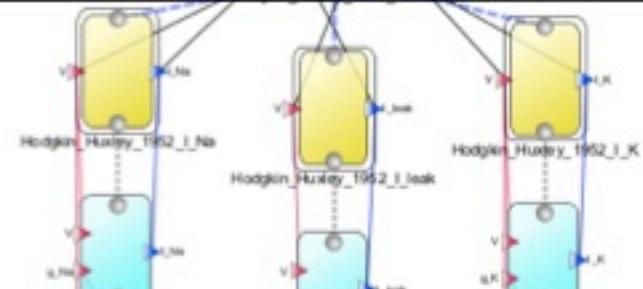


Ionic Currents

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

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

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



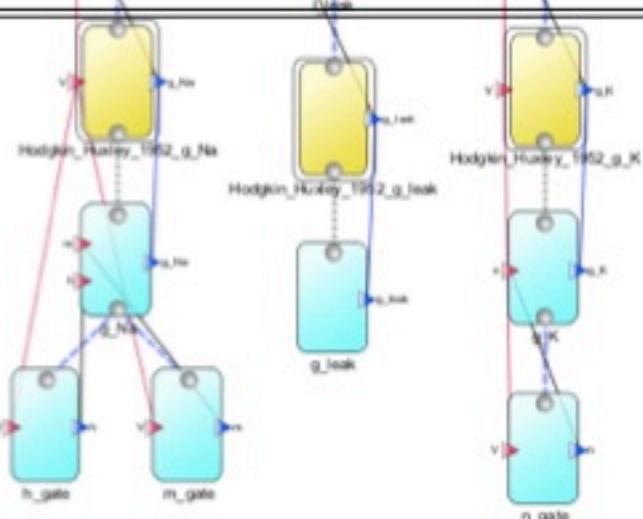
Conductance

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

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

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

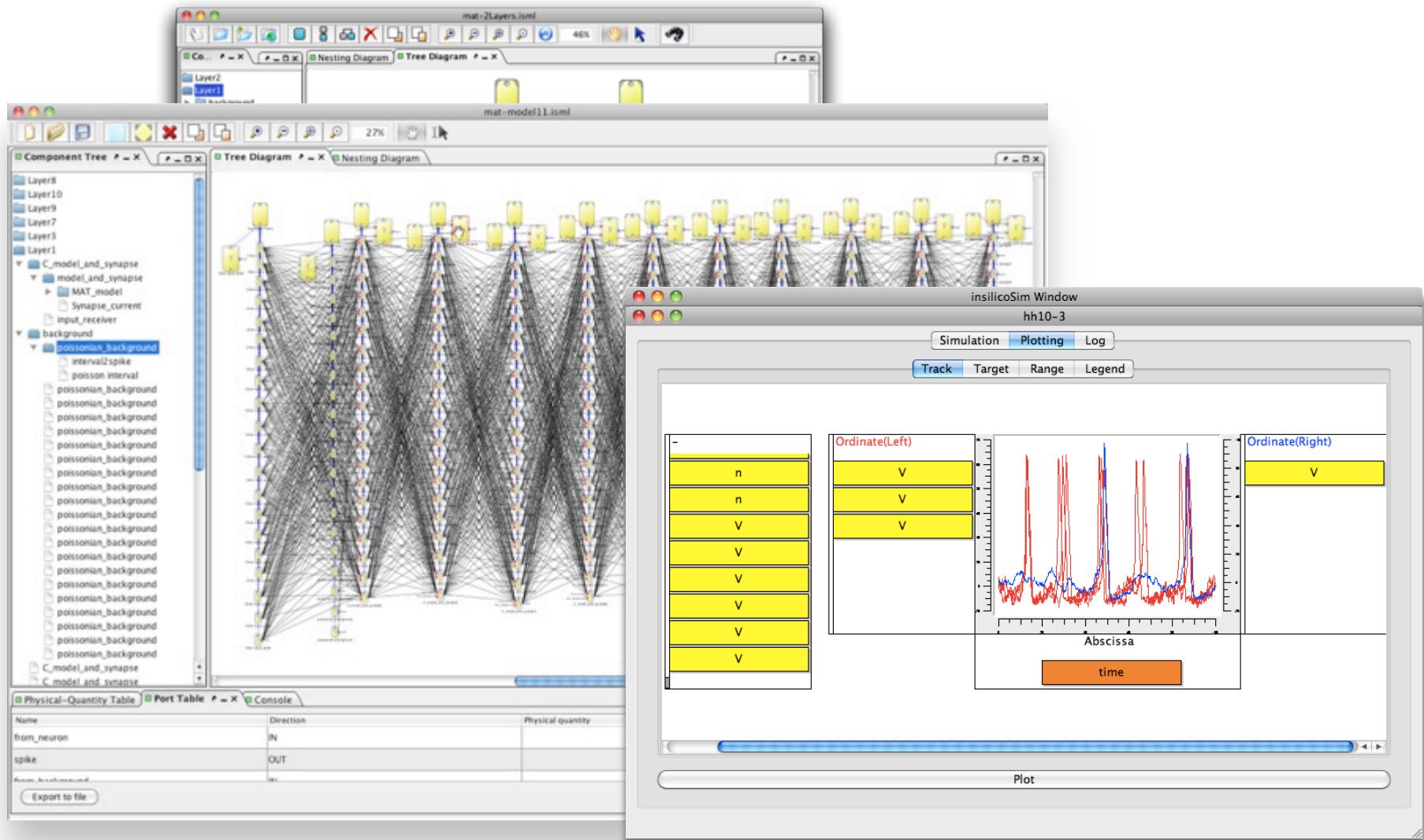
$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$



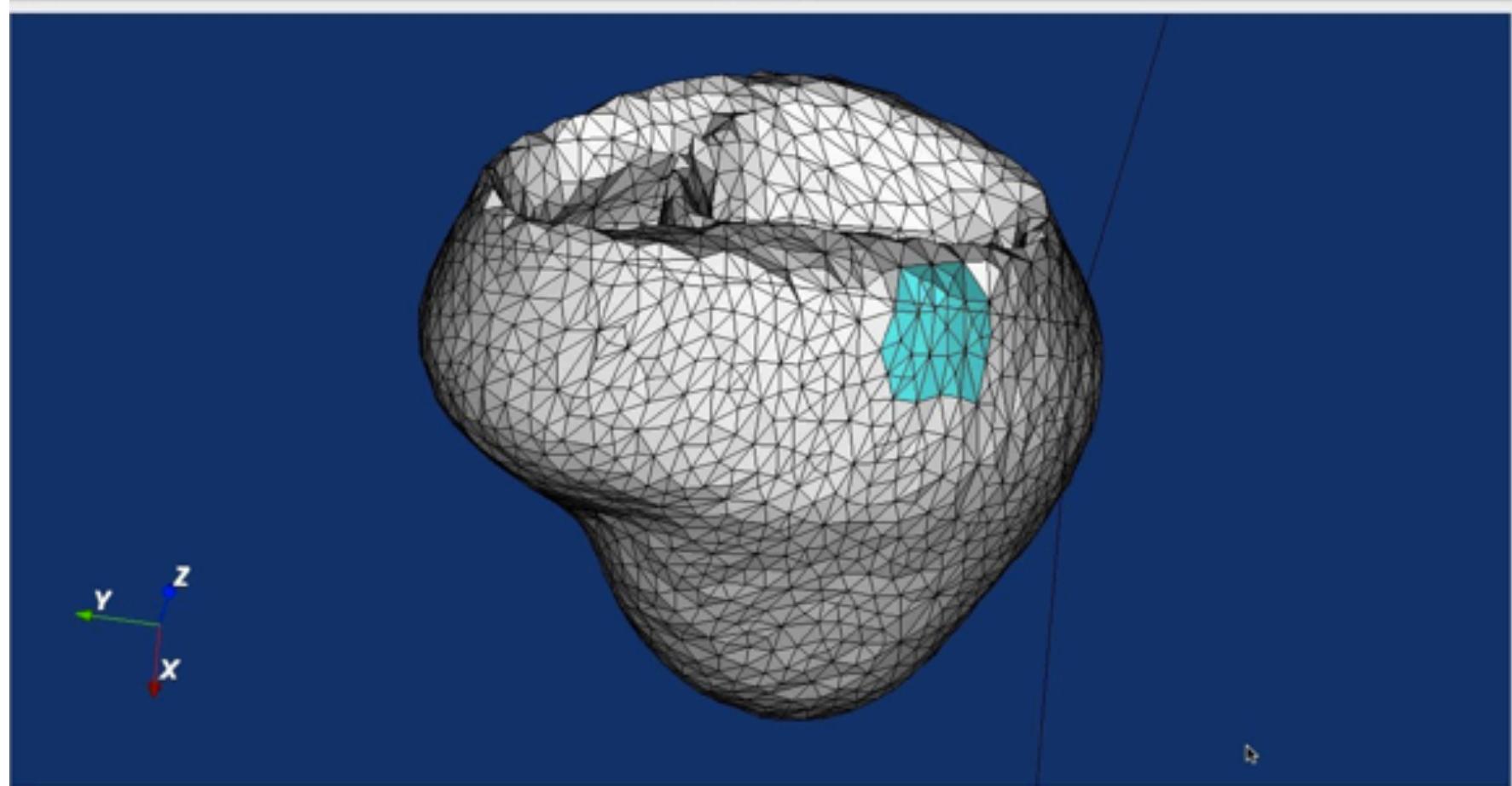
Channel Gate Variables

Use case: Neural network using

Link edges among instances randomly with given parameters
(e.g. 1:8 link for all neurons in Layer 1)



Geometry viewer



View Color

Shading Wireframe Shading+lines Scale

Points select Elements select Lines select

Surface : Rubberband Click Label

Clipping

Mesh

Clip Slice

3D : Option format: mesh :

Physical-quantity

Type	Name	Assigned port	Description
State	drug_vesnarinon	out: drug_vesnarinon	drug effect state
Static-parameter	ay		unbinding rate constant
Variable-parameter	by		binding rate constant

Delete

Basic setting Initial value Domain **Implementation** Extra-implementation Description Problem conditions

Including: Stochastic terms

Definition-type: **ode**

Terms with time delay

$$\frac{d}{d \text{ time}} \text{drug_vesnarinon} = ay \cdot (1 - \text{drug_vesnarinon})$$

Equation:

Export to file

Apply

F= MathML Editor

Close Apply editor1.mml

$\frac{d}{d \text{ time}} \text{drug_vesnarinon} = ay \cdot (1 - \text{drug_vesnarinon}) -$

Expression MathML Text

Relations

- "equals" relational operator
- "not equal to" relational operator
- "greater than" relational operator
- "greater than or equal" relational operator

Arithmetic Operators

Sequences And Series

Calculus And Vector Calculus

Elementary Classical Functions

Linear Algebra

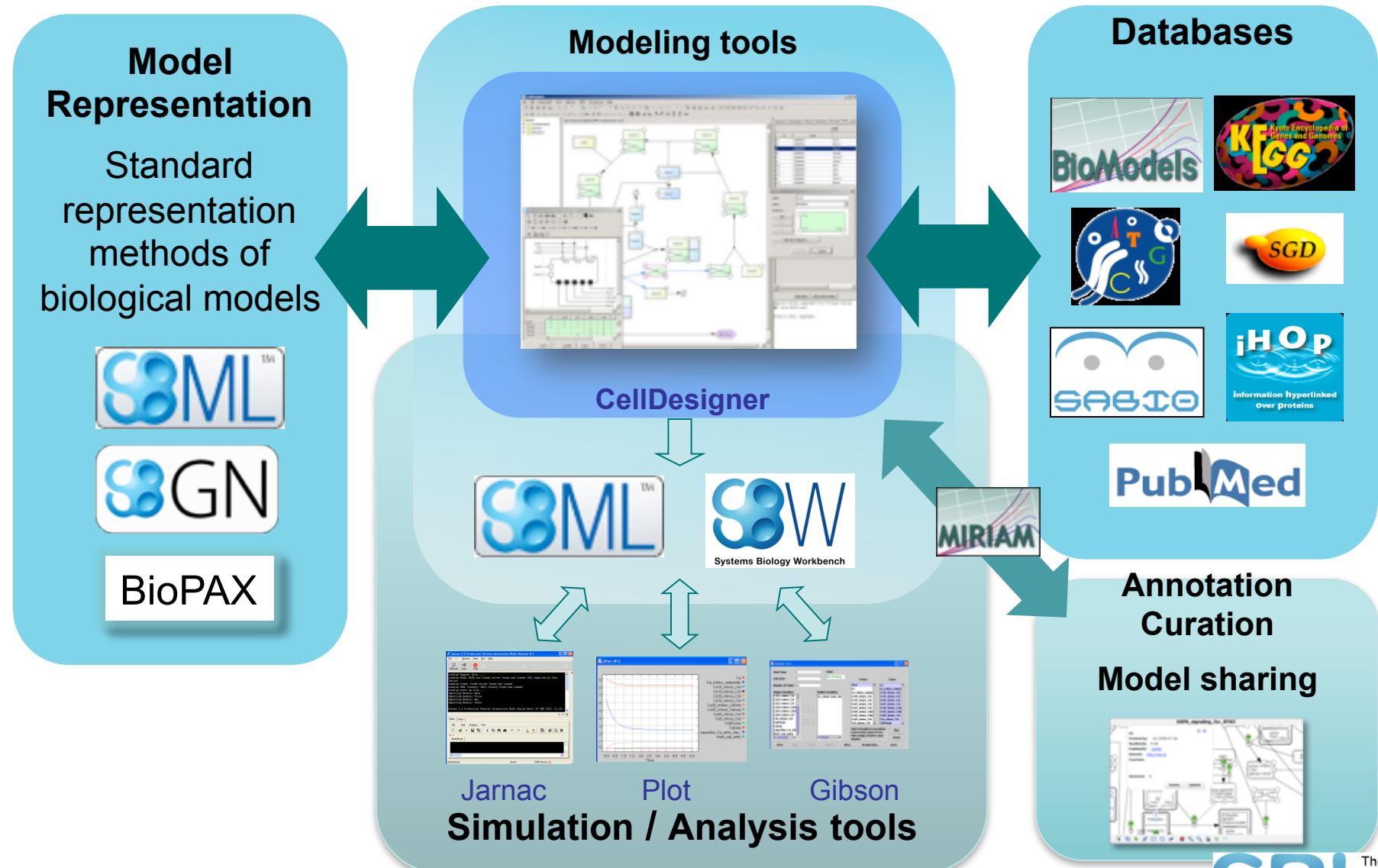
Logic Operators

Constant And Symbol Elements

Function

ISIDE Defined Function

CellDesigner Infrastructure





PHML

● XML-based model descriptive specification.

