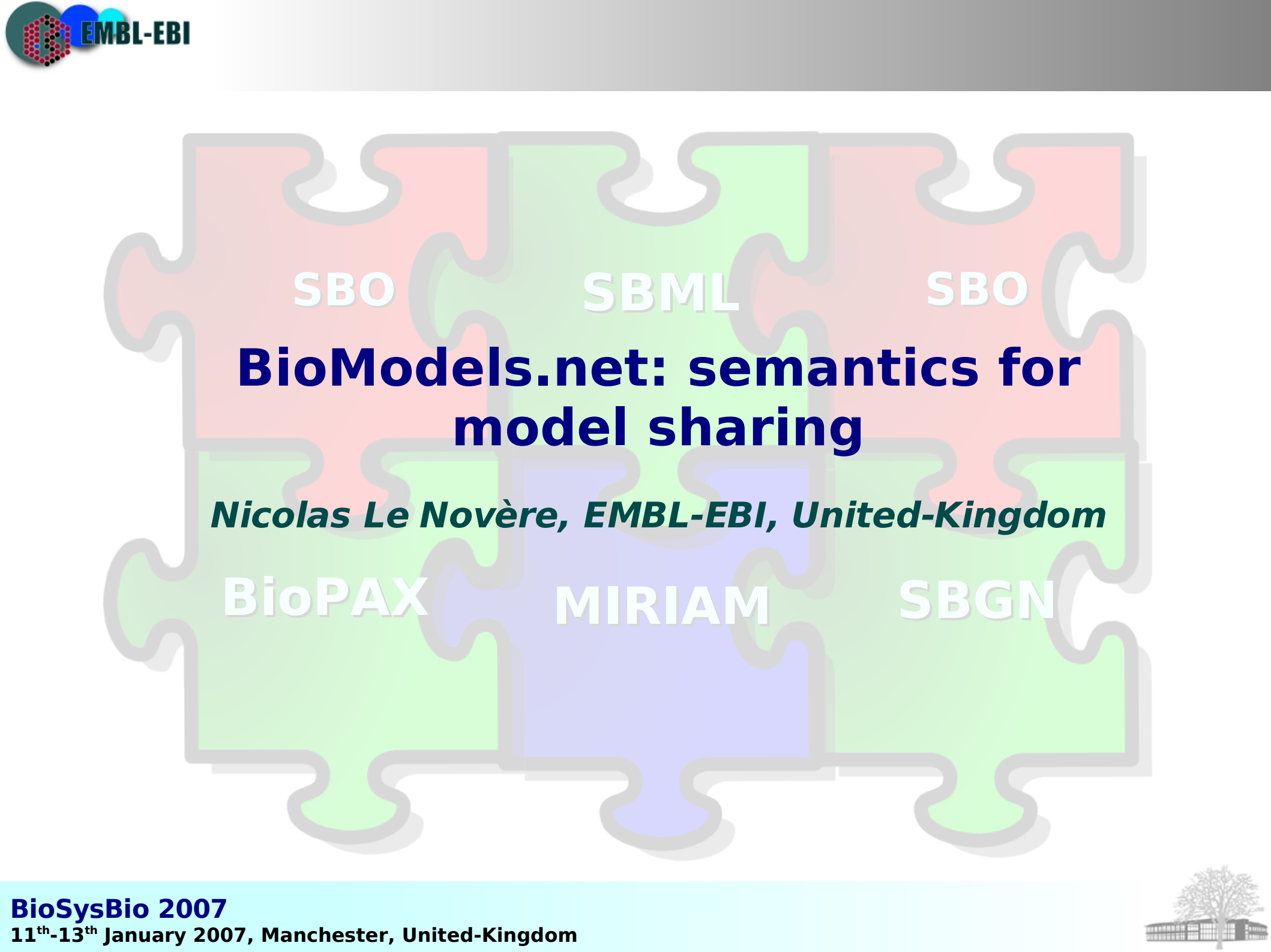
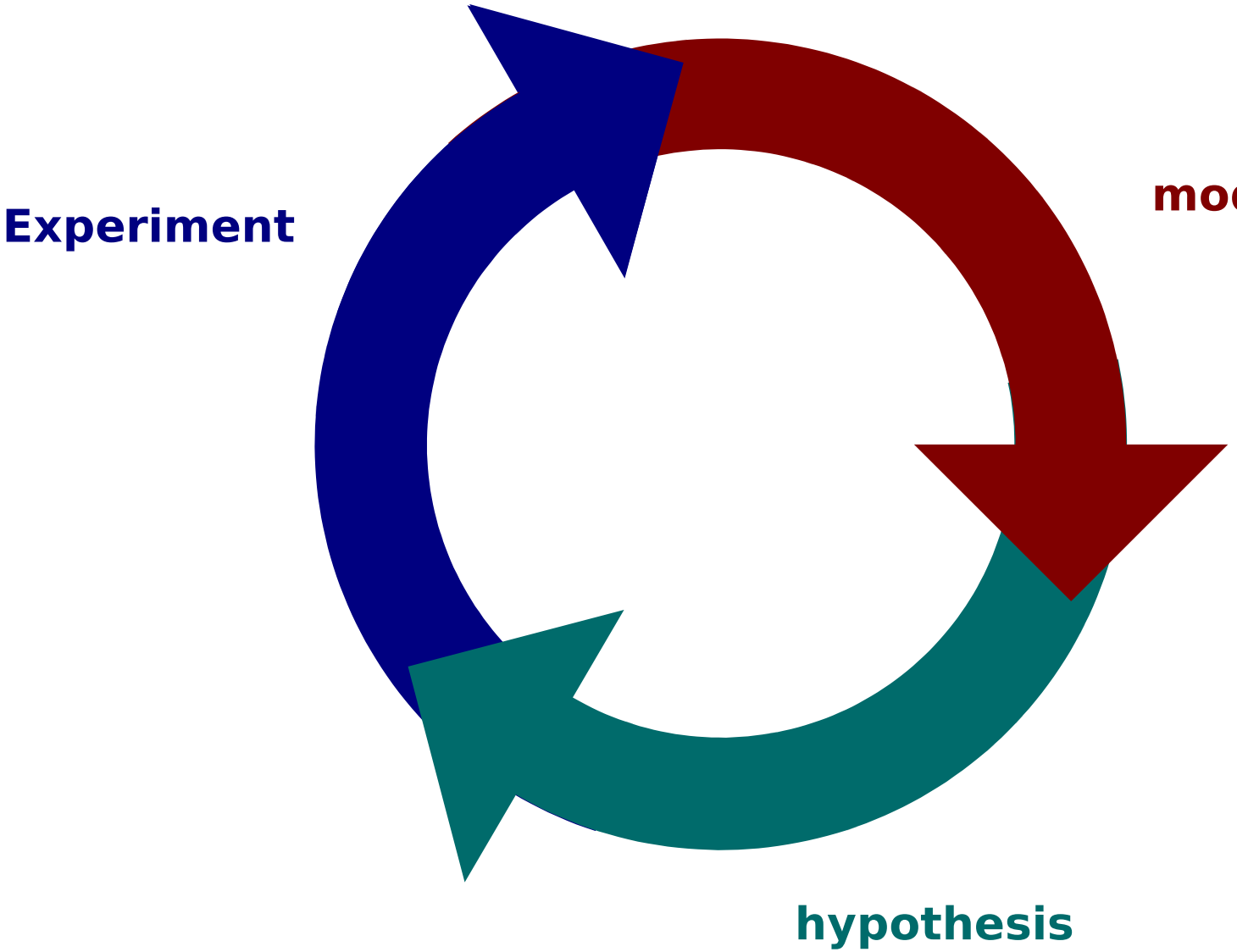
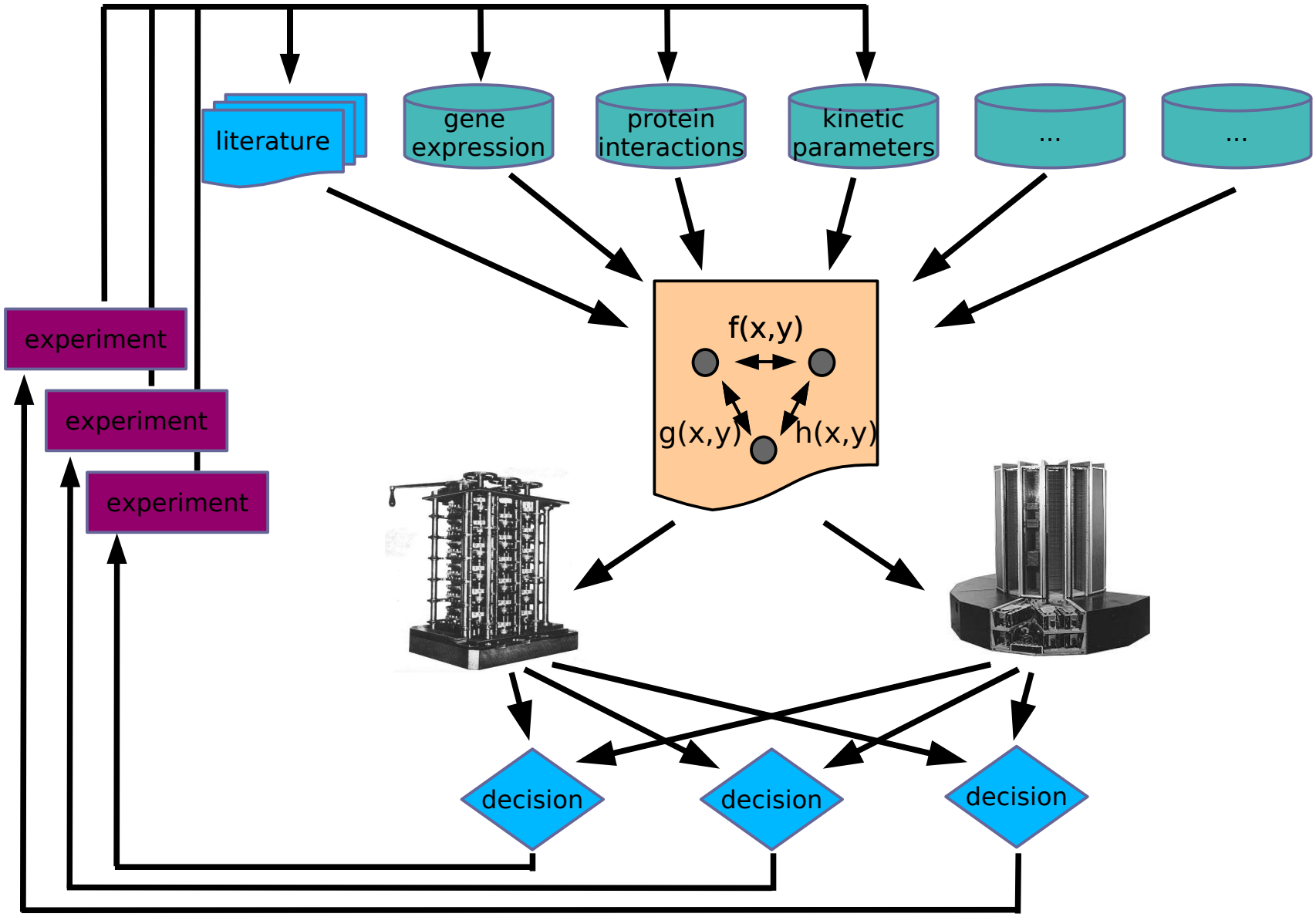


