EMBL-EBI

Sharing enriched computational models, a cornerstone for Integrative Biology

Nicolas Le Novère, EMBL-EBI

Computational Neurobiology

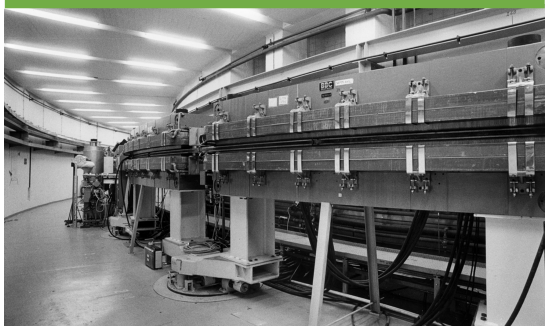
European Molecular Biology Laboratory

- EMBL is a basic research institute funded by public research monies from 20 member states and numerous external funding sources
- 1530 staffs, over 60 nationalities

Heidelberg

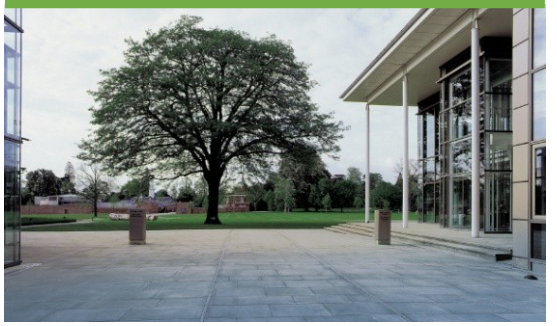
Basic research in molecular biology
Administration
EMBO

Hamburg



Structural biology

Hinxton



Bioinformatics

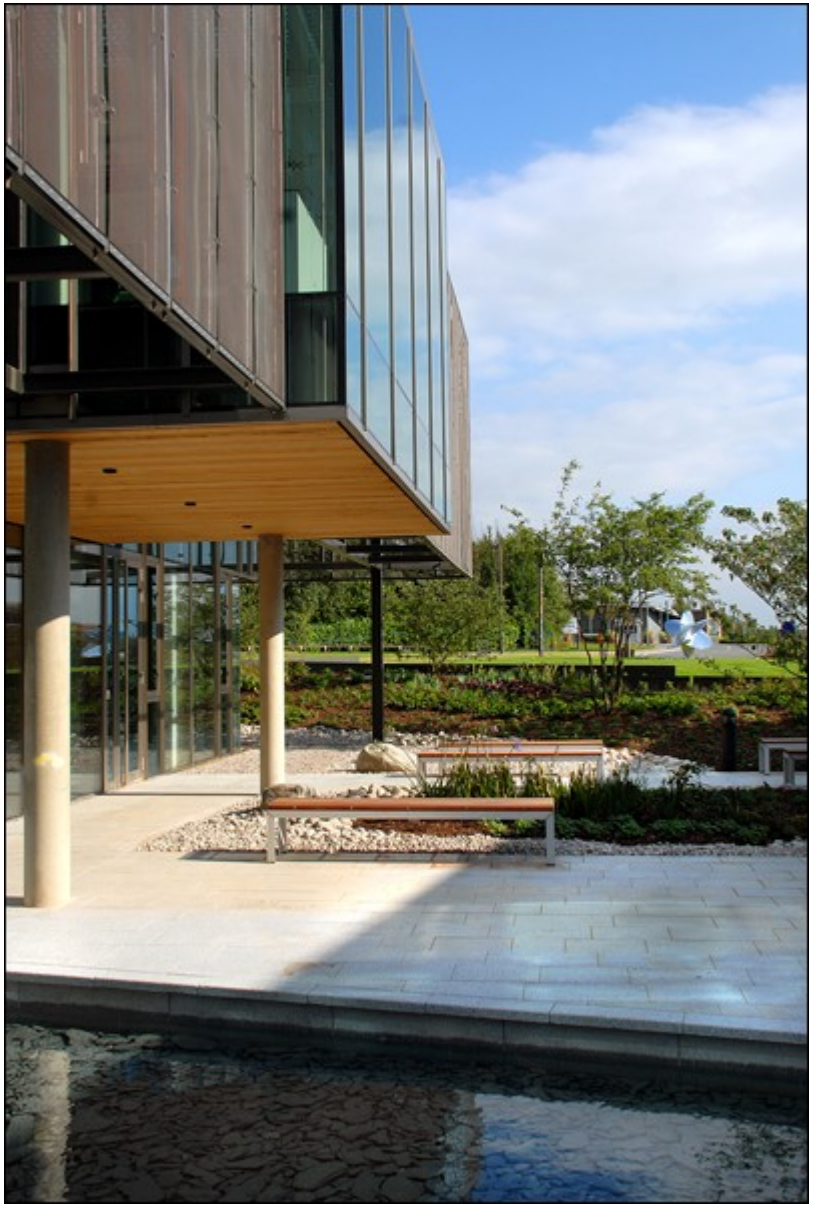
Grenoble

Structural biology

Monterotondo

Mouse biology

EMBL-European Bioinformatics Institute



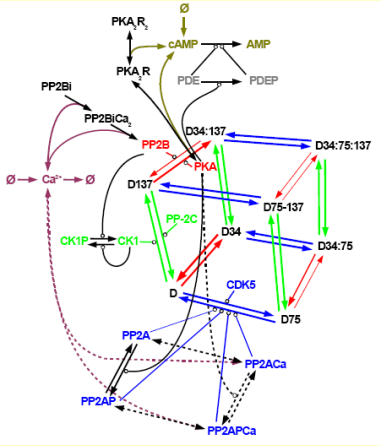
Provision of services, research and training in Bioinformatics

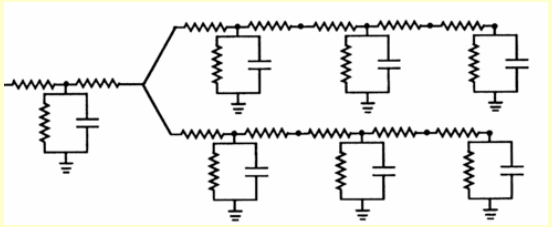
From the molecule to the cell, and the genome to the individual

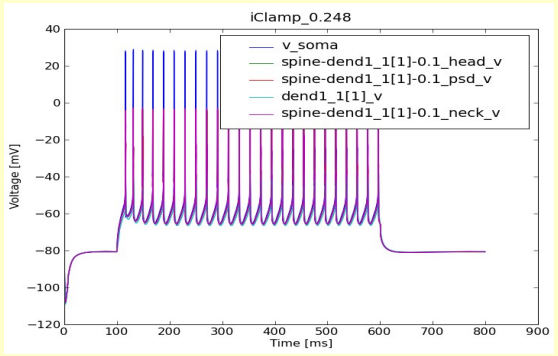
Based on the Wellcome-Trust Genome Campus near Cambridge, UK

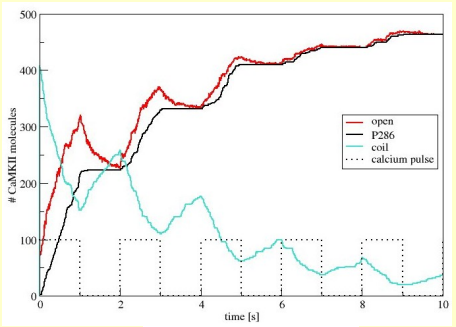
Themes and projects of the “compneur” group

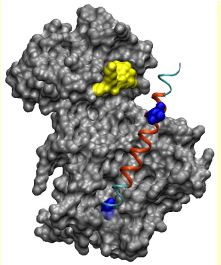
Computational Neurobiology

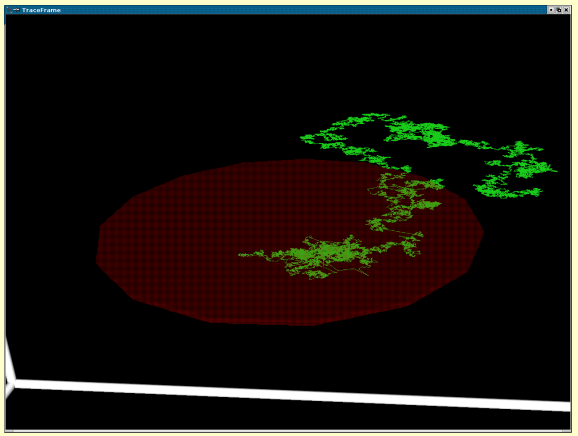




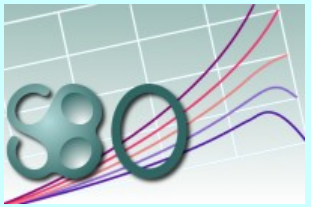


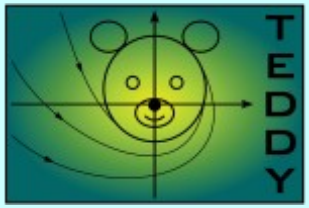


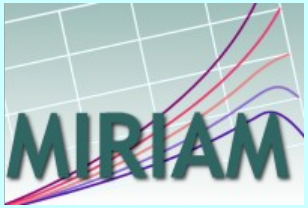


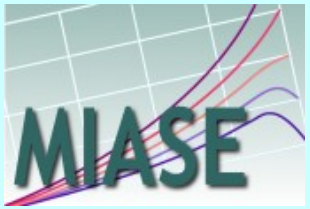


Computational Systems Biology









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

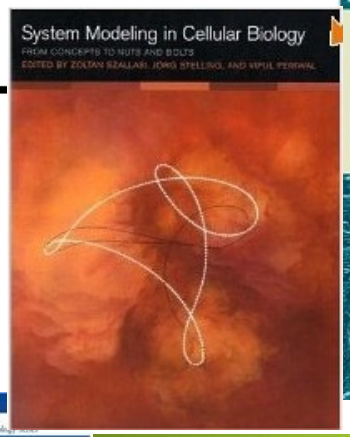
REVIEW

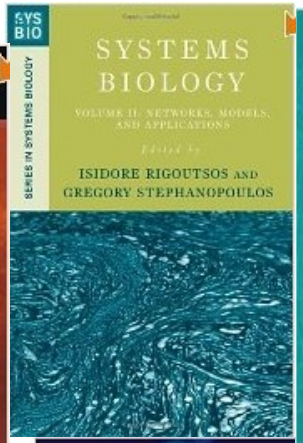
Systems Biology: A Brief Overview

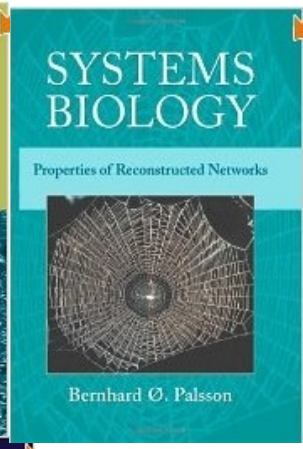
Hiroaki Kitano

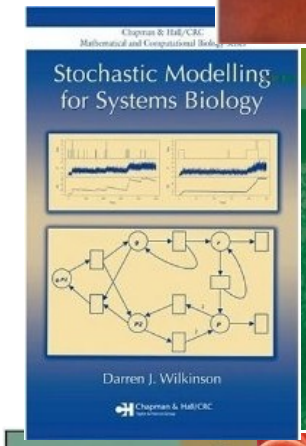
1 MARCH 2002 VOL 295 SCIENCE www.sciencemag.org

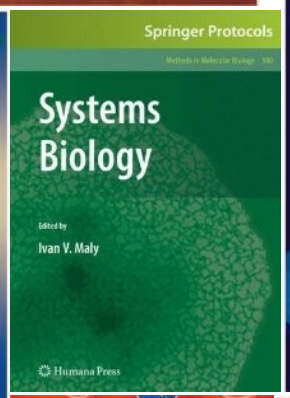
Basic science

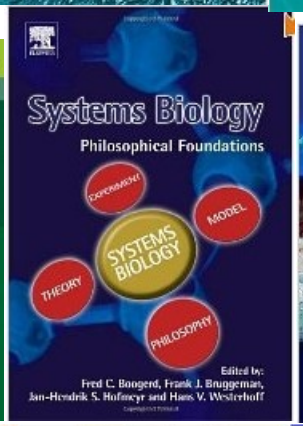


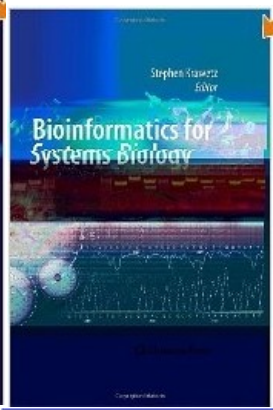


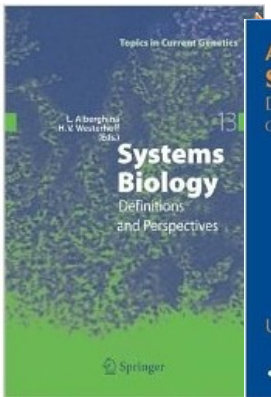


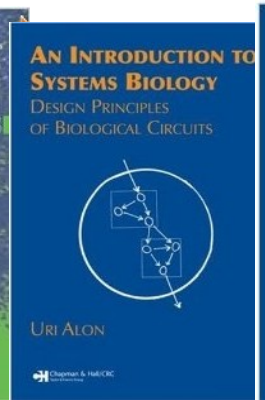


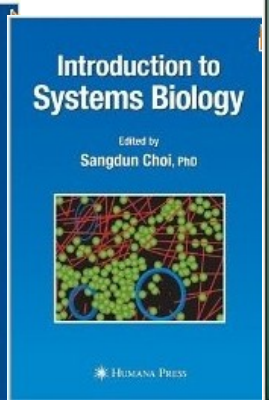


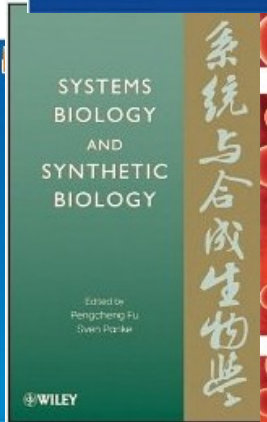


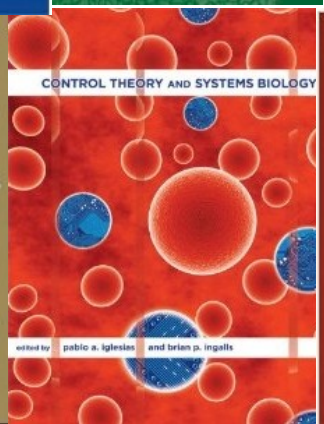


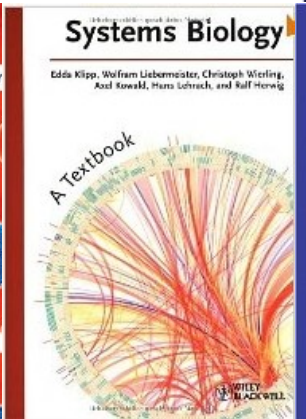


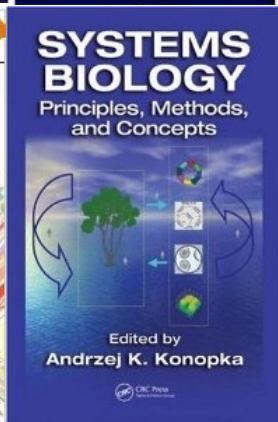












Nobel Symposium on Systems Biology (June 2009)

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

Roger Brent

Lucy Shapiro

Hans Westerhoff

Francois Nedelec

Luis Serrano

Uwe Sauer

Jim Ferrell

Naama Barkai

Jorg Stelling

Jens Nielsen

Edda Klipp

Boris Kholodenko

Bela Novak

Johan Elf

Hiroaki Kitano

Stefan Hohmann

Bernard Palsson

Harley McAdams

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Johan Elf

Hiroaki Kitano

Stefan Hohmann

Bernard Palsson

Harley McAdams

Nicolas Le Novère

William Bialek

Mans Ehrenberg

Avid Regev

Jeff Hasty

Michael Elowitz

Yoshihide Hayashizaki

Richard Young

synthetic biology
cell reprogramming

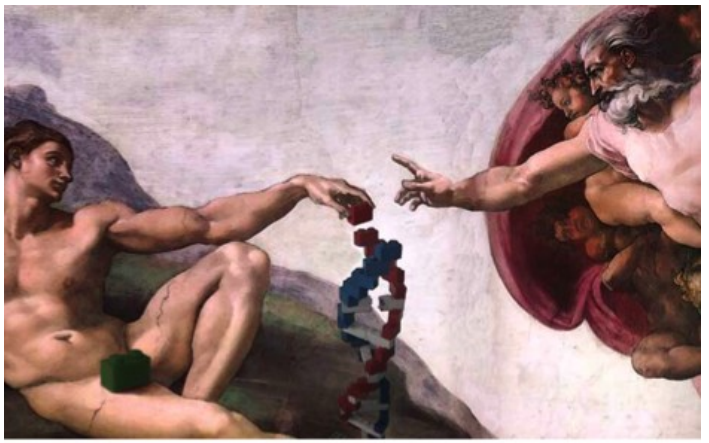
What happened to biology at the end of XXth century?

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



EXTREME GENETIC ENGINEERING

An Introduction to Synthetic Biology

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

Technology

January 2007

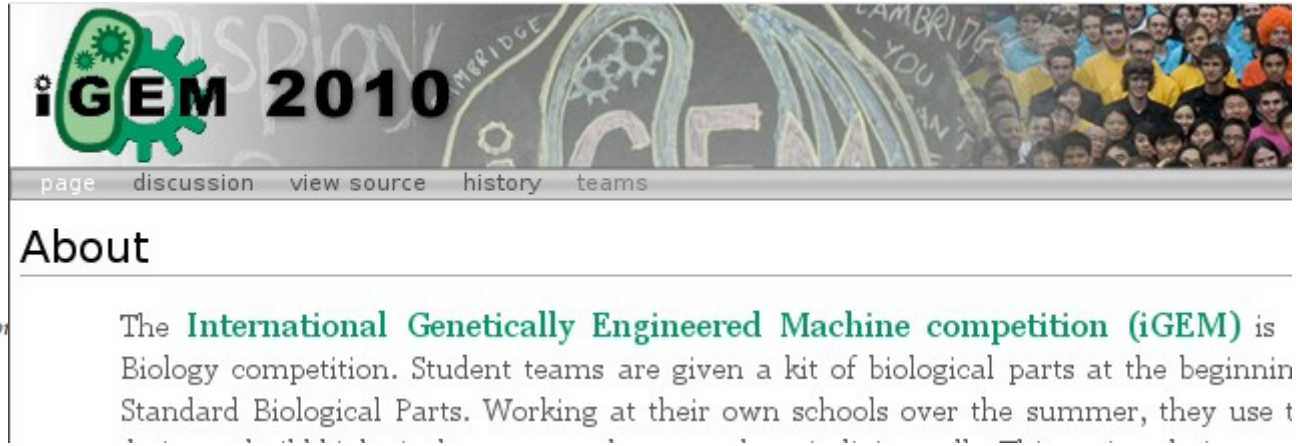
etc group

A synthetic oscillatory network of transcriptional regulators

Michael B. Elowitz & Stanislas Leibler

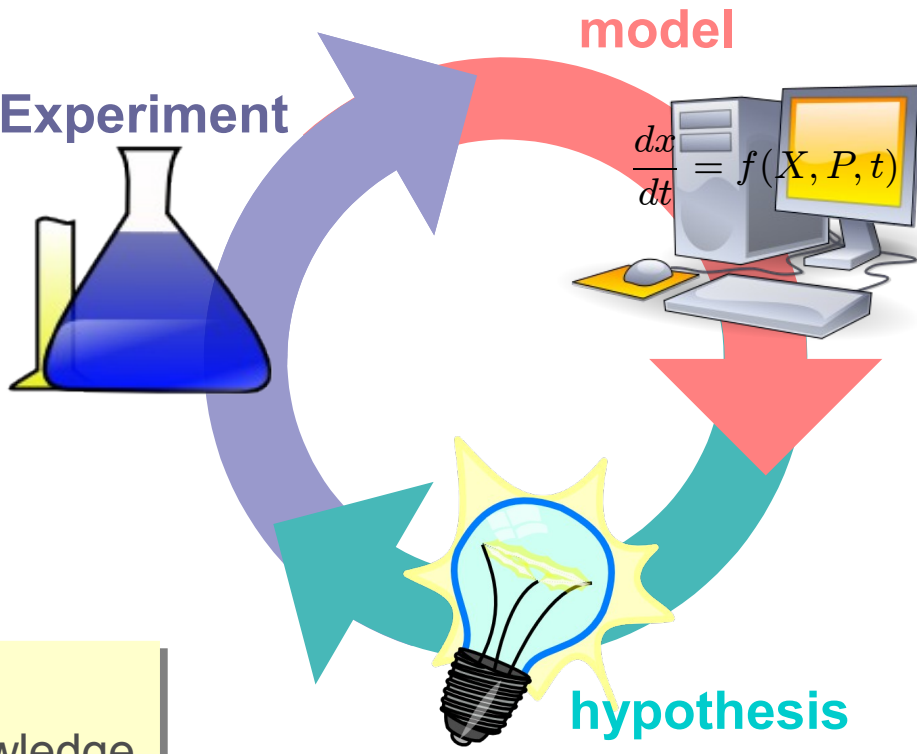
Departments of Molecular Biology and Physics, Princeton University, Princeton New Jersey 08544, USA

