CellDesigner

http://celldesigner.org/

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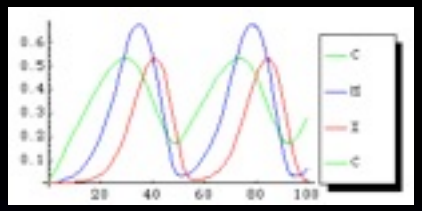
Keio University, Japan
6th Aug. 2017

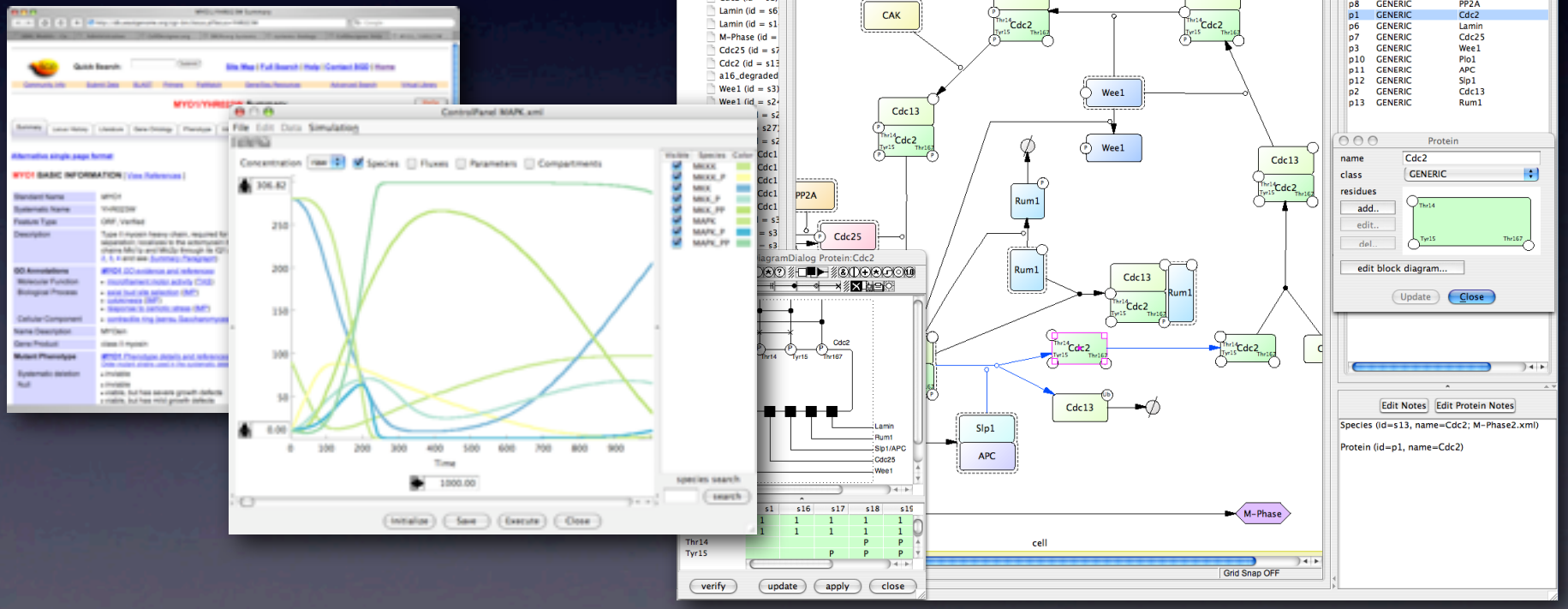
Keio University
1858
CALAMVS
GLADIO
FORTIOR

SBI The Systems Biology Institute

CellDesigner

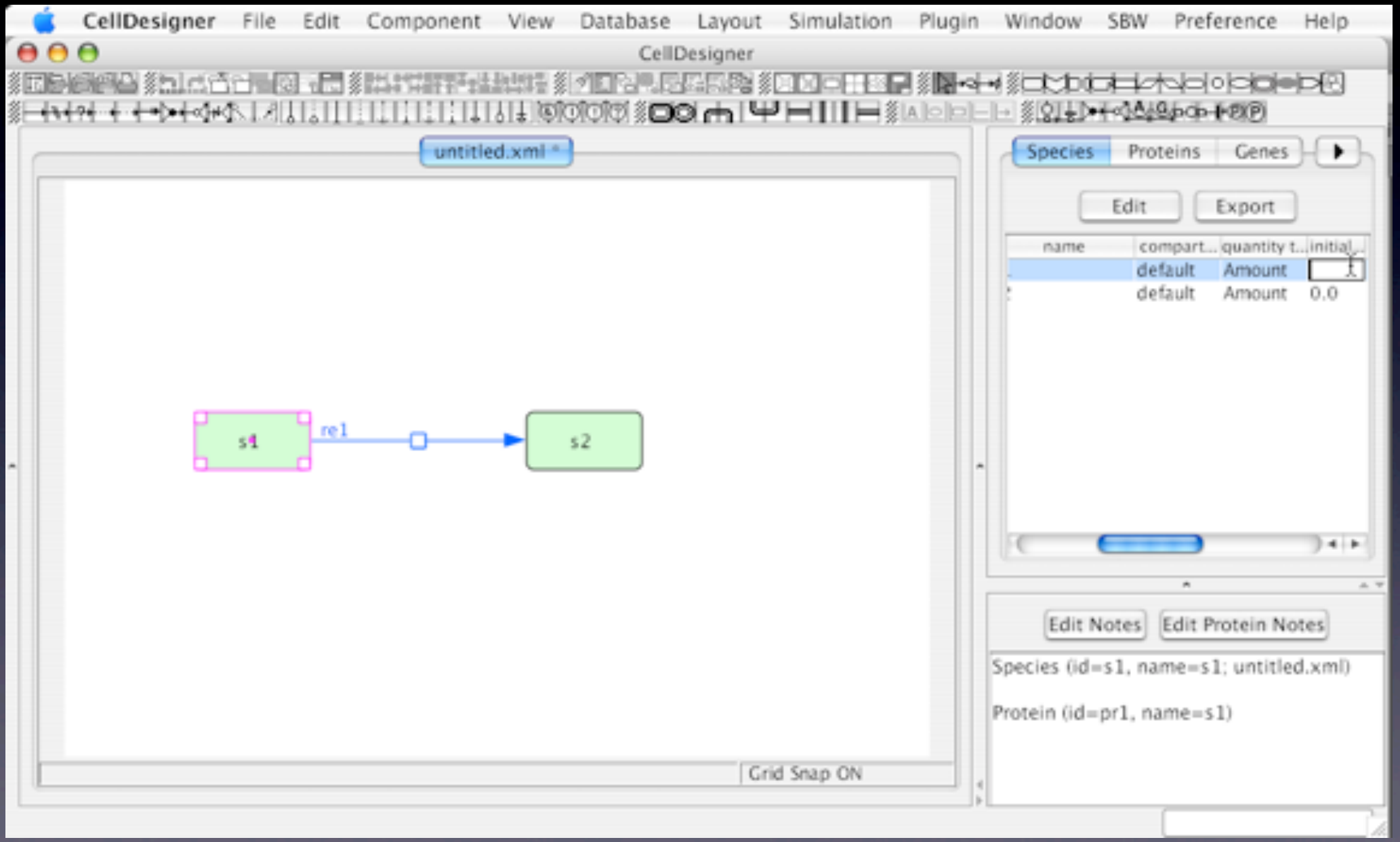
SBML + SBGN +  +

= CellDesigner



Modeling tool for biochemical and gene-regulatory network

CellDesigner



Nature Molecular Systems Biology 4(173) 2008

Comprehensive pathway map

Molecular Systems Biology 4; Article number 173; doi:10.1038/msb.2008.7
Citation: ***Molecular Systems Biology*** **4:173**

www.molecularsystemsbiology.com

molecular systems biology

REVIEW

A comprehensive modular map of molecular interactions in RB/E2F pathway

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We present, here, a detailed and curated map of molecular interactions taking place in the regulation of the cell cycle by the retinoblastoma protein (RB/RB1). Deregulations and/or mutations in this pathway are observed in most human cancers. The map was created using Systems Biology Graphical Notation language with the help of CellDesigner 3.5 software and converted into BioPAX 2.0 pathway description format. In the current state the map contains 78 proteins, 176 genes, 99 protein complexes, 208 distinct chemical species and 165 chemical reactions. Overall, the map recapitulates biological facts from approximately 350 publications annotated in the diagram. The network contains more details about RB/E2F interaction network than existing large-scale pathway databases. Structural analysis of the interaction network revealed a modular organization of the network, which was used to elaborate a more summarized, higher-level representation of RB/E2F network. The simplification of complex networks opens the road for creating realistic computational models of this regulatory pathway.
Molecular Systems Biology 4 March 2008; doi:10.1038/msb.2008.7
Subject Categories: metabolic and regulatory networks; cell cycle
Keywords: cell-cycle regulation; E2F; RB pathway; RB1; systems-biology standards

