

Models For All

*Standards for Describing the
Whole Life-Cycle of Modeling in
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
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A NEW APPROACH TO DECODING LIFE: Systems Biology

Trey Ideker^{1,2}, Timothy Galitski¹, and Leroy Hood^{1,2,3,4,5}
Institute for Systems Biology¹, 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.

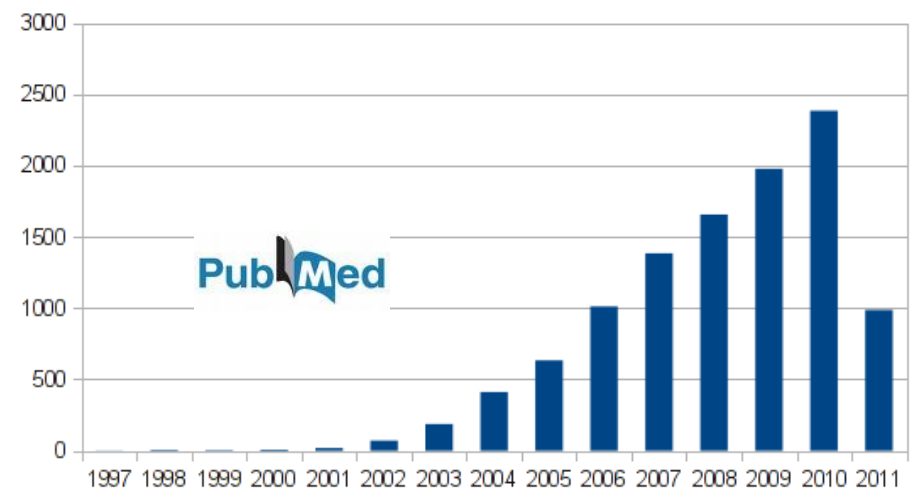
NEW
GENERATION
COMPUTING

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What is Systems Biology?

- First mention of the term: 1928 (L Von Bertalanffy)
- Modern revival of the term: 1998 (L Hood, H Kitano)



*Systems Biology is the study of the **emerging** properties of a biological system, taking into account all the **necessary** constituents, their **relationships** and their **dynamics**.*

Systems-wide analysis (omics)

- Born: 1990s
- Technologies: high-throughput, statistics
- People's background: molecular biologists, mathematicians
- Key lesson: the selection of a phenotype is done at the level of the system, not of the component (gene expression puzzle)

Application of systems-theory

- Born: 1960s
- Technologies: quantitative measurements, modelling
- People's background: biochemists, engineers
- Key lesson: the properties at a certain level are emerging from the dynamic interaction of components at a lower level

Nobel Symposium on Systems Biology (June 2009)

networks

Leroy Hood
Marc Vidal
Mike Snyder
Marc Kirschner
Charlie Boone
Ruedi Aebersold
Terence Hwa
Erin O'Shea
Jussi Taipale

models

Eric Davidson
Stanislas Leibler
Michel Savageau
Lucy Shapiro
Hans Westerhoff
Roger Brent
Luis Serrano
Francois Nedelec
Naama Barkai
Jim Ferrell
Jorg Stelling
Edda Klipp
Boris Kholodenko
Johan Elf
Bela Novak
Hiroaki Kitano
Stefan Hohmann
Bernard Palsson
Harley McAdams
Nicolas Le Novère
William Bialek
Mans Ehrenberg



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Avid Regev
Jeff Hasty
Michael Elowitz
Yoshihide Hayashizaki
Richard Young

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Stefan Hohmann
Harley McAdams
William Bialek
Mans Ehrenberg

synthetic biology
cell reprogramming



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

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

Cell

Kazutoshi Takahashi¹ and Shinya Yamanaka^{1,2,*}

¹Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan

²CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan

*Contact: yamanaka@frontier.kyoto-u.ac.jp

DOI 10.1016/j.cell.2006.07.024

Cell 126, 663–676, August 25, 2006 ©2006 Elsevier Inc. 663



EXTREME GENETIC ENGINEERING

An Introduction to Synthetic Biology

January 2007



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



page discussion view source history teams

About

The **International Genetically Engineered Machine competition (iGEM)** is a Biology competition. Student teams are given a kit of biological parts at the beginning of the year. Working at their own schools over the summer, they use the

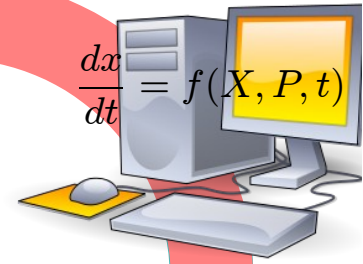
New way of doing biomedical research

Needs for interplay between models and reality tests

Experiment

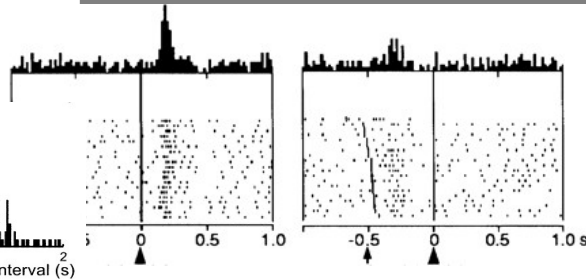
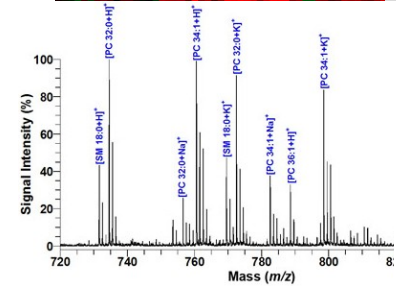
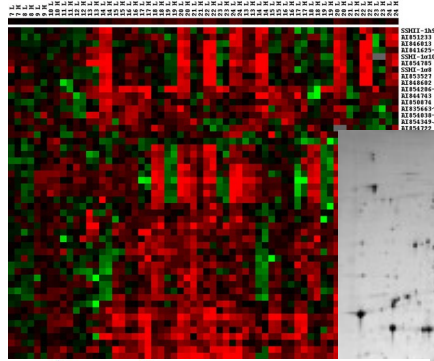
model

$$\frac{dx}{dt} = f(X, P, t)$$

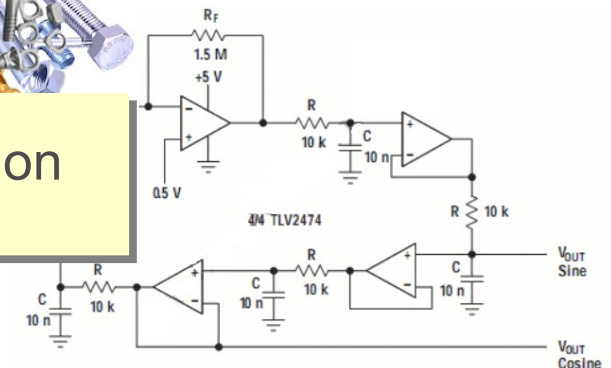


hypothesis

Needs for systems thinking and integration of heterogeneous knowledge



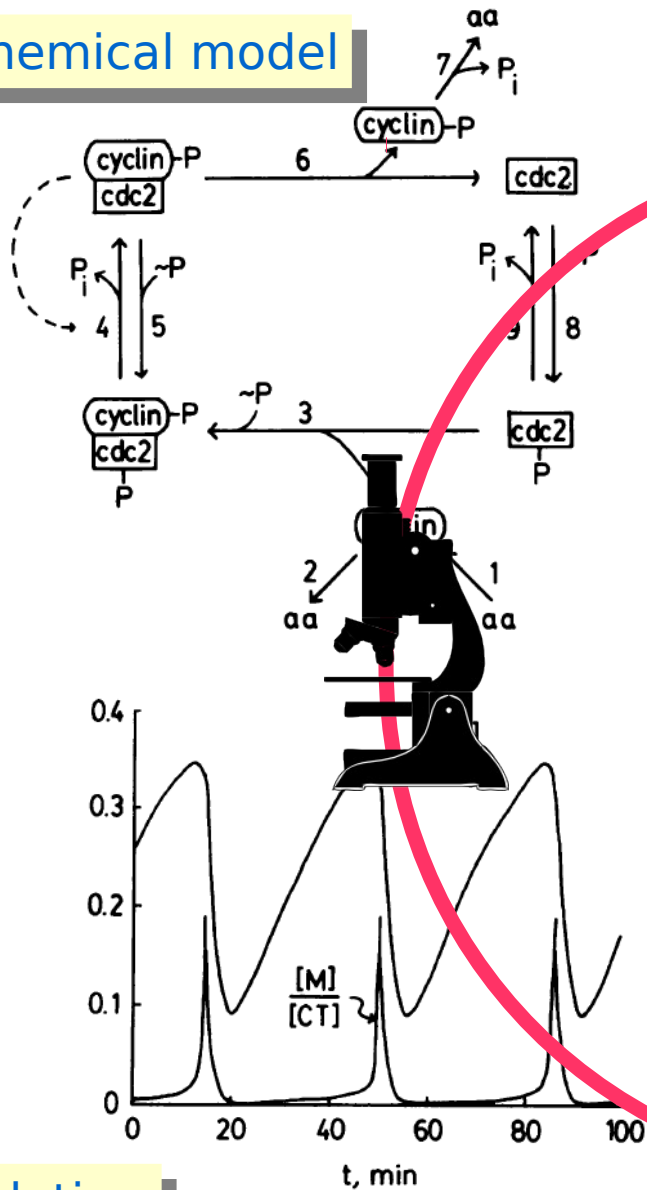
Needs for cooperation and standardisation



The models I am talking about

biochemical model

mathematical model



$$\begin{aligned} \frac{d[C2]}{dt} &= k_6[M] - k_8[\sim P][C2] + k_9[CP] \\ \frac{d[CP]}{dt} &= -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP] \\ \frac{d[pM]}{dt} &= k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M] \\ \frac{d[M]}{dt} &= [pM]F([M]) - k_5[\sim P][M] - k_6[M] \\ \frac{d[Y]}{dt} &= k_1[aa] - k_2[Y] - k_3[CP][Y] \\ \frac{d[YP]}{dt} &= k_6[M] - k_7[YP] \end{aligned}$$

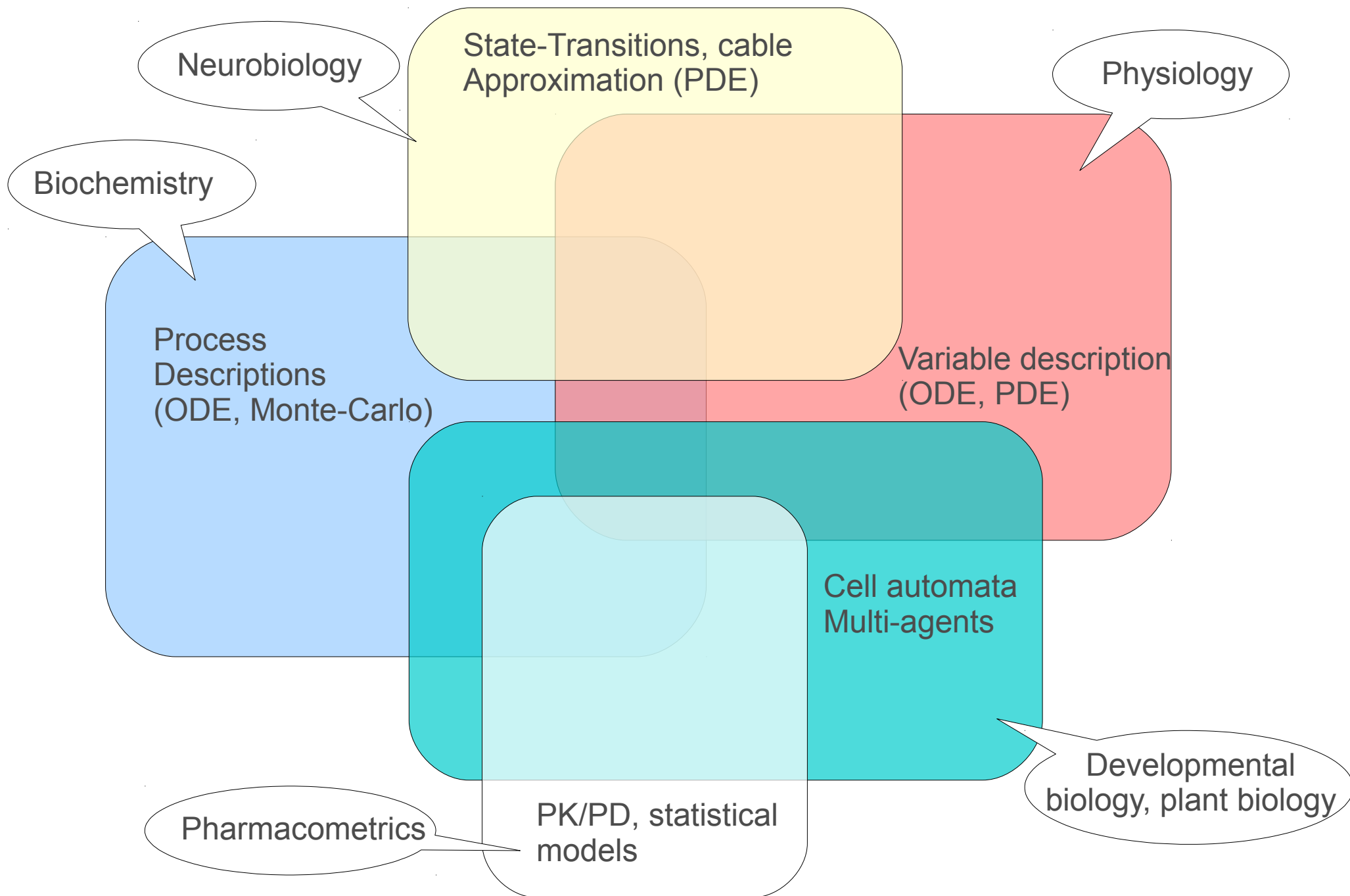
Parameter	Value	Notes
$k_1[aa]/[CT]$	0.015 min^{-1}	*
k_2	0	†
$k_3[CT]$	200 min^{-1}	*
k_4	$10\text{--}1000 \text{ min}^{-1}$ (adjustable)	
k_4'	0.018 min^{-1}	
$k_5[\sim P]$	0	‡
k_6	$0.1\text{--}10 \text{ min}^{-1}$ (adjustable)	
k_7	0.6 min^{-1}	†
$k_8[\sim P]$	$\gg k_9$	§
k_9	$\gg k_6$	§

simulation

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

computational model

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 and 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 al. The I κ B-NF- κ B 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- κ B 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 I κ B protein within the NF- κ B 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- κ B-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](#)

Browse models

- Curated models (326)
- Browse models using [Browse curated models](#)
- Non-curated models (373)

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

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](#).

