EMBL-EBI 

Models For All

Standards for Describing the Whole Life-Cycle of Modeling in Life Sciences

Nicolas Le Novère

What happened to Biology at the end of XXth century?

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

A New Approach to Decoding Life:
Systems Biology

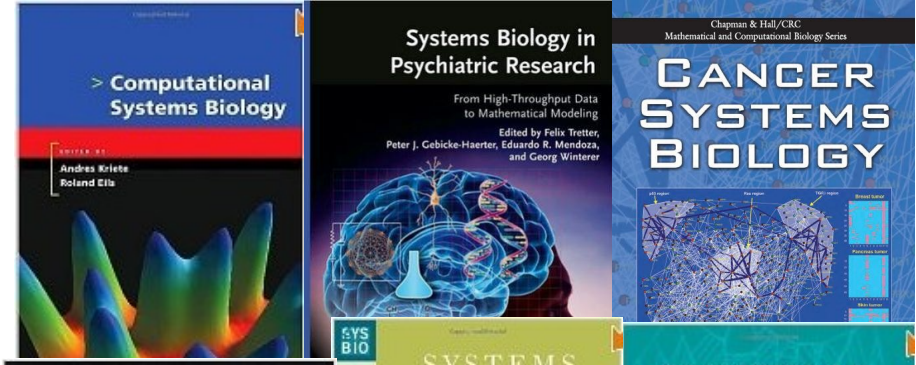
Trey Ideker[1,2], Timothy Galitski[1], and Leroy Hood[1,2,3,4,5]
Institute for Systems Biology[1], Seattle, Washington 98105; Departments of

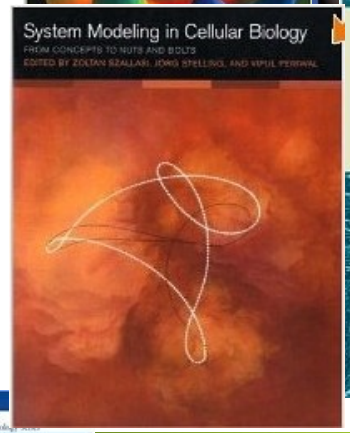
New Generation Computing, 18(2000)199-216
Ohmsha, Ltd. and Springer-Verlag

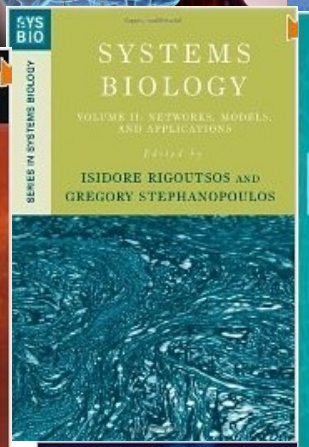
Invited Paper

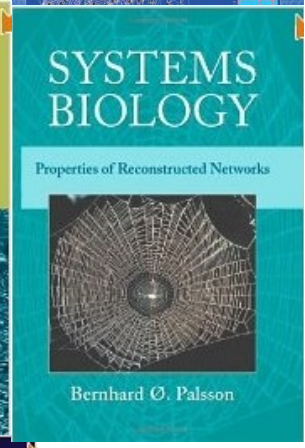
Perspectives on Systems Biology

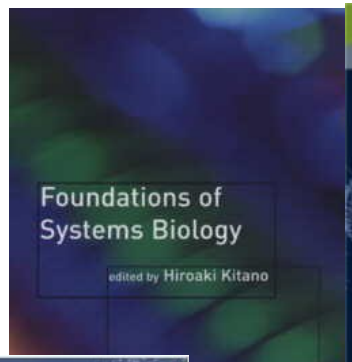
Hiroaki KITANO
Sony Computer Science Laboratories, Inc.

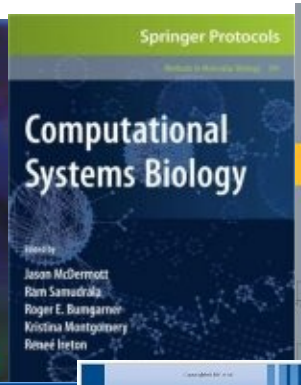


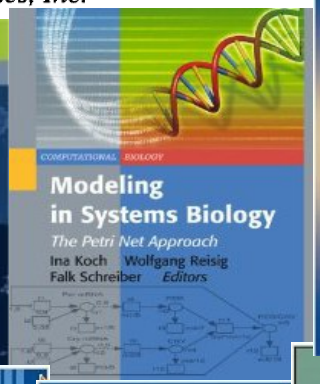


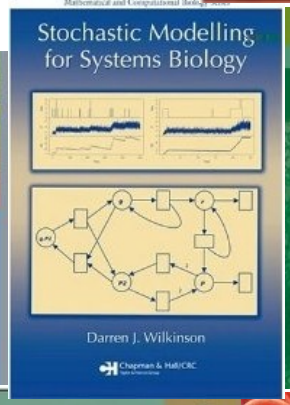


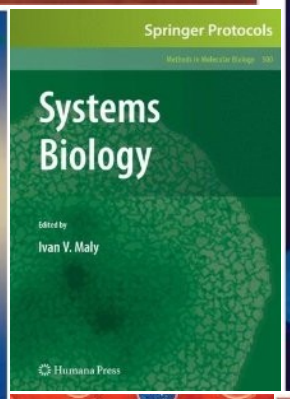


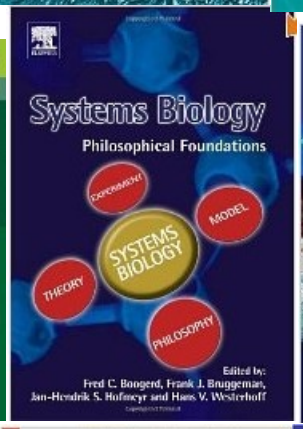


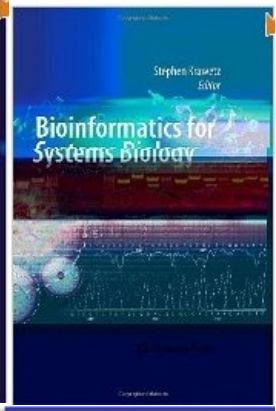


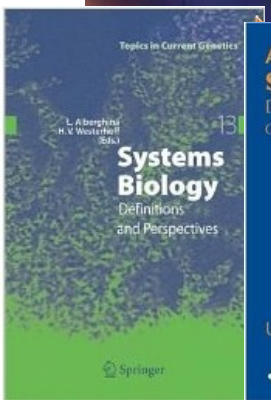


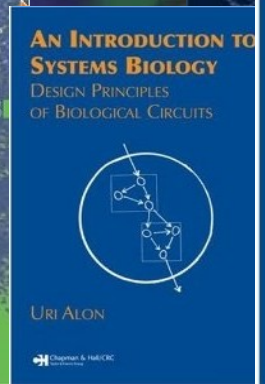


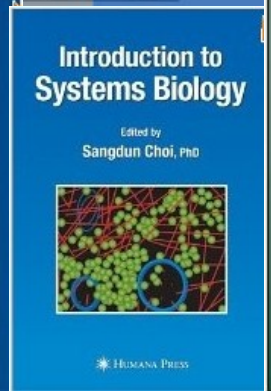


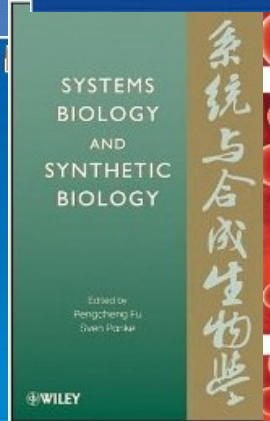


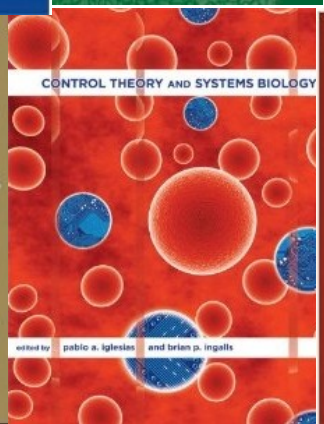


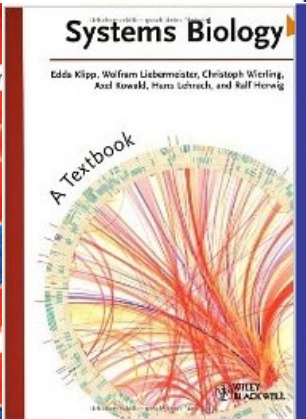


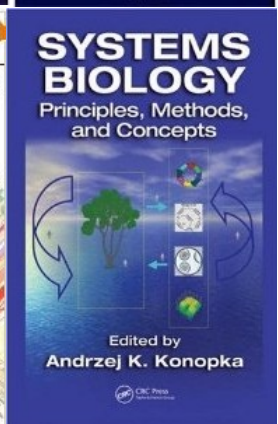




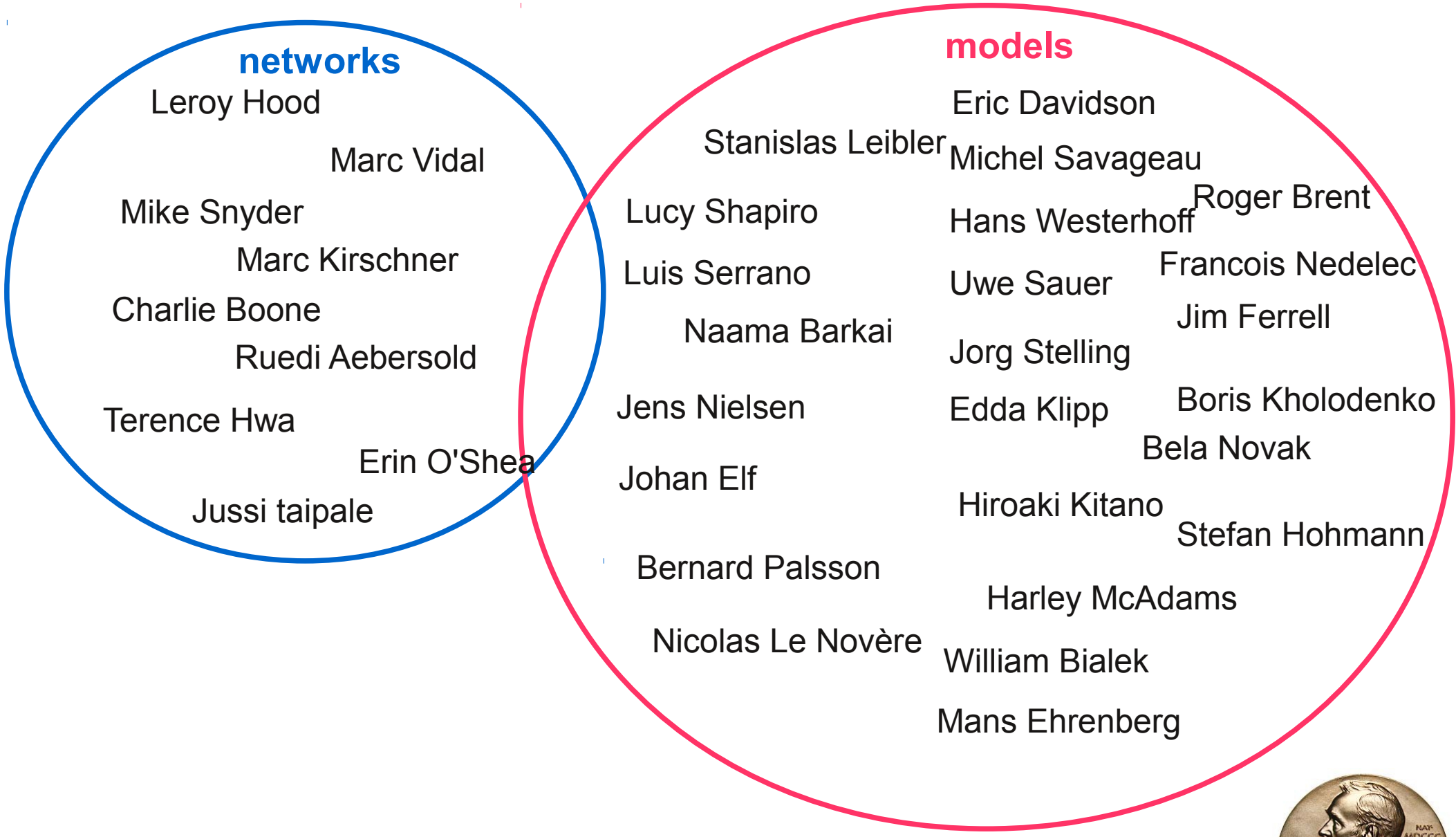








Nobel Symposium on Systems Biology (June 2009)



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

Boris Kholodenko

Jens Nielsen

Edda Klipp

Bela Novak

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

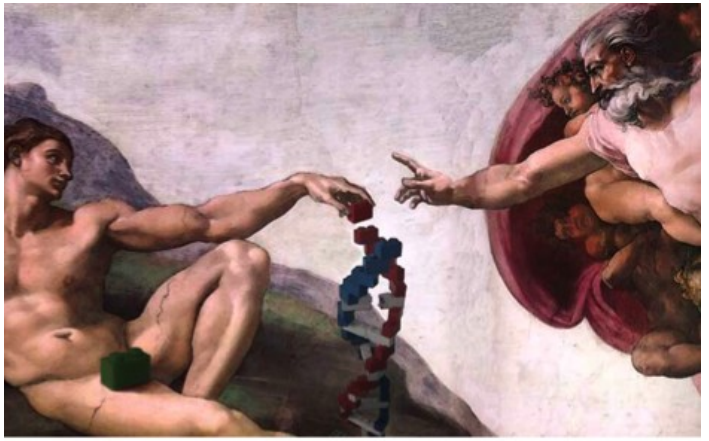
What happened to biology at the end of XXth century?

