# Mathematical modeling with CellDesigner

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SBI The Systems Biology Institute

# Overview

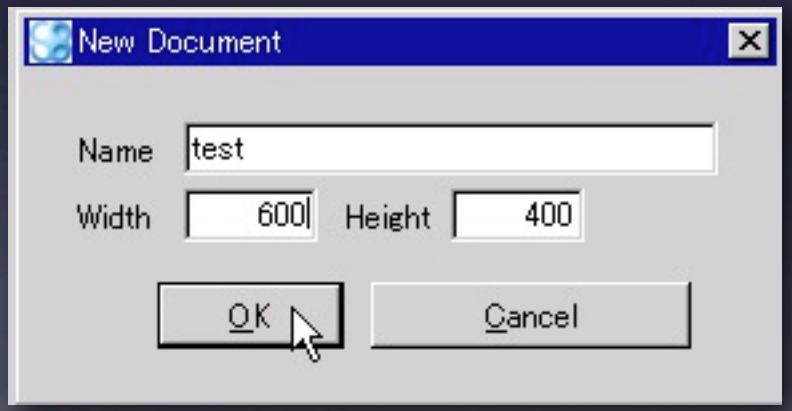
- Introduction of CellDesigner
  - What kind of model you can build
- How to build a model with CellDesigner
  - From scratch
  - Import a model, kinetic law and parameters from existing databases

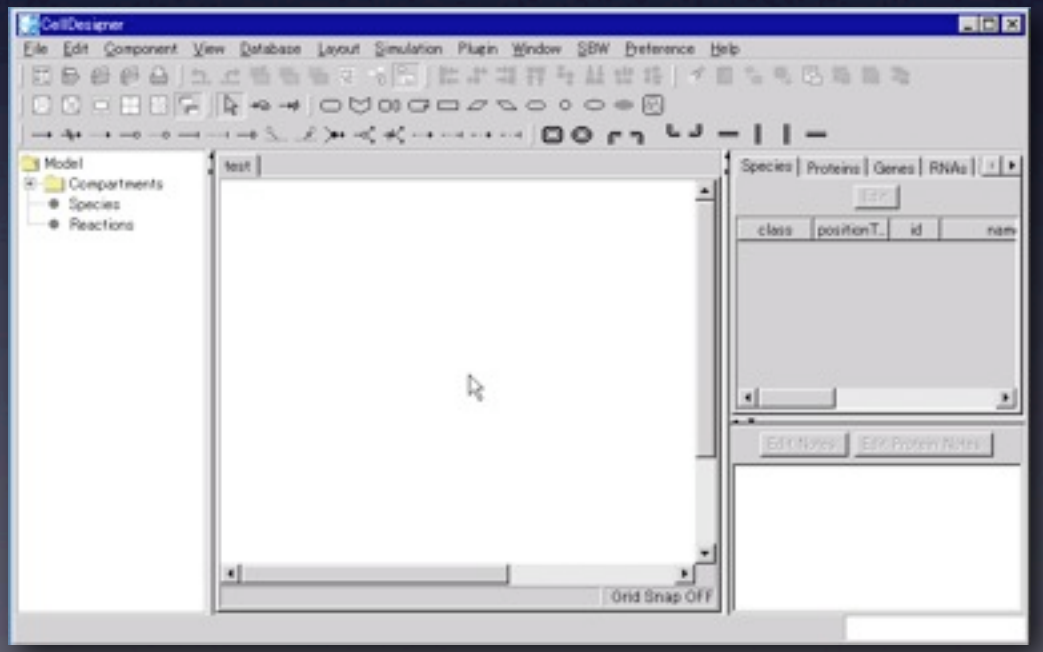
# Installation



# Create model

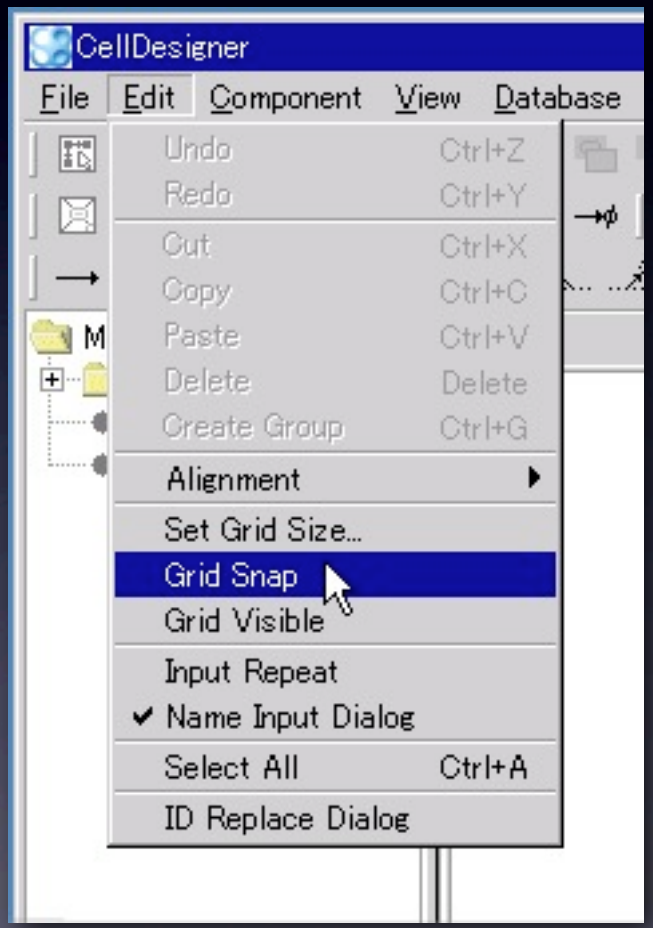
- Create new model:
  - [File] → [New] → input title → [OK]

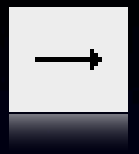



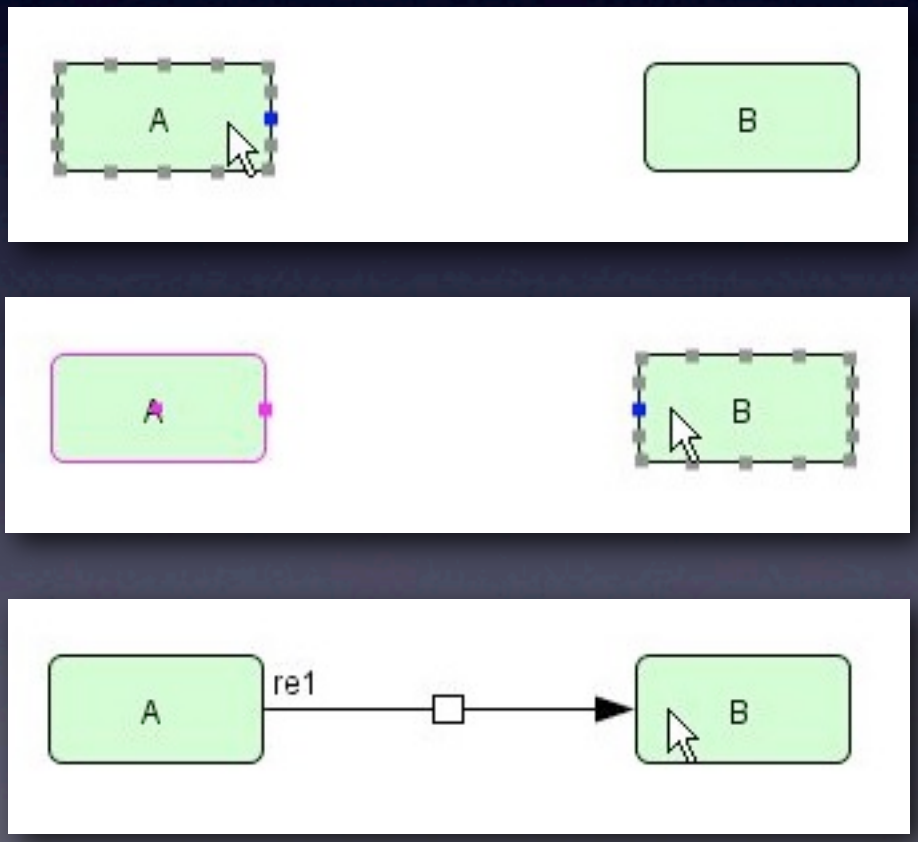
# Tips

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



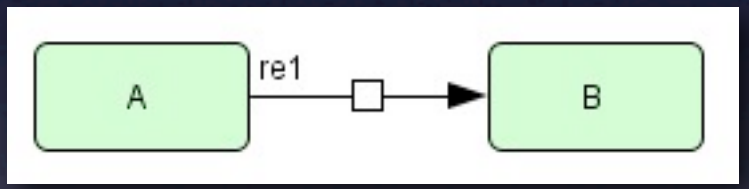
# Create Reaction

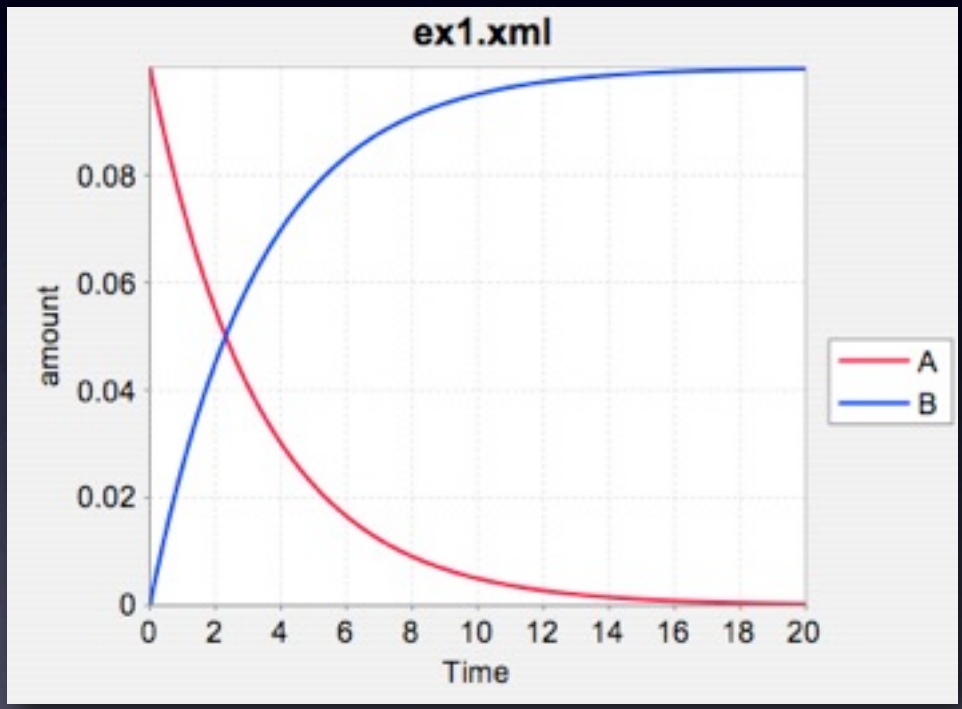
- Create Protein “A” and “B”
- Draw “State transition”  arrow from “A” to “B”



# Simulation (ex1)

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




$$v = k[A]$$

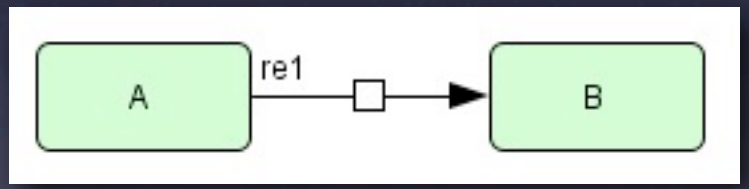
$k = 0.3$

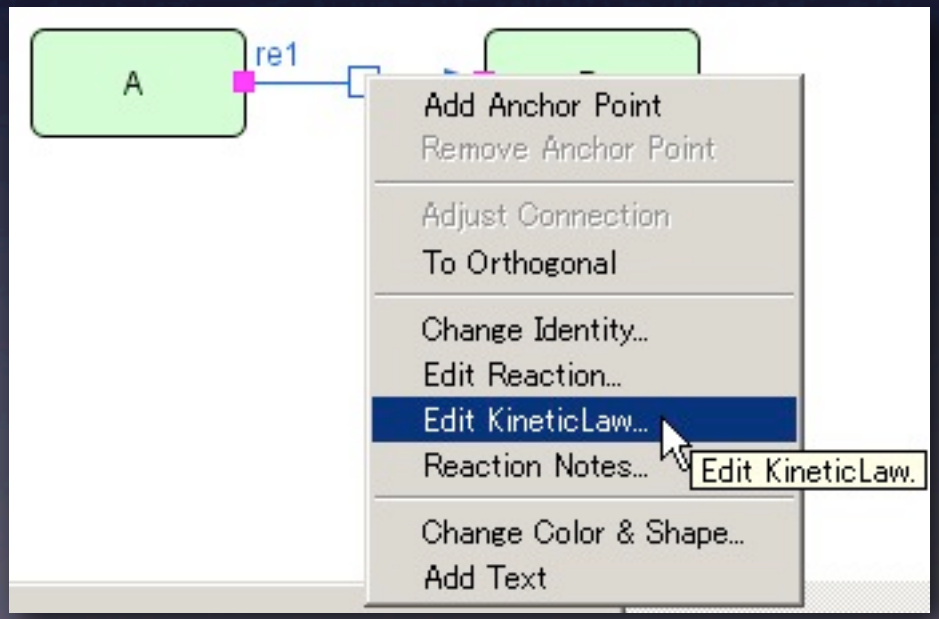
$A = 0.1$

$B = 0$

# Simulation (ex1)

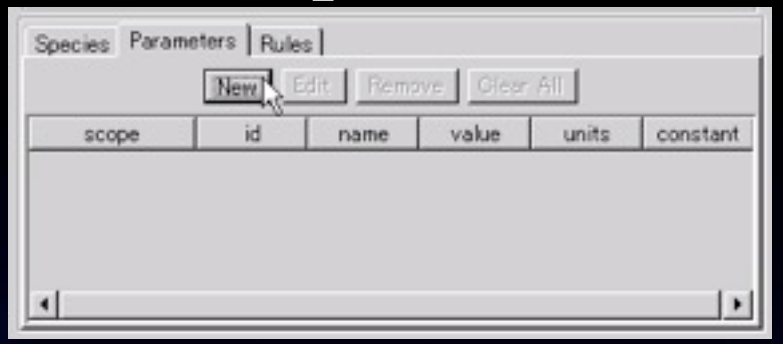
- Right click on the reaction and select [Edit KineticLaw...]



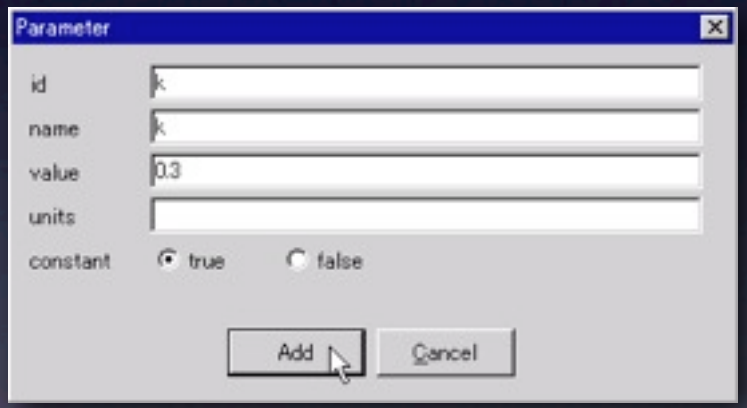



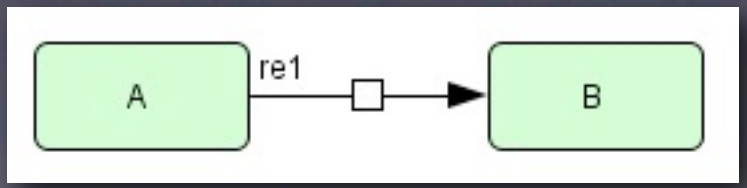
# Simulation (ex1)

- Click [New] button on [Parameters] tab




- Input values as follows:
  - id: k
  - name: k
  - value: 0.3




$$v = k[A]$$

$k = 0.3$

$A = 0.1$

$B = 0$

# Simulation (ex1)

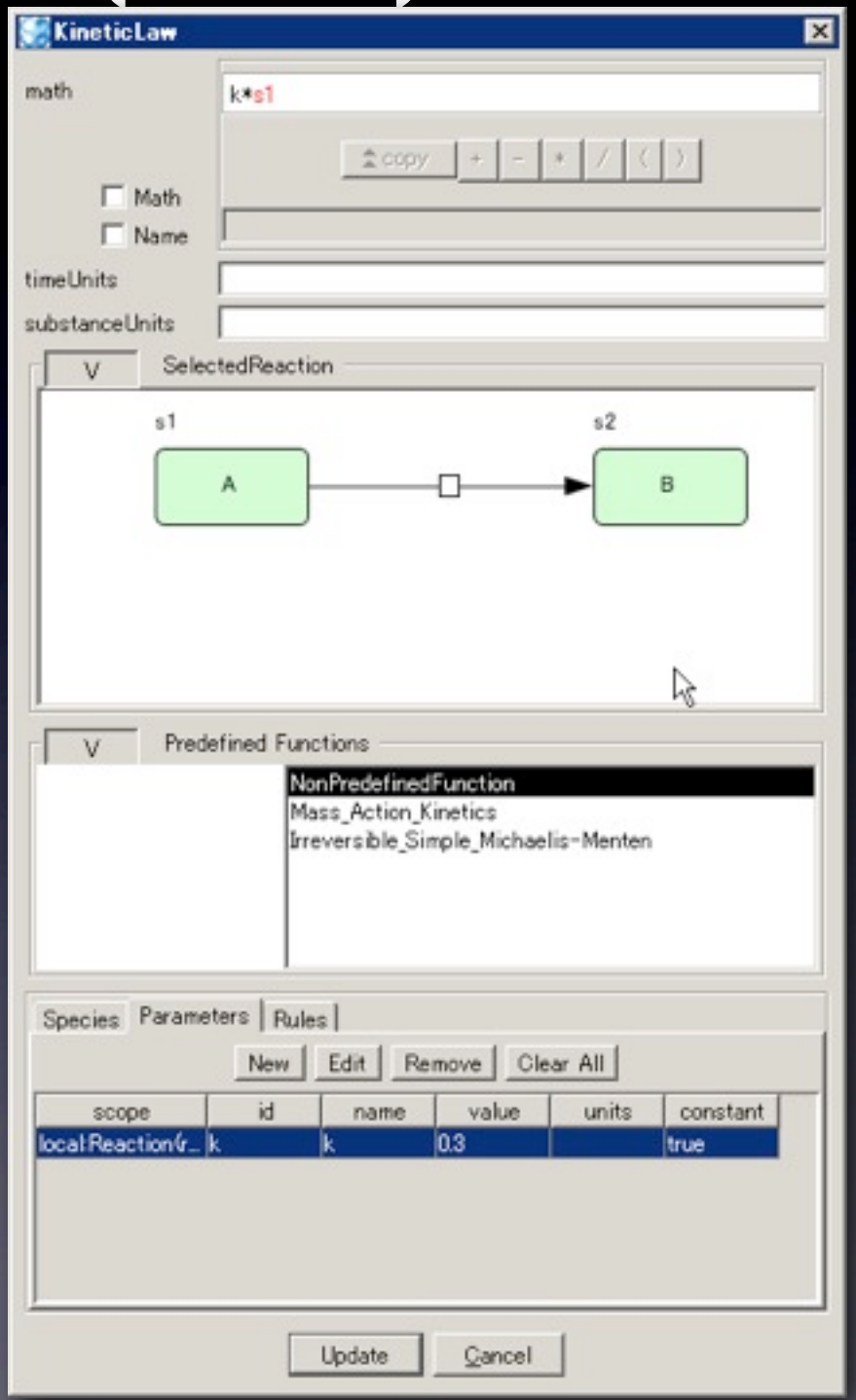
- Click top most text field
- Type k * (k times)
- Select Protein “A”
- Click [Name] checkbox
  ( k*s1 → k*A )

