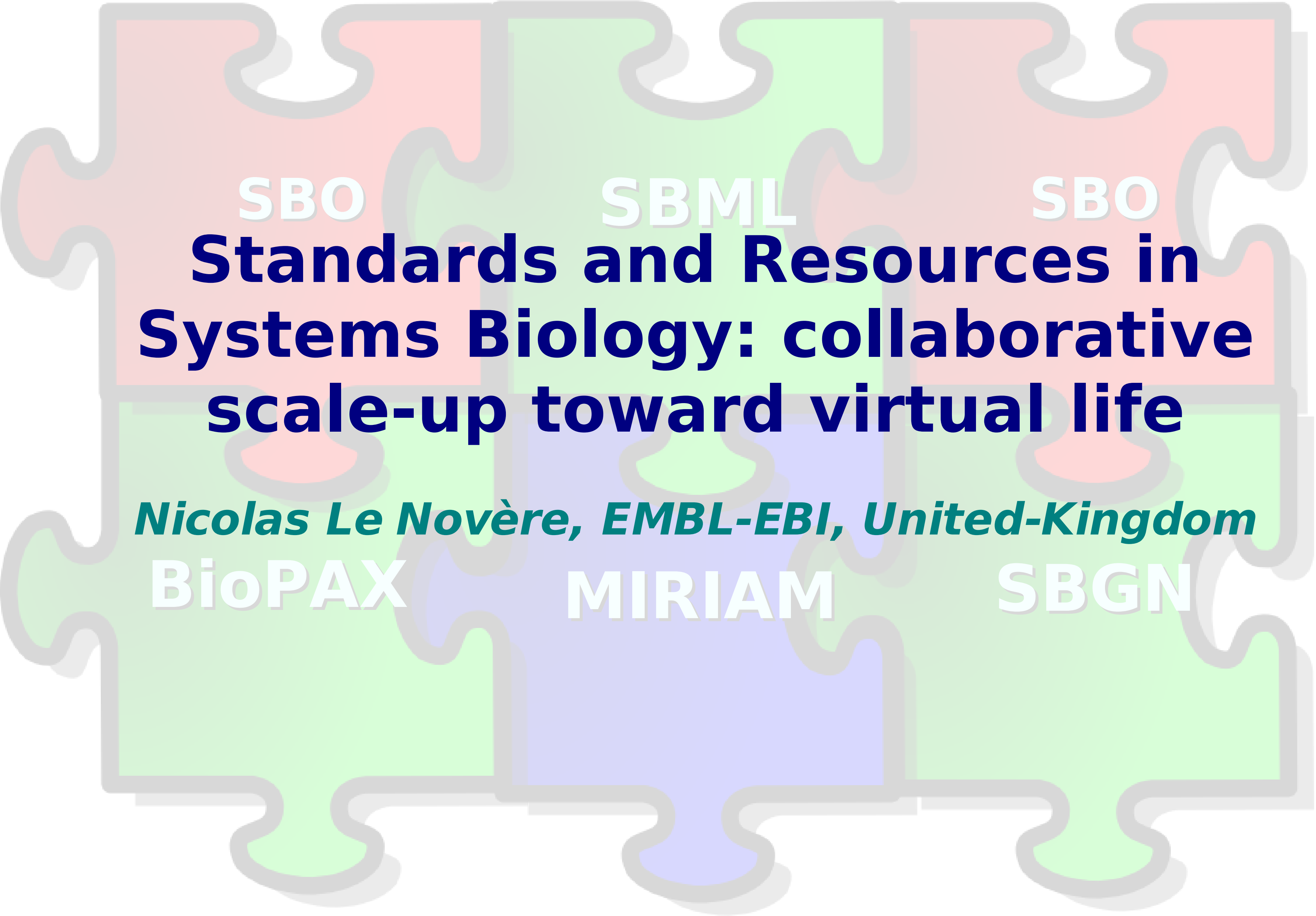
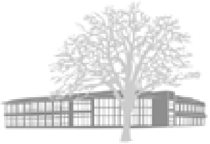


Standards and Resources in Systems Biology: collaborative scale-up toward virtual life

Nicolas Le Novère, EMBL-EBI, United-Kingdom

Annual Meeting 2006, Friday 24th November 2006

November 24 2006, Ghent, Belgium



What is Systems Biology anyway?

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- *« Je tiens impossible de connaître les parties sans connaître le tout, non plus que de connaître le tout sans connaître particulièrement les parties »*   Blaise Pascal, Pensées, 1660.

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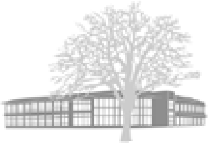
- *“[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems*" Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928



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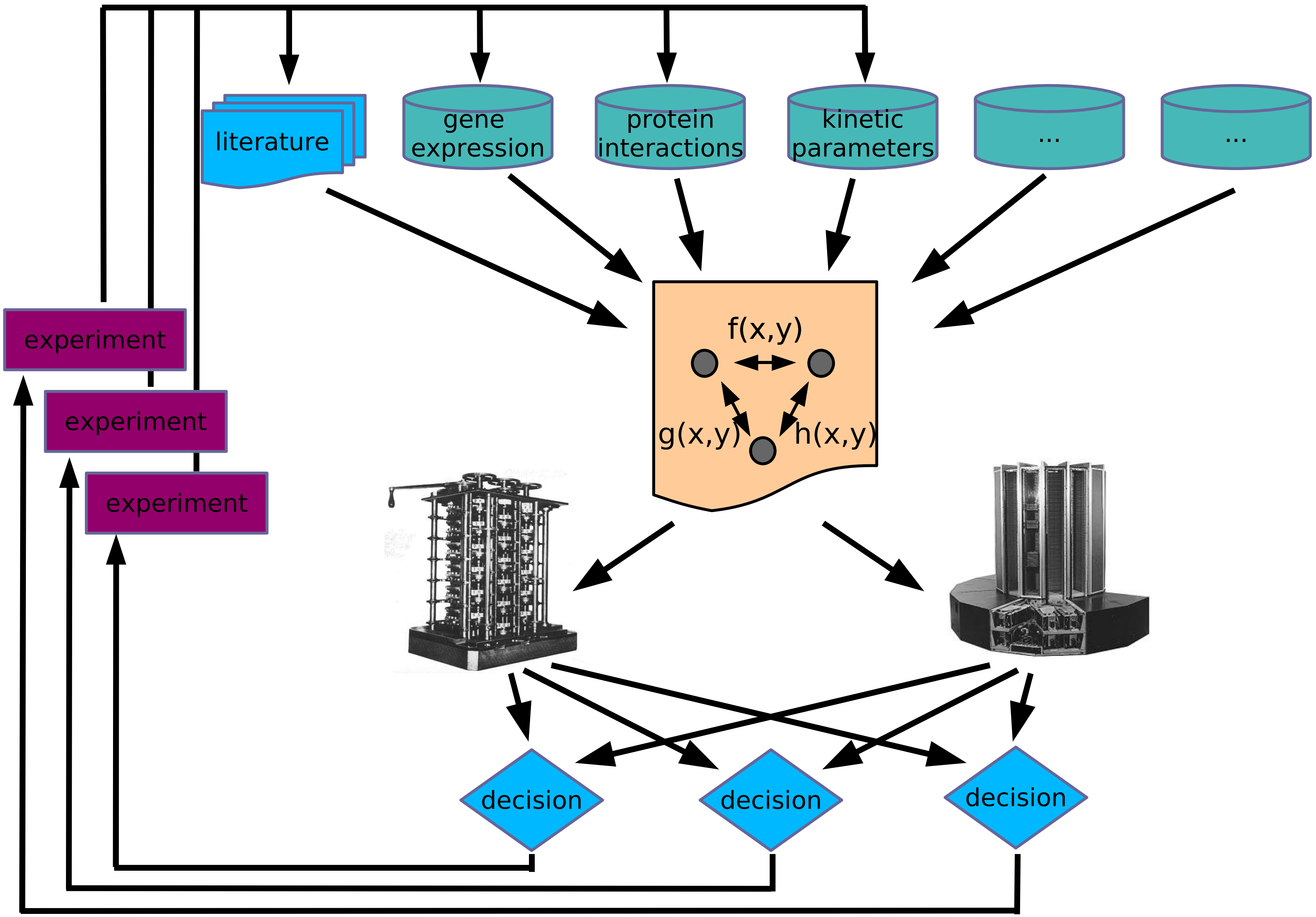
⇒ The question we ask in Systems Biology is not:

“fit my data”

but:

“Surprise-me”

The model as an integrator of knowledge



literature

gene expression

protein interactions

kinetic parameters

...

...

f(x,y)

g(x,y)

h(x,y)

experiment

experiment

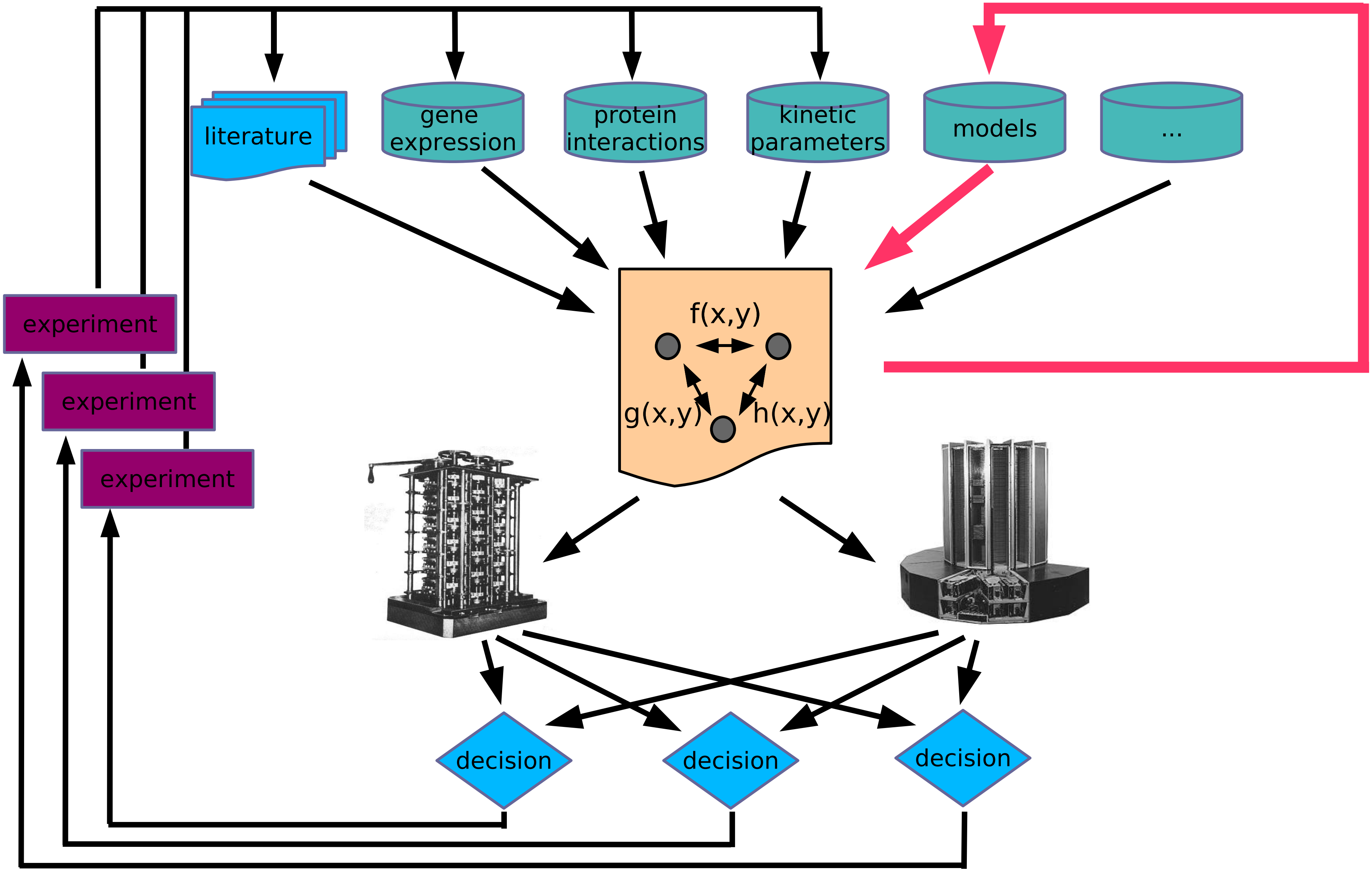
experiment

decision

decision

decision

The model as an integrator of knowledge



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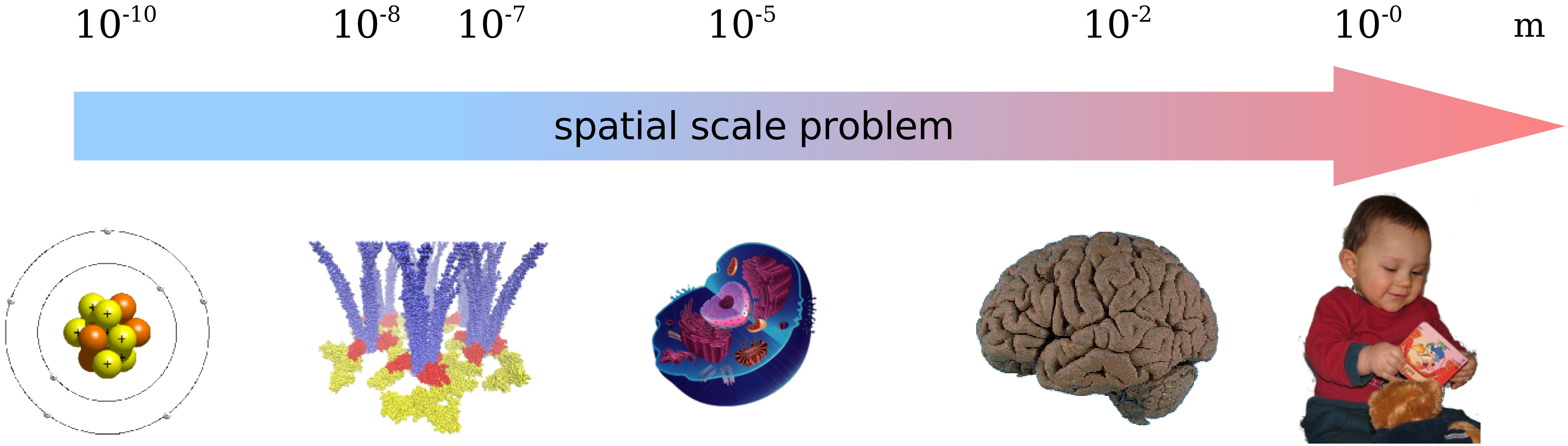
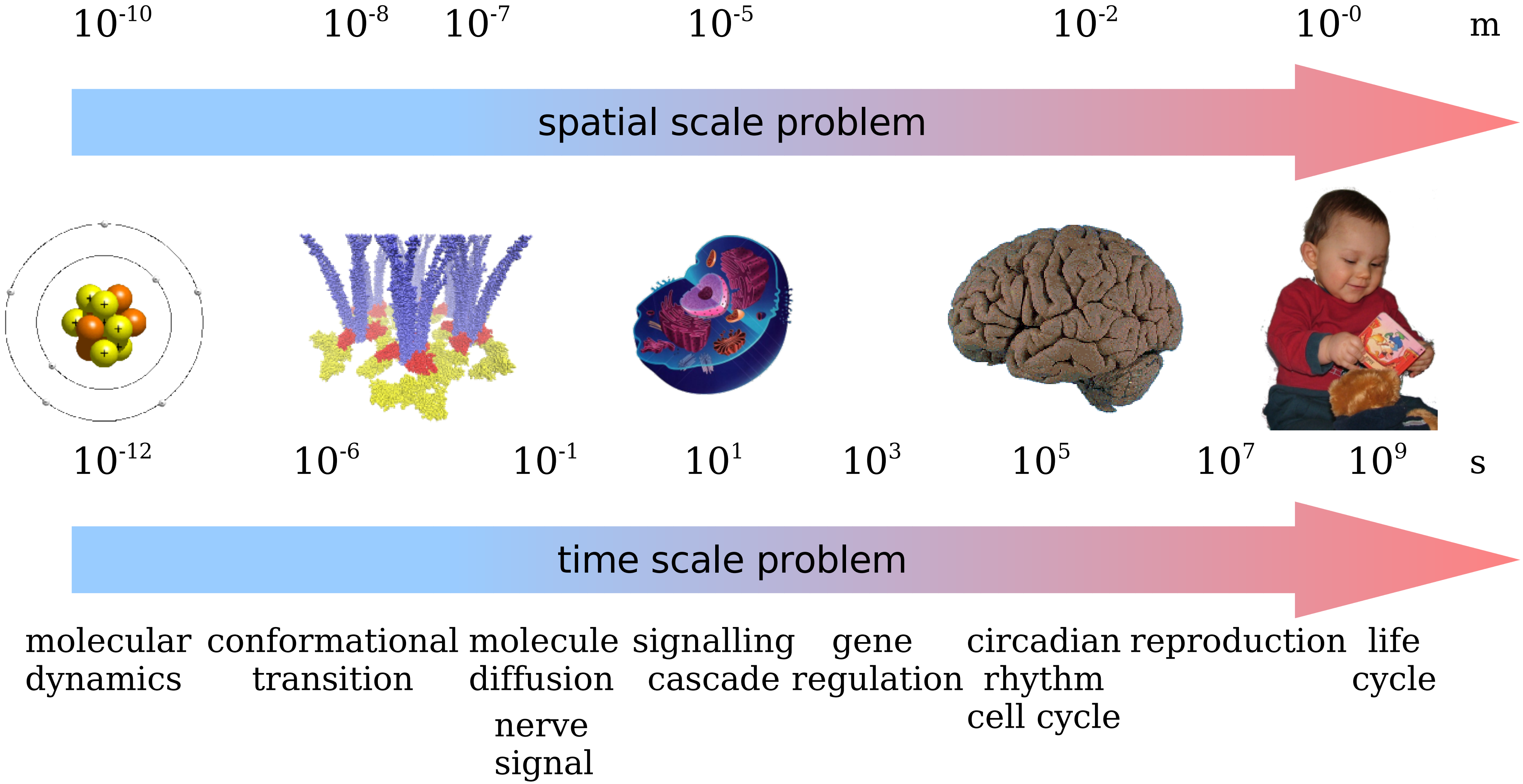
A multiscale problem



A multiscale problem



10^{-10} 10^{-8} 10^{-7} 10^{-5} 10^{-2} 10^{-0} m

spatial scale problem

10^{-12} 10^{-6} 10^{-1} 10^{1} 10^{3} 10^{5} 10^{7} 10^{9} s

time scale problem

- molecular dynamics
- conformational transition
- molecule diffusion
- nerve signal
- signalling cascade
- gene regulation
- circadian rhythm
- cell cycle
- reproduction
- life cycle

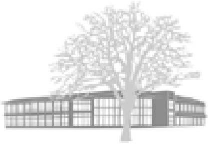
A simulation problem

Molecular dynamics:	to simulate $\propto 10^{-12}$ s	requires $\propto$ 1 s
Particle diffusion:	to simulate $\propto 10^{-6}$ s	requires $\propto$ 1 s
Stochastic chemical kinetics:	to simulate $\propto$ 1 s	requires $\propto$ 1 s
Continuous ODE:	to simulate $\propto 10^{3}$ s	requires $\propto$ 1 s

⇒ Humongous stiffness: the speed of the whole simulation is determined by the quickest event

We need to reuse computational models

- The development of quantitative models of even simple living systems requires an extensive knowledge of biology, from biochemical reactions to physiology.