BioModels.net: semantics for model sharing

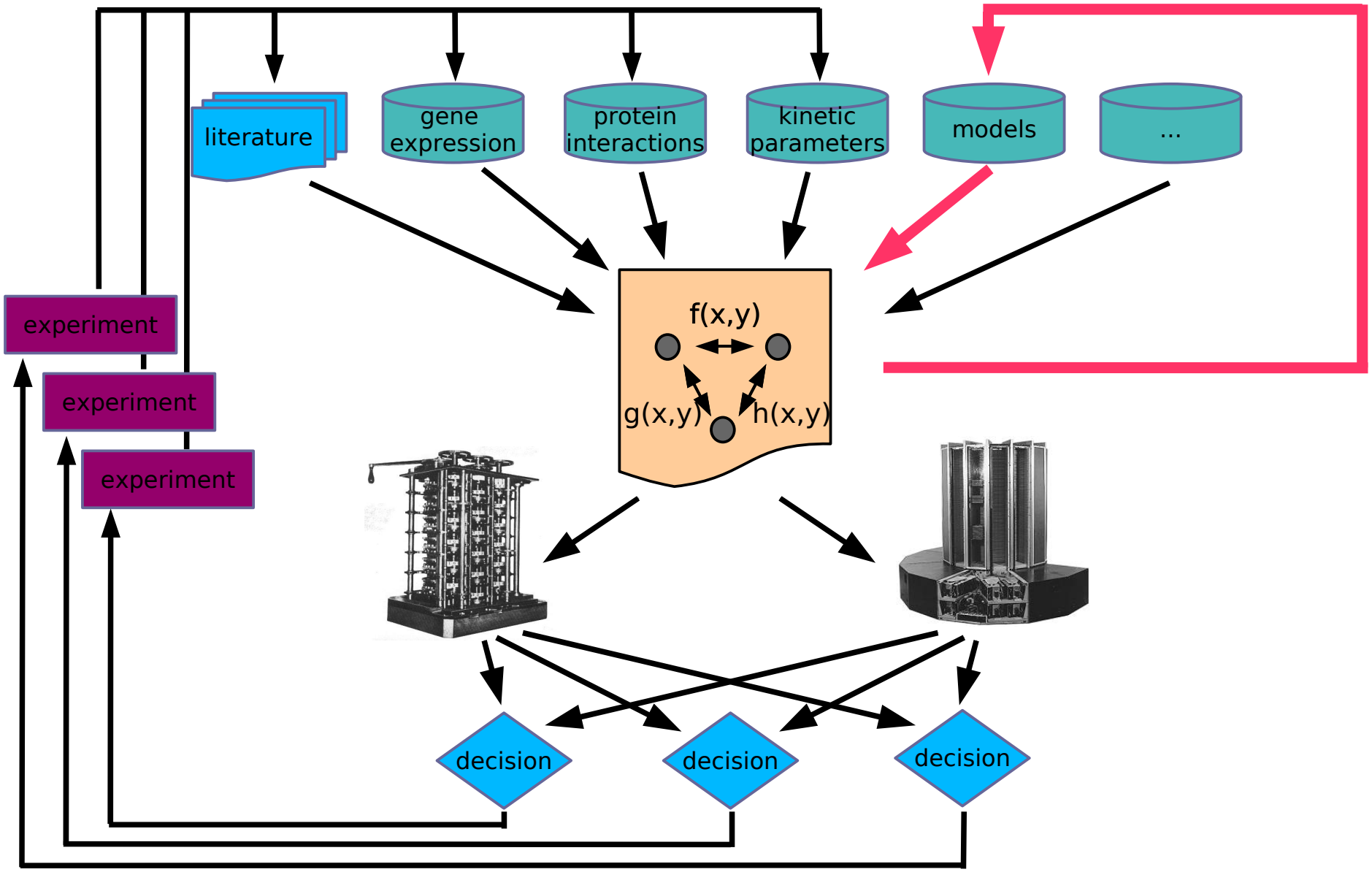
Nicolas Le Novère, EMBL-EBI, United-Kingdom


Experiment
model
hypothesis

The model as an integrator of knowledge



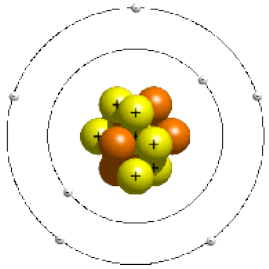
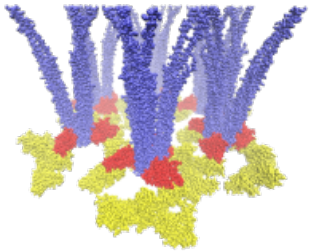
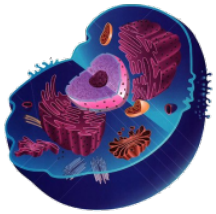
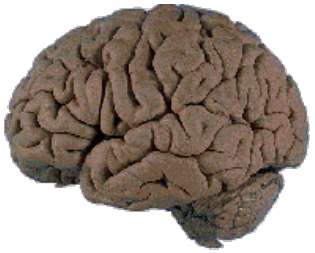
The model as an integrator of knowledge



A multiscale problem

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

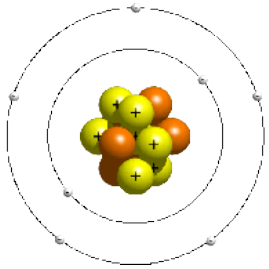
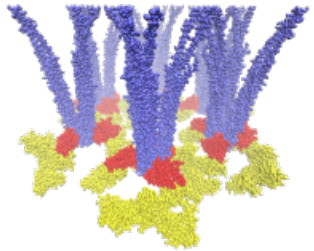
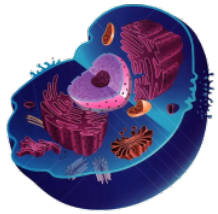
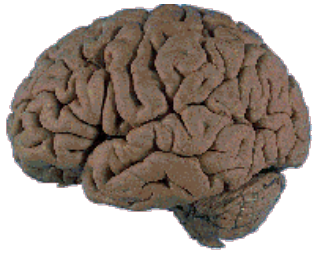
spatial scale problem


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

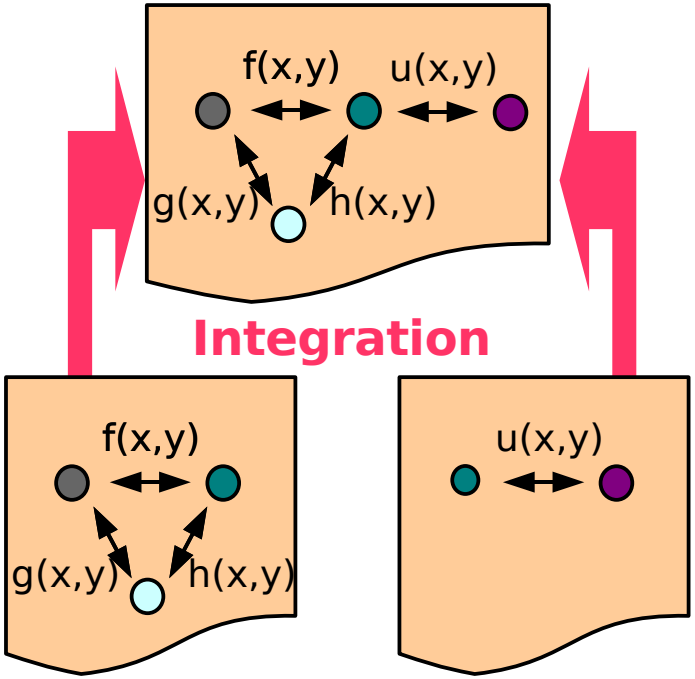
molecular dynamics
conformational transition
molecule diffusion
nerve signal
signalling cascade
gene regulation
circadian rhythm
cell cycle
reproduction
life cycle

A simulation problem

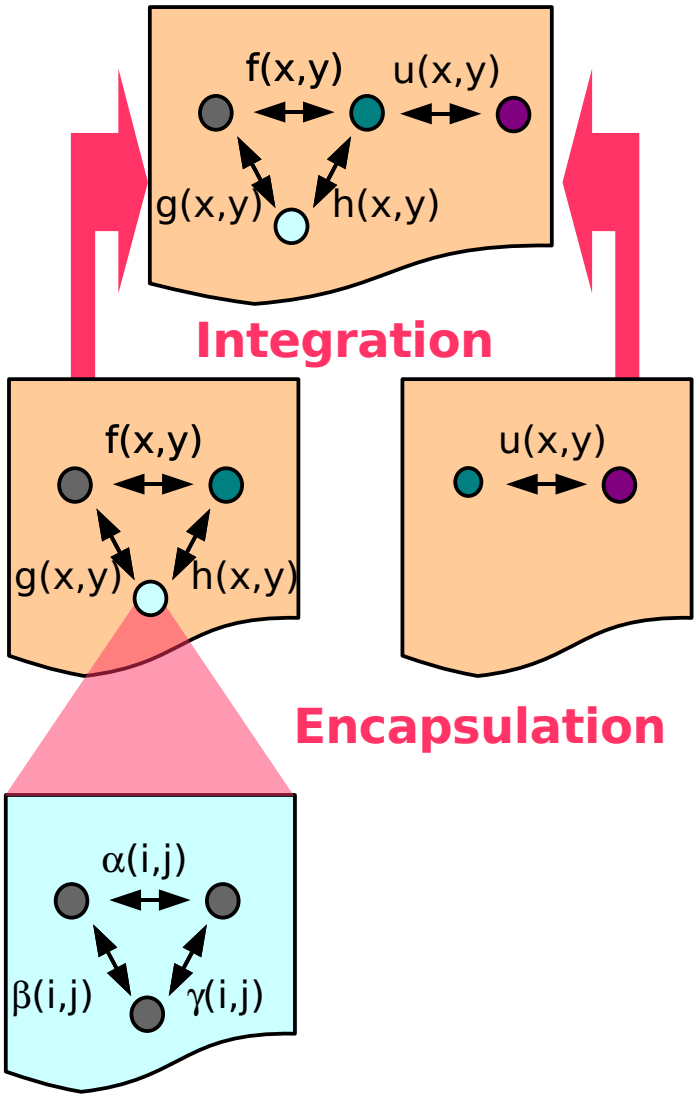
- Molecular dynamics: to simulate $\propto 10^{-12}$ s requires $\propto$ 1 s
- Particle diffusion: to simulate $\propto 10^{-6}$ s requires $\propto$ 1 s
- Stochastic chemical kinetics: to simulate $\propto$ 1 s requires $\propto$ 1 s
- Continuous ODE: to simulate $\propto 10^{3}$ s requires $\propto$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