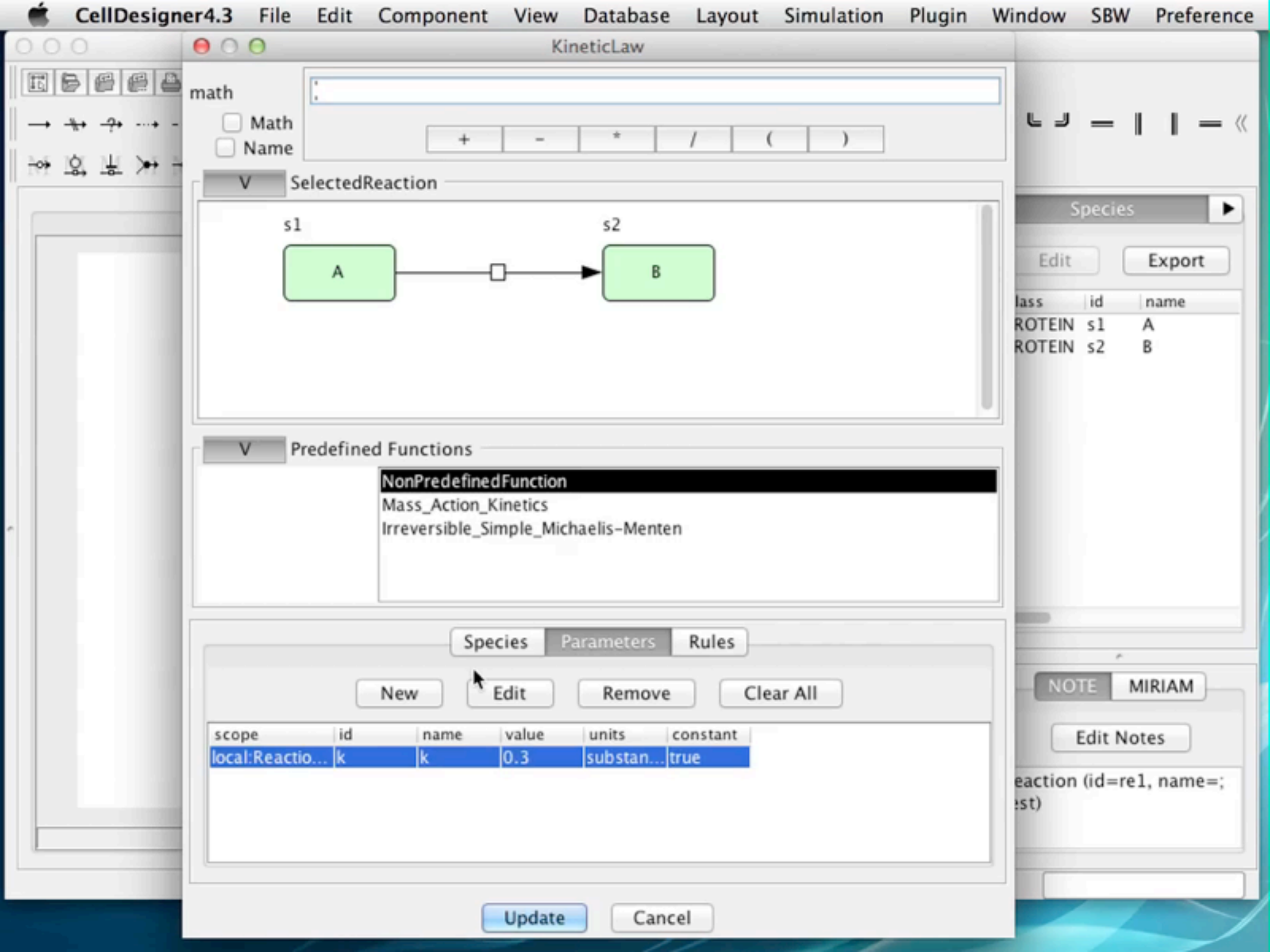
$$v = k[A]$$

$k = 0.3$

$A = 0.1$

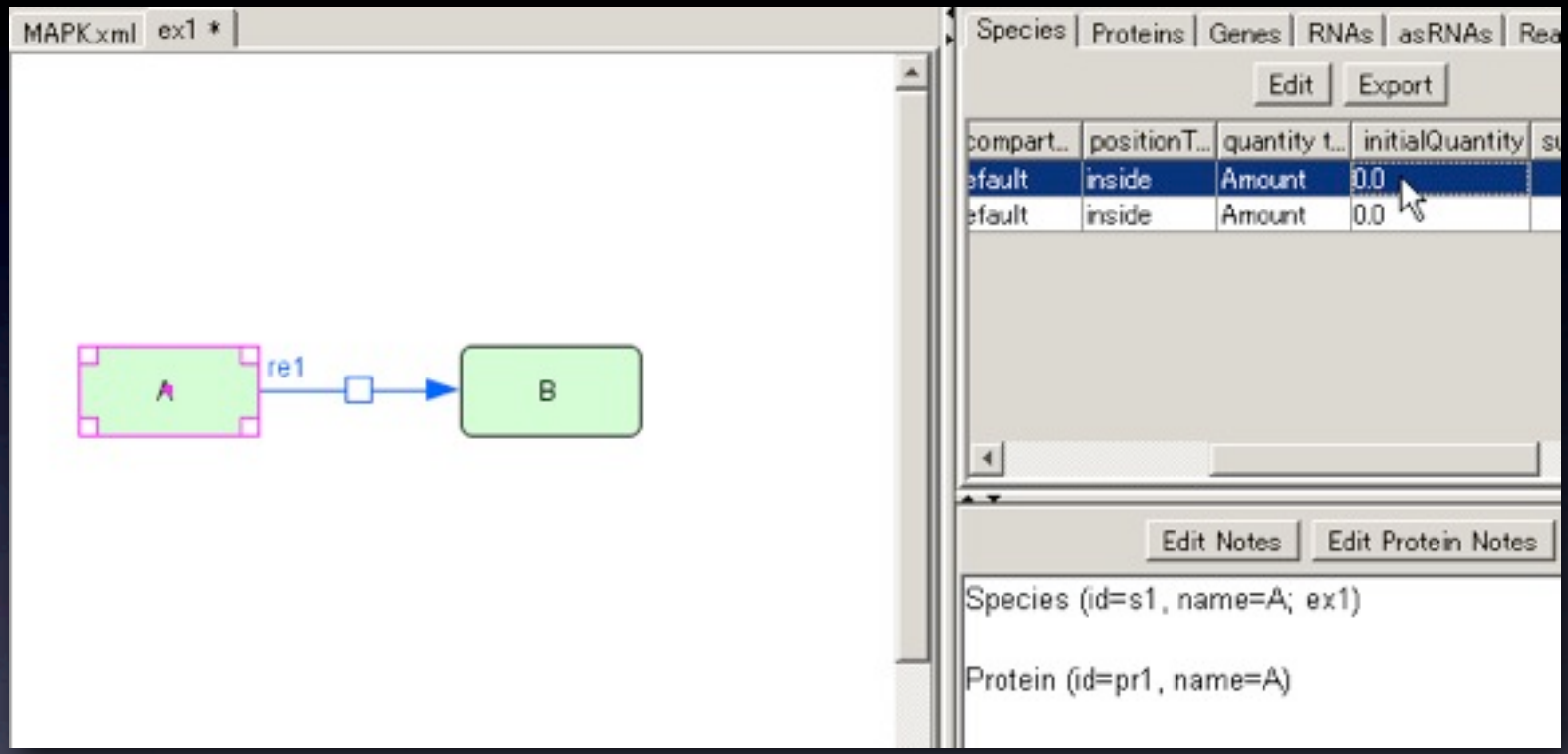
$B = 0$




CellDesigner4.3 File Edit Component View Database Layout Simulation Plugin Window SBW Preference
KineticLaw
math
Math
Name
+ - * / ( )
V SelectedReaction
s1
s2
A
B
V Predefined Functions
NonPredefinedFunction
Mass_Action_Kinetics
Irreversible_Simple_Michaelis-Menten
Species Parameters Rules
New Edit Remove Clear All
scope id name value units constant
local:Reactio... k k 0.3 substan... true
Update Cancel
Species
Edit Export
lass id name
ROTEIN s1 A
ROTEIN s2 B
NOTE MIRIAM
Edit Notes
eaction (id=re1, name=;
st)

# Simulation (ex1)

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




- Set value as 0.1

$$v = k[A]$$

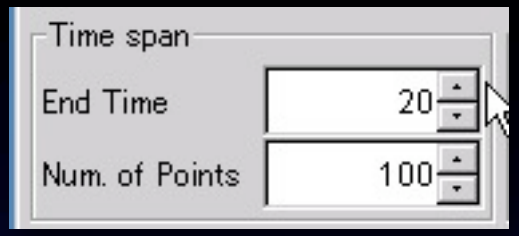
$k = 0.3$

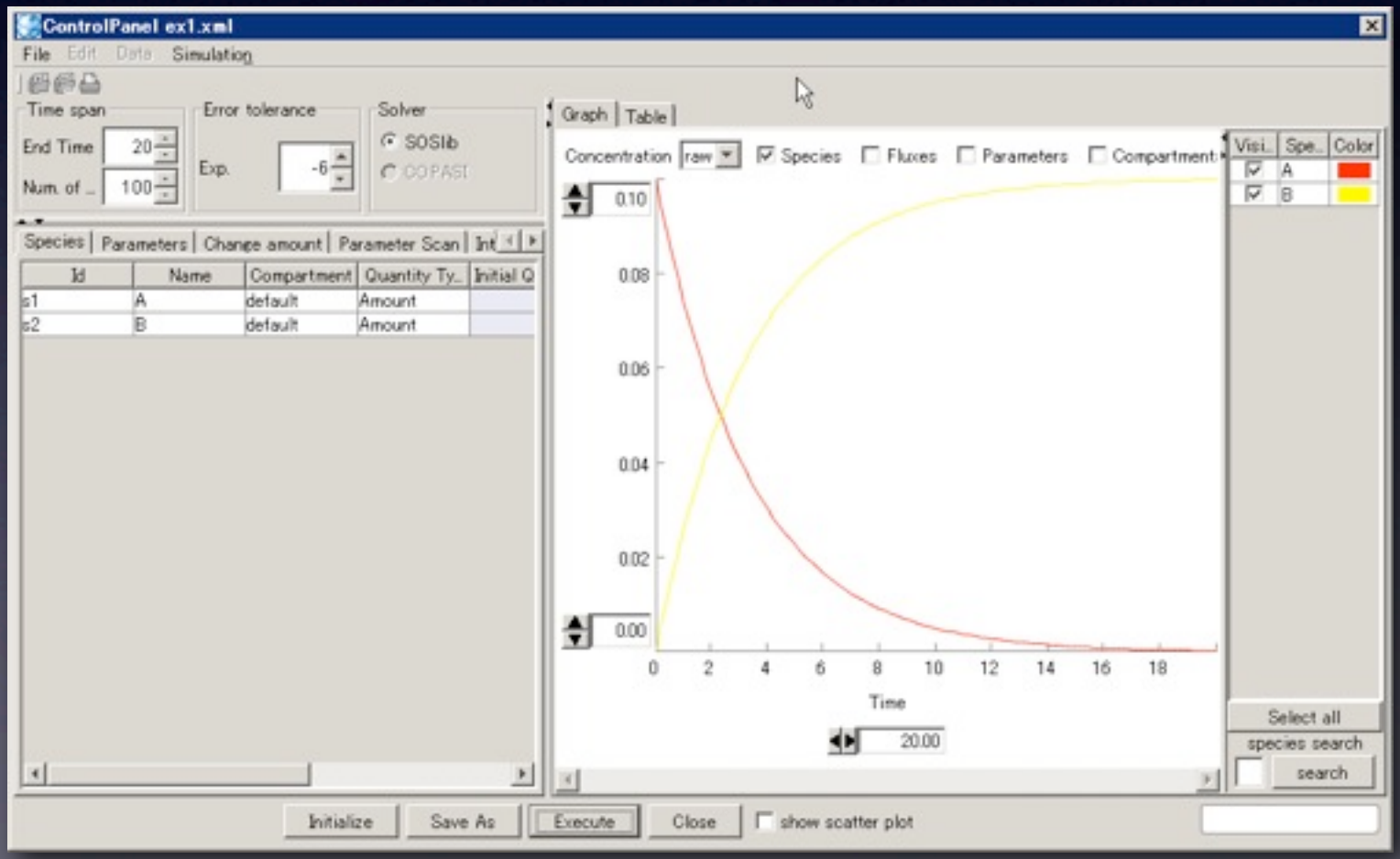
$A = 0.1$

$B = 0$

# Simulation (ex1)

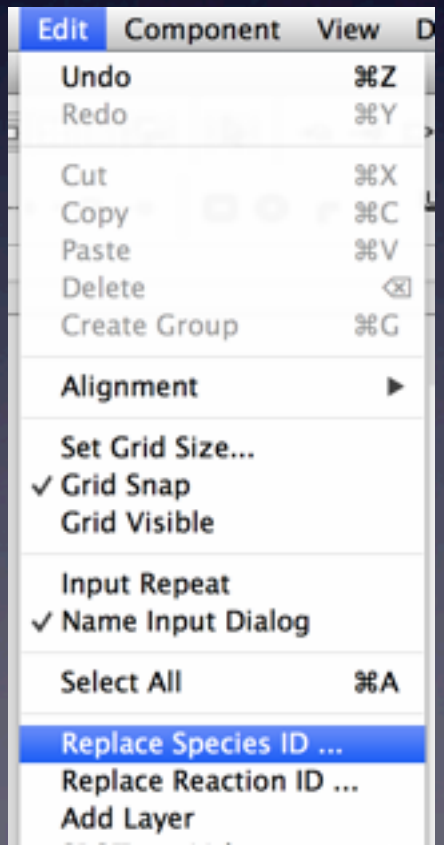
- Click [Simulation] → [ControlPanel]
- Set [End Time] to 20
- Click [Execute] button

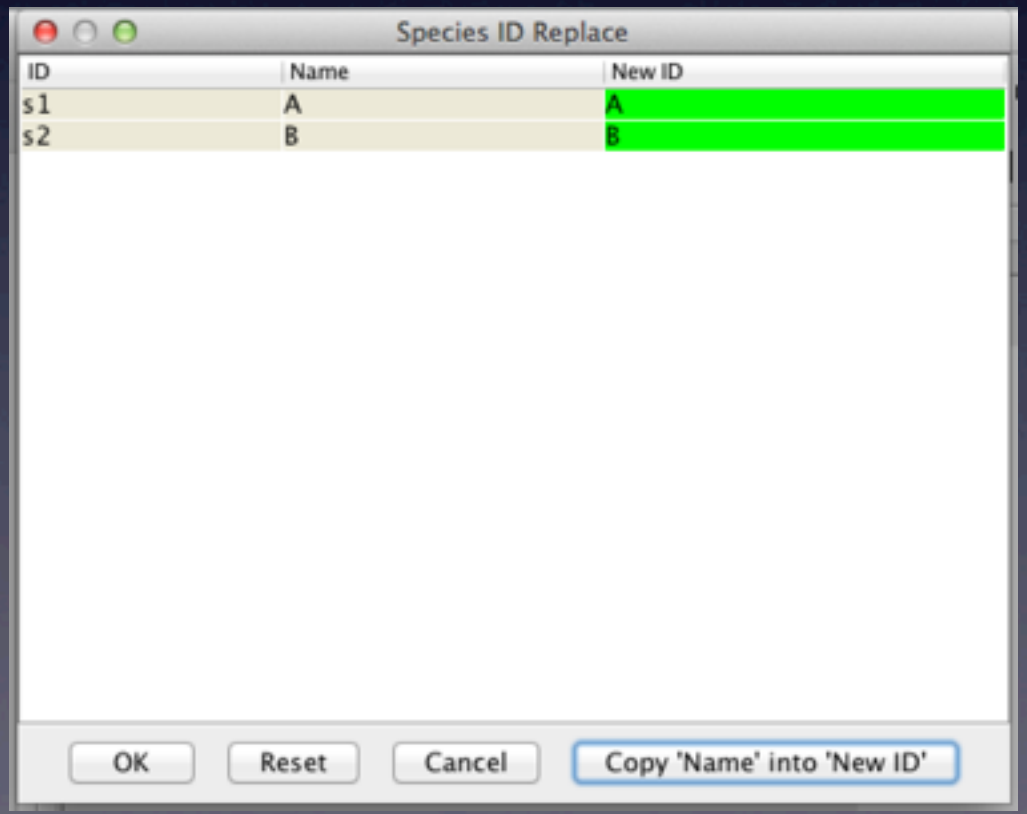


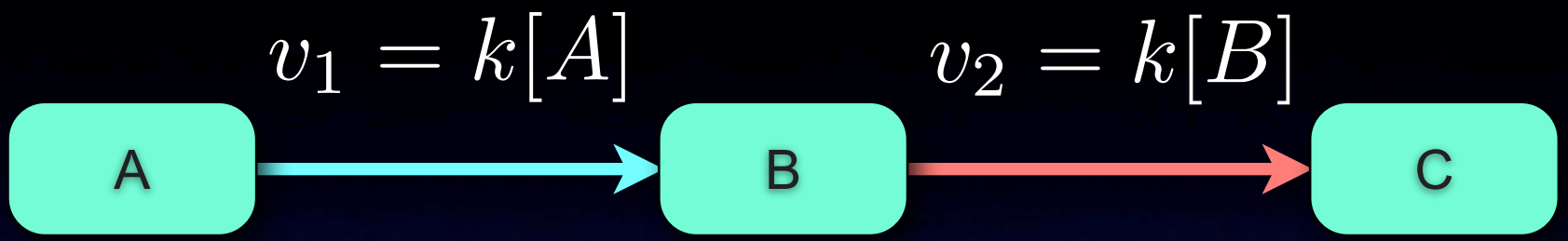
# Rename Species ID (s1 → A)