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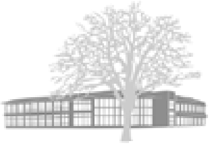

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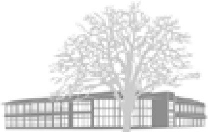
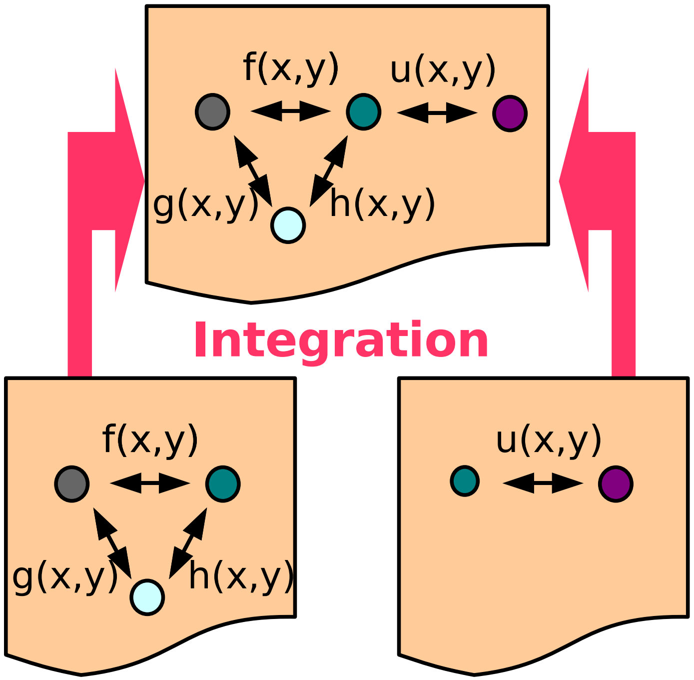
⇒ Nobody possesses the required knowledge. Moreover the time, money and energy necessary are prohibitive



What can-we do?



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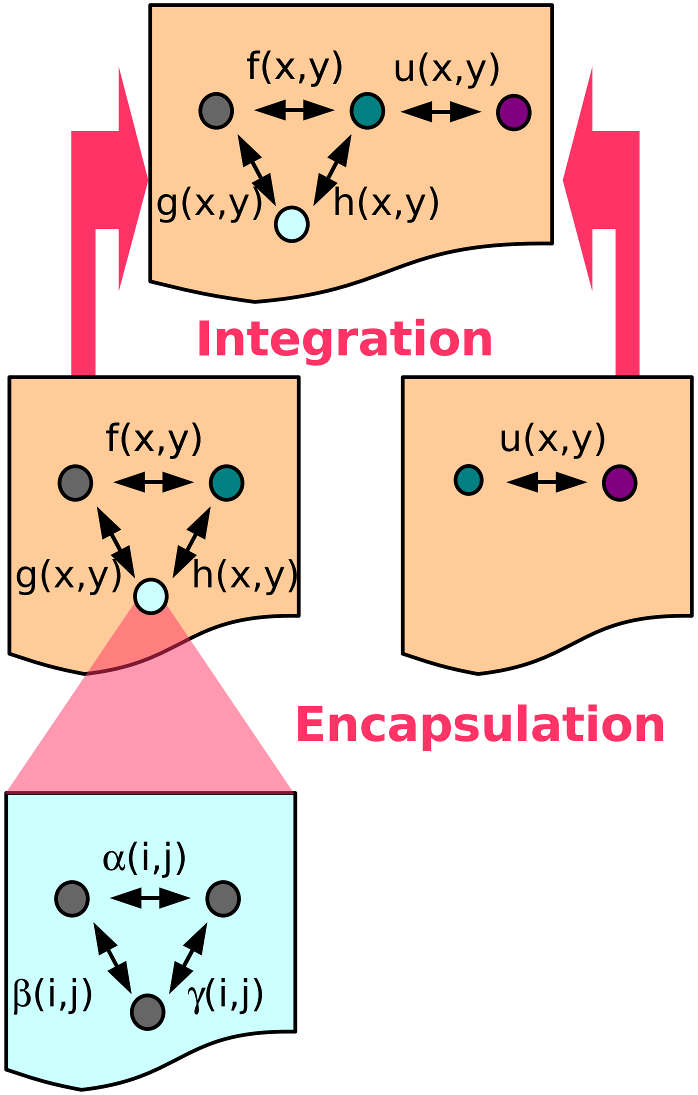

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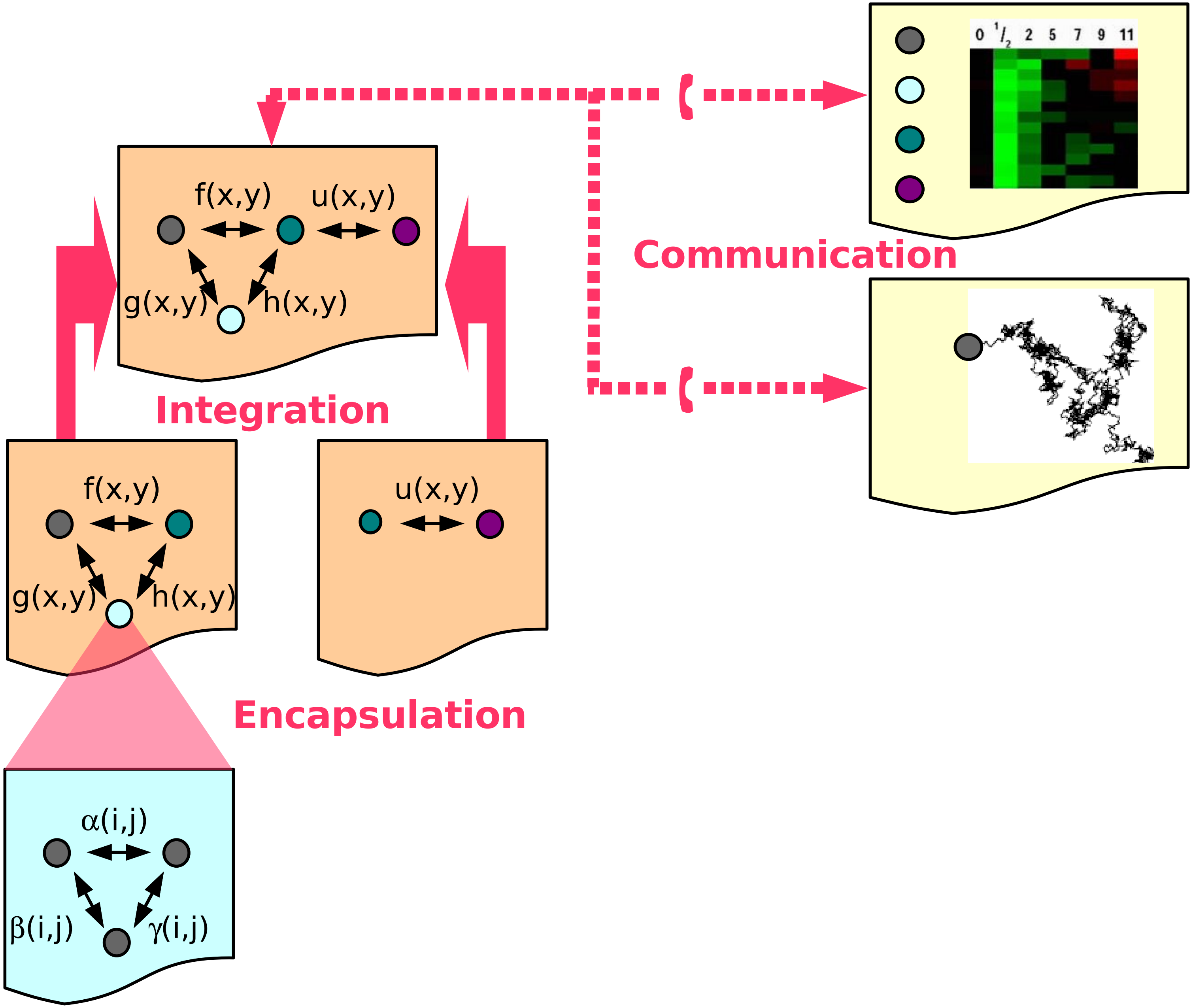

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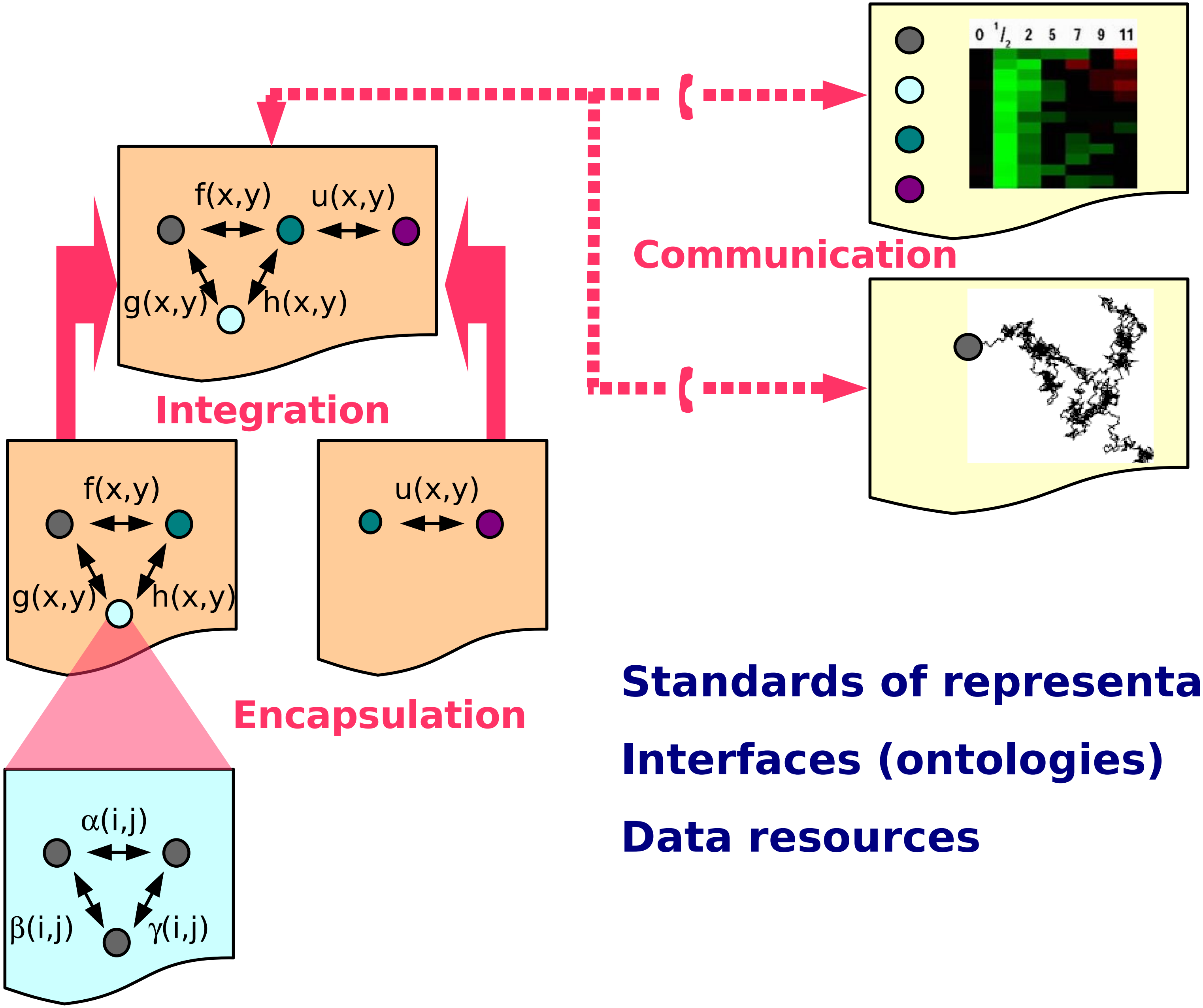


Standards of representation

Interfaces (ontologies)

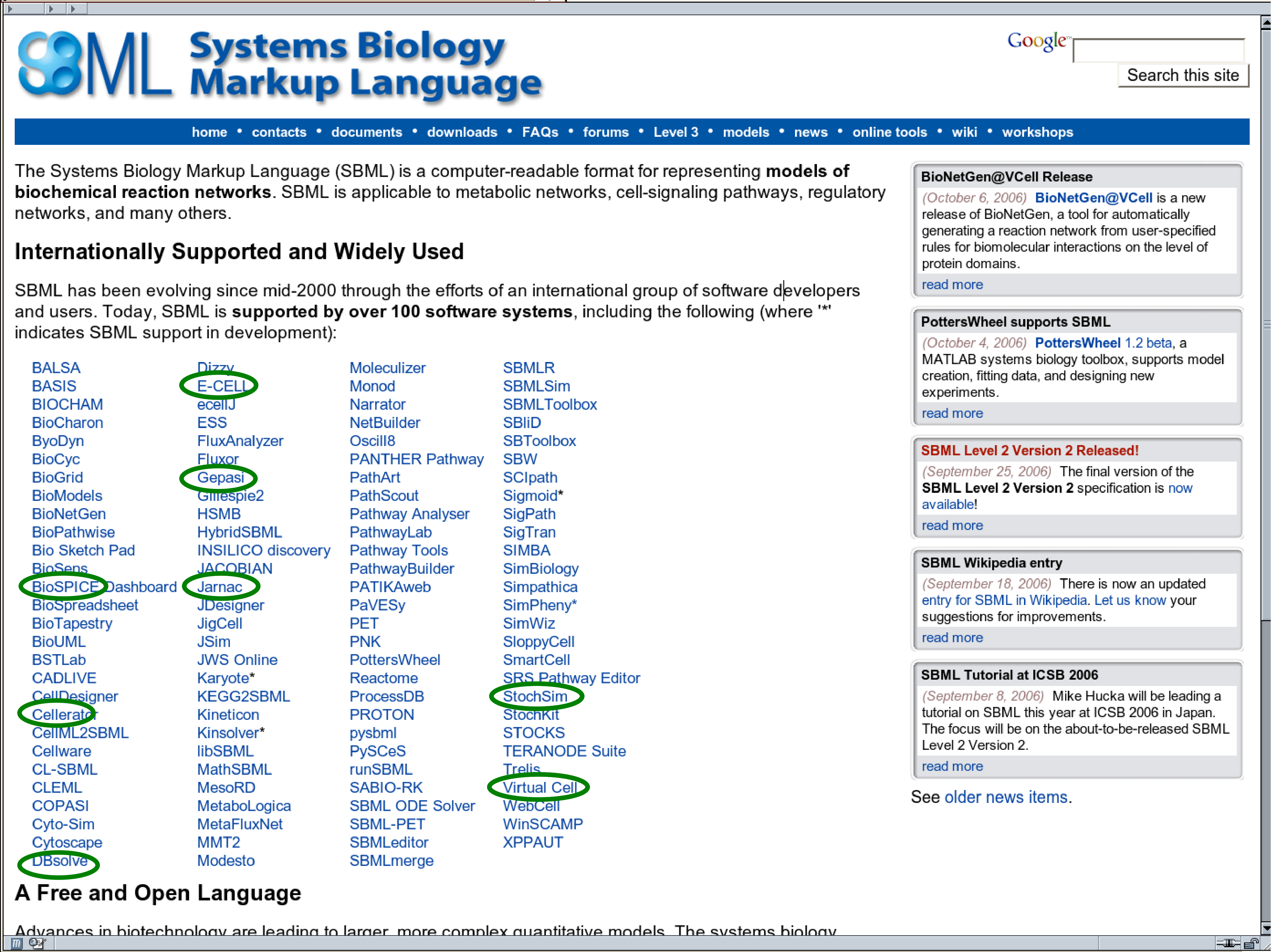
Data resources

Standards of representation

“ The nice thing about standards is that there are so many to choose from”.
Attributed to Andrew S Tanenbaum

Standards of representation

- cellML biology. math. data. knowledge.
  `http://www.cellml.org/`
  Based on modules; scalable;
- NeuroML
  `http://www.neuroml.org/`
  Flexible (expendable set of classes/schemas);
- BrainML.org
  `http://brainml.org/`
  Models are XML-schemas
- <BioPAX>
  `http://www.biopax.org/`
  No kinetics; deep semantics; OWL
- SBGN
  `http://www.sbgn.org/`
  Graphical representation of interactions
- SBML Systems Biology Markup Language
  `http://sbml.org/`
  `Rich kinetics; weak semantics; XML`



Systems Biology Markup Language

The Systems Biology Markup Language (SBML) is a computer-readable format for representing **models of biochemical reaction networks**. SBML is applicable to metabolic networks, cell-signaling pathways, regulatory networks, and many others.

Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is **supported by over 100 software systems**, including the following (where '*' indicates SBML support in development):

- BALSA
- BASIS
- BIOCHAM
- BioCharon
- ByoDyn
- BioCyc
- BioGrid
- BioModels
- BioNetGen
- BioPathwise
- Bio Sketch Pad
- BioSens
- BioSPICE Dashboard
- BioSpreadsheet
- BioTapestry
- BioUML
- BSTLab
- CADLIVE
- CellDesigner
- Cellerator
- CellML2SBML
- Cellware
- CL-SBML
- CLEML
- COPASI
- Cyto-Sim
- Cytoscape
- DBsolve
- Dizzy
- E-CELL
- ecellJ
- ESS
- FluxAnalyzer
- Fluxor
- Gepasi
- Gillespie2
- HSMB
- HybridSBML
- INSILICO discovery
- JACOBIAN
- Jarnac
- JDesigner
- JigCell
- JSim
- JWS Online
- Karyote*
- KEGG2SBML
- Kineticon
- Kinsolver*
- libSBML
- MathSBML
- MesoRD
- MetaboLogica
- MetaFluxNet
- MMT2
- Modesto
- Moleculizer
- Monod
- Narrator
- NetBuilder
- Oscill8
- PANTHER Pathway
- PathArt
- PathScout
- Pathway Analyser
- PathwayLab
- Pathway Tools
- PathwayBuilder
- PATIKAweb
- PaVESy
- PET
- PNK
- PottersWheel
- Reactome
- ProcessDB
- PROTON
- pysbml
- PySCeS
- runSBML
- SABIO-RK
- SBML ODE Solver
- SBML-PET
- SBMLeditor
- SBMLmerge
- SBMLR
- SBMLSim
- SBMLToolbox
- SBliD
- SBToolbox
- SBW
- SCIpath
- Sigmoid*
- SigPath
- SigTran
- SIMBA
- SimBiology
- Simpathica
- SimPheny*
- SimWiz
- SloppyCell
- SmartCell
- SRS Pathway Editor
- StochSim
- StochKit
- STOCKS
- TERANODE Suite
- Trelis
- Virtual Cell
- WebCell
- WinSCAMP
- XPPAUT

A Free and Open Language

Advances in biotechnology are leading to larger, more complex quantitative models. The systems biology

BioNetGen@VCell Release

(October 6, 2006) **BioNetGen@VCell** is a new release of BioNetGen, a tool for automatically generating a reaction network from user-specified rules for biomolecular interactions on the level of protein domains.

read more

PottersWheel supports SBML

(October 4, 2006) **PottersWheel** 1.2 beta, a MATLAB systems biology toolbox, supports model creation, fitting data, and designing new experiments.

read more

SBML Level 2 Version 2 Released!

