EMBL-EBI

Sharing enriched computational models, a cornerstone for Integrative Biology

Nicolas Le Novère, EMBL-EBI

Computational Neurobiology

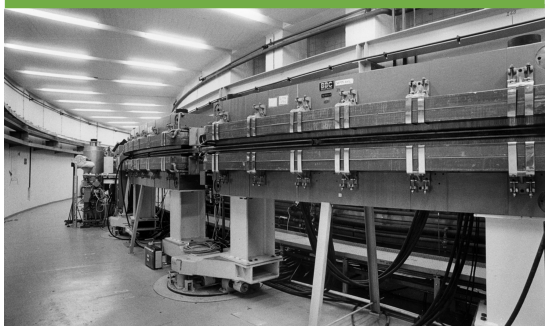
European Molecular Biology Laboratory

- 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

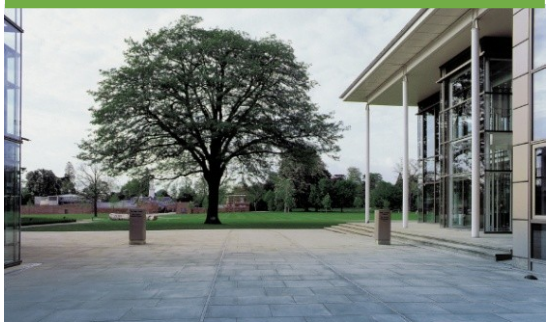
Basic research in molecular biology
Administration
EMBO

Hamburg



Structural biology

Hinxton



Bioinformatics

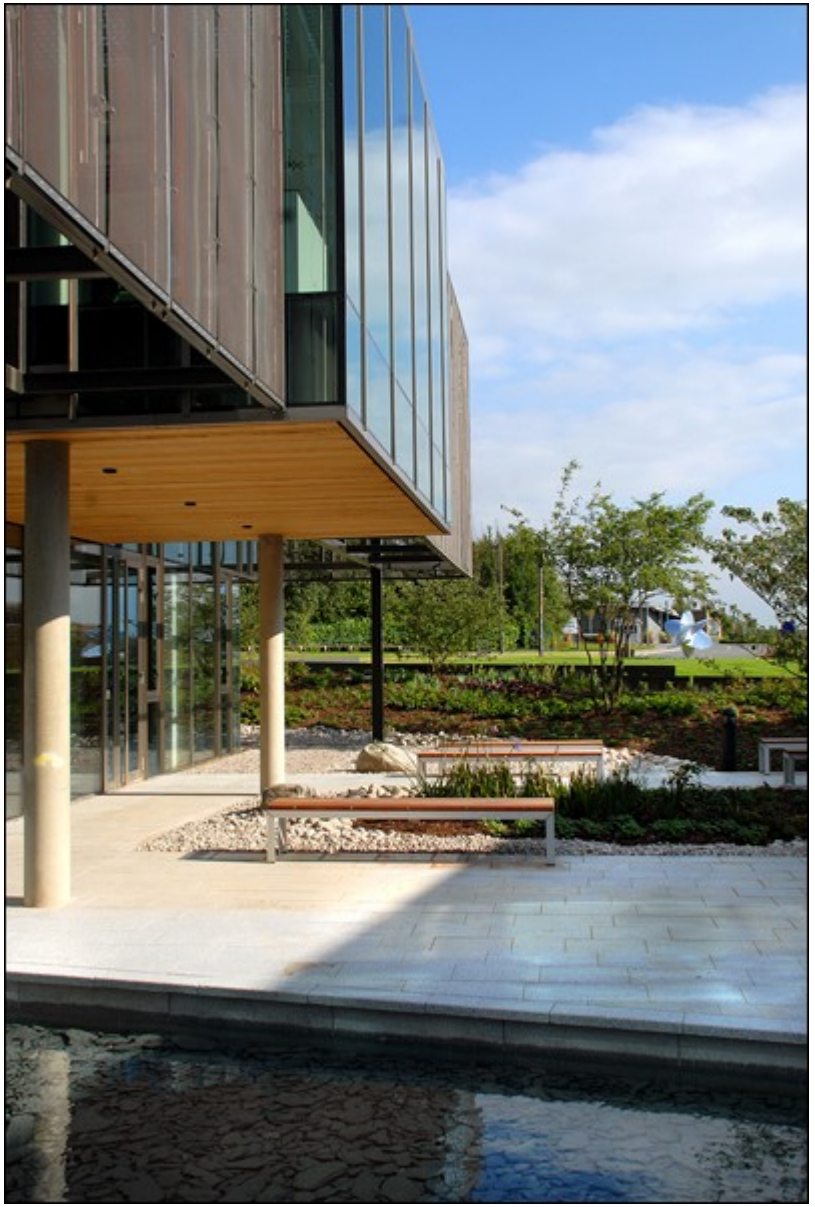
Grenoble

Structural biology

Monterotondo

Mouse biology

EMBL-European Bioinformatics Institute



Provision of services, research and training in Bioinformatics

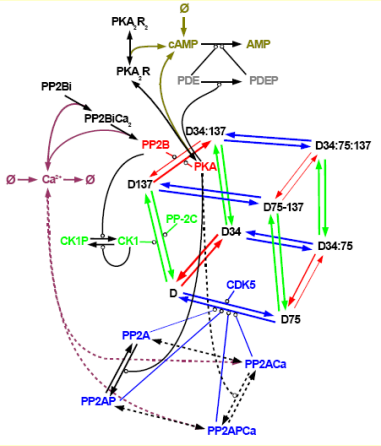
From the molecule to the cell, and the genome to the individual

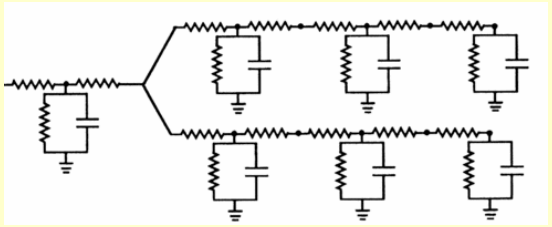
Based on the Wellcome-Trust Genome Campus near Cambridge, UK

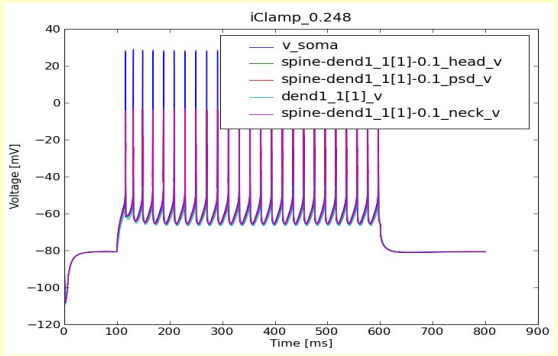
ENA European Nucleotide Archive
Ensembl
UniProt
EMBL-EBI PDBe PROTEIN DATA BANK EUROPE
European Genome-phenome Archive
ArrayExpress
IntAct
PRIDE
BioModels
GO
ChEBI
InterPro
IntEnz
S80

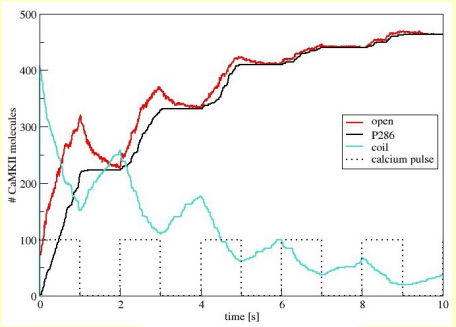
Themes and projects of the “compneur” group

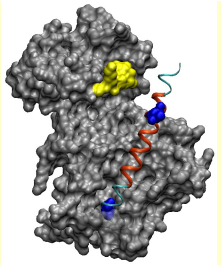
Computational Neurobiology

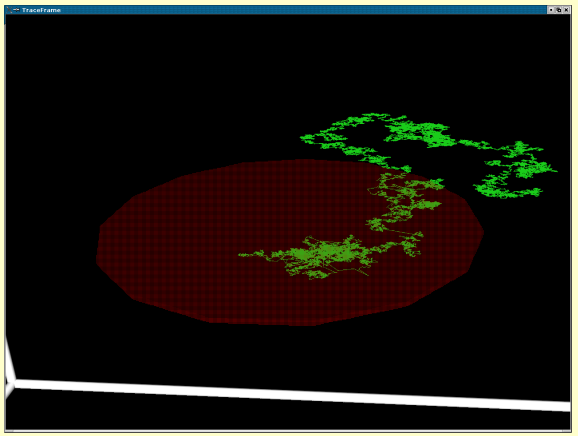










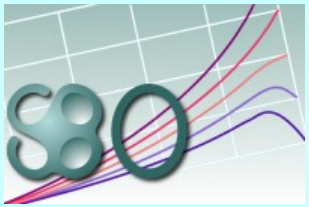


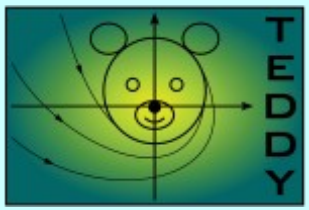
Computational Systems Biology

SED ML

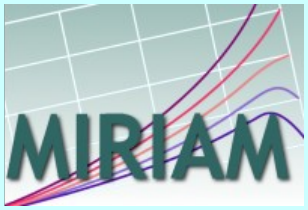
SBML

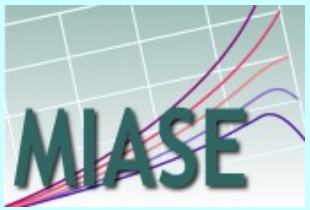
SBGN





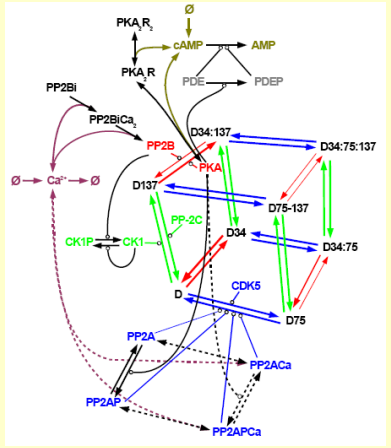
KISAO

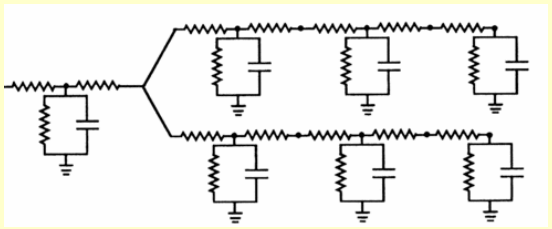


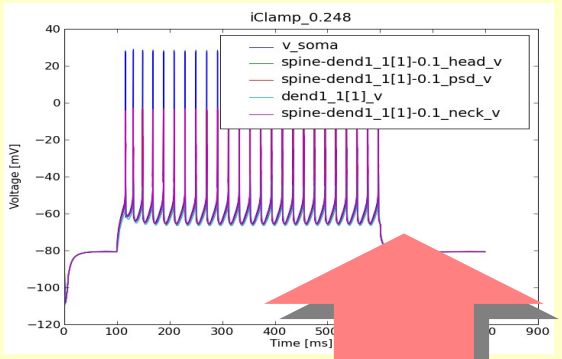


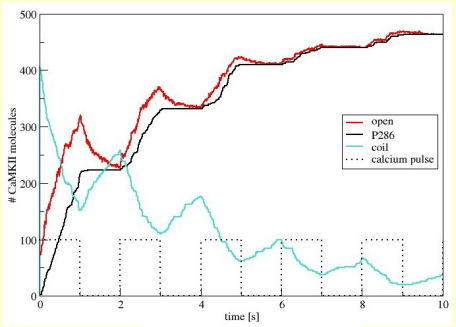
Themes and projects of the “compneur” group

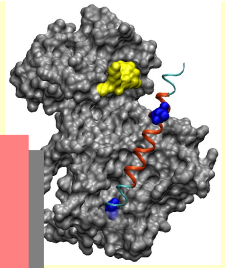
Computational Neurobiology

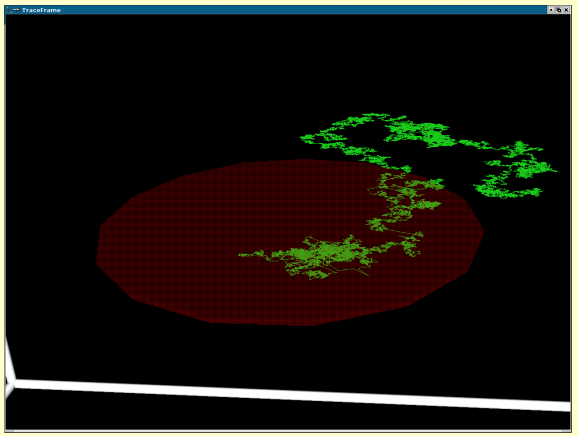




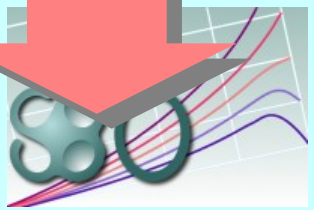


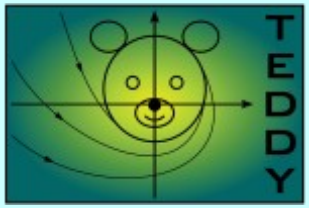


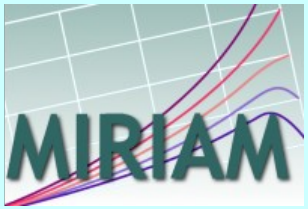


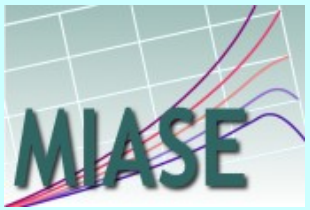


Computational Systems Biology









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

Federal Ministry
of Education
and Research

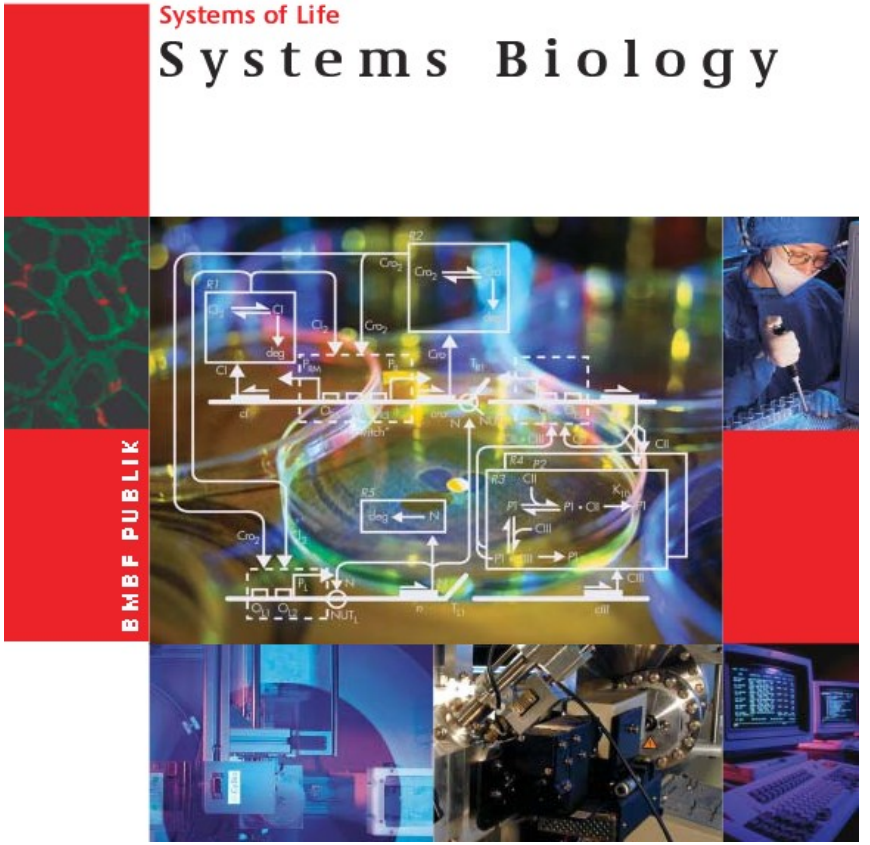
Basic science

REVIEW

Systems Biology: A Brief Overview

Hiroaki Kitano

1 MARCH 2002 VOL 295 SCIENCE www.sciencemag.org



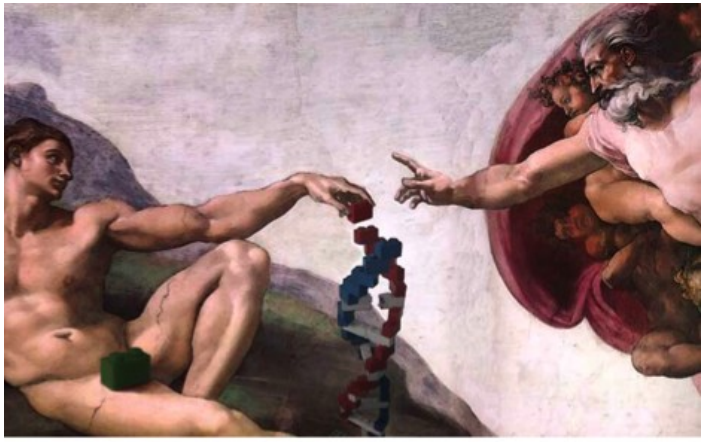
What happened to biology at the end of XXth century?

