Models For All

Standards for describing the whole life-cycle of modeling in the life sciences

Nicolas Le Novère, EMBL-EBI

What happened to Biology at the end of XXth century?

Annu. Rev. Genomics Hum. Genet. 2001. 2:343–72

A New Approach to Decoding Life:
Systems Biology

Trey Ideker[1,2], Timothy Galitski[1], and Leroy Hood[1,2,3,4,5]
Institute for Systems Biology[1], Seattle, Washington 98105; Departments of

New Generation Computing, 18(2000)199-216
Ohmsha, Ltd. and Springer-Verlag

Invited Paper

Perspectives on Systems Biology

Hiroaki KITANO
Sony Computer Science Laboratories, Inc.

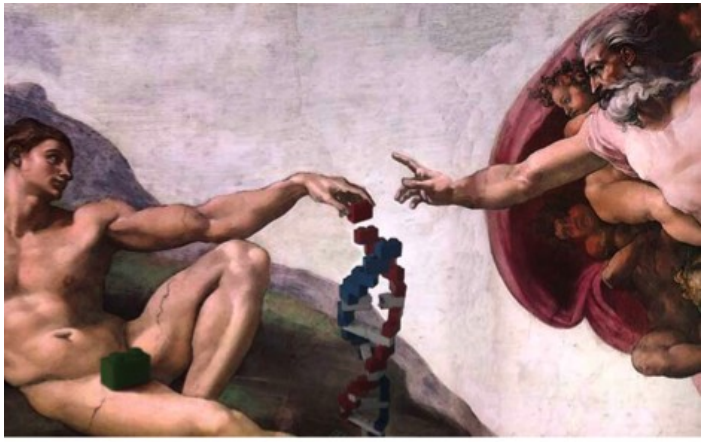
What happened to biology at the end of XXth century?

RESEARCH ARTICLE

Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome

Daniel G. Gibson,[1] John I. Glass,[1] Carole Lartigue,[1] Vladimir N. Noskov,[1] Ray-Yuan Chuang,[1] Mikkel A. Algire,[1] Gwynedd A. Benders,[2] Michael G. Montague,[1] Li Ma,[1] Monzia M. Moodie,[1] Chuck Merryman,[1] Sanjay Vashee,[1] Radha Krishnakumar,[1] Nacyra Assad-Garcia,[1] Cynthia Andrews-Pfannkoch,[1] Evgeniya A. Denisova,[1] Lei Young,[1] Zhi-Qing Qi,[1] Thomas H. Segall-Shapiro,[1] Christopher H. Calvey,[1] Prashanth P. Parmar,[1] Clyde A. Hutchison III,[2] Hamilton O. Smith,[2] J. Craig Venter[1,2]*

2 JULY 2010 VOL 329 SCIENCE www.sciencemag.org



EXTREME GENETIC ENGINEERING

An Introduction to Synthetic Biology

etc group

january 2007

Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Cell

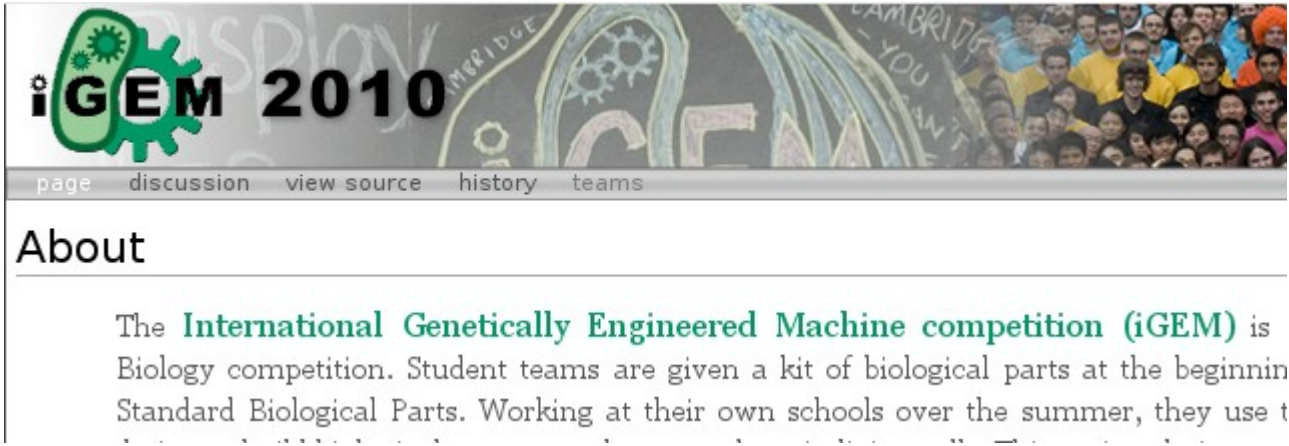
Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]
[1] Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2] CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
*Contact: yamanaka@frontier.kyoto-u.ac.jp
DOI 10.1016/j.cell.2006.07.024

A synthetic oscillatory network of transcriptional regulators

Michael B. Elowitz & Stanislas Leibler

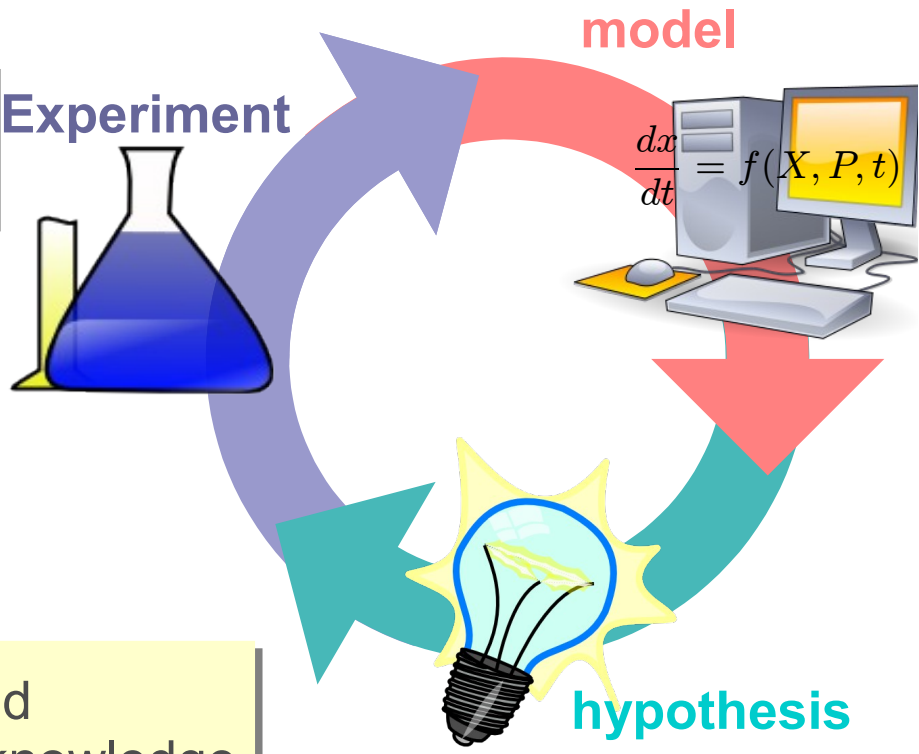
Departments of Molecular Biology and Physics, Princeton University, Princeton, New Jersey 08544, USA

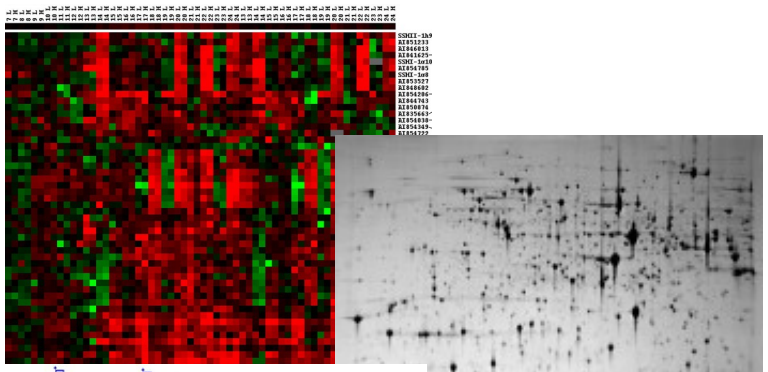
NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com

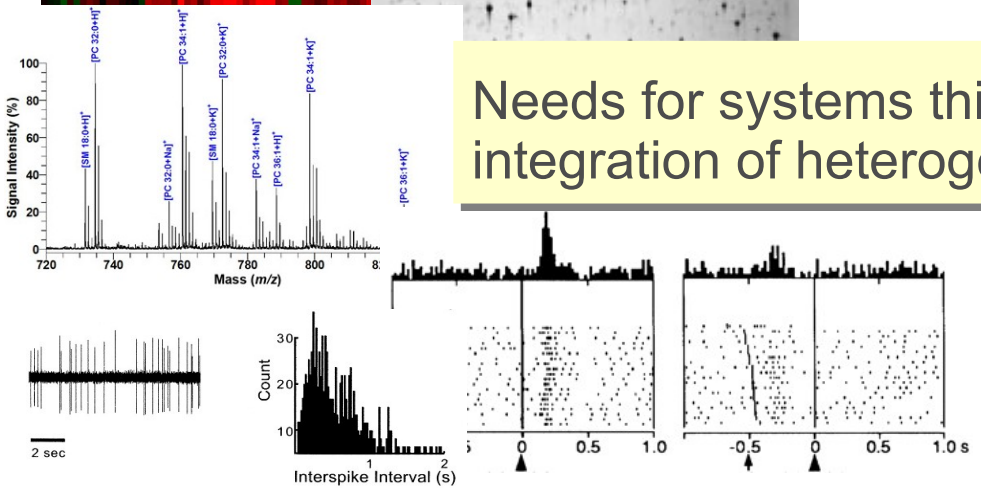


New way of doing biomedical research

Needs for interplay between models and reality tests

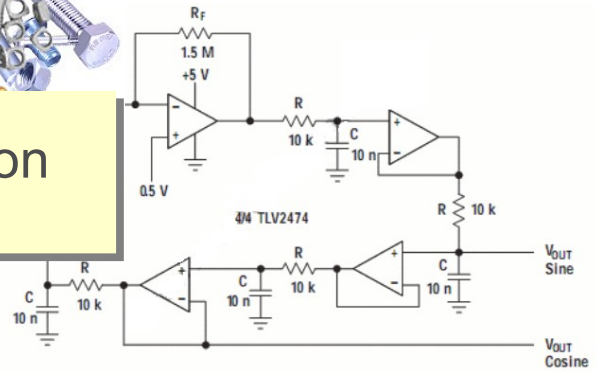






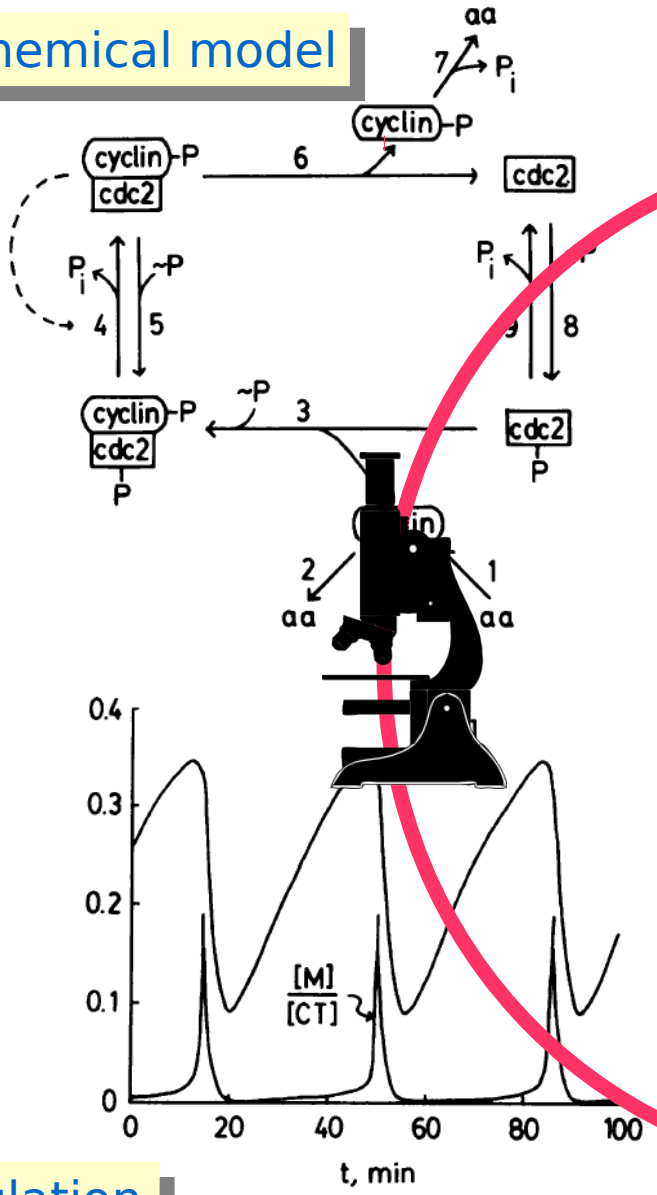
Needs for systems thinking and integration of heterogeneous knowledge

Needs for cooperation and standardisation



The models I am talking about

biochemical model



simulation

mathematical model

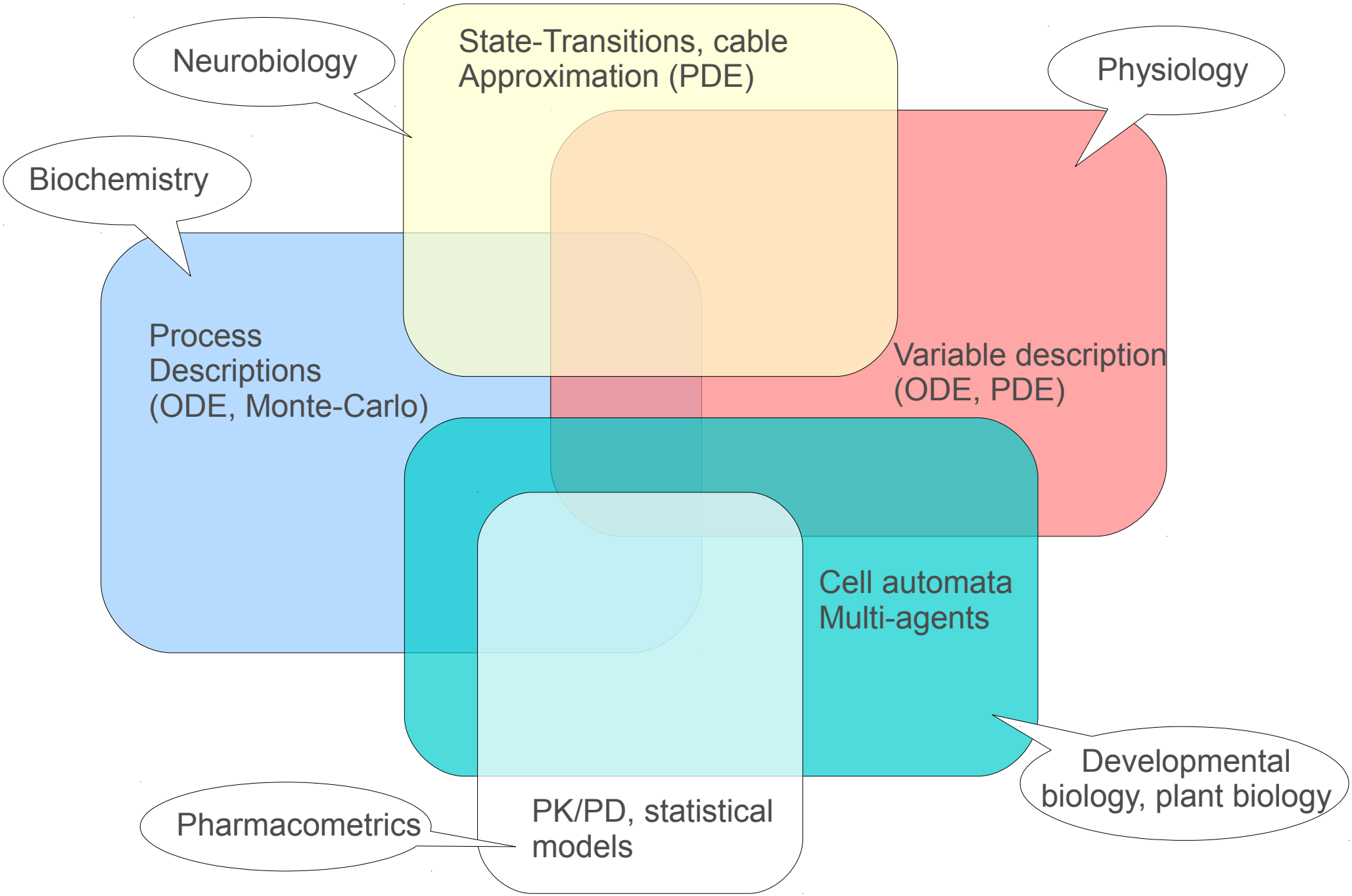
$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
$$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$$
$$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$$
$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
$$d[YP]/dt = k_6[M] - k_7[YP]$$

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	$>>k_6$	§

computational model

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

Many complementary modelling approaches



Computational modelling left the niches

- Metabolic networks Fung et al. A synthetic gene-metabolic oscillator. ***Nature*** 2005; Herrgård et al. A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. ***Nat Biotechnol*** 2008

- Signalling pathways Bray et al. Receptor clustering as a cellular mechanism to control sensitivity. ***Nature*** 1998; Bhalla ad Iyengar. Emergent properties of signaling pathways. ***Science*** 1998; Schoeberl et al. Computational modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors. ***Nat Biotechnol*** 2002; Hoffmann et. The IκB-NF-κB signaling module: temporal control and selective gene activation. ***Science*** 2002; Smith et al. Systems analysis of Ran transport. ***Science*** 2002; Bhalla et al. MAP kinase phosphatase as a locus of flexibility in a mitogen-activated protein kinase signaling network. ***Science*** 2002; Nelson et al. Oscillations in NF-κB Signaling Control the Dynamics of Gene Expression. ***Science*** 2004; Werner et al. Stimulus specificity of gene expression programs determined by temporal control of IKK activity. ***Science*** 2005; Sasagawa et al. Prediction and validation of the distinct dynamics of transient and sustained ERK activation. ***Nat Cell Biol*** 2005; Basak et al. A fourth IkappaB protein within the NF-κB signaling module. ***Cell*** 2007; McLean et al. Cross-talk and decision making in MAP kinase pathways. ***Nat Genet*** 2007; Ashall et al. Pulsatile Stimulation Determines Timing and Specificity of NF-κB-Dependent Transcription. ***Science*** 2009; Becker et al. Covering a broad dynamic range: information processing at the erythropoietin receptor. ***Science*** 2010

- Gene regulatory networks McAdams and Shapiro. Circuit simulation of genetic networks. ***Science*** 1995; Yue et al. Genomic cis-regulatory logic: Experimental and computational analysis of a sea urchin gene. ***Science*** 1998; Von Dassow et al. The segment polarity network is a robust developmental module. ***Nature*** 2000; Elowitz and Leibler. A synthetic oscillatory network of transcriptional regulators. ***Nature*** 2000; Shen-Orr et al, Network motifs in the transcriptional regulation network of Escherichia coli. ***Nat Genet*** 2002; Yao et al. A bistable Rb-E2F switch underlies the restriction point. ***Nat Cell Biol*** 2008; Friedland. Synthetic gene networks that count. ***Science*** 2009

- Pharmacometrics models Labrijn et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. ***Nat Biotechnol*** 2009

- Physiological models Noble. Modeling the heart from genes to cells to the whole organ. ***Science*** 2002; Izhikevich and Edelman. Large-scale model of mammalian thalamocortical systems. ***PNAS*** 2008

- Infectious diseases Perelson et al. HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. ***Science*** 1996; Nowak. Population dynamics of immune responses to persistent viruses. ***Science*** 1996; Neumann et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. ***Science*** 1998

BioModels Database - A Database of Annotated Published Models

BioModels Database is a repository of peer-reviewed, published, computational models. These mathematical models are primarily from the field of systems biology, but more generally are those of biological interest. This resource allows biologists to store, search and retrieve published mathematical models. In addition, models in the database can be used to generate sub-models, can be simulated online, and can be converted between different representational formats. This resource also features programmatic access via Web Services.

All unmodified models in the database are available freely for use and distribution, to all users. This resource is developed and maintained by the BioModels.net initiative. More information about BioModels Database can be found in the Frequently Asked Questions.

Advanced Search

Search | Go to model

Browse models

- Curated models (326)
- Browse models usi
- Non-curated models (373)

Browse curated models

Browse the models in the curated branch. These models have been thoroughly curated, and model elements have been annotated with terms from controlled vocabularies as well as links to relevant data resources.

Simulate in JWS Online

Submit a model

http://www.ebi.ac.uk/biomodels/

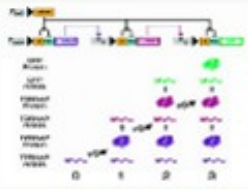
Links

- Main instance at EMBL-EBI, UK
- Mirror at Caltech, USA
- Project on SourceForge
- Web Services
- Download archived models

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

Model of the month

June, 2011



Two complementary synthetic genetic counters in E.*coli* that can count up to three induction events: the first, a riboregulated transcriptional cascade, and the second, a recombinase-based cascade of memory units, has been reported.. *Read more...*

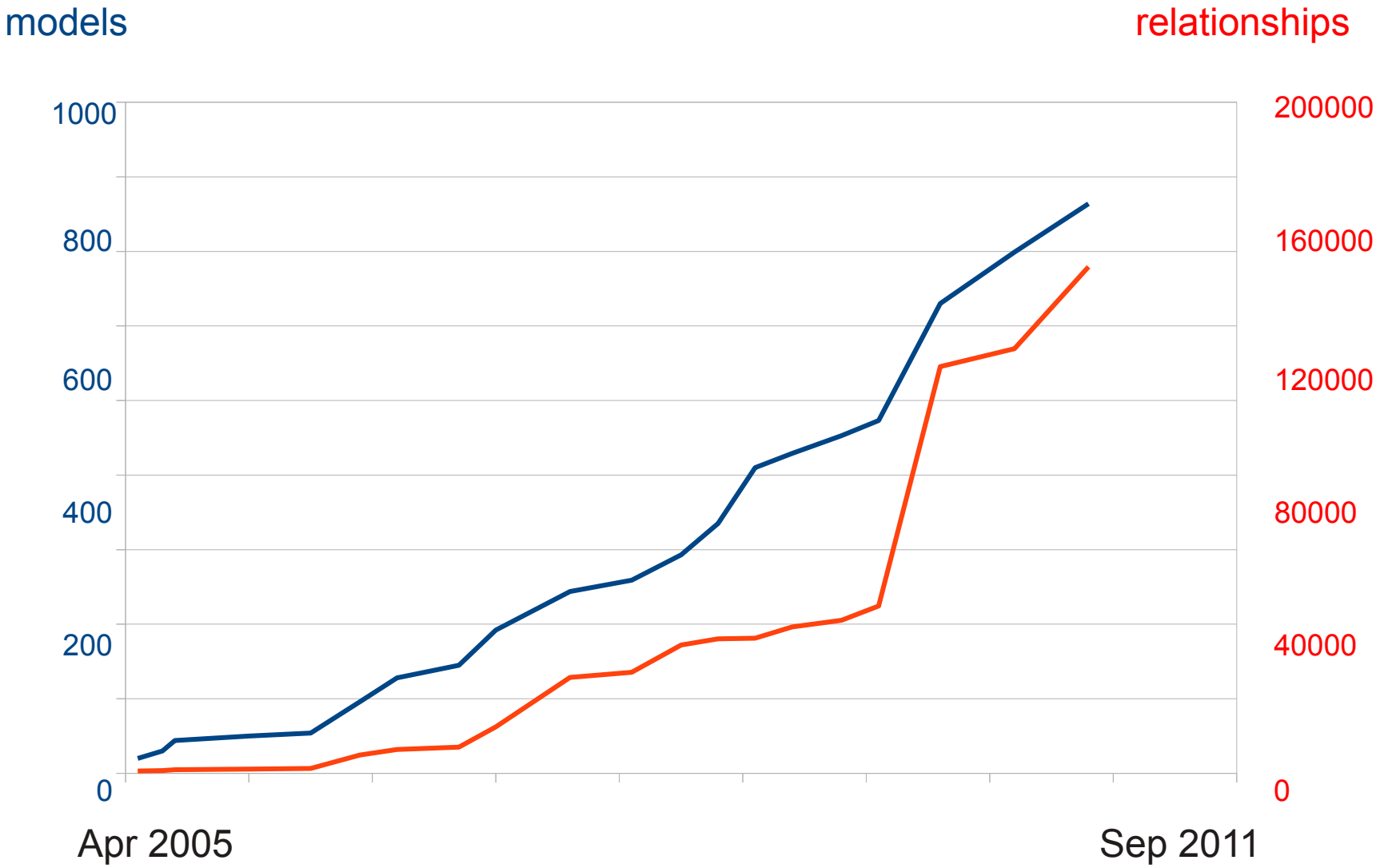
News

15 April 2011 **Nineteenth Release!**
Download All Models Under SBML Format

4 February 2011 **JUMMP: JUst a Model Management Platform**
To provide the worldwide community with a modern tool for the collaborative creation and sharing of models in an efficient and secured way, the Jürgen Eils and Nicolas Le Novère groups are announcing the JUMMP project. It is planned that JUMMP will be used as the software infrastructure running BioModels Database. Read more...