(September 25, 2006) The final version of the **SBML Level 2 Version 2** specification is now available!

read more

SBML Wikipedia entry

(September 18, 2006) There is now an updated entry for SBML in Wikipedia. Let us know your suggestions for improvements.

read more

SBML Tutorial at ICSB 2006

(September 8, 2006) Mike Hucka will be leading a tutorial on SBML this year at ICSB 2006 in Japan. The focus will be on the about-to-be-released SBML Level 2 Version 2.

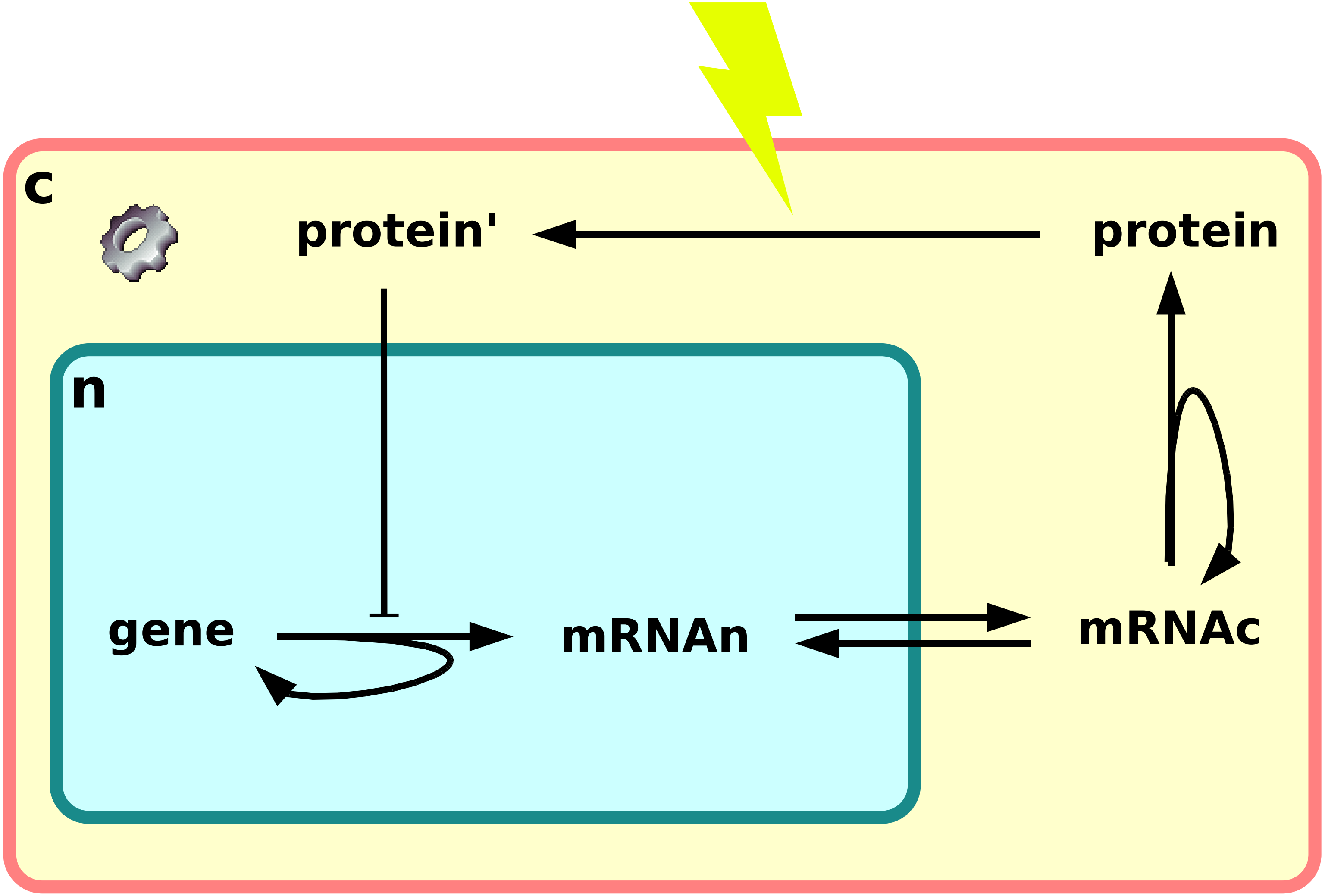
read more

See older news items.

What the heck is SBML

"*The goal of SBML is to help people to disagree as precisely as possible*". Ed Franck, Argonne National Laboratory

What can we encode in SBML?



A → B

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

SBML is not limited to biochemistry!

- Rate Rules can describe the temporal evolution of <u>any quantitative parameter</u>, e.g. transmembrane voltage;
- Events can describe any discontinuous change, e.g. neurotransmitter release;
- A species is an entity participating to a reaction, **not always** a **chemical** entity:
  - It can be a molecule
  - It can be a cell
  - It can be an organ
  - It can be an organism

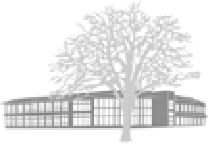
➔ Remember, Systems Biology is scale-free!

SBML Levels

- Level 1 (March 2001)
  - Predefined kinetics functions
  - Only one type of reactive substance
  - ISO646 encoding
- Level 2 (June 2003)
  - User-defined functions
  - Modifier species
  - Events
  - All math in MathML
  - Unicode encoding
  - IETF MIME-Type, see RFC3823
- Level 3 (?)

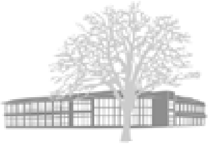
Hucka et al (2003)
Bioinformatics 19: 524-531

Hucka et al (2004)
IEE Systems Biology 1: 41-53



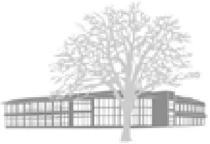
New: SBML Level 2 Version 2

- Released on September 25th 2006
- Simpler and cleaner (units ...)
- Generic entities (compartmentType, speciesType)
  ➔ path to generalised reactions
- Constraints and initialAssignments
- Controlled annotations (+ links to SBO)
- Backward compatible with Level 2 Version 1
- More detailed and bug-free specification ... 145 pages, 10pt, small margin.



SBML Level 3

- Modular SBML, with core + optional packages
- Graph Layout
- Generalised reactions (probable)
- Model composition (probable)
- Complex species (probable)
- Arrays or sets (maybe)
- Geometry (maybe)
- Movements (maybe)
- Dynamic compartments (maybe)
- ???



Is SBML enough? What's missing?

- An SBML model lists physical entities, but does not identify them properly.
- An SBML model contains mathematical expressions, but does not tell-us what they characterise and how.
- An SBML constructed for a certain modelling approach cannot be used straight-away within another modelling framework.

⇒ SBML models cannot be easily searched
SBML models cannot be easily converted
SBML models cannot be easily merged

Minimum Information Requested In the Annotation of biochemical Models

Le Novère N., Finney A., Hucka M., Bhalla U., Campagne F., Collado-Vides J.,
Crampin E., Halstead M., Klipp E., Mendes P., Nielsen P., Sauro H., Shapiro B.,
Snoep J.L., Spence H.D., Wanner B.L.
***Nature Biotechnology* (2005), 23: 1509-1515**

MIRIAM

Reference correspondence

- The model must be encoded in a public, standardized, machine-readable format (SBML, CellML, GENESIS ...)

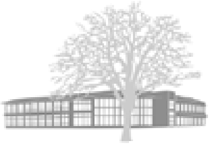
- The model must comply with the standard in which it is encoded!

- The model must be clearly related to a single reference description. If a model is composed from different parts, there should still be a description of the derived/combined model.

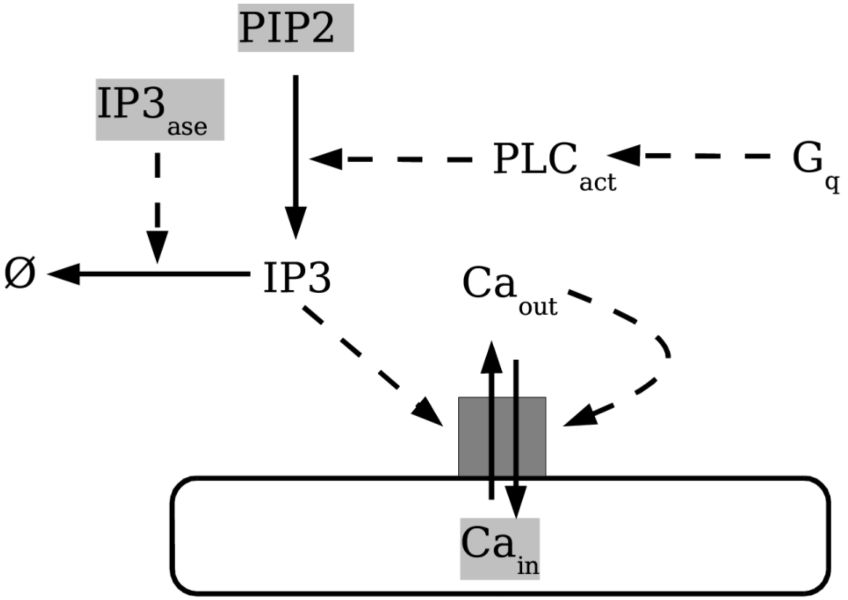
- The encoded model structure must reflect the biological processes listed in the reference description.

- The model must be instantiated in a simulation: All quantitative attributes have to be defined, including initial conditions.

- When instantiated, the model must be able to reproduce all results given in the reference description within an epsilon (algorithms, round-up errors)



Model example



$$k_1 = k_2 = k_3 = 1\ s^{-1}$$

$$Km_1 = 10^{-7}\ M, Km_2 = 10^{-8}, Km_3 = 2.10^{-6}\ M$$

$$K_A = 10^{-11}, m = 4, n = 3, \alpha = 0.001$$

$$[Ca_{in}] = [IP3R] = [PLC_{tot}] = [PIP2] = [IP3_{ase}] = 0.001\ M$$

$$[G_q] = 0.01\ M, [Ca_{out}] = [IP3] = [PLC_{act}] = 0\ M$$

$$\frac{d[Ca_{out}]}{dt} = \frac{k_1[IP3R] * ([Ca_{in}] - [Ca_{out}])}{Km_1 + |[Ca_{in}] - [Ca_{out}]|} * \frac{[IP3]^m}{K_A + [IP3]^m}$$

$$\frac{d[IP3]}{dt} = \frac{k_2[PLC_{act}] * [PIP2]}{Km_2 + [PIP2]} - \frac{k_3[IP3_{ase}] * [IP3]}{Km_3 + [IP3]}$$

$$\frac{d[PLC_{act}]}{dt} = \frac{[G_q]^n}{\alpha + [G_q]^n} * [PLC_{tot}]$$

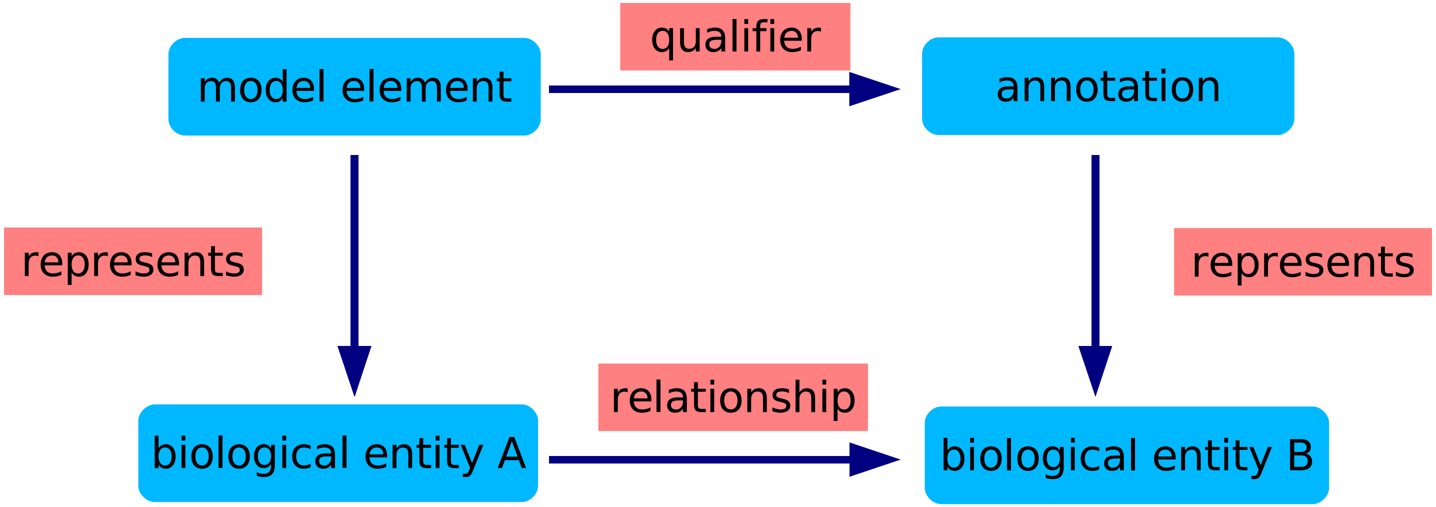
Attribution annotation

- The model has to be named.
- A citation of the reference description must be joined (complete citation, unique identifier, unambigous URL). The citation should permit to identify the *authors* of the model.
- The name and contact of model *creators* must be joined.
- The date and time of creation and last modification should be specified. An history is useful but not required.
- The model should be linked to a precise statement about the terms of distribution. MIRIAM does not require “freedom of use” or “no cost”.

External resource annotation

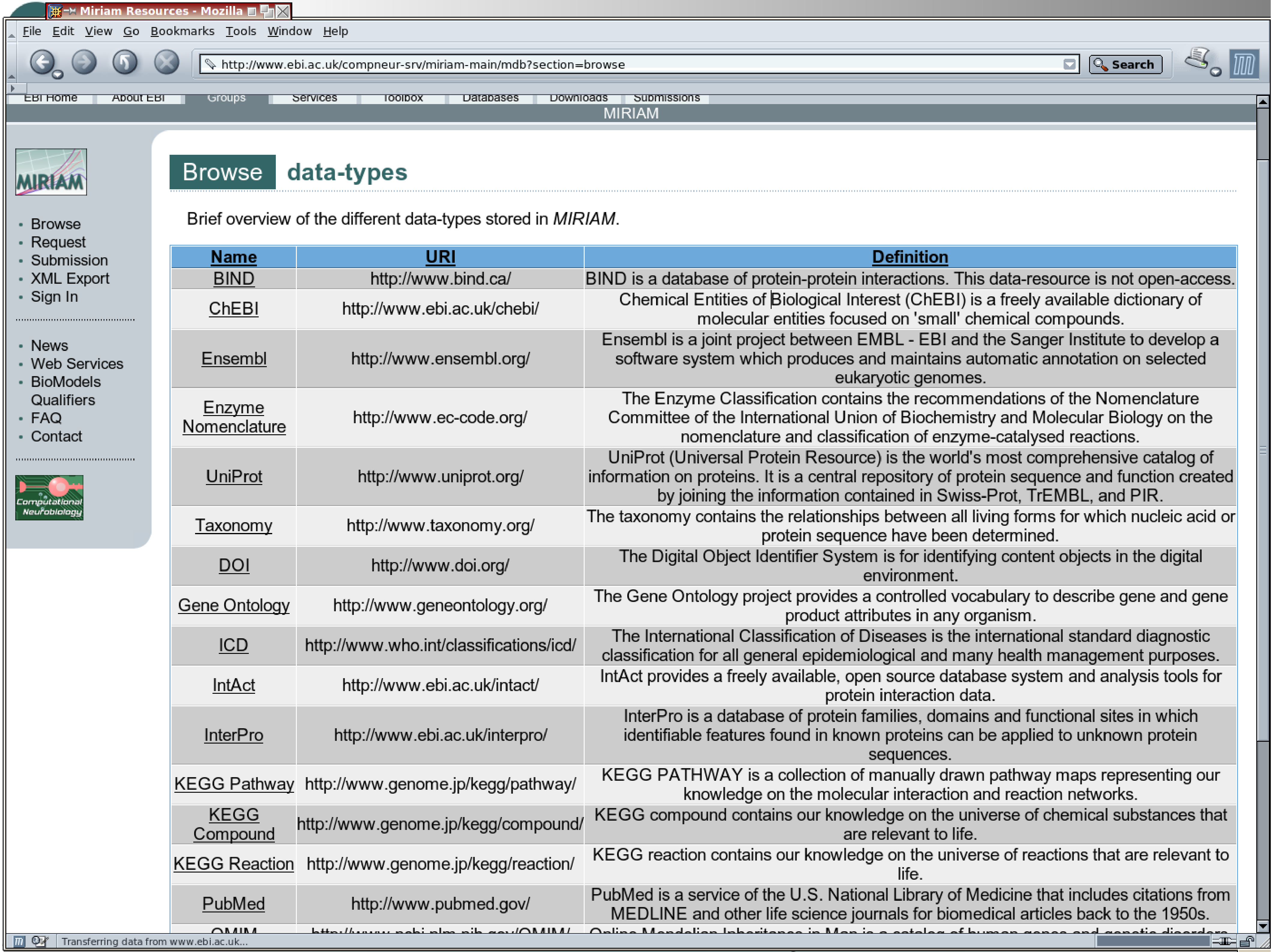
- The annotation must permit to unambiguously relate a piece of knowledge to a model constituent.

