EMBL-EBI

Models For All

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

Nicolas Le Novère

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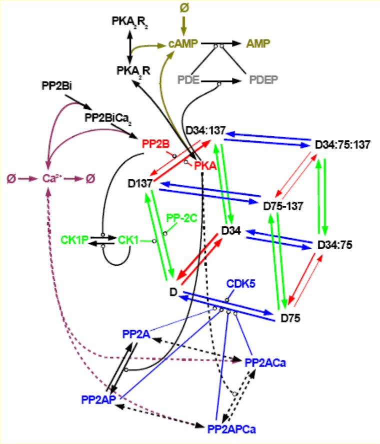
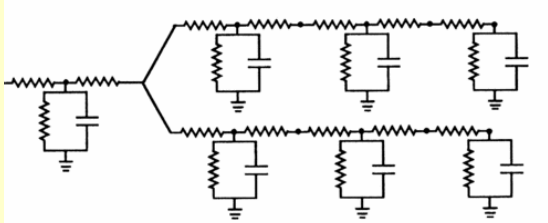
Standards for Describing the Whole Life-Cycle of Modeling in Life Sciences

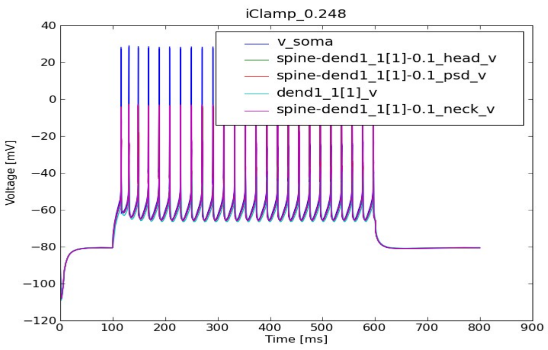
Nicolas Le Novère, EMBL-EBI

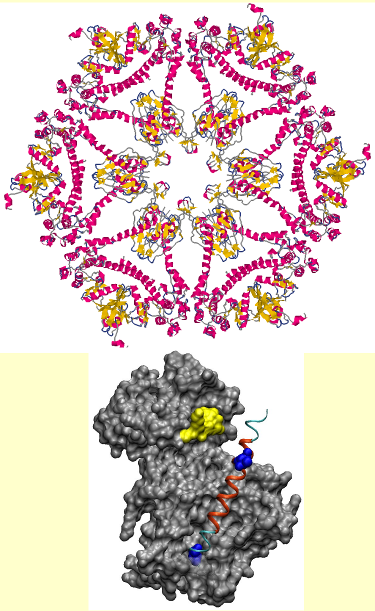
Themes and projects of the Le Novère group

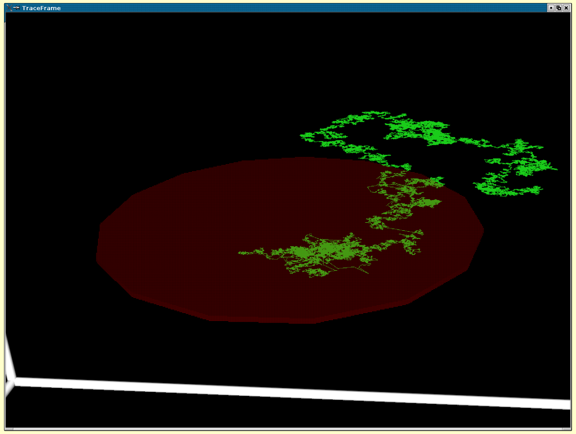
Computational Neurobiology











Computational Systems Biology

SBML™

SBGN

SBO

TEDDY

KISAO

MIRIAM

MIASE

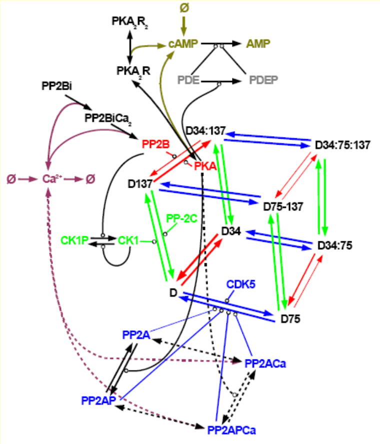
ε-MeP

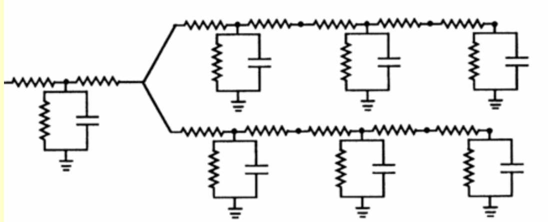
Ligand-Gated Ion Channel database

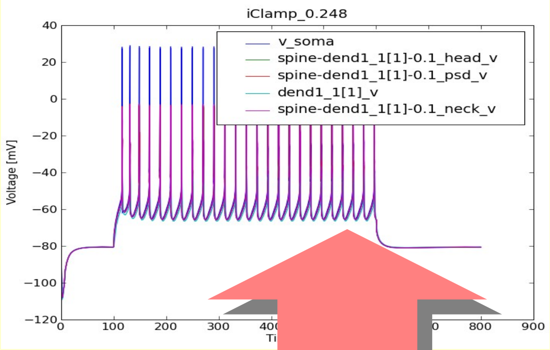
BioModels

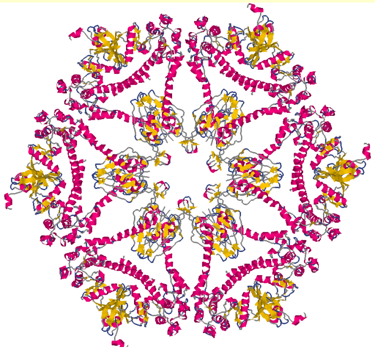
Themes and projects of the Le Novère group

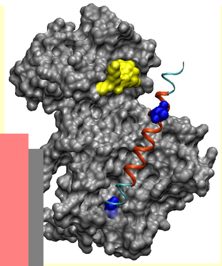
Computational Neurobiology

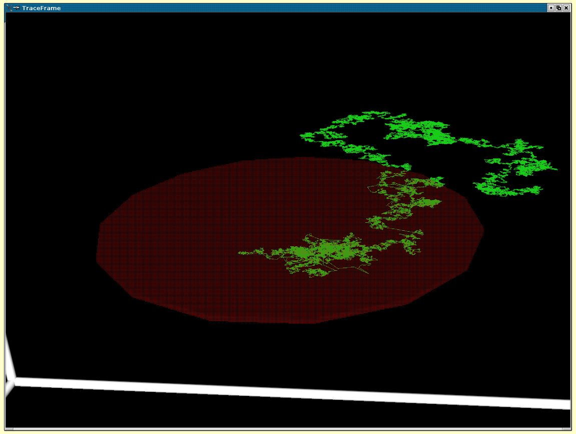












SBML

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Computational Systems Biology

MIRIAM

MIASE

BioModels

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

---

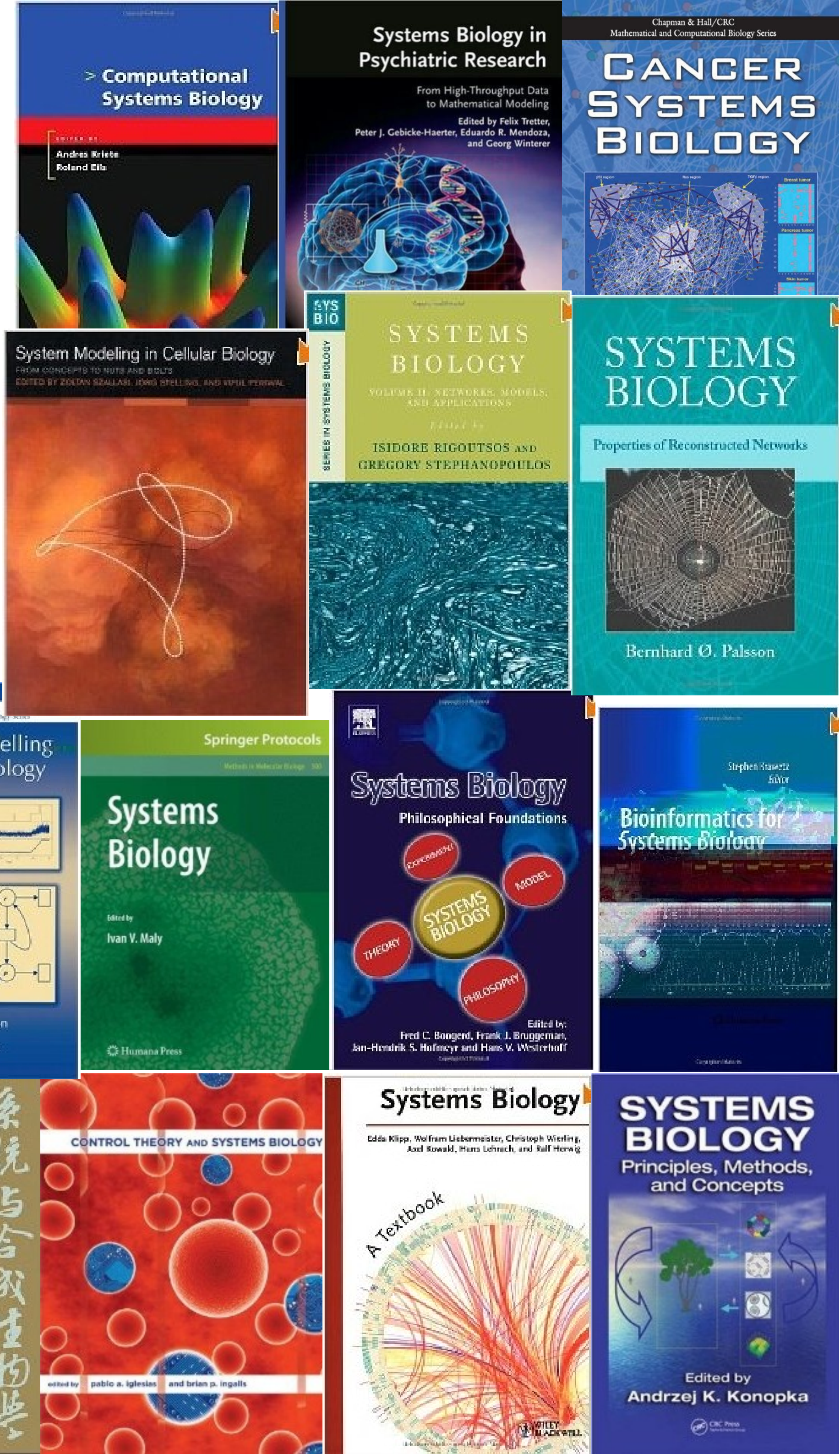
New Generation Computing, 18(2000)199-216
Ohmsha, Ltd. and Springer-Verlag

NEW GENERATION COMPUTING
©Ohmsha, Lt

Invited Paper

Perspectives on Systems Biology

Hiroaki KITANO
Sony Computer Science Laboratories, Inc.


Computational Systems Biology
Edited by Andres Kriete, Roland Eils

Systems Biology in Psychiatric Research
From High-Throughput Data to Mathematical Modeling
Edited by Felix Tretter, Peter J. Gebicke-Haerter, Eduardo R. Mendoza, and Georg Winterer

Chapman & Hall/CRC Mathematical and Computational Biology Series
CANCER SYSTEMS BIOLOGY

System Modeling in Cellular Biology
From Concepts to Nuts and Bolts
Edited by Zoltan Szallasi, Jörg Stelling, and Vipul Periwal

SYSTEMS BIOLOGY
Volume II: Networks, Models, and Applications
Isidore Rigoutsos and Gregory Stephanopoulos

SYSTEMS BIOLOGY
Properties of Reconstructed Networks
Bernhard Ø. Palsson

Springer Protocols
Systems Biology
Edited by Ivan V. Maly
Humana Press

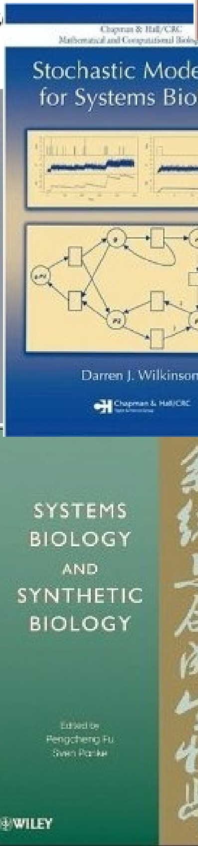
Systems Biology
Philosophical Foundations
Edited by: Fred C. Boogerd, Frank J. Bruggeman, Jan-Hendrik S. Hofmeyr and Hans V. Westerhoff

Stephen Krawetz
Bioinformatics for Systems Biology

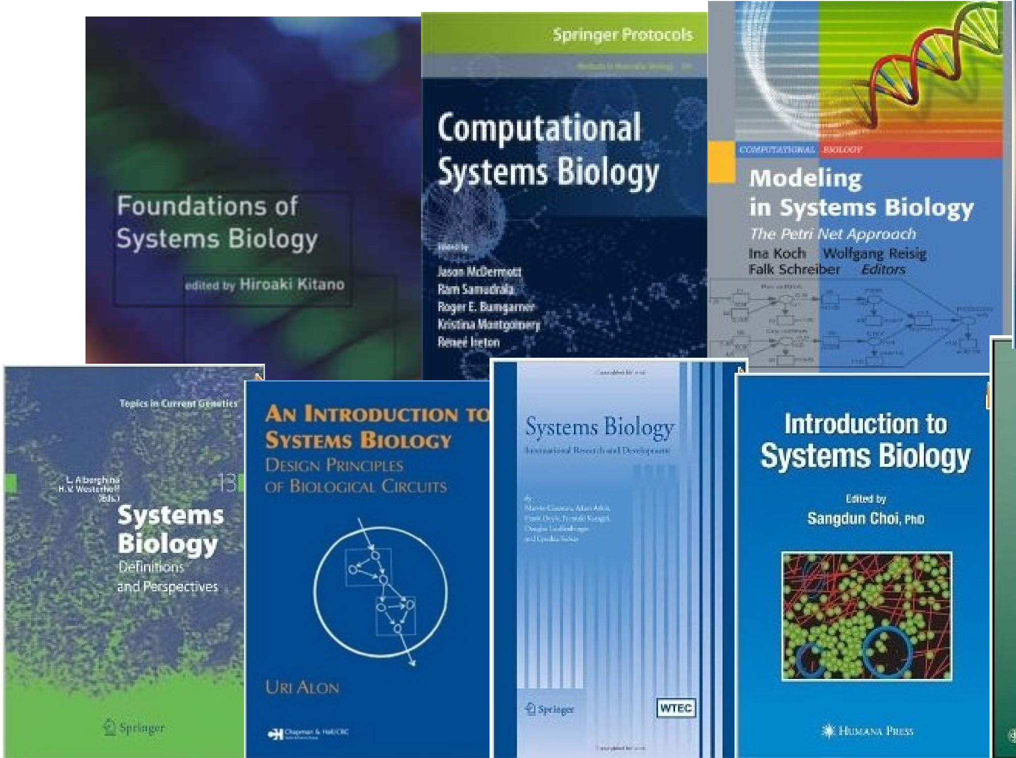
CONTROL THEORY AND SYSTEMS BIOLOGY
edited by pablo a. iglesias and brian p. ingalls

Systems Biology
Edda Klipp, Wolfram Liebermeister, Christoph Wierling, Axel Kowald, Hans Lehrach, and Ralf Herwig
A Textbook
Wiley-Blackwell

SYSTEMS BIOLOGY
Principles, Methods, and Concepts
Edited by Andrzej K. Konopka


Chapman & Hall/CRC Mathematical and Computational Biology Series
Stochastic Modelling for Systems Biology
Darren J. Wilkinson
Chapman & Hall/CRC

SYSTEMS BIOLOGY AND SYNTHETIC BIOLOGY
Edited by Pengcheng Fu, Sven Panke
WILEY
系统与合成生物学


Foundations of Systems Biology
edited by Hiroaki Kitano

Springer Protocols
Computational Systems Biology
Edited by Jason McDermott, Ram Samudrala, Roger E. Bumgarner, Kristina Montgomery, Reneé Ireton

Computational Biology
Modeling in Systems Biology
The Petri Net Approach
Ina Koch, Wolfgang Reisig, Falk Schreiber, Editors

Topics in Current Genetics 13
L. Alberghina, H.V. Westerhoff (Eds.)
Systems Biology
Definitions and Perspectives
Springer

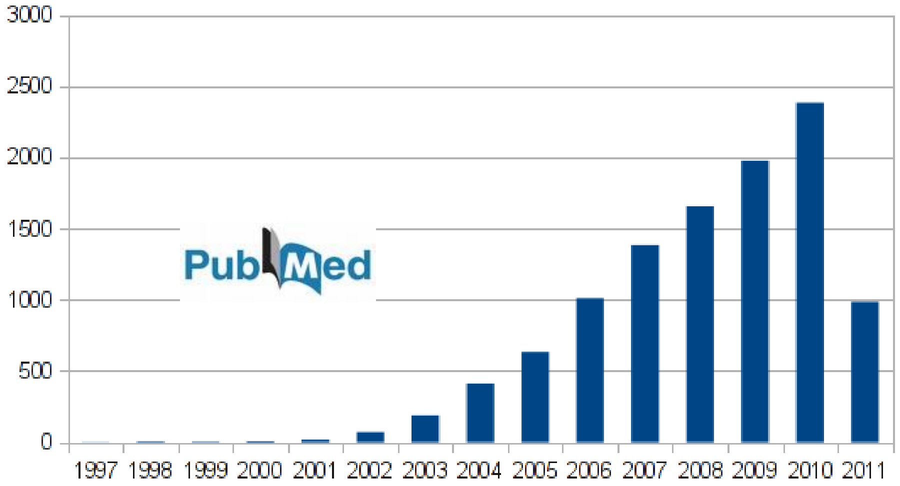
AN INTRODUCTION TO SYSTEMS BIOLOGY
DESIGN PRINCIPLES OF BIOLOGICAL CIRCUITS
URI ALON
Chapman & Hall/CRC

Systems Biology
International Research and Development
Springer
WTEC

Introduction to Systems Biology
Edited by Sangdun Choi, PhD
Humana Press

What is Systems Biology?

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



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

Systems-wide analysis (omics)

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

Application of systems-theory

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

Nobel Symposium on Systems Biology (June 2009)

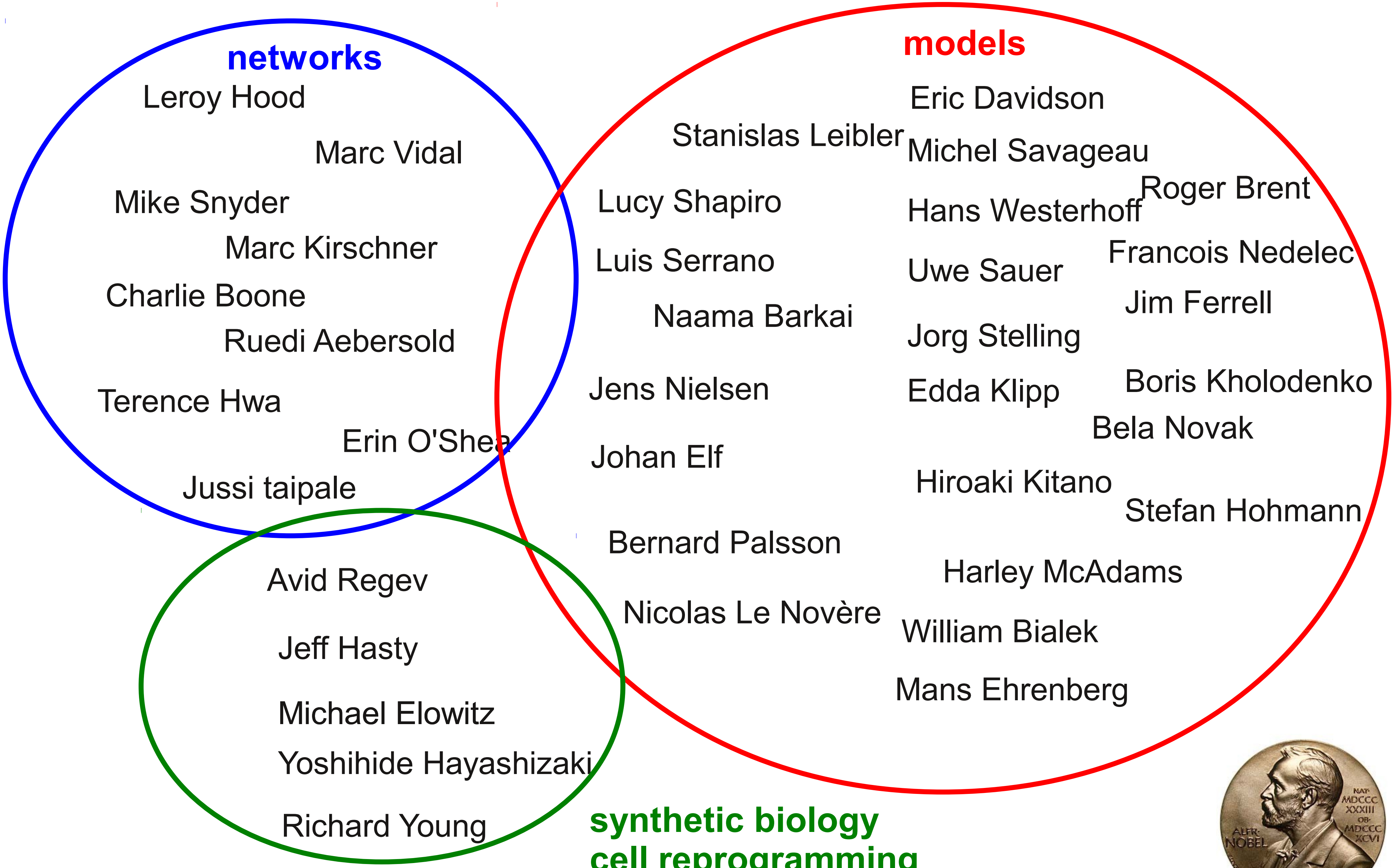
networks

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

models

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

Nobel Symposium on Systems Biology (June 2009)



networks

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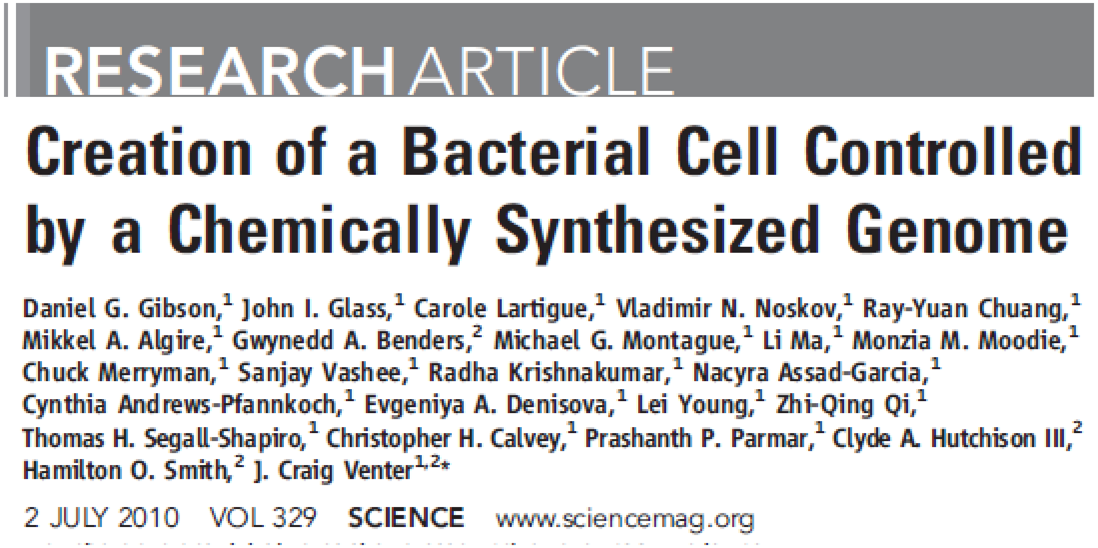
Stefan Hohmann
Bernard Palsson
Harley McAdams
Nicolas Le Novère
William Bialek
Mans Ehrenberg

synthetic biology
cell reprogramming

Avid Regev
Jeff Hasty
Michael Elowitz
Yoshihide Hayashizaki
Richard Young

What happened to biology at the end of XXth century?