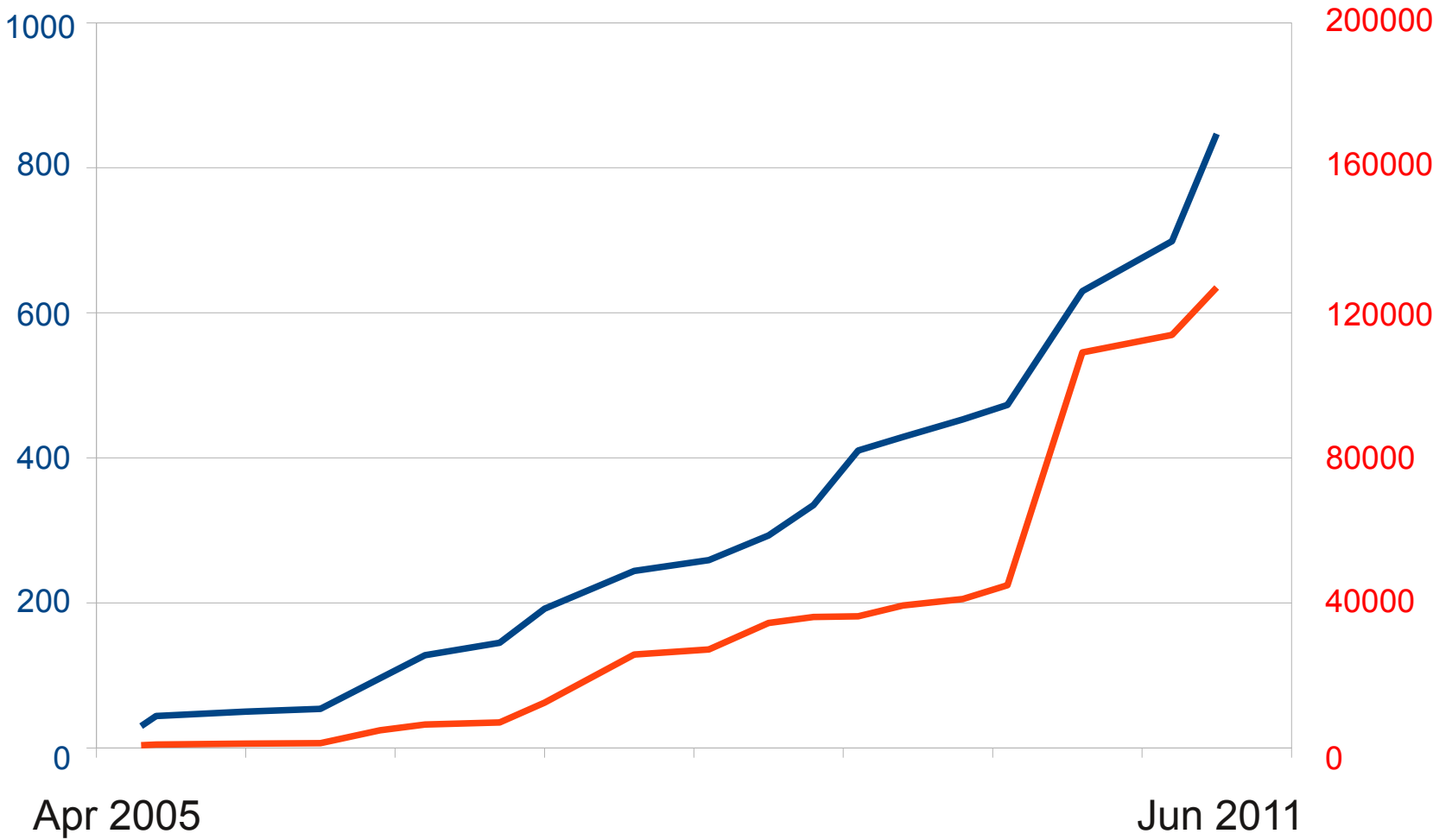
Li et al (2010). BMC Syst Biol, 4: 92



Computational models on the rise

models

relationships



BioModels Database growth since its creation

A language to describe computational models in biology

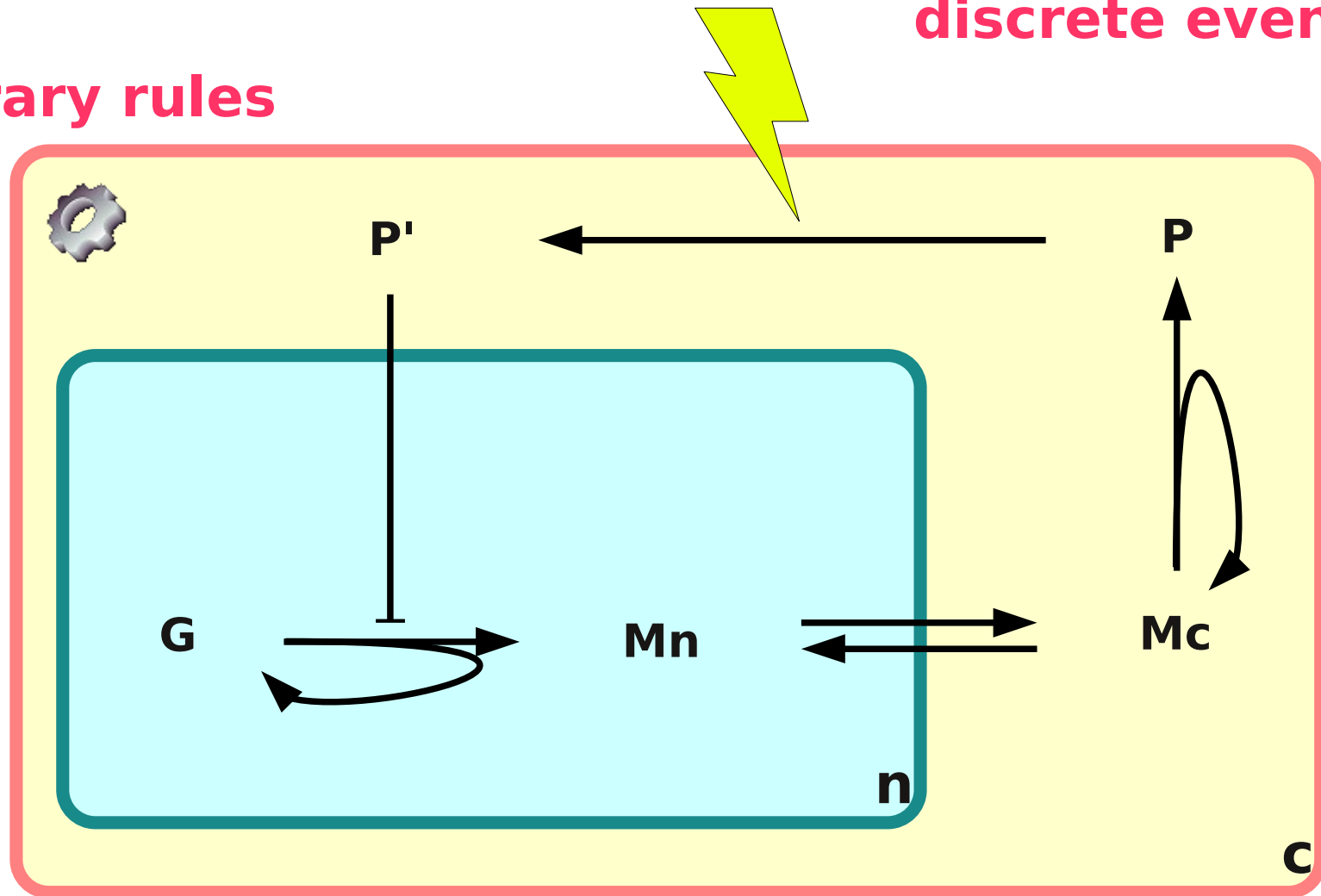
	Model descriptions
Data-models	

Born in Caltech 2000

What can we encode in SBML (core)?

arbitrary rules

discrete events



Why the Extensible Markup Language (XML)?

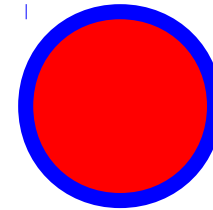
- **HTML**

A **strong word** and an [hyperlink](http://www.w3.org/)

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>
```

B1		   =C11*E11	
	A	B	C
1	1	102	
2			

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

```
<?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

A very simple SBML file (A $\rightarrow$ 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 $\rightarrow$ 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



SimpleSBML - COPASI 4.6 (Build 32) /home/.../2011-03-ModelsIndustry/SimpleSBML.cps

File Tools Help

Concentrations

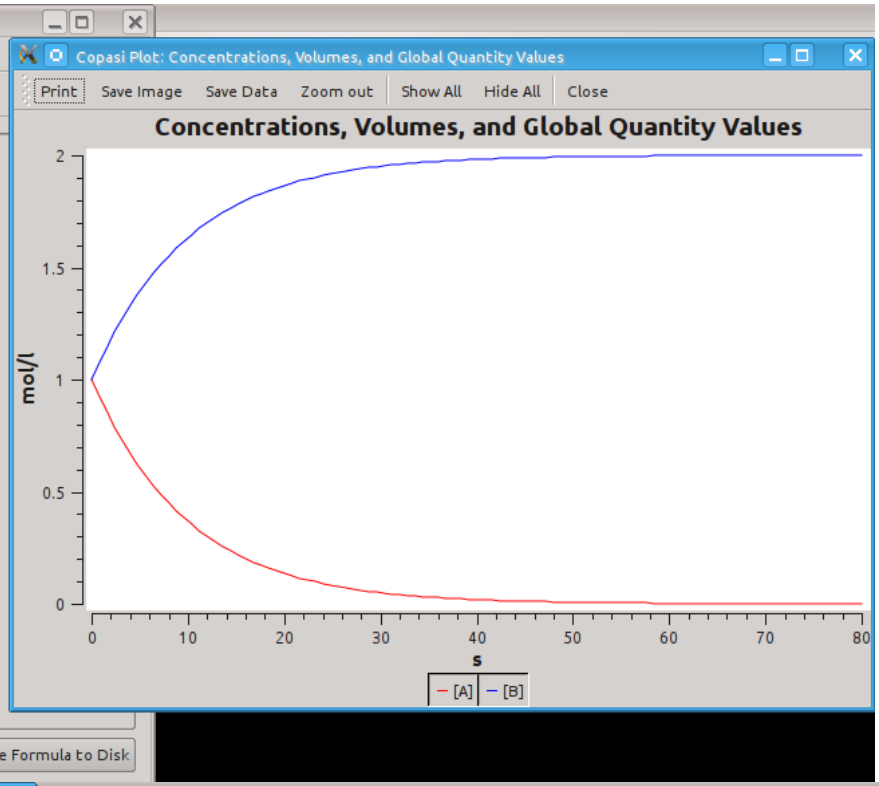
Copasi

- 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**

$$\frac{d([A] \cdot V_{\text{cell}})}{dt} = -V_{\text{cell}} \cdot (k_1 \cdot [A])$$
$$\frac{d([B] \cdot V_{\text{cell}})}{dt} = +V_{\text{cell}} \cdot (k_1 \cdot [A])$$

local parameters display numerical value Save Formula to Disk



CellDesigner

File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help

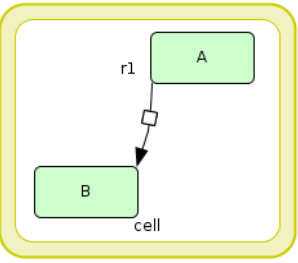
CellDesigner.org

Model

- Compartments
- Species
- Reactions

Layer base

SimpleSBML.xml *



Species Proteins Genes RNAs asRNAs Reactions Compartments Par

Edit Export

class	id	name	speciesType	compar...	positi...	included
PROTEIN	A	A		cell	inside	
PROTEIN	B	B		cell	inside	

ControlPanel SimpleSBML.xml

File Edit Data Simulation

Time span: End Time 80, Num. o... 100

Error tolerance: Exp. -6

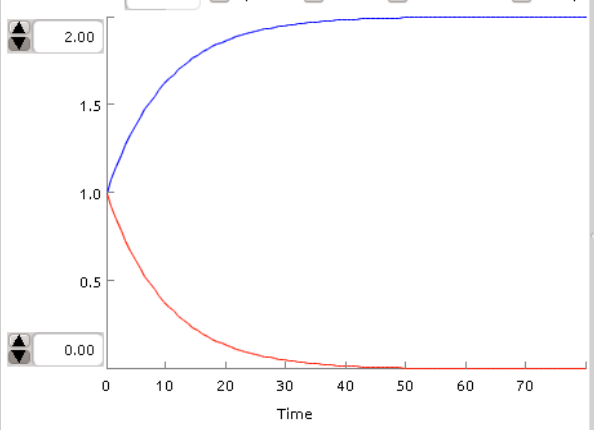
Solver: ☒ SLSlib, ☐ COPASI

Species Parameters Change amount Parameter Scan

Id	Name	Compart...	Quantity ...	Initial
A	A	cell	Concentra...	
B	B	cell	Concentra...	

Graph Table

Concentration raw ☒ Species ☐ Fluxes ☐ Parameters ☐ Comp...



Unselect all species search

search

Initialize Save As Execute Close show scatter plot

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



Difference between SBML L1, L2 and L3

Level 1

(devpt 2000-2003)

- predefined functions
- proprietary infix math notation
- reserved namespaces for annotation
- no controlled annotation
- no discrete events
- monolithic
- default values

Level 2

(devpt 2002-2008)

- function definitions
- all math in MathML
- no reserved namespaces for annotations
- controlled RDF annotation
- discrete events
- monolithic
- default values

Level 3

(devpt 2009-)

- function definitions
- all math in MathML
- no reserved namespaces for annotations
- controlled RDF annotation
- discrete events
- modular
- no default values

Progressive simplification, generalisation and externalisation

~15 software

~135 software

>220 software

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

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

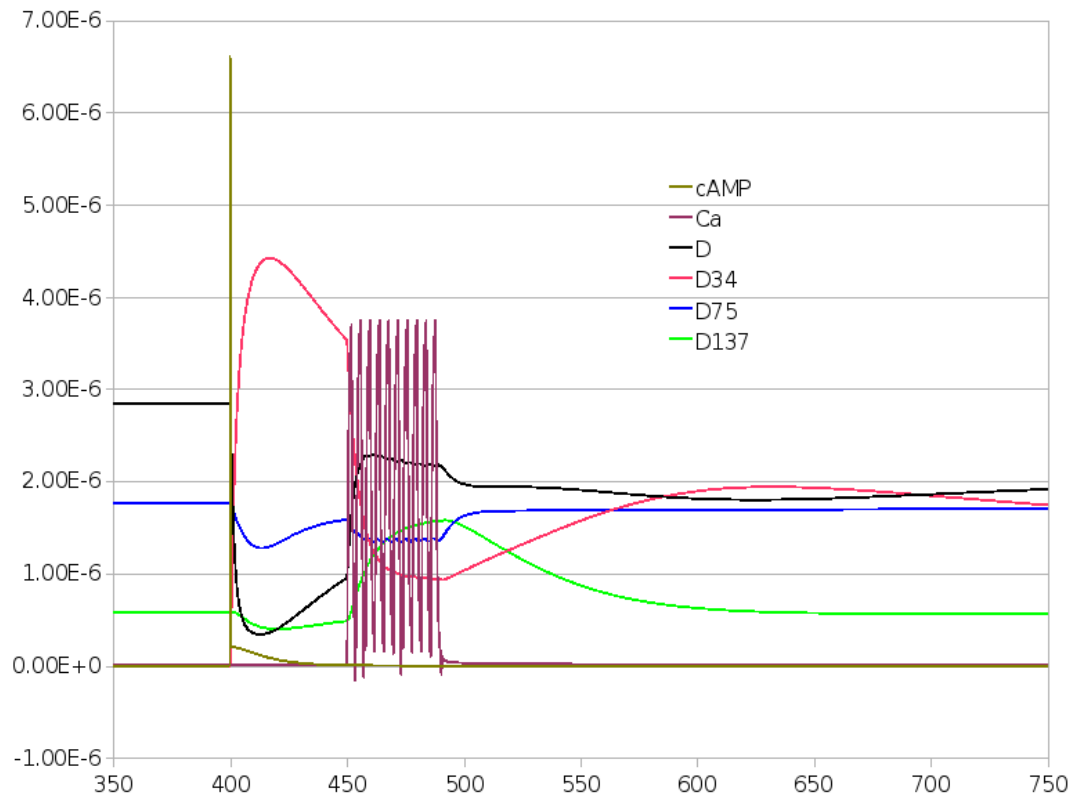
???

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



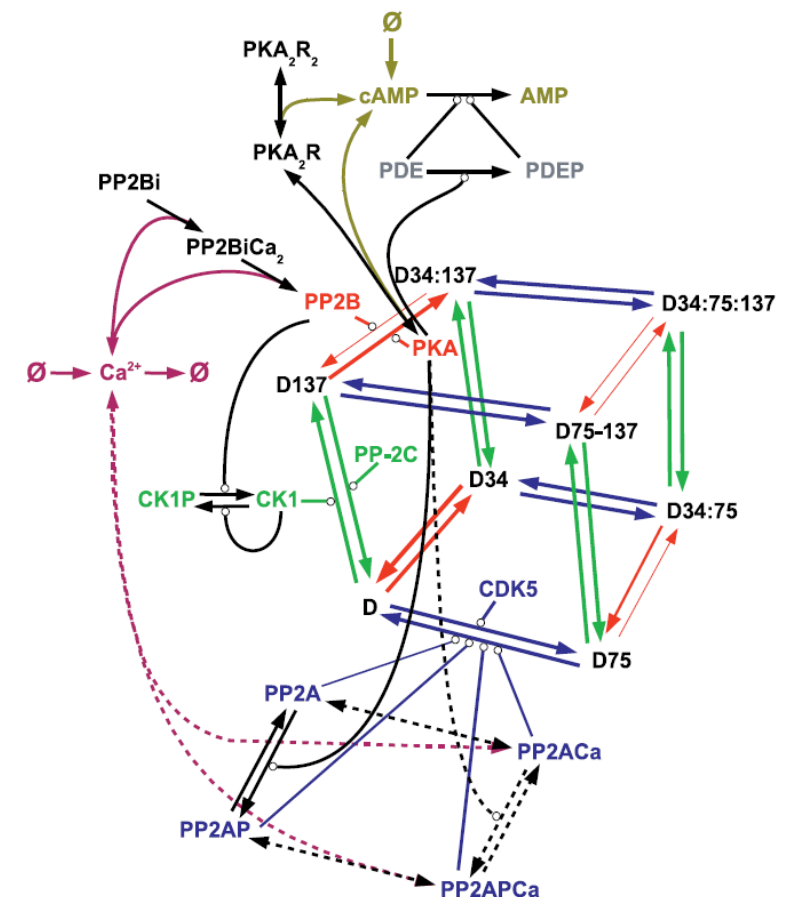
reaction:

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

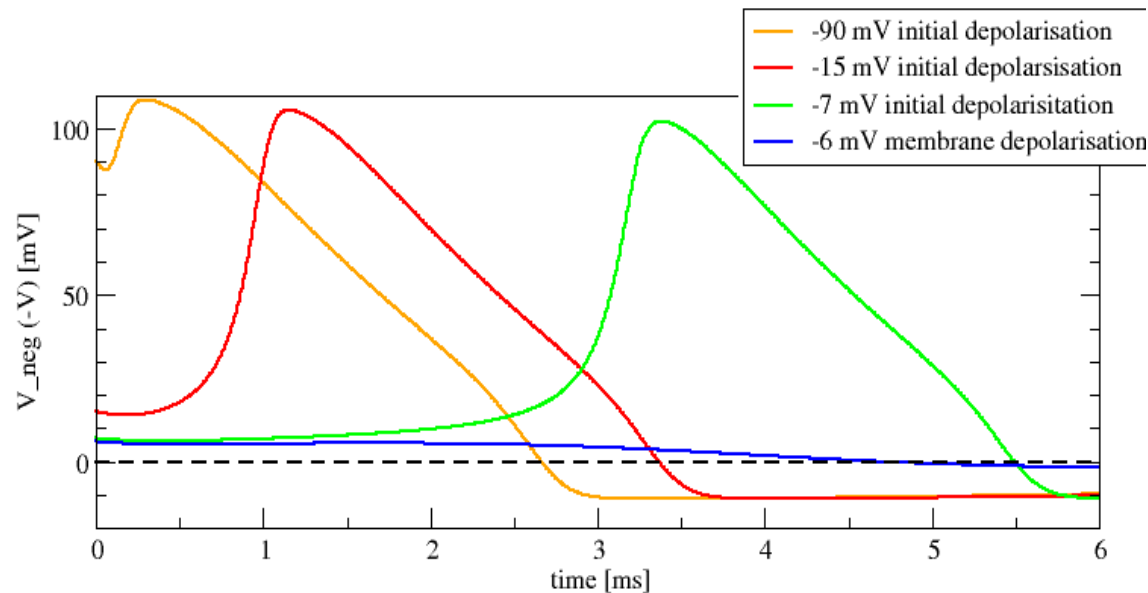
Fernandez et al. DARPP-32 is a robust integrator of dopamine and glutamate signals
PLoS Comput Biol (2006) 2: e176.