PHML has some compatibility with **CellML**, and is developing cooperative frameworks with **SBML**.

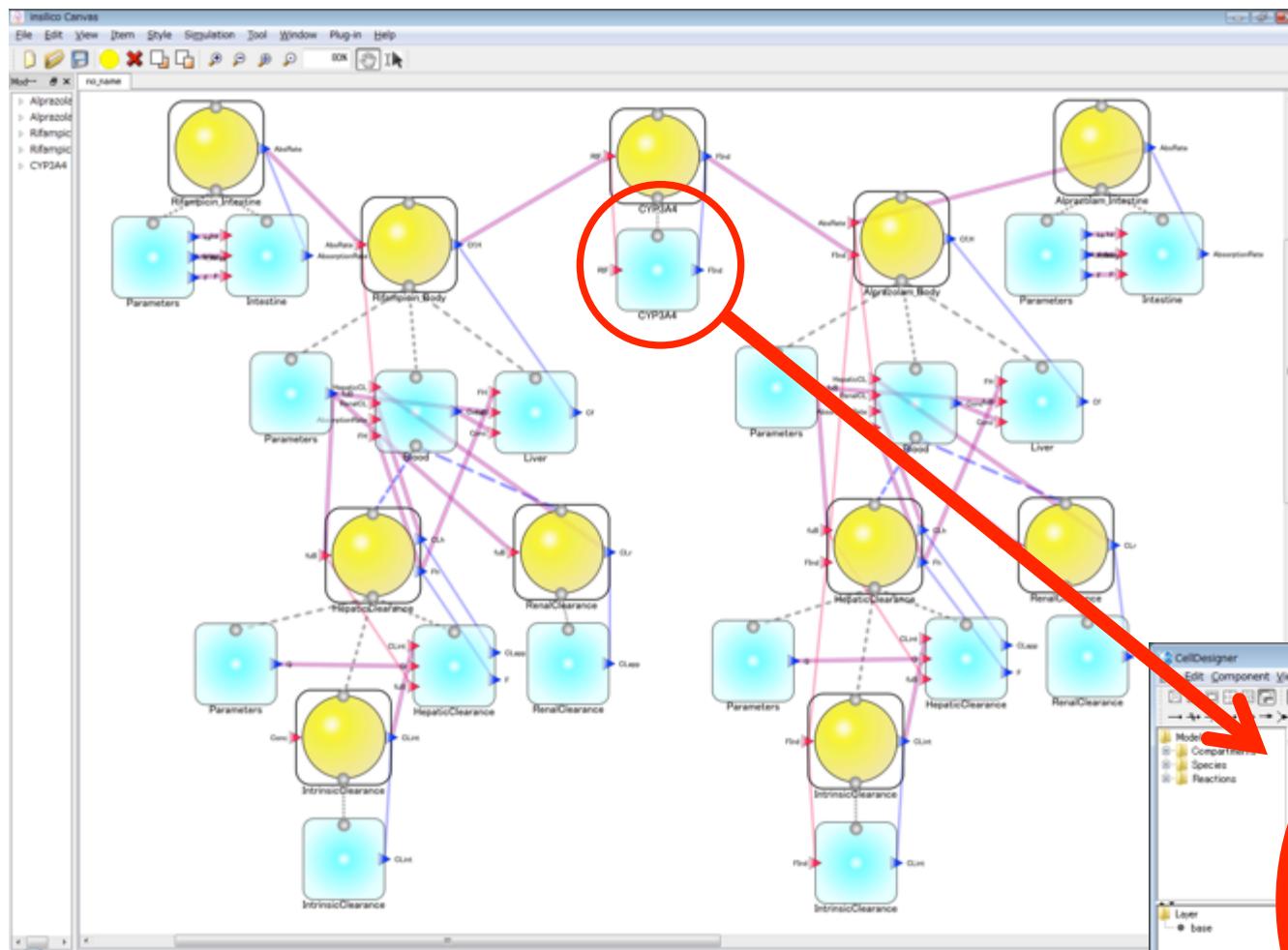
● PHML has some complementary features to describe models.