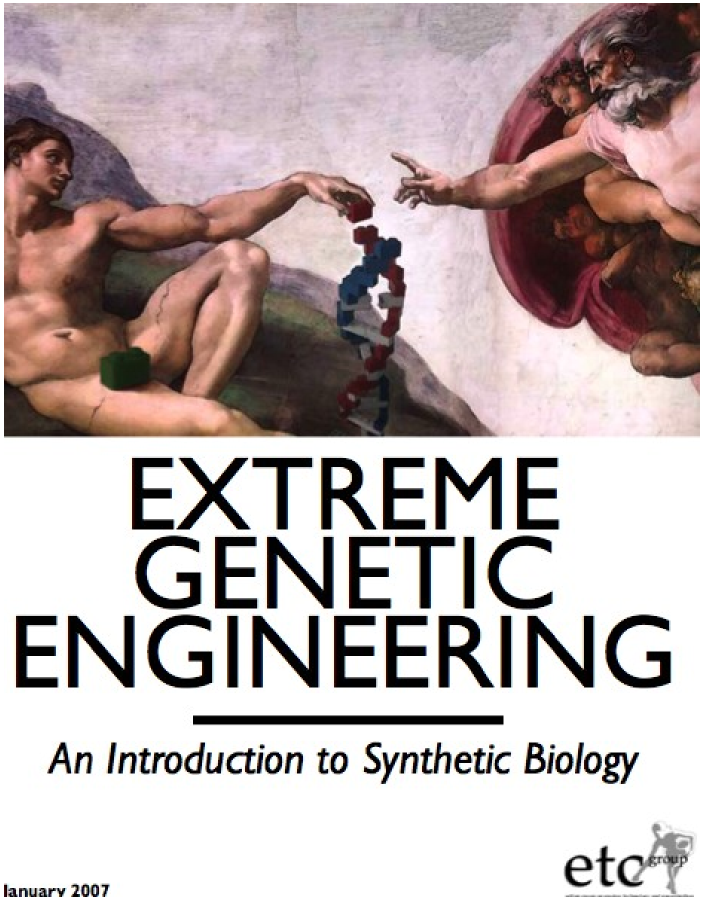


RESEARCH ARTICLE

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

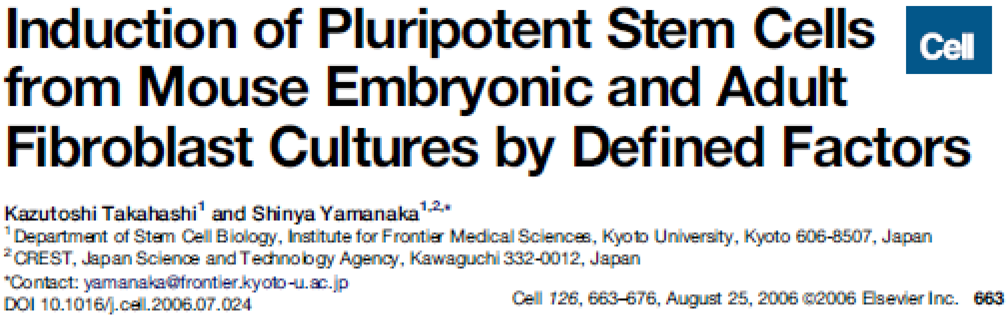


EXTREME GENETIC ENGINEERING

An Introduction to Synthetic Biology

January 2007

etc group



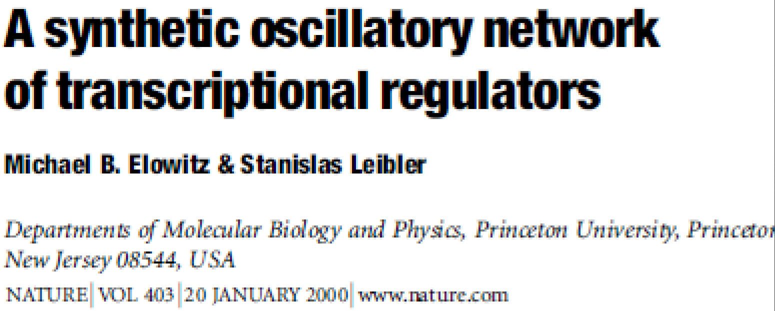
Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

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

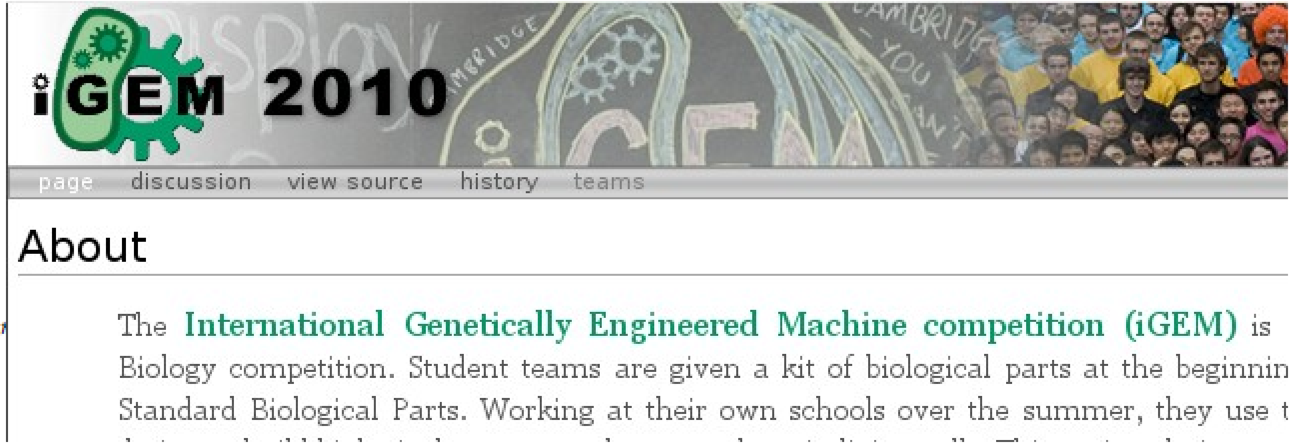


A synthetic oscillatory network of transcriptional regulators

Michael B. Elowitz & Stanislas Leibler

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

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

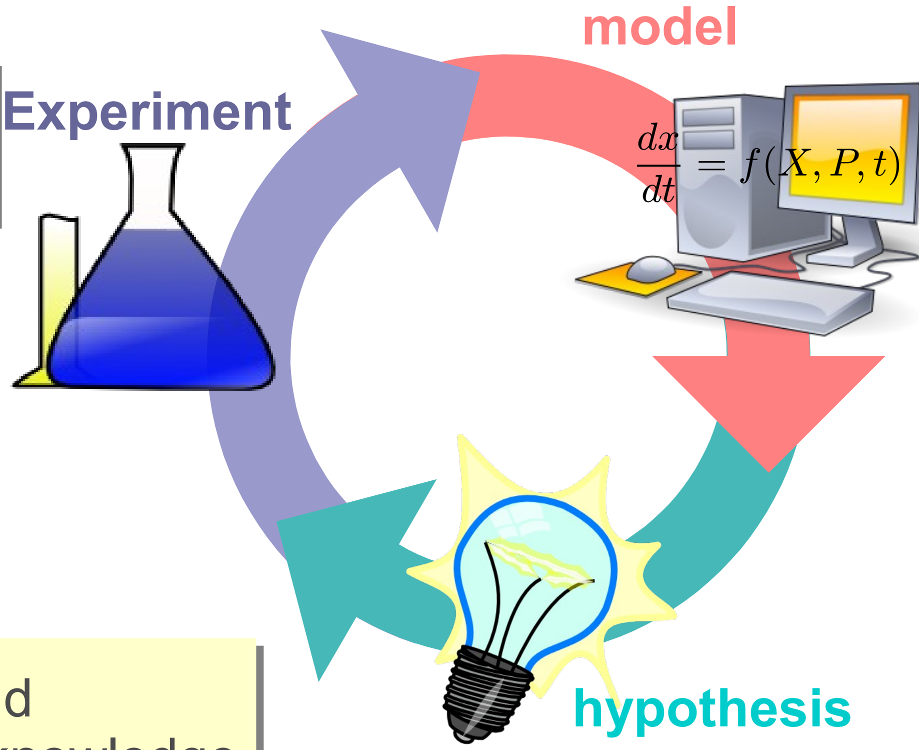


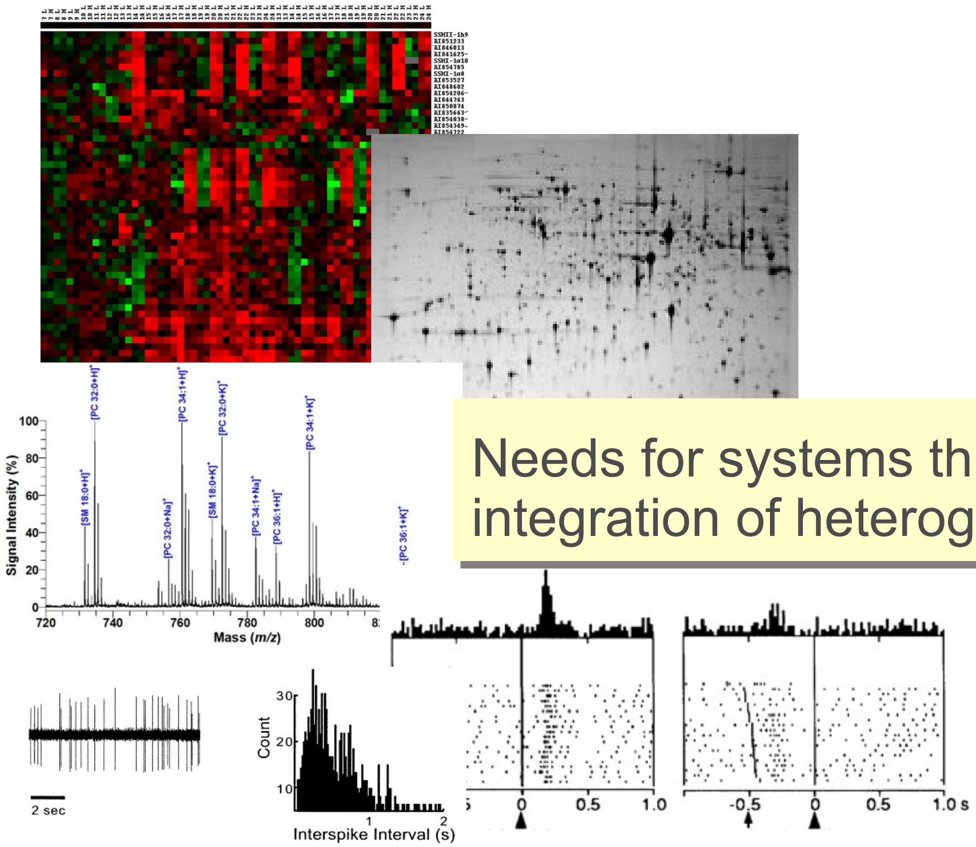
About

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

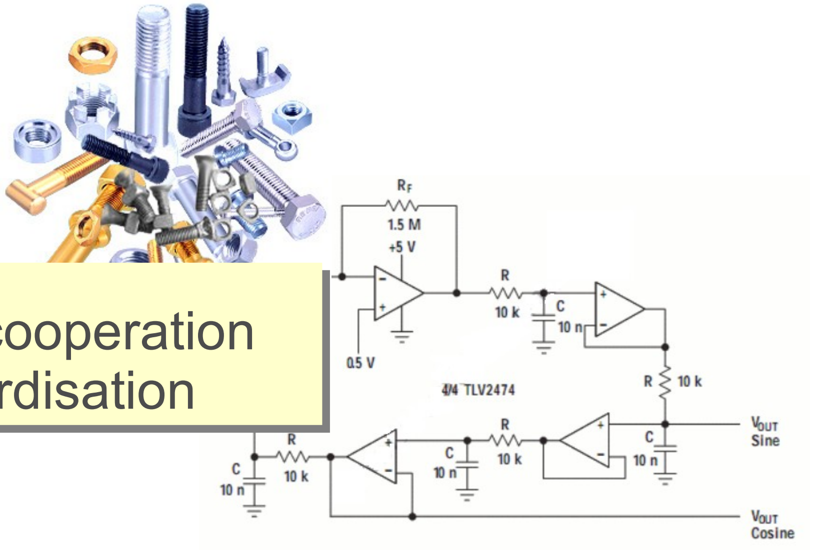
New way of doing biomedical research

Needs for interplay between models and reality tests





Needs for systems thinking and integration of heterogeneous knowledge

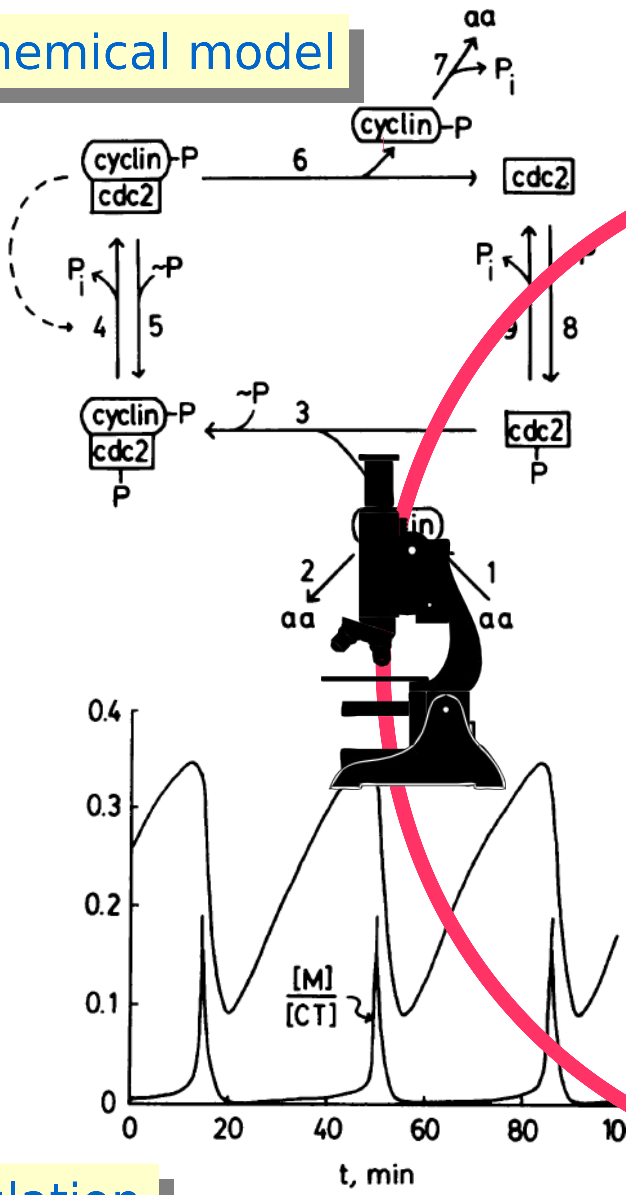


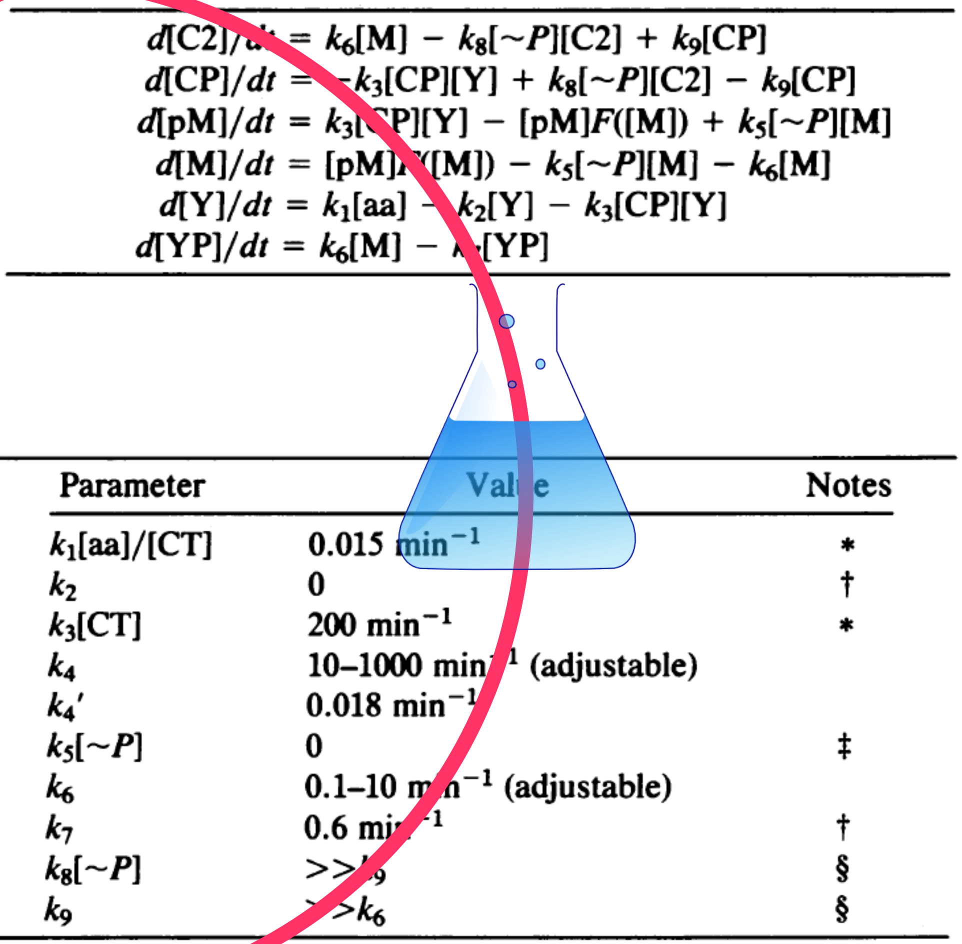
Needs for cooperation and standardisation