BIOMD0000000153



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.



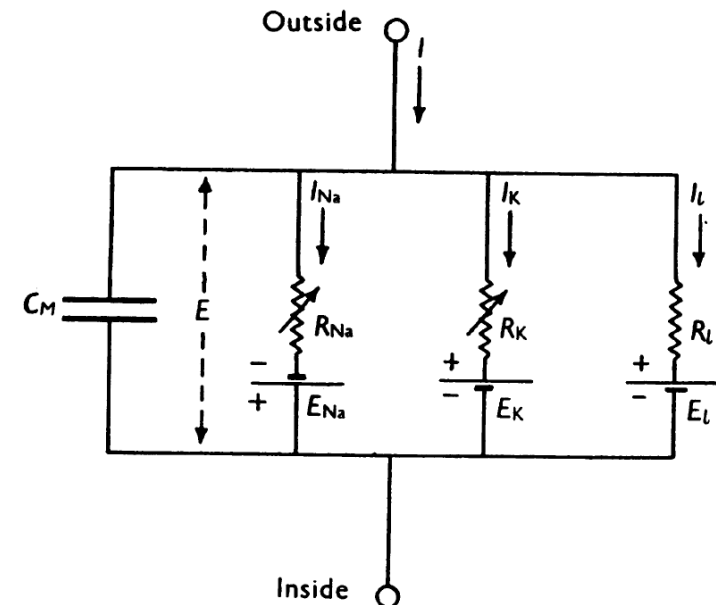
BIOMD0000000020

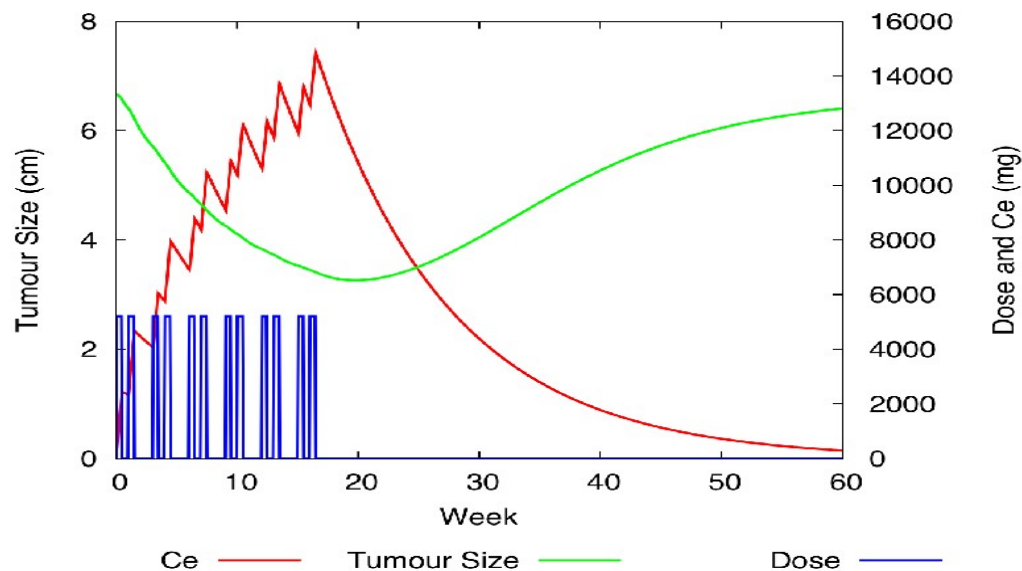
rate rule:

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

assignment rule:

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





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.

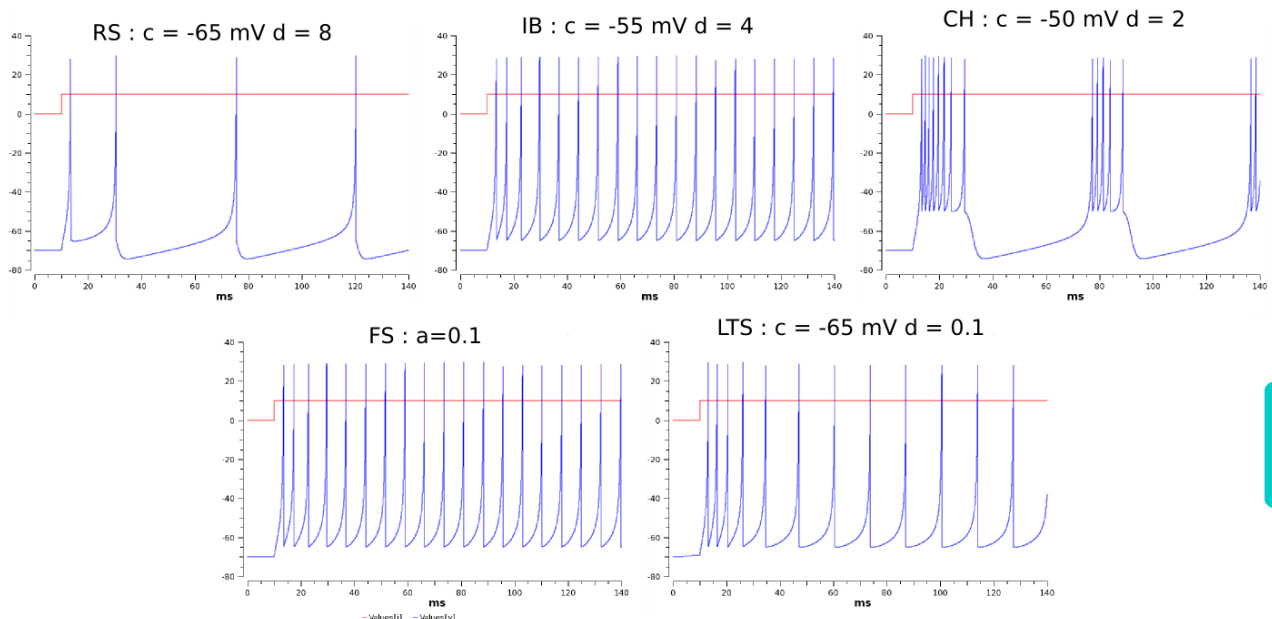


rate rule:

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

assignment rule:

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



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



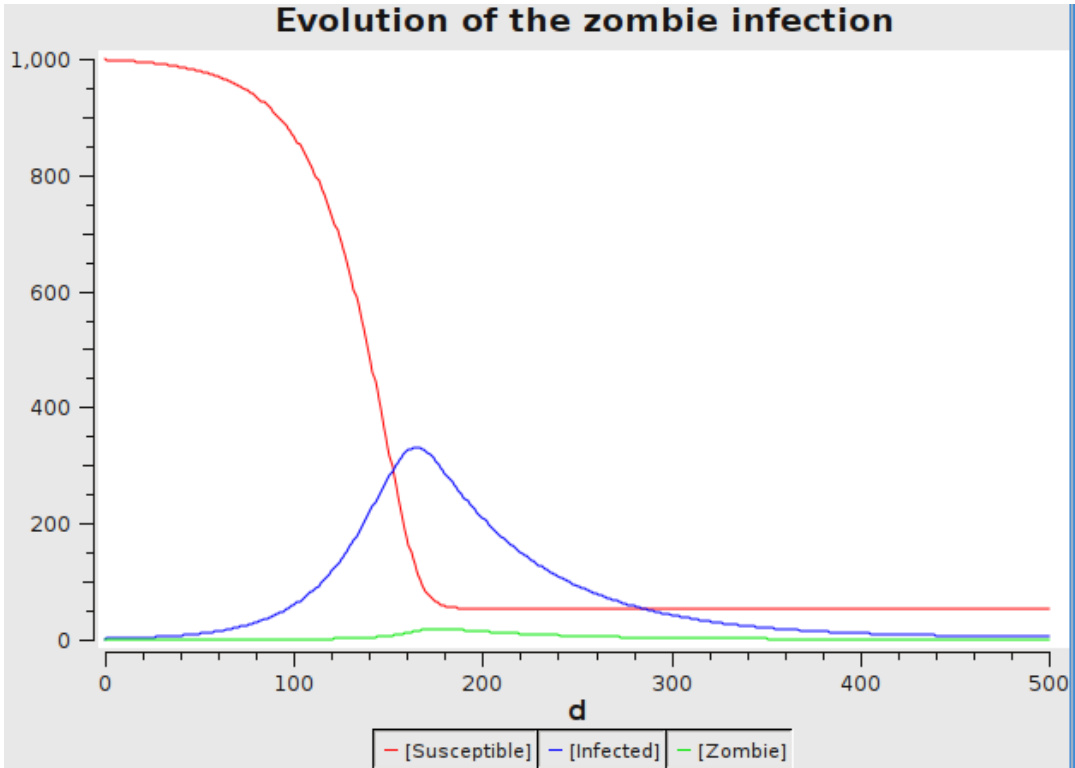
rate rule:

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

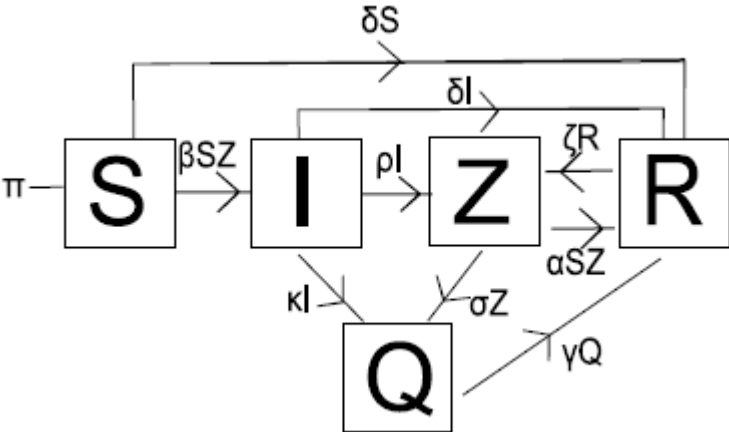
event:

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

Spread of infection diseases ...



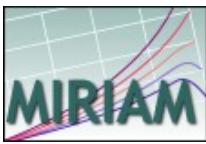
Munz P et al. When zombies attack!: Mathematical modelling of an outbreak of zombie infection. in "Infectious Disease Modelling Research Progress", (2009)133-150



Adding the semantics to the syntax

	Model descriptions
Minimal requirements	 The MIRIAM logo features the word "MIRIAM" in a bold, green, sans-serif font. It is set against a light blue background with a grid pattern and several curved lines in red, orange, and blue.
Data-models	 The SBML logo consists of the letters "SBML" in a blue, sans-serif font. The "S" and "B" are stylized, with the "S" having a circular shape. A small "TM" trademark symbol is located to the right of the "L".
Terminologies	 The SBOL logo features the letters "SBOL" in a green, sans-serif font. It is set against a light blue background with a grid pattern and several curved lines in red, orange, and blue.

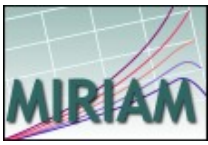
Born in Heidelberg 2004



Minimum Information Required in the Annotation of Models (simplified)

Models must :

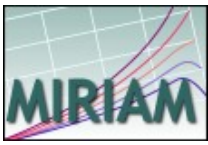
- be encoded in a public machine-readable format
- be clearly linked to a single reference description
- reflect the structure of the biological processes described in the reference paper (list of reactions etc.)
- be instantiable in a simulation (possess initial conditions etc.)
- be able to reproduce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



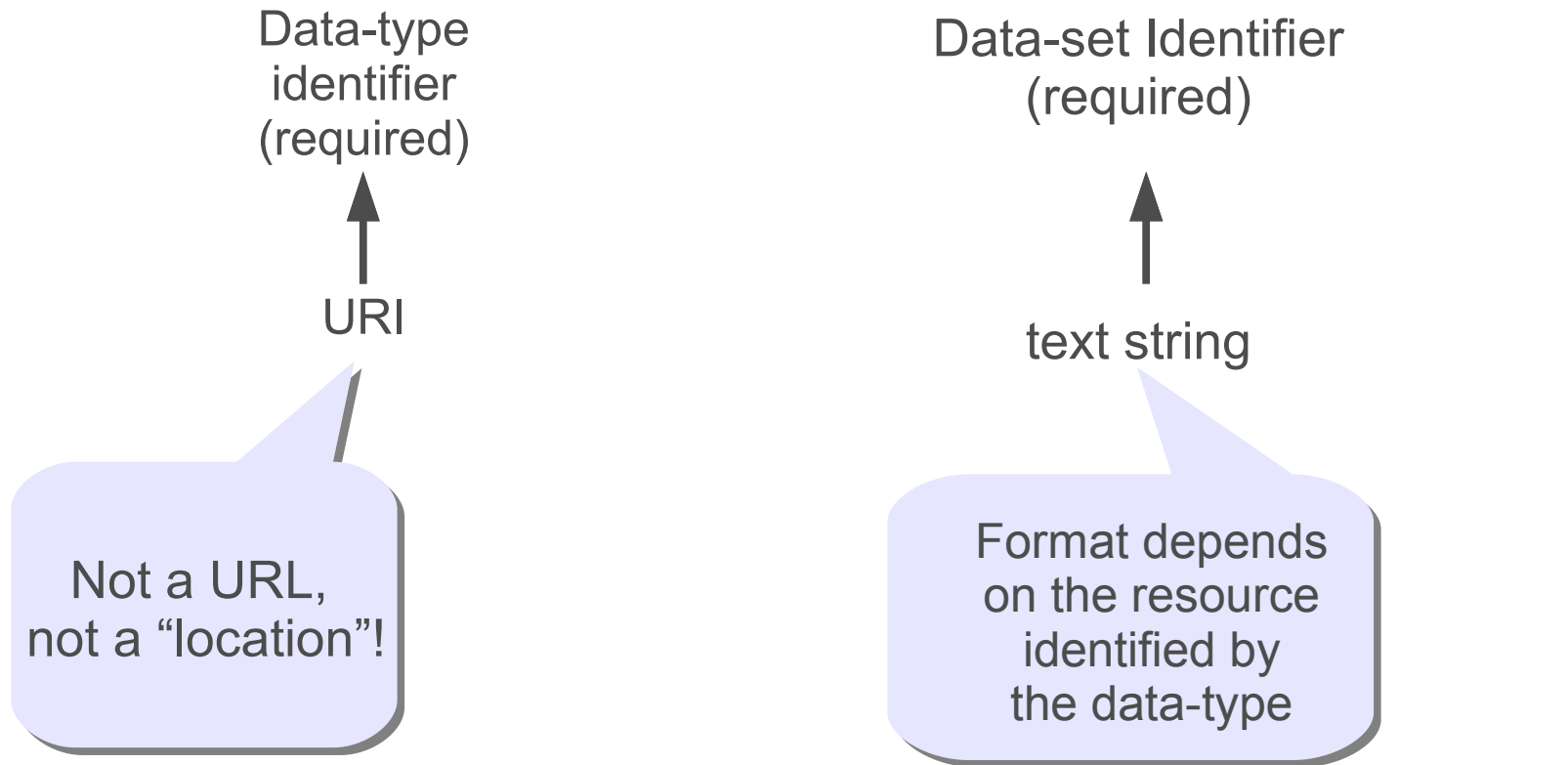
Why are annotations important?