Introduction

The cell cycle is the succession of four phases called G1, S, G2 and M. In dividing cells, DNA replication (S phase) and mitosis (M phase) alternate (Alberts *et al*, 1994), and are separated by two gap phases, G1 and G2 phases. In quiescent cells, the cells are considered to be in G0 phase. When they receive external signals, such as growth factors, a series of activations push the cell from a G0 to a G1 state and enters the cell cycle. The whole process of cell division is mainly orchestrated by complexes composed of two subunits, a kinase and a cyclin partner. These complexes phosphorylate a certain number of proteins, either activating or inhibiting them. Among them, the retinoblastoma tumour suppressor protein RB (RB1) is a key regulator in cell-cycle entry (transition G1/S). It sequesters a family of transcription factors, the E2Fs, responsible for the transcription of many genes involved in cell-cycle regulation, DNA replication and other functions like the activation of the apoptotic pathway (Muller *et al*, 2001). RB functions as a brake in the cell cycle, which is released when external signals trigger S-phase entry. The main targets of the external signals are the G1 cyclin/CDK complexes. Once active, the complexes, among them CycD1/CDK4,6, act as starters of the cell cycle (Novak *et al*, 2007) and phosphorylate RB, which then releases E2F (DeGregori, 2004).

RB is a member of a family of proteins called the pocket proteins (Knudsen and Wang, 1997). These proteins RB, p107 and p130, share sequence similarities, especially in the 'pocket domain' (Stevaux and Dyson, 2002), which is responsible for their repressor function. RB protein contains domains where the binding sites for co-repressors (E2F proteins and viral oncoproteins) are situated. These sites are subjected to most mutations.

RB is a tumour suppressor gene. Because of its implication in so many, if not all, cancers (Sherr and McCormick, 2002), the study of RB regulation requires a special attention.

More specifically, the RB/E2F pathway is commonly deregulated in cancer through genetic or epigenetic mechanisms, resulting in E2F activation. Several common oncogenes (involved in many cancer types) are the activators of the pathway, whereas several common tumour suppressor genes are inhibitors of the pathway. For example, cyclin D1 (CCND1), E2F3 and the two cyclin-dependent kinases CDK4 and CDK6 can be activated by translocation, amplification or mutation, whereas RB (RB1) and the cyclin-dependent kinase inhibitors p16INK4a (CNKN2A) and p15INK4b (CDKN2B) can be inactivated by point mutation, homozygous deletion or DNA methylation. In addition, RB can be inactivated by several oncogenic viral proteins including E7 from human papillomavirus, which is responsible for more than 90% of cervical carcinomas (Munger *et al*, 2001). Tumour suppressor gene inactivation is found not only in sporadic tumours but also in tumour-prone families. Germline mutations of RB1 results in retinoblastoma with a high penetrance early in young individuals and late in life in sarcomas and lung and bladder carcinomas (Knudson, 1971; Nevins, 2001; Giacinti and Giordano, 2006). Germinal mutations of p16INK4a results in

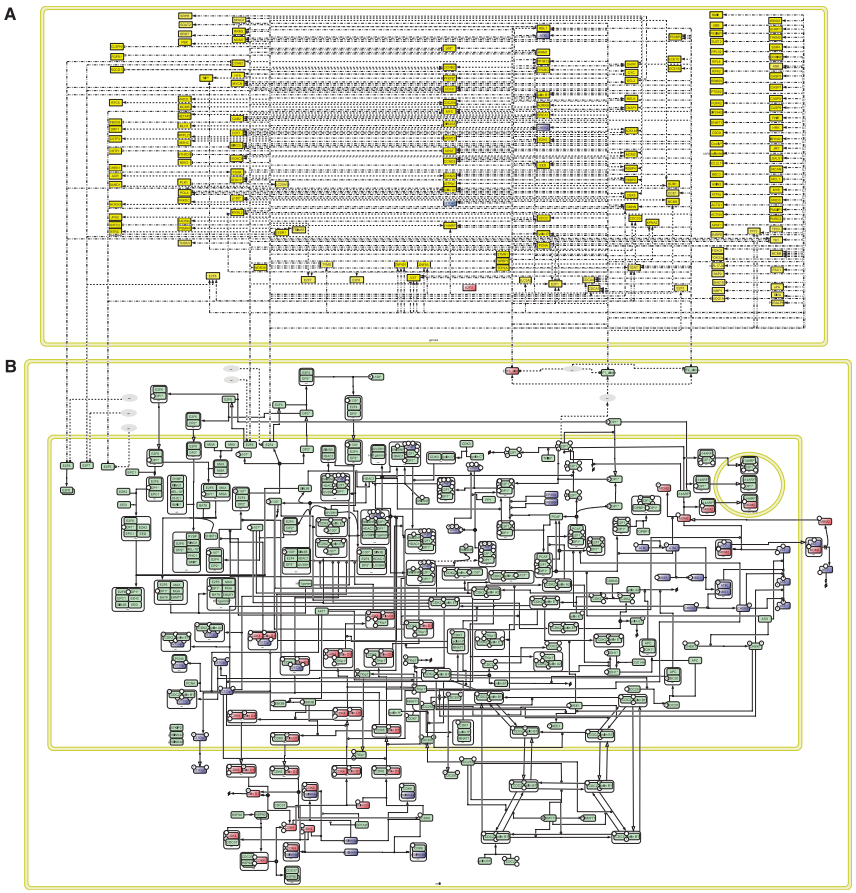


Figure 2 The textbook pathway of RB has been expanded by integrating data from the literature. The E2F transcription factors (represented here by single proteins in the nuclear compartment) are connected by activation and inhibition arrows to their gene targets. (**A**) Map of target genes of E2F transcription factors. Each E2F associates with different cofactors to activate or inhibit the transcription of many genes; pointed arrows mean activation and flat arrows mean inhibitions (**B**) Map of protein–protein interaction network. Each icon on the diagram represents distinct chemical species. See Kitano and co-workers' description of CellDesigner's standard notation (Kitano *et al*, 2005) for a detailed meaning of shapes. When the information is available (from Atlas Oncology web-page: www.atlasgeneticsoncology.org/), tumour suppressor genes and the corresponding proteins are coloured in blue and oncogenes in red, the other proteins are in green. To read and navigate through the map, visit our webpage: http://bioinfo-out.curie.fr/projects/rbpathway/. The map is clickable and allows easy access to all included information (such as literature references or standard protein ids) and hyperlinked to other databases.

are connected by 'activation' and 'inhibition' relations. The information about these relations is derived from the detailed diagram. For example, in the detailed map, E2F1 is phosphorylated by CycA2/CDK2 and is subsequently recognized for degradation, which is translated in the modular map by CycA2/CDK2 module inhibiting E2F1-3 module.