- Click [Edit] → [Replace Species ID]
- Click [Copy ‘Name’ into ...] button
- Use “Species Name” in KineticLaw Editor



# Network → Equation




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

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

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

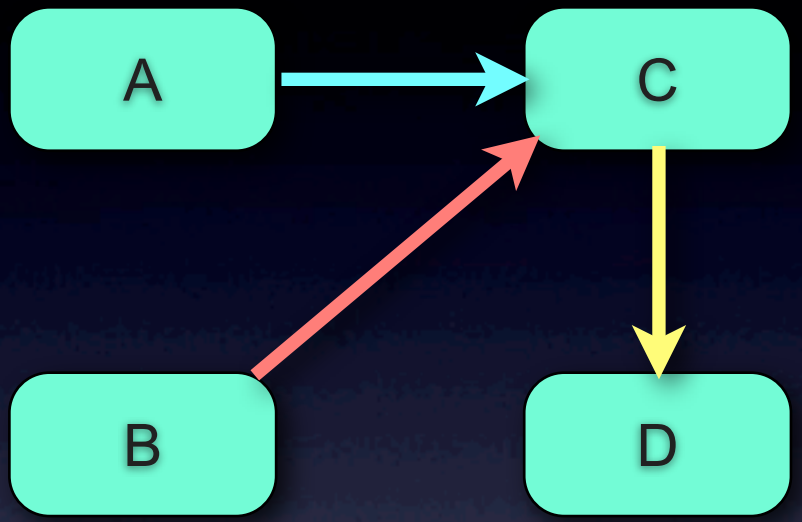
# Equation → Network

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

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

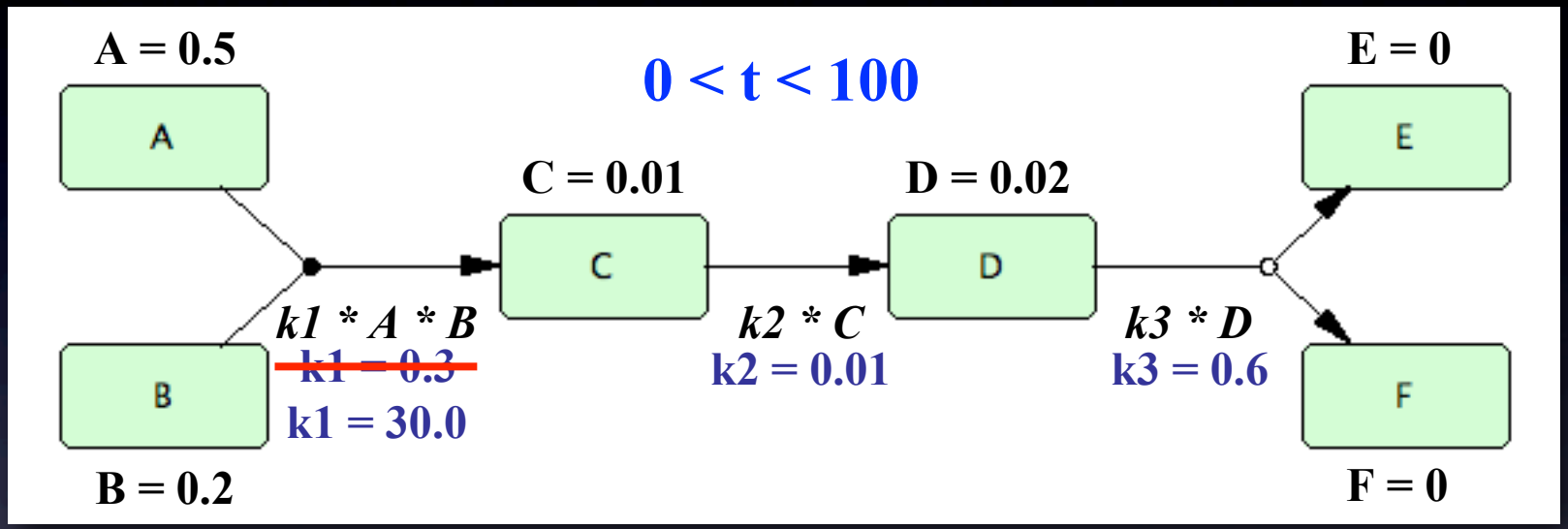
$$\frac{dC}{dt} = k_1 A + k_2 B - k_3 C$$

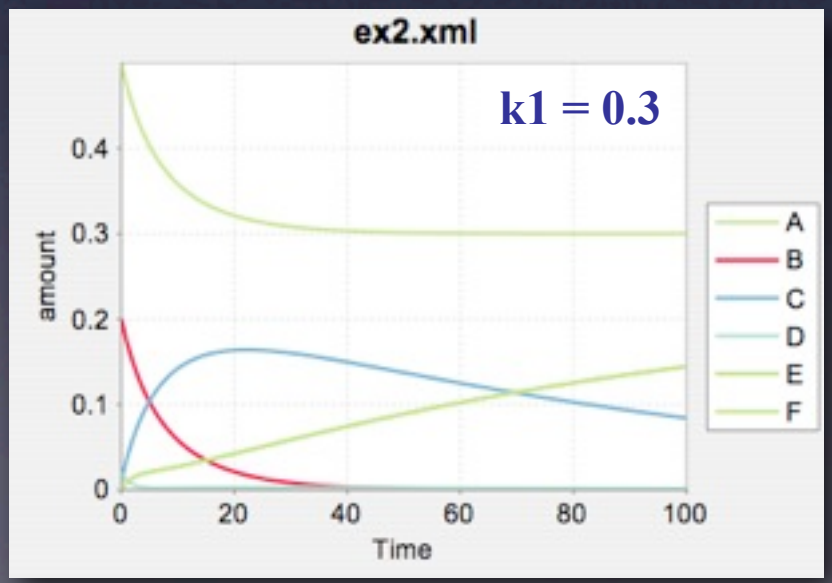
$$\frac{dD}{dt} = k_3 C$$

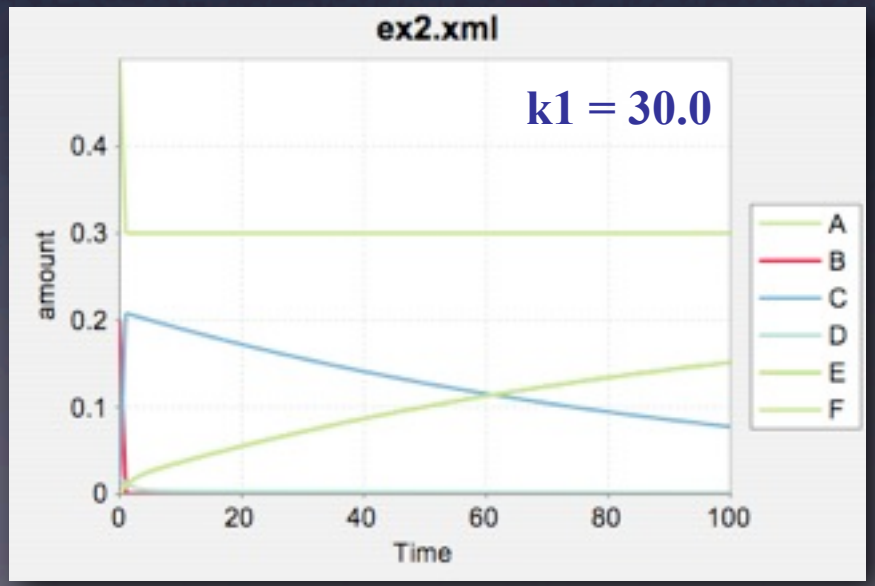


# Simulation (ex2)

- Change parameter k1 to 30.0

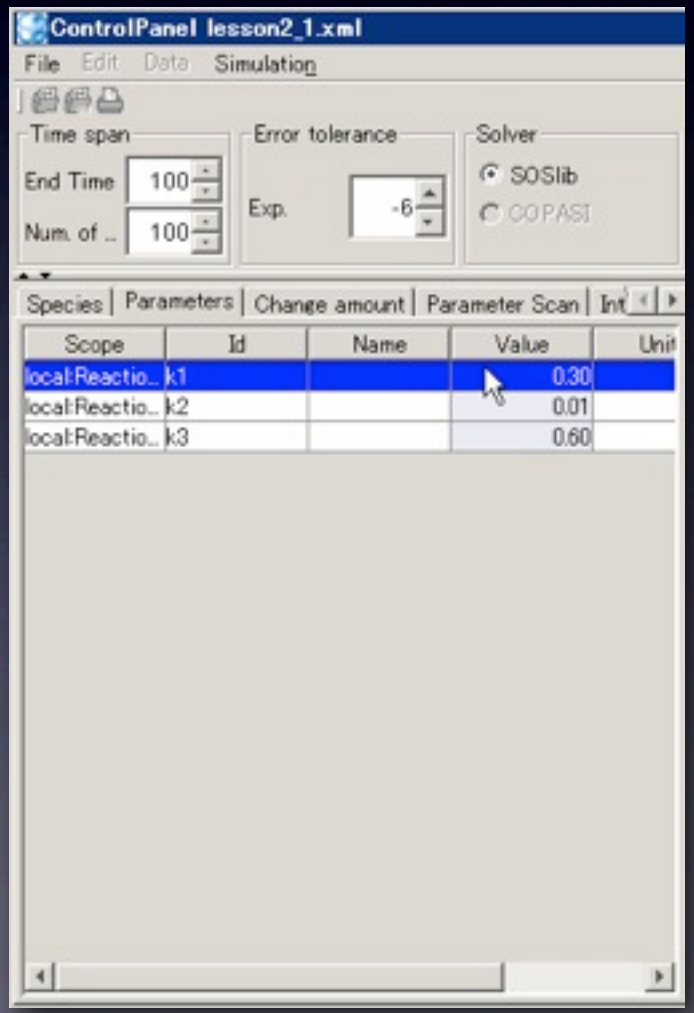


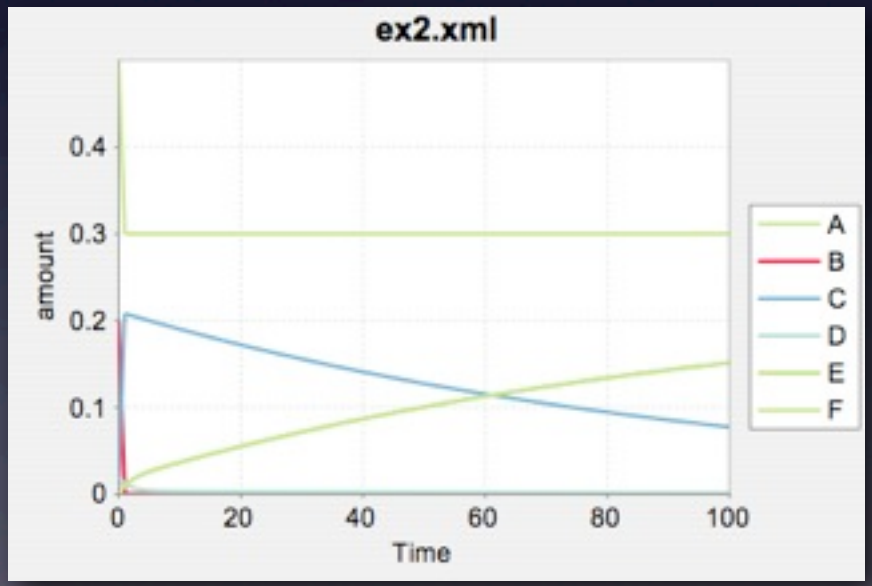



# Simulation (ex2)

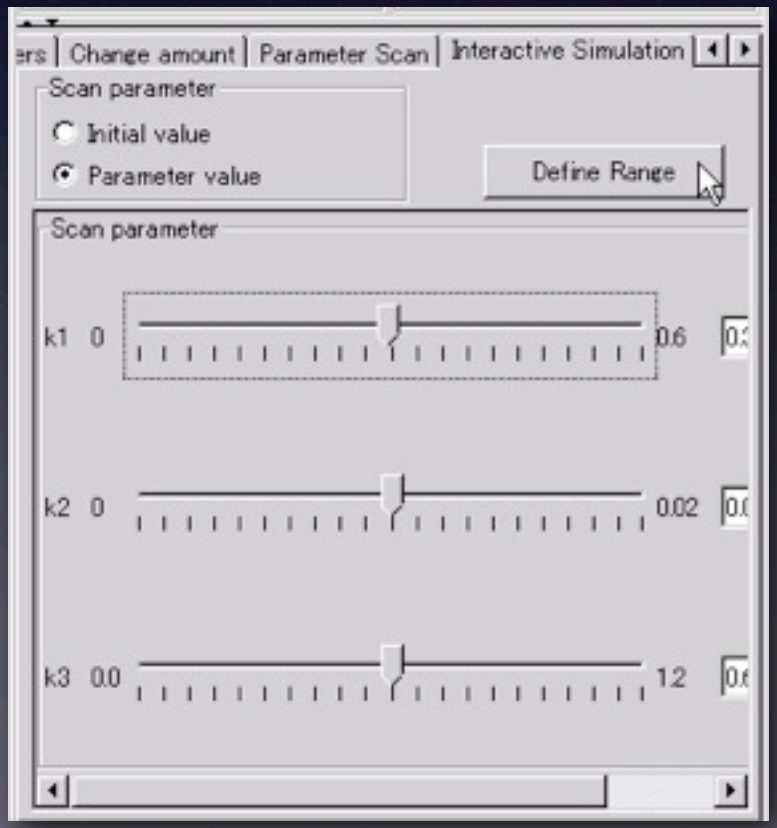
- Click [Parameters] tab
- Double click [Value] column for k1
- Change parameter k1 to 30.0

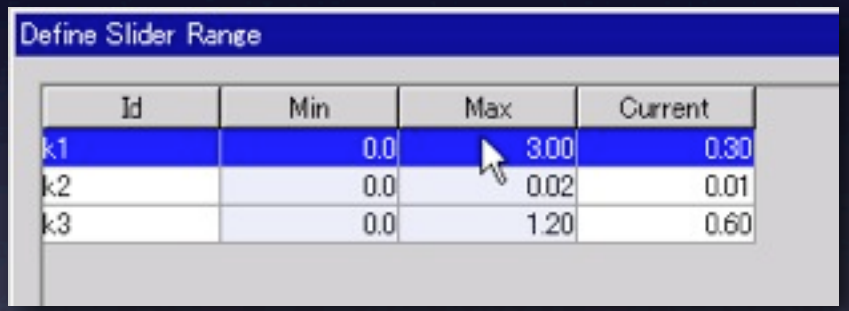


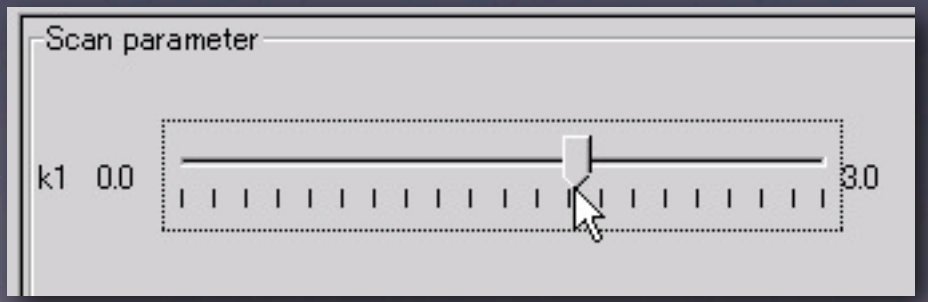
# Simulation (ex2)

- Click [Interactive Simulation] tab
- Click [Parameter value] radio button
- Click [Define Range] button
- Click [Max] column for k1 and set value as 3.0