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

etc group

January 2007

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

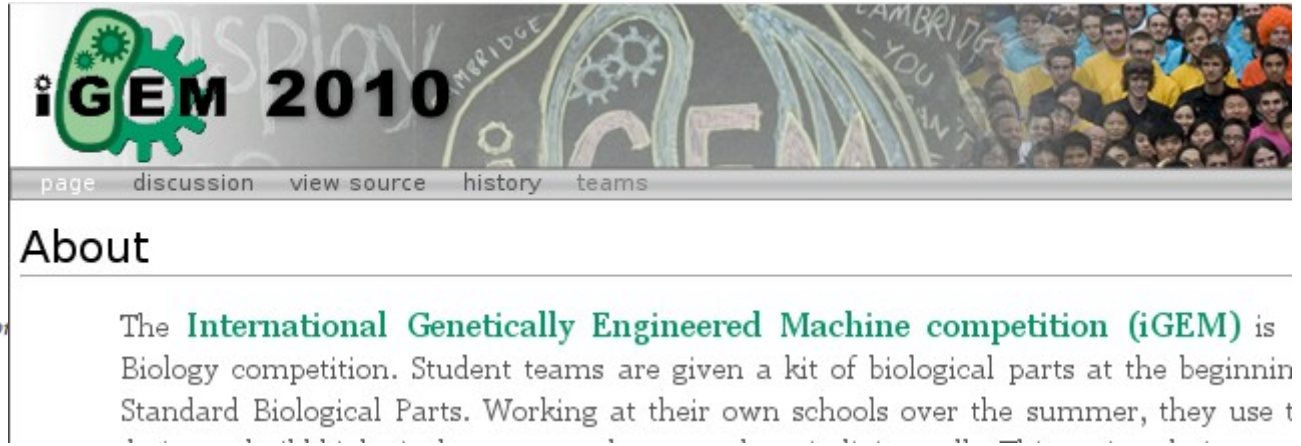
Cell

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]
[1] Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2] CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
*Contact: yamanaka@frontier.kyoto-u.ac.jp
DOI 10.1016/j.cell.2006.07.024 Cell *126*, 663–676, August 25, 2006 ©2006 Elsevier Inc. 663

A synthetic oscillatory network of transcriptional regulators

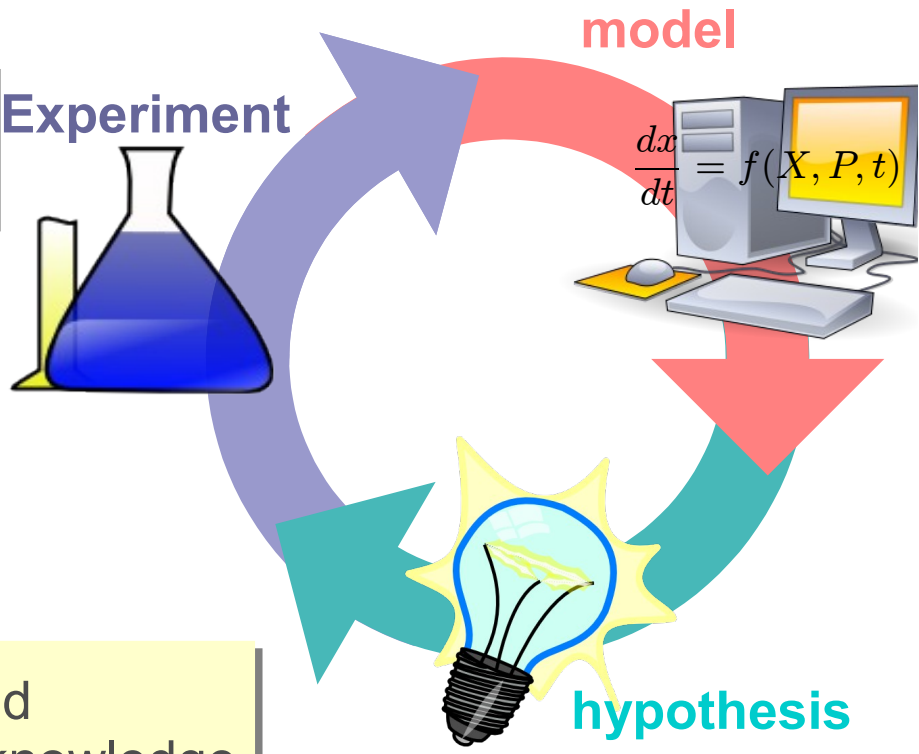
Michael B. Elowitz & Stanislas Leibler

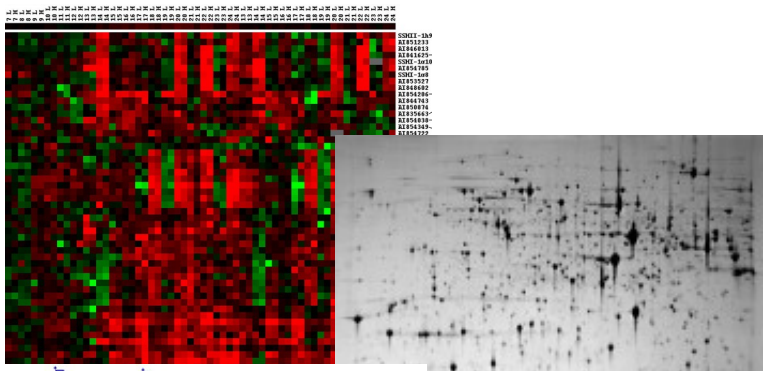
Departments of Molecular Biology and Physics, Princeton University, Princeton New Jersey 08544, USA
NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com

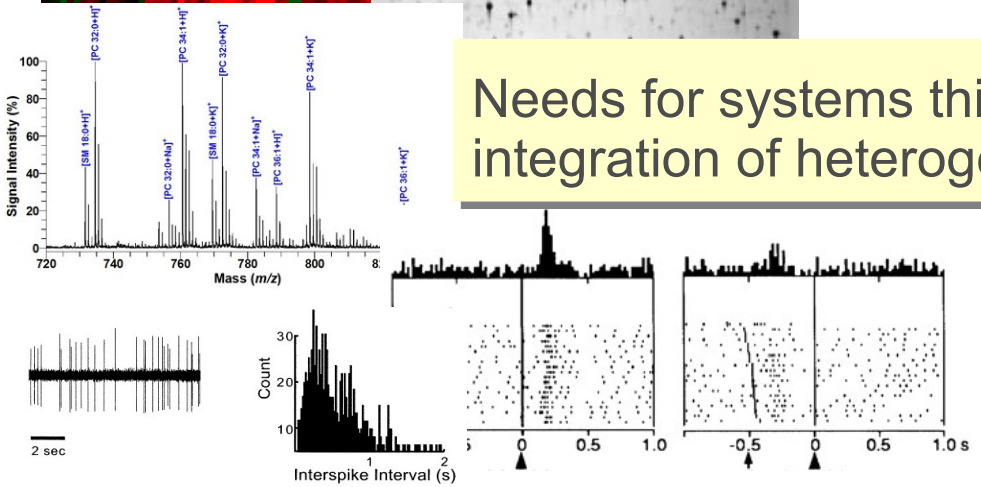


New way of doing biomedical research

Needs for interplay between models and reality tests

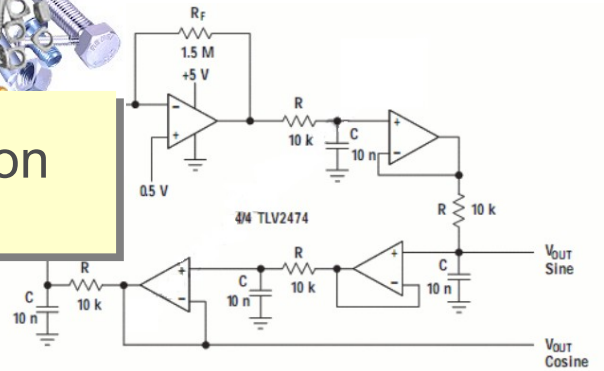






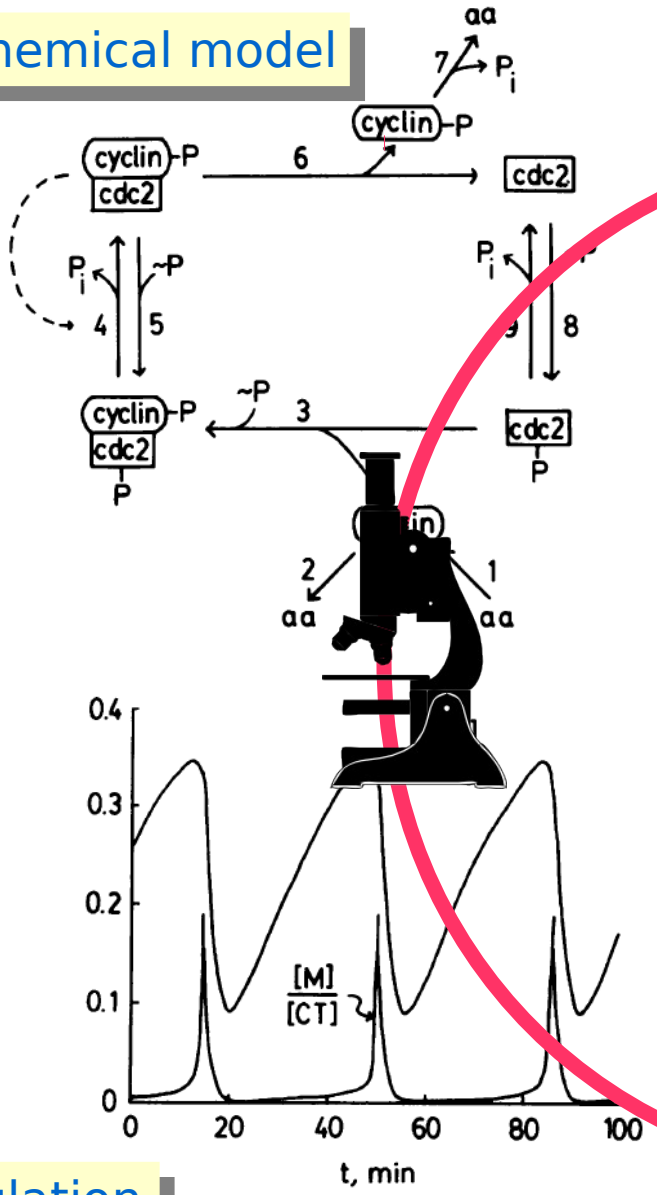
Needs for systems thinking and integration of heterogeneous knowledge

Needs for cooperation and standardisation



The models I am talking about

biochemical model



simulation

mathematical model

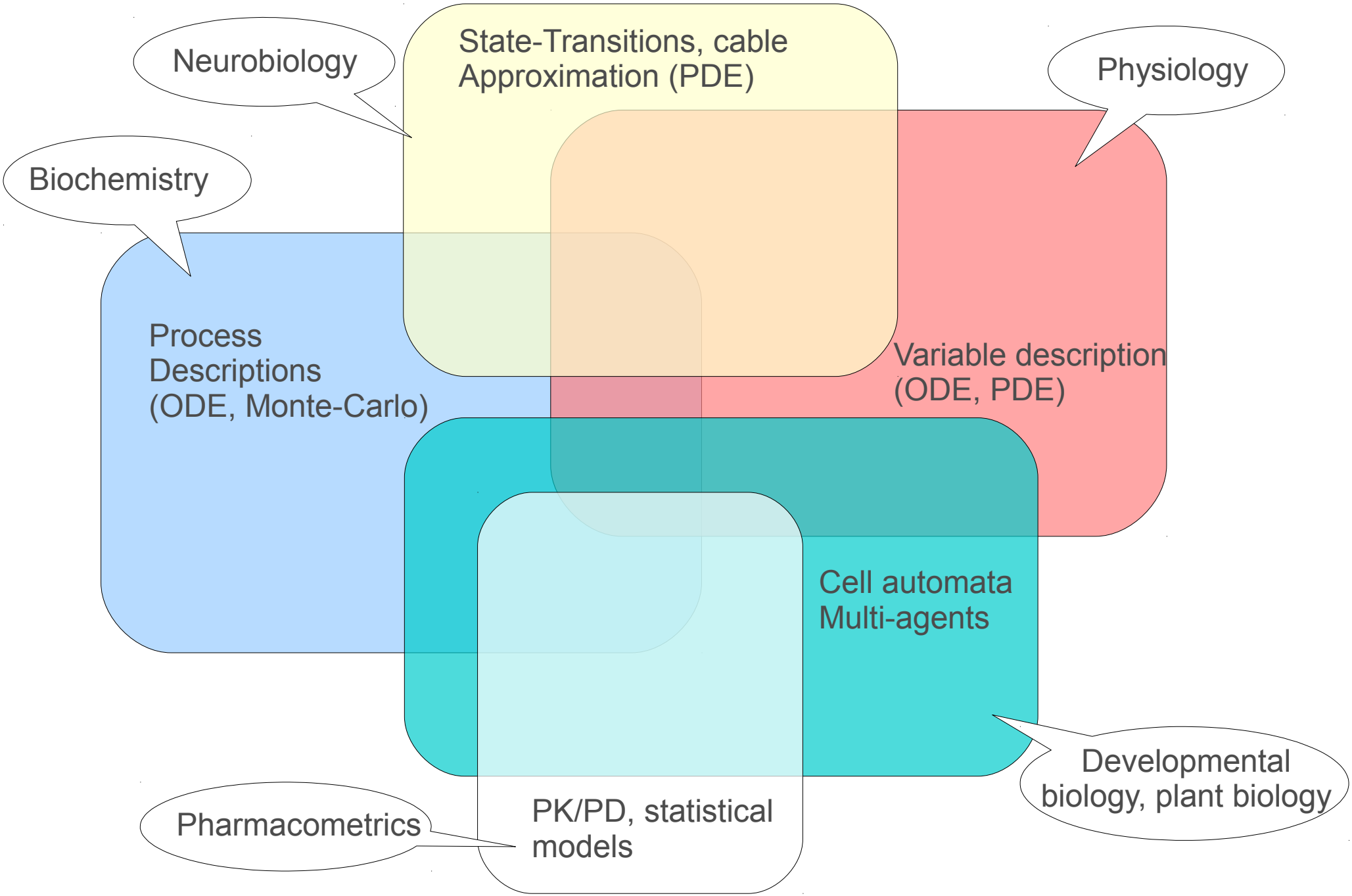
$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
$$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$$
$$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$$
$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
$$d[YP]/dt = k_6[M] - k_7[YP]$$

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

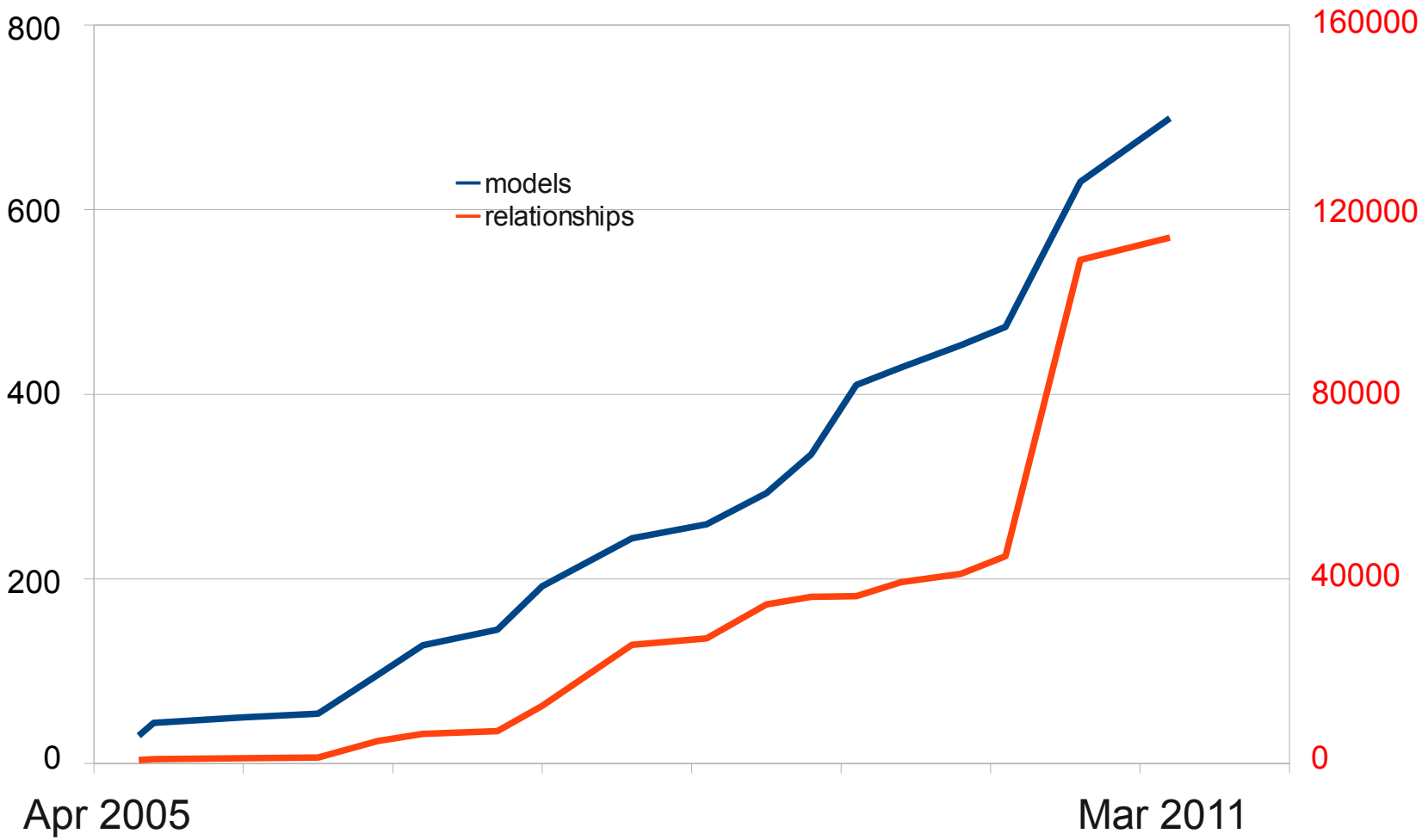
computational model

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

Many complementary modelling approaches



Computational models on the rise



BioModels Database growth since its creation

Computational modelling left the niches

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

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

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

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

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

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

BioModels Database - A Database of Annotated Published Models

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

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

Advanced Search

Search | Go to model

Browse models

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

Browse models using Gene Ontology

Browse the models in the curated branch using the Gene Ontology tree. The number that appears between brackets next to each GO branch represents how many models are related to that GO term.