PLoS One, 7(12): e51000. doi: 10.1371/journal.pone.0051000

Mathematical model

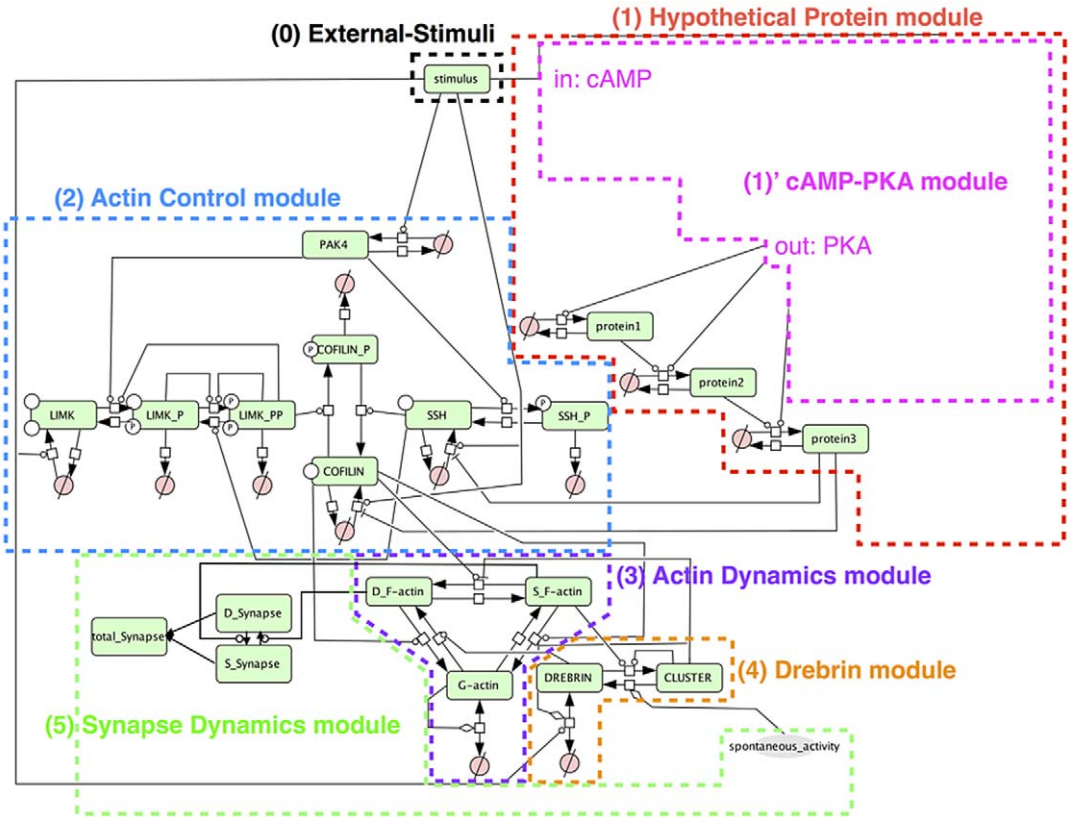


Figure 4. Whole view of the model. The model is written in accordance with Systems Biology Graphical Notation (SBGN) [83]. 0. Black box: External stimulation exists at the most upstream and drives our model. 1. Red box: Hypothetical protein module includes hypothetical proteins which play an important role in possible network succession for long-term synaptic maintenance. 2. Blue box: Actin control module includes actin binding protein: COFILIN and COFILIN kinase/phosphatase. 3. Purple box: Actin dynamics module includes G-actin and F-actin to explain the actin dynamics (polymerization and depolymerization). 4. Orange box: Drebrin module includes the actin binding protein: Drebrin. Drebrin affects actin dynamics and is clustered with F-actin. 5. Green box: Synapse dynamics module includes two kinds of synapses to explain the dynamics of synaptogenesis and synaptic maintenance. The white square boxes linked to two connectors are process nodes, which represent processes that transform one or several entity pools to be identical or different. The circles crossed by a bar linking the upper-right and lower-left corners of an invisible square drawn around the circle (Ø) are empty sets which represent the source or sink [84].
doi:10.1371/journal.pone.0051000.g004

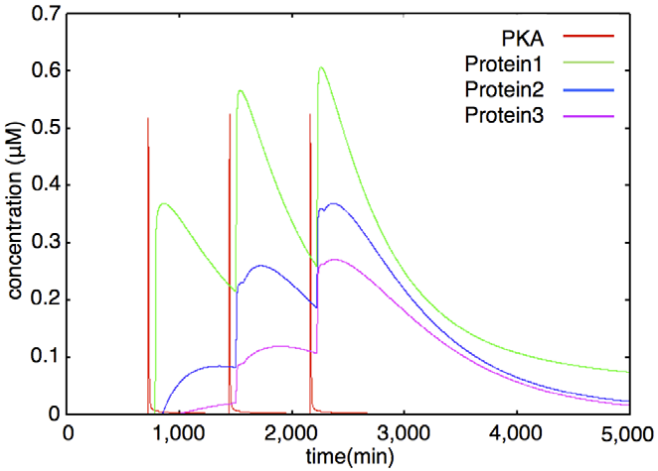
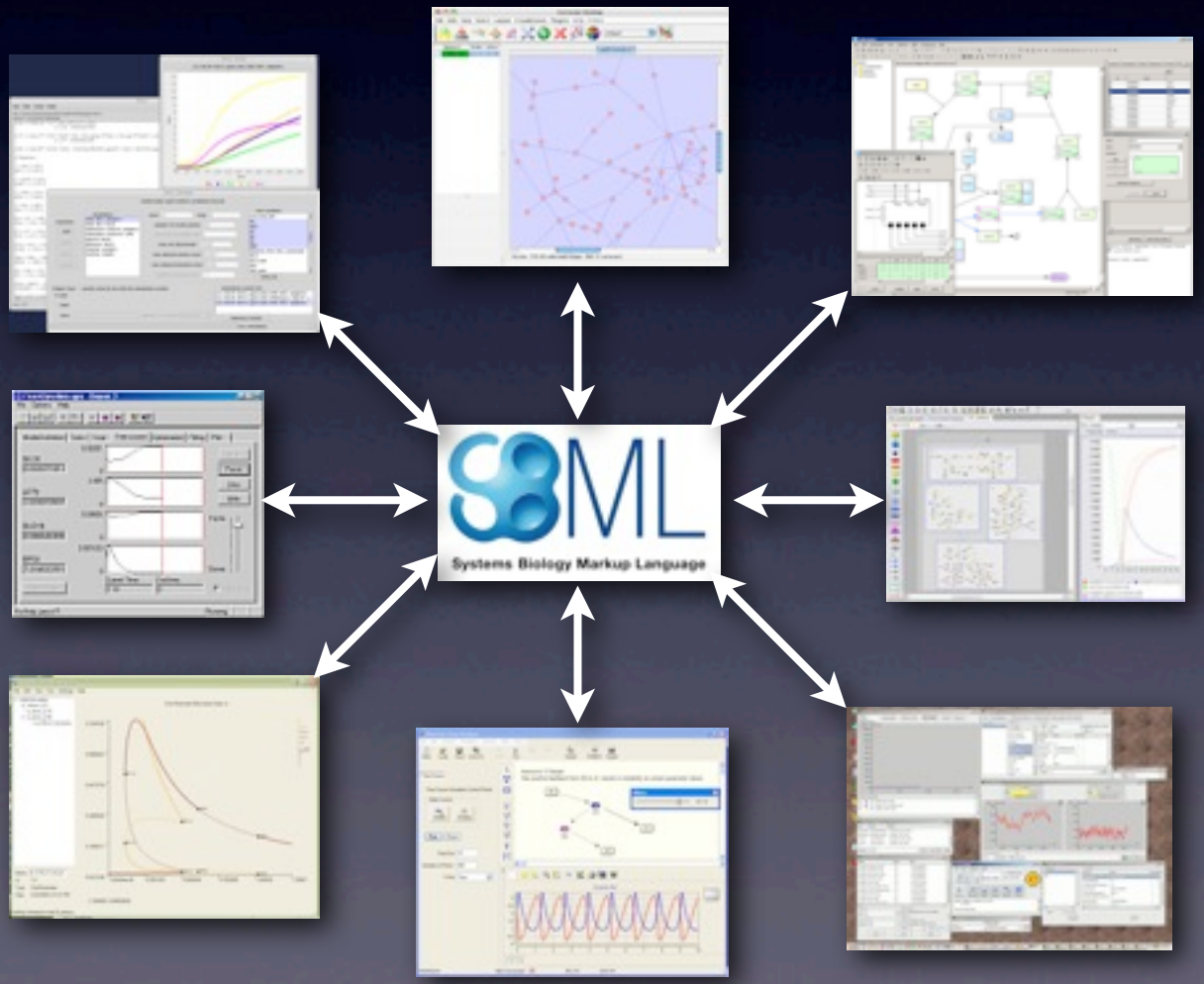


Figure 8. Example of dynamics of PKA, Proteins 1, 2, 3 (interval between stimuli = 720 min). The colored lines show the time-course fluctuations of each of the components. Red: PKA; Green: Protein 1; Blue: Protein 2; Purple: Protein 3. External stimuli increase cAMP level (not shown) and cAMP increases the PKA level. PKA directly increases Protein 1 level. Protein 1 and PKA coordinately increase Protein 2. Protein 2 and PKA coordinately increase Protein 3. Protein generation is time-consuming, so there are time-lags between the PKA increase and protein increase.
doi:10.1371/journal.pone.0051000.g008

Mathematical Modeling of Sustainable Synaptogenesis by Repetitive Stimuli Suggests Signaling Mechanisms in vivo