Drag sliderbar for k1



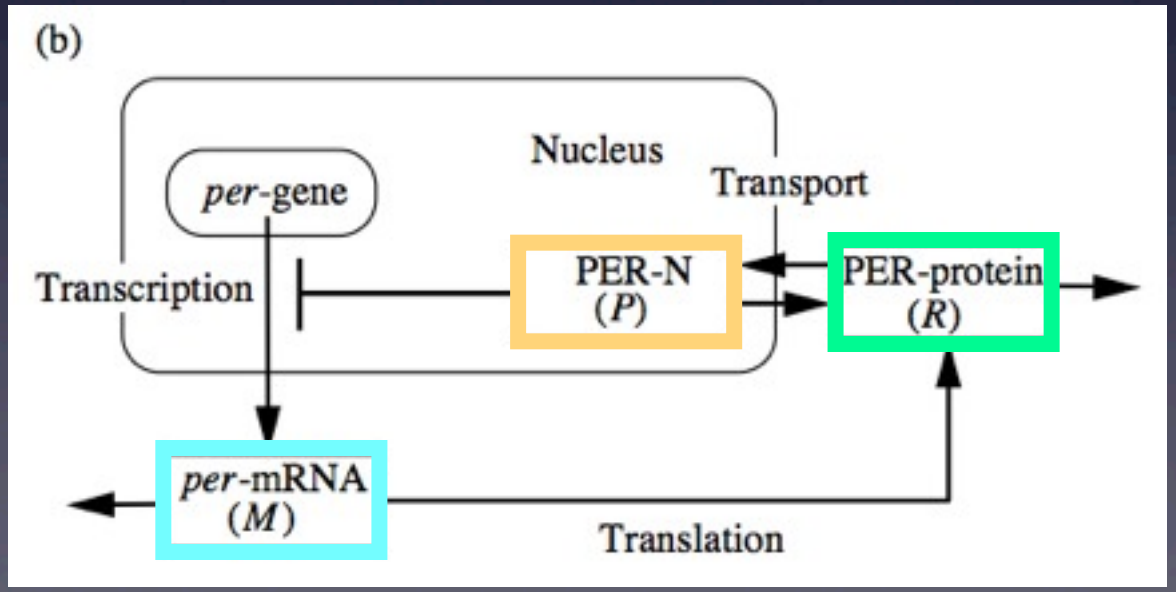
# Circadian clock model

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

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

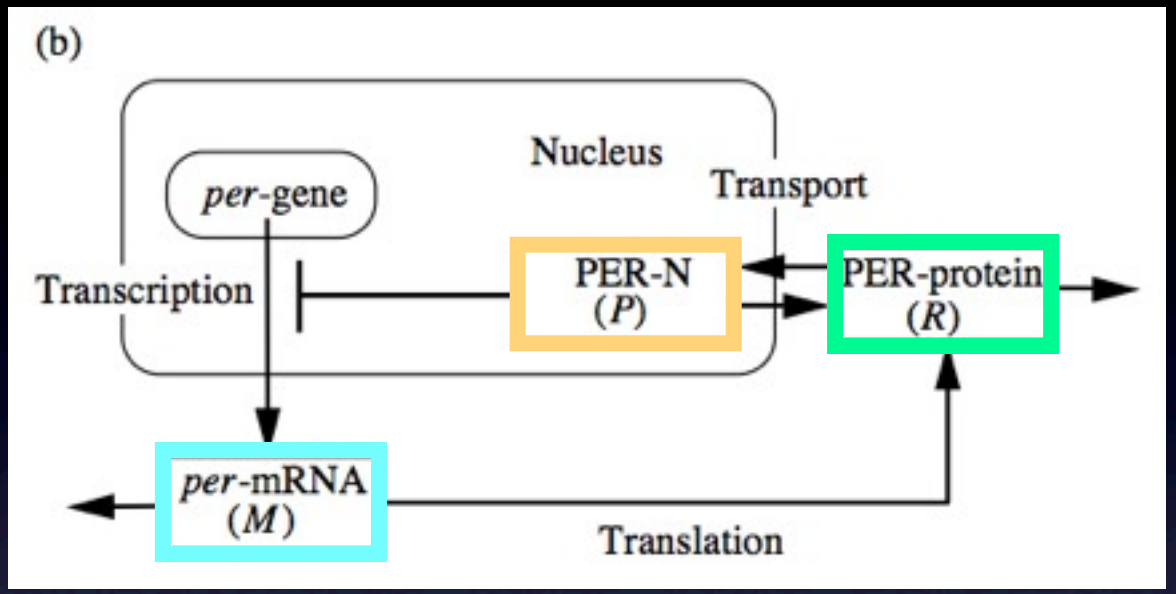
$$\frac{dR}{dt} = sM - (d+u)R + vP$$

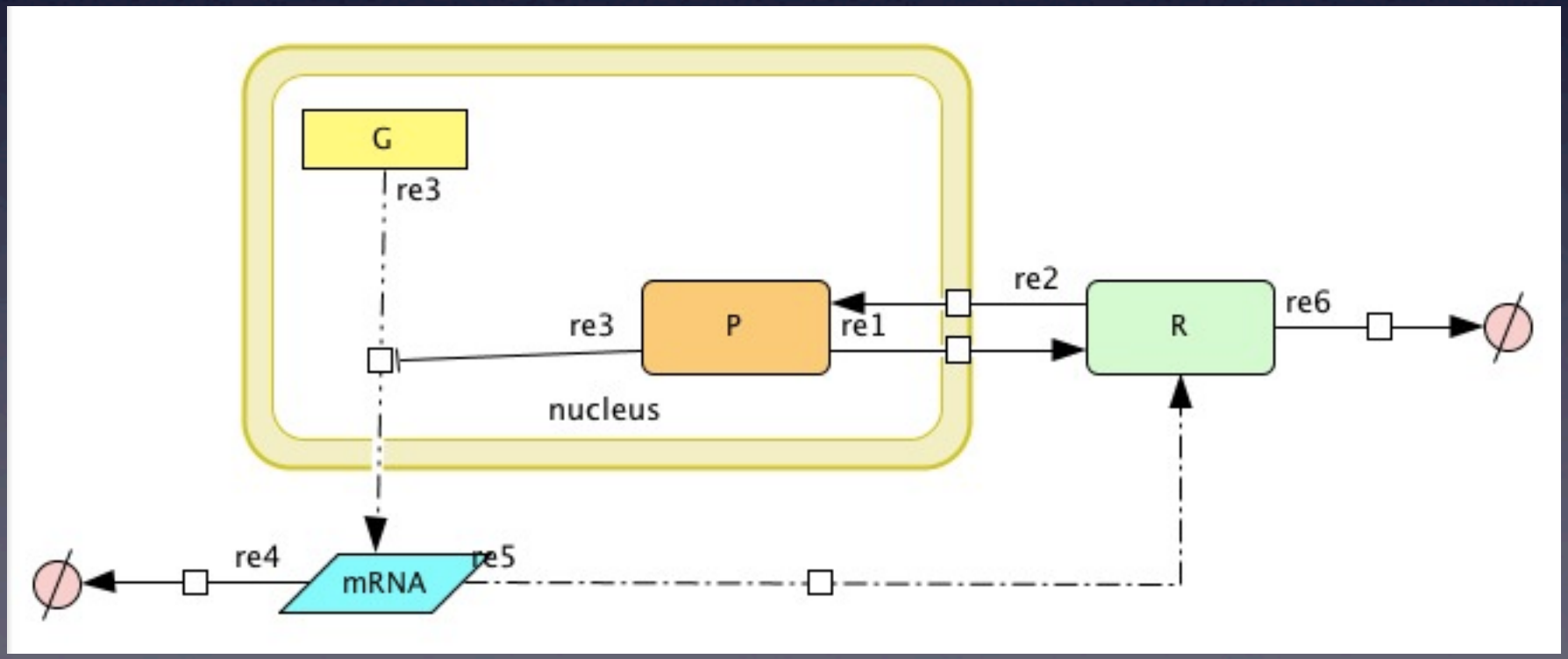
$$\frac{dP}{dt} = uR - vP$$




J. theor. Biol. (2002) 216, 193–208

# Circadian clock model



# Circadian clock model

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

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

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

$x^n = pow(x, n)$

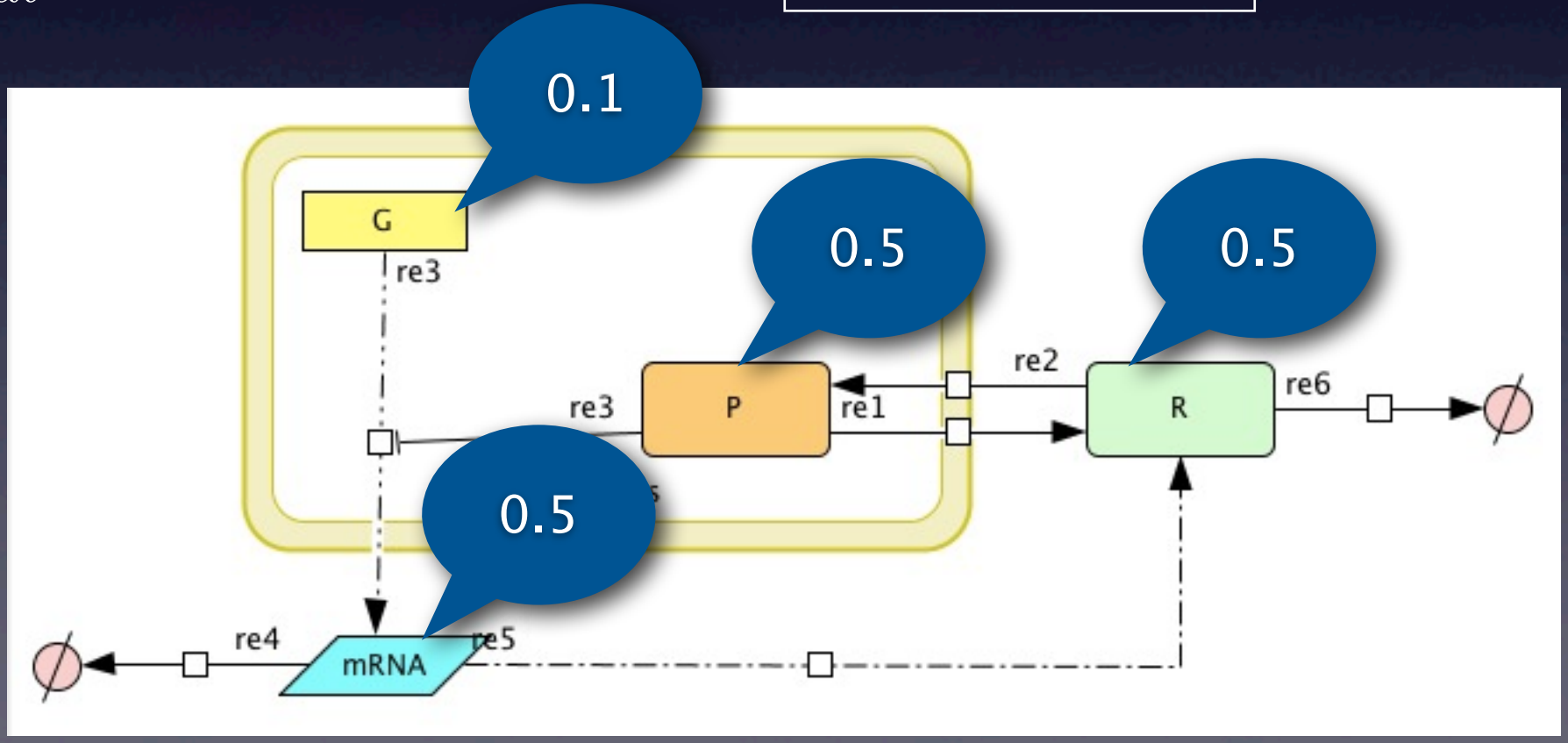
$$a = s = d = v = 1.0$$

$$u = 0.1$$

$$h = 0.01$$

$$n = 40$$

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



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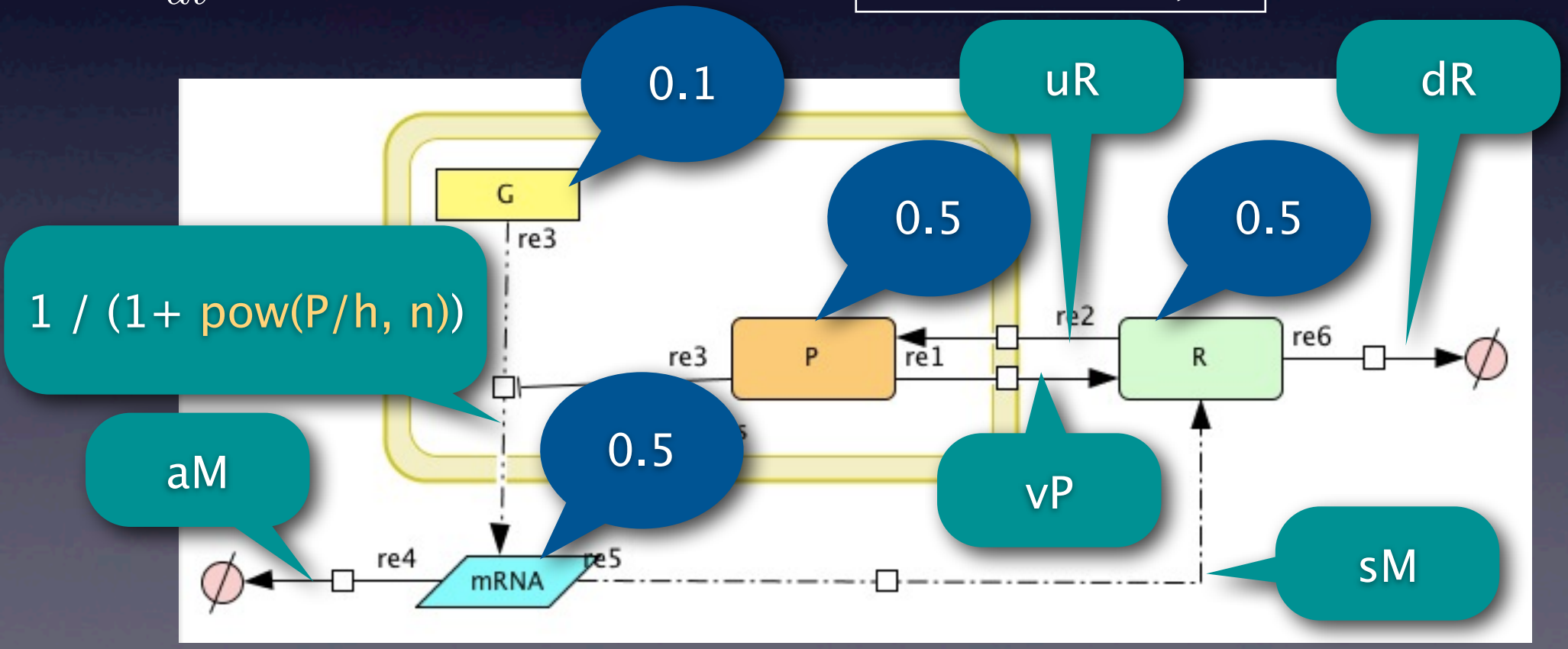
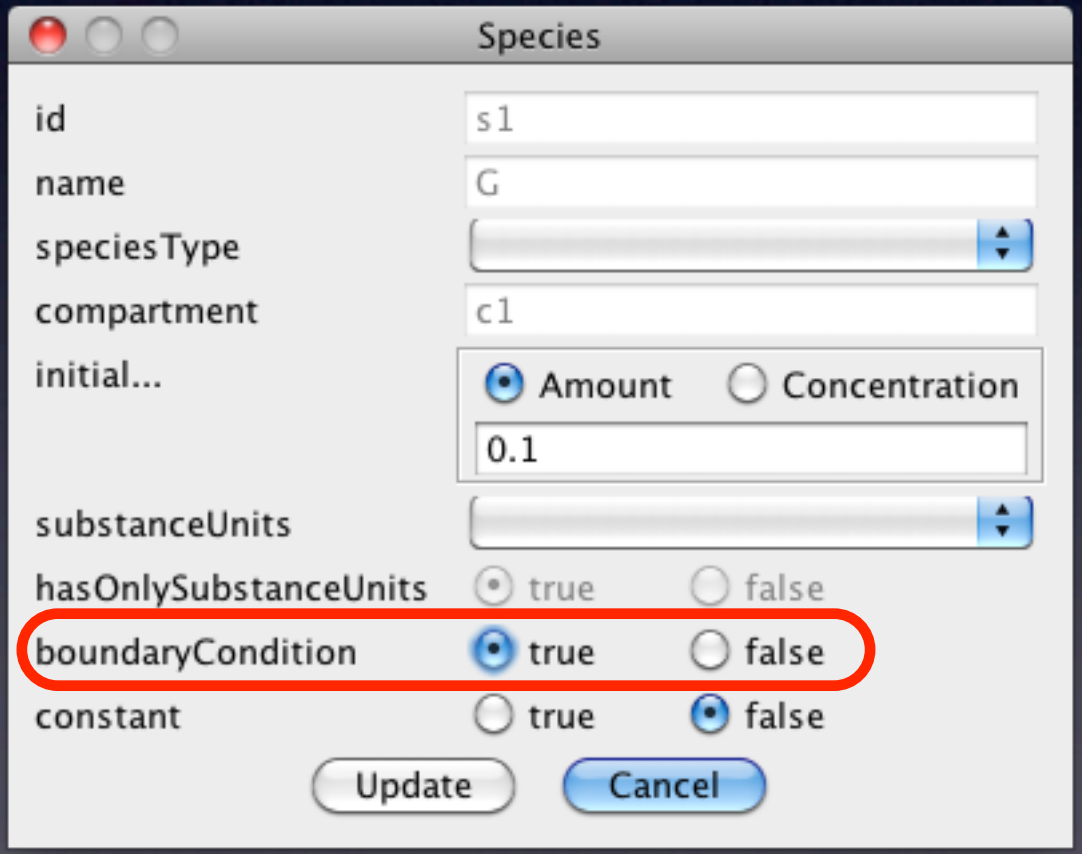
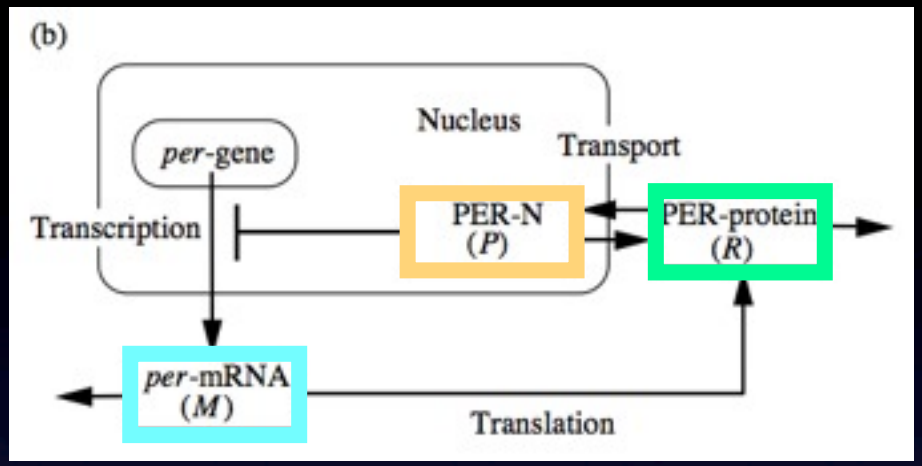


# Boundary condition

| name | speciesType | compar... | 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 |