Requirements

- ★ It can express hierarchy of biophysical functions and structures.
- ★ It can describe dynamics of biophysical functions
 - Ordinary / Partial differential equations, agent based system, boundary conditions, etc
- ★ It can describe structures related to biophysical functions
 - Surface information, Volume information
- ★ It can describe meta-information of the model and physiology.

```
<?xml version="1.0" encoding="UTF-8" standalone="no"?>
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  <is:module module-id="00adeeb8-51c7-4828-979c-92888c58d897">
    <is:property>
      <is:name>m_U</is:name>
      <is:type>functional-unit</is:type>
      <is:capsulation state="true">
        <is:capsulated-by module-id="c2bf70d0-13af-426e-8e5c-fa8c78e91185"/>
      </is:capsulation>
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      <is:description/>
    </is:property>
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        <is:name>v</is:name>
        <is:description/>
      </is:port>
      <is:port port-id="2" direction="out">
        <is:name>u</is:name>
        <is:reference physical-quantity-id="1"/>
      </is:port>
    </is:port-set>
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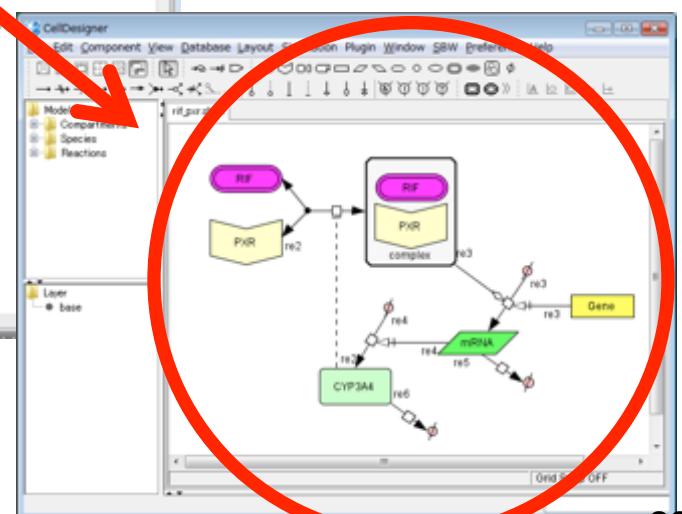
PHML-SBML Hybrid Simulation: Dynamics of In Vivo Pharmacokinetic Drug-Drug Interaction



rifampicin → alprazolam
CYP3A4 induction

Created by PhysioDesigner

Created by CellDesigner 4.2



SBML-PHML Hybrid Simulation

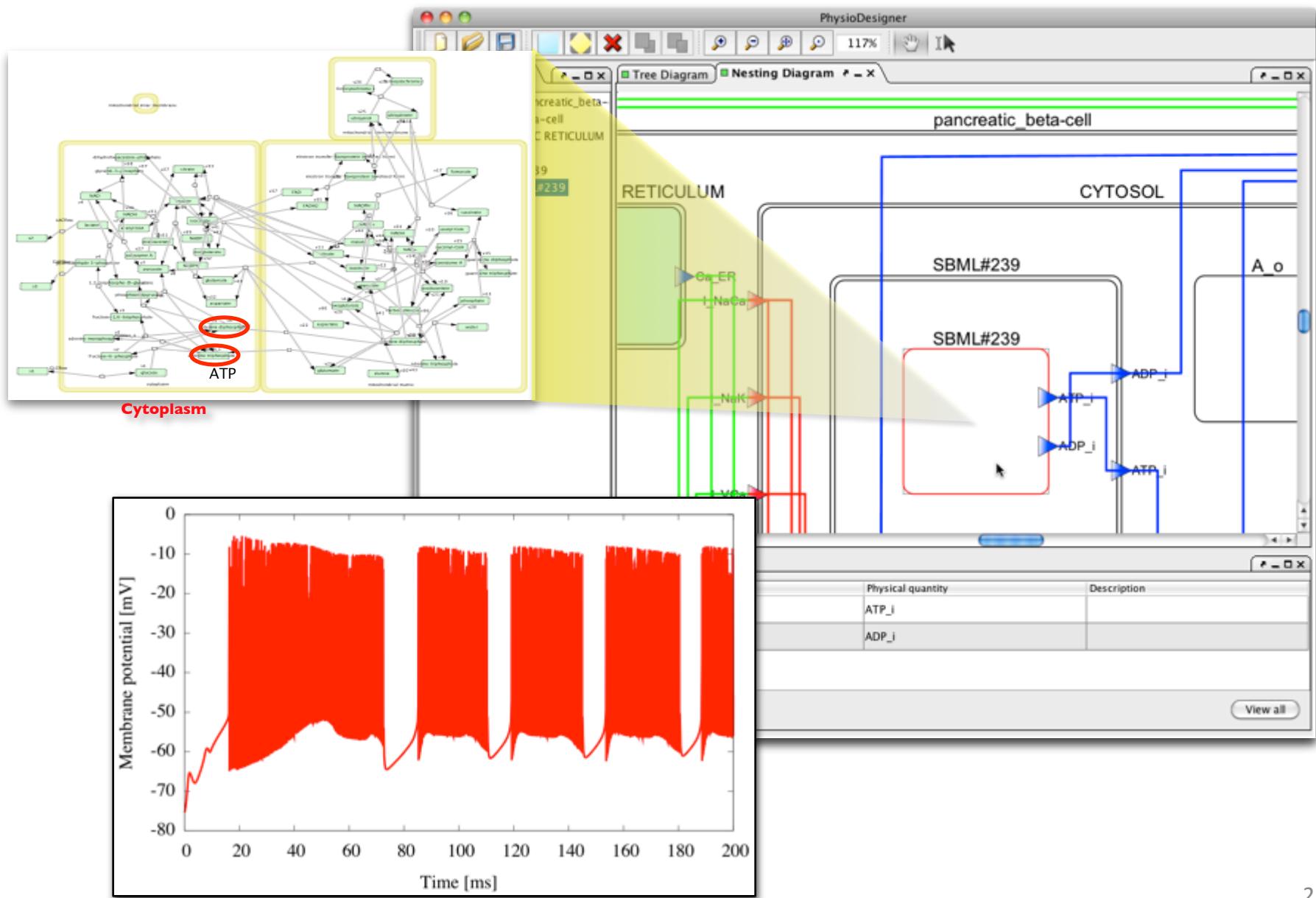
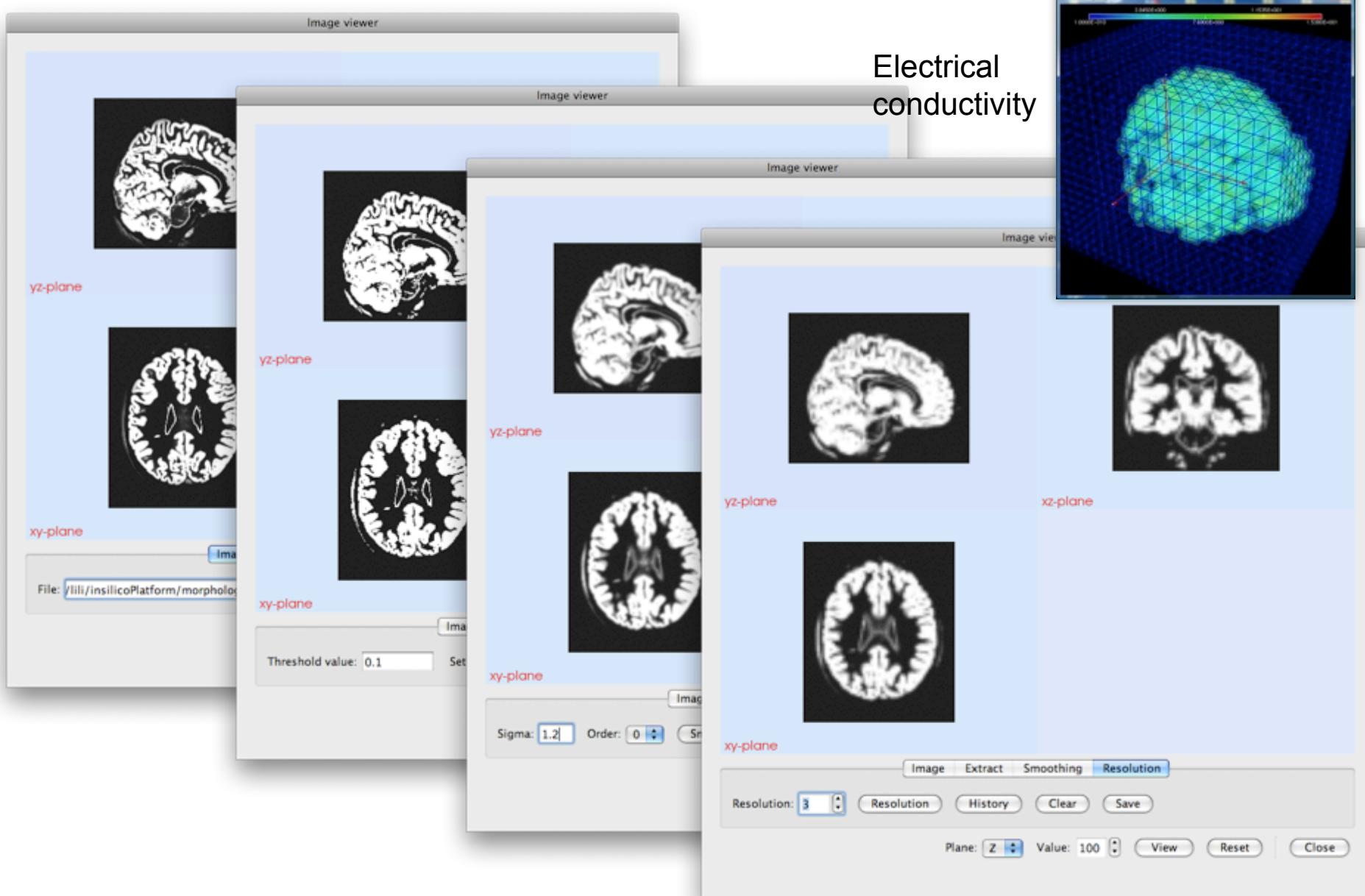


Image processing for integrating morphology

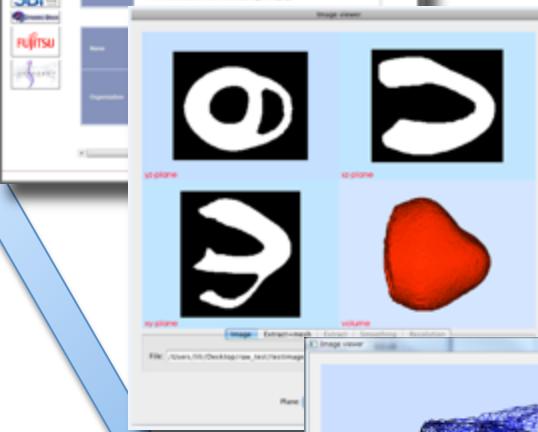


Another scenario

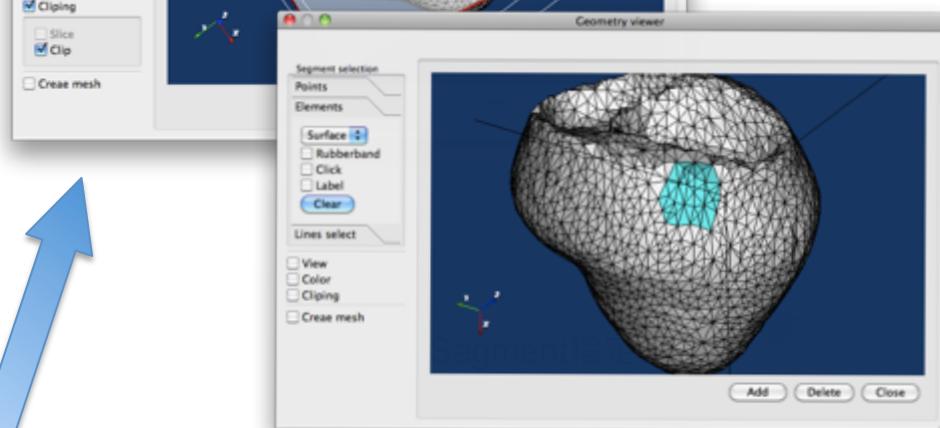
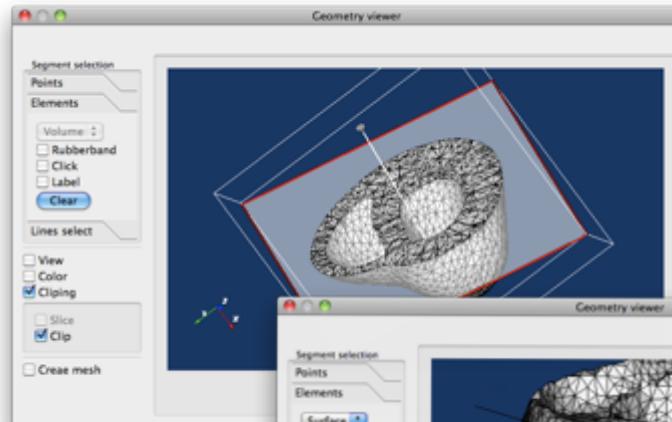
Raw binary image



Image Viewer
Segmentation

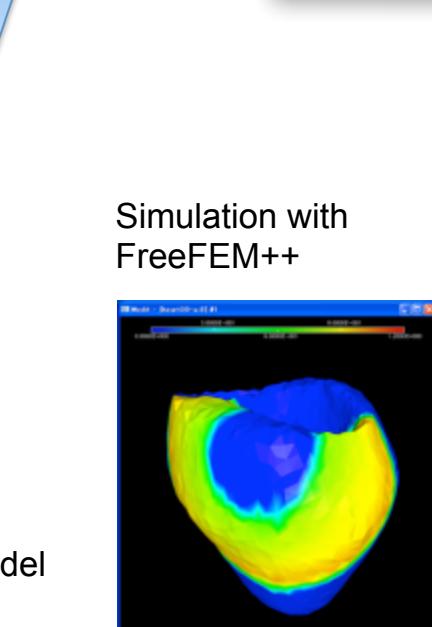


Creation of Surface model

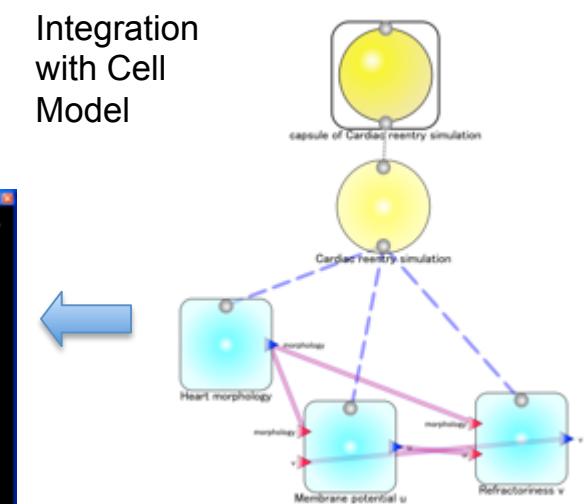


Morphology editor
Create volume mesh

Segment definition



Simulation with
FreeFEM++



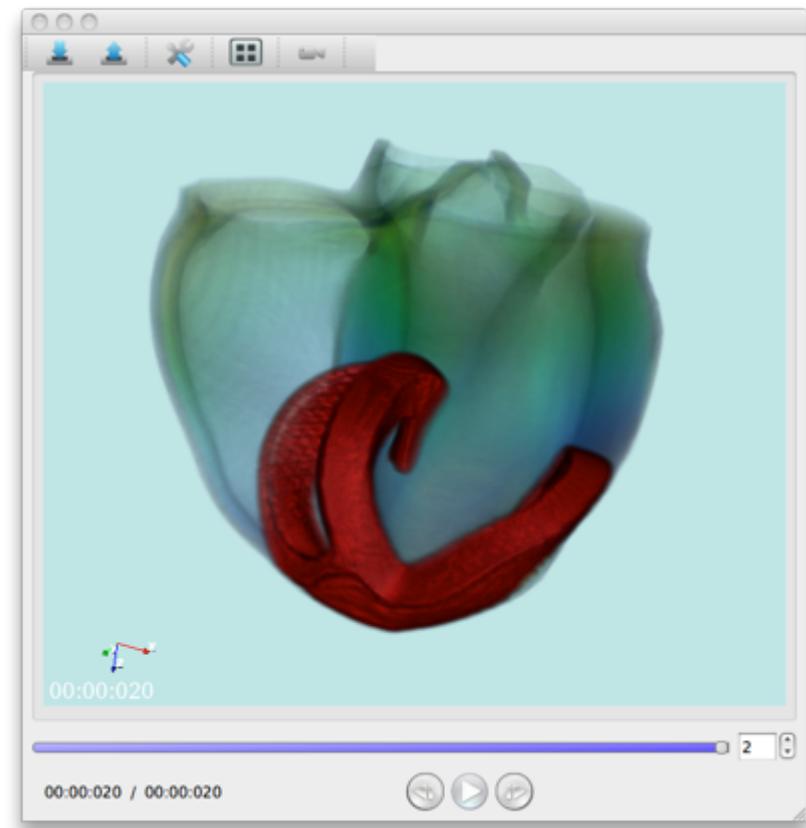
PhysioVisualizer



The screenshot shows the PhysioVisualizer software interface. At the top, there are four panels: two black panels labeled 'R-plane' and 'L-plane' containing white heart outlines, and two blue panels labeled 'M-plane' and 'A-plane' containing a 3D orange heart model. Below these are several windows:

- A central window titled 'heart' displays a schematic diagram of a heart's internal structure with nodes like 'lstm', 'membrane potential', and 'capsule_of_Gap junction'. It includes a 'Template' section and numerical values 2142 and 20.
- To the left, a tree view shows 'membrane potential' expanded to include 'V' (with 'I_Na' and 'I_K' branches) and 'currents'.
