Path2Models

Large-scale harnessing of pathway knowledge to provide pump-priming models for all

http://arxiv.org/abs/1307.7005

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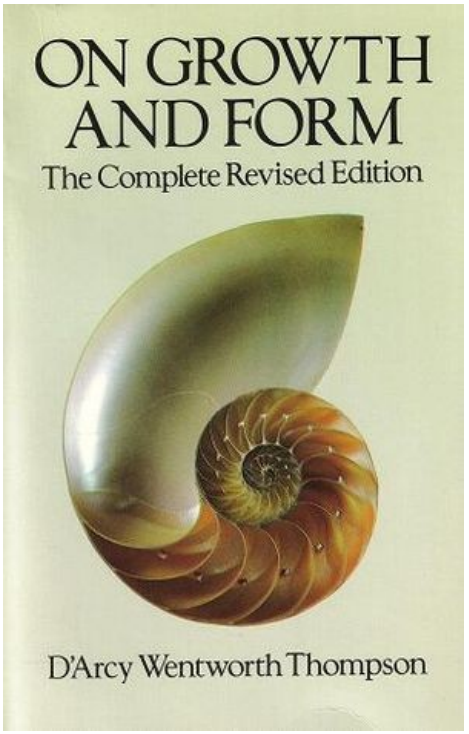
Babraham Institute

Why using mathematical models?

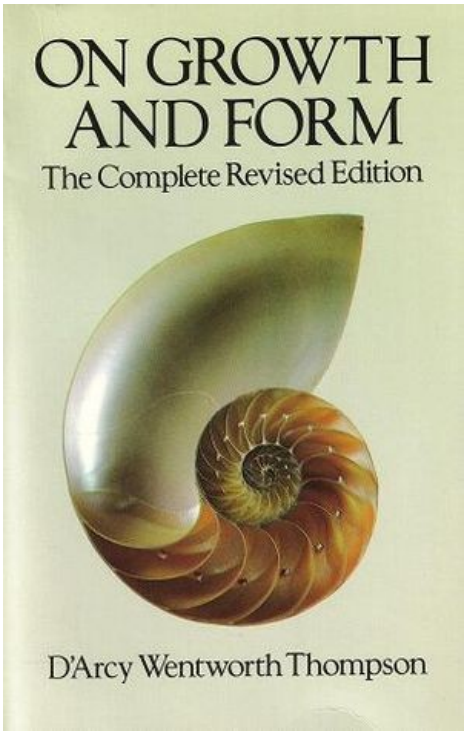
Describe

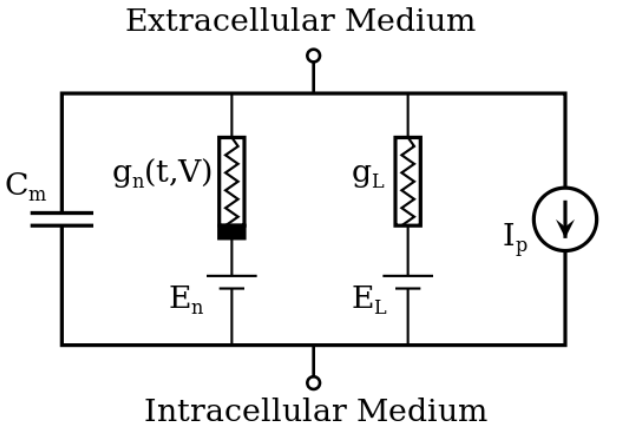


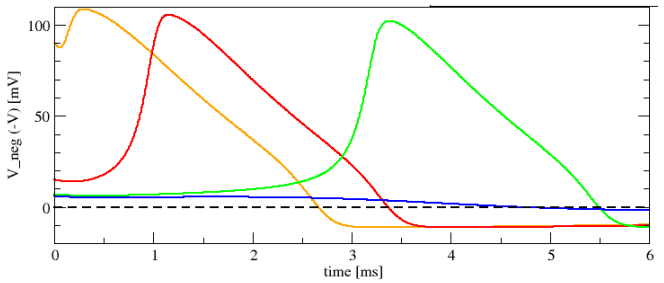
1917

Why using mathematical models?

Describe	Explain





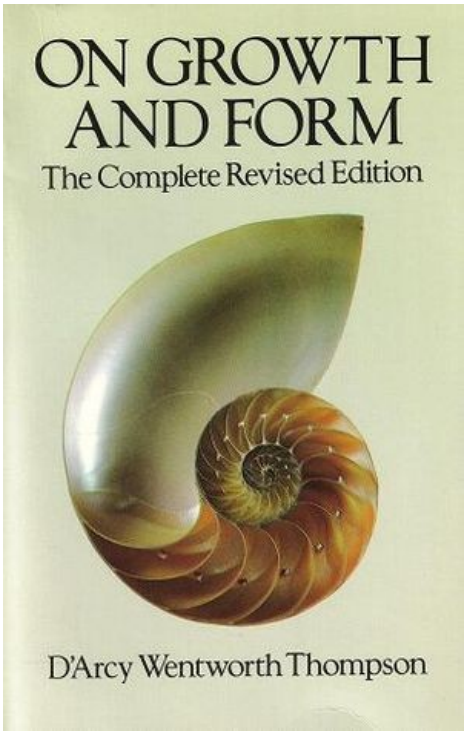


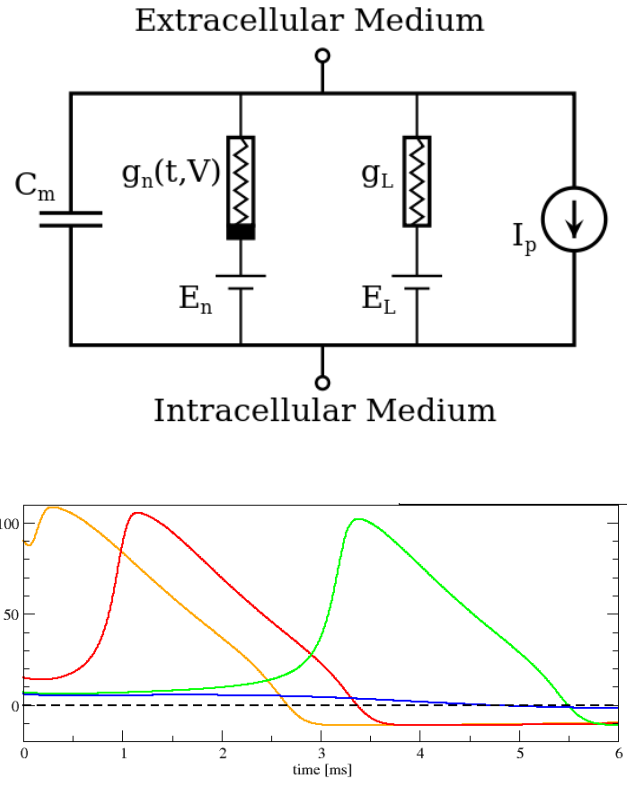
1917

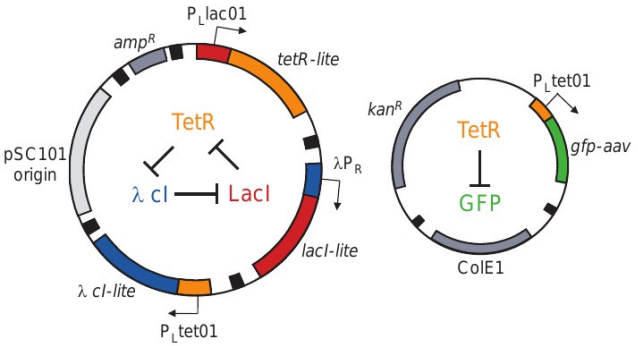
1952

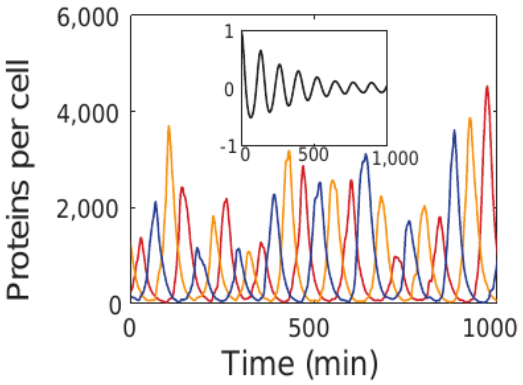
Why using mathematical models?

Describe	Explain	Predict









1917 1952 2000

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

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variables
[x]
Vmax
Kd
EC_{50}
length
$t_{1/2}$

What we want to know or compare with experiments

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

variables
[x]
Vmax
Kd
EC_{50}
length
$t_{1/2}$

relationships

$$K_d = \frac{[A] \cdot [B]}{[AB]}$$

$$d[X]/dt = k \cdot [Y]^2$$

$$\sum_i [X]_i - F(t) = 0$$

$$k(t) \sim N(k, \sigma^2)$$

If $\text{mass}_t > \text{threshold}$
then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$

What we already know or want to test

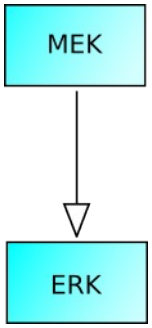
What is a mathematical model?

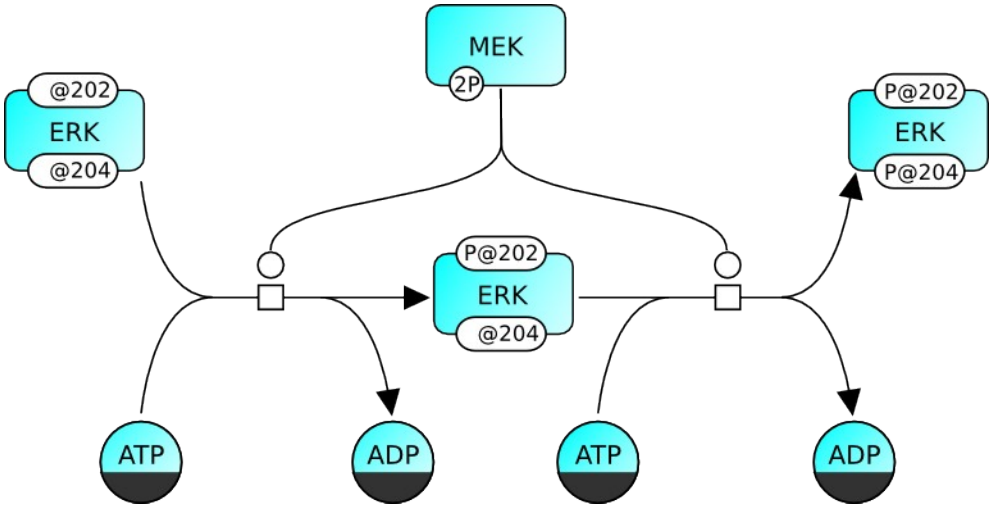
Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

variables	relationships	constraints
[x]	$K_d = \frac{[A] \cdot [B]}{[AB]}$	[x]>0
Vmax	$d[X]/dt = k \cdot [Y]^2$	Energy conservation
Kd	$\sum_i [X]_i - F(t) = 0$	Boundary conditions (v < upper limit)
EC_{50}	$k(t) \sim N(k, \sigma^2)$	Objective functions (maximise ATP)
length	If $\text{mass}_t > \text{threshold}$ then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$	Initial conditions
$t_{1/2}$		

The context or what we want to ignore

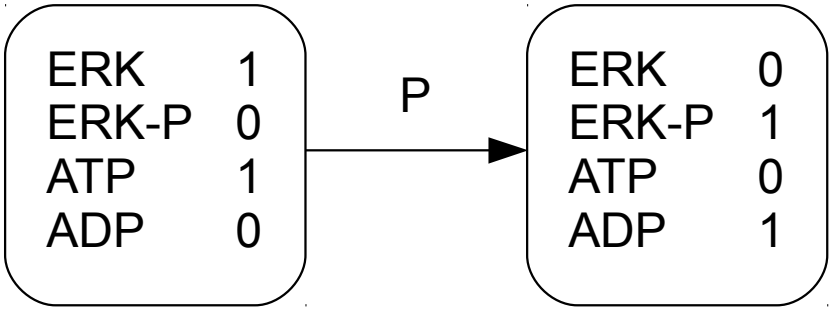
Many levels of “modelling”

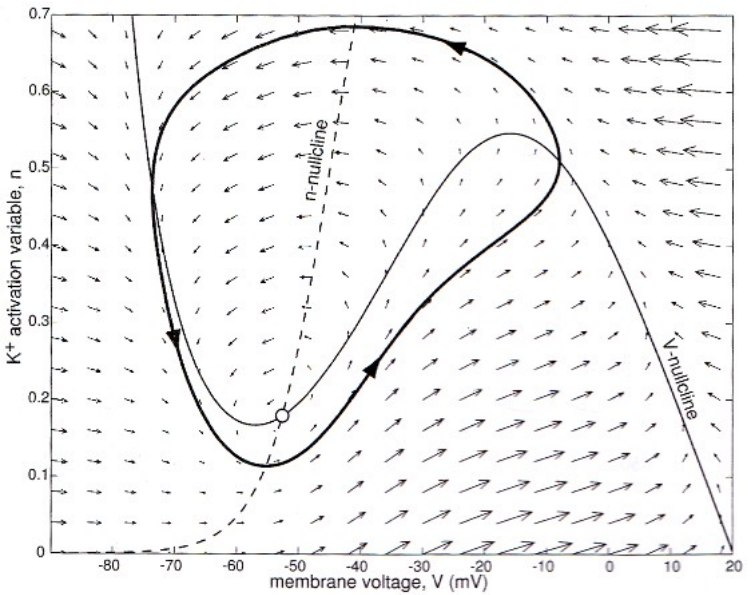




1 ERK + 1 ATP → 1 ERK-P + 1 ADP

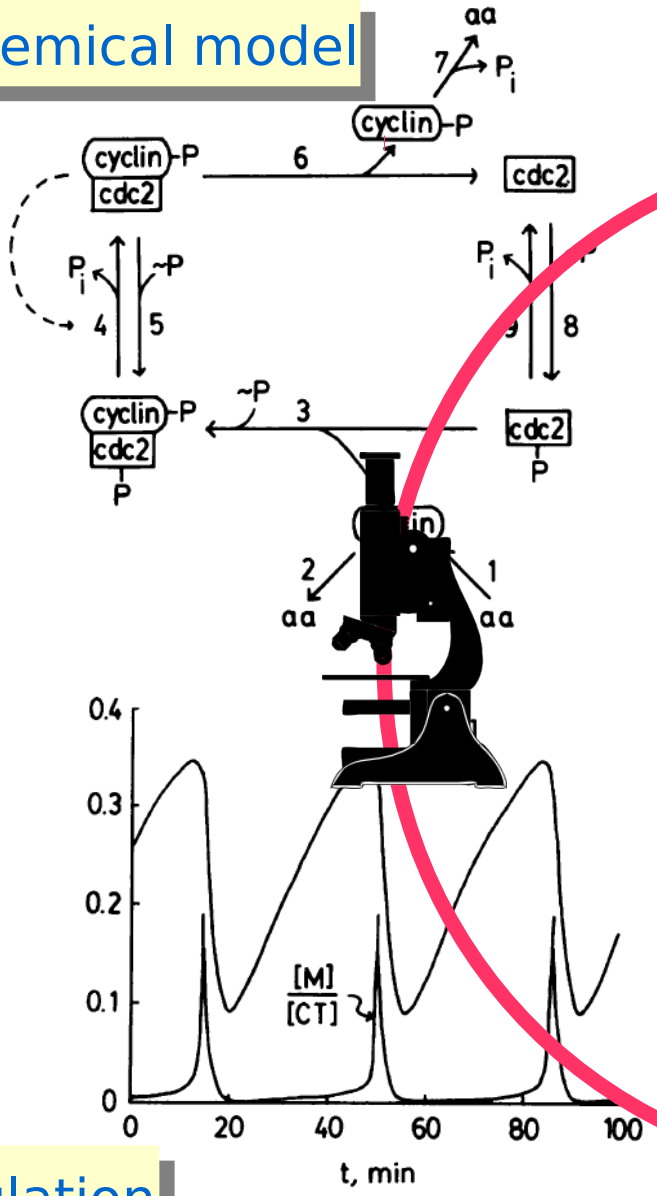
$$\frac{d[ERK-P]}{dt} = V_{\max}\frac{[ERK]}{K_m + [ERK]}$$





The models I am talking about

biochemical model



mathematical model

$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
$$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$$
$$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$$
$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
$$d[YP]/dt = k_6[M] - k_7[YP]$$

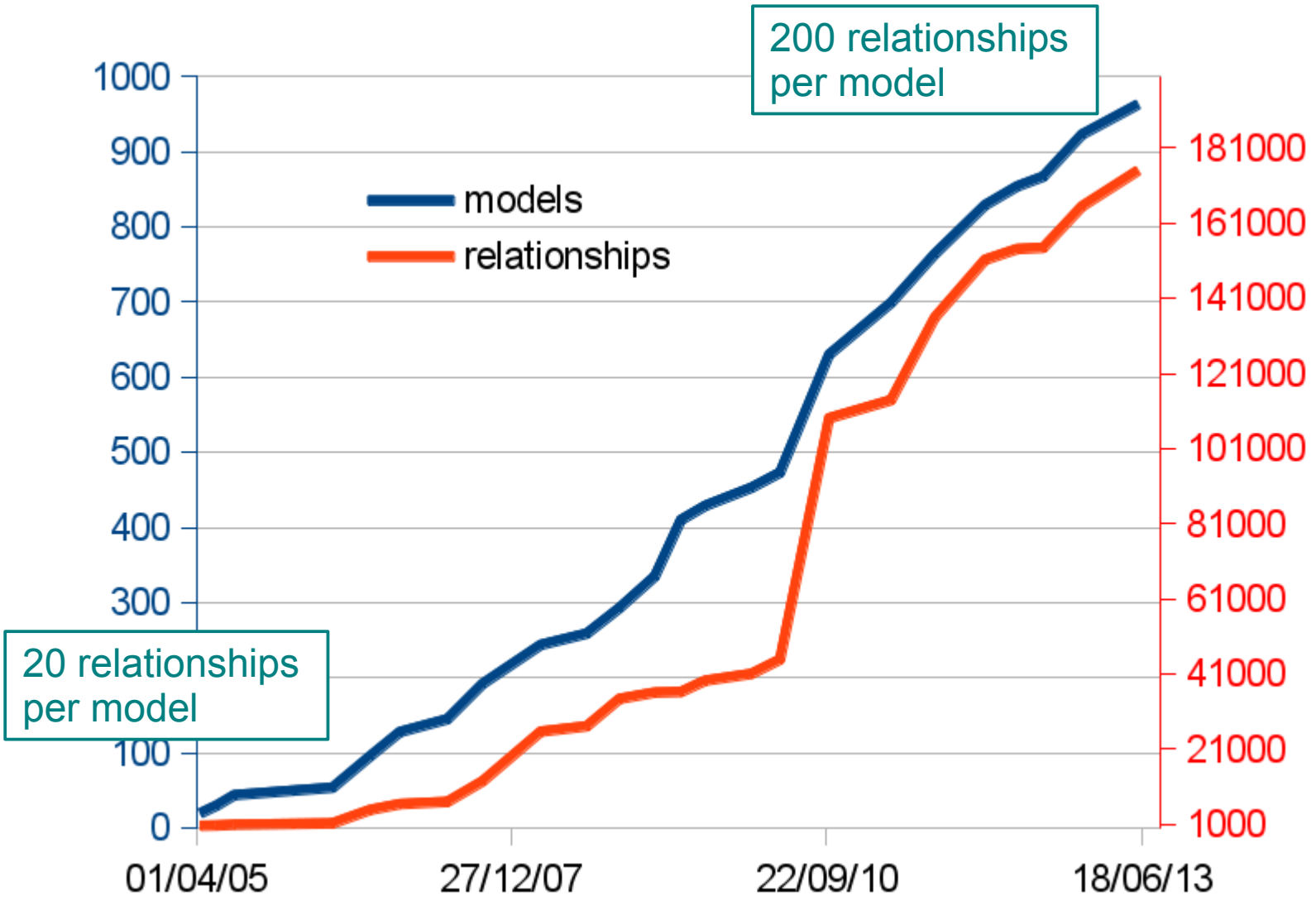
Parameter	Value	Notes
$k_1[aa]/[CT]$	0.015 min^{-1}	*
k_2	0	†
$k_3[CT]$	200 min^{-1}	*
k_4	10–1000 min^{-1} (adjustable)	
k_4'	0.018 min^{-1}	
$k_5[\sim P]$	0	‡
k_6	0.1–10 min^{-1} (adjustable)	
k_7	0.6 min^{-1}	†
$k_8[\sim P]$	$>> k_9$	§
k_9	$> k_6$	§