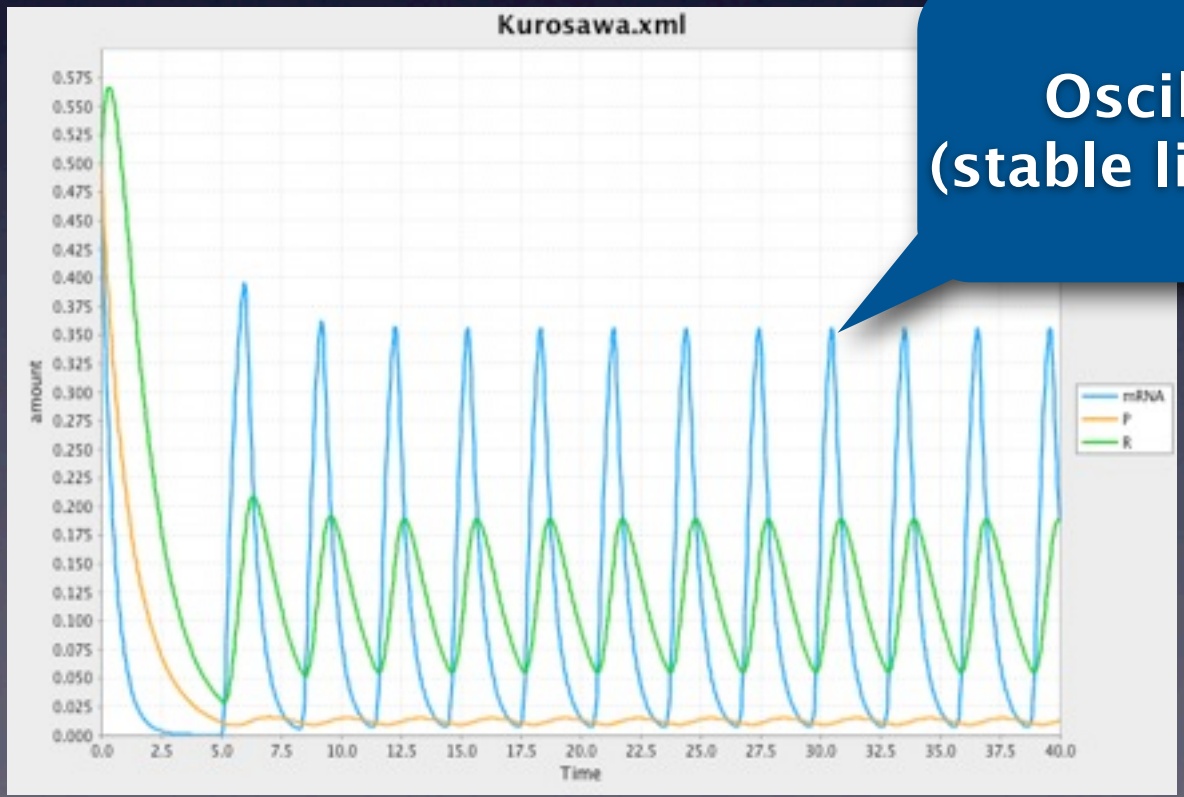
# Qualitative change by ‘n’




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

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

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

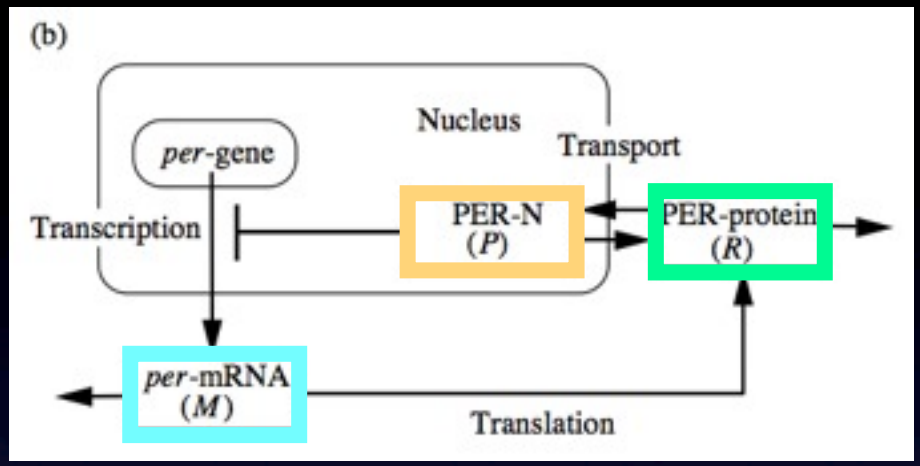



**Oscillation (stable limit cycle)**

n = 40

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

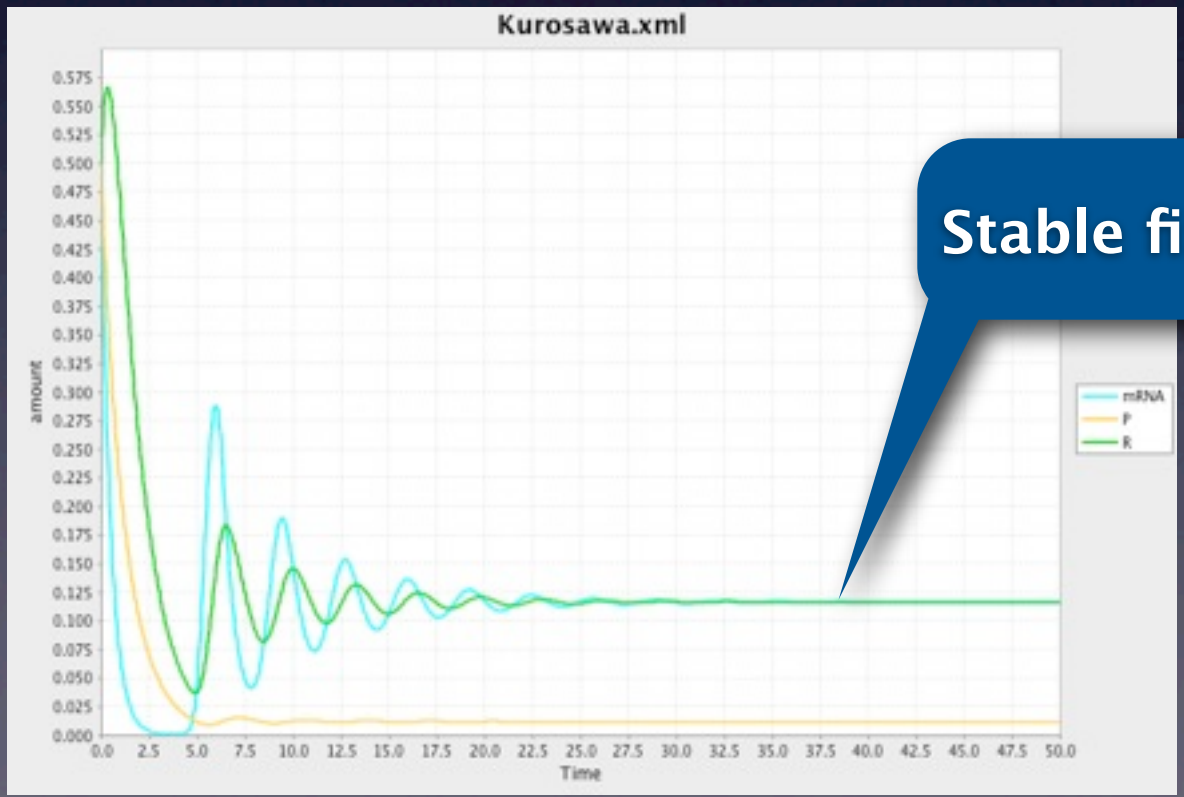
# Qualitative change by ‘n’




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

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

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

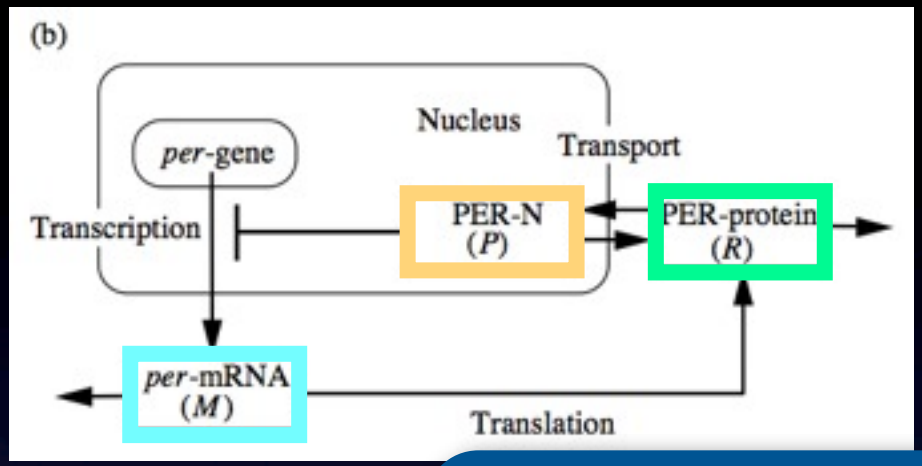



Stable fixed point

n = 8

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

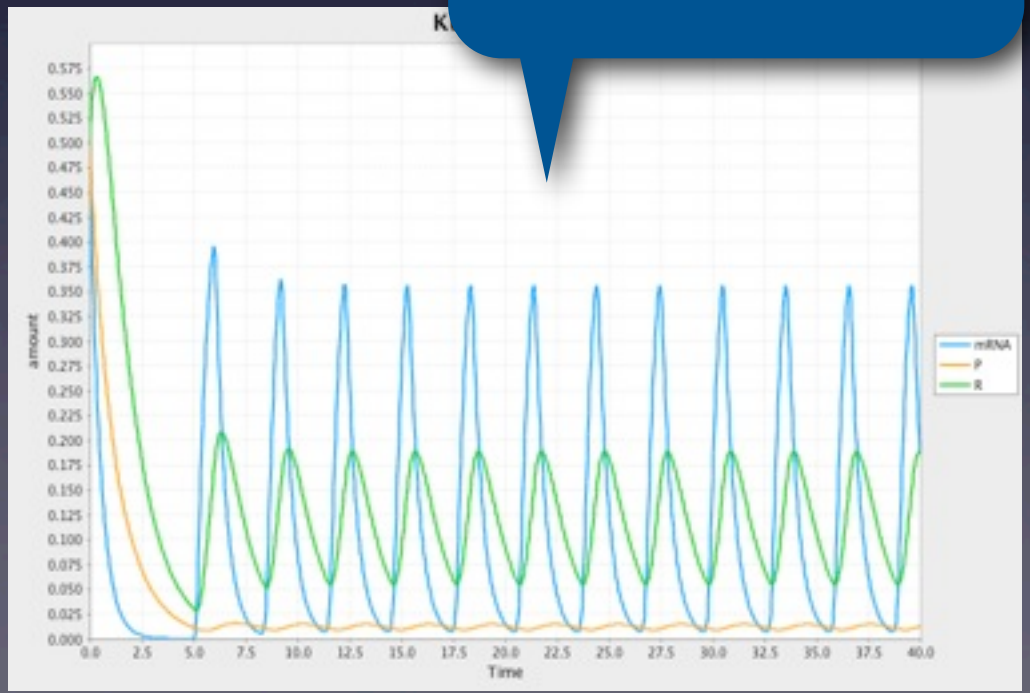
# Why we simulate a model?




Mathematical model and **Quantitative** evaluation (Simulation) will reach a **Qualitative** conclusion

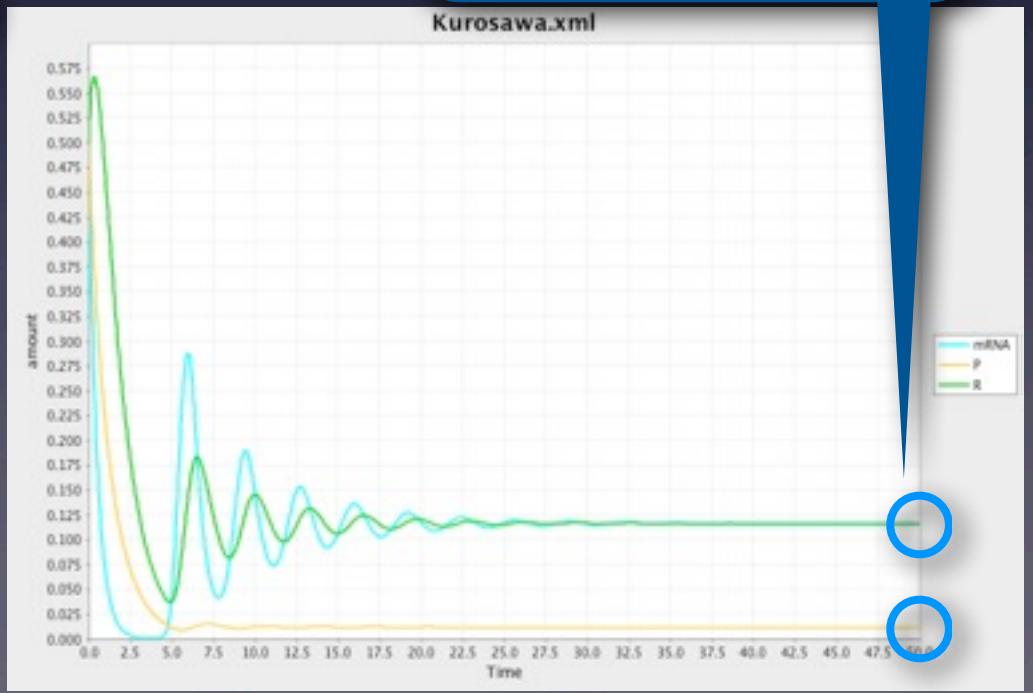
n = 40

Oscillation (stable limit cycle)



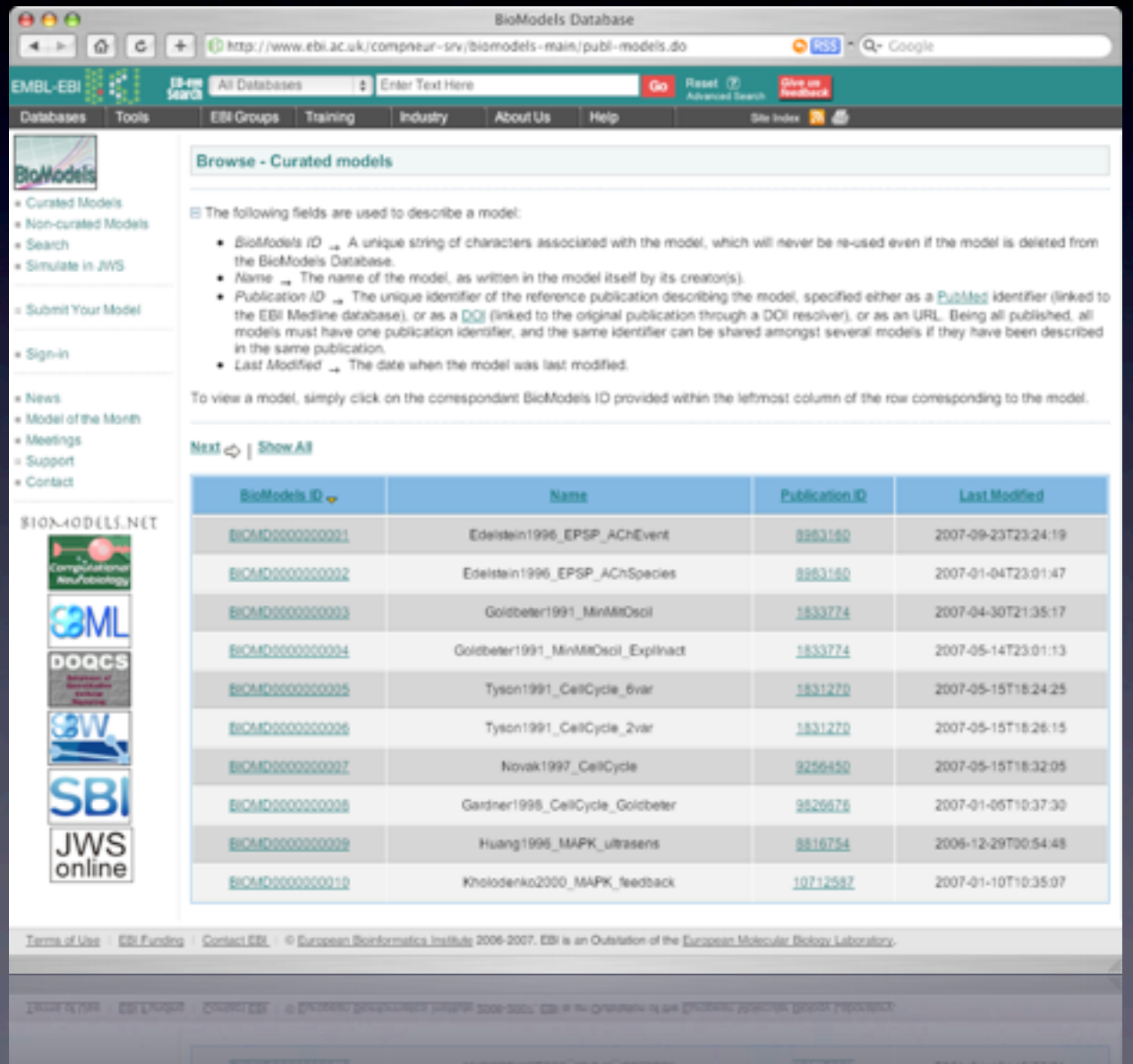

n = 8

Stable fixed point



# Database connection

- Import model from BioModels.net



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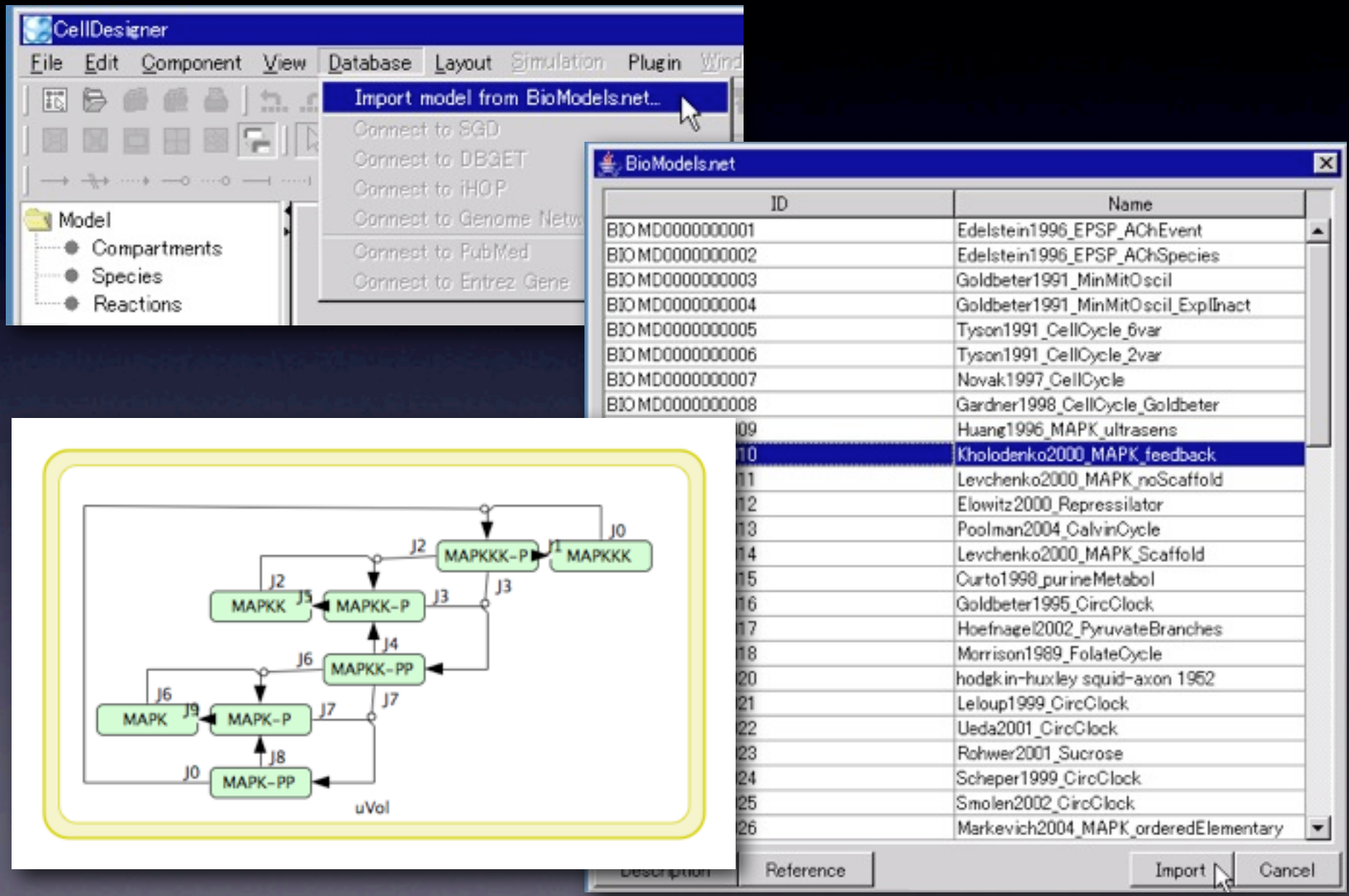


