

CellDesigner

Akira Funahashi & Noriko Hiroi
Keio University, Japan
4th Sep. 2013



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CALAMVS
GLADIO
FORTIOR

SBI The
Systems
Biology
Institute

Overview

- Introduction of CellDesigner
- What kind of model you can build
- How to build a model with CellDesigner
 - From scratch
 - Import a model, kinetic law and parameters from existing databases

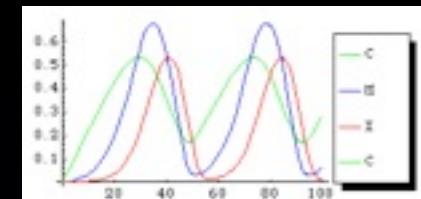
CellDesigner



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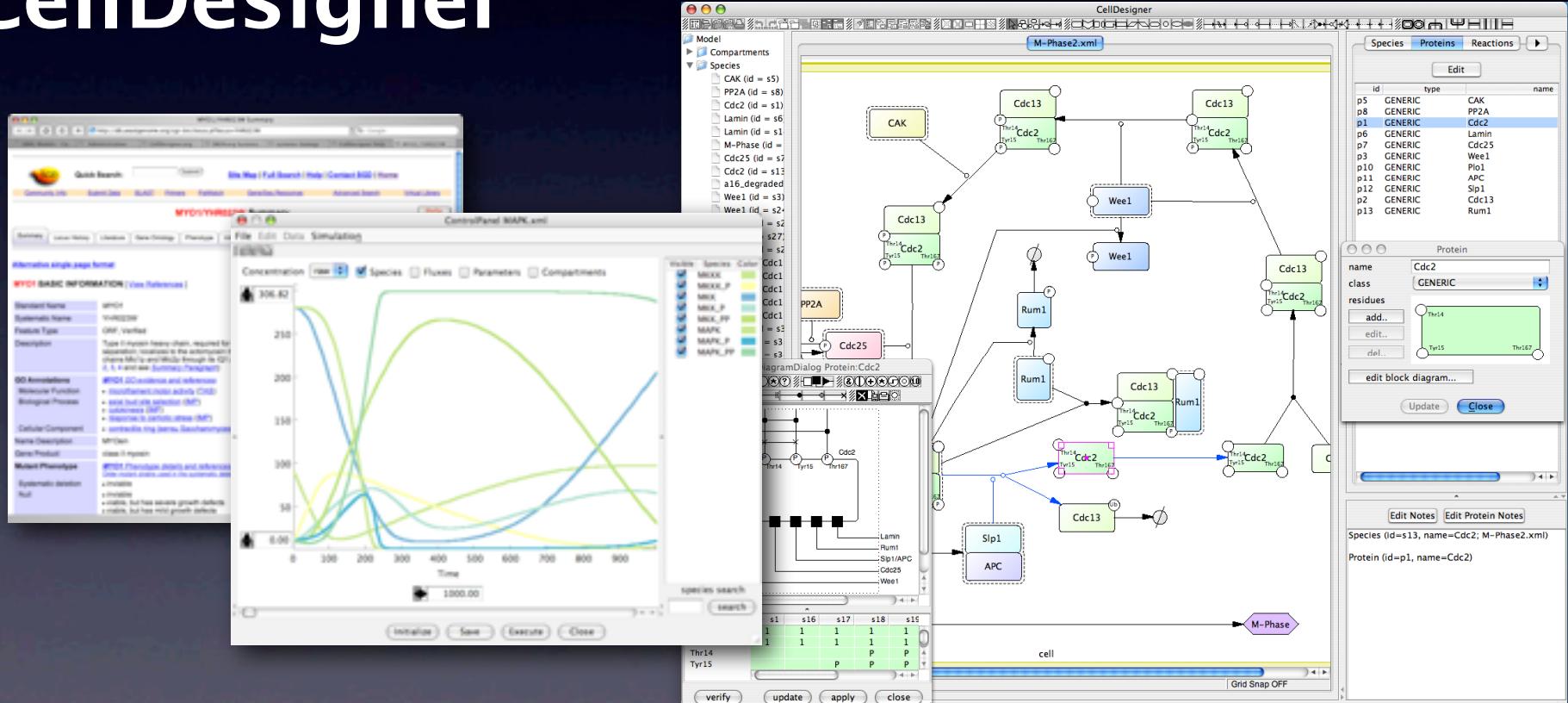
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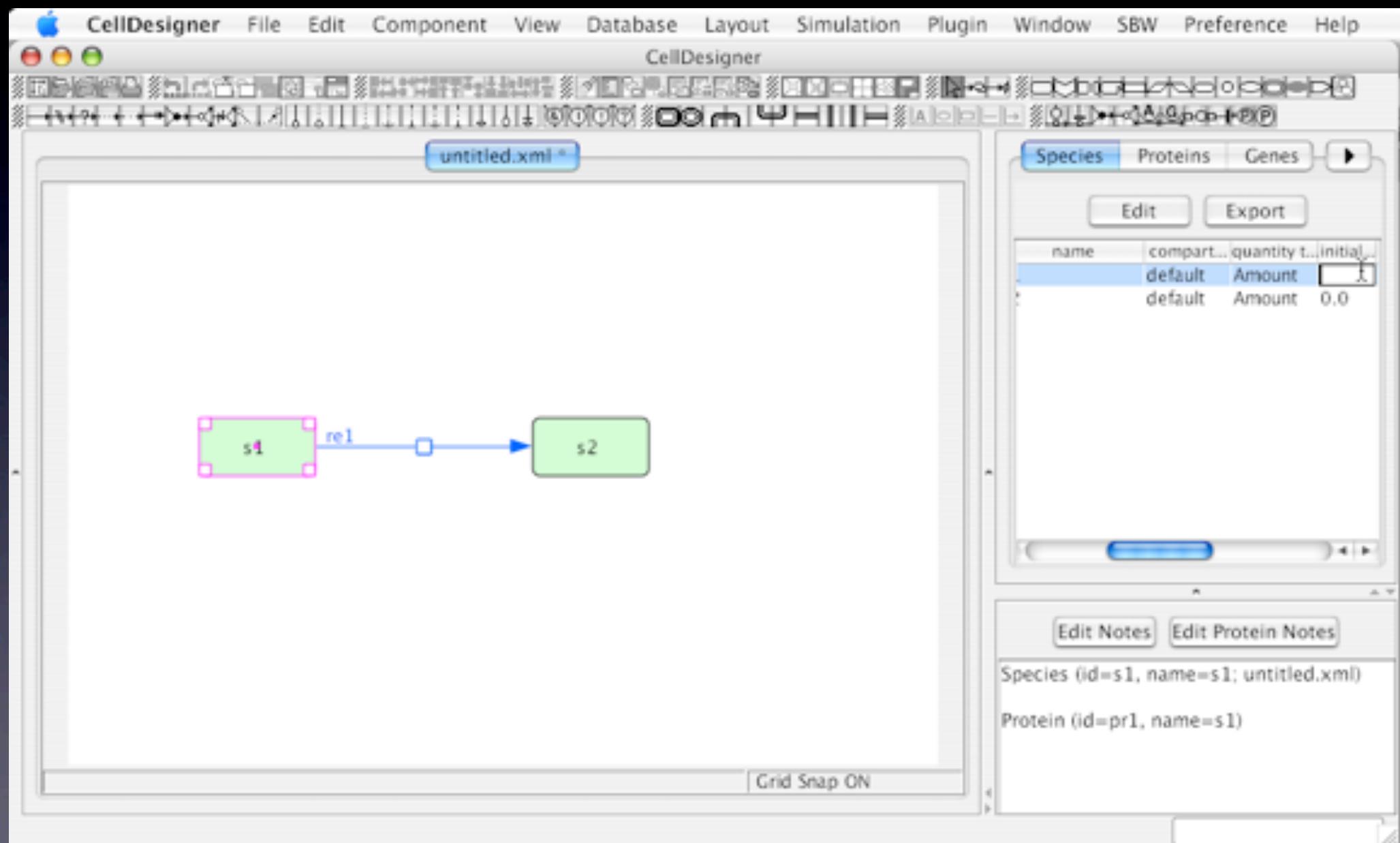


= CellDesigner



Modeling tool for biochemical and gene-regulatory network

CellDesigner



Comprehensive pathway map

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www.molecularsystemsbiology.com

REVIEW

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

Laurence Calzone^{1,2,3,6}, Amélie Gelay^{1,5,6},
 Andrei Zinov'yev^{1,2,3,6,*}, François Radvanyi^{4,5,7}
 and Emmanuel Barillot^{1,2,3,7}

¹ Institut Curie, Service Bioinformatique, Paris,
² INSERM, U900, Paris, F-75248 France,
³ Ecole des Mines de Paris, ParisTech, Fontainebleau, F-77300 France,
⁴ Institut Curie, Centre de Recherche, Paris, F-75248 France and
⁵ Institut Curie, CNRS UMR144, Paris, France

⁶ These authors contributed equally to this work.

⁷ These two authors are the joint senior authors of this paper.

* Corresponding author: Institut Curie, Service Bioinformatique, 26 rue d'Ulm, Paris 75248, France. Tel: + 33 1 53 10 70 50; Fax: + 33 1 44 41 09 08;
 E-mail: andrei.zinovyev@curie.fr

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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

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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

molecular
systems
biology

(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 oncogene products) 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). Germline mutations of p16INK4a results in

A comprehensive map of RB/E2F pathway
 L Calzone *et al*

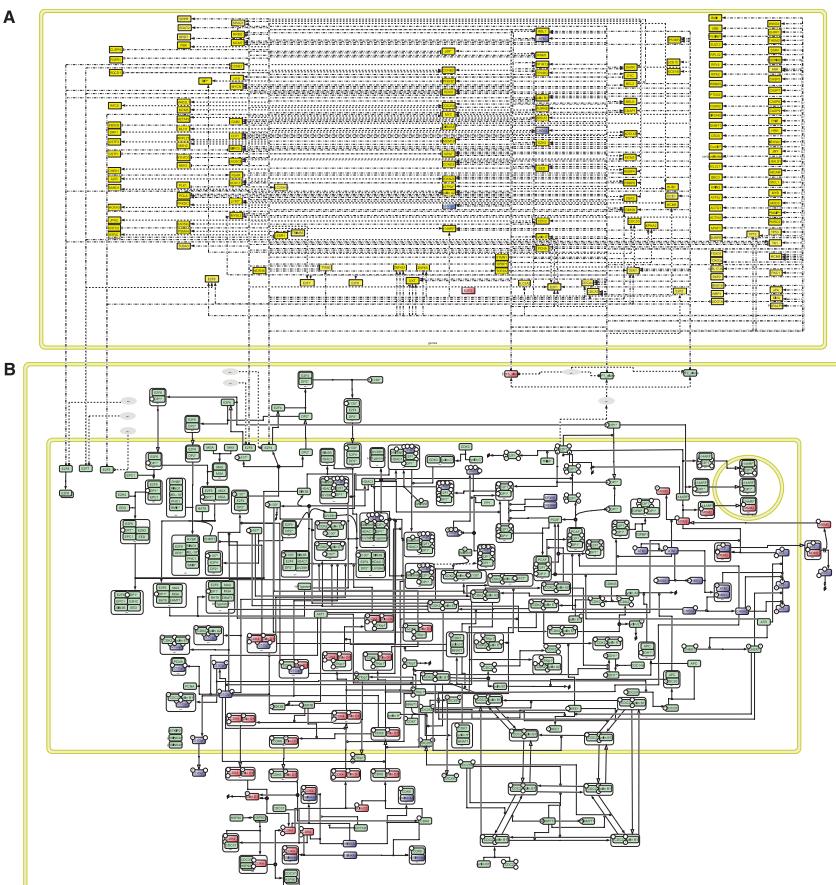


Figure 2 The textbook pathway of RB has been expanded by integrating data from the literature. The E2F transcription factors (represented here by single proteins in the nuclear compartment) are connected by activation and inhibition arrows to their gene targets. Each E2F associates with different cofactors to activate or inhibit the transcription of many genes; pointed arrows mean activation and flat arrows mean inhibition. **(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.curie.fr/projects/bopathway/>. 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 phos-

phorylated by CycA2/CDK2 and is subsequently recognized for degradation, which is translated in the modular map by CycA2/CDK2 module inhibiting E2F1-3 module.