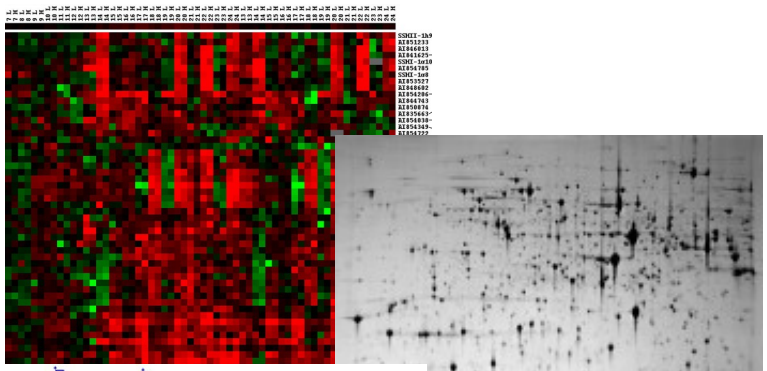
NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com

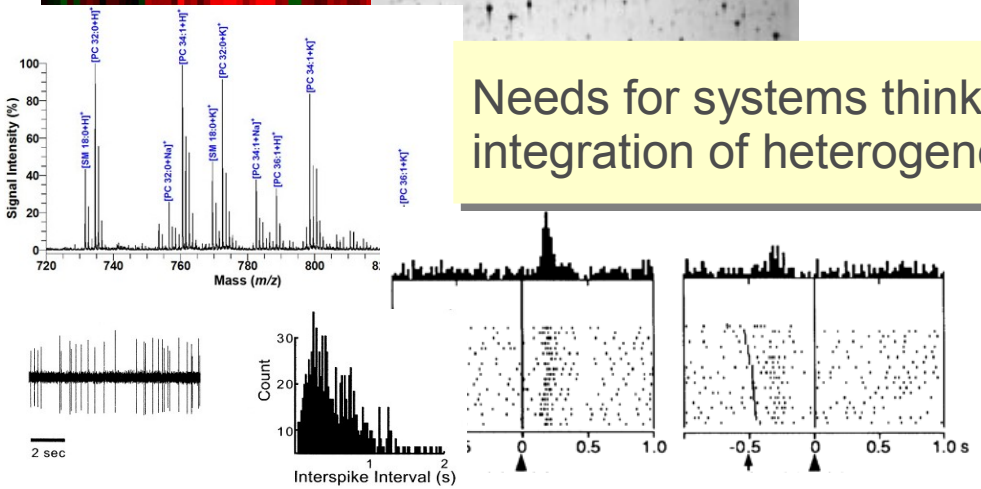


Consequences of this revolution on our activity

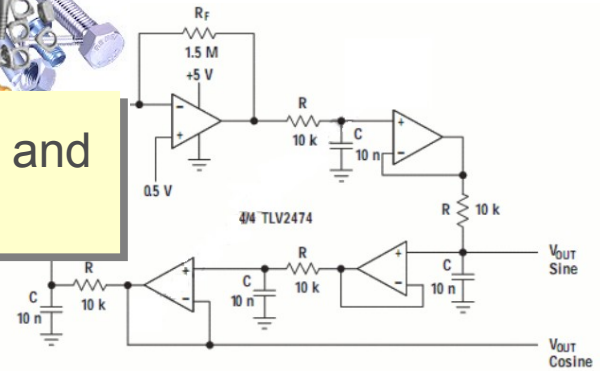
Needs for interplay between models and reality tests







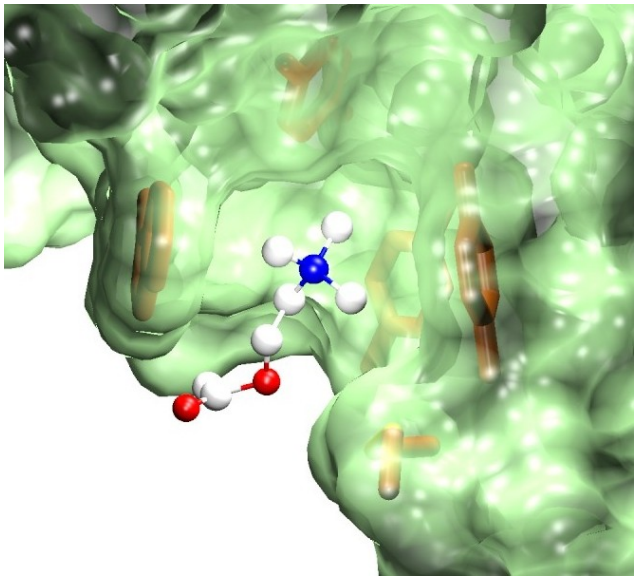
Needs for systems thinking and integration of heterogeneous knowledge

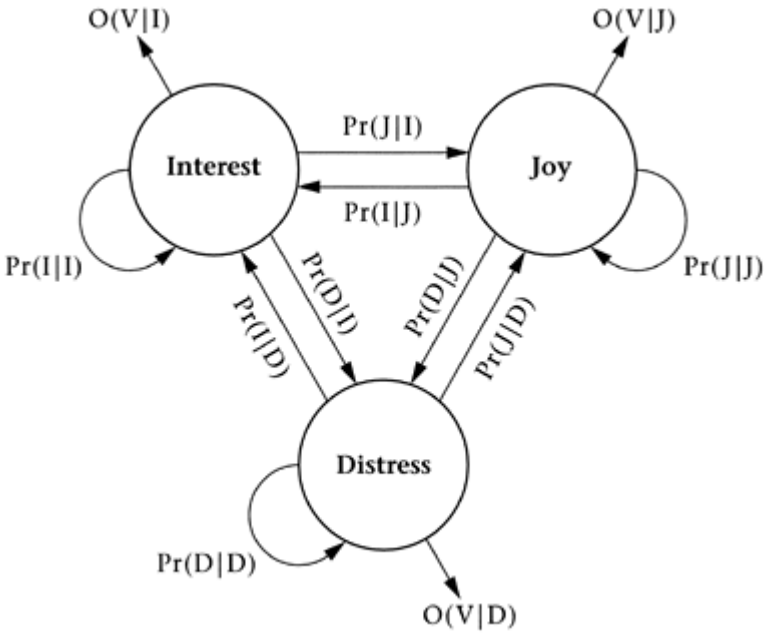


Needs for cooperation and standardisation

The models I am not talking about

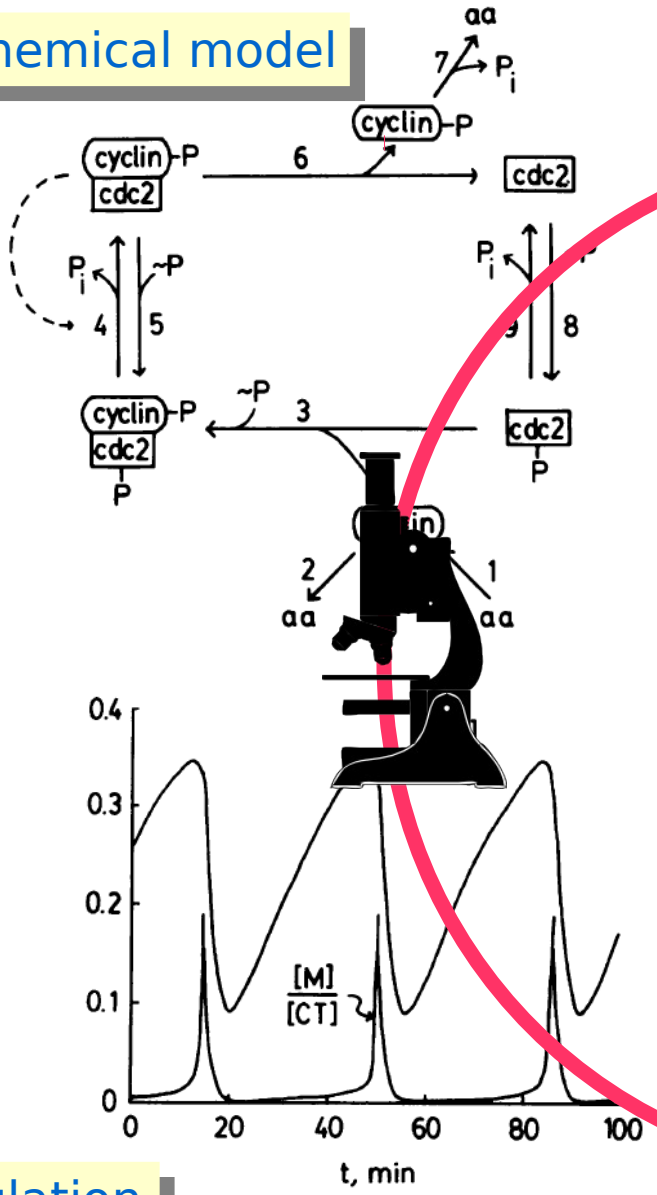
The models I am not talking about





The models I am talking about

biochemical model



simulation

mathematical model

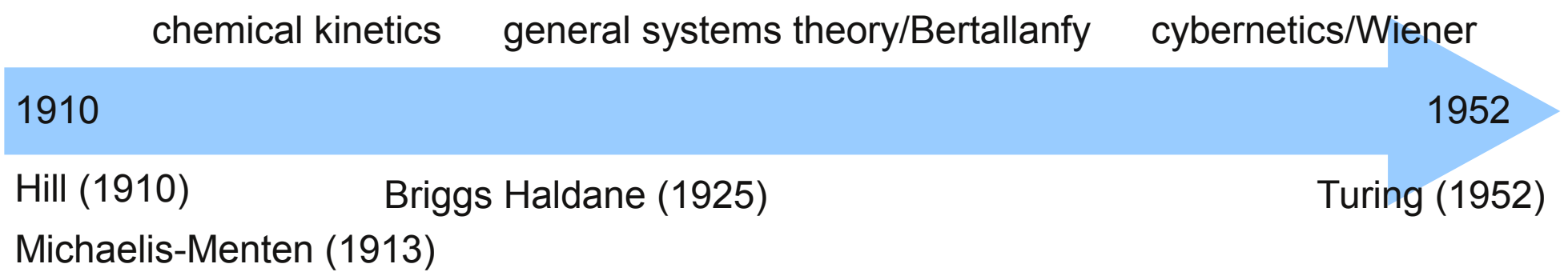
$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
$$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$$
$$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$$
$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
$$d[YP]/dt = k_6[M] - k_7[YP]$$

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

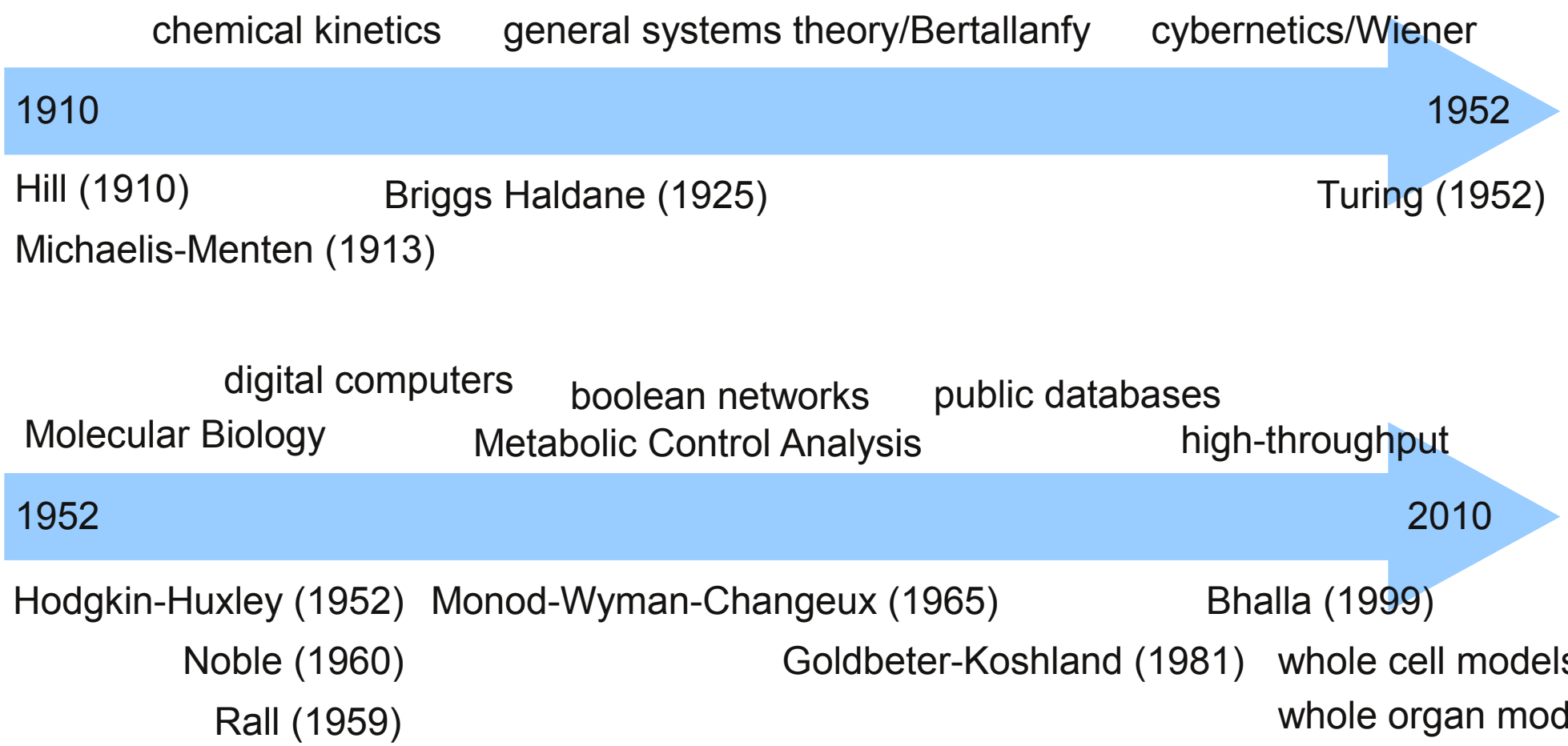
Tyson et al (1991) PNAS 88(1):7328-32

Phenomenological (descriptive) models



Systems Biology: Where it comes from, what it is, and what it does:
http://www.ebi.ac.uk/~lenov/LECTURES/LeNovere_SystemsBiology-EBI_WT.pdf

Mechanistic (explanatory) models

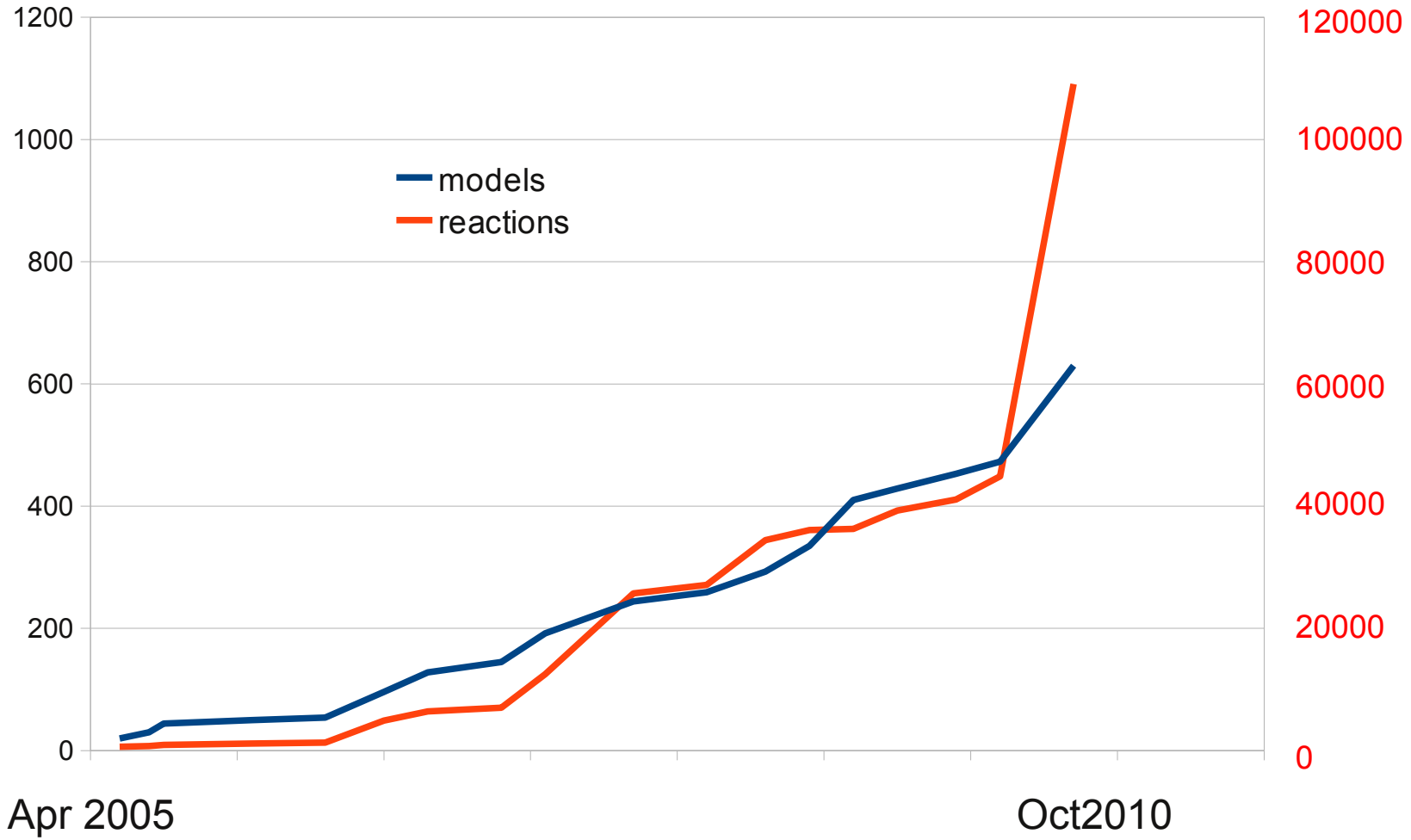


Systems Biology: Where it comes from, what it is, and what it does:
http://www.ebi.ac.uk/~lenov/LECTURES/LeNovere_SystemsBiology-EBI_WT.pdf

Computational modelling for biology and medicine left the niches and is now mainstream