- A 'Template List' window shows entries: 'capsule_of_Gap_junc.' (number 100), 'FSK 2008 AP model in Epi_vesnarin' (number 100), and 'FSK 2008 AP model in Epi_vesnarin' (number 100).
- A 'Physical-Quality Table' window lists variables:

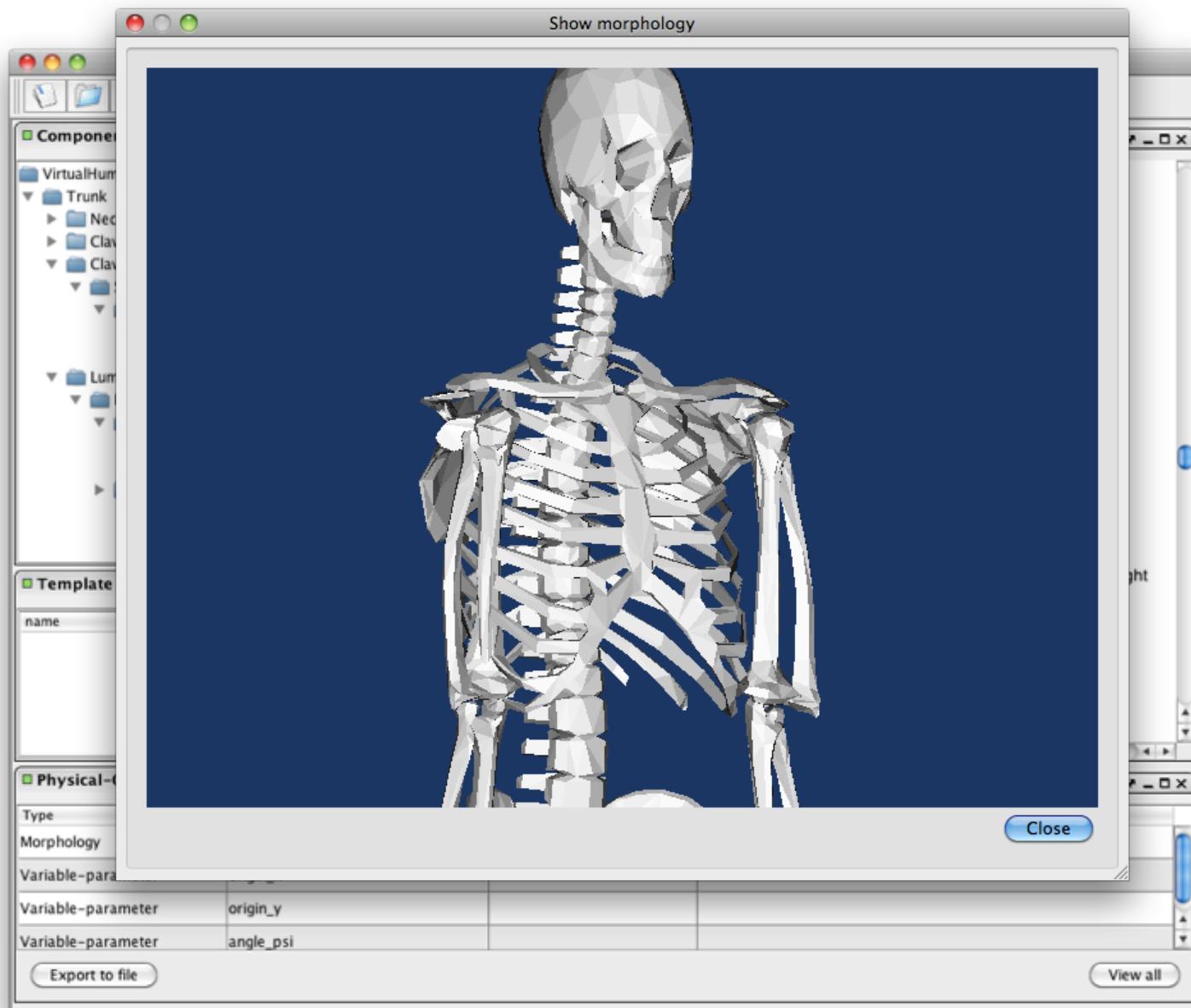
Type	Name	Assigned port	Definition	Initial value	Description
Variable-parameter	I _{Na} _total	in: I _{Na} _total	Port		
Variable-parameter	I _K	in: I _K	Port	$I = (I_{Na_total} + I_K)$	Total current
State	V	out: V	(dV/dt, time) = (-dV)	v = -87.0	membrane potential
Variable-parameter	I _{Na} _total	in: I _{Na} _total	Port		
Variable-parameter	I _K _total	in: I _K _total	Port		
- A 'Port Table' window is also visible.



FLINT



Multiple Geometries in Tree Structure



CellDesigner

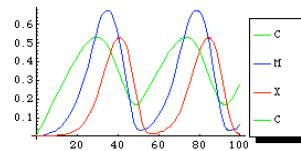
Modeling tool for biochemical and gene-regulatory network

SBML + **SBGN** +

Systems Biology Markup Language

SBGN +

Systems Biology Graphical Notation

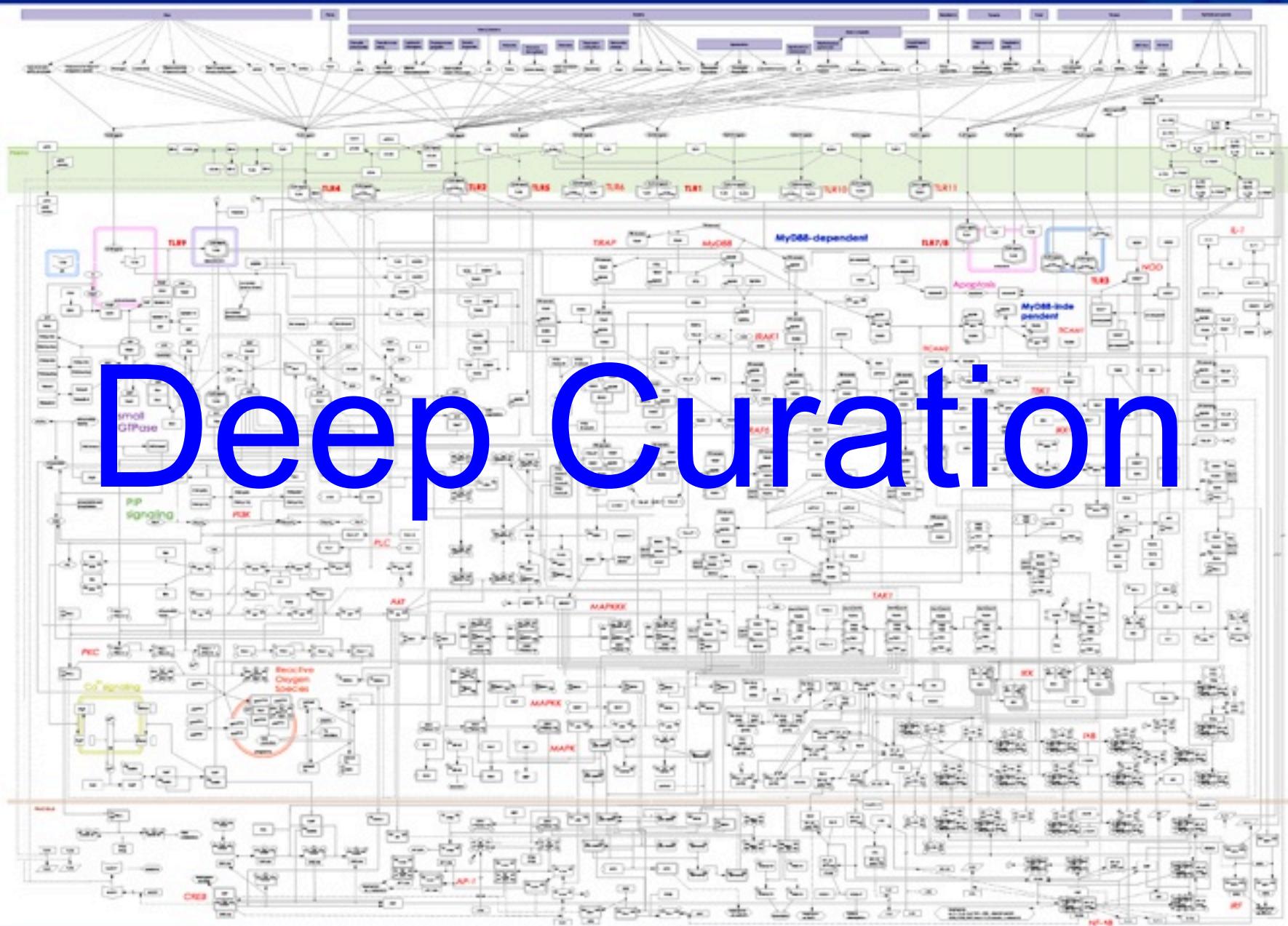


+

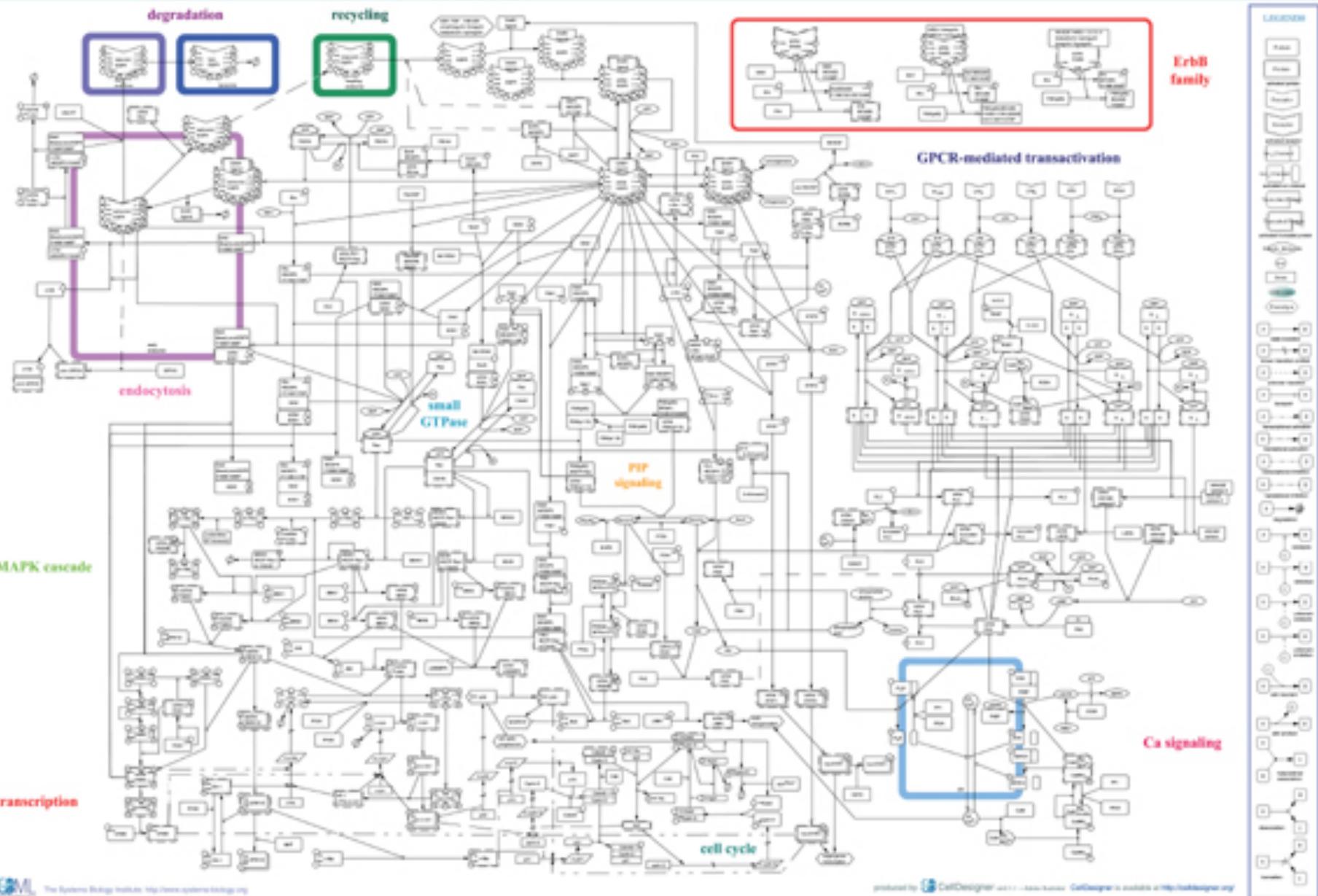


The screenshot displays the CellDesigner interface. On the left, the model structure is shown with components like M9KX and M9K. In the center, a simulation window shows the concentration of various species (M9K, M9KX, M9K_P) over time, with curves for each. On the right, a detailed model summary page is open, providing information about the model's basic information, annotations, cellular components, and other details.

<http://celldesigner.org>



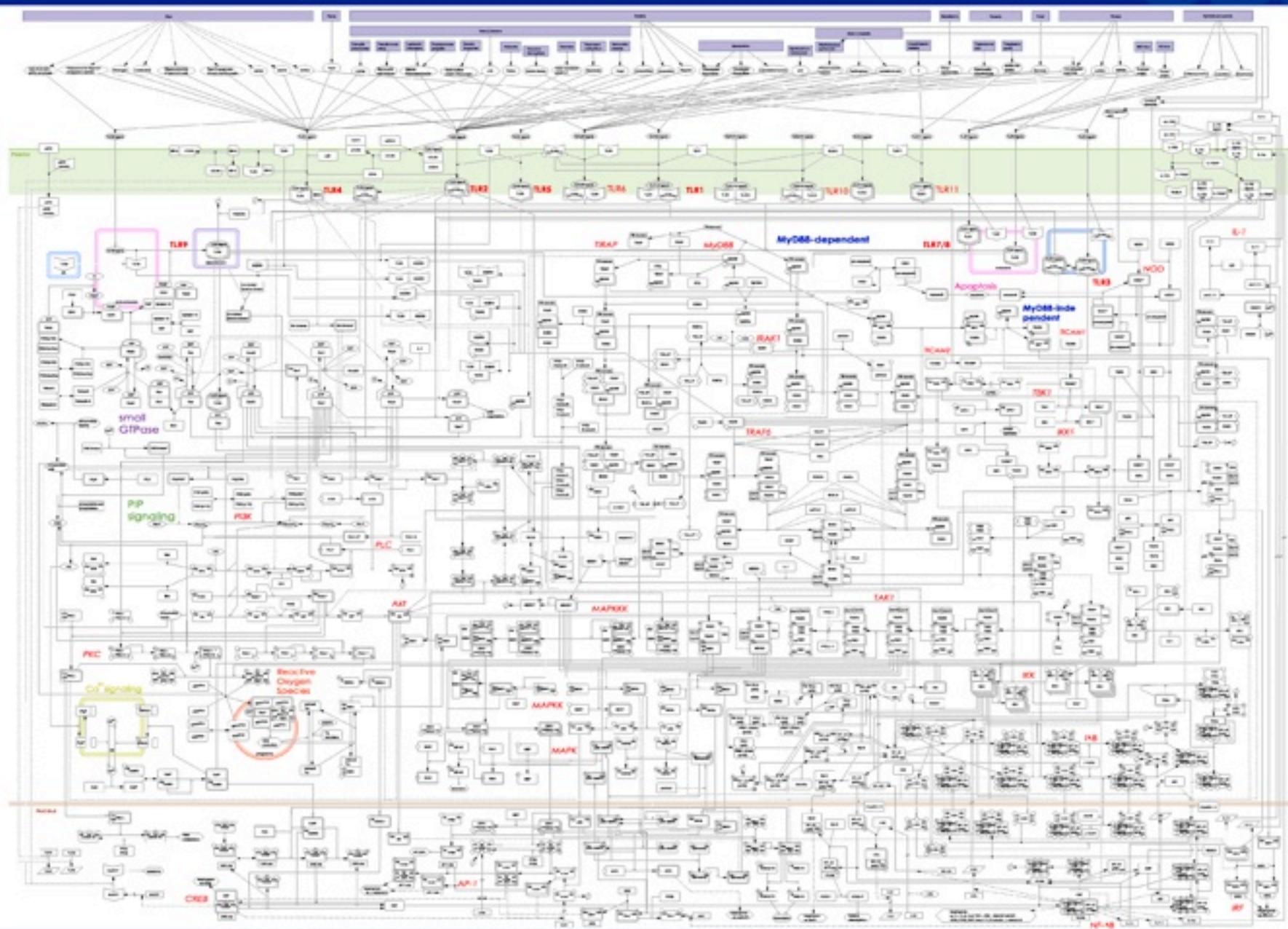
EGF Receptor Cascade



TLR pathway

Review Code (1, 2), Review Status (1, 2, 3)

The Systems Biology Institute, Tokyo, Japan
http://systemsbiology.org

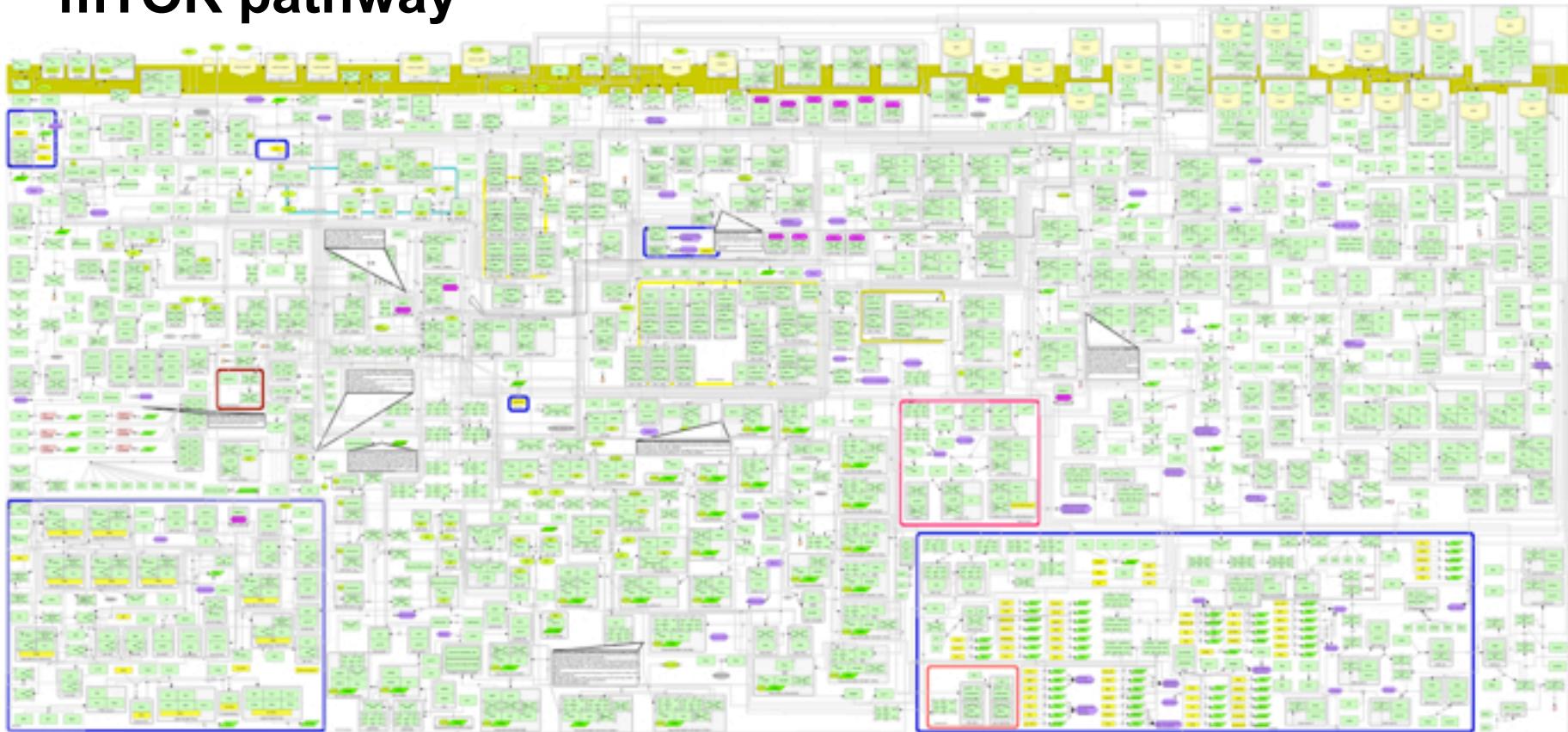


LEGENDS

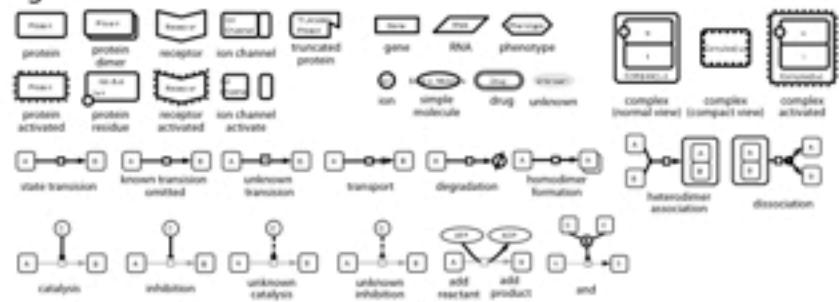


CellDesigner 3.3
CellDesigner is a trademark of the Systems Biology Institute.

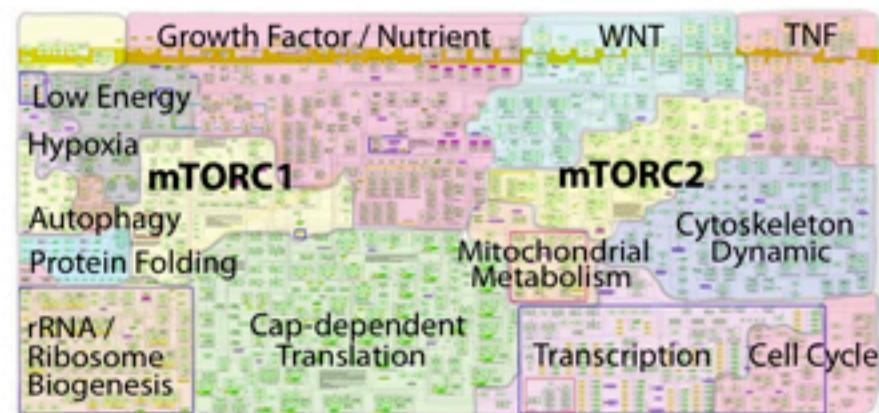
mTOR pathway

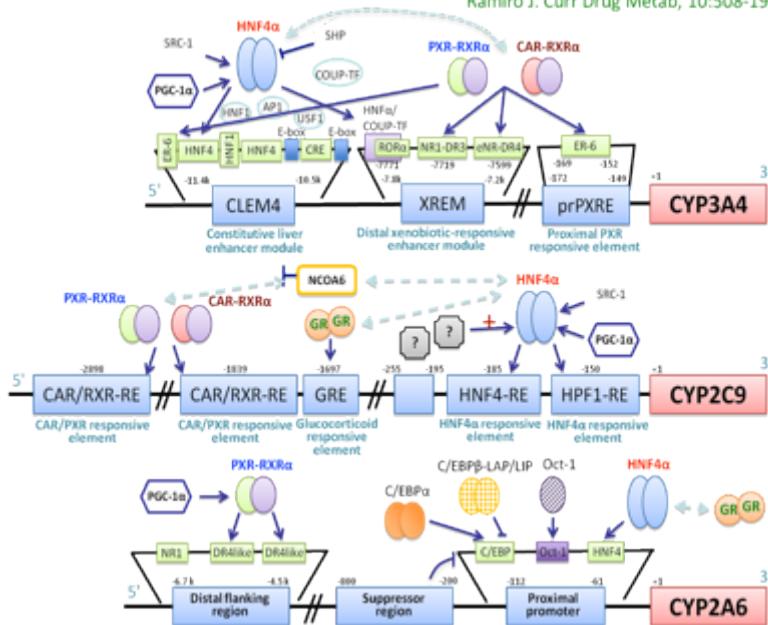


Legend

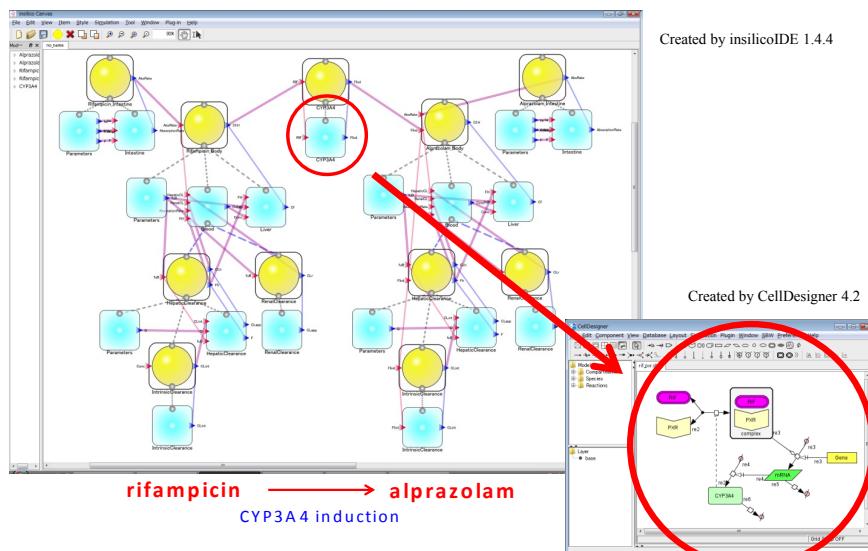


produced by CellDesigner™ ver4.0.1

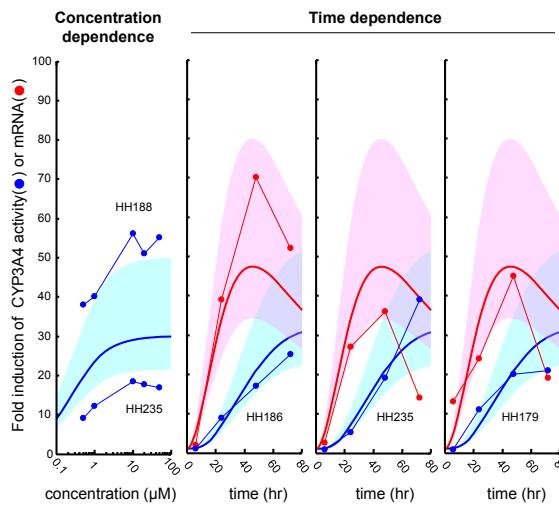




PHML-SBML Hybrid Simulation for In vivo DDI



Extended least squares analysis for CYP3A4 induction by rifampicin in human hepatocytes



$$\frac{dCYP^i}{dt} = a_1 \cdot (RNA^i - CYP^i)$$

$$\frac{dRNA^i}{dt} = a_2 \cdot (1 - RNA^i + a_3 \cdot PXR^{act})$$

$$\frac{dPXR^{act}}{dt} = \frac{Rif}{a_4 + Rif} \cdot \frac{(1 + a_5)}{(1 + a_5 \cdot CYP^i)} - a_6 \cdot PXR^{act}$$

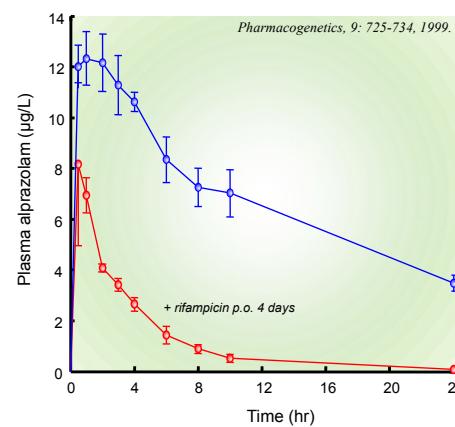
$$(a_3 \propto 1/q_1, \quad a_5 \propto q_1)$$

where,

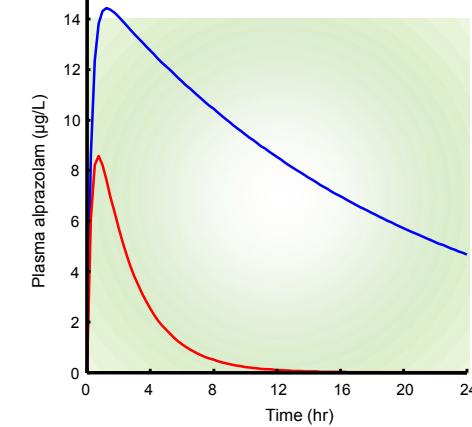
$$CYP^i = \frac{CYP}{CYP_0}, \quad RNA^i = \frac{RNA}{RNA_0}$$