- The referenced information should be described using a triplet {data-type, identifier, qualifier}



- The community has to agree on a set of standard valid data-types. A database and the associated API (WebServices) have been developed at the EBI to provide the generation and interpretation of URIs.

creators	Joe User (juser@eden.com), Anne Other (aother@eden.com)			
creation date	01 January 0000			
last modification	31 May 2005			
Constituent	**Data Type**	**Identifier**	**Qualifier**	**Meaning**
model	http://www.pubmed.gov/	0000000		
	http://www.taxonomy.org/	9606		*Homo sapiens*
	http://www.geneontology.org/	GO:0007204	IsVersionOf	*positive regulation of cytosolic ca2+ concentration*
	http://www.geneontology.org/	GO:0051279	IsVersionOf	*regulation of release of sequestered ca2+ into cytop*
	http://www.genome.jp/kegg/pathway	hsa04020	IsPartOf	*Calcium signaling pathway—H sapiens*
	http://www.genome.jp/kegg/pathway	hsa04070	IsPartOf	*Phosphatidylinositol signaling system—H sapiens*
compartment ER	http://www.geneontology.org/	GO:0005790		*smooth endoplasmic reticulum*
reactant Ca$_{in}$	http://www.ebi.ac.uk/chebi/	CHEBI:29108		*calcium(2+)*
compartment cytoplasm	http://www.geneontology.org/	GO:0005737		*cytoplasm*
reactant Ca$_{out}$	http://www.ebi.ac.uk/chebi/	CHEBI:29108		*calcium(2+)*
reactant IP3	http://www.ebi.ac.uk/chebi/	CHEBI:16595		*1D-myo-inositol 1,4,5-tris(dihydrogen phosphate)*
reactant PIP2	http://www.ebi.ac.uk/chebi/	CHEBI:18348		*1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate*
reactant IP3R	http://www.uniprot.org/	Q14643	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 1*
	http://www.uniprot.org/	Q14571	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 2*
	http://www.uniprot.org/	Q14573	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 3*
reactant PLC$_{act}$	http://www.uniprot.org/	Q9NQ66	IsVersionOf	*PIP2 phosphodiesterase* β*1*
reactant PLC$_{tot}$	http://www.uniprot.org/	Q9NQ66		*PIP2 phosphodiesterase* β*1*
reactant IP3$_{ase}$	http://www.uniprot.org/	Q14642		*Type I inositol-1,4,5-trisphosphate 5-phosphatase*
reactant G$_q$	http://www.uniprot.org/	Q6NT27		*Guanine nucleotide binding protein Gq*
reaction Ca$_{release}$	http://www.geneontology.org/	GO:0005220		*IP3-sensitive calcium-release channel activity*
	http://www.geneontology.org/	GO:0008095	IsVersionOf	*IP3 receptor activity*
reaction IP3$_{production}$	http://www.geneontology.org/	GO:0004435	IsVersionOf	*phosphoinositide phospholipase C activity*
	http://www.ec-code.org/	3.1.4.11	IsVersionOf	*phosphoinositide phospholipase C*
reaction IP3$_{degradation}$	http://www.ec-code.org/	3.1.3.56	IsVersionOf	*inositol-polyphosphate 5-phosphatase*
reaction PLC$_{activation}$	http://www.geneontology.org/	GO:0007200		*G-protein signaling coupled to IP3 2nd messenger*



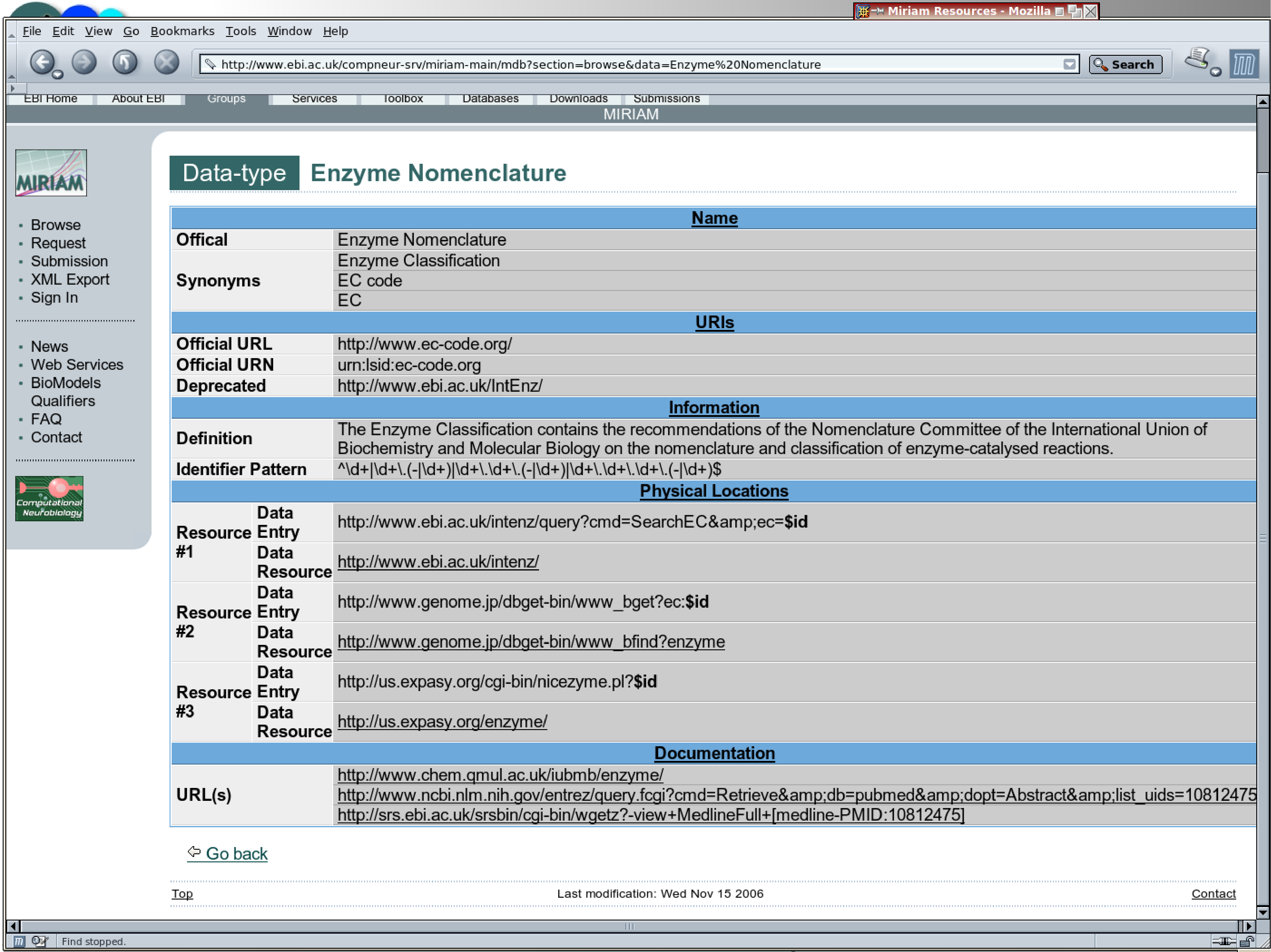
http://www.ebi.ac.uk/compneur-srv/miriam-main/mdb?section=browse

Browse data-types

Brief overview of the different data-types stored in *MIRIAM*.

Name	URI	Definition
BIND	http://www.bind.ca/	BIND is a database of protein-protein interactions. This data-resource is not open-access.
ChEBI	http://www.ebi.ac.uk/chebi/	Chemical Entities of Biological Interest (ChEBI) is a freely available dictionary of molecular entities focused on 'small' chemical compounds.
Ensembl	http://www.ensembl.org/	Ensembl is a joint project between EMBL - EBI and the Sanger Institute to develop a software system which produces and maintains automatic annotation on selected eukaryotic genomes.
Enzyme Nomenclature	http://www.ec-code.org/	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.
UniProt	http://www.uniprot.org/	UniProt (Universal Protein Resource) is the world's most comprehensive catalog of information on proteins. It is a central repository of protein sequence and function created by joining the information contained in Swiss-Prot, TrEMBL, and PIR.
Taxonomy	http://www.taxonomy.org/	The taxonomy contains the relationships between all living forms for which nucleic acid or protein sequence have been determined.
DOI	http://www.doi.org/	The Digital Object Identifier System is for identifying content objects in the digital environment.
Gene Ontology	http://www.geneontology.org/	The Gene Ontology project provides a controlled vocabulary to describe gene and gene product attributes in any organism.
ICD	http://www.who.int/classifications/icd/	The International Classification of Diseases is the international standard diagnostic classification for all general epidemiological and many health management purposes.
IntAct	http://www.ebi.ac.uk/intact/	IntAct provides a freely available, open source database system and analysis tools for protein interaction data.
InterPro	http://www.ebi.ac.uk/interpro/	InterPro is a database of protein families, domains and functional sites in which identifiable features found in known proteins can be applied to unknown protein sequences.
KEGG Pathway	http://www.genome.jp/kegg/pathway/	KEGG PATHWAY is a collection of manually drawn pathway maps representing our knowledge on the molecular interaction and reaction networks.
KEGG Compound	http://www.genome.jp/kegg/compound/	KEGG compound contains our knowledge on the universe of chemical substances that are relevant to life.
KEGG Reaction	http://www.genome.jp/kegg/reaction/	KEGG reaction contains our knowledge on the universe of reactions that are relevant to life.
PubMed	http://www.pubmed.gov/	PubMed is a service of the U.S. National Library of Medicine that includes citations from MEDLINE and other life science journals for biomedical articles back to the 1950s.
OMIM	http://www.ncbi.nlm.nih.gov/OMIM/	Online Mendelian Inheritance in Man is a catalog of human genes and genetic disorders

Transferring data from www.ebi.ac.uk...



Data-type Enzyme Nomenclature

Name		
Offical		Enzyme Nomenclature
Synonyms		Enzyme Classification EC code EC
URIs		
Official URL		http://www.ec-code.org/
Official URN		urn:lsid:ec-code.org
Deprecated		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=**$id**
	Data Resource	http://www.ebi.ac.uk/intenz/
Resource #2	**Data Entry**	http://www.genome.jp/dbget-bin/www_bget?ec:**$id**
	Data Resource	http://www.genome.jp/dbget-bin/www_bfind?enzyme
Resource #3	**Data Entry**	http://us.expasy.org/cgi-bin/nicezyme.pl?**$id**
	Data Resource	http://us.expasy.org/enzyme/
Documentation		
URL(s)		http://www.chem.qmul.ac.uk/iubmb/enzyme/ http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10812475 http://srs.ebi.ac.uk/srsbin/cgi-bin/wgetz?-view+MedlineFull+[medline-PMID:10812475]

Go back

Top	Last modification: Wed Nov 15 2006	Contact

The Systems Biology Ontology

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

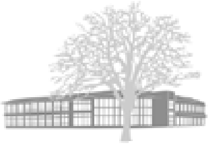
Classifications Vs. Ontologies

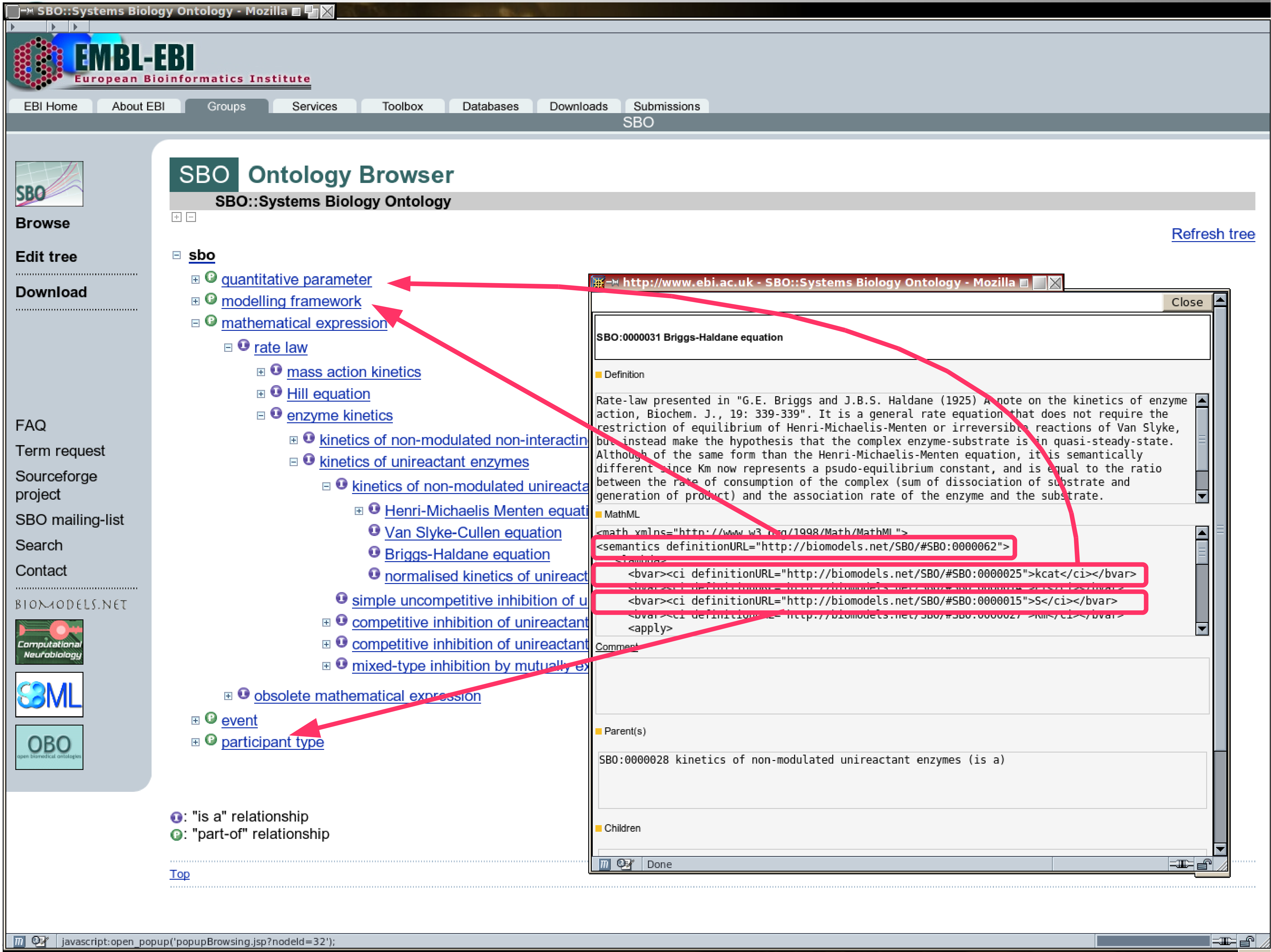
- Ontology: A set of elements of knowledge linked with sense-bearing relationships.

- Each term of an ontology is associated to a perennial identifier. Once created a term is never destroyed. It can be merged with another, or made obsolete, but it still exists.
- An ontology is an evolving structure: It can cope with an increase or refinement of knowledge. No need to reconstruct everything as with the taxonomies.
- An ontology is a Direct Acyclic Graph, and not a hierarchy. A term can possess more than one parent.
- Ontologies are stored in standard machine-readable formats. They can be subjected to automatic treatments.

Systems Biology Ontology vocabularies

- Types and roles of reaction participants, including terms like “substrate”, “catalyst” etc., but also “macromolecule”, or “channel”.
- Parameter used in quantitative models. This vocabulary includes terms like “Michaelis constant” , “forward unimolecular rate constant”etc.
- Mathematical expressions. Examples of terms are “mass action kinetics”, “Henri-Michaelis-Menten equation” etc. Each term contains a precise mathematical expression stored as a MathML lambda function. The variables refer to the CVs described above.
- Modelling framework to precise how to interpret the rate-law. E.g. “continuous modelling”, “discrete modelling” etc.
- Event type, such as “catalysis” or “addition of a chemical group”.





SBO Ontology Browser

SBO::Systems Biology Ontology

- sbo
  - quantitative parameter
  - modelling framework
  - mathematical expression
    - rate law
      - mass action kinetics
      - Hill equation
      - enzyme kinetics
        - kinetics of non-modulated non-interactin
        - kinetics of unireactant enzymes
          - kinetics of non-modulated unireacta
            - Henri-Michaelis Menten equati
            - Van Slyke-Cullen equation
            - Briggs-Haldane equation
            - normalised kinetics of unireact
          - simple uncompetitive inhibition of u
          - competitive inhibition of unireactant
          - competitive inhibition of unireactant
          - mixed-type inhibition by mutually ex
    - obsolete mathematical expression
  - event
  - participant type

I: "is a" relationship

P: "part-of" relationship

http://www.ebi.ac.uk - SBO::Systems Biology Ontology - Mozilla

SBO:0000031 Briggs-Haldane equation

Definition

Rate-law presented in "G.E. Briggs and J.B.S. Haldane (1925) A note on the kinetics of enzyme action, Biochem. J., 19: 339-339". It is a general rate equation that does not require the restriction of equilibrium of Henri-Michaelis-Menten or irreversible reactions of Van Slyke, but instead make the hypothesis that the complex enzyme-substrate is in quasi-steady-state. Although of the same form than the Henri-Michaelis-Menten equation, it is semantically different since Km now represents a psudo-equilibrium constant, and is equal to the ratio between the rate of consumption of the complex (sum of dissociation of substrate and generation of product) and the association rate of the enzyme and the substrate.