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



MIRIAM identifiers



UniProt and P62158 (human calmodulin)

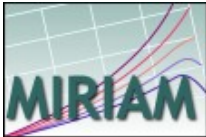
urn:miriam:uniprot:P62158

EC code and 1.1.1.1 (alcohol dehydrogenase)

urn:miriam:ec-code:1.1.1.1

Gene Ontology and GO:0000186 (activation of MAPKK activity)

urn:miriam:obo.go:GO%3A0000186



Private Vs public cross-references

<annotation>

<!-- // -->

<rdf:li rdf:resource="urn:miriam:uniprot:P62158" />

<!-- // -->

</annotation>

- No need to know the resources in advance
- Stable format

<annotation>

**<resource database="UniProt"
accession="P62158" />**

</annotation>

- Need to list the resources
and share the list

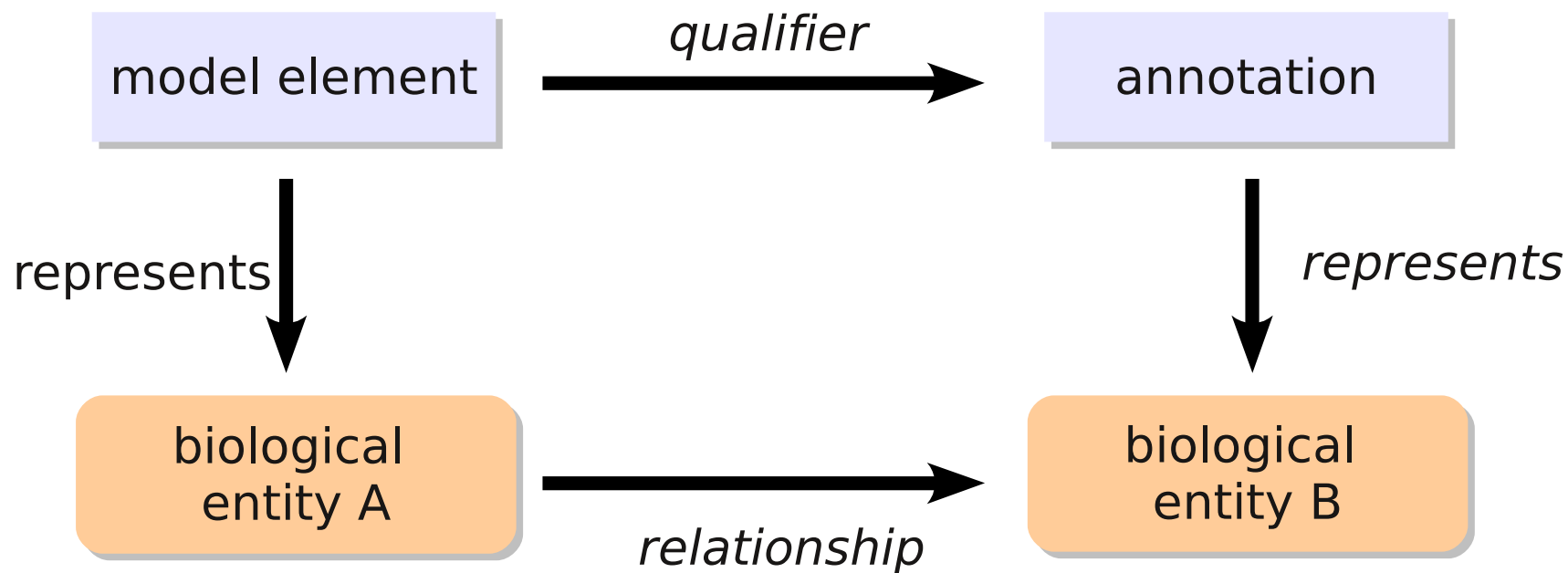
<annotation>

<uniprot>P62158</uniprot>

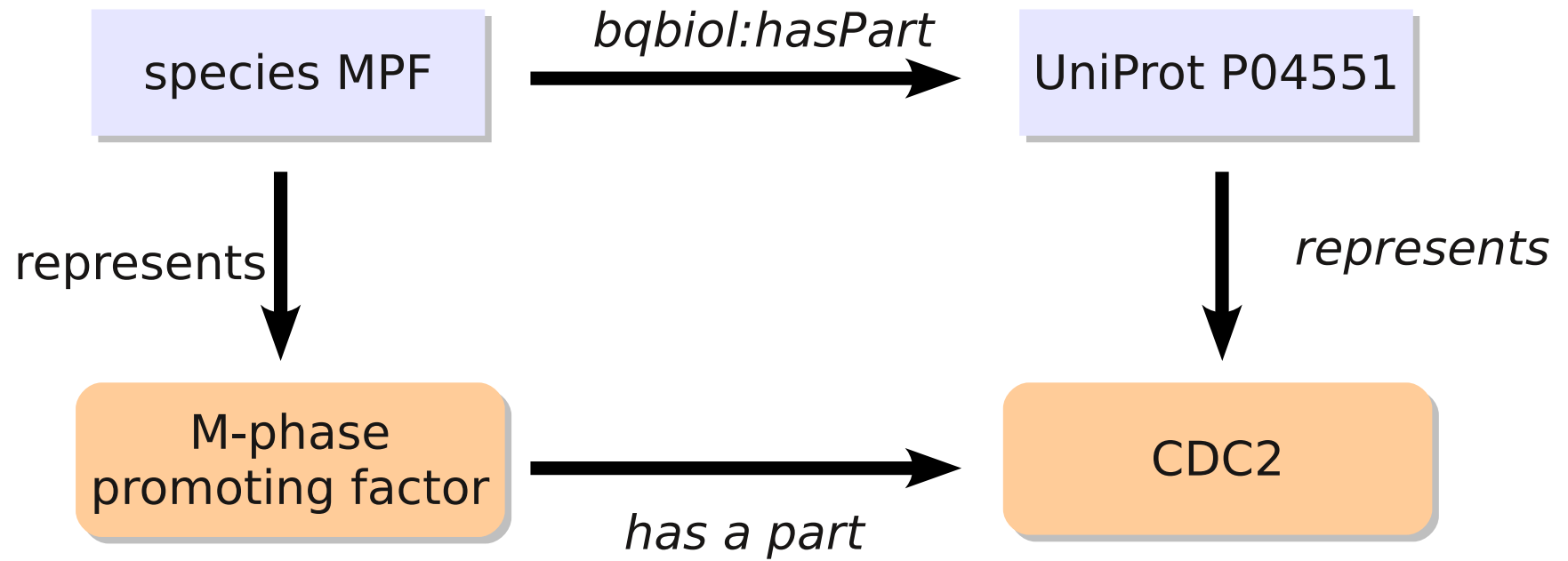
</annotation>

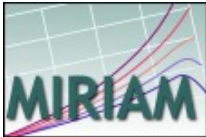
- Need to change the format
to add resources

Qualification of annotation



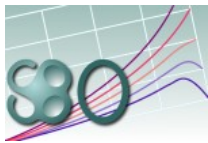
Qualification of annotation





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:hasPart>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P62158"/>
            <rdf:li rdf:resource="urn:miriam:obo.chebi:CHEBI%3A29108"/>
          </rdf:Bag>
        </bqbiol:hasPart>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```



Systems Biology Ontology

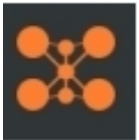
- Download
- Recent changes

- 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

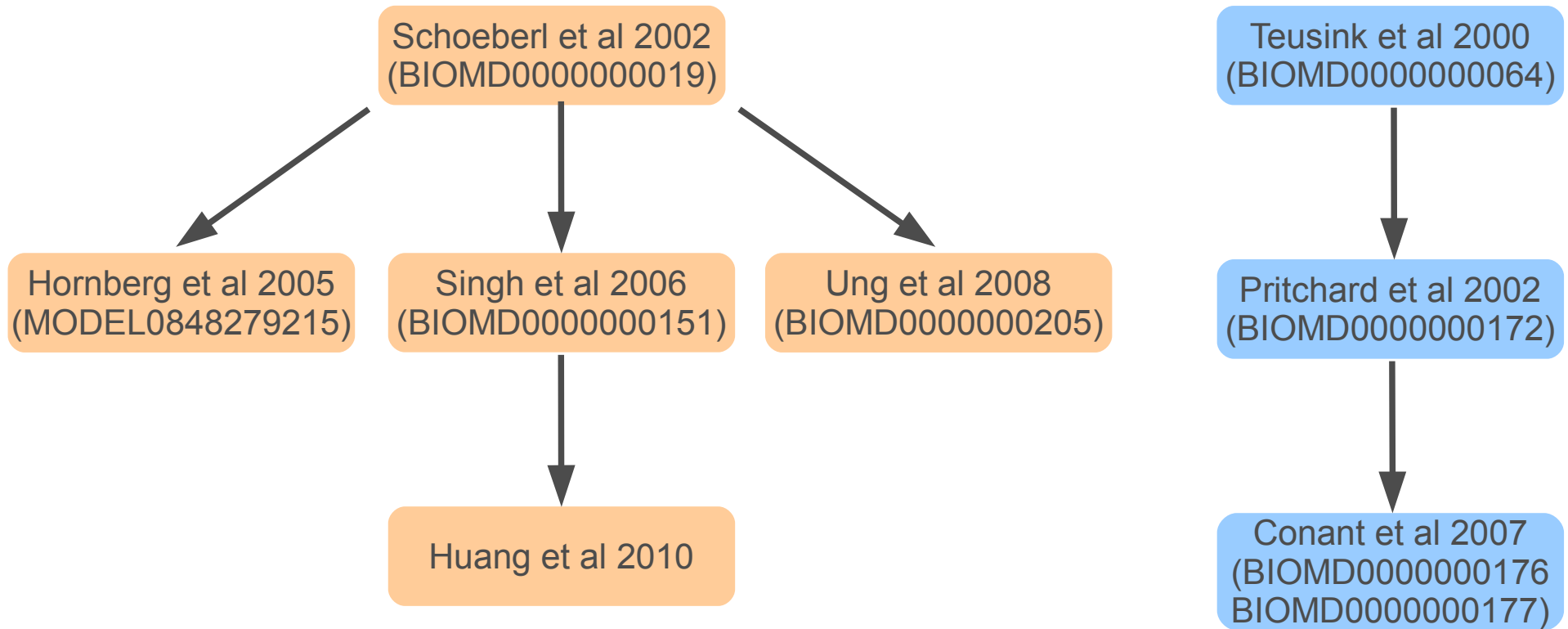
- SBO:0000492 - amplitude
- SBO:0000542 - basic reproductive ratio
- SBO:0000380 - biochemical coefficient
- SBO:0000258 - capacitance
- SBO:0000257 - conductance
- SBO:0000254 - electrical resistance
- SBO:0000308 - equilibrium or steady-state characteristic

Essential activator

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

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

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

Schulz et al. *Mol Syst Biol*, in the press

BIOMD000000000010_0
 BIOMD000000000009_Huang1996_MAPK_ultrasens)
 BIOMD000000000011_Levchenko2000_MAPK_noScaffold)
 BIOMD000000000014_Levchenko2000_MAPK_Scaffold)
 BIOMD000000000026_Markevich2004_MAPK_orderedElementary)
 BIOMD000000000028_Markevich2004_MAPK_phosphoRandomElementary)
 BIOMD000000000030_Markevich2004_MAPK_AllRandomElementary)
 BIOMD000000000029_Markevich2004_MAPK_phosphoRandomMM)
 BIOMD000000000027_Markevich2004_MAPK_orderedMM)
 BIOMD000000000031_Markevich2004_MAPK_orderedMM2kinases)
 BIOMD000000000032_Kofahl2004_pheromone)
 BIOMD000000000016_McClean2007_CrossTalk)
 BIOMD000000000084_Hornberg2005_ERKcascade)
 BIOMD000000000149_Kim2007_Wnt_ERK_Crosstalk)
 BIOMD000000000033_0
 BIOMD000000000048_Kholodenko1999_EGFRsignaling)
 BIOMD000000000049_Sasagawa2005_MAPK)
 BIOMD000000000205_Ung2008_EGFR_Endocytosis)
 BIOMD000000000019_0
 BIOMD000000000175_Birtwistle2007_ErbB_Signaling)

ATP:protein_phosphotransferase_(non-specific)
 RAF_proto-oncogene_serine/threonine-protein_kinase
 inactivation_of_MAPKKK_activity
 inactivation_of_MAPKK_activity
 protein_amino_acid_dephosphorylation
 protein_amino_acid_phosphorylation
 MAP_kinase_kinase_kinase_kinase_activity
 MAP_kinase_kinase_kinase_activity
 activation_of_MAPKKK_activity
 activation_of_MAPKK_activity
 Ras_small_GTPase,_Ras_type
 mitogen-activated_protein_kinase_kinase_kinase_binding
 urn:miriam:reactome:REACT_143
 urn:miriam:reactome:REACT_996
 urn:miriam:reactome:REACT_614
 Serine/threonine-protein_kinase_mos
 urn:miriam:reactome:REACT_525
 Mitogen-activated_protein_kinase_1
 ATP:protein_phosphotransferase_(MAPKKK-activated)
 MAP_kinase_kinase_activity
 activation_of_MAPK_activity
 inactivation_of_MAPK_activity
 Dual_specificity_mitogen-activated_protein_kinase_kinase_1
 urn:miriam:reactome:REACT_136
 urn:miriam:reactome:REACT_2247
 urn:miriam:uniprot:Q90W58
 phosphoprotein_phosphatase_activity
 mitogen-activated_protein_kinase_binding
 mitogen-activated_protein_kinase_kinase_binding
 urn:miriam:reactome:REACT_1780
 urn:miriam:reactome:REACT_495
 peptidyl-threonine_phosphorylation
 peptidyl-tyrosine_phosphorylation

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_ExpInact	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	
	BIOMD0000000073	0.163	5.0e-03	

Schulz *et al.* *Mol Syst Biol*, in the press

See also: Henkel *et al* (2010) *BMC Bioinfo*, 11:423

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	
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Sasagawa2005_MAPK	BIOMD0000000049	0.240	< 1/1000	
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.234	< 1/1000	
Leloup1999_CircClock	BIOMD0000000021	0.229	< 1/1000	
Goldbeter1991_MinMitOscil_ExpInact	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	
	BIOMD0000000073	0.163	5.0e-03	

MAPK

Schulz *et al.* *Mol Syst Biol*, in the press

See also: Henkel *et al* (2010) *BMC Bioinfo*, 11:423

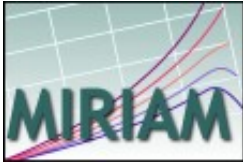
Ranking and retrieval of models

Model	BioModel	Score	p-val num		
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.000	< 1/1000		MAPK
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		Other kinase cascades
Sasagawa2005_MAPK	BIOMD0000000049	0.240	< 1/1000		
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.234	< 1/1000		
Leloup1999_CircClock	BIOMD0000000021	0.229	< 1/1000		
Goldbeter1991_MinMitOscil_ExpInact	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		
	BIOMD0000000073	0.163	5.0e-03		

Schulz *et al.* *Mol Syst Biol*, in the press

See also: Henkel *et al* (2010) *BMC Bioinfo*, 11:423

The interface with all biologists

	Model descriptions
Minimal requirements	
Data-models	
Terminologies	

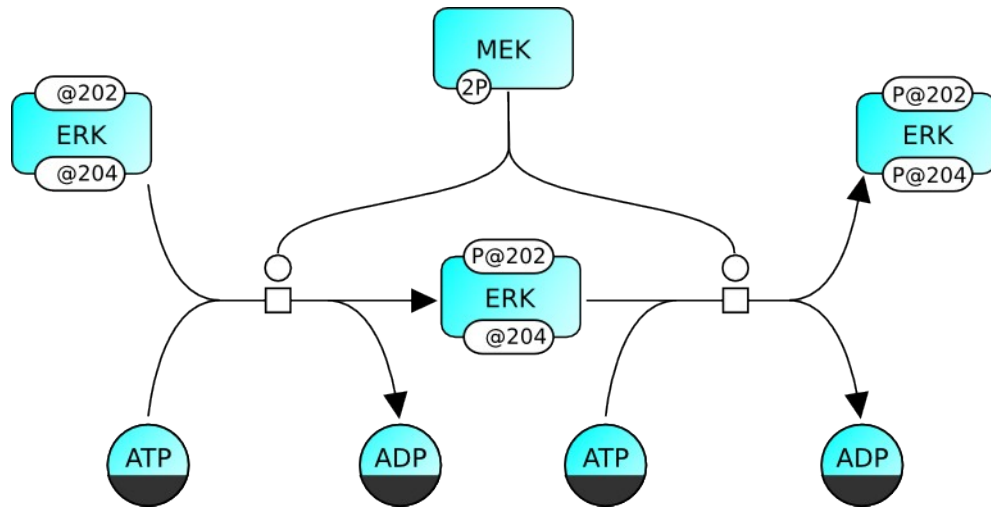
Born in Tokyo 2005

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.