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

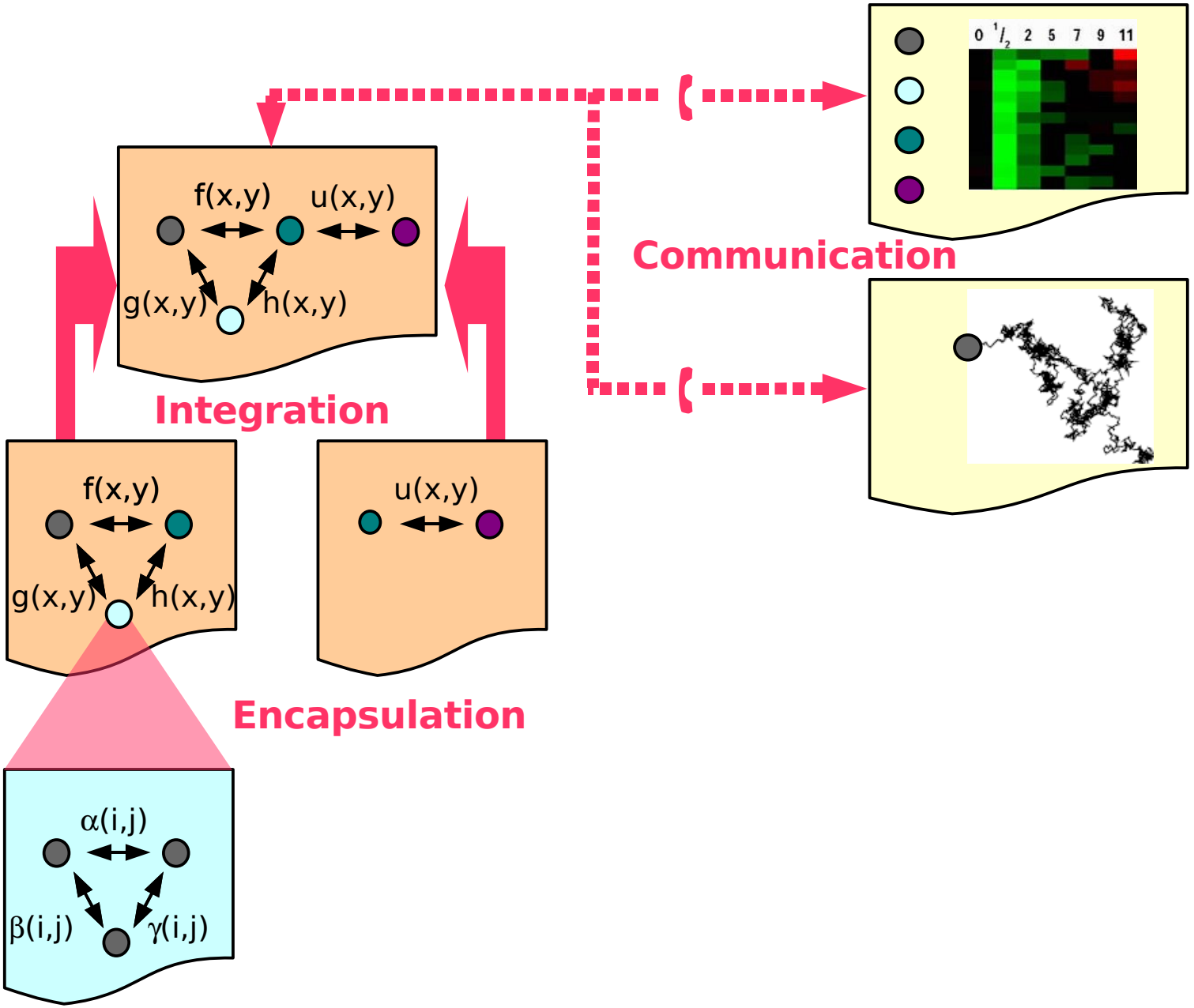
What can-we do?



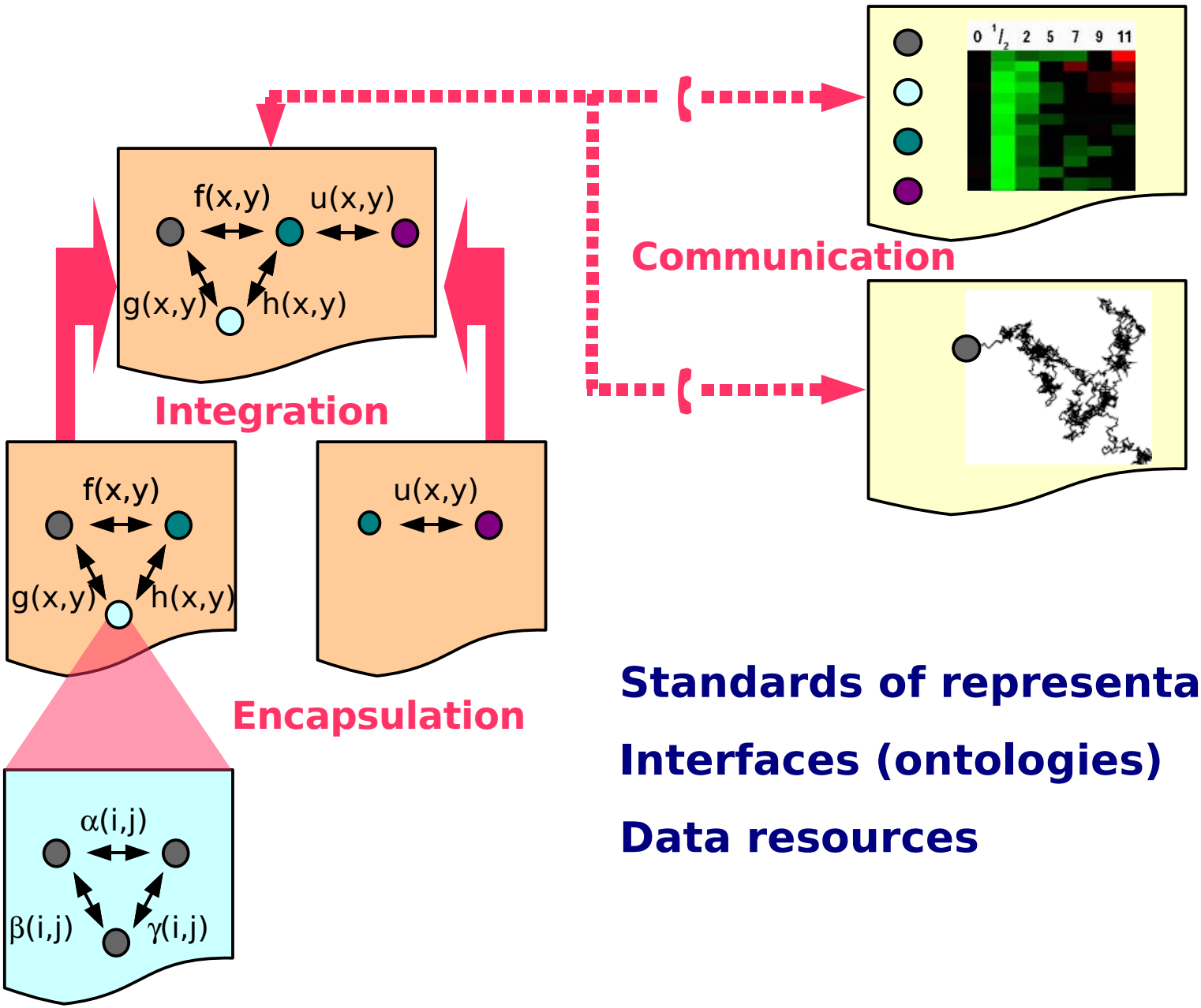
What can-we do?



What can-we do?



What can-we do?



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

- 

http://www.cellml.org/
Based on modules; scalable;

- 

http://www.neuroml.org/
Flexible (expendable set of classes/schemas);

- 

http://brainml.org/
Models are XML-schemas

- 

http://www.biopax.org/
No kinetics; deep semantics; OWL

- 

http://www.sbgn.org/
Graphical representation of interactions

- 

http://sbml.org/
Rich kinetics; weak semantics; XML

SBML Systems Biology Markup Language

Google Search this site

home • contacts • documents • downloads • FAQs • forums • Level 3 • models • news • online tools • wiki • workshops

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.