17 November 2010 **New availability of the Models of the Month**
Models of the Month are now linked from BioMed Central's Systems Biology Gateway.

Computational models on the rise



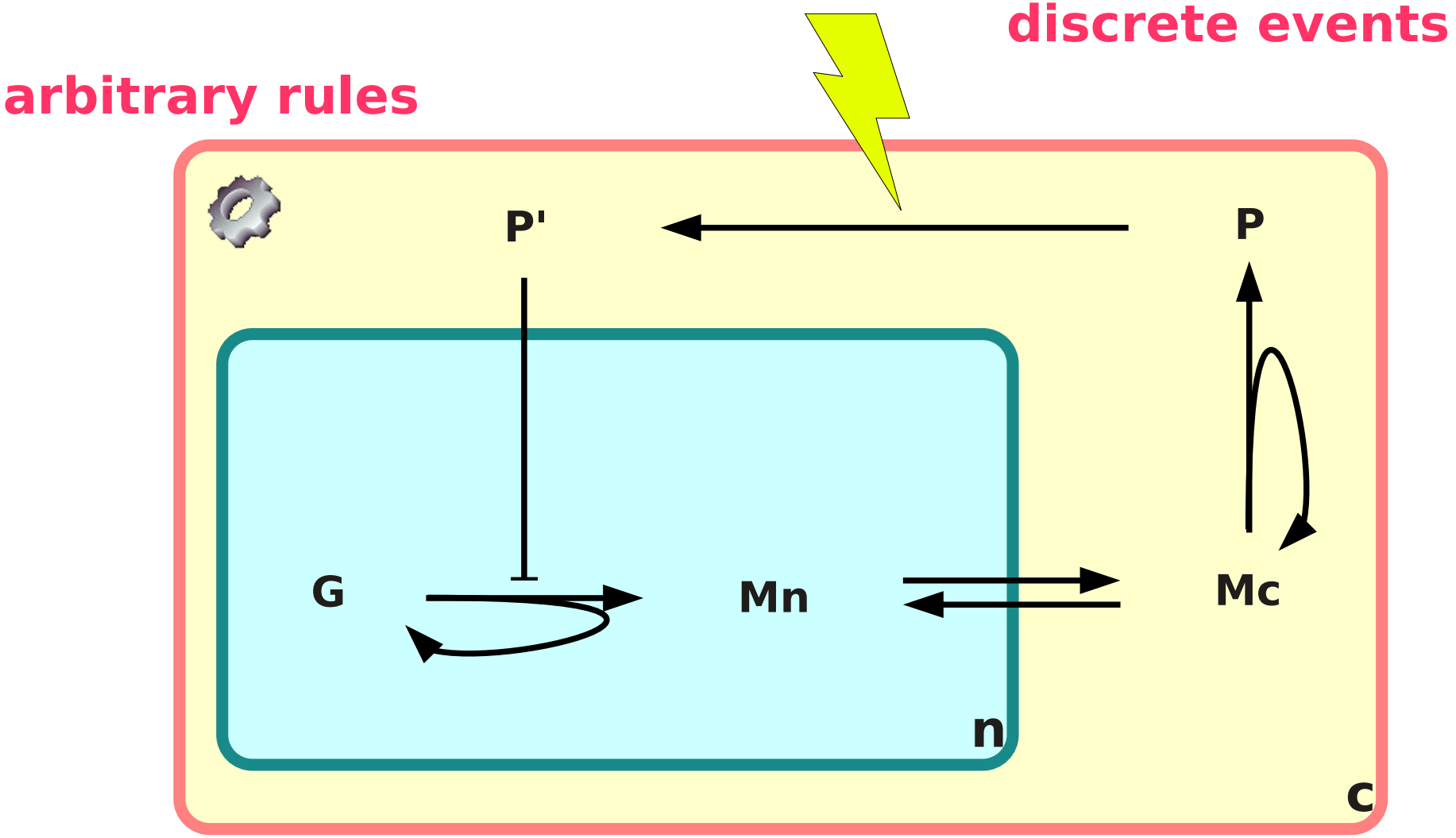
BioModels Database growth since its creation

A language to describe computational models in biology

	Model descriptions
Data-models	

Born in Caltech 2000

What can we encode in SBML (core)?



Why the Extensible Markup Language (XML)?

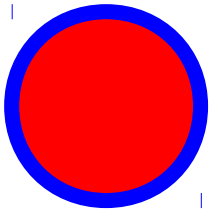
- **HTML**

```
A <strong>strong word</strong> and an
<a href=”http://www.w3.org/”>hyperlink</a>
```

A **strong word** and an hyperlink

- **SVG**

```
<circle r="100" fill="red"
stroke="blue" stroke-width="10"  />
```



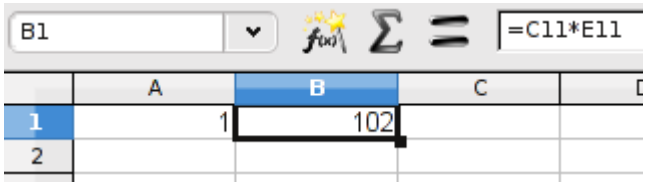
- **MathML**

```
<apply>
  <int/>
  <bvar><ci> x </ci></bvar>
  <lowlimit><cn> 0 </cn></lowlimit>
  <uplimit><ci> a </ci></uplimit>
  <apply><ci> f </ci><ci> x </ci></apply>
</apply>
```

$$\int_0^a f(x)\,dx$$

- **Excel**

```
<row r="1">
  <c r="A1"><v>1</v></c>
  <c r="B1">
    <f>C11*E11</f>
    <v>102</v>
  </c>
</row>
```



Why the Extensible Markup Language (XML)?

- Easy to define and validate
  - Rapid prototyping, processing tools can be generated and thrown away
- Existence of a very large toolkit
  - Libraries in every programming languages
  - A very large number of description formats in life sciences are in XML
- Associated technologies
  - Definition: XML Schema, Schematron (themselves XML)
  - Conversion: XSLT (using XSL in XML)
  - Linking: XPath and XQuery

Global structure of a SBML file

variables

relationships

```
<?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>
```

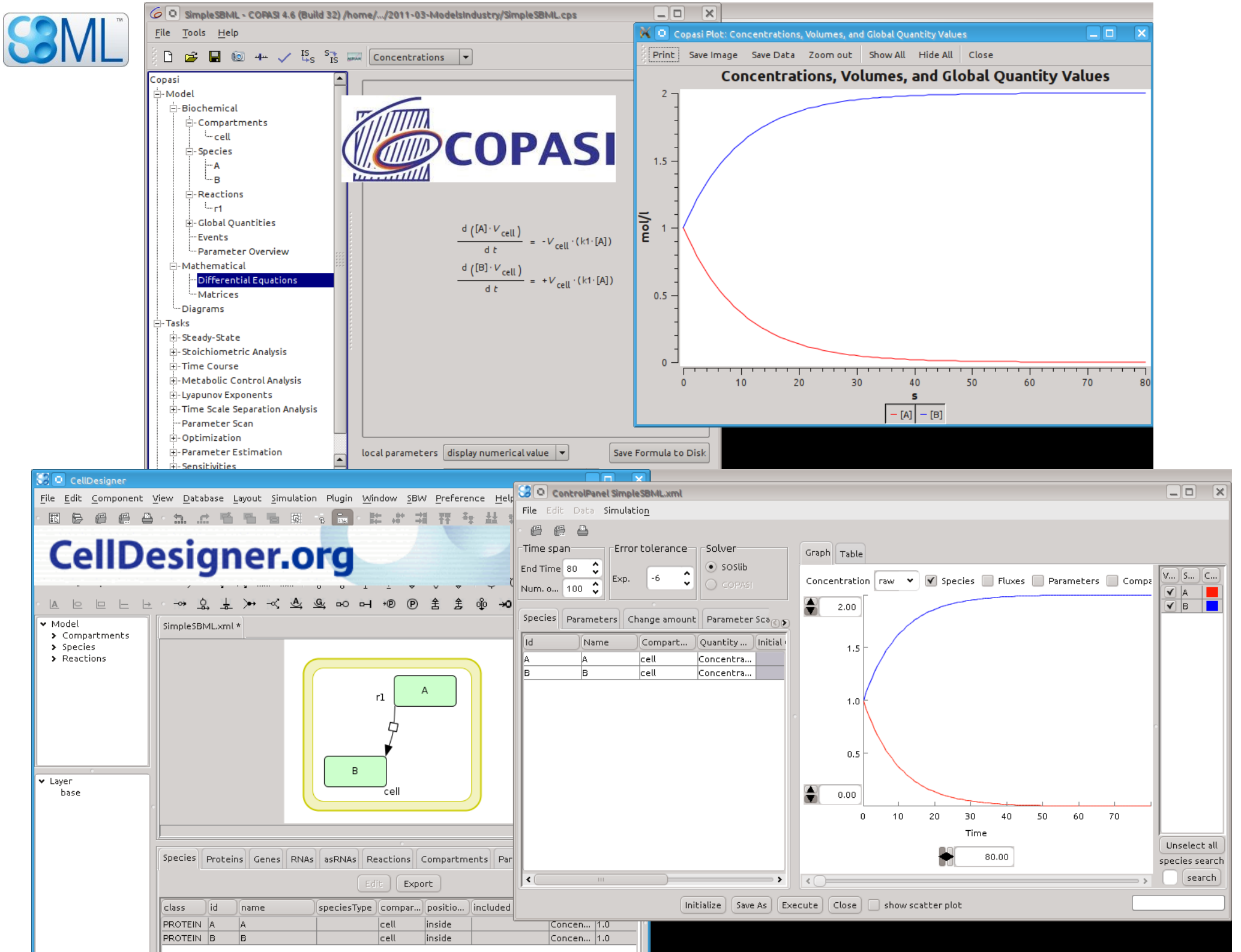
A very simple SBML file (A ⟶ B)

```
<?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>
```

A very simple SBML file (A ⟶ B)

```
<?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>
```

MathML


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
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.org
Model
Compartments
Species
Reactions
Layer
base
SimpleSBML.xml *
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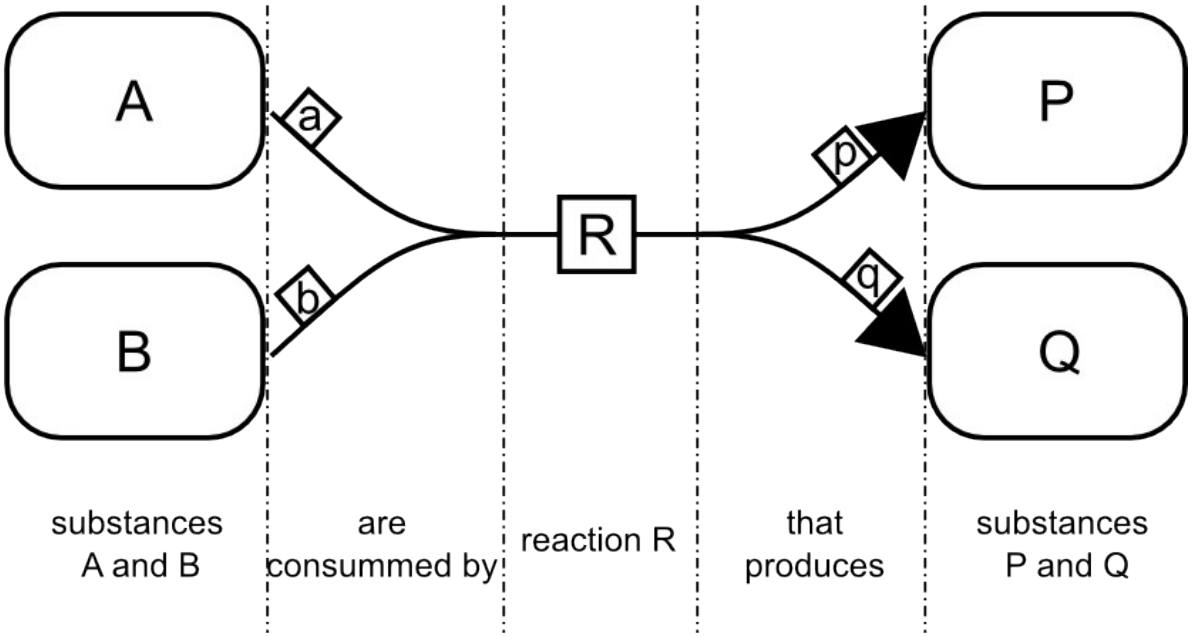
A
B
cell
Species Proteins Genes RNAs asRNAs Reactions Compartments
Edit Export
class id name speciesType compar... positio... included
PROTEIN A A cell inside Concen... 1.0
PROTEIN B B cell inside Concen... 1.0
ControlPanel SimpleSBML.xml
File Edit Data Simulation
Time span
End Time 80
Num. o... 100
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



SBML

Species | Species Reference | Kinetic Law | Species Reference | Species

A more realistic example ...

```
<species·
    id="A"·
    name="a-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF·
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"·
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

A more realistic example ...

```
<species·
    id="A"·
    name="a-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF·
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"·
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

biological semantics: macromolecule

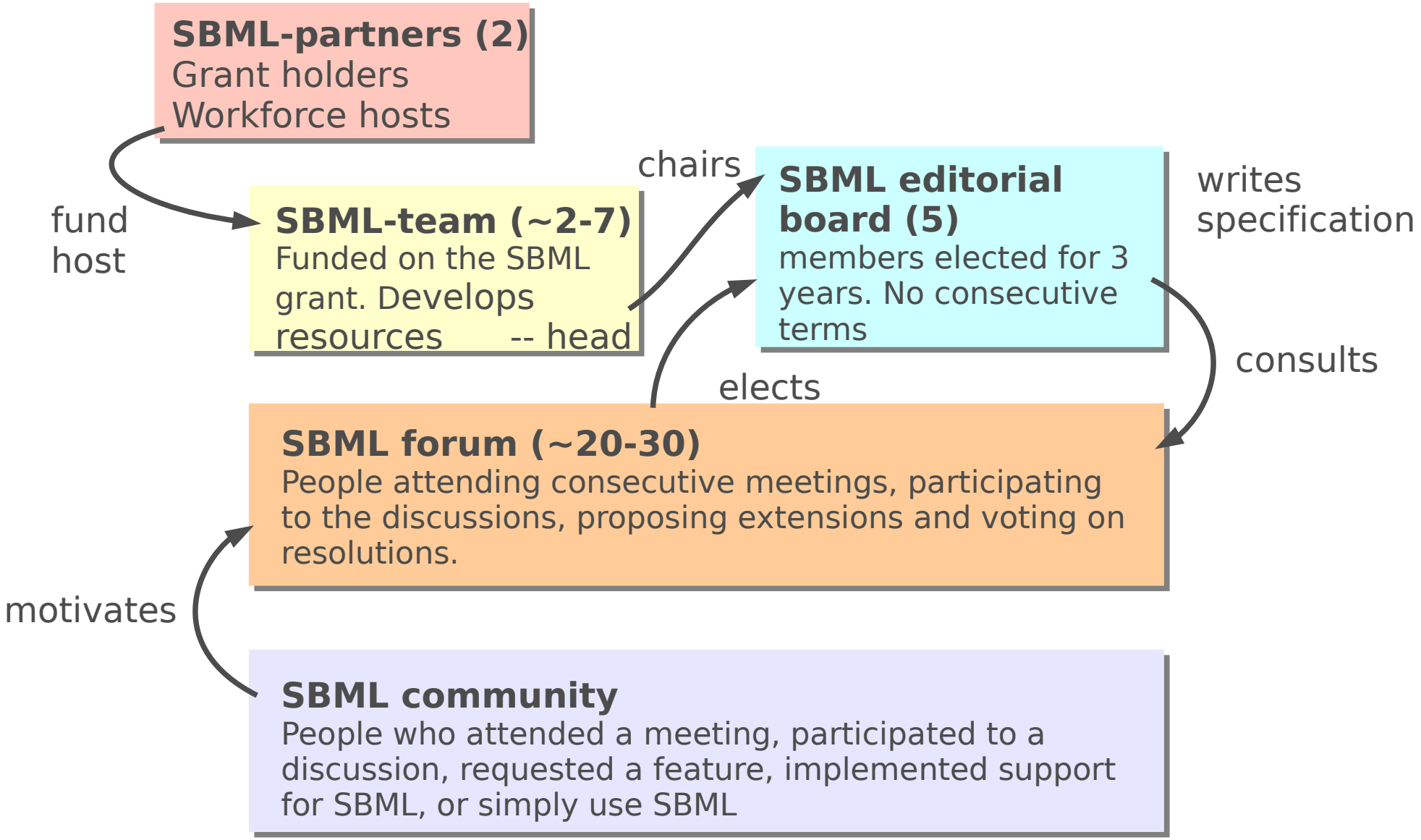
XHTML

RDF

SBML definition and API

- SBML syntax and semantics are very precisely defined
  - SBML specification document: Level 3 Version 1 = 167 pages, small margins
  - XML schema (L1 and L2) and Schematron (forthcoming for L3)
  - Hundreds of validation rules to check compliance
- A standard Application Programming Interface with two implementations
  - LibSBML in C and C++, with binding to C#, Java, Python, Perl, MatLab, Octave, Ruby
  - JSBML, native Java version
- Test suite of 5514 models either testing a feature or a documented error

Current structure of the community



SBML Software Guide

The following summarize all SBML-compatible systems known to us. The *matrix* provides an at-a-glance summary, whereas the *summary* provides longer descriptions of each software or project grouped by themes.

Number of software packages listed in the matrix today: 225.

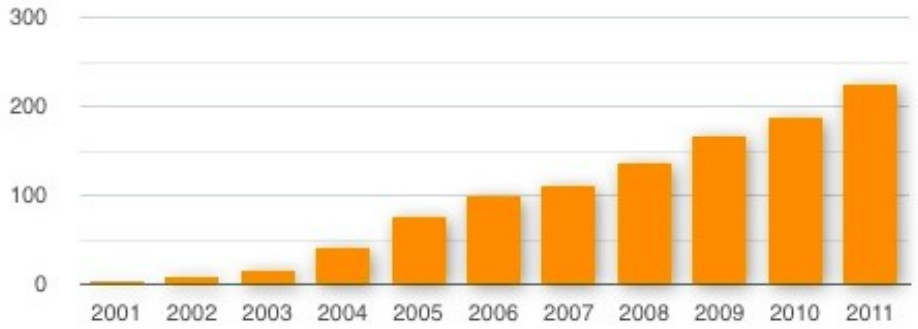
Please **use the survey form** to notify us about additions and suggestions.

Go to the SBML Software Matrix

Go to the SBML Software Summary

Historical trend

The following graph shows the total number of known SBML-compatible software packages each year, as counted by the SBML Team. The counts shown are for approximately the middle of each year.



(Note: the flat period in 2007 is an artifact of inadequate record keeping rather than a lull in SBML software

SBML supporting tools

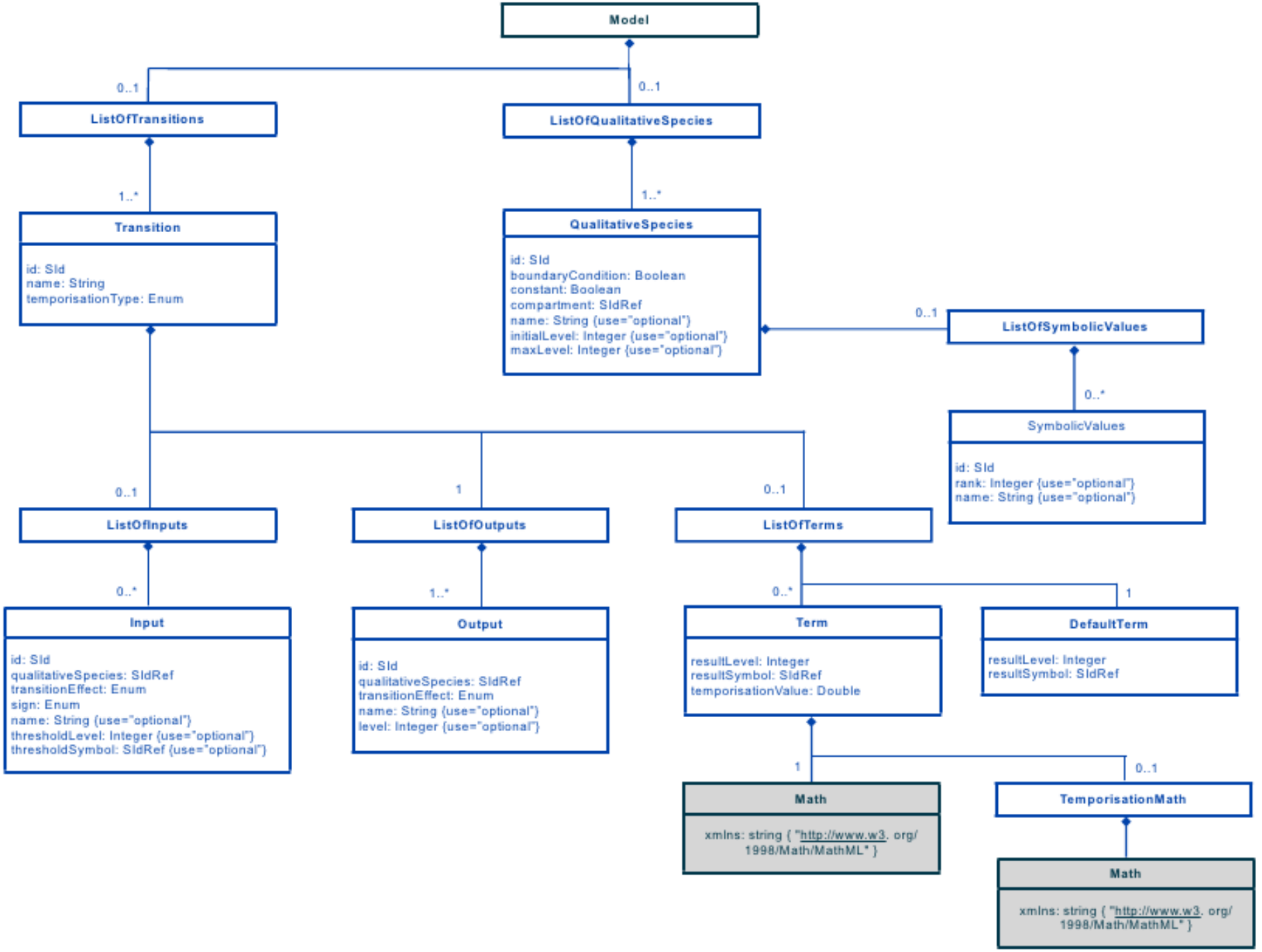
- Simulators
  - Discrete stochastic (25)
  - Continuous deterministic (42)
  - Spatial (4)
- Modelling and simulation environments (29)
  - Based on Mathematica (3)
  - Based on Matlab (12)
  - Based on Python/SciPy (9)
  - Based on R (3)
- Flux/metabolic analysis (16)
- Integrated framework (3)
- Libraries (3)
- Model Management, Data Integration, and Analysis (12)
- Model development tools (18)
- Model visualisation (7)
- Model Repositories, Test Suites, and Databases (16)
- Converters (7)
- Analysis and utility (12)