simulation

computational model

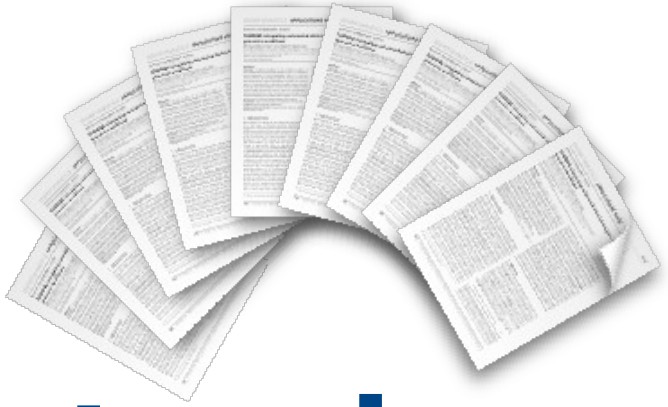
Tyson et al (1991) PNAS 88(1):7328-32

Computational models on the rise



BioModels Database growth (published models branch) since its creation

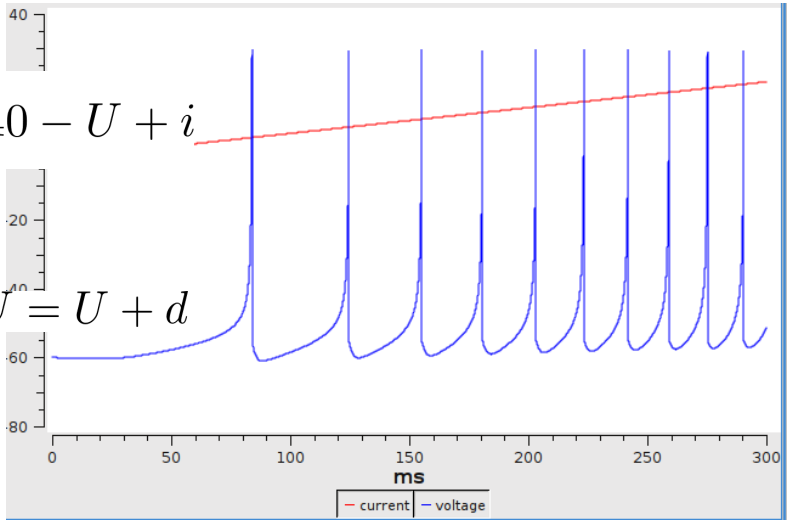
Knowledge-based model creation

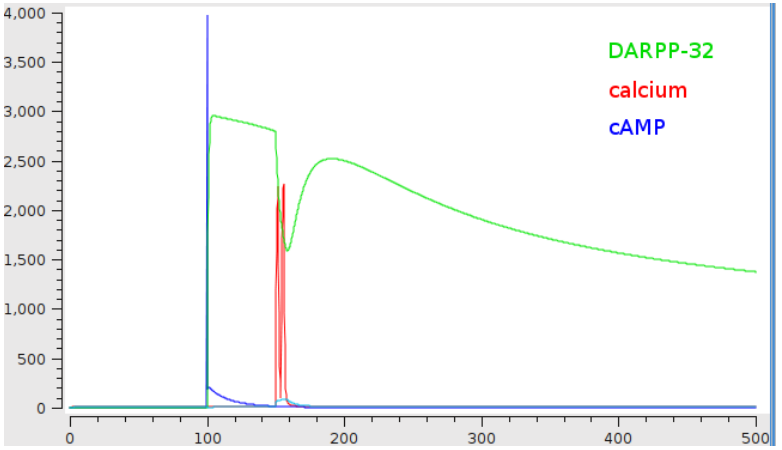


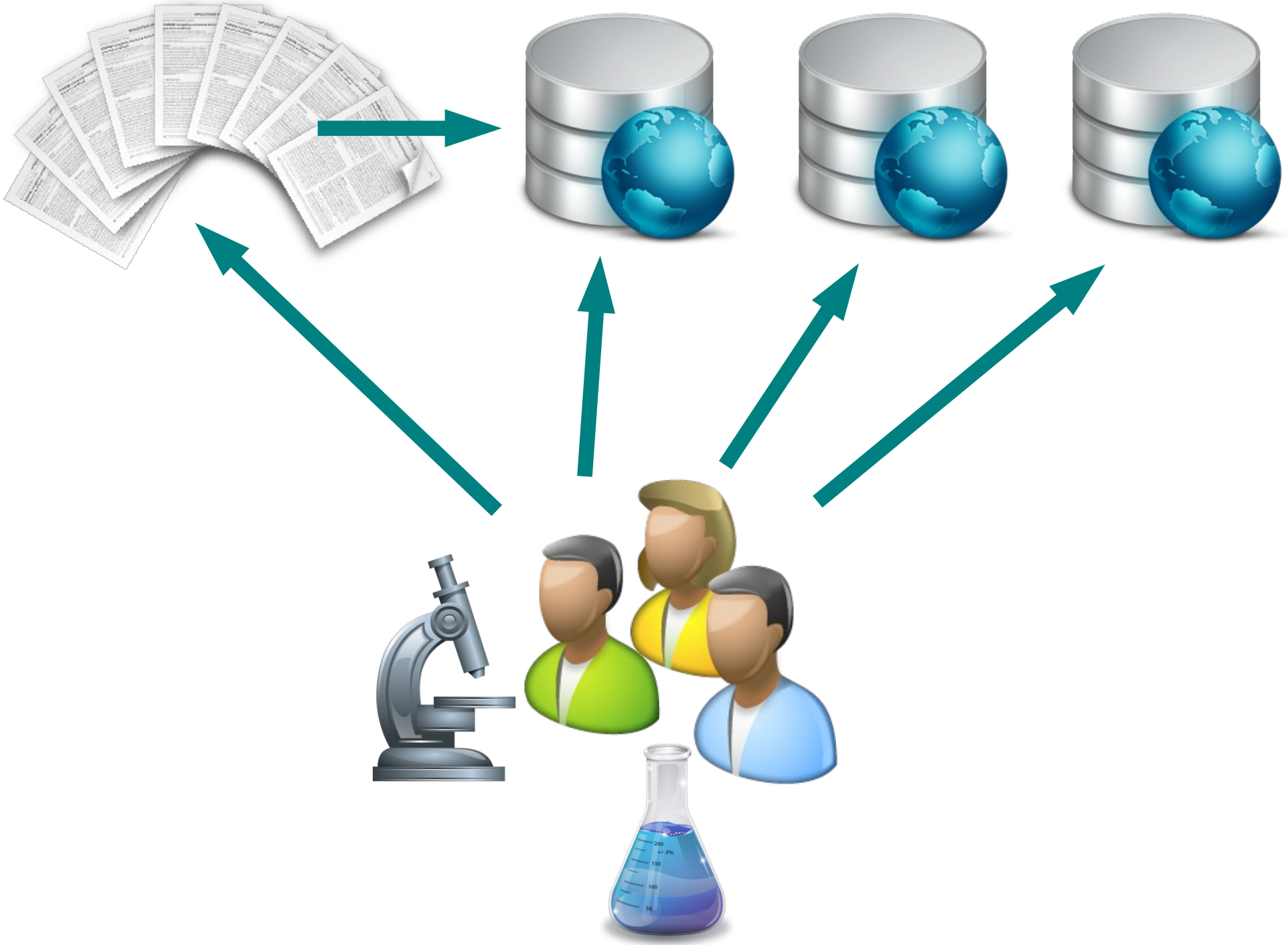
$$\frac{dv}{dt} = 0.04v^2 + 5v + 140 - U + i$$

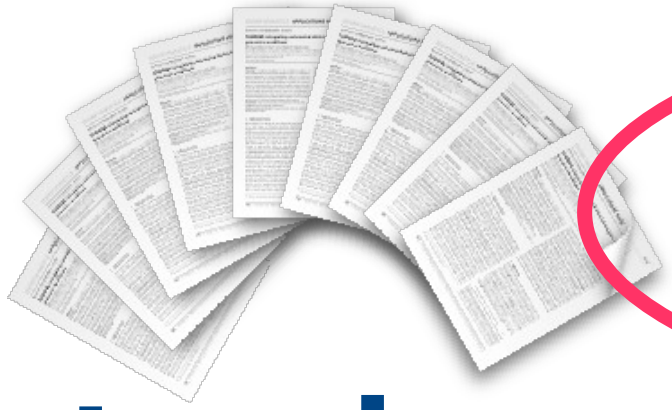
$$\frac{dU}{dt} = a(bv - U)$$

$$v > V_{\text{thresh}} \Rightarrow v = c; U = U + d$$









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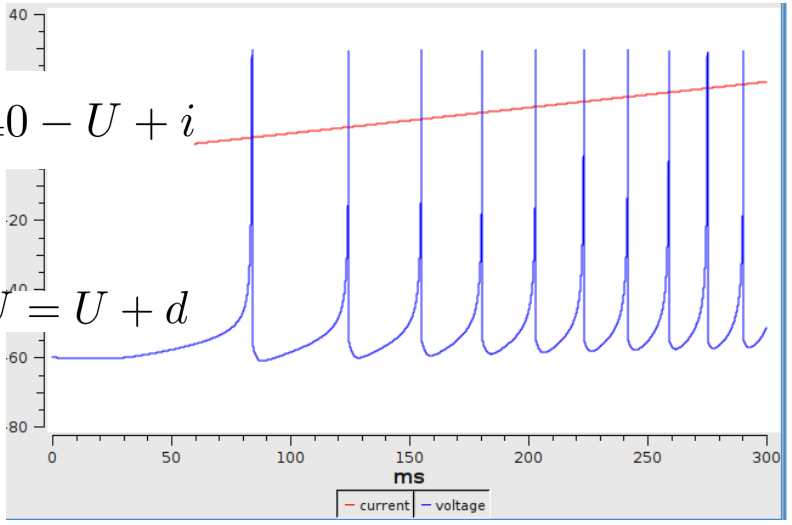

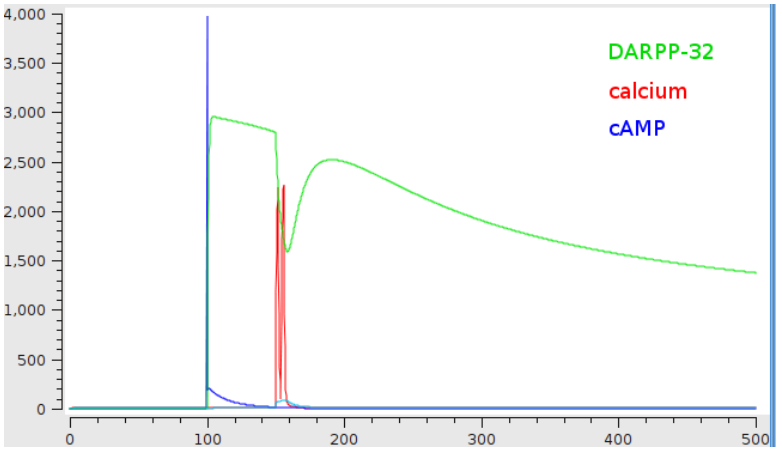

EMBL-EBI Services Research

Training

I want my pathways from KEGG (Kyoto Encyclopedia of Genes and Genomes)

Training Home | Train at EBI | Train outside EBI | Public events | Train Online | Abo

Joint EMBL-EBI-Wellcome Trust Course: In Silico Systems Biology

Venue:
European Bioinformatics Institute, Cambridge, CB10 1SD
United Kingdom
See map: Google Maps
Date: Tuesday, June 25, 2013 - Saturday, June 29, 2013
Organizers:
Laura Emery , EMBL-EBI, UK
Julio Saez-Rodriguez , EMBL-EBI
Nicolas Le Novère , EMBL-EBI
Admin support:
Wellcome Trust Advanced Courses , Wellcome Trust Advanced Courses, UK
Registration Opens Date: Thursday, August 23, 2012
Registration Deadline: Friday, March 8, 2013
Participation: Open application with selection

Overview | Programme | Registration | Trainers |

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Starting on July 1, 2011 the KEGG FTP site for academic users will be transferred from GenomeNet at Kyoto University to NPO Bioinformatics Japan, and it will be available only to paid subscribers. The publicly funded portion, the medicus directory, will continue to be freely accessible at GenomeNet. The KEGG FTP site for commercial customers managed by Pathway Solutions will remain unchanged. The new FTP site is available for free trial until the end of June.

Please register to learn more about the KEGG FTP subscription.

Thank you!

Minoru Kanehisa

EMBL-EBI Services Research

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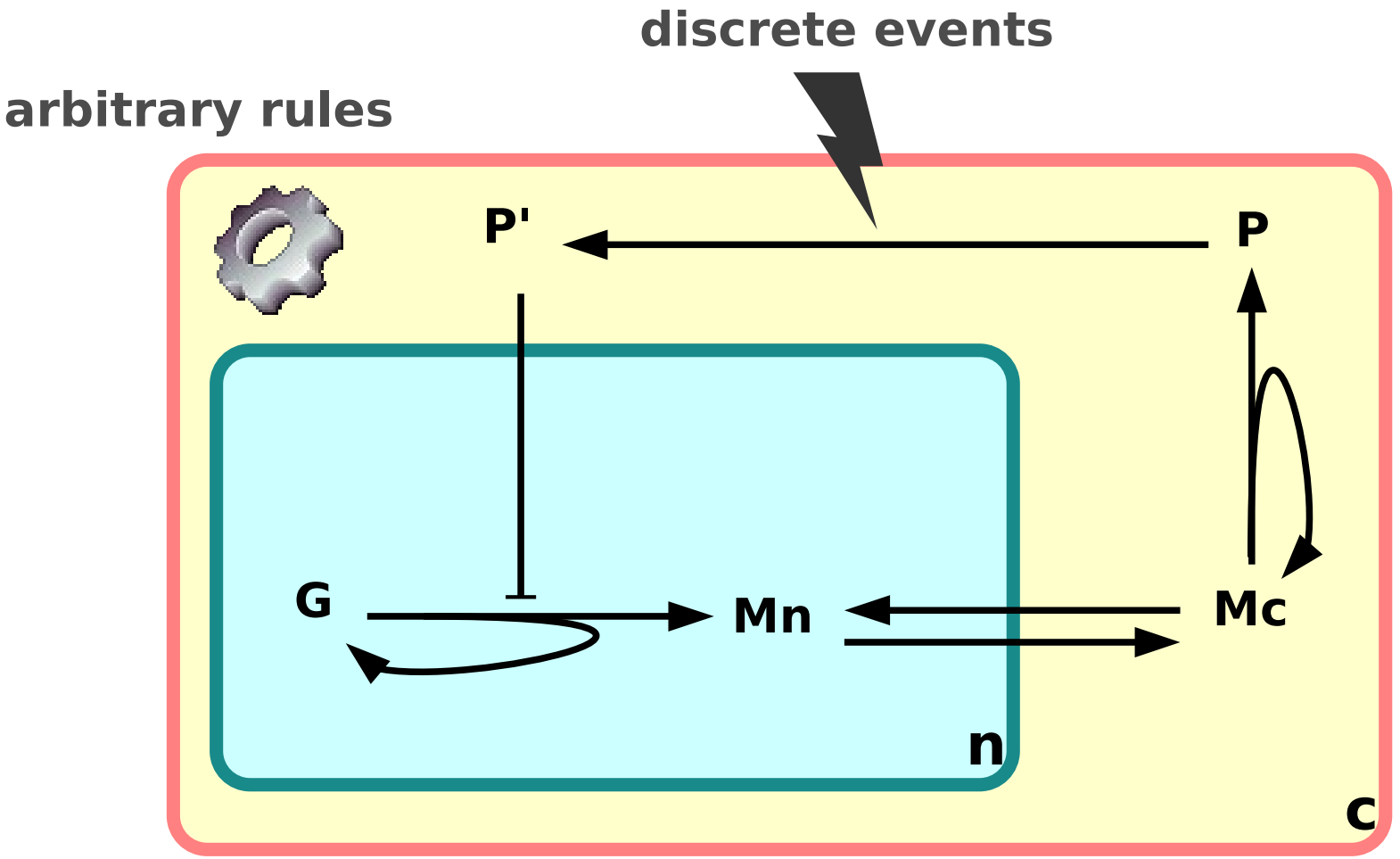
Registration Opens Date: Thurs
Registration Deadline: Friday, M
Participation: Open application wit

Overview | Progra | gistrat | Trainers |

I want my pathways from KEGG

I want my pathways in SBML

Systems Biology Markup Language



Hucka *et al*. The Systems Biology Markup Language (SBML): A Medium for Representation and Exchange of Biochemical Network Models. *Bioinformatics* (2003), 19: 524-531.

Systems Biology Markup Language

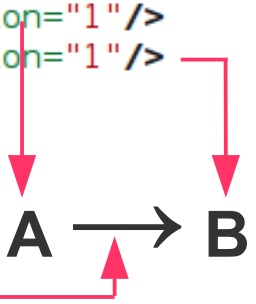
```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="3" version="1"·
      xmlns="http://www.sbml.org/sbml/level3/version1/core">
  <model>
    <listOfFunctionDefinitions> <!-- --> </listOfFunctionDefinitions>
    <listOfUnitDefinitions> <!-- --> </listOfUnitDefinitions>
    <listOfCompartments> <!-- --> </listOfCompartments>
    <listOfSpecies> <!-- --> </listOfSpecies>
    <listOfParameters> <!-- --> </listOfParameters>
    <listOfInitialAssignments> <!-- --> </listOfInitialAssignments>
    <listOfRules> <!-- --> </listOfRules>
    <listOfConstraints> <!-- --> </listOfConstraints>
    <listOfReactions> <!-- --> </listOfReactions>
    <listOfEvents> <!-- --> </listOfEvents>
  </model>
</sbml>
```

variables

relationships

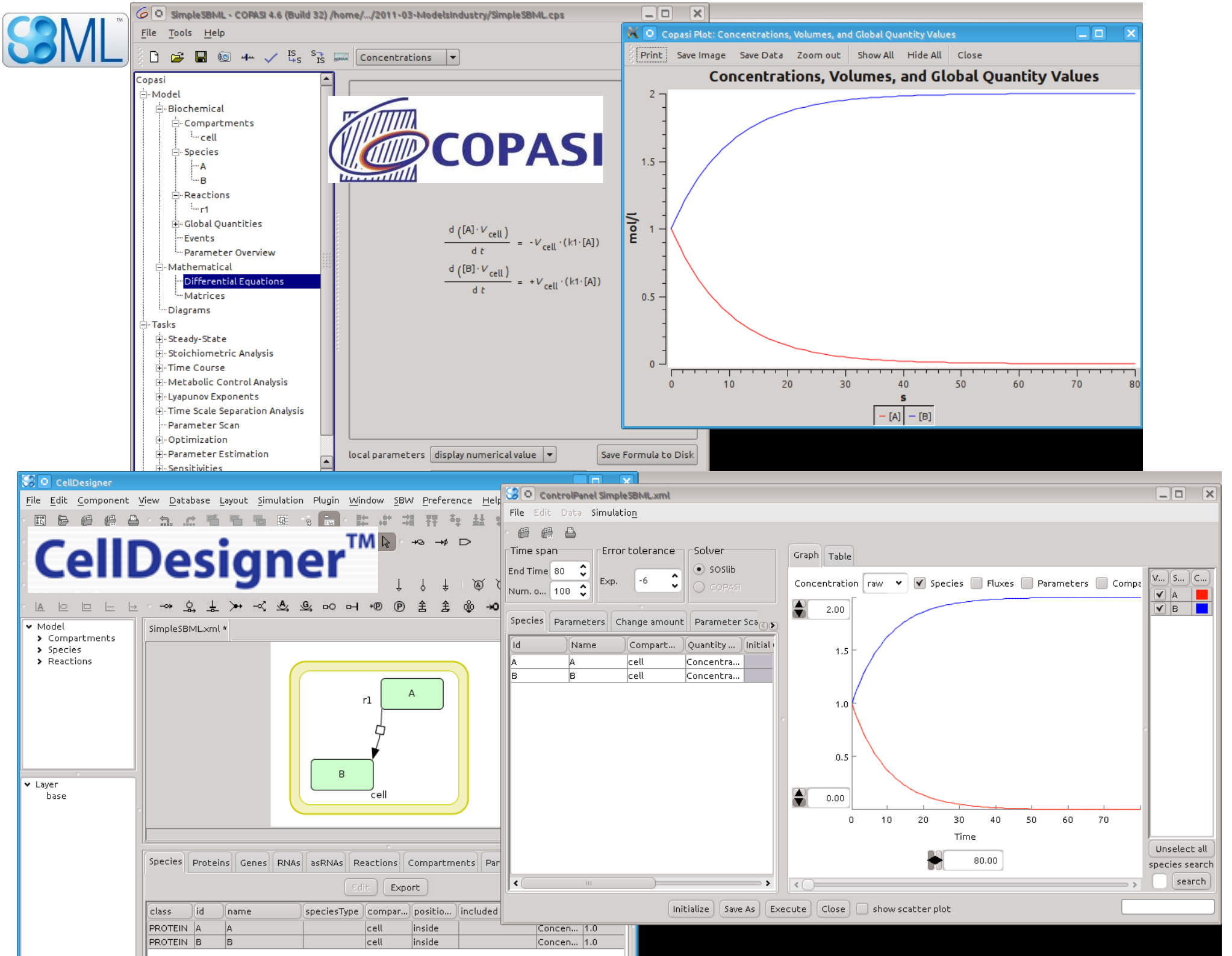
Systems Biology Markup Language

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
  <model name="Simple Model">
    <listOfCompartments>
      <compartment id="cell" size="1" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="1"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="k1" value="0.1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction id="r1" reversible="false">
      <listOfReactants>
          <speciesReference species="A"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci> cell </ci>
              <ci> k1 </ci>
              <ci> A </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```



$$v1 = k1 \times [A] \times V_{cell}$$

A very simple SBML file


SBML
SimpleSBML - COPASI 4.6 (Build 32) /home/.../2011-03-ModelsIndustry/SimpleSBML.cps
File Tools Help
Concentrations
Copasi
Model
Biochemical
Compartments
cell
Species
A
B
Reactions
r1
Global Quantities
Events
Parameter Overview
Mathematical
Differential Equations
Matrices
Diagrams
Tasks
Steady-State
Stoichiometric Analysis
Time Course
Metabolic Control Analysis
Lyapunov Exponents
Time Scale Separation Analysis
Parameter Scan
Optimization
Parameter Estimation
Sensitivities
COPASI
d([A]·V_cell)/dt = -V_cell·(k1·[A])
d([B]·V_cell)/dt = +V_cell·(k1·[A])
local parameters
display numerical value
Save Formula to Disk
Copasi Plot: Concentrations, Volumes, and Global Quantity Values
Print Save Image Save Data Zoom out Show All Hide All Close
Concentrations, Volumes, and Global Quantity Values
mol/l
s
[A] [B]
CellDesigner
File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help
CellDesigner™
Model
Compartments
Species
Reactions
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cell
Species Proteins Genes RNAs asRNAs Reactions Compartments
Edit Export
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PROTEIN B B cell inside Concen... 1.0
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End Time 80
Num. o... 100
Error tolerance
Exp. -6
Solver
SOSlib
COPASI
Species Parameters Change amount Parameter Sca
Id Name Compart... Quantity ... Initial
A A cell Concentra...
B B cell Concentra...
Graph Table
Concentration raw
Species Fluxes Parameters Compa
2.00
0.00
Time
80.00
V... S... C...
A
B
Unselect all
species search
search
Initialize Save As Execute Close show scatter plot

A community-driven global reconstruction of human metabolism

Ines Thiele[1,2,37], Neil Swainston[3,4,37], Ronan M T Fleming[1,5], Andreas Hoppe[6], Swagatika Sahoo[1], Maike K Aurich[1], Hulda Haraldsdottir[1], Monica L Mo[7], Ottar Rolfsson[1], Miranda D Stobbe[8,9], Stefan G Thorleifsson[1], Rasmus Agren[10], Christian Bölling[6], Sergio Bordel[10], Arvind K Chavali[11], Paul Dobson[12], Warwick B Dunn[3,13], Lukas Endler[14], David Hala[15], Michael Hucka[16], Duncan Hull[4], Daniel Jameson[3,4], Neema Jamshidi[7], Jon J Jonsson[5], Nick Juty[17], Sarah Keating[17], Intawat Nookaew[10], Nicolas Le Novère[17,18], Naglis Malys[3,19,20], Alexander Mazein[21], Jason A Papin[11], Nathan D Price[22], Evgeni Selkov, Sr[23], Martin I Sigurdsson[1], Evangelos Simeonidis[22,24], Nikolaus Sonnenschein[25], Kieran Smallbone[3,26], Anatoly Sorokin[21,27], Johannes H G M van Beek[28–30], Dieter Weichart[3,31], Igor Goryanin[21,32], Jens Nielsen[10], Hans V Westerhoff[3,28,33,34], Douglas B Kell[3,35], Pedro Mendes[3,4,36] & Bernhard Ø Palsson[1,7]

Multiple models of human metabolism have been reconstructed, but each represents only a subset of our knowledge. Here we describe Recon 2, a community-driven, consensus 'metabolic reconstruction', which is the most comprehensive representation of human metabolism that is applicable to computational modeling. Compared with its predecessors, the reconstruction has improved topological and functional features, including ~2× more reactions and ~1.7× more unique metabolites. Using Recon 2 we predicted changes in metabolite biomarkers for 49 inborn errors of metabolism with 77% accuracy when compared to experimental data. Mapping metabolomic data and drug information onto Recon 2 demonstrates its potential for integrating and analyzing diverse data types. Using protein expression data, we automatically generated a compendium of 65 cell type–specific models, providing a basis for manual curation or investigation of cell-specific metabolic properties. Recon 2 will facilitate many future biomedical studies and is freely available at http://humanmetabolism.org/.