The models I am talking about

biochemical model

mathematical model





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

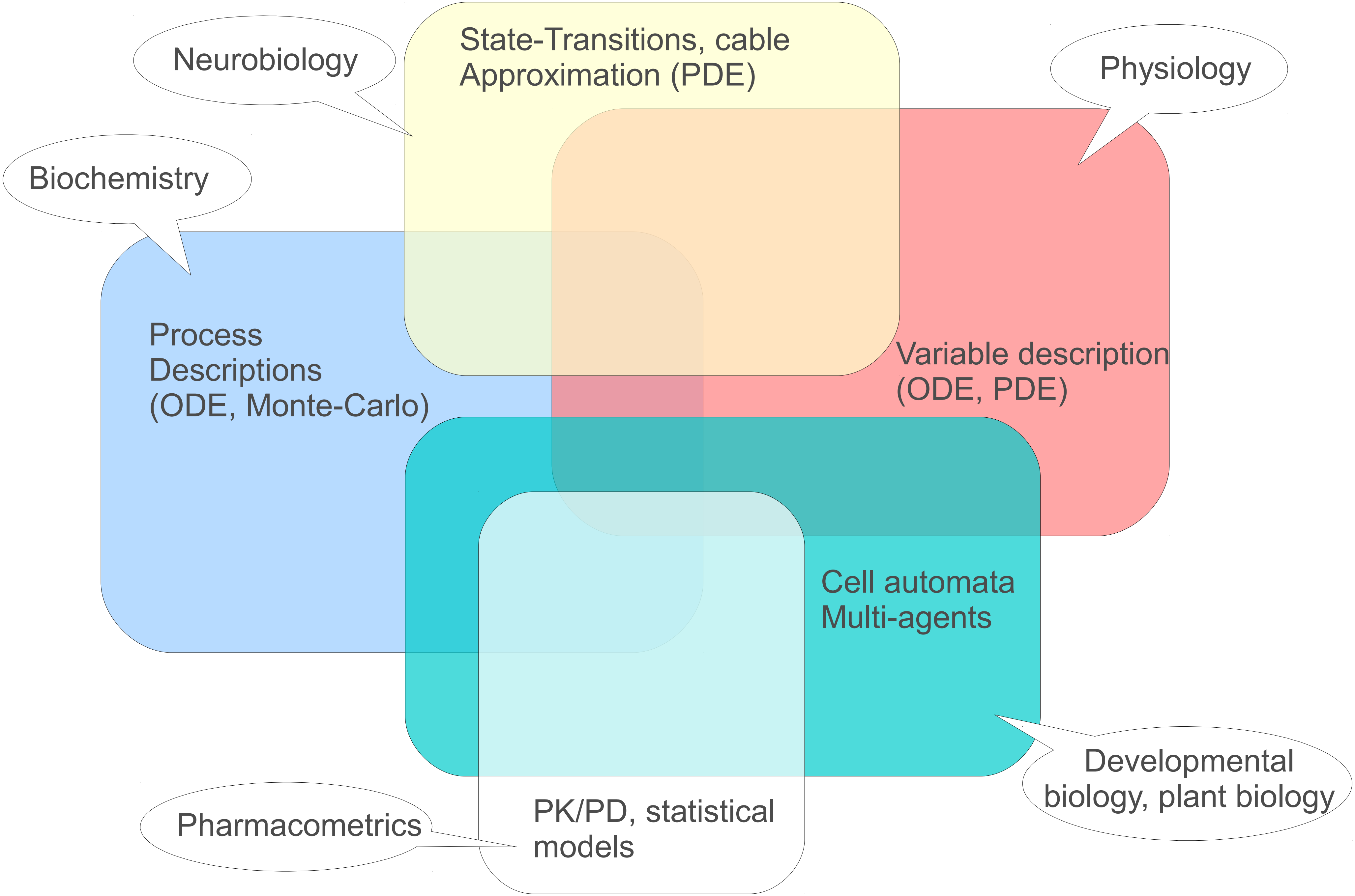
Parameter	Value	Notes
$k_1[\mathrm{aa}]/[\mathrm{CT}]$	0.015 min^{-1}	*
k_2	0	†
$k_3[\mathrm{CT}]$	200 min^{-1}	*
k_4	10–1000 min^{-1} (adjustable)	
k_4'	0.018 min^{-1}	
$k_5[\sim P]$	0	‡
k_6	0.1–10 min^{-1} (adjustable)	
k_7	0.6 min^{-1}	†
$k_8[\sim P]$	$>> k_9$	§
k_9	$>> k_6$	§

simulation

computational model

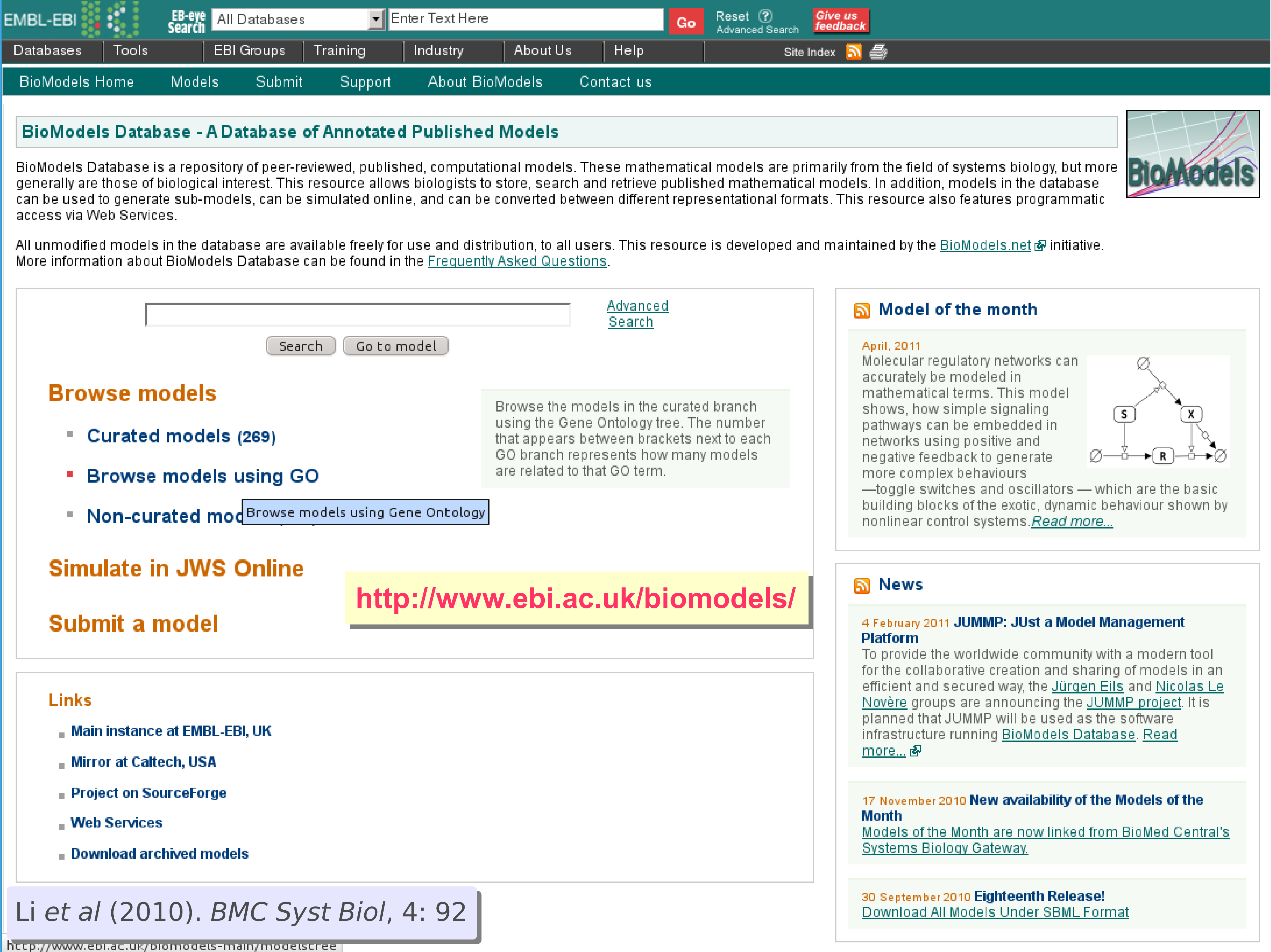
Tyson et al (1991) PNAS 88(1):7328-32

Many complementary modelling approaches



Computational modelling left the niches

- Metabolic networks Fung et al. A synthetic gene-metabolic oscillator. ***Nature*** 2005; Herrgård et al. A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. ***Nat Biotechnol*** 2008
- Signalling pathways Bray et al. Receptor clustering as a cellular mechanism to control sensitivity. ***Nature*** 1998; Bhalla ad Iyengar. Emergent properties of signaling pathways. ***Science*** 1998; Schoeberl et al. Computational modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors. ***Nat Biotechnol*** 2002; Hoffmann et. The IκB-NF-κB signaling module: temporal control and selective gene activation. ***Science*** 2002; Smith et al. Systems analysis of Ran transport. ***Science*** 2002; Bhalla et al. MAP kinase phosphatase as a locus of flexibility in a mitogen-activated protein kinase signaling network. ***Science*** 2002; Nelson et al. Oscillations in NF-κB Signaling Control the Dynamics of Gene Expression. ***Science*** 2004; Werner et al. Stimulus specificity of gene expression programs determined by temporal control of IKK activity. ***Science*** 2005; Sasagawa et al. Prediction and validation of the distinct dynamics of transient and sustained ERK activation. ***Nat Cell Biol*** 2005; Basak et al. A fourth IkappaB protein within the NF-κB signaling module. ***Cell*** 2007; McLean et al. Cross-talk and decision making in MAP kinase pathways. ***Nat Genet*** 2007; Ashall et al. Pulsatile Stimulation Determines Timing and Specificity of NF-κB-Dependent Transcription. ***Science*** 2009; Becker et al. Covering a broad dynamic range: information processing at the erythropoietin receptor. ***Science*** 2010
- Gene regulatory networks McAdams and Shapiro. Circuit simulation of genetic networks. ***Science*** 1995; Yue et al. Genomic cis-regulatory logic: Experimental and computational analysis of a sea urchin gene. ***Science*** 1998; Von Dassow et al. The segment polarity network is a robust developmental module. ***Nature*** 2000; Elowitz and Leibler. A synthetic oscillatory network of transcriptional regulators. ***Nature*** 2000; Shen-Orr et al, Network motifs in the transcriptional regulation network of Escherichia coli. ***Nat Genet*** 2002; Yao et al. A bistable Rb-E2F switch underlies the restriction point. ***Nat Cell Biol*** 2008; Friedland. Synthetic gene networks that count. ***Science*** 2009
- Pharmacometrics models Labrijn et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. ***Nat Biotechnol*** 2009
- Physiological models Noble. Modeling the heart from genes to cells to the whole organ. ***Science*** 2002; Izhikevich and Edelman. Large-scale model of mammalian thalamocortical systems. ***PNAS*** 2008
- Infectious diseases Perelson et al. HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. ***Science*** 1996; Nowak. Population dynamics of immune responses to persistent viruses. ***Science*** 1996; Neumann et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. ***Science*** 1998



BioModels Database - A Database of Annotated Published Models

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

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

Browse models

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

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**

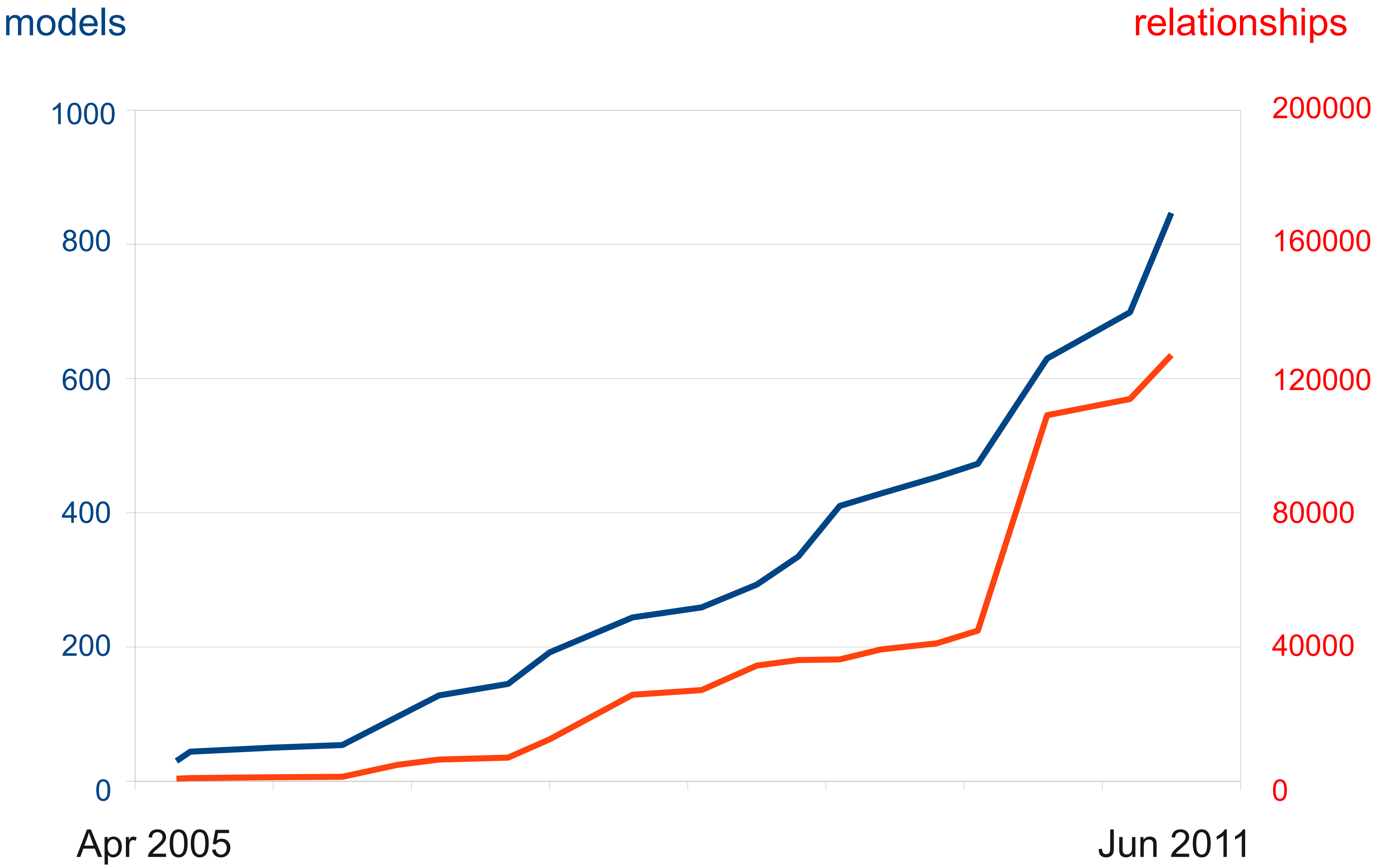
Models of the Month are now linked from BioMed Central's Systems Biology Gateway.

30 September 2010 **Eighteenth Release!**

Download All Models Under SBML Format

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

Computational models on the rise



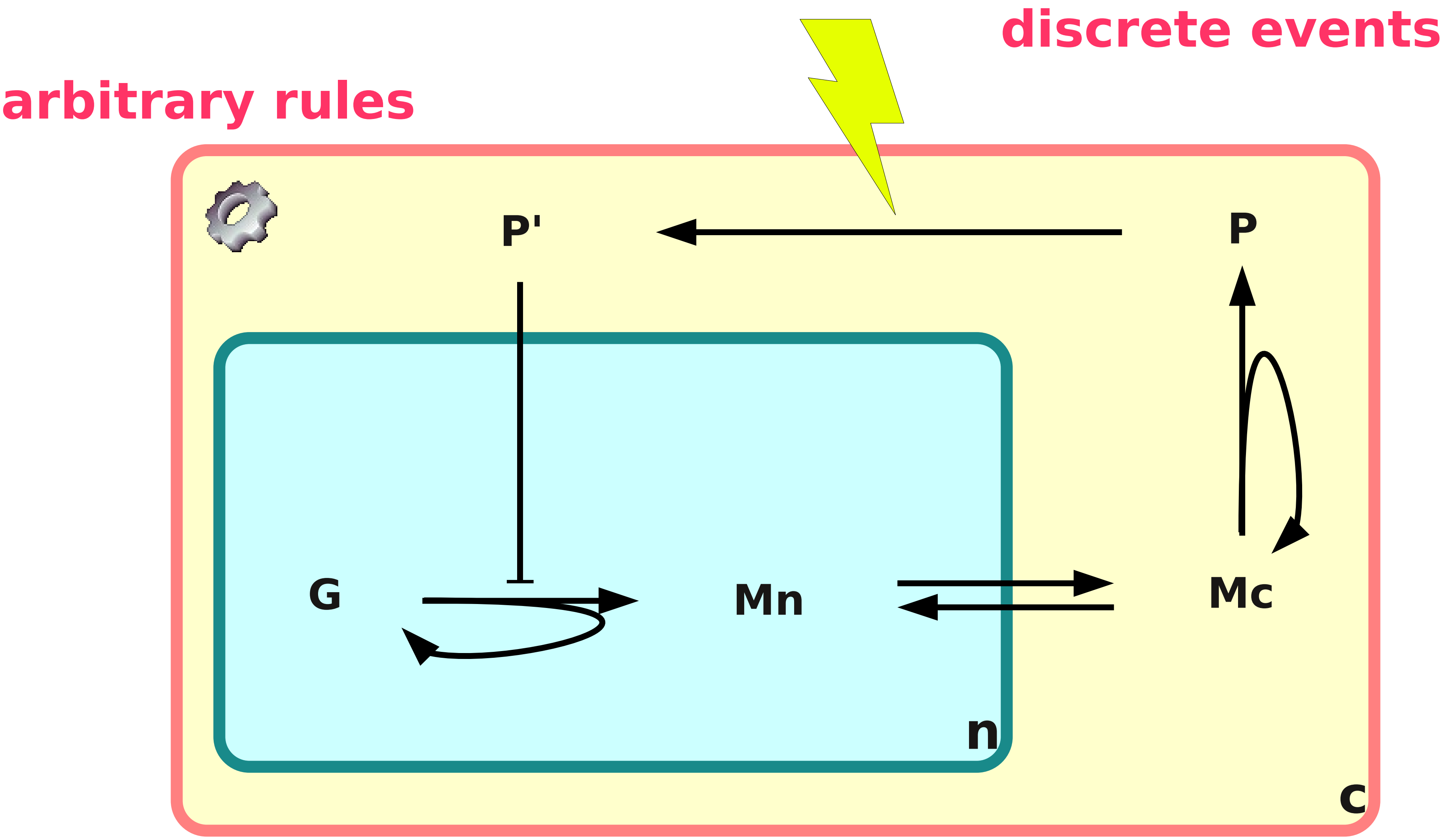
BioModels Database growth since its creation

A language to describe computational models in biology

	Model descriptions
Data-models	SBML™

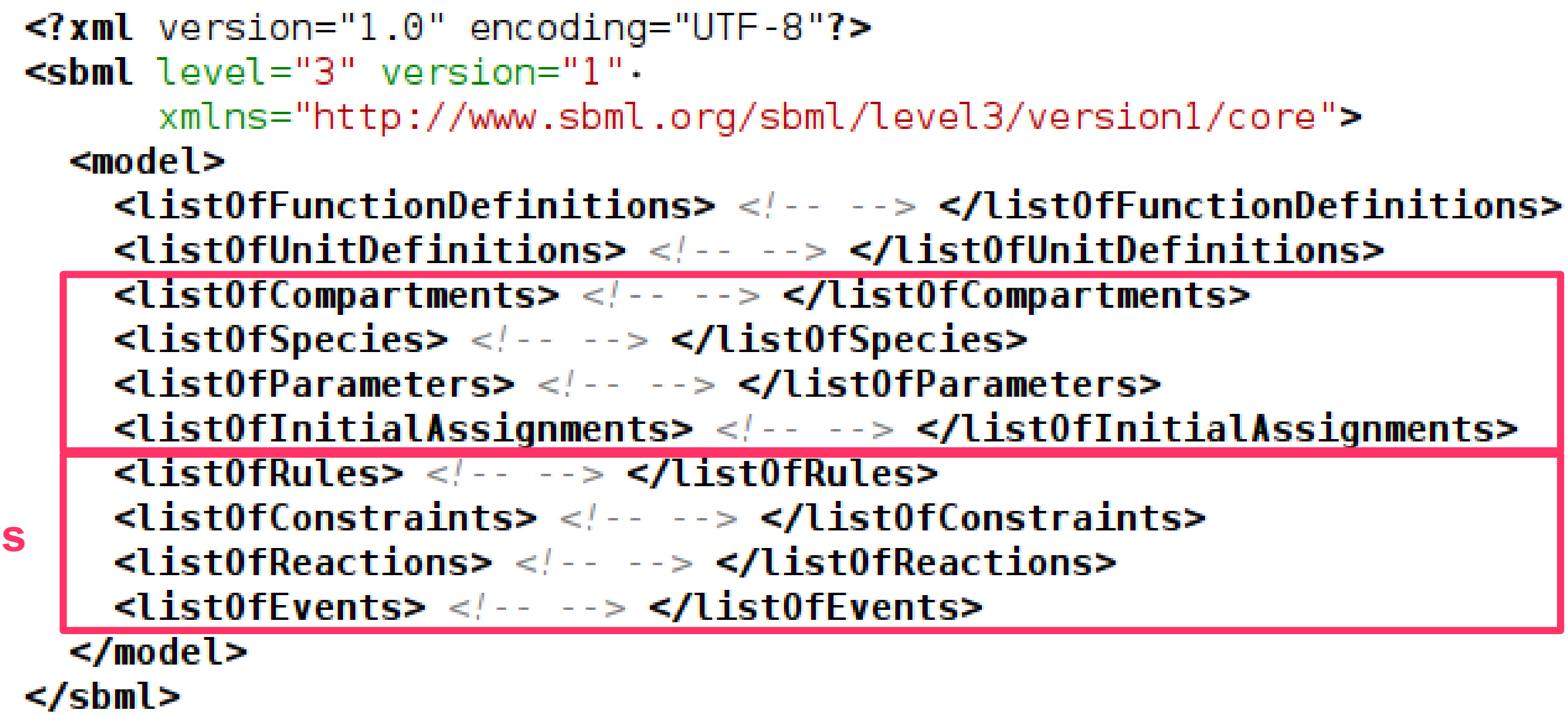
Born in Caltech 2000

What can we encode in SBML (core)?