SBML Level 3 packages

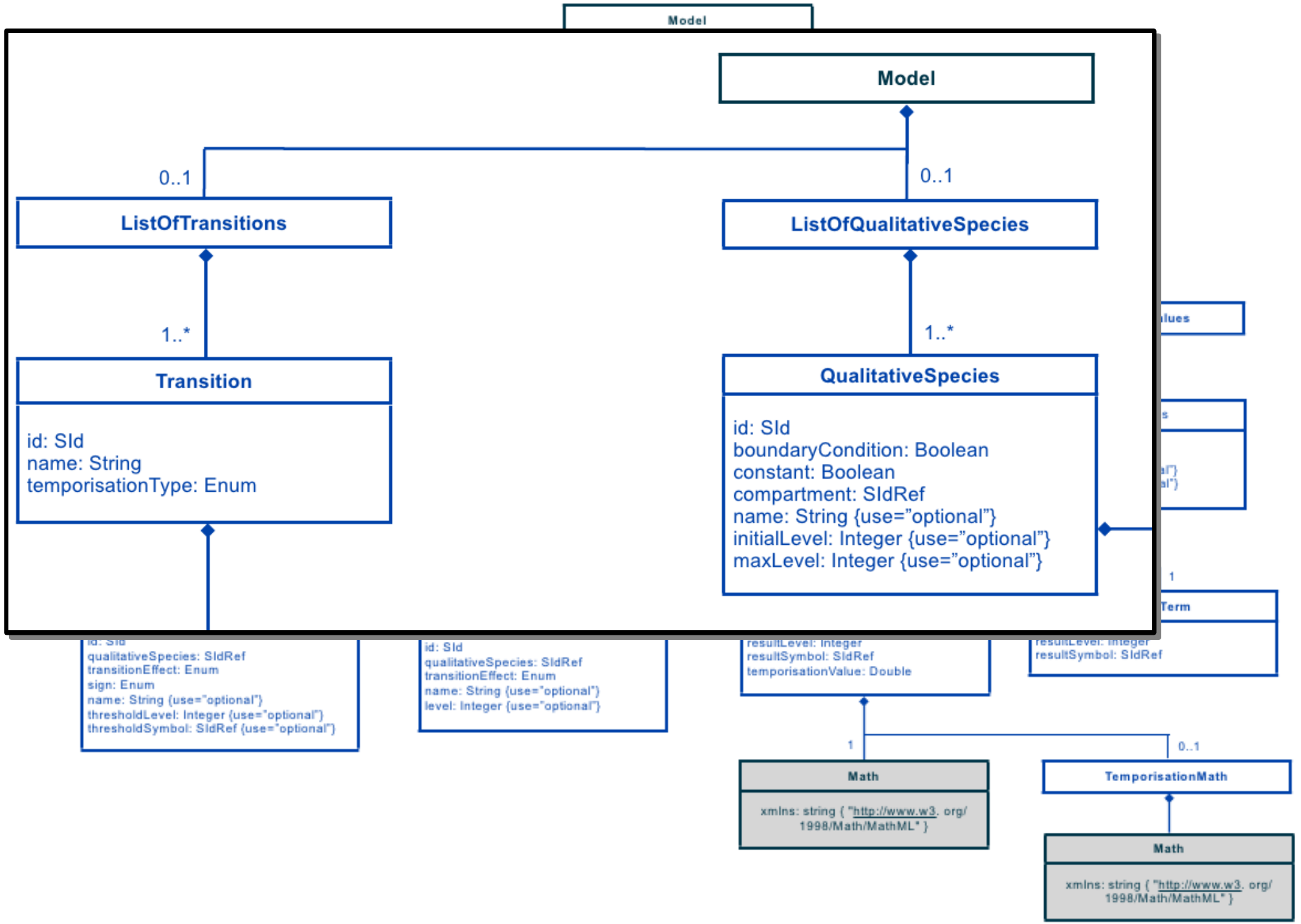
- Core package – public specification
- Graph Layout – specification finalised
- Complex species – specification finalised
- Groups - specification finalised
- Model composition – specification finalised
- Qualitative models – specification finalised
- Flux balance constraint – specification finalised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

???

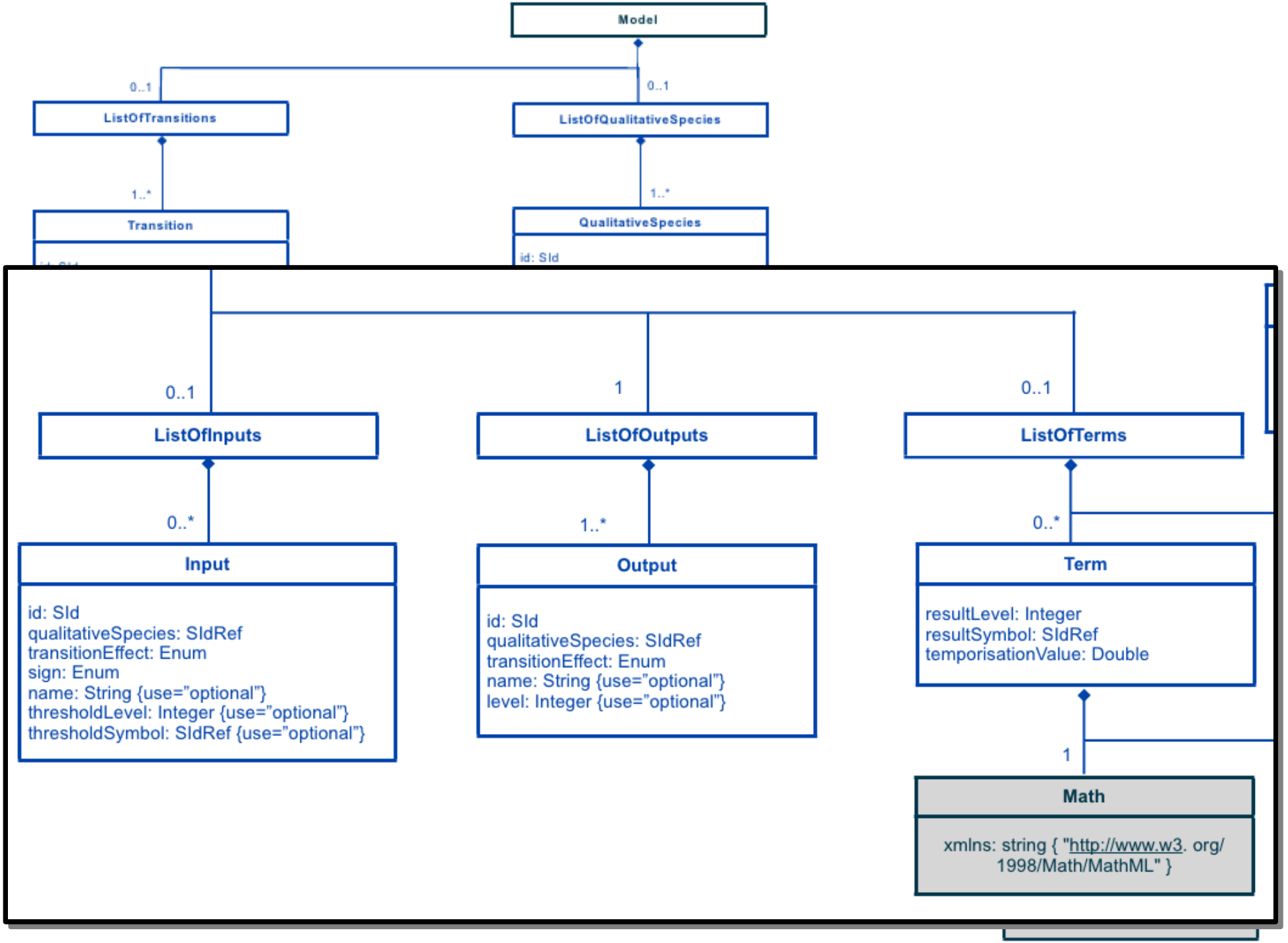
The *qual* package



The *qual* package



The *qual* package

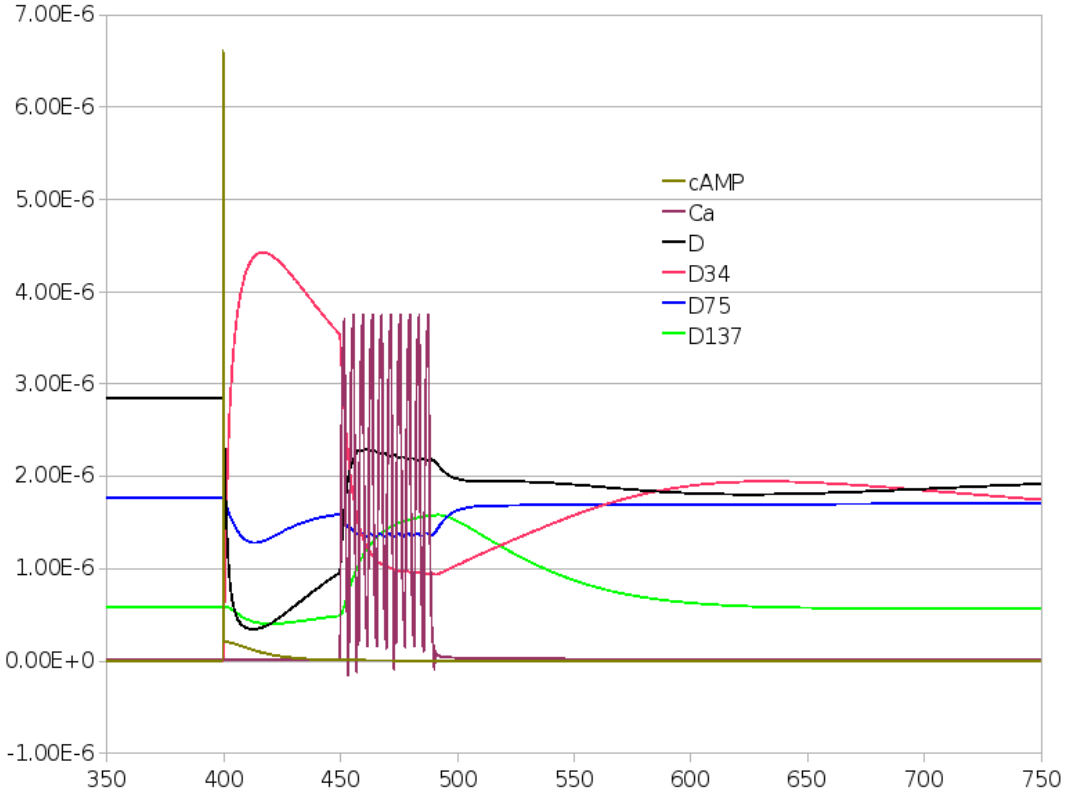


SBML is not limited to biochemistry!

- A species is a pool of entities participating to a reaction, **not always** a **chemical** entity
  - It can be a pool of molecules
  - It can be a pool of cells
  - It can be a pool of organs
  - It can be a population of organi
- Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage, tumour size etc.
- Events can describe any discontinuous change, e.g. neurotransmitter release, repolarisation, cell division etc.

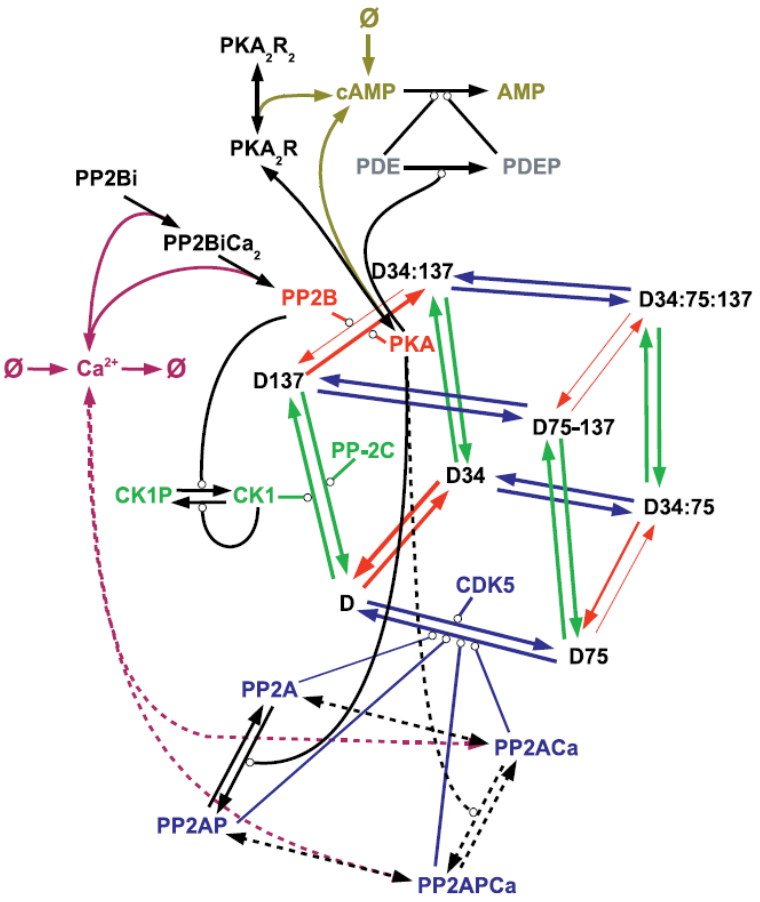
➔ SBML is about process descriptions

Biochemical models



Fernandez et al. DARPP-32 is a robust integrator of dopamine and glutamate signals
PLoS Comput Biol (2006) 2: e176.

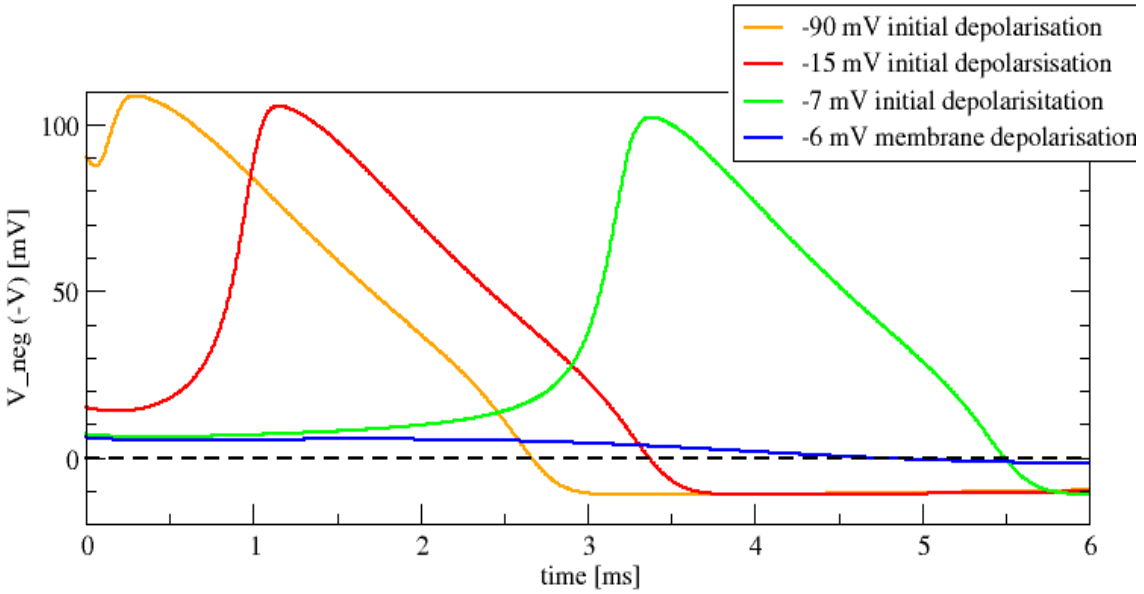
BioModels **BIOMD0000000153**



reaction:

$$v_{on1} = k_{on1} \times [D] \times [CDK5] \times Vol$$

Conductance-based model



Hodgkin AL, Huxley AF.
A quantitative description of membrane current and its application to conduction and excitation in nerve.
J Physiol (1952) 117:500-544.

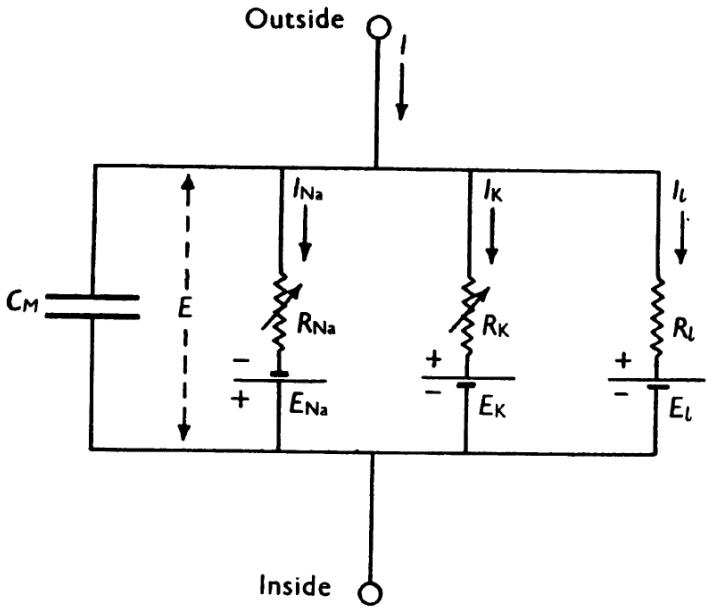
BIOMD0000000020

rate rule:

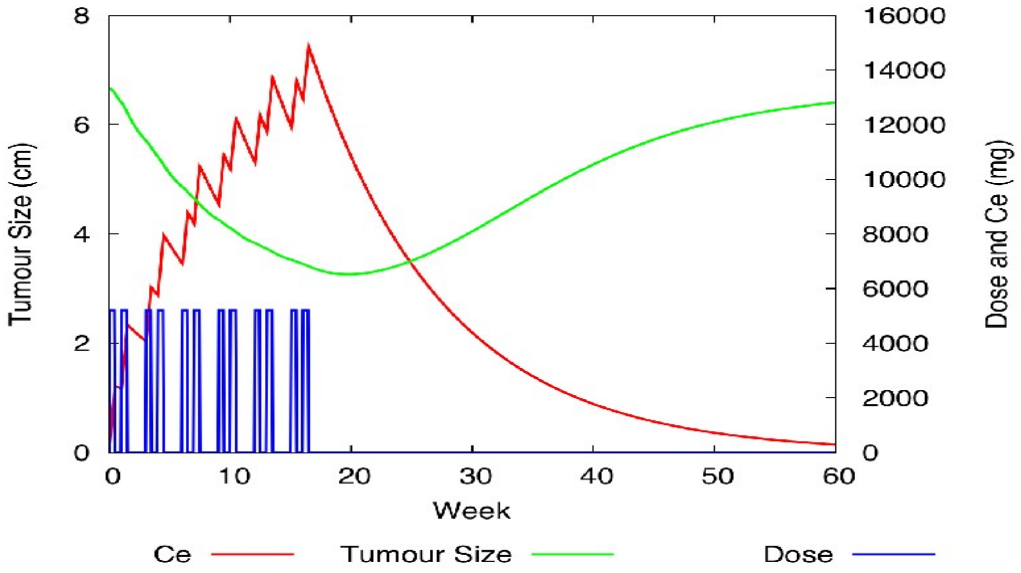
$$\frac{dv}{dt} = \frac{I - (i_{Na} + i_K + i_L)}{C_m}$$

assignment rule:

$$i_{Na} = g_{Na} \times m^3 \times h \times (V - E_{Na})$$



Pharmacometrics models



Tham et al (2008) A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients. *Clin Cancer Res*. 2008 14(13): 4213-8.

BIOMD0000000234

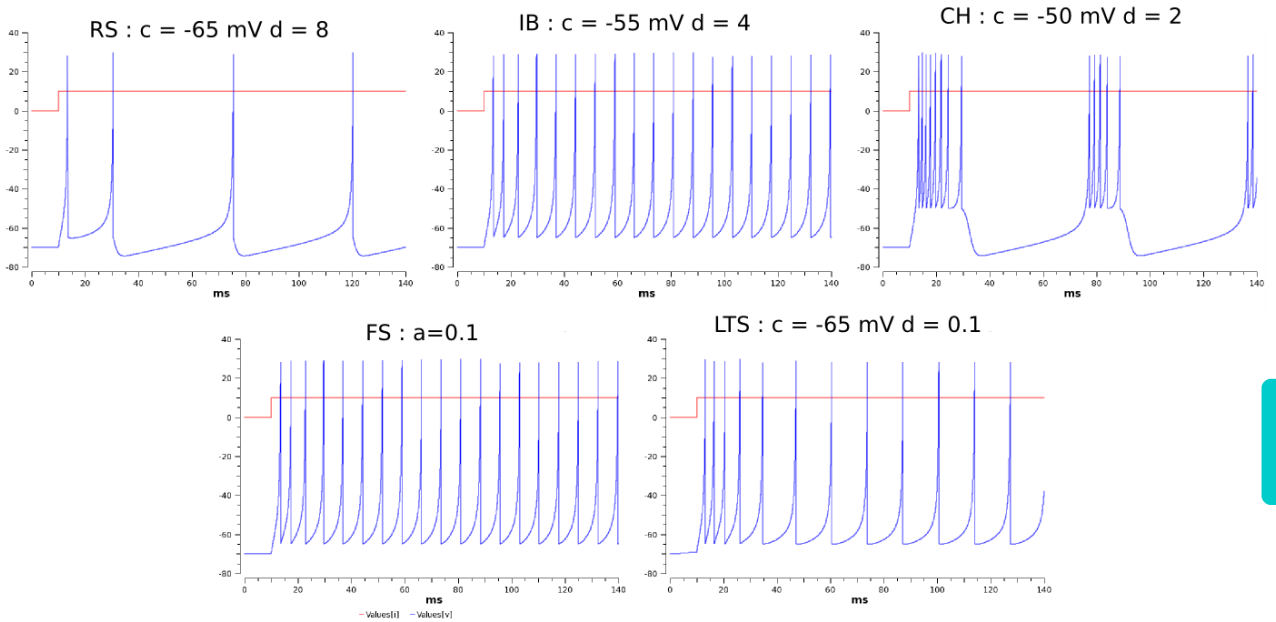
rate rule:

$$\frac{dSize}{dt} = (Rate_{in} \times Effect - K_{over} \times Size) \times Size$$

assignment rule:

$$Effect = 1 - \frac{E_{max} \times Ce}{Amt_{50} + Ce}$$

Single-compartment neurons



Izhikevich EM. Simple model of spiking neurons. *IEEE Trans Neural Netw* (2003) 14(6):1569-1572.