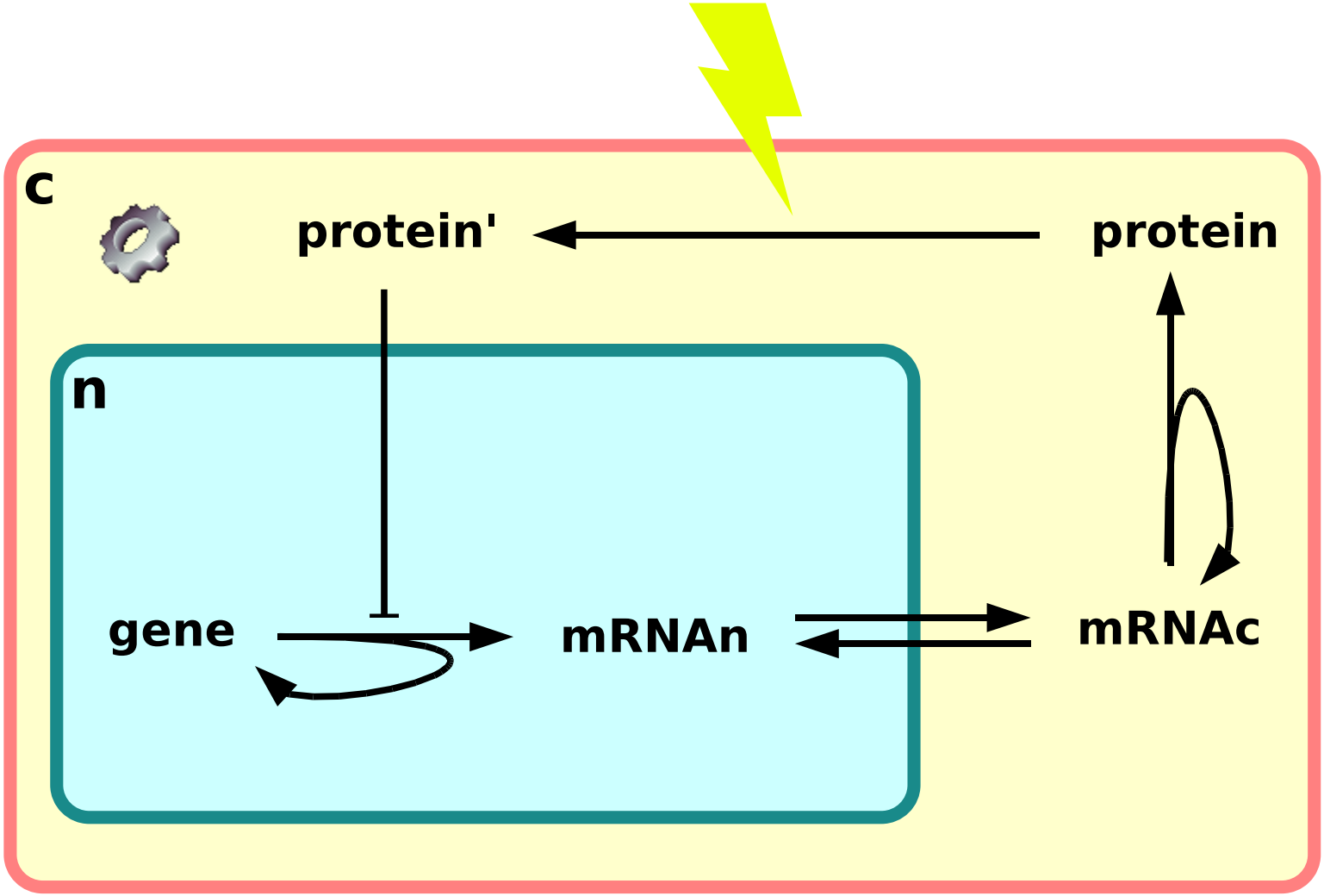
read more

See older news items.

What 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?



```
<?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 any quantitative parameter, 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!

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 (MIRIAM) 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 participants, but does not identify them.
- An SBML model contains mathematical expressions, but does not tell-us what they “mean”, and how they are derived.
- An SBML model 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**

http://www.ebi.ac.uk/compneur-srv/miriam/

Reference correspondence

Thou shalt encode your model in a public, standardized, machine-readable format (SBML, CellML, GENESIS ...)

Thy model shalt comply with the standard in which it is encoded!

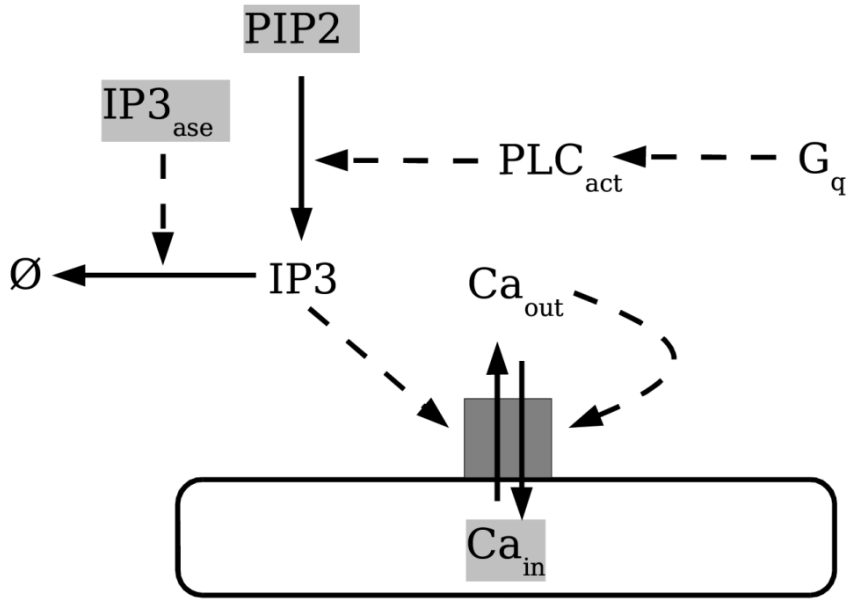
Thy model shalt be clearly related to a single reference description. If thy model is composed from different parts, thou shalt still quote a description of the derived/combined model.

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

Thy model shalt be instantiated in a simulation: All quantitative attributes shalt be defined, including initial conditions.

When instantiated, thy 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

Thy model has to be named.

Thou shalt join a citation of the reference description (complete citation, unique identifier, unambigous URL). The citation shalt permit to identify the *authors* of thy model.

Thou shalt join the name and contact of model *creators*.

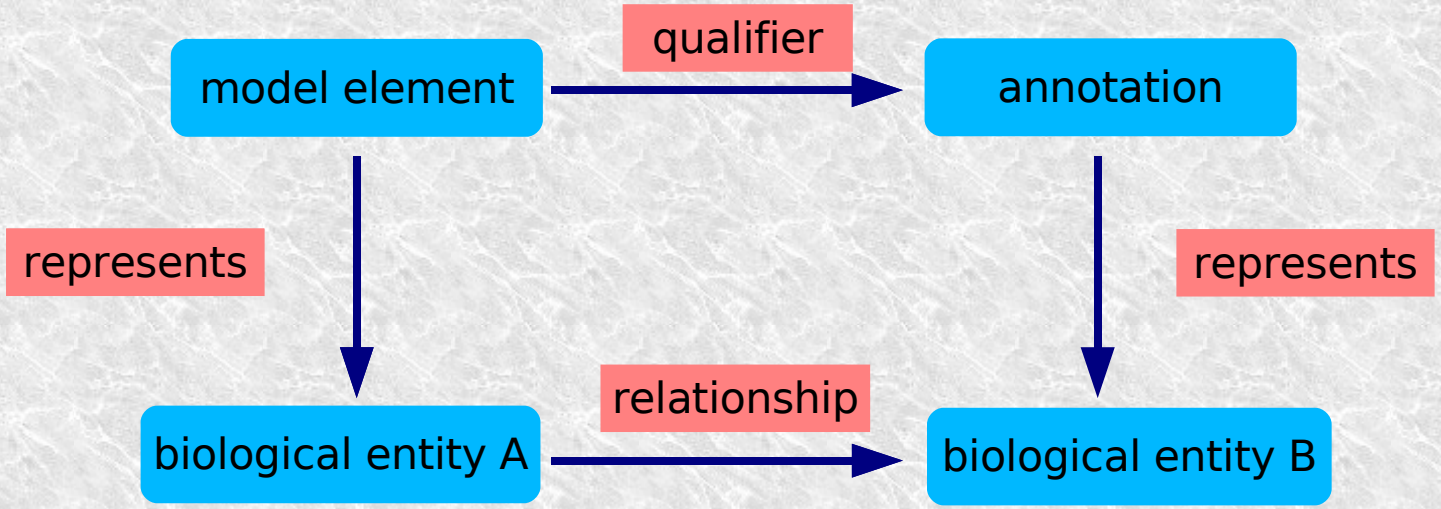
Thou shalt specify the date and time of creation and last modification. An history is useful but not required.

Thou shalt link thy model to a precise statement about the terms of distribution. MIRIAM does not require “freedom of use” or “no cost”.

External resource annotation

Thy annotation shalt permit to unambiguously relate
a piece of knowledge to a model constituent.

Thy referenced information shalt 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.

- Browse
- Request
- Submission
- XML Export
- Sign In

- News
- Web Services
- BioModels Qualifiers
- FAQ
- Contact

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

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]

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Last modification: Wed Nov 15 2006

Contact

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Miriam Web Services

MIRIAM database provides some web services for programmatic access.

WSDL

You can access to the WSDL file here.

Java Library

In order to communicate with the web services of Miriam in a Java program, you can use the library below (distributed under the terms of the GNU General Public License). Two versions are provided:

- simple version (you need a couple of external jars to use it)
- standalone version (all the dependencies are included in the jar)

Here are the dependencies:

- axis
- commons-discovery
- commons-logging
- jaxrpc
- log4j
- saaj
- wsdl4j
- activation
- mail

Note: you can find the latest version of each of these packages on their official web site.

Documentation

The documentation (javadoc) can be found here.

Tutorial

Here is a sample program to show how to use the library:

```
import uk.ac.ebi.miriam.lib.*;

public class WebServicesTesting
{
  public static void main(String[] args)
  {
   // creation of the link to the web services
   MiriamLink link = new MiriamLink();

   // changes the default address
```

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 β1*
reactant PLC_{tot}	http://www.uniprot.org/	Q9NQ66		*PIP2 phosphodiesterase β1*
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*

Annotated SBML

```
<species metaid="metaid_0000055"
     id="boundEGFReceptor"
     compartment="cell"
     initialConcentration="0">
    <annotation>
        <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
             xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
         xmlns:bqmodel="http://biomodels.net/model-qualifiers/">
            <rdf:Description rdf:about="#metaid_0000055">
                <bqbiol:hasPart>
                    <rdf:Bag>
                        <rdf:li rdf:resource="http://www.uniprot.org/#Q9QX70"/>
                        <rdf:li rdf:resource="http://www.uniprot.org/#P07522"/>
                    </rdf:Bag>
                </bqbiol:hasPart>
            </rdf:Description>
        </rdf:RDF>
    </annotation>
</species>
```

Epidermal Growth Factor receptor

Epidermal Growth Factor

Hidden assumptions