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

Global structure of a SBML file



```
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<sbml level="3" version="1"·
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  <model>
    <listOfFunctionDefinitions> <!-- --> </listOfFunctionDefinitions>
    <listOfUnitDefinitions> <!-- --> </listOfUnitDefinitions>
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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 (A ⟶ B)

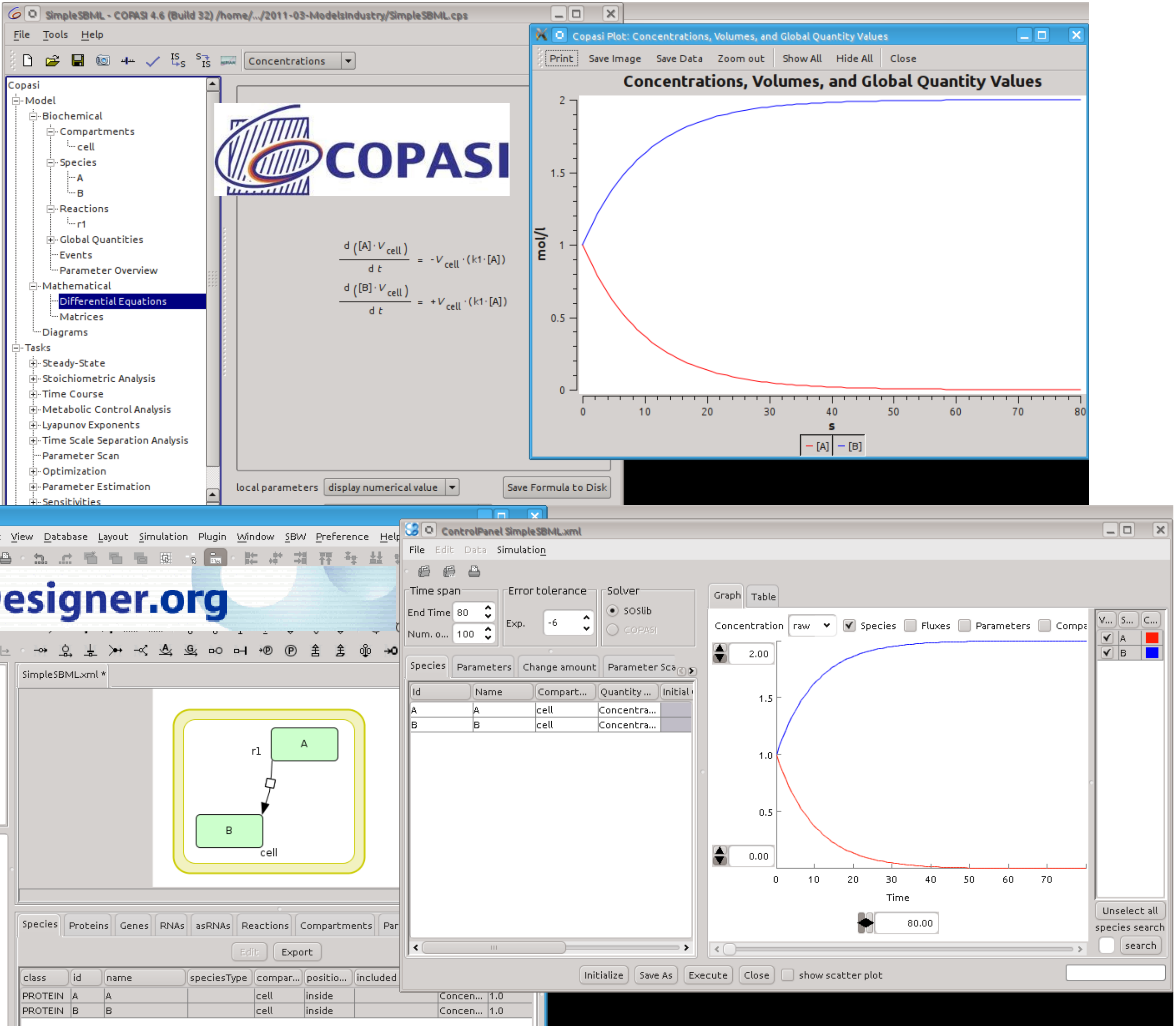
```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
  <model name="Simple Model">
    <listOfCompartments>
      <compartment id="cell" size="1" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell"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

A very simple SBML file (A ⟶ B)

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

MathML

SBML



$$\frac{d\left([A]\cdot V_{cell}\right)}{dt} = -V_{cell}\cdot(k1\cdot[A])$$

$$\frac{d\left([B]\cdot V_{cell}\right)}{dt} = +V_{cell}\cdot(k1\cdot[A])$$

End Time 80

Num. o... 100

Exp. -6

● SOSlib

○ COPASI

Concentration raw ☑ Species ☐ Fluxes ☐ Parameters ☐ Compa

☑ A 🟥

☑ B 🟦

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

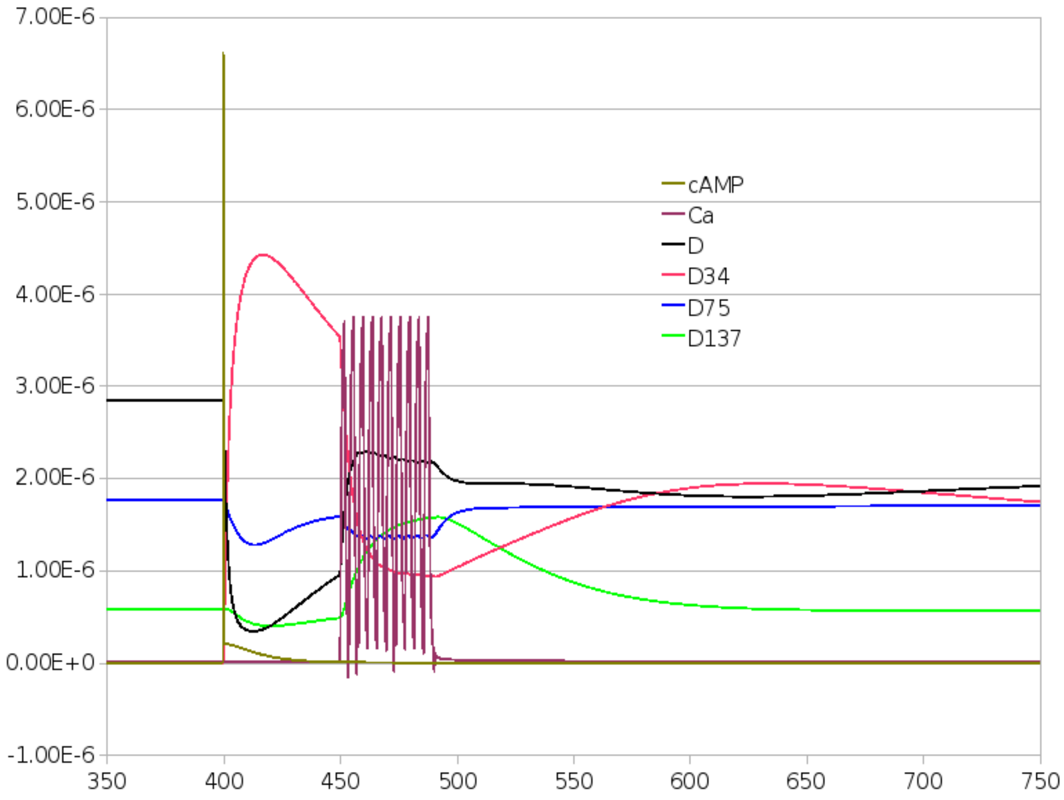
class	id	name	speciesType	compar...	positio...	included		
PROTEIN	A	A		cell	inside		Concen...	1.0
PROTEIN	B	B		cell	inside		Concen...	1.0

SBML is not limited to biochemistry!

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

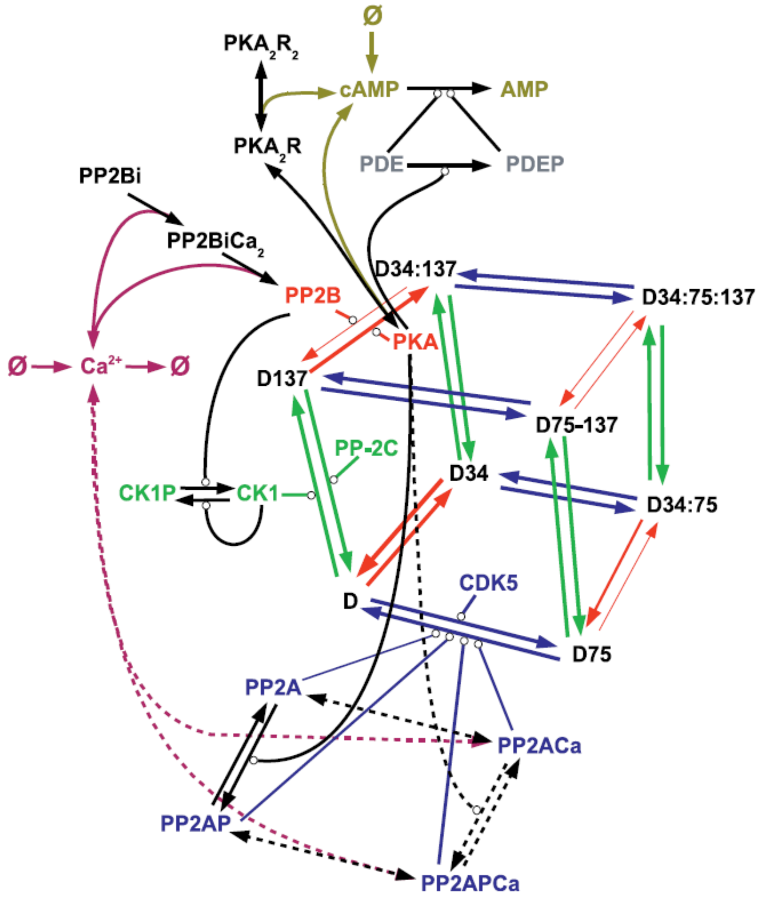
➔ SBML is about process descriptions

Biochemical models



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

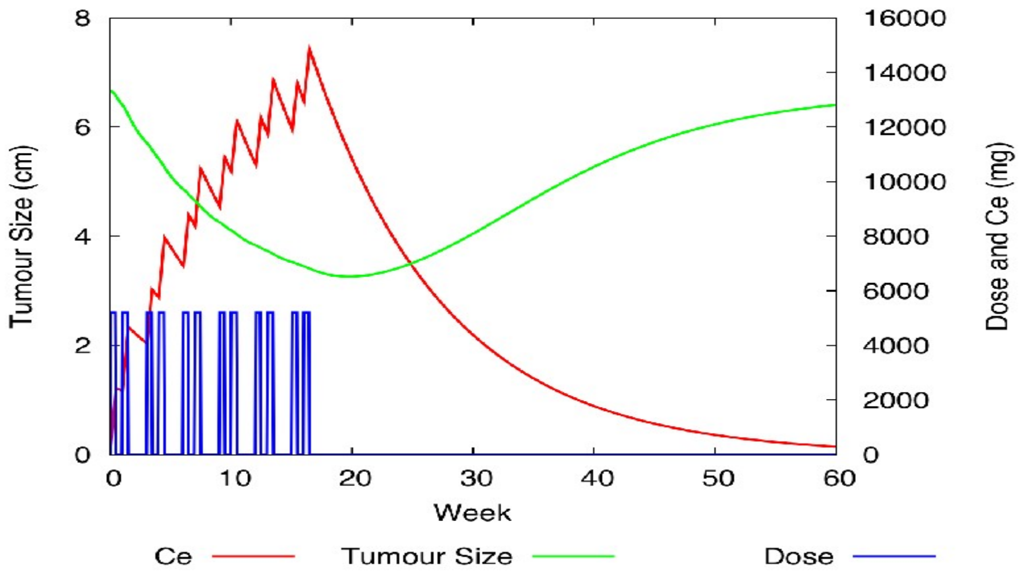
BIOMD0000000153



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

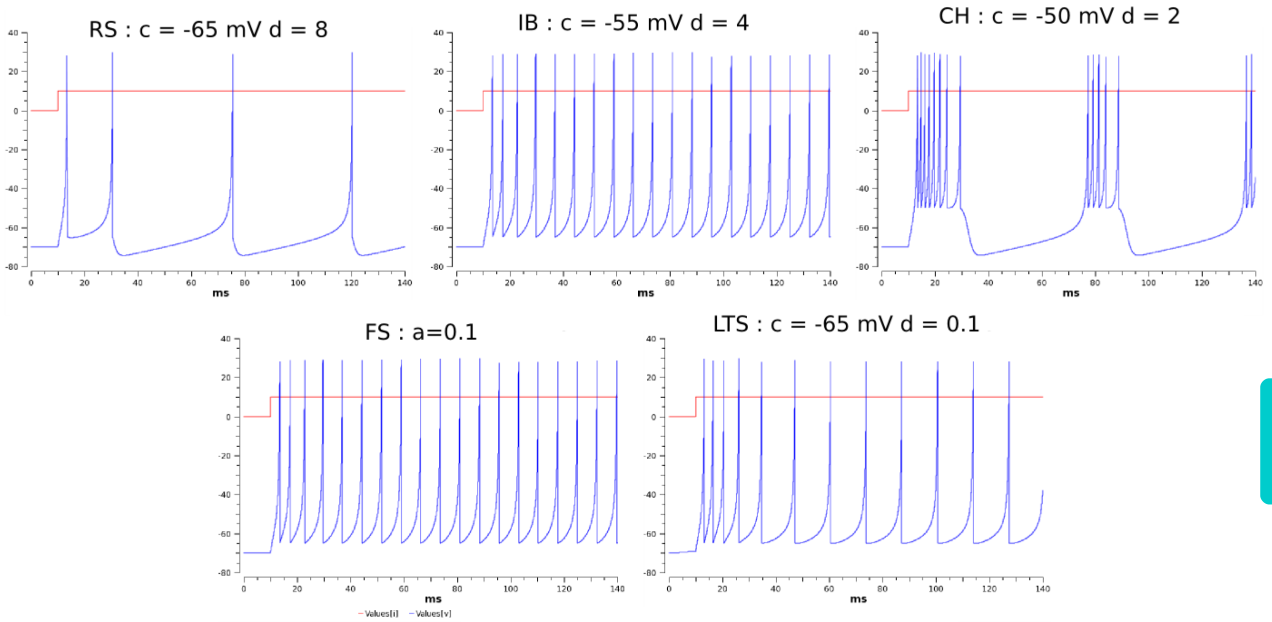
rate rule:

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

assignment rule:

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

Single-compartment neurons



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

BIOMD0000000127

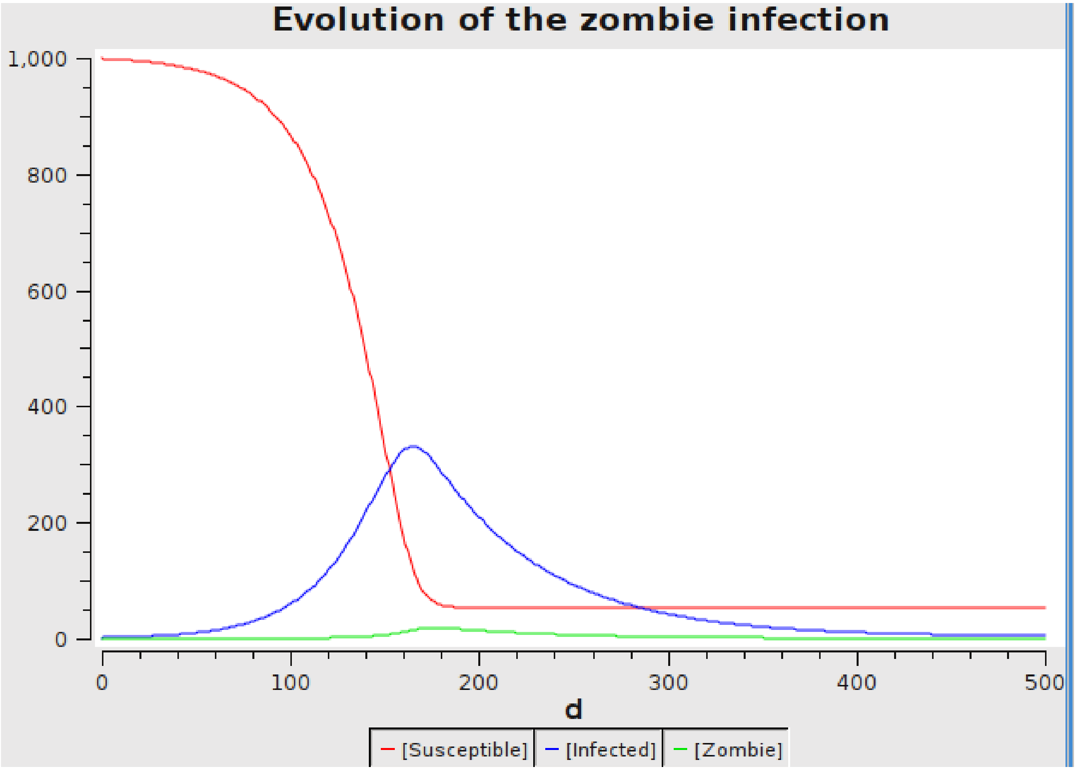
rate rule:

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

event:

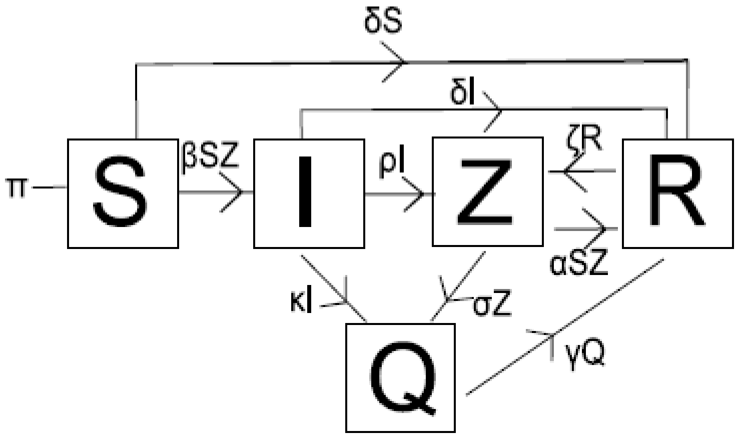
$$\text{when}\, v > V_{thresh} \begin{cases} v = c \\ U = U + d \end{cases}$$

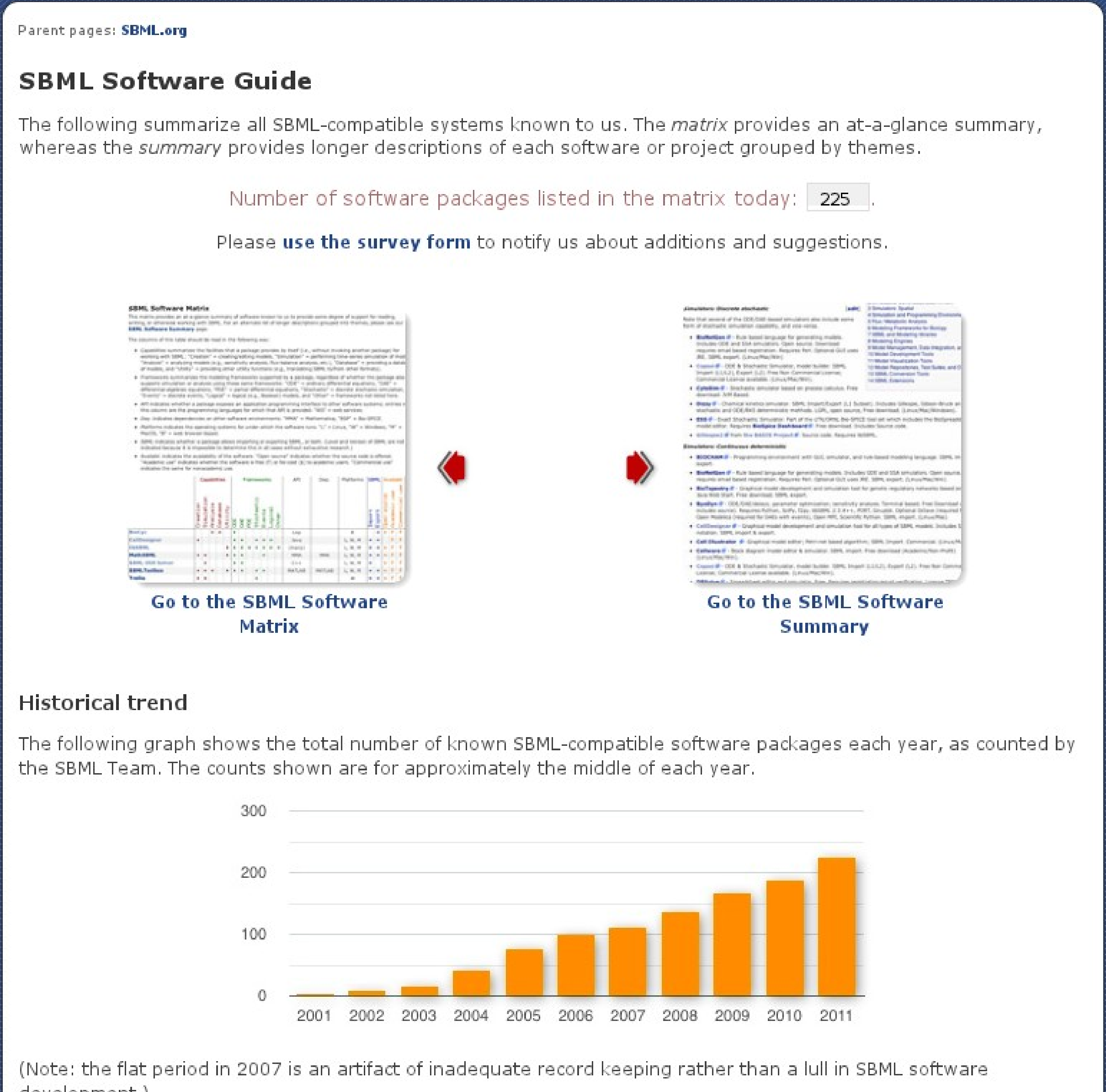
Spread of infection diseases ...