Simulate in JWS Online

Submit a model

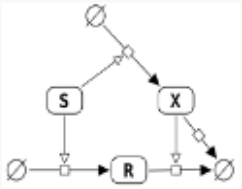
http://www.ebi.ac.uk/biomodels/

Links

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

Model of the month

April, 2011



Molecular regulatory networks can accurately be modeled in mathematical terms. This model shows, how simple signaling pathways can be embedded in networks using positive and negative feedback to generate more complex behaviours —toggle switches and oscillators — which are the basic building blocks of the exotic, dynamic behaviour shown by nonlinear control systems. *Read more...*

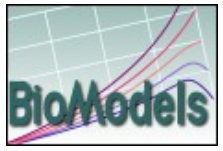
News

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

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

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

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



See presentation by Camille Laibe
at 11:00

A language to describe computational models in biology

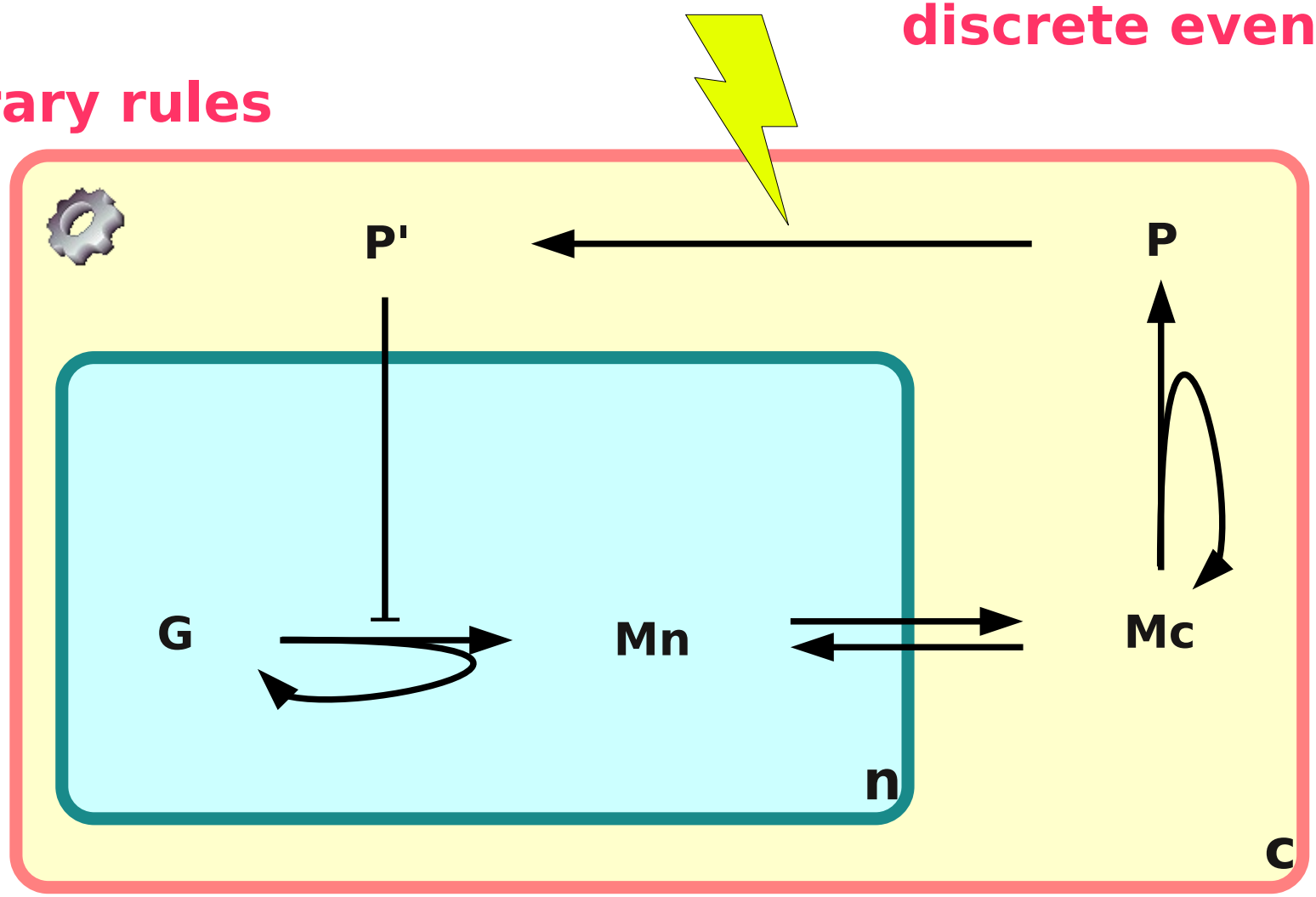
	Models
Data-models	

Born in Caltech 2000

What can we encode in SBML (core)?

discrete events

arbitrary rules



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

Why the Extensible Markup Language (XML)?

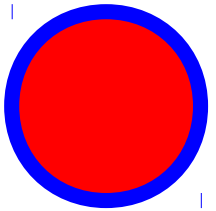
- **HTML**

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

A **strong word** and an hyperlink

- **SVG**

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



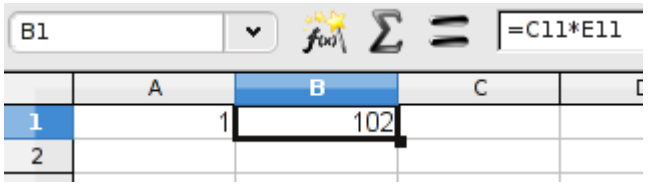
- **MathML**

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

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

- **Excel**

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



Why the Extensible Markup Language (XML)?

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

Global structure of a SBML file

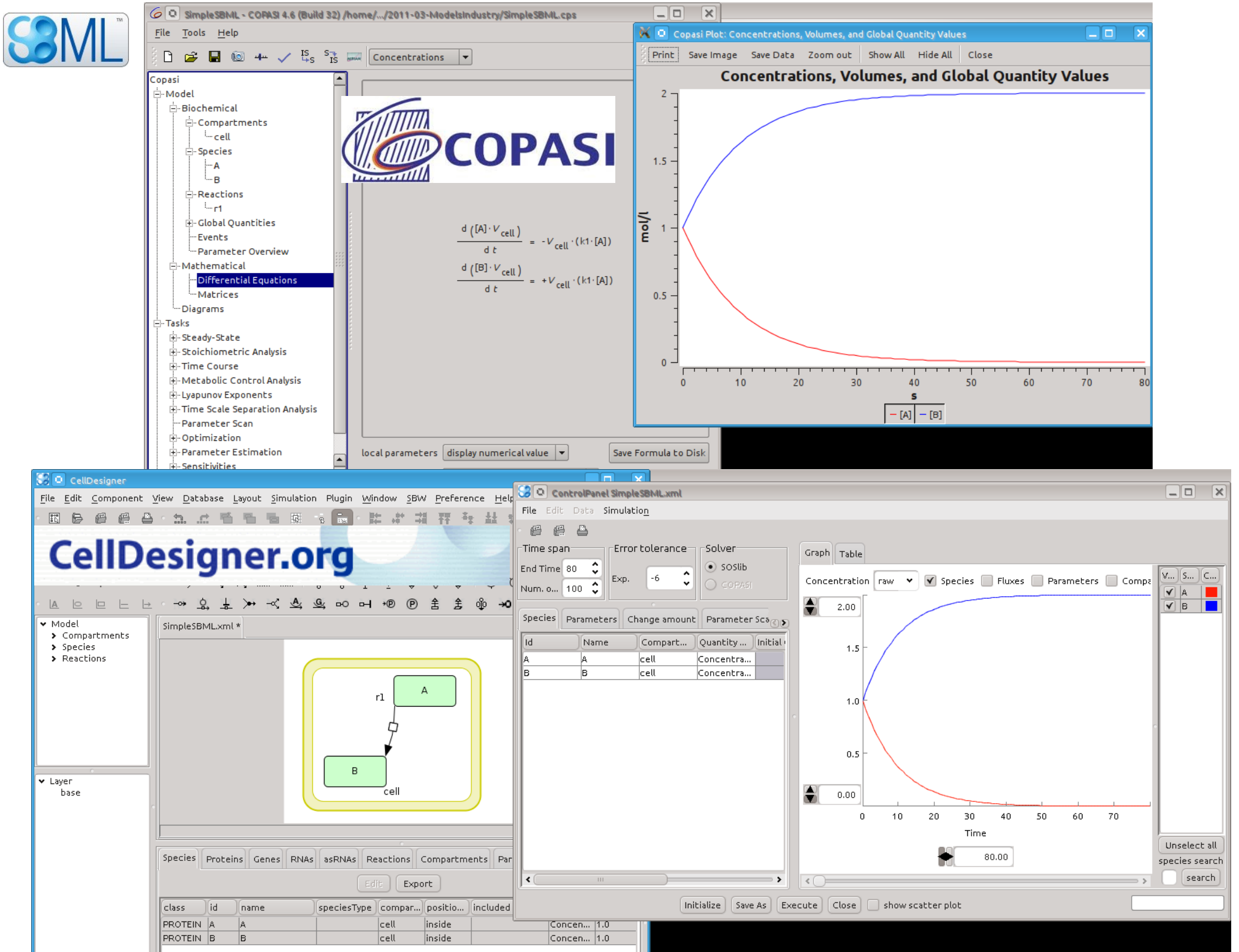
variables

relationships

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

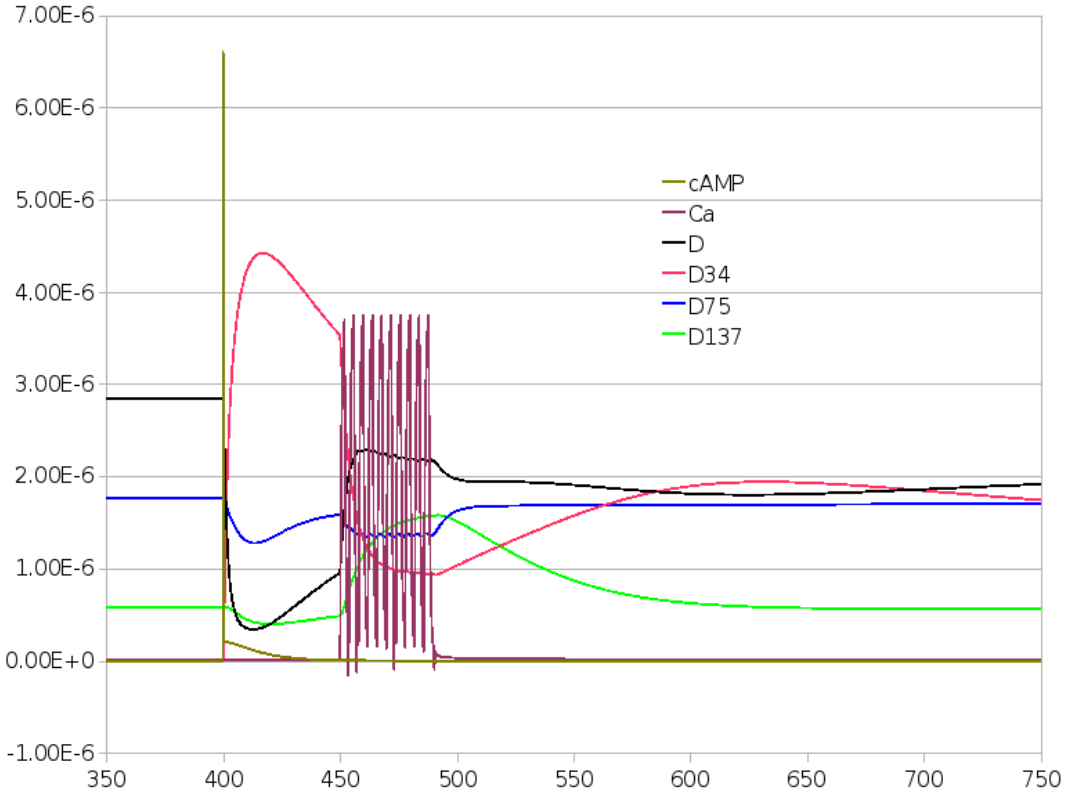
A very simple SBML file (A ⟶ B)

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


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

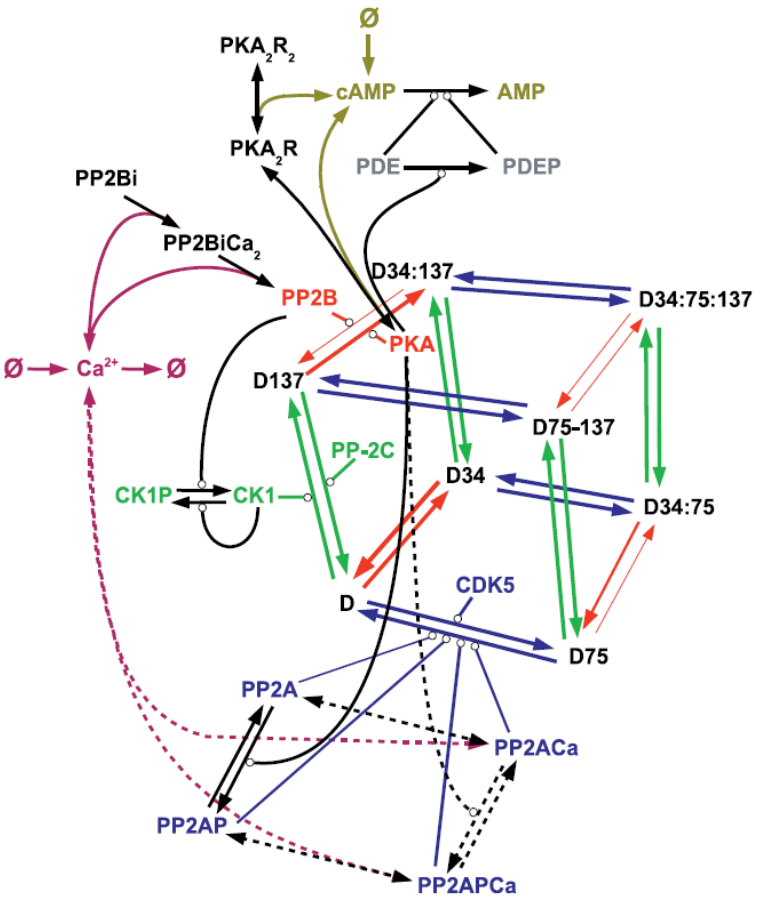
See presentation by Sven Sahle
tomorrow at 10:00