Mathematical model

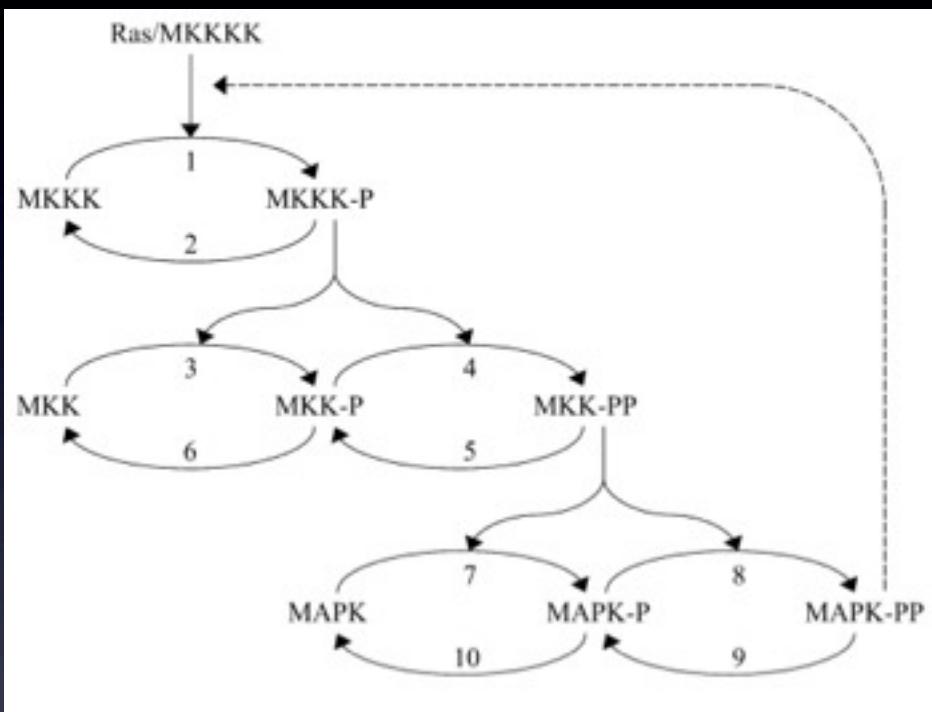
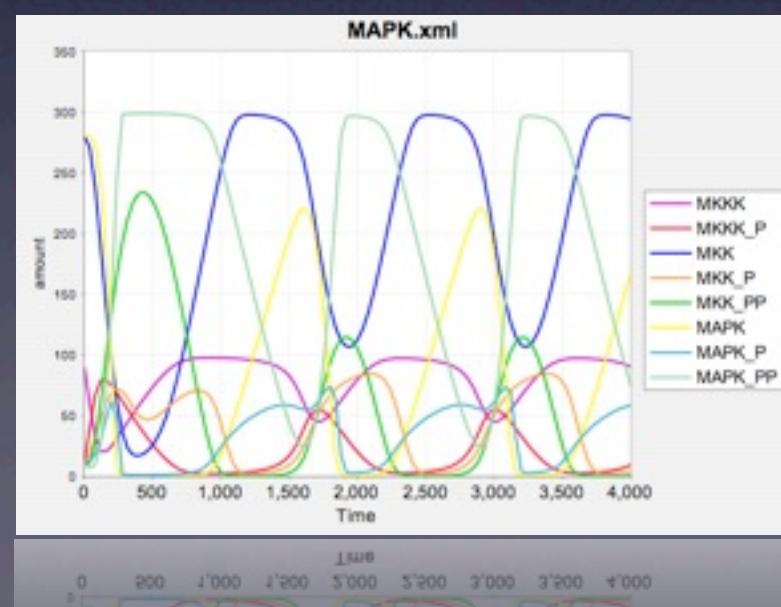
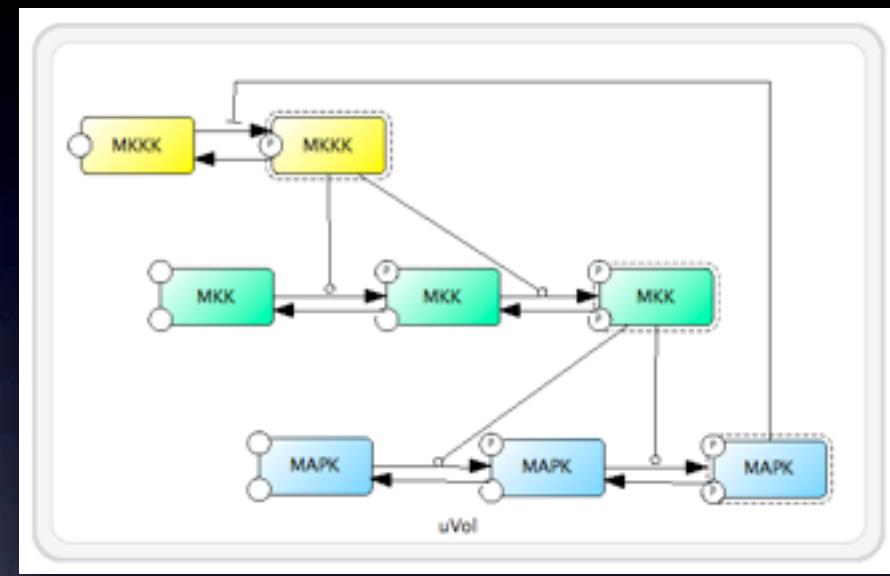
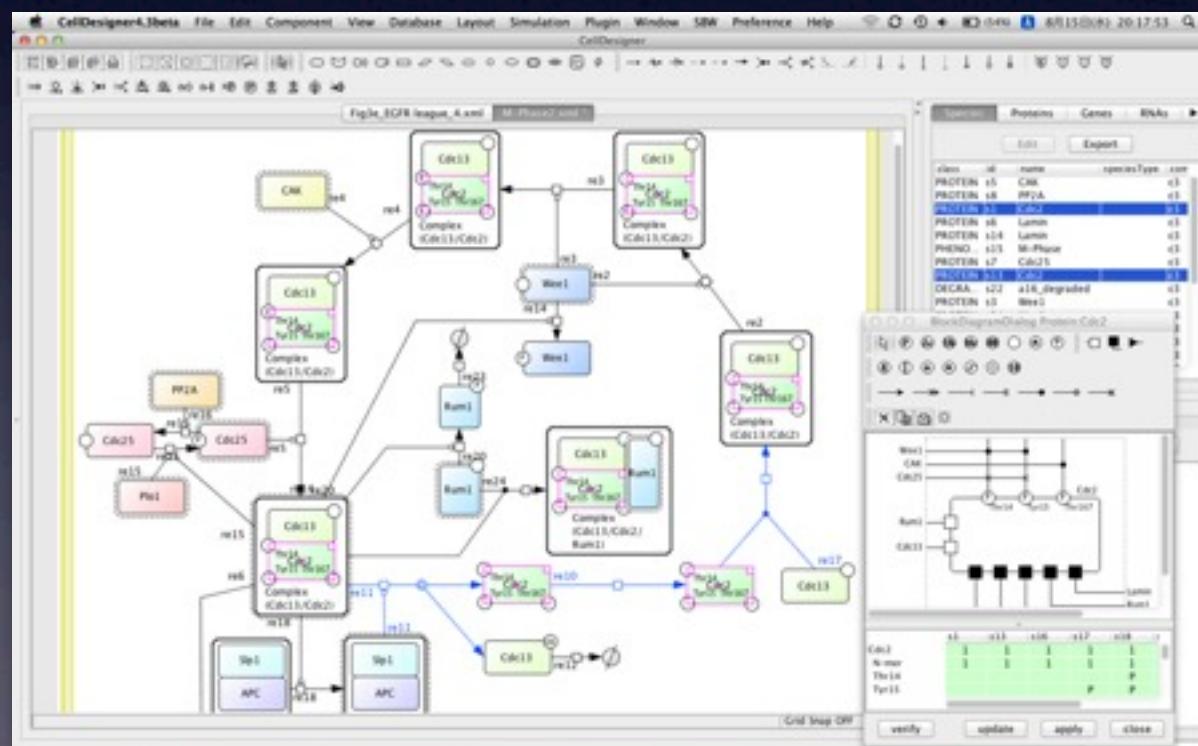


Fig. 1. Kinetic scheme of the MAPK cascade.
Feedback effect of MAPK on the rate of
MKKK phosphorylation is shown schematically
by the dashed line. Numbering of individual
steps corresponds to kinetic equations in
Tables 1 and 2.



CellDesigner 4.3

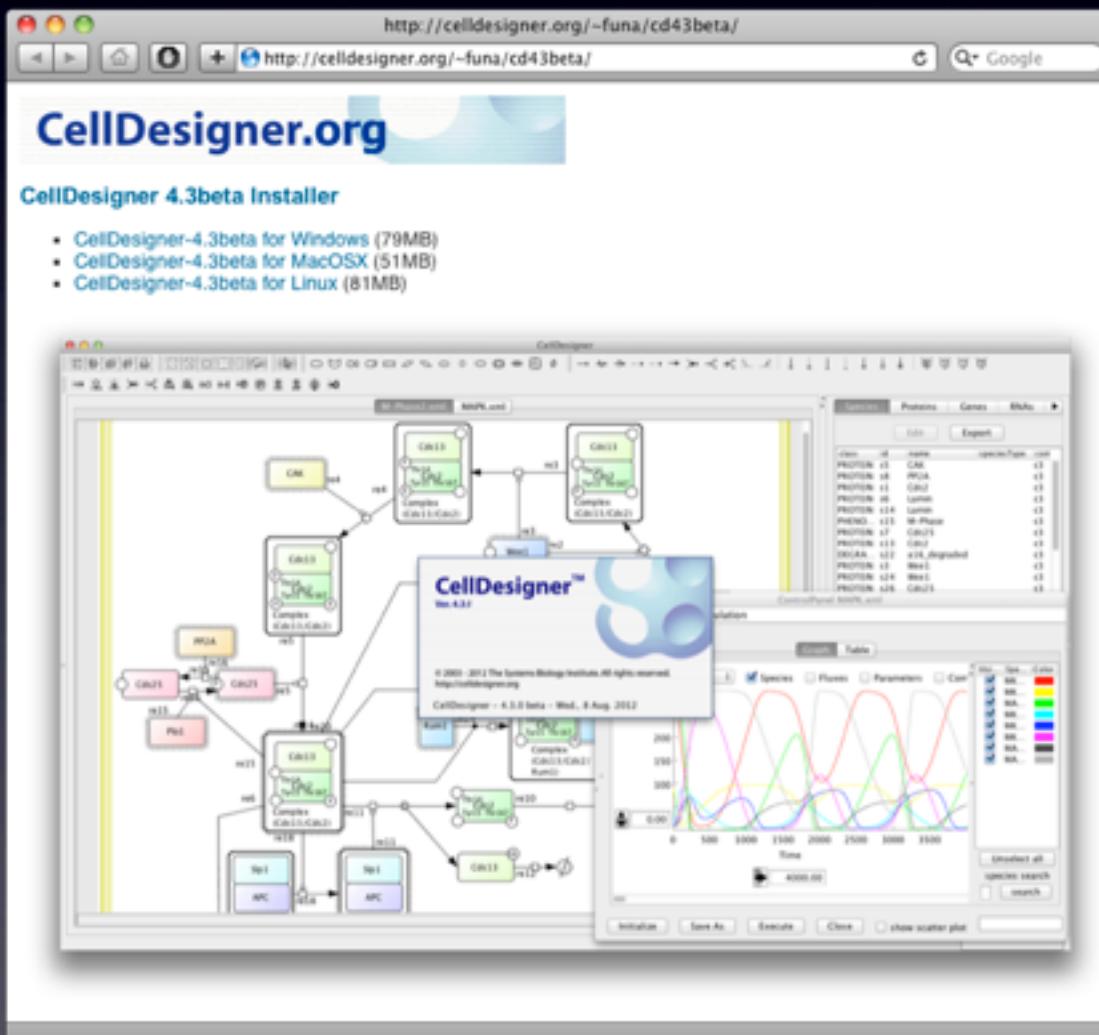
- SBML Level 2 version 4 support
- Graphical notation (SBGN Viewer, **SBGN-ML export**)
- Built-in simulator (SOSlib, COPASI, Simulation Core)
- Database connection (BioModels.net, **SABIO-RK**, PANTHER, JWS Online)
- MIRIAM, SBO, **SED-ML**
- Plugin architecture
- Export to PDF, PNG.
- Freely available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



<http://celldesigner.org>

Before we start

- Please download & install CellDesigner 4.3 from <http://celldesigner.org/>



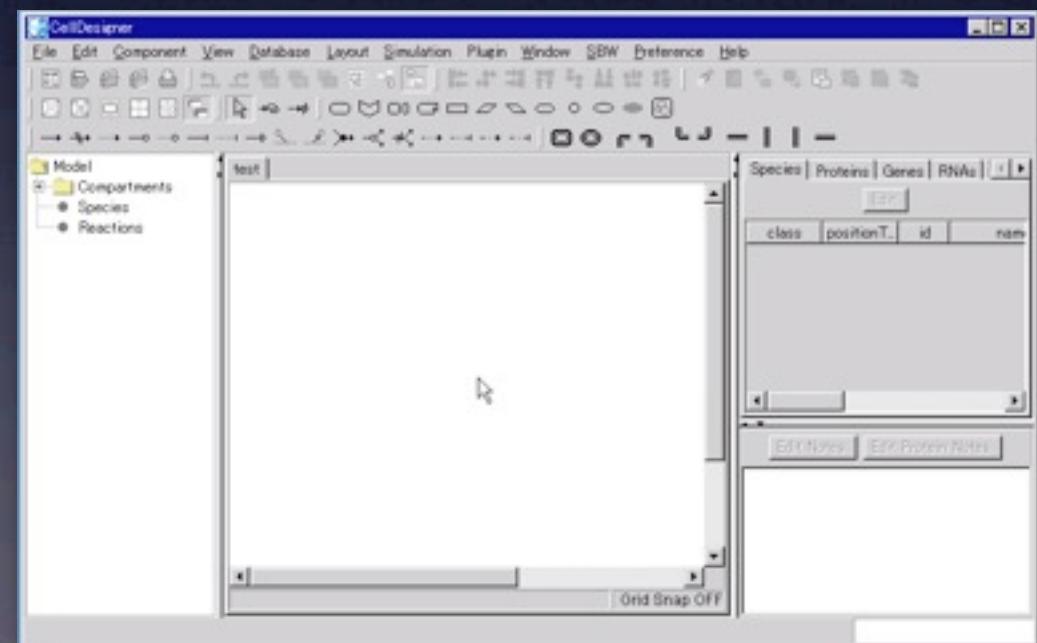
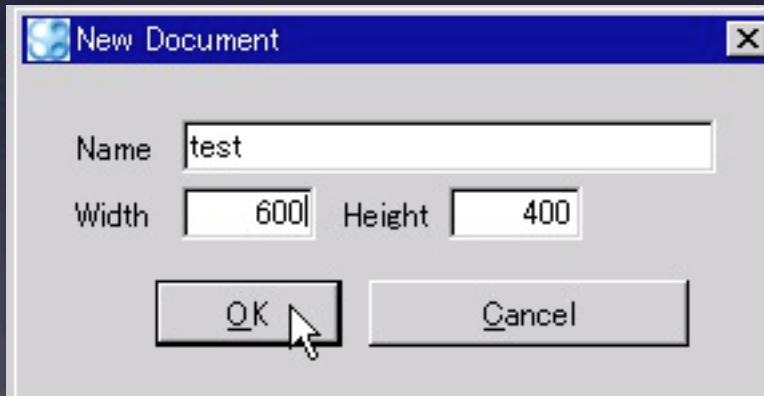
Installation