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

MODEL1008060001





Parent pages: **SBML.org**

SBML Software Guide

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

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

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

Go to the SBML Software Matrix

Go to the SBML Software Summary

Historical trend

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

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

Adding the semantics to the syntax

	Model descriptions
Minimal requirements	MIRIAM
Data-models	SBML™
Terminologies	SBO

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

Data-type identifier (required)

URI

Not a URL, not a “location”!

Data-set Identifier (required)

text string

Format depends on the resource identified by the data-type

`UniProt and P62158 (human calmodulin)`

`urn:miriam:uniprot:P62158`

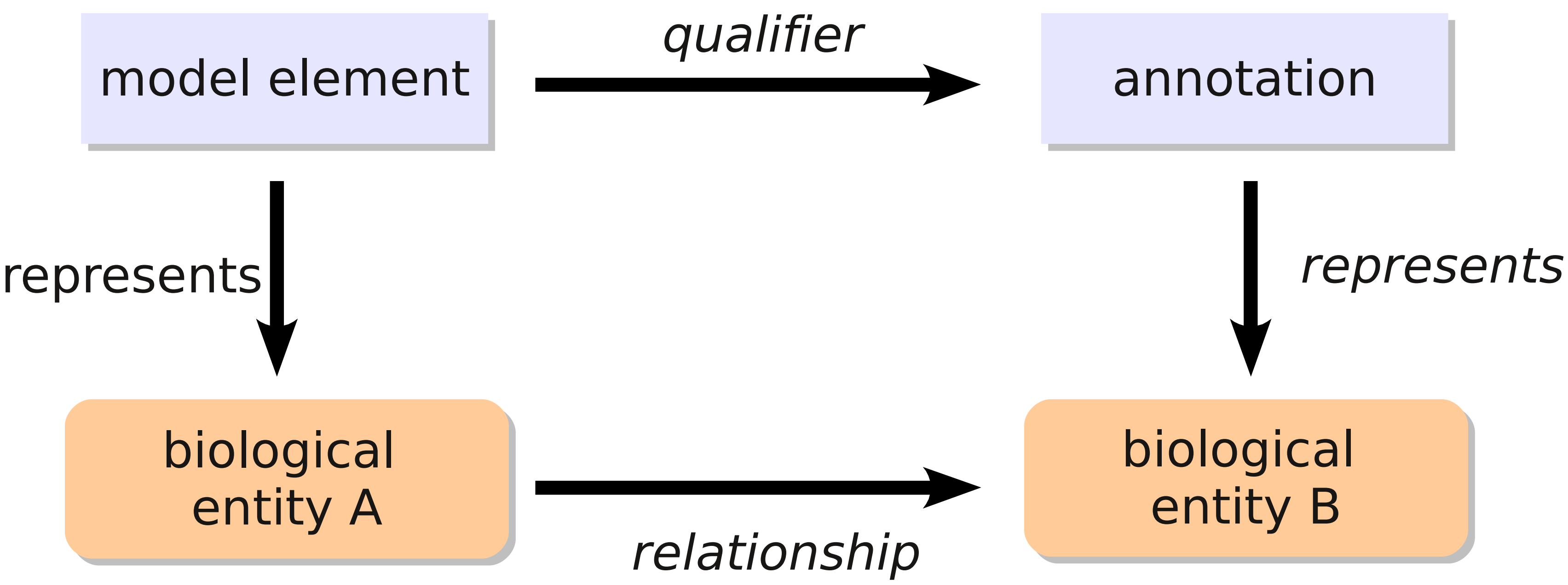
`EC code and 1.1.1.1 (alcohol dehydrogenase)`

`urn:miriam:ec-code:1.1.1.1`

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

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

Qualification of annotation



model element

qualifier

annotation

represents

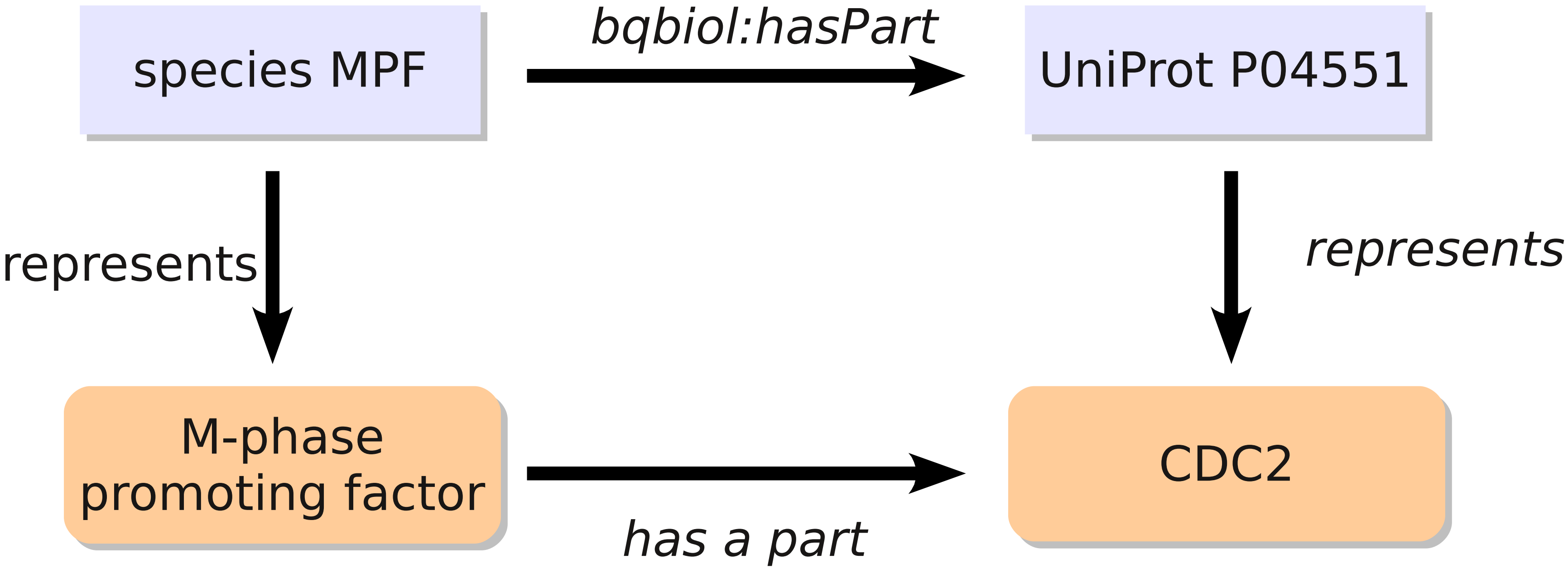
represents

biological entity A

relationship

biological entity B

Qualification of annotation



species MPF

bqbiol:hasPart

UniProt P04551

represents

represents

M-phase promoting factor

CDC2

has a part

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>
```

Private Vs public cross-references

```
<annotation>
  <!-- // -->
   <rdf:li rdf:resource=”urn:miriam:uniprot:P62158” />
   <!-- // -->
</annotation>
```

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

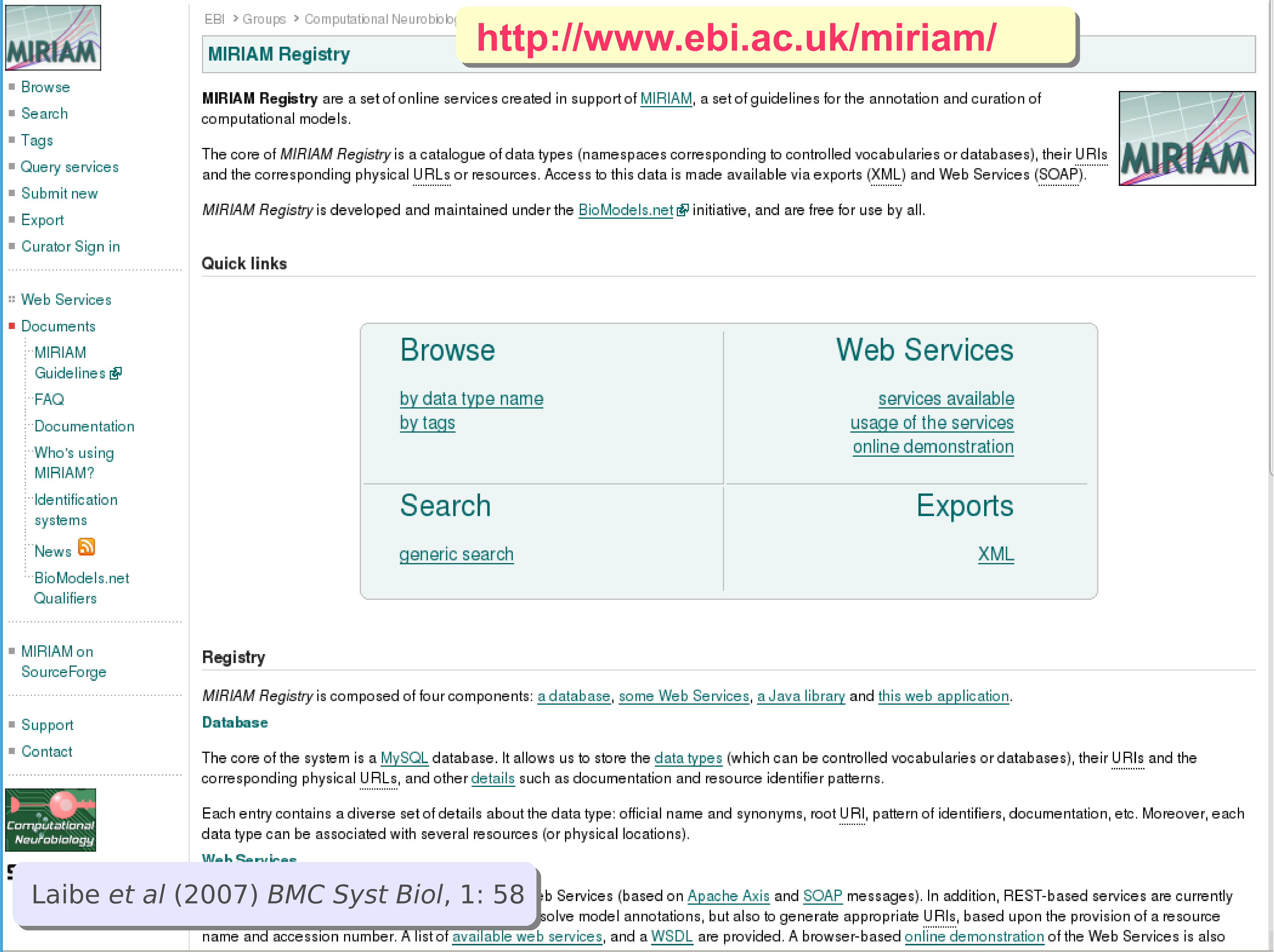
```
<annotation>
      <resource database=”UniProt”
                accession=”P62158” />
</annotation>
```

- Need to list the resources
  and share the list