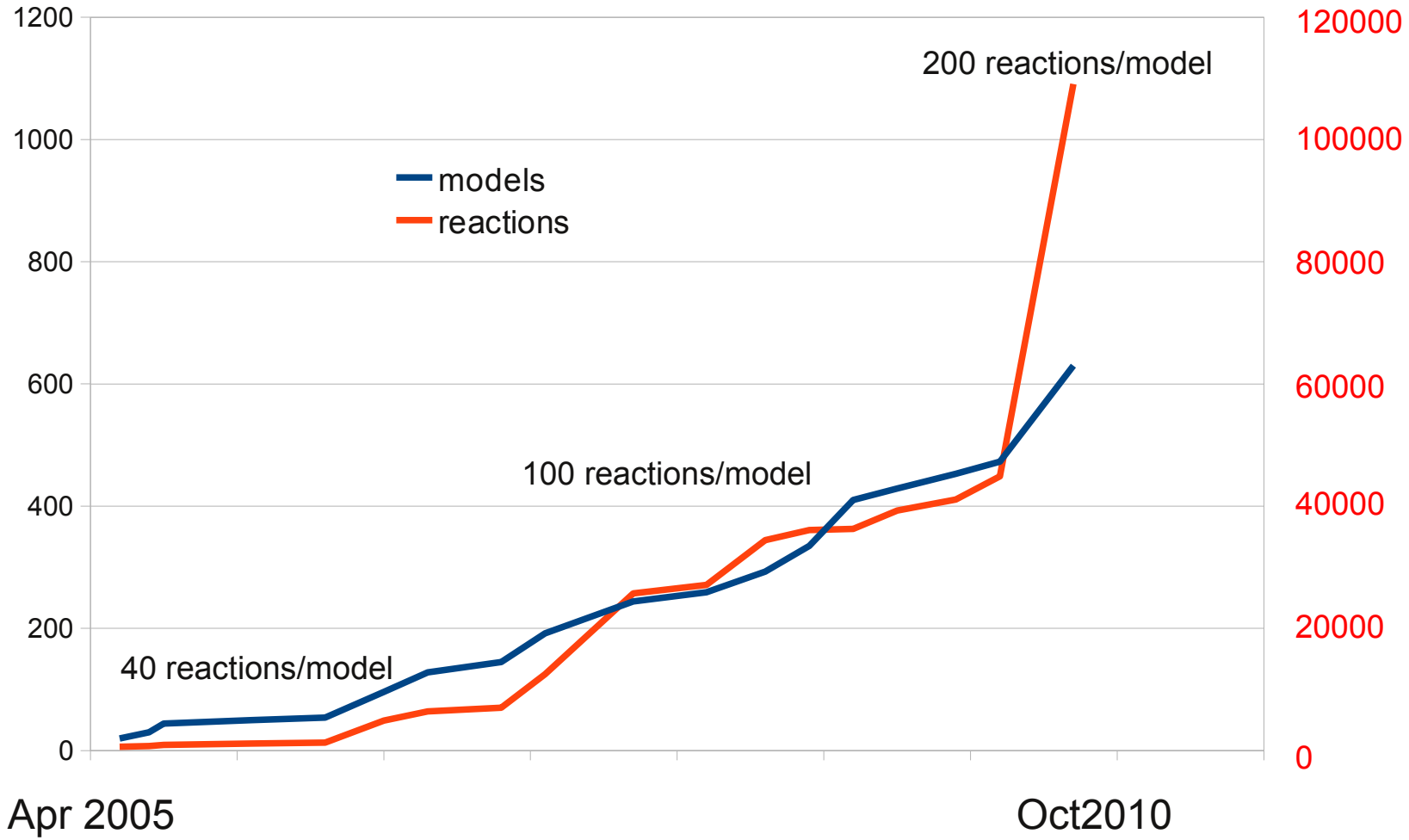
- Metabolic networks (Herrgård et al. A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. ***Nat Biotechnol*** 2008)
- Signalling pathways (Bray et al. Receptor clustering as a cellular mechanism to control sensitivity. ***Nature*** 1998; Bhalla ad 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; Nelson et al. Oscillations in NF-kB Signaling Control the Dynamics of Gene Expression. ***Science*** 2004; Ashall et al. Pulsatile Stimulation Determines Timing and Specificity of NF-kappa B-Dependent Transcription. ***Science*** 2009)
- 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)
- Pharmacokinetic/dynamic 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; Neumann et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. ***Science*** 1998)

Computational models on the rise



Growth of BioModels Database between its creation and release 18

Computational models on the rise



Growth of BioModels Database between its creation and release 18

EMBL-EBI EB-eye Search All Databases Enter

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

Databases | Tools | EBI Groups | Training | Ind

BioModels Home | Models | Submit | Support | About BioModels | Contact us

BioModels Database - A Database of Annotated Published Models

BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and controlled vocabularies.
BioModels Database also allows users to generate sub-models, provides access to online simulation tools and features programmatic access via Web Services.

Advanced Search

Search | Go to model

Browse models

- Curated models (269)
- Browse models using GO
- Non-curated models (361)

Simulate in JWS Online

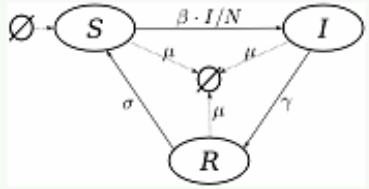
Submit a model

Links

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

Model of the month

November, 2010



The evolution of virulence and the occurrence of cross-immunity are of great importance for the development of pathogens and epidemics and they are rarely modelled in combination. Here is the model that explores both in one framework...
Read more...

News

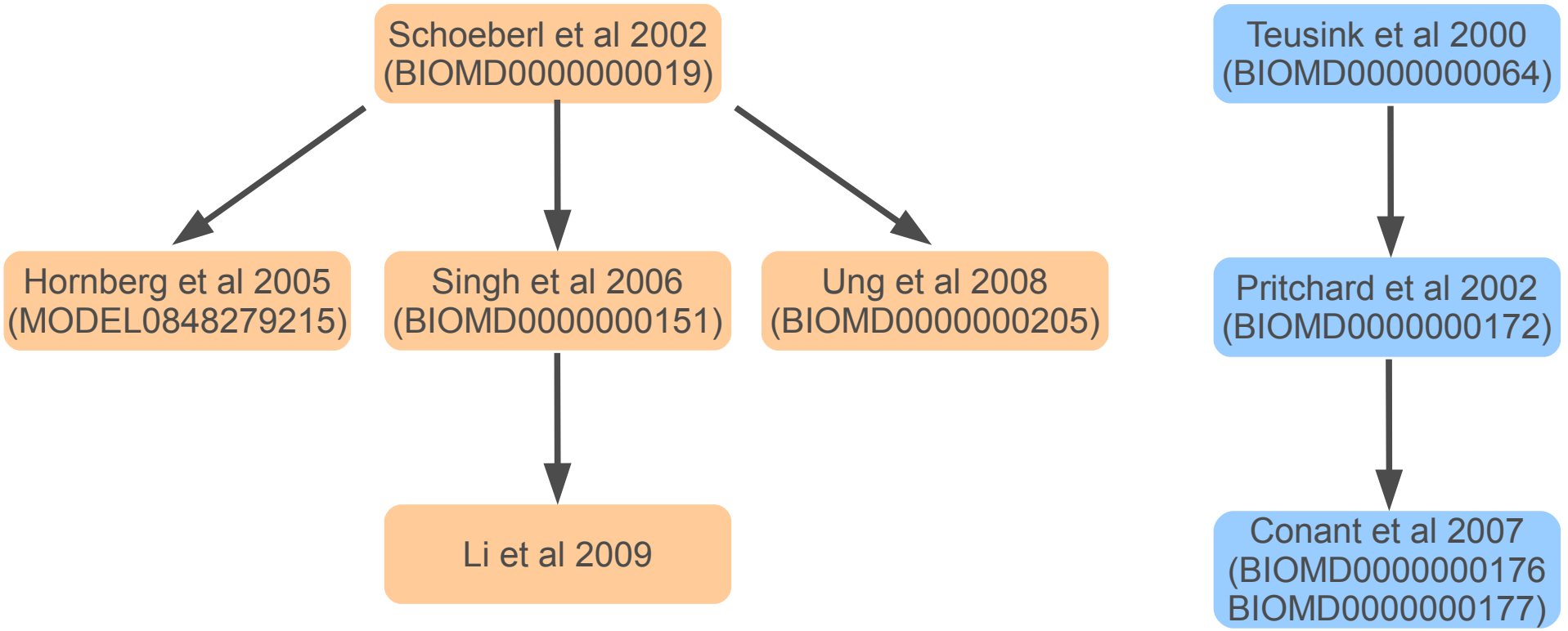
17 November 2010 **New availability of the Models of the Month**
Models of the Month are now linked from BioMed Central's Systems Biology Gateway.

30 September 2010 **Eighteenth Release!**
Download All Models Under SBML Format

29 June 2010 **New BioModels Database publication**
New BioModels Database paper published in *BMC Systems Biology*: BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models.

Le Novère *et al* (2006) *Nucleic Acids Research,* 34: D689-D691

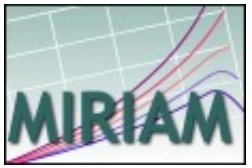
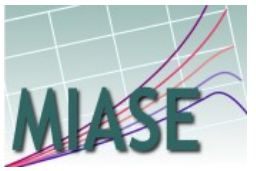
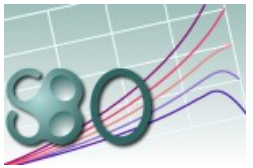
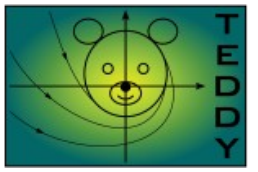
Direct model re-use: EGFR signalling and glycolysis



A “complete” (?) mosaic of standards for Computational Systems Biology models

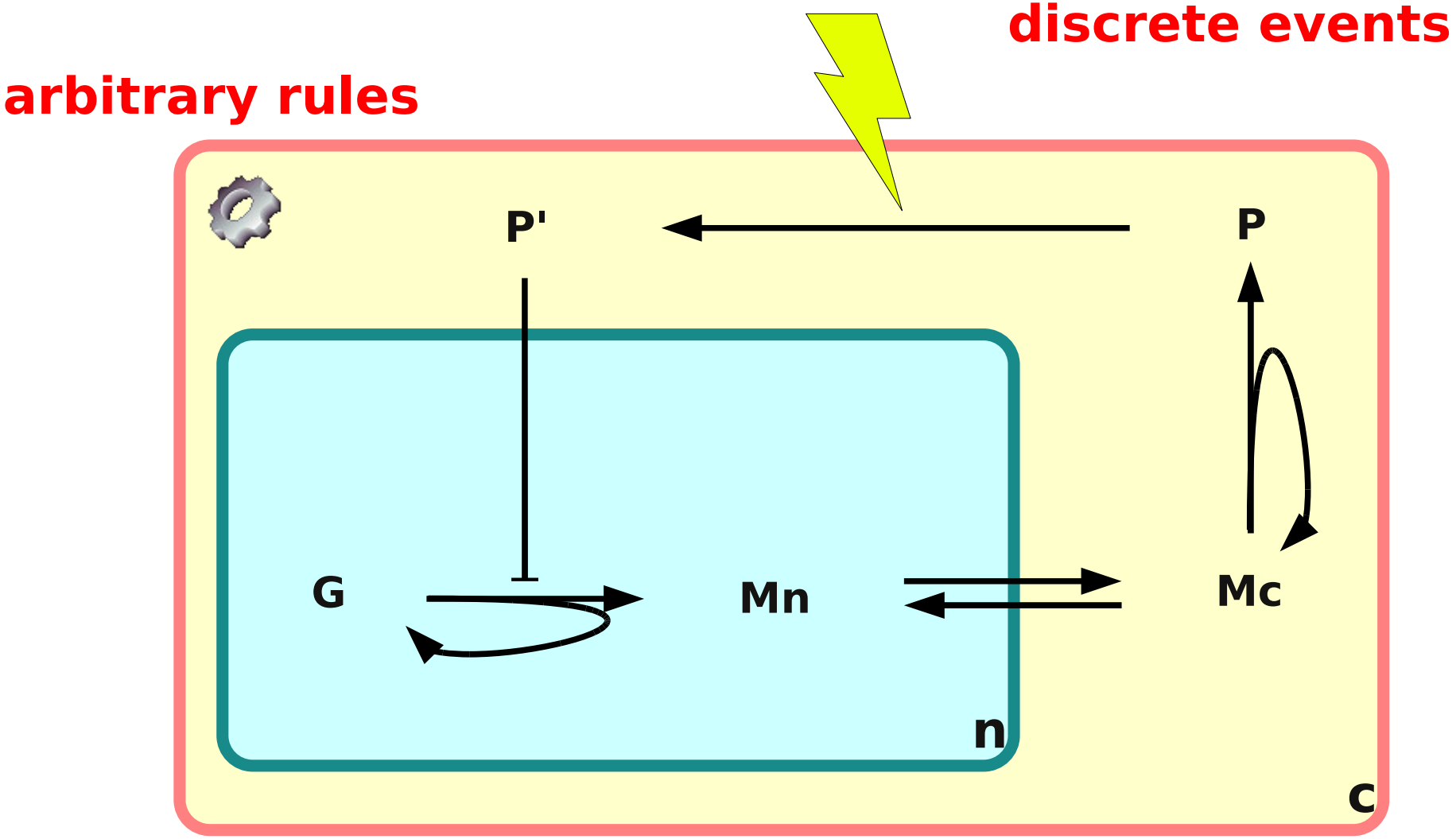
	Models	Simulation	Results
Minimal requirements	MIRIAM	MIASE	
Data-models	SBML, SBGN	SED ML	SBRML
Ontologies	SBO	KISAO	TEDDY

Model description

	Models	Simulation	Results
Minimal requirements			
Data-mode			SBRML
Ontologies			

Hucka *et al* (2003). *Bioinformatics*, 19: 524-531

What can we encode in SBML (core)?