Biochemical models



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

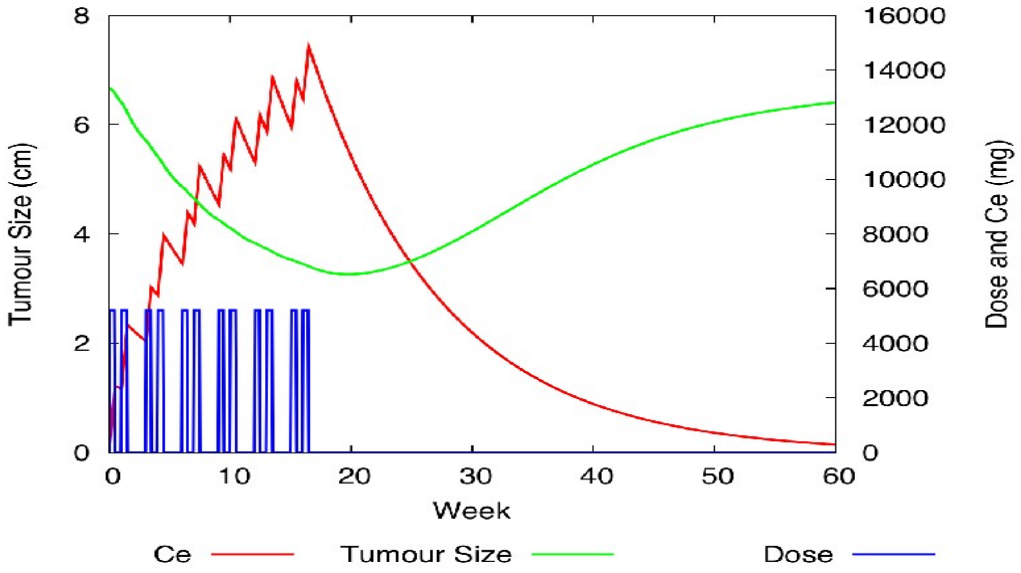
BioModels **BIOMD0000000153**



reaction:

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

Pharmacometrics models



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

BIOMD0000000234

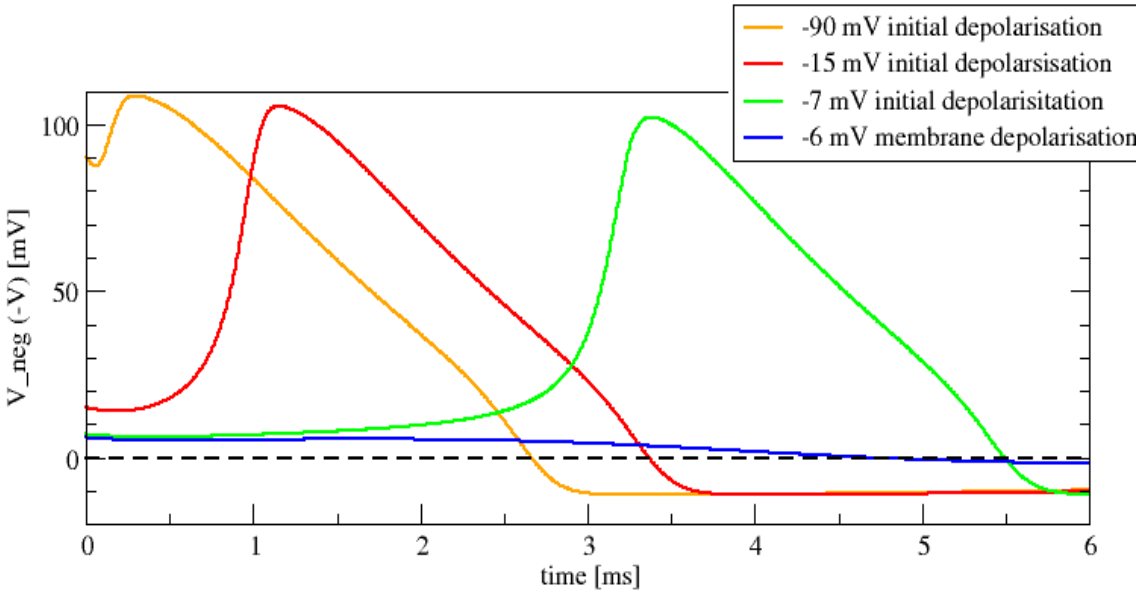
rate rule:

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

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.

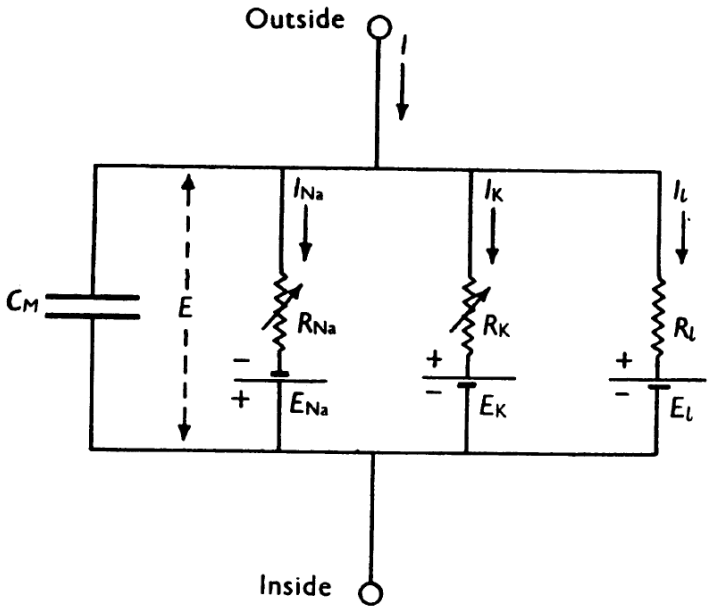
BIOMD0000000020

rate rule:

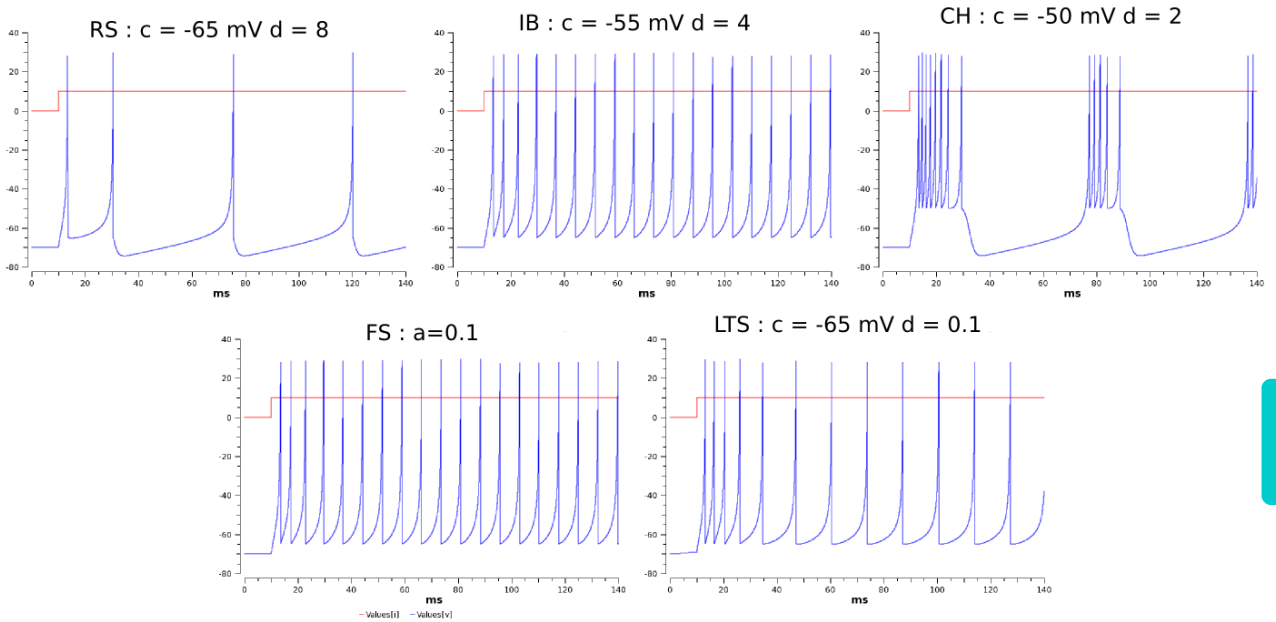
$$\frac{dv}{dt} = \frac{I - (i_{Na} + i_K + i_L)}{C_m}$$

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

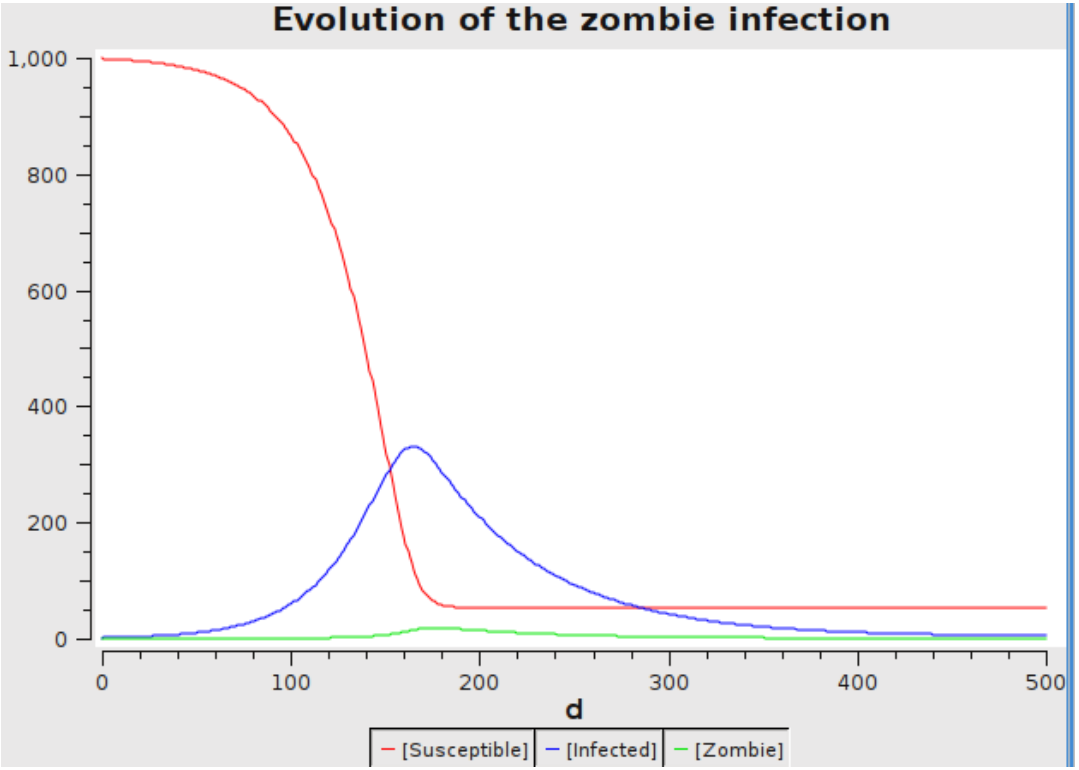
rate rule:

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

event:

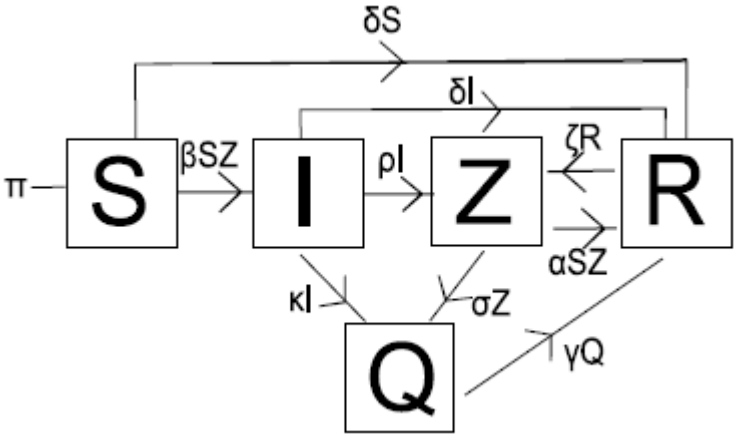
$$\text{when } v > V_{thresh} \begin{cases} v = c \\ U = U + d \end{cases}$$

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

BioModels 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: **214.**

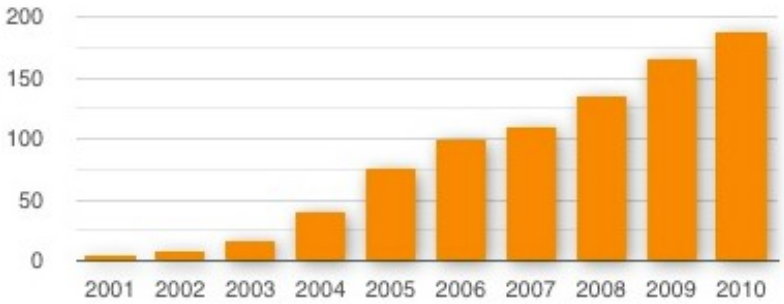
Please **use the survey form** to notify us about additions and suggestions.

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.

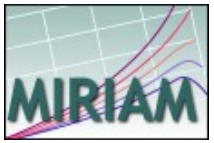


(Note: the flat period in 2007 is an artifact of inadequate record keeping rather than a lull in SBML software development.)