Simulation of DDI for alprazolam with rifampicin

(A) Clinical Data



(B) Simulation



Pharmacokinetic parameters of alprazolam were obtained from Kato et al., Pharm. Res. 25: 1891-1901 (2008).



"PAYAO"

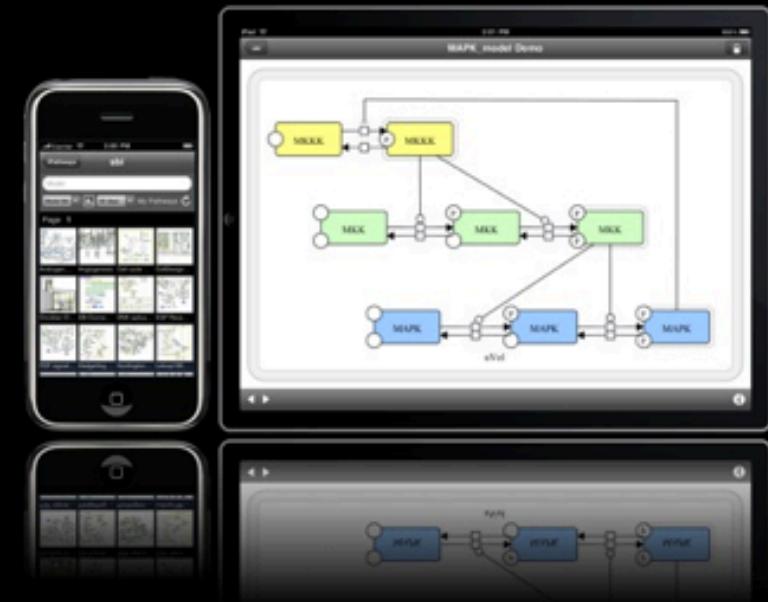
Community Tagging System to SBML models.



- A community tool to work on the same pathway models simultaneously, insert tags to the specific parts of the model, exchange comments, record the discussions and eventually update the models accurately and concurrently.
- Reads SBML models, display them with CellDesigner

The screenshots illustrate the PAYAO platform's features:

- Left Screenshot:** Shows a search results page for "My Models". It lists several SBML models with their names, registration dates, owners, and brief descriptions. Buttons for "View", "Add to Favorite", and "Delete" are available for each entry.
- Middle Screenshot:** Shows a "Search Tags" interface. It displays a "Tag Sets" section with checkboxes for "Publications", "Text", and "Guest". Below this is a "Other Tag Sets" section with a "Notes" entry. A "readable" tag is highlighted with a green dot. A "Show Disabled Tags" checkbox is also present.
- Right Screenshot:** Shows a detailed view of an SBML model named "EGFR_signalling_for_RTKC". The model diagram includes various nodes like "EGFR", "GDP", "ATP", "PIP2", "PIP3", "Rac", "Cdc42", and "PI3K". Annotations are shown as green dots with text like "readable", "test", and "comment". A "Comment" section allows users to add text. At the bottom, there are tabs for "Species", "Proteins", "Genes", "RNAs", "ncRNAs", "Reacts", "Complex", "Param", "Func", "Units", "Roles", and "Events". A table at the bottom right provides detailed information for selected species and complexes.



Available on the iPhone
App Store

Over 6500 registered users!!
iPathways 1.2 for iPhone/iPad is available now!!

What's new in 1.2

- Extended pathway library (over 200 pathways)
- Explore pathway channels: Cancer, Signaling, Panther pathways, KEGG metabolic pathways
- View pathways in black and white (night mode)
- Save pathways to view in offline mode
- Rate the pathways

Welcome to **iPathways**, your mobile explorer for biological pathways!

Subscribe

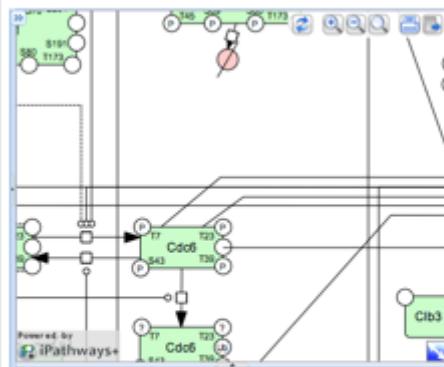
We will keep you informed on new features.

Email ► **Submit**

Embedding the map to the website

My WorkPlace

Current Project



[View Larger Map](#)

This is the workplace for building the pathway model..... The project members are....

Link Out



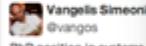
Discussion Twitter Link

#systemsbiology



Vangelis Simeonikos
PhD position in systems biology
human metabolism | Luxembourg
email:msimeonikos@ipb.ac.be