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>
```

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 ⟶ B)

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="4" xmlns="http://www.sbml.org/sbml/level2/version4">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

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 is not limited to biochemistry!

Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage, tumour size etc.

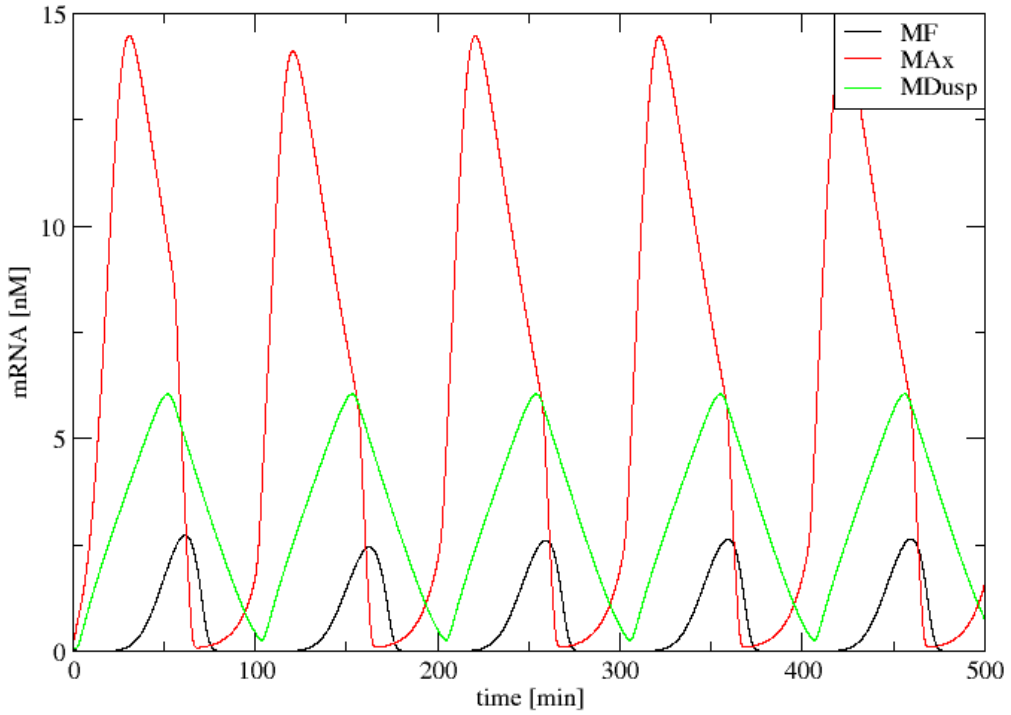
Events can describe any discontinuous change, e.g. neurotransmitter release, repolarisation, cell division etc.

A species is an entity participating to a reaction, **not always** a **chemical** entity:

- It can be a molecule
- It can be a cell
- It can be an organ
- It can be an organism

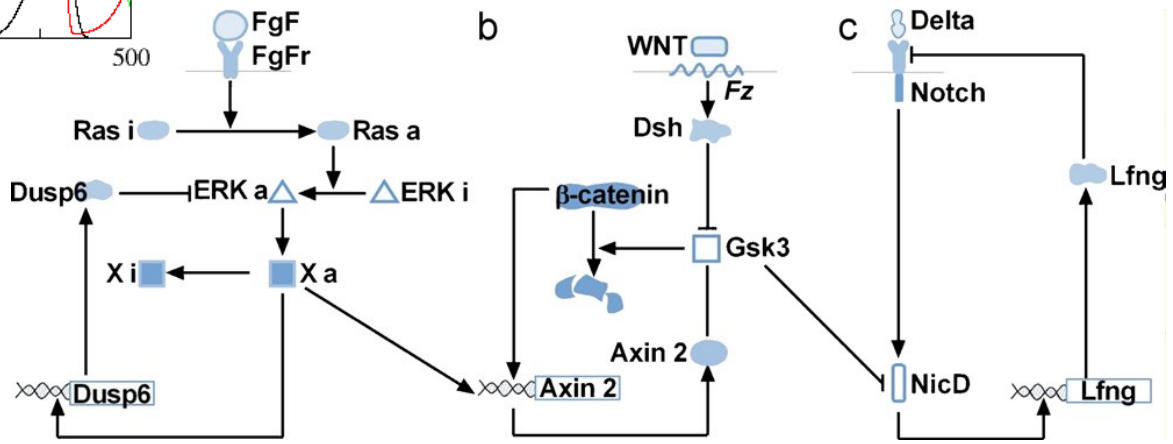
➔ SBML is about process descriptions

Models of signalling pathways



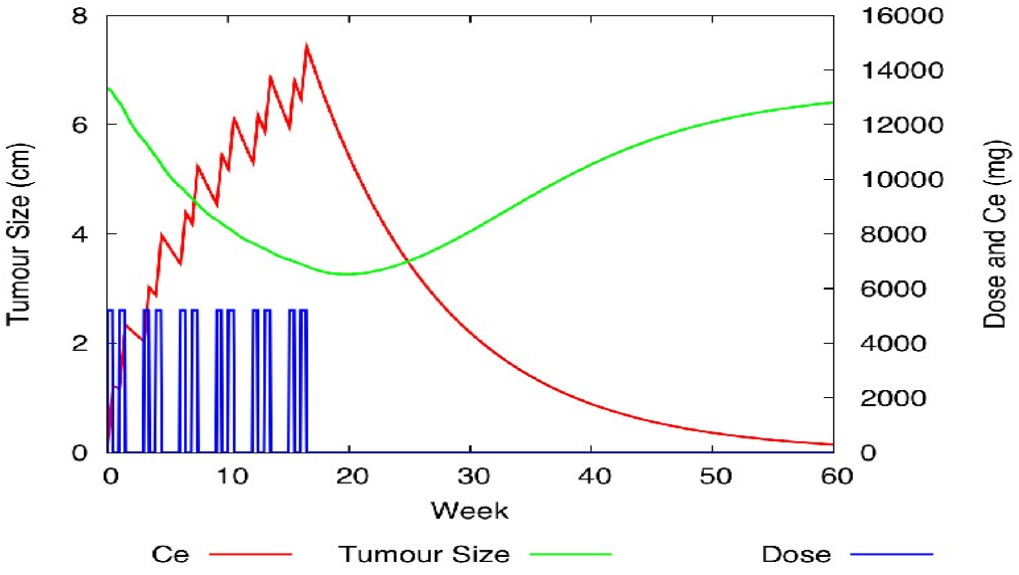
Goldbeter and Pourquié. Modeling the segmentation clock as a network of coupled oscillations in the Notch, Wnt and FGF signaling pathways.
J Theor Biol 2008 252: 574-585.

BIOMD0000000201



$$\frac{dM_F}{dt} = \varepsilon \times \left(v_{sF} \times \frac{Na_n^p}{K_A^p + Na_n^p} - v_{mF} \times \frac{M_F}{K_{dmF} + M_F} \right)$$

Pharmacokinetic/dynamic model



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

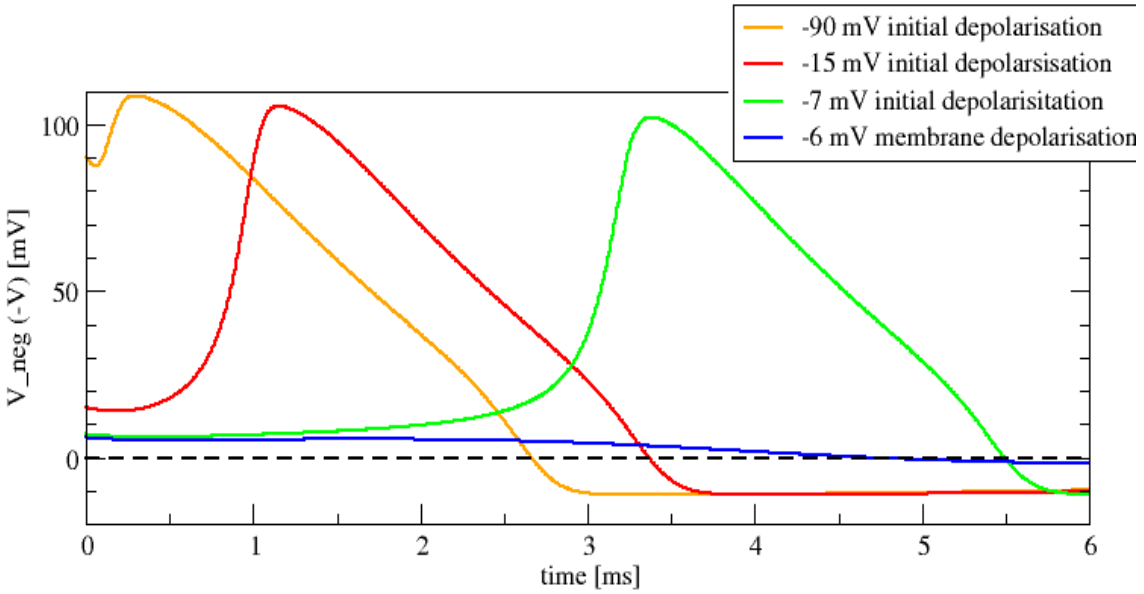
rate rule:

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

assignment rule:

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

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.

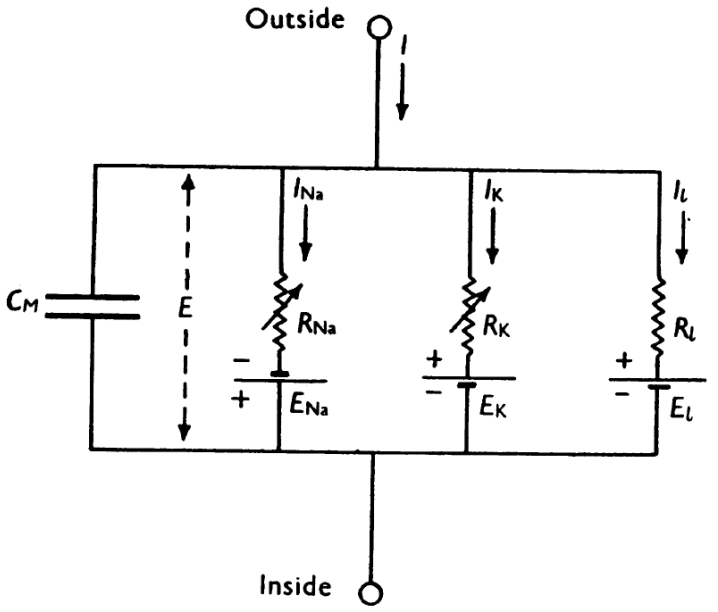
BIOMD0000000020

rate rule:

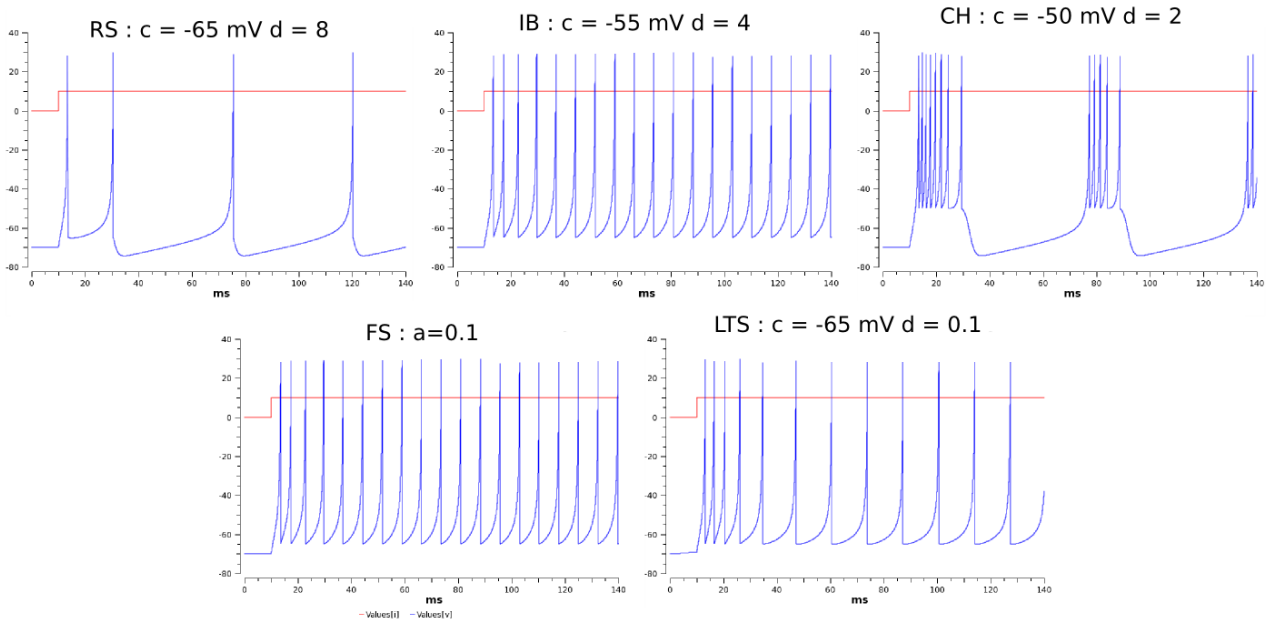
$$\frac{dv}{dt} = \frac{I - (i_{Na} + i_K + i_L)}{C_m}$$

assignment rule:

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



Single-compartment neurons



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

BIOMD0000000127

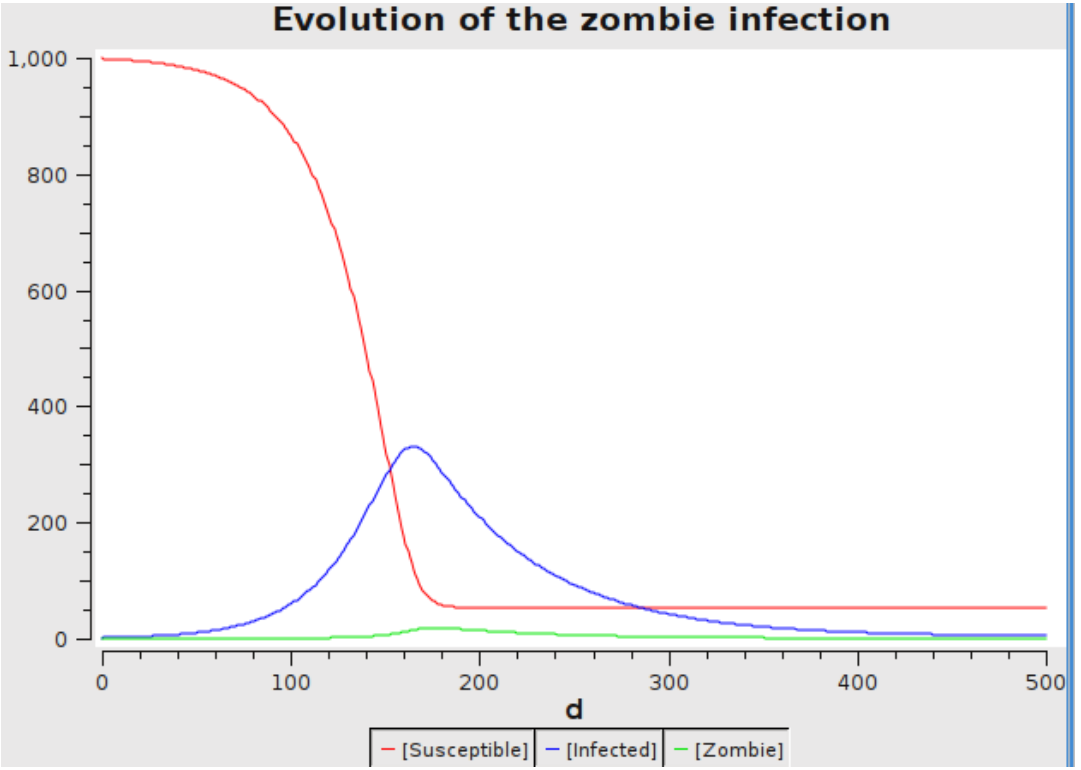
rate rule:

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

event:

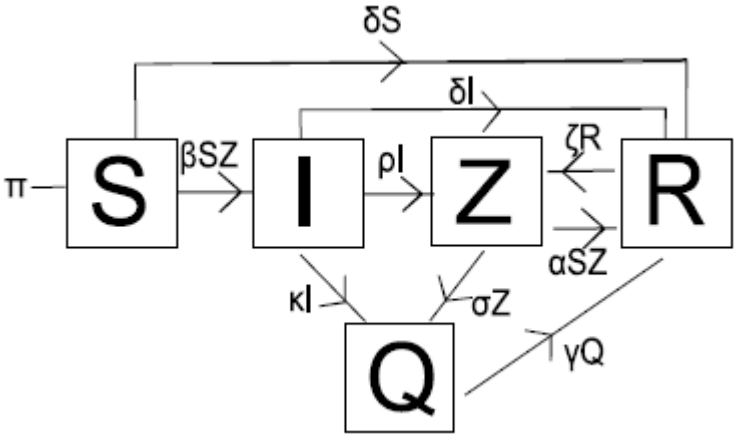
$$\text{when } v > V_{thresh} \begin{cases} v = c \\ U = U + d \end{cases}$$

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

MODEL1008060001



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: **205**

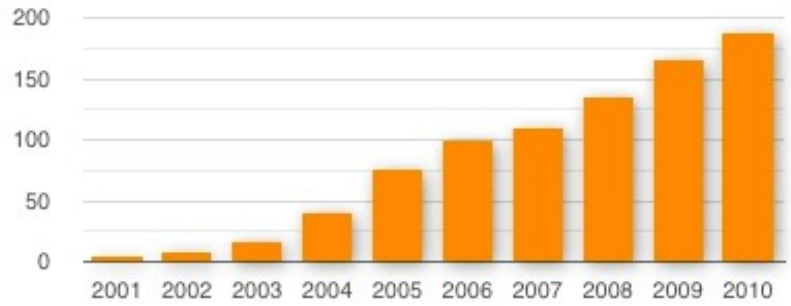
Please **use the survey form** to notify us about additions and suggestions.

Go to the SBML Software Matrix

Go to the SBML Software Summary

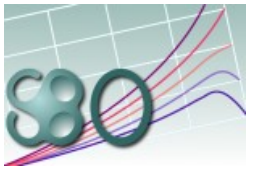
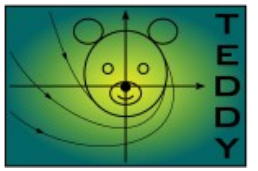
Historical trend

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 development.)

Model semantics

	Models	Simulation	Results
Minimal requiremer			
Data-models			SBRML
Ontologies			

MIRIAM compliance (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

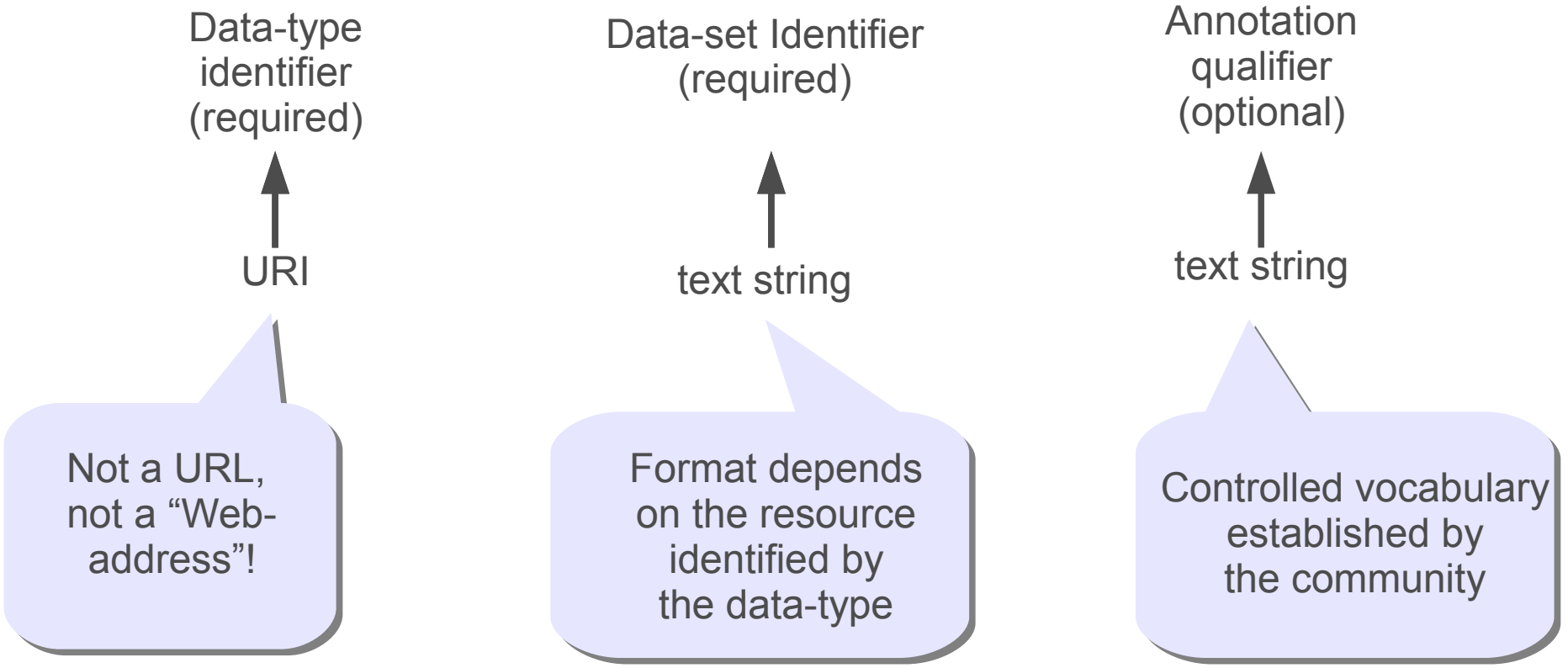
Le Novère *et al* (2005) *Nature Biotechnology*, 23: 1509-1515

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 cross-references



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

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

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

EMBL-EBI EB-eye Search All Databases Enter T Advanced Search

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EBI > Groups > Computational Neurobiology > Research > MIRIAM Resources

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- Query services
- Submit new
- Export
- Sign In

- Web Services
- Documents
  - MIRIAM Standard
  - FAQ
  - Documentation
  - News
  - BioModels.net Qualifiers

- MIRIAM on SourceForge

- Support
- Contact

MIRIAM Resources

MIRIAM Resources are a set of online services created to support MIRIAM Standard.