BIOMD0000000127

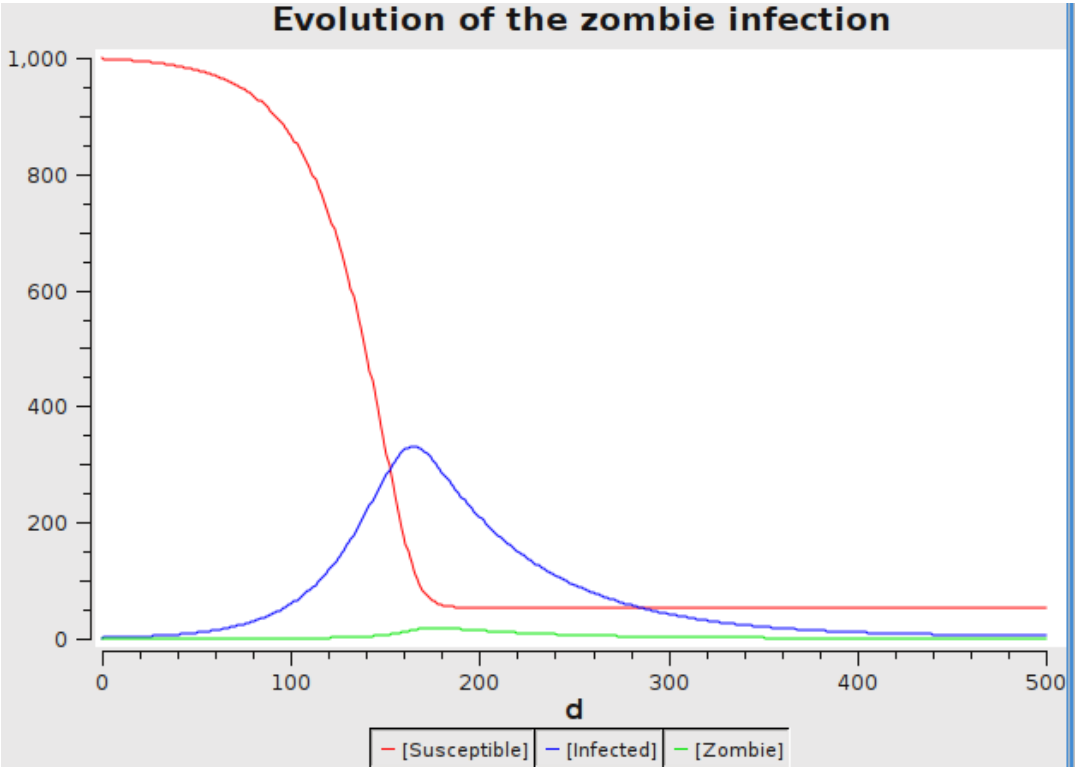
rate rule:

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

event:

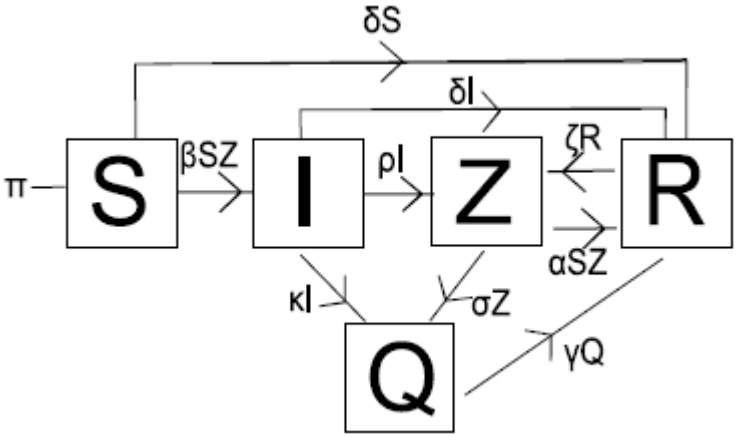
$$\text{when } v > V_{thresh} \begin{cases} v = c \\ U = U + d \end{cases}$$

Spread of infection diseases ...

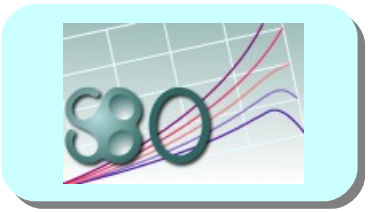


Munz P et al. When zombies attack!: Mathematical modelling of an outbreak of zombie infection. in "Infectious Disease Modelling Research Progress", (2009)133-150

BioModels MODEL1008060001



Adding the semantics to the syntax

	Model descriptions
Minimal requirements	
Data-models	
Terminologies	

Born in Heidelberg 2004

Minimum Information Required in the Annotation of Models (simplified)

Models must :

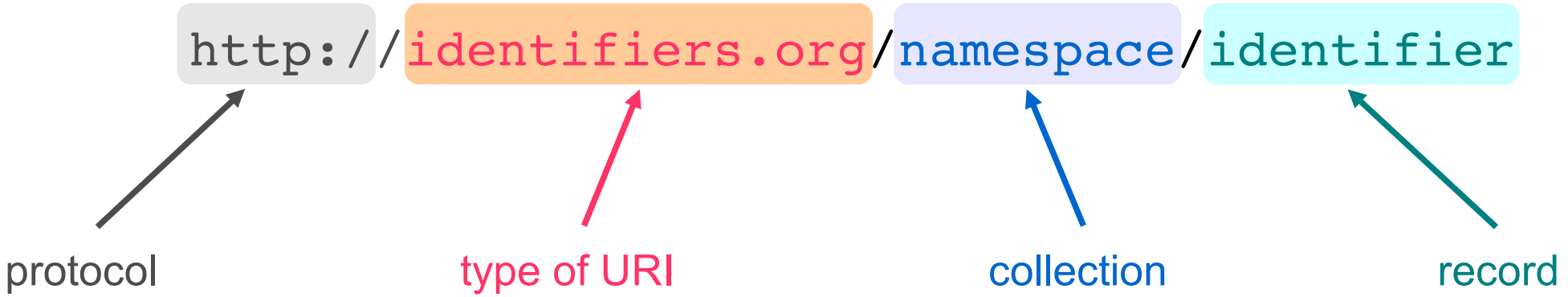
- be encoded in a public machine-readable format
- be clearly linked to a single reference description
- reflect the structure of the biological processes described in the reference paper (list of reactions etc.)
- be instantiable in a simulation (possess initial conditions etc.)
- be able to reproduce the results given in the reference paper
- contain creator's contact details
- annotation to unambiguously identify each model constituent

Why are annotations important?

Annotation of model components are essential to:

- allow efficient search strategies
- unambiguously identify model components
  - improve understanding the structure of the model
  - allow easier comparison of different models
  - ease the integration of models
- add a semantic layer to the model
  - improve understanding of the biology behind the model
  - allow conversion and reuse of the model
  - ease the integration of model and biological knowledge

Enters Identifiers.org (aka new MIRIAM URIs)



http://identifiers.org/uniprot/P62158

http://identifiers.org/ec-code/1.1.1.1

http://identifiers.org/obo.go/GO:0000186

identifiers.org

- Browse
- Search
- Tags
- Query services
- Submit new
- Export
- Curator Sign in

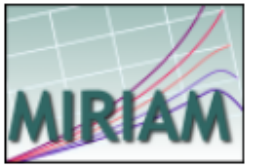
- Web Services
- Documents
  - MIRIAM Guidelines
  - FAQ
  - Documentation
  - Who's using MIRIAM?
  - Identification systems
  - News
  - BioModels.net Qualifiers

- MIRIAM on SourceForge

- Support
- Contact

MIRIAM Registry

MIRIAM Registry are a set of online services created in support of MIRIAM, a set of guidelines for the annotation and curation of computational models.



The core of *MIRIAM Registry* is a catalogue of data collections (corresponding to controlled vocabularies or databases), their URIs and the corresponding physical URLs or resources. Access to this data is made available via exports (XML) and Web Services (SOAP).

MIRIAM Registry is developed and maintained under the BioModels.net initiative, and are free for use by all.

Quick links

Browse

by data collection name
by tags

Web Services

services available
usage of the services
online demonstration

Search

generic search

Exports

XML

Registry

MIRIAM Registry is composed of four components: a database, some Web Services, a Java library and this web application.

Database

The core of the system is a MySQL database. It allows us to store the data collections (which can be controlled vocabularies or databases), their URIs and the corresponding physical URLs, and other details such as documentation and resource identifier patterns.

Each entry contains a diverse set of details about the data collection: official name and synonyms, root URI, pattern of identifiers, documentation, etc. Moreover, each data collection can be associated with several resources (or physical locations).

Web Services

Data type: *Enzyme Nomenclature*

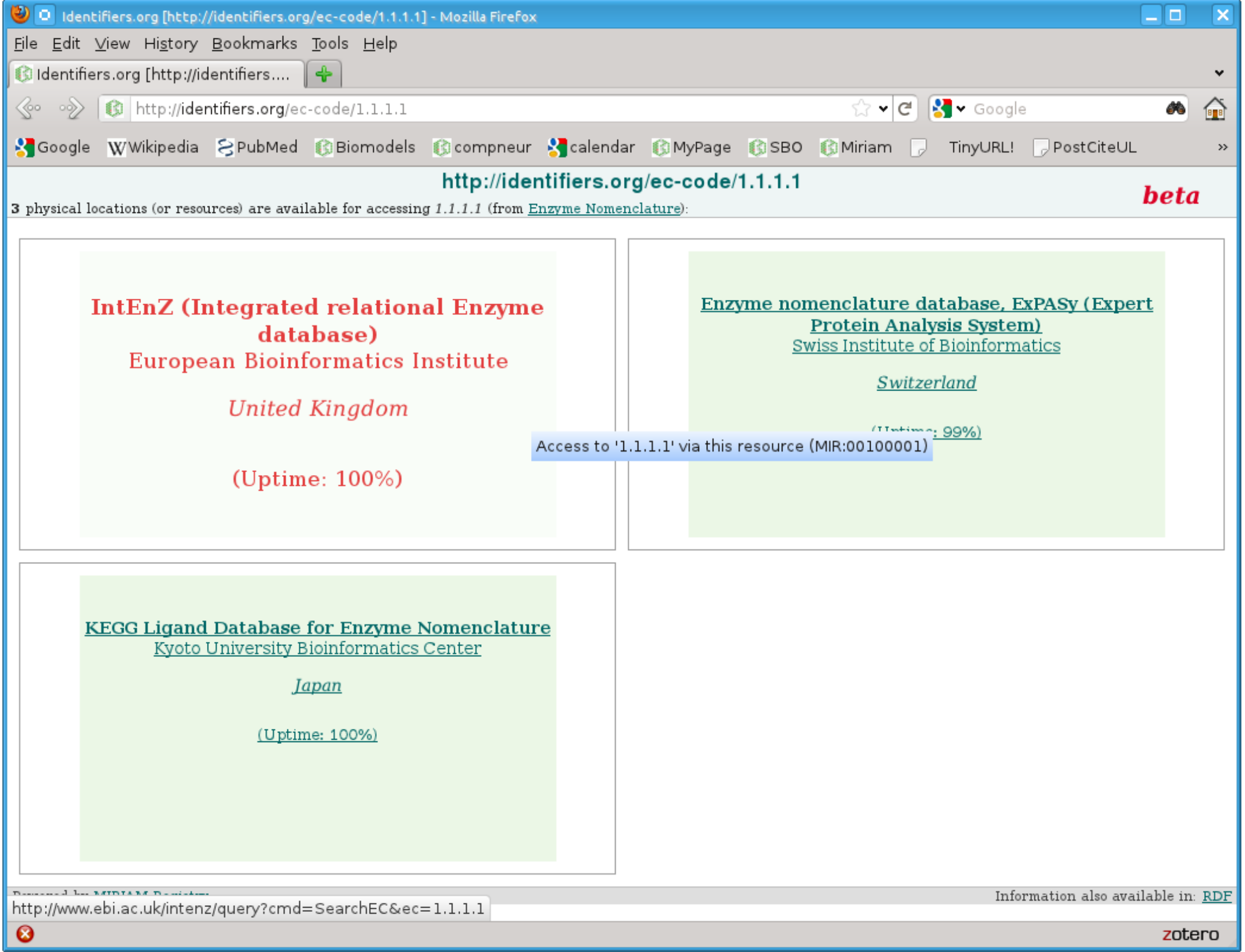
General | Tags | Annotation

General information about the data type

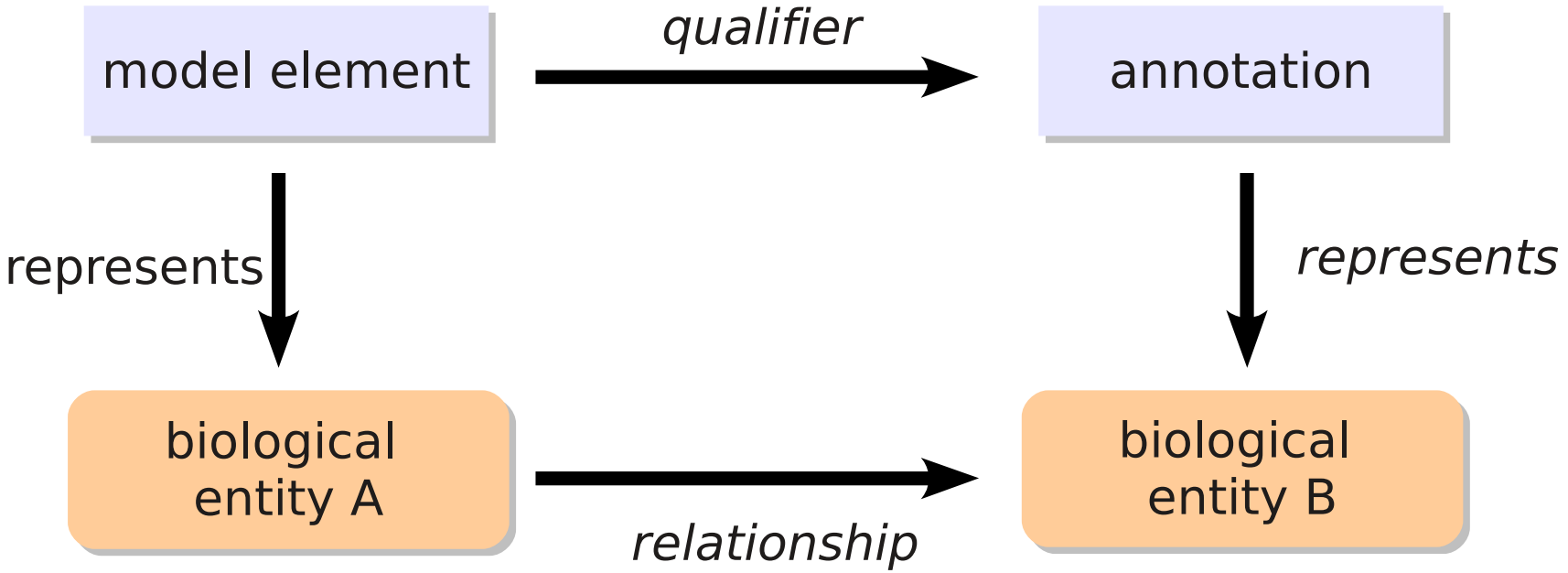
Name		
Identifier		MIR:00000004
Name		Enzyme Nomenclature
Synonyms		EC code
		Enzyme Classification
		EC
URIs		
Official URN		urn:miriam:ec-code
Deprecated		http://www.ec-code.org/
		urn:lsid:ec-code.org
		http://www.ebi.ac.uk/IntEnz/
Information		
Definition		The Enzyme Classification contains the recommendations of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology on the nomenclature and classification of enzyme-catalysed reactions.
Identifier Pattern		^\d+\.-\.-\.-|\d+\.\d+\.-\.-|\d+\.\d+\.\d+\.-|\d+\.\d+\.\d+\.\d+$
Physical Locations		
Resource #1	**Data Entry**	http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&ec=**$id** [Example: 1.1.1.1]
	Data Resource	http://www.ebi.ac.uk/intenz/
	Information	IntEnZ (Integrated relational Enzyme database)
	Institution	European Bioinformatics Institute, United Kingdom
Resource #2	**Data Entry**	http://www.genome.jp/dbget-bin/www_bget?ec:**$id** [Example: 1.1.1.1]
	Data Resource	http://www.genome.jp/dbget-bin/www_bfind?enzyme
	Information	KEGG Ligand Database for Enzyme Nomenclature
	Institution	Kyoto University Bioinformatics Center, Japan
Resource #3	**Data Entry**	http://us.expasy.org/cgi-bin/nicezyme.pl?**$id** [Example: 1.1.1.1]
	Data Resource	http://us.expasy.org/enzyme/
	Information	Enzyme nomenclature database, ExPASy (Expert Protein Analysis System)
	Institution	Swiss Institute of Bioinformatics, Switzerland
Documentation		
URL(s)		http://www.chem.qmul.ac.uk/iubmb/enzyme/
		⊞ http://srs.ebi.ac.uk/srsbin/cgi-bin/wgetz?-view+MedlineFull+[medline-PMID:10812475]
Miscellaneous		
Date of creation		2006-08-14 19:38:06 GMT
Date of last modification		2009-05-08 14:59:31 GMT

Go back to the list of data types

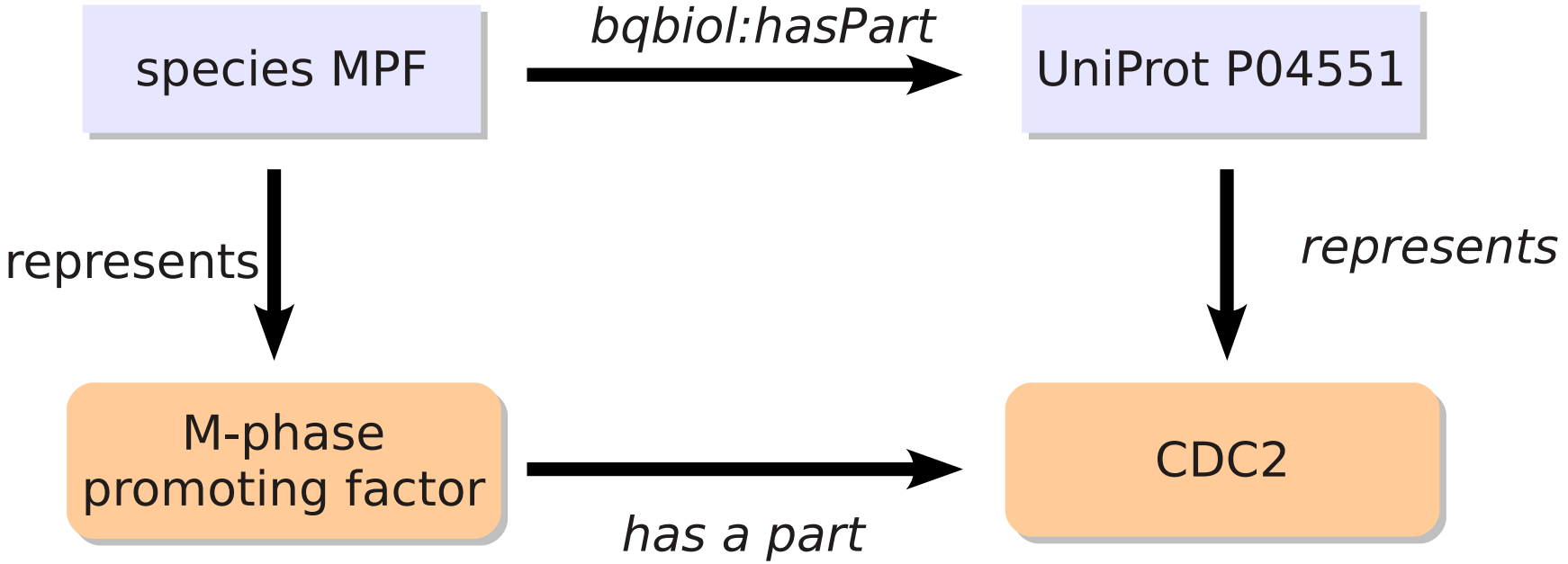
Edit this data type


Identifiers.org [http://identifiers.org/ec-code/1.1.1.1] - Mozilla Firefox
File Edit View History Bookmarks Tools Help
Identifiers.org [http://identifiers....
http://identifiers.org/ec-code/1.1.1.1
Google
Google Wikipedia PubMed Biomodels compneur calendar MyPage SBO Miriam TinyURL! PostCiteUL
http://identifiers.org/ec-code/1.1.1.1
beta
3 physical locations (or resources) are available for accessing 1.1.1.1 (from Enzyme Nomenclature):
IntEnZ (Integrated relational Enzyme database)
European Bioinformatics Institute
United Kingdom
(Uptime: 100%)
Enzyme nomenclature database, ExPASy (Expert Protein Analysis System)
Swiss Institute of Bioinformatics
Switzerland
(Uptime: 99%)
Access to '1.1.1.1' via this resource (MIR:00100001)
KEGG Ligand Database for Enzyme Nomenclature
Kyoto University Bioinformatics Center
Japan
(Uptime: 100%)
Information also available in: RDF
http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&ec=1.1.1.1
zotero