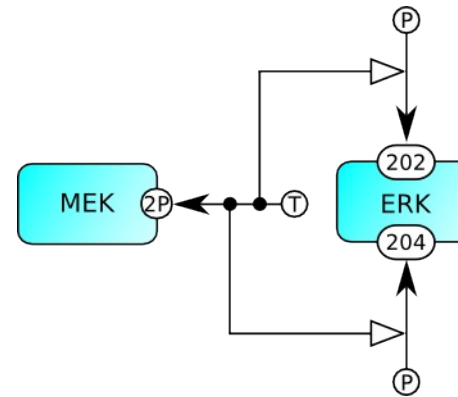
Graph trinity: three languages in one notation

Process Descriptions



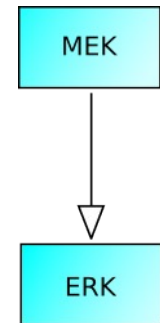
- Unambiguous
- Mechanistic
- Sequential
- Combinatorial explosion

Entity Relationships



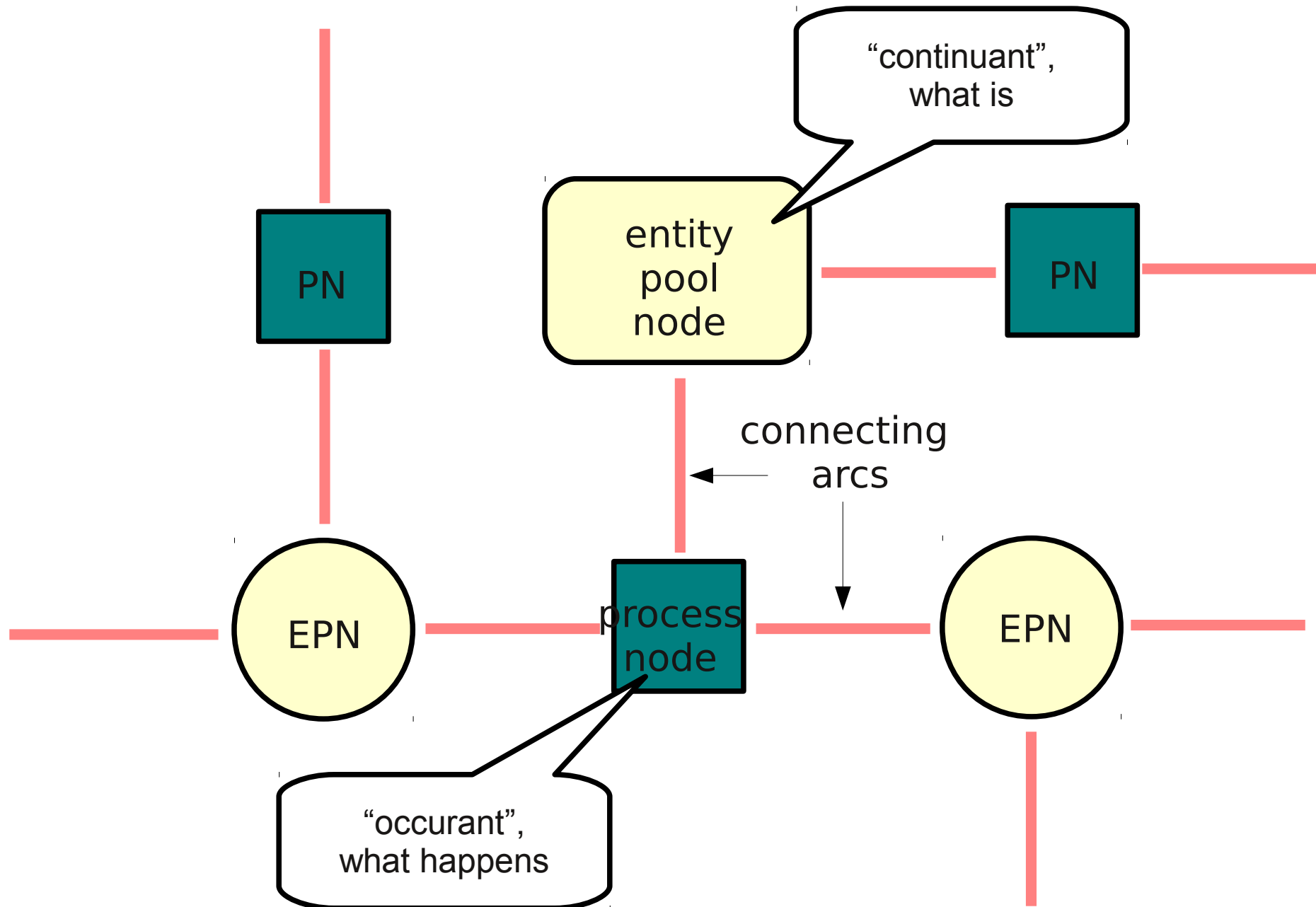
- Unambiguous
- Mechanistic
- Non-sequential
- Independence of relationships

Activity Flows

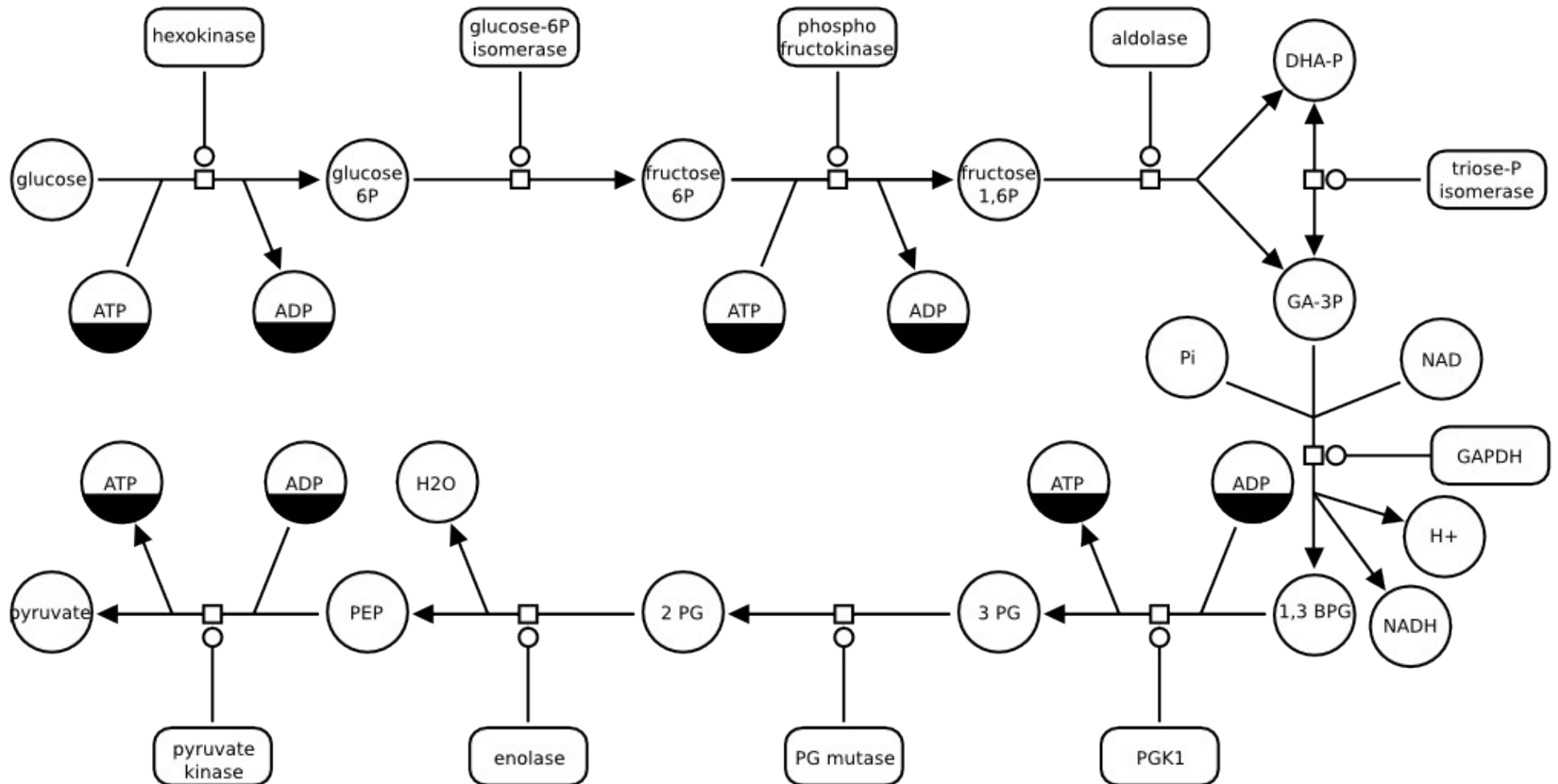


- Ambiguous
- Conceptual
- Sequential

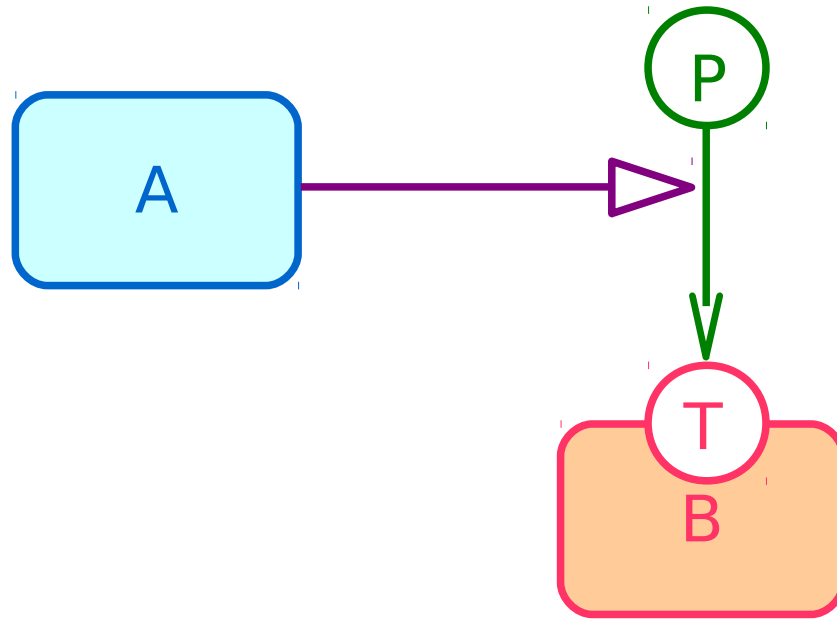
Process Descriptions are bipartite graphs



Metabolic network in Process Description Language



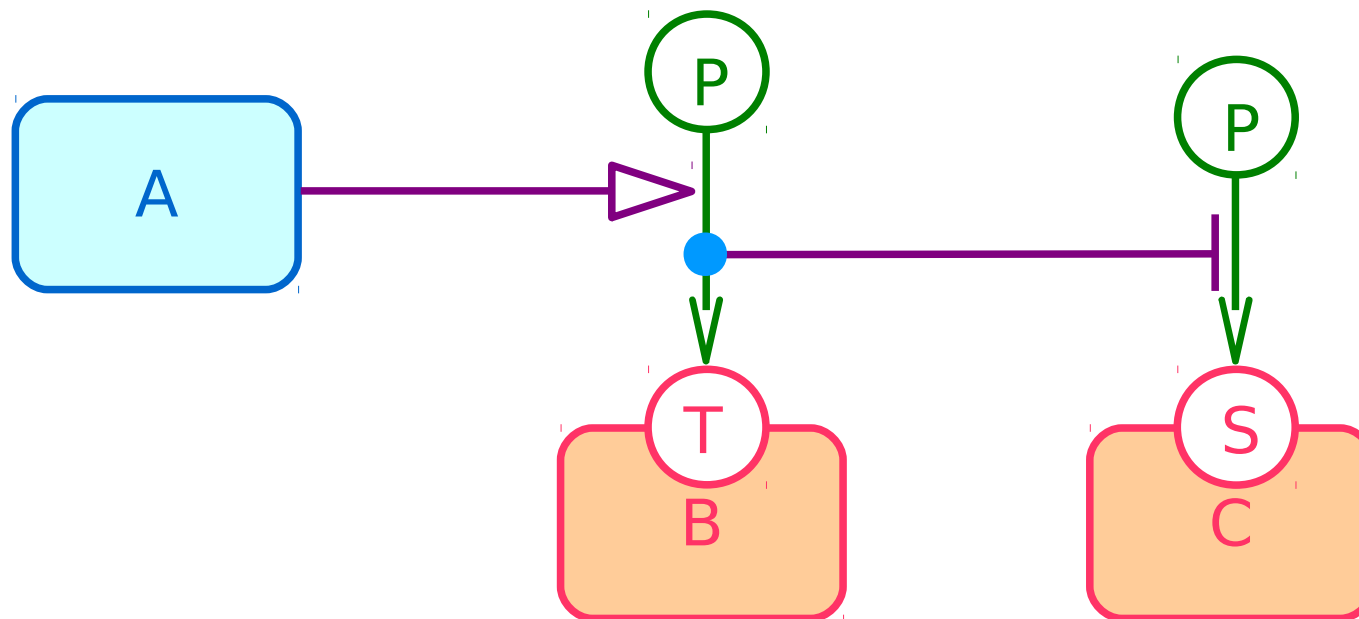
Entity Relationships can be viewed as rules



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**)

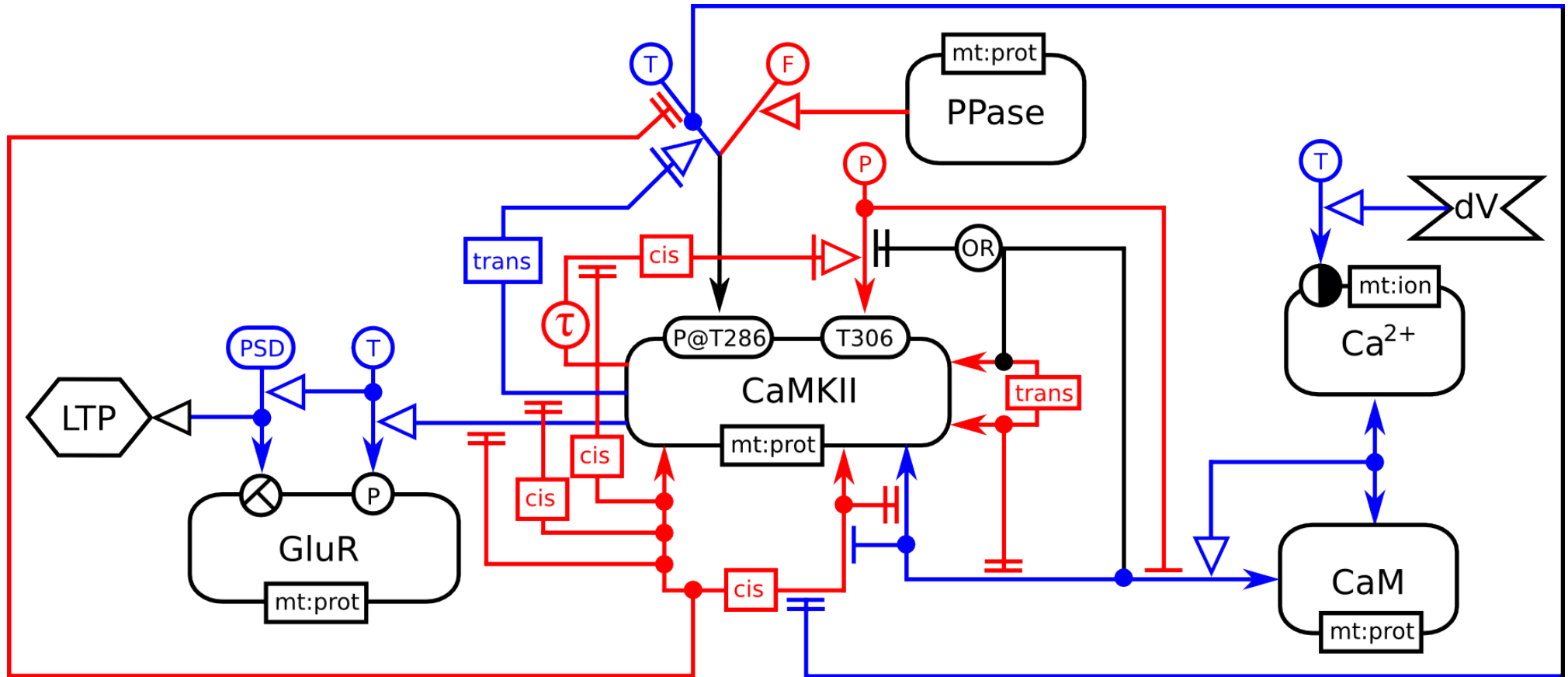
Entity Relationships can be viewed as rules