Adding the semantics to the syntax

	Models
Minimal requirements	
Data-models	
Ontologies	

Born in Heidelberg 2004



Minimum Information Required in the Annotation of Models (simplified)

Models must :

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

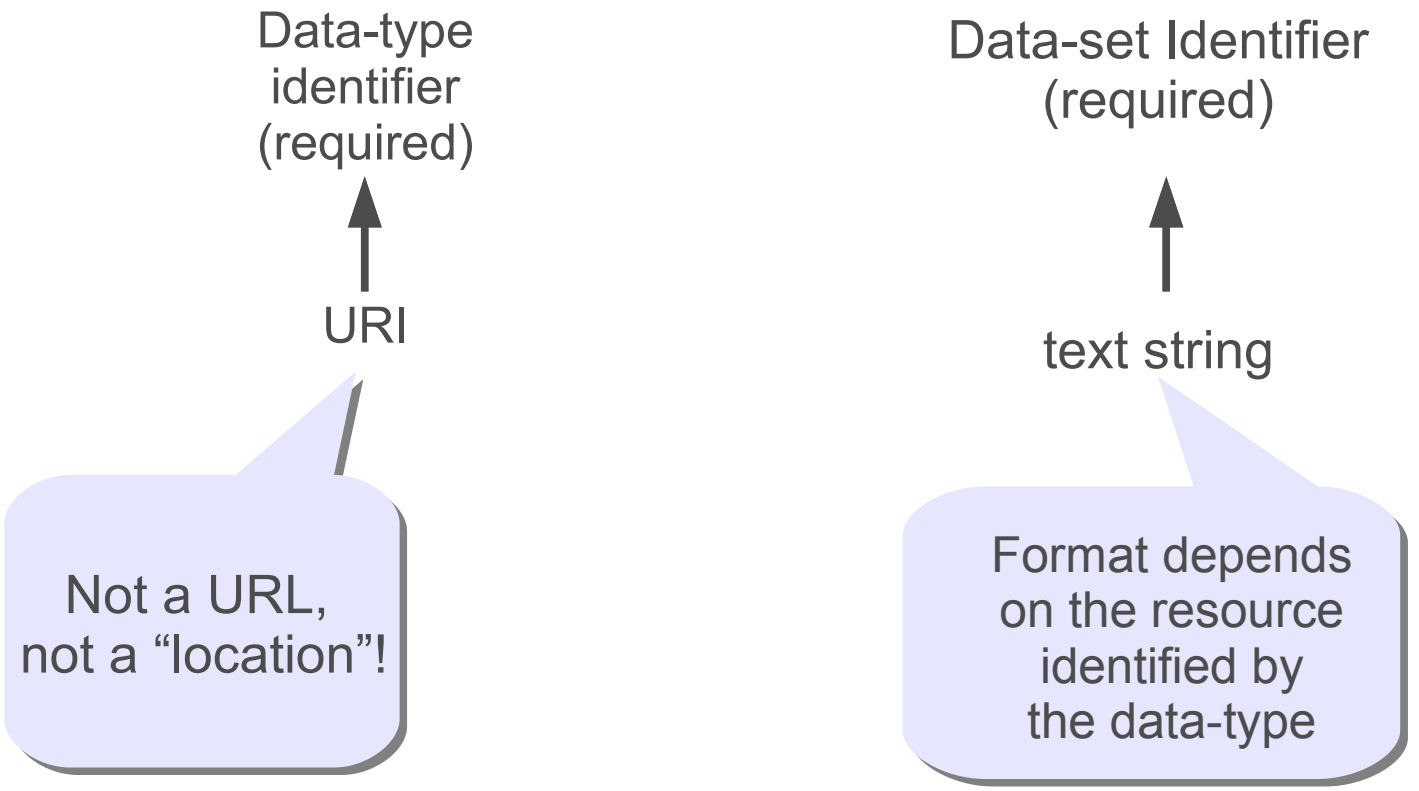
Le Novère *et al* (2005) *Nat Biotechnol*, 23: 1509-1515

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 identifiers



UniProt and P62158 (human calmodulin)
→ urn:miriam:uniprot:P62158

EC code and 1.1.1.1 (alcohol dehydrogenase)
→ urn:miriam:ec-code:1.1.1.1

Gene Ontology and GO:0000186 (activation of MAPKK activity)
→ urn:miriam:obo.go:GO%3A0000186

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

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

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

Databases | Tools | EBI Groups | Training | Industry | About Us | Help | Site Index

EBI > Groups > Computational Neurobiology > Research > MIRIAM Resources

- 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.

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).

eb Services (based 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 Syst Biol*, 1: 58