Qualification of annotation



Qualification of annotation



SBML and MIRIAM cross-references

```
<species id="ca_calmodulin" metaid="cacam">
  <annotation>
    <rdf:RDF
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/">
      <rdf:Description rdf:about="#cacam">
        <bqbiol:hadPart>
          <rdf:Bag>
            <rdf:li rdf:resource="http://identifiers.org/uniprot/62158"/>
            <rdf:li rdf:resource="http://identifiers.org/chebi/CHEBI:29108"/>
          </rdf:Bag>
        </bqbiol:hasPart>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

Systems Biology Ontology

- Download
- Recent changes
- Term request
- Edit tree
- Web Services
- FAQ
- News
- Project on SourceForge
- Contact

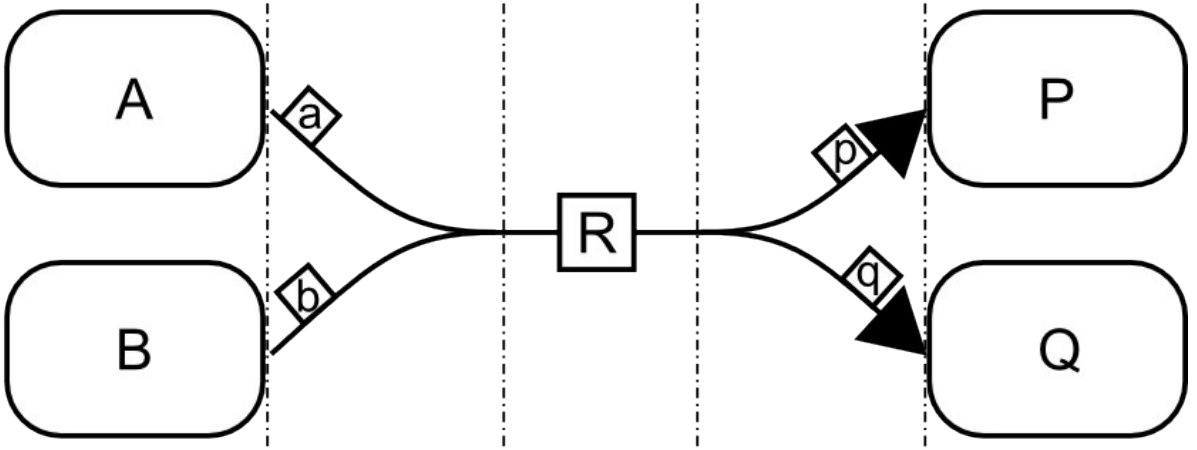
BIOMODELS.NET

- **SBO:0000000 - systems biology representation**
  - SBO:0000064 - mathematical expression
    - SBO:0000355 - conservation law
    - SBO:0000474 - convenience function
    - SBO:0000001 - rate law
    - SBO:0000391 - steady state expression
  - SBO:0000544 - metadata representation
  - SBO:0000004 - modelling framework
  - SBO:0000231 - occurring entity representation
  - SBO:0000003 - participant role
  - SBO:0000236 - physical entity representation
  - SBO:0000545 - systems description parameter
    - SBO:0000546 - qualitative systems description parameter
    - SBO:0000002 - quantitative systems description parameter
      - SBO:0000492 - amplitude
      - SBO:0000542 - basic reproductive ratio
      - SBO:0000380 - biochemical coefficient
      - SBO:0000258 - capacitance
      - SBO:0000257 - conductance
      - SBO:0000254 - electrical resistance
      - SBO:0000308 - equilibrium or steady-state characteristic

Essential activator

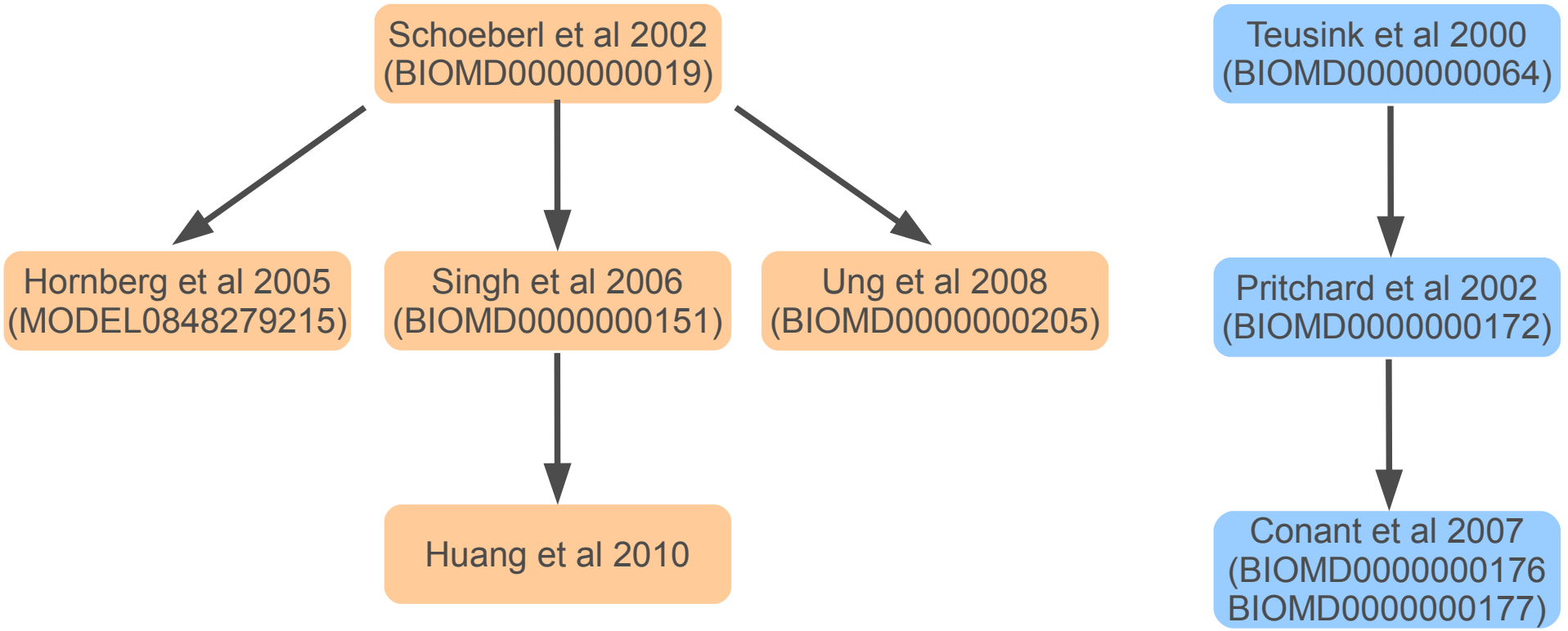
```
<listOfModifiers>
    <modifierSpeciesReference
      sboTerm="SBO:0000461"
      species="Y"/>
 </listOfModifiers>
```

http://www.ebi.ac.uk/sbo/



substances A and B	are consummed by	reaction R	that produces	substances P and Q
SBO:0000240 material entity	SBO:0000394 consumption	SBO:0000375 process	SBO:0000393 production	SBO:0000240 material entity
Species	Species Reference	Kinetic Law	Species Reference	Species

Direct model re-use: e.g. EGFR signalling and glycolysis



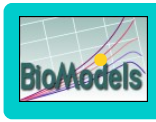
Standard formats generate new research

- Herrgård et al (2008) A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. *Nature Biotechnol*, 26: 1155-1160

MODEL0072364382: 2152 species, 1857 reactions

  - stoichiometric map, no concentrations, no kinetics

- Smallbone et al (2010) Towards a genome-scale kinetic model of cellular metabolism. *BMC Syst Biol*, 4:6



MODEL1001200000: 1748 species, 1059 reactions

  - Concentrations and flux from BioModels Database
  - Constraint-based model and simplified linlog kinetics

- Dobson et al (2010) Further developments towards a genome-scale metabolic model of yeast. *BMC Syst Biol,* 4:145

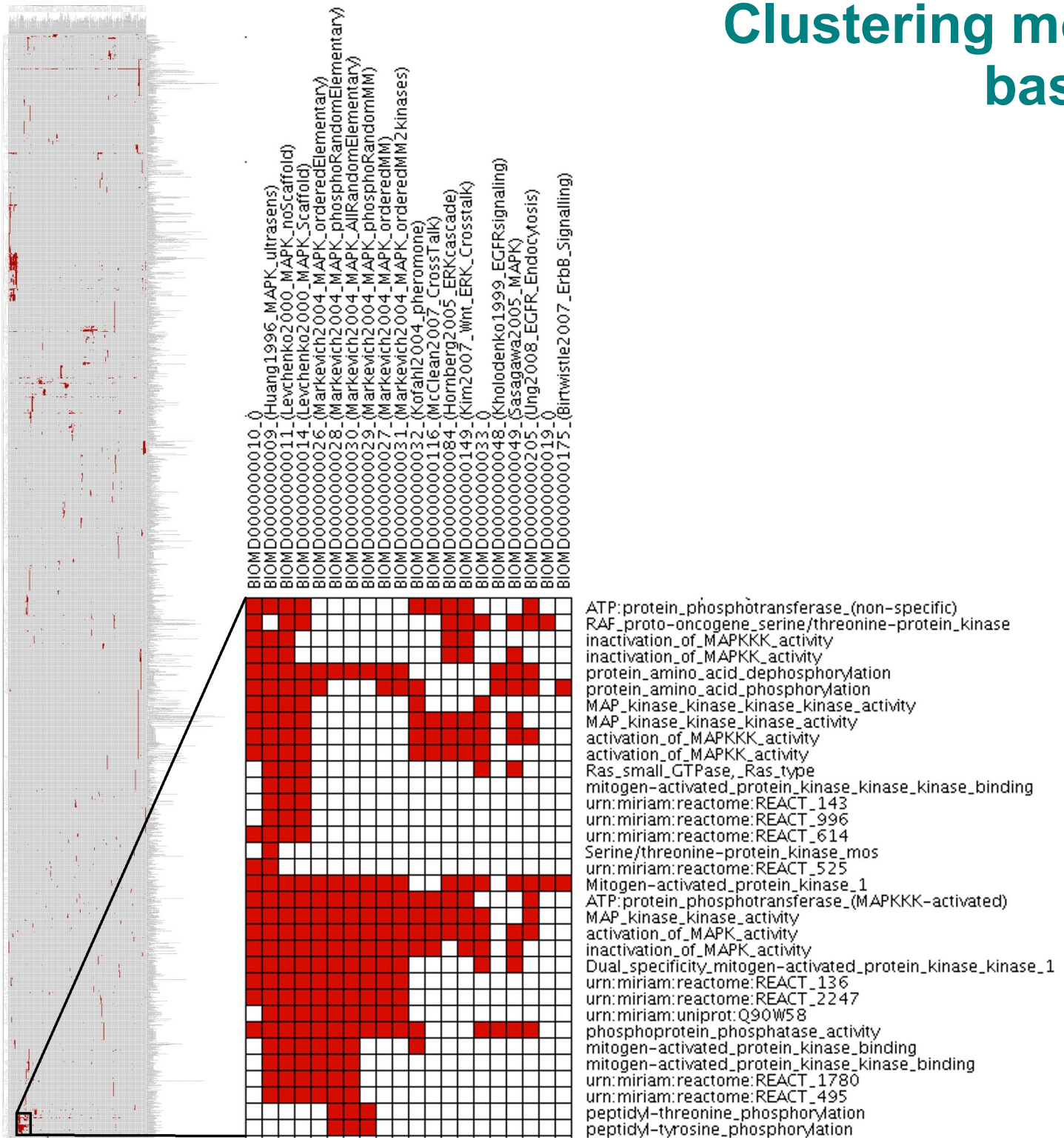
MODEL1012110000: 2657 species, 1865 reactions

- Li et al (2010) Systematic integration of experimental data and models in systems biology. *BMC Bioinfo,* 11: 582

MODEL1012110001

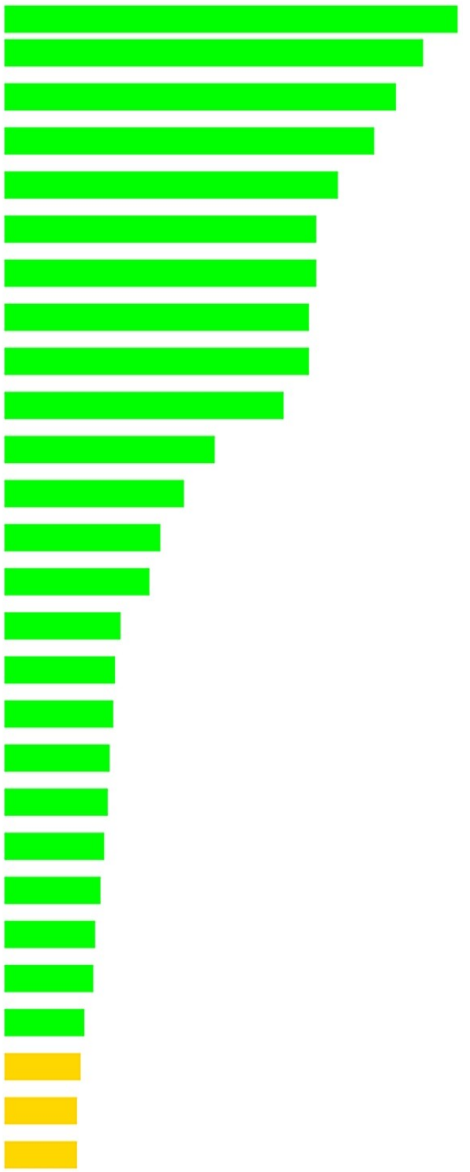
  - Workflows using experimental kinetic information database (SABIO-RK) plus metabolomics and proteomics database
  - Full quantitative chemical kinetics descriptions

Clustering models (and data) based on metadata

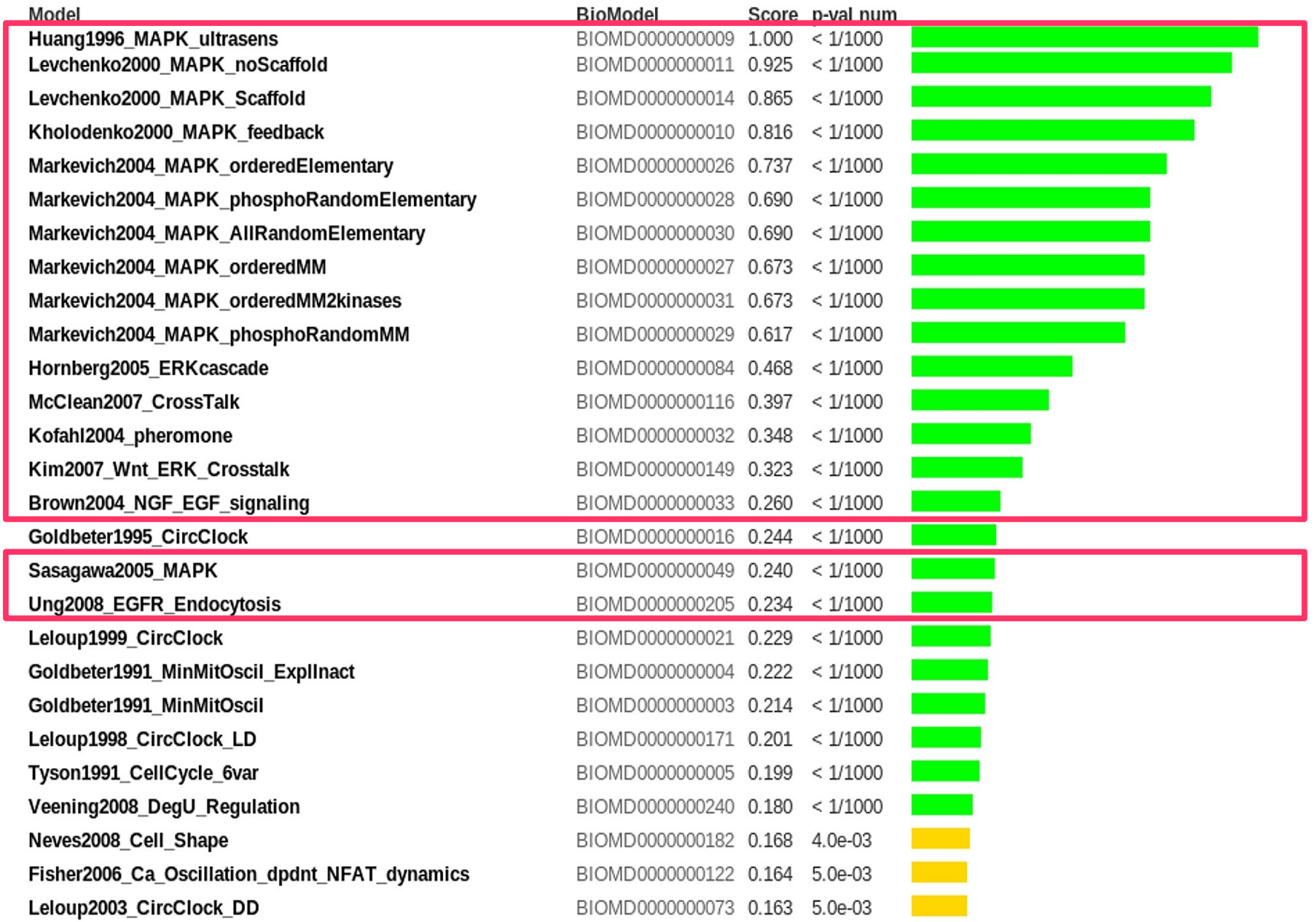


Ranking and retrieval of models

Model	BioModel	Score	p-val num