# SABIO-RK

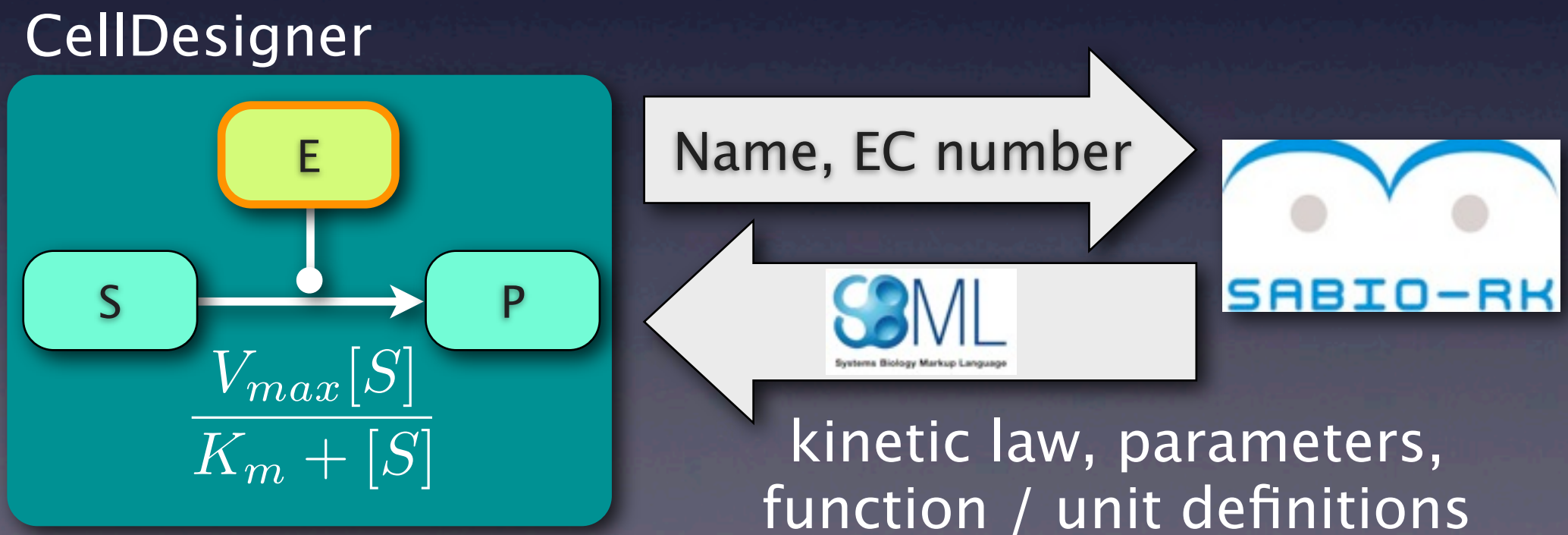
- Web-accessible database
- http://sabio.h-its.org/
- Contains information about biochemical reactions, related kinetic equations and parameters


Heidelberg Institute for Theoretical Studies

HITS

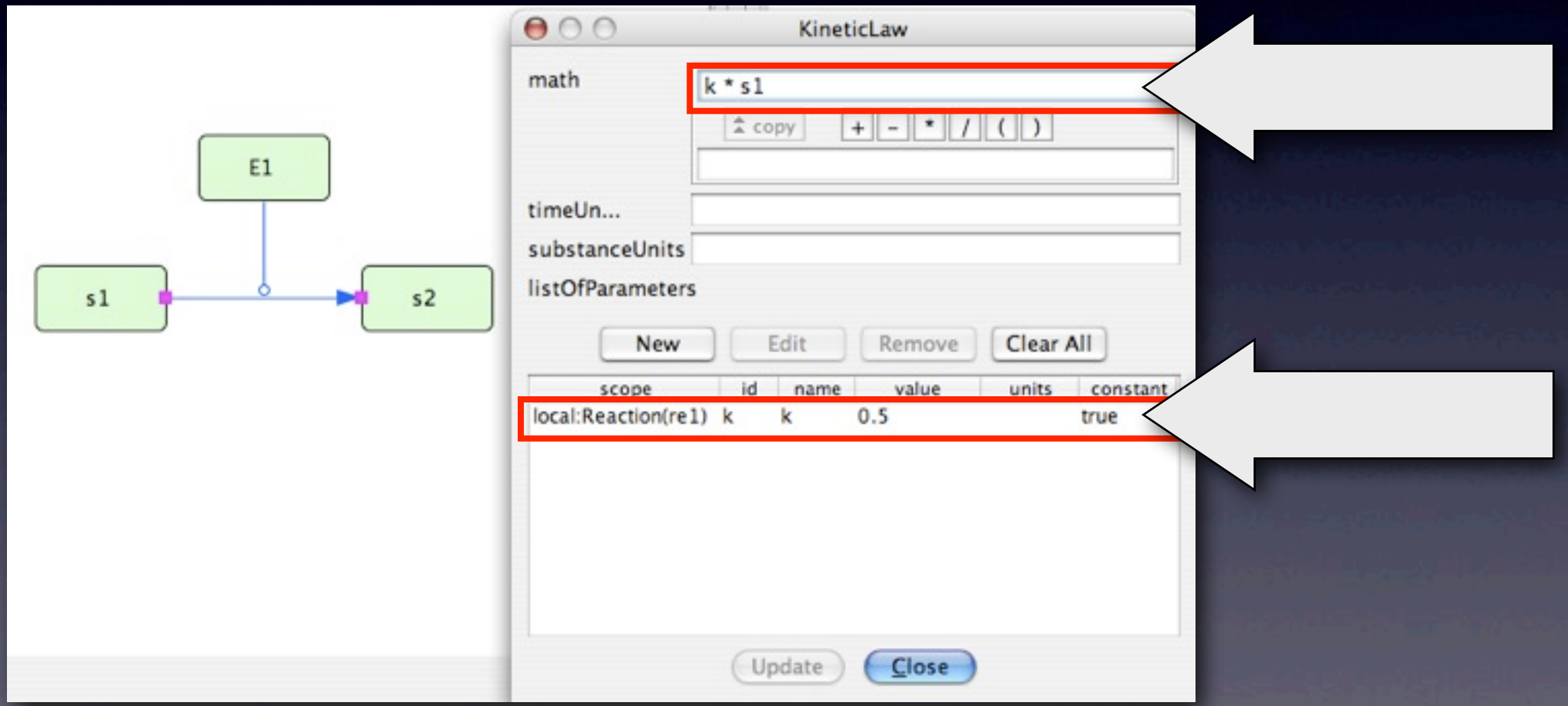
# CellDesigner ⇔ SABIO RK

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



# Integration

- Import kinetic law, parameters to the model from SABIO-RK



# Annotating a model

Akira Funahashi & Noriko Hiroi & Yuta Tokuoka
Keio University, Japan
6th Aug. 2017

Keio University
1858
CALAMVS
GLADIO
FORTIOR

SBI The Systems Biology Institute

# IGF signaling pathway

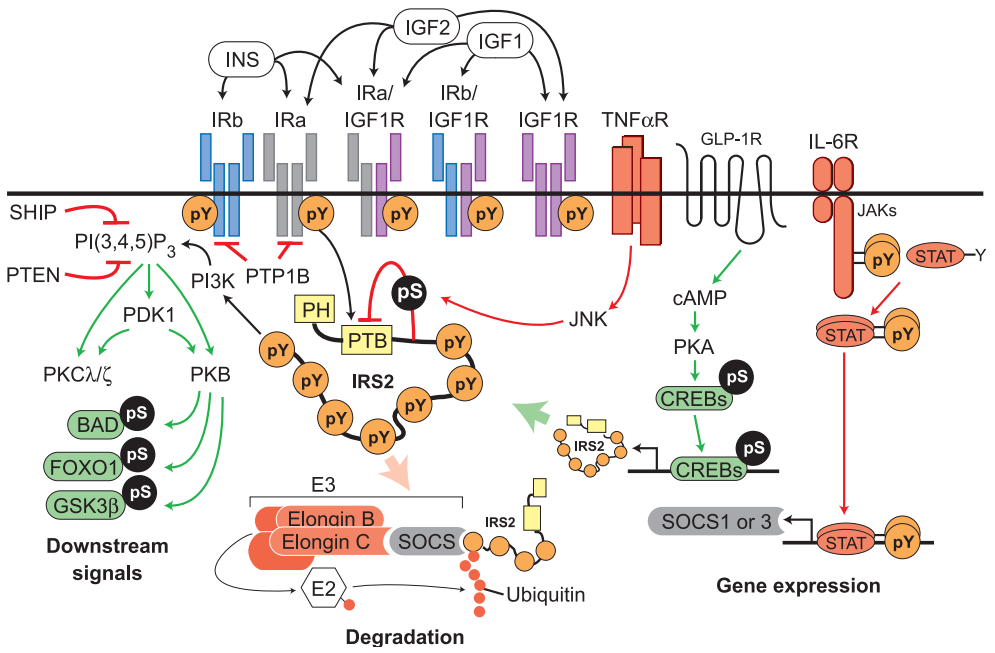
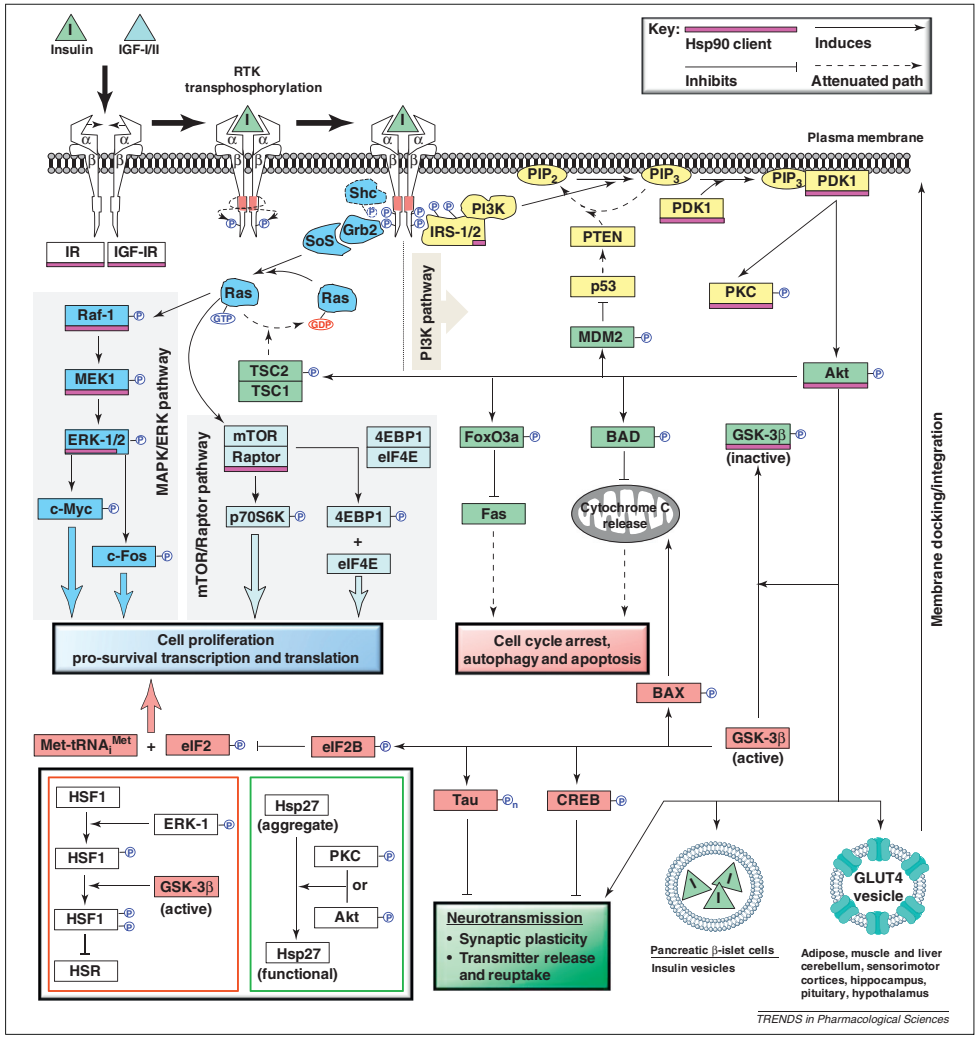


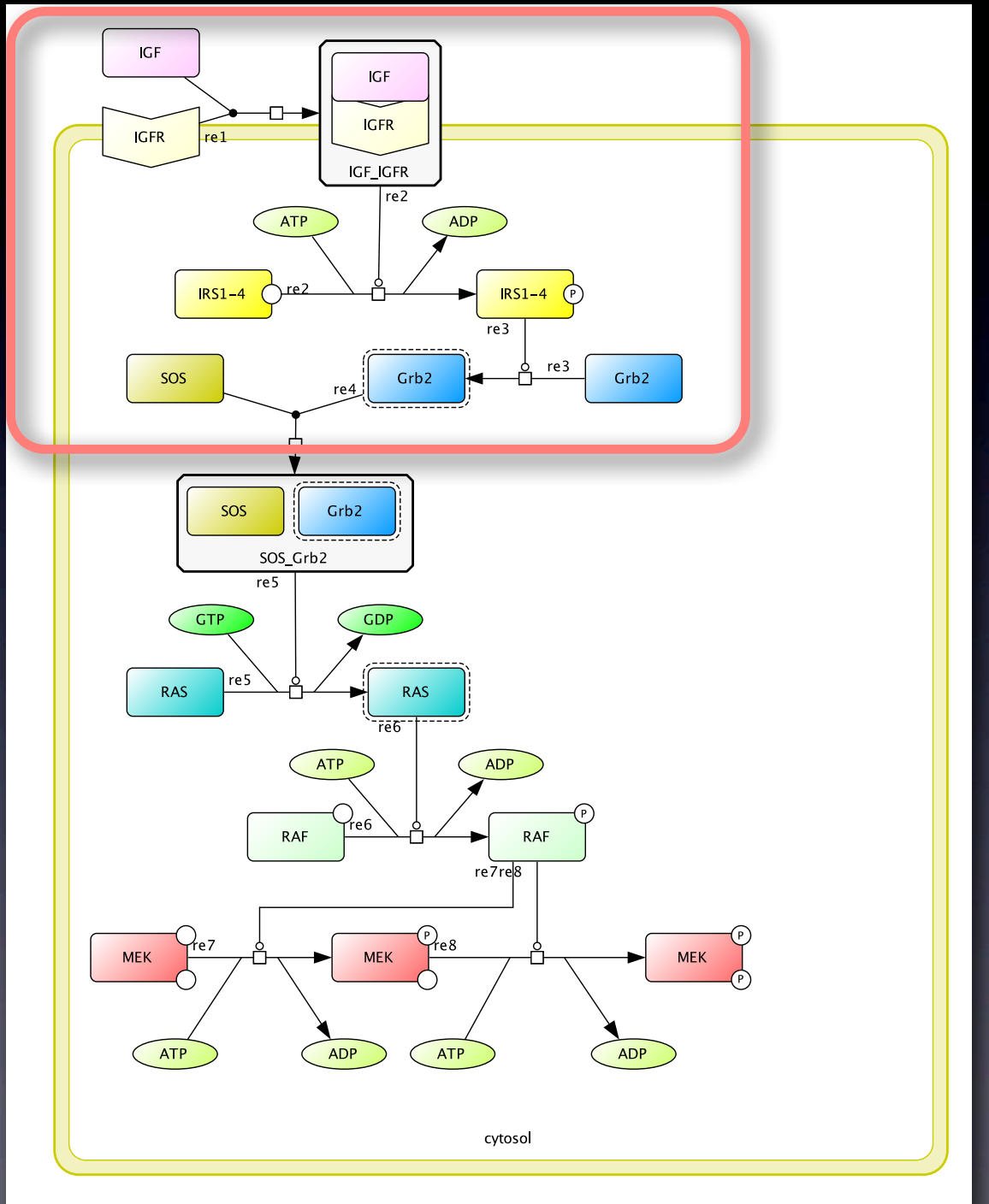

**Fig. 1.** Regulation of insulin and IGF signaling. Insulin and IGF1 receptors form hybrids that modulate the selectivity and affinity for insulin and insulin-like growth factors (IGF1 and IGF2). Insulin or IGF binding stimulates tyrosine autophosphorylation in the receptor β subunits, which activates the kinase and recruits cellular substrates—IRS1 and IRS2—for tyrosine phosphorylation. Recruitment is regulated by serine phosphorylation of the IRS proteins, which inhibits the interaction between its PTB domain and the phosphorylated receptor. Proinflammatory cytokines increase the synthesis of SOCS1 or SOCS3, which promote ubiquitination and degradation of IRS1 and IRS2. Production of cAMP enhances expression of IRS2 through the activity of phosphorylated CREB. Tyrosine phosphorylation of IRS1 or IRS2 recruits and activates various SH2 domain–containing proteins, including the PI 3-kinase, which activates the PKB cascade. Abbreviations: pY, phosphotyrosine; pS, phosphoserine; PKCλ/ζ, protein kinase C λ or ζ; E2, ubiquitin conjugating enzymes; TNFαR, tumor necrosis factor–α receptor; GLP-1R, glucagon-like peptide–1 receptor; IL6R, interleukin-6 receptor; for other abbreviations, see the text.