#PD #iron

Kazuhiro Takemoto
Kazuhiro Takemoto



Vangelis Simeonikos
PhD position in systems biology
human metabolism | Luxembourg
email:msimeonikos@ipb.ac.be
#PD #iron

Scott Wagers
Scott Wagers

MT @amostenacher: #SystemsBiology reductionistic? Good point, more top-down. I use go #SystemsMedicine

f Share This Link

Share On your own timeline

Write something...



Kaizu2010_BuddingYeastCellCycle

<http://ipathwaysplus.unit.oist.jp/mc>

Creators: Kazunari Kaizu (mail address), Samik Ghosh, Yukiko Matsuoka, Hisao Moriya, Yuki Shimizu-Yoshida, Hiroaki Kitano Creation date: Jan 2009 ...

< > 1 of 1 Choose a thumbnail

No thumbnail

[Friends](#) [Share link](#) [Cancel](#)

iPathways+ Mail form

Your name (required)

Your Mail Address info@abc.com (required)

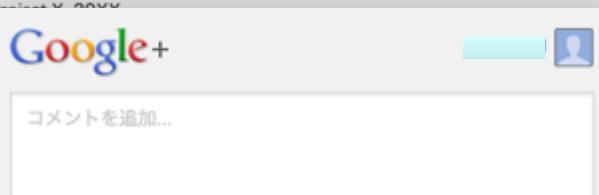
Send to Address info@def.com (required)

Subject Model Link (required)

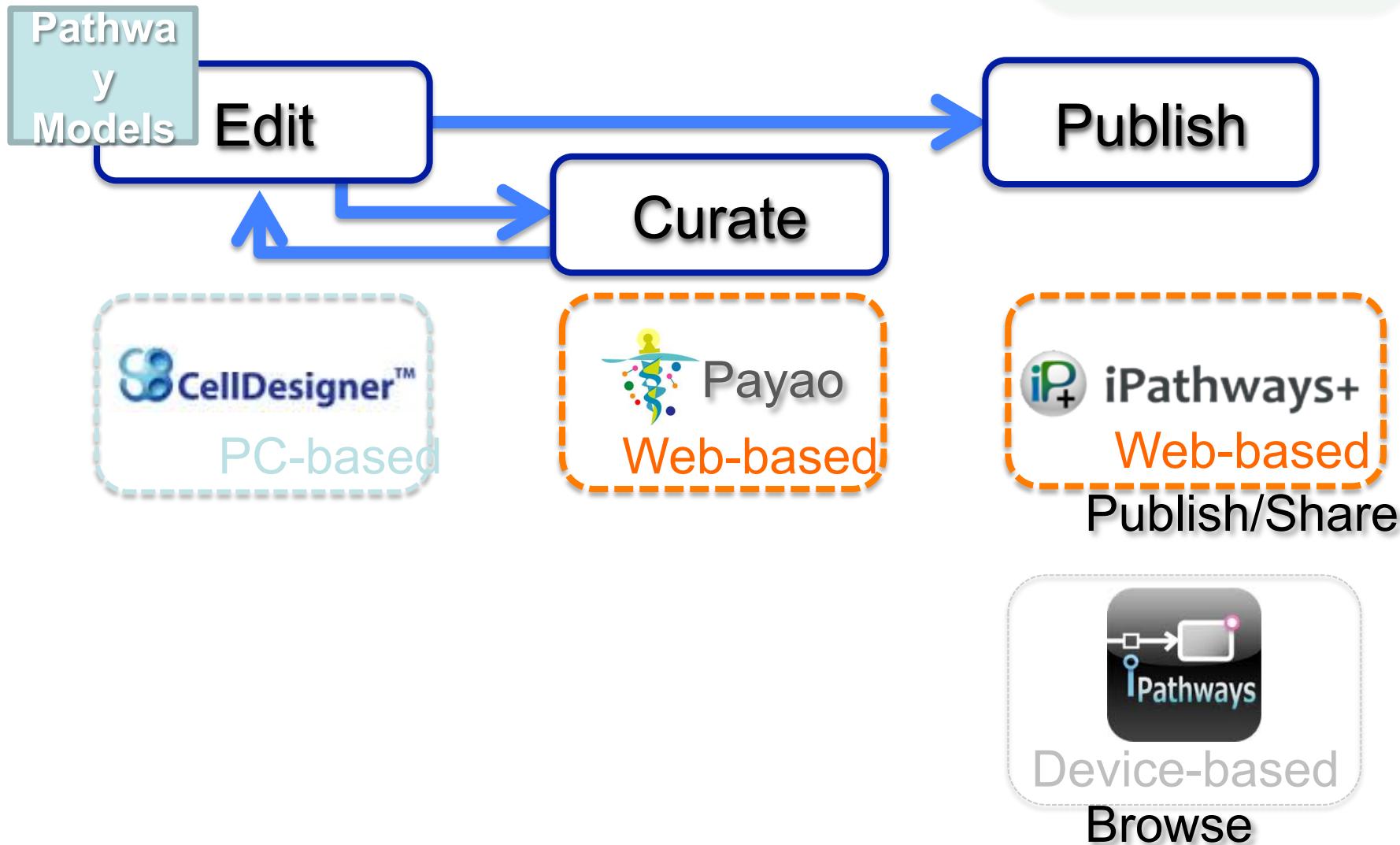
body(required)
<http://ipathwaysplus.unit.oist.jp/ipp/QtNuai>

Model map provided by iPathways+

[send](#) [clear](#)



Tools for Pathway Modeling



iPathways+ vs. Payao



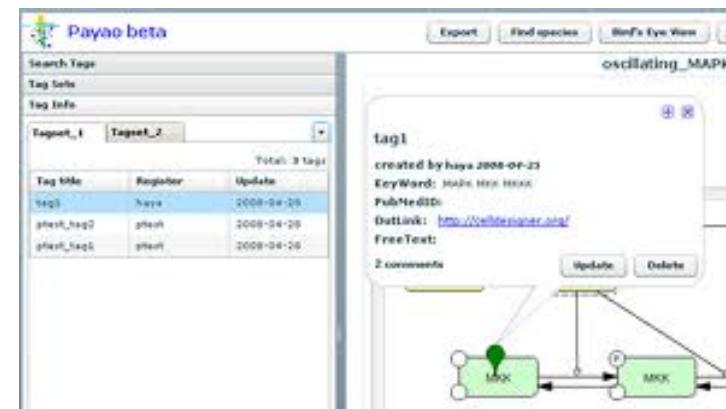
iPathways+

- www.ipathways.org/plus
- Publish & Share
 - Share link/cropped image with SNS and mail
 - Embed the pathway model into your website/blog
- Access control



Payao

- www.payaologue.org
- Curation
 - Add comments
 - Update tags
- Access control



iPathways+ vs. iPathways



iPathways+

- Web-based
- Browse Public Pathways
 - From Panther Pathways (86 selection)
- Register your own pathways
- Share your pathways
 - Via eMail
 - Via SNS
 - Via embedding to website/blog



iPathways

- Device-based (iAPP)
- Browse Public Pathways
- Channel Feature
 - KEGG
 - Panther Pathways (approx. 150 models)



Simulation

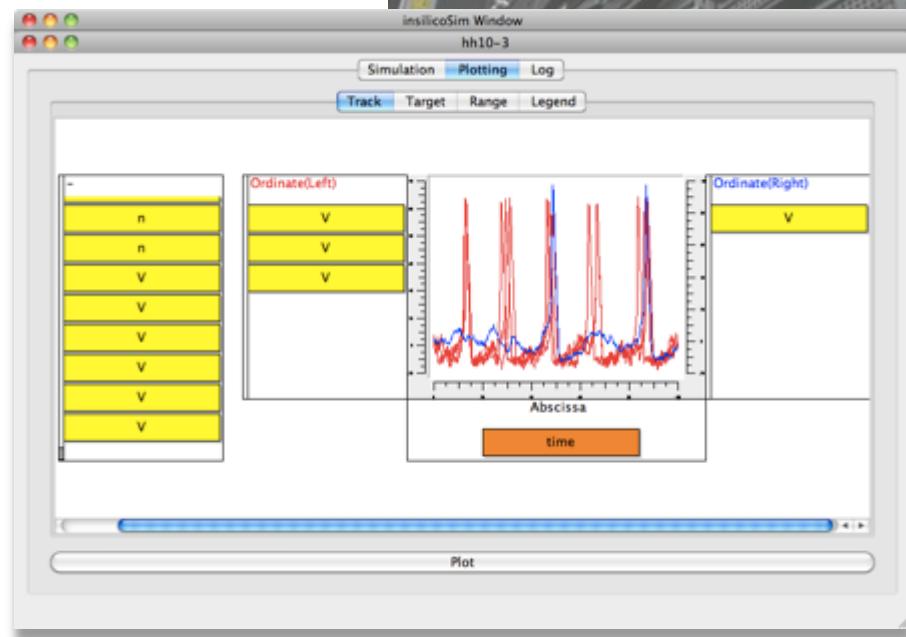
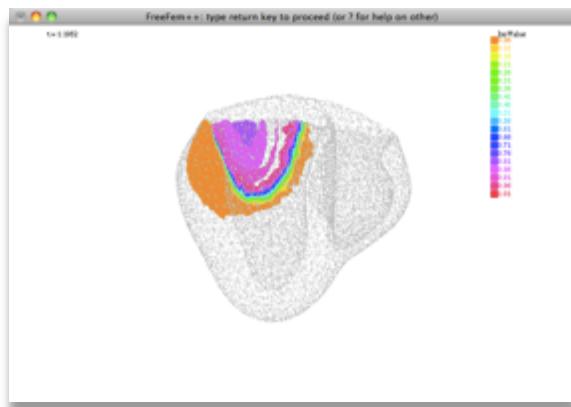
Simulator  FLINT

Supports SBML as well as PHML

Supports parallel computation

Export to C++, JAVA

Export to FreeFEM format



on Cloud



Flint K3

Interface Server is at somewhere in the internet.

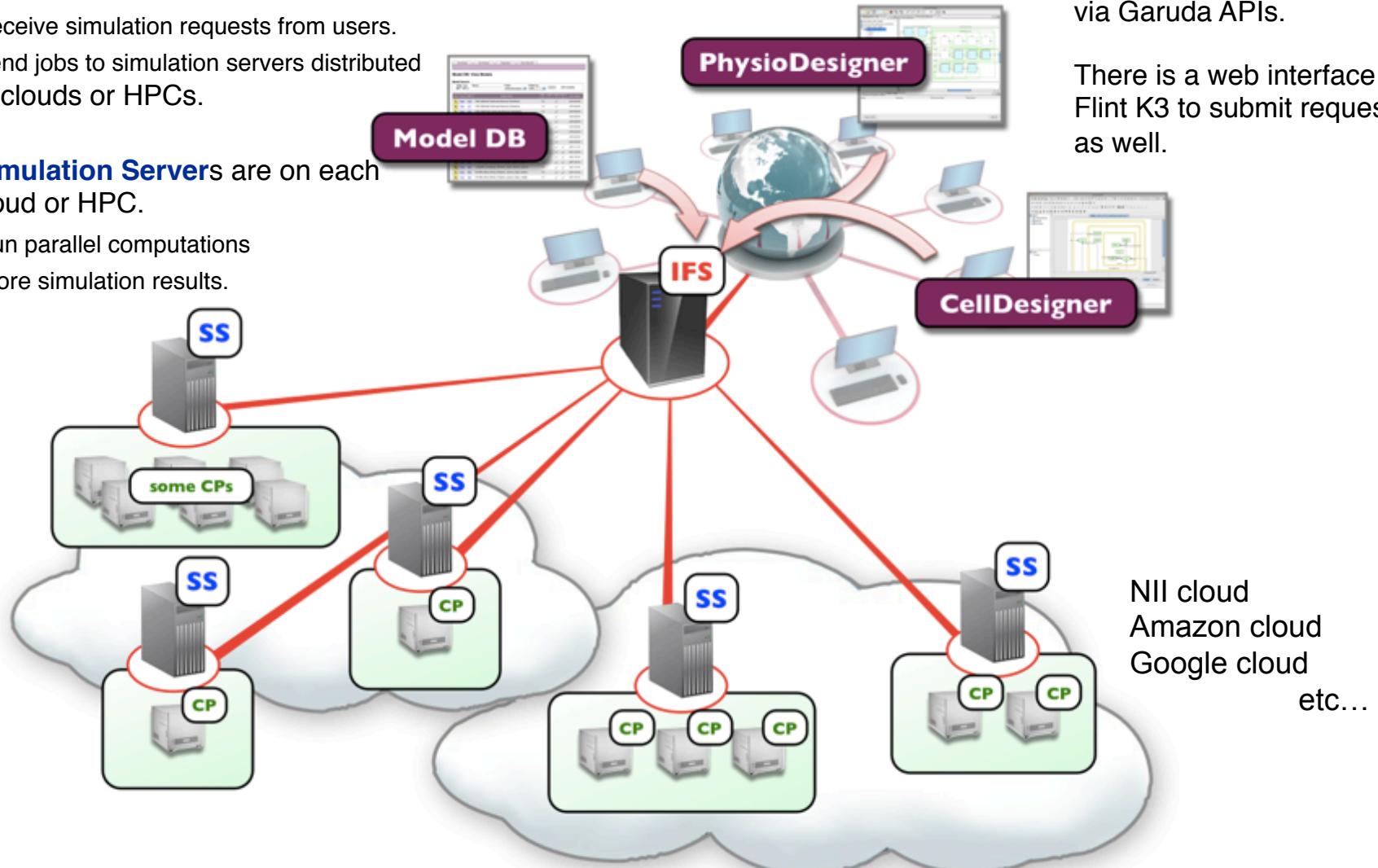
- Receive simulation requests from users.
- Send jobs to simulation servers distributed on clouds or HPCs.

Simulation Servers are on each cloud or HPC.

- Run parallel computations
- Store simulation results.

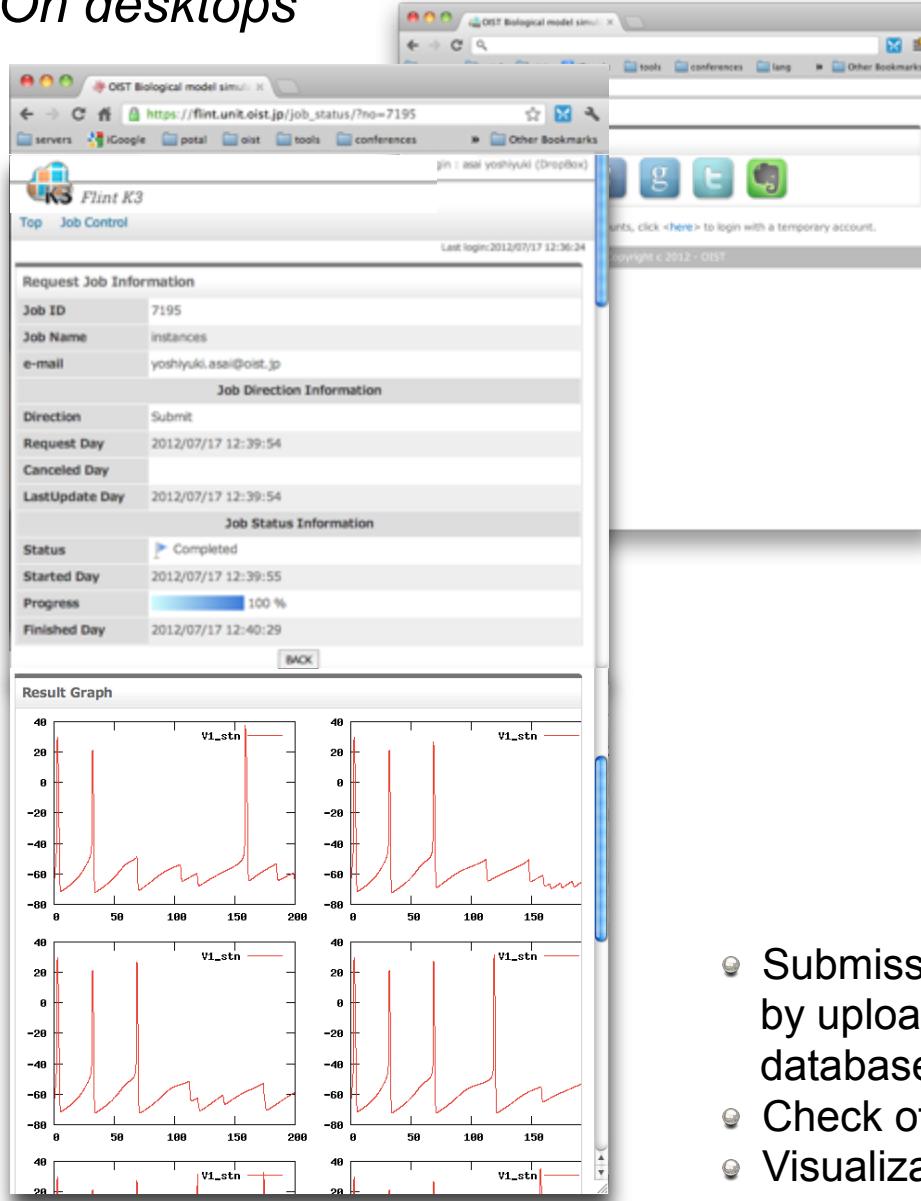
Garuda alliance member applications can send simulation jobs to Flint K3 via Garuda APIs.

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

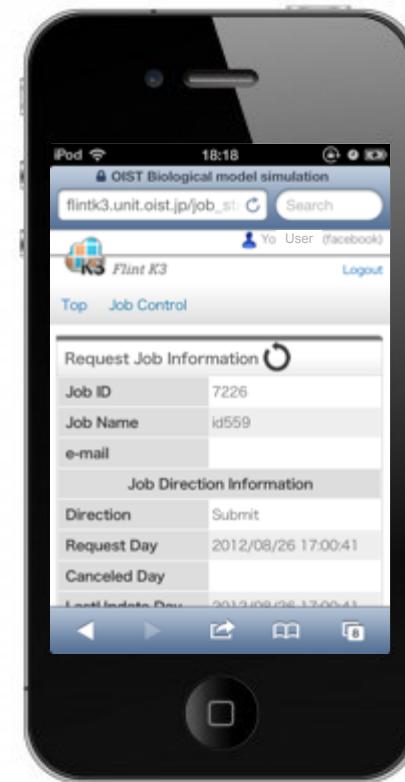


Flint K3

On desktops

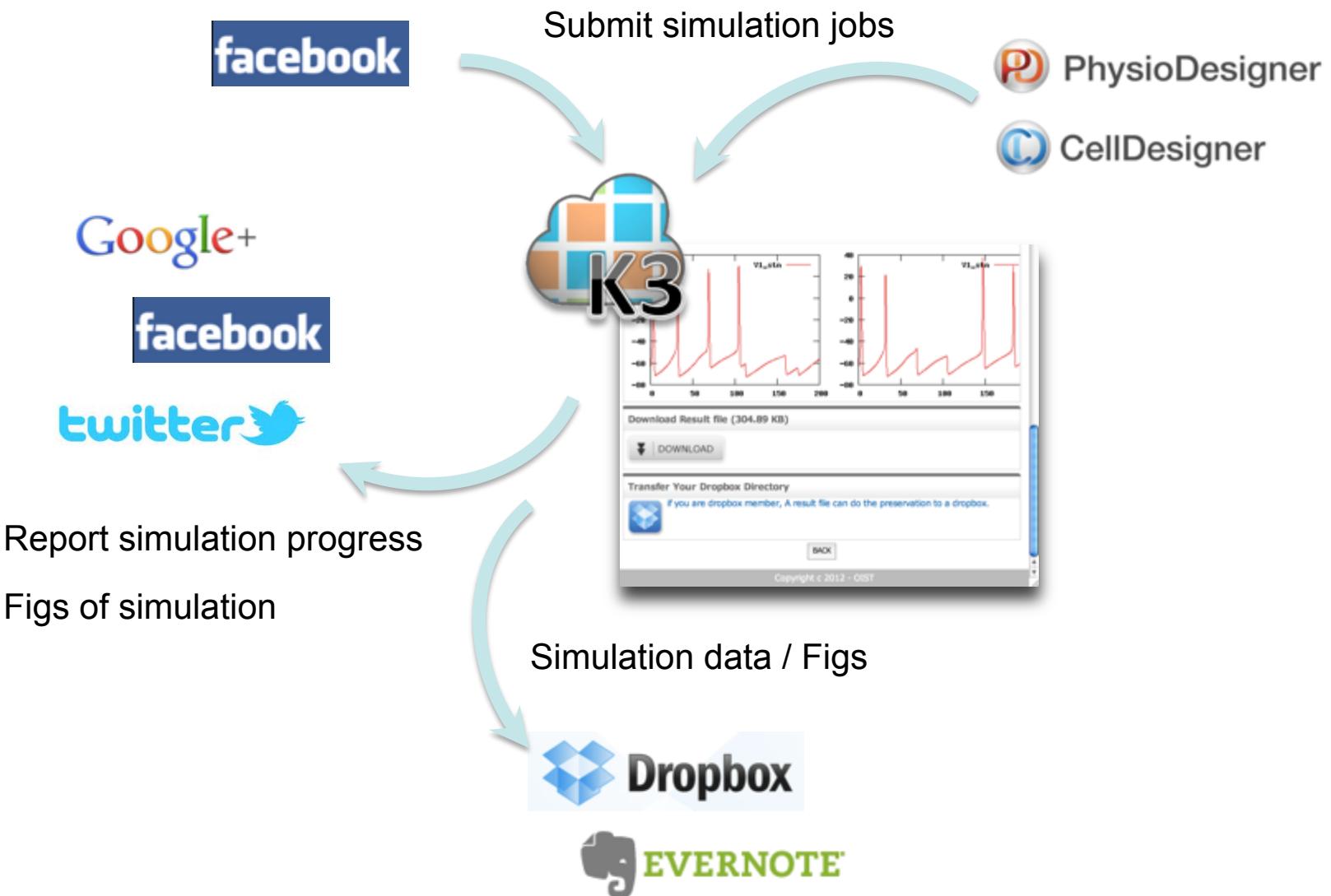


On smart devices



- Submission of simulation requests by uploading models or providing model ID in open databases