MathML

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
<semantics definitionURL="http://biomodels.net/SBO/#SBO:0000062">
  <lambda>
    <bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000025">kcat</ci></bvar>
    <bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000015">S</ci></bvar>
    <bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000027">Km</ci></bvar>
    <apply>
```

Comment

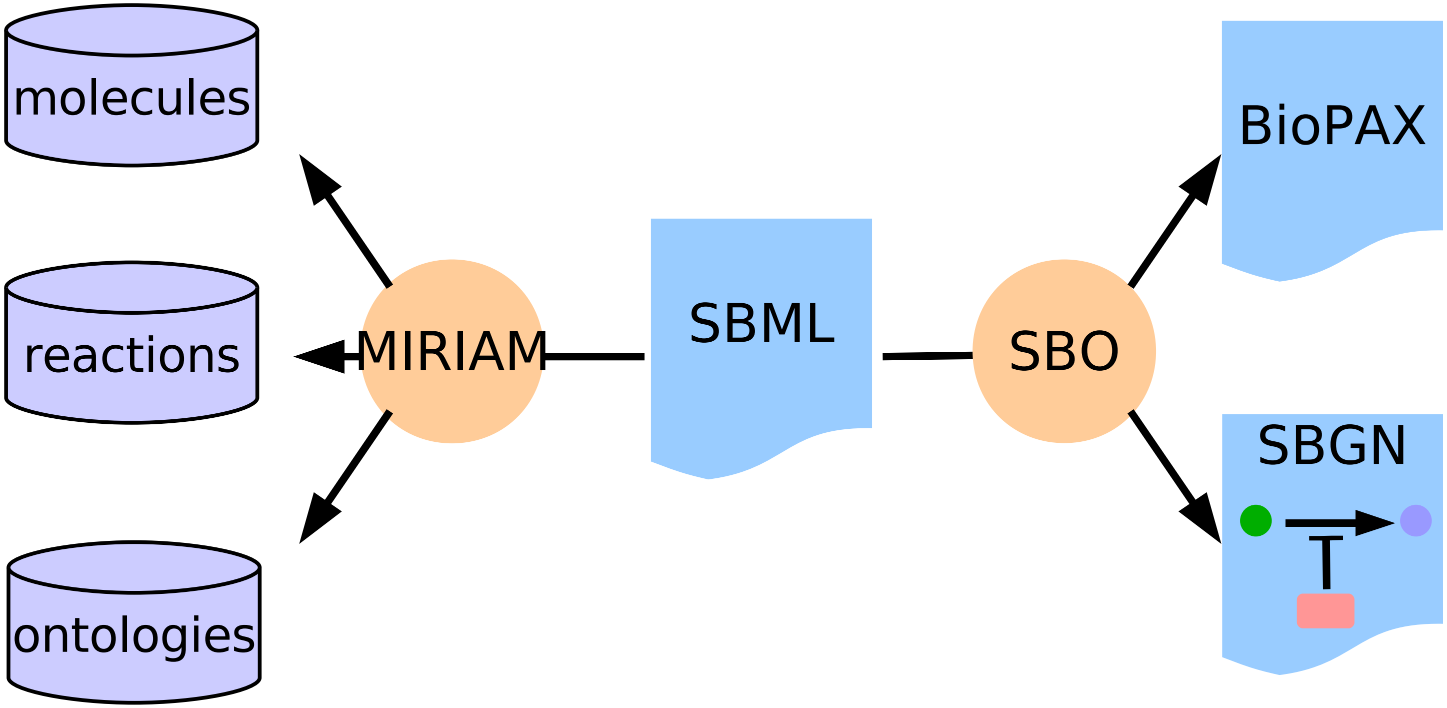
Parent(s)

SBO:0000028 kinetics of non-modulated unireactant enzymes (is a)

Children

javascript:open_popup('popupBrowsing.jsp?nodeId=32');

Shall-we interface?



molecules

reactions

ontologies

MIRIAM

SBML

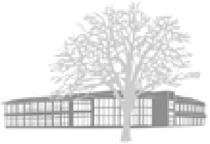
SBO

BioPAX

SBGN

Requirements for a unified model resource

- Neither focussed on a particular biological substrate or process, nor specialised on a given modelling approach
- Real “searchable“ database rather than mere repository
- Models thoroughly verified, structure and results, and annotated
- International collaboration rather than a one-group effort
- Freely available and reusable
- Long-term commitment and secure funding



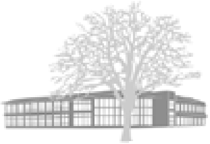
BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems

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.
***Nucleic Acids Research*, (2006), 34: D689-D691**

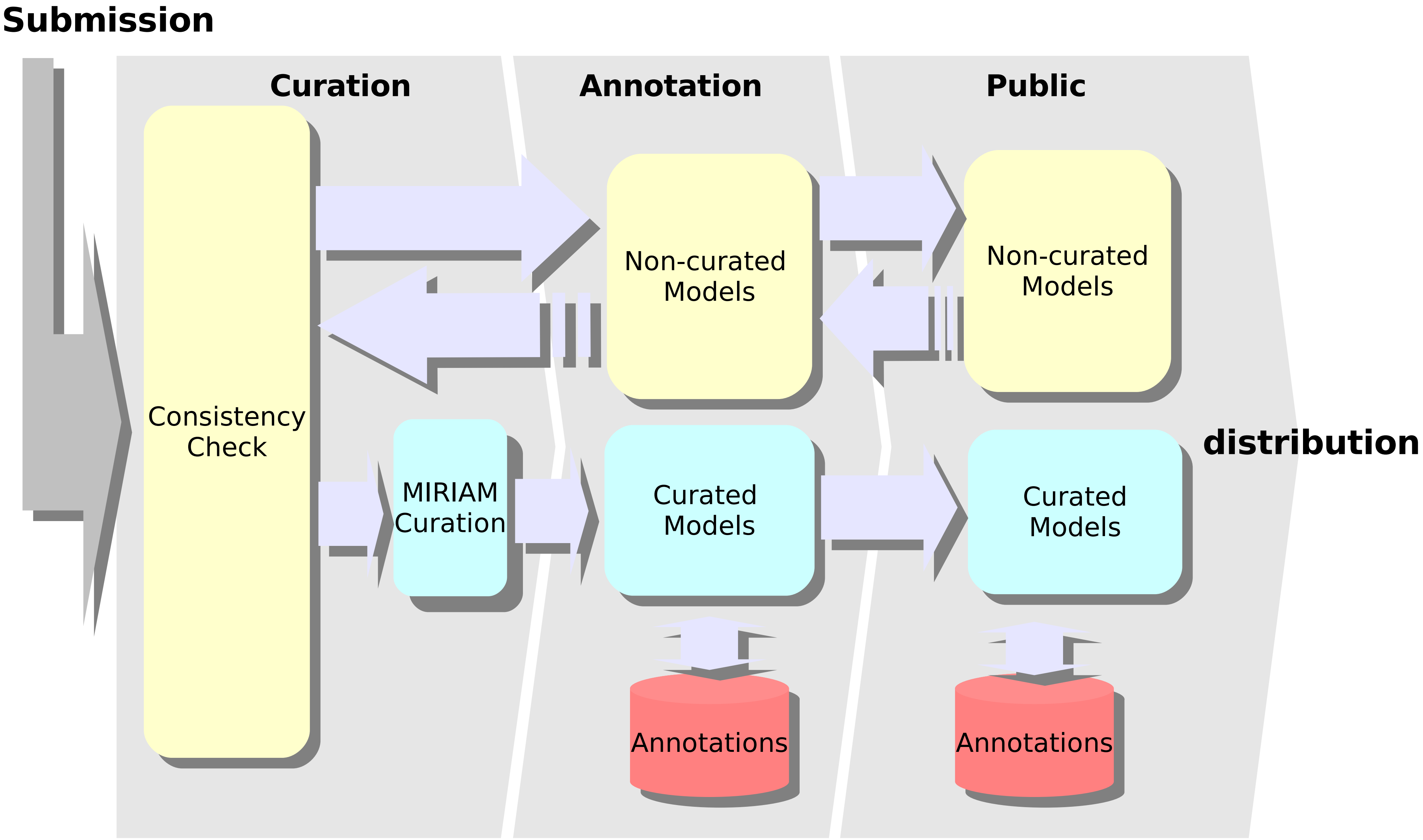
http://www.ebi.ac.uk/biomodels/

What is BioModels Database?

- Store and serve quantitative models of biomedical interest
- Only models described in the peer-reviewed scientific literature.
- Models are curated: computer software check the syntax, while human curators check the semantics.
- Models are simulated to check the reference correspondence
- Model components are annotated, to improve identification and retrieval.
- Models are accepted in several formats, and served in several others.
- Aims to be the “UniProt” of quantitative modelling.



Structure of BioModels Database



Submission

Curation

Annotation

Public

Consistency Check

MIRIAM Curation

Non-curated Models

Curated Models

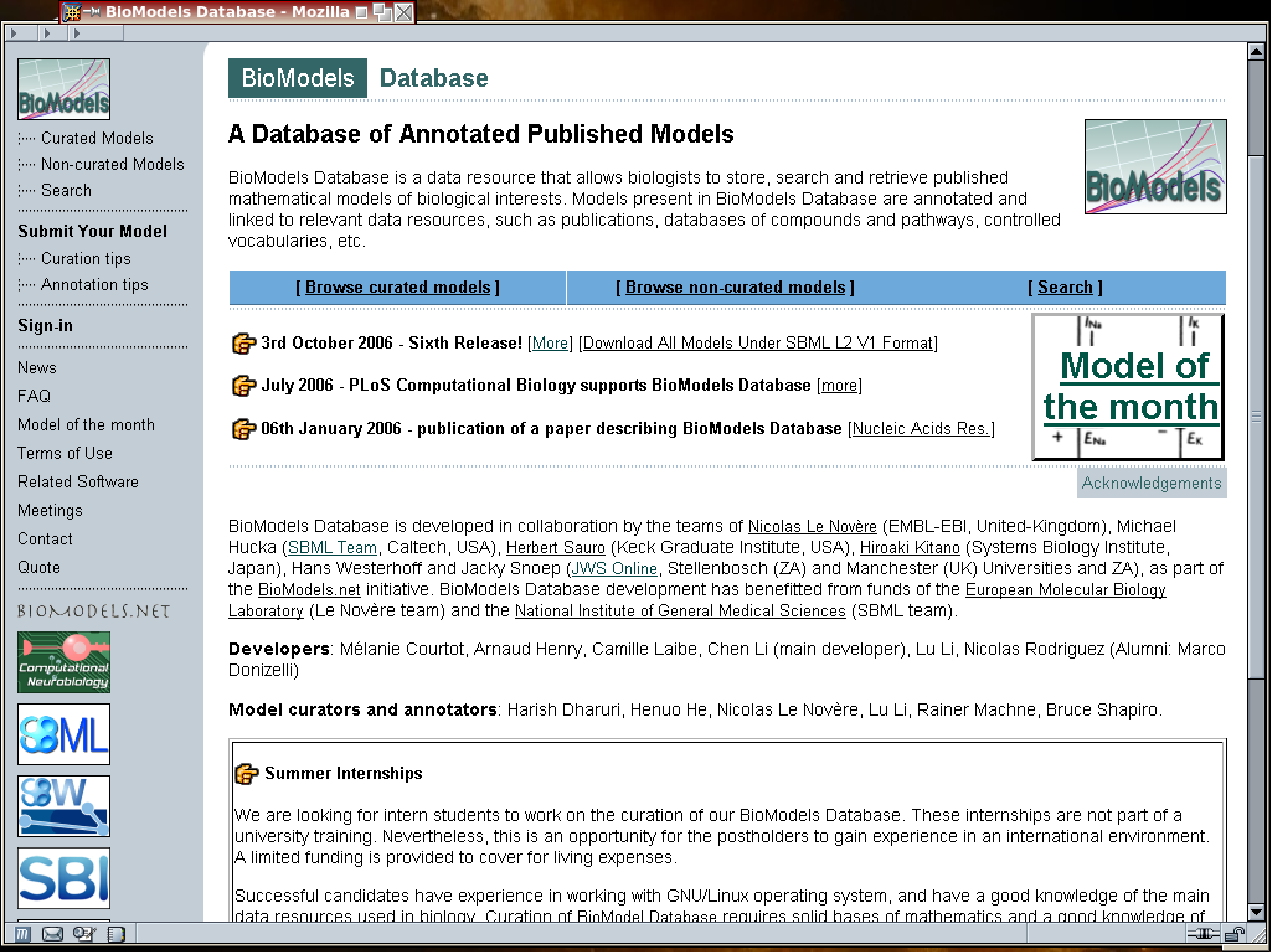
Annotations

Non-curated Models

Curated Models

Annotations

distribution



A Database of Annotated Published Models

BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, controlled vocabularies, etc.

3rd October 2006 - Sixth Release! [More] [Download All Models Under SBML L2 V1 Format]

July 2006 - PLoS Computational Biology supports BioModels Database [more]

06th January 2006 - publication of a paper describing BioModels Database [Nucleic Acids Res.]

BioModels Database is developed in collaboration by the teams of Nicolas Le Novère (EMBL-EBI, United-Kingdom), Michael Hucka (SBML Team, Caltech, USA), Herbert Sauro (Keck Graduate Institute, USA), Hiroaki Kitano (Systems Biology Institute, Japan), Hans Westerhoff and Jacky Snoep (JWS Online, Stellenbosch (ZA) and Manchester (UK) Universities and ZA), as part of the BioModels.net initiative. BioModels Database development has benefitted from funds of the European Molecular Biology Laboratory (Le Novère team) and the National Institute of General Medical Sciences (SBML team).

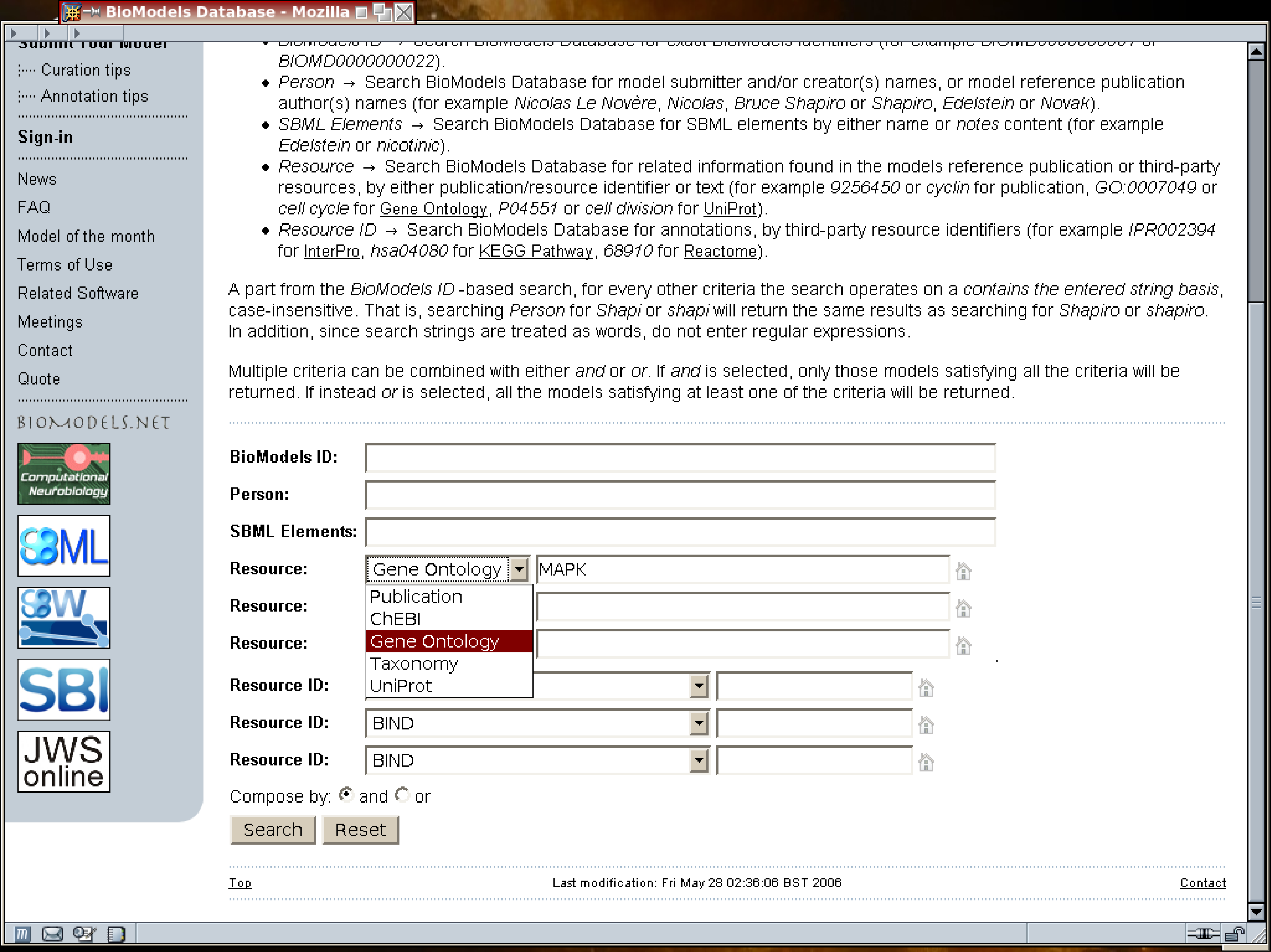
Developers: Mélanie Courtot, Arnaud Henry, Camille Laibe, Chen Li (main developer), Lu Li, Nicolas Rodriguez (Alumni: Marco Donizelli)

Model curators and annotators: Harish Dharuri, Henuo He, Nicolas Le Novère, Lu Li, Rainer Machne, Bruce Shapiro.

Summer Internships

We are looking for intern students to work on the curation of our BioModels Database. These internships are not part of a university training. Nevertheless, this is an opportunity for the postholders to gain experience in an international environment. A limited funding is provided to cover for living expenses.

Successful candidates have experience in working with GNU/Linux operating system, and have a good knowledge of the main data resources used in biology. Curation of BioModel Database requires solid bases of mathematics and a good knowledge of



BIOMD0000000022).