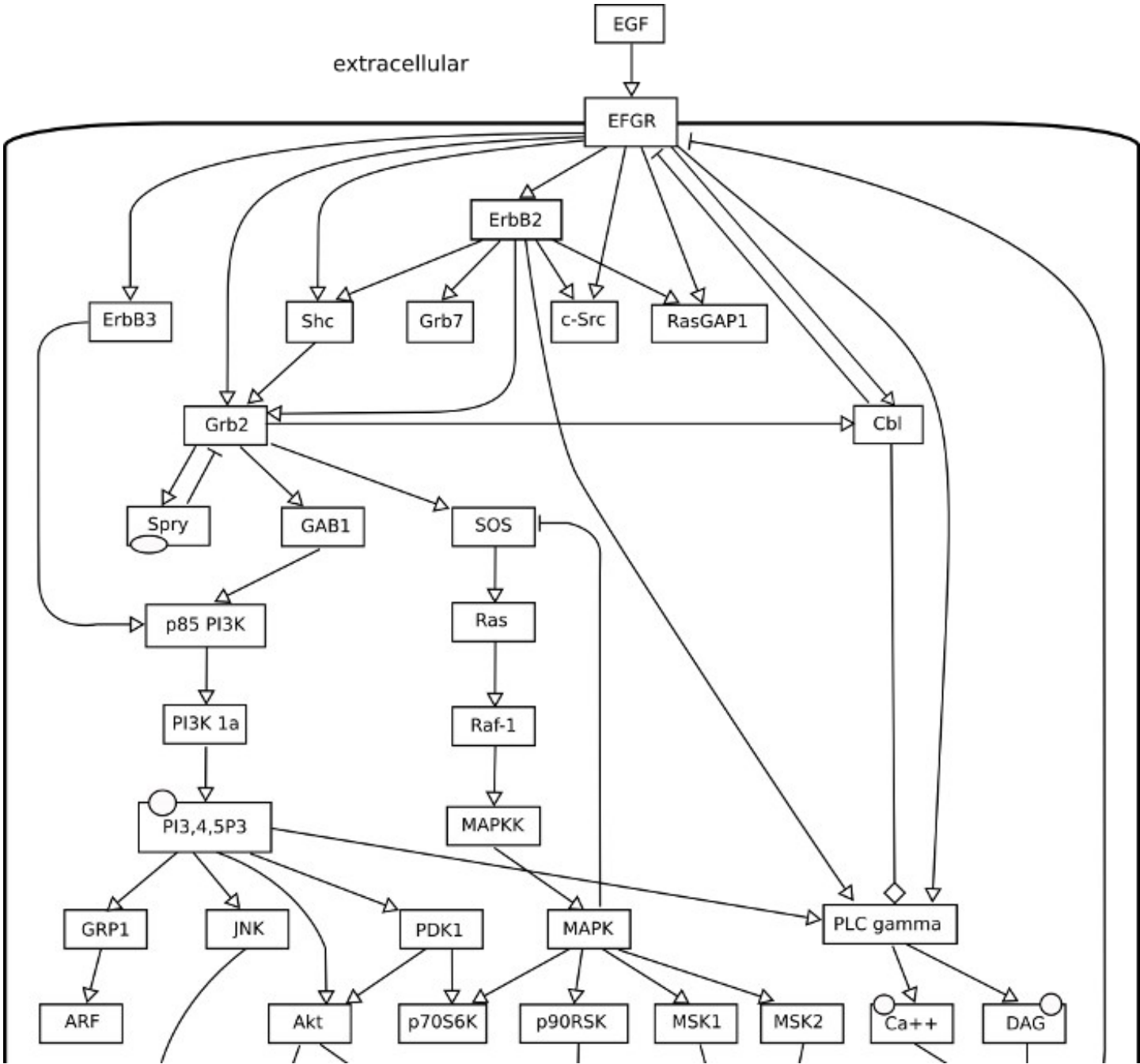
If **A exists**, the **assignment of the value P** to the **state variable T of B** is **increased**

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**

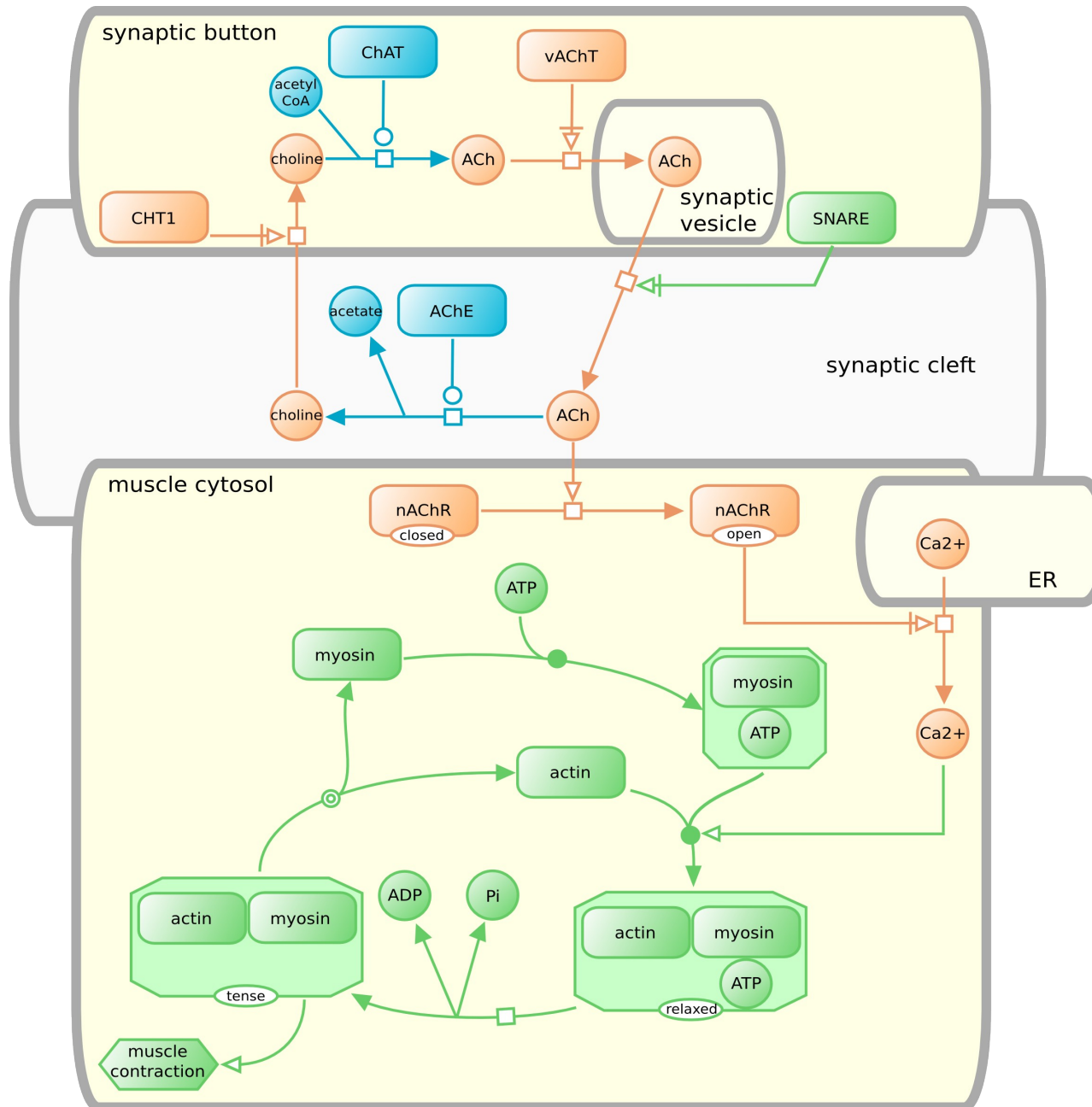
GN ER map of calcium-regulated synaptic plasticity



Example of Activity Flow map



Linking SBGN maps to external information

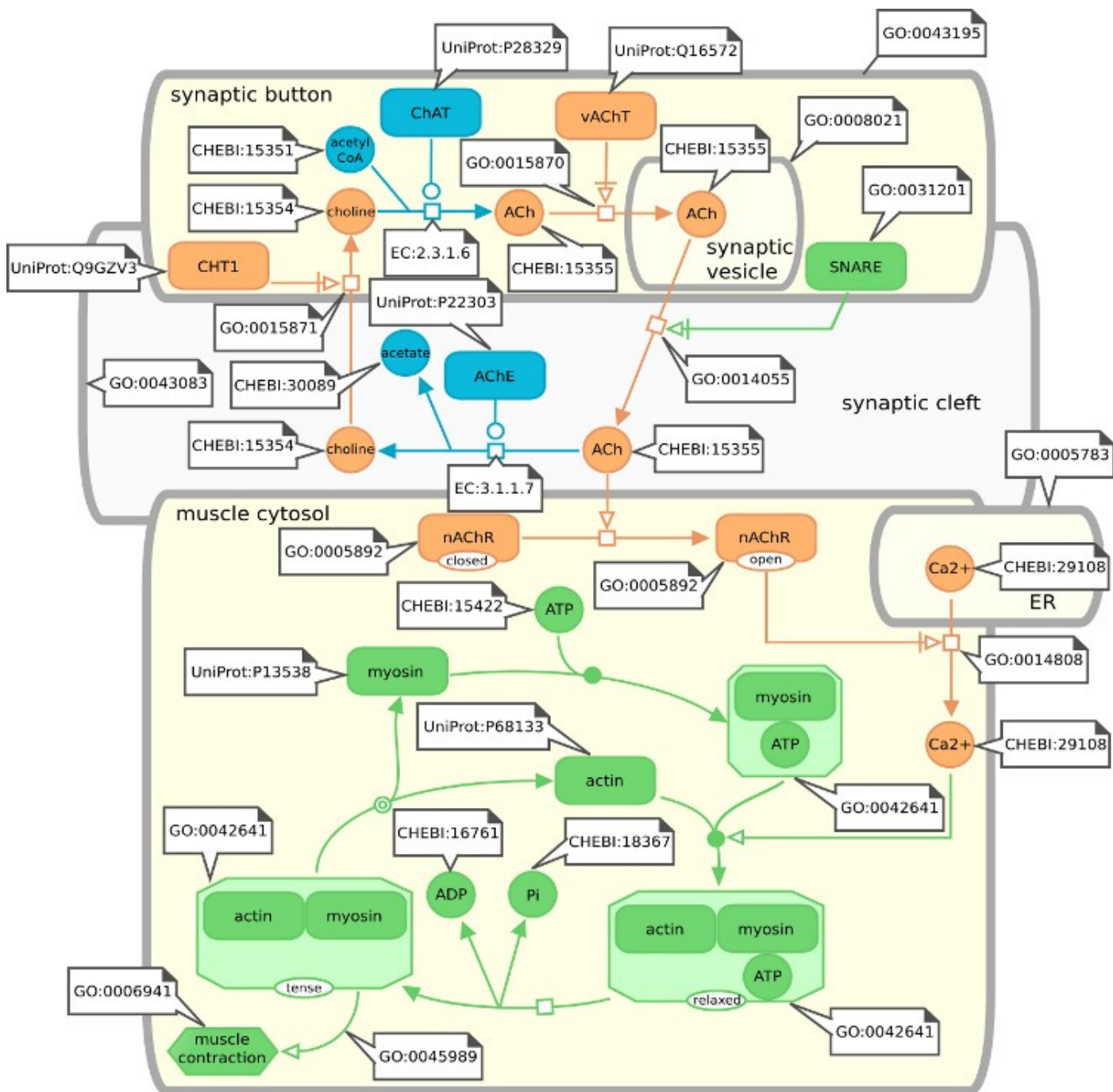


catalytic processes

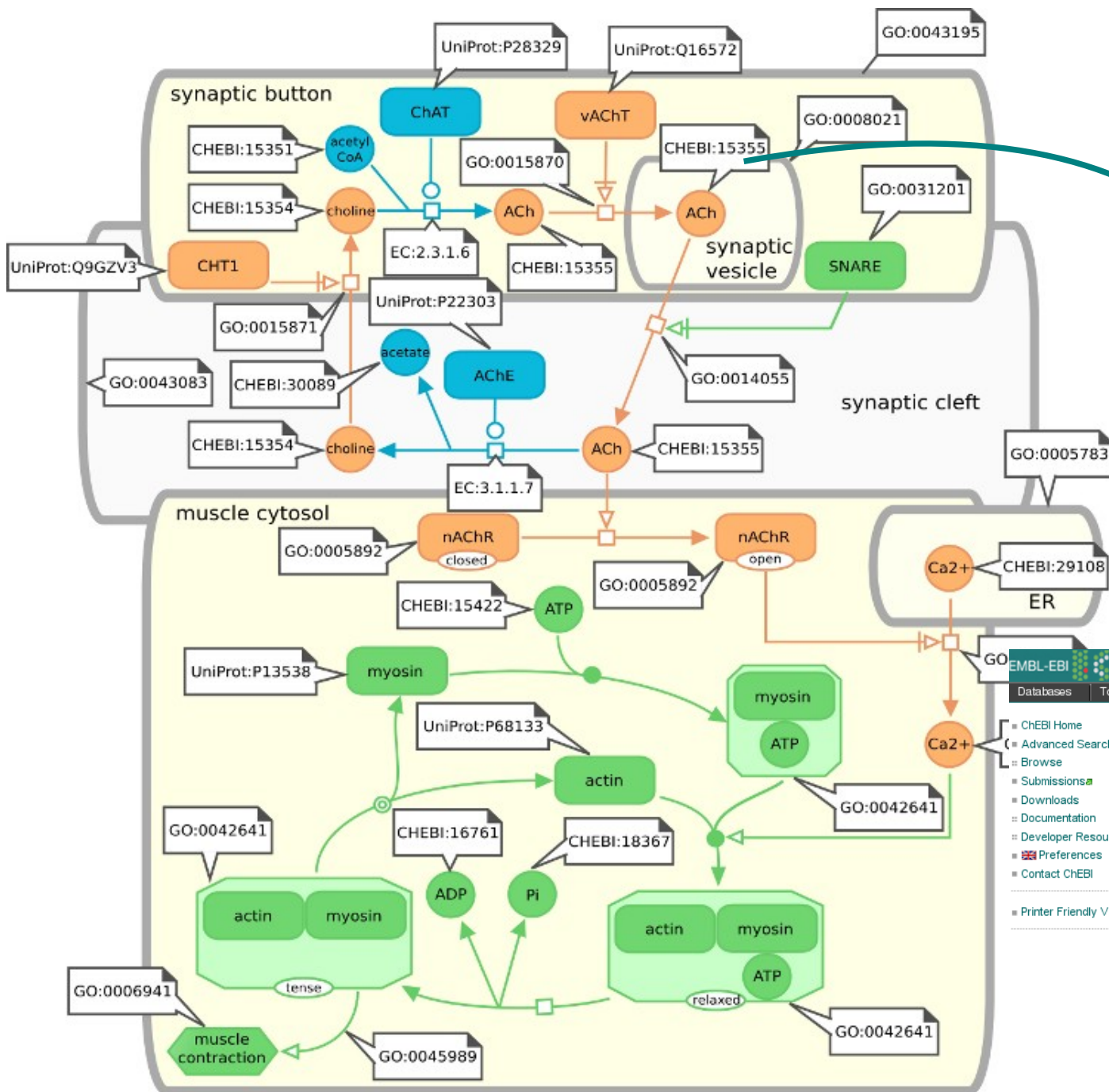
transport processes

contractile proteins

Linking SBGN maps to external information



Linking SBGN maps to external information



EBI Databases > Small Molecules > ChEBI > Main

acetylcholine (CHEBI:15355)

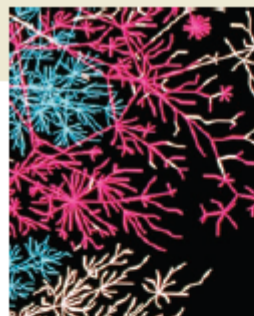
Main | Automatic Xrefs

ChEBI Name: **acetylcholine**
 ChEBI ID: **CHEBI:15355**
 Definition: Acetylcholine is an ester of ace
 Last Modified: 21 December 2009
 Stars: ★★ This entity has
 Secondary ChEBI IDs: CHEBI:12686, CHEBI:13715, CI

☒ Image
☐ Applet
[more structures >>](#)

[Molfile](#)

InChI: 1/C7H16NO2/c1-7(9)10-6-5-8(2,3)4/h5-6H2,1-4H3/q+1
 InChIKey: OIPLFWXSMYKGL-UHFFFAOYAY