```
<annotation>
   <uniprot>P62158</uniprot>
</annotation>
```

- Need to change the format
  to add resources

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



EBI > Groups > Computational Neurobiolog

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

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

- MIRIAM on SourceForge

- Support
- Contact

Computational Neurobiology

MIRIAM Registry

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

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

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

Quick links

Browse	Web Services
by data type name by tags	services available usage of the services online demonstration
Search	**Exports**
generic search	XML

Registry

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

Database

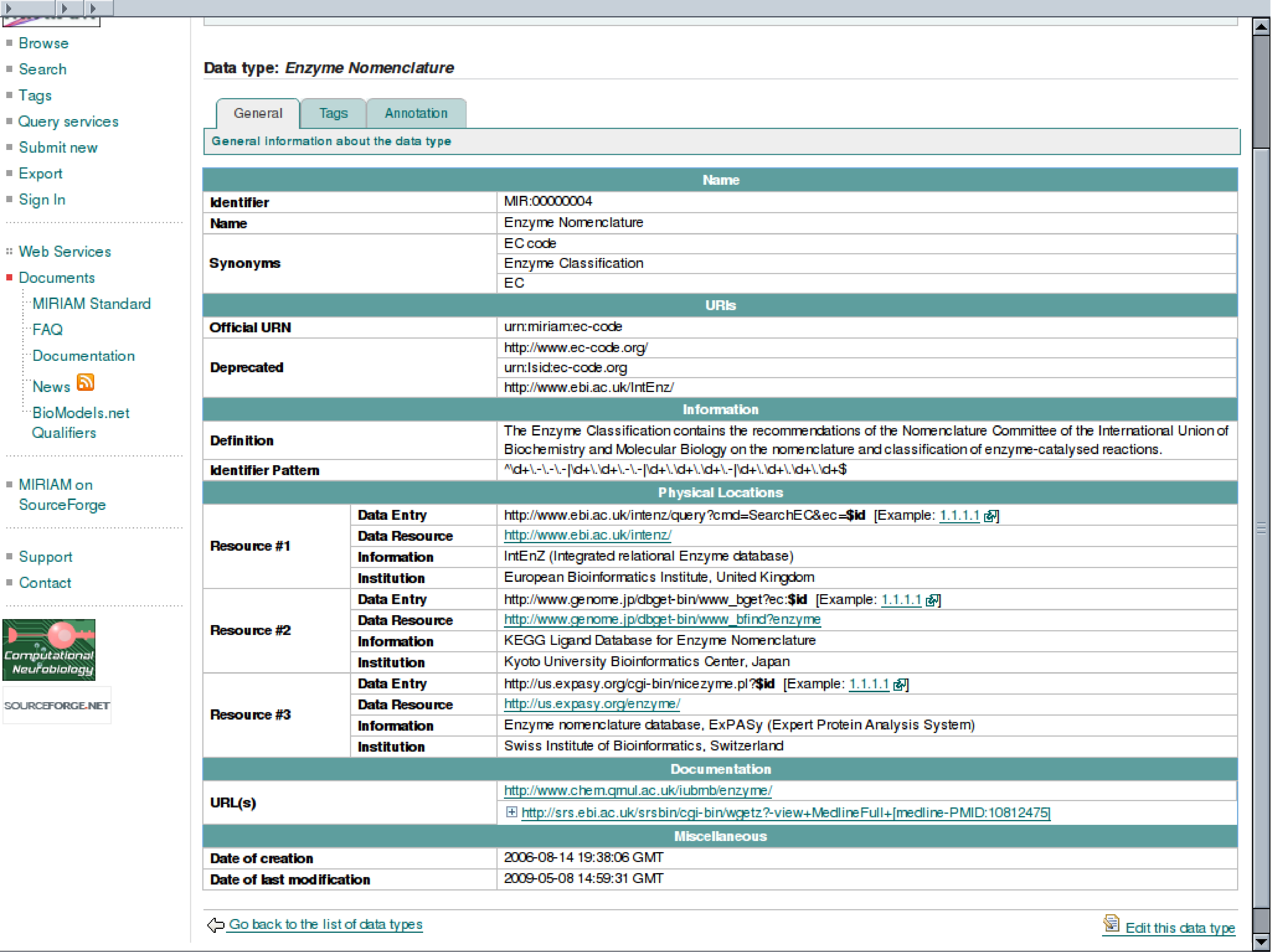
The core of the system is a MySQL database. It allows us to store the data types (which can be controlled vocabularies or databases), their URIs and the corresponding physical URLs, and other details such as documentation and resource identifier patterns.

Each entry contains a diverse set of details about the data 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).

Web Services

b Services (based on Apache Axis and SOAP messages). In addition, REST-based services are currently solve model annotations, but also to generate appropriate URIs, based upon the provision of a resource name and accession number. A list of available web services, and a WSDL are provided. A browser-based online demonstration of the Web Services is also

Laibe *et al* (2007) *BMC Syst Biol*, 1: 58



Data type: ***Enzyme Nomenclature***

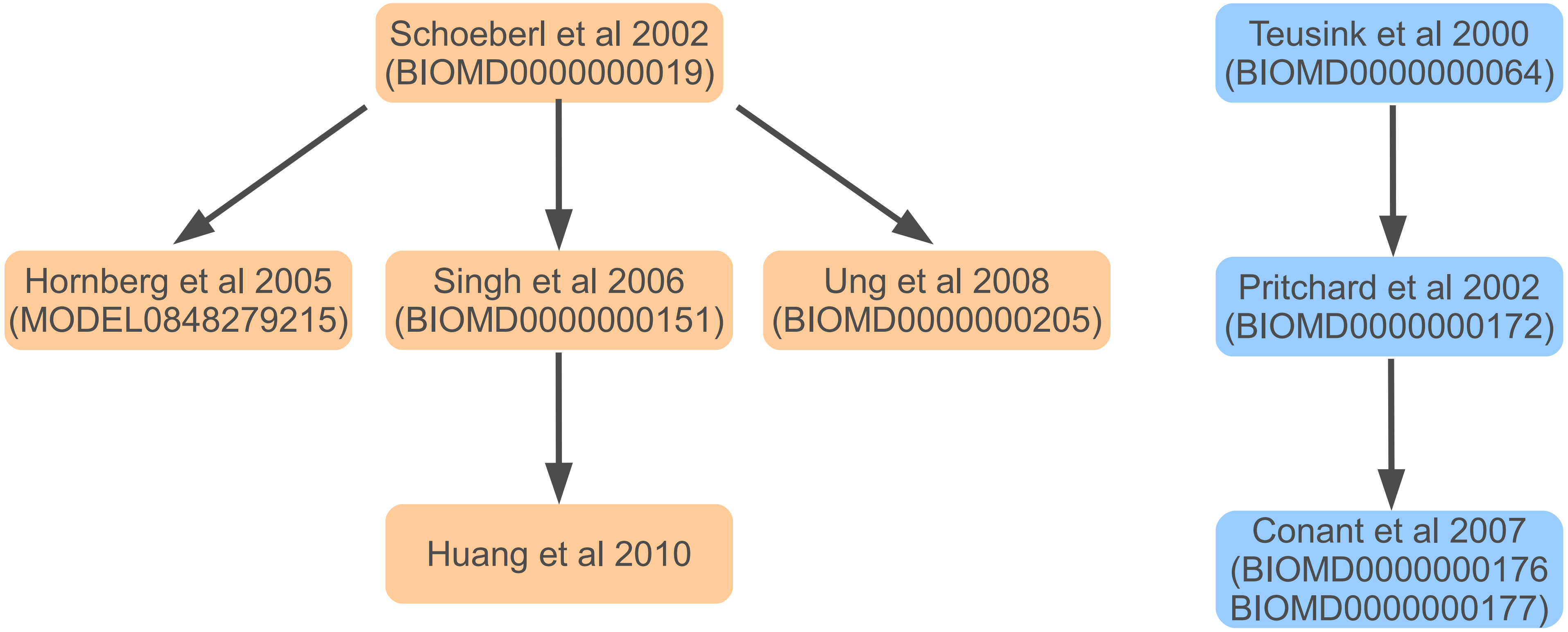
General information about the data type

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

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


Schoeberl et al 2002 (BIOMD0000000019)

Hornberg et al 2005 (MODEL0848279215)

Singh et al 2006 (BIOMD0000000151)

Ung et al 2008 (BIOMD0000000205)

Huang et al 2010

Teusink et al 2000 (BIOMD0000000064)

Pritchard et al 2002 (BIOMD0000000172)

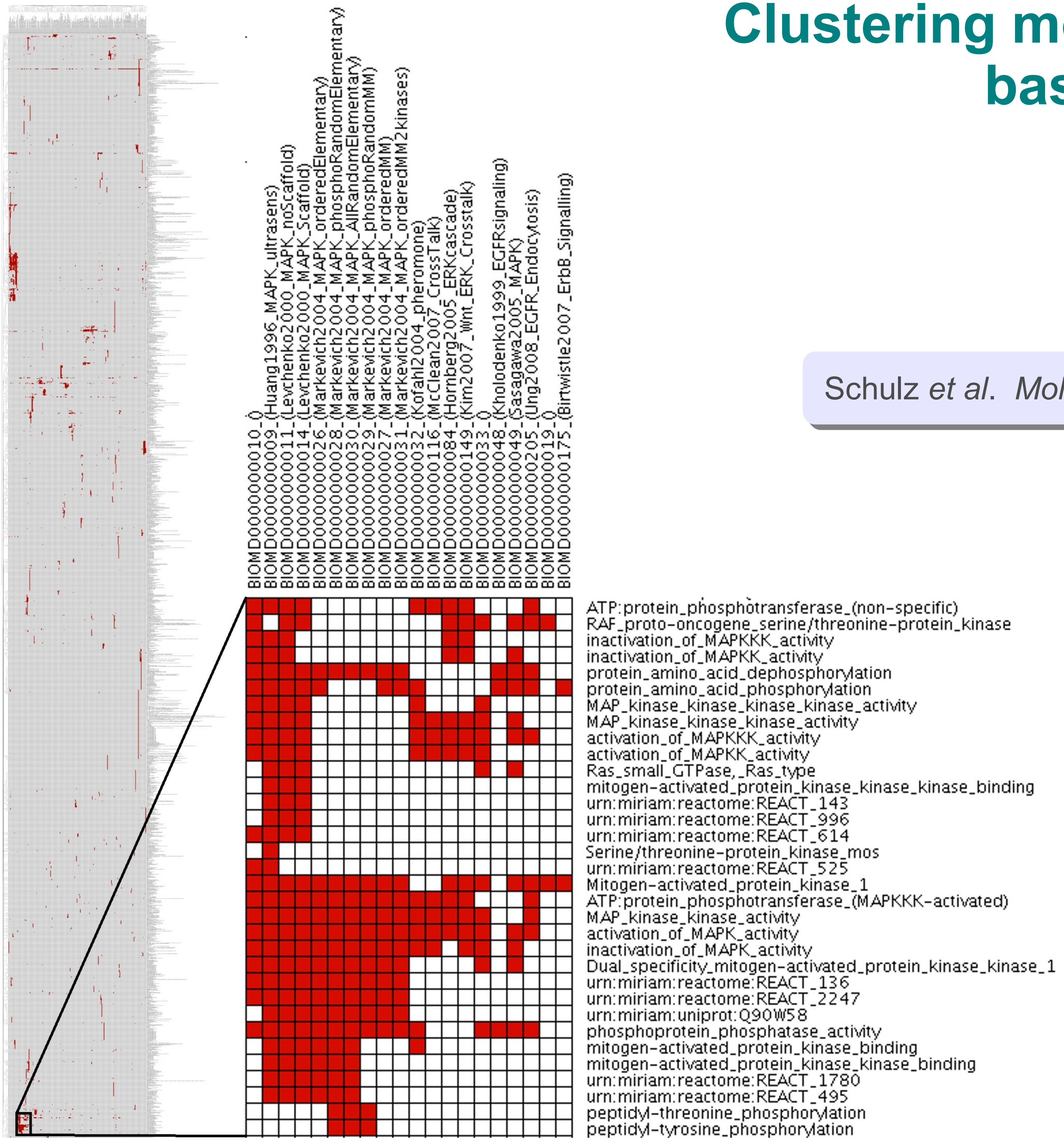
Conant et al 2007 (BIOMD0000000176 BIOMD0000000177)

Standard formats generate new research

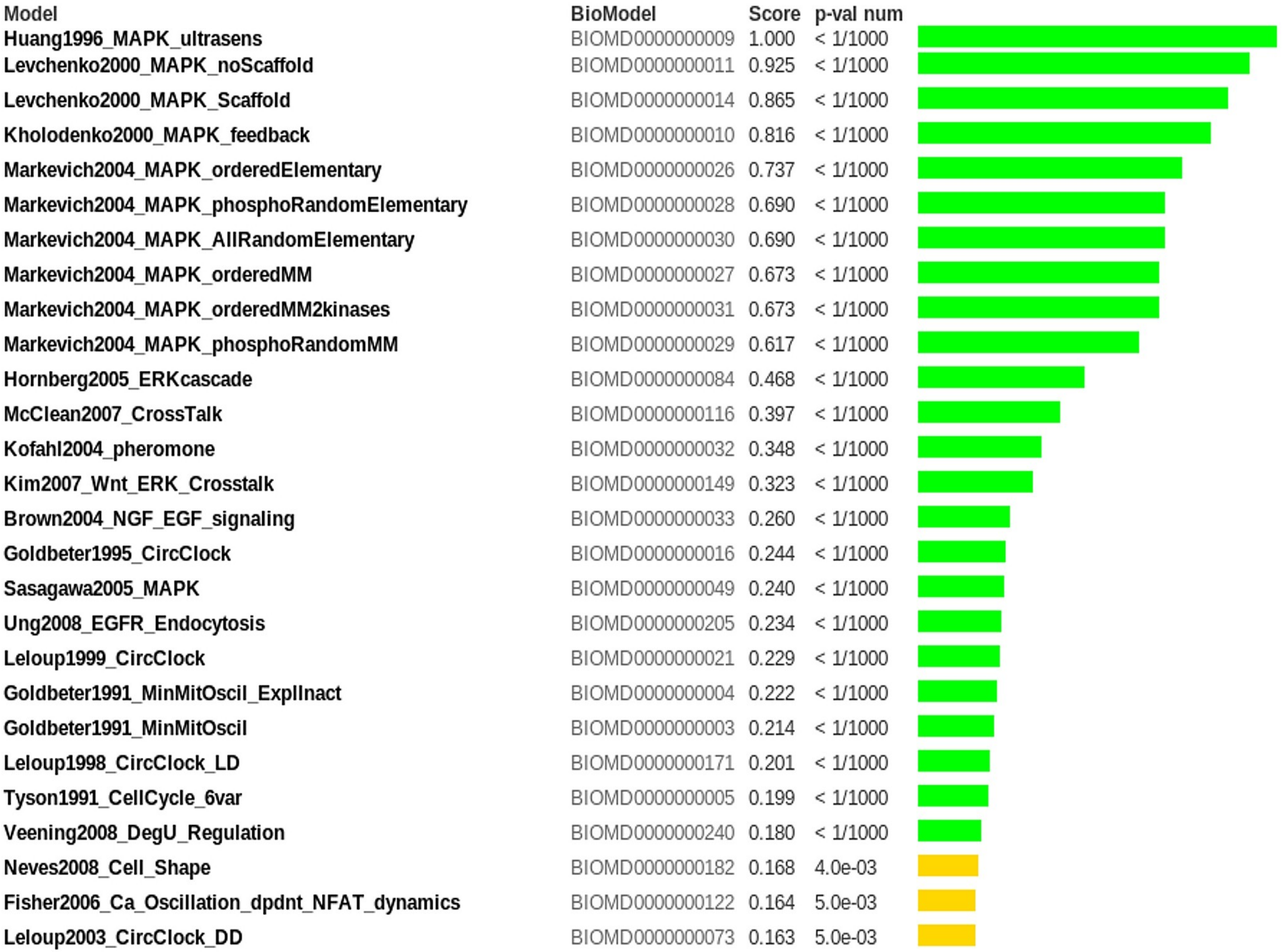
- Herrgård et al (2008) A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. *Nature Biotechnol*, 26: 1155-1160
  - MODEL0072364382: 2152 species, 1857 reactions
  - stoichiometric map, no concentrations, no kinetics
- Smallbone et al (2010) Towards 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	🟨

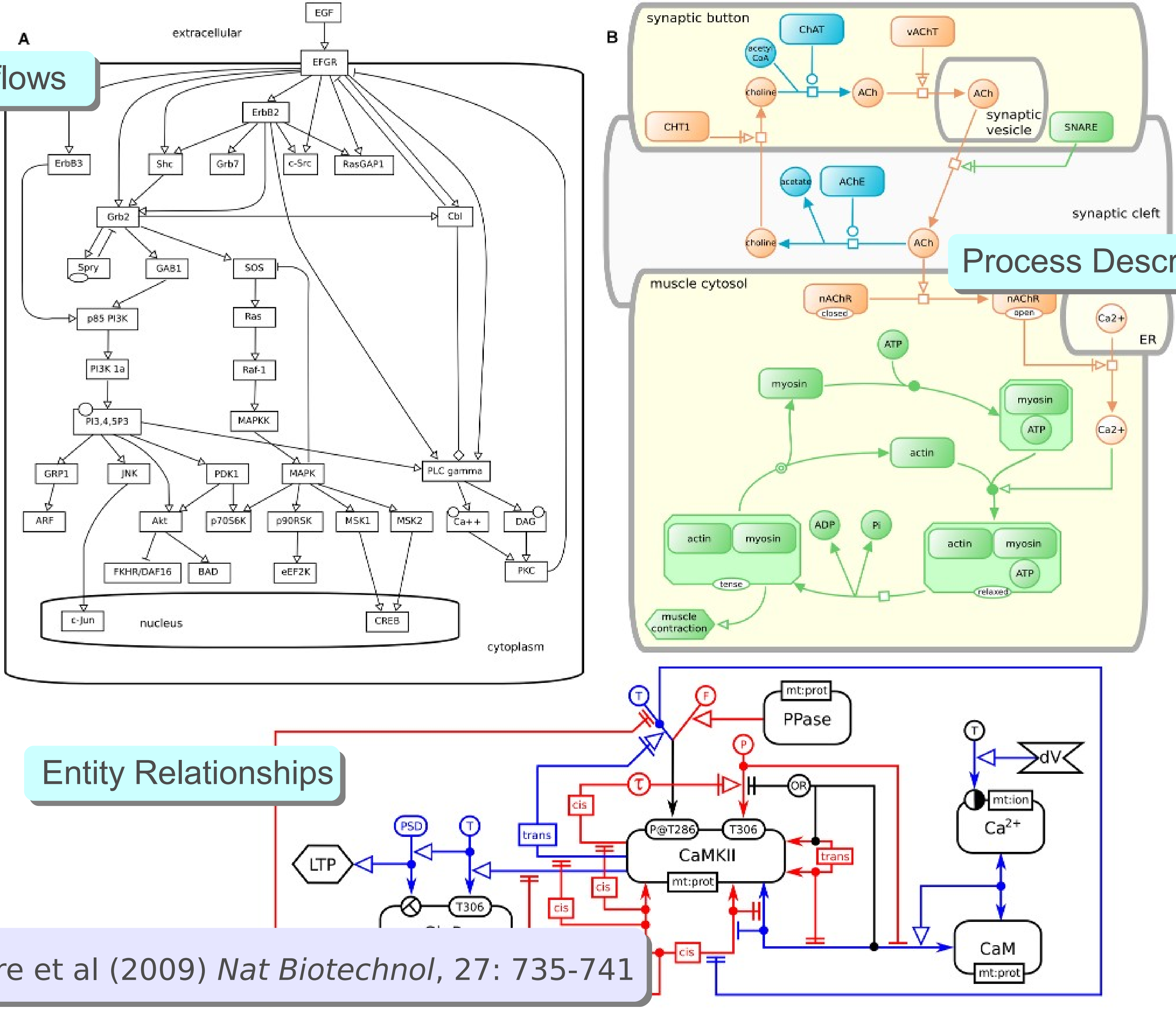
See also: Henkel *et al* (2010) *BMC Bioinfo*, 11:423

The interface with all biologists

	Model descriptions
Minimal requirements	MIRIAM
Data-models	SBMI™ SBGN
Terminologies	SBO

Born in Tokyo 2005

Systems Biology Graphical Notation

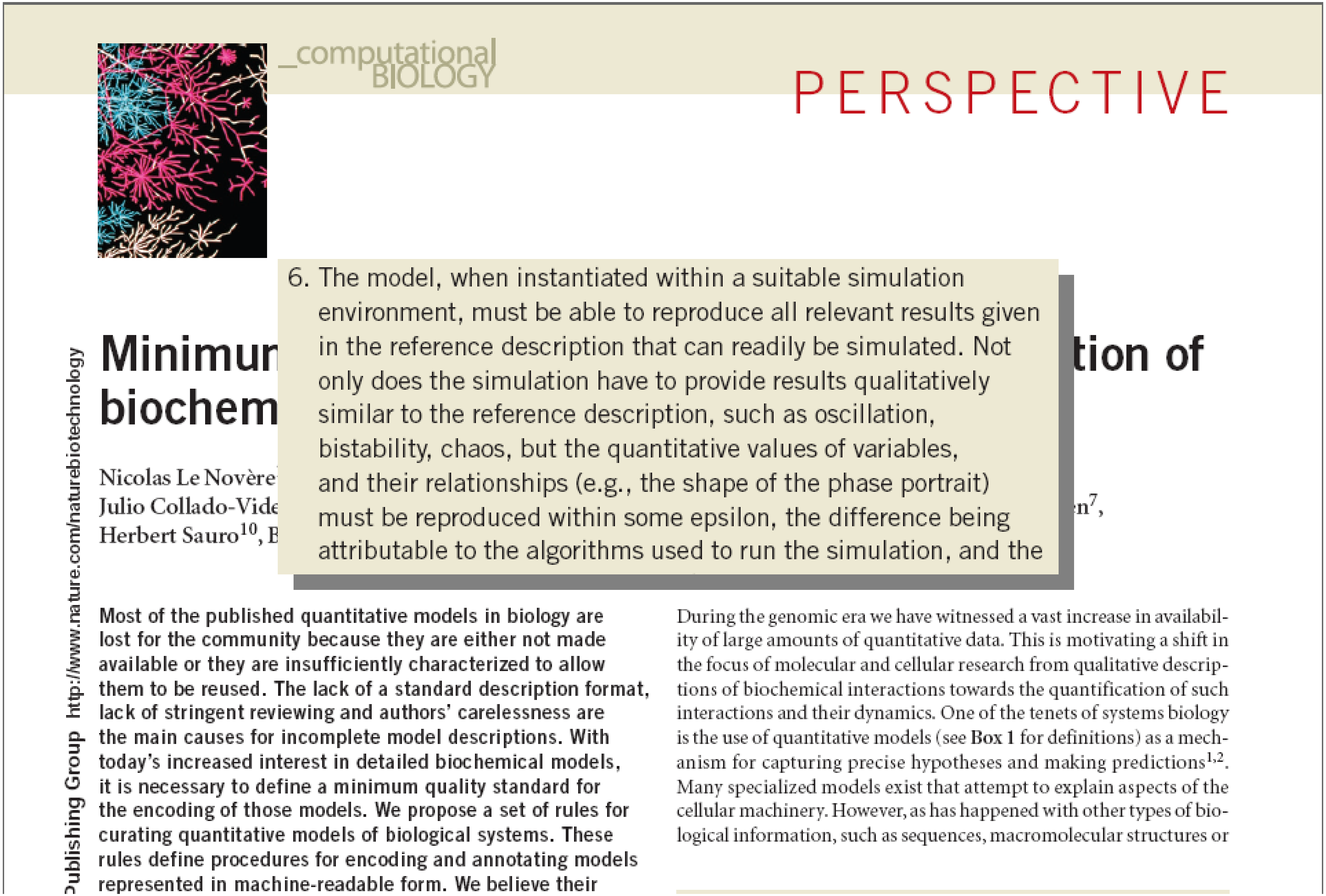


Activity flows

Process Descriptions

Entity Relationships

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



_computational BIOLOGY

PERSPECTIVE

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

Minimu … tion of biochem

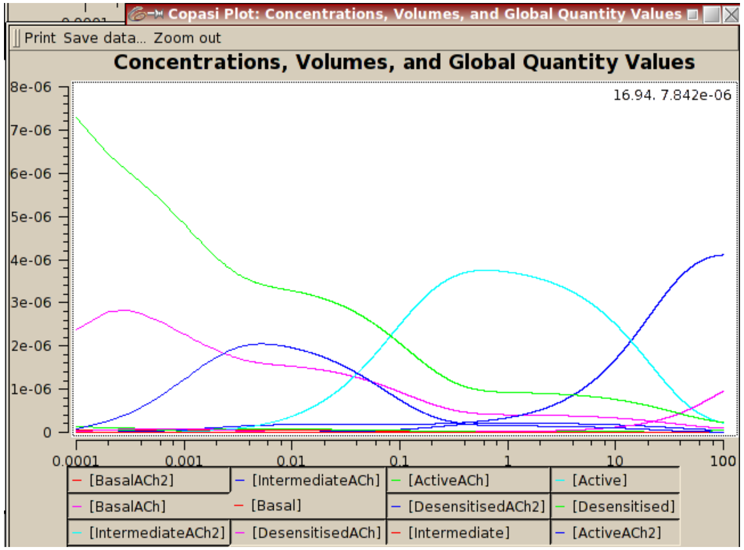
Nicolas Le Novère
Julio Collado-Vide … n[7],
Herbert Sauro[10], B

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

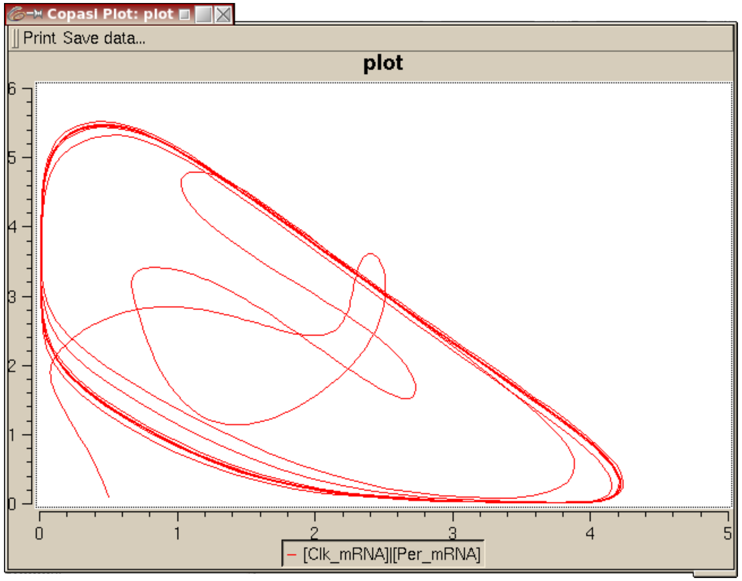
During the genomic era we have witnessed a vast increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their dynamics. One of the tenets of systems biology is the use of quantitative models (see **Box 1** for definitions) as a mechanism for capturing precise hypotheses and making predictions[1,2]. Many specialized models exist that attempt to explain aspects of the cellular machinery. However, as has happened with other types of biological information, such as sequences, macromolecular structures or

Reproduction of published simulation results

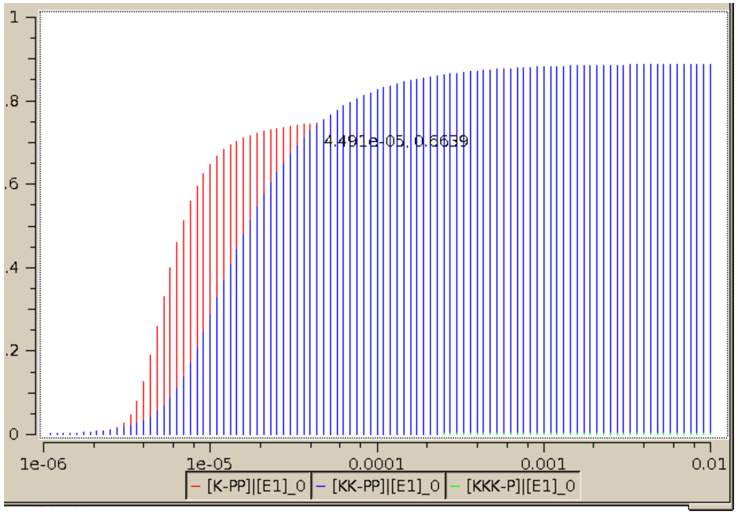
Edelstein et al 1996 (BIOMD0000000002)



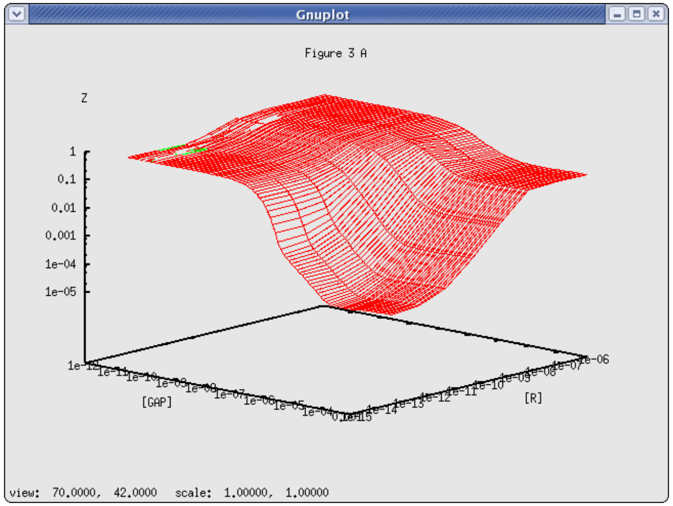
Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)



Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)



Description of simulations and analyses

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

Born in Hinxton 2007

Description of model simulation and analysis

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

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

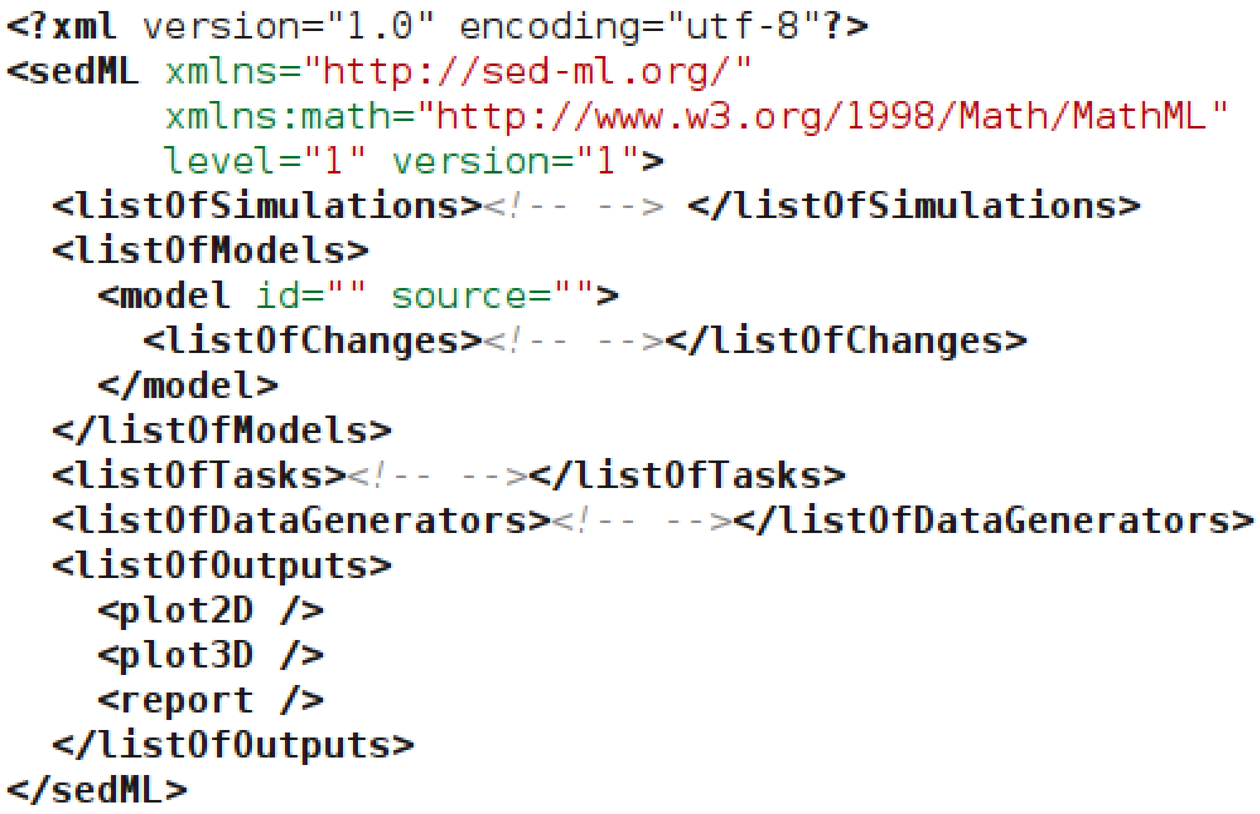
Simulation Experiment Description Markup Language (SED-ML) XML-based format for encoding simulation experiments, following the requirements defined in the MIASE guidelines

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">
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  <listOfModels>
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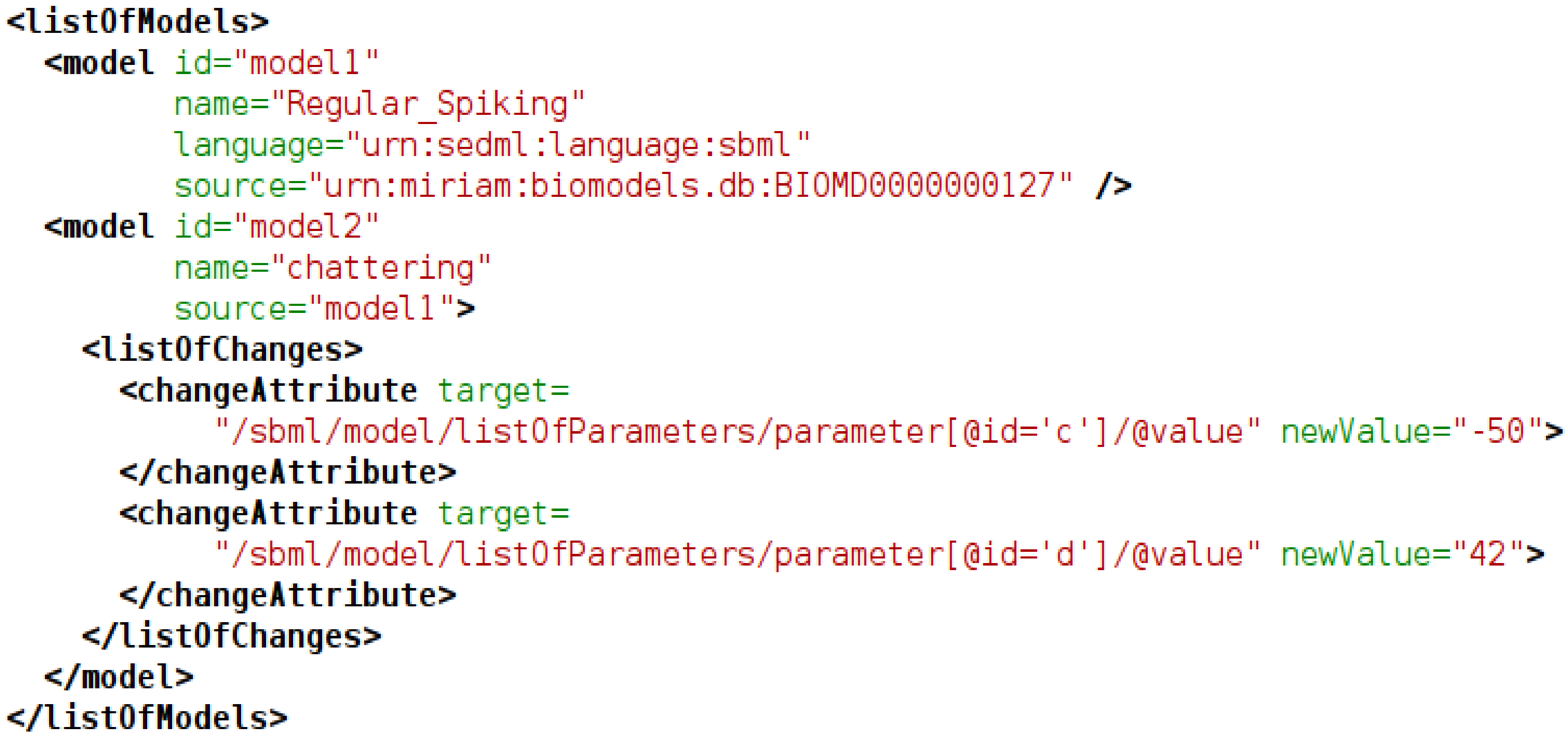
  </listOfModels>
  <listOfTasks><!-- --></listOfTasks>
  <listOfDataGenerators><!-- --></listOfDataGenerators>
  <listOfOutputs>
    <plot2D />
    <plot3D />
    <report />
  </listOfOutputs>
</sedML>
```