- *Person* → Search BioModels Database for model submitter and/or creator(s) names, or model reference publication author(s) names (for example *Nicolas Le Novère*, *Nicolas*, *Bruce Shapiro* or *Shapiro*, *Edelstein* or *Novak*).
- *SBML Elements* → Search BioModels Database for SBML elements by either name or *notes* content (for example *Edelstein* or *nicotinic*).
- *Resource* → Search BioModels Database for related information found in the models reference publication or third-party resources, by either publication/resource identifier or text (for example *9256450* or *cyclin* for publication, *GO:0007049* or *cell cycle* for Gene Ontology, *P04551* or *cell division* for UniProt).
- *Resource ID* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for InterPro, *hsa04080* for KEGG Pathway, *68910* for Reactome).

A part from the *BioModels ID* -based search, for every other criteria the search operates on a *contains the entered string basis*, case-insensitive. That is, searching *Person* for *Shapi* or *shapi* will return the same results as searching for *Shapiro* or *shapiro*. In addition, since search strings are treated as words, do not enter regular expressions.

Multiple criteria can be combined with either *and* or *or*. If *and* is selected, only those models satisfying all the criteria will be returned. If instead *or* is selected, all the models satisfying at least one of the criteria will be returned.

BioModels ID:

Person:

SBML Elements:

Resource: Gene Ontology MAPK

Resource:

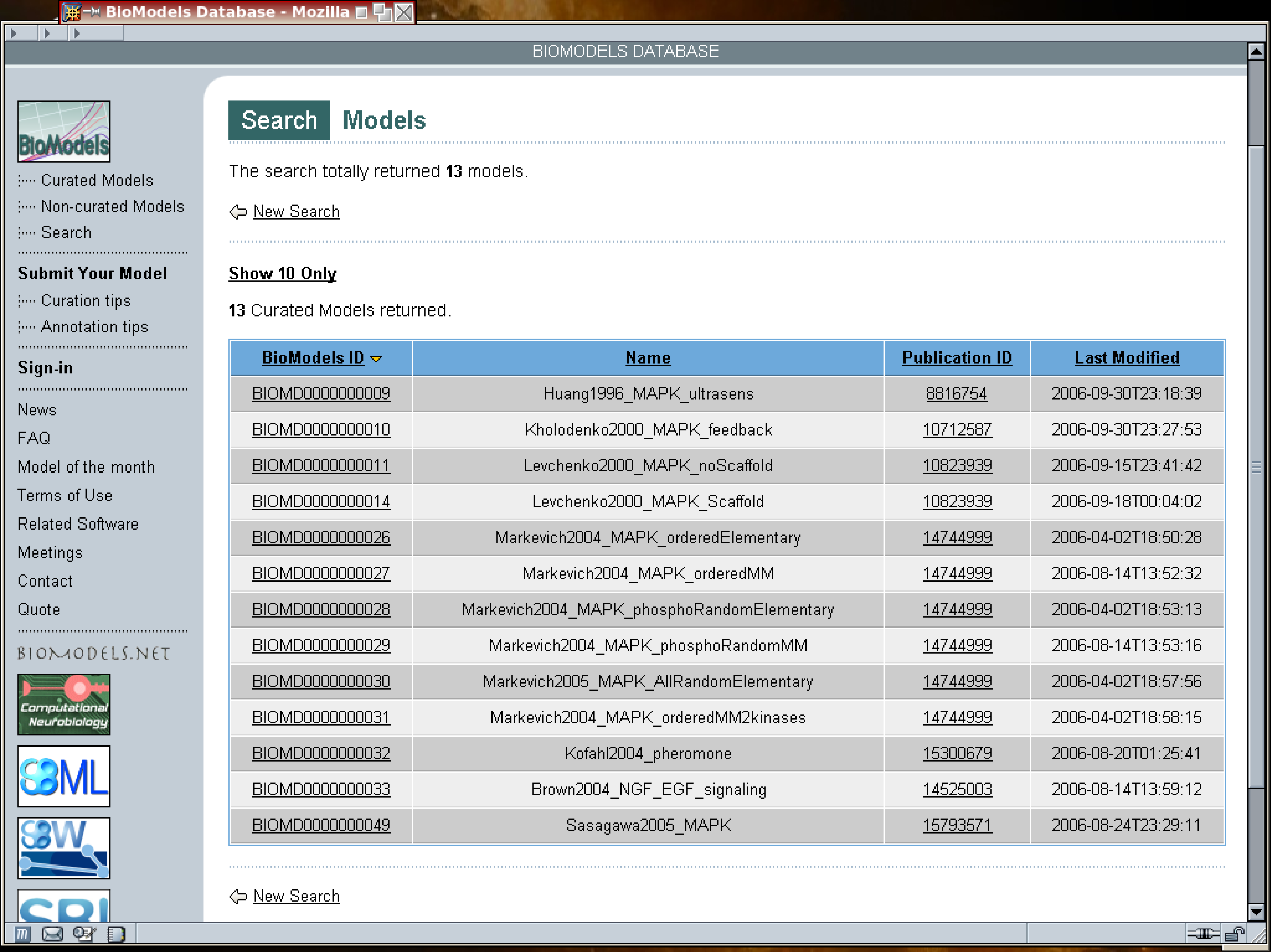
Resource:

Resource ID:

Resource ID: BIND

Resource ID: BIND

Compose by: ● and ○ or



Search Models

The search totally returned **13** models.

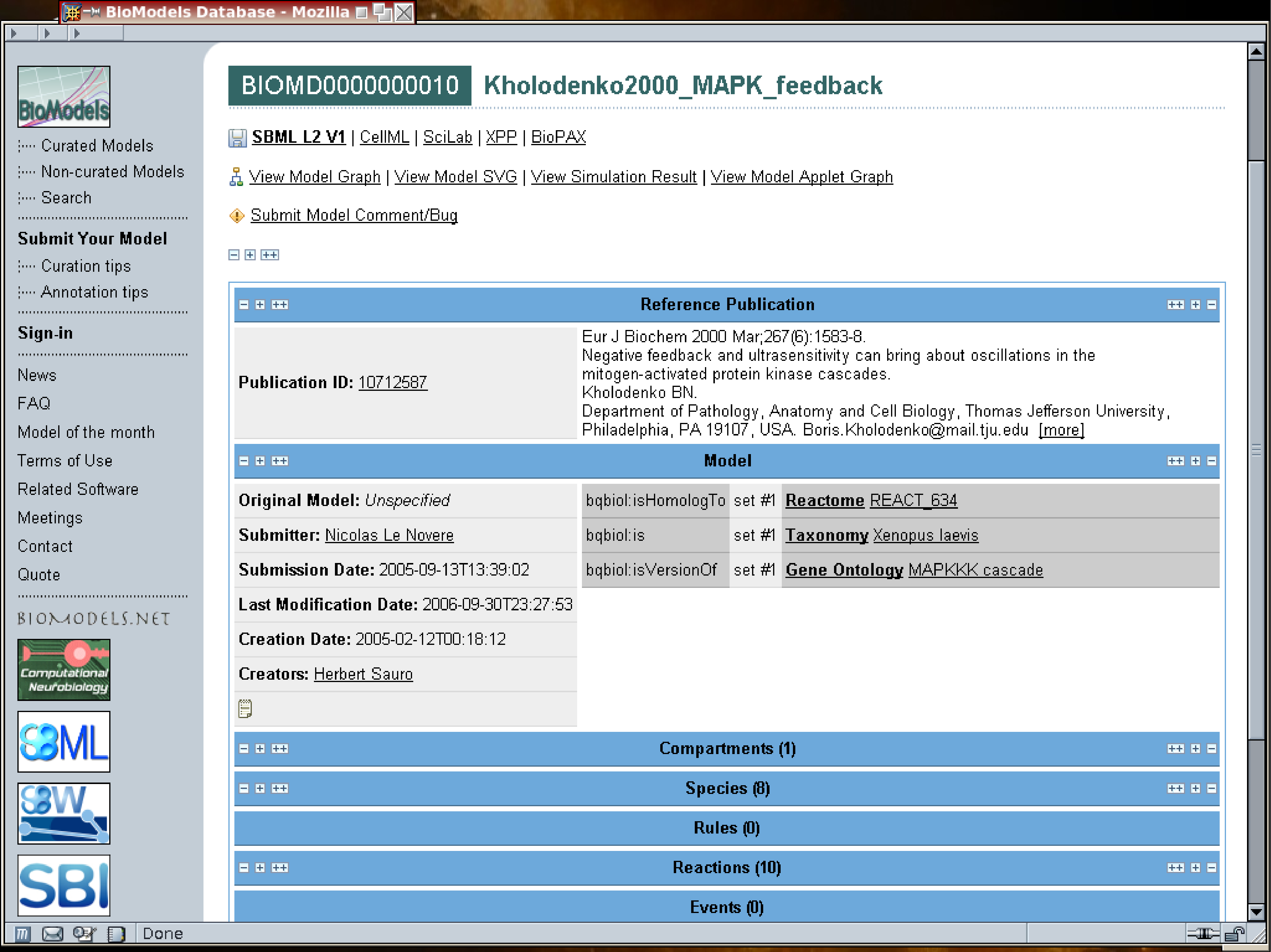
New Search

Show 10 Only

13 Curated Models returned.

BioModels ID	Name	Publication ID	Last Modified
BIOMD0000000009	Huang1996_MAPK_ultrasens	8816754	2006-09-30T23:18:39
BIOMD0000000010	Kholodenko2000_MAPK_feedback	10712587	2006-09-30T23:27:53
BIOMD0000000011	Levchenko2000_MAPK_noScaffold	10823939	2006-09-15T23:41:42
BIOMD0000000014	Levchenko2000_MAPK_Scaffold	10823939	2006-09-18T00:04:02
BIOMD0000000026	Markevich2004_MAPK_orderedElementary	14744999	2006-04-02T18:50:28
BIOMD0000000027	Markevich2004_MAPK_orderedMM	14744999	2006-08-14T13:52:32
BIOMD0000000028	Markevich2004_MAPK_phosphoRandomElementary	14744999	2006-04-02T18:53:13
BIOMD0000000029	Markevich2004_MAPK_phosphoRandomMM	14744999	2006-08-14T13:53:16
BIOMD0000000030	Markevich2005_MAPK_AllRandomElementary	14744999	2006-04-02T18:57:56
BIOMD0000000031	Markevich2004_MAPK_orderedMM2kinases	14744999	2006-04-02T18:58:15
BIOMD0000000032	Kofahl2004_pheromone	15300679	2006-08-20T01:25:41
BIOMD0000000033	Brown2004_NGF_EGF_signaling	14525003	2006-08-14T13:59:12
BIOMD0000000049	Sasagawa2005_MAPK	15793571	2006-08-24T23:29:11

New Search



BIOMD0000000010 Kholodenko2000_MAPK_feedback

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

View Model Graph | View Model SVG | View Simulation Result | View Model Applet Graph

Submit Model Comment/Bug

Reference Publication

Publication ID: 10712587	Eur J Biochem 2000 Mar;267(6):1583-8. Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. Kholodenko BN. Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu [more]

Model

Original Model: *Unspecified*	bqbiol:isHomologTo	set #1	**Reactome** REACT_634
Submitter: Nicolas Le Novere	bqbiol:is	set #1	**Taxonomy** Xenopus laevis
Submission Date: 2005-09-13T13:39:02	bqbiol:isVersionOf	set #1	**Gene Ontology** MAPKKK cascade
Last Modification Date: 2006-09-30T23:27:53			
Creation Date: 2005-02-12T00:18:12			
Creators: Herbert Sauro			

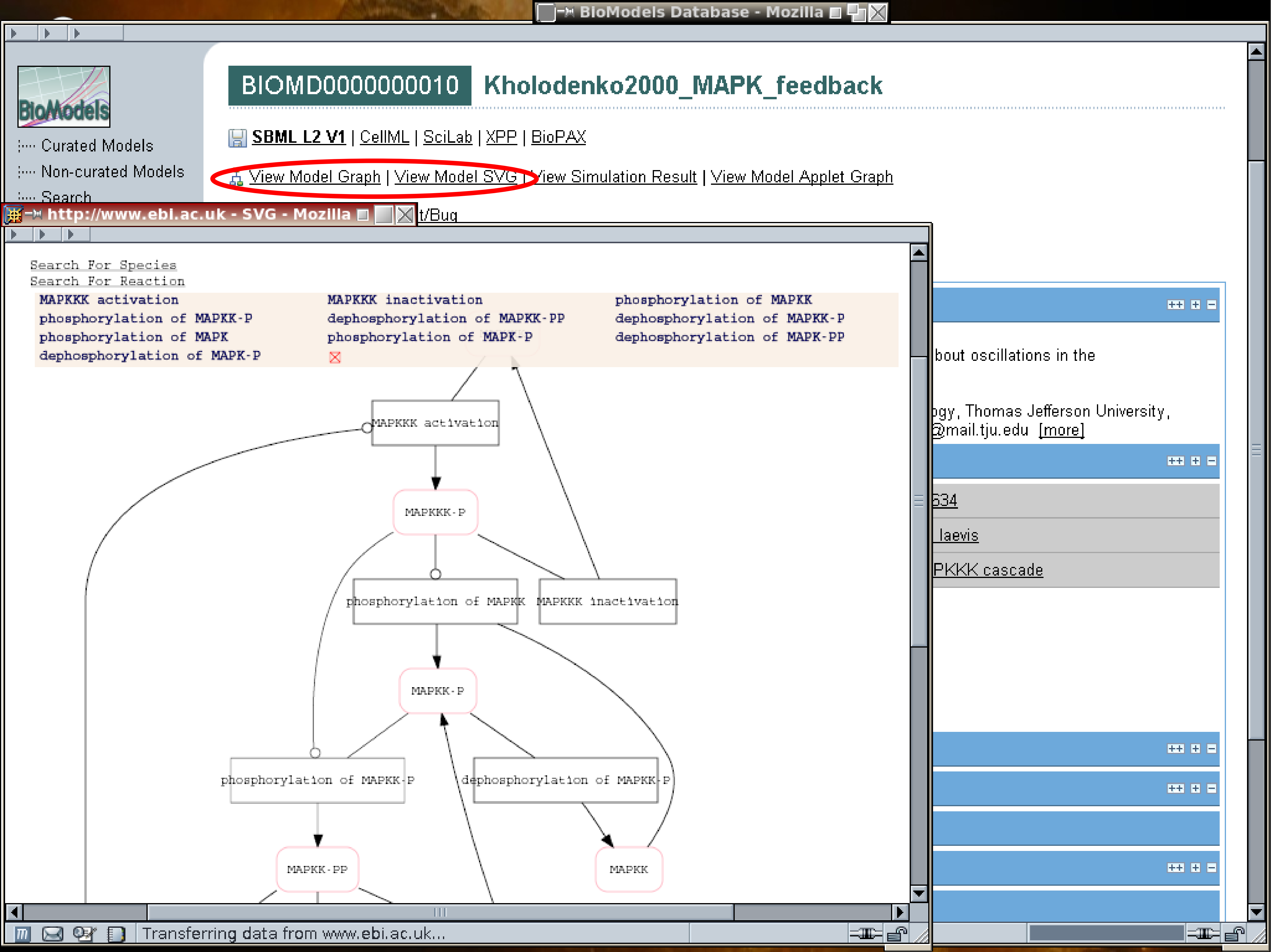
Compartments (1)

Species (8)

Rules (0)

Reactions (10)

Events (0)



BioModels Database - Mozilla

BIOMD0000000010 Kholodenko2000_MAPK_feedback

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

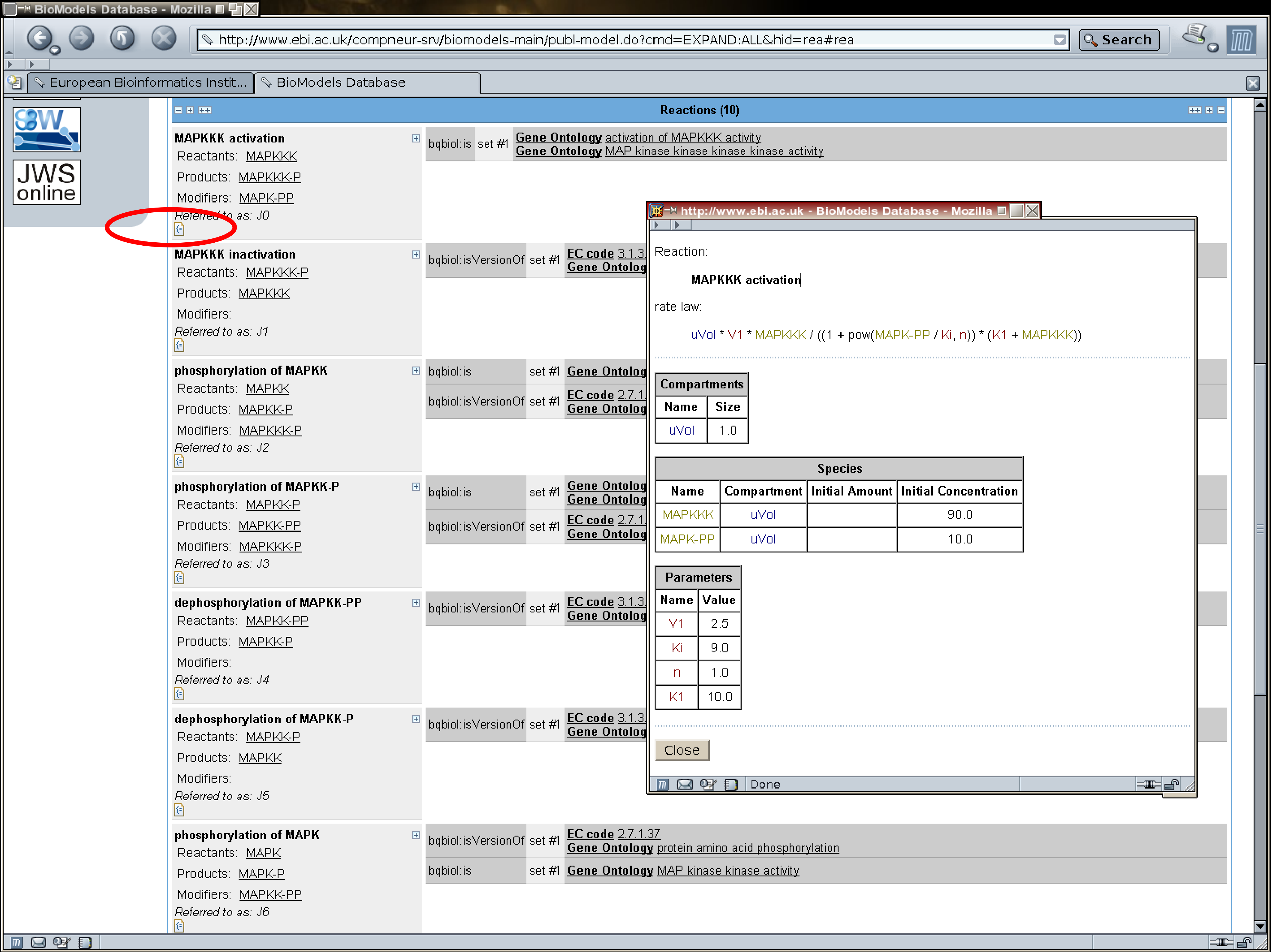
View Model Graph | View Model SVG | View Simulation Result | View Model Applet Graph

http://www.ebi.ac.uk - SVG - Mozilla

Search For Species
Search For Reaction