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

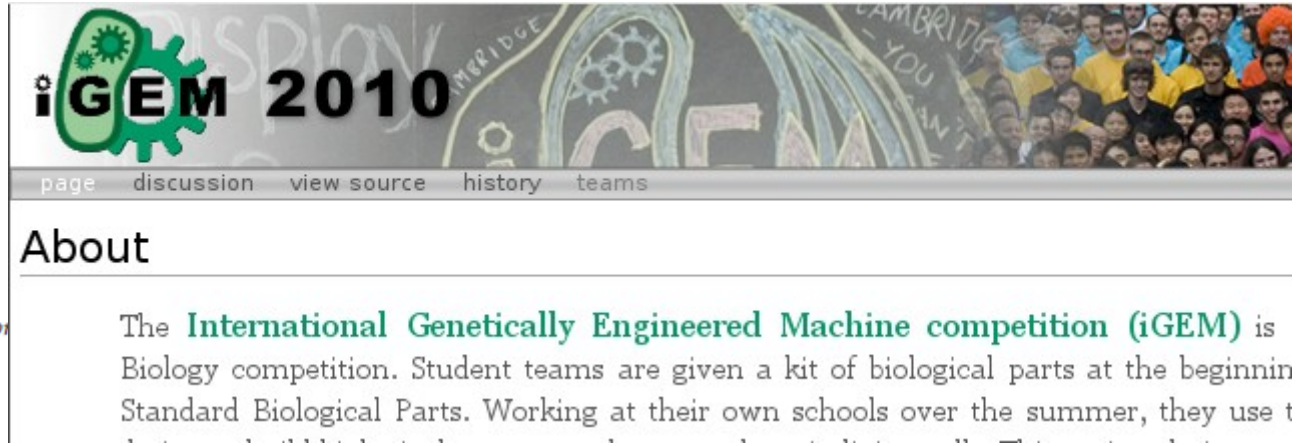
etc group

A synthetic oscillatory network of transcriptional regulators

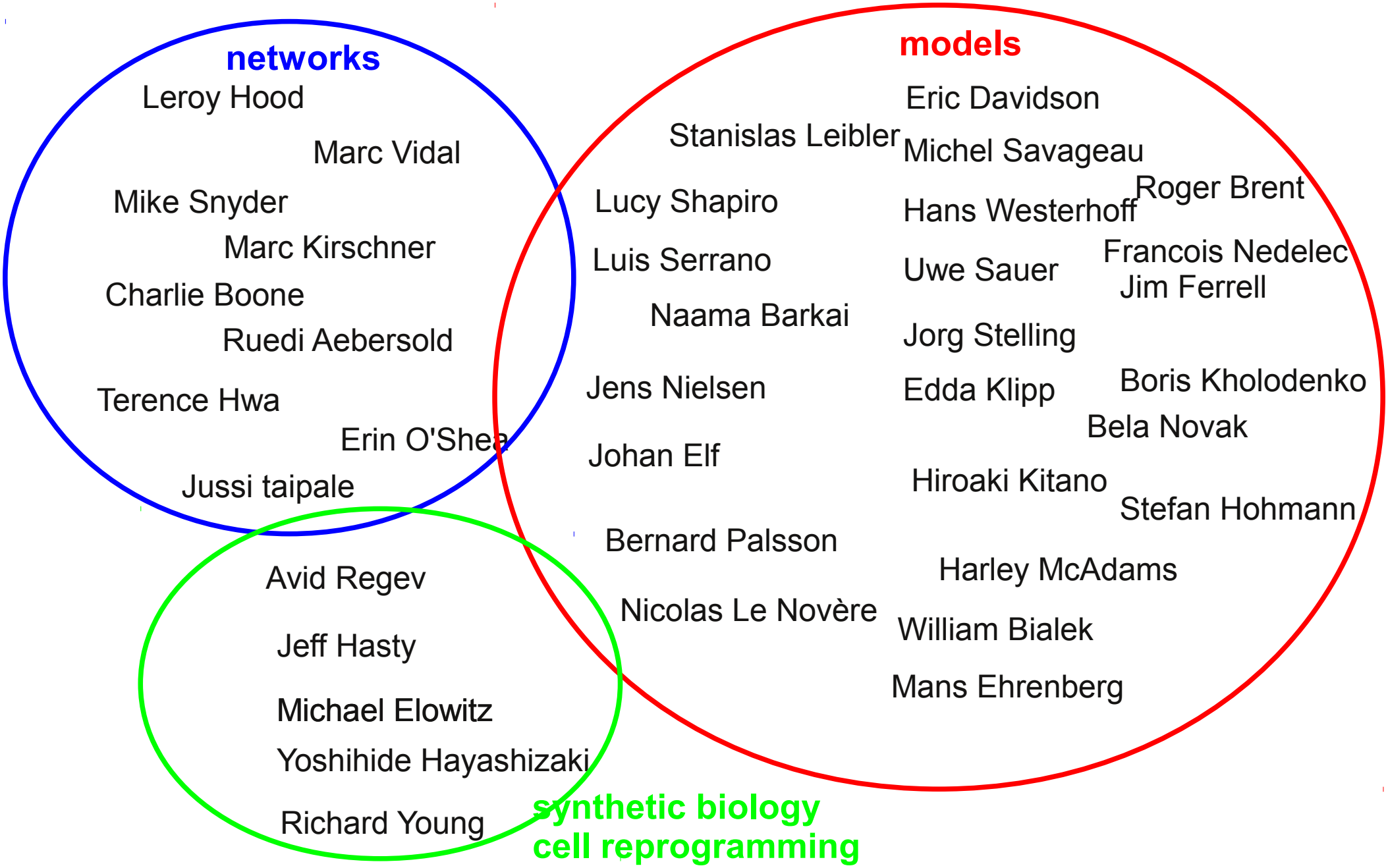
Michael B. Elowitz & Stanislas Leibler

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

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

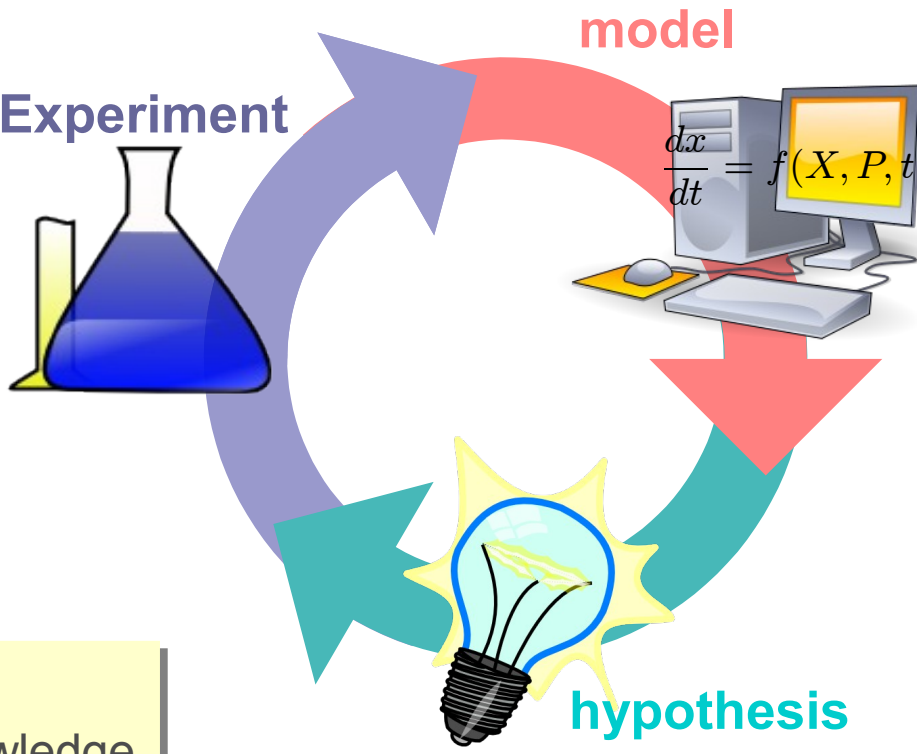


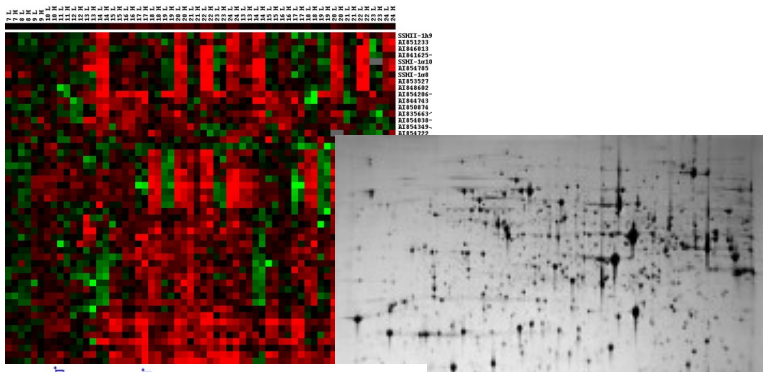
Nobel Symposium on Systems Biology (June 2009)

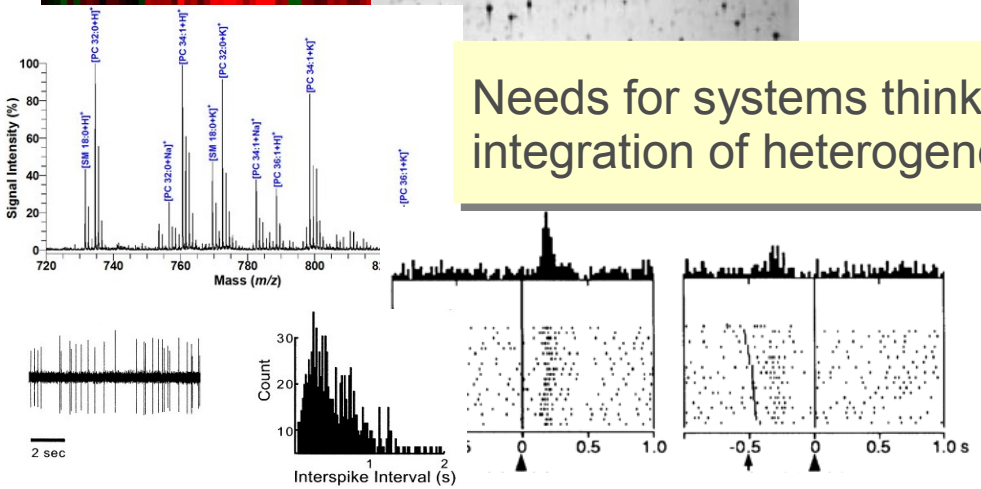


Consequences of this revolution on our activity

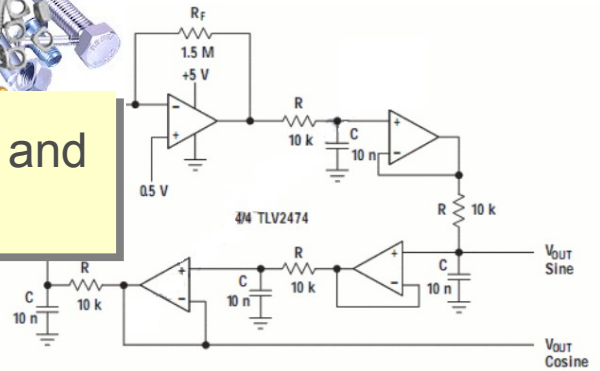
Needs for interplay between models and reality tests







Needs for systems thinking and integration of heterogeneous knowledge

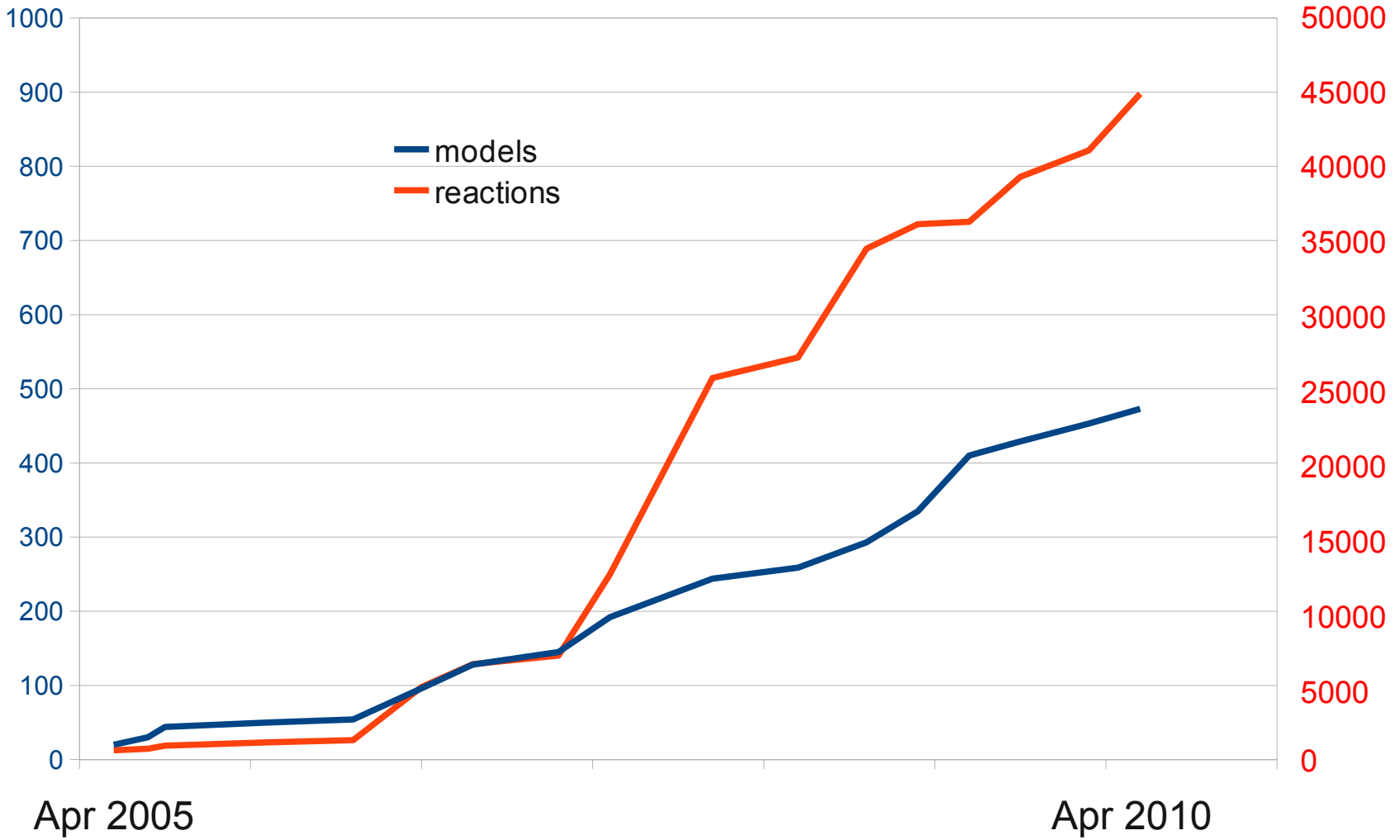


Needs for cooperation and standardisation

Computational modelling for biology and medicine left the niches in the last decades

- 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 17

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

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 pathways, controlled vocabularies, etc.

Search | Go to the model | Advanced search

Browse models

- Curated models (249)
- Browse models using GO
- Non-curated models (224)

Simulate in JWS Online

Submit a model

Mirror at California Institute of Technology http://biomodels.caltech.edu

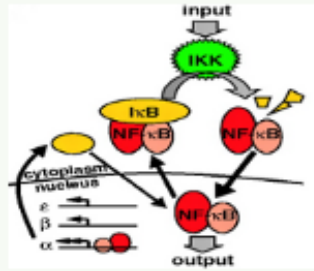
BioModels AT SourceForge http://sourceforge.net/projects/biomodels/

Web Services http://www.ebi.ac.uk/biomodels-main/webservices

Download archived models http://www.ebi.ac.uk/biomodels/models-main/tars/

Model of the month

July, 2010



The activity of the transcription factor NF-κB, is largely controlled by three IκB isoforms (IκBα, IκBβ, IκBε) which upon binding to NF-κB, prevents its association with DNA causing its localization to the cytoplasm. A computational model that describes the temporal control of NF-κB activation by IκB proteins is described here.
Read more...

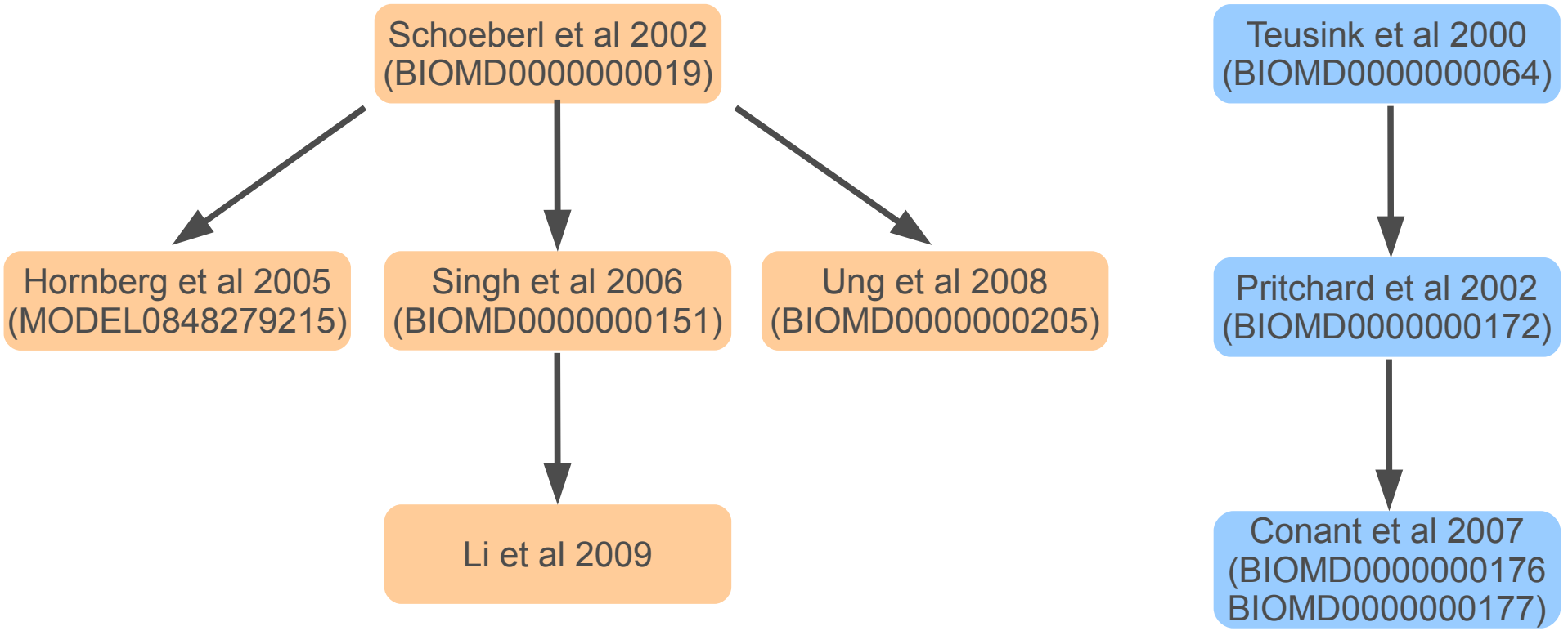
News

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.

2nd June 2010 **SBML to VCML converter updated**
The Virtual Cell recently released a new version of

N. Le Novère, B. Bornstein, A. Broicher, M. Courtot, M. Donizelli, H. Dharuri, L. Li, H. Sauro, M. Schilstra, B. Shapiro, J.L. Snoep, M. Hucka. BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems. (2006) *Nucleic Acids Research*, 34: D689-D691.

Direct model re-use: EGFR signalling and glycolysis



Models at the core of integrative systems bio/physio/neurobiology

- As any kind of output from scientific research, models must be available to the scientific community: Results based on a model that is not distributed cannot be verified and falsified. This is not valid and useful science
- Computational models must be exchanged:
  computer storable and readable
- Computational models must be related to relevant experimental datasets:
  expressive relationships and robust links
- Computational models must be amenable to many different analyses:
  standard API
- Computational models must allow modification, split, merge:
  Encoded according a suitable design

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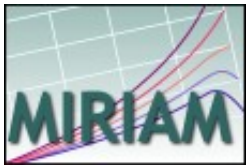
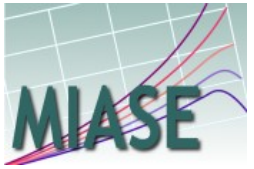
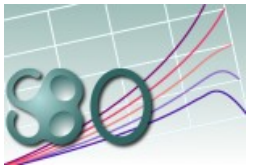
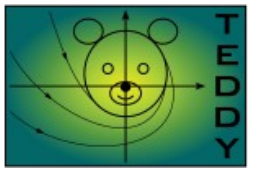
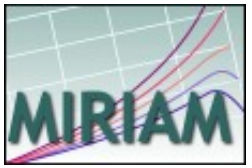
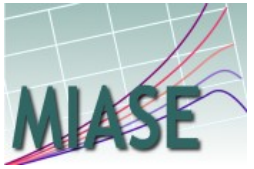
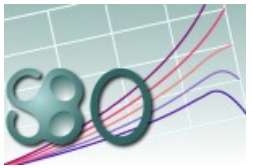
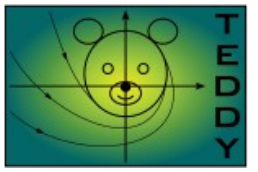
➔ Standardisation is unavoidable!