Data type: *Enzyme Nomenclature*

General | Tags | Annotation

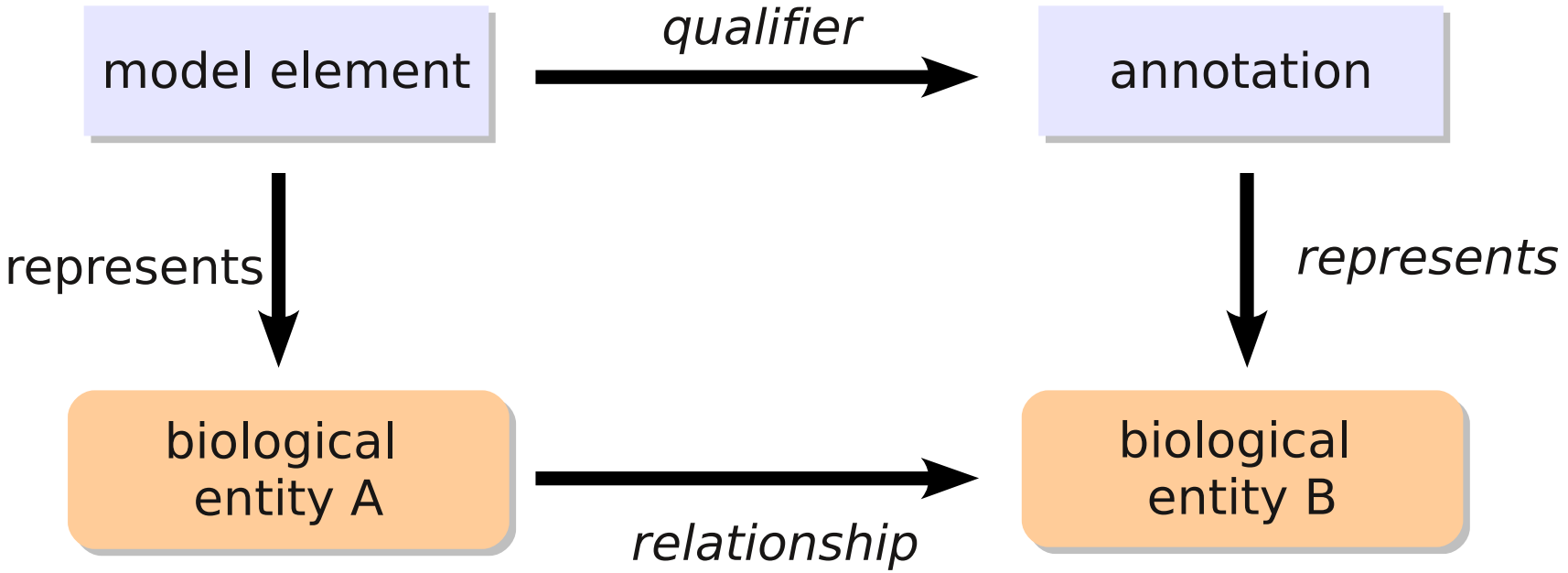
General information about the data type

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

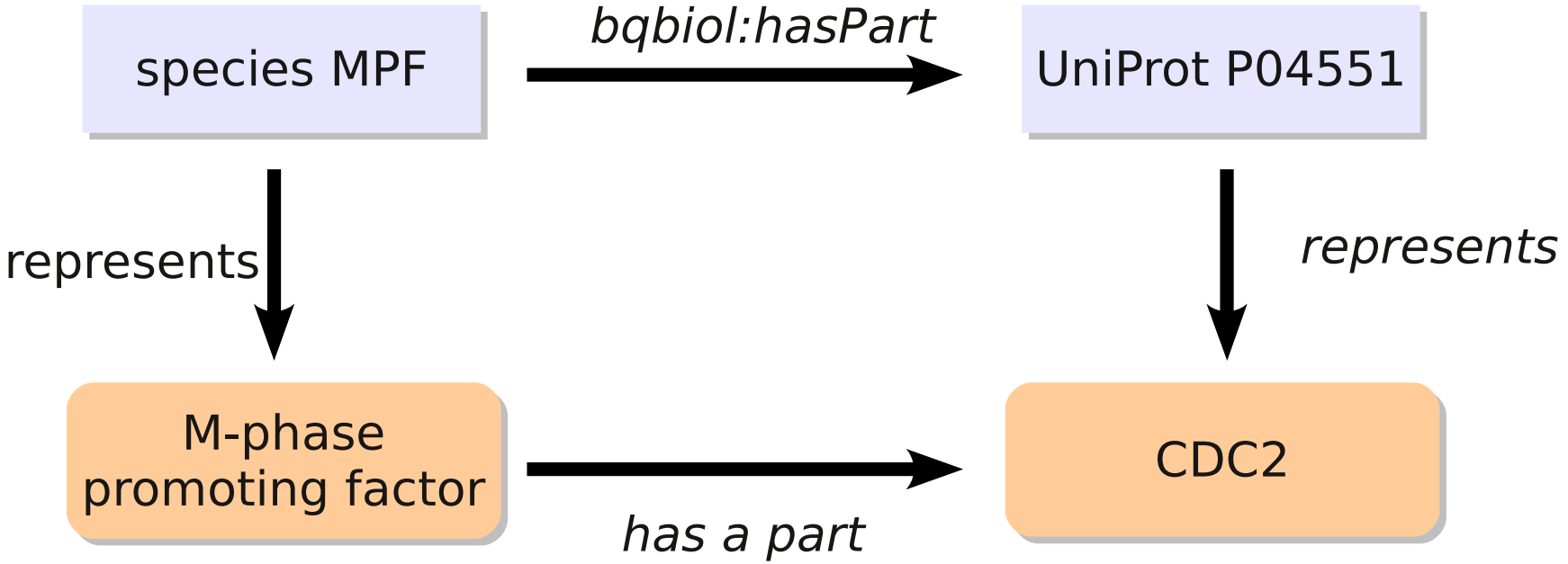
Go back to the list of data types

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>
```

Systems Biology Ontology

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

BIOMODELS.NET

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

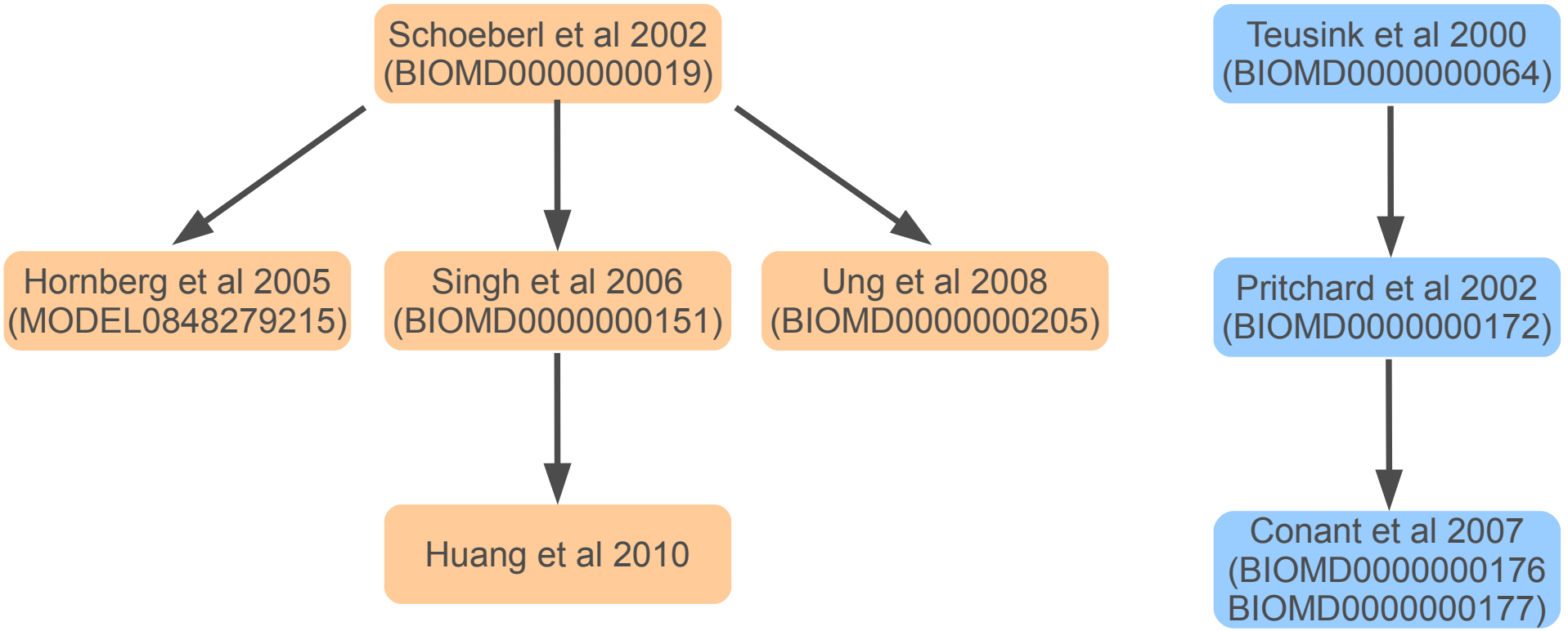
Essential activator

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

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

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

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



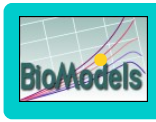
Standard formats generate new research

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

MODEL0072364382: 2152 species, 1857 reactions

  - stoichiometric map, no concentrations, no kinetics

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



MODEL1001200000: 1748 species, 1059 reactions

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

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

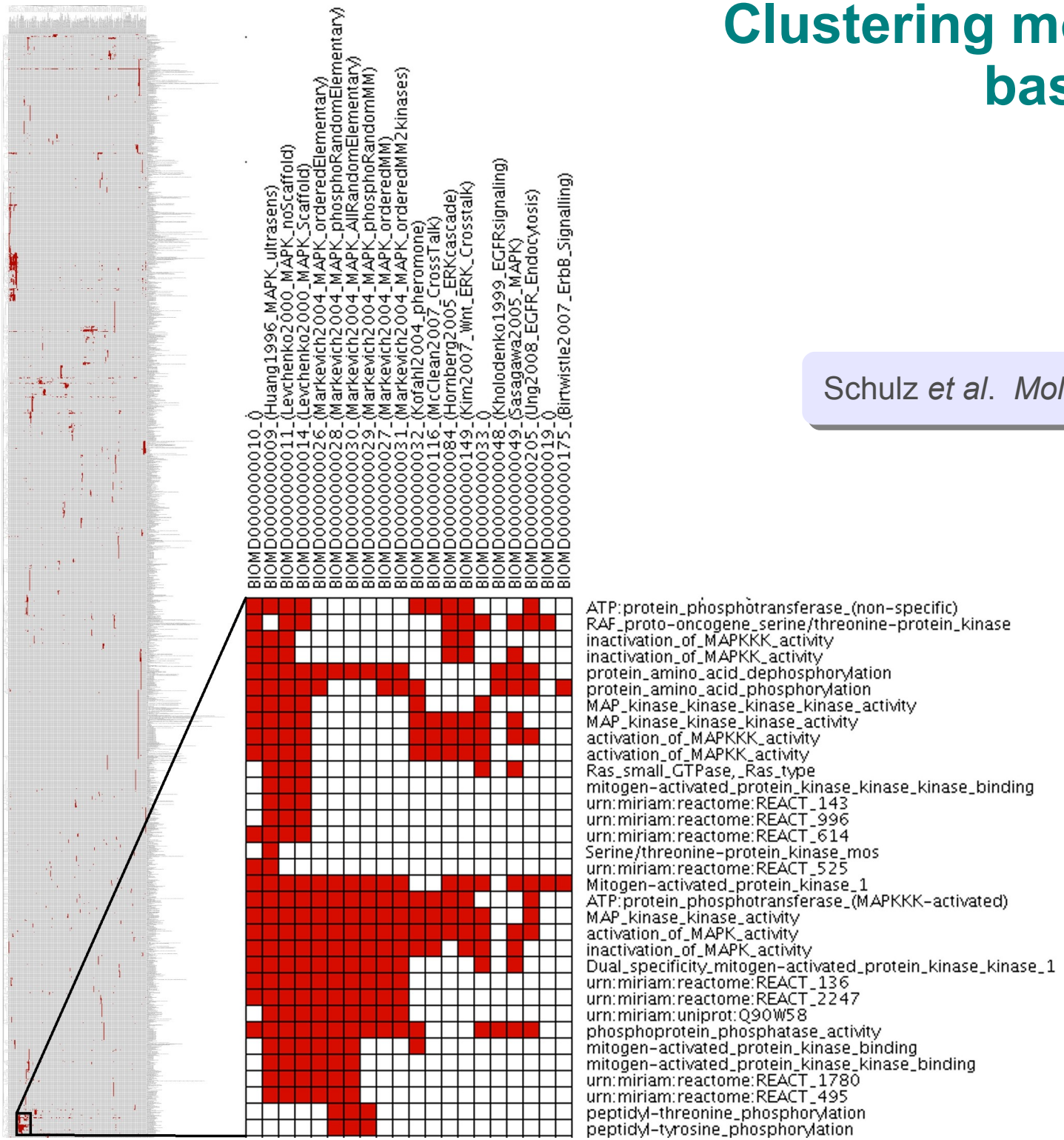
MODEL1012110000: 2657 species, 1865 reactions

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

MODEL1012110001

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

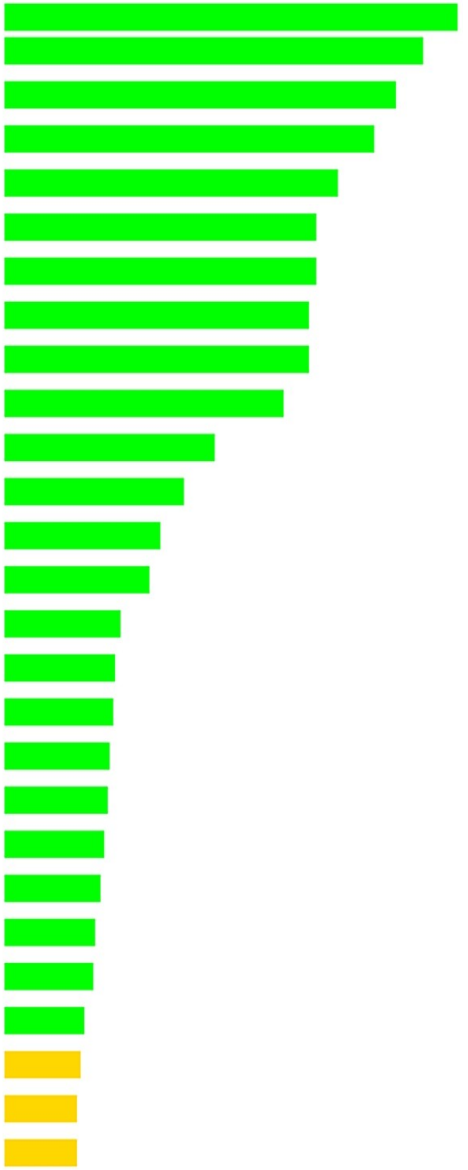
Clustering models (and data) based on metadata



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

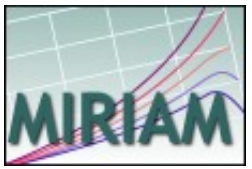
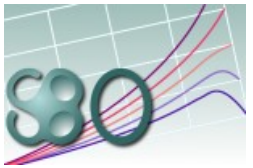
Ranking and retrieval of models

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