Create model

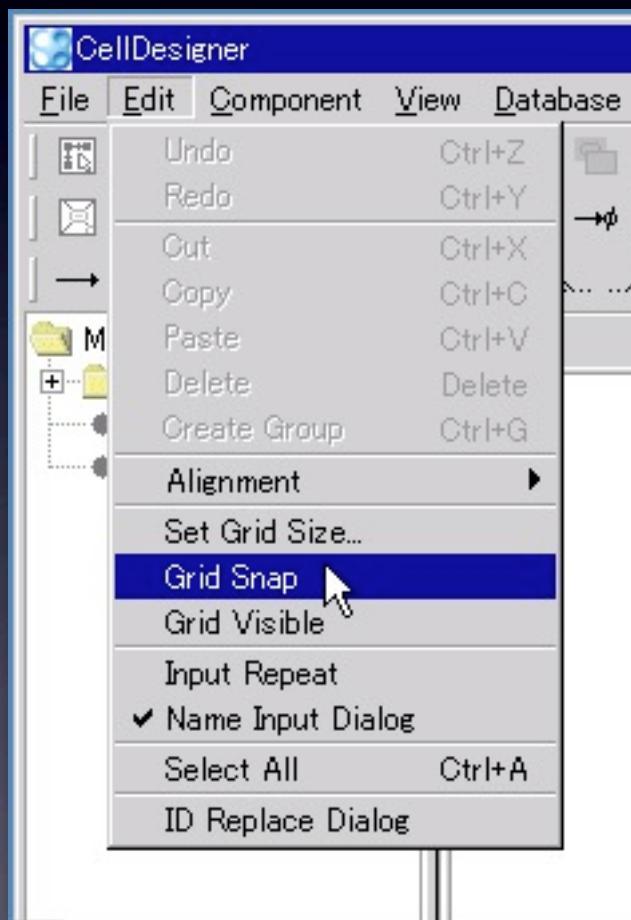
- Create new model:

- [File] → [New] → input title → [OK]



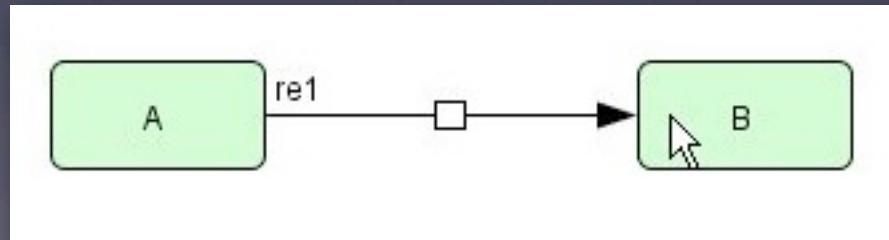
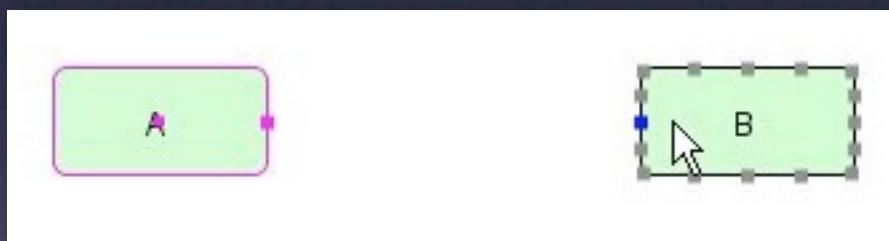
Tips

- Enable [Grid Snap] will help you draw your model much easier



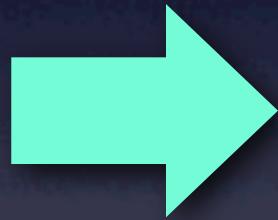
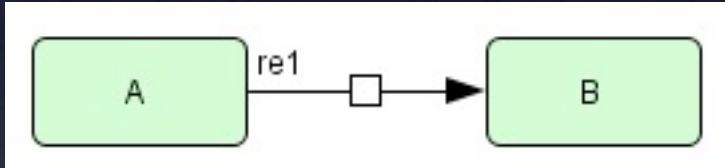
Create Reaction

- Create Protein “A” and “B”
- Draw “State transition” arrow from “A” to “B”



Simulation (ex1)

- Create following biochemical reaction
- Click [Simulation] → [ControlPanel]
and call SBML ODE Solver

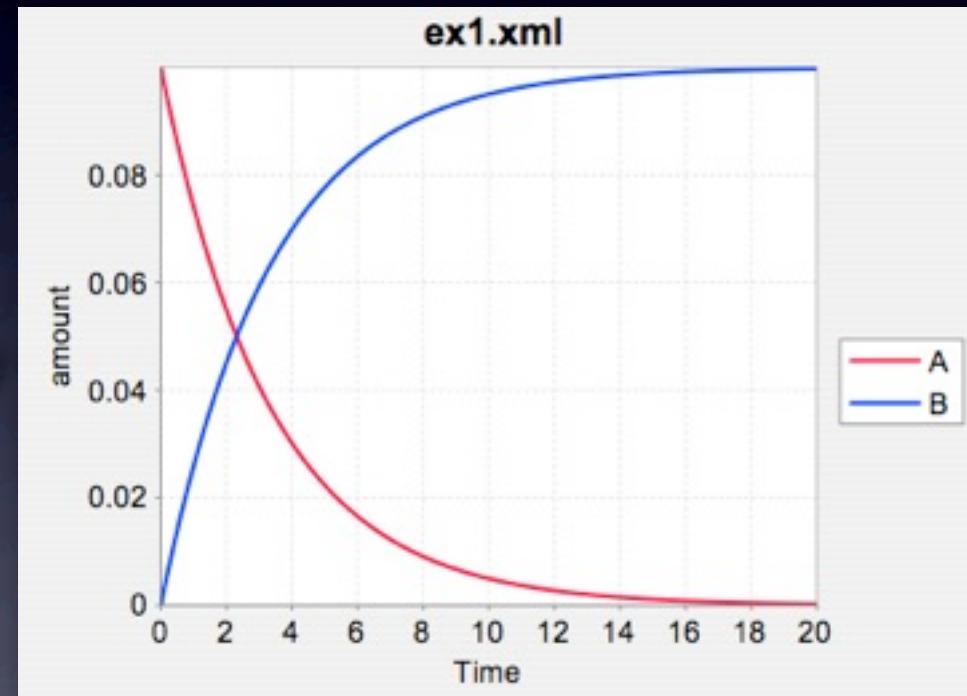


$$\frac{d[B]}{dt} = k[A]$$

$$k = 0.3$$

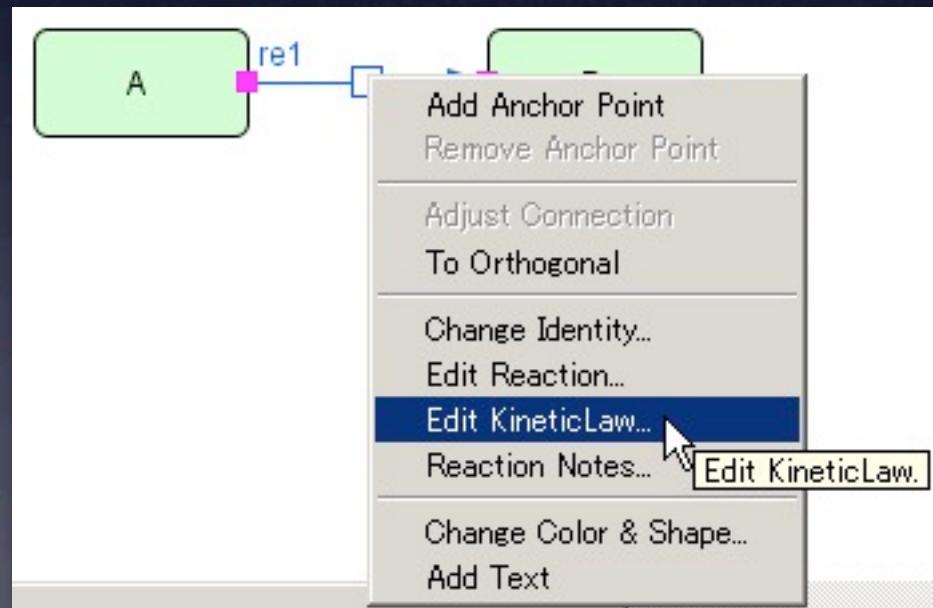
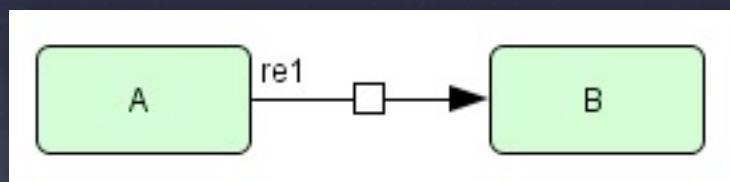
$$A = 0.1$$

$$B = 0$$



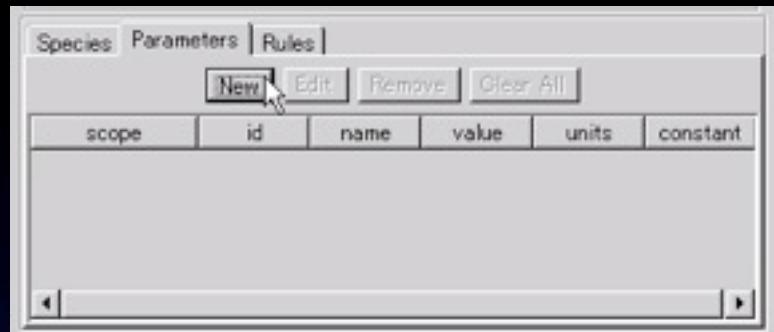
Simulation (ex1)

- Right click on the reaction and select [Edit KineticLaw...]



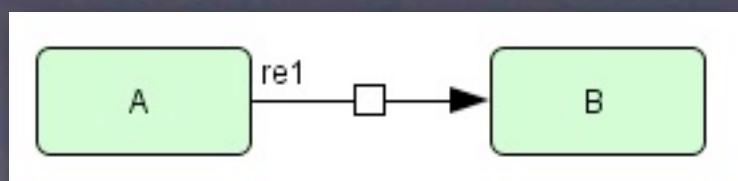
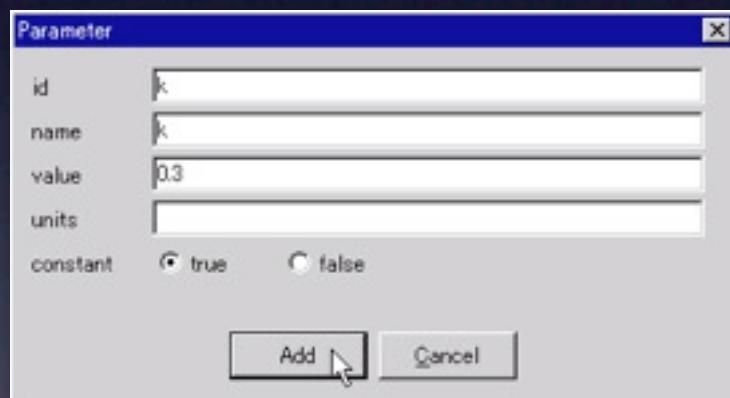
Simulation (ex1)

- Click [New] button on [Parameters] tab



- Input values as follows:

- id: k
- name: k
- value: 0.3



$$\frac{d[B]}{dt} = k[A]$$

k = 0.3

A = 0.1

B = 0

Simulation (ex1)