MAPKKK activation	MAPKKK inactivation	phosphorylation of MAPKK
phosphorylation of MAPKK-P	dephosphorylation of MAPKK-PP	dephosphorylation of MAPKK-P
phosphorylation of MAPK	phosphorylation of MAPK-P	dephosphorylation of MAPK-PP
dephosphorylation of MAPK-P		

Transferring data from www.ebi.ac.uk...



Reactions (10)

MAPKKK activation
Reactants: MAPKKK
Products: MAPKKK-P
Modifiers: MAPK-PP
Referred to as: J0

bqbiol:is set #1 **Gene Ontology** activation of MAPKKK activity
Gene Ontology MAP kinase kinase kinase kinase activity

MAPKKK inactivation
Reactants: MAPKKK-P
Products: MAPKKK
Modifiers:
Referred to as: J1

bqbiol:isVersionOf set #1 **EC code** 3.1.3.
Gene Ontolog

phosphorylation of MAPKK
Reactants: MAPKK
Products: MAPKK-P
Modifiers: MAPKKK-P
Referred to as: J2

bqbiol:is set #1 **Gene Ontolog**
bqbiol:isVersionOf set #1 **EC code** 2.7.1.
Gene Ontolog

phosphorylation of MAPKK-P
Reactants: MAPKK-P
Products: MAPKK-PP
Modifiers: MAPKKK-P
Referred to as: J3

bqbiol:is set #1 **Gene Ontolog**
Gene Ontolog
bqbiol:isVersionOf set #1 **EC code** 2.7.1.
Gene Ontolog

dephosphorylation of MAPKK-PP
Reactants: MAPKK-PP
Products: MAPKK-P
Modifiers:
Referred to as: J4

bqbiol:isVersionOf set #1 **EC code** 3.1.3.
Gene Ontolog

dephosphorylation of MAPKK-P
Reactants: MAPKK-P
Products: MAPKK
Modifiers:
Referred to as: J5

bqbiol:isVersionOf set #1 **EC code** 3.1.3.
Gene Ontolog

phosphorylation of MAPK
Reactants: MAPK
Products: MAPK-P
Modifiers: MAPKK-PP
Referred to as: J6

bqbiol:isVersionOf set #1 **EC code** 2.7.1.37
Gene Ontology protein amino acid phosphorylation
bqbiol:is set #1 **Gene Ontology** MAP kinase kinase activity

Reaction:

MAPKKK activation

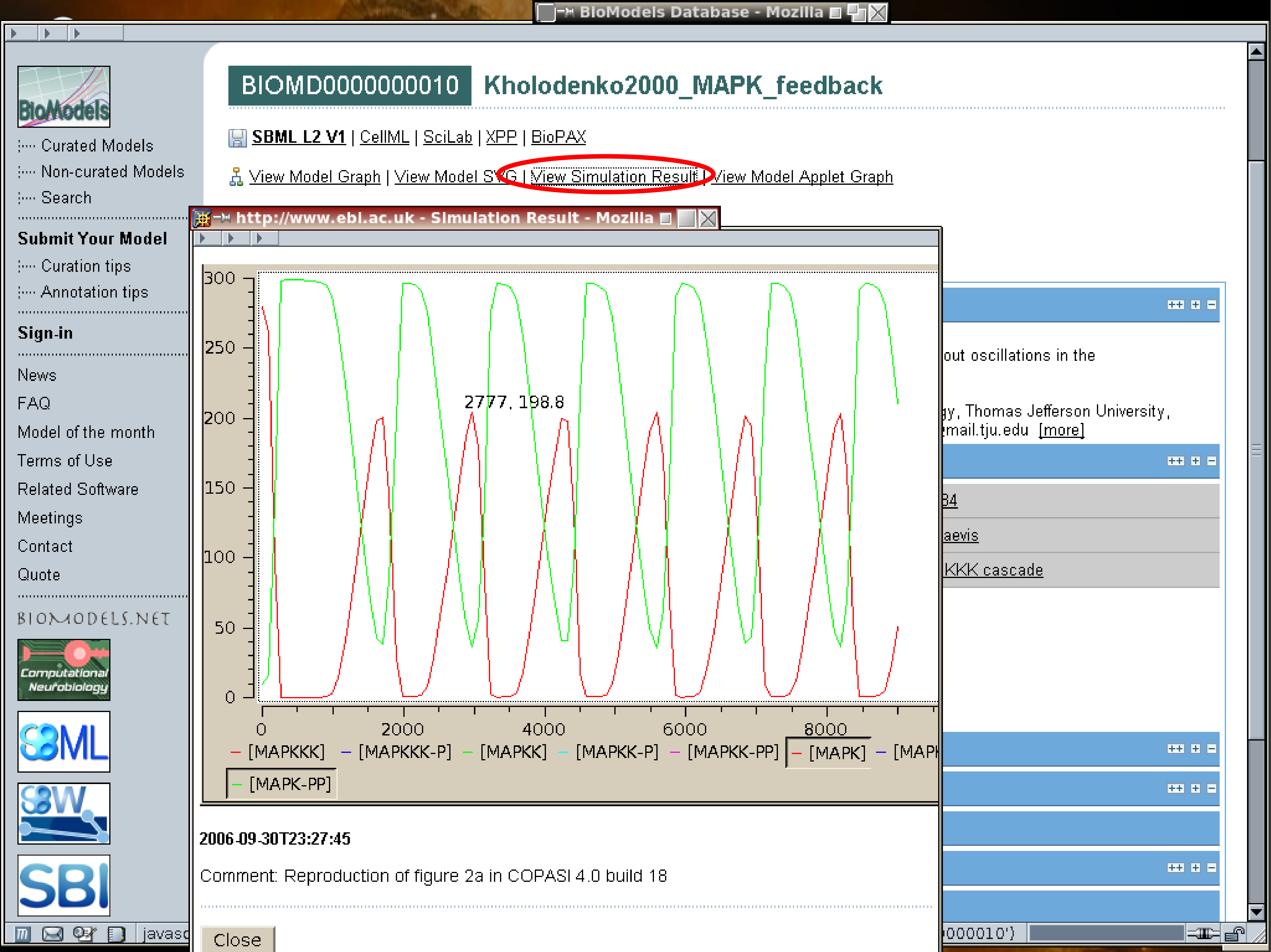
rate law:

uVol * V1 * MAPKKK / ((1 + pow(MAPK-PP / Ki, n)) * (K1 + MAPKKK))

Compartments	
Name	**Size**
uVol	1.0

Species			
Name	**Compartment**	**Initial Amount**	**Initial Concentration**
MAPKKK	uVol		90.0
MAPK-PP	uVol		10.0

Parameters	
Name	**Value**
V1	2.5
Ki	9.0
n	1.0
K1	10.0



BioModels Database - Mozilla

- Curated Models
- Non-curated Models
- Search

Submit Your Model

- Curation tips
- Annotation tips

Sign-in

News

FAQ

Model of the month

Terms of Use

Related Software

Meetings

Contact

Quote

BIOMODELS.NET

BIOMD0000000010 Kholodenko2000_MAPK_feedback

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

View Model Graph | View Model SVG | View Simulation Result | View Model Applet Graph

out oscillations in the

gy, Thomas Jefferson University,

mail.tju.edu [more]

84

aevis

KKK cascade

http://www.ebi.ac.uk - Simulation Result - Mozilla

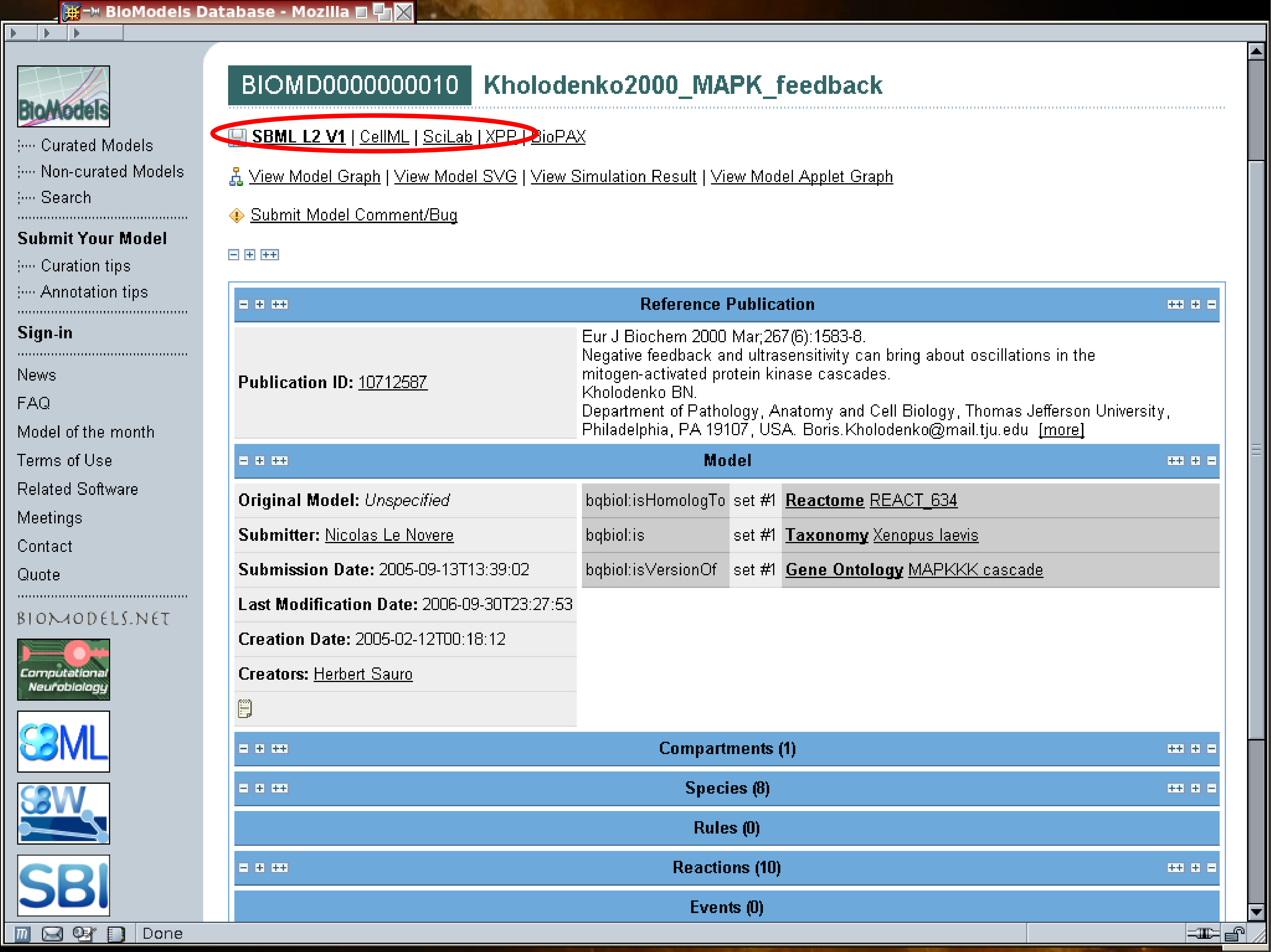
2006-09-30T23:27:45

Comment: Reproduction of figure 2a in COPASI 4.0 build 18

Close

javasc

000010')



BIOMD0000000010 Kholodenko2000_MAPK_feedback

Reference Publication

Publication ID: 10712587

Eur J Biochem 2000 Mar;267(6):1583-8.
Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades.
Kholodenko BN.
Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu [more]

Model

Original Model: *Unspecified*

Submitter: Nicolas Le Novere

Submission Date: 2005-09-13T13:39:02

Last Modification Date: 2006-09-30T23:27:53

Creation Date: 2005-02-12T00:18:12

Creators: Herbert Sauro

bqbiol:isHomologTo	set #1	**Reactome** REACT_634
bqbiol:is	set #1	**Taxonomy** Xenopus laevis
bqbiol:isVersionOf	set #1	**Gene Ontology** MAPKKK cascade

Compartments (1)

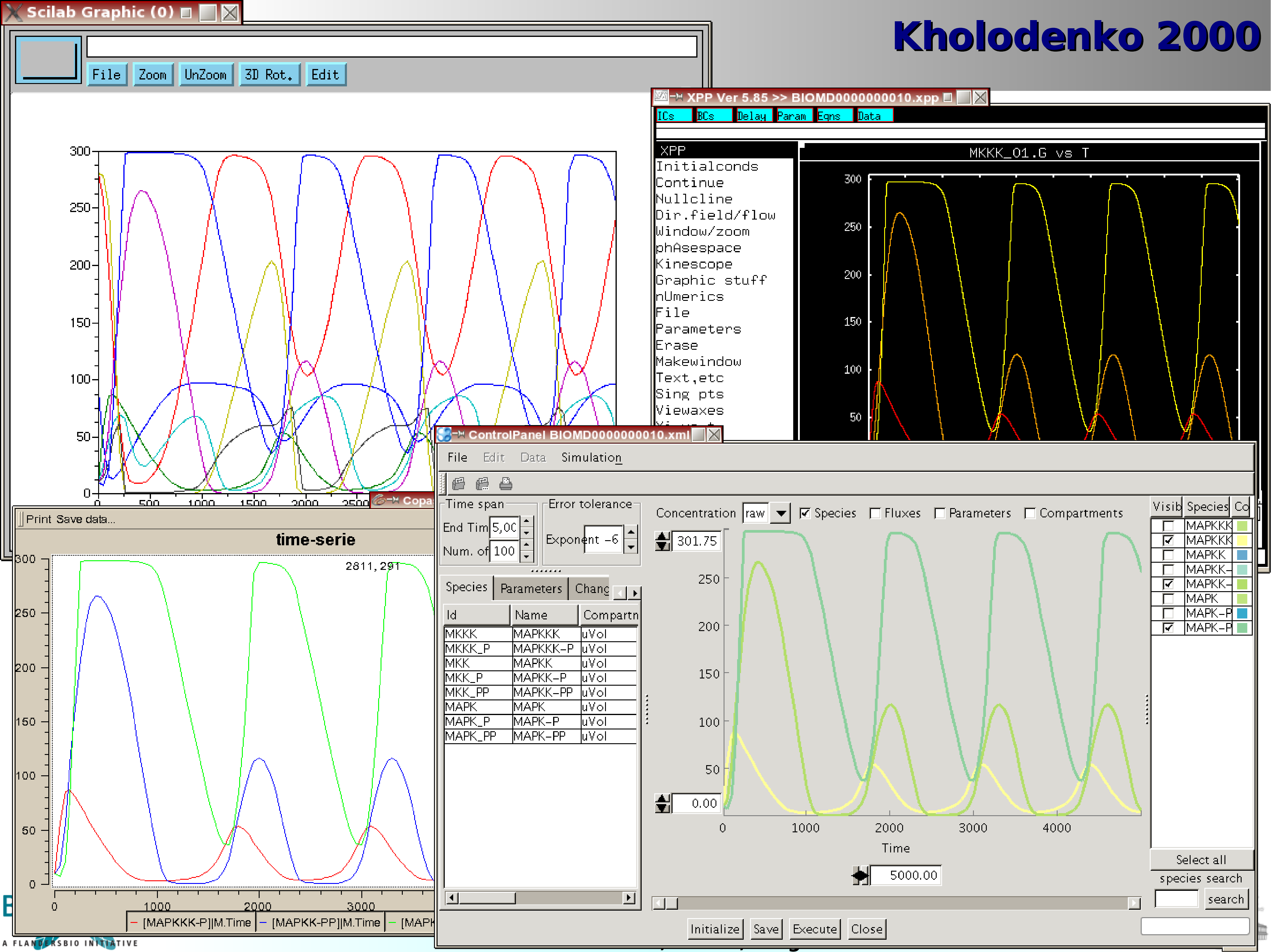
Species (8)

Rules (0)

Reactions (10)

Events (0)

Kholodenko 2000



End Tim 5,00

Num. of 100

Exponent −6

Concentration raw

301.75

0.00

5000.00

Id	Name	Compartn
MKKK	MAPKKK	uVol
MKKK_P	MAPKKK-P	uVol
MKK	MAPKK	uVol
MKK_P	MAPKK-P	uVol
MKK_PP	MAPKK-PP	uVol
MAPK	MAPK	uVol
MAPK_P	MAPK-P	uVol
MAPK_PP	MAPK-PP	uVol

Visib	Species
☐	MAPKKK
☑	MAPKKK
☐	MAPKK
☐	MAPKK–
☑	MAPKK–
☐	MAPK
☐	MAPK–P
☑	MAPK–P

Where are the models coming from

I) Existing model repositories

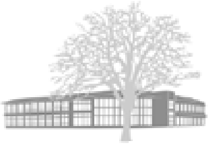
- old SBML repository
- JWS Online
- Database Of Quantitative Cell Signalling (Release on December 4th)
- CellML repository

II) Individuals