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

	Models	Simulation	Results
Minimal requirements			
Data-models			SBRML
Ontologies			

Model description

	Models	Simulation	Results
Minimal requirements			
Data-mode			SBRML
Ontologies			

Hucka M., Bolouri H., Finney A., Sauro H.M., Doyle J.C., Kitano H.Arkin A.P., Bornstein B.J., Bray D., Cornish-Bowden A., Cuellar A.A., Dronov S., Ginkel M., Gor V., Goryanin I.I., Hedley W.J., Hodgman T.C., Hunter P.J., Juty N.S., Kasberger J.L., Kremling A., Kummer U., Le Novère N., Loew L.M., Lucio D., Mendes P., Mjolsness E.D., Nakayama Y., Nelson M.R., Nielsen P.F., Sakurada T., Schaff J.C., Shapiro B.E., Shimizu T.S., Spence H.D., Stelling J., Takahashi K., Tomita M., Wagner J., Wang J.et al (2003). The Systems Biology Markup Language (SBML): A Medium for Representation and Exchange of Biochemical Network Models. *Bioinformatics*, 19: 524-531.

What is SBML?

The Systems Biology Markup Language is a way to **exchange and reuse** (and hopefully **interface**) descriptions of quantitative models in "Systems Biology", in fact mostly well-stirred chemical kinetics so far.

It is not a procedural language.

It is not a programming language.

It is not a format for specific software configuration files

(only 3 of the 7 SBML founding software are still maintained today).

Development philosophy: Start small, get good support, extend.

SBML itself re-uses other standards: XML, MathML, XHTML, RDF, existing ontologies.

It is supported by a community large, diverse, active and **evolving.**

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>
```

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    <listOfSpecies> <!-- --> </listOfSpecies>
    <listOfParameters> <!-- --> </listOfParameters>
    <listOfInitialAssignments> <!-- --> </listOfInitialAssignments>
    <listOfRules> <!-- --> </listOfRules>
    <listOfConstraints> <!-- --> </listOfConstraints>
    <listOfReactions> <!-- --> </listOfReactions>
    <listOfEvents> <!-- --> </listOfEvents>
  </model>
</sbml>
```

variables

relationships

A very simple SBML file

```
<?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>
```

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              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

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    <listOfSpecies>
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              <ci>A</ci>
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          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

A very simple SBML file

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              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

A very simple SBML file

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<?xml version="1.0" encoding="UTF-8"?>
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    <listOfSpecies>
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              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

MathML

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

XHTML

RDF

SBML is not limited to biochemistry!

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

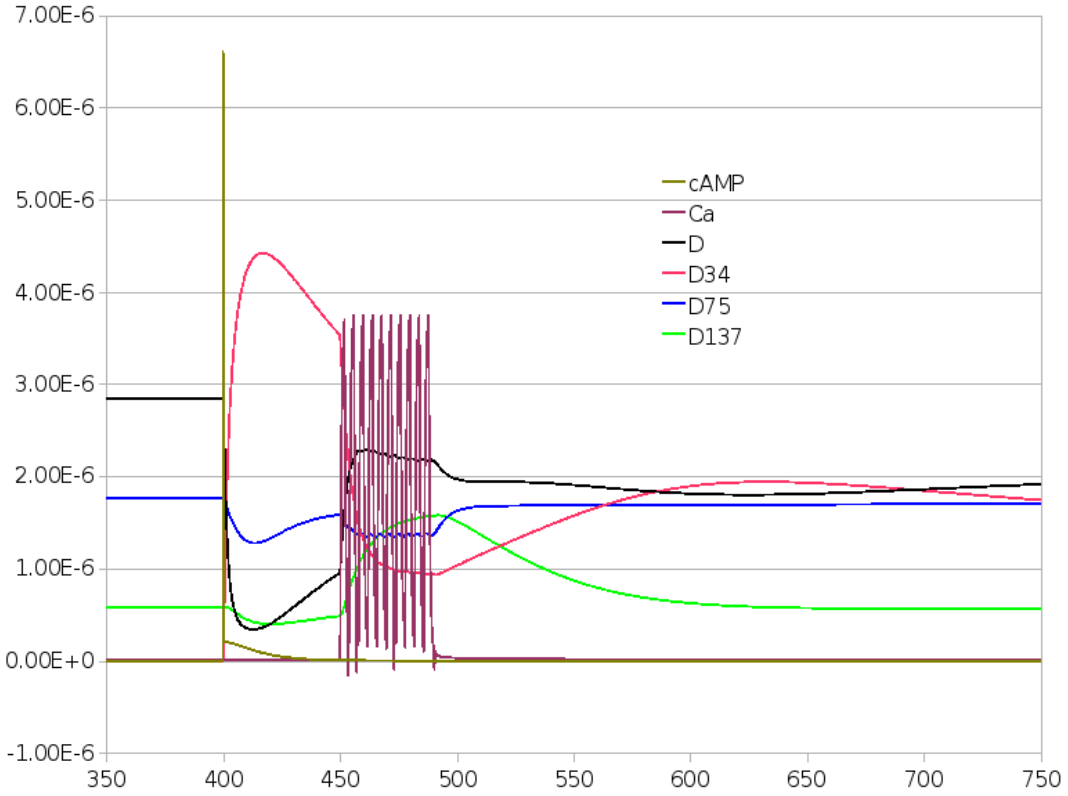
Events can describe any discontinuous change, e.g. neurotransmitter release or repolarisation;

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

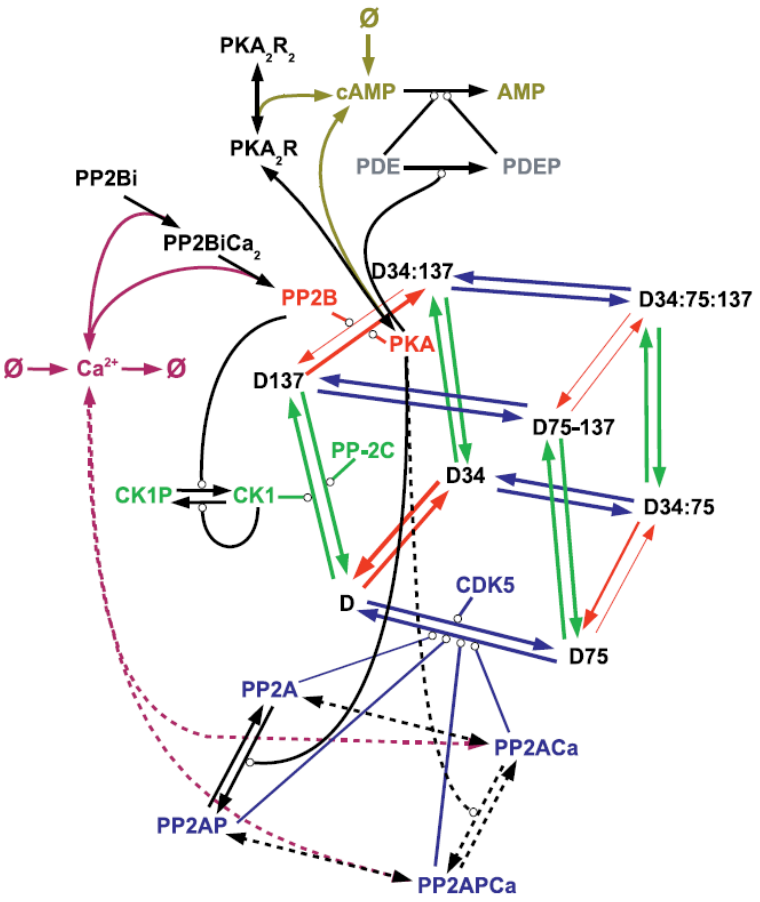
➔ SBML is about process descriptions

Model of signalling pathways



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

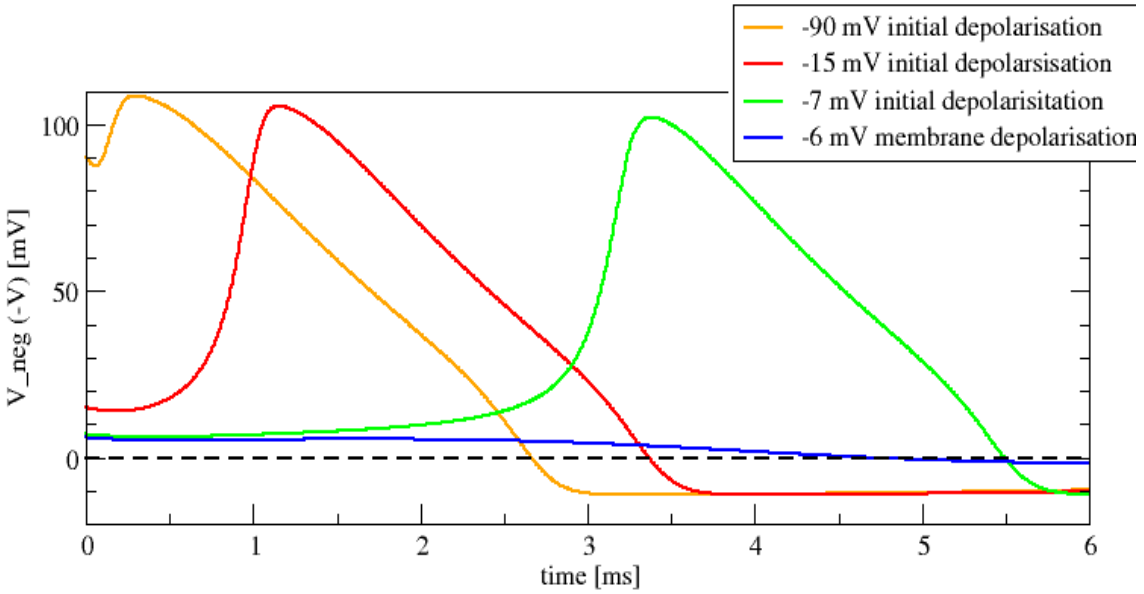
BIOMD0000000153



reaction:

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

Conductance-based model



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

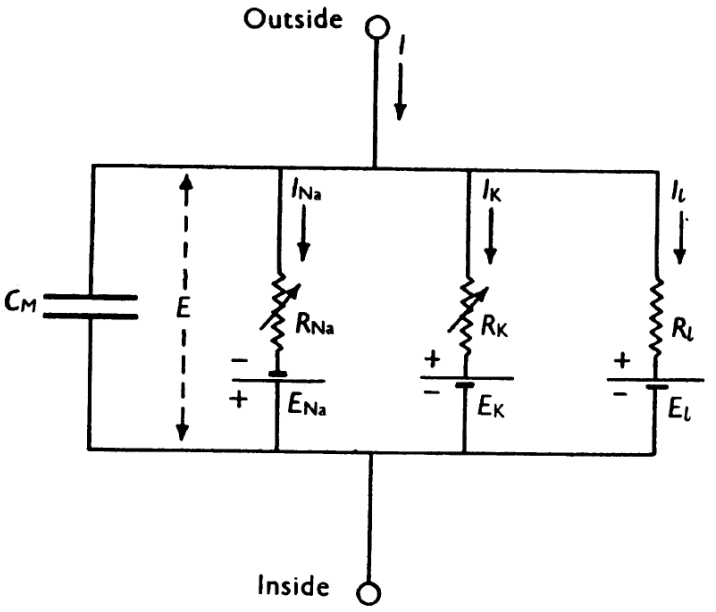
BIOMD0000000020

rate rule:

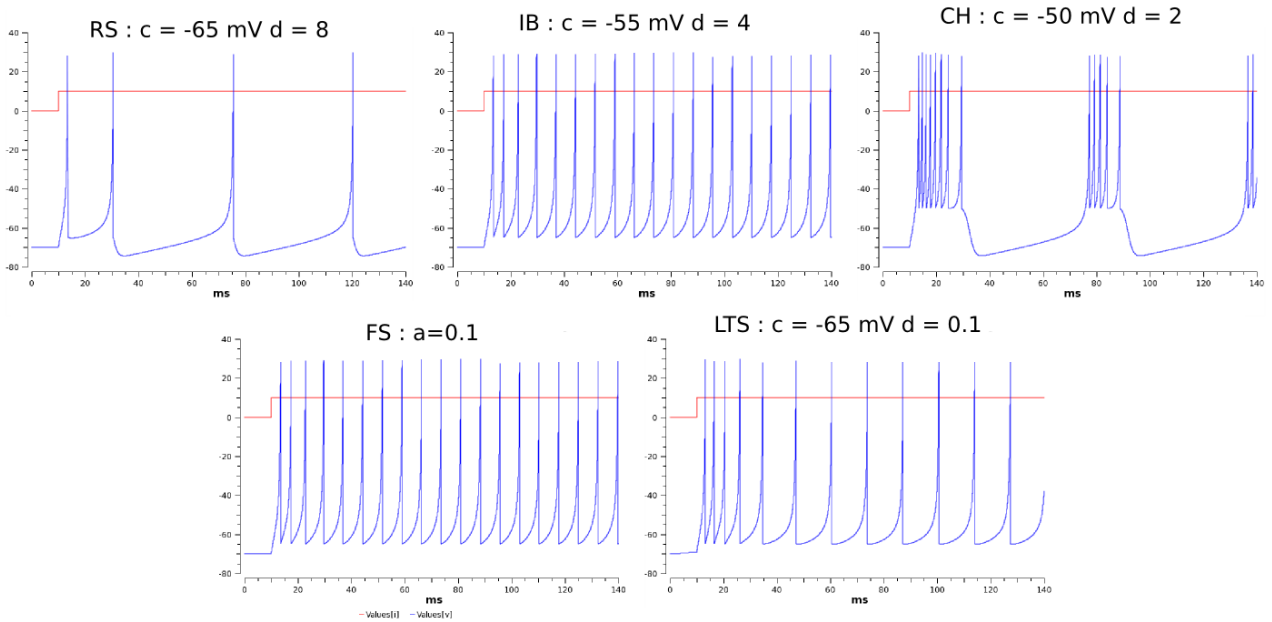
$$\frac{dv}{dt} = \frac{I - (i_{Na} + i_K + i_L)}{C_m}$$

assignment rule:

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



Single-compartment neurons



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

BIOMD0000000127

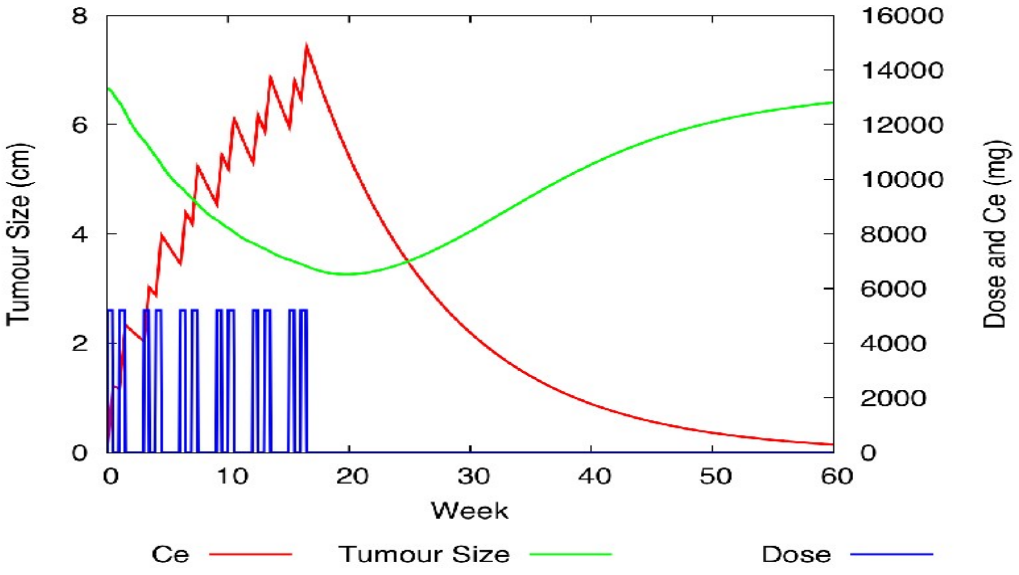
rate rule:

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

event:

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

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

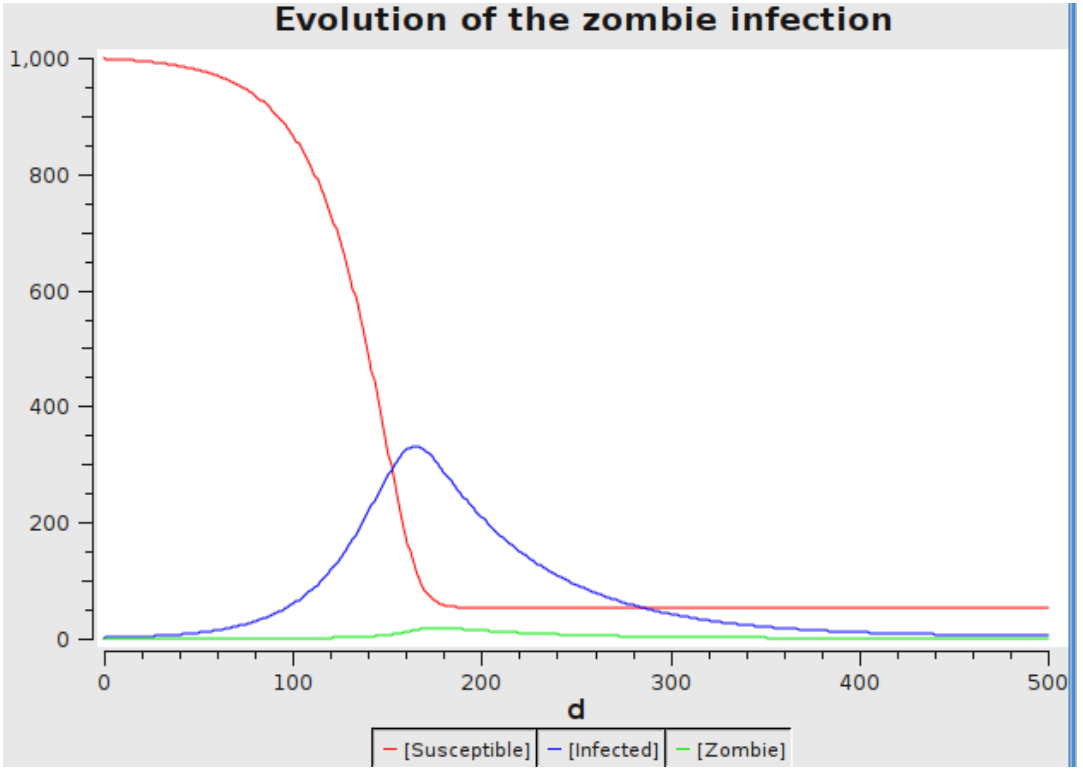
rate rule:

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

assignment rule:

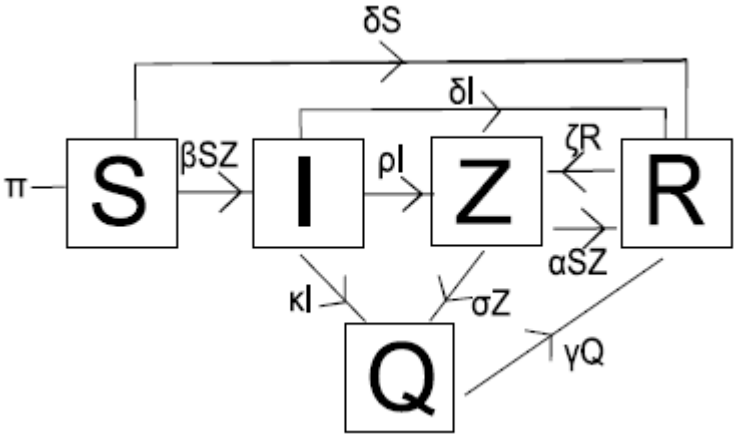
$$Effect = 1 - \frac{E_{max} - Ce}{Amt_{50} + Ce}$$

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



Difference between SBML L1, L2 and L3

L1	L2	L3
predefined functions	function definitions	function definitions
proprietary infix math notation	all math in MathML	all math in MathML
reserved namespaces for annotation	no reserved namespaces for annotations	no reserved namespaces for annotations
no controlled annotation	controlled RDF annotation	controlled RDF annotation
no discrete events	discrete events	discrete events
monolithic	monolithic	modular
default values	default values	no default values

Progressive simplification, generalisation and externalisation

SBML Level 3 packages

- Core package – Release candidate
- Graph Layout – specification finalised
- Complex species – specification finalised
- Groups - specification finalised
- Model composition – specification under discussion
- Qualitative models – specification under discussion
- Distributions and ranges - specification under discussion
- Graph rendering – specification proposed
- Arrays and sets – specifications proposed
- Geometry - specification proposed
- Spatial diffusion – specification proposed
- Dynamic structures - needed

???