The core of *MIRIAM Resources* is a catalogue of data types (these can be 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).

Quick links

Browse
- by data type name
- by tags

Web Services
- services available
- usage of the services
- online demonstration

Search
- generic search

Exports
- XML

Resources

MIRIAM Resources are 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 types (which can be controlled vocabularies or databases), their URIs and the corresponding physical URLs or resources.

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

sed on Apache Axis and SOAP messages). This API permits not only to resolve model annotations, but also to generate the correct URIs based on resource name and accession numbers. You have access to the list of services available, an

Laibe *et al* (2007) *BMC Systems Biology*, 1: 58

Data type: *Enzyme Nomenclature*

General | Tags | Annotation

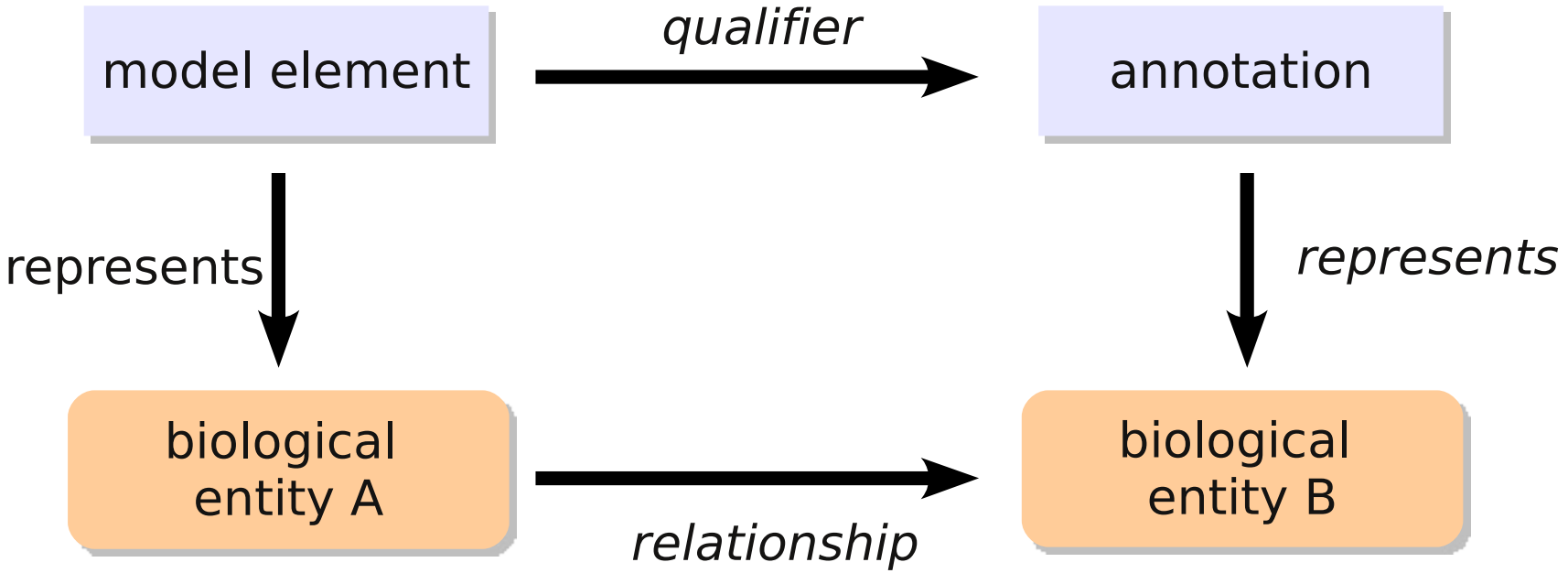
General information about the data type

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

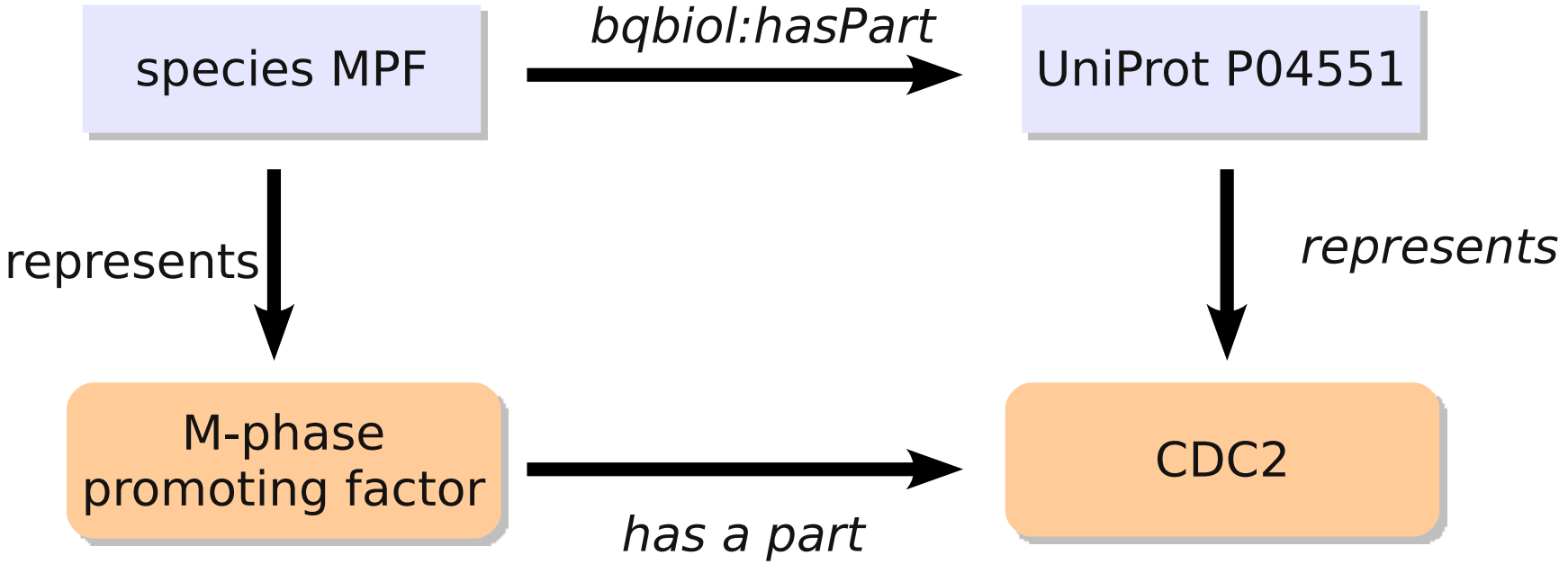
Go back to the list of data types

Edit this data type

Qualification of annotation



Qualification of annotation



SBML and MIRIAM cross-references

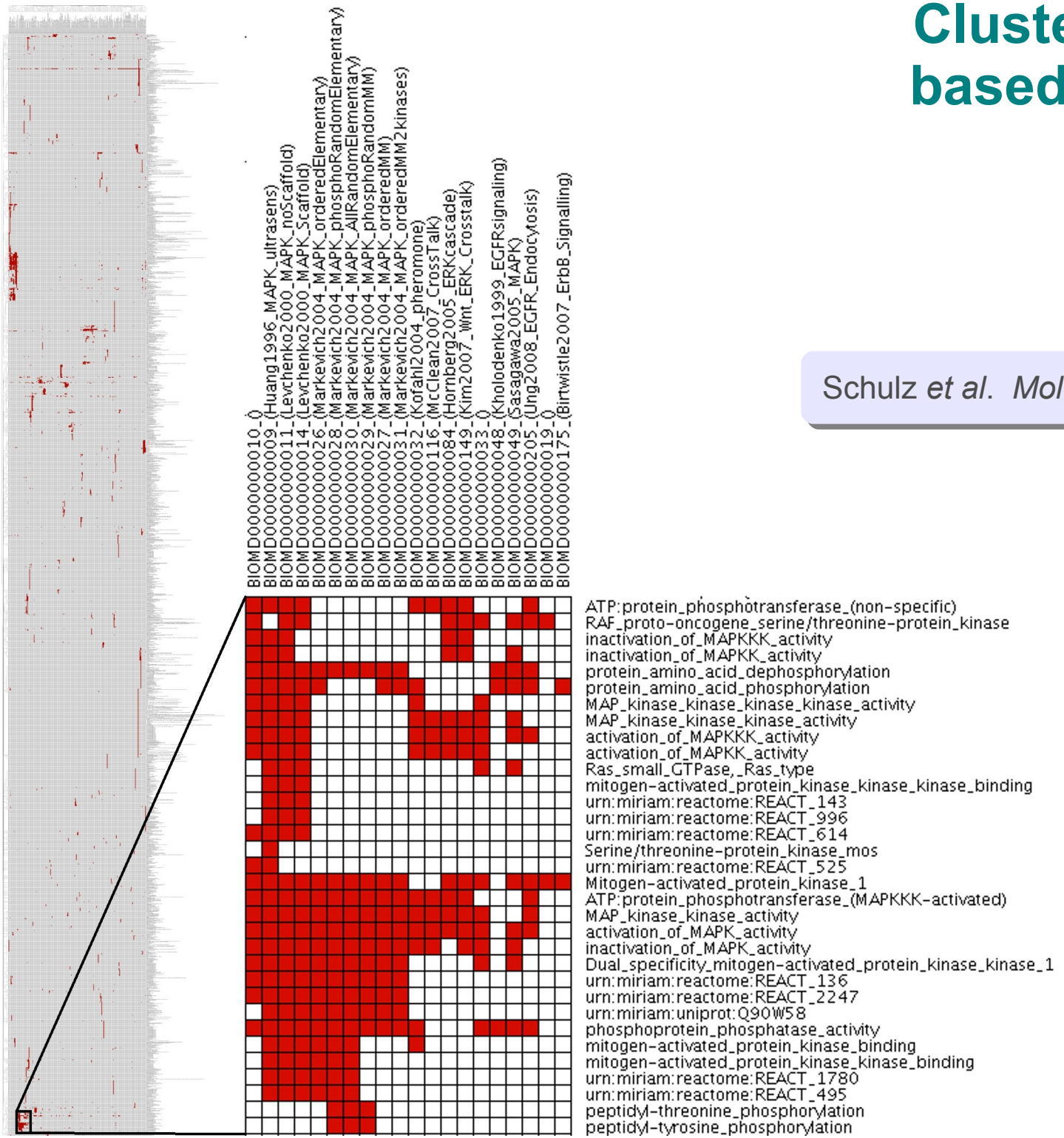
```
<species id="Ca_calmodulin" metaid="cacam">
  <annotation>
    <rdf:RDF
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/">
      <rdf:Description rdf:about="#cacam">
        <bqbiol:hasPart>
          <rdf:Bag>
            <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>
```

Tools developing support for MIRIAM identifiers

- Data resources
  - BioModels Database (kinetic models)
  - PSI consortium (protein interactions)
  - Reactome (pathways)
  - Pathway commons (pathways)
  - SABIO-RK (reaction kinetics)
  - Yeast consensus model database
  - Human consensus model database
  - E-MeP (structural genomics)
- Discussion started with publishers
  - Elsevier
  - Wiley
  - Nature Mol Syst Biol
  - BiomedCentral

- Application software
  - ARCADIA (graph editor)
  - BIOUML (modeling and simulation)
  - COPASI (Simulation)
  - libAnnotationSBML
  - libSBML
  - SAINT (semantic annotation)
  - SBML2BioPAX
  - SBML2LaTeX
  - SBMLeditor (model editor)
  - SemanticSBML (annotation and merging)
  - Snazer (Network analysis, Simulations)
  - Systems Biology Workbench (model design and simulation)
  - The Virtual Cell (Simulation)

Clustering models based on metadata



Schulz *et al*. *Mol Syst Biol, under revision*

BIOMD0000000010_()
BIOMD0000000009_(Huang1996_MAPK_ultrasens)
BIOMD0000000011_(Levchenko2000_MAPK_noScaffold)
BIOMD0000000014_(Levchenko2000_MAPK_Scaffold)
BIOMD0000000026_(Markevich2004_MAPK_orderedElementary)
BIOMD0000000028_(Markevich2004_MAPK_phosphoRandomElementary)
BIOMD0000000030_(Markevich2004_MAPK_AllRandomElementary)
BIOMD0000000029_(Markevich2004_MAPK_phosphoRandomMM)
BIOMD0000000027_(Markevich2004_MAPK_orderedMM)
BIOMD0000000031_(Markevich2004_MAPK_orderedMM2kinases)
BIOMD0000000032_(Kofahl2004_pheromone)
BIOMD0000000116_(McClean2007_CrossTalk)
BIOMD0000000084_(Hornberg2005_ERKcascade)
BIOMD0000000149_(Kim2007_Wnt_ERK_Crosstalk)
BIOMD0000000033_()
BIOMD0000000048_(Kholodenko1999_EGFRsignaling)
BIOMD0000000049_(Sasagawa2005_MAPK)
BIOMD0000000205_(Ung2008_EGFR_Endocytosis)
BIOMD0000000019_()
BIOMD0000000175_(Birtwistle2007_ErbB_Signalling)
ATP:protein_phosphotransferase_(non-specific)
RAF_proto-oncogene_serine/threonine-protein_kinase
inactivation_of_MAPKKK_activity
protein_amino_acid_dephosphorylation
protein_amino_acid_phosphorylation
MAP_kinase_kinase_kinase_kinase_activity
MAP_kinase_kinase_kinase_activity
activation_of_MAPKKK_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