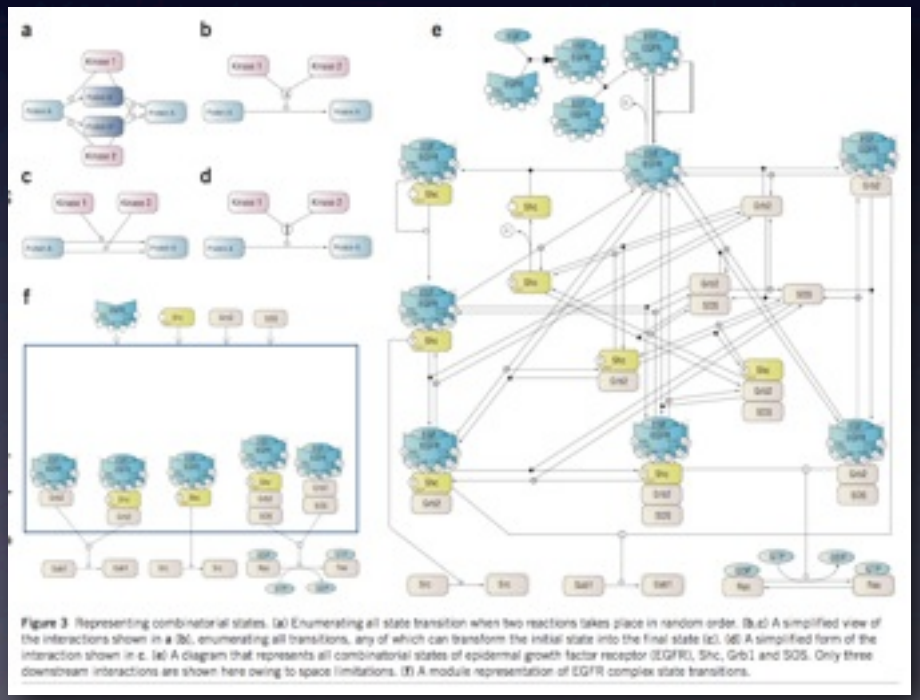
CellDesigner↔SBML

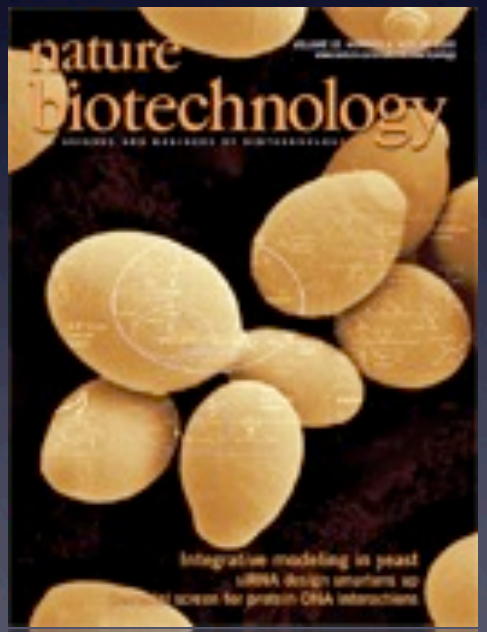
- 290 software packages support SBML
- http://sbml.org



Graphical Notation

- Graphical Notation for representing biological interactions
- protein-protein interaction, gene regulatory networks

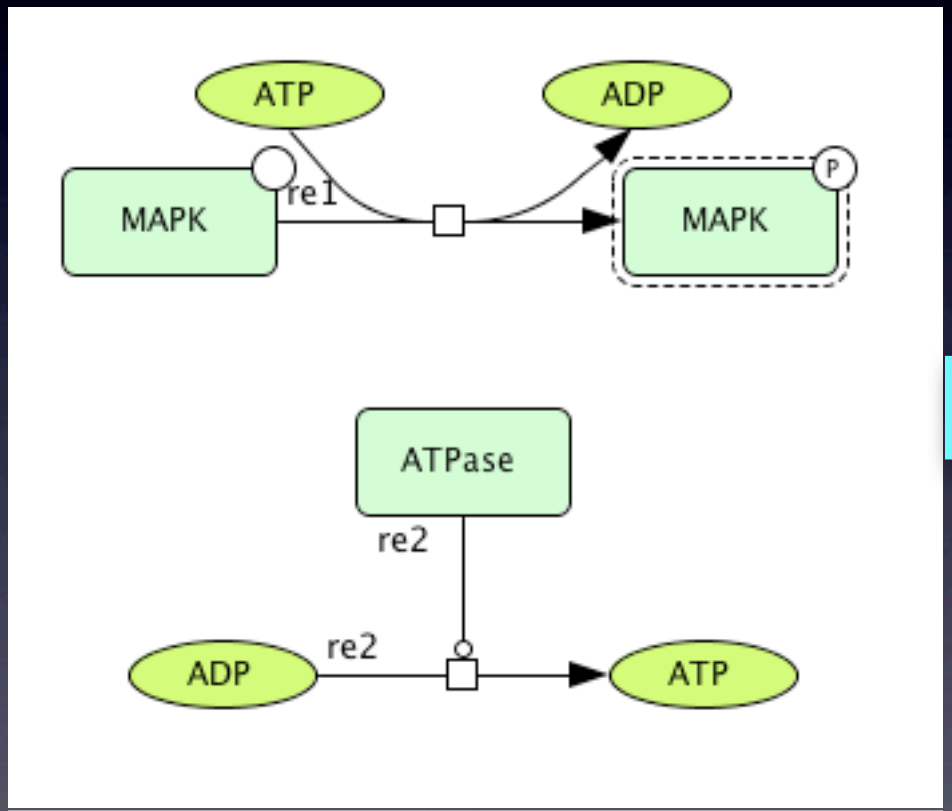




Kitano, H. et al. "Using process diagrams for the graphical representation of biological networks", *Nature Biotechnology* 23(8), 961 - 966 (2005)