An understanding of metabolism is fundamental to comprehending the phenotypic behavior of all living organisms, including humans, where metabolism is integral to health and is involved in much of human disease. High quality, genome-scale 'metabolic reconstructions' are at the heart of bottom-up systems biology analyses and represent the entire network of metabolic reactions that a given organism is known to exhibit[1]. The metabolic-network reconstruction procedure is now well-established[2] and has been applied to a growing number of model organisms[3]. Metabolic reconstructions allow for the conversion of biological knowledge into a mathematical format and the subsequent computation of physiological states[1,4,5] to address a variety of scientific and applied questions[3,6]. Reconstructions enable network-wide mechanistic investigations of the genotype-phenotype relationship. A high-quality reconstruction of the metabolic network is thus

[1]Center for Systems Biology, University of Iceland, Reykjavik, Iceland. [2]Faculty of Industrial Engineering, Mechanical Engineering and Computer Science, University of Iceland, Reykjavik, Iceland. [3]Manchester Centre for Integrative Systems Biology, University of Manchester, Manchester Institute of Biotechnology, Manchester, UK. [4]School of Computer Science, University of Manchester, Manchester, UK. [5]Department of Biochemistry and Molecular Biology, University of Iceland, Reykjavik, Iceland. [6]Computational Systems Biochemistry Group, Charité– Universitätsmedizin Berlin, Berlin, Germany. [7]Department of Bioengineering, University of California, San Diego, La Jolla, California, USA. [8]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. [9]Netherlands Bioinformatics Centre, Nijmegen, the Netherlands. [10]Department of Chemical and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden. [11]Department of Biomedical Engineering, University of Virginia, Charlottesville, Virginia, USA. [12]Department of Chemical and Biological Engineering, University of Sheffield, Sheffield, UK. [13]Centre for Advanced Discovery and Experimental Therapeutics (CADET), Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK. [14]Institute for Theoretical Chemistry, University of Vienna, Vienna, Austria. [15]Department of Biology, University of North Texas, Denton, Texas, USA. [16]Computing and Mathematical Sciences Department, California Institute of Technology, Pasadena, California, USA. [17]European Molecular Biology Laboratory, European Bioinformatics Institute, Hinxton, UK. [18]Babraham Institute, Babraham Research Campus, Cambridge, UK. [19]Faculty of Life Sciences, University of Manchester, Manchester, UK. [20]School of Life Sciences, Gibbet Hill Campus, University of Warwick, Coventry, UK. [21]School of Informatics, University of Edinburgh, Edinburgh, UK. [22]Institute for Systems Biology, Seattle, Washington, USA. [23]Genome Designs, Inc., Walnut Creek, California, USA. [24]Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Campus Belval, Esch-sur-Alzette, Luxembourg. [25]School of Engineering and Science, Jacobs University Bremen, Bremen, Germany. [26]School of Mathematics, University of Manchester, Manchester, UK. [27]Institute of Cell Biophysics, Russian Academy of Sciences, Moscow region, Pushchino, Russia. [28]Department of Molecular Cell Physiology, Vrije Universiteit, Amsterdam, the Netherlands. [29]Section Medical Genomics, Department of Clinical Genetics, Vrije Universiteit University Medical Centre, Amsterdam, the Netherlands. [30]Netherlands Consortium for Systems Biology, Amsterdam, The Netherlands. [31]School of Dentistry, The University of Manchester, Manchester, UK. [32]Okinawa Institute Science and Technology, Okinawa, Japan. [33]School of Chemical Engineering and Analytical Science, University of Manchester, Manchester, UK. [34]Swammerdam Institute for Life Sciences, Faculty of Science, University of Amsterdam, Amsterdam, The Netherlands. [35]School of Chemistry, The University of Manchester, Manchester, UK. [36]Virginia Bioinformatics Institute, Virginia Tech, Blacksburg, Virginia, USA. [37]These authors contributed equally to this work. Correspondence should be addressed to I.T. (ines.thiele@gmail.com).

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A not so simple SBML file (Recon2)

- 8 compartments
- 5 063 metabolites
- 2 194 proteins
- 7 440 reactions

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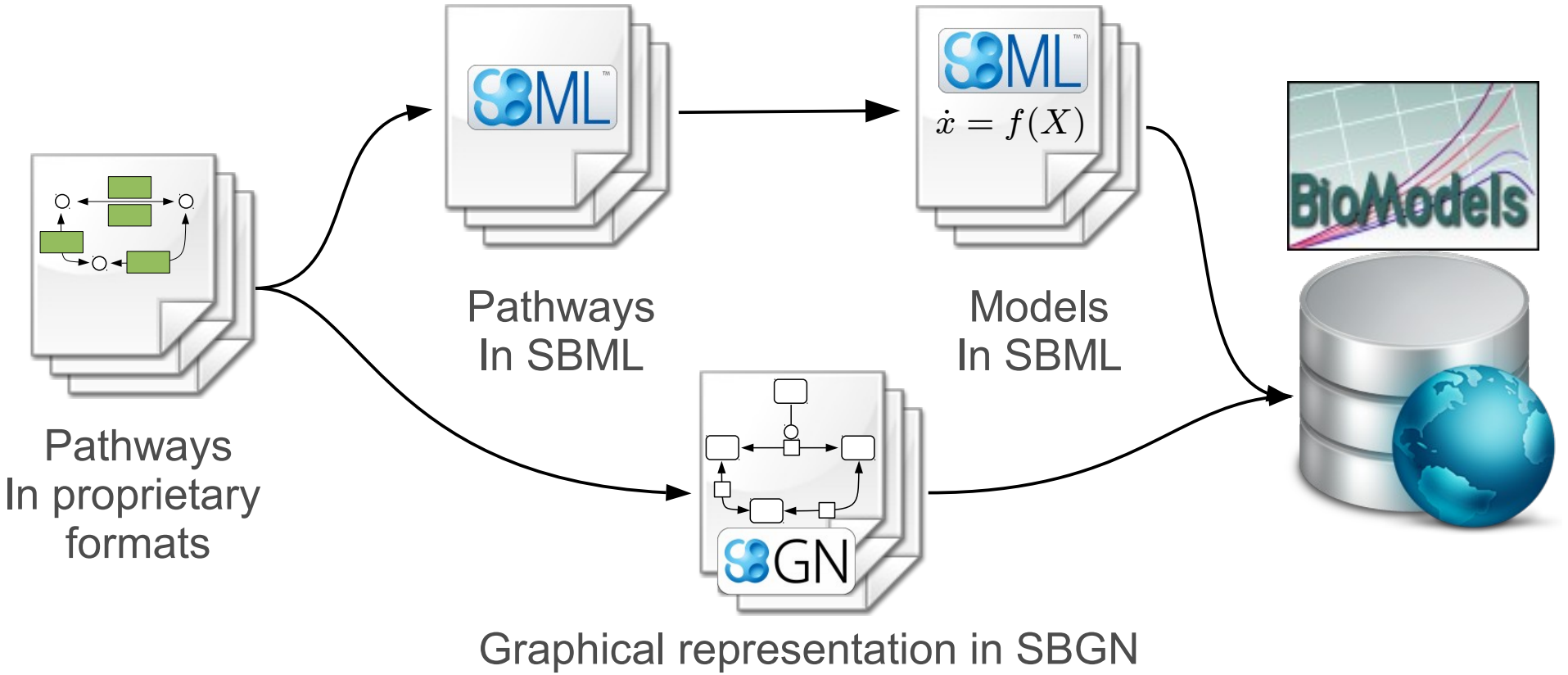
- Core package – public specification
- Flux balance constraint – public specification
- Model composition – public specification
- Qualitative models – public specification
- Graph Layout – public specification
- Graph rendering – specification finalised
- Complex species – specification finalised
- Groups - specification finalised
- Distributions and ranges - specification under discussion
- Spatial diffusion – specification under discussion
- Enhanced metadata – specification under discussion
- Arrays and sets – specification proposed
- Dynamic structures - discussed

SBML Level 3 is modular

Aims of the Path2Models project

- To re-use existing pathway data to generate biochemically based models
- To provide a starting point to model as many biochemical pathways as possible in as many species as possible
- To provide models in a standard format readable by most systems biology software



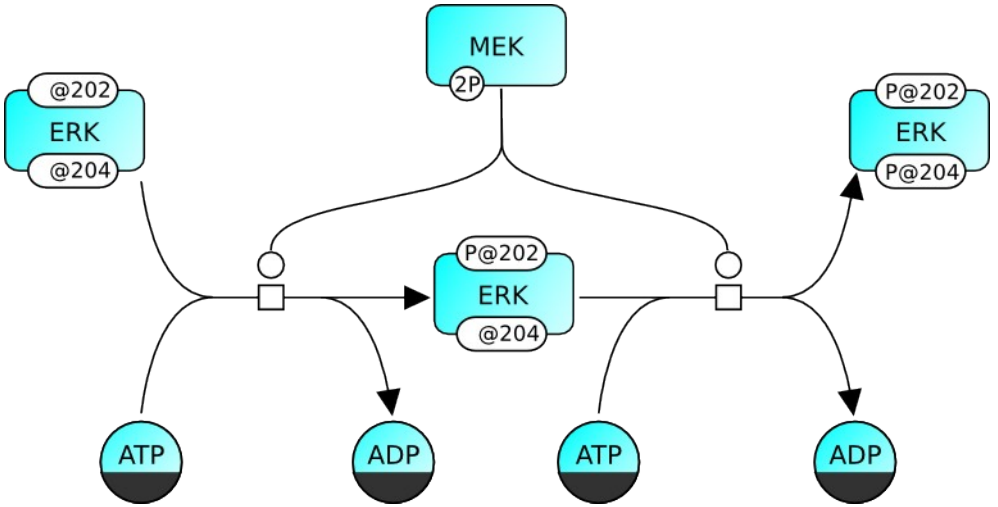
What is SBGN?

- An unambiguous way of graphically describing and interpreting biochemical and cellular events: “biological circuit diagrams”
- Limited amount of symbols
  Re-use existing symbols
  ☞ Smooth learning curve
- Can represent logical or mechanistic models, biochemical pathways, at different levels of granularity
- Detailed technical specification, precise data-models, standard API and growing software support
- Developed over four years by a diverse community, including biologists, modellers, computer scientists etc.

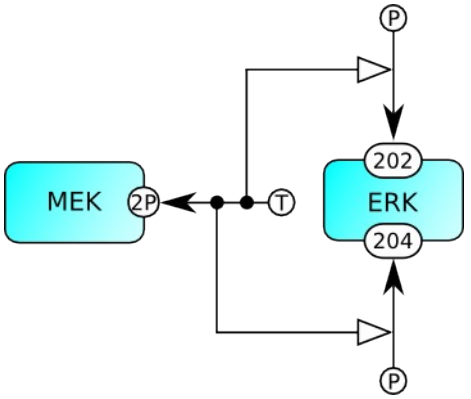
Le Novère et al. The Systems Biology Graphical Notation.
Nat Biotechnol (2009), 27: 735-741

Graph trinity: three languages in one notation

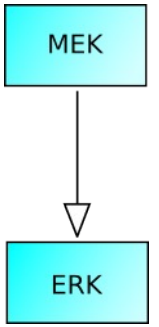
Process Descriptions

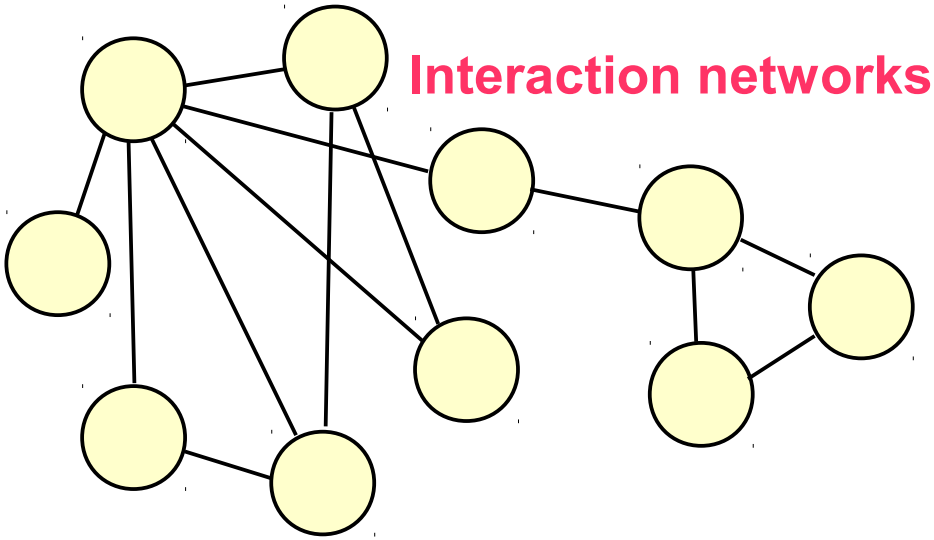


Entity Relationships



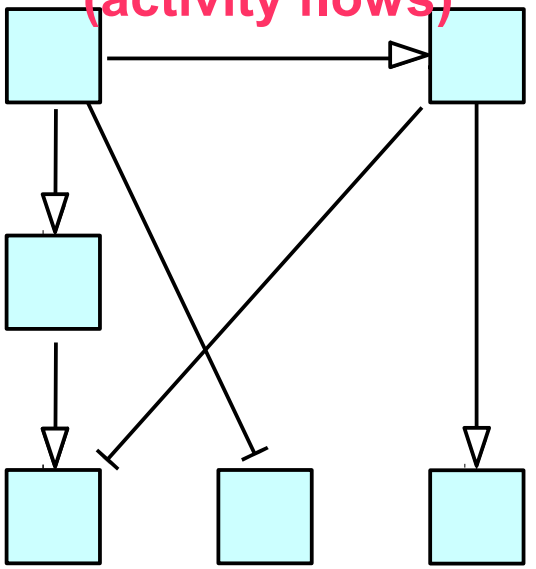
Activity Flows



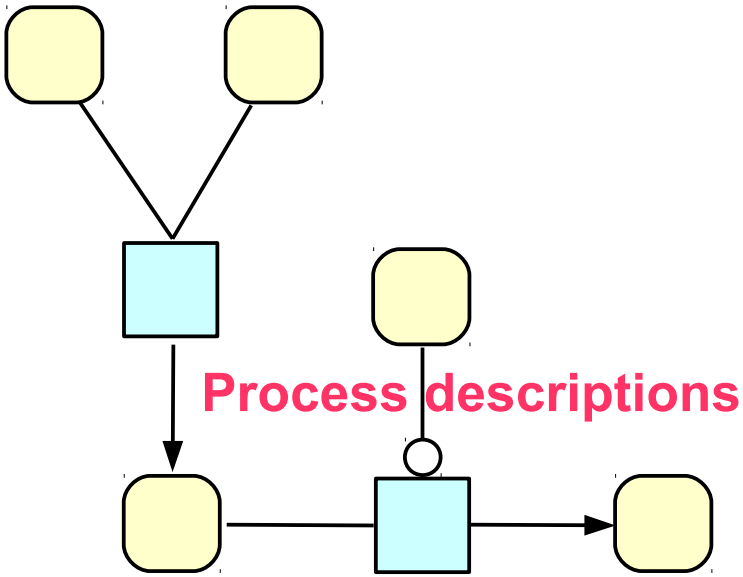


Interaction networks

Influence diagrams
(activity flows)