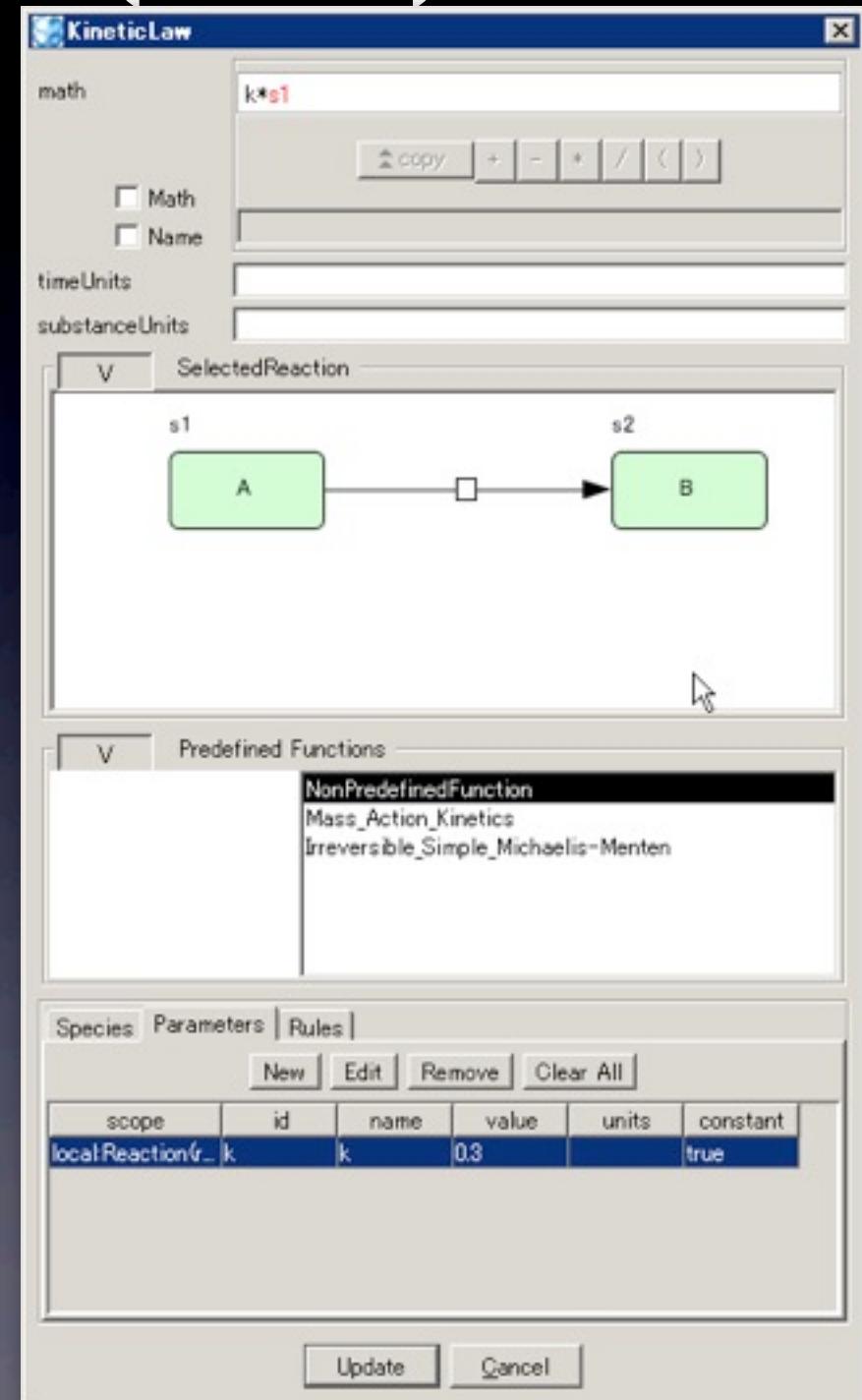
- Click top most text field
- Type $k * (k \text{ times})$
- Select Protein “A”
- Click [Name] checkbox
($k^*s1 \rightarrow k^*A$)

$$\frac{d[B]}{dt} = k[A]$$

$$k = 0.3$$

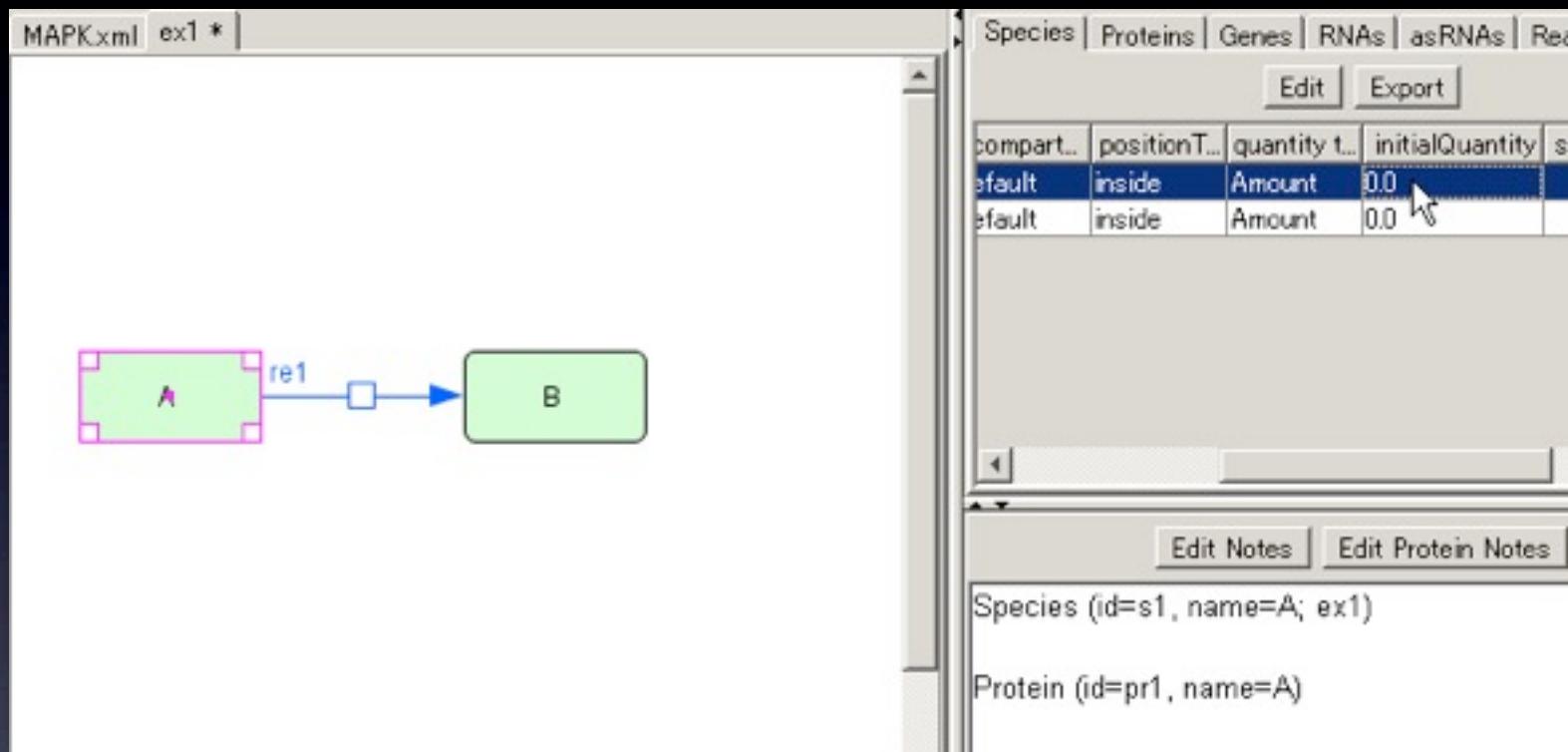
$$A = 0.1$$

$$B = 0$$



Simulation (ex1)

- Double click [initialQuantity] column for Protein “A”



- Set value as 0.1

$$\frac{d[B]}{dt} = k[A]$$

$$k = 0.3$$

$$A = 0.1$$

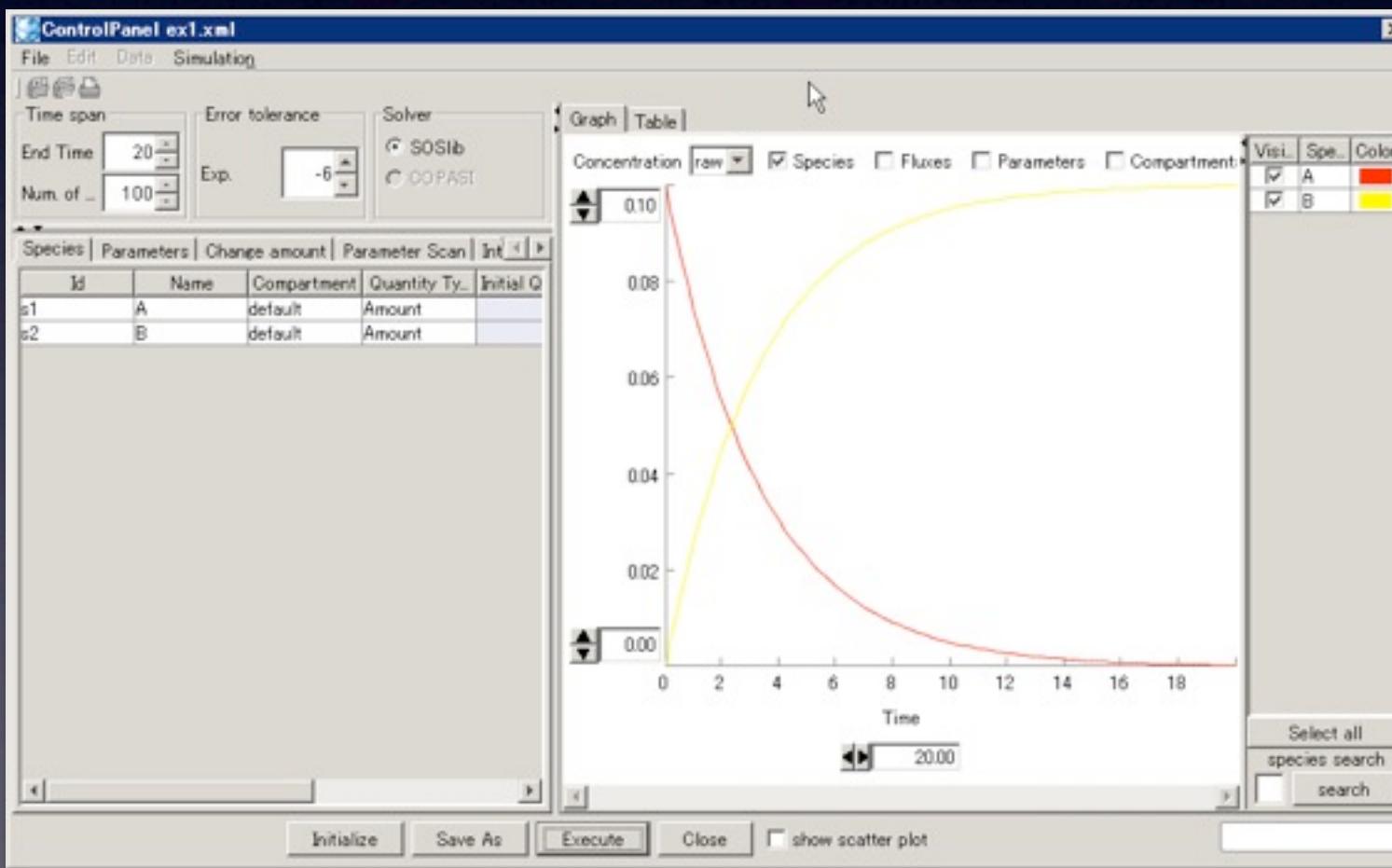
$$B = 0$$

Simulation (ex1)

- Click [Simulation] → [ControlPanel]
- Set [End Time] to 20
- Click [Execute] button

Time span

End Time	20
Num. of Points	100



Network → Equation

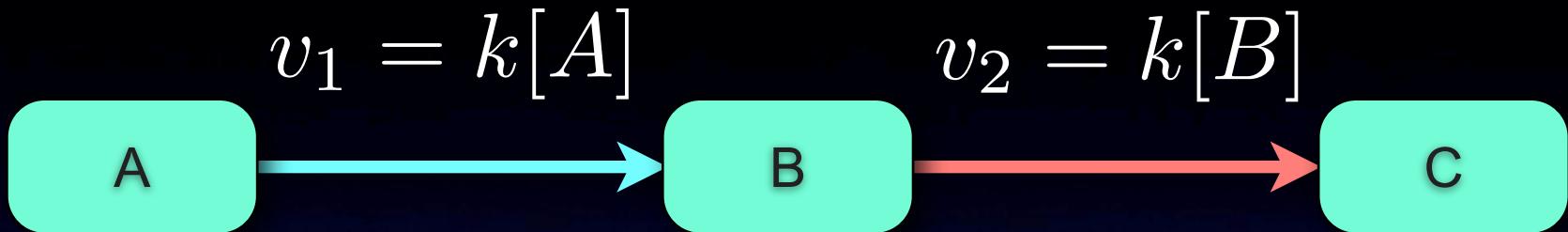
$$v_1 = k[A]$$



$$\frac{d[A]}{dt} = -k[A]$$

$$\frac{d[B]}{dt} = k[A]$$

Network → Equation



$$\frac{d[A]}{dt} = -k[A]$$

$$\frac{d[B]}{dt} = k[A] - k[B]$$

$$\frac{d[C]}{dt} = k[B]$$

Equation → Network

$$\frac{dA}{dt} = -k_1 A$$

A

$$\frac{dB}{dt} = -k_2 B$$

B

$$\frac{dC}{dt} = k_1 A + k_2 B - k_3 C$$

C

$$\frac{dD}{dt} = k_3 C$$

D

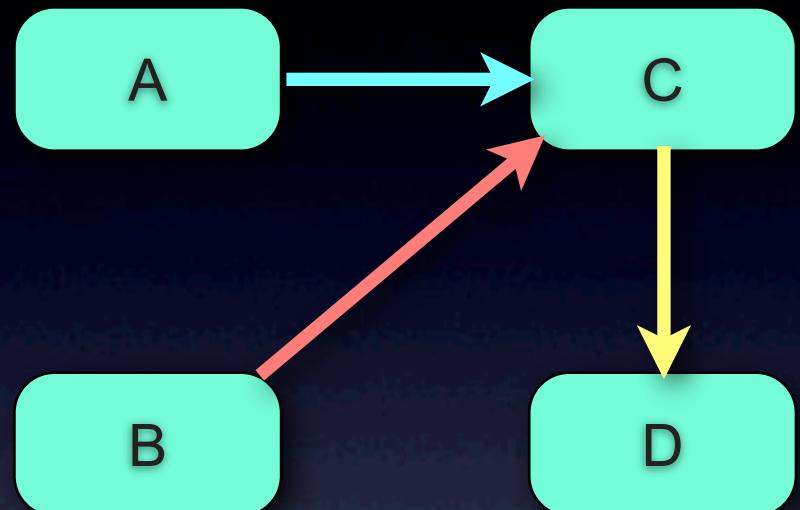
Equation → Network

$$\frac{dA}{dt} = -k_1 A$$

$$\frac{dB}{dt} = -k_2 B$$

$$\frac{dC}{dt} = k_1 A + k_2 B - k_3 C$$

$$\frac{dD}{dt} = k_3 C$$



Database connection

Import model from BioModels.net

The screenshot shows a web browser window for the BioModels Database. The URL is <http://www.ebi.ac.uk/compteur-srv/biomodels-main/publ-models.do>. The page title is "BioModels Database". The left sidebar includes links for Curated Models, Non-curated Models, Search, Simulate in JWS, Submit Your Model, Sign-in, News, Model of the Month, Meetings, Support, and Contact. Logos for SBML, DOQCS, SBW, SBI, and JWS online are also present. The main content area is titled "Browse - Curated models". It contains a list of fields used to describe a model: BioModels ID, Name, Publication ID, and Last Modified. Below this is a table listing ten curated models:

BioModels ID	Name	Publication ID	Last Modified
BIOMD0000000001	Edelstein1996_EPSP_AChEvent	883160	2007-09-23T23:24:19
BIOMD0000000002	Edelstein1996_EPSP_AChSpecies	883160	2007-01-04T23:01:47
BIOMD0000000003	Goldbeter1991_MinMitOscil	1833774	2007-04-30T21:35:17
BIOMD0000000004	Goldbeter1991_MinMitOscil_Explain	1833774	2007-05-14T23:01:13
BIOMD0000000005	Tyson1991_CellCycle_6var	1831270	2007-05-15T18:24:25
BIOMD0000000006	Tyson1991_CellCycle_2var	1831270	2007-05-15T18:26:15
BIOMD0000000007	Novak1997_CellCycle	9256150	2007-05-15T18:32:05
BIOMD0000000008	Gardner1998_CellCycle_Goldbeter	9826676	2007-01-06T10:37:30
BIOMD0000000009	Huang1996_MAPK_ultrasens	8816754	2006-12-29T00:54:48
BIOMD0000000010	Kholodenko2000_MAPK_feedback	10712587	2007-01-10T10:35:07

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Database connection



Import model from BioModels.net

CellDesigner

File Edit Component View Database Layout Simulation Plugin Window

Import model from BioModels.net...

Connect to SGD
Connect to DBGET
Connect to iHOP
Connect to Genome Network
Connect to PubMed
Connect to Entrez Gene

Model
● Compartments
● Species
● Reactions

BioModels.net

ID	Name
BIO MD000000000001	Edelstein1996_EPSP_AChEvent
BIO MD000000000002	Edelstein1996_EPSP_AChSpecies
BIO MD000000000003	Goldbeter1991_MinMitOscil
BIO MD000000000004	Goldbeter1991_MinMitOscil_ExplInact
BIO MD000000000005	Tyson1991_CellCycle_6var
BIO MD000000000006	Tyson1991_CellCycle_2var
BIO MD000000000007	Novak1997_CellCycle
BIO MD000000000008	Gardner1998_CellCycle_Goldbeter
10	Huang1996_MAPK_ultrasens
11	Kholodenko2000_MAPK_feedback
12	Levchenko2000_MAPK_noScaffold
13	Elowitz2000_Repressilator
14	Poolman2004_CalvinCycle
15	Levchenko2000_MAPK_Scaffold
16	Curto1998_purineMetabol
17	Goldbeter1995_CircClock
18	Hoefnagel2002_PyruvateBranches
19	Morrison1989_FolateCycle
20	hodgkin-huxley squid-axon 1952
21	Leloup1999_CircClock
22	Ueda2001_CircClock
23	Rohwer2001_Sucrose
24	Scheper1999_CircClock
25	Smolen2002_CircClock
26	Markevich2004_MAPK_orderedElementary

Description Reference Import Cancel

```
graph TD; MAPK-PP -- J10 --> MAPK-P; MAPK-P -- J8 --> MAPK-PP; MAPK-P -- J7 --> MAPKK-P; MAPK-P -- J9 --> MAPK-PP; MAPKK-P -- J6 --> MAPK-P; MAPKK-P -- J5 --> MAPKK-P; MAPKK-P -- J4 --> MAPKK-PP; MAPKK-PP -- J3 --> MAPKK-P; MAPKK-PP -- J2 --> MAPKK-P; MAPKK-PP -- J1 --> MAPKKK-P; MAPKKK-P -- J0 --> MAPKK-PP; MAPKKK-P -- J2 --> MAPKK-PP; MAPKKK-P -- J1 --> MAPKKK
```

SABIO-RK

- Web-accessible database
- <http://sabio.h-its.org/>
- Contains information about biochemical reactions, related kinetic equations and parameters

The screenshot shows the SABIO-RK web interface. At the top, there's a navigation bar with links for CONTACT, HELP, and IMPRINT. Below it, a search bar contains the text "Search Reaction". To the right, there's a section titled "Kinetic Data Availability" with three categories: "Kinetic data available matching the search criteria" (green), "Kinetic data available, but not matching all search criteria" (yellow), and "No kinetic data available" (red). A link "Click here to view your search criteria" is also present. The main content area displays a table of search results:

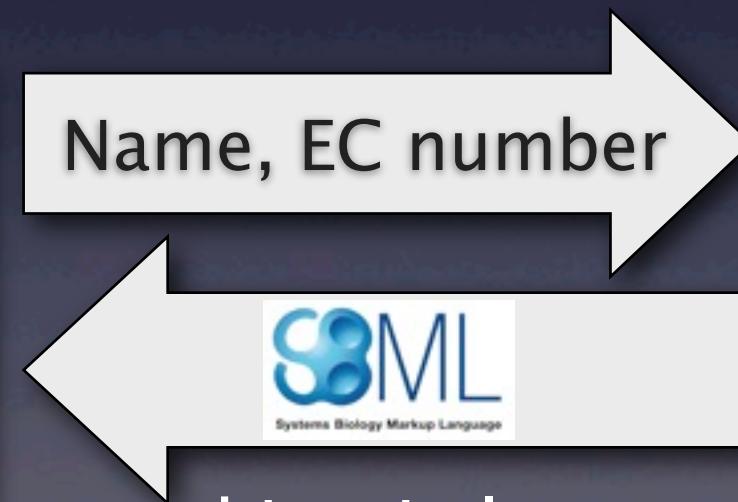
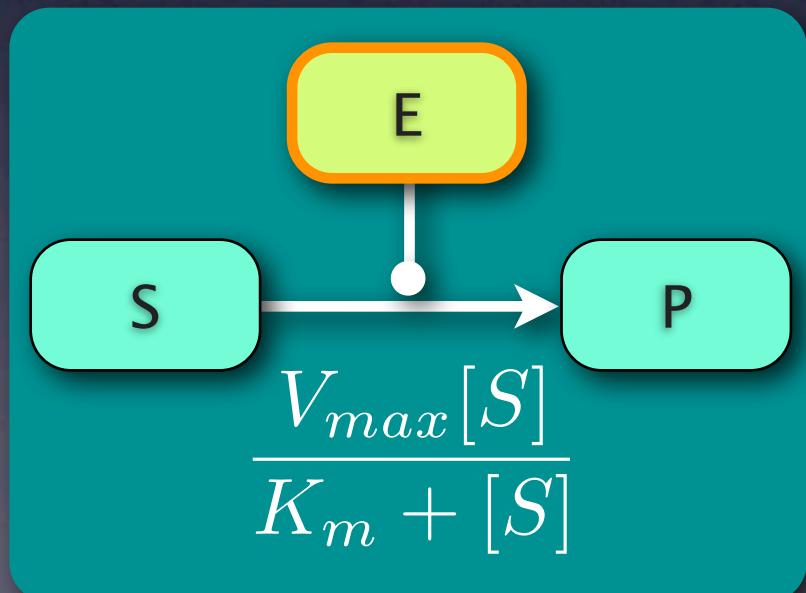
Reactions	Select Reaction(s) (<input type="checkbox"/> Select All)	Kinetic Data for this reaction (<input type="checkbox"/> Click to View)	Enzyme ECF	Kinetic data for enzymes (<input type="checkbox"/> Click to View)
D-Glucose + ATP <=> D-Glucose-1-phosphate EAL1	<input type="checkbox"/>	<input type="checkbox"/>	2.7.3.1 2.7.3.2	<input type="checkbox"/> <input type="checkbox"/>
ATP + Glucose-1<->ADP + Glucose-6 GNGT65	<input type="checkbox"/>	<input type="checkbox"/>	2.7.3.1 2.7.3.2	<input type="checkbox"/> <input type="checkbox"/>
			3.6.3.16 3.6.4.1 2.7.3.1 3.6.2.1 3.1.3.29	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>



CellDesigner ↔ SABIO RK

- Users can import additional information to each object (reaction) on-the-fly
- SBML (Systems Biology Markup Language) is used to exchange information

CellDesigner



kinetic law, parameters,
function / unit definitions



Example

CellDesigner4.3beta File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help ⌂ (100%) 8月17日(金) 17:40:34

CellDesigner

TCA cycle

- Add Anchor Point
- Remove Anchor Point
- Adjust Connection
- To Orthogonal
- Change Identity...
- Edit Reaction...
- Edit KineticLaw...
- Reaction Notes...
- Change Color & Shape...
- Add Text
- Import KineticLaw from SABIO-RK...
- Import reaction information from SABIO-RK...

Species Proteins Genes RNAs

class	id	name	speciesType	com
SIMPLE_...	s2	Acetyl-CoA	def:	
PROTEIN	s3	Pyruvate_br_D...	def:	
SIMPLE_...	s4	Citrate	def:	
SIMPLE_...	s5	H_sub_2_ends...	def:	
PROTEIN	s7	coA	def:	
SIMPLE_...	s9	cis-Aconitate	def:	
PROTEIN	s10	Aconitase	def:	
SIMPLE_...	s11	IsoCitrate	def:	
SIMPLE_...	s12	Oxalosuccinate	def:	
PROTEIN	s13	Isocitrate_br...	def:	
SIMPLE_...	s14	NAD_super_+	def:	
SIMPLE_...	s15	NADH+H ⁺ ...	def:	
SIMPLE_...	s16	alpha_Ketogl...	def:	
SIMPLE_...	s17	CO_sub_2_en...	def:	

NOTE MIRIAM

Edit Notes Edit Protein Notes

Reaction (id=r23, name=: TCA cycle)

Grid Snap OFF

Example

CellDesigner4.3beta File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help 8月17日(金) 17:42:54

Import kineticLaw from SABIO-RK

Search query: Citrate Synthase

Organism: saccharomyces cerevisiae

Tissue: id

Search

Import KineticLaw Close

Grid Snap OFF

TCA cycle

Example

CellDesigner4.3beta File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help 8月17日(金) 17:43:38

Import kineticLaw from SABIO-RK

Search query: Citrate Synthase
Organism: saccharomyces cerevisiae
Tissue:

Search

id	Equation
10225	$\text{H}_2\text{O} + \text{Acetyl-CoA} + \text{Oxaloacetate} \rightleftharpoons \text{Coenzyme A} + \text{Citrate}$

B concentration Acetyl-CoA 0.0125 0.125 - mM -
Kb Km Acetyl-CoA 1.3 - 0.01 μM -
Kd Kd Oxaloacetate 3.7 - 0.02 mM -
Et concentration Enzyme - - - -
kcatKa kcat/Km Oxaloacetate 9.8 - 0.7 M^(-1)s^(-1) -
A concentration Oxaloacetate 10.0 50.0 - mM -
kcatKb kcat/Km Oxaloacetate 200000.0 - 0.1E5 M^(-1)s^(-1) -
Ki Ki Oxaloacetate 140.0 - 1 mM -
kcat kcat - 0.3 - 0.02 s^(-1) -
Ka Km Oxaloacetate 25.5 - 0.1 mM -

Import KineticLaw Close

Grid Snap OFF

TCA cycle

Example

CellDesigner4.3beta File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help 8月17日(金) 17:44:00

Mapping Species References ID

Reactants ID/Name Mapping

Species id(name) [CellDesigner] Species id(name) [SABIO-RK]

s2 (Acetyl-CoA)	SPC_1276_Cell(Acetyl-CoA)
s23 (Oxaloacetate)	SPC_1915_Cell(Oxaloacetate)
s5 (H _{sub} 2_endsub_O)	SPC_40_Cell(H ₂ O)

Products ID/Name Mapping

Species id(name) [CellDesigner] Species id(name) [SABIO-RK]

s7 (CoA)	SPC_1265_Cell(Coenzyme A)
s4 (Citrate)	SPC_1952_Cell(Citrate)

Modifiers ID/Name Mapping

Species id(name) [CellDesigner] Species id(name) [SABIO-RK]

s32 (Citrate_bSynthase)	ENZ_53518_Cell(homocitrate synthase(Enzyme) wildtype)
-------------------------	---

Apply Cancel

The diagram illustrates a metabolic pathway involving Citrate Synthase and other TCA cycle enzymes. Citrate Synthase (r13) converts Acetyl-CoA and Oxaloacetate to Citrate, releasing H₂O. Citrate is then converted to α-Ketoglutarate by α-Ketoglutarate Dehydrogenase (r16), which uses NAD⁺ and CoA, releasing CO₂. α-Ketoglutarate is further converted to Succinate by α-Ketoglutarate Dehydrogenase (r17), which uses NADH + H⁺ and CoA, releasing CO₂. Succinate is then converted to Succinyl-CoA by Succinyl CoA Synthetase (r18), which uses GTP and CoA, releasing GDP + P_i. Finally, Succinyl-CoA is converted to Succinate by Succinate Dehydrogenase, which uses NADH + H⁺ and CoA, releasing GTP.