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

Description of models



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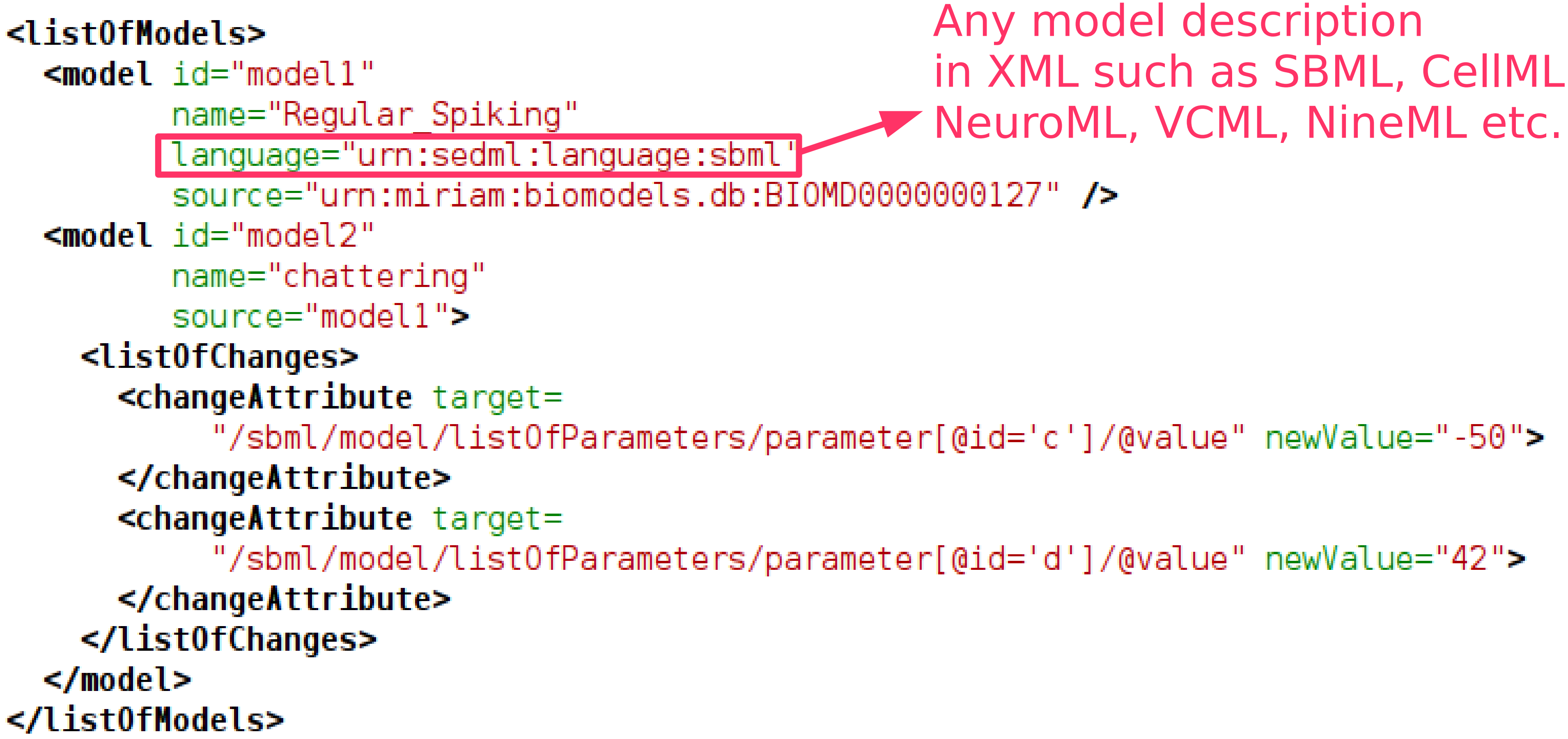
Description of models



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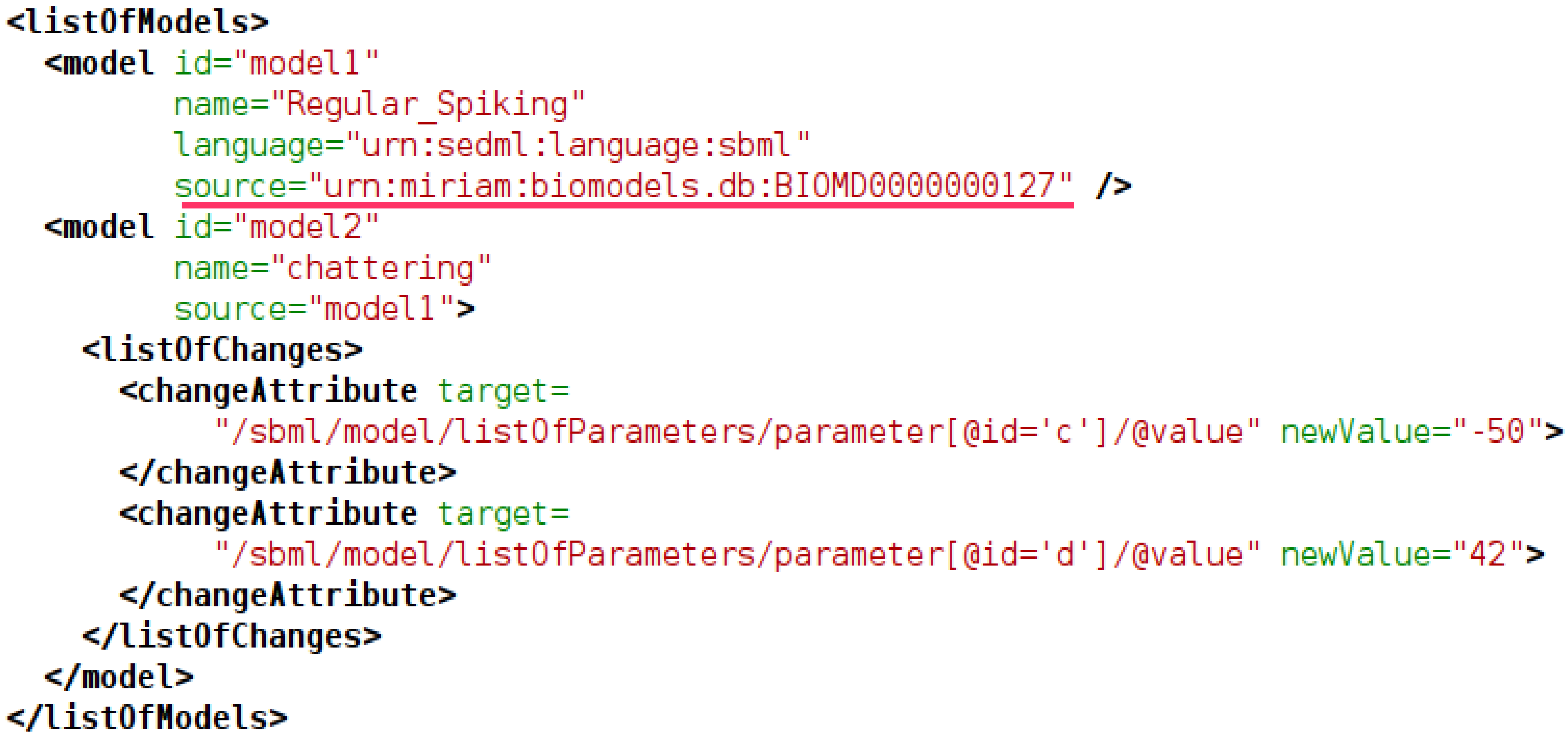
    </listOfChanges>
  </model>
</listOfModels>
```

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

Description of models