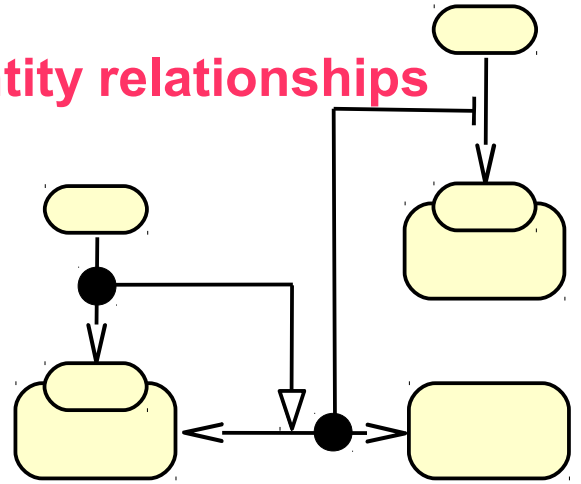


Four types of networks in systems biology

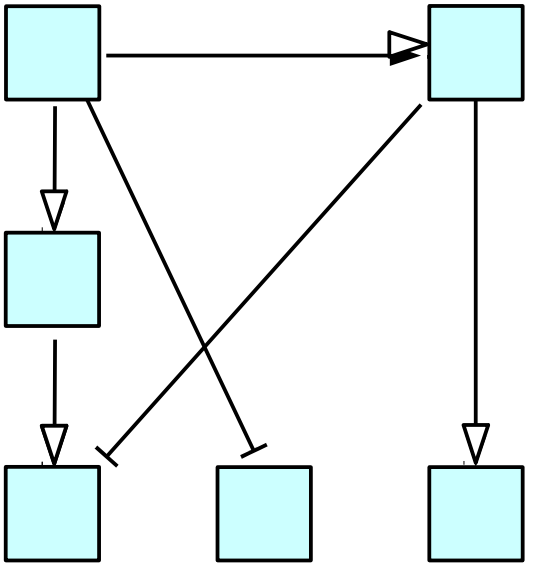


Process descriptions

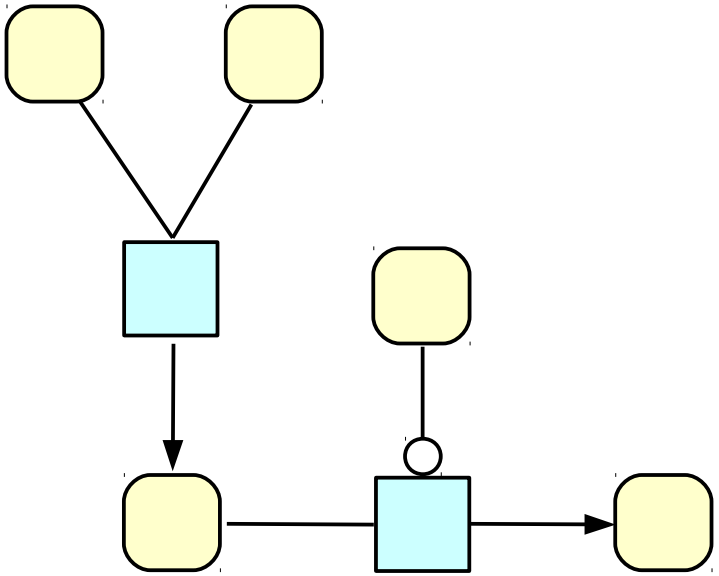
Entity relationships



Activity flows

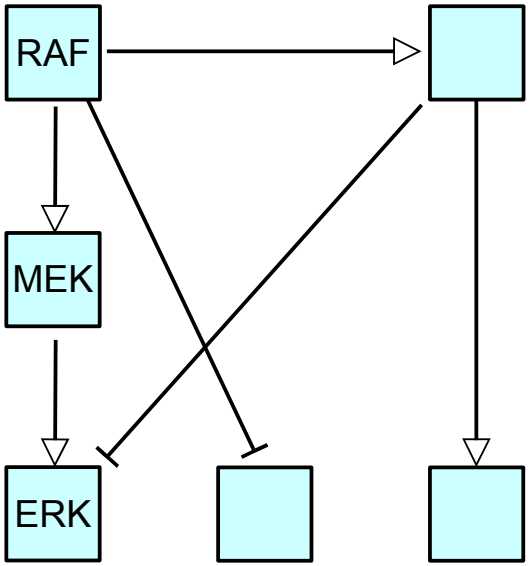


Path2models focus



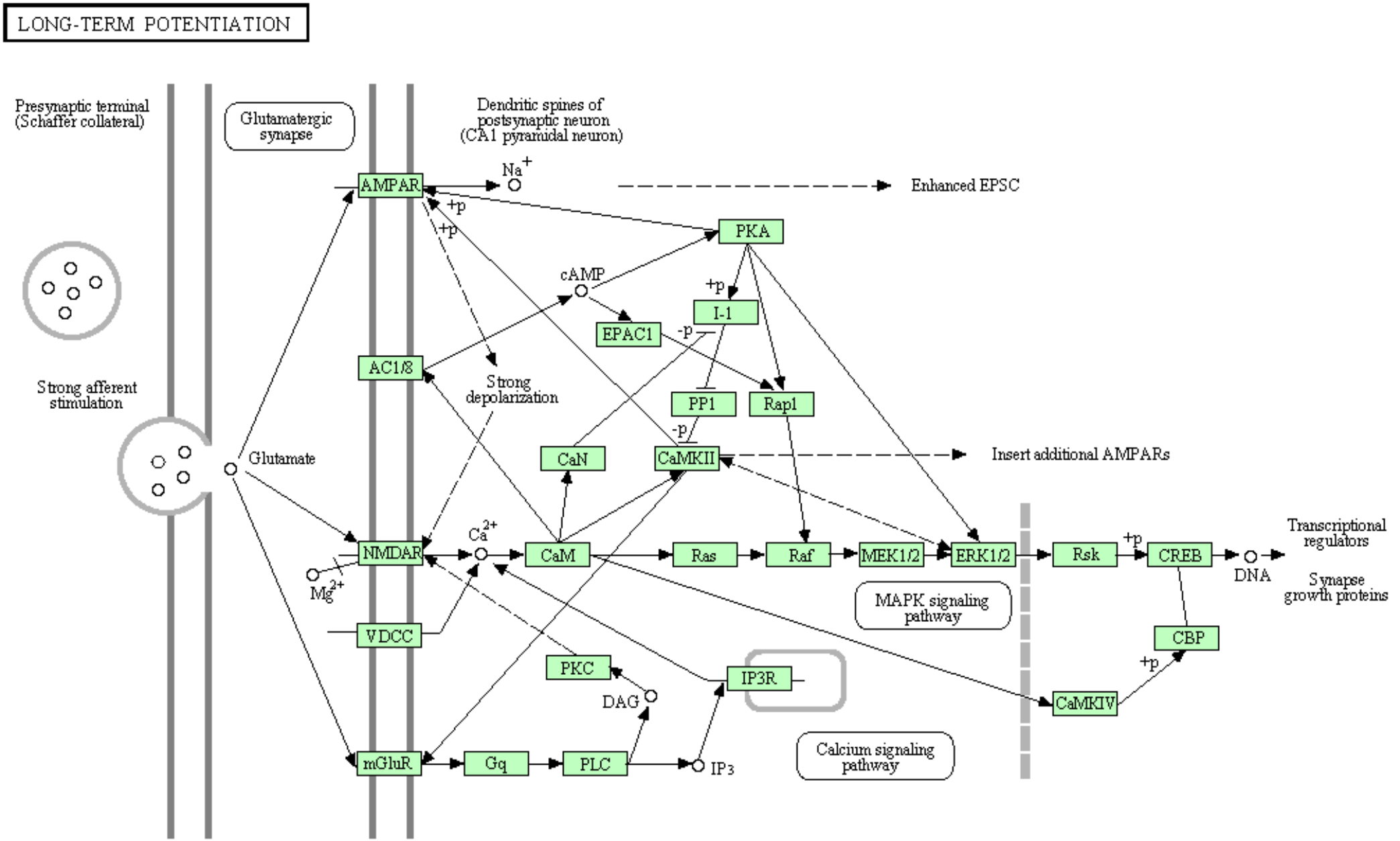
Process descriptions

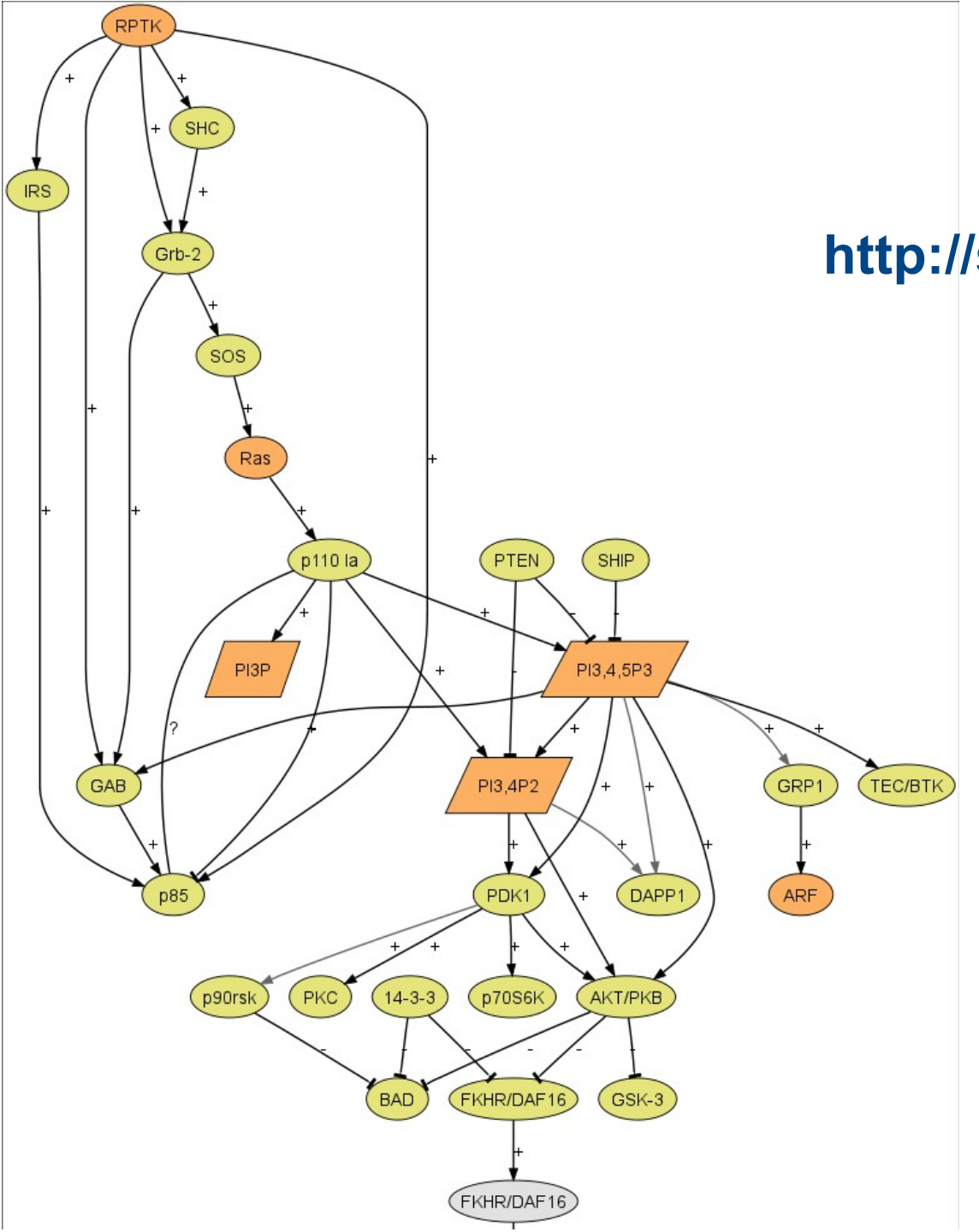
Influence diagrams (activity-flows)



- Signalling pathways, gene regulatory networks
- Nodes represent activities
- Directional
- Sequential
- Non-mechanistic
- Logical modelling

http://www.genome.jp/kegg/pathway.html





http://stke.sciencemag.org/cm/

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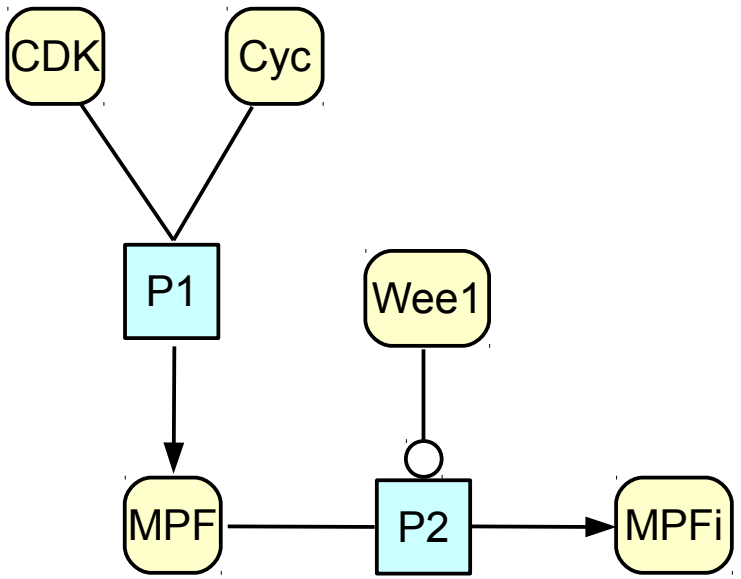
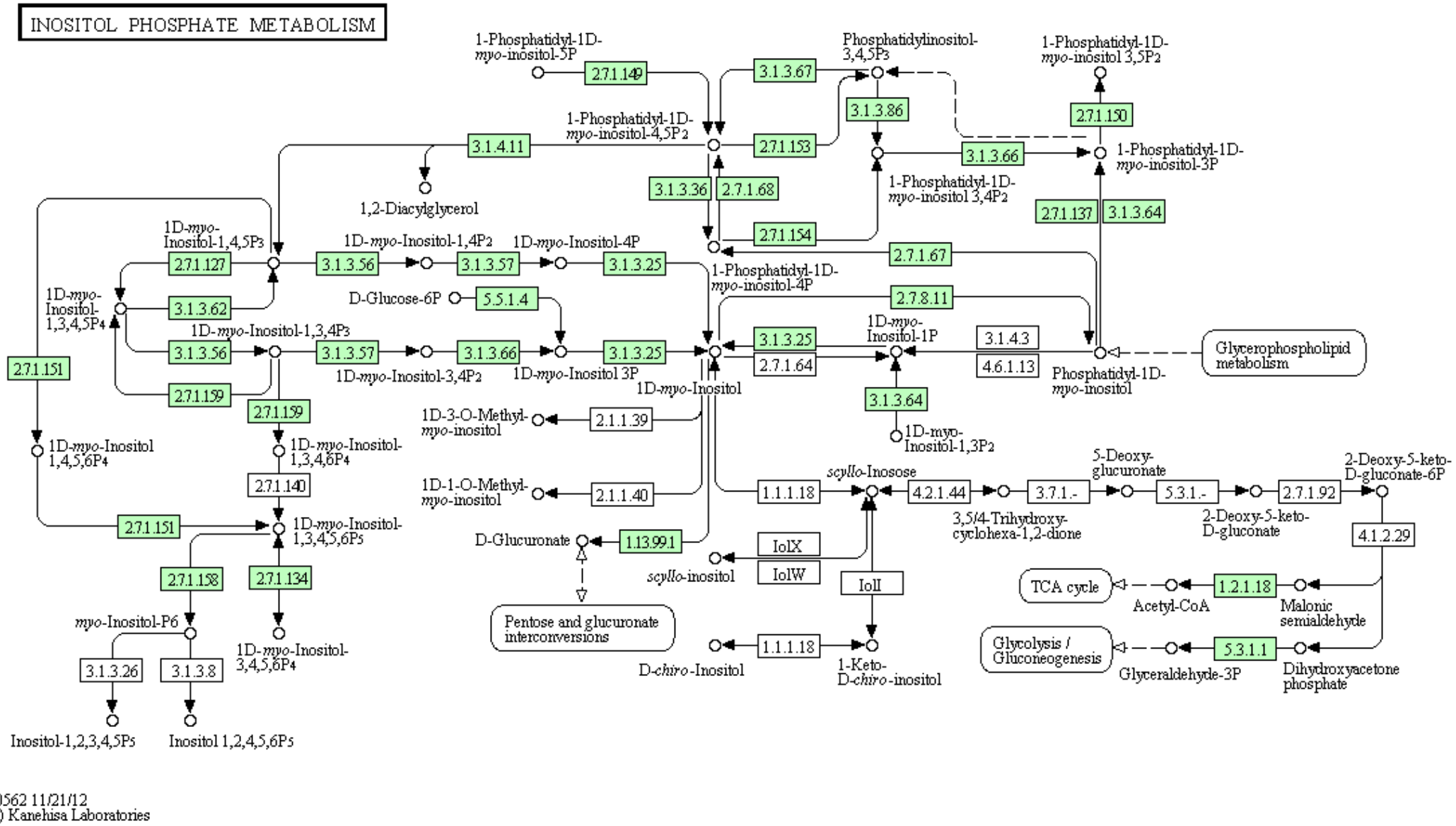
Process Descriptions

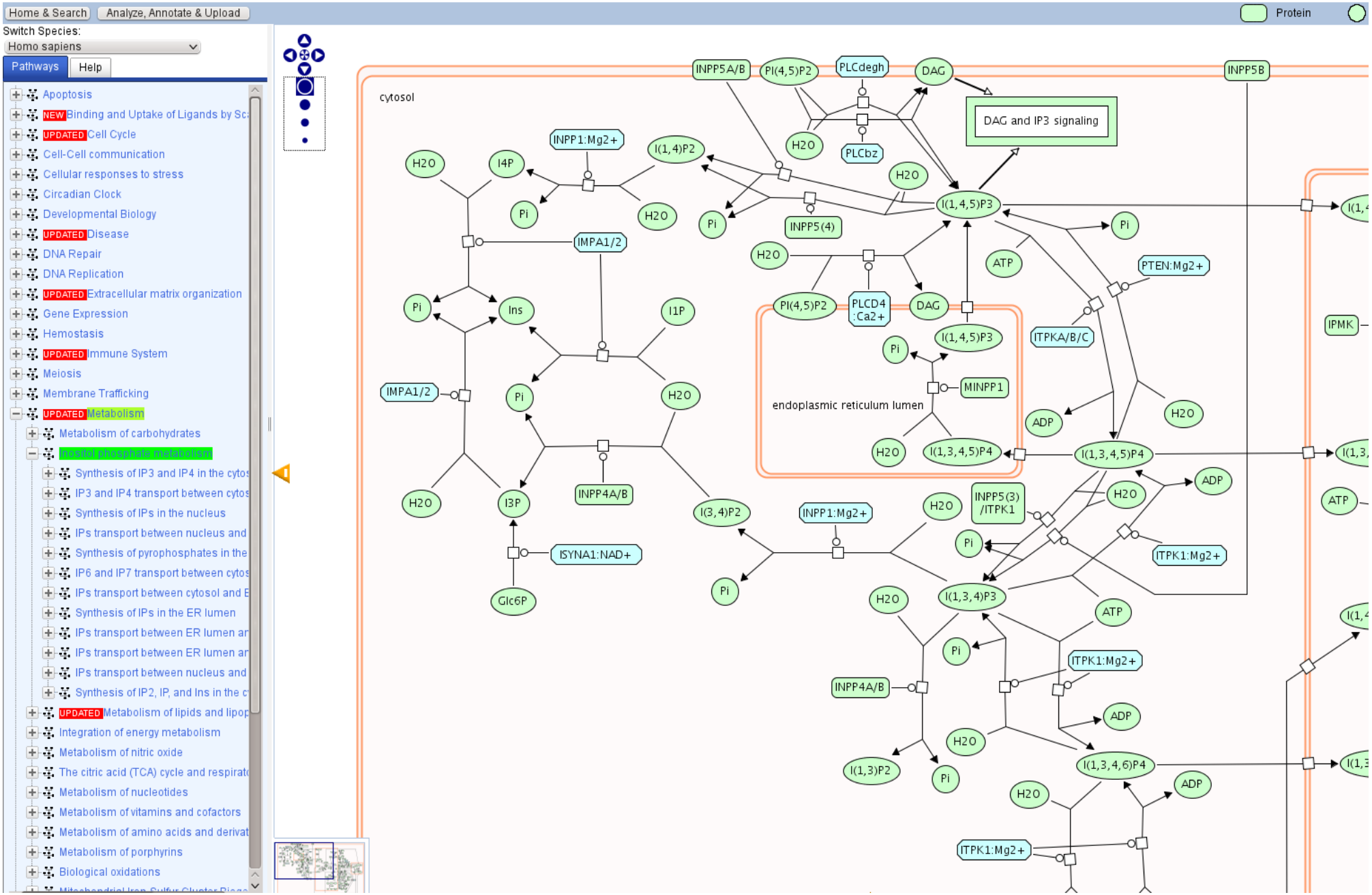


- Biochemistry, Metabolic networks
- Nodes represent populations of reactants and reactions
- Directional
- Sequential
- Mechanistic
- Subjected to combinatorial explosion
- Process modelling (ODE, SSA)

http://www.genome.jp/kegg/pathway.html



http://www.reactome.org



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Three parallel workflows

Signalling Pathways

+

Logical models
of individual signalling pathways

Three parallel workflows

Signalling Pathways

+

Logical models
of individual signalling pathways

Metabolic Networks

Chemical kinetics models
of individual metabolic pathways

Three parallel workflows

Signalling Pathways

+

Logical models
of individual signalling pathways

Metabolic Networks

Chemical kinetics models
of individual metabolic pathways

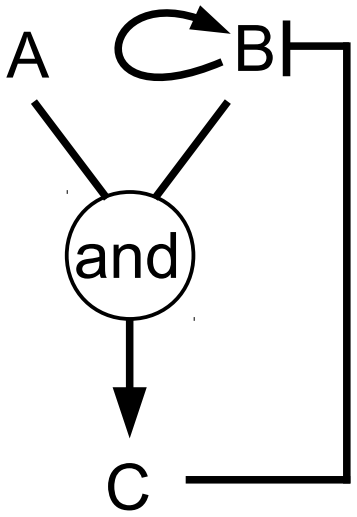
Metabolic Networks

+

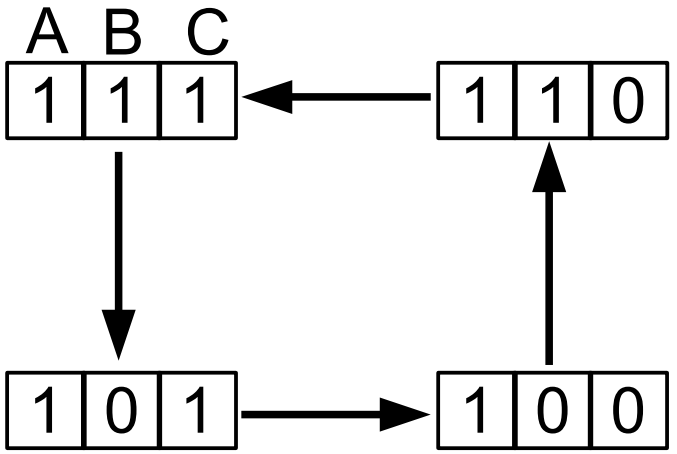
Flux Balance Analysis
of whole genome reconstructions

Signalling pathways: Logical models

- Variables can take a discrete number of values, at least 2
- Transitions of output are expressed as logical combinations of input values
- Simulations can be:
  synchronous: all the nodes are updated at once
  asynchronous: nodes are updated one after the other
- One can add delays, inputs etc.



Influence diagram



state diagram

Qual

From KEGG metabolic pathways to full kinetic models

KGML

From KEGG metabolic pathways to full kinetic models

KEGGtranslator

KGML → SBML

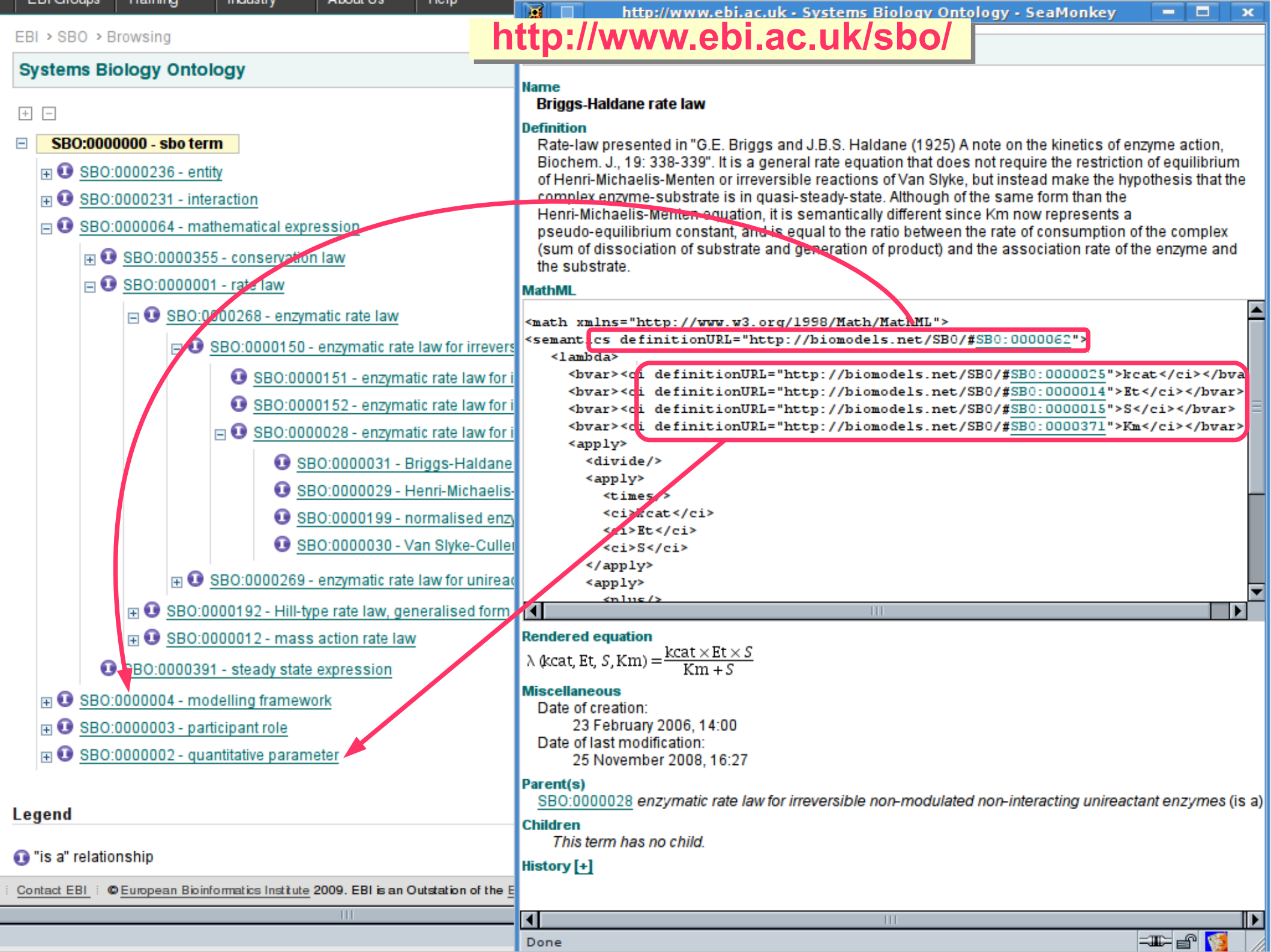
Core

From KEGG metabolic pathways to full kinetic models

Systems Biology Ontology vocabularies

- Entities, that is existing objects, whether functional or material, such as "macromolecule", or "channel".
- Roles of reaction participants, including terms like "substrate", "catalyst" etc.
- Parameter used in quantitative models. This vocabulary includes terms like "Michaelis constant", "forward unimolecular rate constant"etc. A term may contain a precise mathematical expression stored as a MathML lambda function. The variables refer to other parameters.
- Mathematical expressions. Examples of terms are "mass action kinetics", "Henri-Michaelis-Menten equation" etc. A term may contain a precise mathematical expression stored as a MathML lambda function. The variables refer to the other vocabularies.
- Modelling framework to precise how to interpret the rate-law. E.g. "continuous modelling", "discrete modelling" etc.
- Event type, such as "catalysis" or "addition of a chemical group".