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

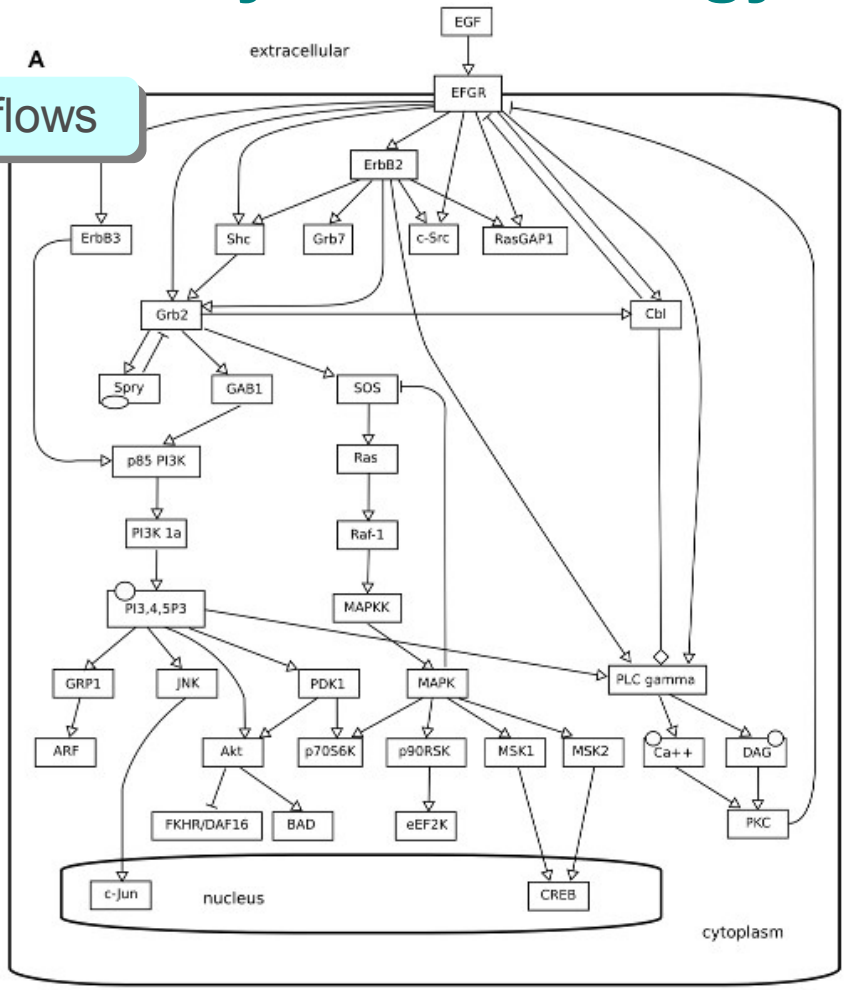
The interface with all biologists

	Models
Minimal requirements	
Data-models	
Ontologies	

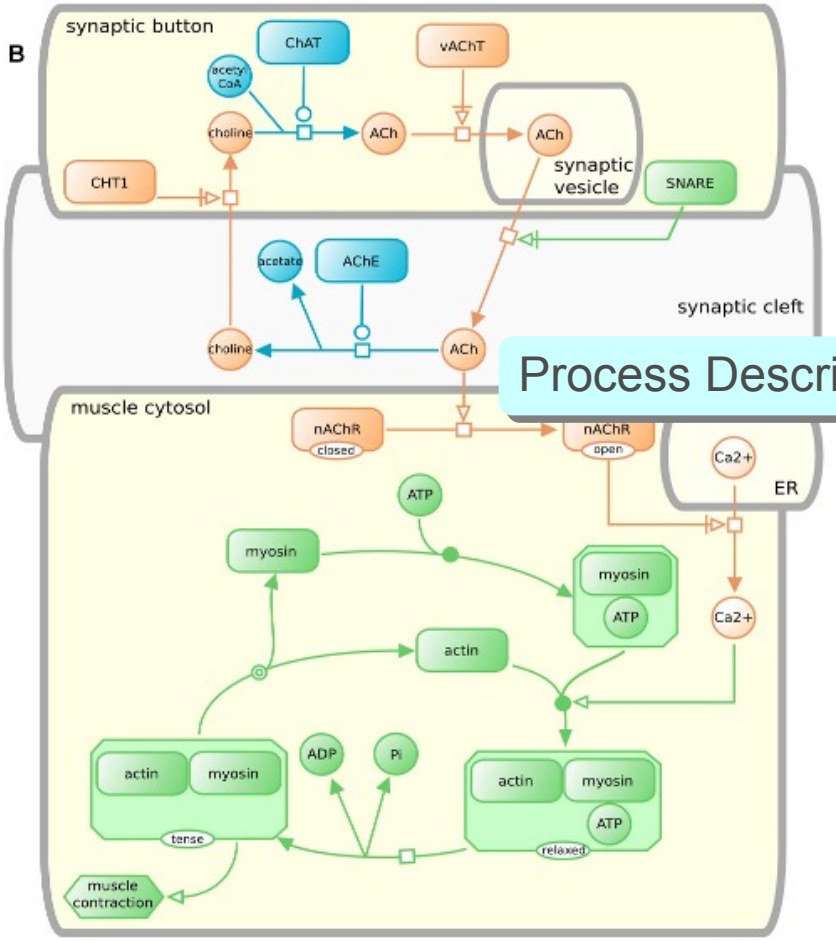
Born in Tokyo 2005

Systems Biology Graphical Notation

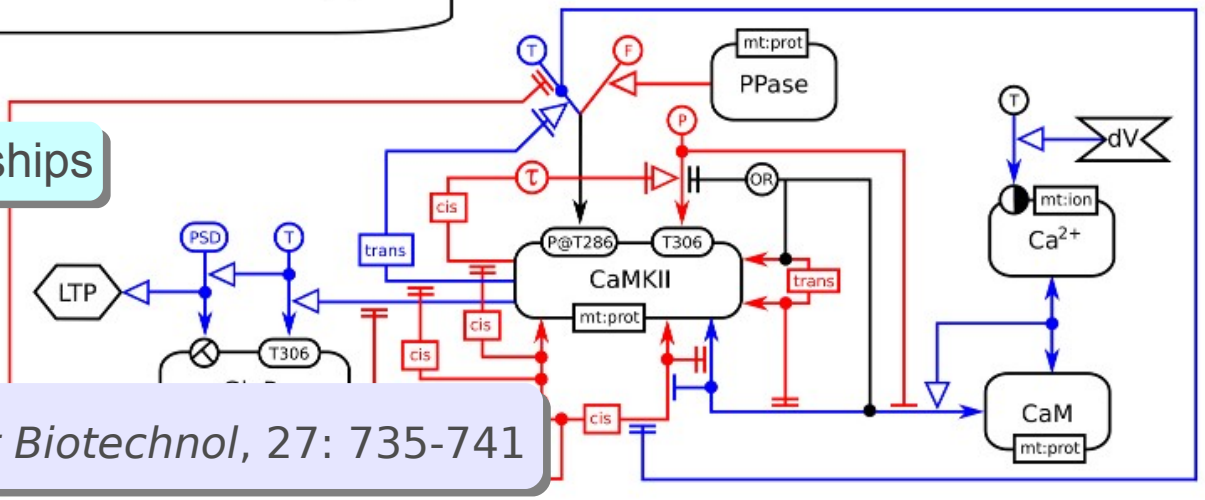
Activity flows



Process Descriptions

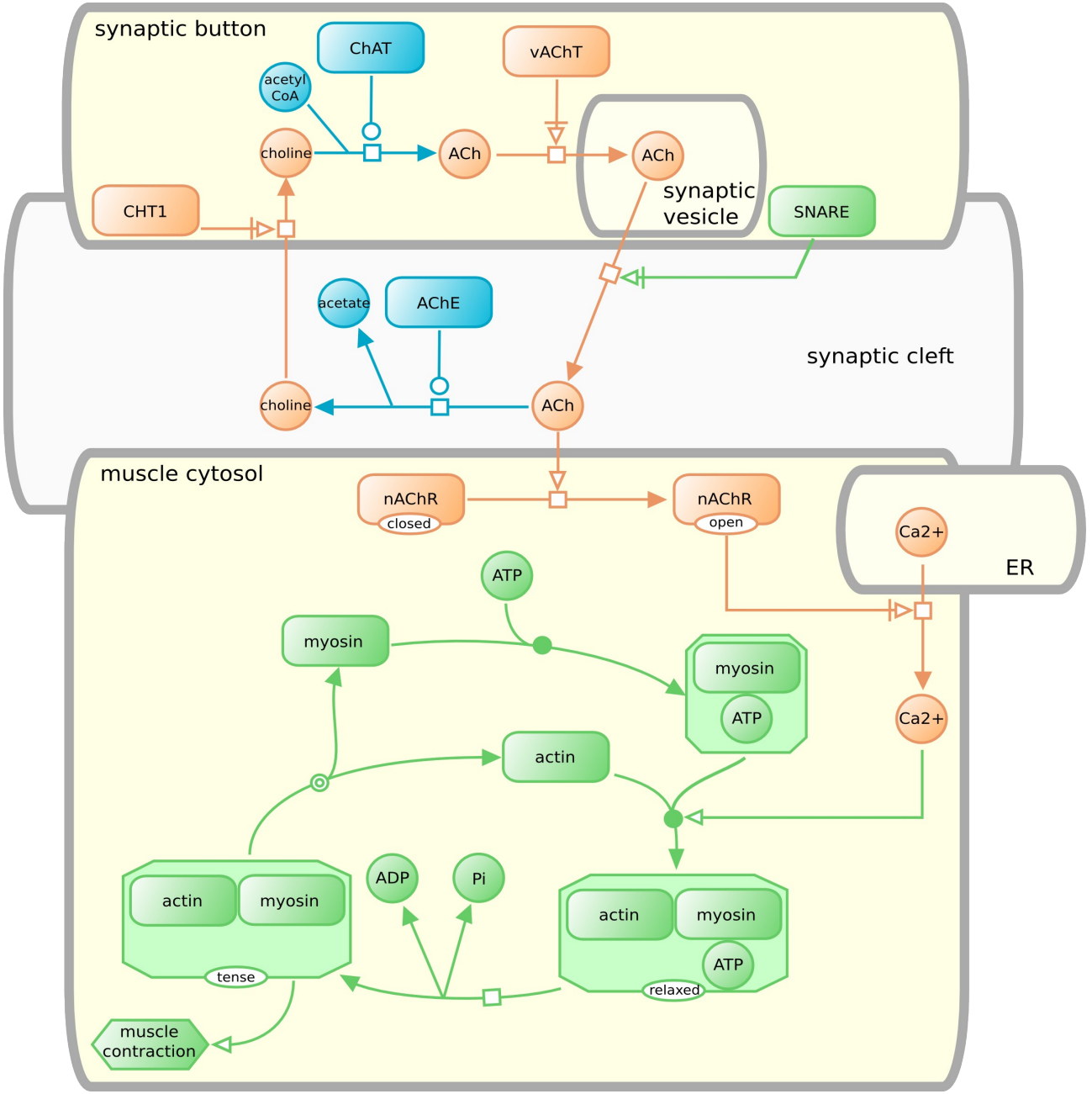


Entity Relationships



Le Novère et al (2009) *Nat Biotechnol*, 27: 735-741

Linking SBGN maps to external information

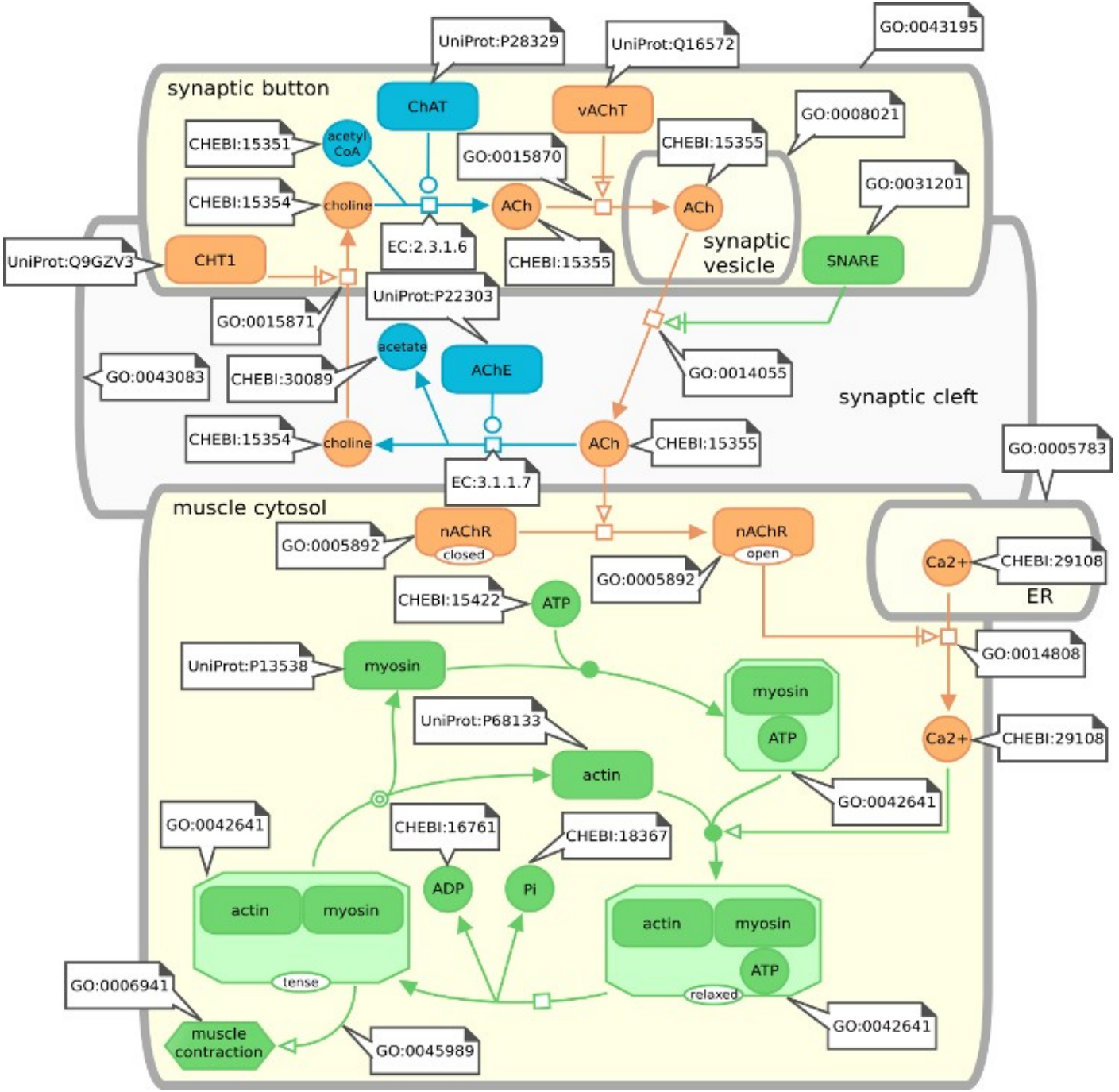


catalytic processes

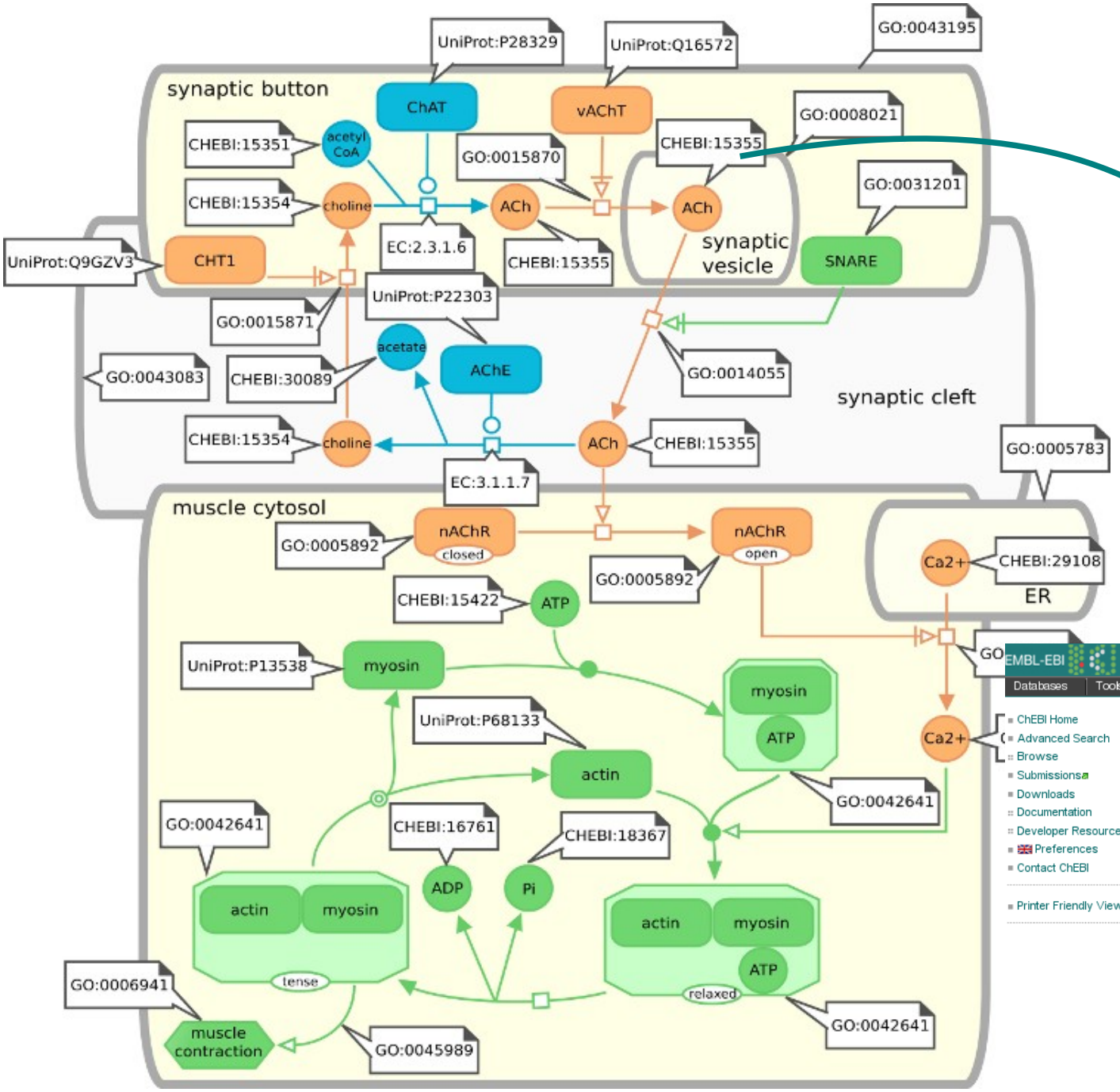
transport processes

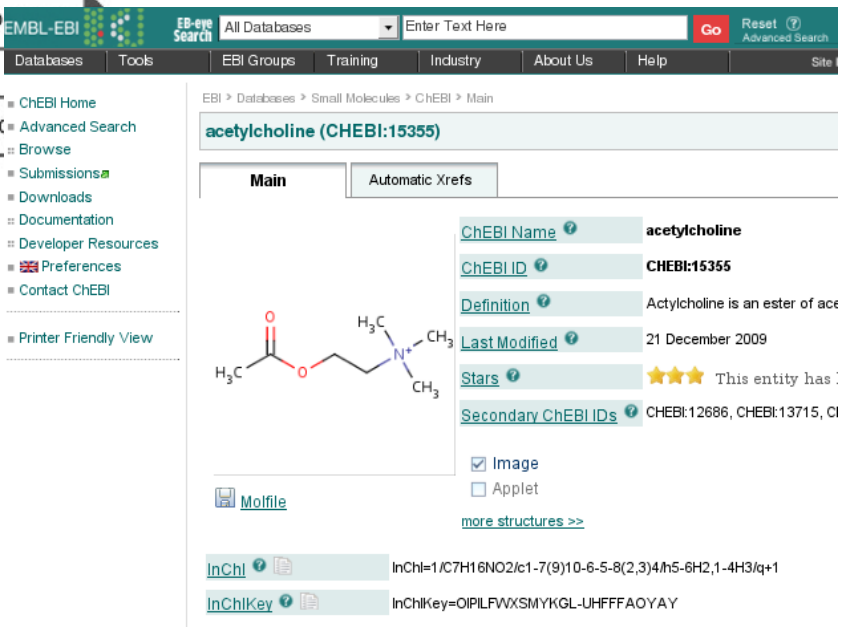
contractile proteins

Linking SBGN maps to external information



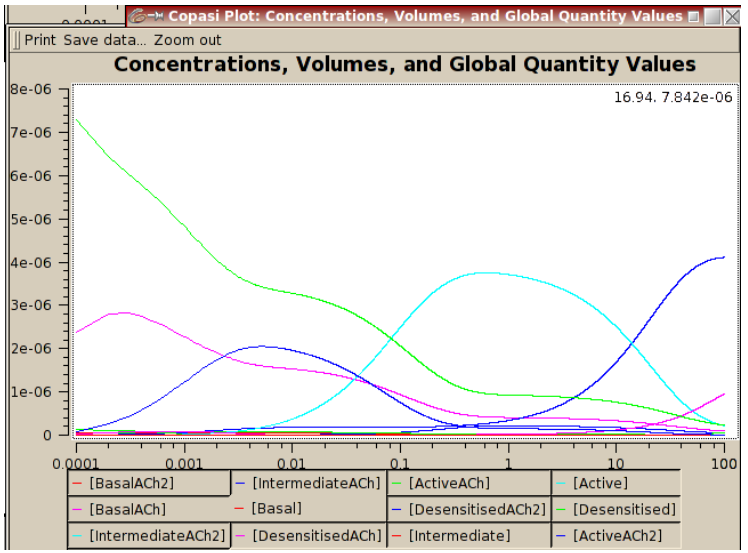
Linking SBGN maps to external information



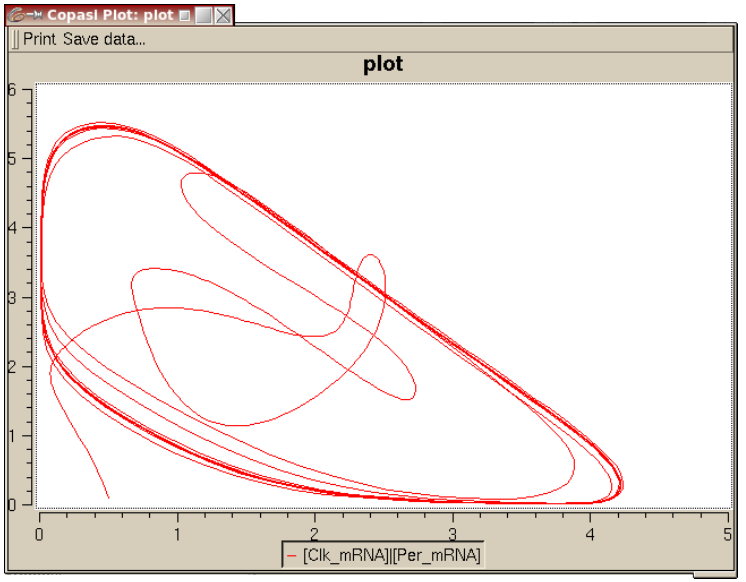


Reproduction of published simulation results

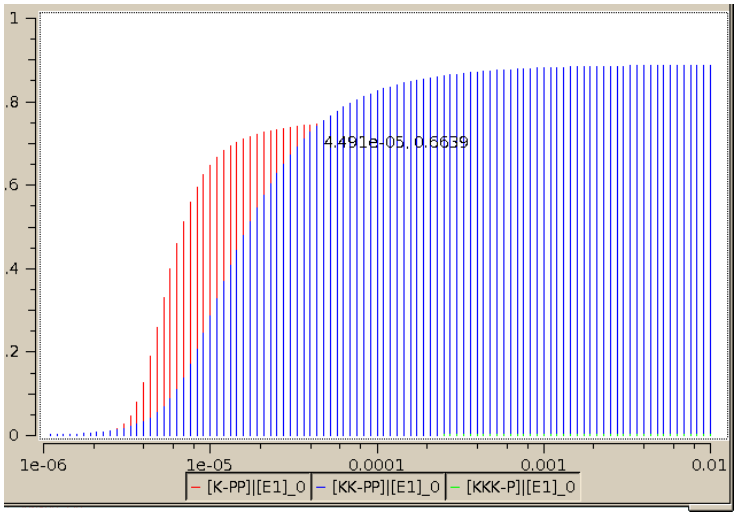
Edelstein et al 1996 (BIOMD0000000002)



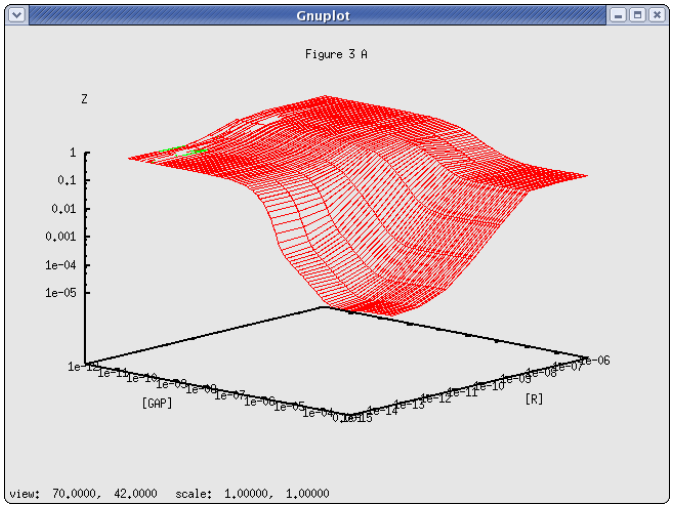
Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)



Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)



Description of simulations and analyses

	Models	Simulations and analysis
Minimal requirements	MIRIAM	MIASE
Data-models	SBML, SBGN	SED-ML
Ontologies	SBO	KISAO

Born in Hinxton 2007

Description of model simulation and analysis

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

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

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

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

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

Courtot et al *submitted*

General structure of SED-ML

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