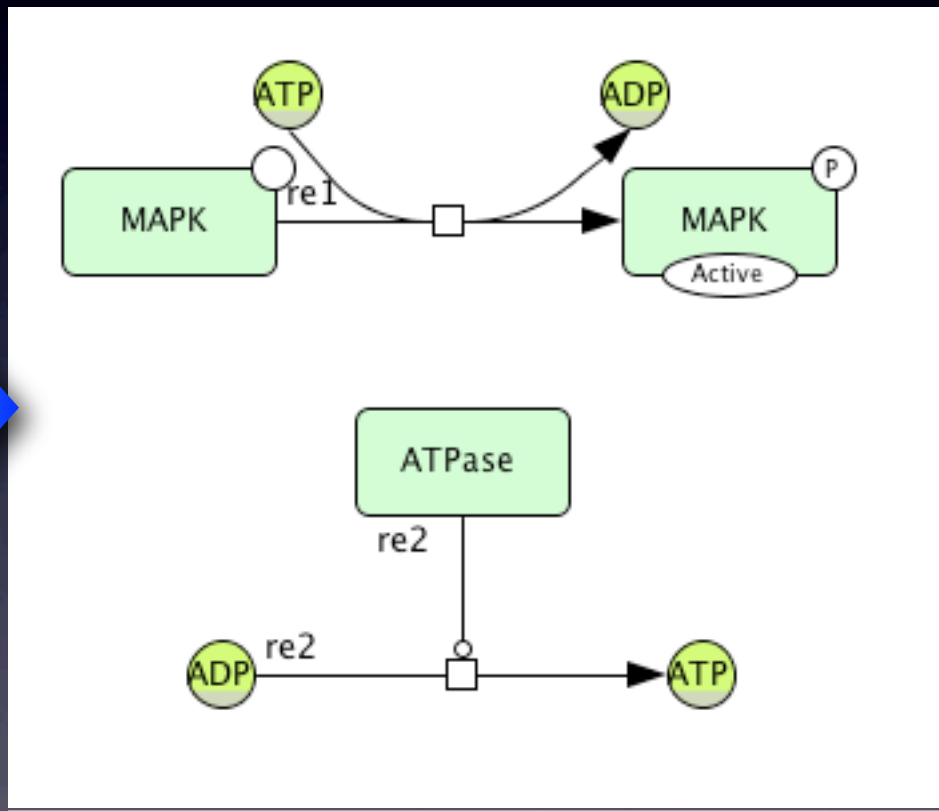
SBGN viewer

CellDesigner notation



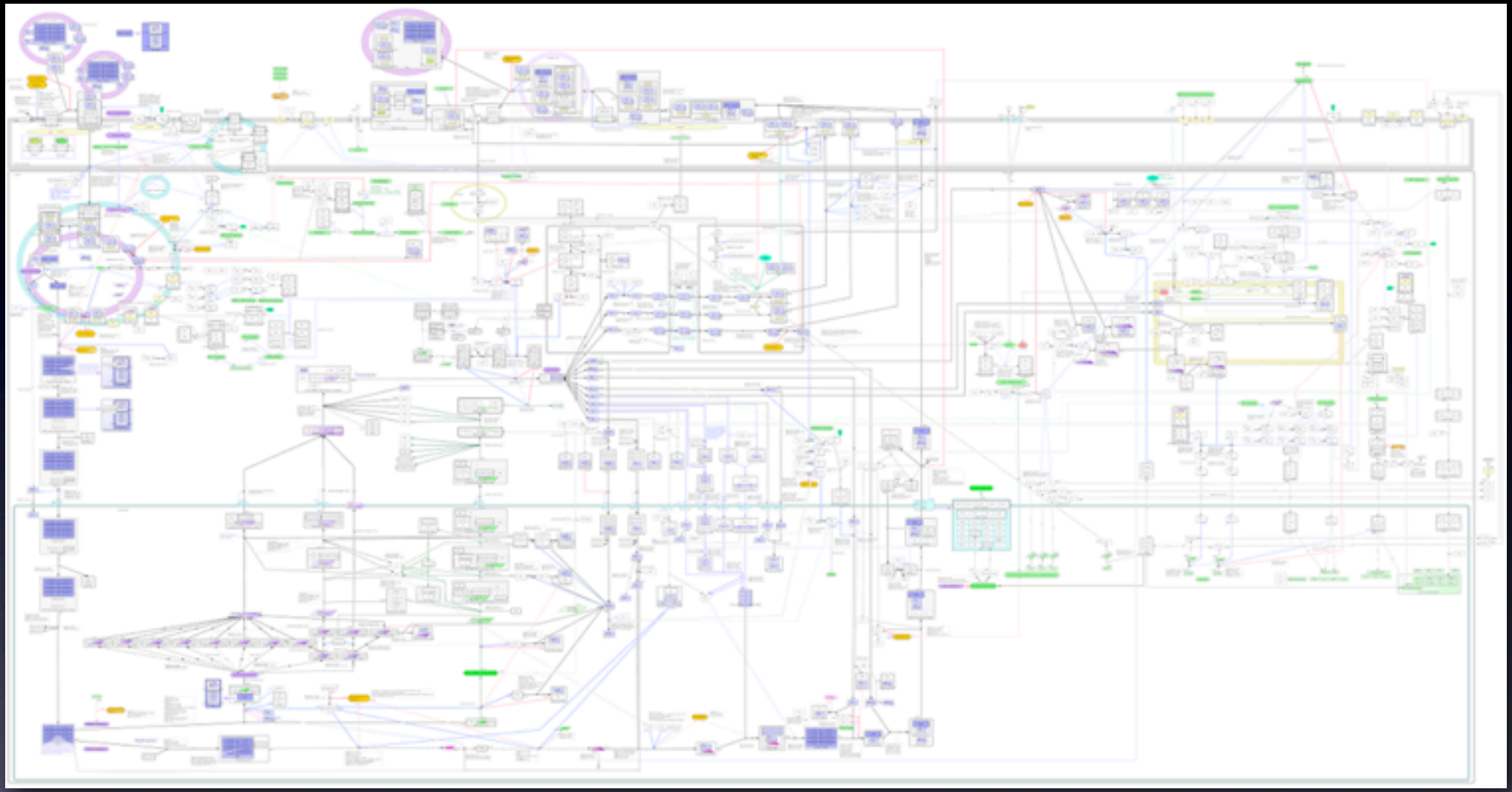
Nature Biotechnology, 23(8), pp.961-66, (2005)

SBGN PD



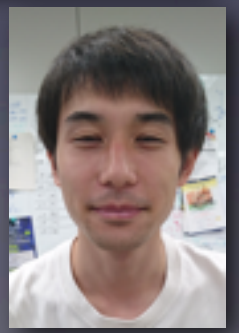
Nature Biotechnology, 27(8), pp.735-41, (2009)