Minimum biochem

Nicolas Le Novère
Julio Collado-Vides
Herbert Sauro¹⁰, B

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

tion of

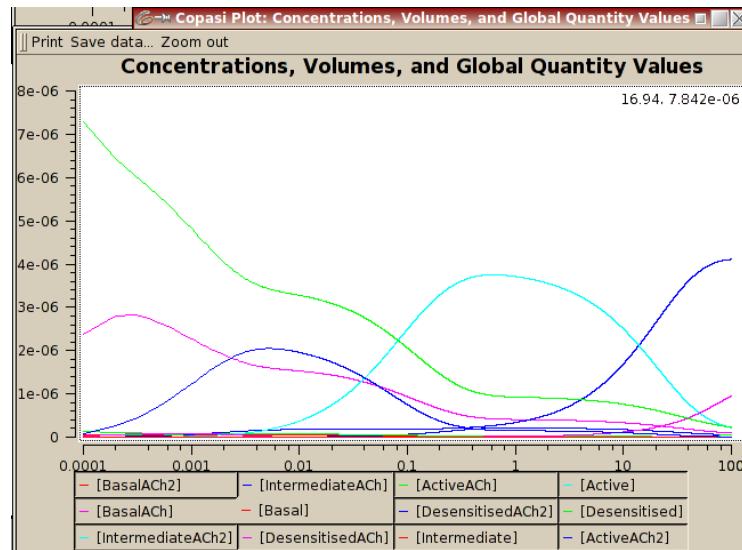
n⁷,

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

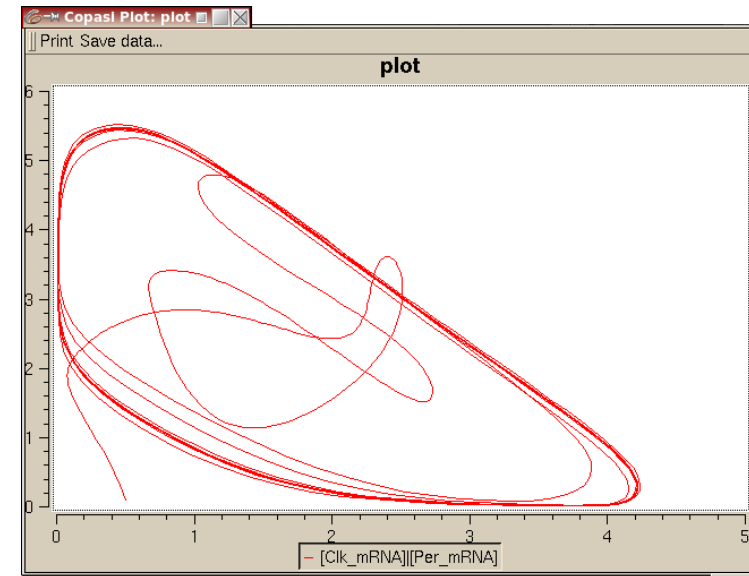
During the genomic era we have witnessed a vast increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their 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

Reproduction of published simulation results

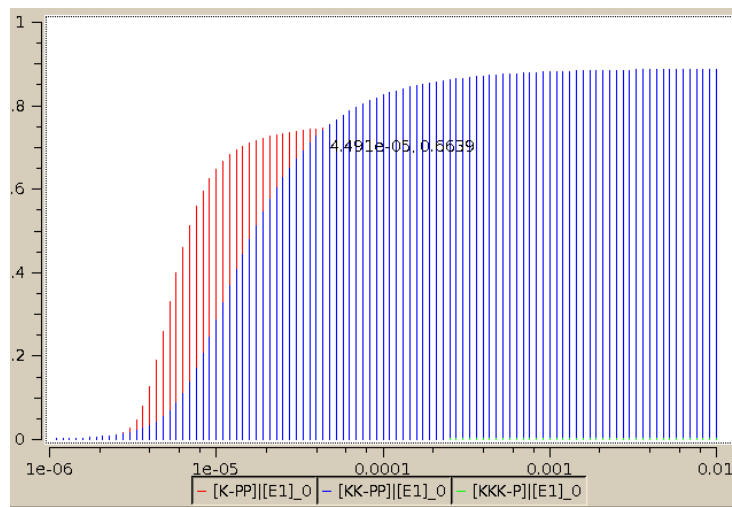
Edelstein et al 1996 (BIOMD0000000002)



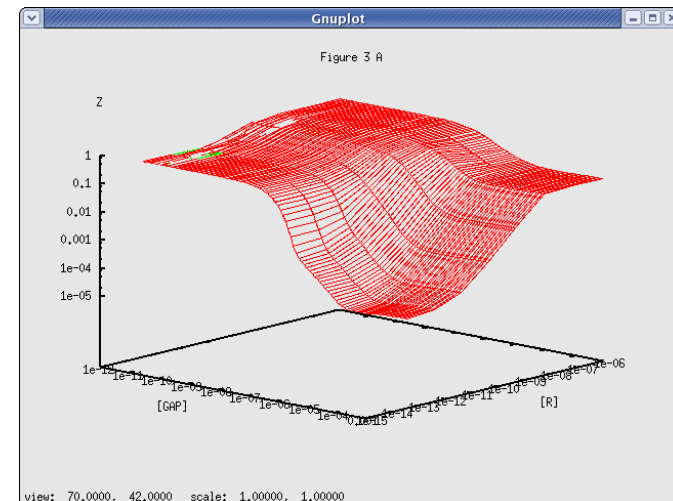
Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)



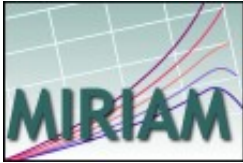
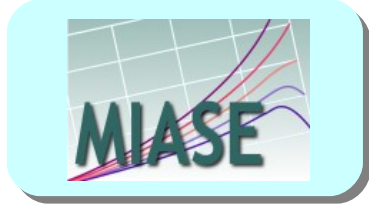
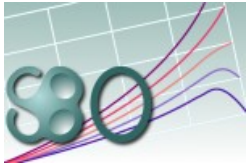
Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)



Description of simulations and analyses

	Model descriptions	Simulations and analysis
Minimal requirements		
Data-models		
Terminologies		

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

Waltemath et al (2011) *PloS Comput Biol*, 7(4): e1001122

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

Köhn D, Le Novère N (2008) *Lect Notes Bioinfo*, 5307: 176-190

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

Courtot et al *submitted*

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns="http://sed-ml.org/"
        xmlns:math="http://www.w3.org/1998/Math/MathML"
        level="1" version="1">
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  <listOfModels>
    <model id="" source="">
      <listOfChanges><!-- --></listOfChanges>
    </model>
  </listOfModels>
  <listOfTasks><!-- --></listOfTasks>
  <listOfDataGenerators><!-- --></listOfDataGenerators>
  <listOfOutputs>
    <plot2D />
    <plot3D />
    <report />
  </listOfOutputs>
</sedML>
```

```
<listOfModels>
  <model id="model1"
    name="Regular_Spiking"
    language="urn:sedml:language:sbml"
    source="urn:miriam:biomodels.db:BIOMD00000000127" />
  <model id="model2"
    name="chattering"
    source="model1">
    <listOfChanges>
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  </model>
</listOfModels>
```

```

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  </model>
</listOfModels>

```

Any model description in XML such as SBML, CellML, NeuroML, VCML, NineML etc.

```
<listOfModels>
  <model id="model1"
    name="Regular_Spiking"
    language="urn:sedml:language:sbml"
    source="urn:miriam:biomodels.db:BIOMD00000000127" />
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  </model>
</listOfModels>
```

Retrieving models



MIRIAM Resources
Data type: <i>BioModels Database</i>
General Tags Annotation
General information about the data type

Name	
Identifier	MIR:00000007
Name	BioModels Database
Synonyms	BioModels
URIs	
Official URN	urn:miriam:biomodels.db
Deprecated	http://www.ebi.ac.uk/biomodels/
Information	
Definition	BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests.

[BioModels Home](#) [Models](#) [Submit](#) [Sign in](#) [Support](#) [About BioModels](#)

Identifier Pattern	
^(BIOMD MODEL)\d{10}\$	
Physical entities	
Resource #1	Data Entry
	Data Resource
	Information
	Institution
Resource #2	Data Entry
	Data Resource
	Information
	Institution
Documentation	
URL(s)	
Miscellaneous	
Date of creation	
Date of last modification	

BIOMD0000000127 - Izhikevich2003_SpikingNeuron

SBML formats | Other formats (auto-generated) | Actions | [Submit Model Comment/Bug](#)

Model Overview Math Physical entities Parameters Curation

Reference Publication	
Publication ID: 18244602	IEEE Trans Neural Netw 2003;14(6):1569-72. Simple model of spiking neurons. Izhikevich EM. The Neurosciences Inst., San Diego, CA, USA. [more]

Model	
Original Model: BIOMD0000000127.xml origin	set #1 bqbiol:isVersionOf Gene Ontology regulation of action potential in neuron Gene Ontology regulation of membrane potential Gene Ontology regulation of action potential
Submitter: Enno He	set #2 bqmodel:isDescribedBy DOI 10.1109/TNN.2003.820440
Submission ID: MODEL4880479792	set #3 bqbiol:is Taxonomy Mammalia
Submission Date: 27 Jul 2007 20:22:14 UTC	
Last Modification Date: 21 Apr 2009 16:46:12 UTC	
Creation Date: 16 Jul 2007 09:41:14 UTC	
Encoders: Enno He	

For more information see the [terms of use](#).

Notes	
This model originates from BioModels Database: A Database of Annotated Published Models. It is copyright (c) 2005-2010 The BioModels Team.	

For more information see the [terms of use](#).
To cite BioModels Database, please use [Le Novère N., Bornstein B., Broicher A., Courtot M., Donizelli M., Dharuri H., Li L., Sauro H., Schilstra M., Shapiro B., Snoep J.L., Hucka M. \(2006\) BioModels Database: A Free, Centralized, and Comprehensive Resource for the Description and Analysis of Biological Models. *Biochemical and Cellular Systems Nucleic Acids Res.*, 34: D689-D691.](#)

FS:a=0.1b=0.2c=-65,d=2

LTS:a=0.02,b=0.25,c=-65,d=2

FS:a=0.1b=0.2c=-65,d=2

LTS:a=0.02,b=0.25,c=-65,d=2

This model originates from BioModels Database: A Database of Annotated Published Models. It is copyright (c) 2005-2010 The BioModels Team.

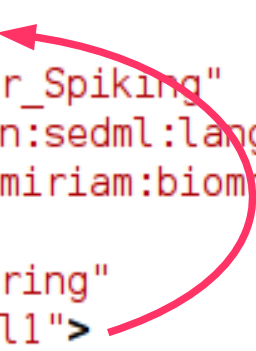
For more information see the [terms of use](#).

To cite BioModels Database, please use [Le Novère N., Bornstein B., Broicher A., Courtot M., Donizelli M., Dharuri H., Li L., Sauro H., Schilstra M., Shapiro B., Snoep J.L., Hucka M. \(2006\) BioModels Database: A Free, Centralized, and Comprehensive Resource for the Description and Analysis of Biological Models. *Biochemical and Cellular Systems Nucleic Acids Res.*, 34: D689-D691.](#)

```

<listOfModels>
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    language="urn:sedml:language:sbml"
    source="urn:miriam:biomodels.db:BIOMD00000000127" />
  <model id="model2"
    name="chattering"
    source="model1">
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      </changeAttribute>
      <changeAttribute target=
        "/sbml/model/listOfParameters/parameter[@id='d']/@value" newValue="42">
      </changeAttribute>
    </listOfChanges>
  </model>
</listOfModels>

```



```

<listOfModels>
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    name="Regular_Spiking"
    language="urn:sedml:language:sbml"
    source="urn:miriam:biomodels.db:BIOMD00000000127" />
  <model id="model2"
    name="chattering"
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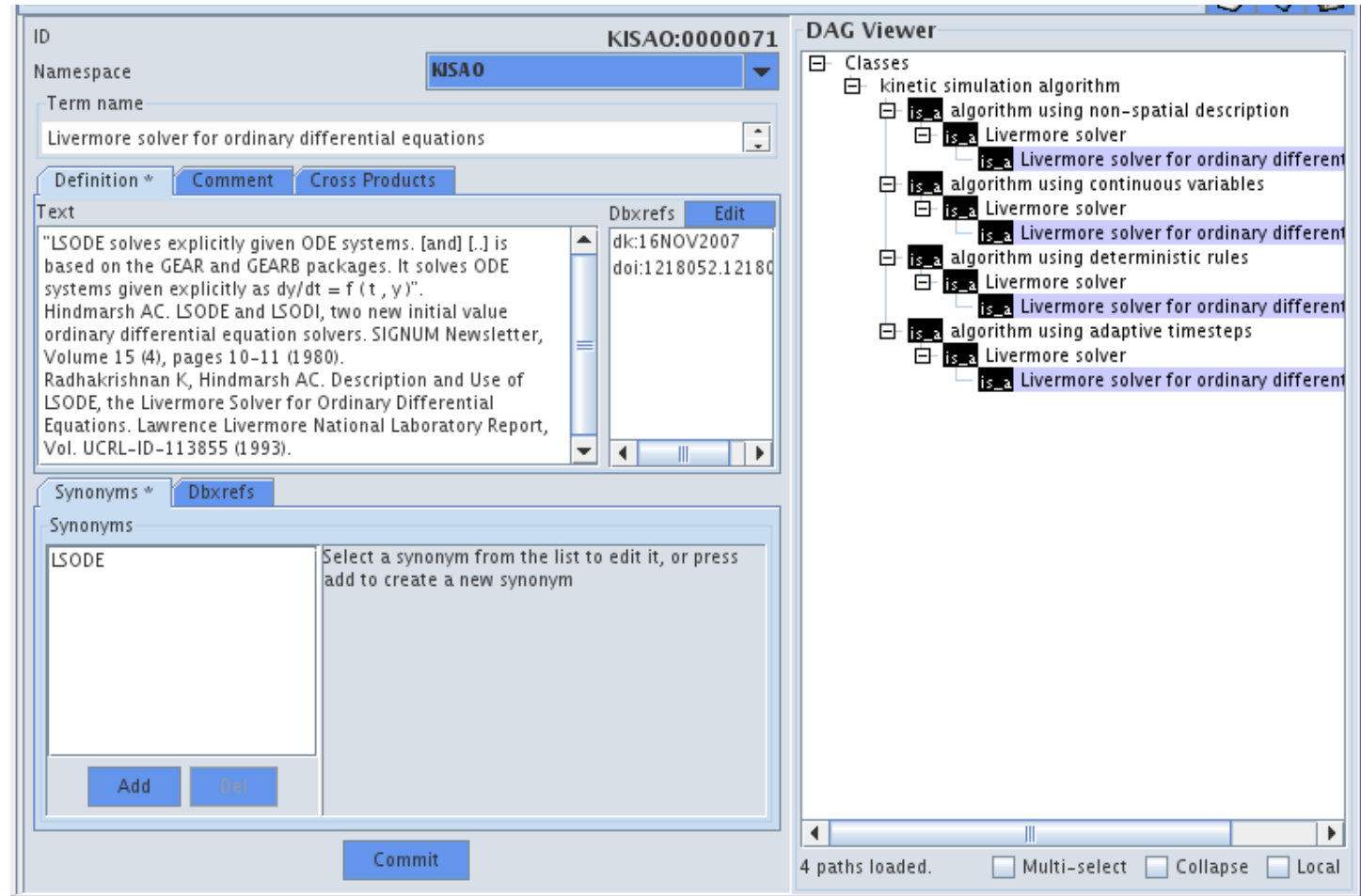
```

XHTML

```
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  <uniformTimeCourse id="simulation1"  
    initialTime="0"  
    outputStartTime="0"  
    outputEndTime="140"  
    numberOfPoints="1000">  
    <algorithm kisaoID="KiSAO:0000030"/>  
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</listOfSimulations>
```

Simulation approach