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: **188**

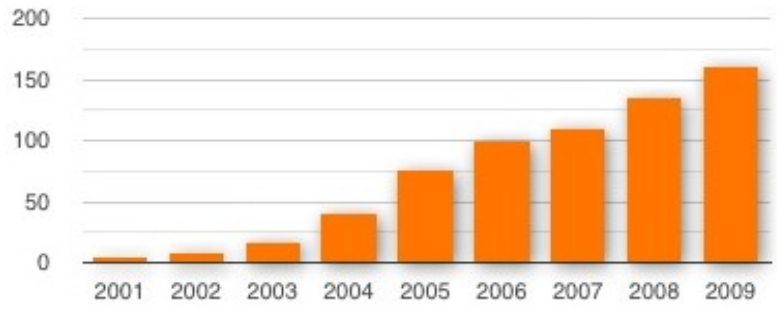
Please **use the survey form** to notify us about additions and suggestions.

Go to the SBML Software Matrix

Go to the SBML Software Summary

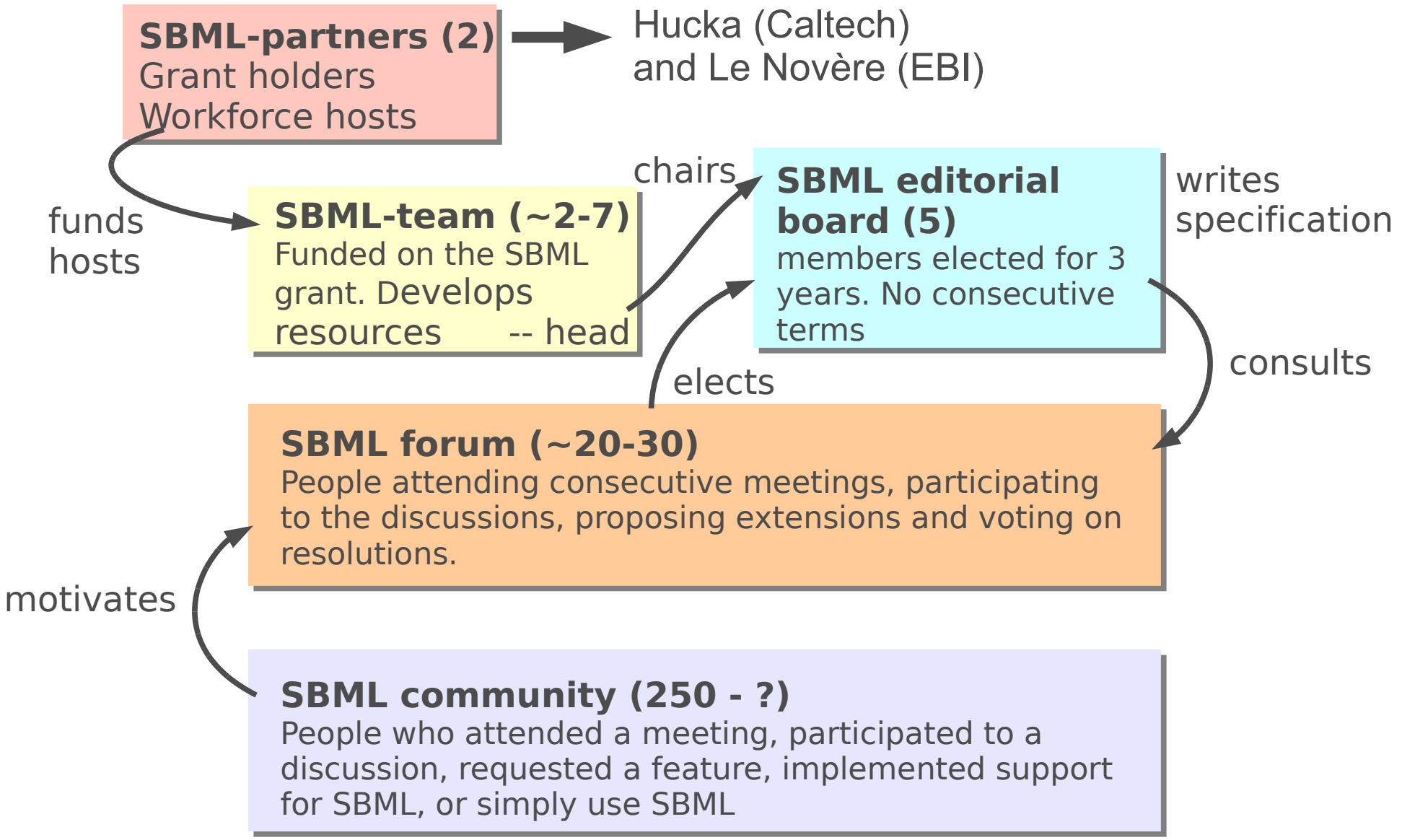
Historical trend

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.

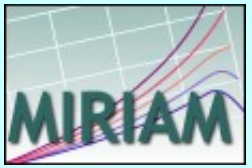
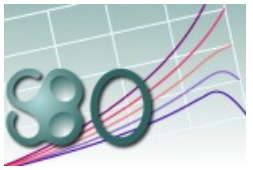
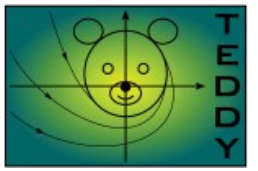


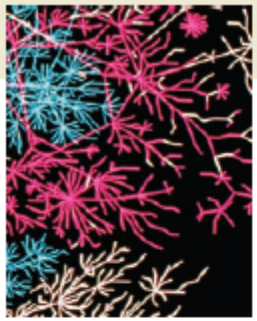
(Note: the flat period in 2007 is an artifact of inadequate record keeping rather than a lull in SBML software development.)

Current structure of the SBML community



Model semantics

	Models	Simulation	Results
Minimal requirements			
Data-models			SBRML
Ontologies			



_computational BIOLOGY

PERSPECTIVE

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

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

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

Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main causes for incomplete model descriptions. With today's increased interest in detailed biochemical models, it is necessary to define a minimum quality standard for the encoding of those models. We propose a set of rules for curating quantitative models of biological systems. These rules define procedures for encoding and annotating models represented in machine-readable form. We believe their

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

MIRIAM compliance

Models must :

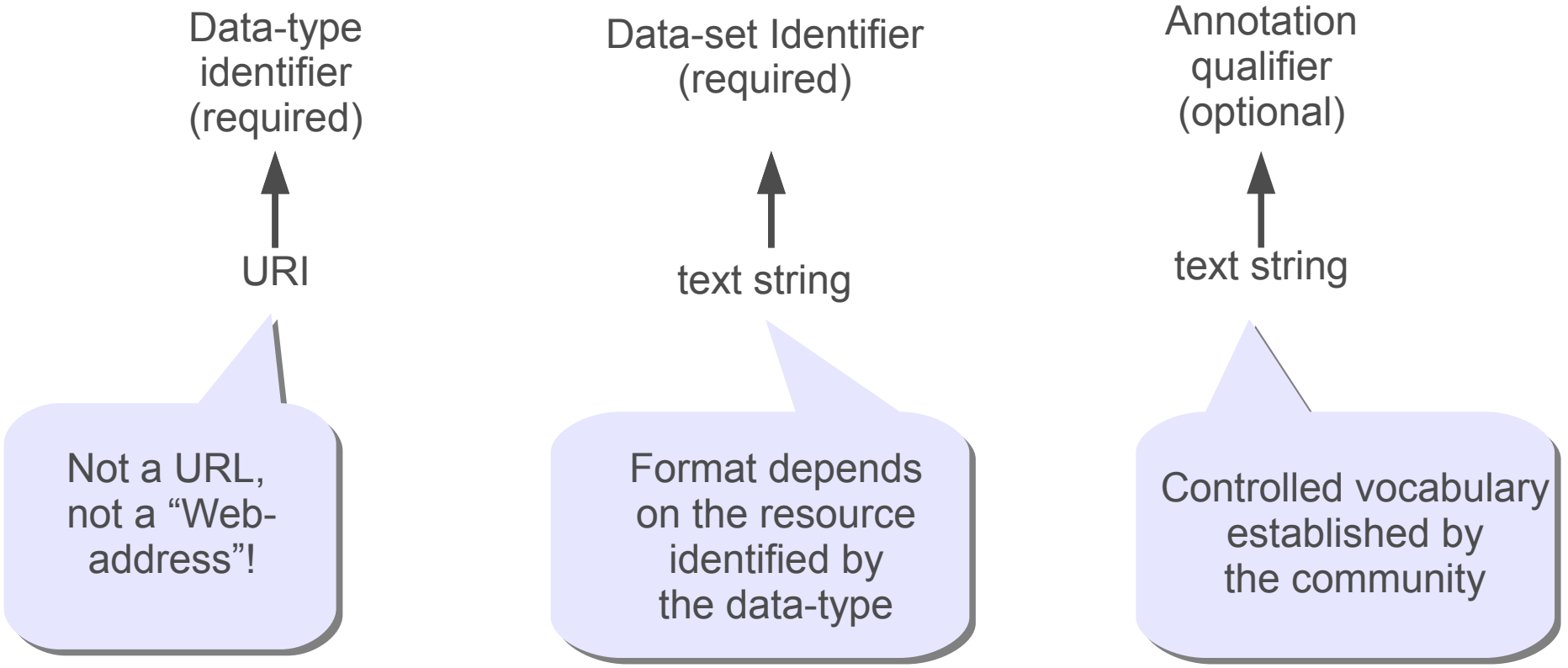
- be encoded in a public machine-readable format
- be clearly linked to a single reference description
- reflect the structure of the biological processes described in the reference paper (list of reactions etc.)
- be instantiable in a simulation (possess initial conditions etc.)
- be able to reproduce 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 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

- Browse
- Search
- Tags
- 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.

Moreover,

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 C., Le Novère N. MIRIAM Resources: tools to generate and resolve robust cross-references in Systems Biology. BMC Systems Biology (2007), 1: 58.

Data type: *Enzyme Nomenclature*

General | Tags | Annotation

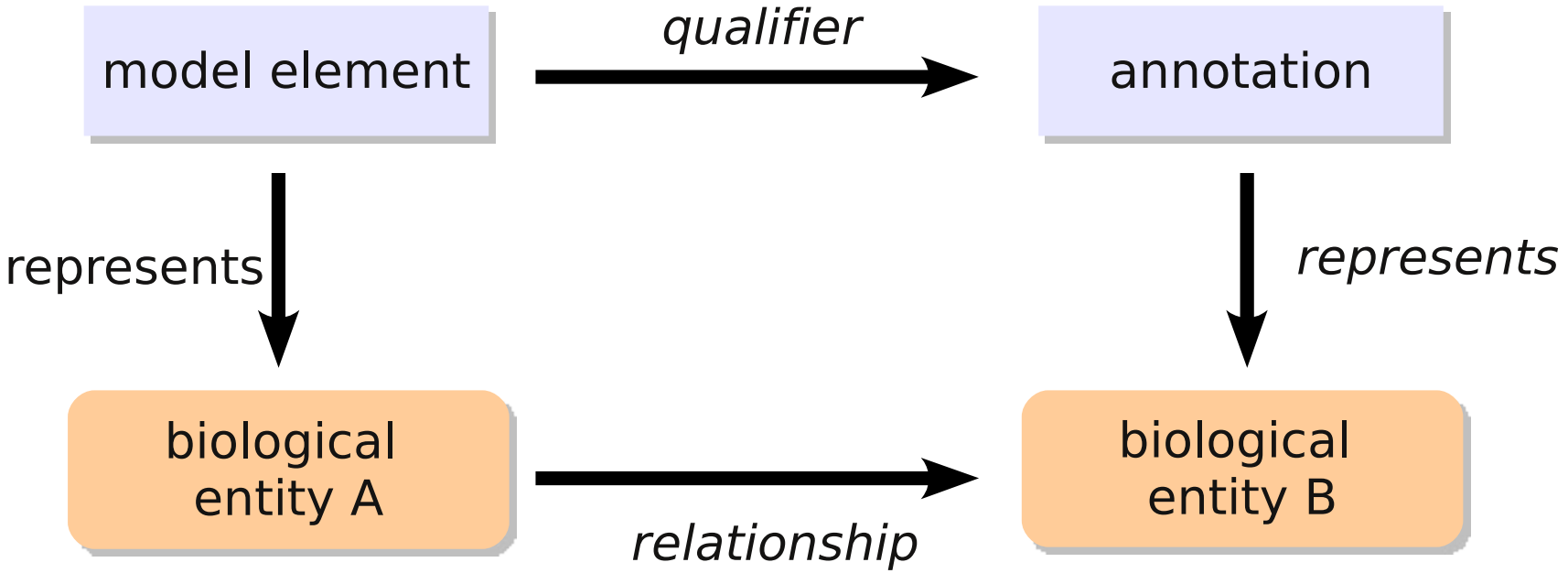
General information about the data type

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

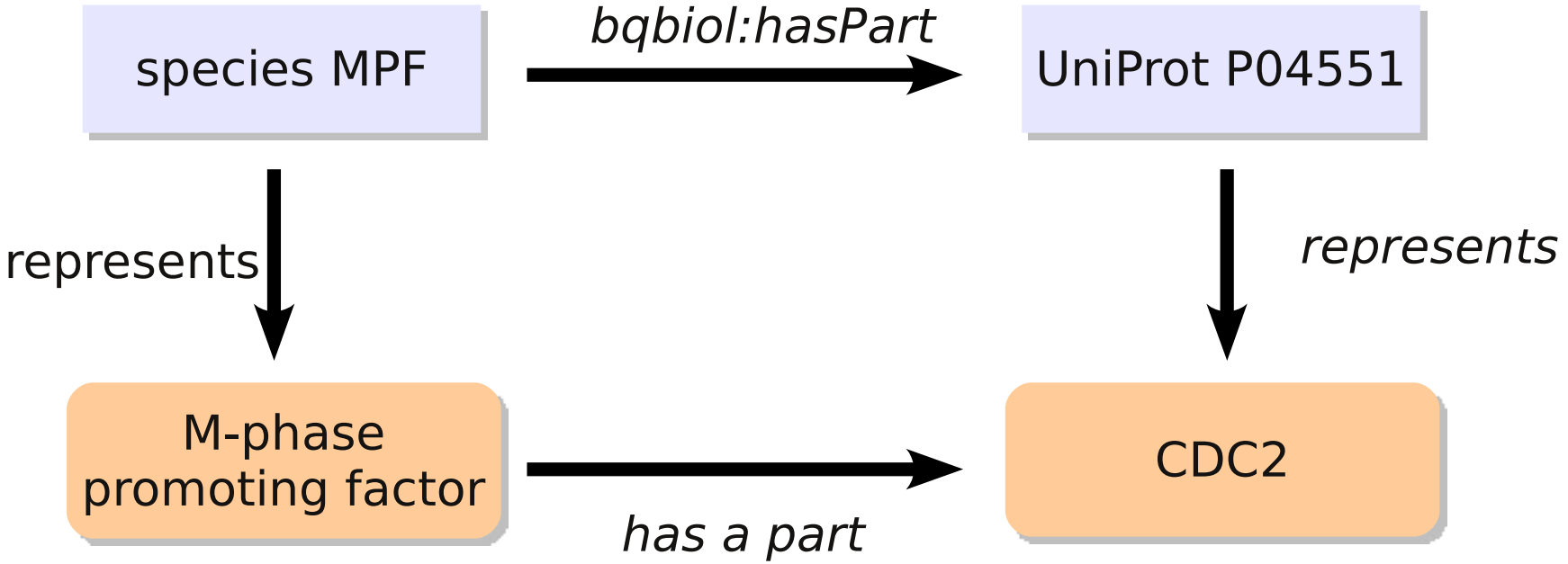
Go back to the list of data types

Edit this data type

Qualification of annotation



Qualification of annotation



SBML and MIRIAM cross-references

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  <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)
- MIRIAM Resources statistics
  - ~5000 web page requests per month
  - ~550000 web service requests per month
- 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)


0
KEGG_Reaction:R01429
042 Nielsen1998_Glycolysis
015 Curto1998_purineMetabol
070 Holzhutter2004_Erythrocyte_Metabolism
051 Chassagnole2002_Carbon_Metabolism
088 Maeda2006_MyosinPhosphorylation
071 Bakker2001_Glycolysis
064 Teusink2000_Glycolysis
063 Galazzo1990_pathway_kinetics
061 Hynne2001_Glycolysis
042 Nielsen1998_Glycolysis
013 Poolman2004_CalvinCycle
018 Morrison1989_FolateCycle
017
056 Chen2004_CellCycle
106 Yang2007_ArachidonicAcid
049 Sasagawa2005_MAPK

http://www.semanticsbml.org/semanticSBML/default/cluster/0

Semantic SBML

semanticSBML 2.0

- HOME
- REST API

Login

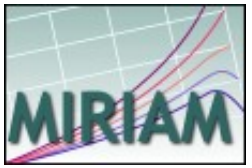
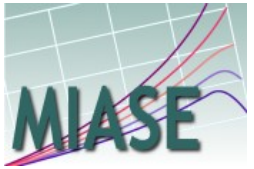
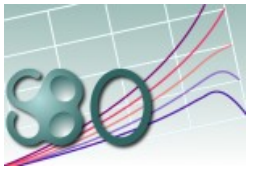
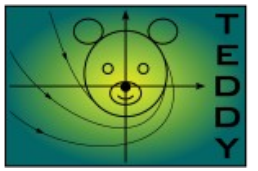
BioModels Similar to BIOMD0000000009.xml