CellDesigner ↔ SBML Layout

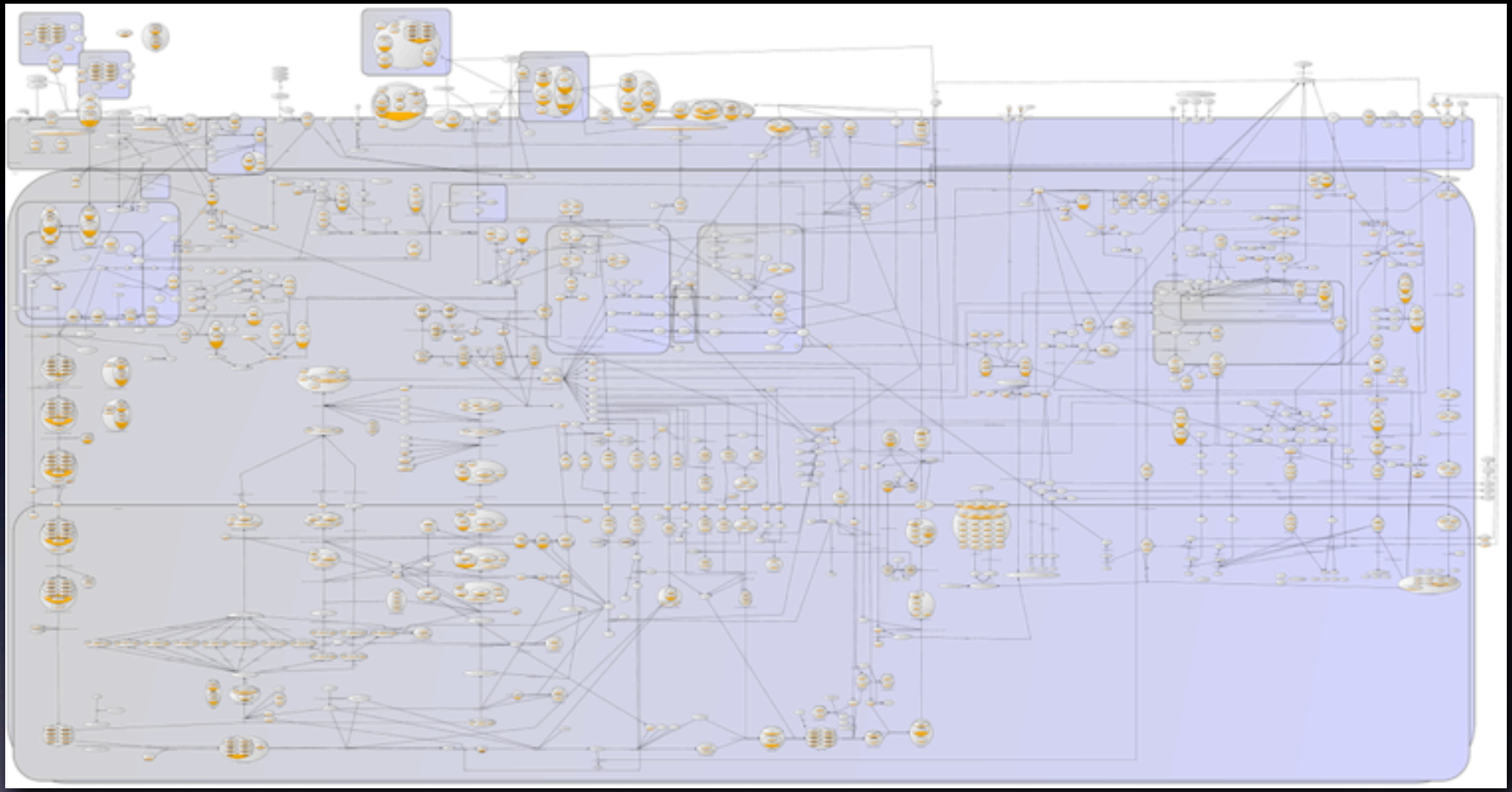


Implemented by Kaito Ii, as part of Google Summer of Code 2016

https://github.com/funasoul/celldesigner-parser



CellDesigner ↔ SBML Layout



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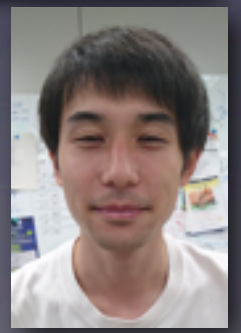
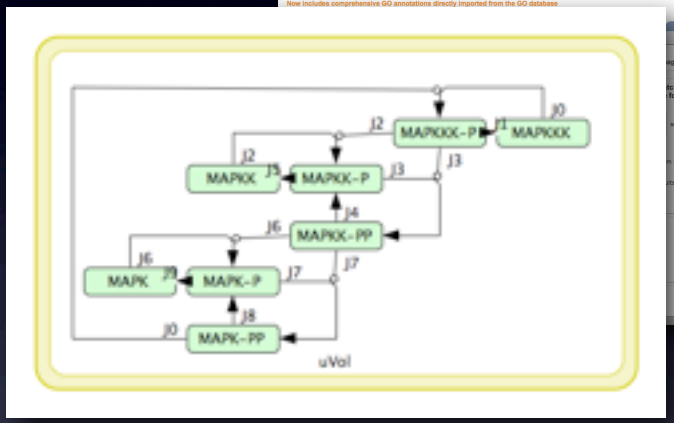
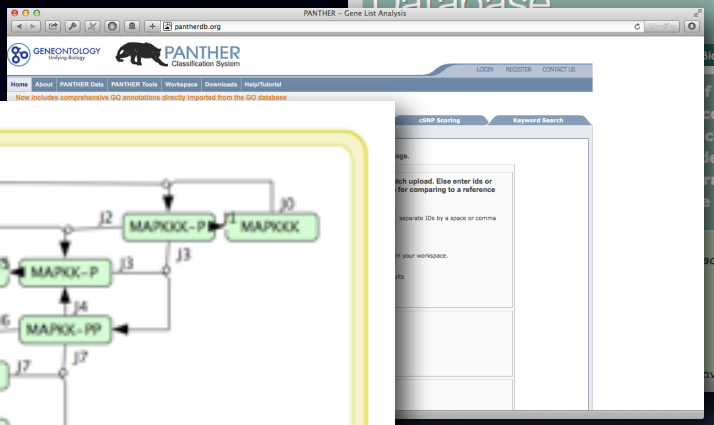
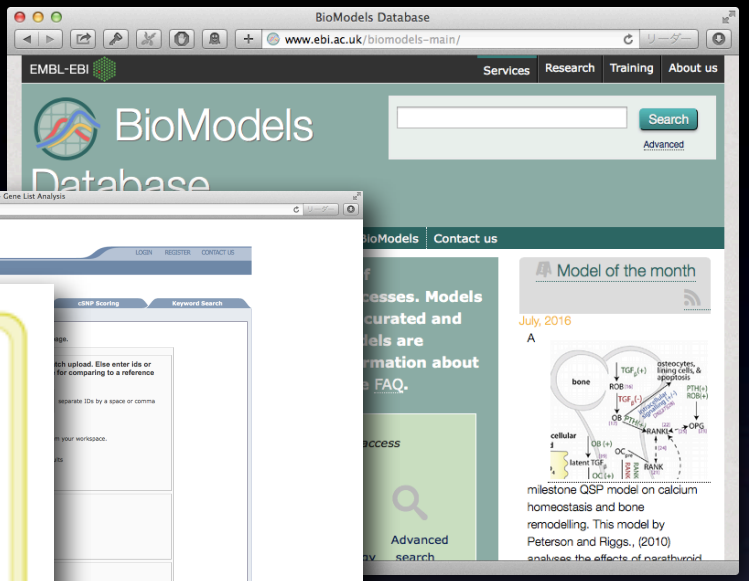


Database connection

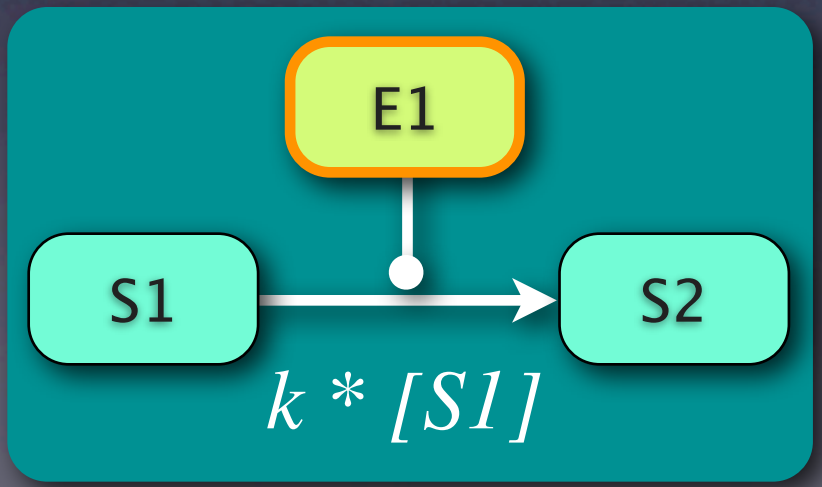
- Import a model from
  - BioModels.net
  - PANTHER







- Import kinetic law etc. from SABIO-RK



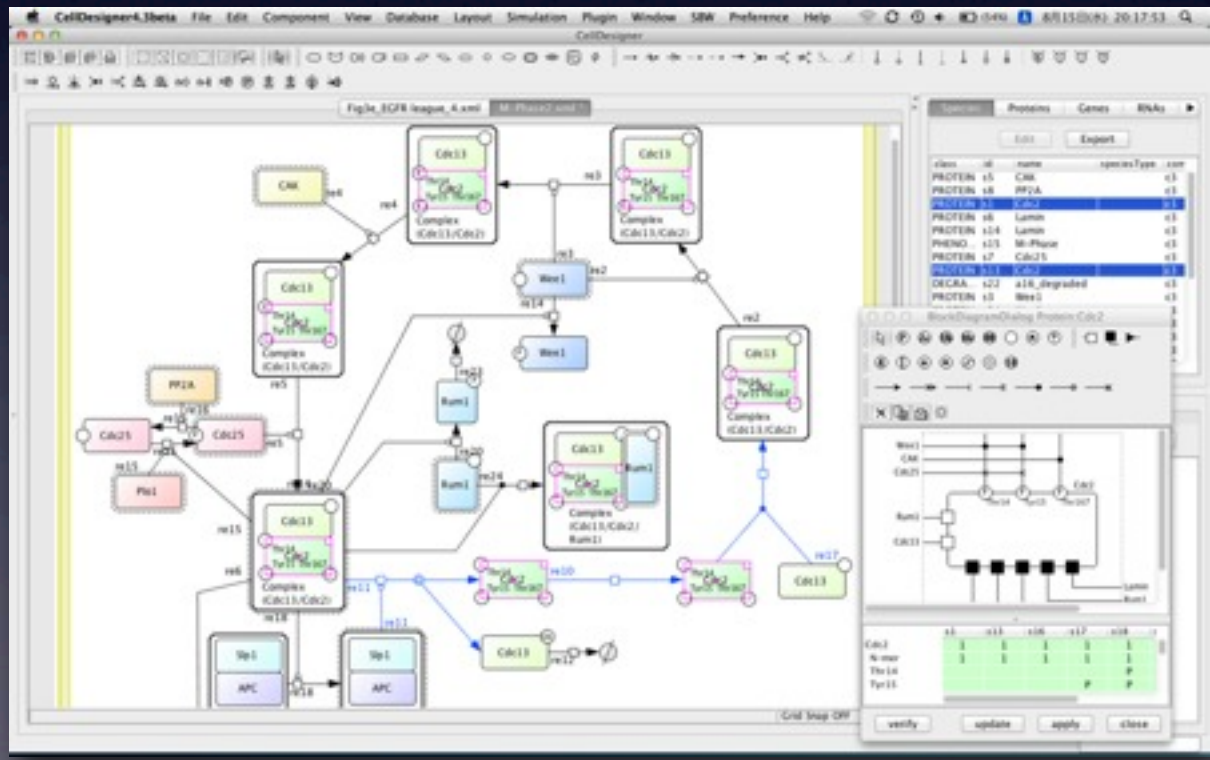
Name, EC number

SBML
Systems Biology Markup Language

SABIO-RK

CellDesigner 4.4

- SBML Level 2 version 4 support
- Graphical notation (SBGN Viewer, SBGN-ML export)
- Built-in simulator (SOSlib, COPASI, Simulation Core)
- Database connection (BioModels.net, SABIO-RK, PANTHER, JWS Online)
- MIRIAM, SBO, SED-ML
- Plugin API
- Export to PDF, PNG.
- Freely available
  - Windows (XP or later)
  - Mac OS X
  - Linux



http://celldesigner.org

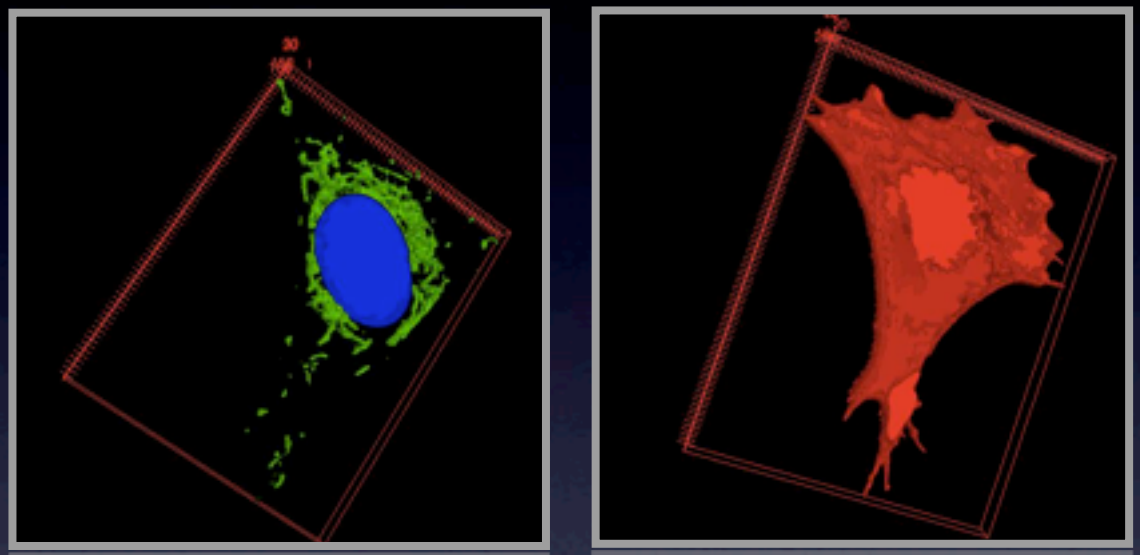
Future Plan (CellDesigner 4.5 & 5)