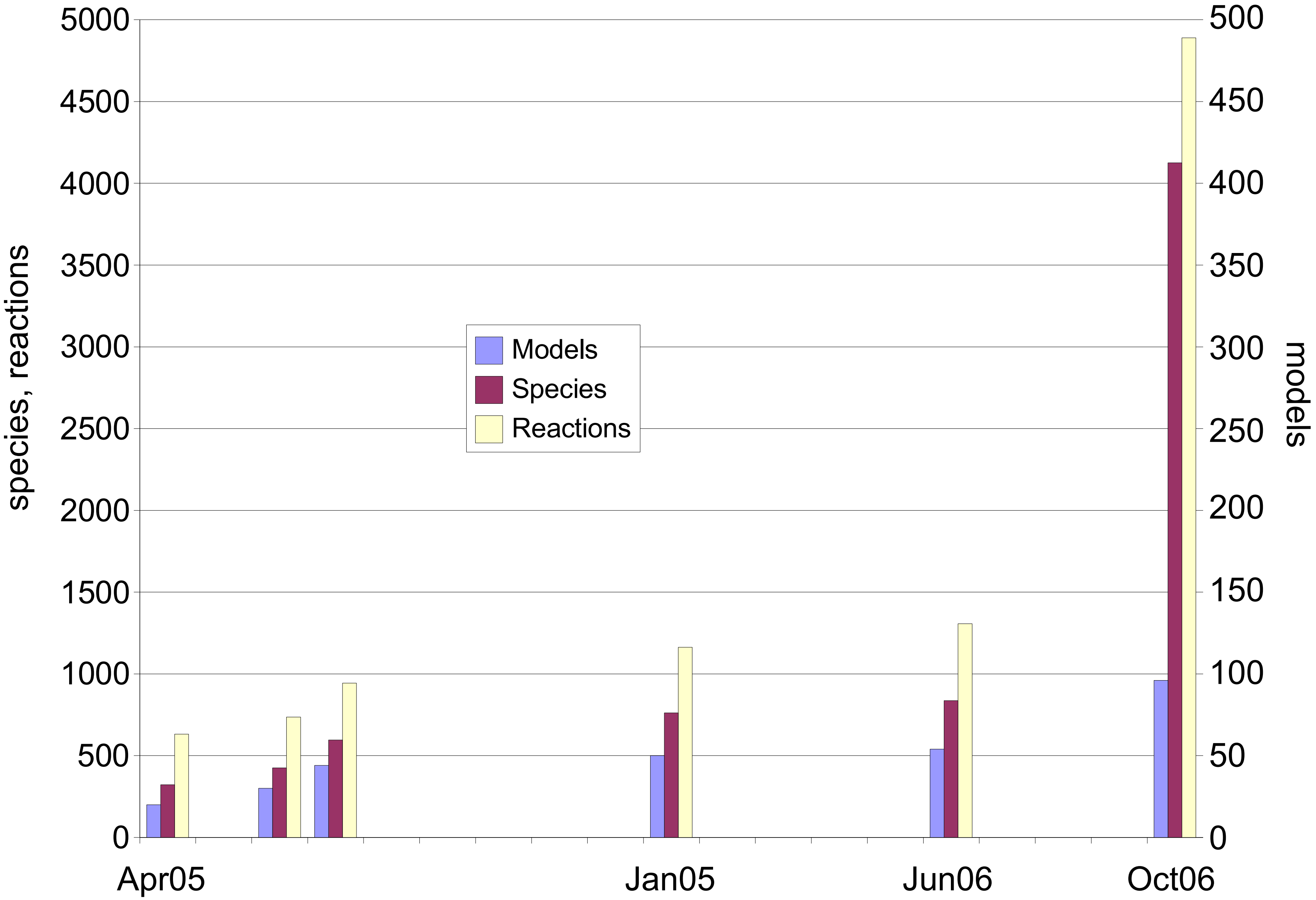
- Members of the SBML community (developers+modellers)
- Authors (prior to grant application, before publication etc.)

III) Journals (Molecular Systems Biology and PloS Computational Biology advise deposition)

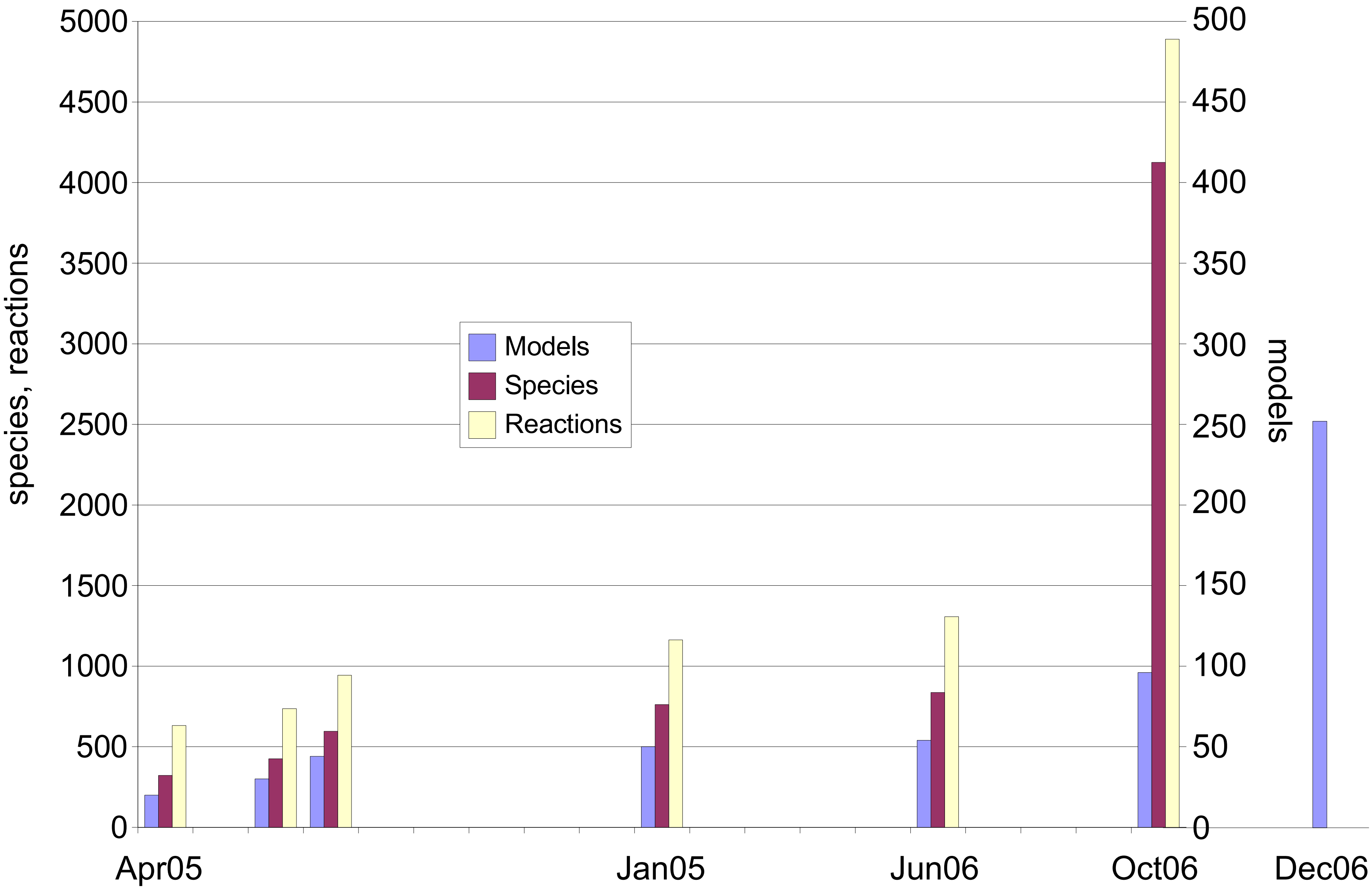
IV) BioModels DB curators encode new models from literature



Steady increase



Steady increase



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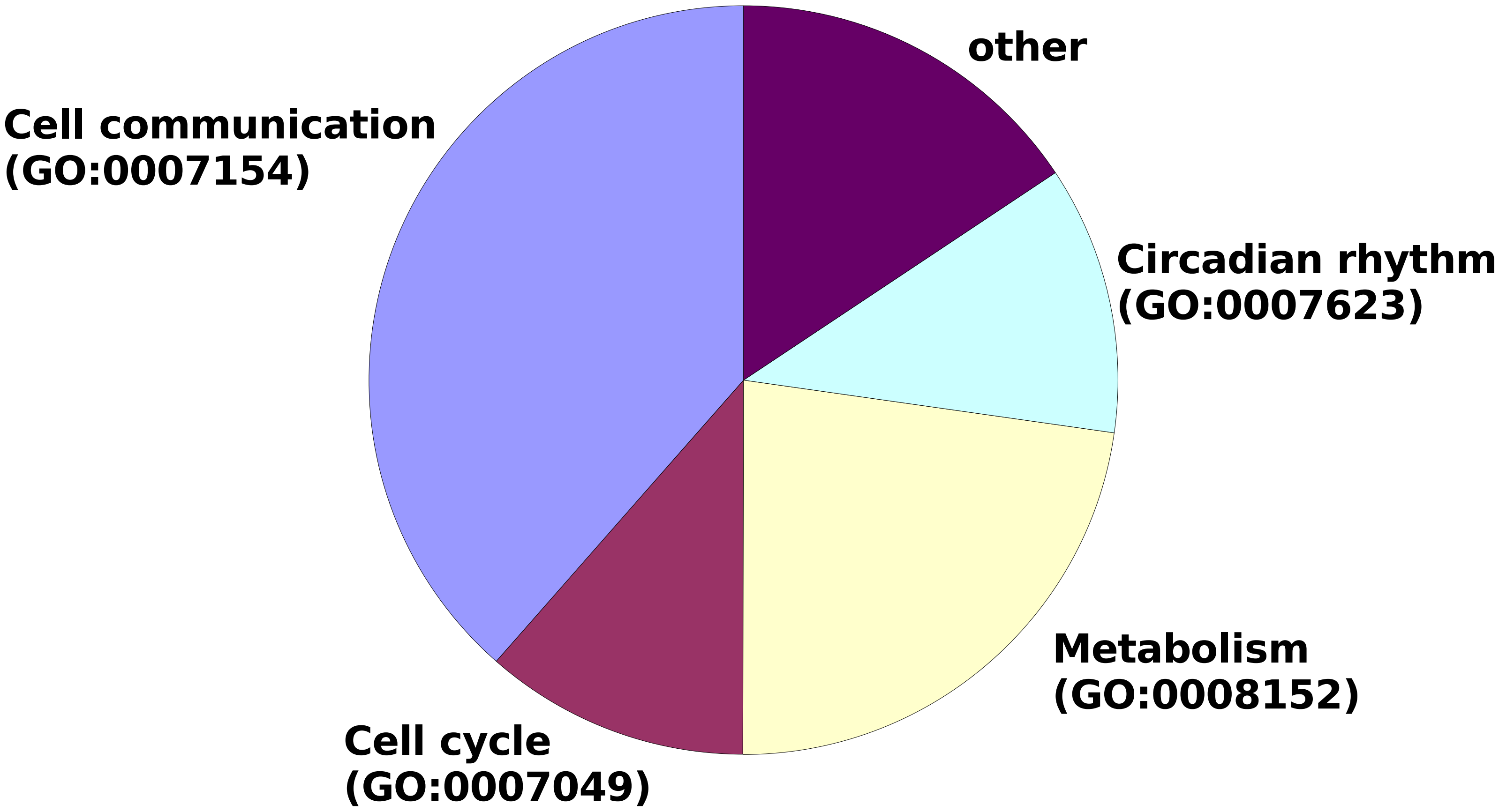
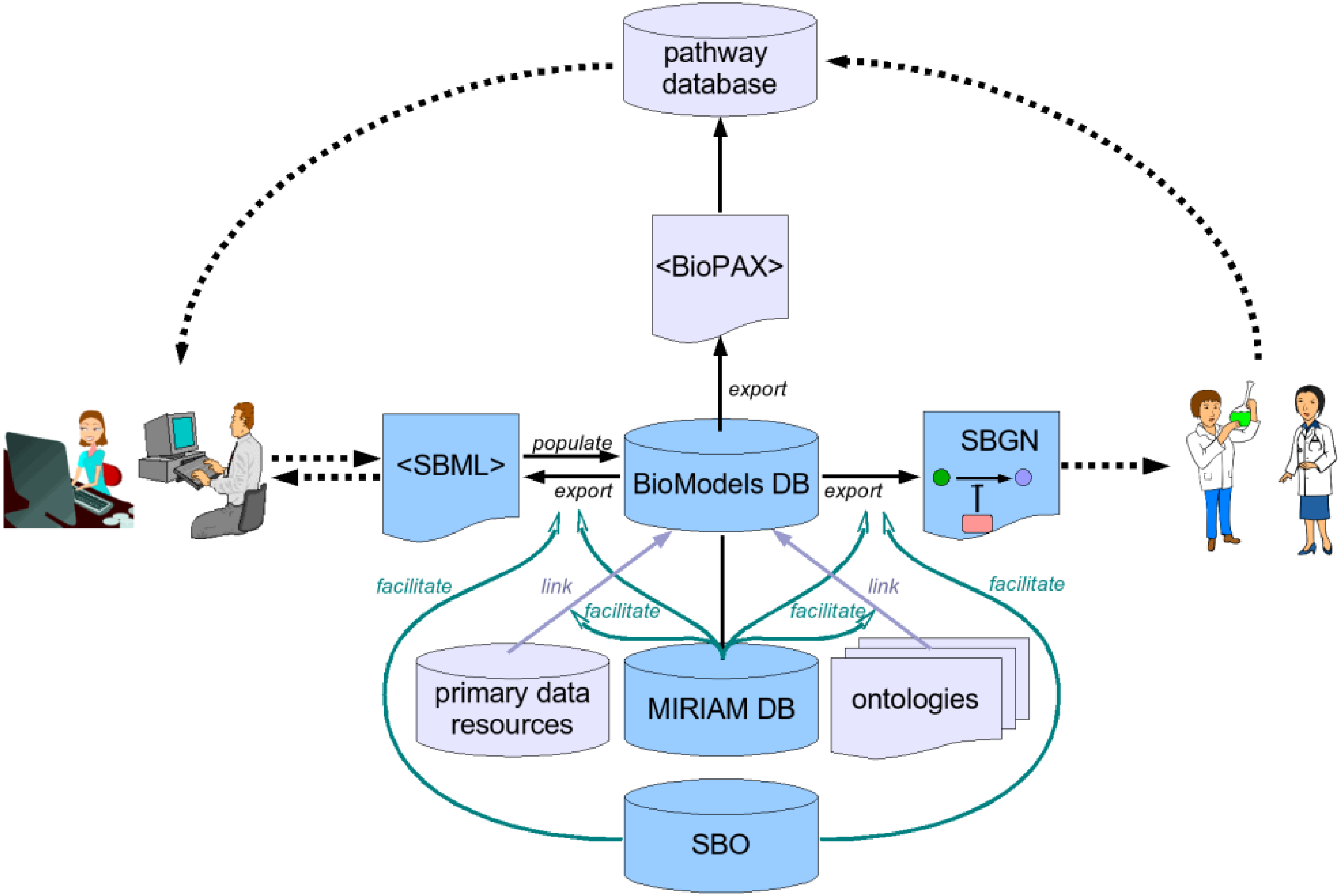


Is the mosaic complete?



The BioModels.net team

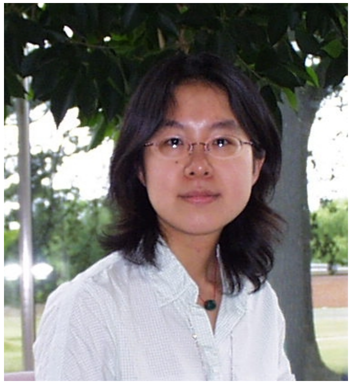

Enuo He


Melanie Courtot

Nicolas
Le Novère

Chen Li

Lu Li




Harish
Dharuri

Camille Laibe

Marco Donizelli

Arnaud Henry

Michael
Hucka

An international collaboration

- EBI
  - Nicolas Le Novère
  - Marco Donizelli
  - Chen Li
  - Mélanie Courtot
  - Lu Li
  - Camille Laibe
  - Arnaud Henry
  - Enuo He
  - Nicolas Rodriguez
  - Alexander Broicher
- SBML team
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  - Andrew Finney
  - Bruce Shapiro
  - Benjamin Borstein
  - Maria Schilstra
  - Sarah Keating
  - Harish Dharuri
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  - Harsha Rani
- Keck Graduate Institute
  - Herbert Sauro
- Vienna TBI
  - Rainer Machne
- Systems Biology Institute
  - Hiroaki Kitano
  - Akira Funahashi
- JWS Online
  - Jacky Snoep
  - Hans Westerhoff
- Journals supporting BioModels Database
  - Molecular Systems Biology
  - PLoS Computational Biology
  -
- Programs used for curation
  - CellDesigner/SBMLodeSolver
  - COPASI
  - Jarnac/JDesigner
  - MathSBML
  - SBMLeditor
  - XPP-Aut

The community of Systems Biology for their contributions of models and comments.

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  - Transcriptomics, Proteomics pathways, models
  - Controlled vocabularies and dictionaries
- Research groups
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  - Molecular Evolution (Goldman)
  - Text-Mining (Rebholz-Schumman)
  - Computational Systems Biology (Le Novère)
  - Statistical array analysis (Huber)
  - Genomic analysis of regulatory systems (Luscombe)
  - Systems Biology of ES cells (Bertone)

Marie Curie Training site Fellowships: PhD 3-6 months. Fully funded.
Undergraduate trainees: 5-6 months.

BioModels ID ▽	Name	Publication ID	Last Modified
MODEL0995500644	Rodriguez2005_denovo_pyrimidine_biosynthesis	15784266	2006-09-30T21:48:57
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MODEL5662377562	Feist2006_methanogenesis_OptiAcetate	10.1038/msb4100046...	2006-10-02T16:46:28
MODEL5662398146	Feist2006_methanogenesis_OptiH2-CO2	10.1038/msb4100046...	2006-10-02T16:47:09
MODEL5662425708	Feist2006_methanogenesis_OptiPyruvate	10.1038/msb4100046...	2006-10-02T16:50:56
MODEL5974712823	FangeElf2006_MinSystem_MesoRD	16846247	2006-09-29T22:28:23
MODEL6623597435	Fuentes2005_ZymogenActivation	15634334	2006-09-29T22:39:28
MODEL6623610941	Hornberg2005_ERKcascade	15634347	2006-09-29T22:50:28
MODEL6623617994	Lambeth2002_Glycogenolysis	12220081	2006-09-30T21:46:54
MODEL6623628741	Kolomeisky2003_myosin	12609867	2006-09-29T23:36:52
MODEL6624091635	Hoefnagel2002_Glycolysis	12241048	2006-09-29T22:45:45
MODEL6624139162	Cronwright2003_GlycerolSynthesis	12200299	2006-09-29T22:34:13
MODEL6624199343	Martins2001_glyoxalase	11453985	2006-10-02T10:53:31
MODEL6762427183	plant_1981_version01	7252375	2006-09-30T18:30:12
MODEL7944007619	Maeda2006_MyosinPhosphorylation	16923126	2006-09-30T18:25:23
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MODEL8568434338	Raman2006_MycolicAcid	16261191	2006-09-29T23:24:10
MODEL8583955822	Singh_Ghosh2006_TCA_eco_glucose	10.1186/1742-4682-3-...	2006-09-29T23:47:42
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MODEL8584292730	Singh_Ghosh2006_TCA_mtu_model1	10.1186/1742-4682-3-...	2006-09-29T23:48:15
MODEL8584468482	Singh_Ghosh2006_TCA_mtu_model2	10.1186/1742-4682-3-...	2006-09-29T23:49:52

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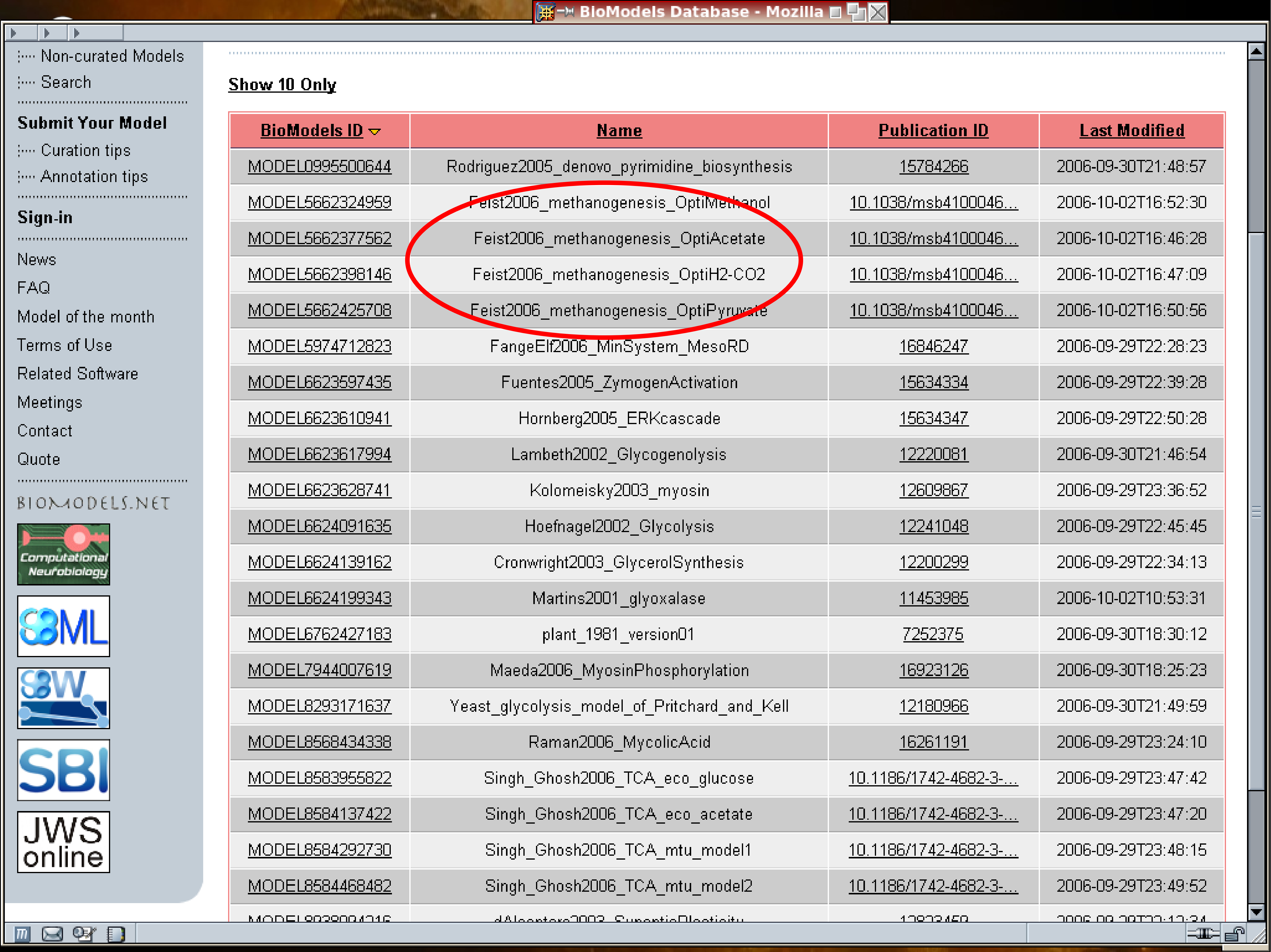

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