Courtot et al. Controlled vocabularies and semantics in Systems Biology.
Mol Syst Biol (2011), 7: 543


http://www.ebi.ac.uk/sbo/
EBI > SBO > Browsing
Systems Biology Ontology
SBO:0000000 - sbo term
SBO:0000236 - entity
SBO:0000231 - interaction
SBO:0000064 - mathematical expression
SBO:0000355 - conservation law
SBO:0000001 - rate law
SBO:0000268 - enzymatic rate law
SBO:0000150 - enzymatic rate law for irrevers
SBO:0000151 - enzymatic rate law for i
SBO:0000152 - enzymatic rate law for i
SBO:0000028 - enzymatic rate law for i
SBO:0000031 - Briggs-Haldane
SBO:0000029 - Henri-Michaelis-
SBO:0000199 - normalised enzy
SBO:0000030 - Van Slyke-Culle
SBO:0000269 - enzymatic rate law for unireac
SBO:0000192 - Hill-type rate law, generalised form
SBO:0000012 - mass action rate law
SBO:0000391 - steady state expression
SBO:0000004 - modelling framework
SBO:0000003 - participant role
SBO:0000002 - quantitative parameter
Legend
"is a" relationship
Contact EBI
© European Bioinformatics Institute 2009. EBI is an Outstation of the E
http://www.ebi.ac.uk - Systems Biology Ontology - SeaMonkey
Name
Briggs-Haldane rate law
Definition
Rate-law presented in "G.E. Briggs and J.B.S. Haldane (1925) A note on the kinetics of enzyme action, Biochem. J., 19: 338-339". It is a general rate equation that does not require the restriction of equilibrium of Henri-Michaelis-Menten or irreversible reactions of Van Slyke, but instead make the hypothesis that the complex enzyme-substrate is in quasi-steady-state. Although of the same form than the Henri-Michaelis-Menten equation, it is semantically different since Km now represents a pseudo-equilibrium constant, and is equal to the ratio between the rate of consumption of the complex (sum of dissociation of substrate and generation of product) and the association rate of the enzyme and the substrate.
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Date of last modification:
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SBML and SBO

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SBML and SBO

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functional compartment

simple chemical

simple chemical

enzyme

catalysis

substrate

product

catalyst

Briggs-Haldane equation

Km

kcat

Conversion between modeling frameworks

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discrete simulator

$$v1 = \frac{(k_{-1} + V)}{U} \cdot [A] \cdot [C]$$

$$v2 = k_{-1} \cdot [D]$$

$$v3 = V \cdot [D]$$

continuous simulator

$$\nu = \frac{C \cdot V \cdot [A]}{(U + [A])}$$

SBML to SBGN conversion using SBO

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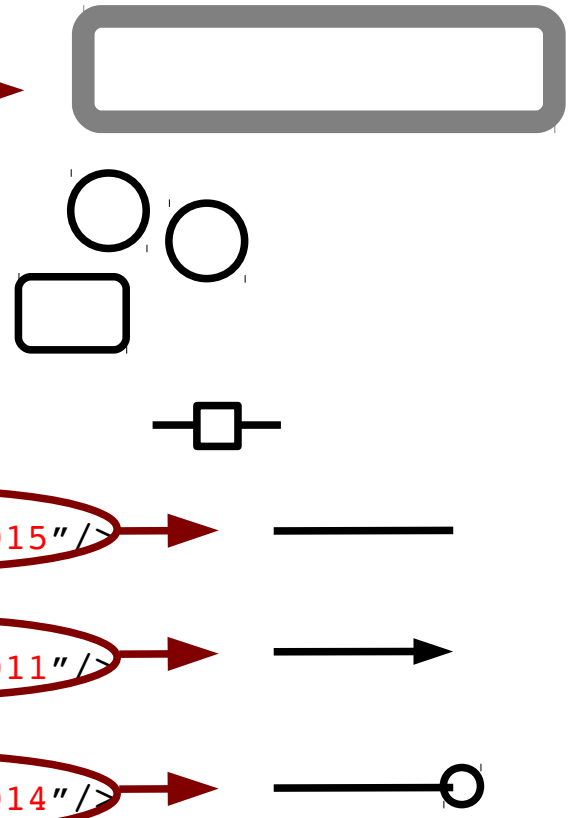
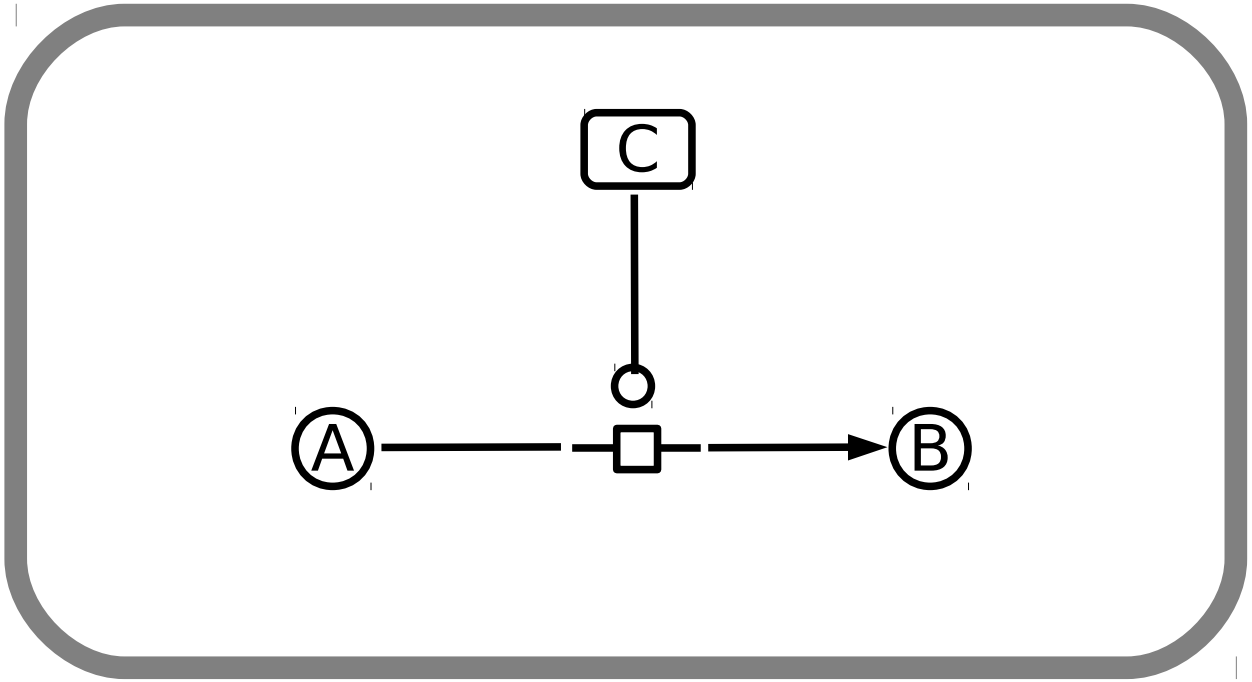
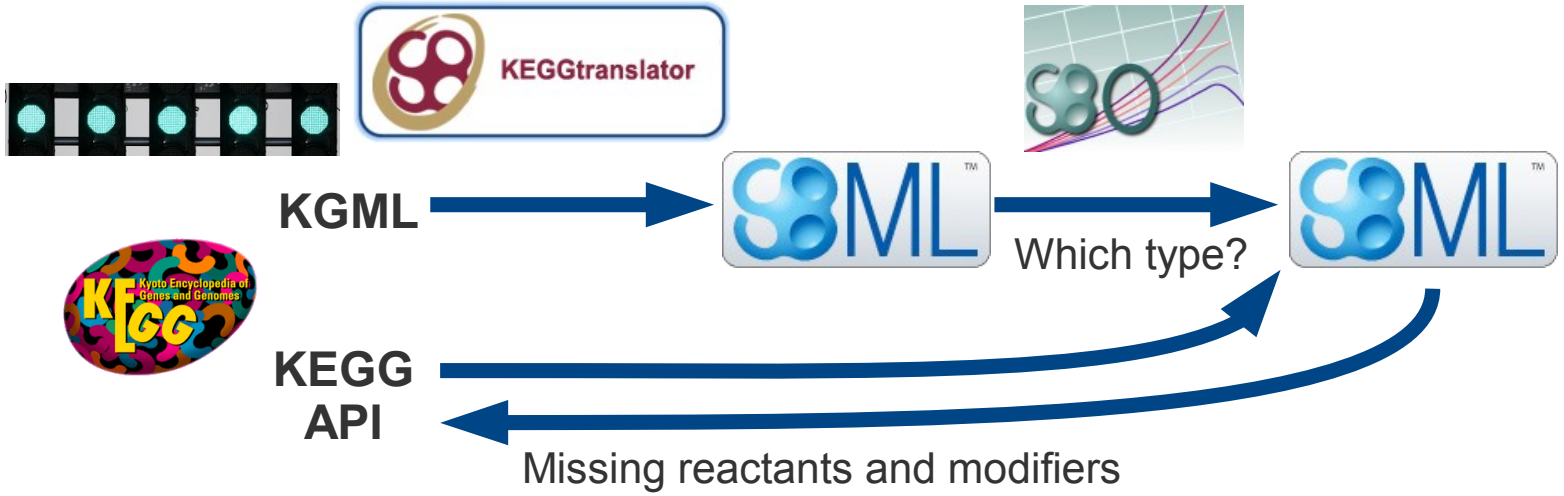


http://www.sbgn.org/

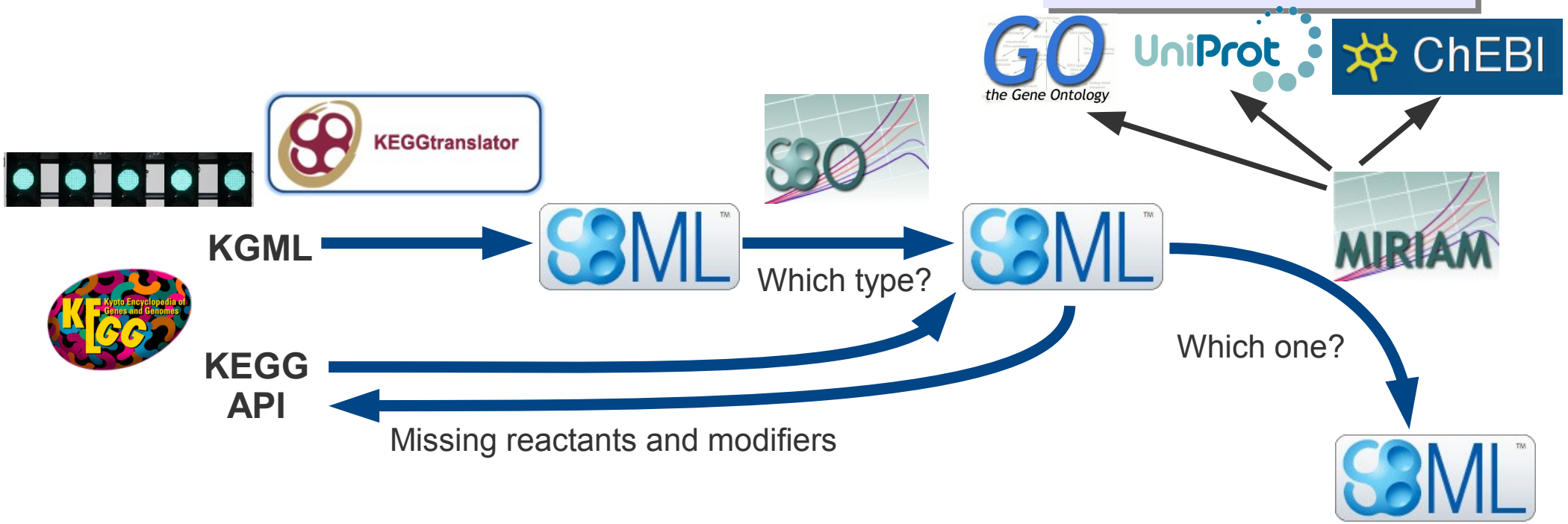
SBML to SBGN conversion using SBO



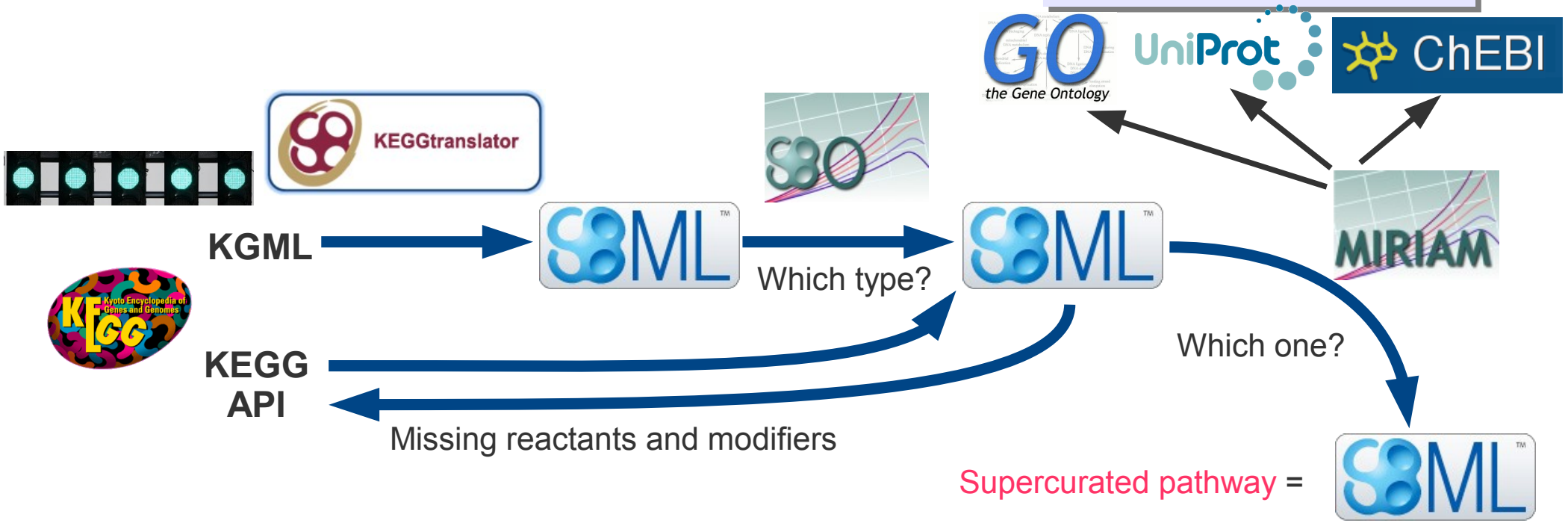
From KEGG metabolic pathways to full kinetic models



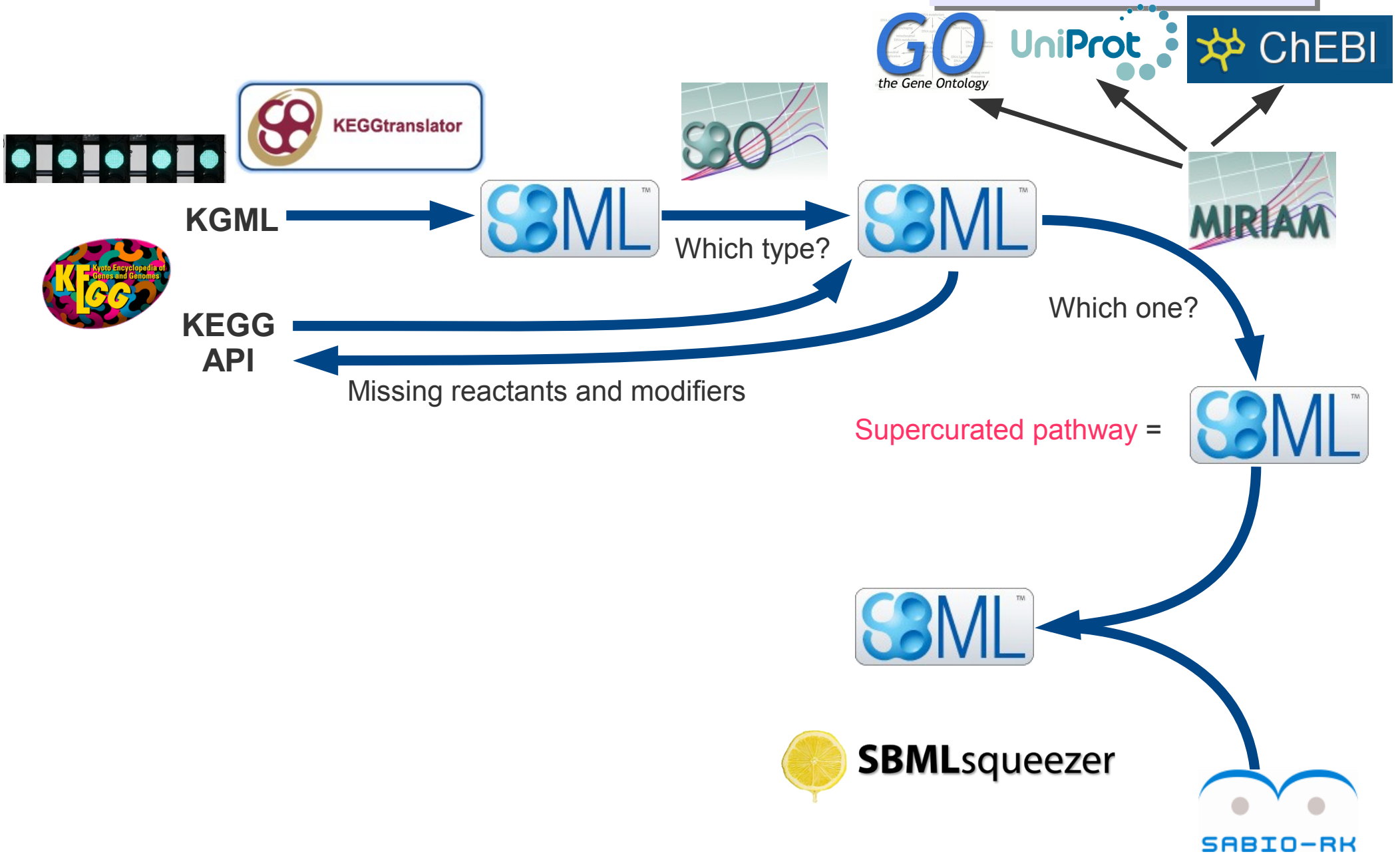
From KEGG metabolic pathways to full kinetic models



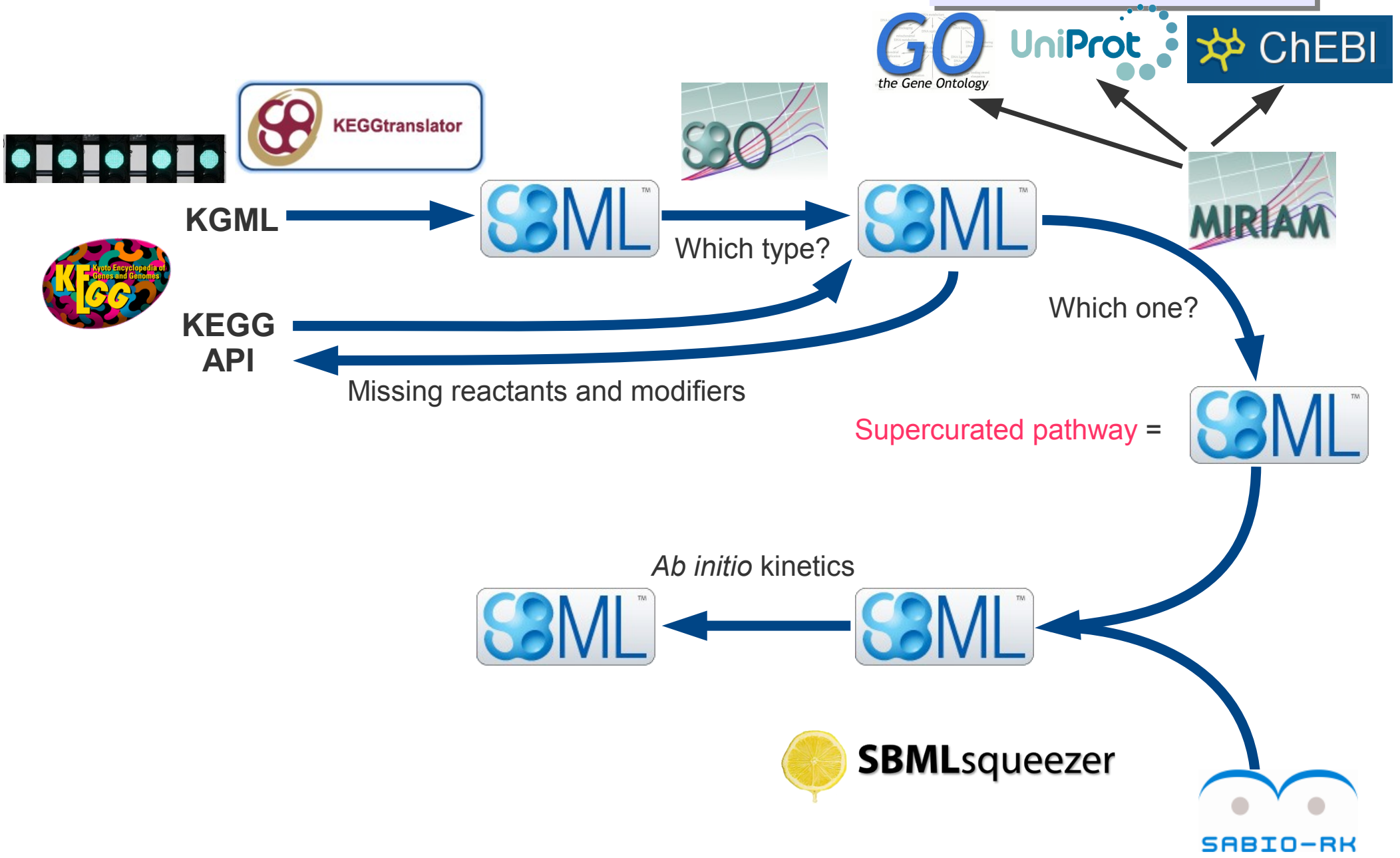
From KEGG metabolic pathways to full kinetic models