```
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  <model id="model2"
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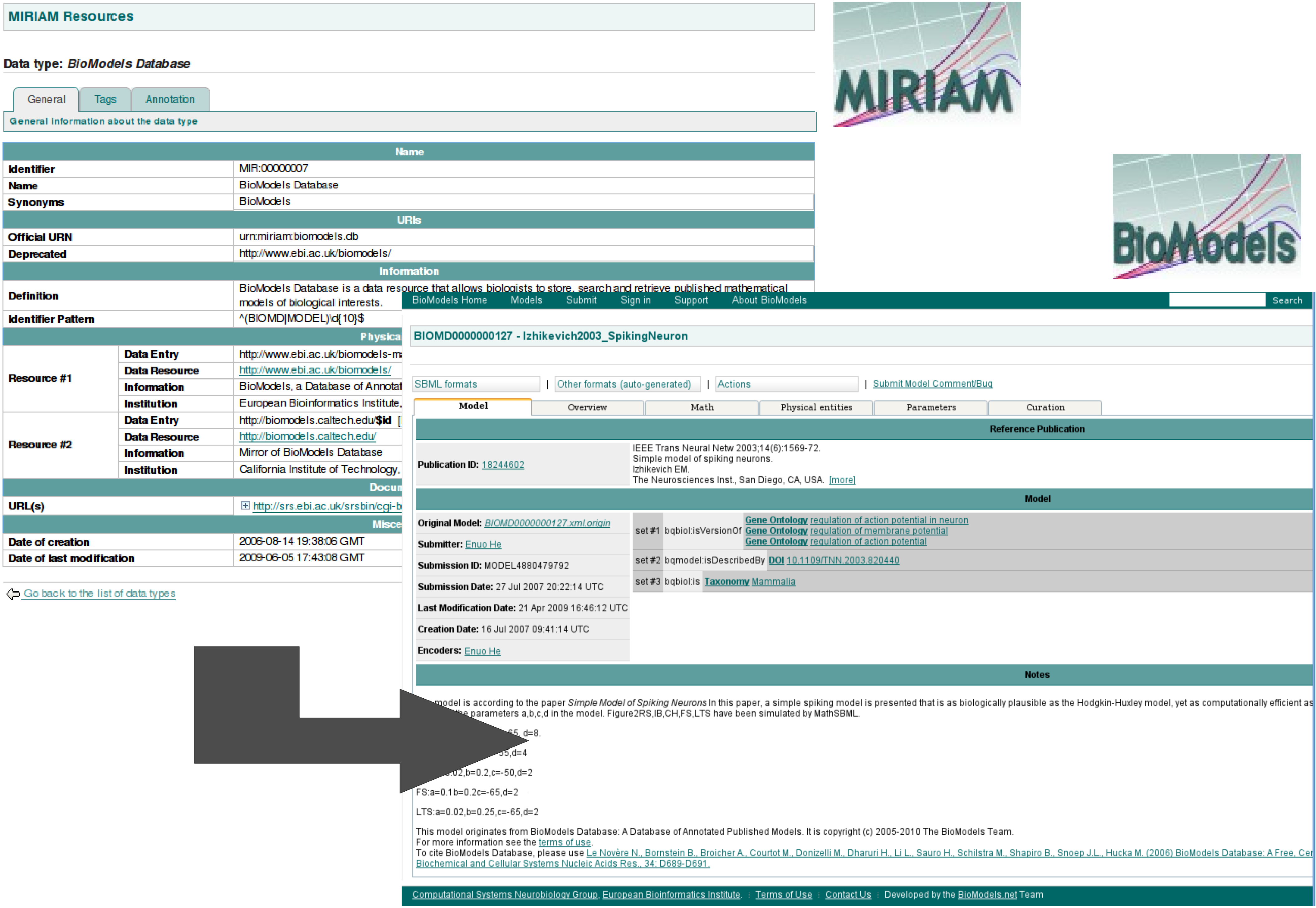
      </changeAttribute>
    </listOfChanges>
  </model>
</listOfModels>
```

Retrieving models



MIRIAM Resources

Data type: ***BioModels Database***

General information about the data type

Name	
Identifier	MIR:00000007
Name	BioModels Database
Synonyms	BioModels
URIs	
Official URN	urn:miriam:biomodels.db
Deprecated	http://www.ebi.ac.uk/biomodels/
Information	
Definition	BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests.
Identifier Pattern	^(BIOMD|MODEL)\d{10}$

Physica		
Resource #1	**Data Entry**	http://www.ebi.ac.uk/biomodels-m
	Data Resource	http://www.ebi.ac.uk/biomodels/
	Information	BioModels, a Database of Annotat
	Institution	European Bioinformatics Institute,
Resource #2	**Data Entry**	http://biomodels.caltech.edu/$id [
	Data Resource	http://biomodels.caltech.edu/
	Information	Mirror of BioModels Database
	Institution	California Institute of Technology,

Docun	
URL(s)	⊞ http://srs.ebi.ac.uk/srsbin/cgi-b
Misce	
Date of creation	2006-08-14 19:38:06 GMT
Date of last modification	2009-06-05 17:43:08 GMT

Go back to the list of data types

BIOMD0000000127 - Izhikevich2003_SpikingNeuron

Reference Publication

Publication ID: 18244602

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

Model

Original Model: *BIOMD0000000127.xml.origin*

Submitter: Enuo He

Submission ID: MODEL4880479792

Submission Date: 27 Jul 2007 20:22:14 UTC

Last Modification Date: 21 Apr 2009 16:46:12 UTC

Creation Date: 16 Jul 2007 09:41:14 UTC

Encoders: Enuo He

set #1	bqbiol:isVersionOf	**Gene Ontology** regulation of action potential in neuron **Gene Ontology** regulation of membrane potential **Gene Ontology** regulation of action potential
set #2	bqmodel:isDescribedBy	**DOI** 10.1109/TNN.2003.820440
set #3	bqbiol:is	**Taxonomy** Mammalia

Notes

model is according to the paper *Simple Model of Spiking Neurons* In this paper, a simple spiking model is presented that is as biologically plausible as the Hodgkin-Huxley model, yet as computationally efficient as the parameters a,b,c,d in the model. Figure2RS,IB,CH,FS,LTS have been simulated by MathSBML.

65, d=8.

55,d=4

.02,b=0.2,c=-50,d=2

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

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

This model originates from BioModels Database: A Database of Annotated Published Models. It is copyright (c) 2005-2010 The BioModels Team.
For more information see the terms of use.
To cite BioModels Database, please use Le Novère N., Bornstein B., Broicher A., Courtot M., Donizelli M., Dharuri H., Li L., Sauro H., Schilstra M., Shapiro B., Snoep J.L., Hucka M. (2006) BioModels Database: A Free, Cer Biochemical and Cellular Systems Nucleic Acids Res., 34: D689-D691.

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Characterising dynamical behaviours

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

Is the matrix of standards complete?

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

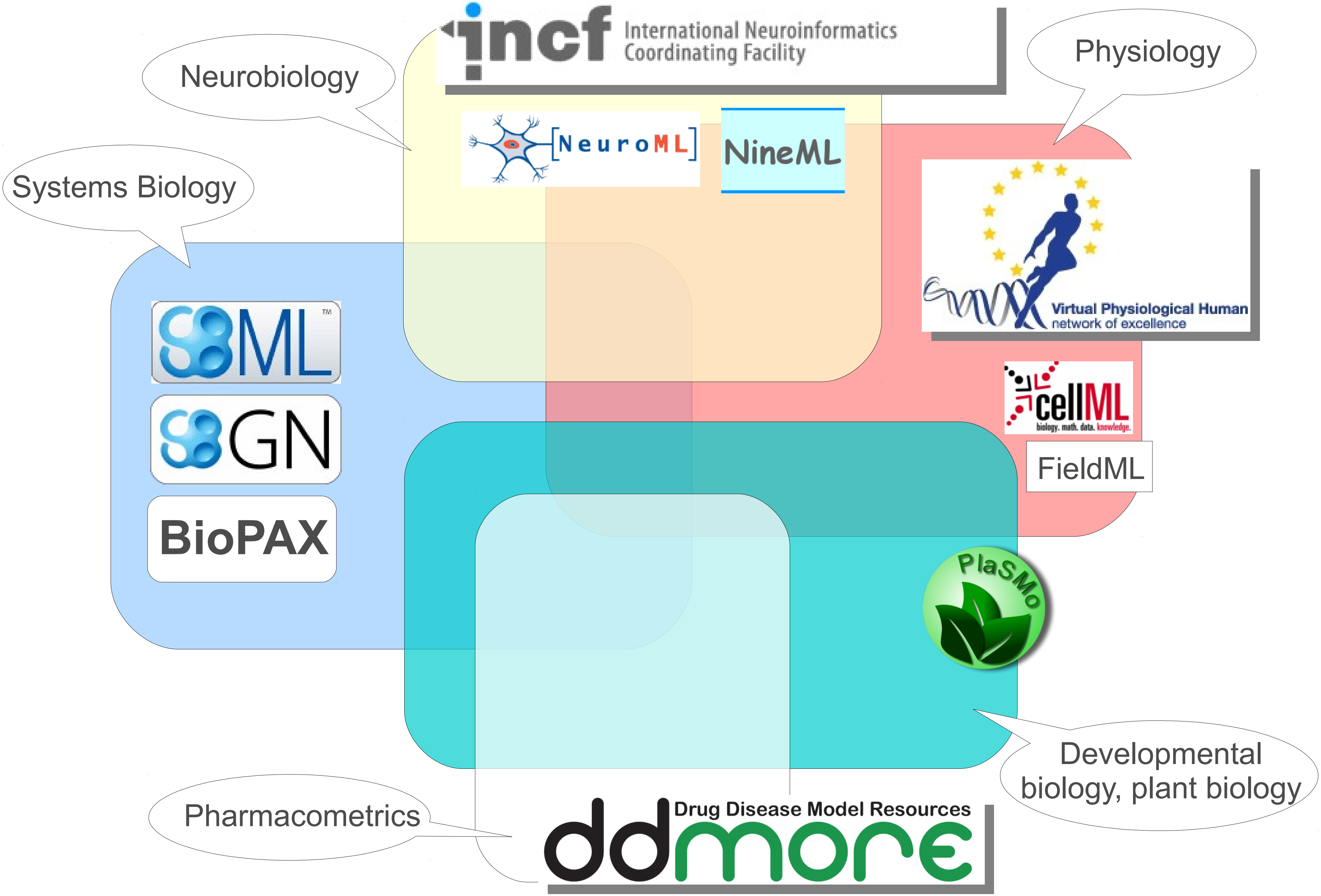
Is the matrix of standards complete?

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

Covering the entire model life-cycle

Model generation	Model structure	Parametrisation	Simulations and analysis	Numerical results
?	SBML™	?	SED ML	SBRML

Parallel and redundant efforts



incf International Neuroinformatics Coordinating Facility

Neurobiology

Physiology

Systems Biology

NeuroML

NineML

SBML

SBGN

BioPAX

Virtual Physiological Human network of excellence

cellML biology. math. data. knowledge.

FieldML

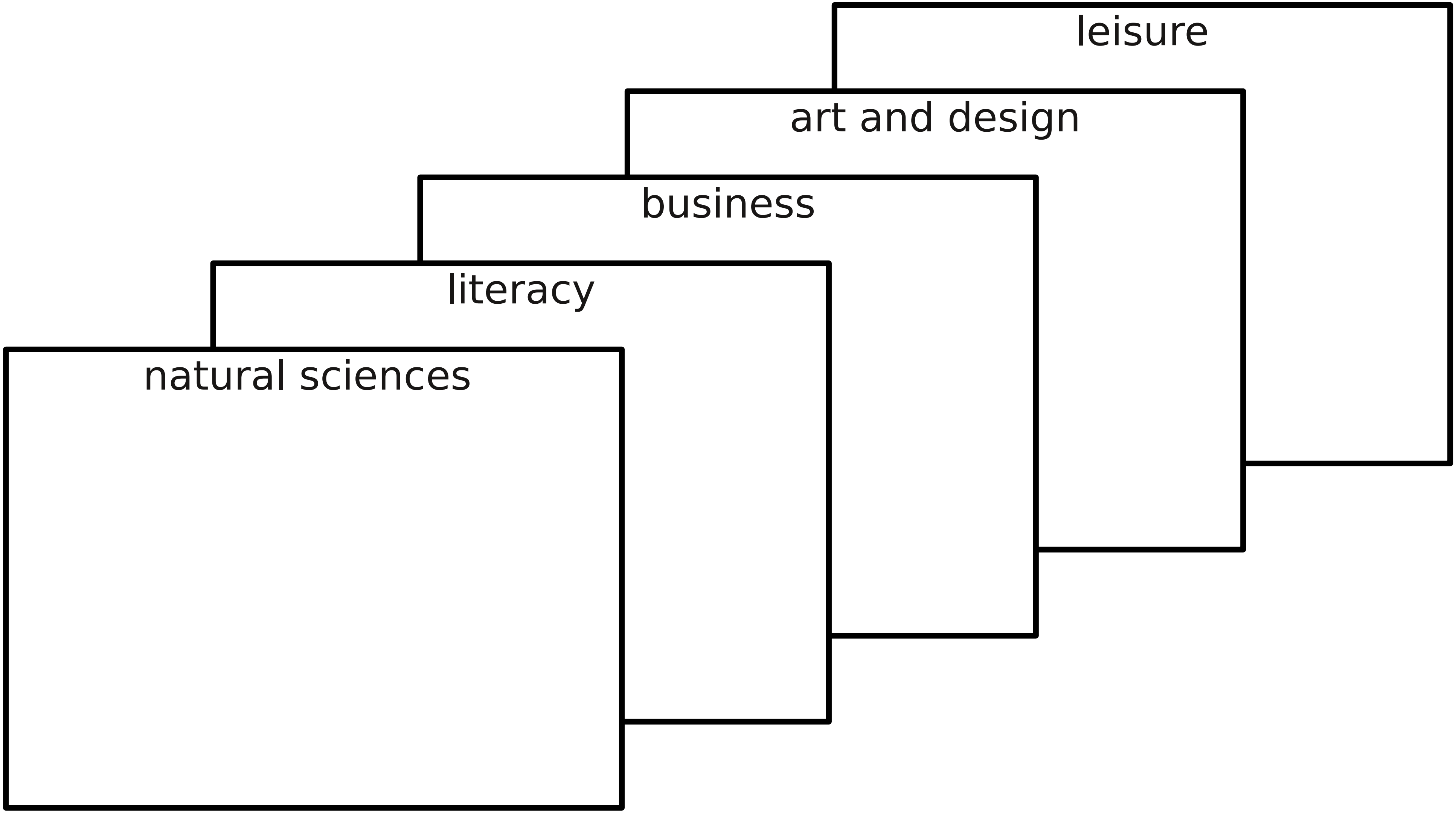
PlaSMo

Developmental biology, plant biology

Pharmacometrics

ddmore Drug Disease Model Resources

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



leisure

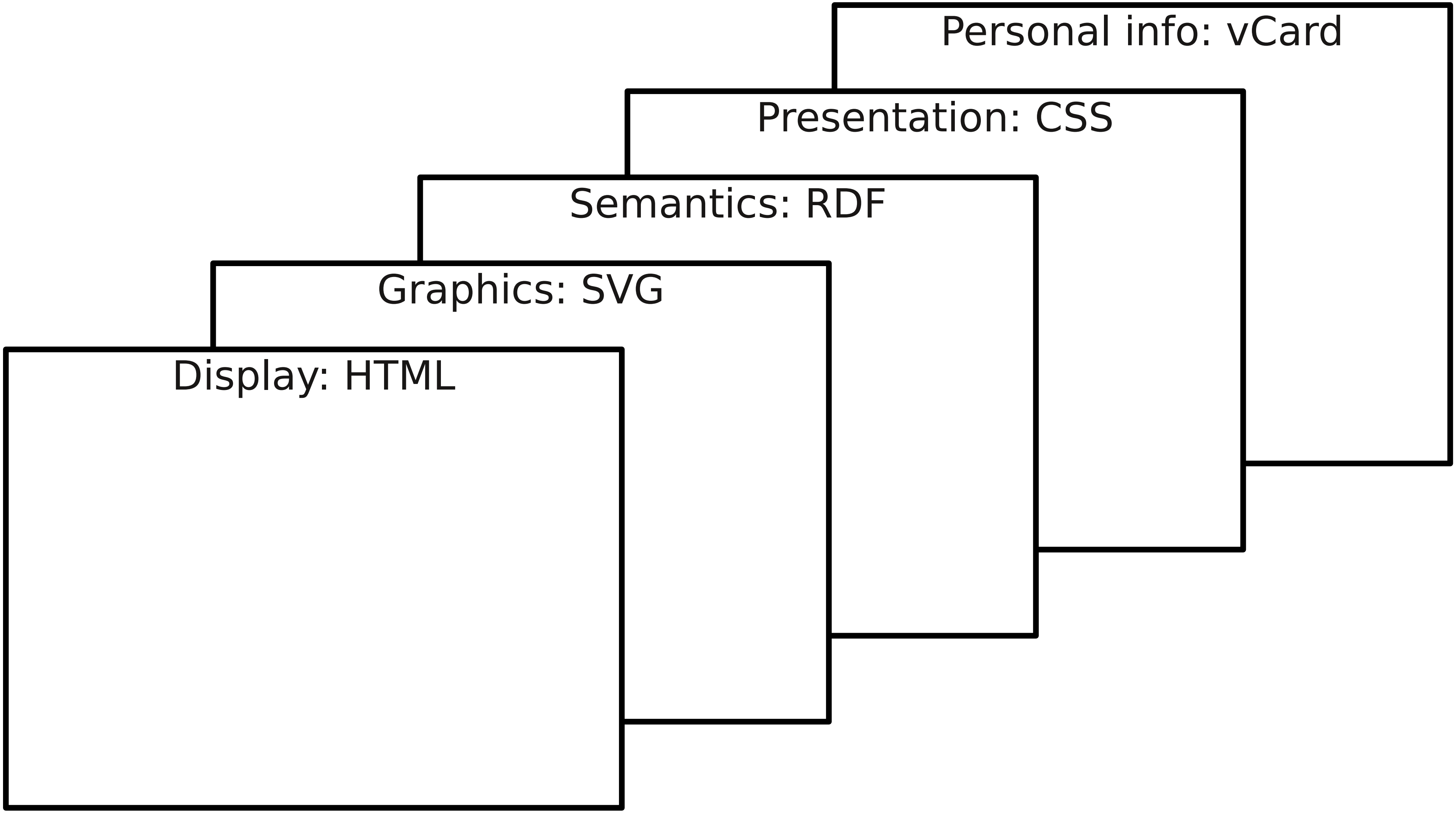
art and design

business

literacy

natural sciences

The correct way to do it



Personal info: vCard

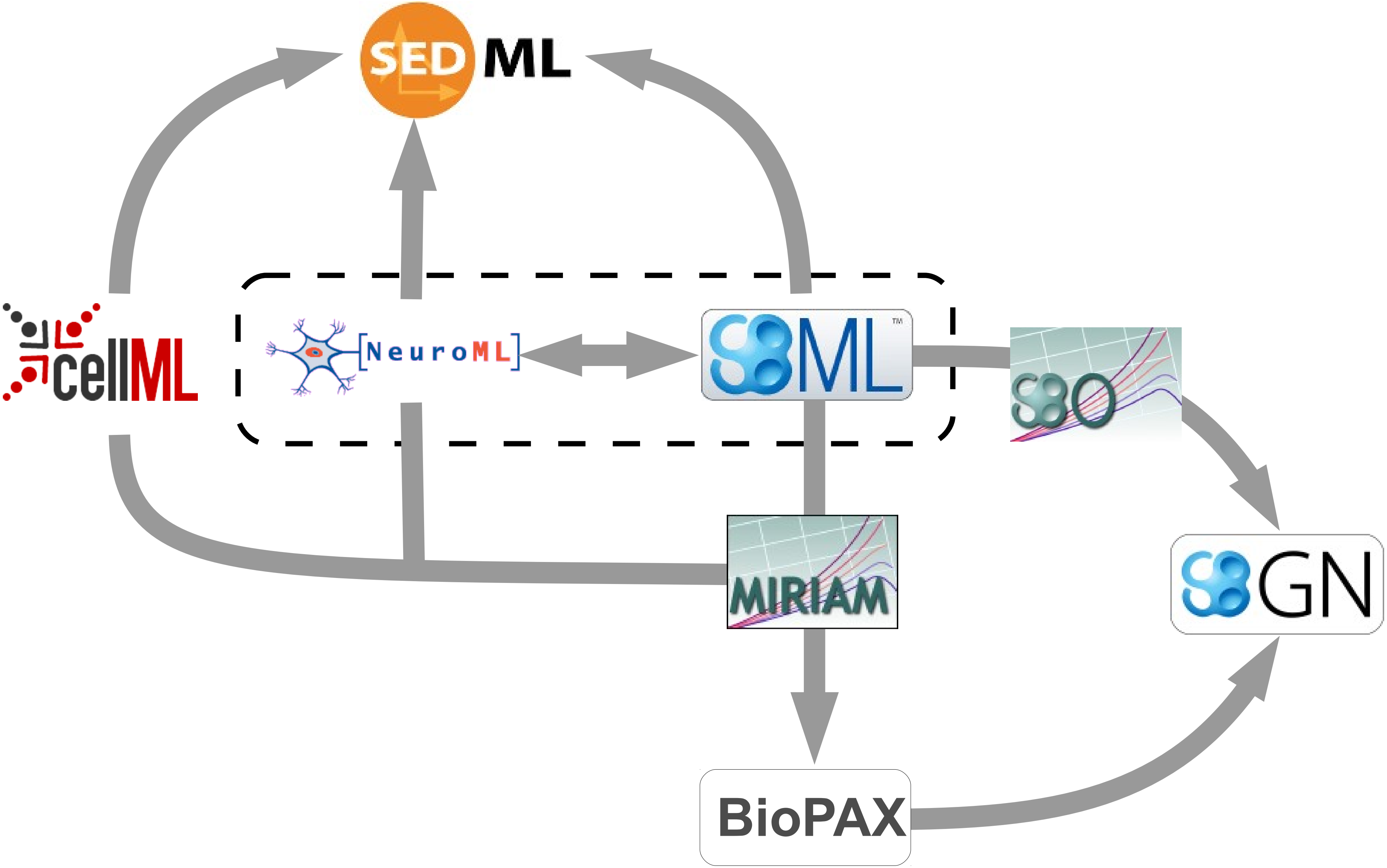
Presentation: CSS

Semantics: RDF

Graphics: SVG

Display: HTML

Existing standards interoperability



Overarching standardisation structure

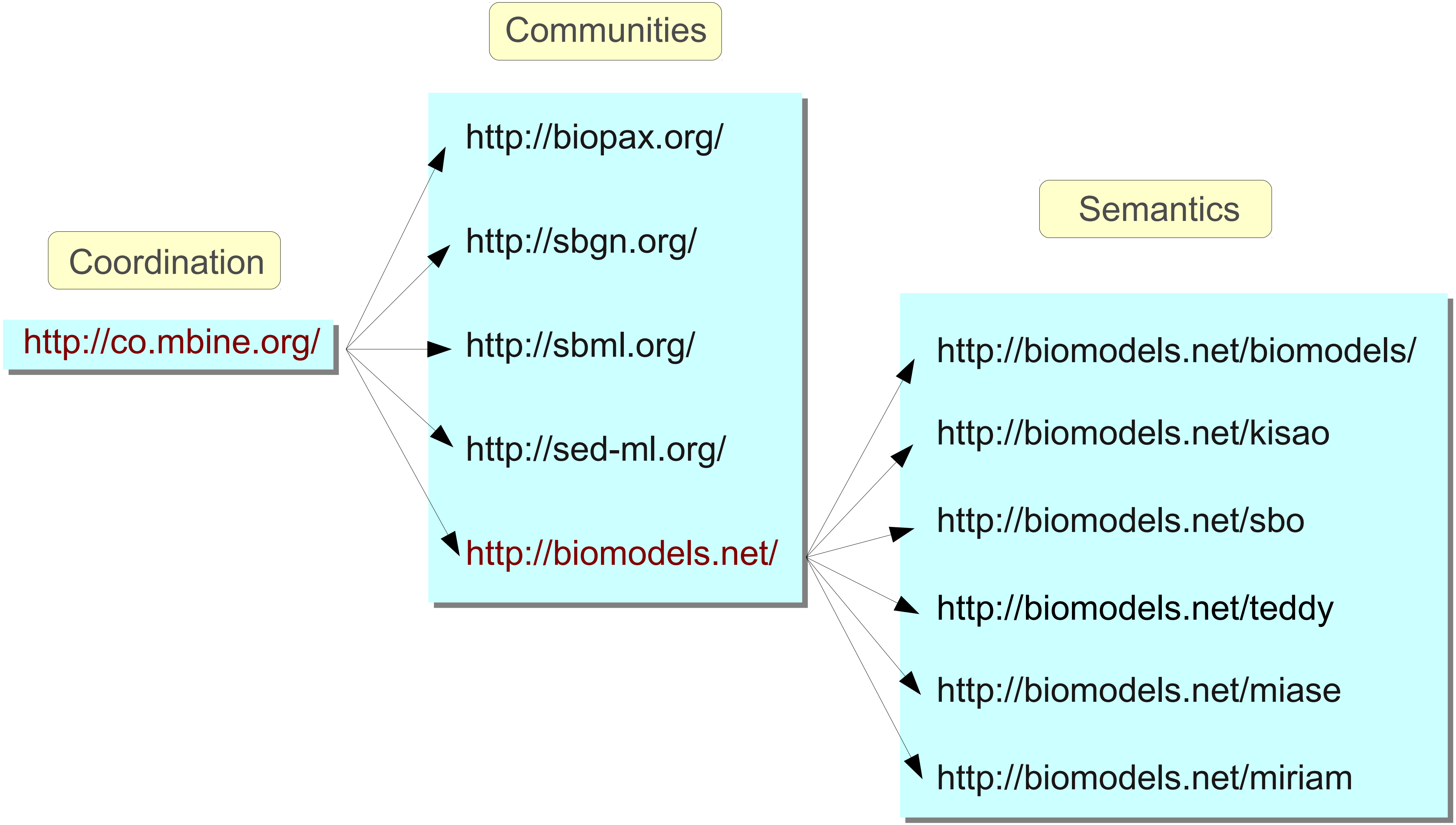
the combine
computational modeling in biology network

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

- HARMONY 2011
  - 18 to 22 April 2011, New-York
  - http://www.biopax.org/harmony.php
- COMBINE 2011
  - 3 to 7 September 2011, Heidelberg
  - http://co.mbine.org/events/COMBINE_2011

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

Where to find more information?



Coordination

http://co.mbine.org/

Communities

http://biopax.org/

http://sbgn.org/

http://sbml.org/

http://sed-ml.org/

http://biomodels.net/

Semantics

http://biomodels.net/biomodels/

http://biomodels.net/kisao

http://biomodels.net/sbo

http://biomodels.net/teddy

http://biomodels.net/miase

http://biomodels.net/miriam

Acknowledgements

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

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The EBI group Computational Systems Neurobiology

NIGMS

BBSRC
bioscience for the future

NEDO

EMBL

ELIXIR

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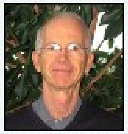
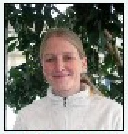
 Nicolas Le Novère Group Leader Joint appointement with the Mouse Biology Unit	 Tracey Andrew Administrative assistant	 Benedetta Frida Baldi PhD student	 Stuart Edelstein Visiting professor
 Kathryn Hardwick Administrative assistant	 Christine Hoyer PhD student	 Massimo Lai Research Scientist	 Lu Li Post-doc
 Michele Mattioni PhD student	Yang Zhan Post-doc Joint appointement with Cornelius Gross	 Junmei Zhu Research Scientist	

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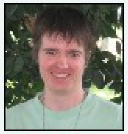
 Camille Laibe BioModels.net coordinator	 Vijayalakshmi Chelliah Database curator	 Lukas Endler Database curator	 Gael Jalowicki Summer intern
 Nick Juty Database and Ontology Curator	 Sarah Keating Software Developer	 Nicolas Rodriguez Scientific Programmer	 Michael Schubert Summer intern
 Anna Zhukova Summer intern			

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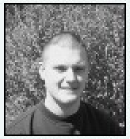
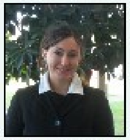
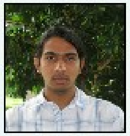
 Duncan Berenguier Trainee	 Alexander Broicher Trainee	 Mélanie Courtot Software Developer	 Marie-Ange Djite Trainee
 Koray Dogan Kaya Marie Curie PhD	 Marco Donizelli Software Engineer	 Marine Dumousseau Software developer	 Ranjita Dutta-Roy Trainee
 Éric Fernandez Postdoctoral fellow	 Enuo He Trainee	 Ron Henkel Visitor	 Arnaud Henry Trainee
 Noriko Hiroi Postdoctoral fellow	 Christian Knuepfer Marie Curie PhD	 Dagmar Koehn Marie Curie PhD	 Chen Li Software Engineer
 Catherine Lloyd Visitor	 David Marshall Trainee	 Antonia Mayer Trainee	 Daniel McGreal Database engineer
 Kedar Nath Natarajan Trainee	 Anika Oellrich Trainee	 Jean-Baptiste Pettit Trainee	 Renaud Schiappa Trainee
 Melanie Stefan PhD student and Post-doc	 Karim Tazibt Trainee	 Dominic Tölle PhD student	 Sarala Wimalaratne Ontology curator