```
<listOfSimulations>
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    outputEndTime="140"
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    <algorithm kisaoID="KISA0:0000030"/>
  </uniformTimeCourse>
</listOfSimulations>
```



The screenshot displays the KISA0:0000071 interface, which is used for defining and managing kinetic simulation algorithms. The main window is titled "KISA0:0000071" and shows the "Definition" tab for the "Livermore solver for ordinary differential equations".

Definition Tab:

- Text:** "LSODE solves explicitly given ODE systems. [and] [...] is based on the GEAR and GEARB packages. It solves ODE systems given explicitly as $dy/dt = f(t, y)$ ". Hindmarsh AC. LSODE and LSODI, two new initial value ordinary differential equation solvers. SIGNUM Newsletter, Volume 15 (4), pages 10-11 (1980). Radhakrishnan K, Hindmarsh AC. Description and Use of LSODE, the Livermore Solver for Ordinary Differential Equations. Lawrence Livermore National Laboratory Report, Vol. UCRL-ID-113855 (1993).
- Dbxrefs:** dk:16NOV2007, doi:1218052.12180

Synonyms Tab:

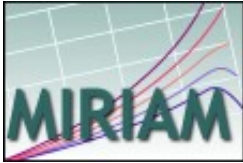
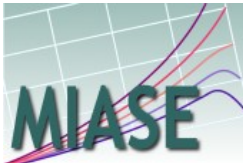
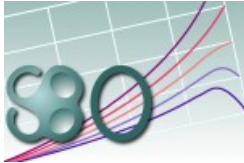
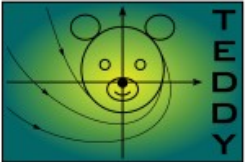
- Synonyms:** LSODE
- Select a synonym from the list to edit it, or press add to create a new synonym**

DAG Viewer:

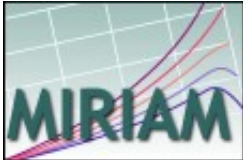
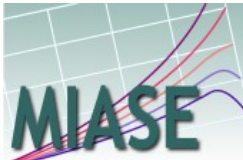
- Classes:**
 - kinetic simulation algorithm
 - is_a algorithm using non-spatial description
 - is_a Livermore solver
 - is_a Livermore solver for ordinary differential equations
 - is_a algorithm using continuous variables
 - is_a Livermore solver
 - is_a Livermore solver for ordinary differential equations
 - is_a algorithm using deterministic rules
 - is_a Livermore solver
 - is_a Livermore solver for ordinary differential equations
 - is_a algorithm using adaptive timesteps
 - is_a Livermore solver
 - is_a Livermore solver for ordinary differential equations

4 paths loaded. ☐ Multi-select ☐ Collapse ☐ Local

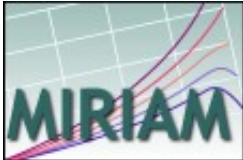
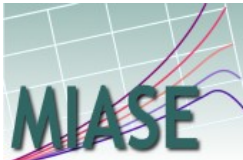
Characterising dynamical behaviours

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

Is the matrix of standards complete?

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

Is the matrix of standards complete?

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

Covering the entire model life-cycle

Model generation	Model structure	Parametrisation	Simulations and analysis	Numerical results
?		?		SBRML

Disentangling the level of discourse



Graphical representation

BioPAX

Biological semantics

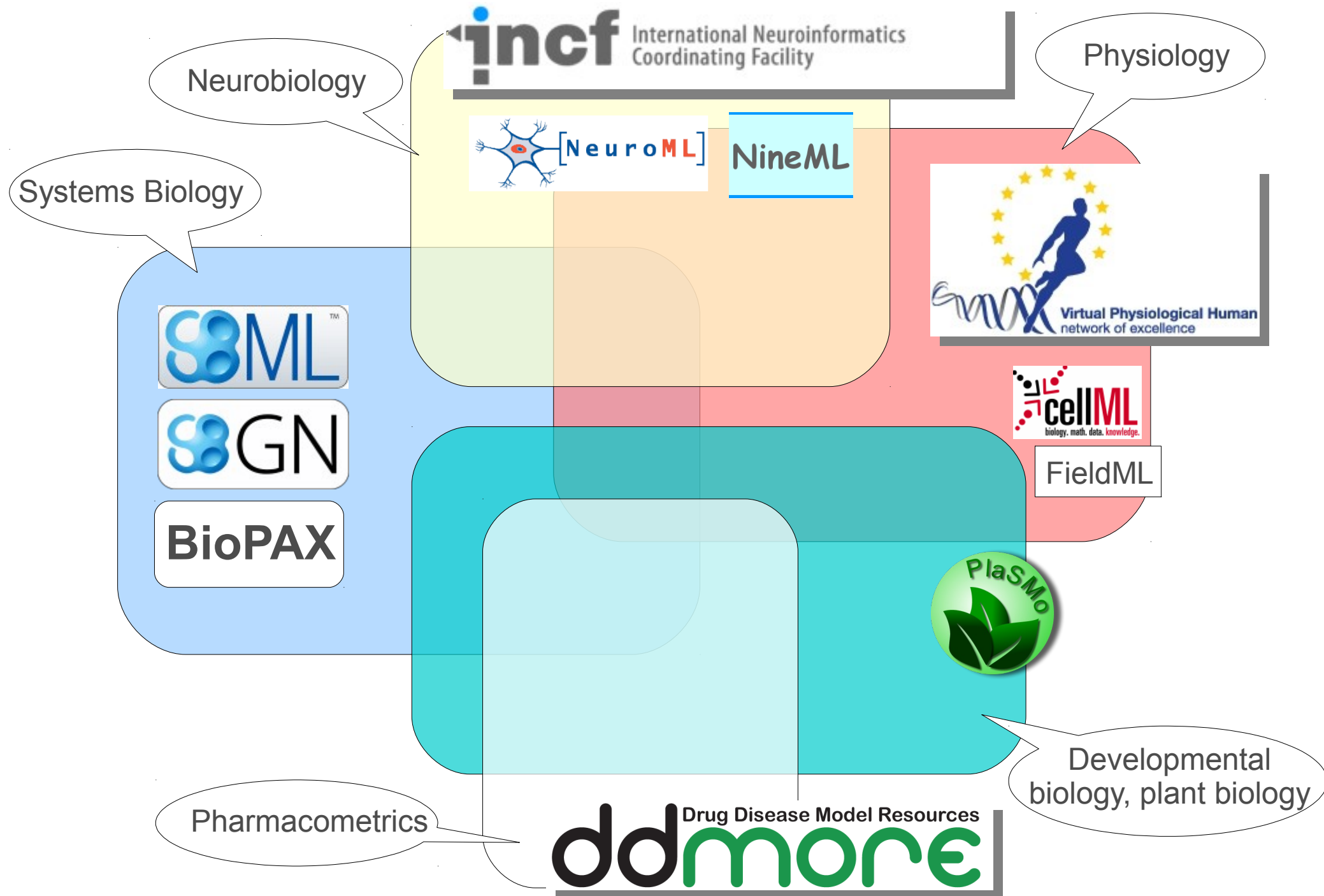


Initial conditions (numbers)

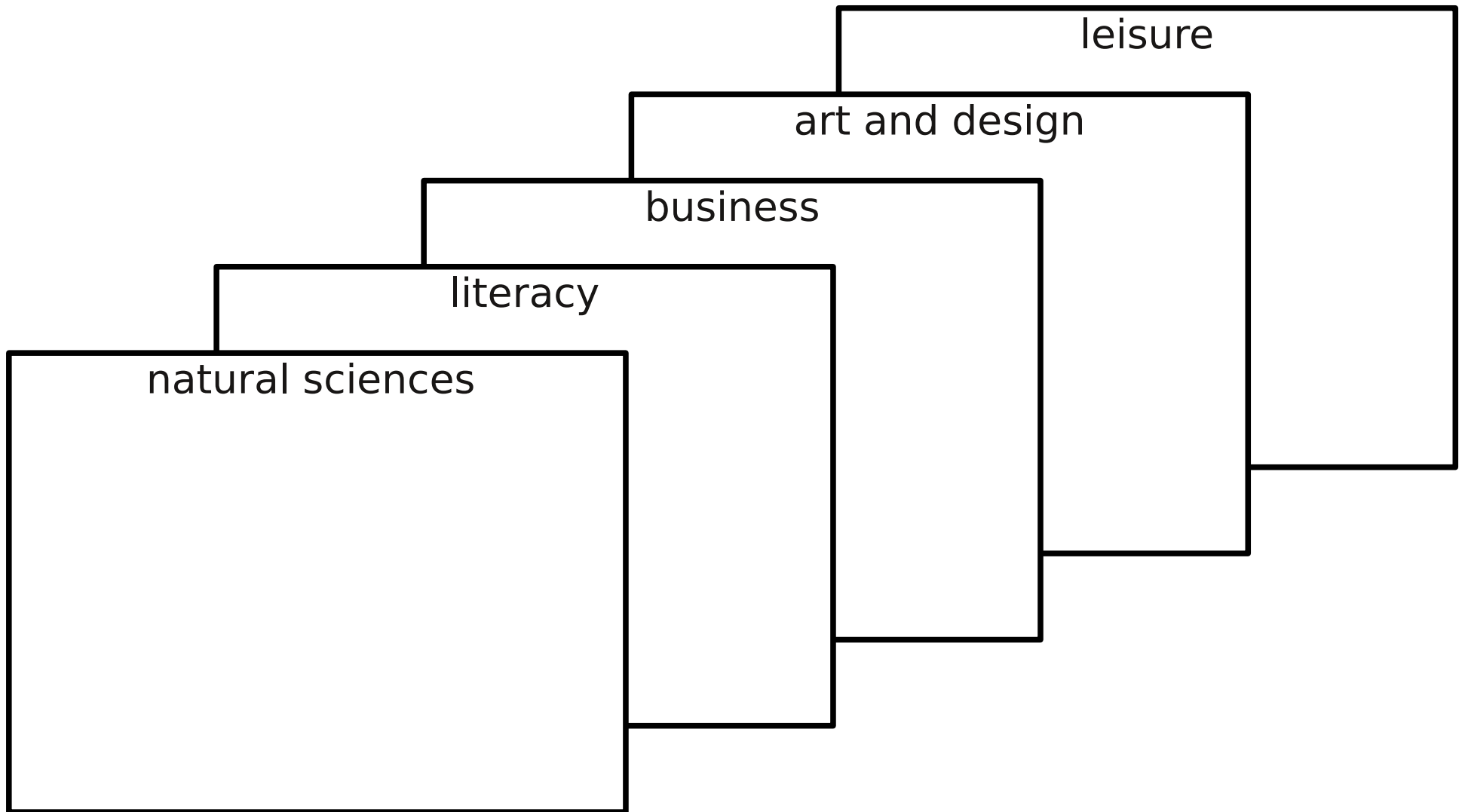


Model semantics (structure)

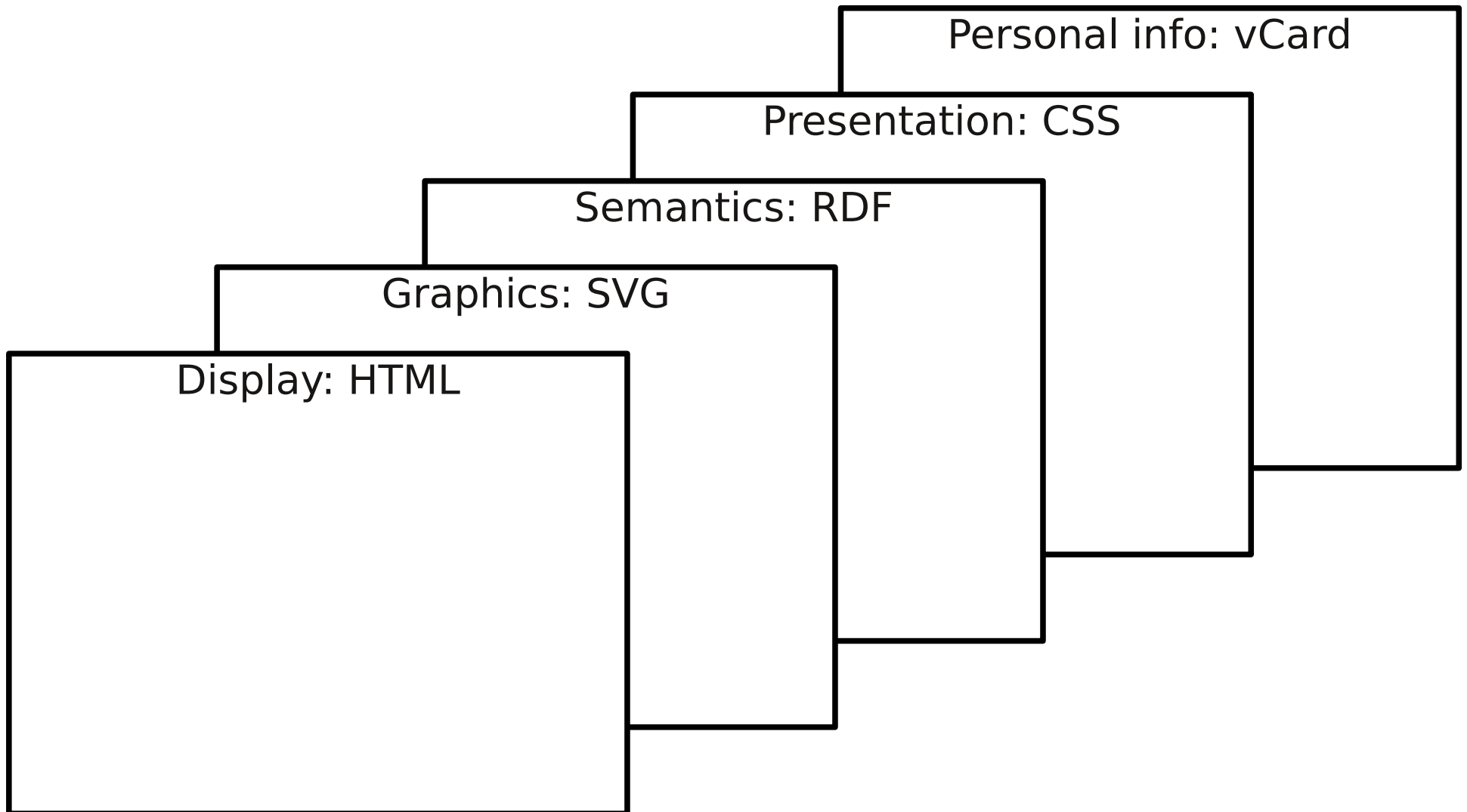
Parallel and redundant efforts



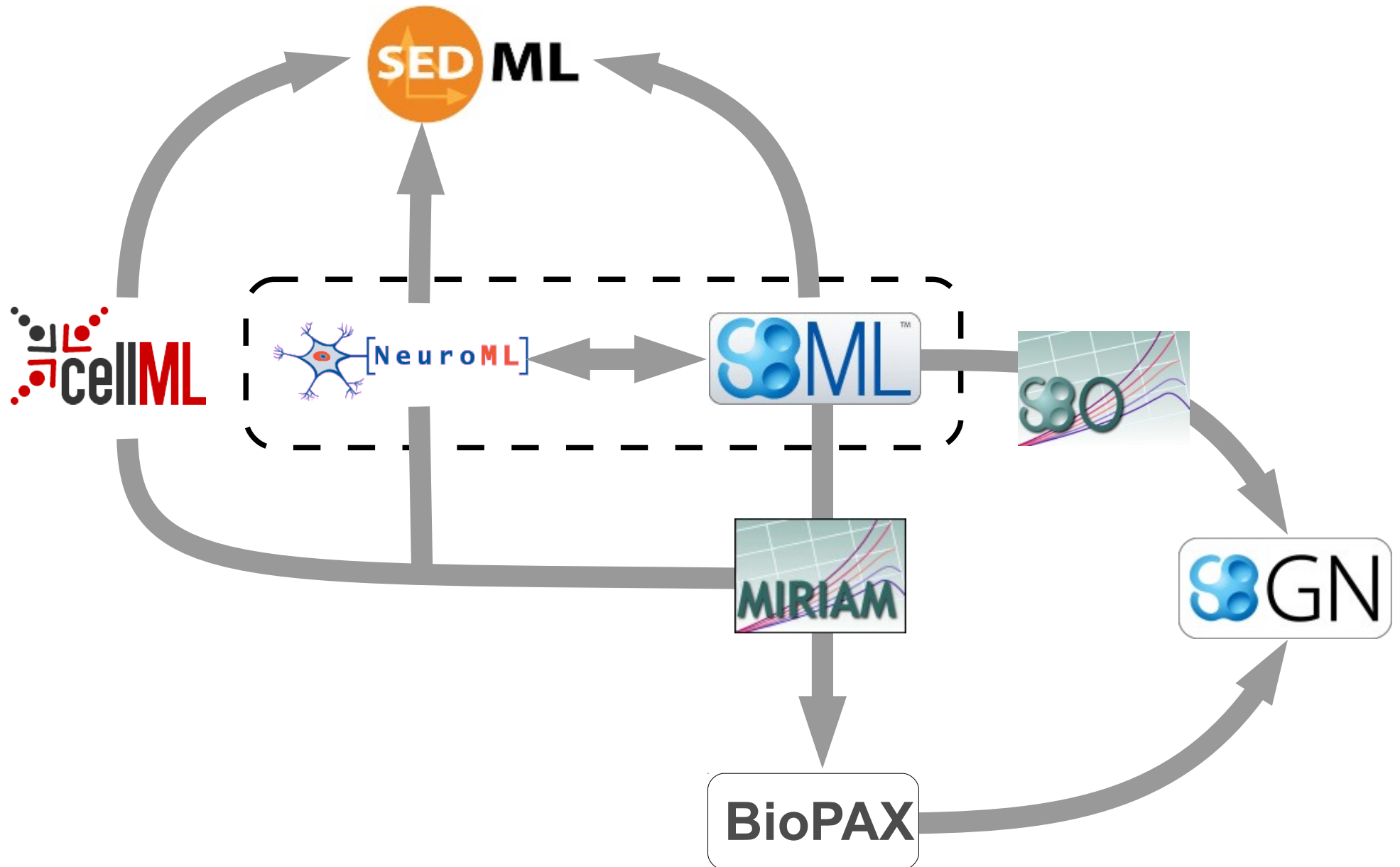
What if the world-wide web was built like this?



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 2011
 - 18 to 22 April 2011, New-York
 - <http://www.biopax.org/harmony.php>
- COMBINE 2011
 - 3 to 7 September 2011, Heidelberg
 - http://co.mbine.org/events/COMBINE_2011
- Standard Operating Procedures
 - Technical requirements
 - Governance
- Single voice
 - Discussions with Industry
 - Financial support

Where to find more information?

Communities

Semantics

Coordination

<http://co.mbine.org/>

<http://biopax.org/>

<http://sbgn.org/>

<http://sbml.org/>

<http://sed-ml.org/>

<http://biomodels.net/>

<http://biomodels.net/biomodels/>

<http://biomodels.net/kisao>

<http://biomodels.net/sbo>

<http://biomodels.net/teddy>

<http://biomodels.net/miase>

<http://biomodels.net/miriam>

Acknowledgements

Visionary: **Hiroaki Kitano**

SBML editors: Frank Bergmann, *Andrew Finney*, *Stefan Hoops*, ***Michael Hucka***, *Nicolas Le Novère*, Sarah Keating, Chris Myers, *Sven Sahle*, *Herbert Sauro*, Jim Schaff, Lucian Smith, *Darren Wilkinson*

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

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