- Standards:
  - SBML Level-3 support*
  - Enhance SBO, SED-ML, MIRIAM support*
  - Garuda gadget*
- Simulation:
  - High performance ODE, SSA simulator using GPGPU *Proc. NOLTA*, 2012 & *Frontiers in Physiology*, 6, 2015
  - Spatial simulator*

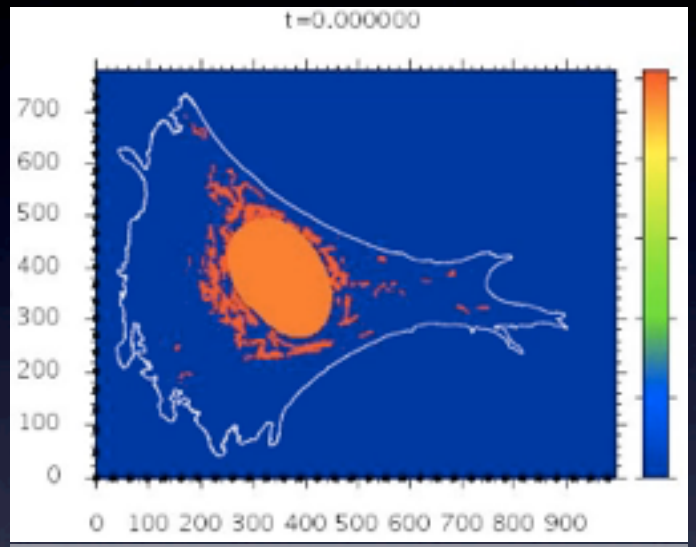
* will be included in CellDesigner4.5

Spatial Simulator

Microscopic Image → 3D reconstruction

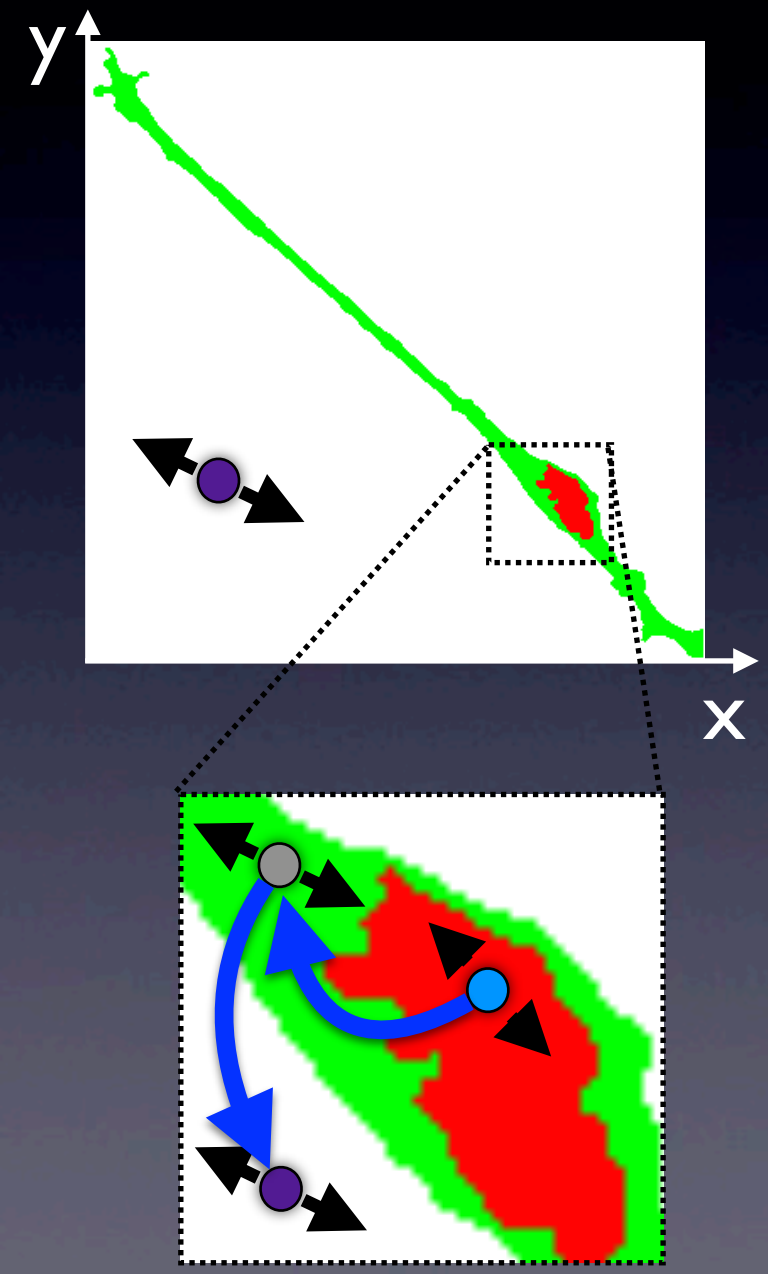


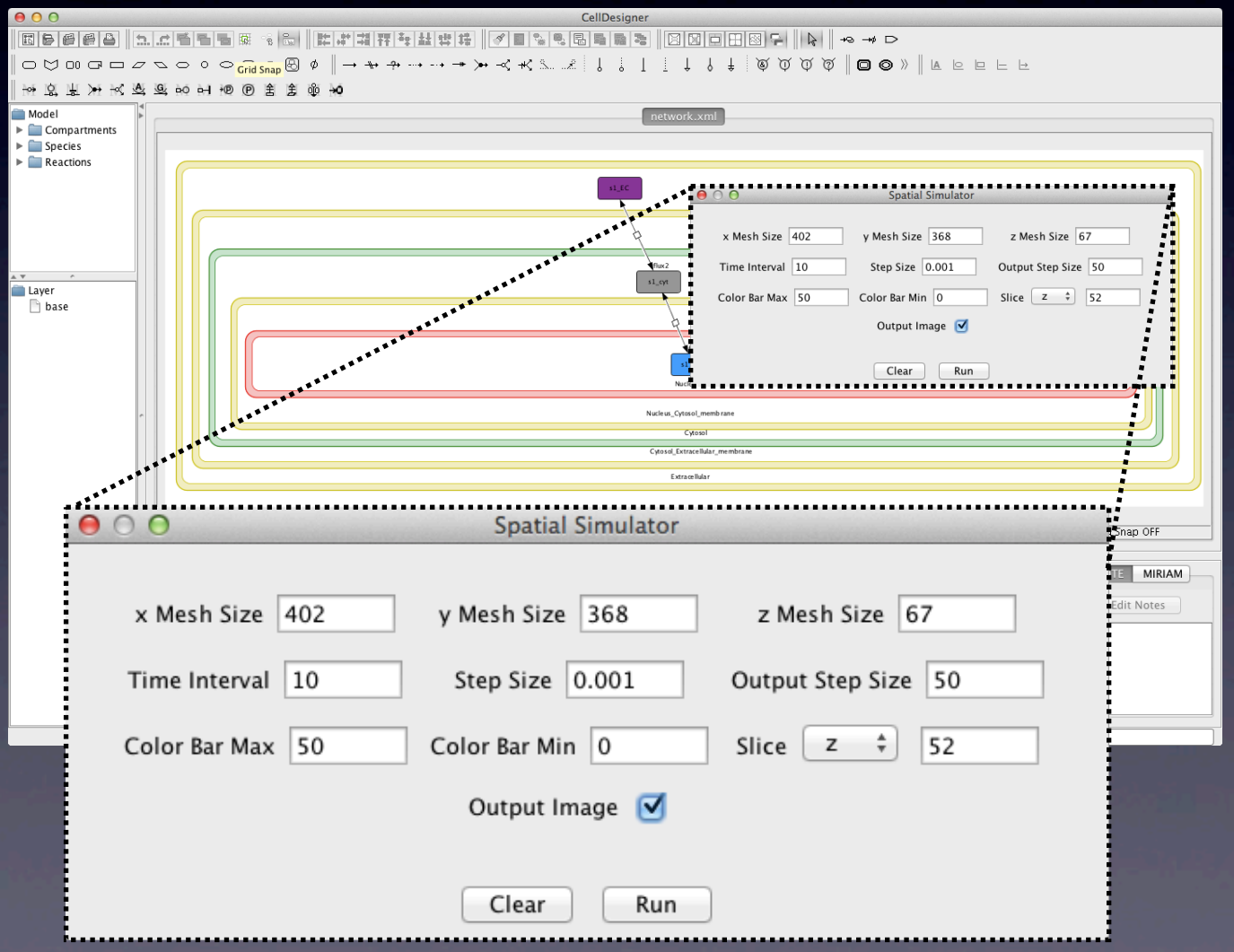
Simulation



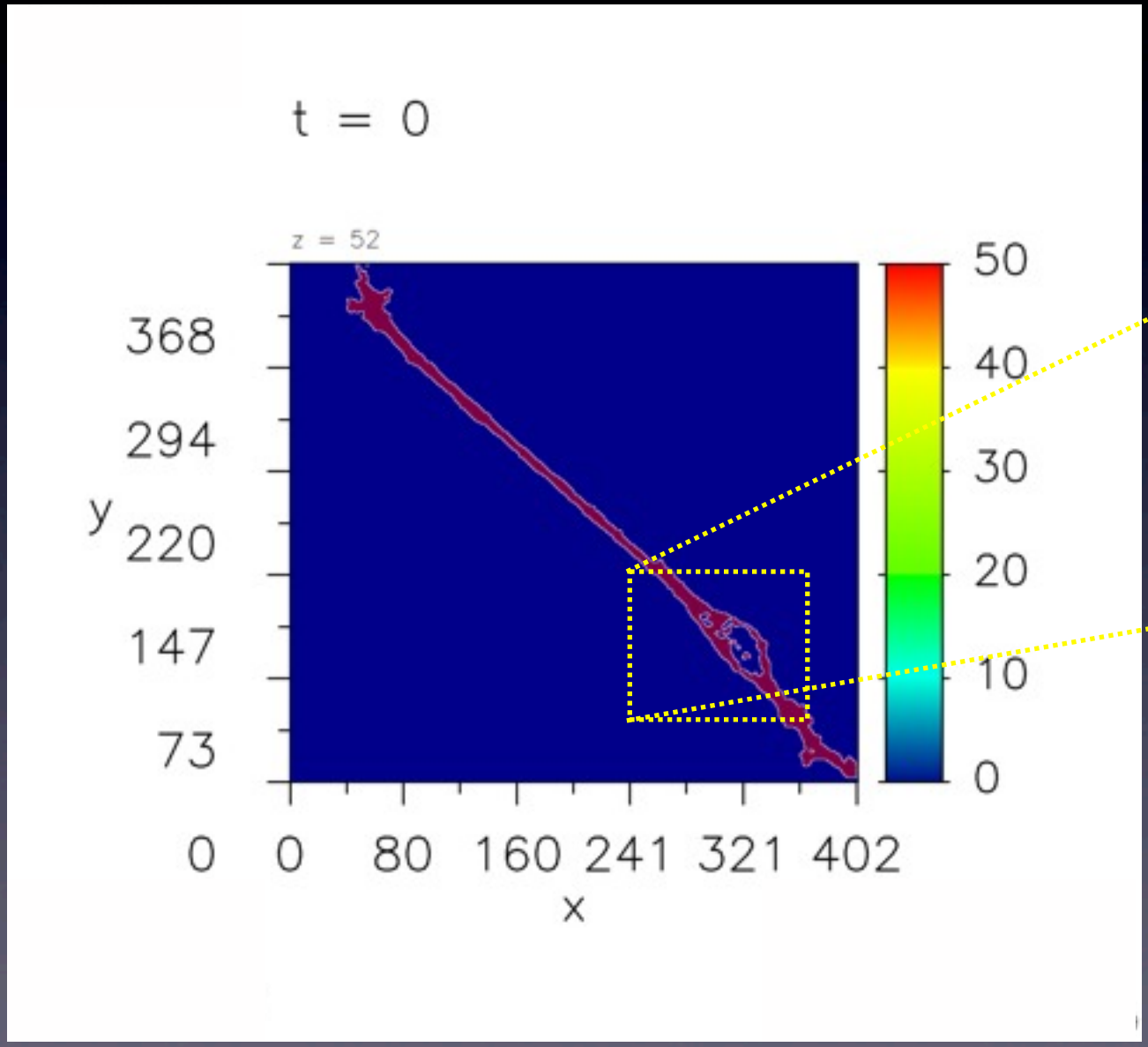
- Automatically create an SBML (+spatial extension) model from microscopic image https://github.com/spatialsimulator/XitoSBML
- 52x (advection), 63x (diffusion) performance improvement with GPGPU