- Check of simulation progress
- Visualization of the simulation results and download

FLINT K3 with SNS or other services

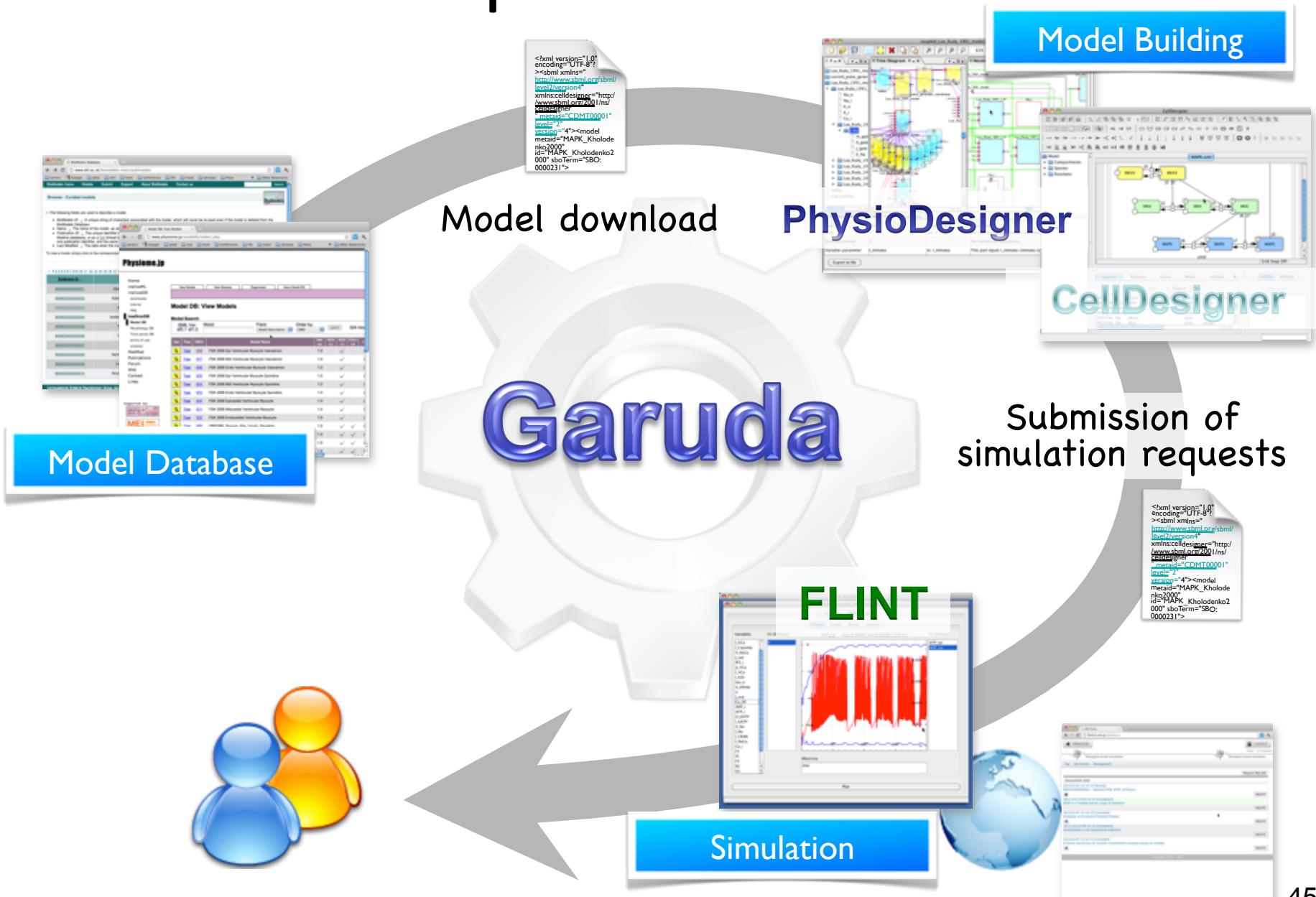


Flint on “K” Peta-flops computer



©RIKEN

Example of workflow



Social engineering for virtual 'big science' in systems biology

Hiroaki Kitano, Samik Ghosh & Yukiko Matsuoka

A new type of big science is emerging that involves knowledge integration and collaboration among small sciences. Because open collaboration involves participants with diverse motivations and interests, social dynamics have a critical role in making the project successful. Thus, proper 'social engineering' will have greater role in scientific project planning and management in the future.

Kitano, Ghosh, Matsuoka, Nature Chemical Biology, May 2011

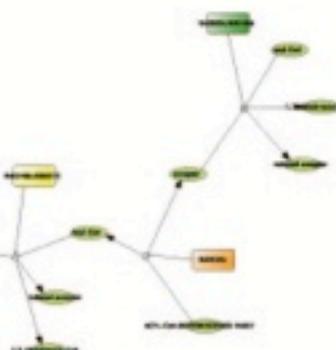
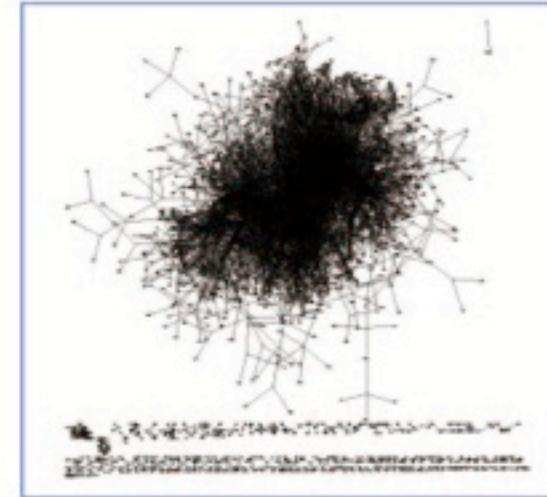
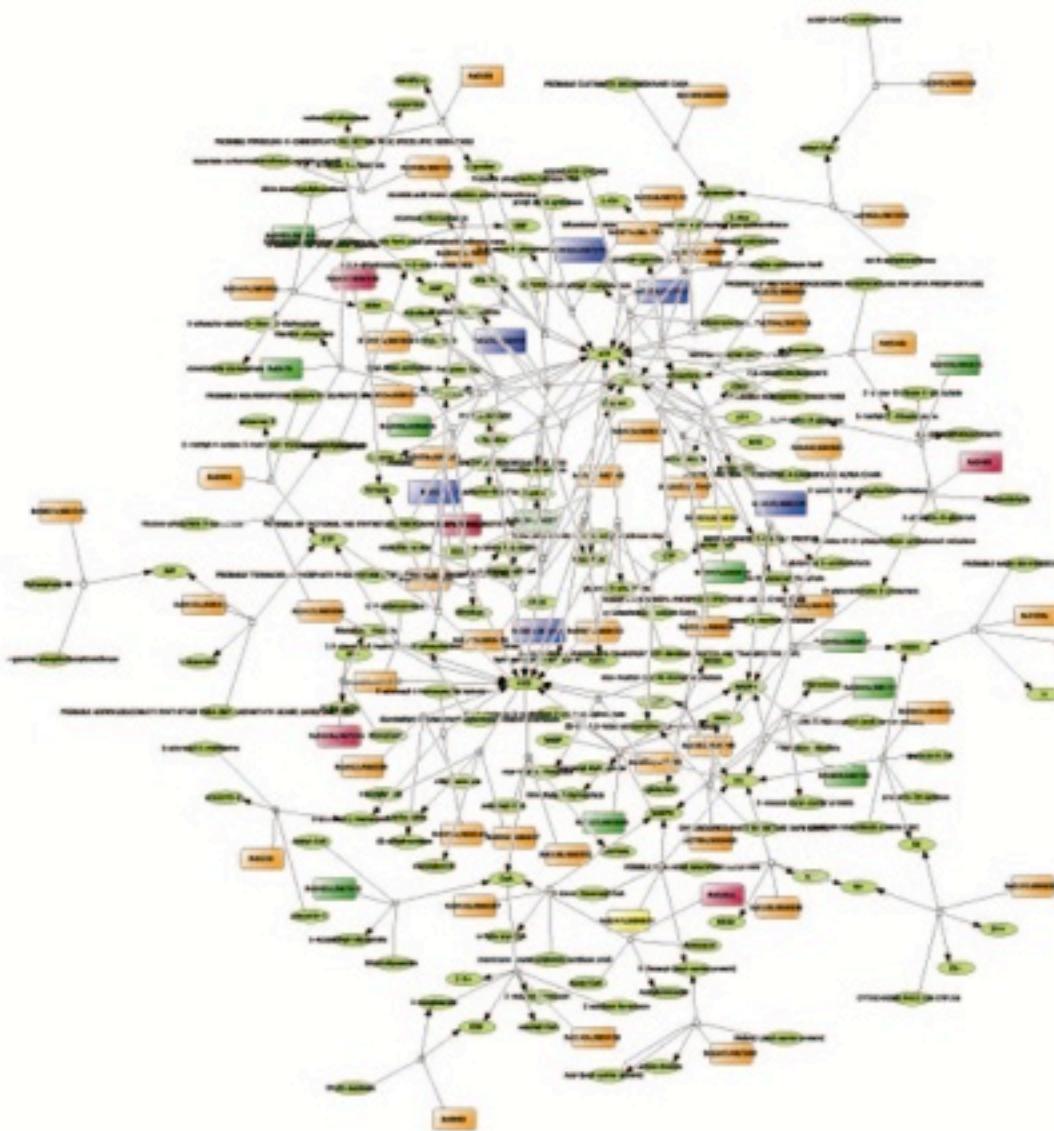


The First Molecular
Interaction Map of TB
OSDD-SBI
collaboration

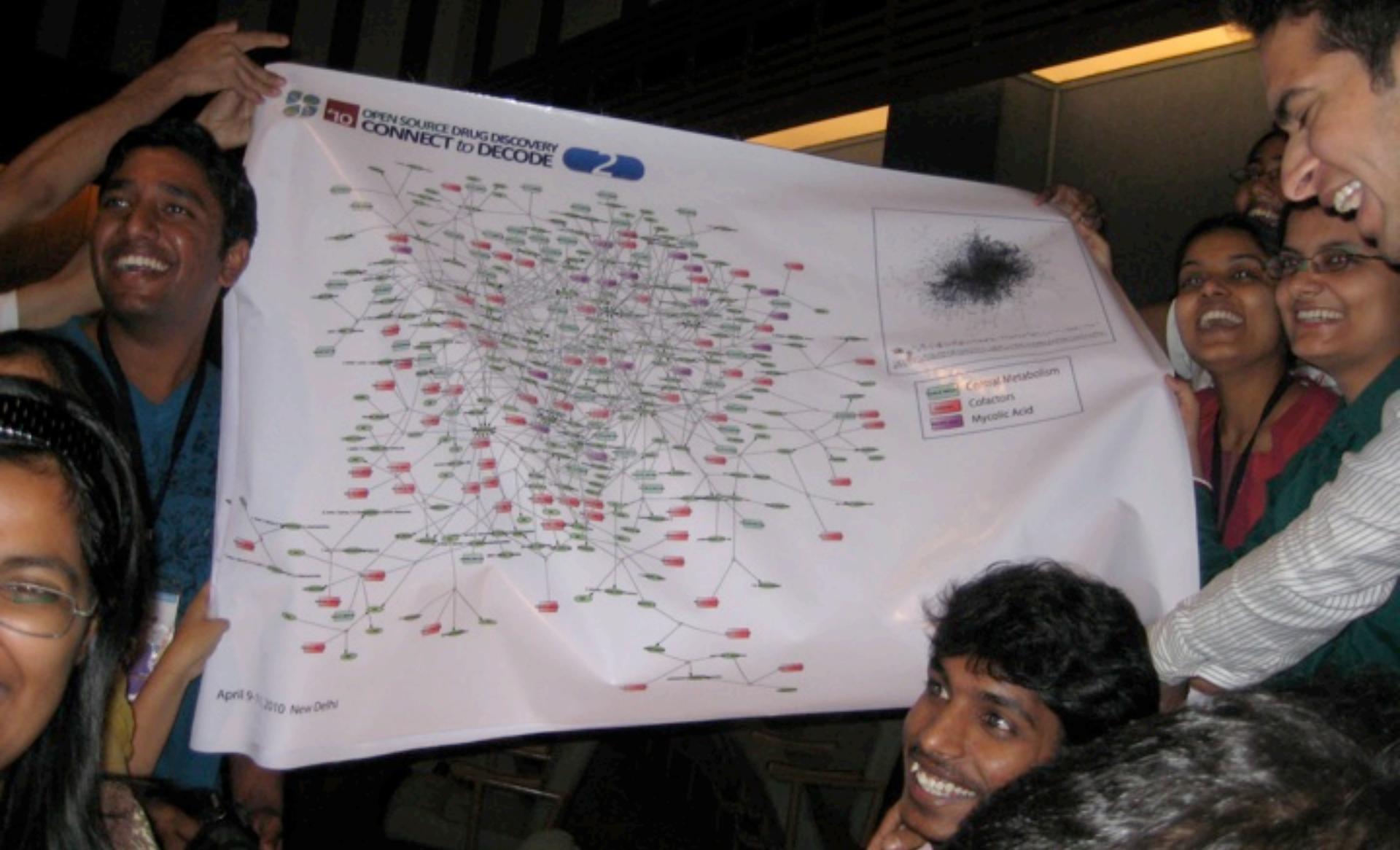




'10 OPEN SOURCE DRUG DISCOVERY
CONNECT to DECODE



Central Metab Chocolate
Energy Metab Pink
Cell Wall Blue
Pthiocerol Green
Cofactors
Mycobactin Red
Mycolic acid Violet
Lipd
Fatty Acid



Kitano, Ghosh, Matsuoka, Nature Chemical Biology, May 2011

Systems Toxicology Project

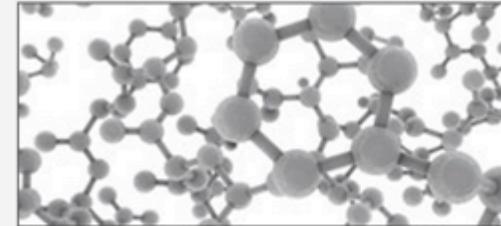
Project Background

Developing new approaches to better understand how drugs lead to adverse effects is a high priority within the field of regulatory science. One approach FDA is exploring to improve our understanding of and ability to predict drug toxicity is the use of "systems biology". Systems biology is an emerging scientific discipline that blends biology with computational modeling to untangle the intricate networks of interactions between genes, proteins, metabolites, and other small molecules within cells. In order to fully understand all the potential effects of a drug, we need to better understand these complex networks. This has proven difficult using the traditional tools of pharmacology and toxicology, but by combining new scientific methods along with modern computing power, systems biology present us with new potential to understand the depth of this complexity.

The FDA is in the process of developing a mechanism-based drug safety assessment and prediction program and the application of systems biology is a cornerstone of this program. RUF is working with FDA and other stakeholders to launch a systems biology-based pilot project to examine the cardiac side effects of Tyrosine Kinase Inhibitors (TKIs), a common and very useful class of cancer drugs. This area was chosen because it is a growing problem — as treatments for cancer have improved and patients are living longer, the incidence of chronic adverse effects associated with treatment are increasing.