Model	BioModel	Score	Bar Chart
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.0	
Levchenko2000_MAPK_noScaffold	BIOMD0000000011	0.925093068877	
Levchenko2000_MAPK_Scaffold	BIOMD0000000014	0.86507748228	
Kholodenko2000_MAPK_feedback	BIOMD0000000010	0.816212542046	
Markevich2004_MAPK_orderedElementary	BIOMD0000000026	0.737035170293	
Markevich2004_MAPK_phosphoRandomElementary	BIOMD0000000028	0.68757623681	
Markevich2004_MAPK_AllRandomElementary	BIOMD0000000030	0.68757623681	
Markevich2004_MAPK_orderedMM	BIOMD0000000027	0.67292654353	
Markevich2004_MAPK_orderedMM2kinases	BIOMD0000000031	0.67292654353	
Markevich2004_MAPK_phosphoRandomMM	BIOMD0000000029	0.614419563376	
Hornberg2005_ERKcascade	BIOMD0000000084	0.467502293047	
McClean2007_CrossTalk	BIOMD0000000116	0.396968852299	
Kofahl2004_pheromone	BIOMD0000000032	0.347654497489	
Kim2007_Wnt_ERK_Crosstalk	BIOMD0000000149	0.323862350322	
Brown2004_NGF_EGF_signaling	BIOMD0000000033	0.259659012885	
Goldbeter1995_CircClock	BIOMD0000000016	0.243985892215	
Sasagawa2005_MAPK	BIOMD0000000049	0.239991163172	
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.233723629425	
Leloup1999_CircClock	BIOMD0000000021	0.22918483858	
Goldbeter1991_MinMitOscil_ExpInact	BIOMD0000000004	0.222401483635	
Goldbeter1991_MinMitOscil	BIOMD0000000003	0.213676433868	
Leloup1998_CircClock_LD	BIOMD0000000171	0.201464719898	
Tyson1991_CellCycle_6var	BIOMD0000000005	0.199125864464	
Veening2008_DegU_Regulation	BIOMD0000000240	0.179667408207	
Neves2008_Cell_Shape	BIOMD0000000182	0.168237862604	
Fisher2006_Ca_Oscillation_dpdnt_NFAT_dynamics	BIOMD0000000122	0.163742528861	
Leloup2003_CircClock_DD	BIOMD0000000073	0.163249339887	
Leloup2003_CircClock_LD	BIOMD0000000078	0.163249339887	
Novak2001_FissionYeast_CellCycle	BIOMD0000000111	0.158121867453	
Kholodenko1999_EGFRsignaling	BIOMD0000000048	0.157261597224	
Swat2004_Mammalian_G1_S_Transition	BIOMD0000000228	0.153857976349	
Chen2004_CellCycle	BIOMD0000000056	0.153626692372	

R. Henkel, L. Endler, A. Peters, N. Le Novère, D. Waltemath (2010) Ranked Retrieval of Computational Biology Models. *BMC Bioinformatics*, 11:423

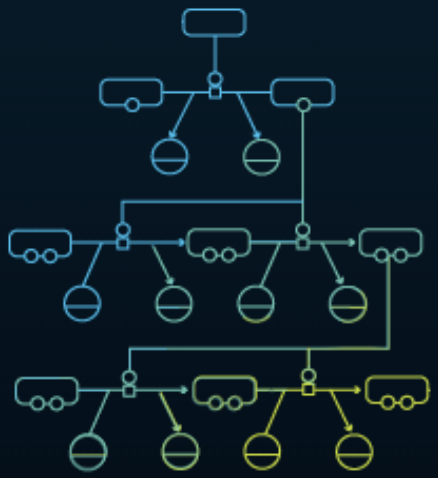
M Schulz, F Krause, N Le Novère, E Klipp, and W Liebermeister: Comparison and clustering of biochemical network models based on semantic annotations. *submitted*

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,

SBGN News

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

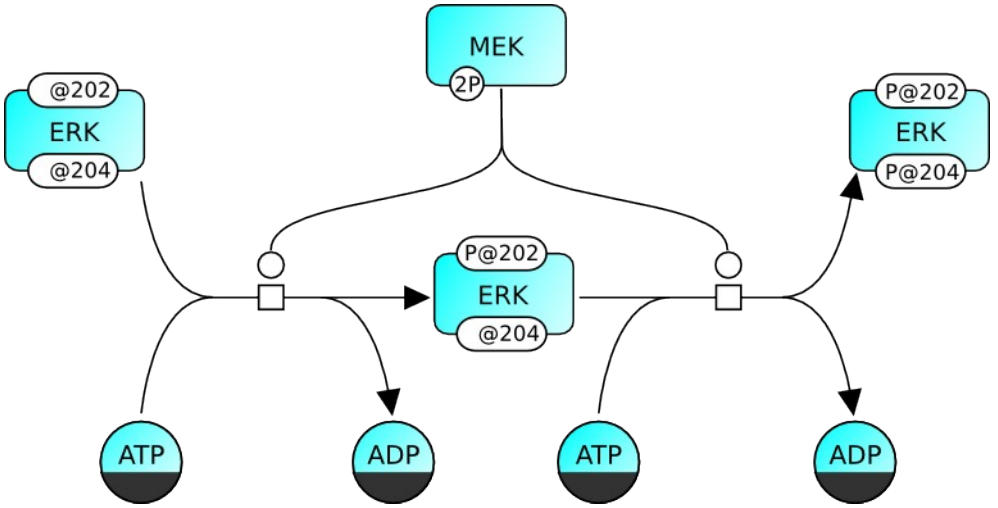
N. Le Novère, M. Hucka, H. Mi, S. Moodie, F. Shreiber, A. Sorokin, et al (2009). The Systems Biology Graphical Notation. *Nature Biotechnology*, 27: 735-741.

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.

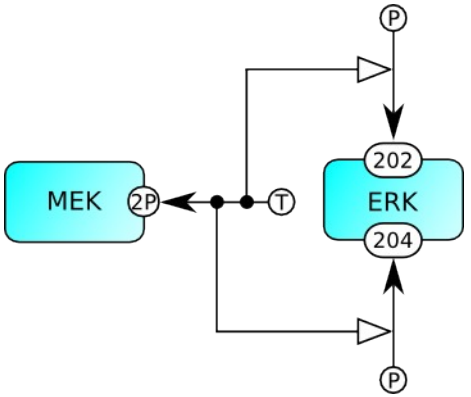
Graph trinity: three languages in one notation

Process Descriptions



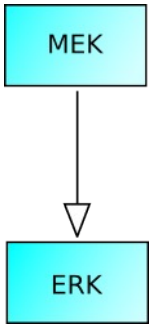
- Unambiguous
- Mechanistic
- Sequential
- Combinatorial explosion

Entity Relationships



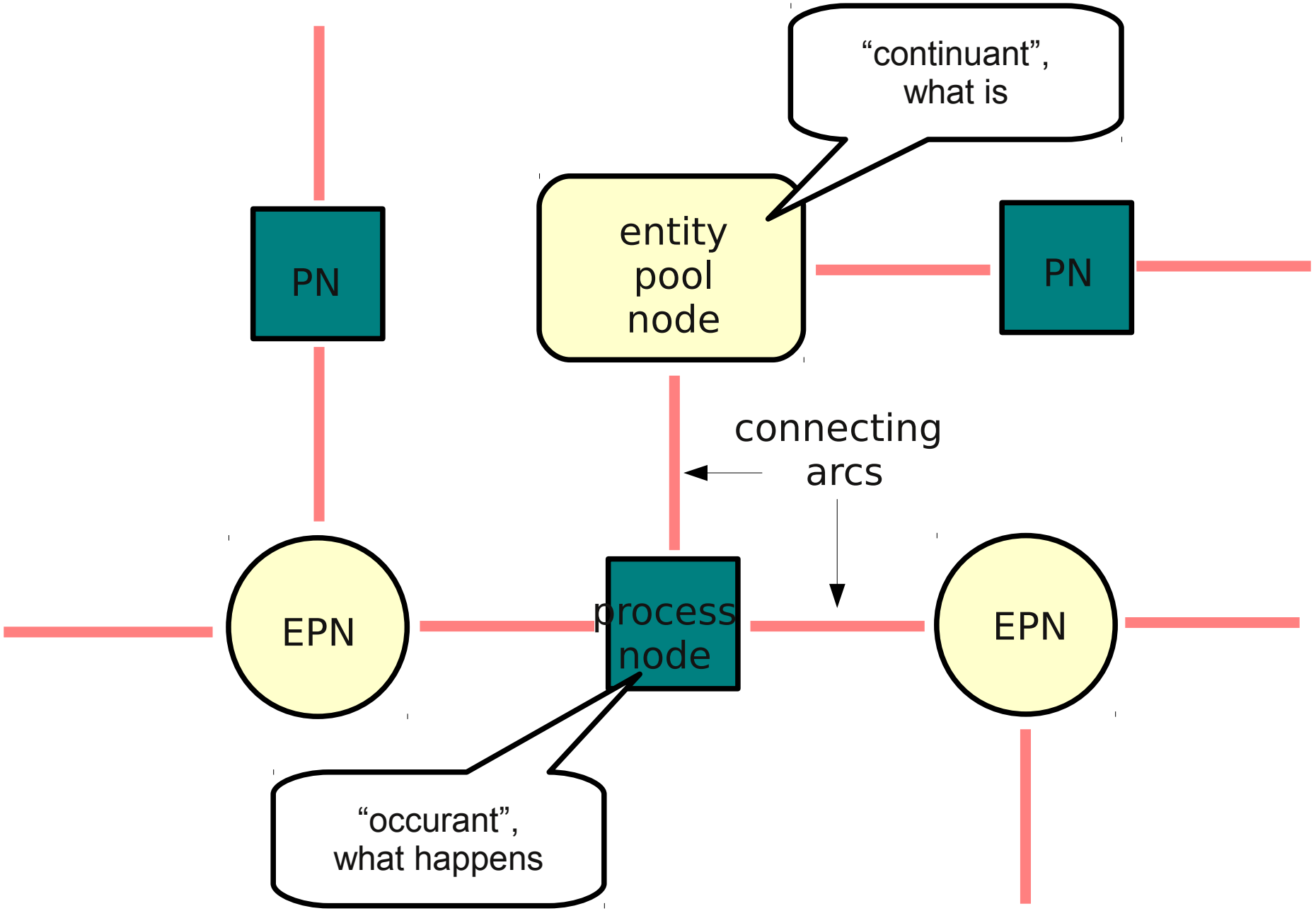
- Unambiguous
- Mechanistic
- Non-sequential
- Independence of relationships

Activity Flows

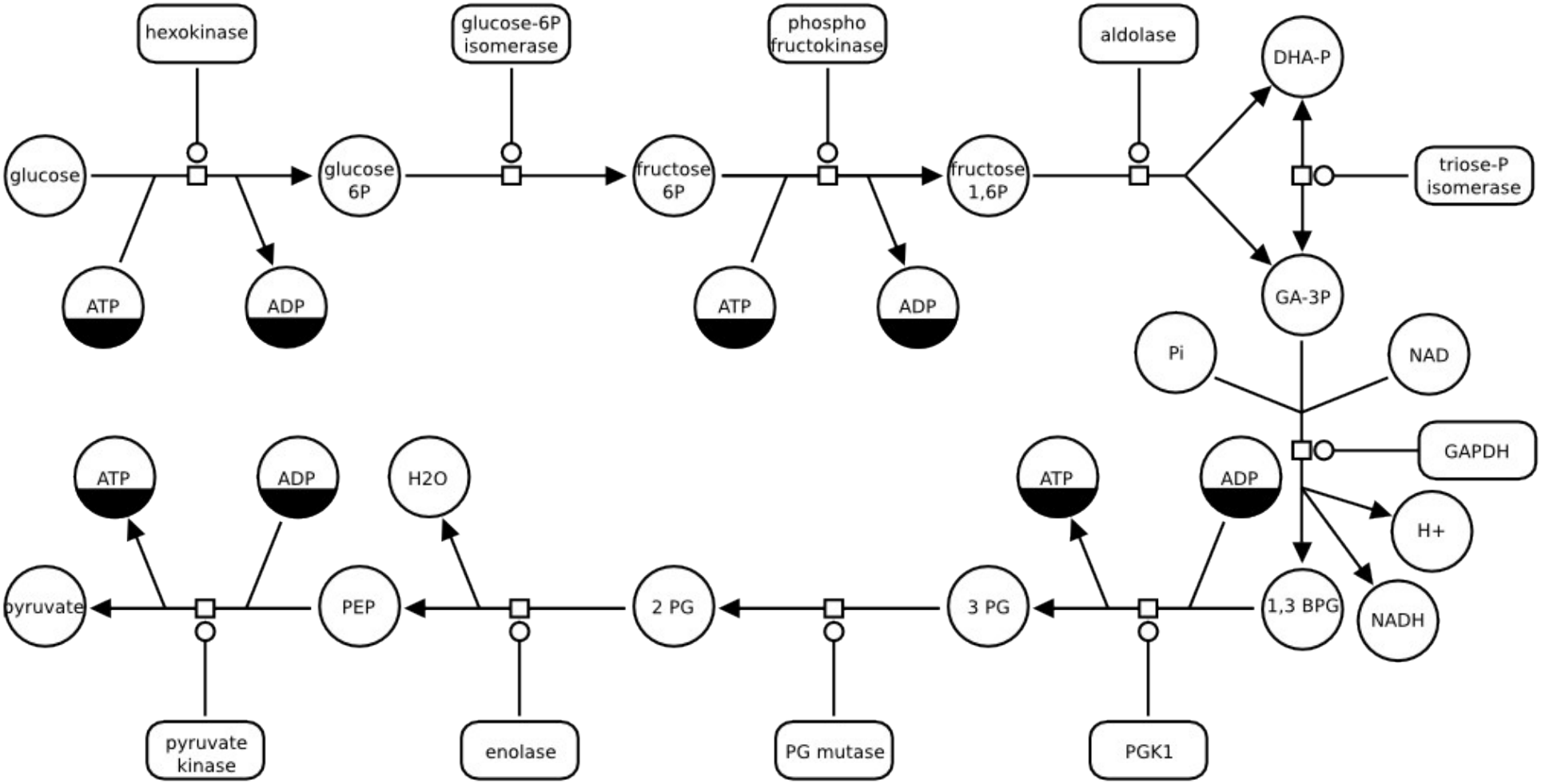


- Ambiguous
- Conceptual
- Sequential

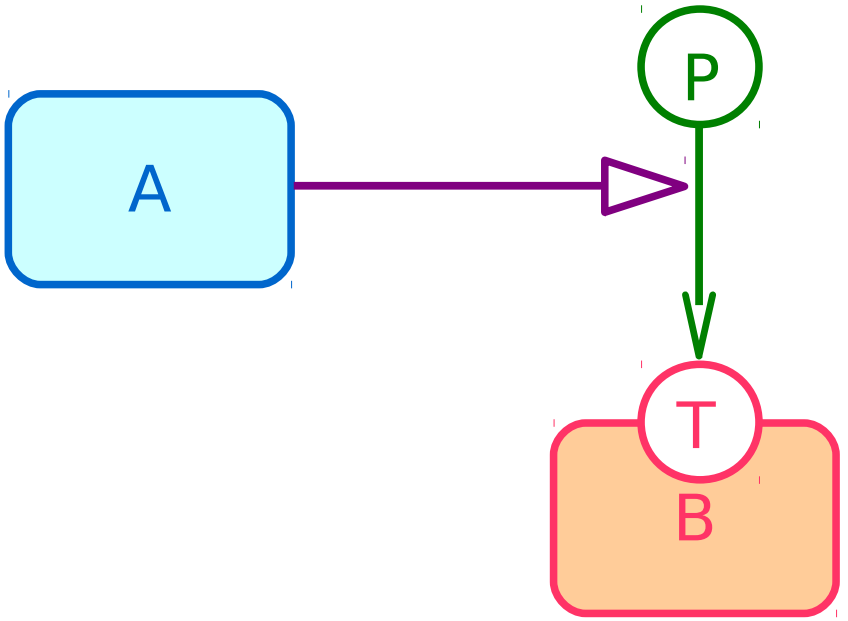
Process Descriptions are bipartite graphs



Metabolic network in Process Description Language



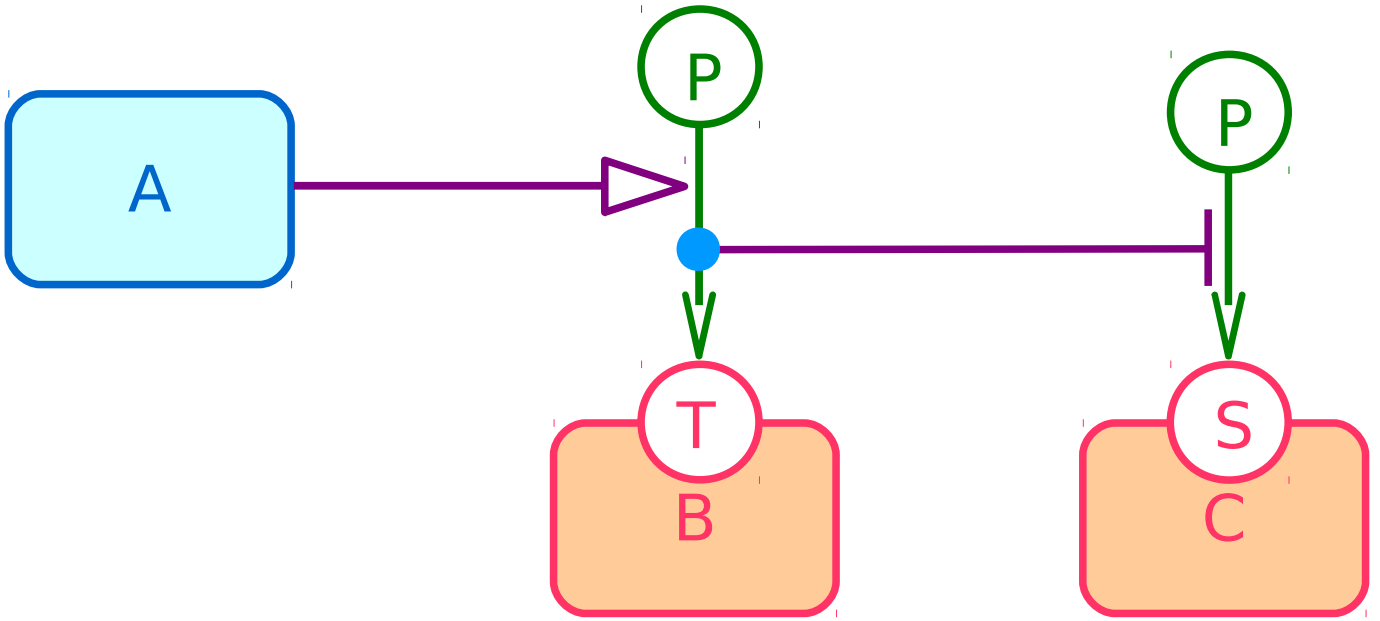
Entity Relationships can be viewed as rules