Köhn D.,Le Novère N. *Lect Notes Bioinfo*, 5307: 176-190.

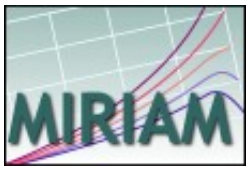
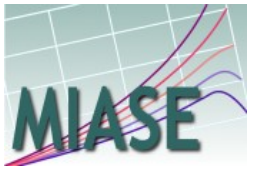
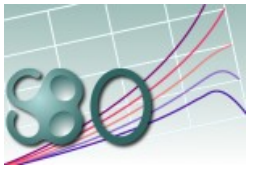
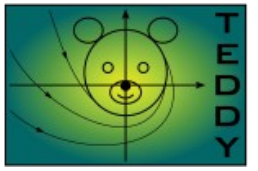
Characterising dynamical behaviours

	Models	Simulations and analysis	results
Minimal requirements	MIRIAM	MIASE	
Data-models	SBML, SBGN	SED ML	SBRML
Ontologies	SBO	KISAO	TEDDY

Is the matrix of standards complete?

	Models	Simulations and analysis	results
Minimal requirements	MIRIAM	MIASE	
Data-models	SBML, SBGN	SED ML	SBRML
Ontologies	SBO	KISAO	TEDDY

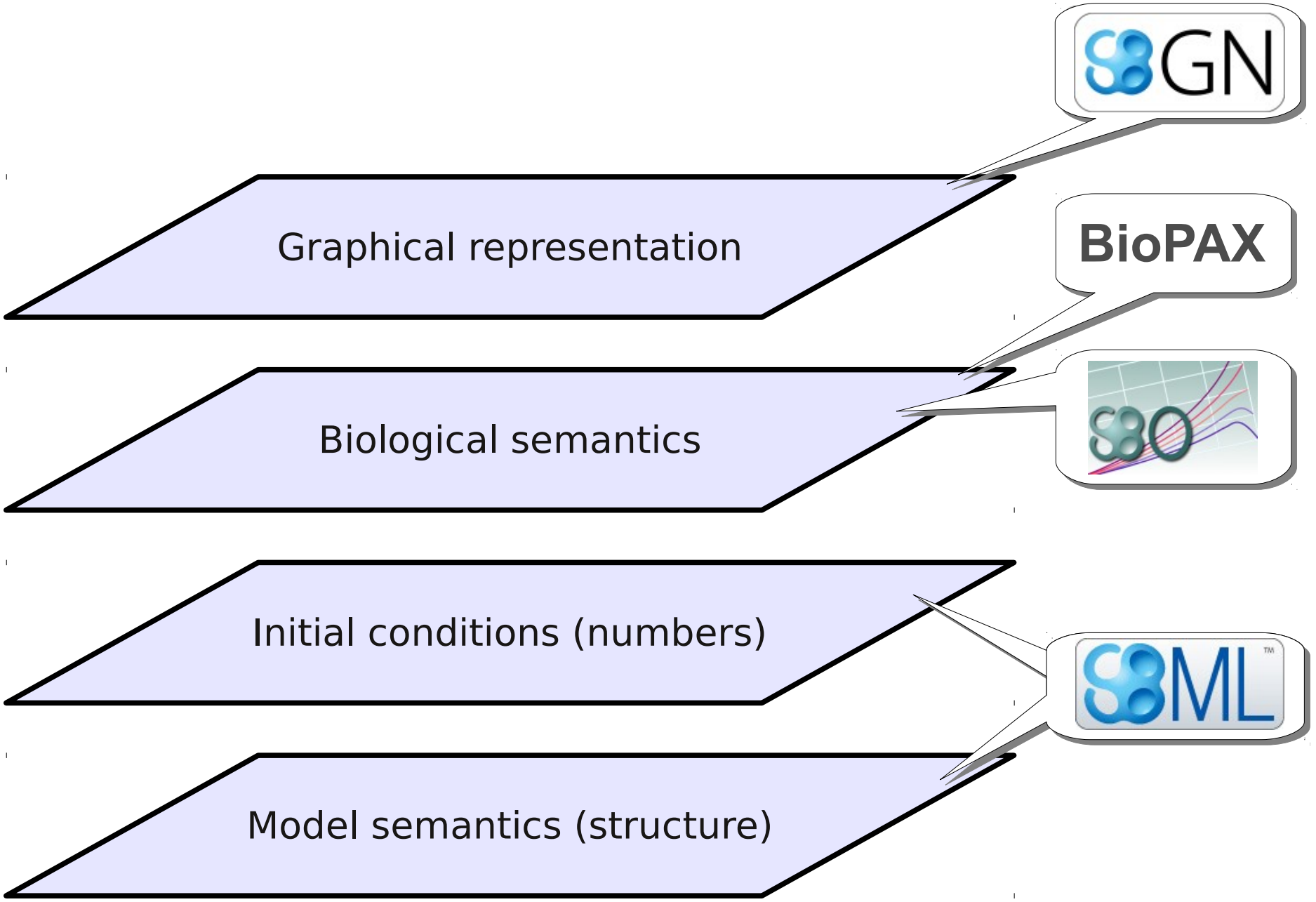
Is the matrix of standards complete?

	Models	Simulations and analysis	results
Minimal requirements			
Data-models			SBRML
Ontologies			

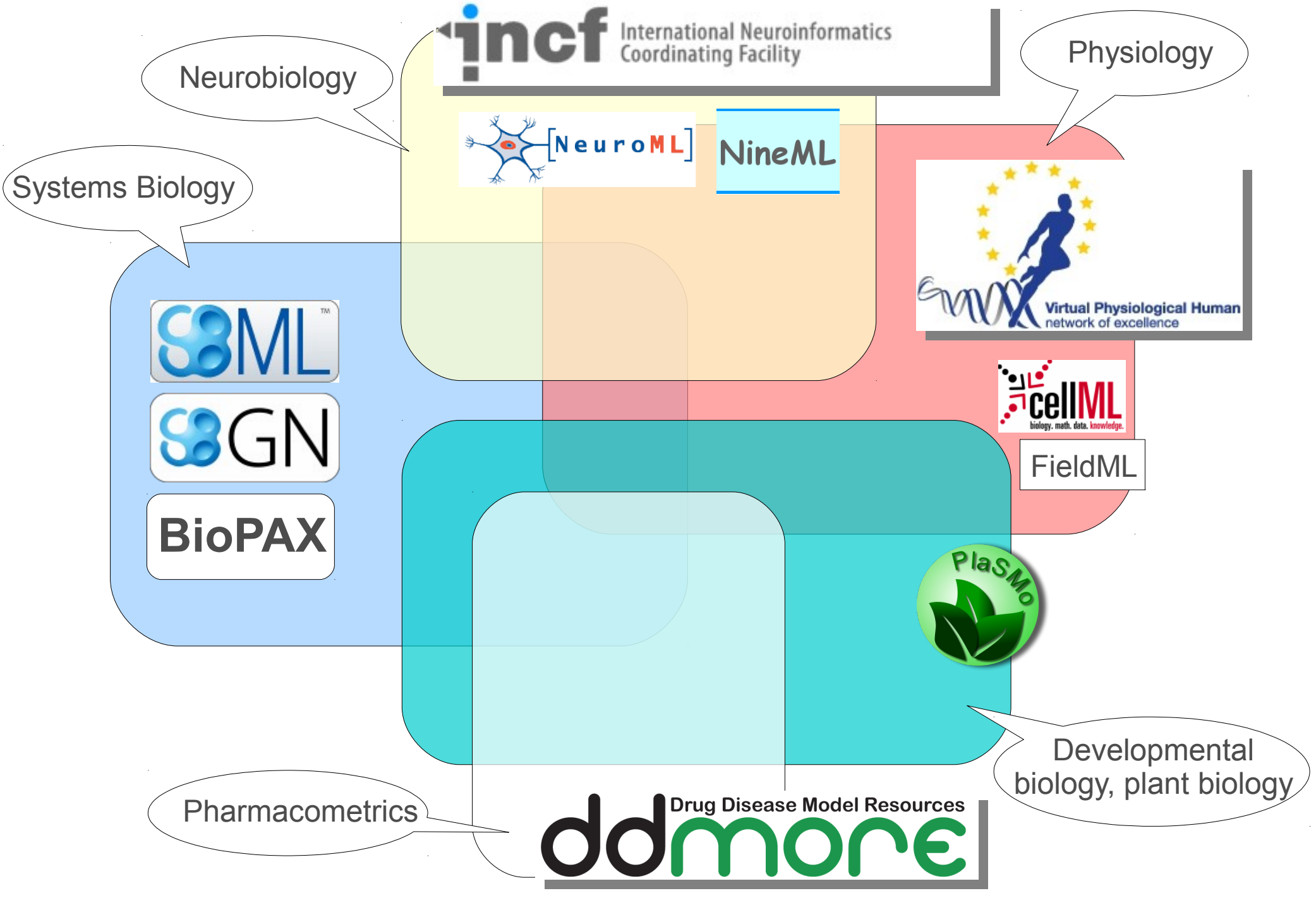
Covering the entire model life-cycle

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

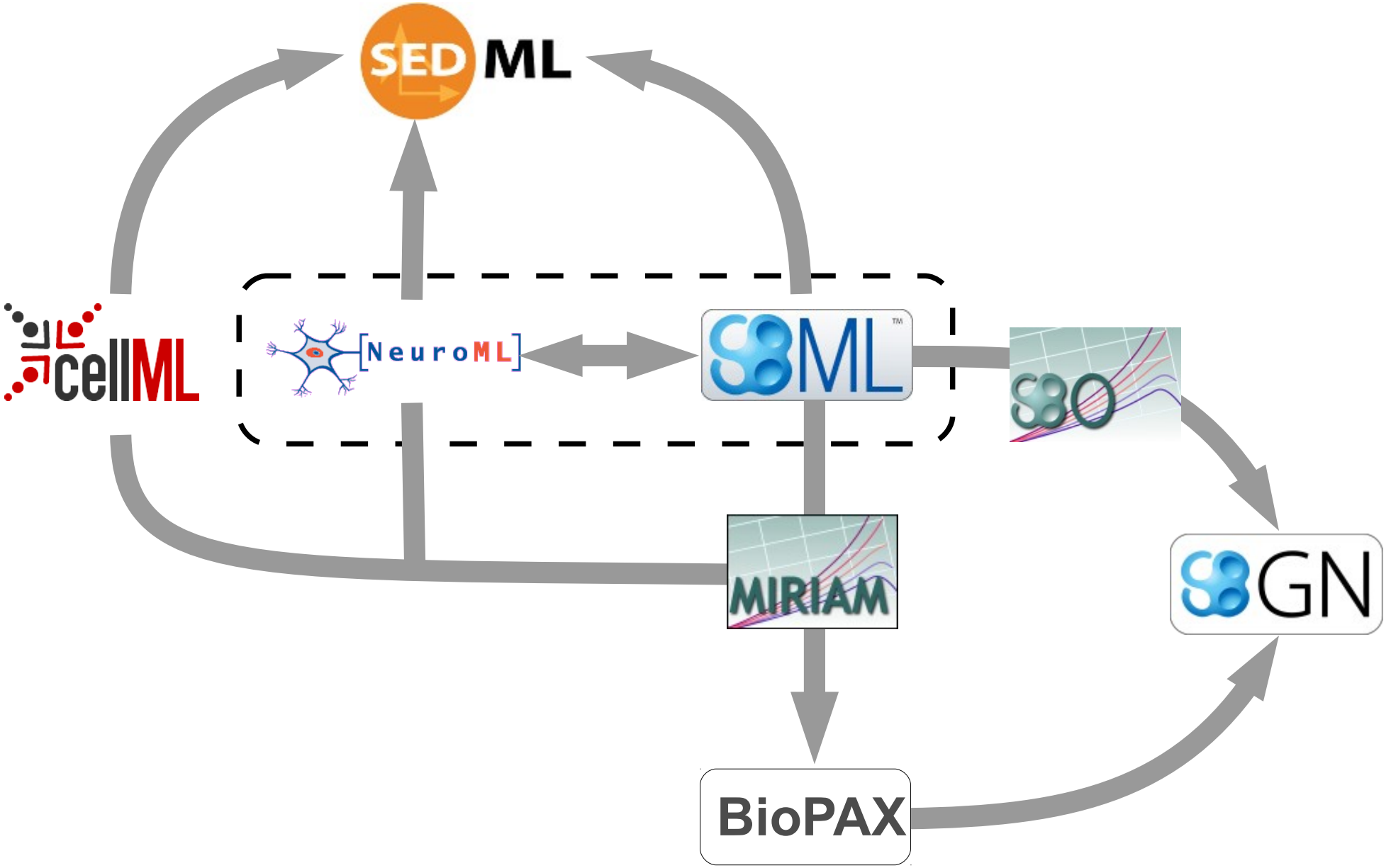
Disentangling the level of discourse



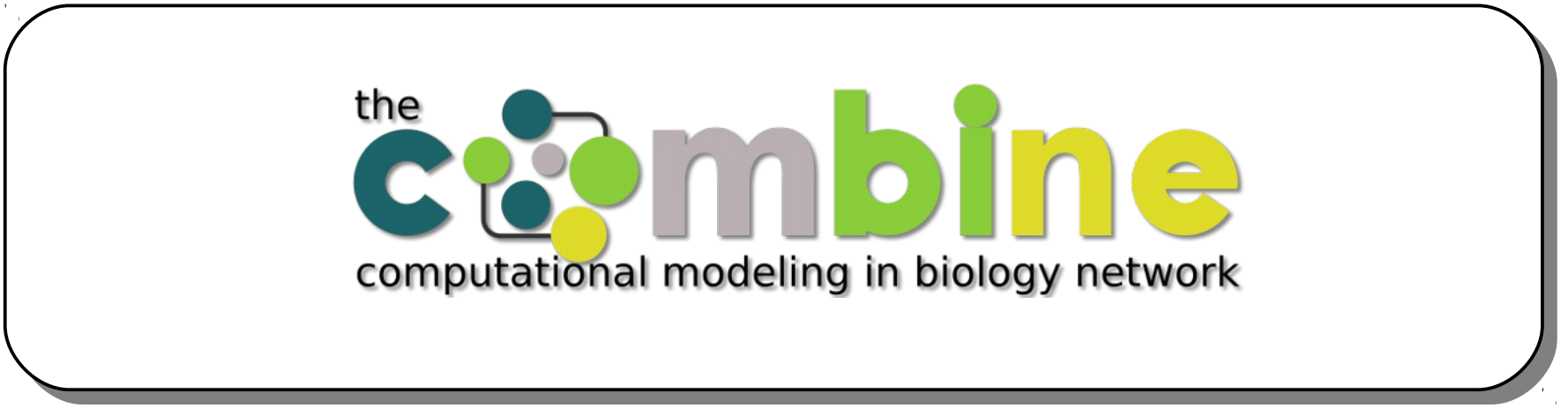
Parallel and redundant efforts



Existing standards interoperability



Overarching standardisation structure



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

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

General data resources

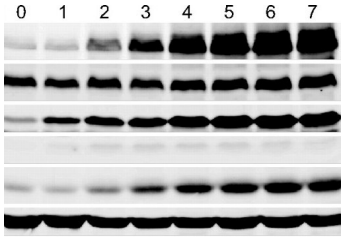
Biomedical literature

Specialist data resources

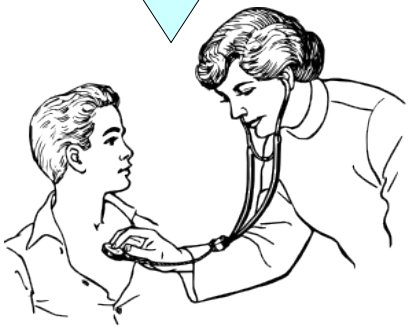
Standard interoperable formats to encode models and metadata

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

Theoretical models



Basic biochemistry and cell biology



Clinical and pharmaceutical models

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The whole community of Computational Systems Biology

The EBI group Computational Systems Neurobiology