From KEGG metabolic pathways to full kinetic models



From KEGG metabolic pathways to full kinetic models



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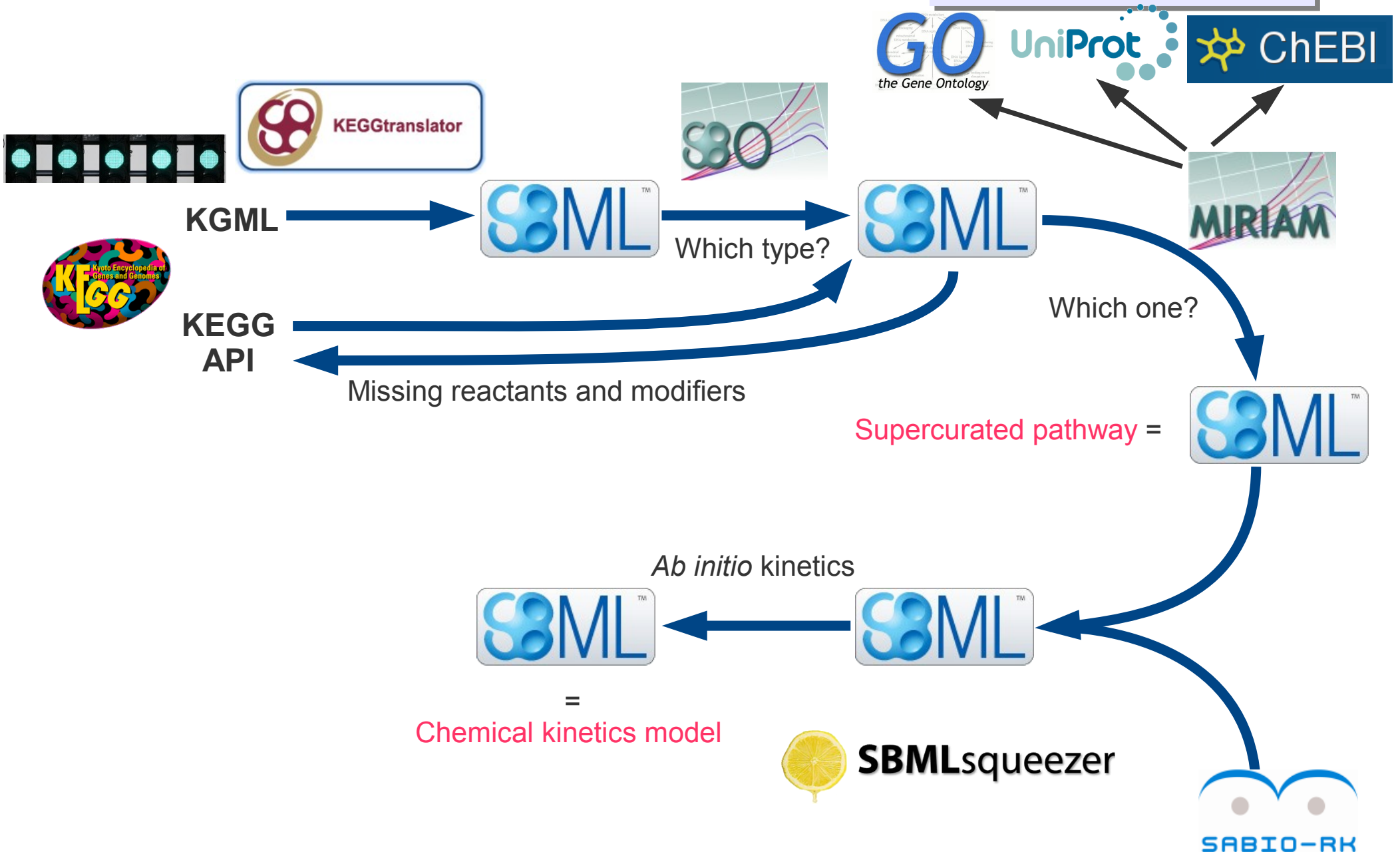
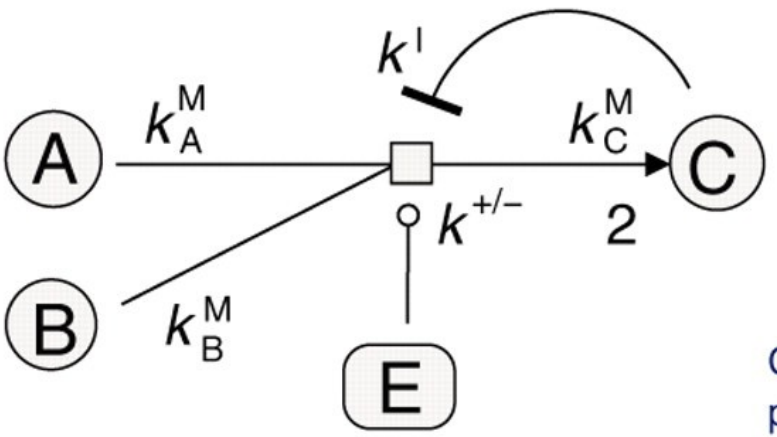
From KEGG metabolic pathways to full kinetic models



Metabolic reactions: Common modular rate-law



Reaction rate

Enzyme level

Stoichiometry, 3 parametrizations

$$v = u\, f\, \frac{T}{D + D^{reg}}$$

Complete or partial regulation

5 rate laws

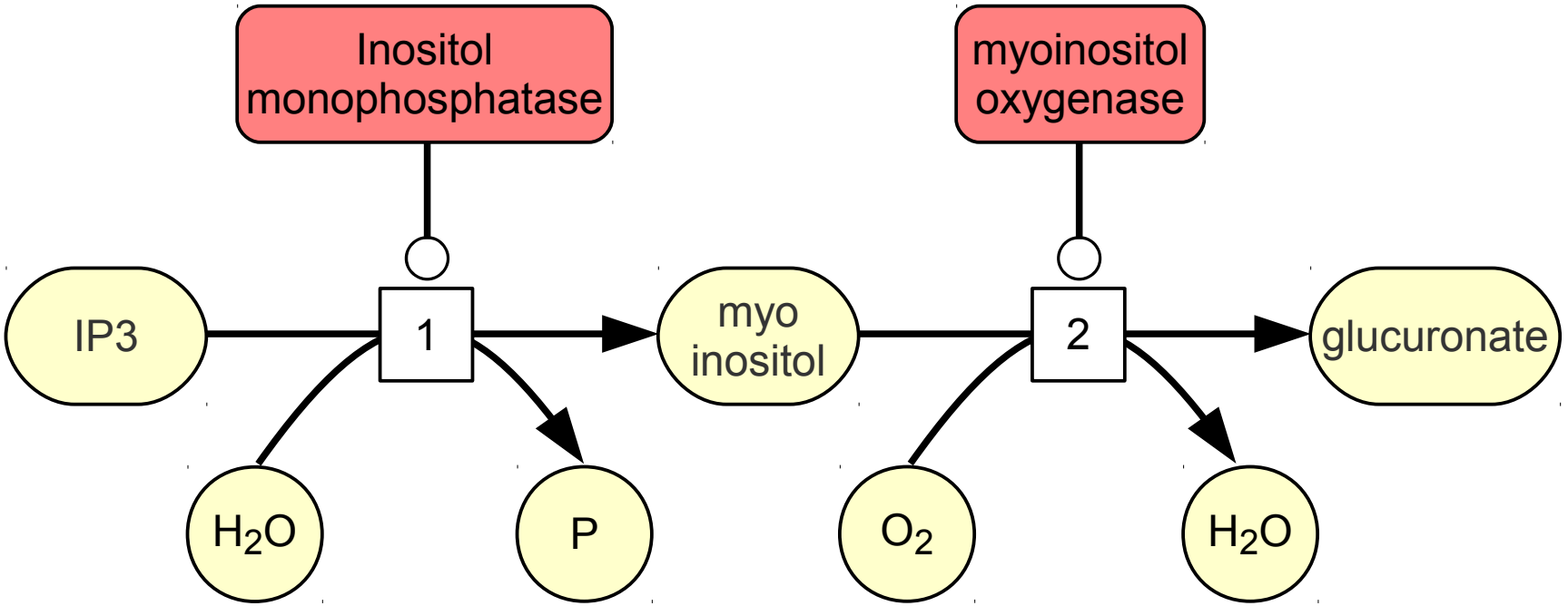
Specific regulation

- Common rate law
- Direct binding rate law
- Simultaneous binding rate law
- Force dependent rate law
- Power Law

$$T = k_r^+ \prod_i \left(\frac{c_i}{k_{ri}^M} \right)^{m_{ri}^+} - k_r^- \prod_i \left(\frac{c_i}{k_{ri}^M} \right)^{m_{ri}^-}$$

Liebermeister, Uhlendorf, Klipp (2010) Modular rate laws for enzymatic reactions: thermodynamics, elasticities and implementation. *Bioinformatics* 26: 1528-1534

Unparametrised Vs. known kinetics



$$v1 = [IMPA] \times k_{\text{cat}} \times \frac{[\text{IP3}]}{K_{\text{m}} + [\text{IP3}]}$$

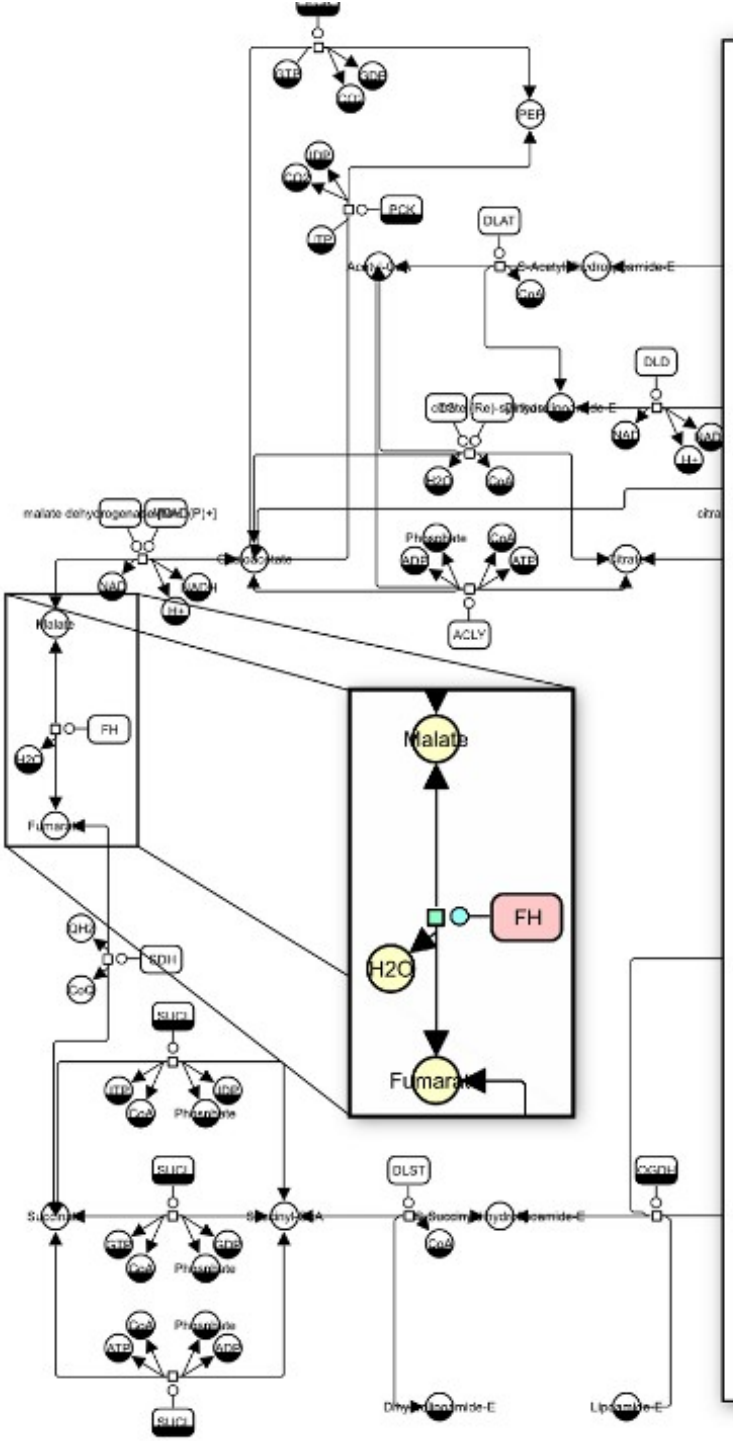
To estimate

$$v2 = V_{\text{max}} \times \frac{[\text{myoinositol}]}{K_{\text{m}} + [\text{myoinositol}]}$$

$3.5 \cdot 10^{-5}\,\text{mol} \cdot \text{s}^{-1} \cdot \text{g}^{-1}$ $0.0033\,\text{M}$

Model BMID000000038685 "Inositol phosphate metabolism"

SABIO-RK

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From KEGG metabolic pathways to full kinetic models

KEGGtranslator

KGML

Which type?

KEGG API

Missing reactants and modifiers

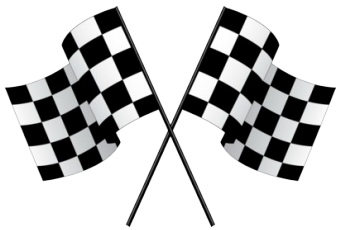
Which one?

Supercurated pathway =

Ab initio kinetics

=

Chemical kinetics model



SBMLsqueezer

SABIO-RK

$$
\mathbf{S}\cdot\mathbf{v}=\dot{\mathbf{x}}
$$

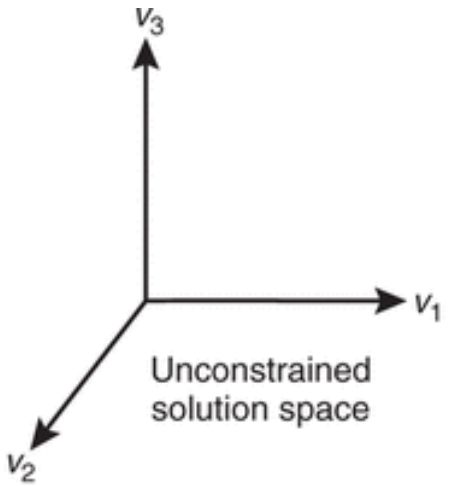
S	Reaction 1	Reaction 2	Reaction 3	Reaction 4	…	Reaction n
Reactant 1	-1	-1	0	0	⋯	1
Reactant 2	0	-1	0	-2	⋯	0
Reactant 3	-1	1	-1	0	⋯	0
…	…	…	…	…	…	…
Reactant m	2	0	1	0	⋯	0

X

v
Flux 1
Flux 2
Flux 3
Flux 4
…
Flux n

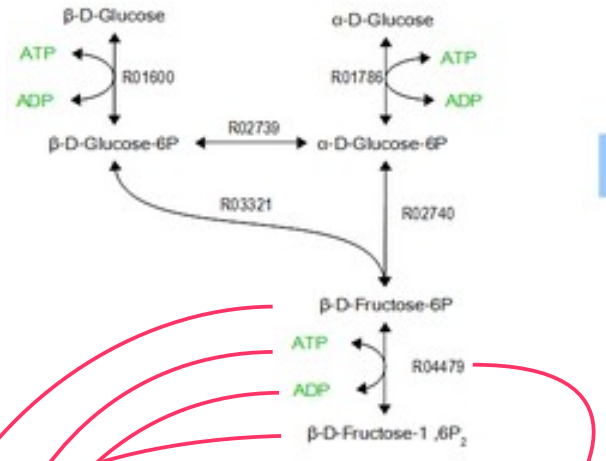
=

ẋ
d[x1]/dt
d[x2]/dt
d[x3]/dt
…
d[xm]/dt

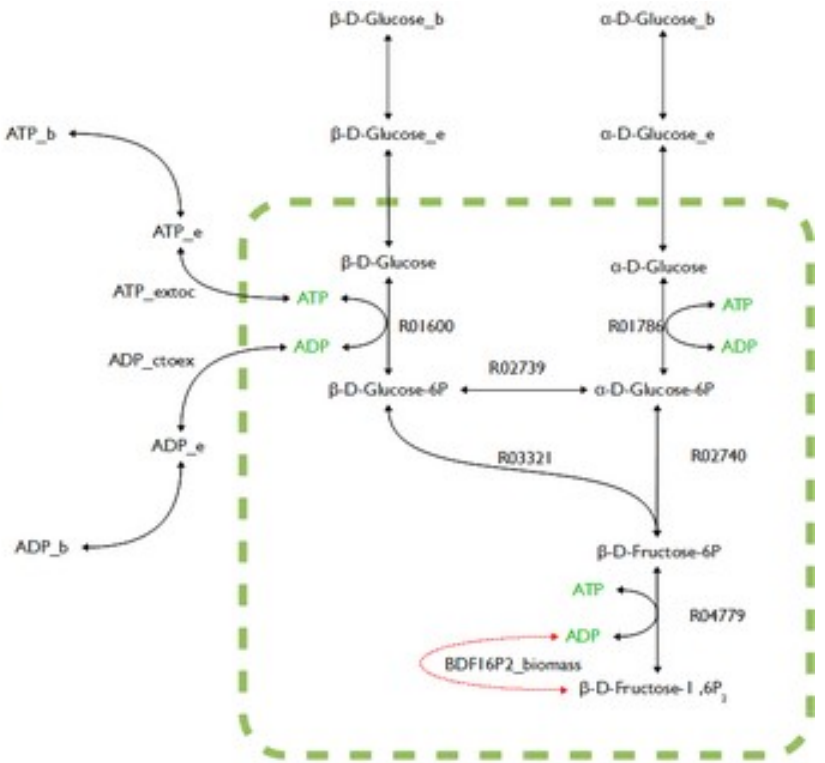


Whole genome reconstructions:

Flux balance analysis models



Prepare for FBA



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C00002	0	0	0	-1	-1	-1
C00008	0	0	0	1	1	1
C00221	0	0	0	-1	0	0
C00267	0	0	0	0	-1	0
C00668	-1	0	-1	0	1	0
C01172	1	-1	0	1	0	0
C05345	0	1	1	0	0	-1
C05378	0	0	0	0	0	1

	R02739_c	R03321_c	R02740_c	R01600_c	R01786_c	R04779_c	ATP_extoc_tr	ADP_ctoex_tr	BDG_extoc_tr	ADG_extoc_tr	BDF16P2_biomass_tr
C00002[c]	0	0	0	-1	-1	-1	1	0	0	0	0
C00002[e]	0	0	0	0	0	0	-1	0	0	0	0
C00008[c]	0	0	0	1	1	1	0	-1	0	0	1
C00008[e]	0	0	0	0	0	0	0	1	0	0	0
C00221[c]	0	0	0	-1	0	0	0	0	1	0	0
C00221[e]	0	0	0	0	0	0	0	0	-1	0	0
C00267[c]	0	0	0	0	-1	0	0	0	0	1	0
C00267[e]	0	0	0	0	0	0	0	0	0	-1	0
C00668[c]	-1	0	-1	0	1	0	0	0	0	0	0
C01172[c]	1	-1	0	1	0	0	0	0	0	0	0
C05345[c]	0	1	1	0	0	-1	0	0	0	0	0
C05378[c]	0	0	0	0	0	1	0	0	0	0	-1

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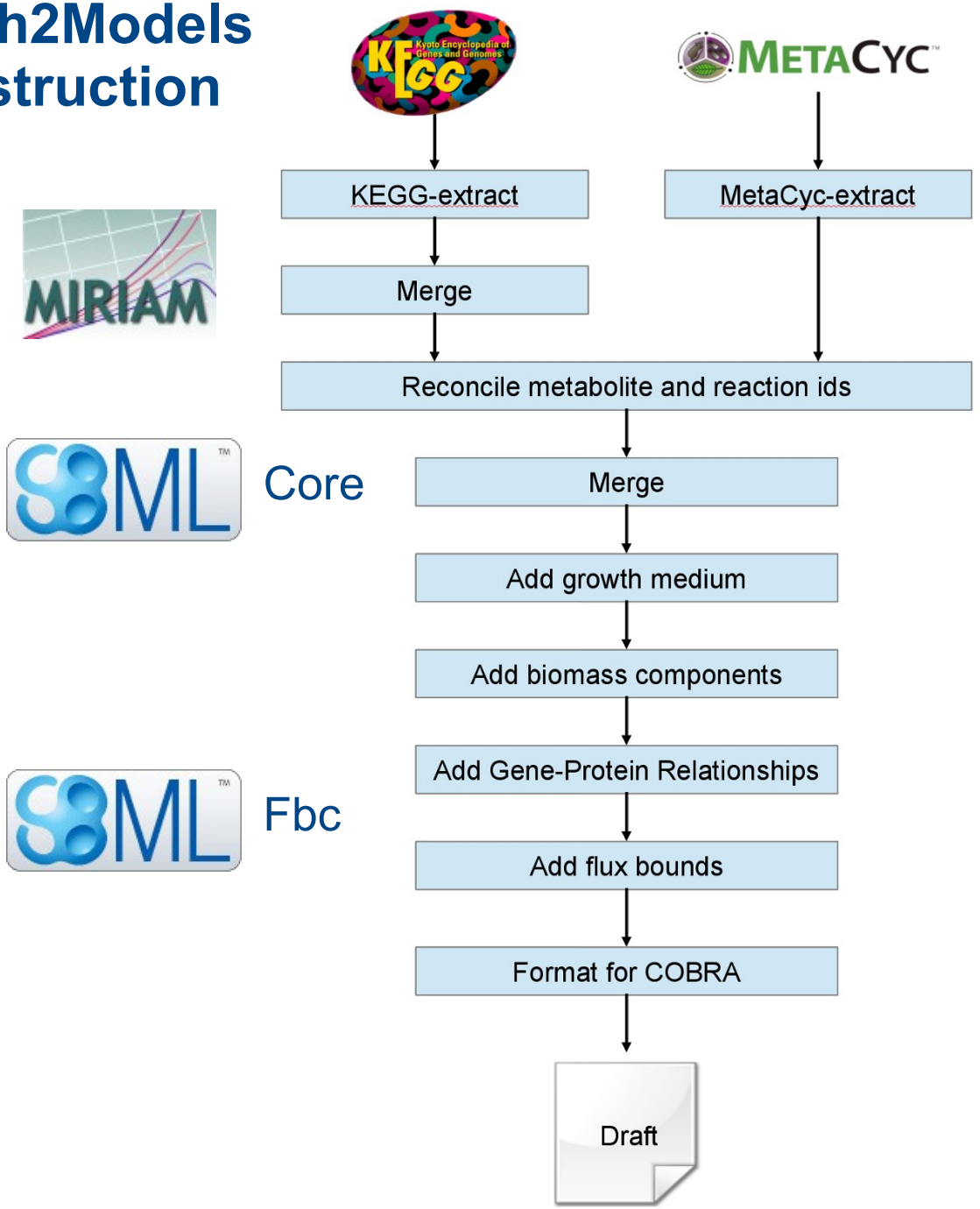
Workflow to build a Path2Models whole genome reconstruction