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.000	< 1/1000
Levchenko2000_MAPK_noScaffold	BIOMD0000000011	0.925	< 1/1000
Levchenko2000_MAPK_Scaffold	BIOMD0000000014	0.865	< 1/1000
Kholodenko2000_MAPK_feedback	BIOMD0000000010	0.816	< 1/1000
Markevich2004_MAPK_orderedElementary	BIOMD0000000026	0.737	< 1/1000
Markevich2004_MAPK_phosphoRandomElementary	BIOMD0000000028	0.690	< 1/1000
Markevich2004_MAPK_AllRandomElementary	BIOMD0000000030	0.690	< 1/1000
Markevich2004_MAPK_orderedMM	BIOMD0000000027	0.673	< 1/1000
Markevich2004_MAPK_orderedMM2kinases	BIOMD0000000031	0.673	< 1/1000
Markevich2004_MAPK_phosphoRandomMM	BIOMD0000000029	0.617	< 1/1000
Hornberg2005_ERKcascade	BIOMD0000000084	0.468	< 1/1000
McClean2007_CrossTalk	BIOMD0000000116	0.397	< 1/1000
Kofahl2004_pheromone	BIOMD0000000032	0.348	< 1/1000
Kim2007_Wnt_ERK_Crosstalk	BIOMD0000000149	0.323	< 1/1000
Brown2004_NGF_EGF_signaling	BIOMD0000000033	0.260	< 1/1000
Goldbeter1995_CircClock	BIOMD0000000016	0.244	< 1/1000
Sasagawa2005_MAPK	BIOMD0000000049	0.240	< 1/1000
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.234	< 1/1000
Leloup1999_CircClock	BIOMD0000000021	0.229	< 1/1000
Goldbeter1991_MinMitOscil_ExplInact	BIOMD0000000004	0.222	< 1/1000
Goldbeter1991_MinMitOscil	BIOMD0000000003	0.214	< 1/1000
Leloup1998_CircClock_LD	BIOMD0000000171	0.201	< 1/1000
Tyson1991_CellCycle_6var	BIOMD0000000005	0.199	< 1/1000
Veening2008_DegU_Regulation	BIOMD0000000240	0.180	< 1/1000
Neves2008_Cell_Shape	BIOMD0000000182	0.168	4.0e-03
Fisher2006_Ca_Oscillation_dpdnt_NFAT_dynamics	BIOMD0000000122	0.164	5.0e-03
Leloup2003_CircClock_DD	BIOMD0000000073	0.163	5.0e-03



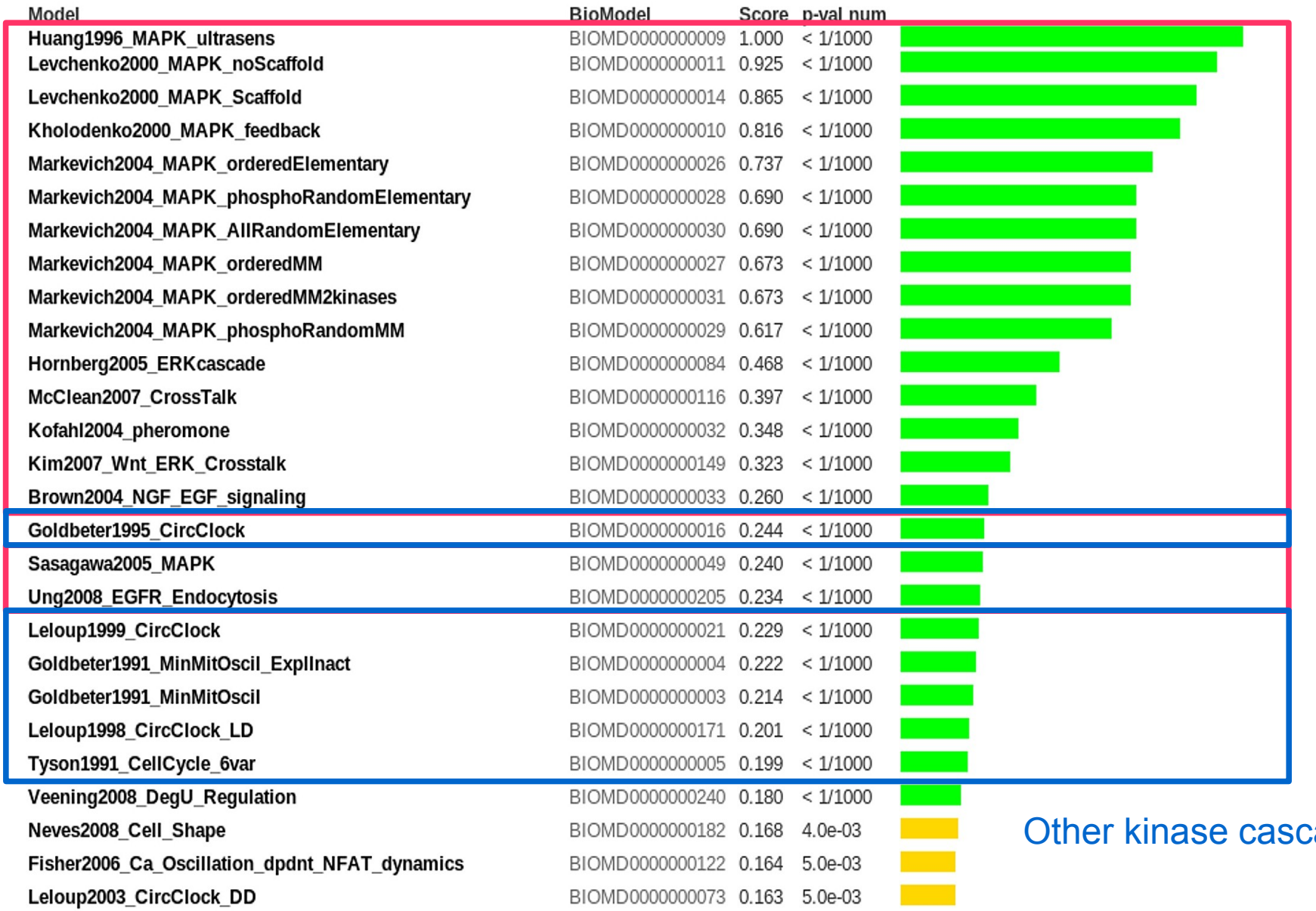
Ranking and retrieval of models



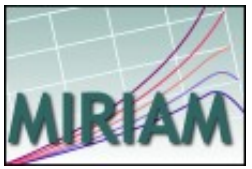
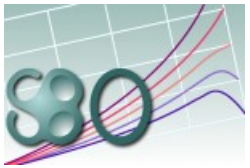
Model	BioModel	Score	p-val num
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.000	< 1/1000
Levchenko2000_MAPK_noScaffold	BIOMD0000000011	0.925	< 1/1000
Levchenko2000_MAPK_Scaffold	BIOMD0000000014	0.865	< 1/1000
Kholodenko2000_MAPK_feedback	BIOMD0000000010	0.816	< 1/1000
Markevich2004_MAPK_orderedElementary	BIOMD0000000026	0.737	< 1/1000
Markevich2004_MAPK_phosphoRandomElementary	BIOMD0000000028	0.690	< 1/1000
Markevich2004_MAPK_AllRandomElementary	BIOMD0000000030	0.690	< 1/1000
Markevich2004_MAPK_orderedMM	BIOMD0000000027	0.673	< 1/1000
Markevich2004_MAPK_orderedMM2kinases	BIOMD0000000031	0.673	< 1/1000
Markevich2004_MAPK_phosphoRandomMM	BIOMD0000000029	0.617	< 1/1000
Hornberg2005_ERKcascade	BIOMD0000000084	0.468	< 1/1000
McClean2007_CrossTalk	BIOMD0000000116	0.397	< 1/1000
Kofahl2004_pheromone	BIOMD0000000032	0.348	< 1/1000
Kim2007_Wnt_ERK_Crosstalk	BIOMD0000000149	0.323	< 1/1000
Brown2004_NGF_EGF_signaling	BIOMD0000000033	0.260	< 1/1000
Goldbeter1995_CircClock	BIOMD0000000016	0.244	< 1/1000
Sasagawa2005_MAPK	BIOMD0000000049	0.240	< 1/1000
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.234	< 1/1000
Leloup1999_CircClock	BIOMD0000000021	0.229	< 1/1000
Goldbeter1991_MinMitOscil_ExplInact	BIOMD0000000004	0.222	< 1/1000
Goldbeter1991_MinMitOscil	BIOMD0000000003	0.214	< 1/1000
Leloup1998_CircClock_LD	BIOMD0000000171	0.201	< 1/1000
Tyson1991_CellCycle_6var	BIOMD0000000005	0.199	< 1/1000
Veening2008_DegU_Regulation	BIOMD0000000240	0.180	< 1/1000
Neves2008_Cell_Shape	BIOMD0000000182	0.168	4.0e-03
Fisher2006_Ca_Oscillation_dpdnt_NFAT_dynamics	BIOMD0000000122	0.164	5.0e-03
Leloup2003_CircClock_DD	BIOMD0000000073	0.163	5.0e-03

MAPK

Ranking and retrieval of models