```
<reaction>
   <listOfReactants>
     <speciesReference species="S" />
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="P" />
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="E" />
   </listOfModifiers>
   <kineticLaw>
     <listOfParameters>
       <parameter id="Km"/>
       <parameter id="kp"/>
     </listOfParameters>
     <math xmlns="http://www.w3.org/1998/Math/MathML">
       <apply>
         <divide/><apply>
                    <times/><ci>E</ci>
                            <ci>kp</ci>
                            <ci>S</ci>
                  </apply>
                  <apply>
                    <plus/><ci>Km</ci>
                           <ci>S</ci>
                  </apply>
       </apply>
     </math>
   </kineticLaw>
 </reaction>
```

E

$S \rightarrow P$

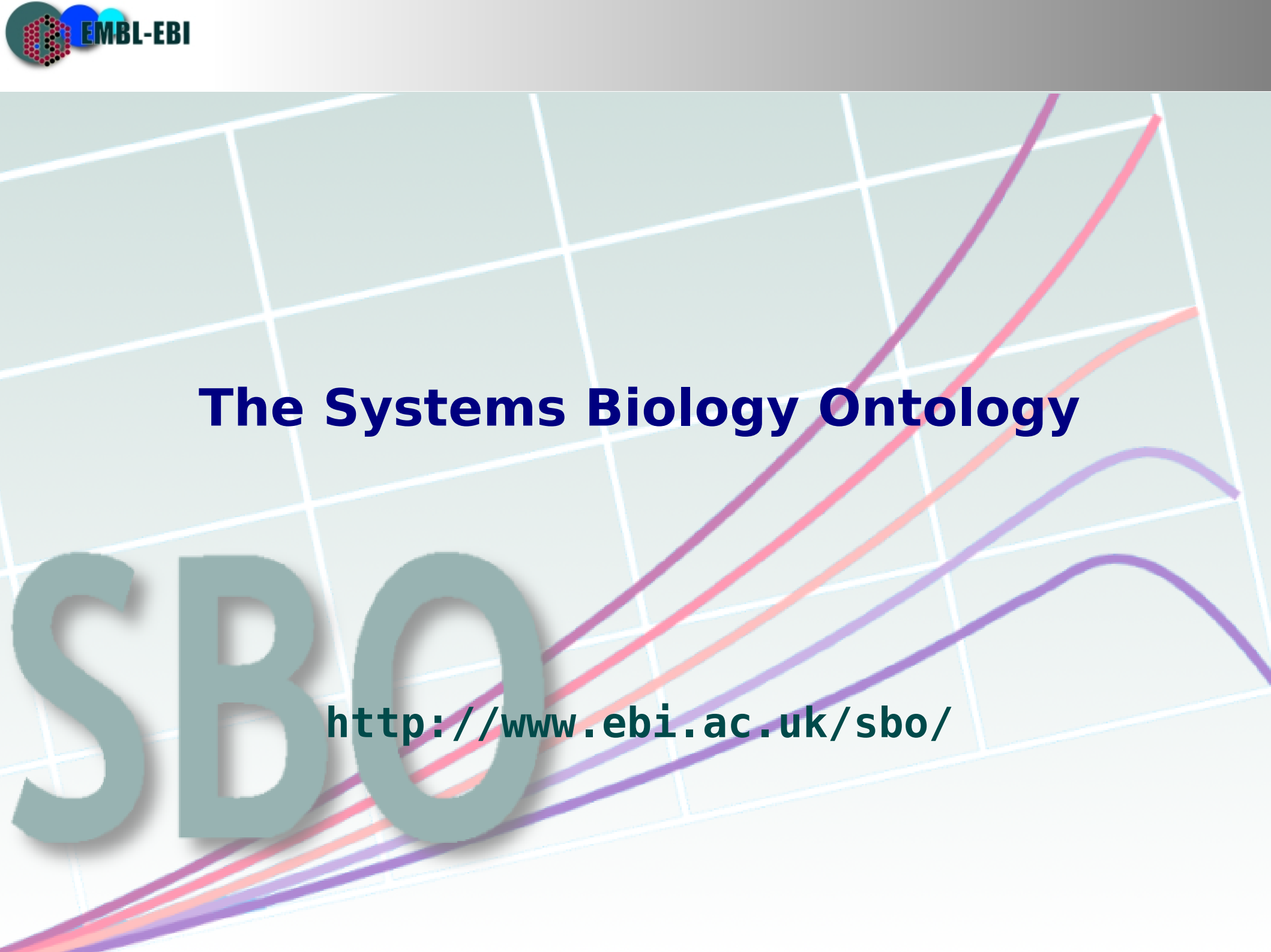
Import in a discrete simulator

$E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_p} E+P \; ; \; k_1 = k_{-1}/K_m$

$E+S \xrightarrow{k_1} ES \xrightarrow{k_p} E+P \; ; \; k_1 = k_p/K_m$

$E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_p} E+P \; ; \; k_1 = (k_{-1}+k_p)/K_m$

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

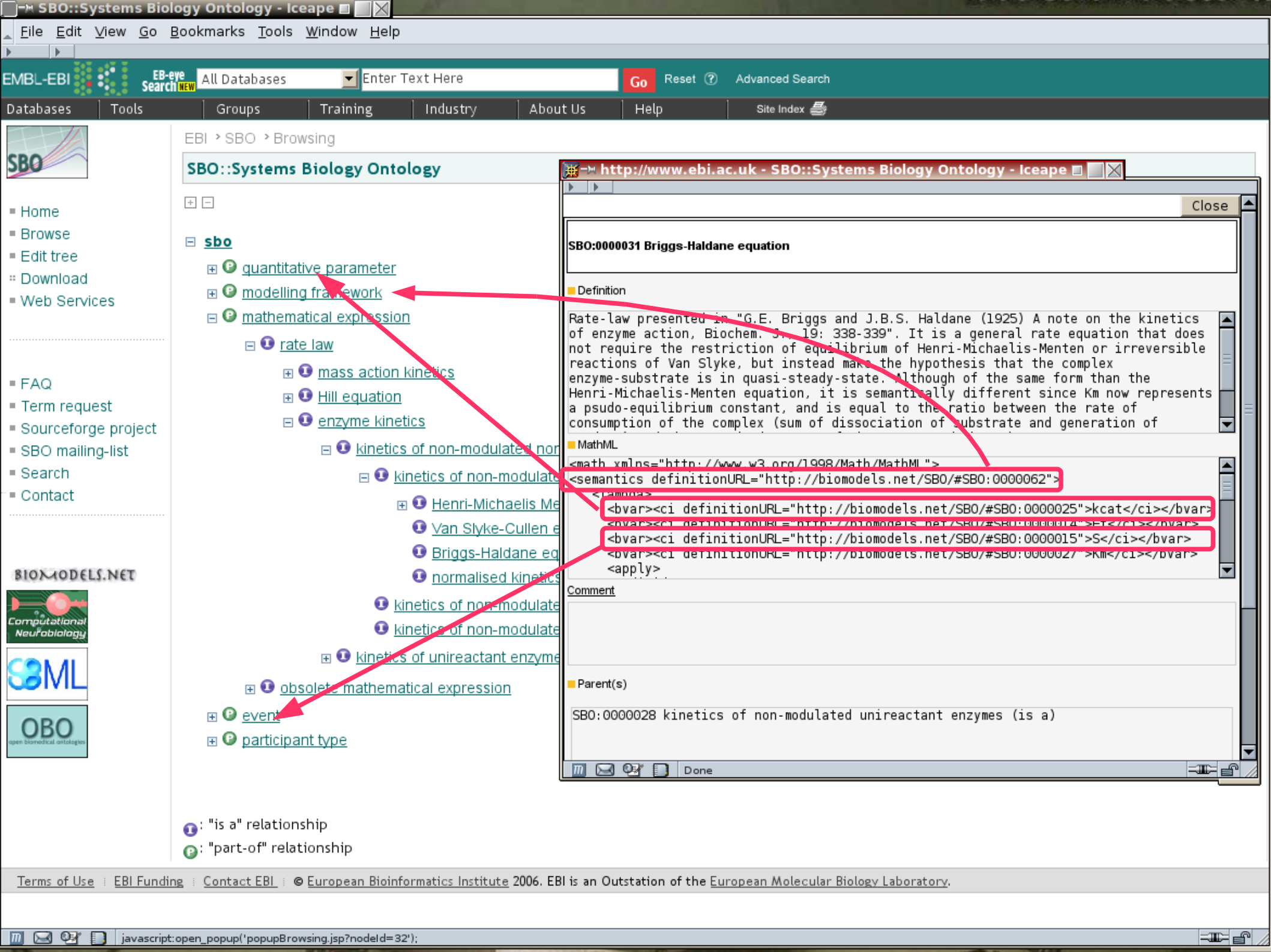
- Types and roles of reaction participants, including terms like "substrate", "catalyst" etc., but also "macromolecule", or "channel".

- Parameter used in quantitative models. This vocabulary includes terms like "Michaelis constant" , "forward unimolecular rate constant"etc. A term may contain a precise mathematical expression stored as a MathML lambda function. The variables refer to other parameters.

- Mathematical expressions. Examples of terms are "mass action kinetics", "Henri-Michaelis-Menten equation" etc. A term may contain a precise mathematical expression stored as a MathML lambda function. The variables refer to the other vocabularies.

- 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::Systems Biology Ontology - Iceape
File Edit View Go Bookmarks Tools Window Help
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Enter Text Here
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Advanced Search
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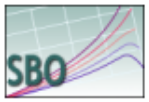
sbo
quantitative parameter
modelling framework
mathematical expression
rate law
mass action kinetics
Hill equation
enzyme kinetics
kinetics of non-modulated nor
kinetics of non-modulate
Henri-Michaelis Me
Van Slyke-Cullen e
Briggs-Haldane eq
normalised kinetics
kinetics of non-modulate
kinetics of non-modulate
kinetics of unireactant enzyme
obsolete mathematical expression
event
participant type
: "is a" relationship
: "part-of" relationship
http://www.ebi.ac.uk - SBO::Systems Biology Ontology - Iceape
Close
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: 338-339". 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
MathML
<math xmlns="http://www.w3.org/1998/Math/MathML">
<semantics definitionURL="http://biomodels.net/SBO/#SBO:0000062">
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000025">kcat</ci></bvar>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000015">S</ci></bvar>
<apply>
Comment
Parent(s)
SBO:0000028 kinetics of non-modulated unireactant enzymes (is a)
Done
Terms of Use | EBI Funding | Contact EBI | © European Bioinformatics Institute 2006. EBI is an Outstation of the European Molecular Biology Laboratory.
javascript:open_popup('popupBrowsing.jsp?nodeId=32');



SBO::Systems Biology Ontology

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- Term request
- Sourceforge project
- SBO mailing-list
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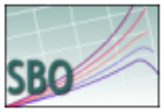
To download any file, click the mouse right button on the link below, and select the *Save Link As...* or *Save Link Target As...* option (browser-dependant).

- Click on the links below to quickly download the last automatic export from the database (generated daily at 6am UK time)
  - SBO_OBO.obo
  - SBO_XML.xml
  - SBO_OWL.owl
- Click on the links below to download the SBO XML schemas
  - SBO_XML_schema.xsd
  - SBO_MathML_schema.xsd
- You can also generate your own version of the files, based on the current info in the database. Your file will be generated automatically: this will take a few moments to complete.
  - OBO Flat file format
  - SBO-XML format
  - OWL format



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Java Library

In order to communicate with the SBO Web Services in a Java program, you can use the library below (distributed under the terms of the GNU General Public License). Two versions are provided:

- SBOWSLib-basic-20070110.jar (simple version, you need a couple of external jars to use it)
- SBOWSLib-20070110.jar (standalone version, all the dependencies are included in the jar)

Here are the dependencies:

- axis
- commons-discovery
- commons-logging
- jaxrpc
- jakarta-oro
- log4j
- saaj
- wsdl4j
- xml-apis
- xerces
- activation
- mail

Note: you can find the latest version of each of these packages on their official web site.

WSDL

The Javadoc API for these methods can be found here.

The full WSDL documentation can be found here [HTML][Download as a PDF]

WDSL file

This WSDL was generated using Axis tools to fulfill the following interface contract:

```
public interface SBOProvider  {
    public java.lang.String sayHi(java.lang.String in0);
    public uk.ac.ebi.sbo.castorExport.Term getTermById(int in0);
    public uk.ac.ebi.sbo.castorExport.Term[] searchPossibleCompletions(java.lang.String in0);
```

Revealed assumptions

```
<reaction>
  <listOfReactants>
    <speciesReference species="A" sboTerm="SBO:0000015"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="B" sboTerm="SBO:0000011"/>
  </listOfProducts>
  <listOfModifiers>
    <speciesReference species="C" sboTerm="SBO:0000014"/>
  </listOfModifiers>
  <kineticLaw sboTerm="SBO:0000031">
    <listOfParameters>
      <parameter id="U" sboTerm="SBO:0000008"/>
      <parameter id="V" sboTerm="SBO:0000025"/>
    </listOfParameters>
  </kineticLaw>
</reaction>
```

substrate

product

catalyst

Briggs-Haldane equation

Km

kcat

continuous simulator

$$v = [C] \cdot V \cdot \left(\frac{[A]}{(U + [A])}\right)$$

discrete simulator

$$v1 = \frac{(k_{-1} + V)}{U} \cdot [A] \cdot [C]$$

$$v2 = k_{-1} \cdot [D]$$

$$v3 = V \cdot [D]$$

[complete model, with links in species and etc.]