Search query: Citrate Synthase
Organism: saccharomyces cerevisiae
Tissue:
Search

id Equation
10225 H₂O + Acetyl-CoA + Oxaloacetate <--> Coenzyme A + Citrate

B	concentration	Acetyl-CoA	0.0125	0.125	-	mM	-
K _b	K _m	Acetyl-CoA	1.3	-	0.01	μM	-
K _d	K _d	Oxaloacetate	3.7	-	0.02	mM	-
E _t	concentration	Enzyme	-	-	-	-	-
k _{cat} /K _m	k _{cat} /K _m	Oxaloacetate	9.8	-	0.7	M ⁶ (-1) ⁴ s ⁶ (-1)	-
A	concentration	Oxaloacetate	10.0	50.0	-	mM	-
k _{cat} /K _b	k _{cat} /K _m	Oxaloacetate	200000.0	-	0.1E5	M ⁶ (-1) ⁴ s ⁶ (-1)	-
K _i _a	K _i	Oxaloacetate	140.0	-	1	mM	-
k _{cat}	k _{cat}	-	0.3	-	0.02	s ⁶ (-1)	-
K _a	K _m	Oxaloacetate	25.5	-	0.1	mM	-

Import KineticLaw Close

Grid Snap OFF

Example

CellDesigner4.3beta File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help 8月17日(金) 17:44:14 Q

Import kineticLaw from SABIO-RK

Search query: Citrate Synthase
organism: saccharomyces cerevisiae

Equation: H₂O + Acetyl-CoA + Oxaloacetate <--> Coenzyme A + Citrate

The following KineticLaw (in Reaction "r23") and its dependent elements (if any) will be imported by clicking "OK" button below.

KineticLaw FunctionDefinition UnitDefinition

Math

```
KL_10225(kcatKb_SPC_1915_Cell, s23, Kd_SPC_1915_Cell, kcatKa_SPC_1915_Cell, Kia_SPC_1915_Cell, s2, Kb_SPC_1276_Cell, kcat, s32, Ka_SPC_1915_Cell)
```

Local Parameters

id	name	value	units	constant
kcatKb_SPC_1915_Cell	kcatKb_Oxaloacetate	200000.0	M ⁻¹ (-1) ⁰ s ⁰ (-1)	true
Kd_SPC_1915_Cell	Kd_Oxaloacetate	0.0037	M	true
kcatKa_SPC_1915_Cell	kcatKa_Oxaloacetate	9.8	M ⁻¹ (-1) ⁰ s ⁰ (-1)	true
Kia_SPC_1915_Cell	Kia_Oxaloacetate	0.14	M	true
Kb_SPC_1276_Cell	Kb_AcetylCoA	1.3E-6	M	true
kcat	kcat	0.3	s ⁰ (-1)	true

concentration Acetyl-CoA 0.0125 0.125 - mM -
Km Acetyl-CoA 1.3 - 0.01 μM -
Kd Oxaloacetate 3.7 - 0.02 mM -
concentration Enzyme - - - -
kKa kcat/Km Oxaloacetate 9.8 - 0.7 M⁰(-1)⁰s⁰(-1) -
concentration Oxaloacetate 10.0 50.0 - mM -
kKb kcat/Km Oxaloacetate 200000.0 - 0.1E5 M⁰(-1)⁰s⁰(-1) -
Ki Oxaloacetate 140.0 - 1 mM -
kcat - 0.3 - 0.02 s⁰(-1) -
Km Oxaloacetate 25.5 - 0.1 mM -

Import KineticLaw Close

Grid Snap OFF

```
graph TD; SC[Succinyl CoA Synthetase] -- r17 --> SC_Synthetase[Succinyl-CoA]; SC_Synthetase -- r17 --> GDP_Pi[GDP + Pi]; SC_Synthetase -- r17 --> NADH_NADP[NADH + H+]; SC_Synthetase -- r17 --> NAD_NADP[NAD+]; SC_Synthetase -- r17 --> coA[coA]; SC_Synthetase -- r17 --> CO2[CO2]; SC_Synthetase -- r17 --> AKG[αKetoglutarate]; AKG -- r16 --> AKG_NADH[NADH + H+]; AKG -- r16 --> AKG_NAD[NAD+]; AKG -- r16 --> AKG_CO2[CO2]; AKG -- r16 --> IDH[Isocitrate Dehydrogenase]; IDH -- r15 --> IDH_Oxalosuccinate[Oxalosuccinate]; IDH -- r15 --> IDH_CO2[CO2]
```

Example

CellDesigner4.3beta File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help 8月17日(金) 17:45:19

CellDesigner

TCA cycle *

KineticLaw

math

SelectedReaction

```

graph LR
    s2[Acetyl-CoA] --> s4[Citrate]
    s23[Oxaloacetate] --> s4
    s5[H2O] --> s7[coA]
    s7 --> s4
    
```

V Predefined Functions

- NonPredefinedFunction
- Mass_Action_Kinetics
- Irreversible_Simple_Michaelis-Menten

Species	Parameters	Rules
Acetyl-CoA		
Pyruvate		
Citrate		
H2O		
coA		
cis-Aconitate		
Aconitase		

Species Parameters Rules

class	id	name	speciesType	compar...	positio...	included	quantit...
SIMPLE...	s2	Acetyl-CoA		default	inside		Amount
PROTEIN	s3	Pyruvate_b...		default	inside		Amount
SIMPLE...	s4	Citrate		default	inside		Amount
SIMPLE...	s5	H_sub_2_end...		default	inside		Amount
PROTEIN	s7	coA		default	inside		Amount
SIMPLE...	s9	cis-Aconitate		default	inside		Amount
PROTEIN	s10	Aconitase		default	inside		Amount

Update Close

Grid Snap OFF

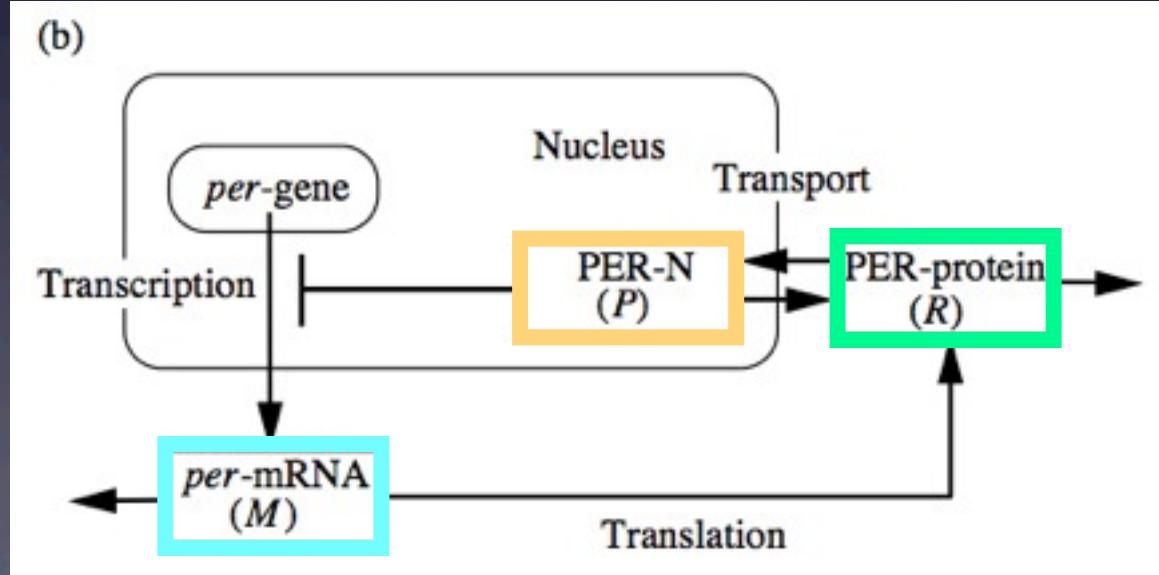
Circadian clock model

- Protein (P) **inhibits** transcription of mRNA (M)
- M is translated to Protein (R)
- P / R will be transported to cytosol / nucleus

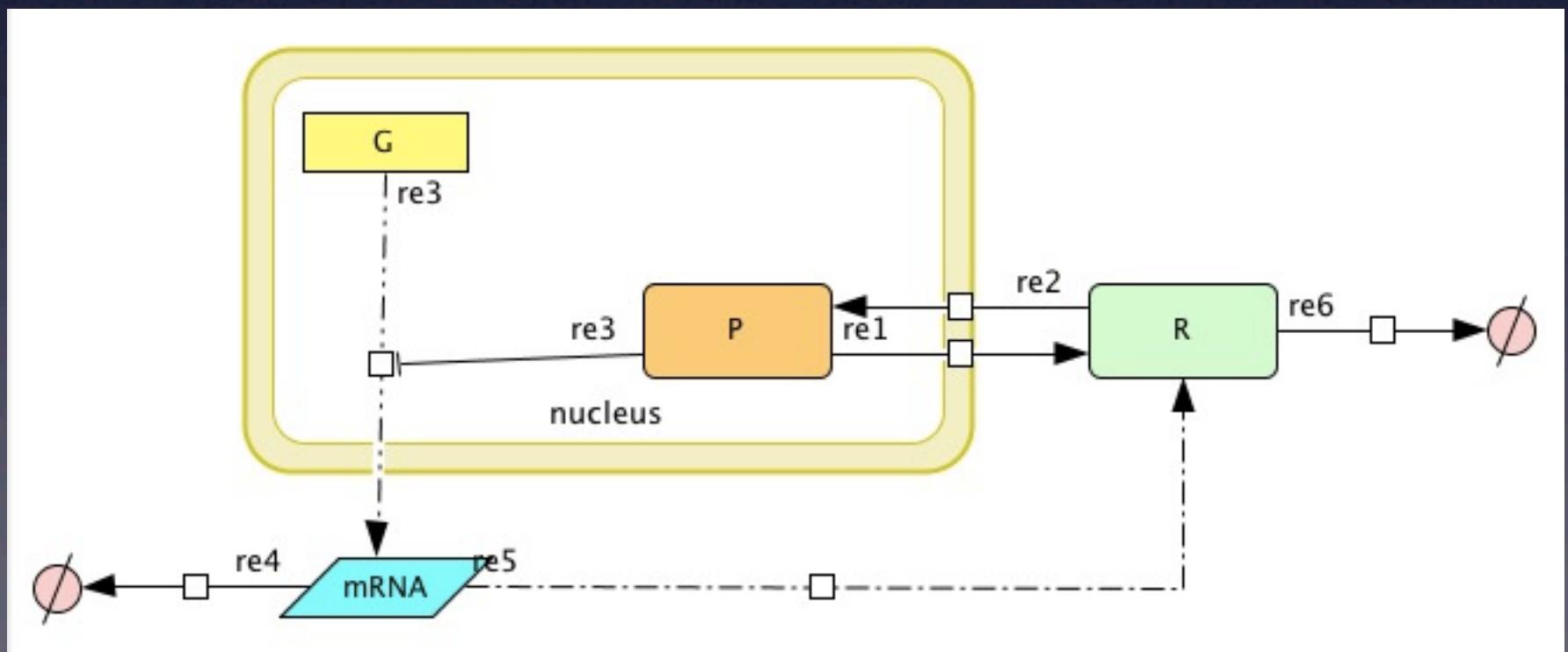
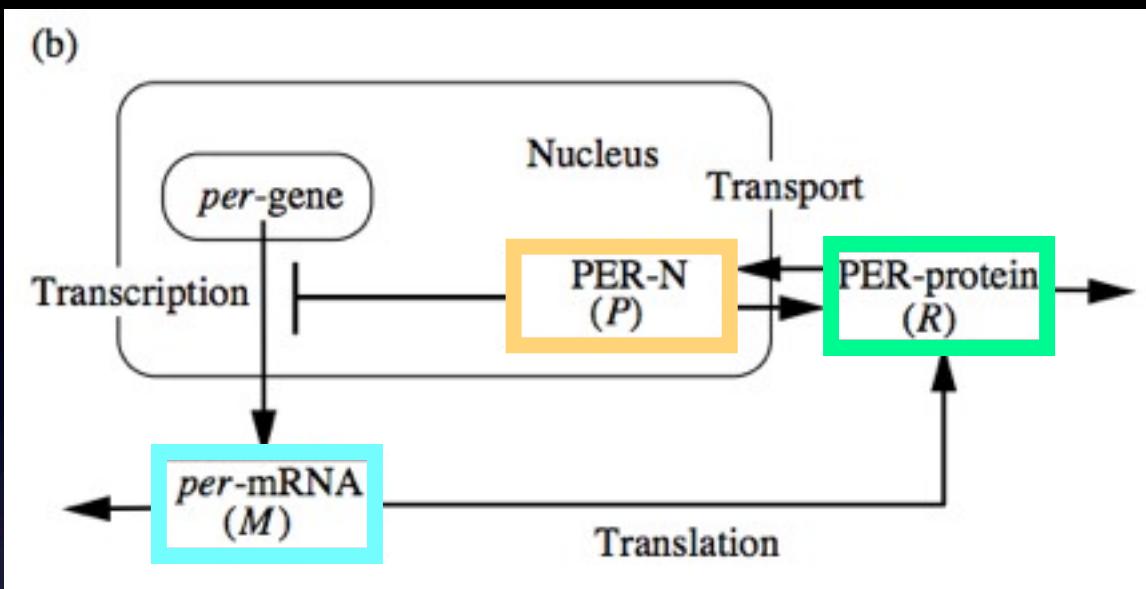
$$\frac{dM}{dt} = \frac{1}{1 + (P/h)^n} - aM - sM$$