Steady-states:
Concentrations do not vary
Inputs = outputs

$$\mathbf{S}\mathbf{v} = 0$$

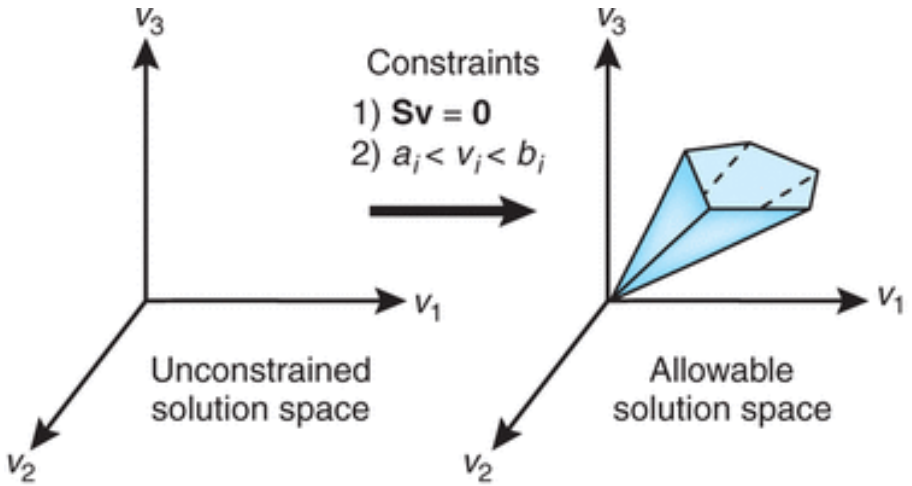
	Reaction 1	Reaction 2	Reaction 3	Reaction 4	…	Reaction n
Reactant 1	-1	-1	0	0	⋯	1
Reactant 2	0	-1	0	-2	⋯	0
Reactant 3	-1	1	-1	0	⋯	0
…	…	…	…	…	…	…
Reactant m	2	0	1	0	⋯	0

$\times$

$\mathbf{v}$
Flux 1
Flux 2
Flux 3
Flux 4
…
Flux n

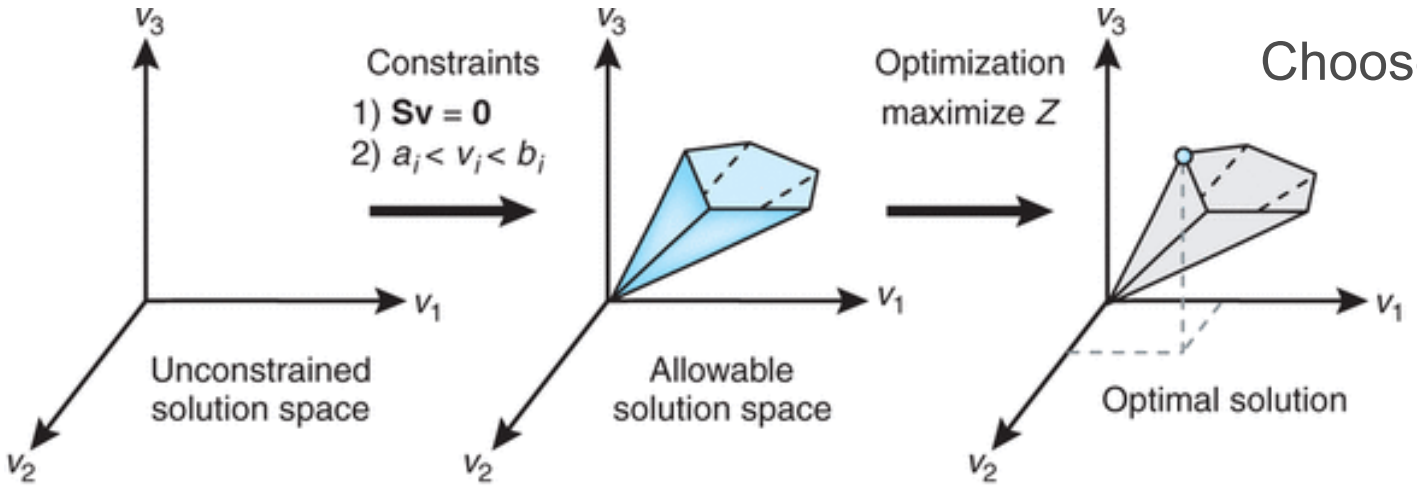
$= 0$

More reactions than reactants = undetermined (more variables than equations)



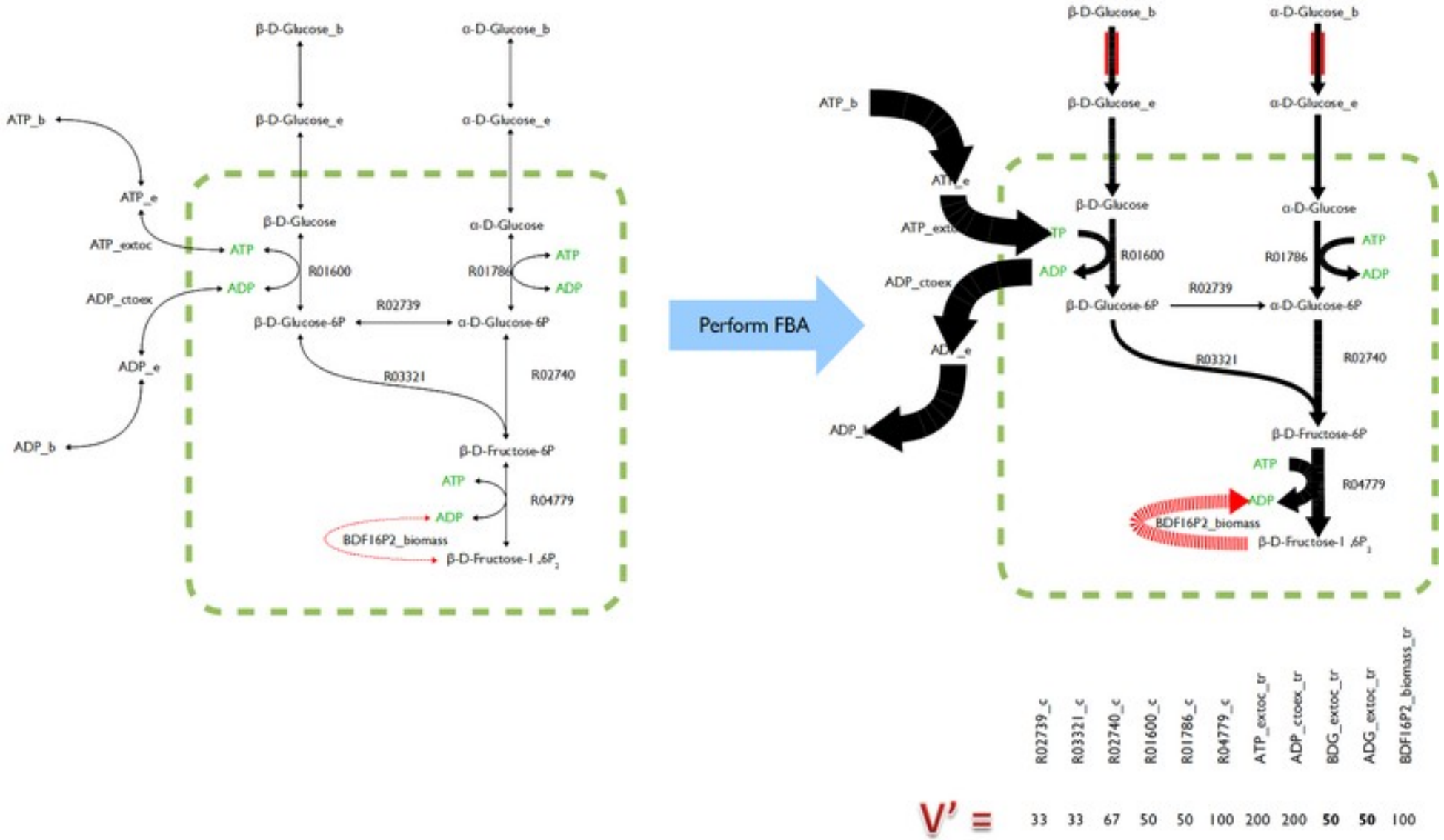
$$
\mathbf{S}\begin{array}{c}
\begin{array}{cccccc} \text{Reaction 1} & \text{Reaction 2} & \text{Reaction 3} & \text{Reaction 4} & \cdots & \text{Reaction n} \end{array} \\
\begin{pmatrix}
-1 & -1 & 0 & 0 & \cdots & 1 \\
0 & -1 & 0 & -2 & \cdots & 0 \\
-1 & 1 & -1 & 0 & \cdots & 0 \\
\cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\
2 & 0 & 1 & 0 & \cdots & 0
\end{pmatrix}
\end{array}
\begin{array}{l}
\text{Reactant 1} \\ \text{Reactant 2} \\ \text{Reactant 3} \\ \cdots \\ \text{Reactant m}
\end{array}
\quad X \quad
\mathbf{v}\begin{pmatrix}
\text{Flux 1} \\ \text{Flux 2} \\ \text{Flux 3} \\ \text{Flux 4} \\ \cdots \\ \text{Flux n}
\end{pmatrix}
\quad = \quad 0
$$

More reactions than reactants = undetermined (more variables than equations)



Choose an objective function (maximise biomass or ATP production)

Application of FBA



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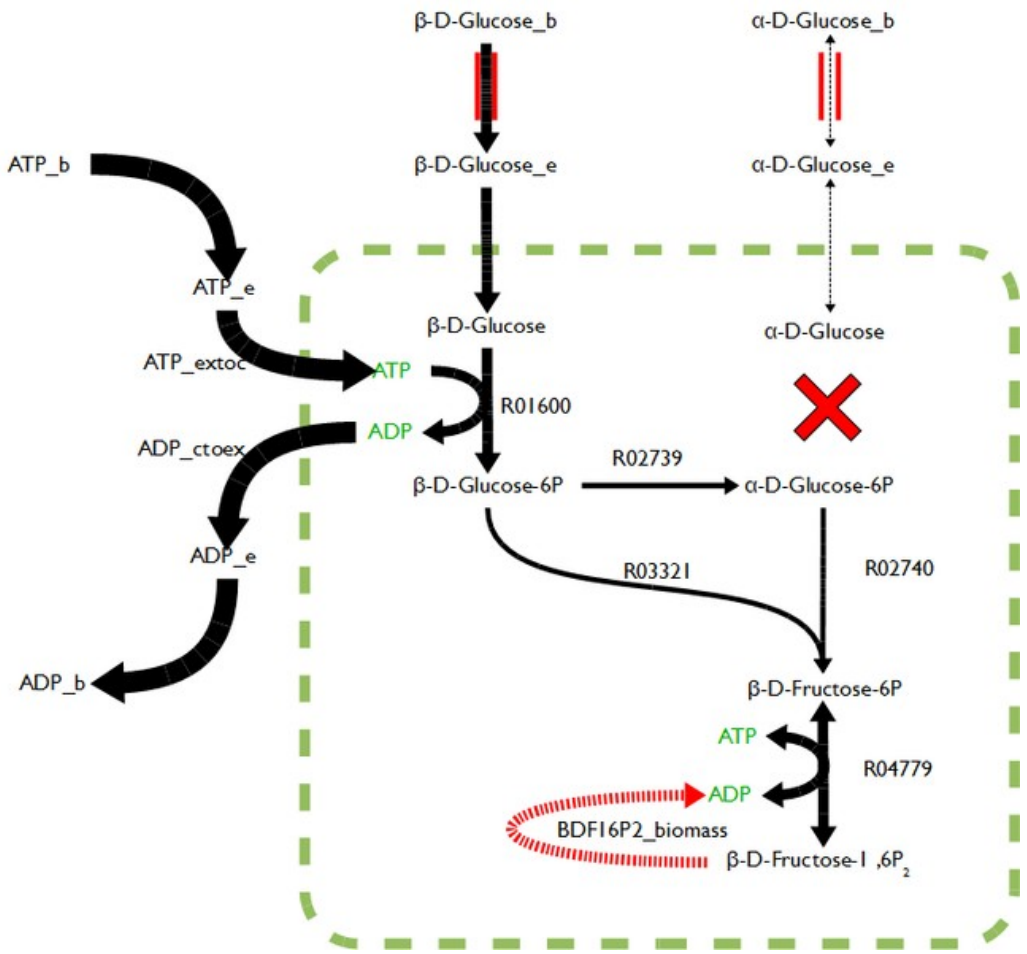
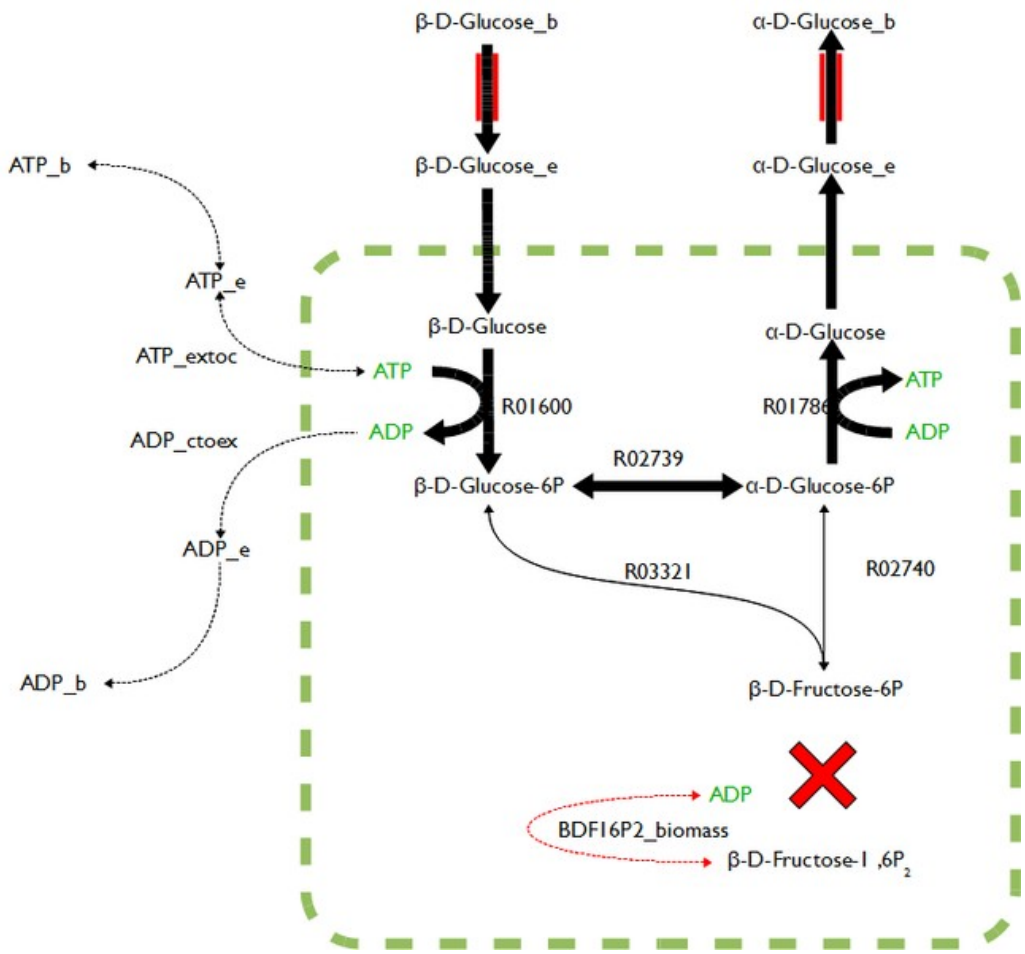
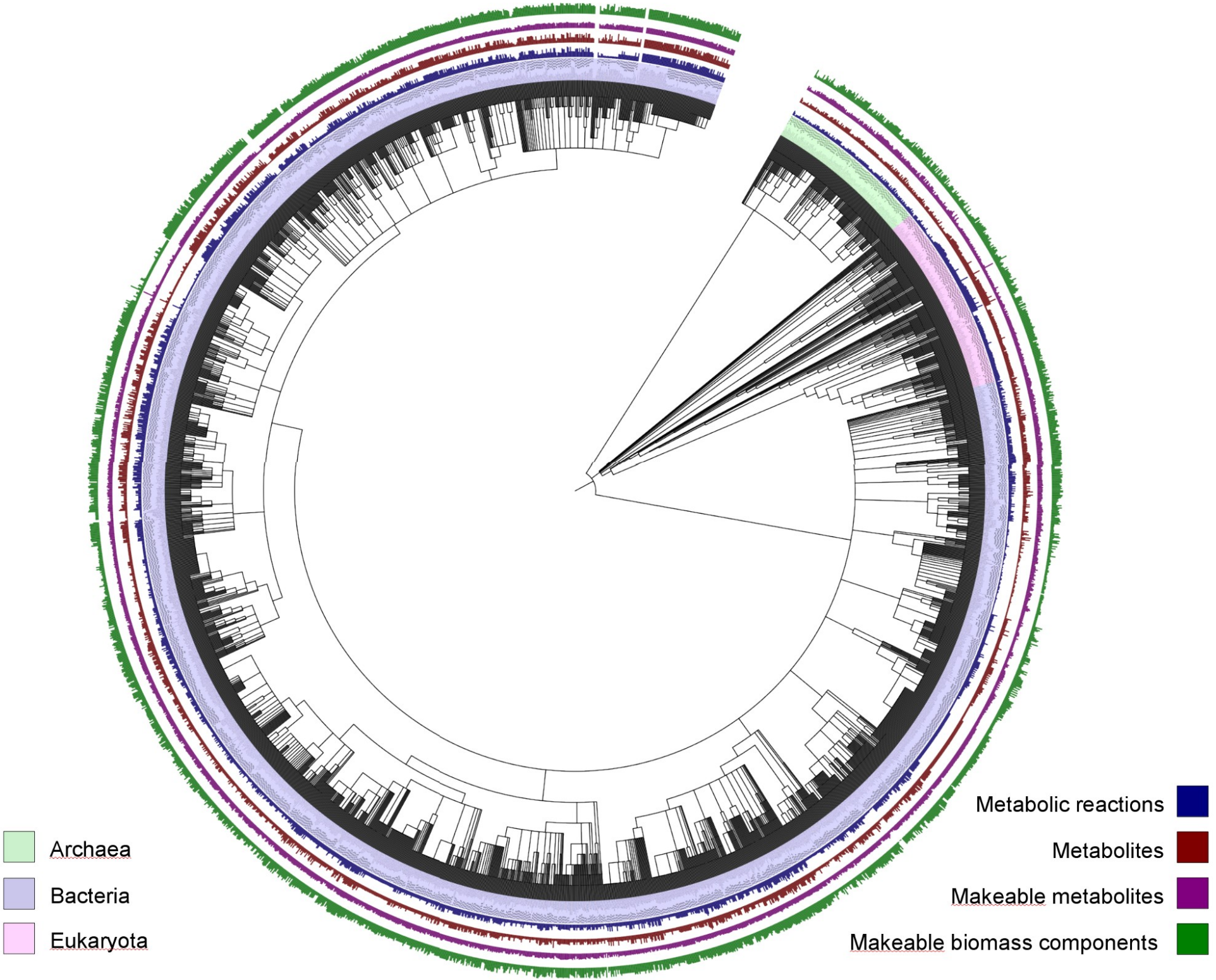
Perturbations



Non-lethal mutation



lethal mutation


Archaea
Bacteria
Eukaryota
Metabolic reactions
Metabolites
Makeable metabolites
Makeable biomass components