```
<listOfSpecies>
  <species id="A" sboTerm="SBO:0000247" />
  <species id="B" sboTerm="SBO:0000247" />
  <species id="C" sboTerm="SBO:0000245" />
</listOfSpecies>
<listOfreactions>
       <reaction sboTerm="SBO:0000172">
    <listOfReactants>
      <speciesReference species="A" sboTerm="SBO:0000015"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="B" sboTerm="SBO:0000011"/>
    </listOfProducts>
    <listOfModifiers>
      <speciesReference species="C" sboTerm="SBO:0000014"/>
    </listOfModifiers>
    <kineticLaw sboTerm="SBO:0000031">
      <listOfParameters>
        <parameter id="U" sboTerm="SBO:0000008"/>
        <parameter id="V" sboTerm="SBO:0000025"/>
      </listOfParameters>
    </kineticLaw>
  </reaction>
</listOfreactions>
```

simple chemical

simple chemical

macromolecule

catalysis

substrate

product

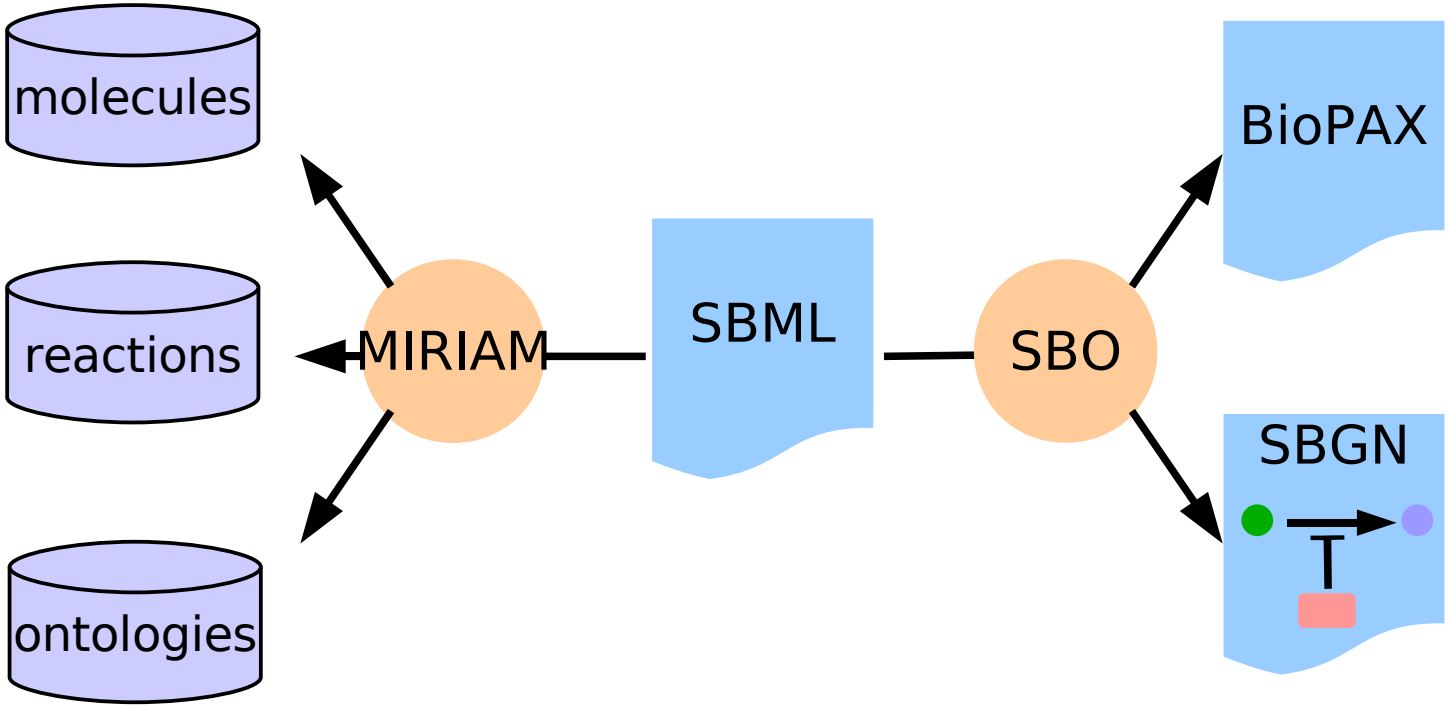
catalyst

Briggs-Haldane equation

Km

kcat

Shall-we interface?



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.

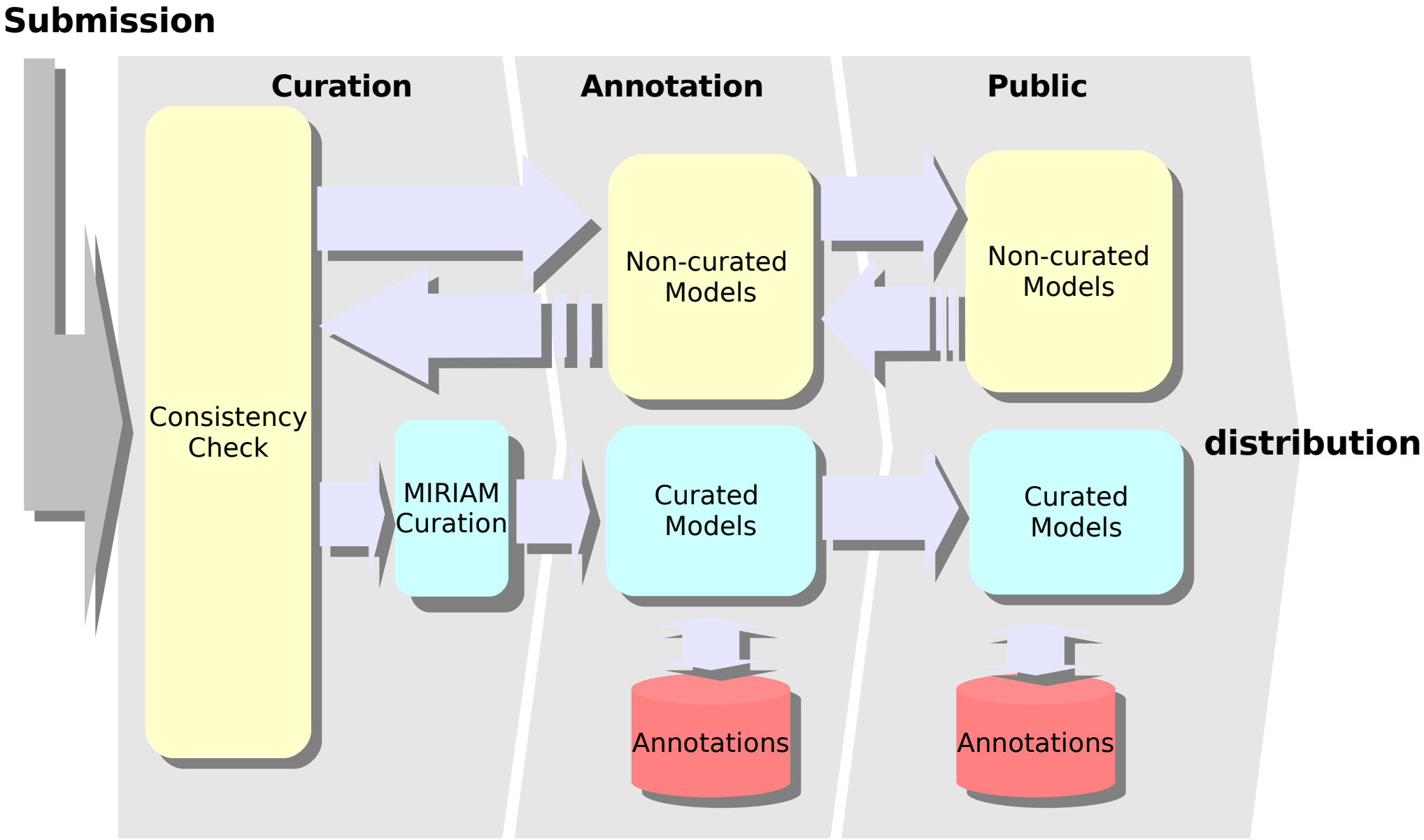
Nucleic Acids Research, (2006), 34: D689-D691

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.

Structure of BioModels Database



;.... Curated Models
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;.... Search

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BioModels Database

A Database of Annotated Published Models

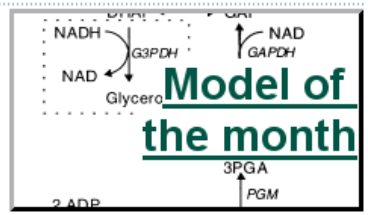
BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, controlled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

[Browse curated models] | [Browse non-curated models] | [Search]

05th January 2007 - Seventh Release! [More] [Download All Models Under SBML L2 V1 Format]

4th December 2006 - BioModels Database and DOQCS join forces [More]

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



Acknowledgements

BioModels Database is developed in collaboration by the teams of Nicolas Le Novère (EMBL-EBI, United-Kingdom), Michael Hucka (SBML Team, Caltech, USA) in collaboration with Upinder Bhalla (DOQCS, National Center for Biological Sciences, India), 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 Stellenbosh University, 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, Enuo He, Nicolas Le Novère, Lu Li, Rainer Machne, Bruce Shapiro (Alumni: Maria Schilstra)