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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

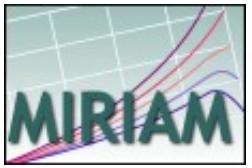
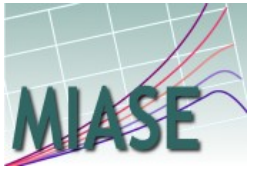
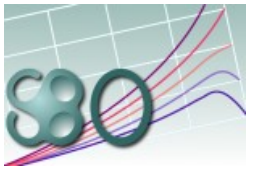
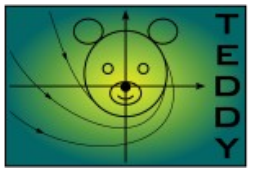
Model	BioModel	Score	p-val num
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.000	< 1/1000
Levchenko2000_MAPK_noScaffold	BIOMD0000000011	0.925	< 1/1000
Levchenko2000_MAPK_Scaffold	BIOMD0000000014	0.865	< 1/1000
Kholodenko2000_MAPK_feedback	BIOMD0000000010	0.816	< 1/1000
Markevich2004_MAPK_orderedElementary	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

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

Standard formats provide new approaches for modelling

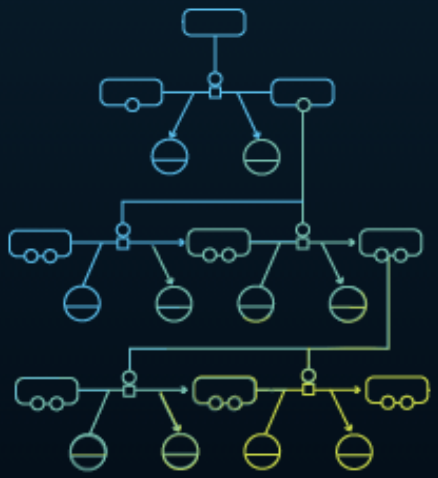
- Herrgård et al (2008) A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. *Nature Biotechnology*, 26: 1155-1160
  - MODEL0072364382: 2152 species, 1857 reactions
  - stoichiometric map, no concentrations, no kinetics
- Smallbone et al (2010) Towards a genome-scale kinetic model of cellular metabolism. *BMC Systems Biology*, 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 Systems Biology,* 4:145
  - MODEL1012110000: 2657 species, 1865 reactions
- Li et al (2010) Systematic integration of experimental data and models in systems biology. *BMC Bioinformatics,* 11: 582
  - MODEL1012110001
  - Workflows using experimental kinetic information database (SABIO-RK) plus metabolomics and proteomics database
  - Full quantitative chemical kinetics descriptions

Visual representation of models

	Models	Simulation	Results
Minimal requirements			
Data-mode	 		SBRML
Ontologies			

SBGN Systems Biology Graphical Notation

Home | News | Documents | Lists | Community | Events | About | Google Site Search.



A Visual Notation for Network Diagrams in Biology

SBGN.org is the global portal for documentation, news, and other information about the Systems Biology Graphical Notation (SBGN) project, an effort to standardize the graphical notation used in maps of biochemical and cellular processes studied in systems biology.

Standardizing the visual representation is crucial for more efficient and accurate transmission of biological knowledge between different communities in research, education, publishing, and more. When biologists are as familiar with the notation as electronics engineers are familiar with the notation of circuit schematics, they can save the time and effort required to familiarize themselves with different notations, and instead spend more time thinking about the biology being depicted.

SBGN is made up of three orthogonal languages, representing different visions of biological systems. Each language defines a comprehensive set of symbols with precise semantics, together with detailed syntactic rules how maps are to be interpreted.

On this site, you can browse some example maps to get a feeling for SBGN, read the SBGN specification documents , software supporting SBGN, get answers to frequent questions about SBGN, access join online discussions, see current working documents in the SBGN wiki, and much more.

SBGN is the work of many people. It would not have been possible without the generous support of multiple organizations over the years, for which we are very thankful.

To quote SBGN as a whole, please use:

Le Novère N, Hucka M, Mi H, Moodie S, Schreiber F, Sorokin A, Demir E, Wegner K, Aladjem MI, Wimalaratne SM, Bergman FT, Gauges R, Ghazal P, Kawaji H, Li L, Matsuoka Y, Villéger A, Boyd SE, Calzone L, Courtot M, Dogrusoz U, Freeman TC, Funahashi A, Ghosh S, Jouraku A, Kim S, Kolpakov F, Luna A, Sahle S, Schmidt E, Watterson S, Wu G, Goryanin I, Kell DB, Sander C, Sauro H, Snoep JL, Kohn K, Kitano H. The Systems Biology Graphical Notation. Nat Biotechnol. 2009 27(8):735-41.