Critical Path to Tuberculosis Drug Regimens (CPTR) Project

Systems Toxicology Project



Learn More About Our Work

The Reagan-Udall Foundation leads and collaborates on programs, projects and other initiatives that advance its mission in support of the FDA. [Find Out More »](#)



Standard Platform



Software platform for HD-Physiology

- To be used throughout the project without exception, including experimental teams if they want to model their system
- Dedicated software development team
- Extensive tutorials throughout the project duration

Standardization

- The Garuda Alliance
- CellDesigner (SBML, SBGN)
- PhysioDesigner (PHML, SBML)
- Flint simulation package
- Other group of software packages
- all comply with the Garuda API set



GARUDA
THE WAY BIOLOGY CONNECTS

Garuda Alliance (snapshot May 2013)



Software problems

- Software for biomedical research is the critical components for success of research
- Nobody can develop entire software systems alone
- However
 - Tools are developed independently
 - Different GUI, different operating procedure, different APIs, etc.
 - Need to launch tools independently
 - No direct data sharing, etc
- Inter-operability is missing!!!!
- Extra work needed for users and developers

[Organisation](#)[Member Airlines](#)[Initiatives](#)[Campaigns](#)[print](#)

The Way the Earth Connects

The Star Alliance network is the leading global airline network, with the highest number of member airlines, daily flights, destinations and countries flown to. It was established in 1997 as the first truly global airline alliance to offer customers convenient worldwide reach and a smoother travel experience.

In this section you'll find information on the Star Alliance member airlines, the organisation and its initiatives and campaigns.



Member airlines »

The Star Alliance network is proud to have some of the world's most respected airlines as members, offering you convenience, comfort and efficiency when travelling the globe. And the alliance continues to grow so that it can better serve your need for a smooth travel experience.

Initiatives »

The Star Alliance network pursues its initiatives as a measure of corporate responsibility, to care for the environment and thought leadership, to connect people, inspire and share ideas.

Campaigns »



Organisation »



Designing Grand Challenges in Systems Biology

- What are scientific challenges?
- What are engineering challenges?
- Grand challenges are suitable for engineering challenge, not scientific challenge because scientific discoveries are unpredictable