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)

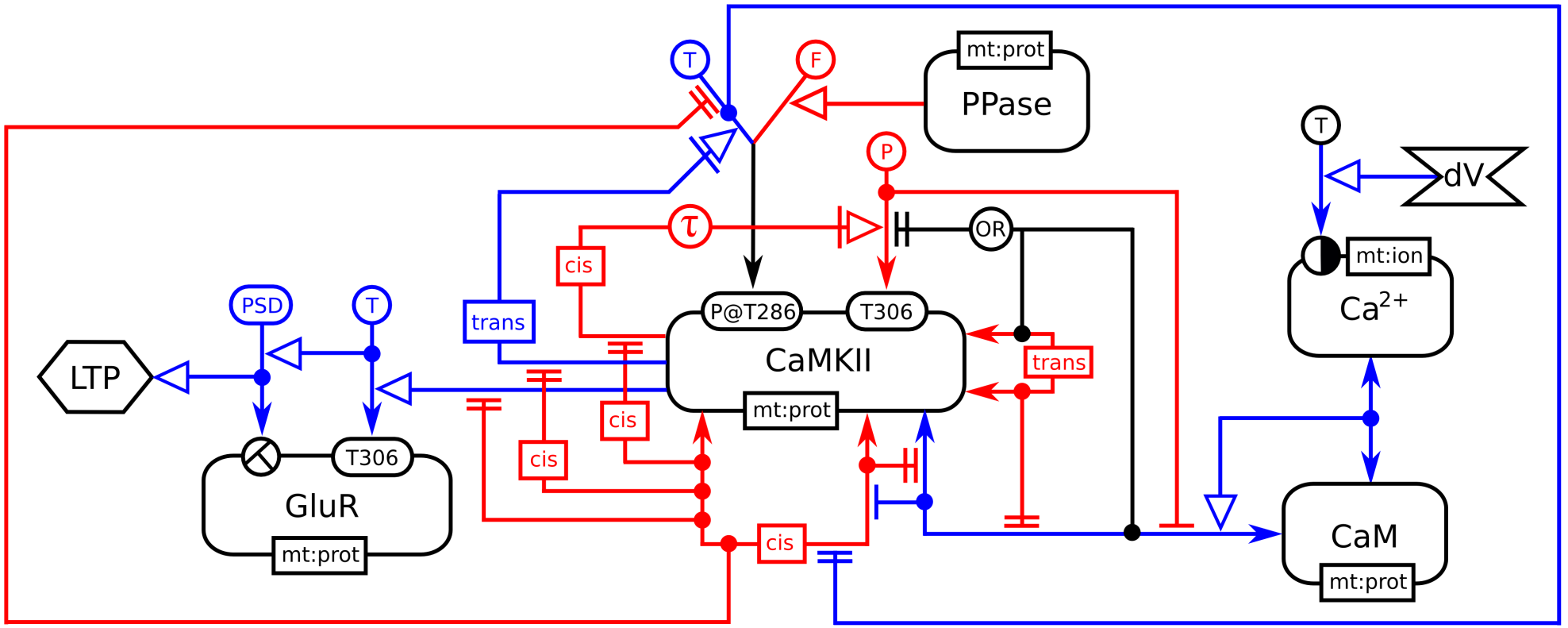
Entity Relationships can be viewed as rules



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

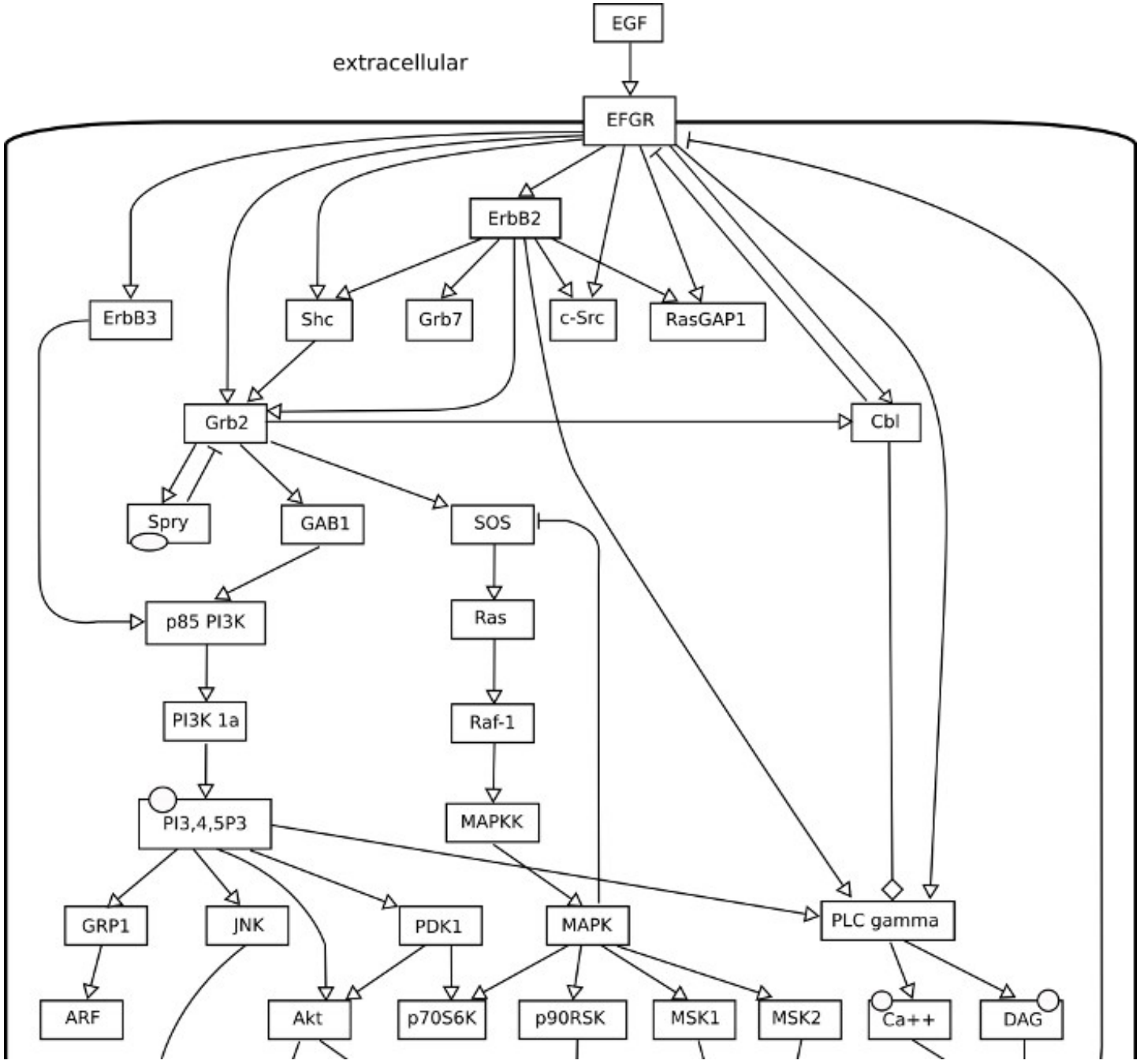
SBGN ER map of calcium-regulated synaptic plasticity