SBGN News

(23 Apr.'10) The first annual competition is opened, with categories such as Best Software, Best Map and Best Outreach.

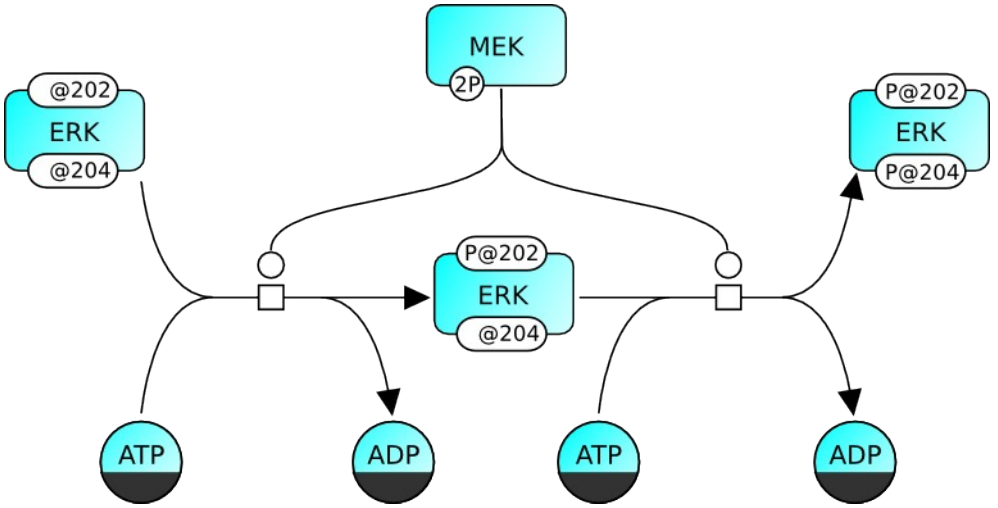
Le Novère *et al* (2008). *Nature Biotechnology, 27: 735-741*

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.

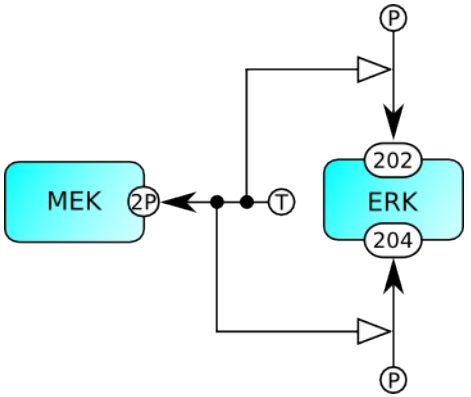
Graph trinity: three languages in one notation

Process Descriptions



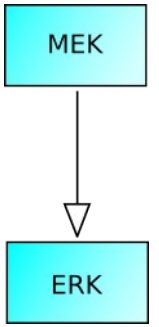
- Unambiguous
- Mechanistic
- Sequential
- Combinatorial explosion

Entity Relationships



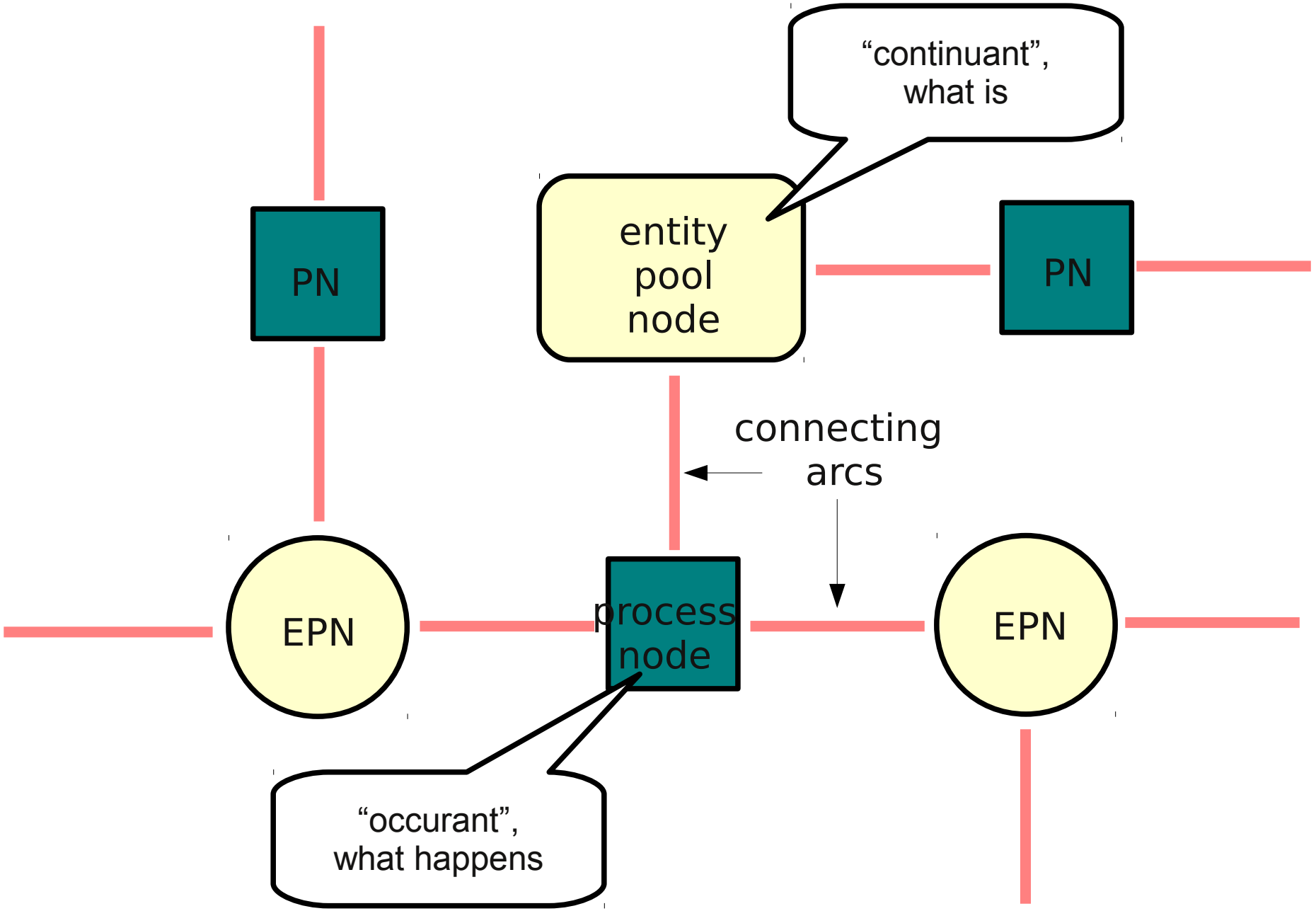
- Unambiguous
- Mechanistic
- Non-sequential
- Independence of relationships

Activity Flows

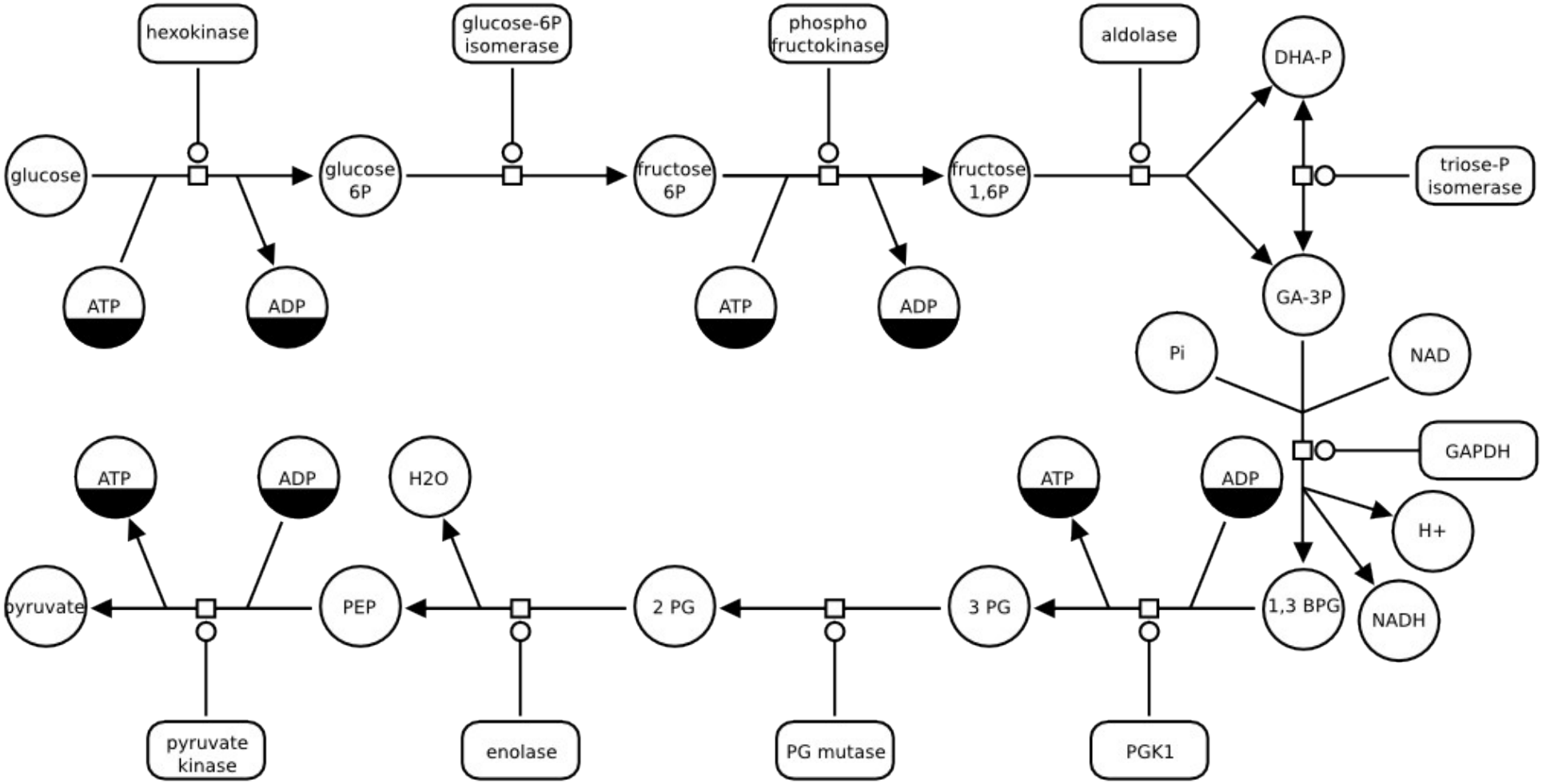


- Ambiguous
- Conceptual
- Sequential

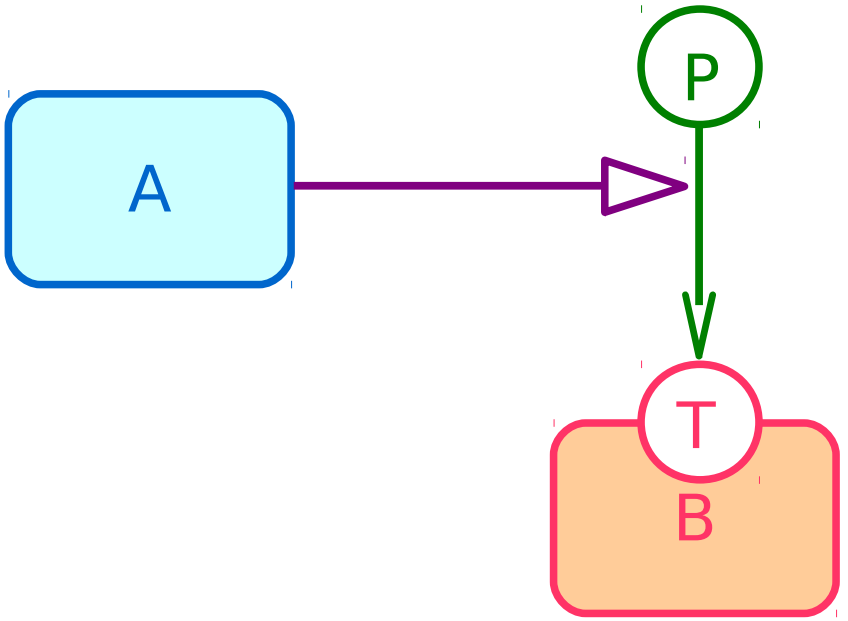
Process Descriptions are bipartite graphs



Metabolic network in Process Description Language



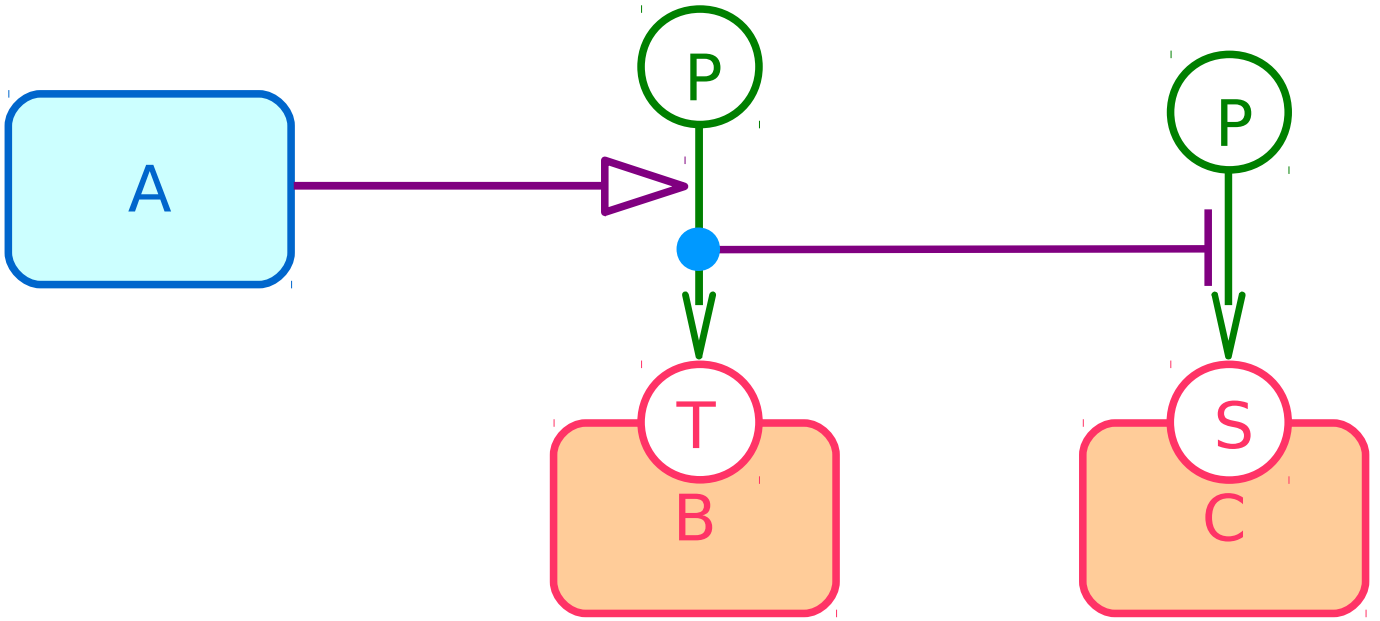
Entity Relationships can be viewed as rules



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

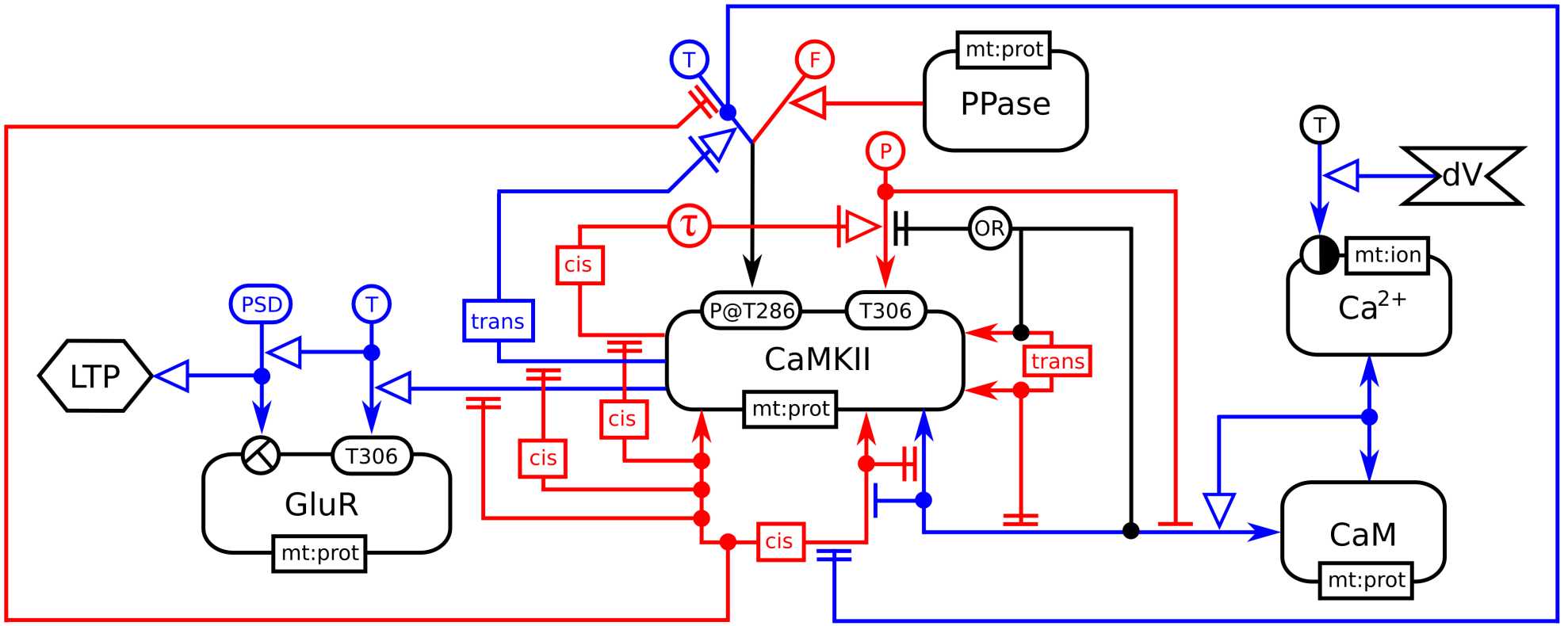


If A exists, the assignment of the value P to the state variable T of B is increased

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

(AThe phosphorylation of B inhibits the phosphorylation of C)

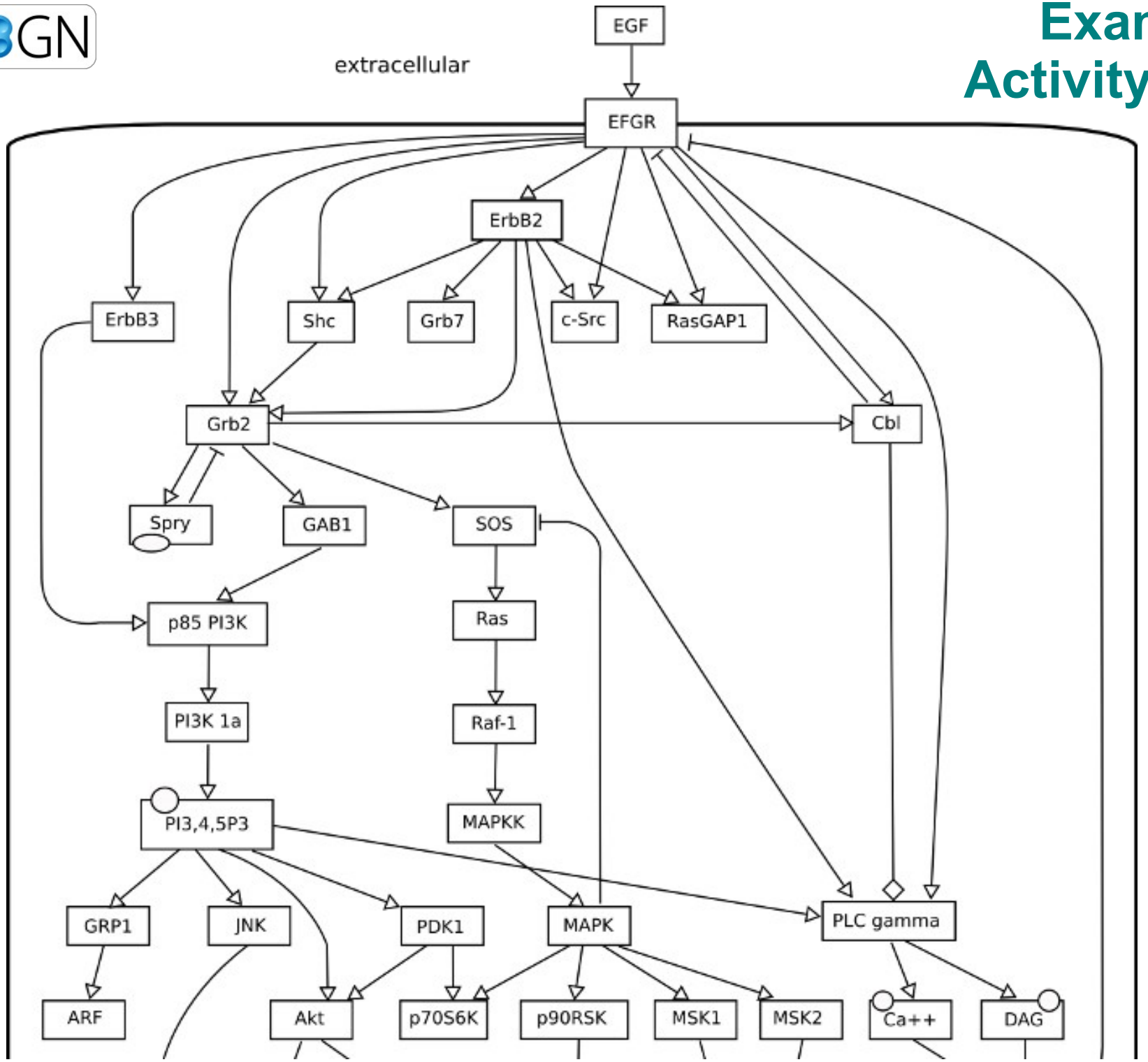
SBGN ER map of calcium-regulated synaptic plasticity

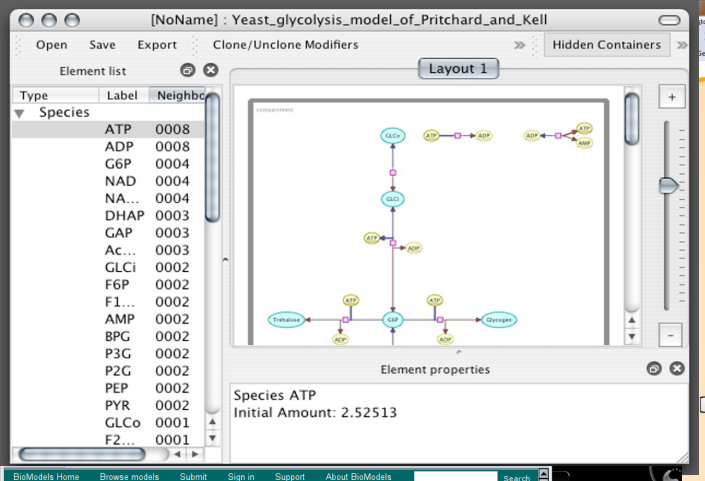


increases synaptic weight

decreases synaptic weight

Example of Activity Flow map

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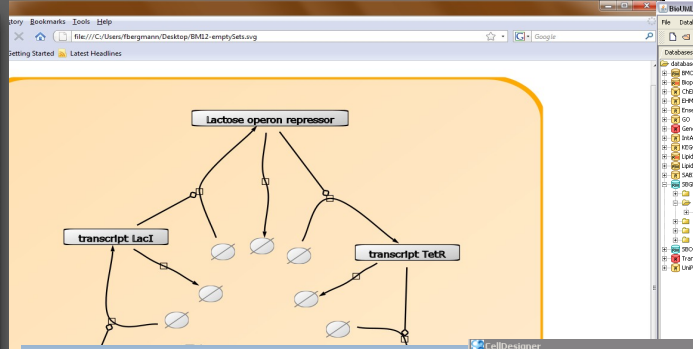
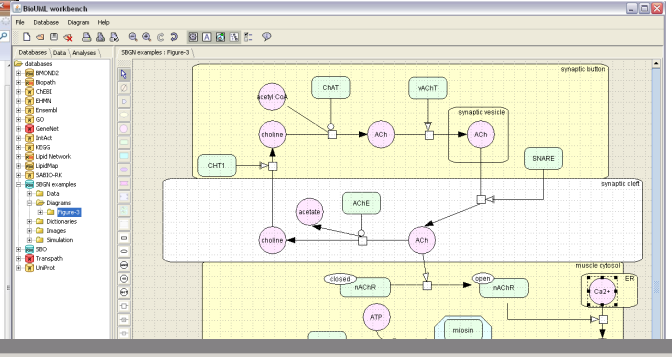
Open
Save
Export
Clone/Unclone Modifiers
Hidden Containers
Element list
Layout 1
Type
Label
Species
ATP 0008
ADP 0008
G6P 0004
NAD 0004
DHAP 0003
GAP 0003
BPG 0002
P3G 0002
P2G 0002
PEP 0002
PYR 0002
GLCo 0001
Element properties
Species ATP
Initial Amount: 2.52513


Lactose operon repressor
transcript LacI
transcript TetR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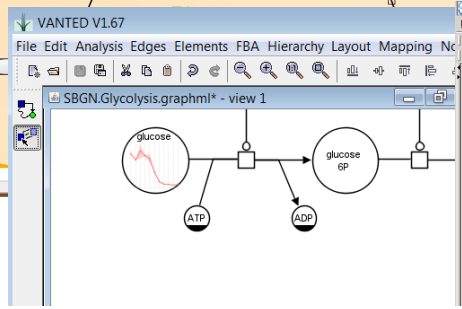
synaptic vesicle
synaptic cleft
muscle cytosol
ACh
choline
acetate
SNARE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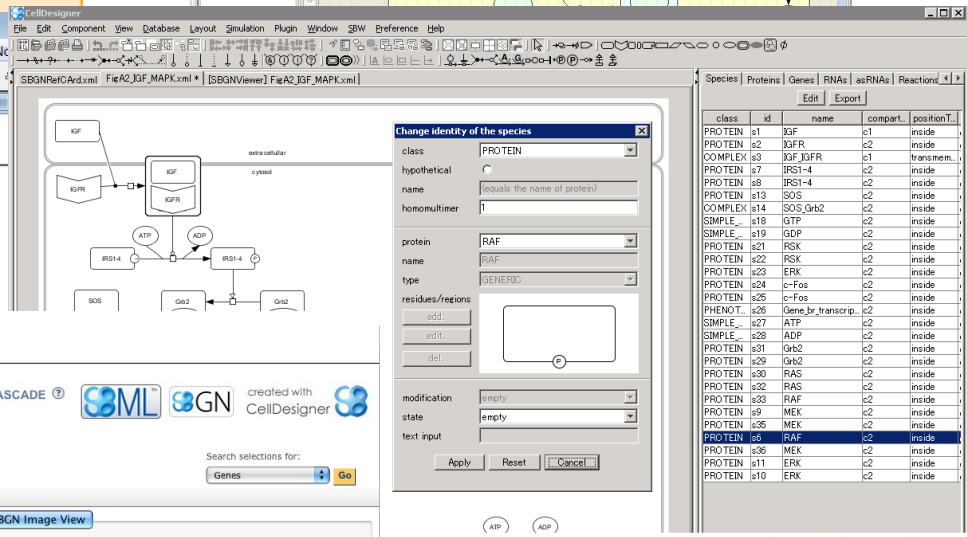
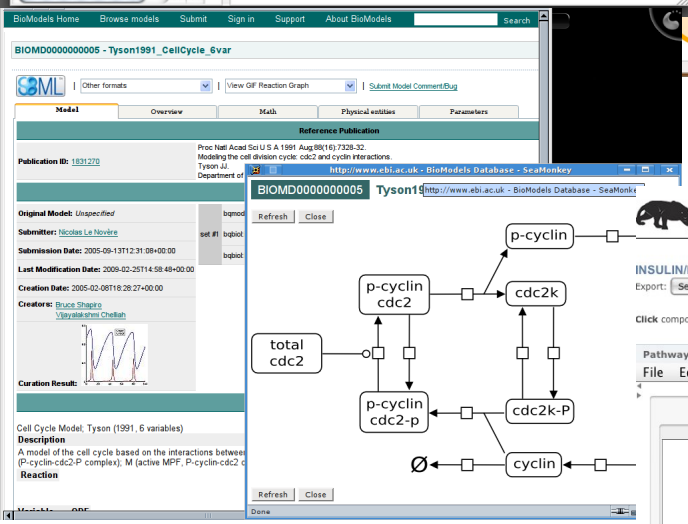
glucose 6P
ATP
ADP


CellDesigner
Change identity of the species
class
PROTEIN
hypothetical
name
homomultimer
protein
RAF
type
residues/regions
modification
state
empty
text input
Apply
Reset
Cancel


BioModels Home
Browse models
Submit
Sign in
Support
About BioModels
BIOMD0000000005 - Tyson1991_CellCycle_6var
Reference Publication
Cell Cycle Model; Tyson (1991, 6 variables)
Description
Reaction

BIOMD0000000005
Refresh
Close
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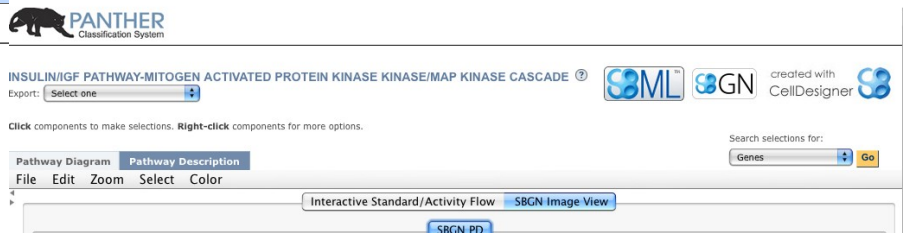
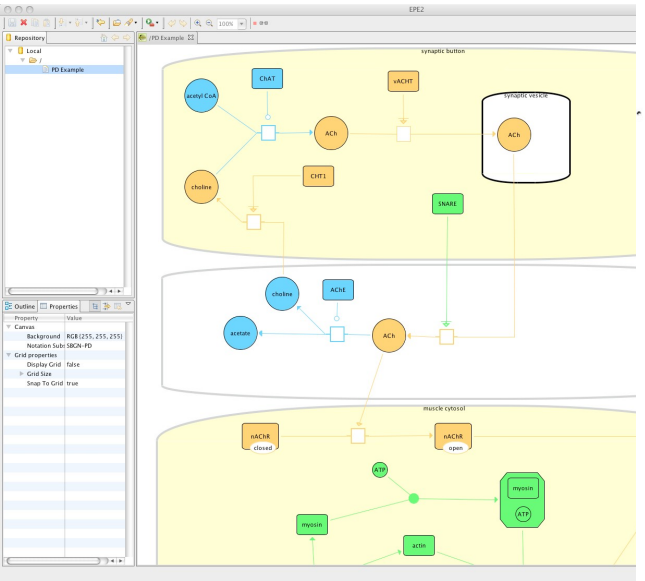
p-cyclin cdc2
cdc2k
total cdc2
p-cyclin cdc2-p
cdc2k-P
cyclin


PANTHER
Classification System
INSULIN/IGF PATHWAY-MITOGEN ACTIVATED PROTEIN KINASE KINASE/MAP KINASE CASCADE
created with CellDesigner
Pathway Diagram
Pathway Description
File Edit Zoom Select Color
Interactive Standard/Activity Flow
SBGN Image View
SBGN PD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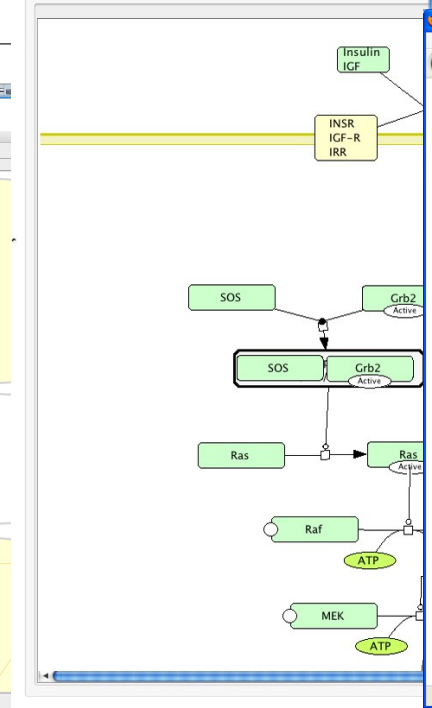
synaptic button
synaptic vesicle
muscle cytosol
ACh
choline
acetate
SNARE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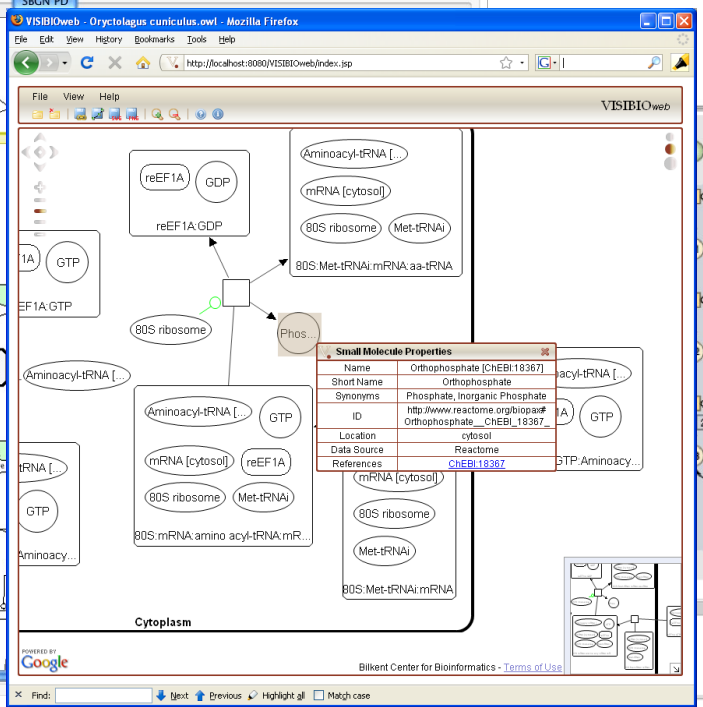
IGF-R
IRR
SOS
Grb2
Active
Ras
Raf
ATP
MEK
ATP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VISIBIOweb
reEF1A
GDP
reEF1A:GDP
Aminoacyl-tRNA [...
mRNA [cytosol]