Create & Simulate Spatial Model on CellDesigner4.5α





Simulation Result

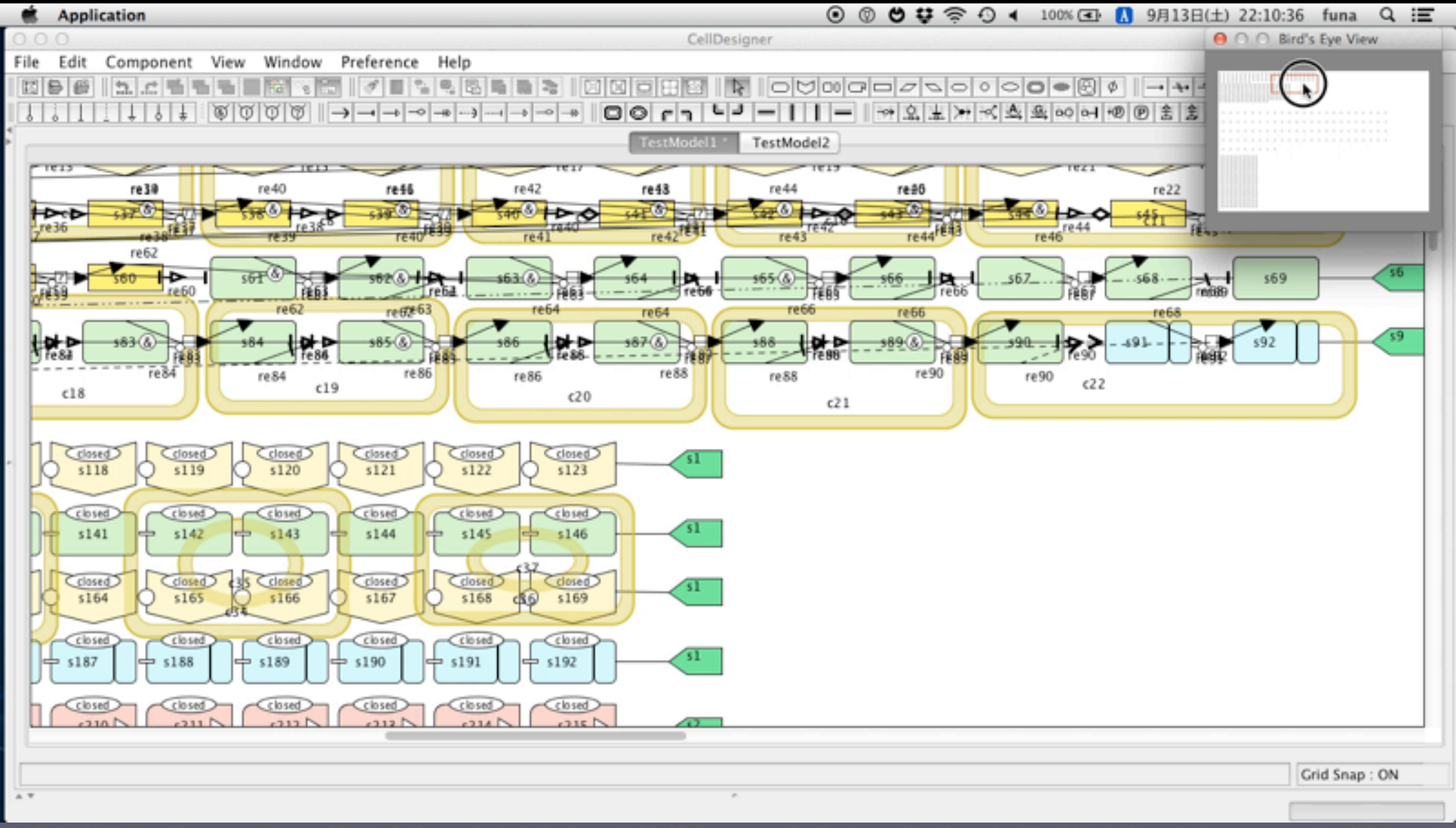


CellDesigner 5

- Completely rewritten from scratch
- SBML Level 3 core support
- Scalable

CellDesigner 5

- Completely rewritten from scratch



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SBML
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SBGN
* SBGN community

SBW
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* Christoph Flamm

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COPASI (Univ. of Heidelberg)
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* Sven Sahle
* Ursula Kummer

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- Google Summer of Code