**Insulin Signaling in Health and Disease**
Science **302** (5651), 2003, 1710.

**Heat shock response and insulin–associated neurodegeneration**
Trends in Pharmacological Sciences, **33**(3), 2012, 129–137

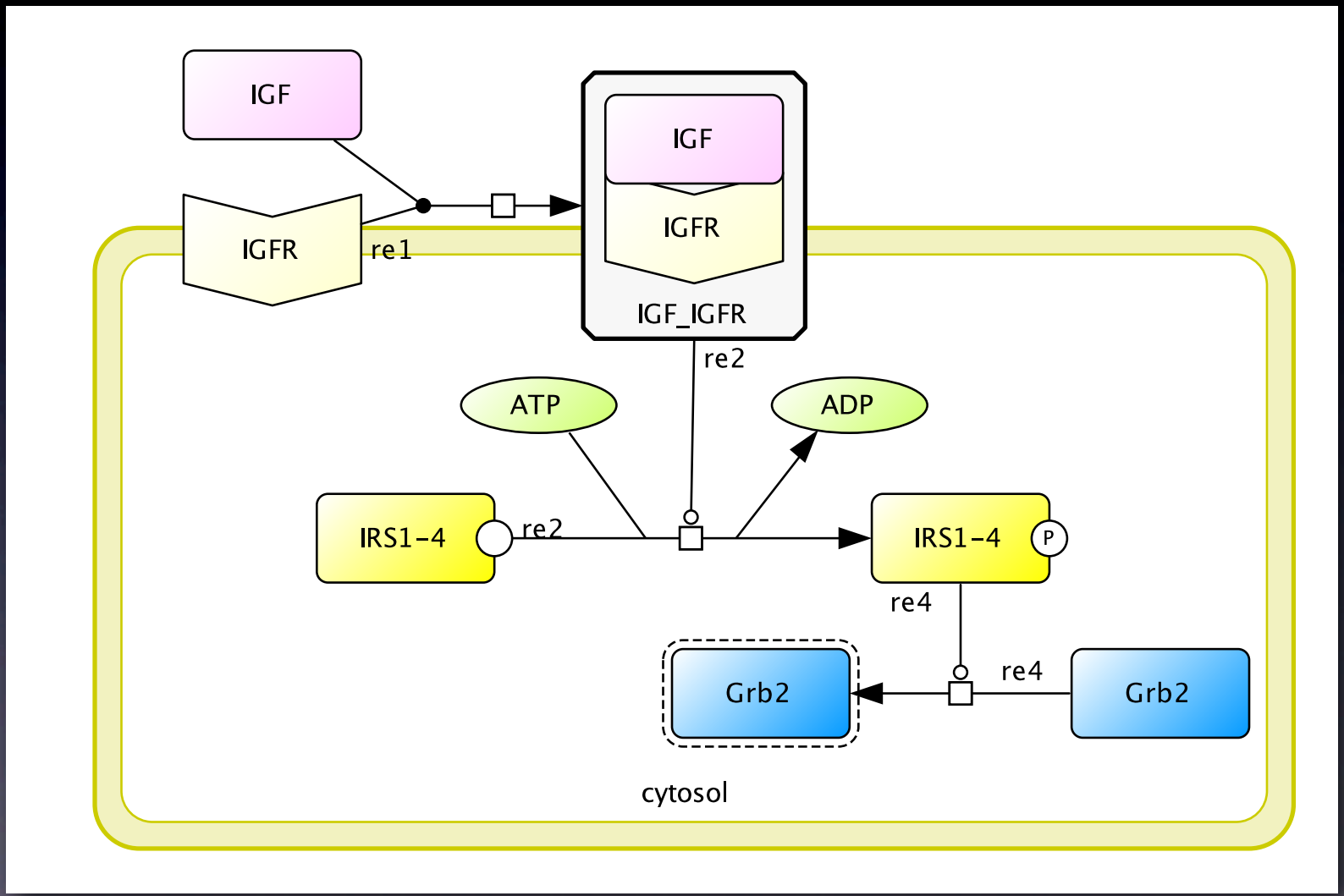
# IGF signaling pathway




http://www.sbgn.org/Documents/PD_L1_Examples

# Exercise

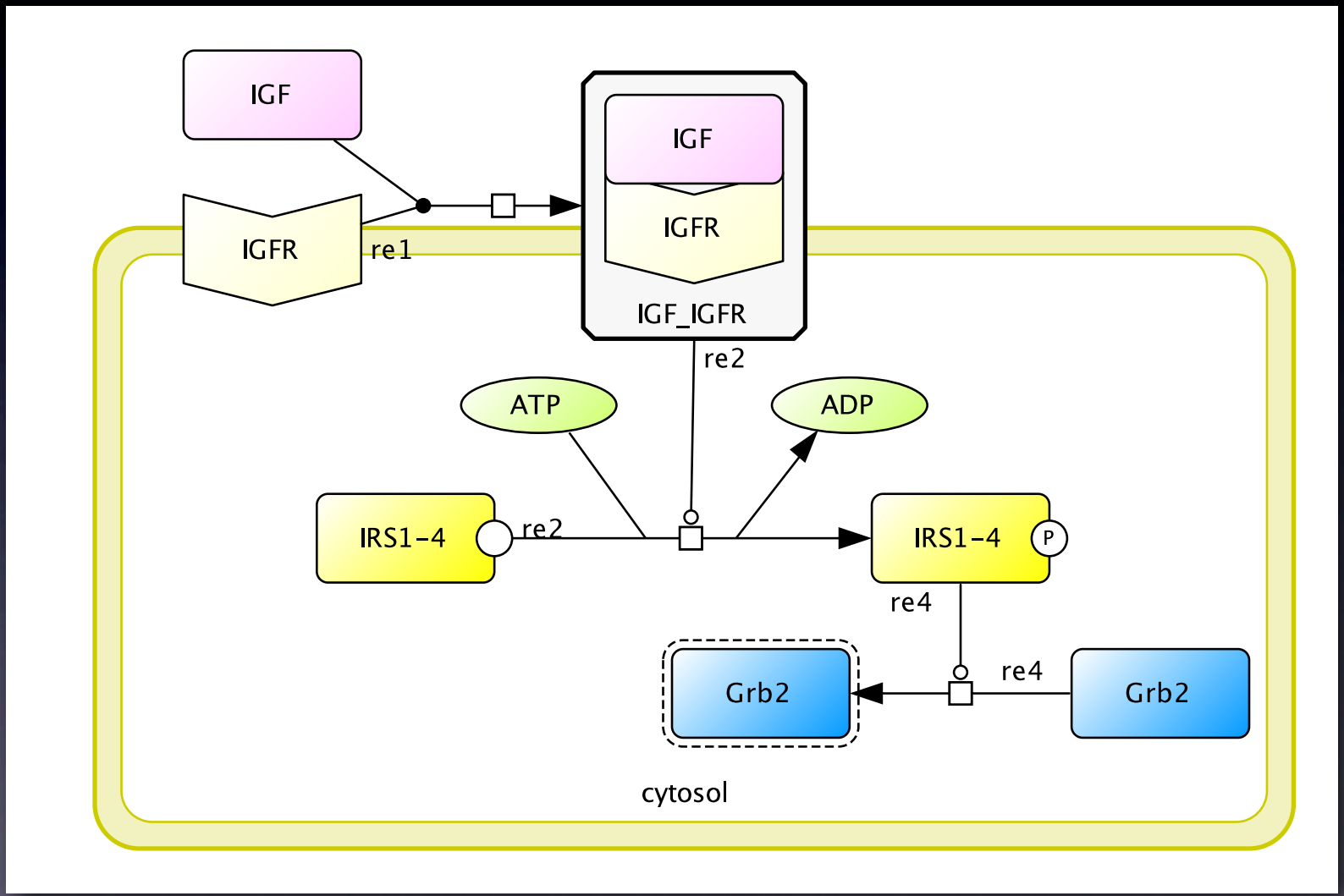
- Create a following model on CellDesigner




http://www.sbgn.org/Documents/PD_L1_Examples

# Exercise

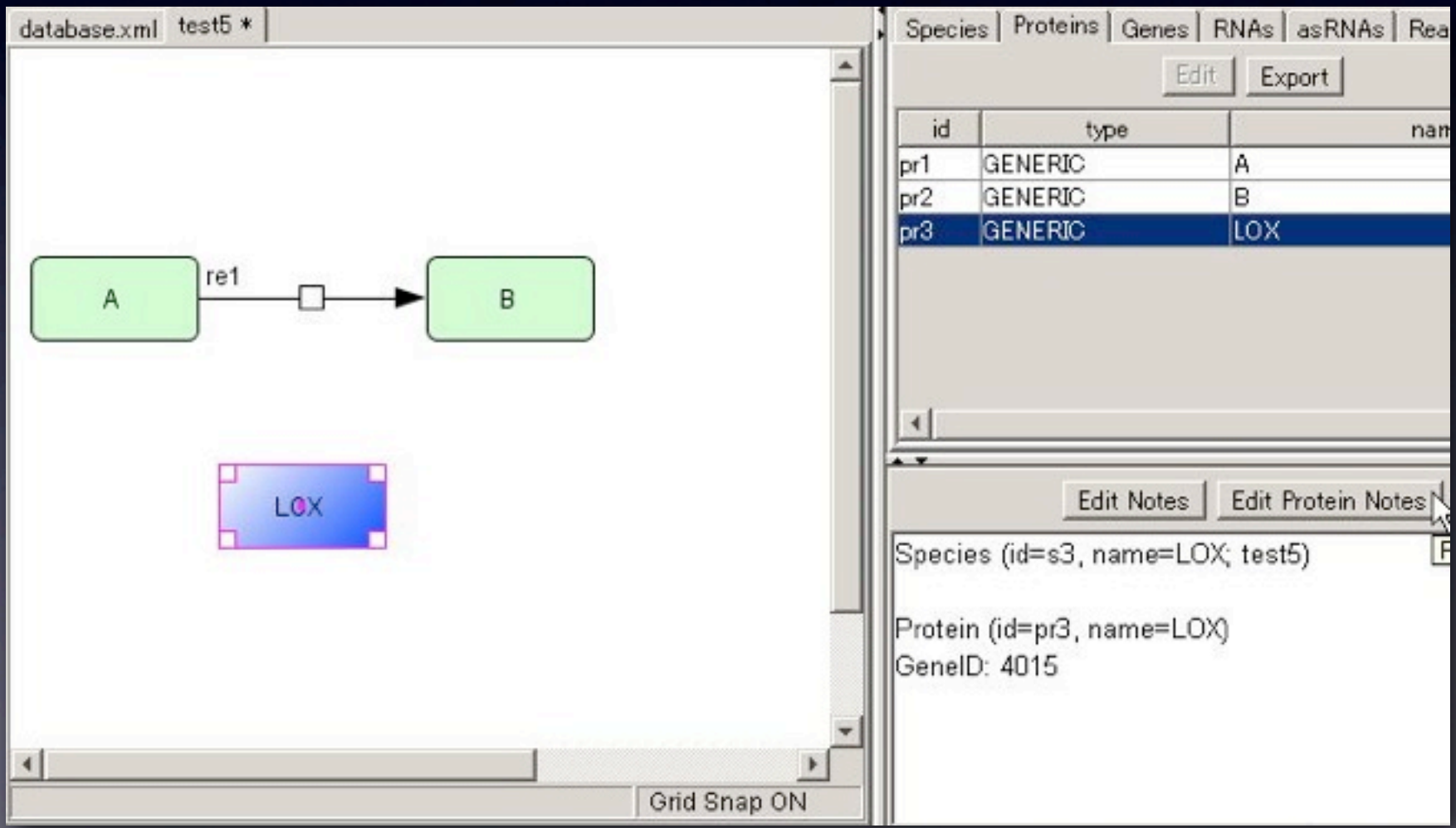
- Search Database from CellDesigner




http://www.sbgn.org/Documents/PD_L1_Examples

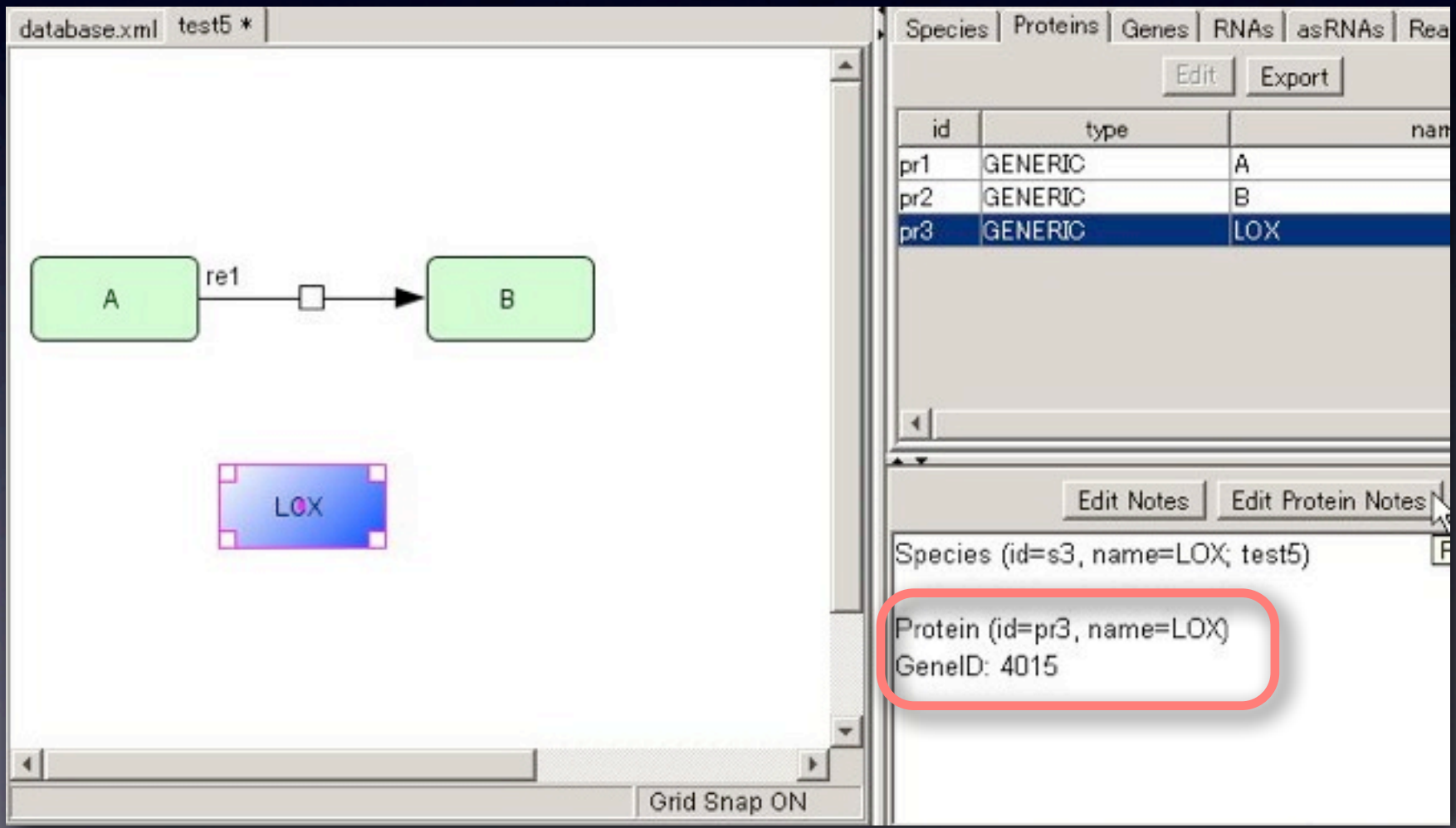
# Database Connection

- Search Database by Notes:
  - PubMed: PMID: 123456
  - Entrez Gene: GeneID: 4015



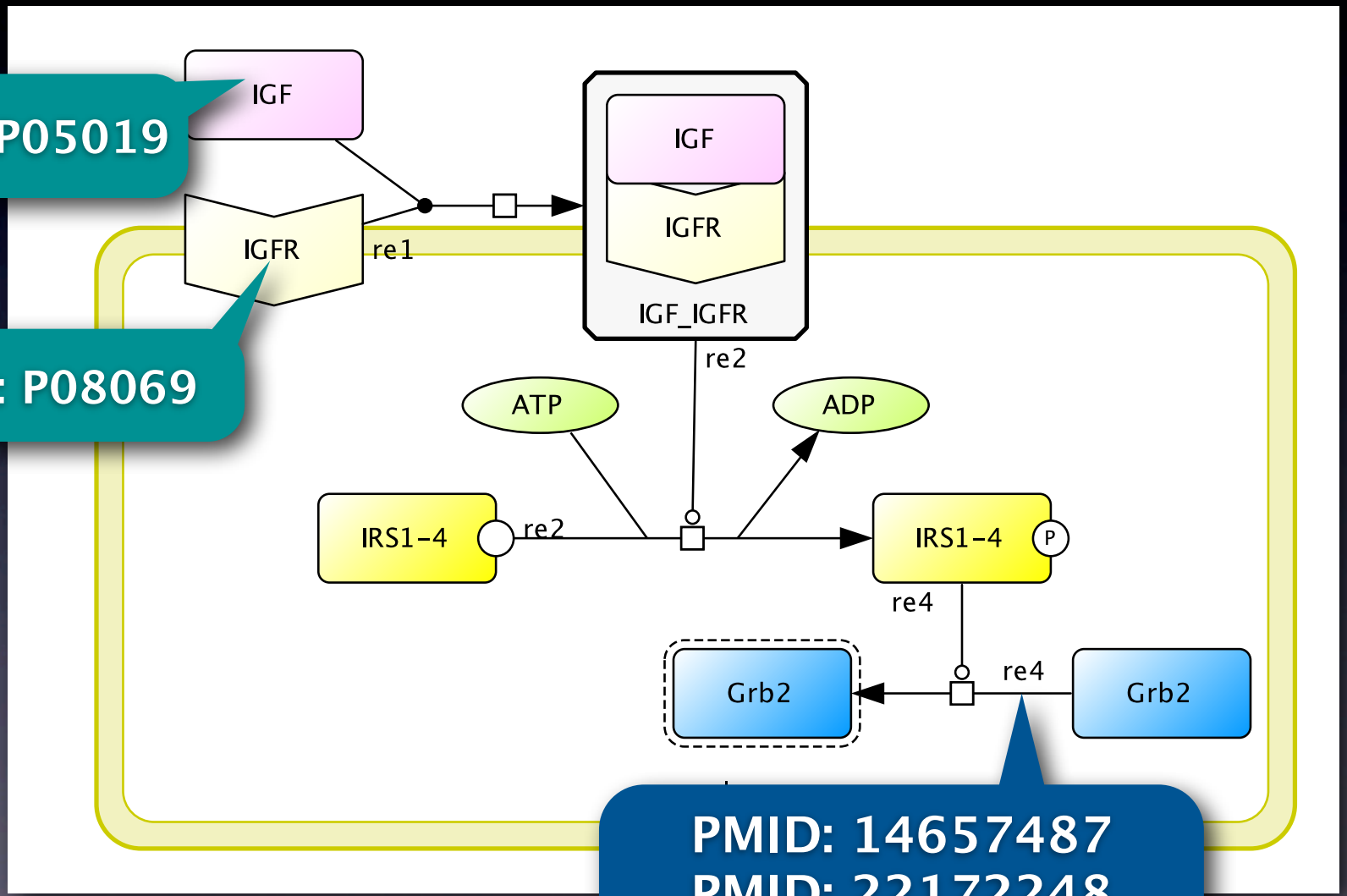
# Database Connection

- Search Database by Notes:
  - PubMed: PMID: 123456
  - Entrez Gene: GeneID: 4015