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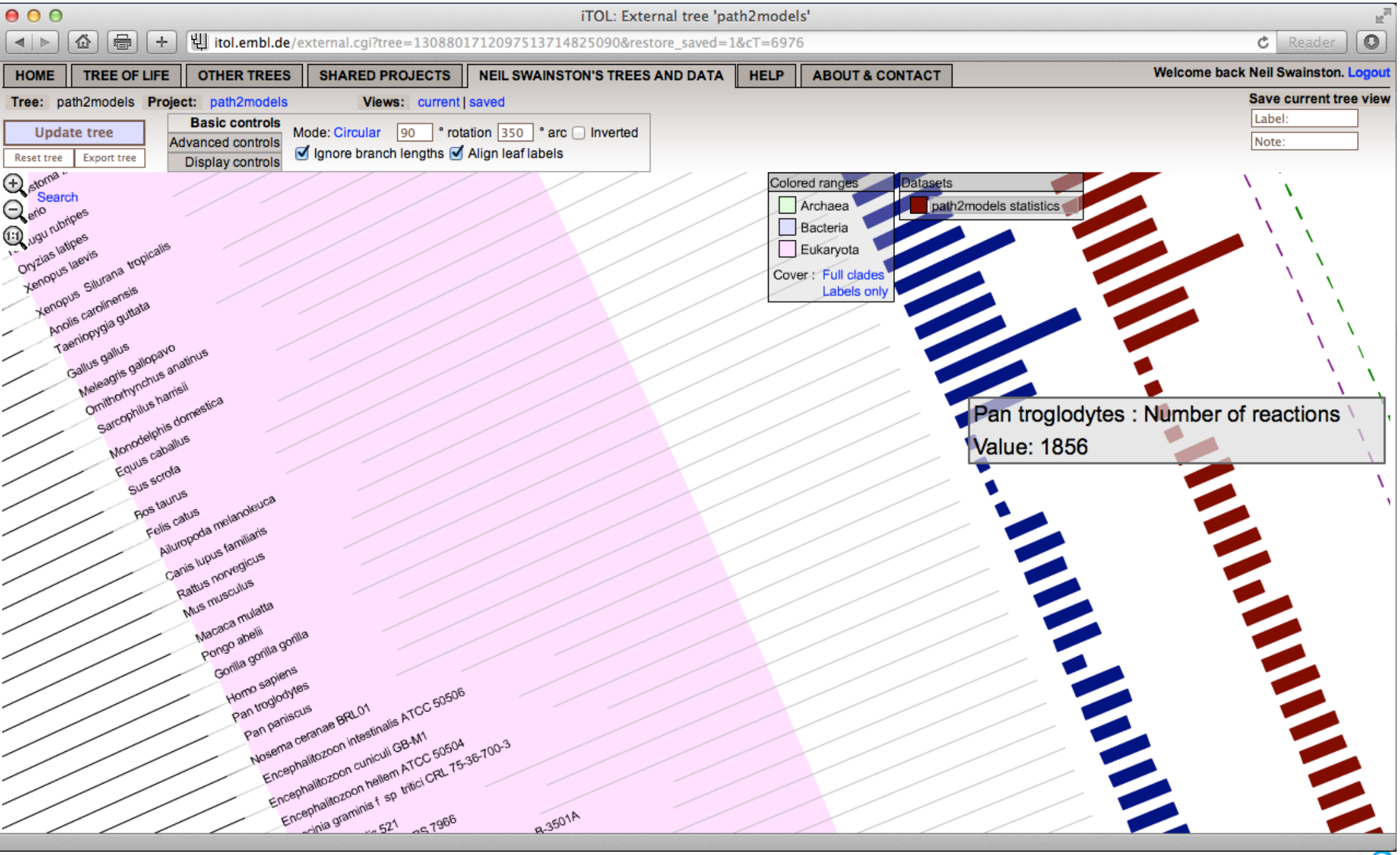

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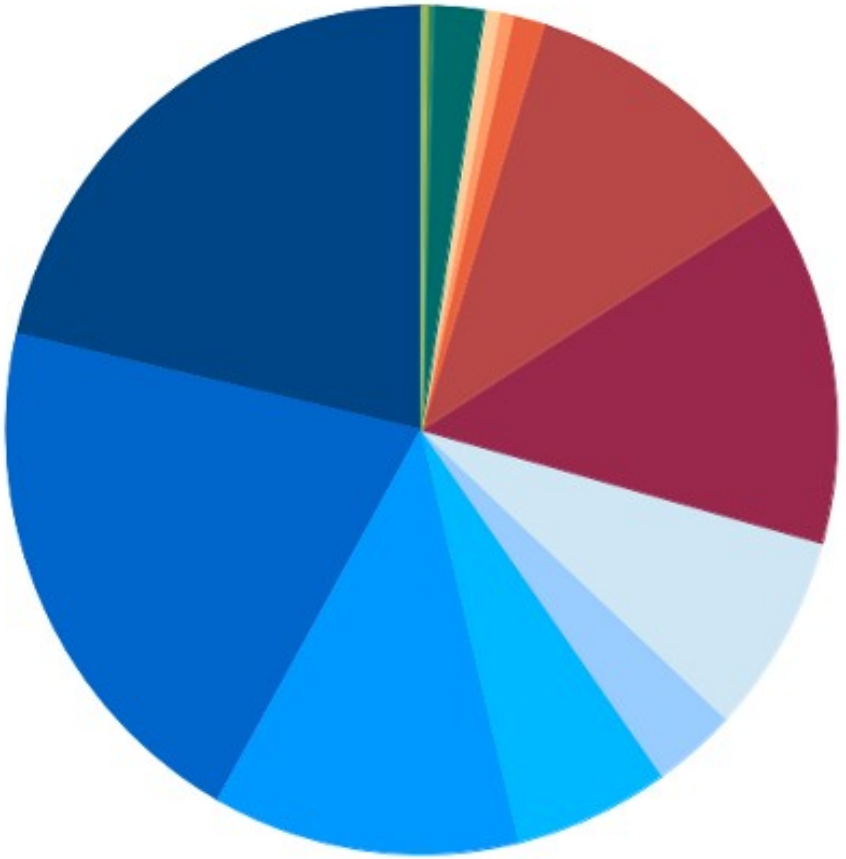
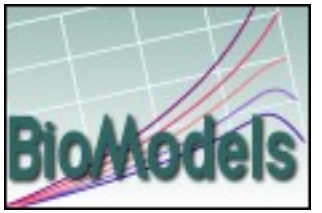
Gene Ontology Coverage



- amino-acid metabolism
- biosynthesis
- saccharide metabolism
- lipid metabolism
- nucleic acid metabolism
- metabolism (other)
- transport and secretion
- genome function
- intracellular signaling
- Intracellular membrane system
- protein processing
- cytoskeletton
- physiological function
- cell division, development and differentiation
- cell interaction
- other

26th BioModels Database release



- October 2013 – 5th release of Path2Models data
- 112 898 common modular rate law models of metabolic networks
- 27 306 qualitative models of signalling pathways
- 2 630 whole genome flux balance analysis models
- 12 280 007 mathematical relations
- 432 154 677 cross references
- http://www.ebi.ac.uk/biomodels-main/path2models

Inositol phosphate metabolism - Mus musculus

Download SBML | Additional files | Send feedback

Model information

Identifier: BMID000000038685
Format: SBML L3 V1 (Layout)
Project: path2models
Categories: metabolic
Submission: 17 May 2012 22:37:29 UTC
Last modified: 10 Dec 2012 03:55:58 UTC
Published: 19 May 2012 23:49:21 UTC

Annotations

isDescribedBy	inositol metabolic process	*Gene Ontology*
occursIn	Mus musculus	*Taxonomy*
isDerivedFrom	Inositol phosphate metabolism	*KEGG Pathway*

Model of "Inositol phosphate metab

Graphical representation of 'Inositol phosphat
(PNG image hosted by the Kyoto Encyclopedi

This model has been automatically generated
formats. Wrzodek C, Dräger A, Zell A. *Bioinfor*
Some kinetic information were added from SA
The missing kinetic equations were added by

This model has been produced by the path2m

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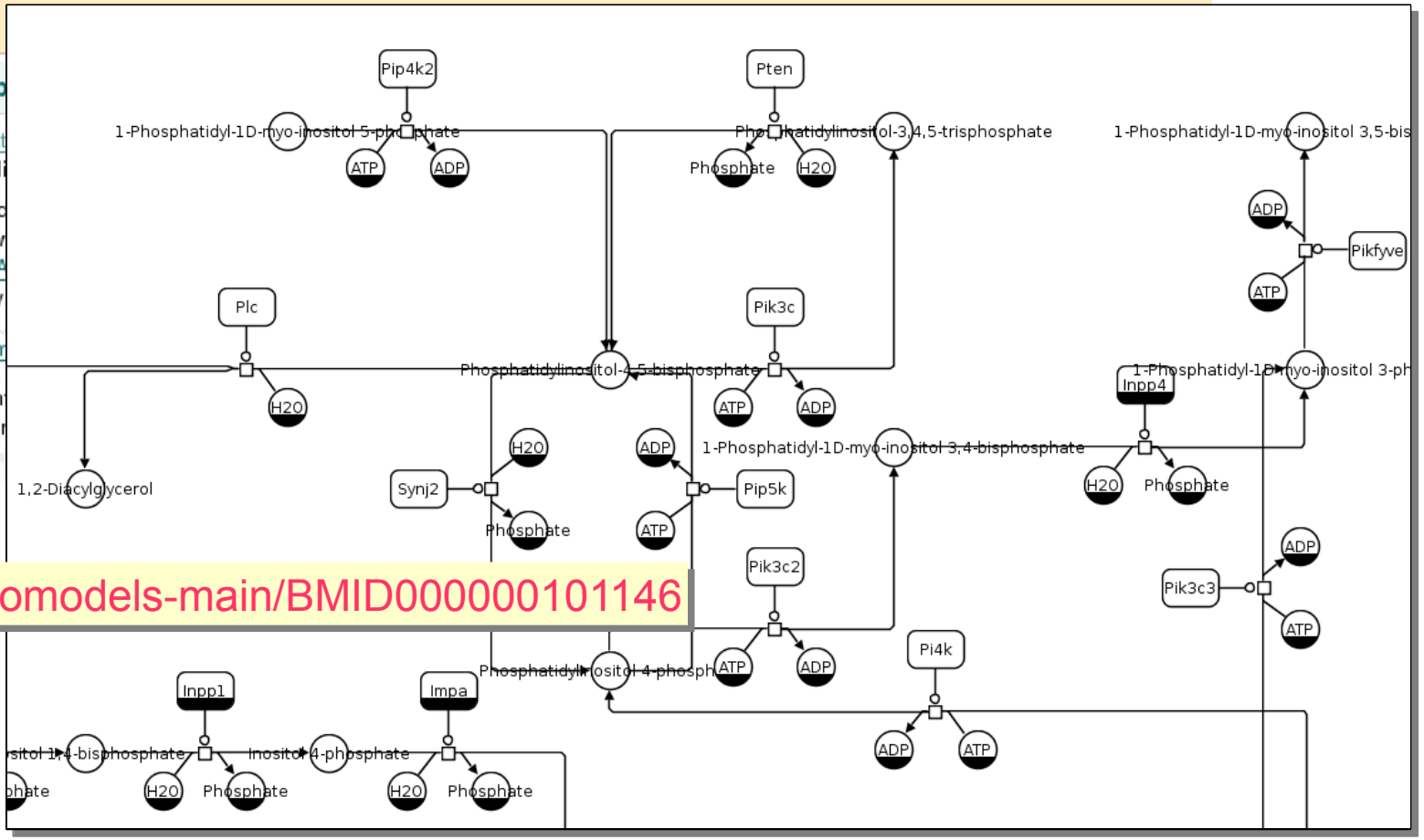
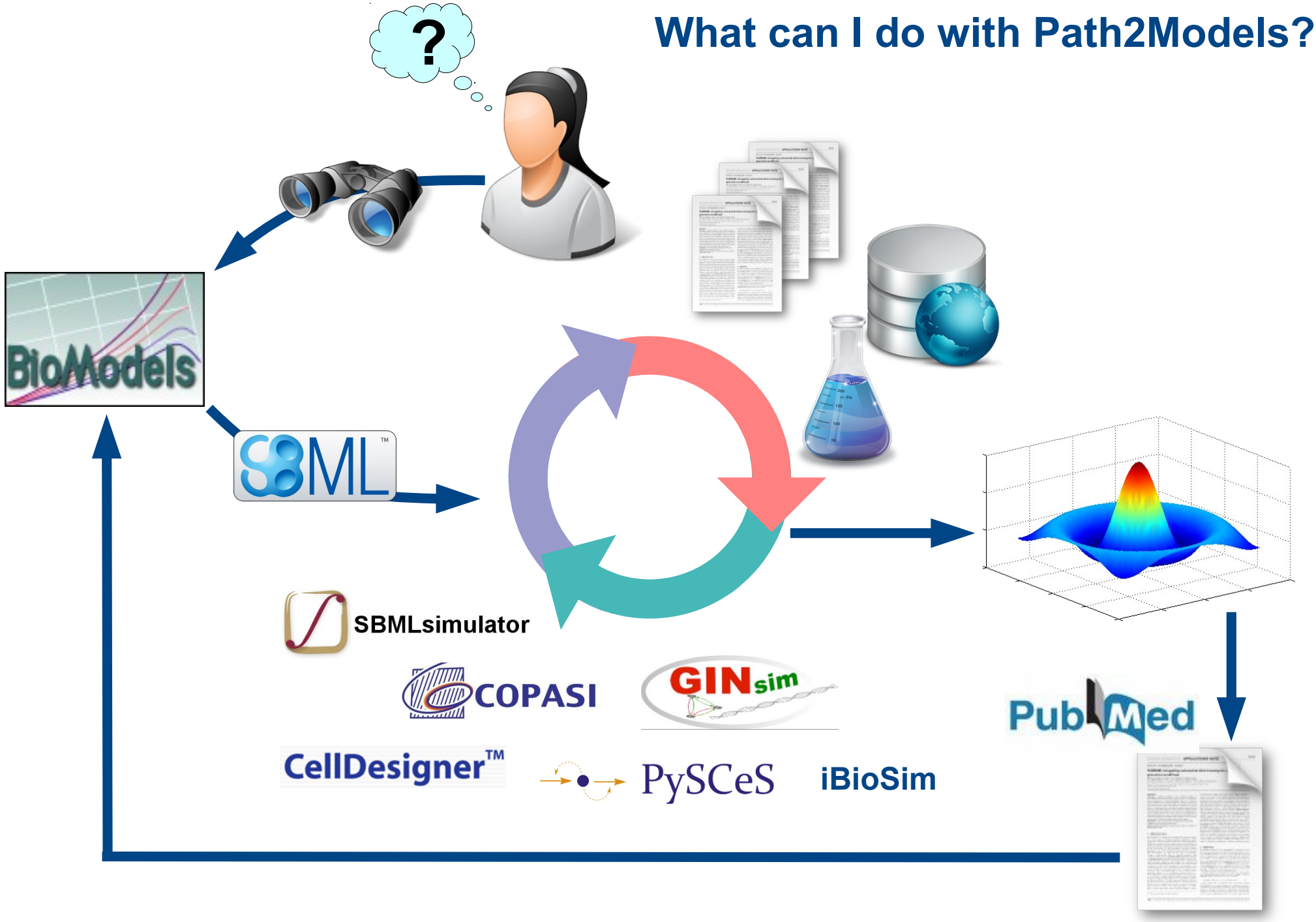


http://www.ebi.ac.uk/biomodels-main/BMID000000101146

What can I do with Path2Models?



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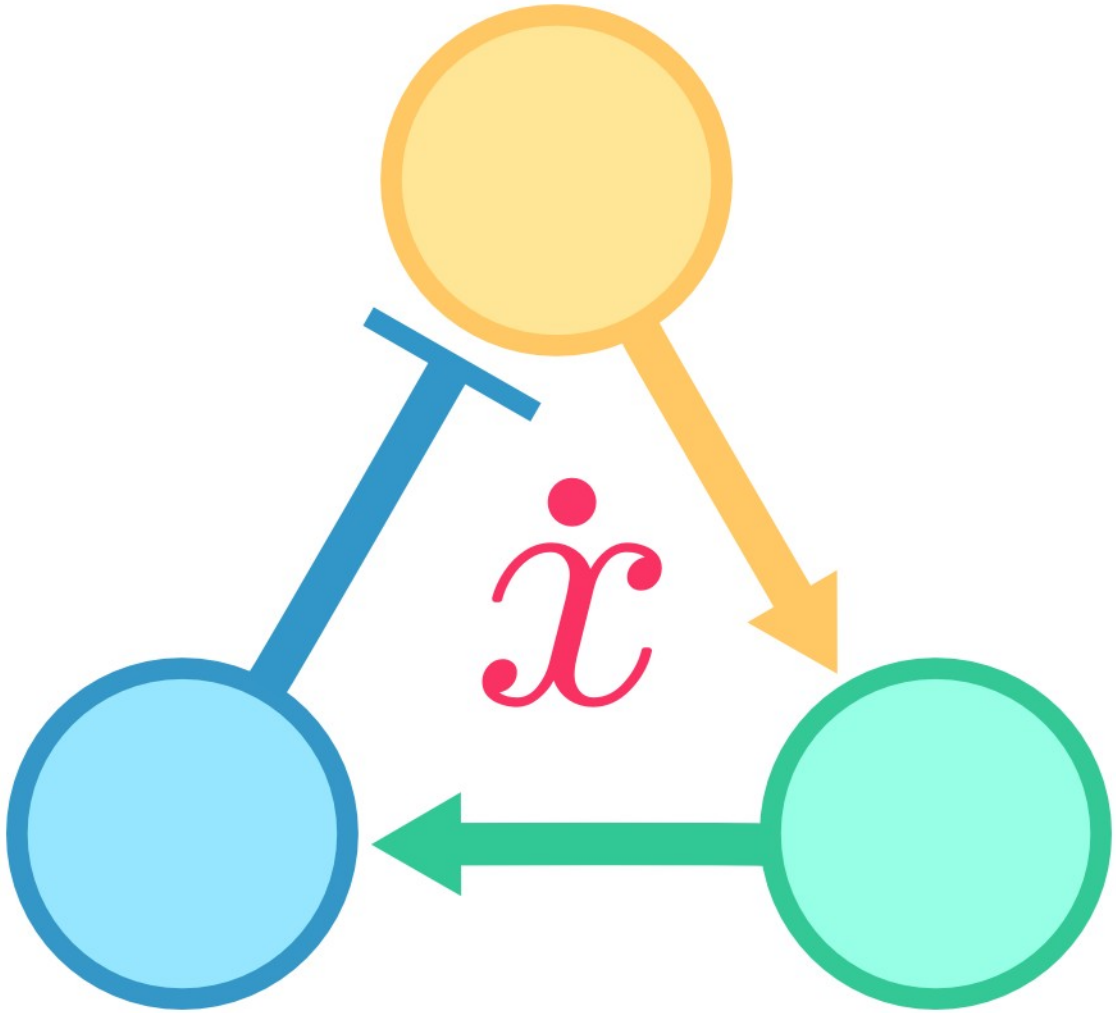
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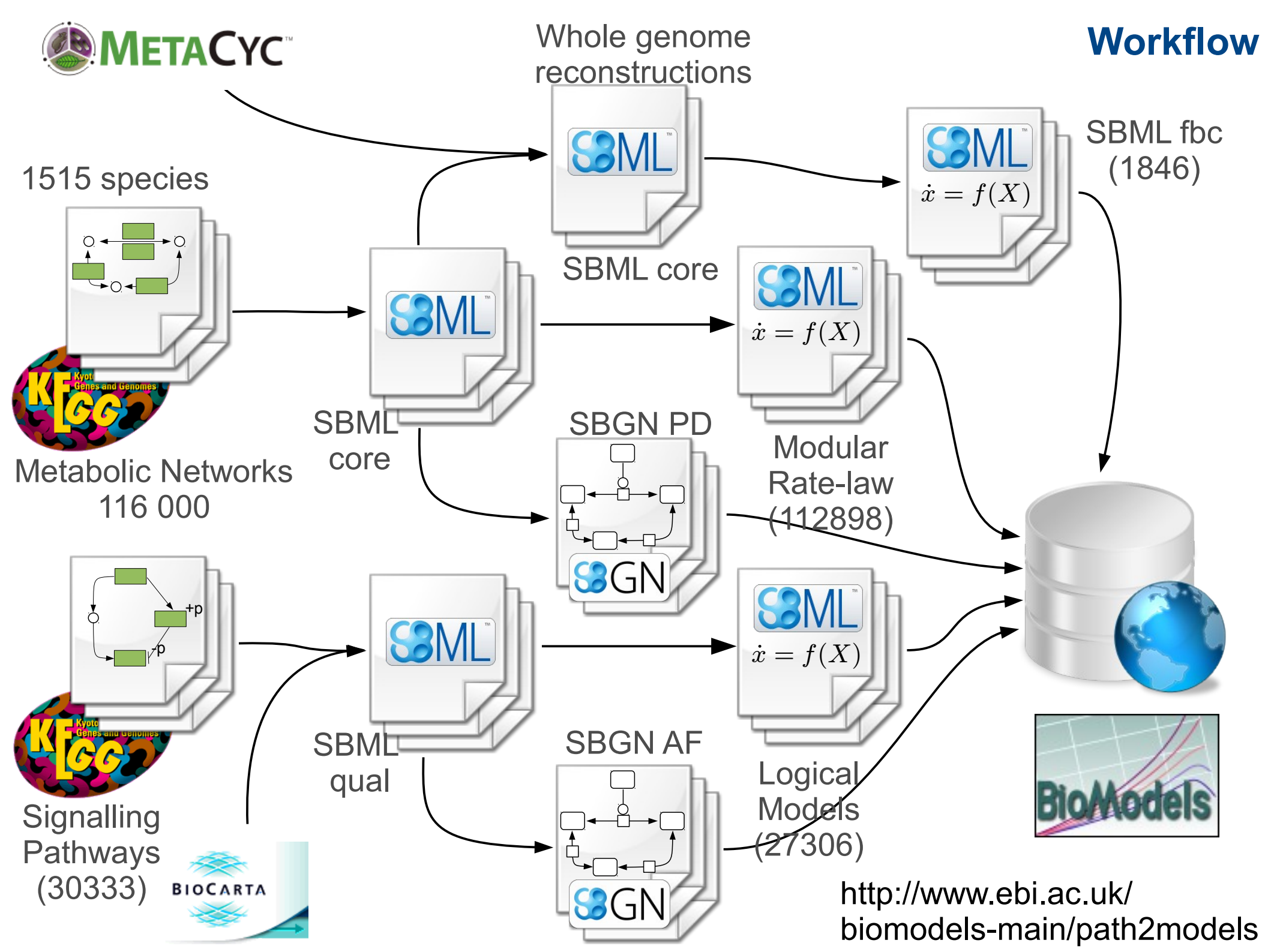
Workflow


METACYC
Whole genome reconstructions
SBML core
SBML fbc (1846)
1515 species
KEGG
Metabolic Networks 116 000
SBML core
SBGN PD
Modular Rate-law (112898)
SBML qual
SBGN AF
Logical Models (27306)
Signalling Pathways (30333)
BIOCARTA
BioModels
http://www.ebi.ac.uk/biomodels-main/path2models