The interface with all biologists

	Model descriptions
Minimal requirements	
Data-models	
Terminologies	

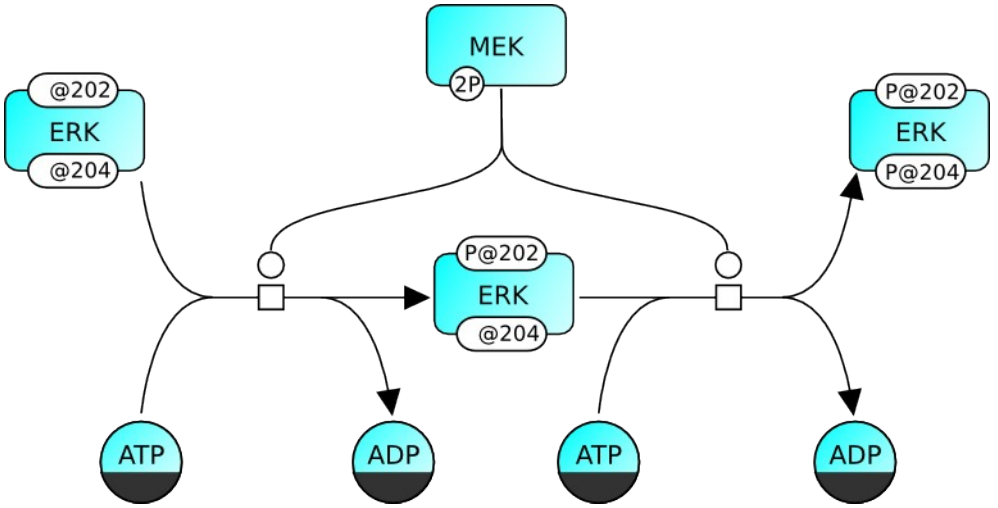
Born in Tokyo 2005

What is SBGN?

- An unambiguous way of graphically describing and interpreting biochemical and cellular events
- 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 and growing software support
- Developed over four years by a diverse community, including biologists, modellers, computer scientists etc.

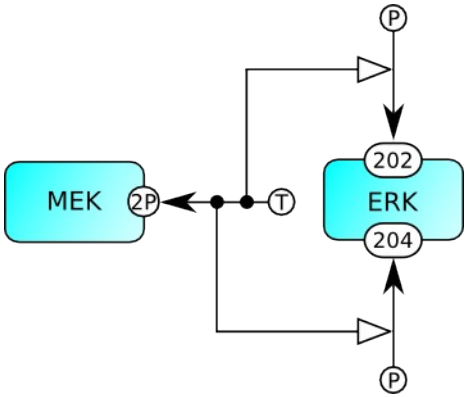
Graph trinity: three languages in one notation

Process Descriptions



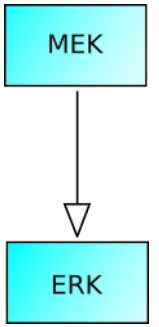
- Unambiguous
- Mechanistic
- Sequential
- Combinatorial explosion

Entity Relationships



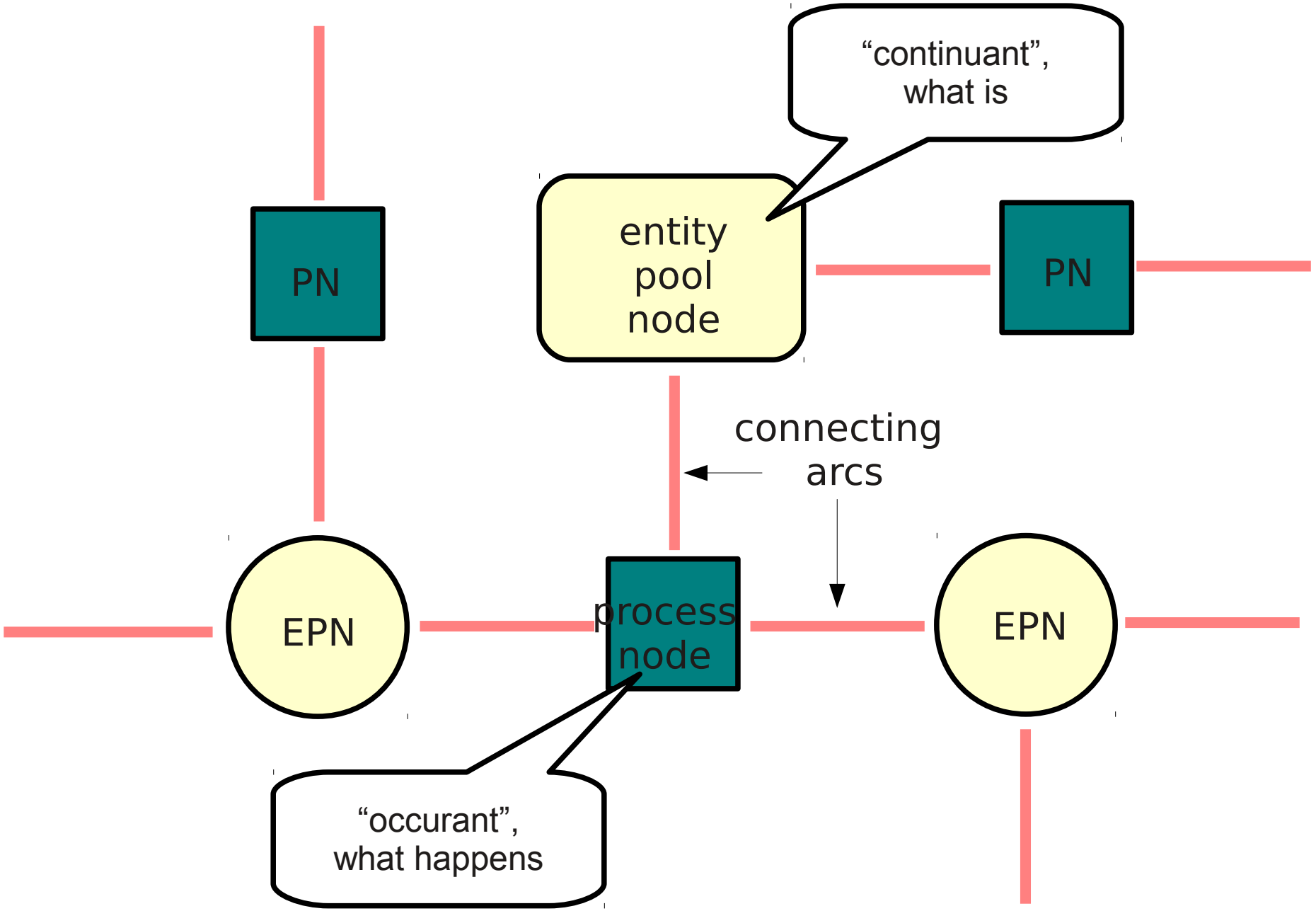
- Unambiguous
- Mechanistic
- Non-sequential
- Independence of relationships

Activity Flows

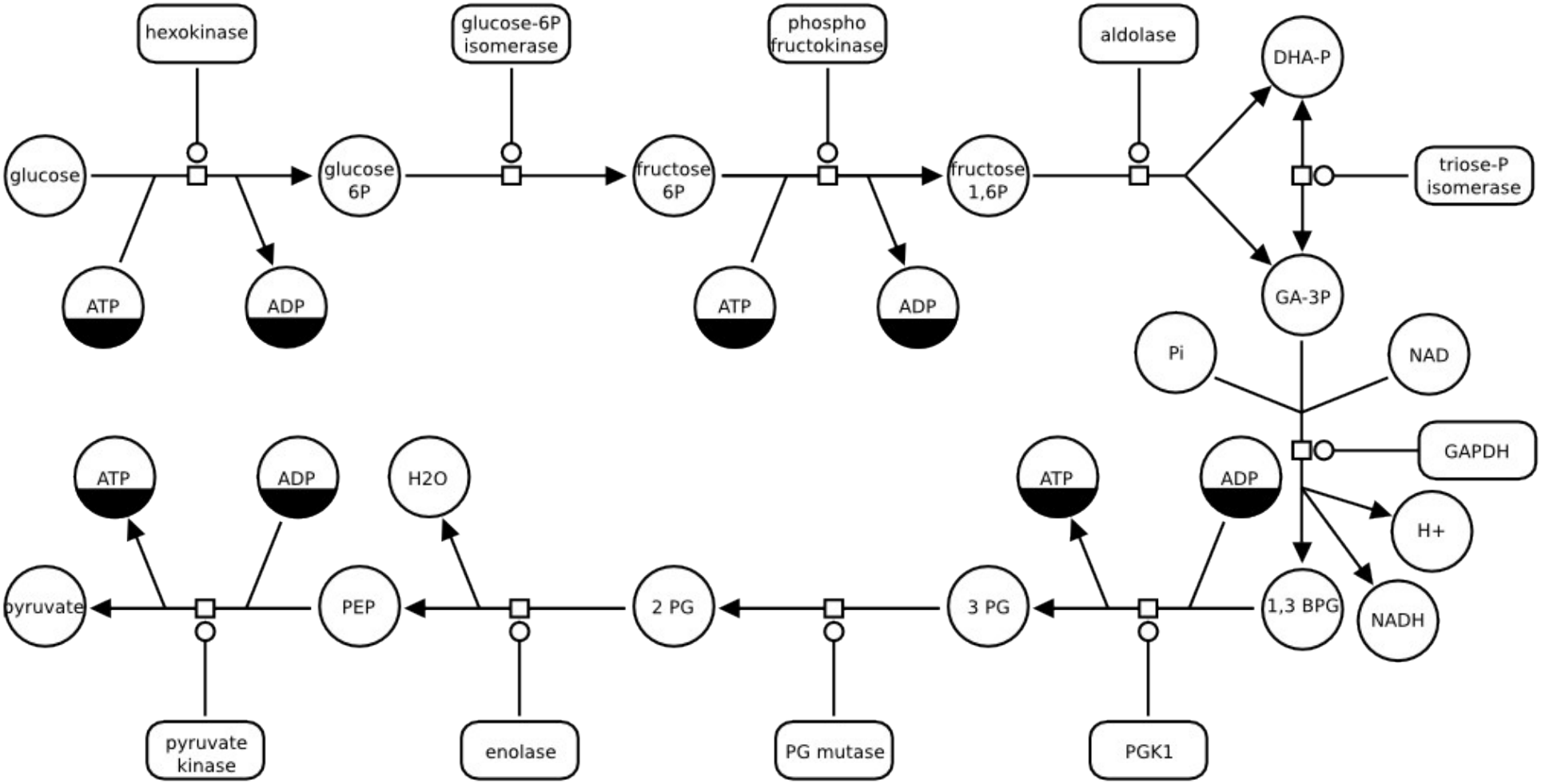


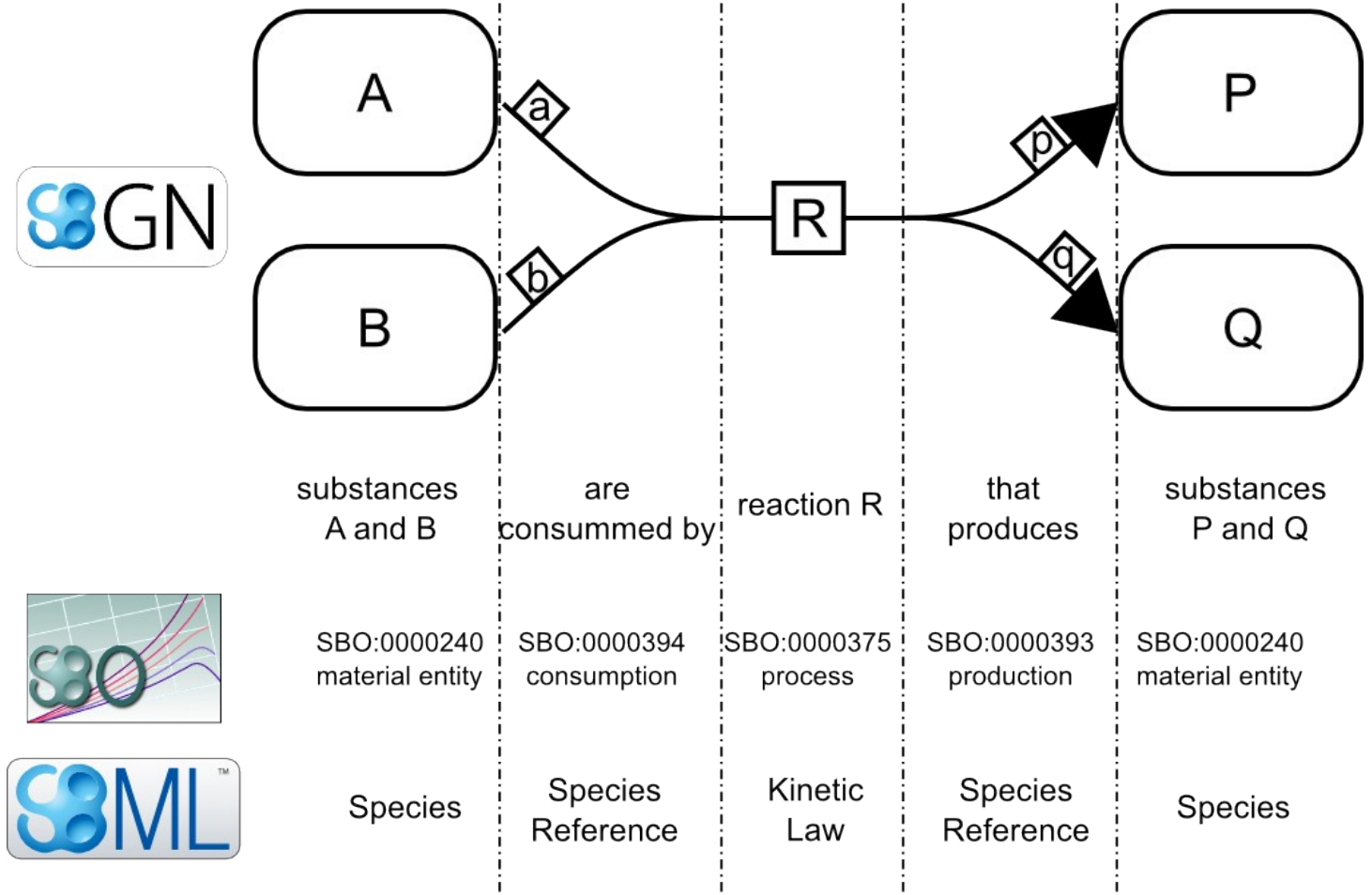
- Ambiguous
- Conceptual
- Sequential

Process Descriptions are bipartite graphs

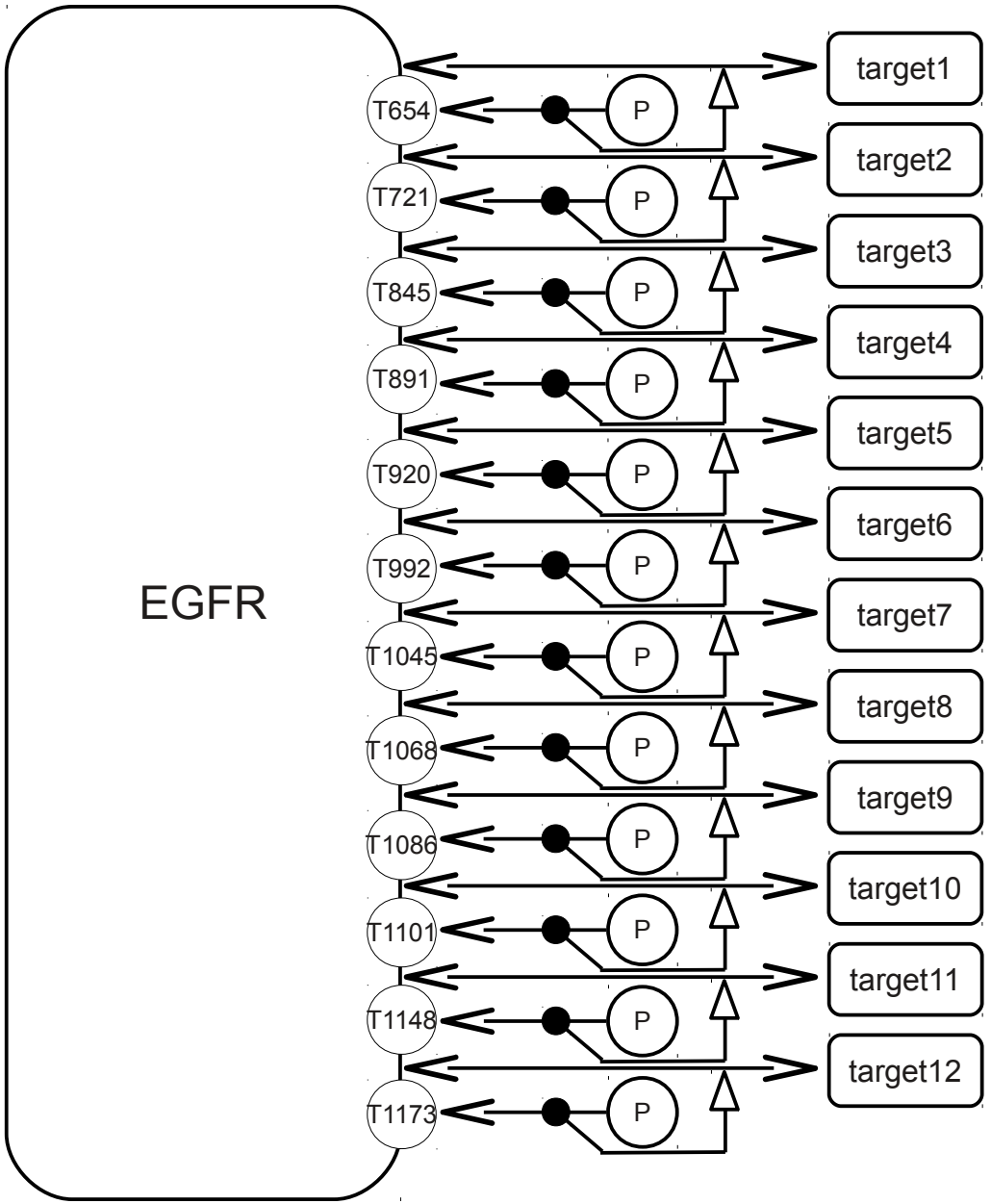


Metabolic network in Process Description Language




A
B
a
b
R
p
q
P
Q
substances A and B
are consummed by
reaction R
that produces
substances P and Q
SBO:0000240 material entity
SBO:0000394 consumption
SBO:0000375 process
SBO:0000393 production
SBO:0000240 material entity
Species
Species Reference
Kinetic Law
Species Reference
Species

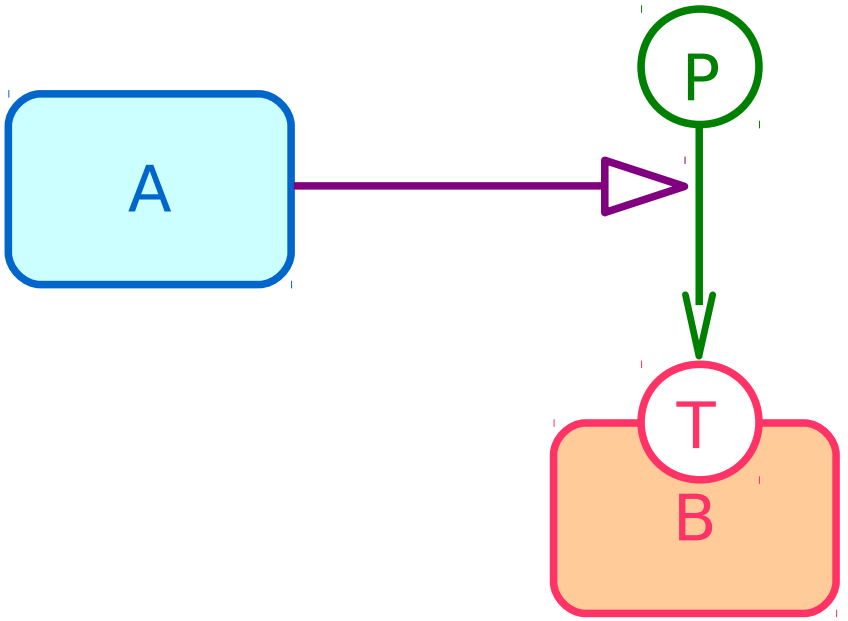
Multi-state and combinatorial explosion



Process Descriptions:
“once a state variable value,
always a state variable value”

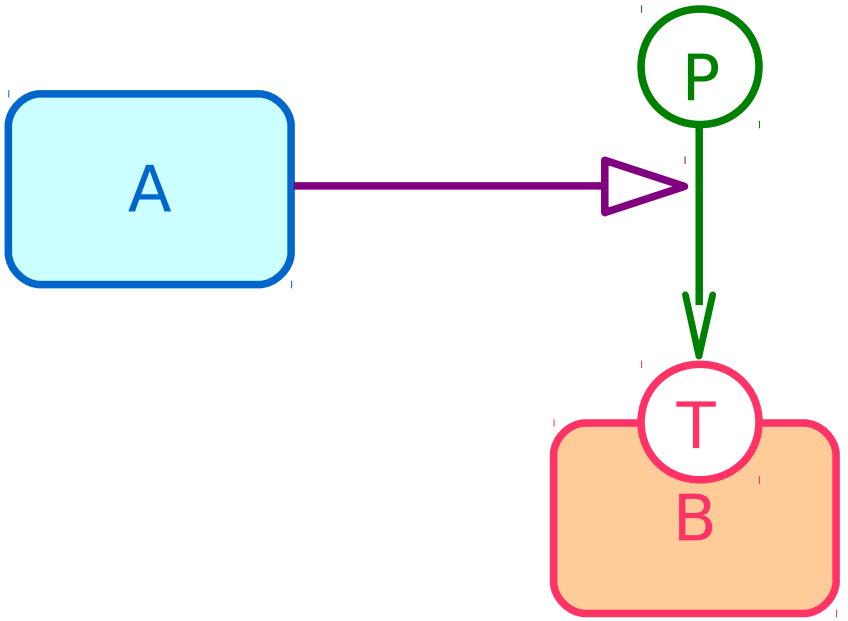
2^{12} = 4096 states
(i.e. EPN glyphs) for EGFR
and 4096 complexes between
EGFR and targets

Entity Relationships can be viewed as rules



If A exists, the assignment of the value P to the state variable T of B is increased

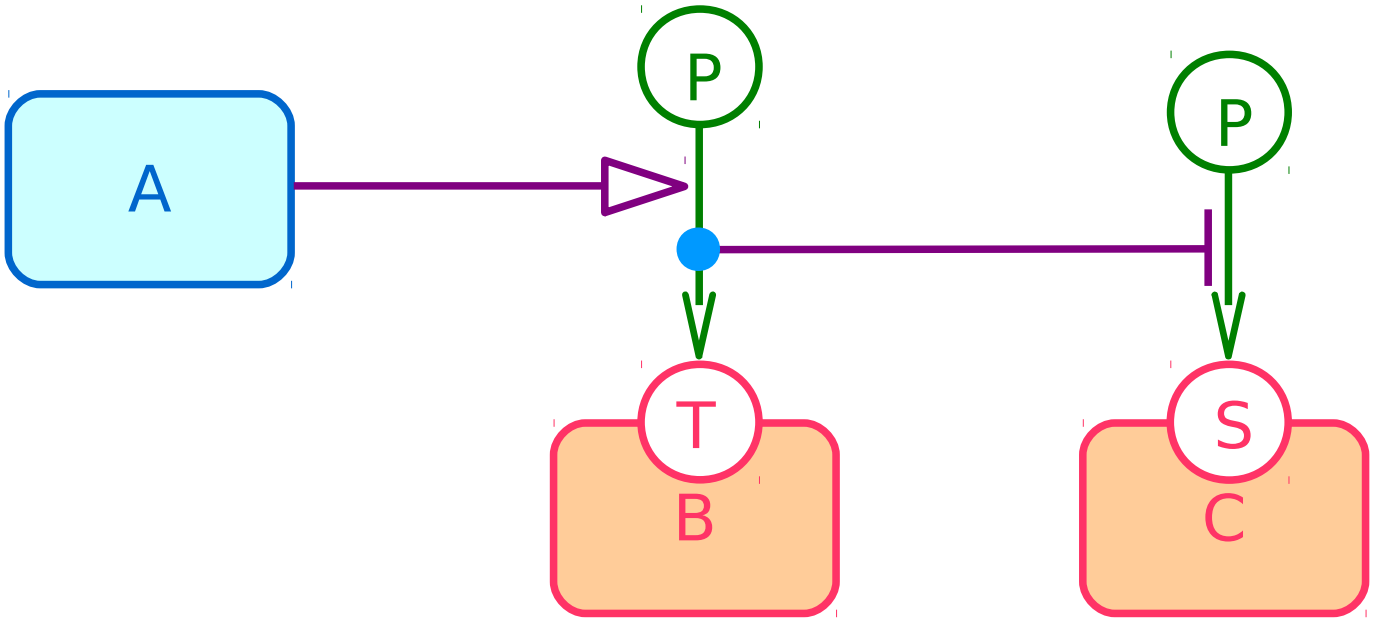
Entity Relationships can be viewed as rules



If A exists, the assignment of the value P to the state variable T of B is increased

(A stimulates the phosphorylation of B on the threonine)

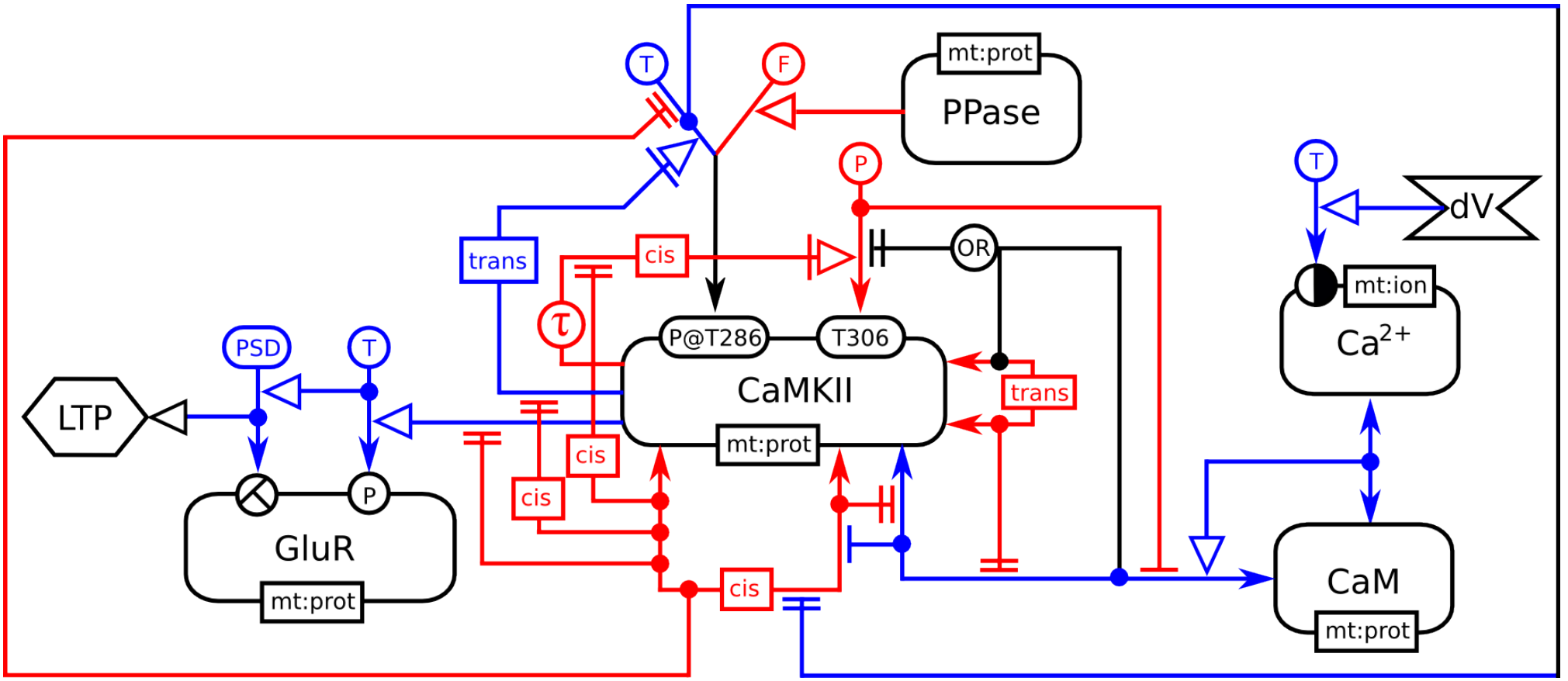
Entity Relationships can be viewed as rules



If A exists, the assignment of the value P to the state variable T of B is increased

If P is assigned to the state variable T of B, the assignment of the value P to the state variable S of B is decreased

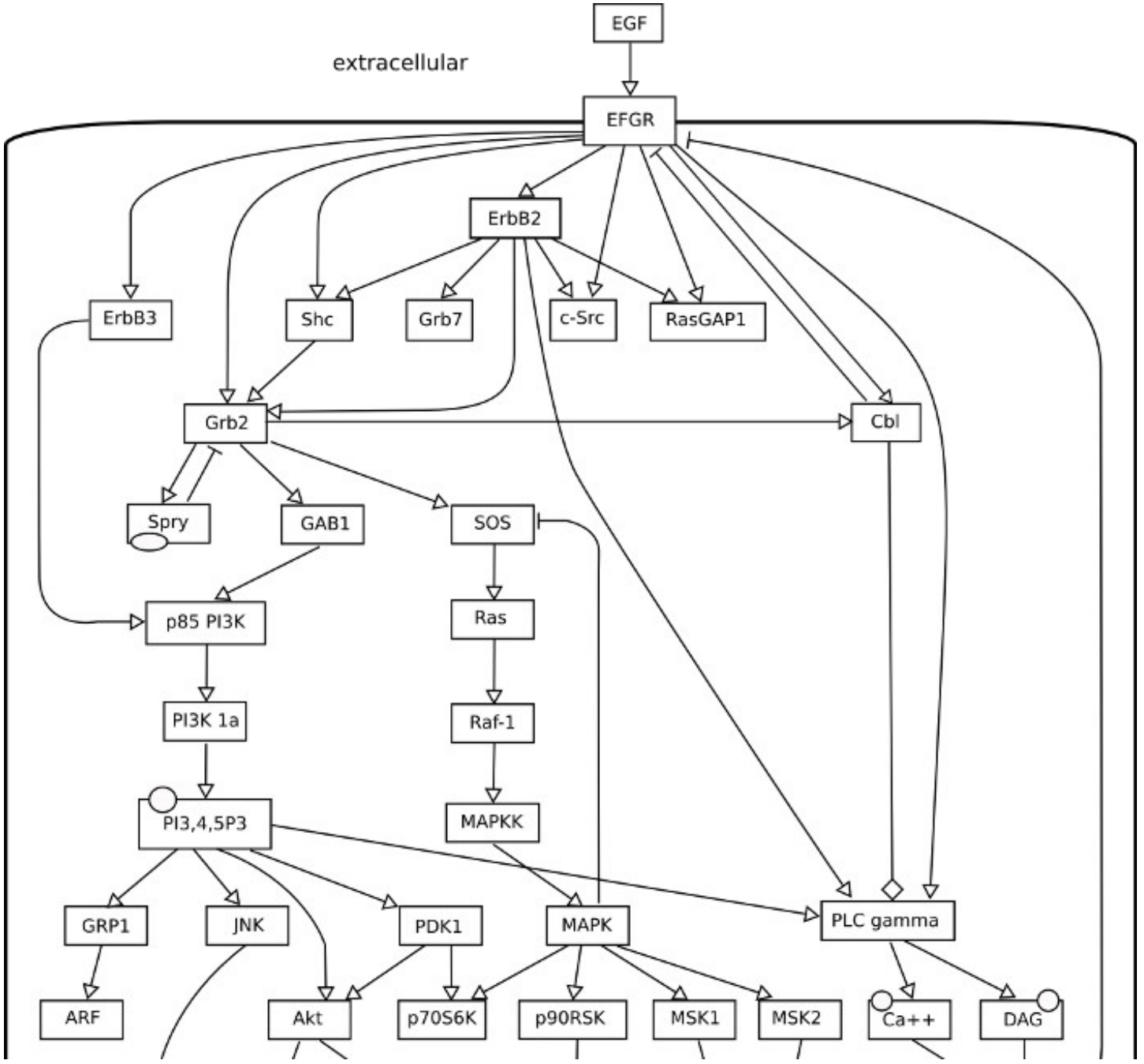
SBGN ER map of calcium-regulated synaptic plasticity



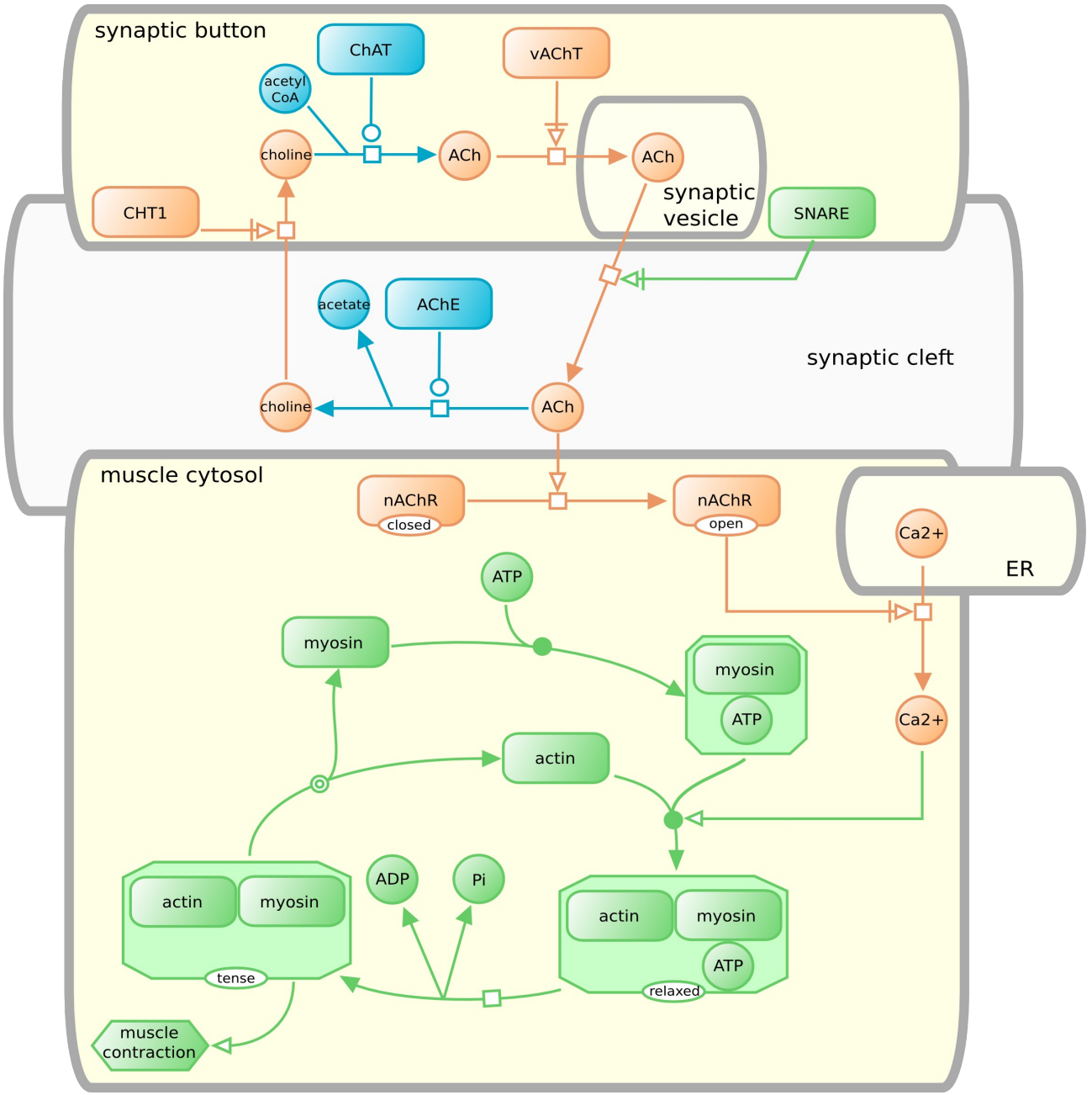
increases synaptic weight

decreases synaptic weight

Example of Activity Flow map



Linking SBGN maps to external information

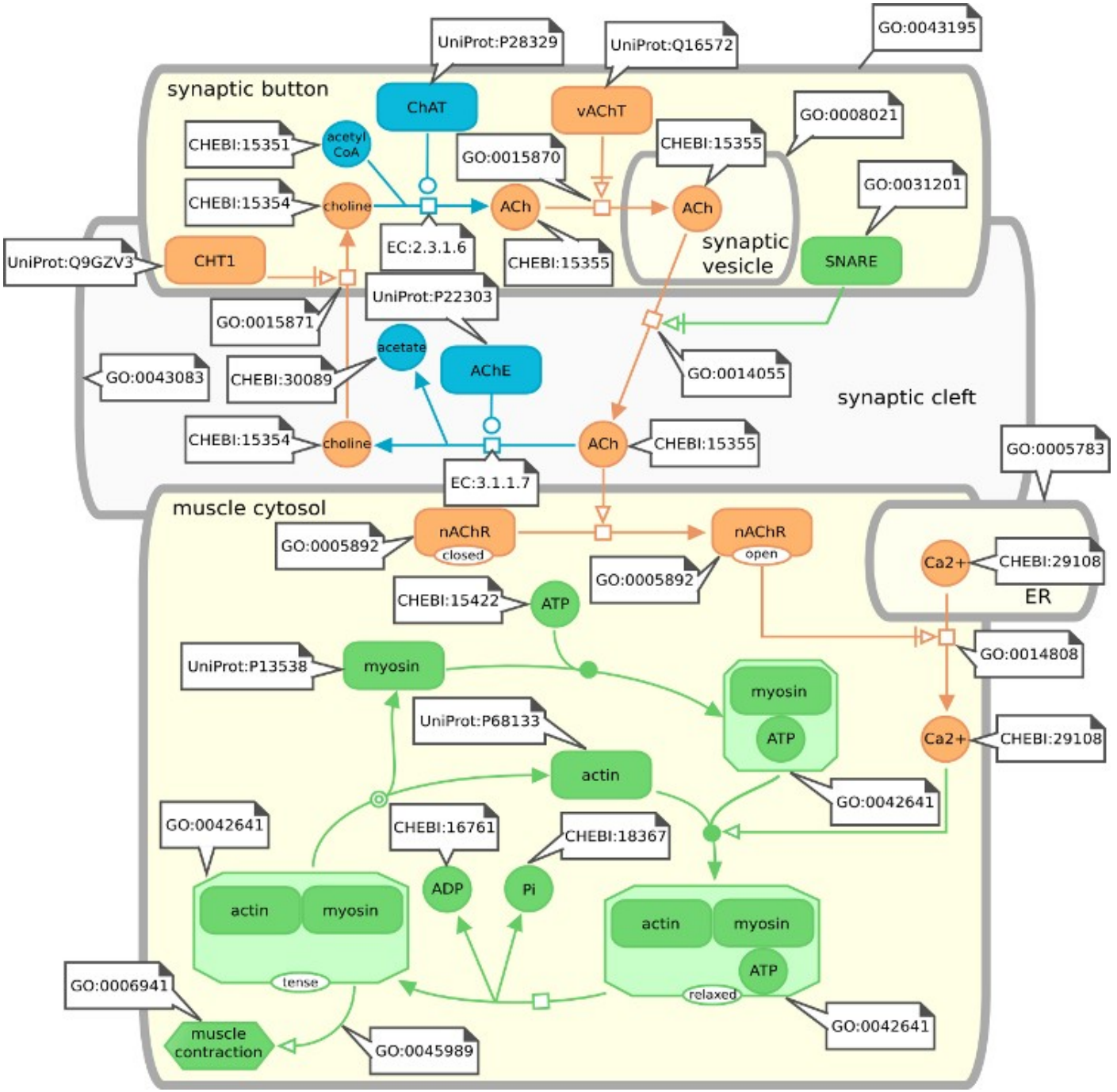


catalytic processes

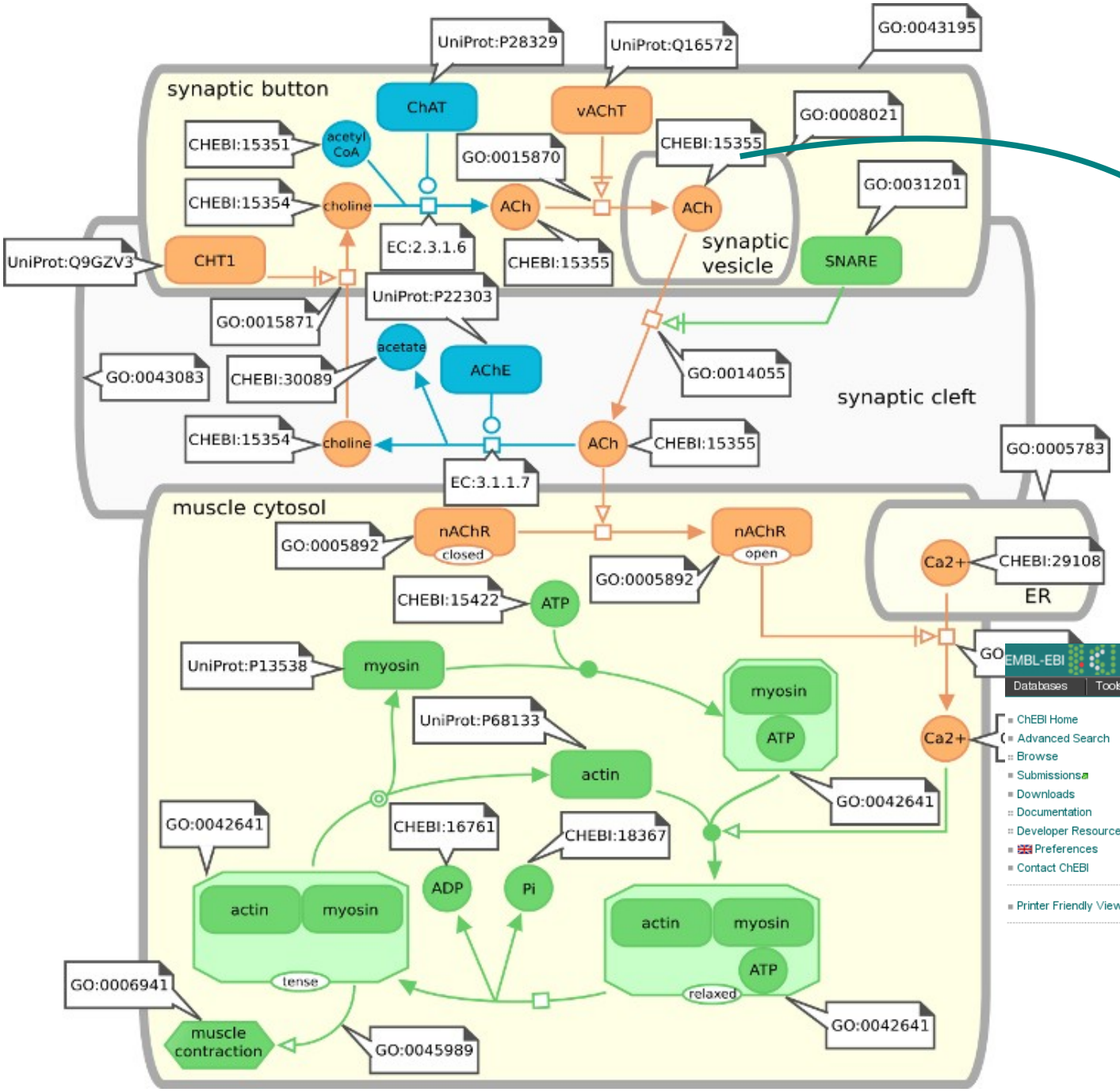
transport processes

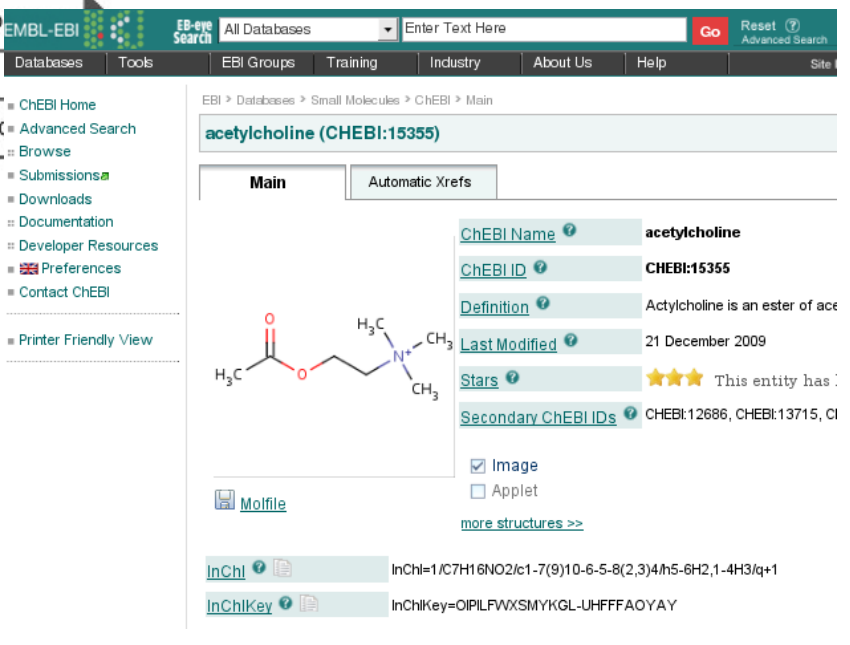
contractile proteins

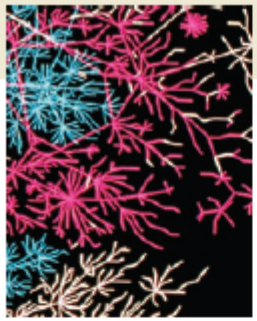
Linking SBGN maps to external information



Linking SBGN maps to external information







PERSPECTIVE

6. The model, when instantiated within a suitable simulation environment, must be able to reproduce all relevant results given in the reference description that can readily be simulated. Not only does the simulation have to provide results qualitatively similar to the reference description, such as oscillation, bistability, chaos, but the quantitative values of variables, and their relationships (e.g., the shape of the phase portrait) must be reproduced within some epsilon, the difference being attributable to the algorithms used to run the simulation, and the