80S ribosome
Met-tRNAi
80S:Met-tRNAi:mRNA:aa-tRNA
GTP
Small Molecule Properties
Name
Orthophosphate [ChEBI:18367]
Short Name
Orthophosphate
Synonyms
Phosphate, Inorganic Phosphate
ID
http://www.reactome.org/biopax#Orthophosphate__ChEBI_18367_
Location
cytosol
Data Source
Reactome
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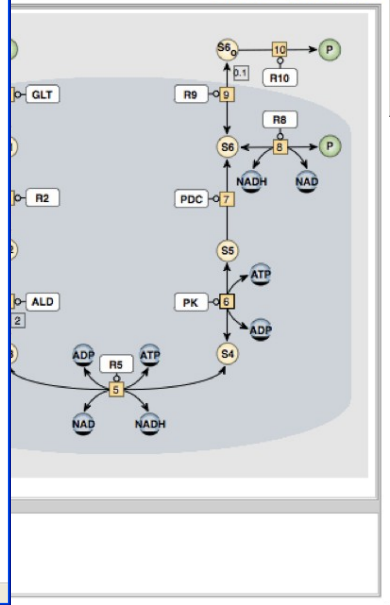
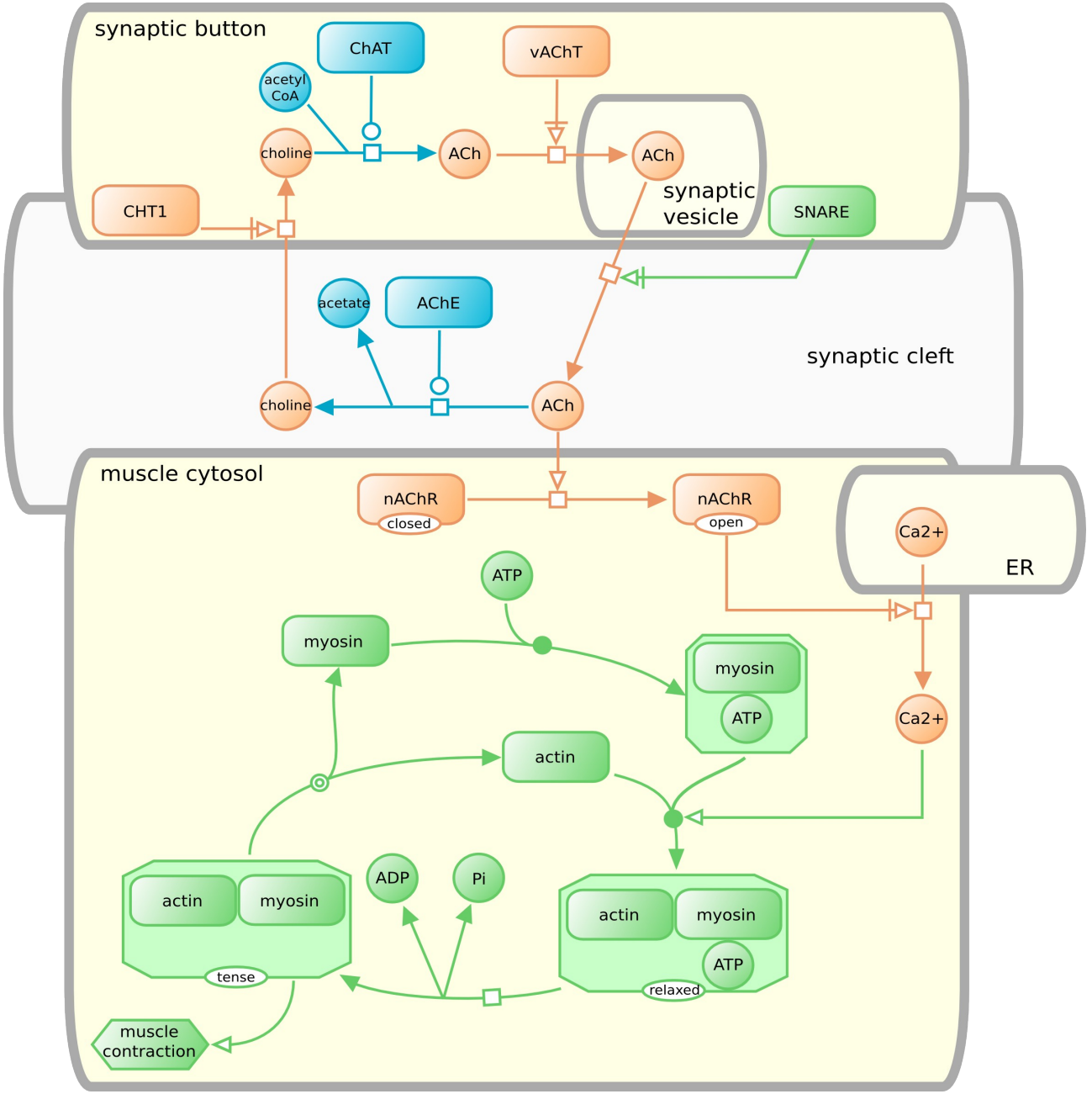
Cytoplasm
Bilkent Center for Bioinformatics - Terms of Use


JWS Online
Search | Upload | About | Help
GLT
R9
R8
S6
NADH
NAD
R2
PDC
S5
ALD
PK
ATP
ADP
S4
R5
NAD
NADH

Linking SBGN maps to external information

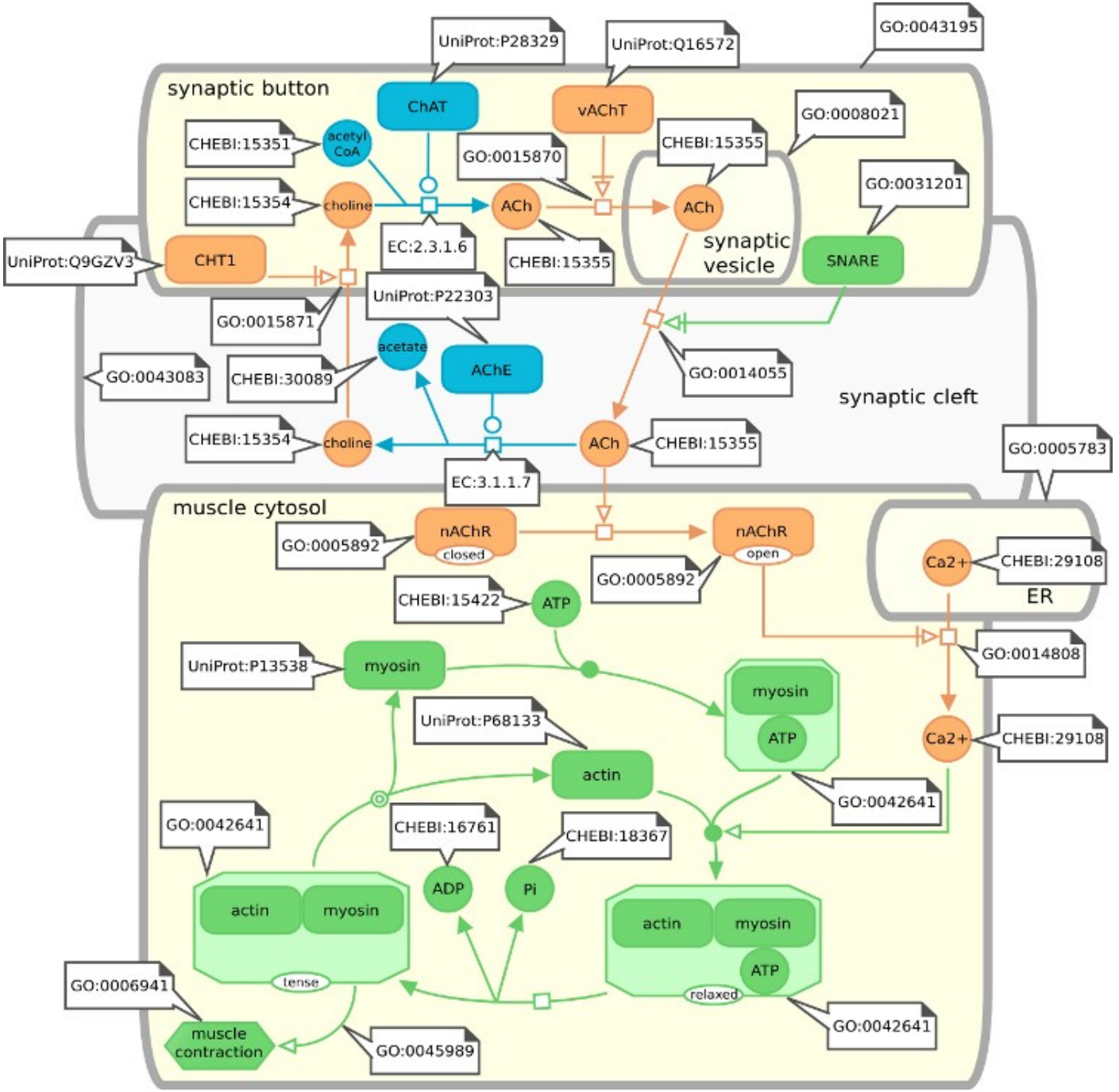


catalytic processes

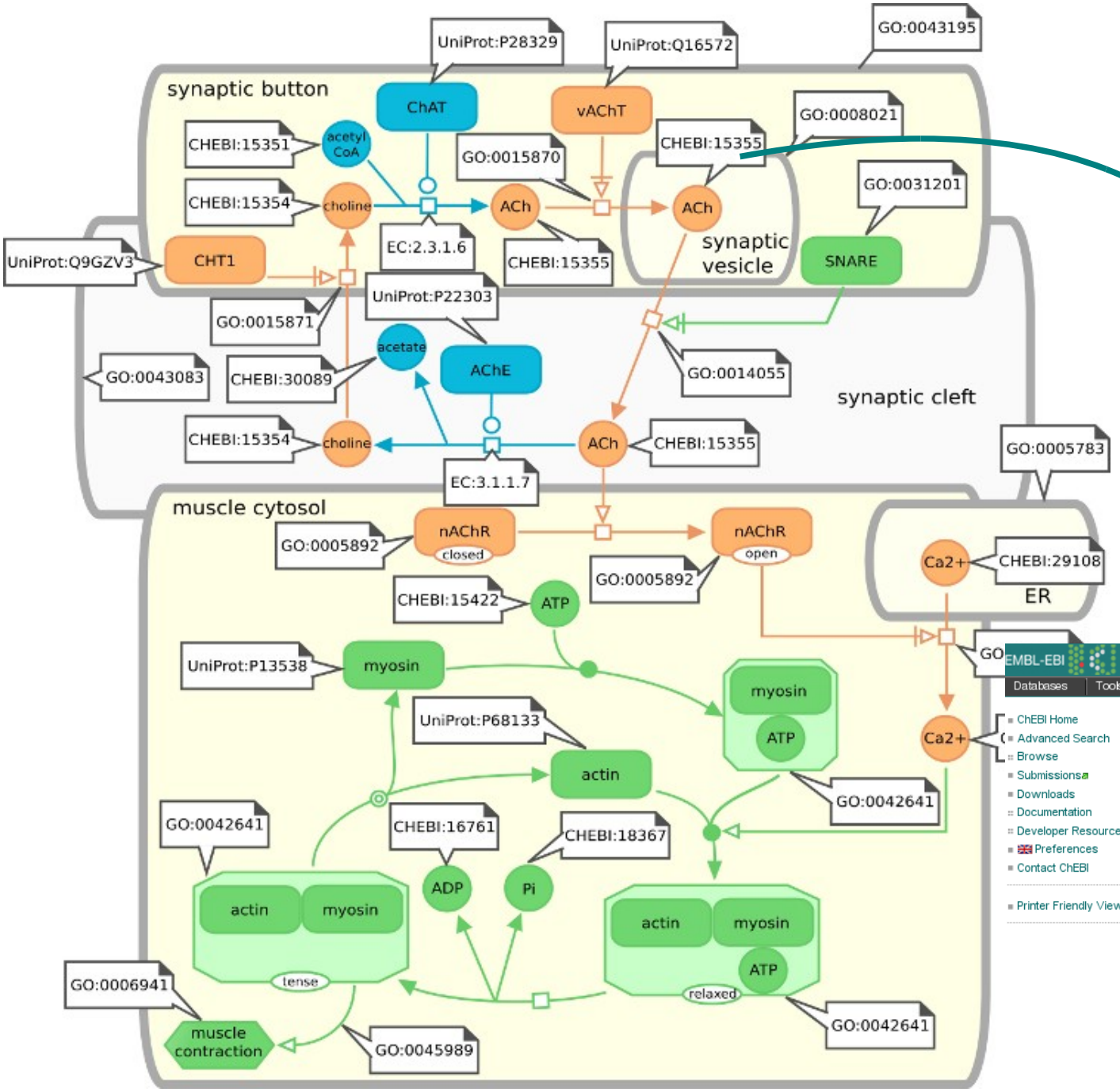
transport processes

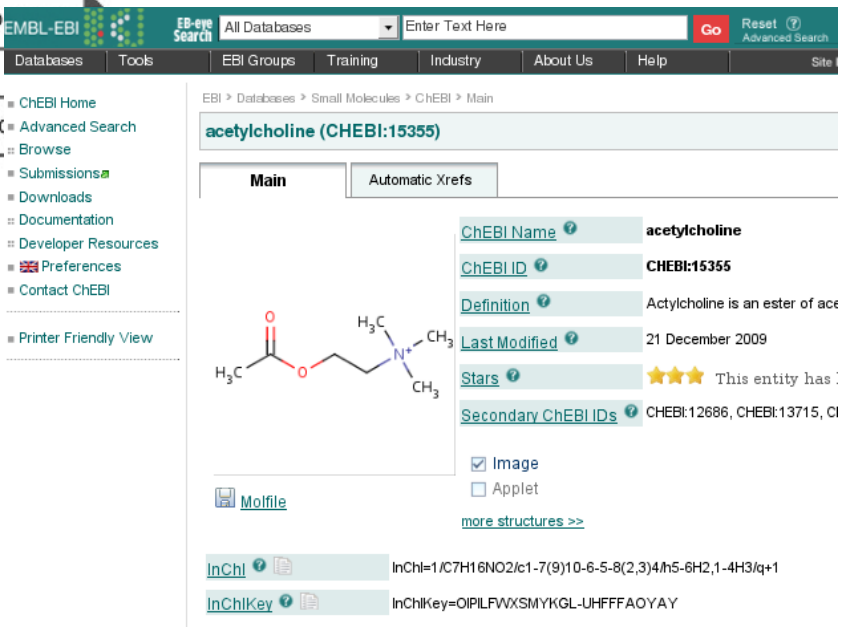
contractile proteins

Linking SBGN maps to external information



Linking SBGN maps to external information

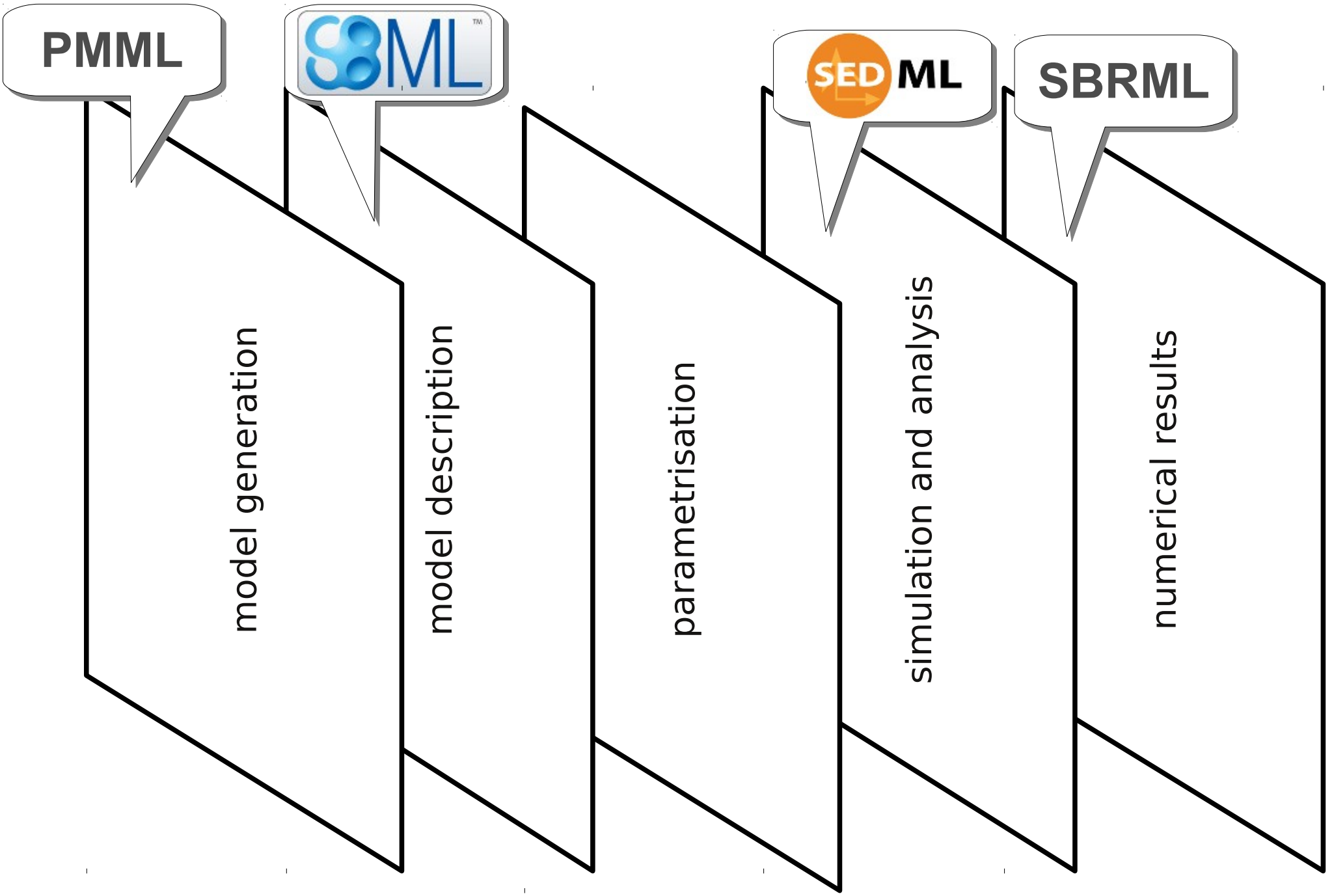




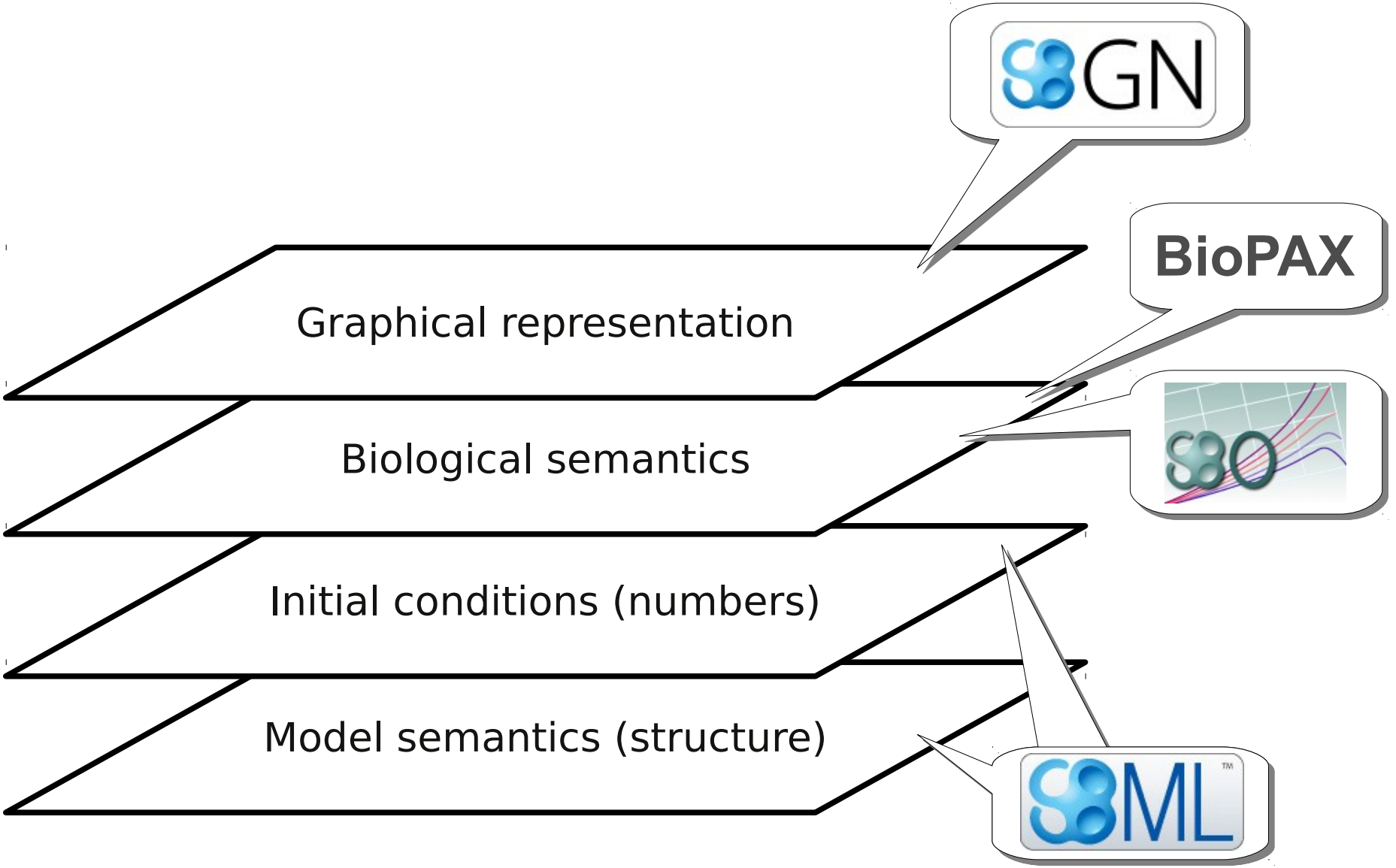
Is the mosaic of standards complete?

	Models	Simulation	Results
Minimal requirements	MIRIAM	MIASE	
Data-models	SBML, SBGN	SED ML	SBRML
Ontologies	SBO	KISAO	TEDDY

Disentangling the model life-cycle



Disentangling the level of discourse



Biological semantics

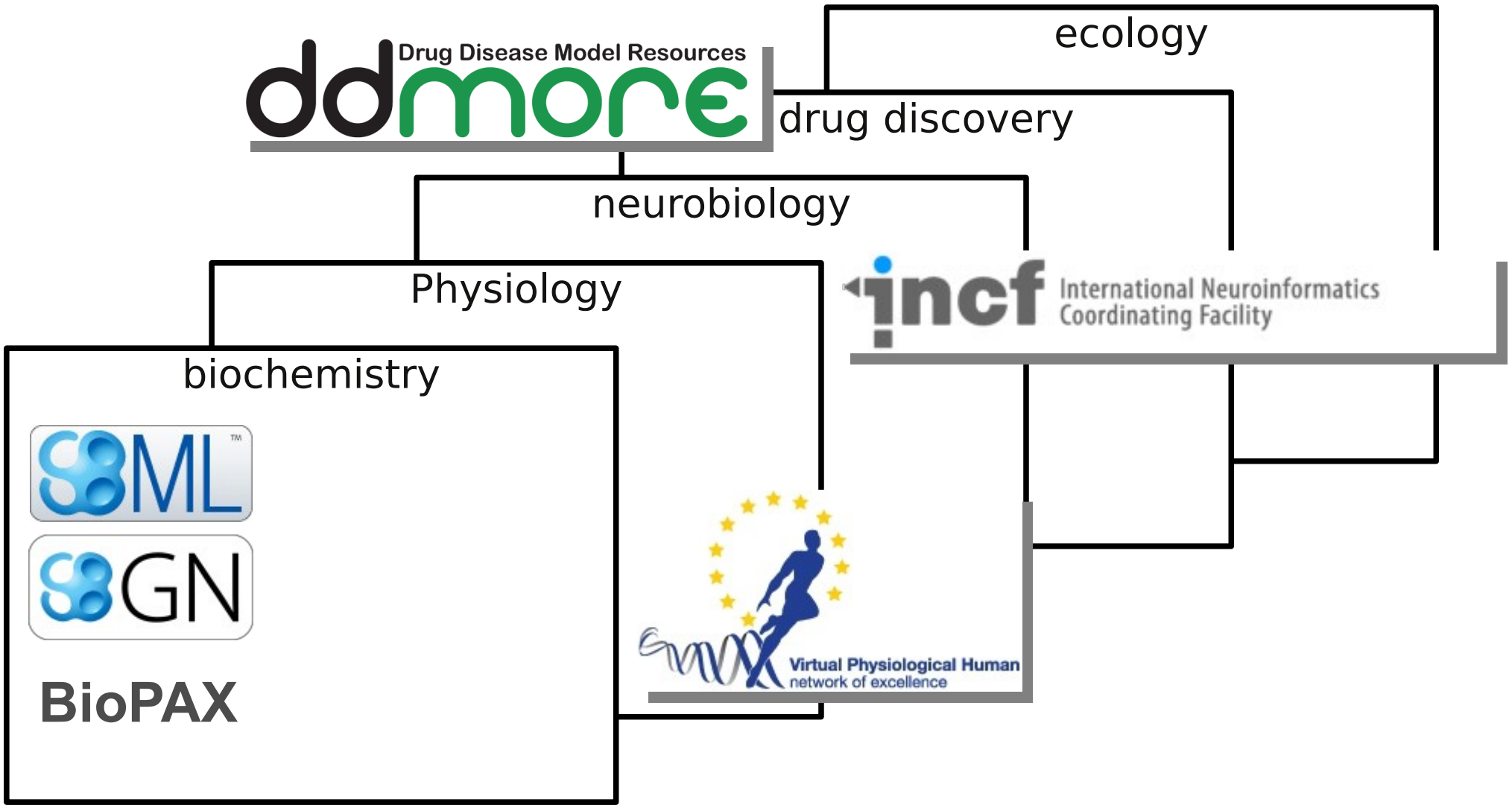
Systems Biology Ontology (SBO) Set of linked controlled vocabularies, defining and relating concepts used in computational modelling in biology. Used in SBML, SBGN, NeuroML

Le Novère et al (2007) *Proc 2nd Intl Symp Exp Std Cond Enz Charact*, 137-153.

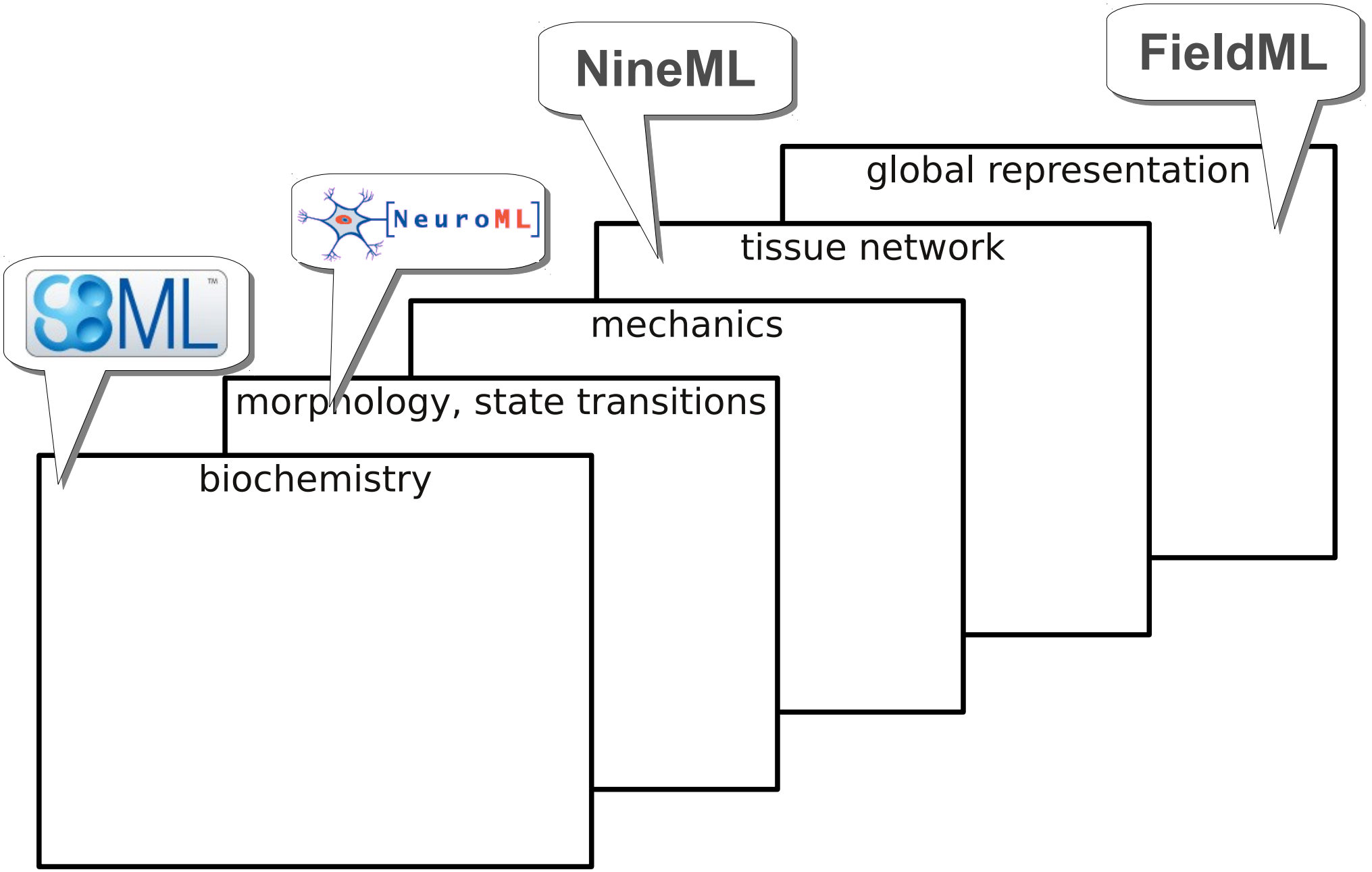
Biological Pathway Exchange (BioPAX) Standard language to represent biological pathways at the molecular and cellular level and to facilitate the exchange of pathway data. Used by most major pathways databases

Demir *et al* (2010) *Nature Biotechnology*, 28: 935–942

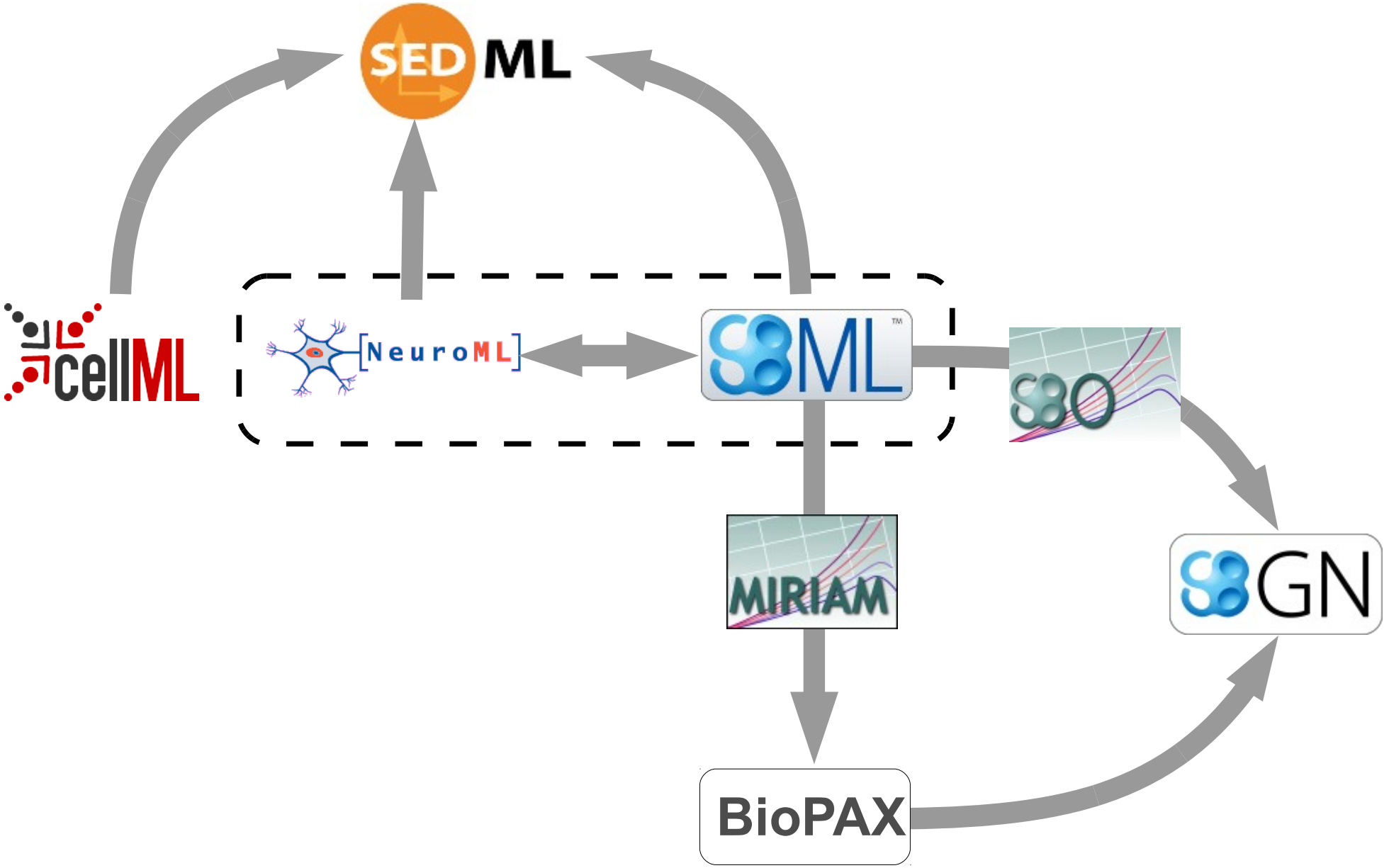
Parallel and redundant efforts



Non-overlapping languages to cover all models



Standards interoperability along the 3 dimensions



Requirements for a overarching standardisation structure

- What?
  - Set of interoperable description languages
  - Cover all aspects of modelling and simulation, all types of descriptions / views of the real
  - Role of community-maintained ontologies.
- How?
  - Independence towards Institutions, funders and individuals
  - Role of European Research Infrastructures? (ELIXIR, ISBE)
- Who?
  - Communities developing their standards: Systems Biology, Physiology (VPH), Neuroscience (INCF), Drug discovery (DDMoRe)
  - Other players in knowledge-representation (W3C, ...)
  - Academic and corporate users: Modeling platforms (MatWorks ...), Pharma (Pistoia alliance) ...

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COmputational Modeling in Biology NEtwork (COMBINE)

The “WorldWide Web consortium” of modelling in biology

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COMBINE 2010

- 6 to 9 October 2010, Edinburgh, before the ICSB
- 81 attendees (forecast was 50 max ...)
- 14 sessions, plus breakouts, 42 presentations, 30 posters

Physiome standards
SED-ML
SBGN languages
libSBGN and SBGN support

Encoding graph layouts
Interactions and reactions
Semantics and metadata resources
Encoding and using semantics

Format conversion
Software support
BioPAX levels
What is not covered yet

SBML Level 3
libSBML and SBML support

followed by:

SBML 10th anniversary

http://sbml.org/Events/Forums/COMBINE_2010

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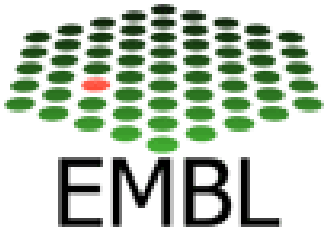
The whole community of Computational Systems Biology

The EBI group Computational Systems Neurobiology



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