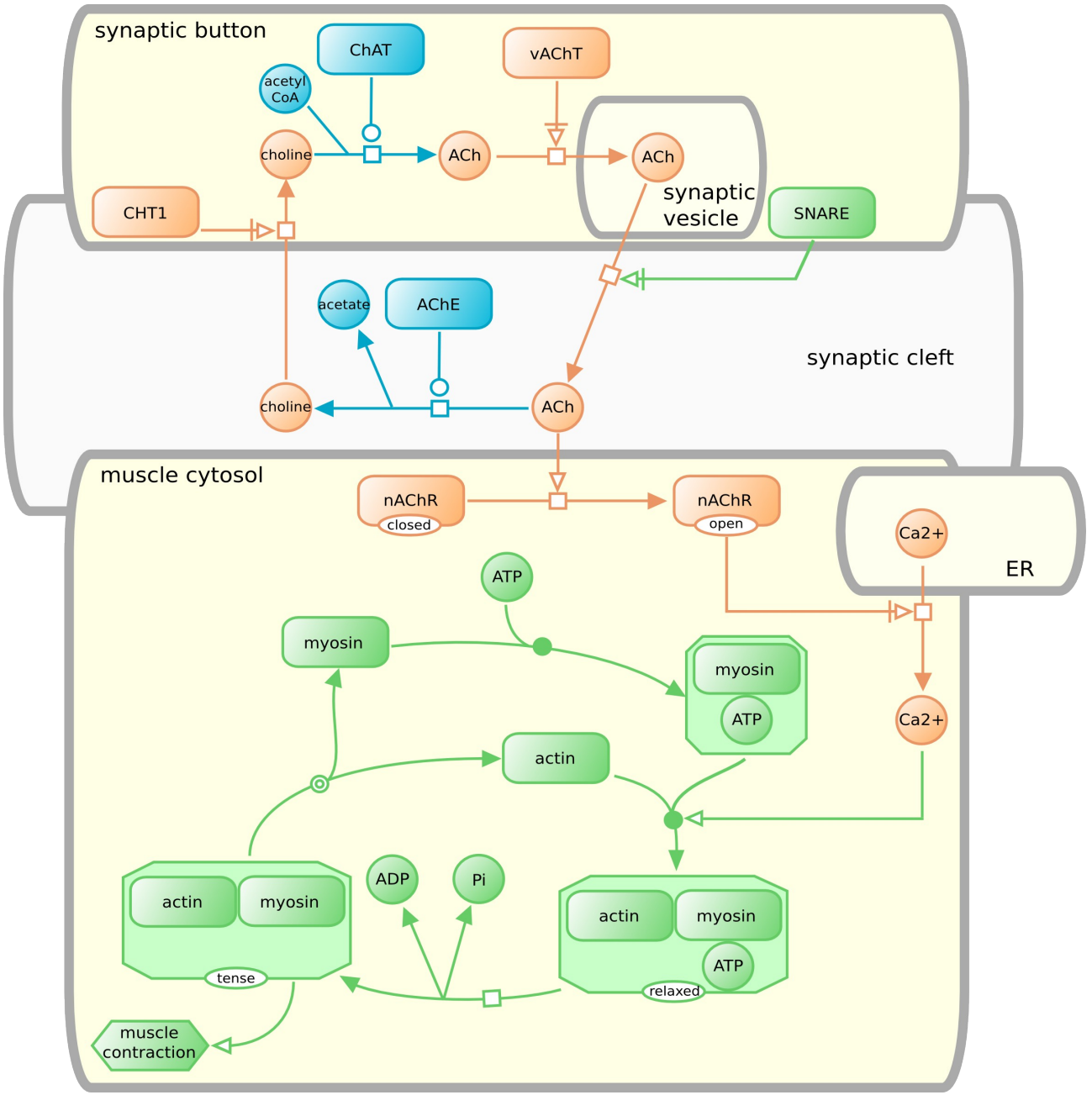
increases synaptic weight

decreases synaptic weight

Example of Activity Flow map



Linking SBGN maps to external information

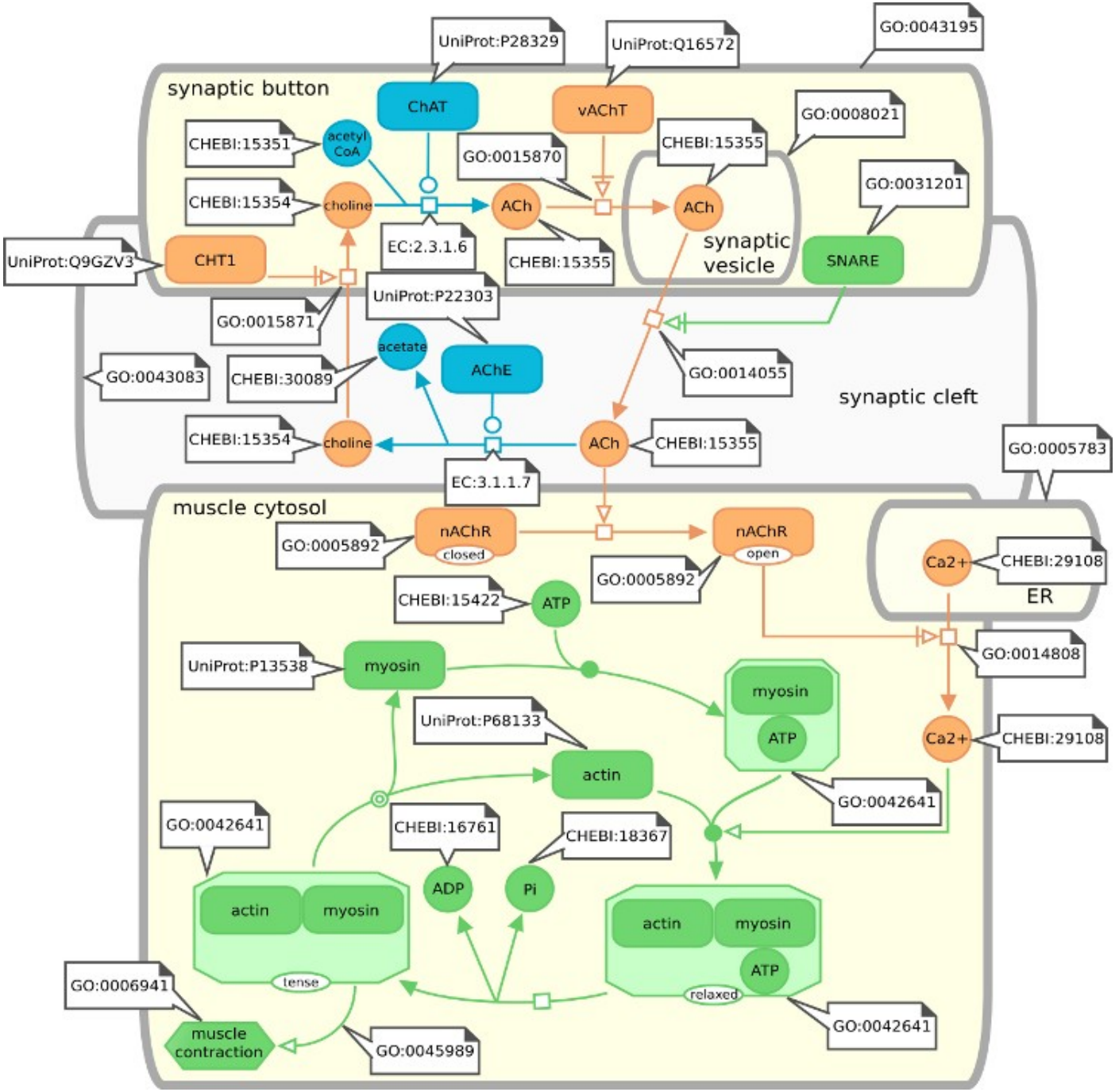


catalytic processes

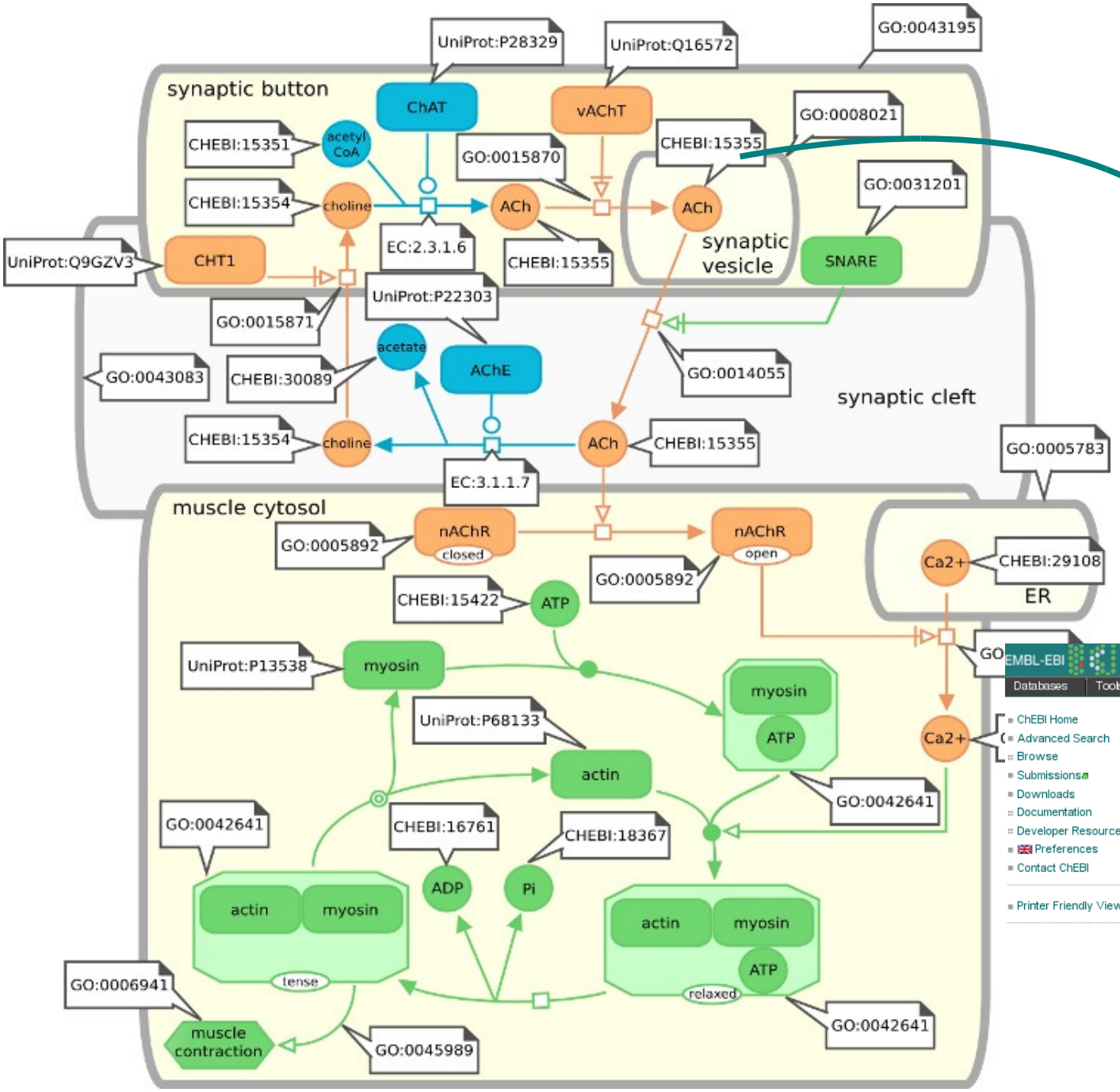
transport processes

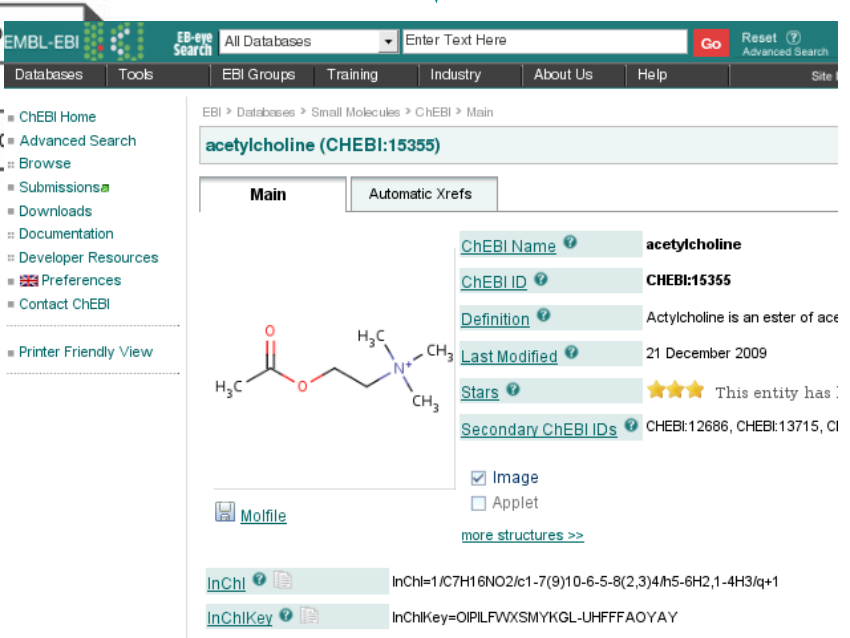
contractile proteins

Linking SBGN maps to external information

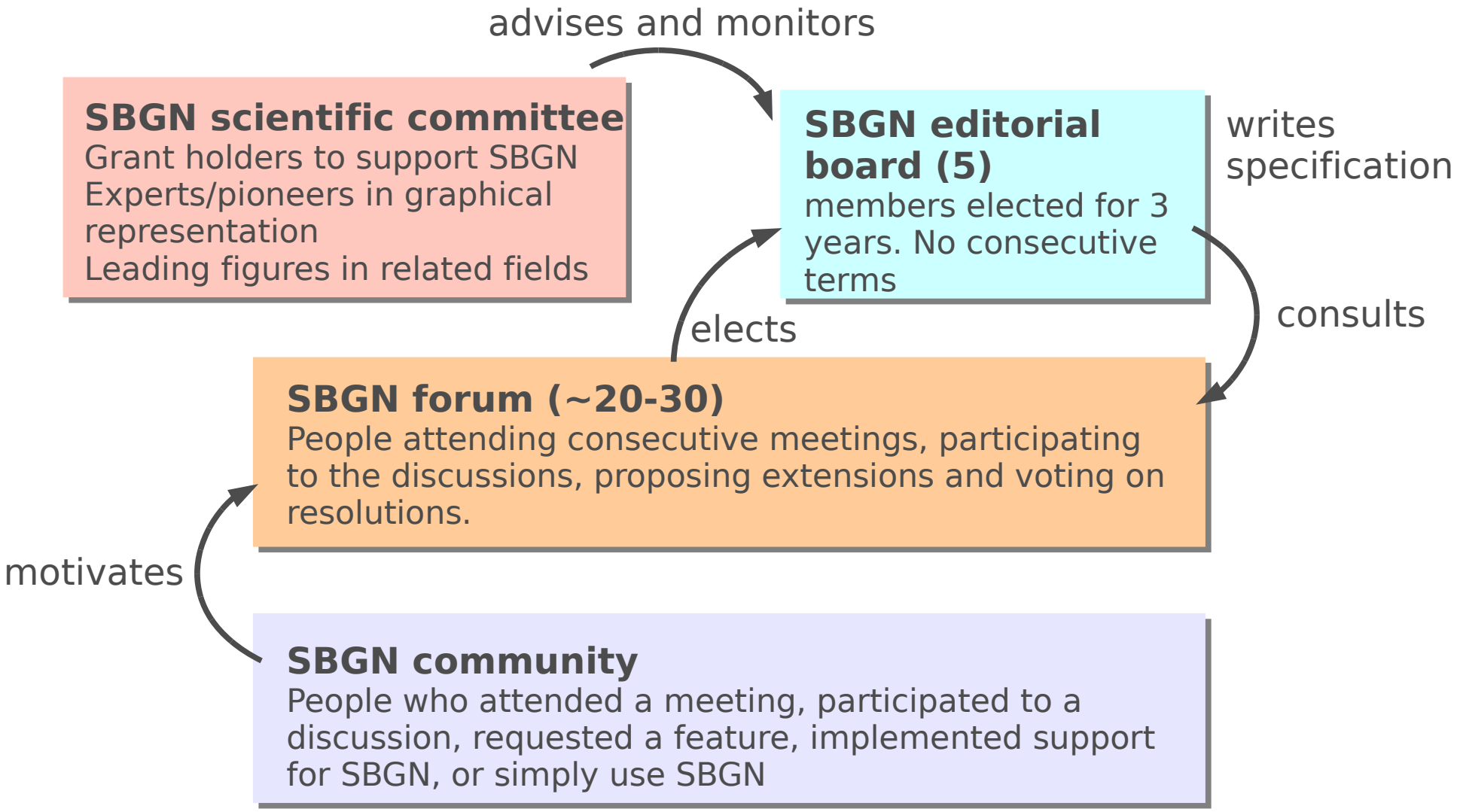


Linking SBGN maps to external information





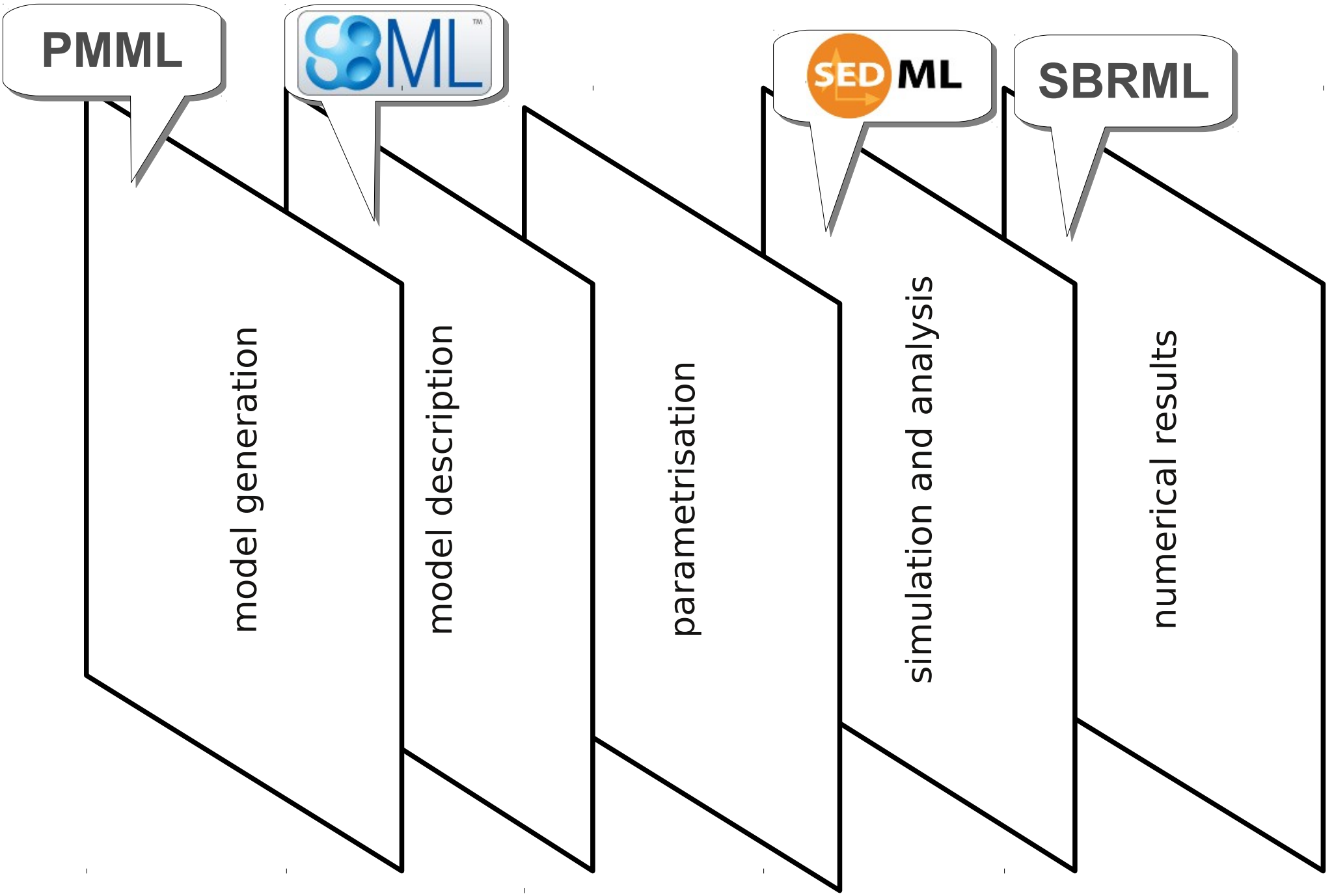
Current structure of the SBGN community



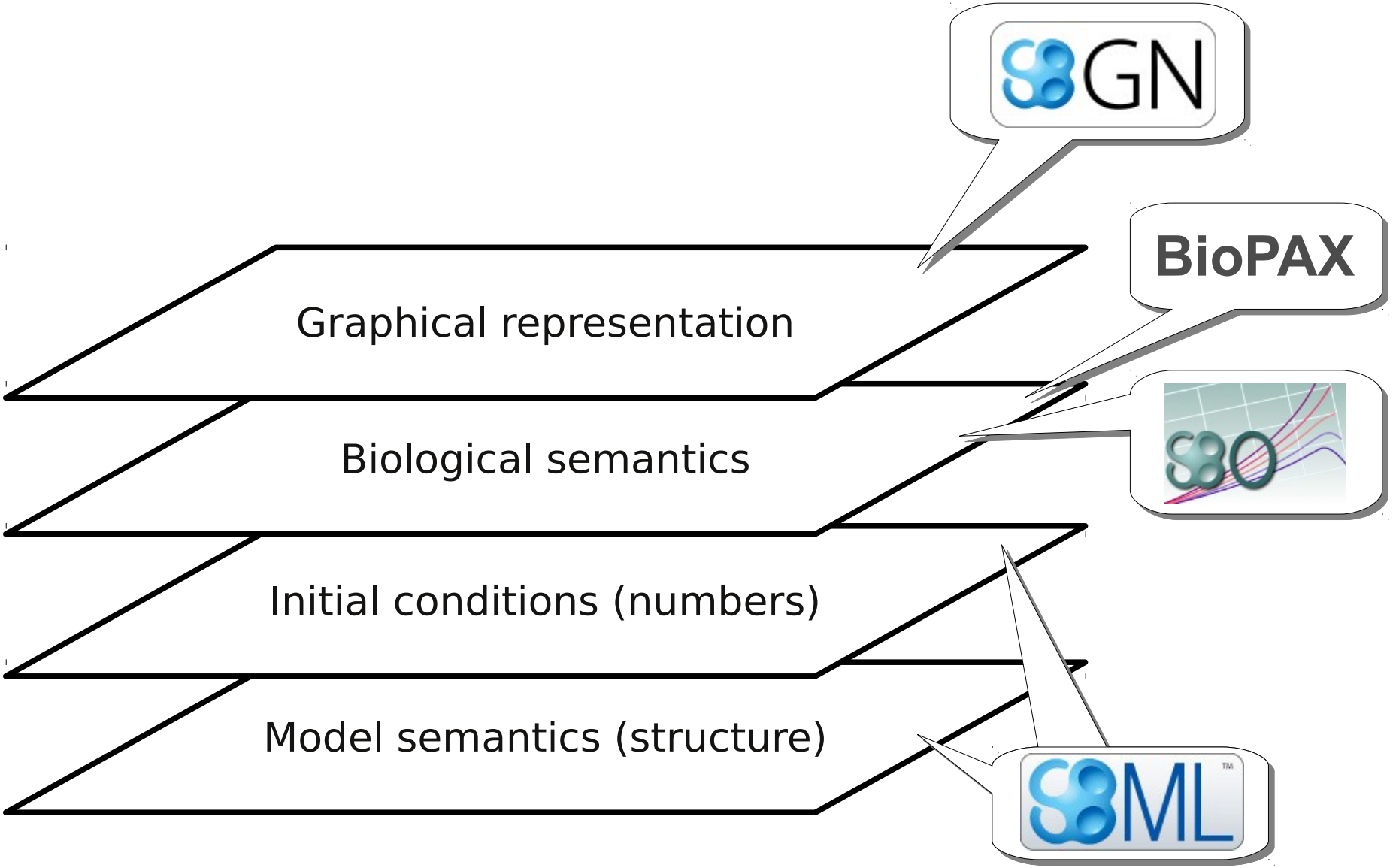
Is the mosaic of standards complete?

	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

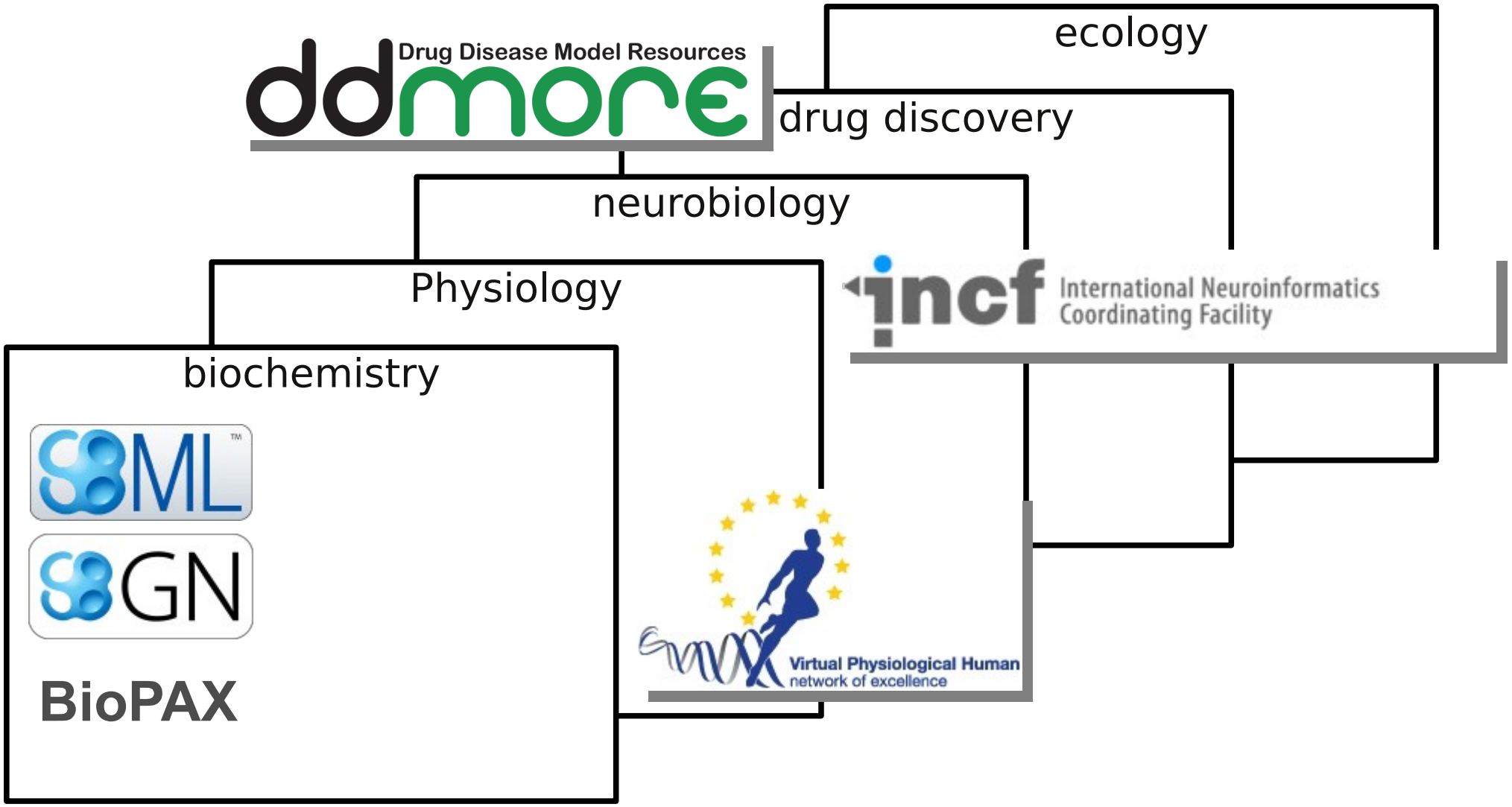
Systems Biology Ontology (SBO) Set of linked controlled vocabularies, defining and relating concepts used in computational modelling in biology. Used in SBML, SBGN, NeuroML

Le Novère N., Courtot M., Laibe C. Adding semantics in kinetics models of biochemical pathways. *Proc 2nd Intl Symp on experimental standard conditions of enzyme characterizations* (2007), 137-153.