$$\frac{dR}{dt} = sM - (d + u)R + vP$$

$$\frac{dP}{dt} = uR - vP$$



Circadian clock model



Circadian clock model

$$\frac{dM}{dt} = \frac{1}{1 + (P/h)^n} - aM - sM$$

$$a = s = d = v = 1.0$$

$$\frac{dR}{dt} = sM - (d + u)R + vP$$

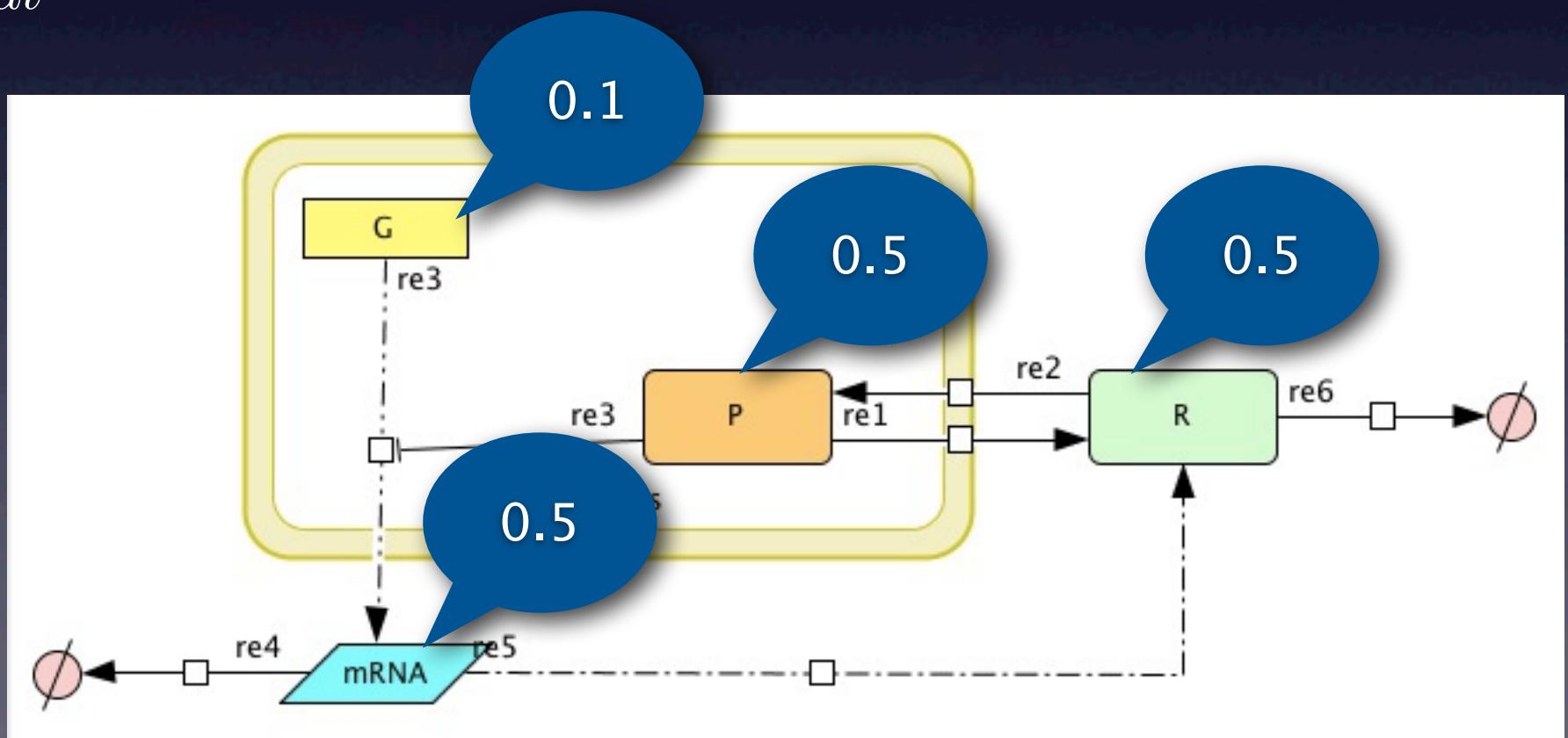
$$u = 0.1$$

$$\frac{dP}{dt} = uR - vP$$

$$h = 0.01$$

$$n = 40$$

$$x^n = \text{pow}(x, n)$$



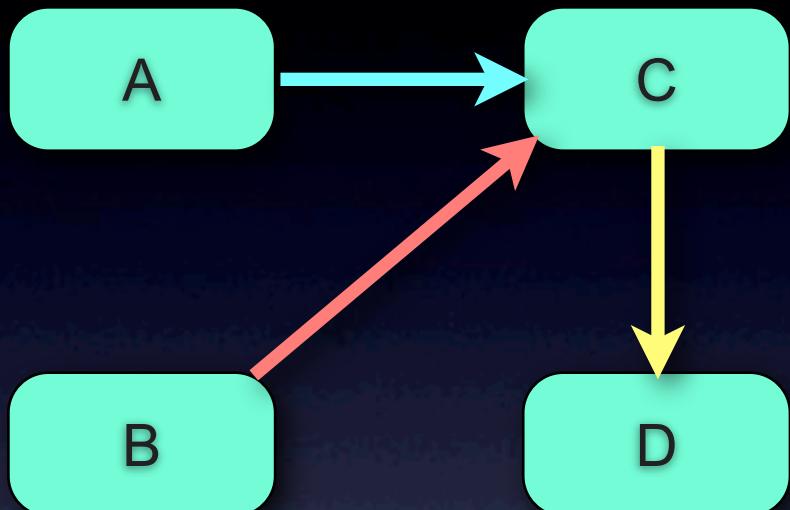
ODE \leftrightarrow Network

$$\frac{dA}{dt} = -k_1 A$$

$$\frac{dB}{dt} = -k_2 B$$

$$\frac{dC}{dt} = k_1 A + k_2 B - k_3 C$$

$$\frac{dD}{dt} = k_3 C$$



Circadian clock model

$$\frac{dM}{dt} = \frac{1}{1 + (P/h)^n} - aM - sM$$

$$a = s = d = v = 1.0$$

$$\frac{dR}{dt} = sM - (d + u)R + vP$$

$$u = 0.1$$

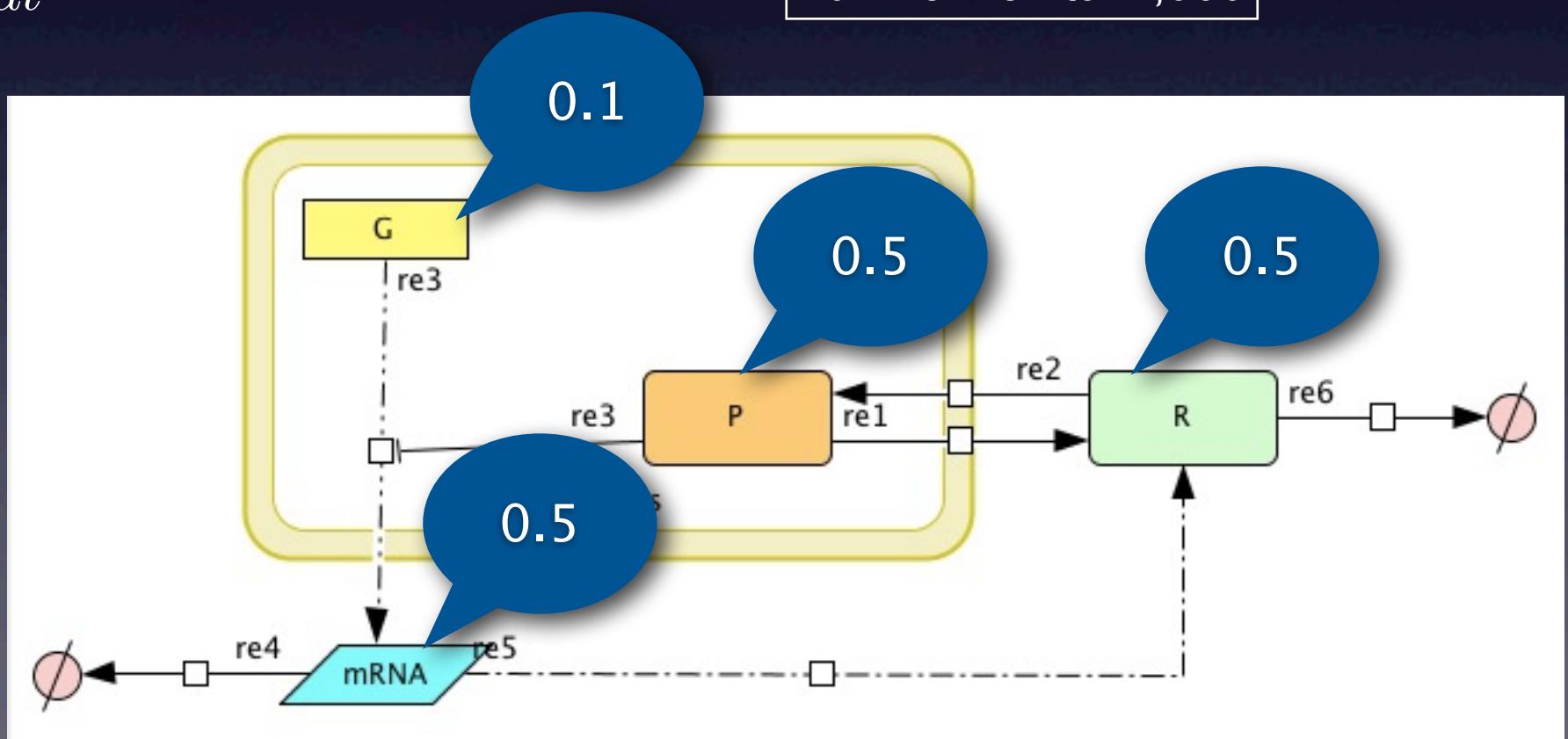
$$\frac{dP}{dt} = uR - vP$$

$$h = 0.01$$

$$x^n = \text{pow}(x, n)$$

$$n = 40$$

End Time: 50
Num. of Points: 1,000



Circadian clock model

$$\frac{dM}{dt} = \frac{1}{1 + (P/h)^n} - aM - sM$$

$$a = s = d = v = 1.0$$

$$\frac{dR}{dt} = sM - (d + u)R + vP$$

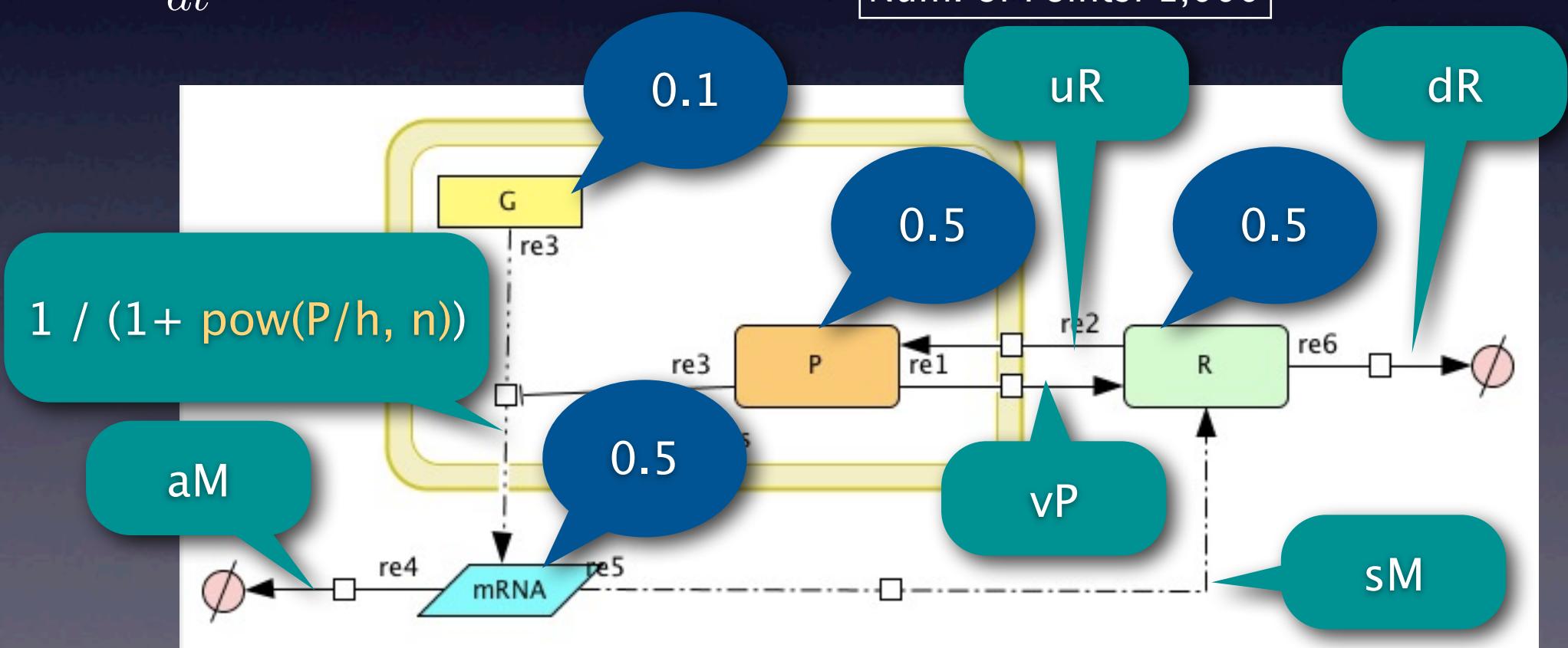
$$u = 0.1$$

$$\frac{dP}{dt} = uR - vP$$

$$h = 0.01$$

$$n = 40$$

End Time: 50
Num. of Points: 1,000



Boundary condition



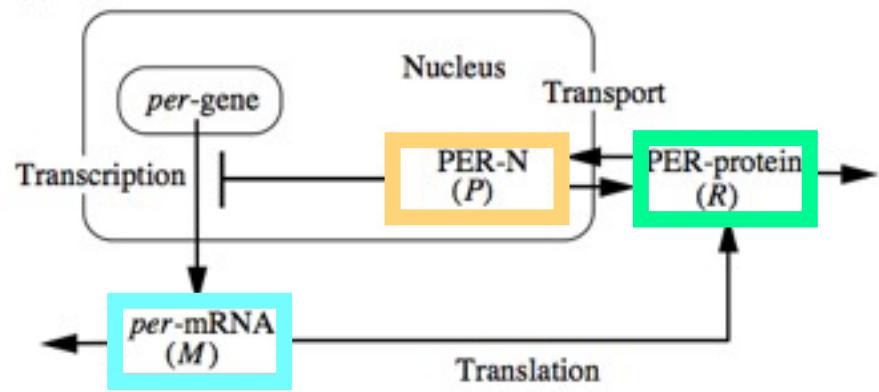
name	speciesType	compart...	positio...	included	quantit...	initialQuantity	sub...	hasO...	b.c.
G		c1	inside		Amount	0.1		true	true
mRNA		default	inside		Amount	0.5		true	false
P		c1	inside		Amount	0.5		true	false