# Exercise

- Add UniProt ID for Proteins, PubMed ID for reactions and call “Connect to UniProt”




UniProt: P05019

UniProt: P08069

PMID: 14657487
PMID: 22172248

# MIRIAM annotation

_computational BIOLOGY

PERSPECTIVE

## Minimum information requested in the annotation of biochemical models (MIRIAM)

Nicolas Le Novère[1,15], Andrew Finney[2,15], Michael Hucka[3], Upinder S Bhalla[4], Fabien Campagne[5], Julio Collado-Vides[6], Edmund J Crampin[7], Matt Halstead[7], Edda Klipp[8], Pedro Mendes[9], Poul Nielsen[7], Herbert Sauro[10], Bruce Shapiro[11], Jacky L Snoep[12], Hugh D Spence[13] & Barry L Wanner[14]



**Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main causes for incomplete model descriptions. With today's increased interest in detailed biochemical models, it is necessary to define a minimum quality standard for the encoding of those models. We propose a set of rules for curating quantitative models of biological systems. These rules define procedures for encoding and annotating models represented in machine-readable form. We believe their application will enable users to (i) have confidence that curated models are an accurate reflection of their associated reference descriptions, (ii) search collections of curated models with precision, (iii) quickly identify the biological phenomena that a given curated model or model constituent represents and (iv) facilitate model reuse and composition into large subcellular models.**

[1]European Bioinformatics Institute, Hinxton, CB10 1SD, UK. [2]Physiomics PLC, Magdalen Centre, Oxford Science Park, Oxford, OX4 4GA,K. [3]Control and Dynamical Systems, California Institute of Technology,Pasadena, California 91125, USA. [4]National Centre for Biological Sciences, TIFR, UAS-GKVK Campus, Bangalore 560065, India. [5]Institute for Computational Biomedicine, Weill Medical College of Cornell University, New York, New York 10021, USA. [6]Center for Genomic Sciences, Universidad Nacional Autónoma de México, Av. Universidad s/n, Cuernavaca, Morelos, 62100, Mexico. [7]Bioengineering Institute and Department of Engineering Science, The University of Auckland, Private Bag 92019, Auckland, New Zealand. [8]Max-Planck Institute for Molecular Genetics, Berlin Center for Genome based Bioinformatics (BCB), Ihnestr. 73, 14195 Berlin, Germany. [9]Virginia Bioinformatics Institute, Virginia Tech, Washington St., Blacksburg, Virginia 24061-0477, USA. [10]Keck Graduate Institute, 535 Watson Drive, Claremont, California 91711, USA. [11]Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California 91109, USA. [12]Triple-J Group for Molecular Cell Physiology, Department of Biochemistry, Stellenbosch University, Private Bag X1, Matieland 7602, South Africa. [13]Department of Scientific Computing & Mathematical Modeling, GlaxoSmithKline Research & Development Limited, Medicines Research Centre, Gunmels Wood Road, Stevenage, Herts, SG1 2NY, UK. [14]Purdue University, Department of Biological Sciences, Lilly Hall of Life Sciences, 915 W. State Street, West Lafayette, Indiana 47907-2054, USA. [15]These authors have contributed equally to the work. Correspondence should be addressed to N.L.N. (e-mail: lenov@ebi.ac.uk).

Published online 6 December 2005; doi:10.1038/nbt1156

During the genomic era we have witnessed a vast increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their dynamics. One of the tenets of systems biology is the use of quantitative models (see **Box 1** for definitions) as a mechanism for capturing precise hypotheses and making predictions[1,2]. Many specialized models exist that attempt to explain aspects of the cellular machinery. However, as has happened with other types of biological information, such as sequences, macromolecular structures or

**Box 1 Glossary**

Some terms are used in a very specific way throughout the article. We provide here a precise definition of each one.

**Quantitative biochemical model.** A formal model of a biological system, based on the mathematical description of its molecular and cellular components, and the interactions between those components.

**Encoded model.** A mathematical model written in a formal machine-readable language, such that it can be systematically parsed and employed by simulation and analysis software without further human translation.

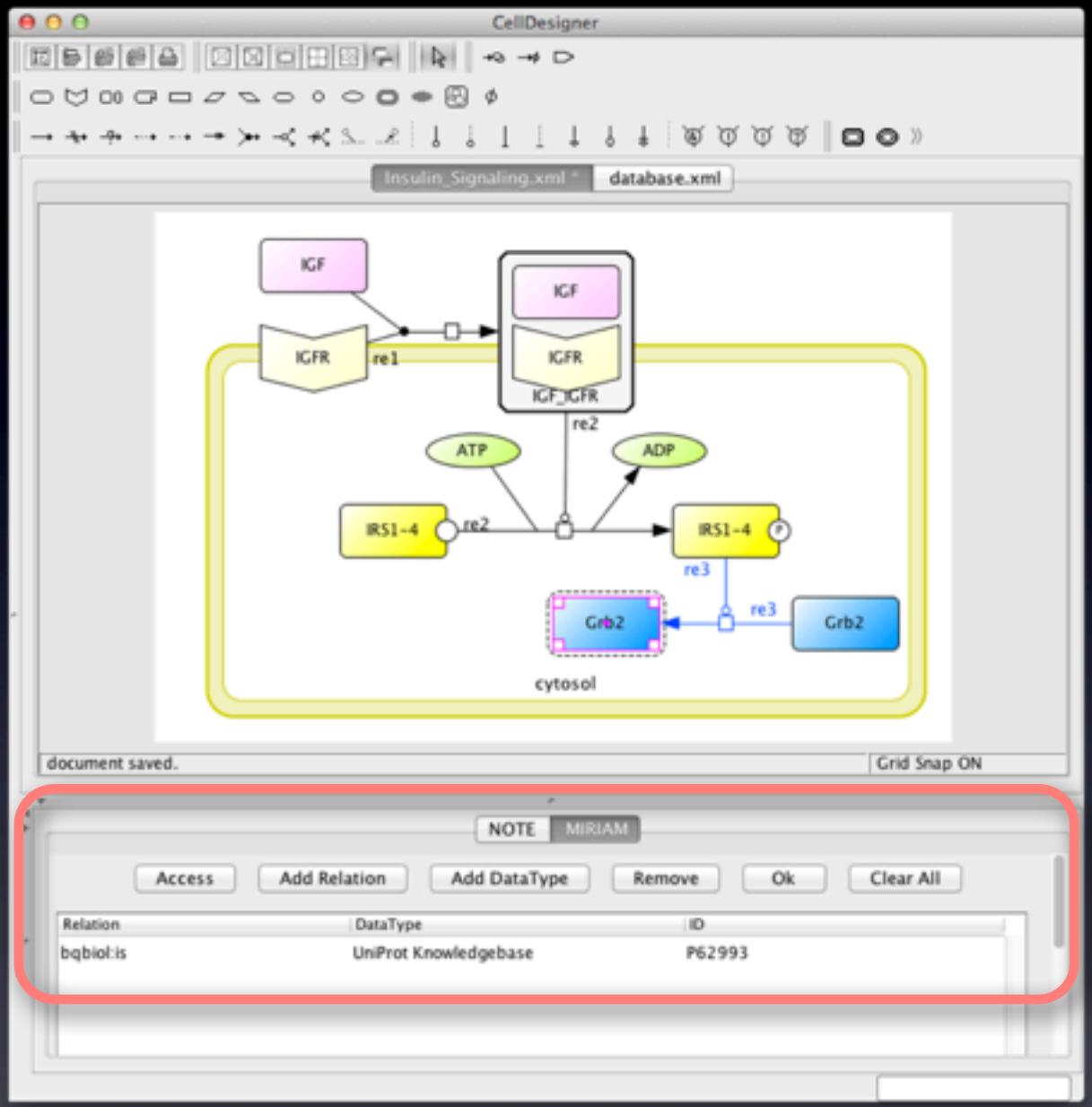
**MIRIAM-compliant model.** A model that passes all the tests and fulfills all the conditions listed in MIRIAM.

**Reference description.** A unique document that describes, or references the description of the model, the structure of the model, the numerical values necessary to instantiate a simulation from the model, or to perform a mathematical analysis of the model, and the results one expects from such a simulation or analysis.

**Curation process.** The process by which the compliance of an encoded model with MIRIAM is achieved and/or verified. The curation process may encompass some or all of the following tasks: encoding of the model, verification of the reference correspondence and annotation of the model.

**Reference correspondence.** The fact that the structure of a model and the results of a simulation or an analysis match the information present in the reference description.

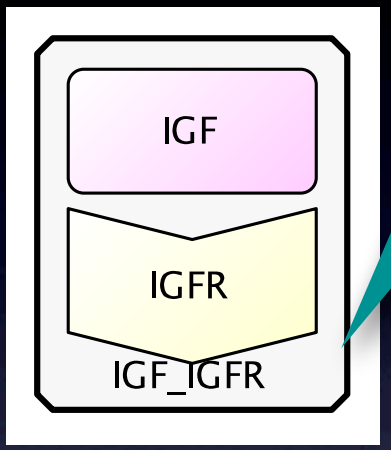




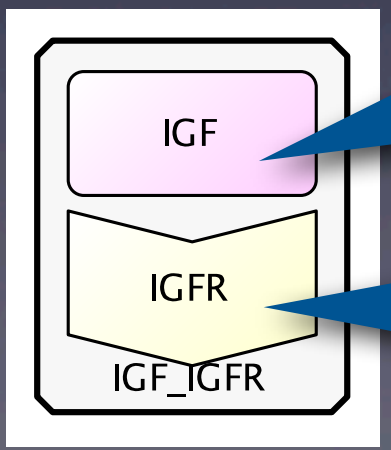

**Minimum information requested in the annotation of biochemical models (MIRIAM)**
Nature Biotechnology 23, 1509 – 1515 (2005)

# MIRIAM annotation

- http://www.ebi.ac.uk/miriam/main/qualifiers/
  - is
  - hasPart
  - isPartOf
  - hasVersion (isoform)
  - isVersionOf (superclass, parent)




IGF_IGFR hasPart: IGF
IGF_IGFR hasPart: IGFR

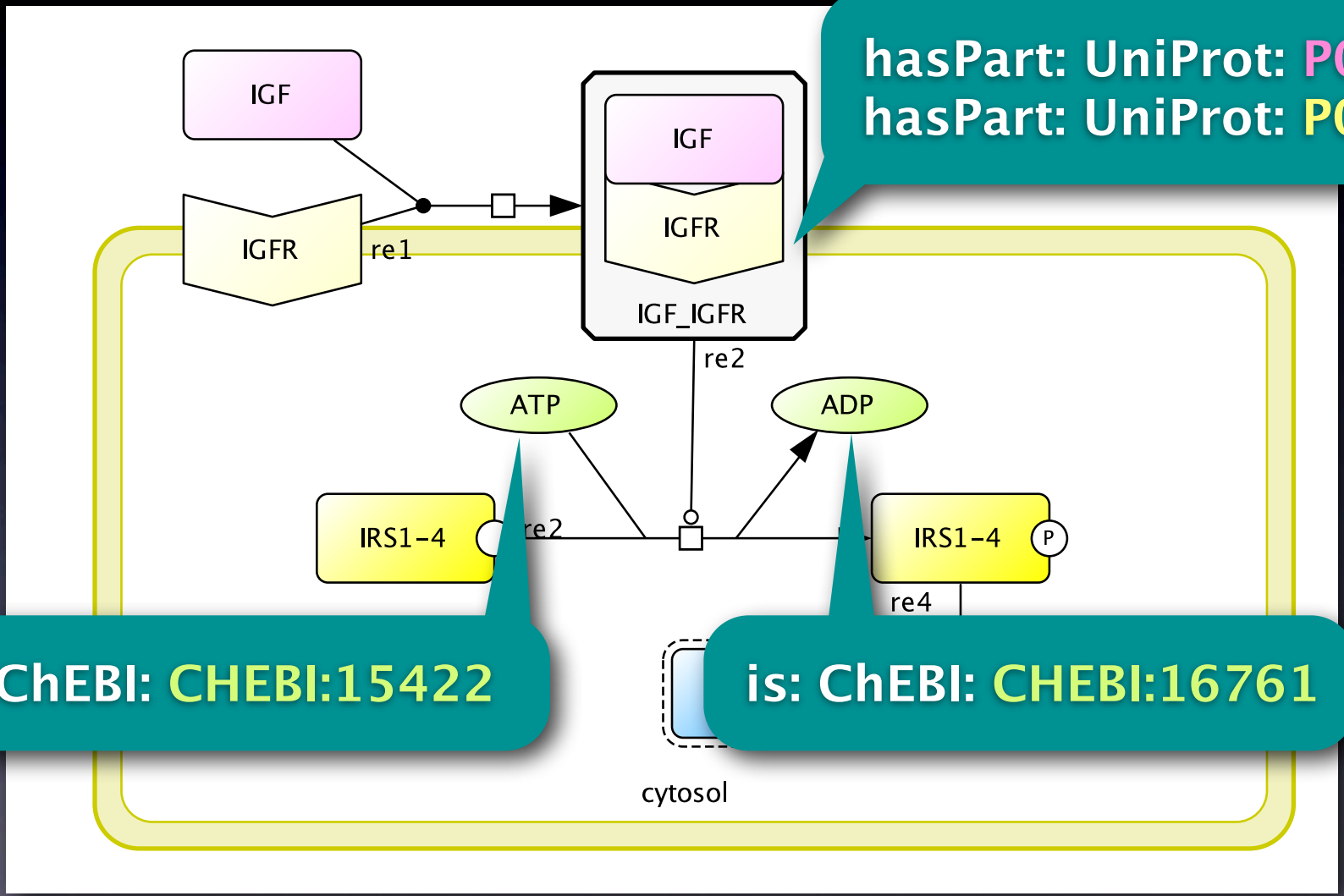



IGF isPartOf: IGF_IGFR

IGFR isPartOf: IGF_IGFR

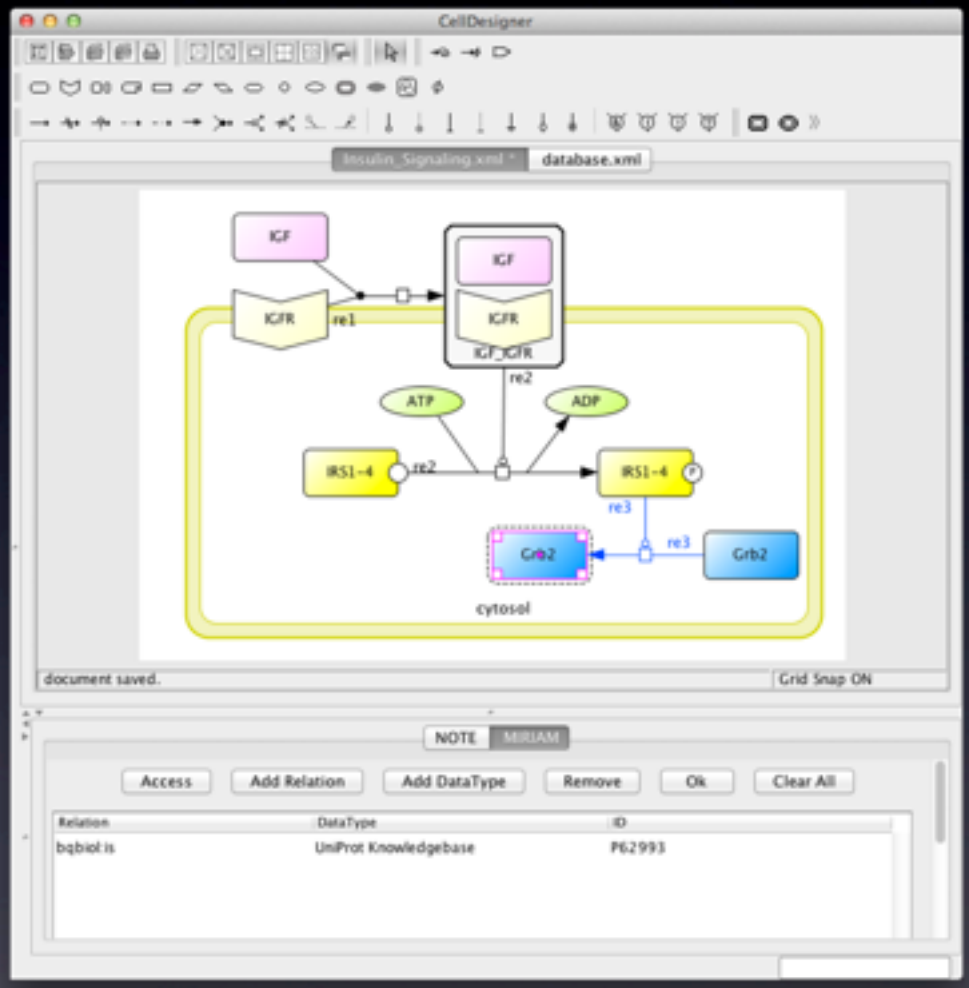
# Exercise

- Add MIRIAM annotation



# Notes or MIRIAM?

- CellDesigner Notes
  - Easy to add (text)
- MIRIAM
  - Tool neutral (SBML)
  - Precise annotation



# Summary

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