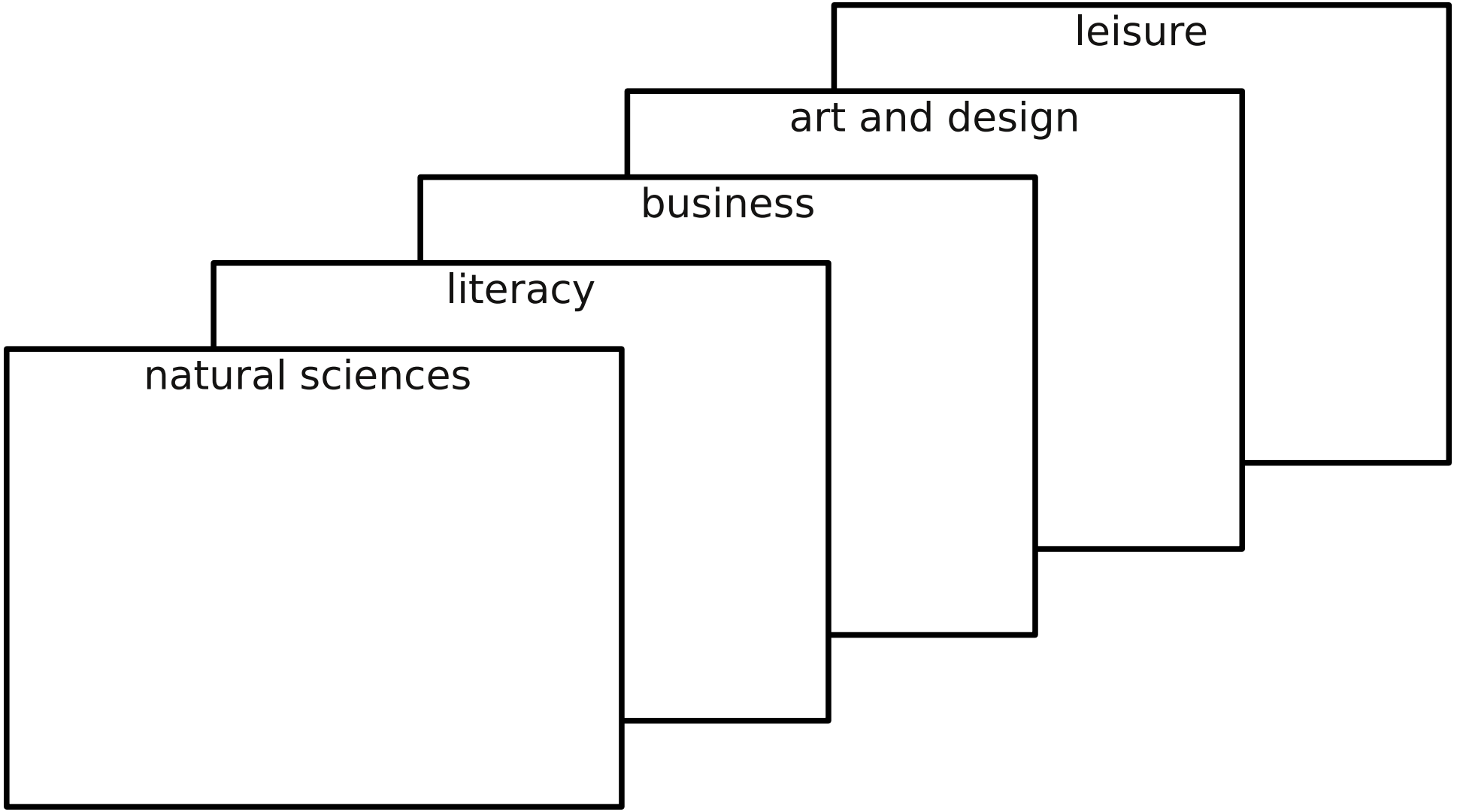
Biological Pathway Exchange (BioPAX) Standard language to represent biological pathways at the molecular and cellular level and to facilitate the exchange of pathway data. Used by most major pathways databases

Demir E, Cary MP, Paley S, Fukuda K, Lemer C, Vastrik I, Wu G, D'Eustachio P, Schaefer C, Luciano J, Schacherer F, Martinez-Flores I, Hu Z, Jimenez-Jacinto V, Joshi-Tope G, Kandasamy K, Lopez-Fuentes AC, Mi H, Pichler E, Rodchenkov I, Splendiani A, Tkachev S, Zucker J, Gopinathrao G, Rajasimha H, Ramakrishnan R, Shah I, Syed M, Anwar N, Babur O, Blinov M, Brauner E, Corwin D, Donaldson S, Gibbons F, Goldberg R, Hornbeck P, Luna A, Murray-Rust P, Neumann E, Reubenacker O, Samwald M, van Iersel M, WimalaratneS, Allen K, Braun B, Carrillo M, Cheung KH, Dahlquist K, Finney A, Gillespie M, Glass E, Gong L, Haw R, Honig M, Hubaut O, Kane D, Krupa S, Kutmon M, Leonard J, Marks D, Merberg D, Petri V, Pico A, Ravenscroft D, Ren L, Shah N, Sunshine M, Tang R, Whaley R, Letovksy S, Buetow KH, Rzhetsky A, Schachter V, Sobral BS, Dogrusoz U, McWeeney S, Aladjem M, Birney E, Collado-Vides J, Goto S, Hucka M, Le Novère N, Maltsev N, Pandey A, Thomas P, Wingender E, Karp PD, Sander C, Bader GD. BioPAX – A Community Standard for Pathway Data Sharing. *Nat Biotechnol* (2010), 28: 935–942

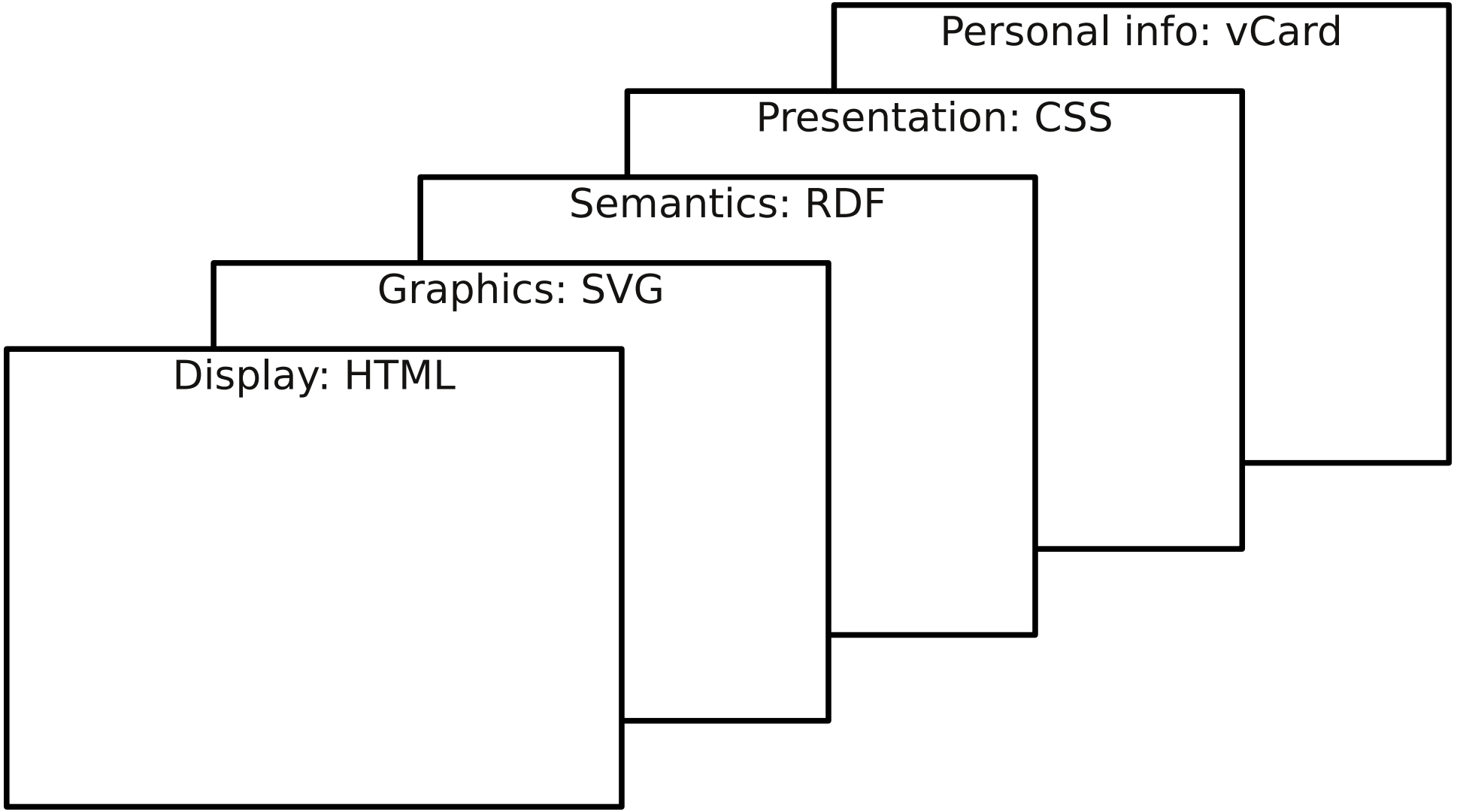
Parallel and redundant efforts



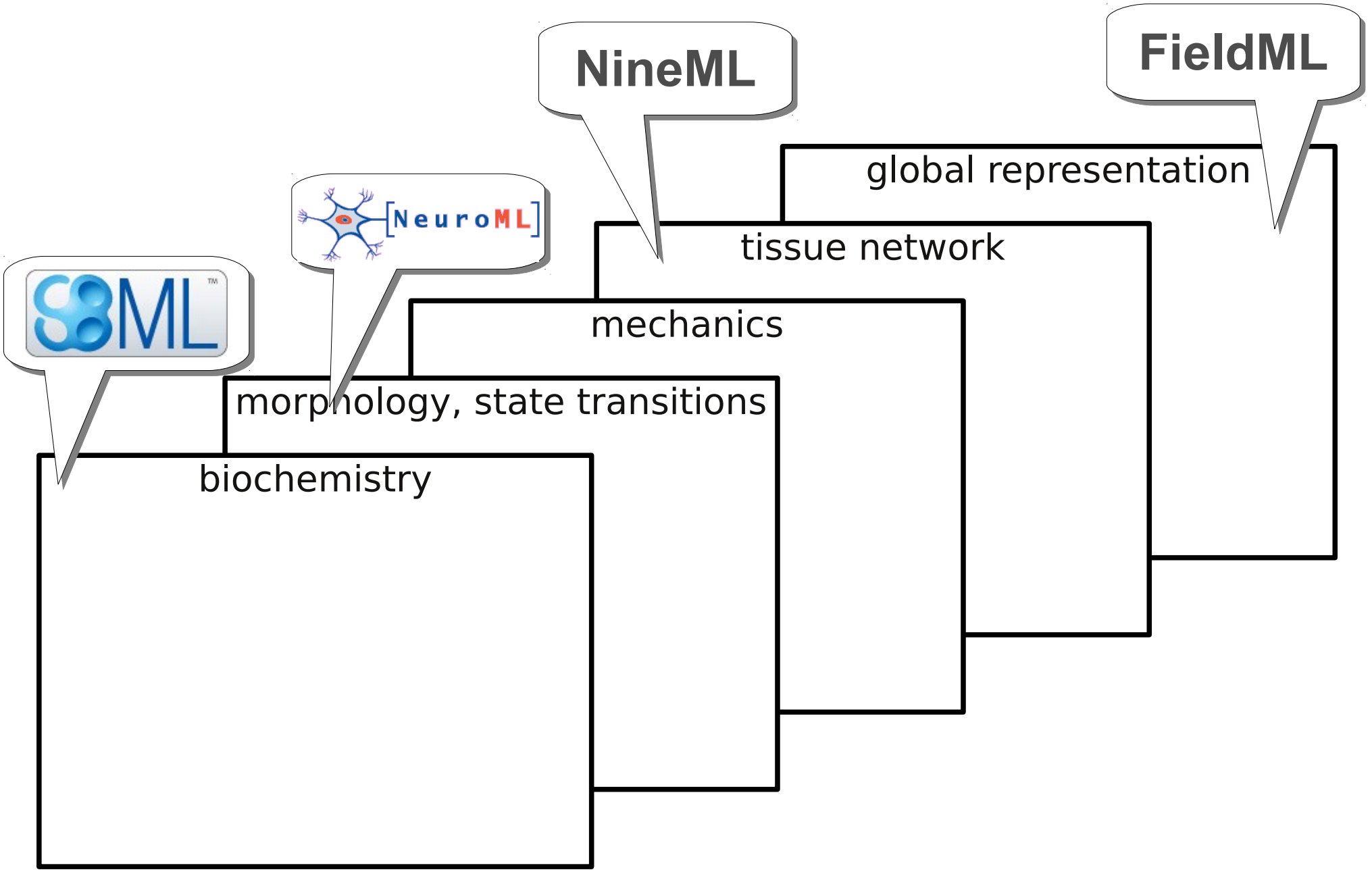
What if the world-wide web was built like this?



The correct way to do it



Non-overlapping languages to cover all models



Standards interoperability along the 3 dimensions

- SBML to BioPAX: conversion using metadata (MIRIAM annotations and SBO terms), e.g.
  - mapping between Species and PhysicalEntity
  - mapping between Reactions and PhysicalInteraction
- Conversion of SBML or BioPAX descriptions to SBGN map
- Usage of SBML descriptions (or CellML or VCML) in SED-ML: Identification of variables using XPath
- Descriptions using SBML and NeuroML: Interface based on XPath

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), Clinical data (CDISC) ...
  - Other players in knowledge-representation: W3C ...
  - Academic and corporate users: Modeling platforms (MatWorks ...), Pharma (Pistoia alliance) ...

Requirements for a overarching standardisation structure

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COmputational Modeling in Biology NEtwork (COMBINE) forthcoming: http://co.mbine.org

COMBINE 2010

- 6 to 9 October 2010, Edinburgh, before the ICSB
- 77 registrations so far (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

W3C

- Standards
- Participate
- Membership
- About W3C
- Member Home

ABOUT W3C

The World Wide Web Consortium (W3C) is an international community where Member organizations, a full-time staff, and the public work together to develop Web standards. Led by Web inventor Tim Berners-Lee and CEO Jeffrey Jaffe, W3C's mission is to lead the Web to its full potential. Contact W3C for more information.

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- Contact
- Staff
- Help and FAQ
- Systems Status (outages)

W3C Mission

- Principles, vision, …

Facts About W3C

- People, organization, revenues, process, patent policy, history, …

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- Press releases, requests for photos and interviews, …

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- Support for W3C operations, validator service, …

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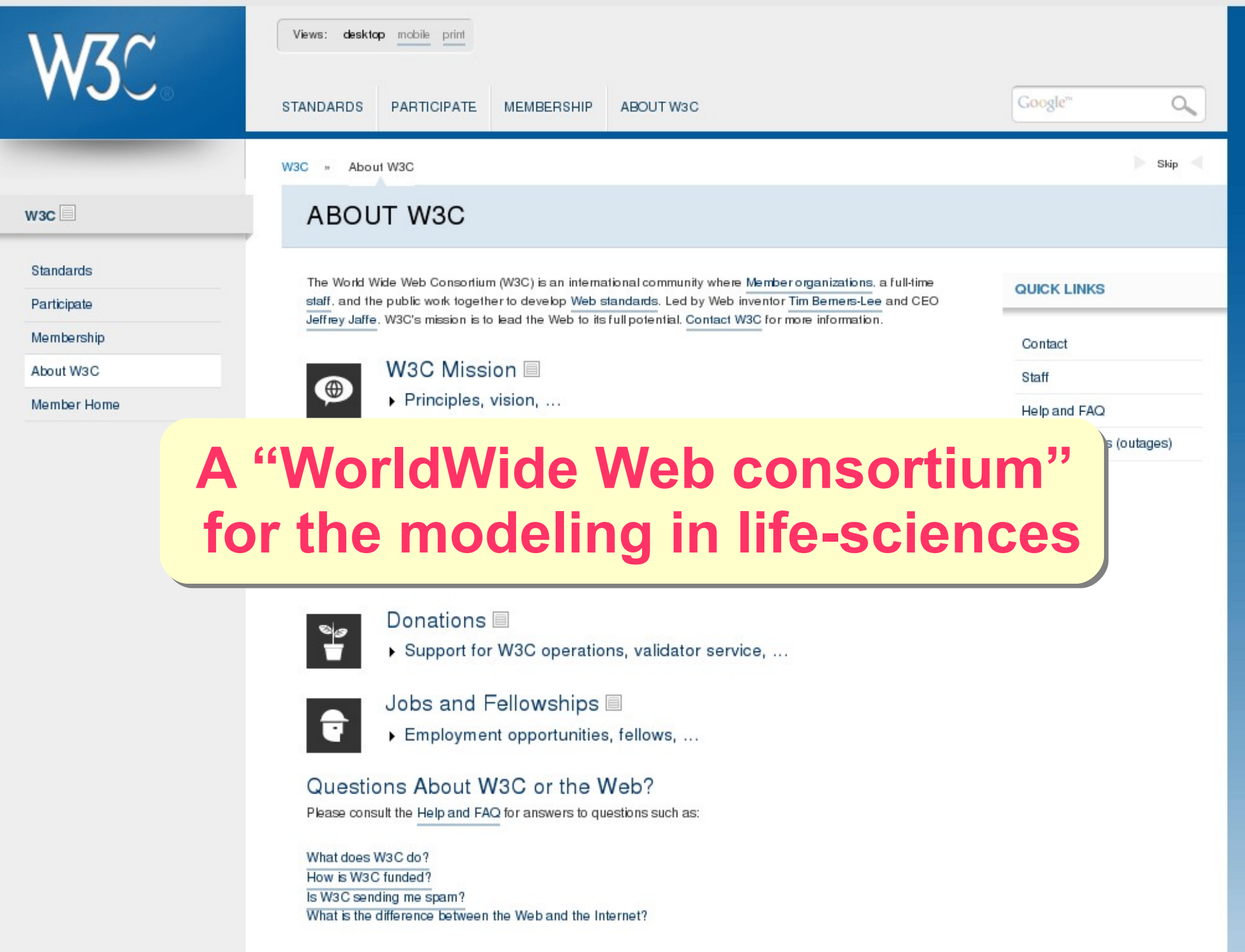
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Research perspectives

- Change of scale for the support of Systems Biology
  - Towards a coherent set of interoperable standards to represent models and simulations at all levels
  - Development of ontologies for model semantics in biology and their integration with experimental and clinical data

    ☞ ”W3C” for modelling in biology
  - Scaling up BioModels Database to cover all mathematical models in biology
- Multi-scale models of neuronal transmission in basal ganglia
  - 4D models of post-synaptic density
  - Forest of kinase signalling linked by phosphatases
  - Integration of biochemical cascades and eletrophysiological behaviours
  - Mechanical models: spine volume, dendritic remodelling
  - Modelling the basic unit of basal ganglia

Multi-approach, multi-scale models in neuroscience

- Models and simulations in neuroscience cover all scales and approaches: Reaction-diffusion, biochemistry, electrophysiology (cable approximation), mechanical (neurite growth), networks, field approaches (EEG)
- Multi-scale biological problems are concrete:
  Molecular basis of synaptic plasticity -> transmission of signal by neuron -> cognitive function
  mutations -> molecular aggregates -> neuronal death -> behavioural pathologies
- Versatile simulation tools exist that cover all levels.
- An expertise is building up on hybrid models:
  Biochemistry/electrophysiology; networks/fields
- There is a political will: role of the *International Neuroinformatics Coordination Facility*: Development of standards, ontologies and simulation tools.
- Neurobiology can make real the aims of the *Virtual Physiological Human* by développing integrated models from the molecule to the organ, and by using them to understand normal functions, emergence of pathologies, and to propose/test new treatments *in silico.*

Scientific environment in Bordeaux

- **Molecule-synapse:** CNRS UMR 5091 Physiologie cellulaire de la synapse (dir. Christophe Mulle), soon INES, on the Neurocampus, and in particular the group of Daniel Choquet for receptor dynamics
- **Neuron**: INSERM U 862 - Physiopathologie de la plasticité neuronale, Neurocentre Magendie (dir. Pier Vincenzo Piazza), on the Neurocampus, for the dendritic remodelling
- **Networks**: CNRS UMR 5228 - Centre de Neurosciences Intégratives et Cognitives (dir. Georges Di Scala), for the modelling of basal ganglia
- **Tissue, organism, pathology:** CNRS UMR 5227 - Mouvement - Adaptation – Cognition (dir. Jean-Rene Cazalets), and in particular the group of Erwan Bezard/Bertrand Bloch, soon institute of neurodegenerative diseases on the Neurocampus

- **Computational resources for Systems Biology:** CBiB, Antoine de Daruvar and soon Macha Nikolskaia
- **Data visualisation and manipulation**: MaBioVis/Gravite, Guy Melançon
- **Event driven simulations**: MAGNOME, David Sherman
- **Advanced numerical methods**: MC2, Thierry Colin
- **High performance simulation**: HiePACS, Jean Roman
- ....

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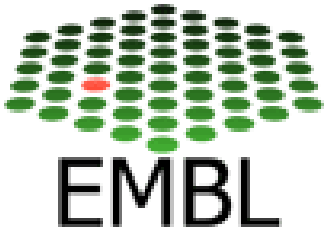
The whole community of Computational Systems Biology

The EBI group Computational Systems Neurobiology



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