R		default	inside		Amount	0.5		true	false
waste		default	inside		Amount	0.0		true	true
waste2		default	inside		Amount	0.0		true	true

Species

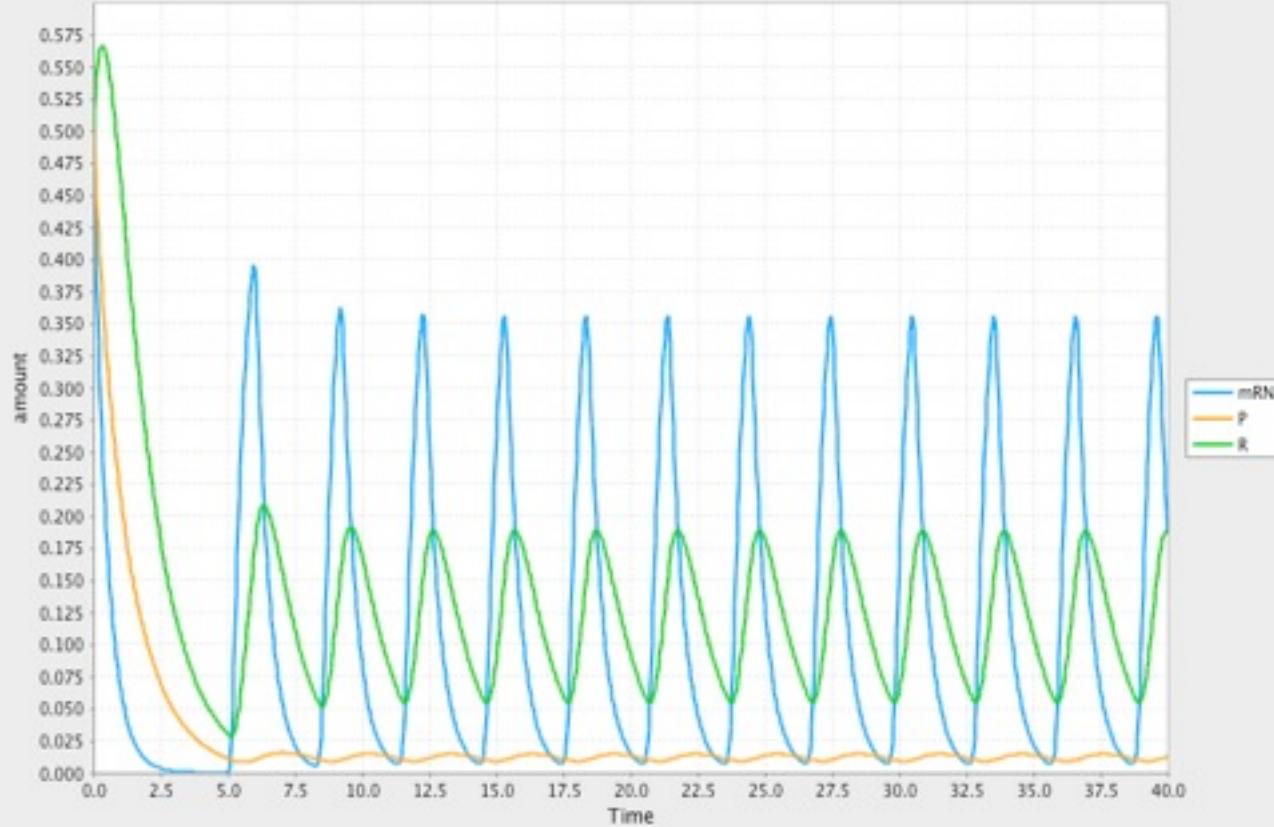
id	s1
name	G
speciesType	<input type="button" value="▼"/>
compartment	c1
initial...	<input checked="" type="radio"/> Amount <input type="radio"/> Concentration 0.1
substanceUnits	<input type="button" value="▼"/>
hasOnlySubstanceUnits	<input checked="" type="radio"/> true <input type="radio"/> false
boundaryCondition	<input checked="" type="radio"/> true <input type="radio"/> false
constant	<input type="radio"/> true <input checked="" type="radio"/> false
	<input type="button" value="Update"/> <input type="button" value="Cancel"/>

Circadian clock model

(b)

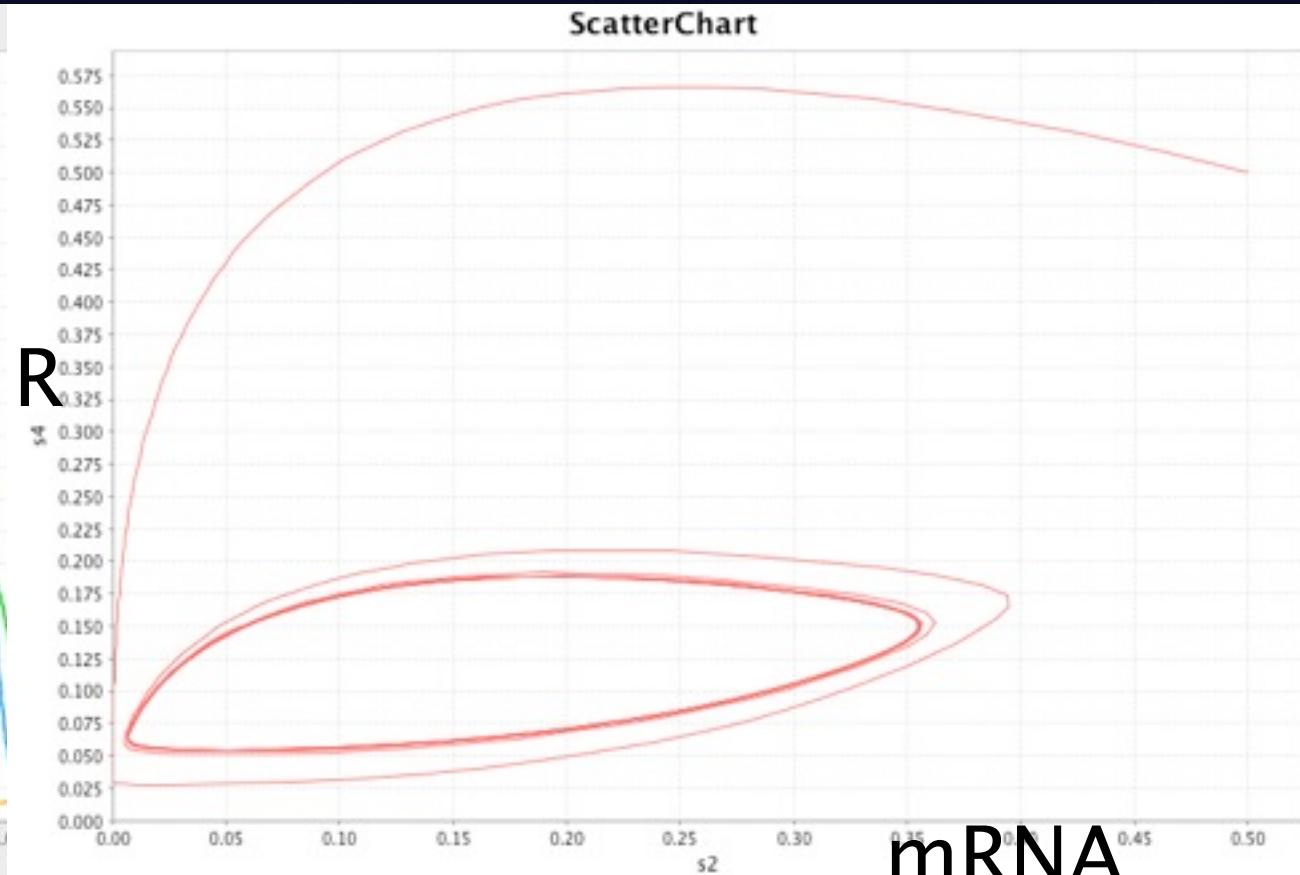
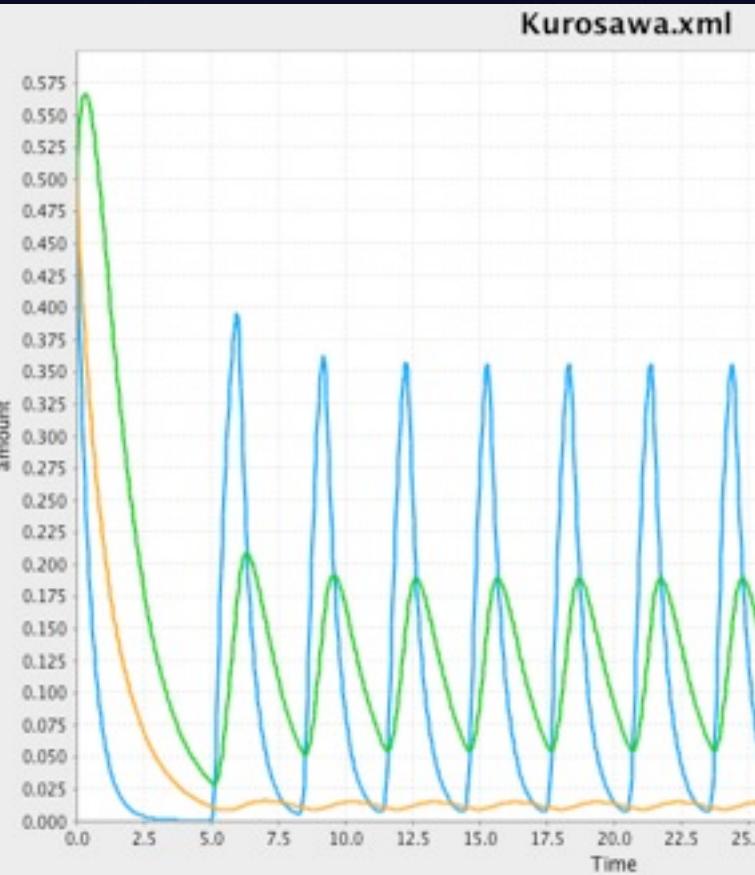
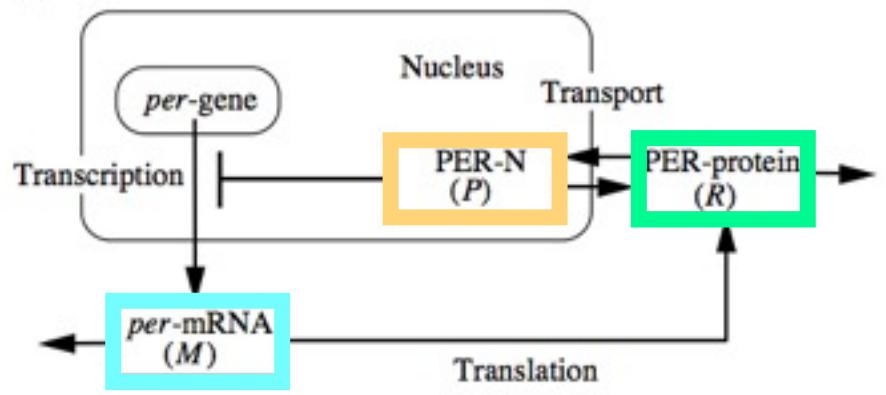


Kurosawa.xml



Circadian clock model

(b)



Summary

- Introduction of CellDesigner
- What kind of model you can build
 - Pathway map
 - Mathematical model
- How to build a model with CellDesigner
 - From scratch
 - Import a model from BioModels.net
 - Import kinetic law and parameters from SABIO-RK

Information

- **Slides:**

Will be uploaded on ICSB 2013 workshop web page

- **Documents:**

C:\Program Files\CellDesigner4.3\documents

/Applications/CellDesigner4.3/documents

Acknowledgement

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SBGN

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