Minimum … tion of biochem…

Nicolas Le Novère[1], Julio Collado-Vide[2], Herbert Sauro[10], B… n[7],

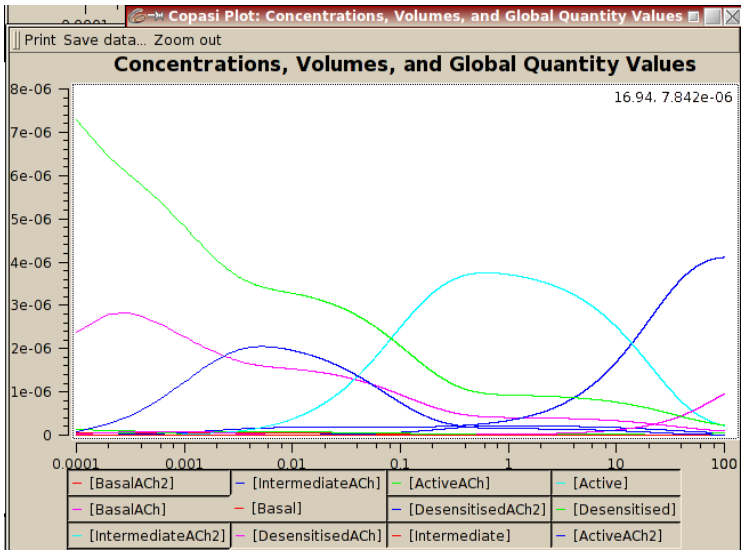
Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main 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

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

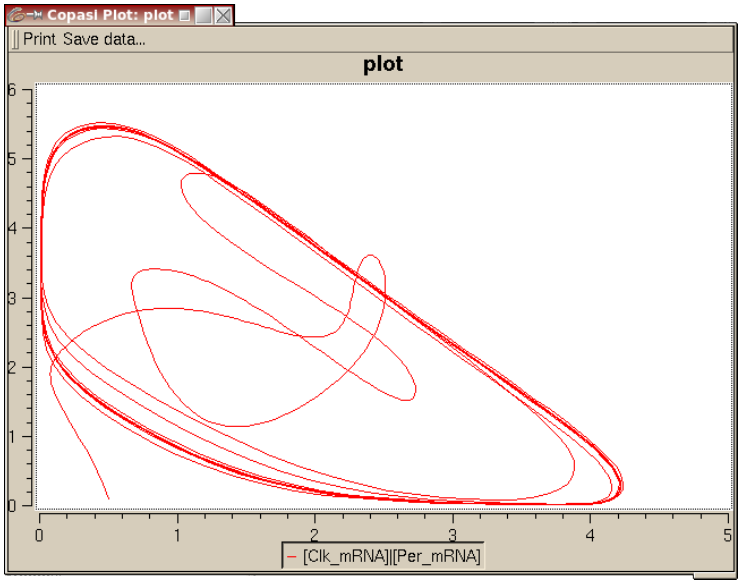
Publishing Group http://www.nature.com/naturebiotechnology

Reproduction of published simulation results

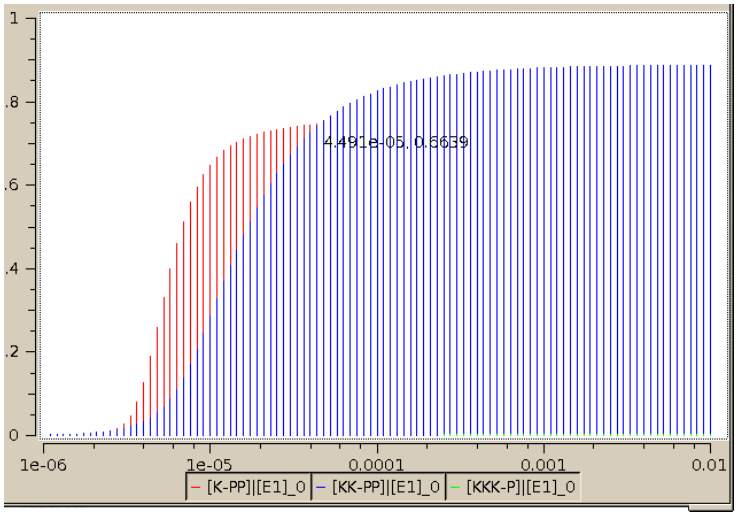
Edelstein et al 1996 (BIOMD0000000002)



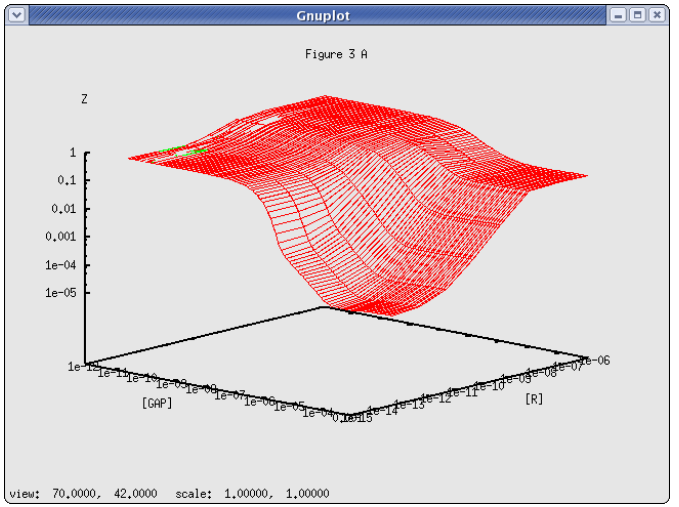
Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)



Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)



Description of simulations and analyses

	Model descriptions	Simulations and analysis
Minimal requirements	MIRIAM	MIASE
Data-models	SBML, SBGN	SED-ML
Terminologies	SBO	KISAO

Born in Hinxton 2007

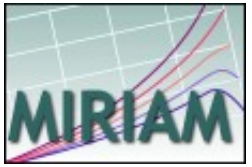
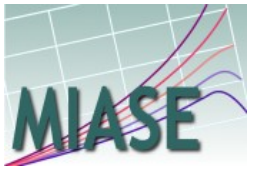
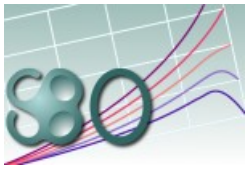
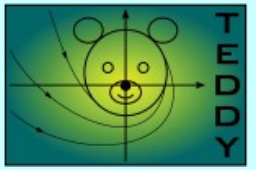
Description of model simulation and analysis

Minimum Information About a Simulation Experiment (MIASE) common set of information a modeller needs to provide in order to enable the execution and reproduction of a numerical simulation experiment, derived from a given set of quantitative models

Simulation Experiment Description Markup Language (SED-ML) XML-based format for encoding simulation experiments, following the requirements defined in the MIASE guidelines

Kinetic Simulation Algorithm Ontology (KiSAO) covers the most important simulation algorithms and simulation methods used to simulate biological kinetic models and puts those algorithms and methods into relation

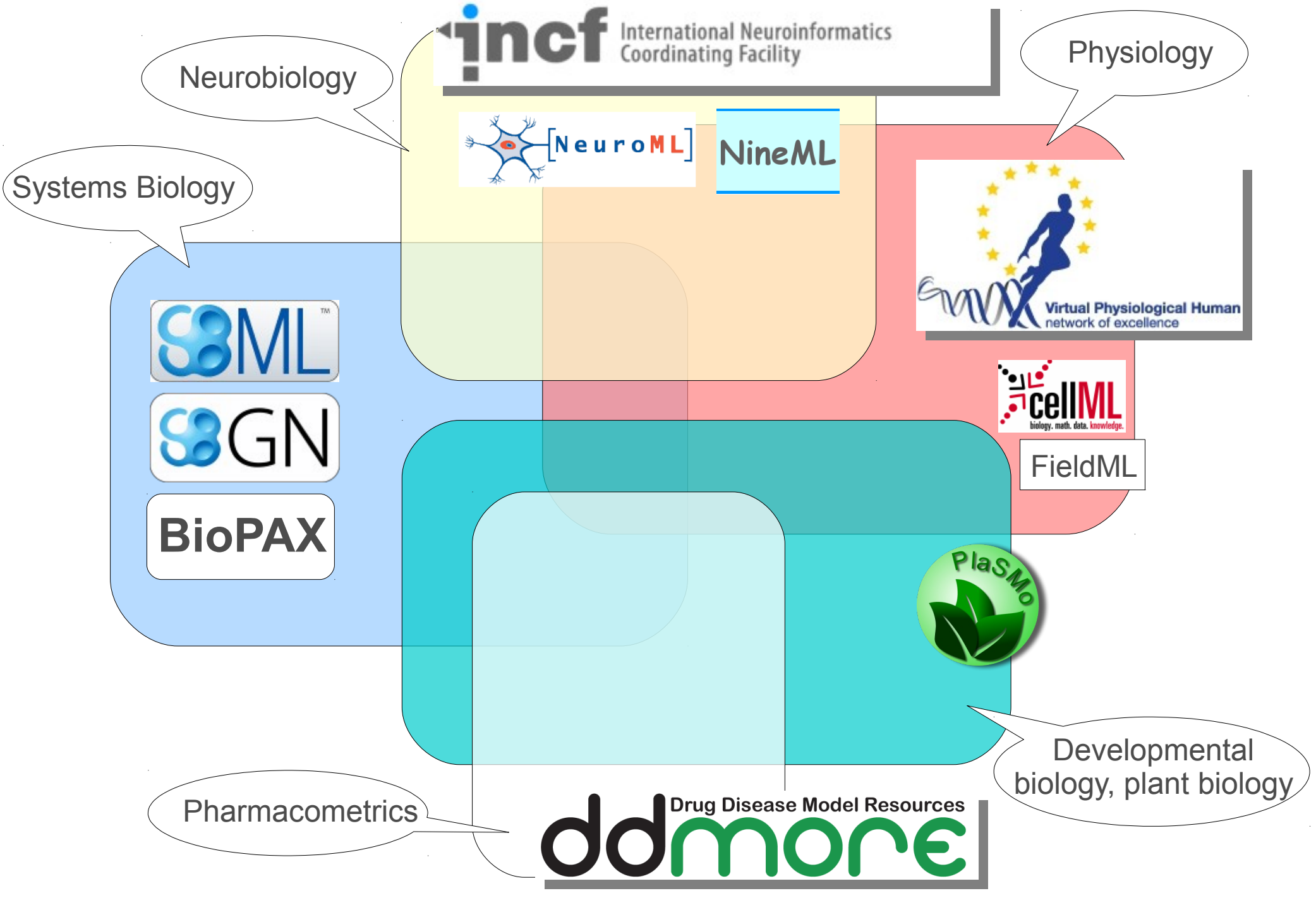
Characterising dynamical behaviours

	Model descriptions	Simulations and analysis	results
Minimal requirements			
Data-models			NuML
Terminologies			

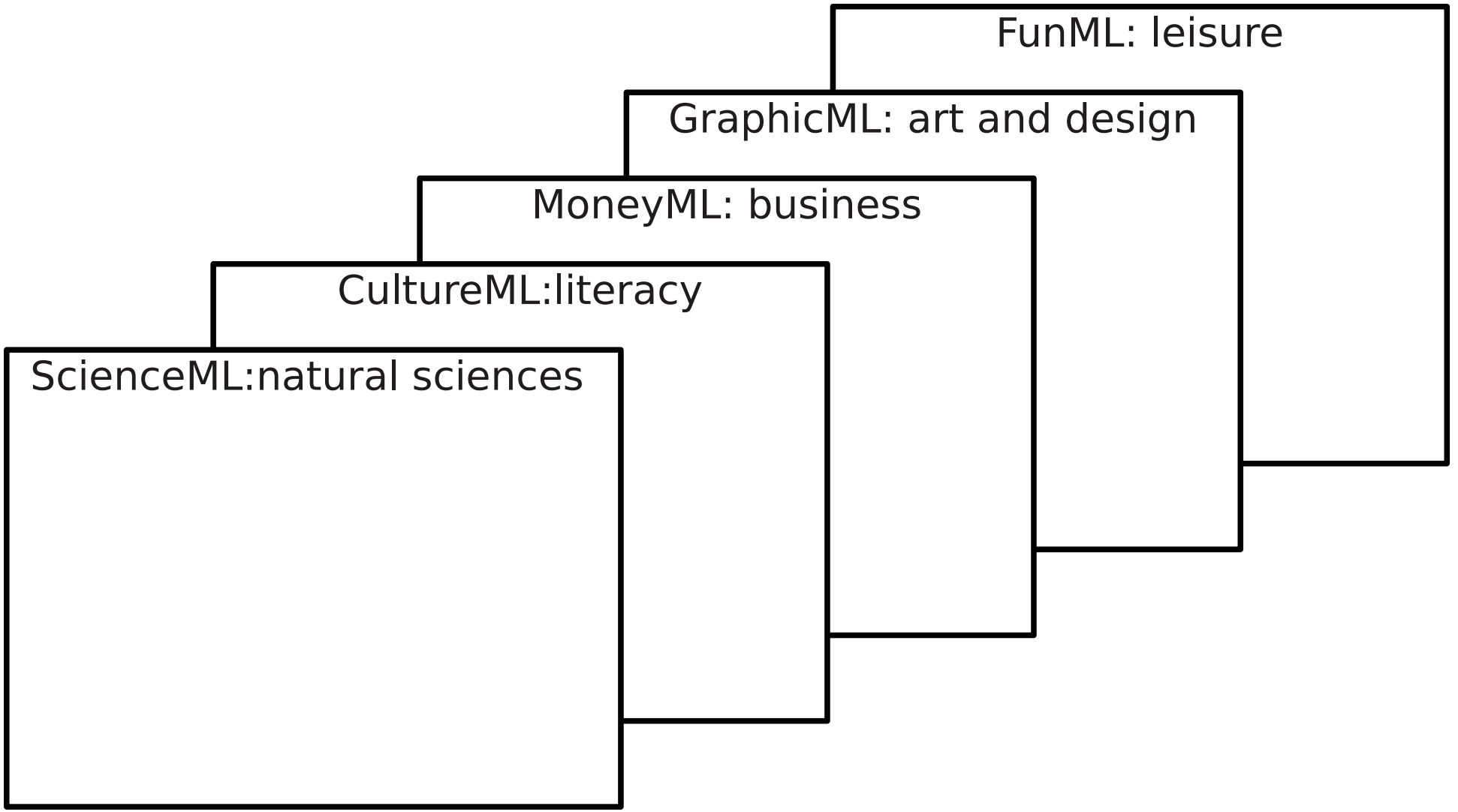
Is the matrix of standard complete?

	Model descriptions	Simulations and analysis	results
Minimal requirements	MIRIAM	MIASE	
Data-models	SBML, SBGN	SED ML	NuML
Terminologies	SBO	KISAO	TEDDY

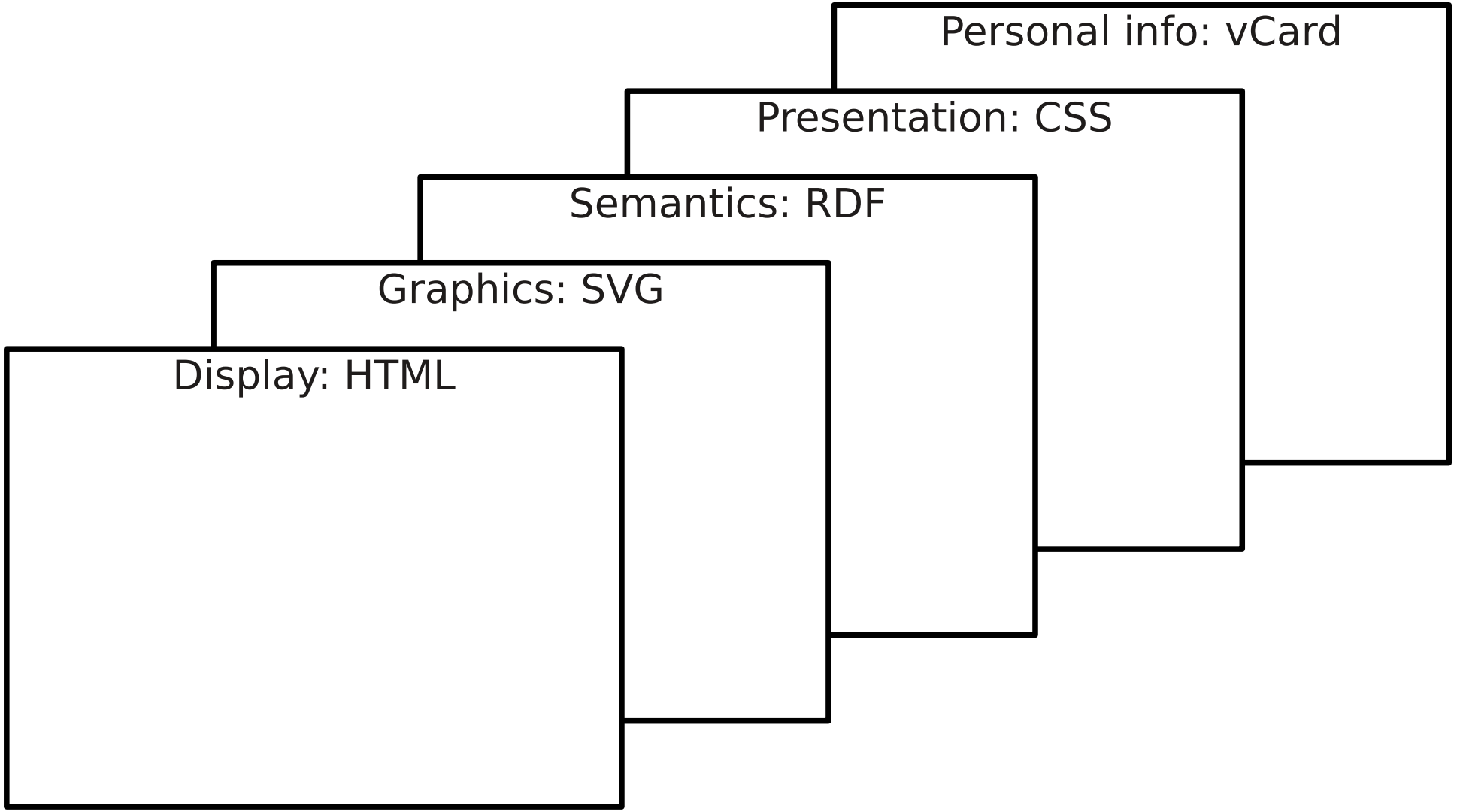
Parallel and redundant efforts



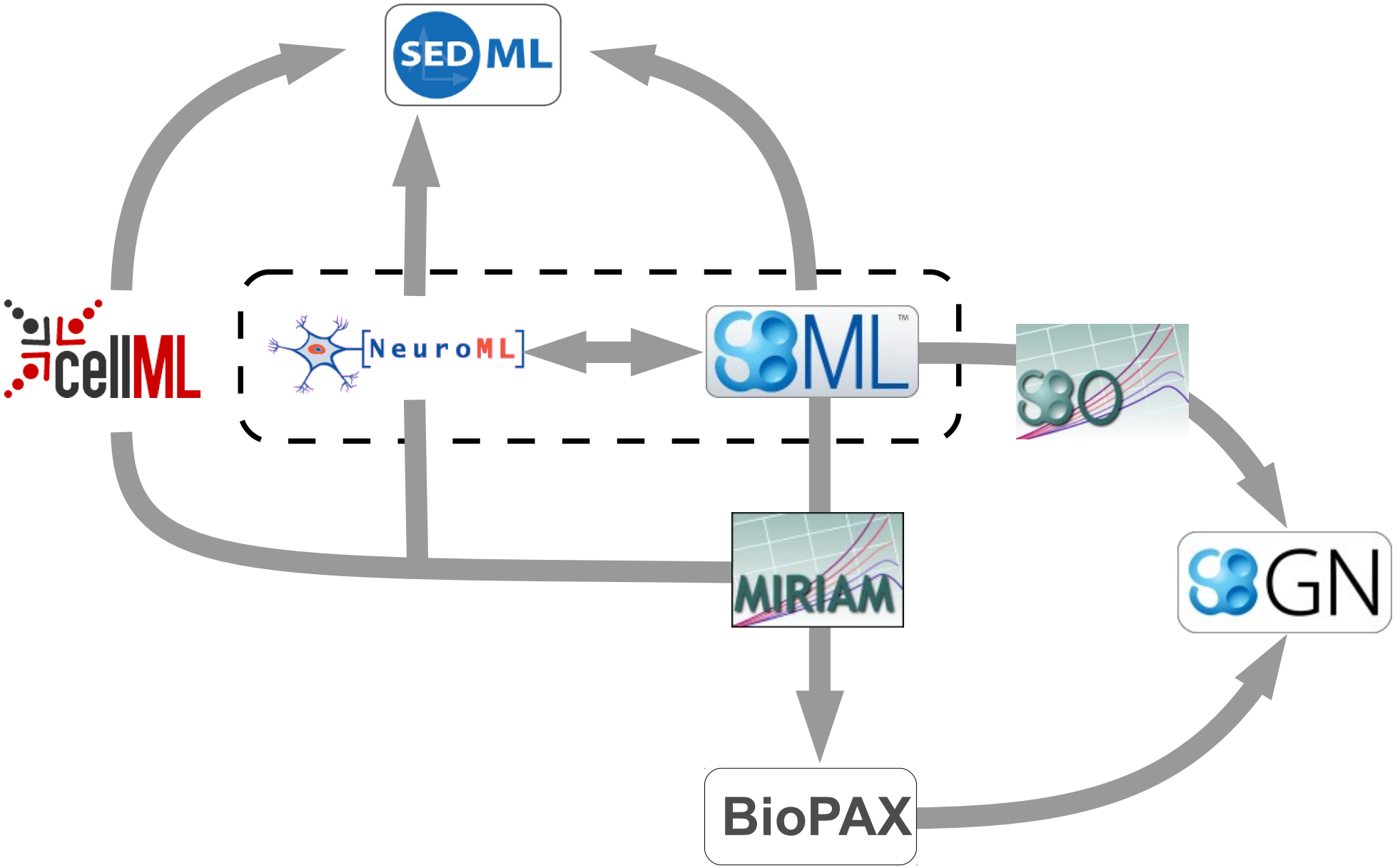
What if the world-wide web was built like this?



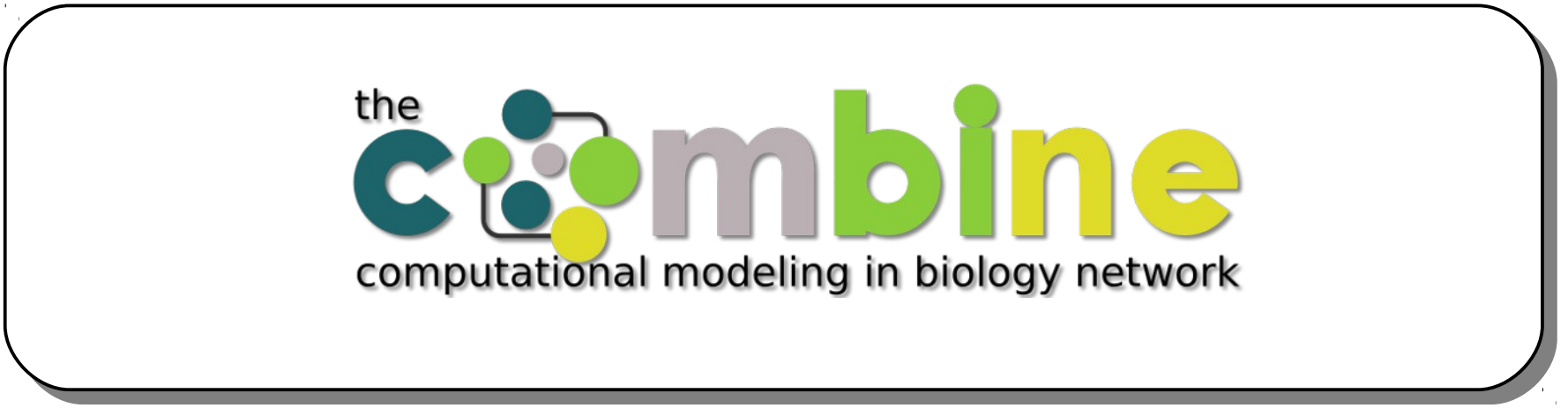
The correct way to do it



Existing standards interoperability



Overarching standardisation structure

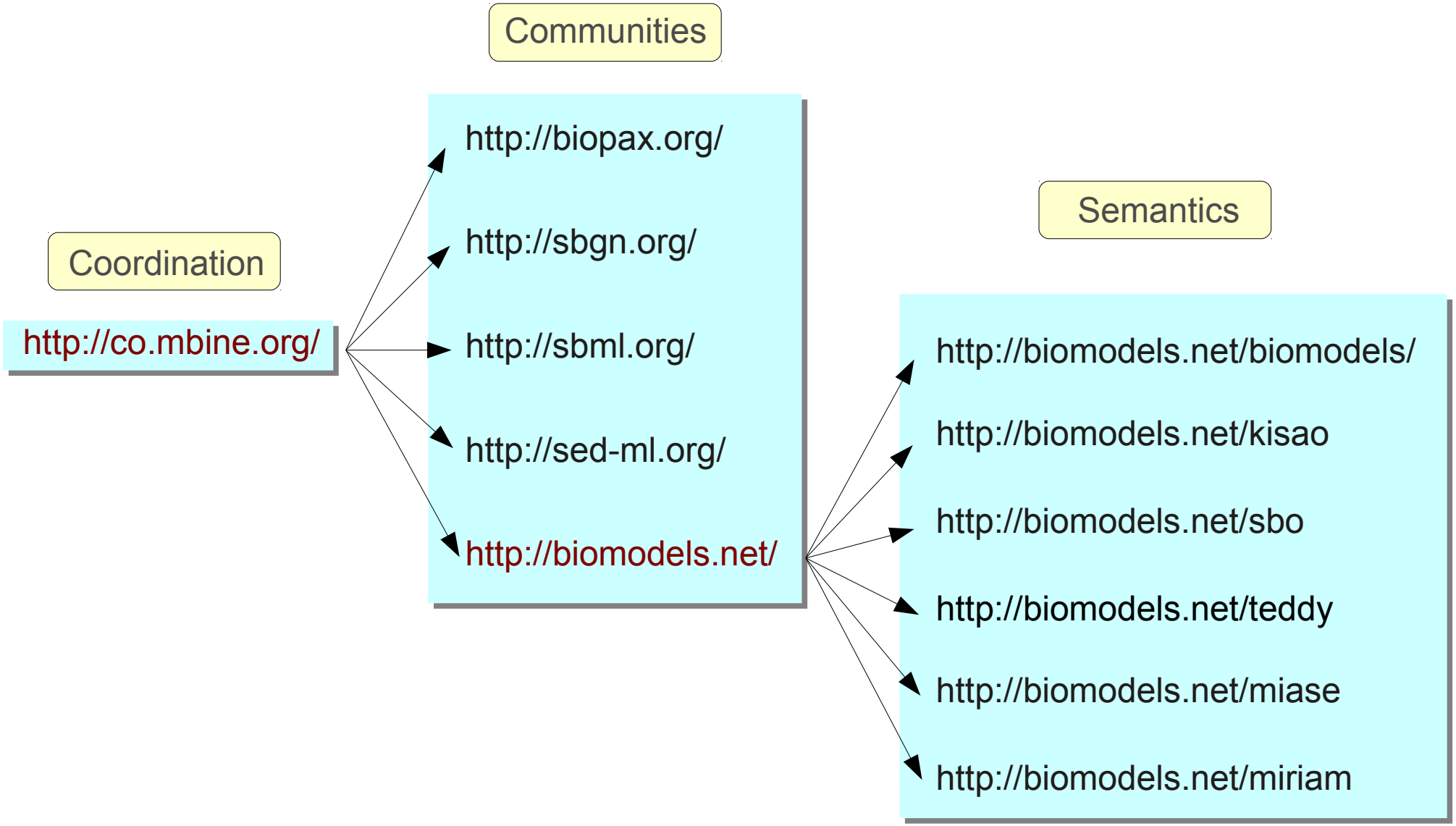


The “WorldWide Web consortium” of modelling in biology
http://co.mbine.org/

- HARMONY 2012
  - 21 to 25 May 2012, Maastricht
  - http://co.mbine.org/events/HARMONY_2012
  - 59 attendees
- COMBINE 2012
  - 14 to 19 August 2012, Toronto
  - http://co.mbine.org/events/COMBINE_2012

- Standard Operating Procedures
  - Technical requirements
  - Governance
- Single voice
  - Discussions with Industry
  - Financial support

Where to find more information?



Acknowledgements

Visionary: **Hiroaki Kitano**

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SBGN editors: Emek Demir, Nicolas Le Novère, *Huaiyu Mi*, *Stuart Moodie*, Falk Schreiber, Anatoly Sorokin, Alice Villéger

SED-ML editors: Richard Adams, Franck Bergmann, *Nicolas Le Novère,* Andrew Miller, David Nickerson, Dagmar Waltemath

Metadata: Mélanie Courtot, Nick Juty, Camille Laibe, Anna Zhukova

The whole community of Computational Systems Biology

The EBI group Computational Systems Neurobiology