External contributors: BioModels Database would not exists without the continuous support of many peopler, whether by ther contribution of models, of software, or by their constructive comments and criticisms. It is unfortunately impossible keep track and to to acknowledge all of them here, without risking to be unfair. Therefore, a big collective thank-you all.

BioModels Database is built thanks to many third-party free software such as libSBML, Jakarta Tomcat, Xindice, Xalan, Xerces, Jena and MySQL.

Main software used to curate models: CellDesigner, COPASI, Jarnac, MathSBML, XPP-Aut, SBMLdeSolver, SBMLeditor and SBMLmerge.

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- *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:

Publication
ChEBI
Gene Ontology
Taxonomy
UniProt

Resource ID:

Resource ID: BIND

Resource ID: BIND

Compose by: and or

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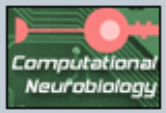

Search Models

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

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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)

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- Non-curated Models
- Search

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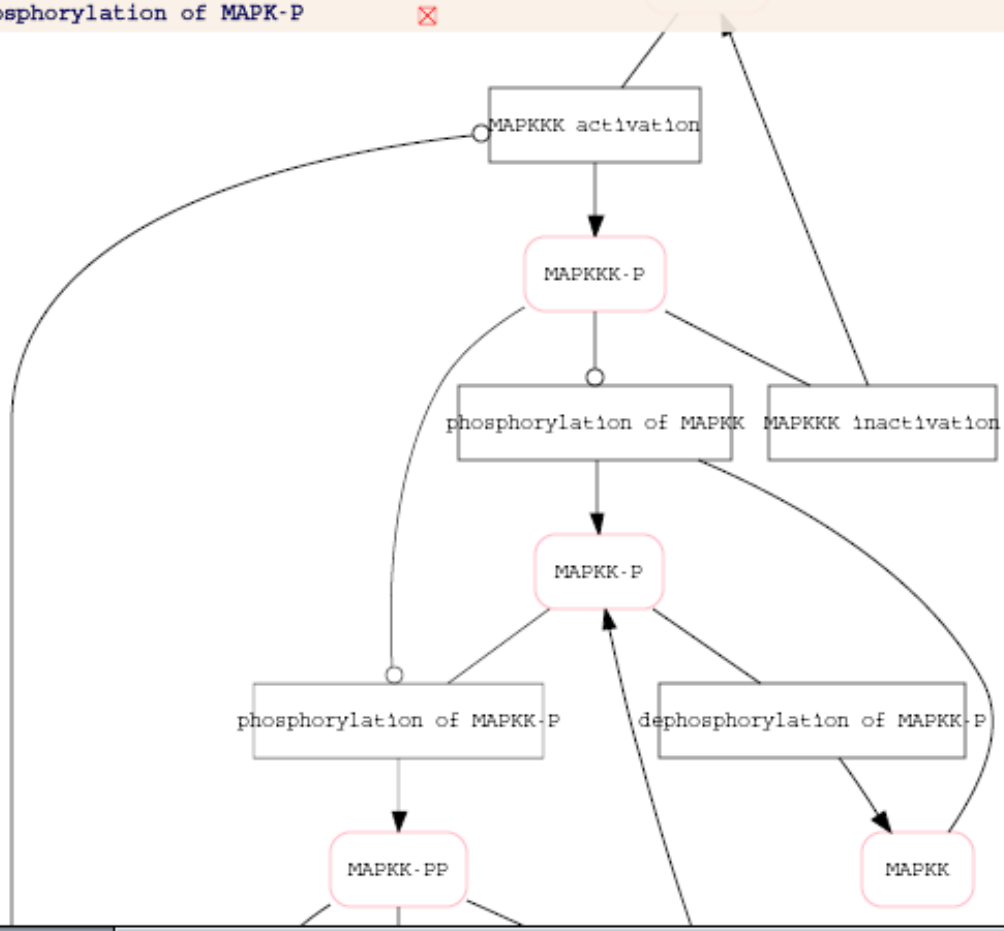
http://www.ebi.ac.uk - SVG - Mozilla

t/Bug

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		



bout oscillations in the

gy, Thomas Jefferson University,
@mail.tju.edu [more]

634
laevis
PKKK cascade

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

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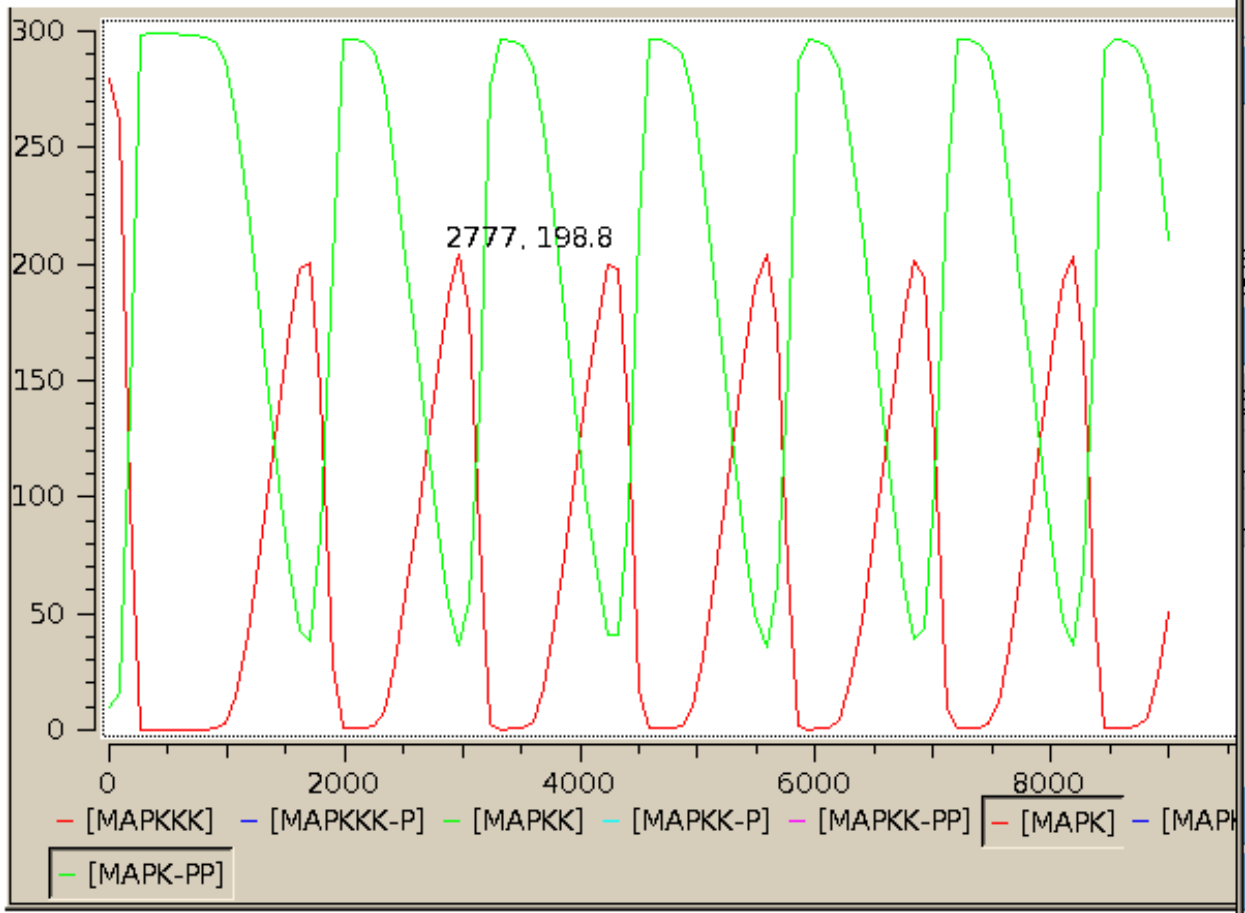

2006-09-30T23:27:45

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

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out oscillations in the

gy, Thomas Jefferson University,
mail.tju.edu [more]

84

aevis

KKK cascade

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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)

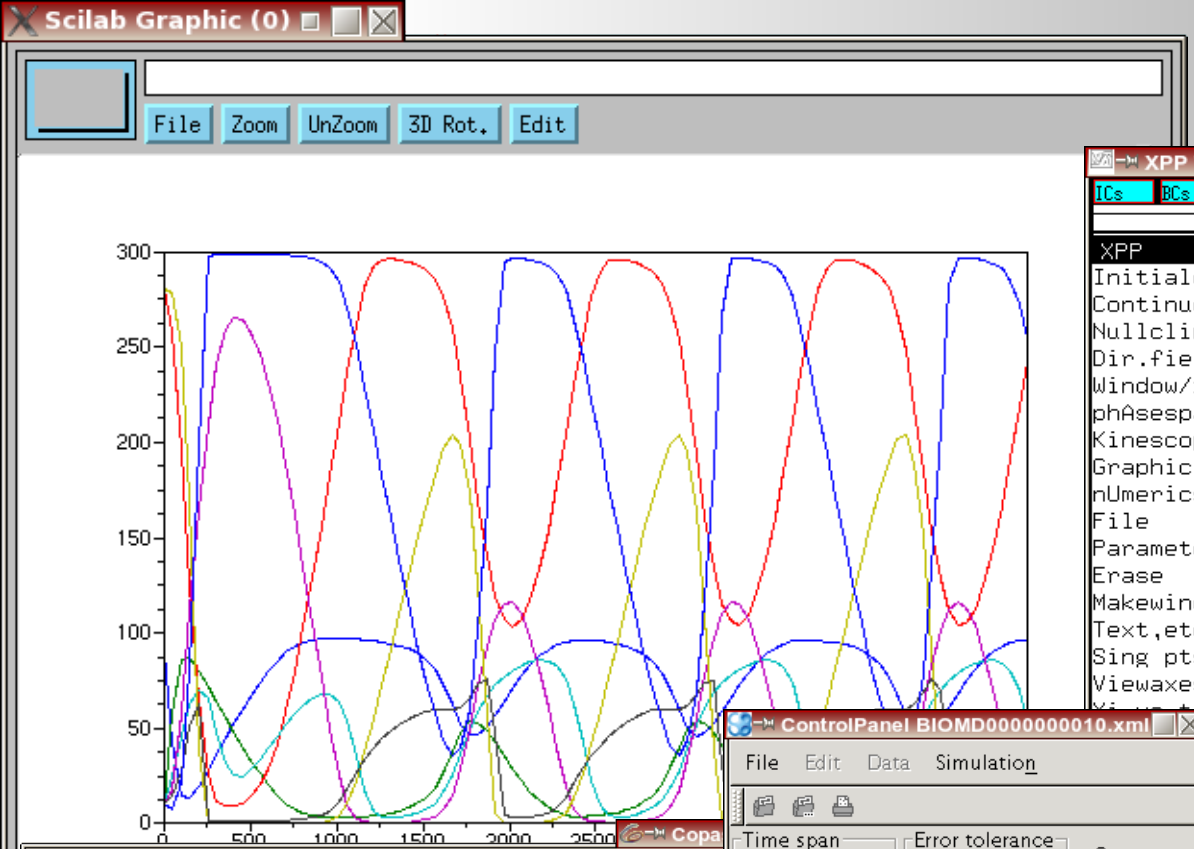
Species (8)

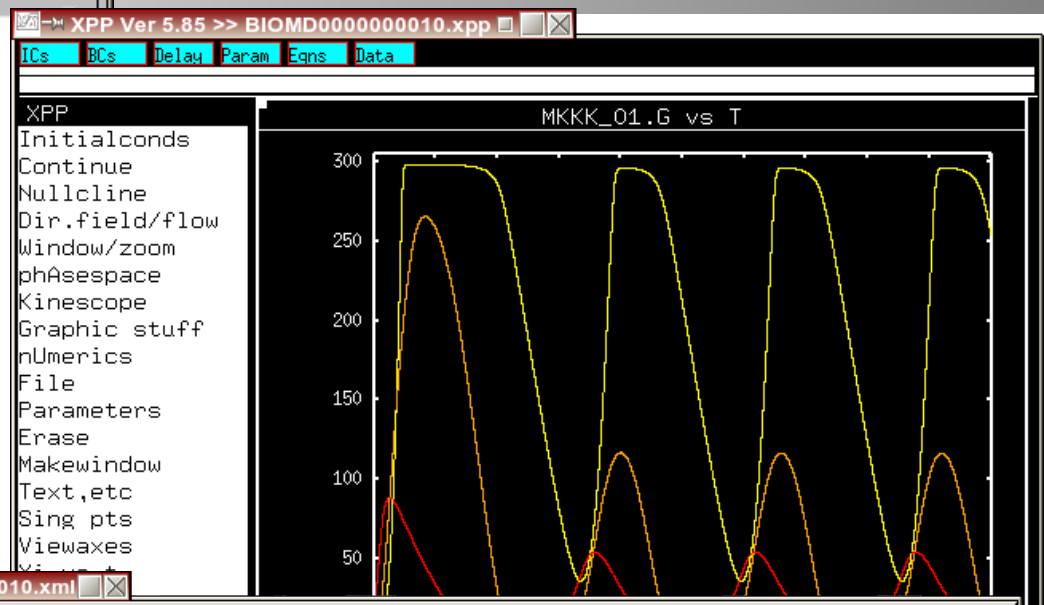
Rules (0)

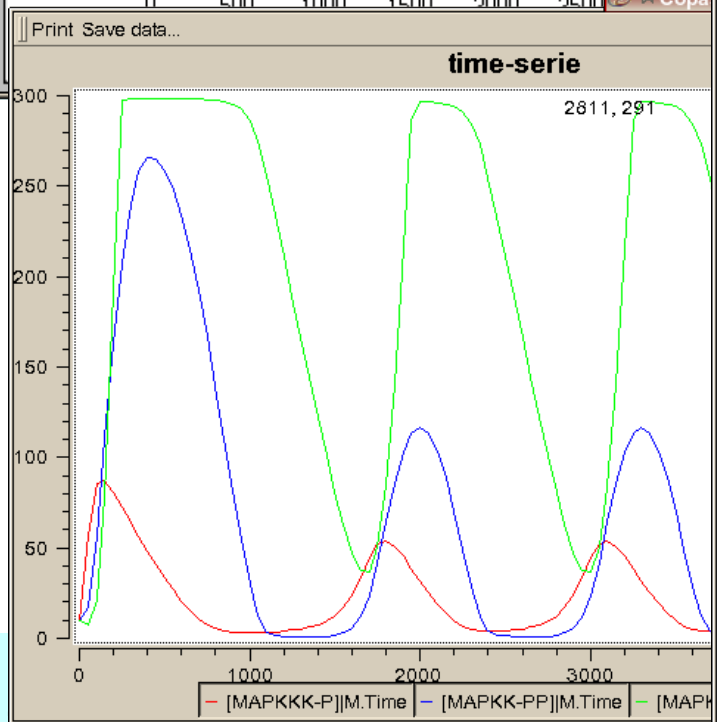
Reactions (10)

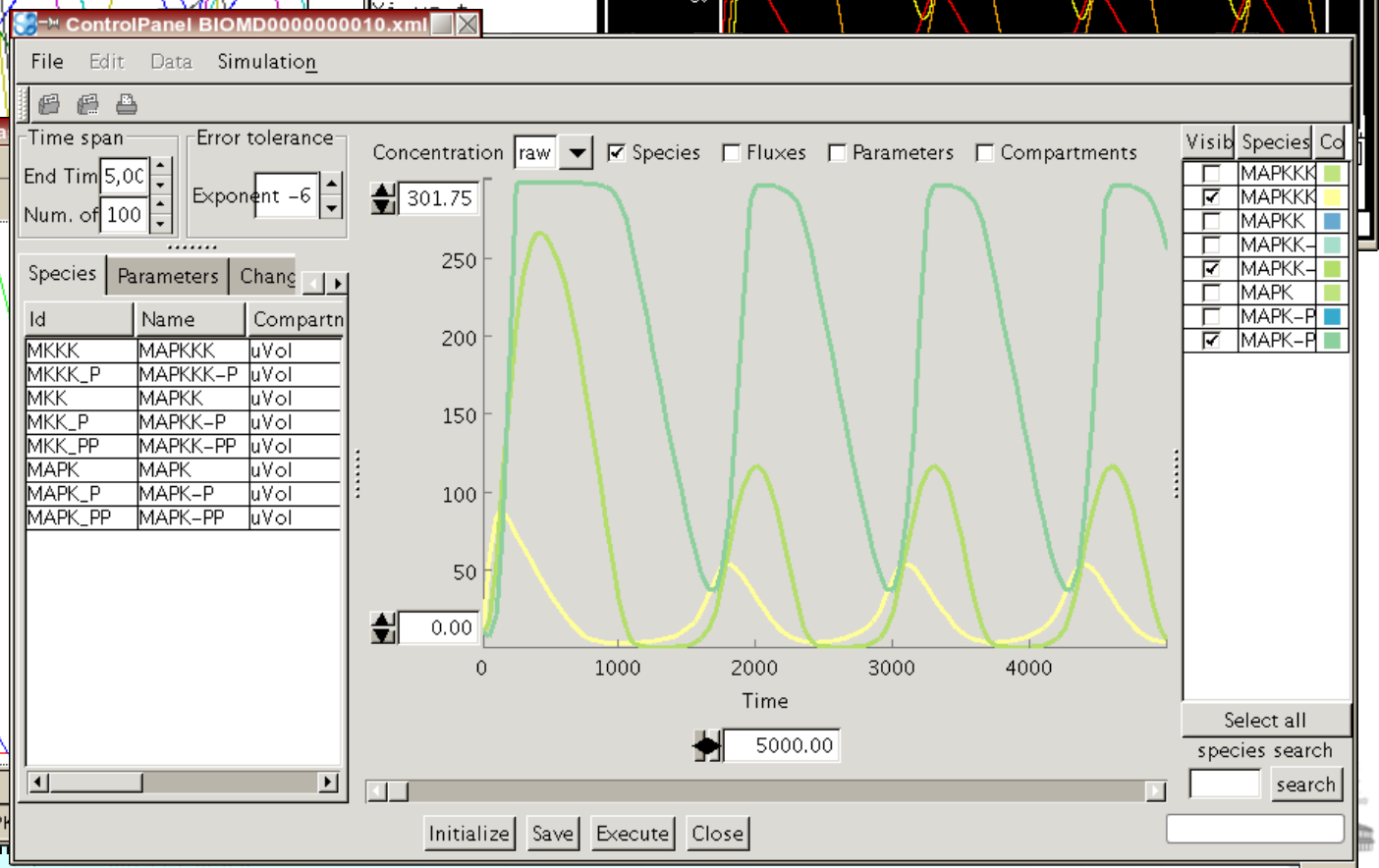
Events (0)

Kholodenko 2000









Where are the models coming from

I) Existing model repositories

- old SBML repository
- JWS Online
- Database Of Quantitative Cell Signalling
- CellML repository
- the Virtual Cell

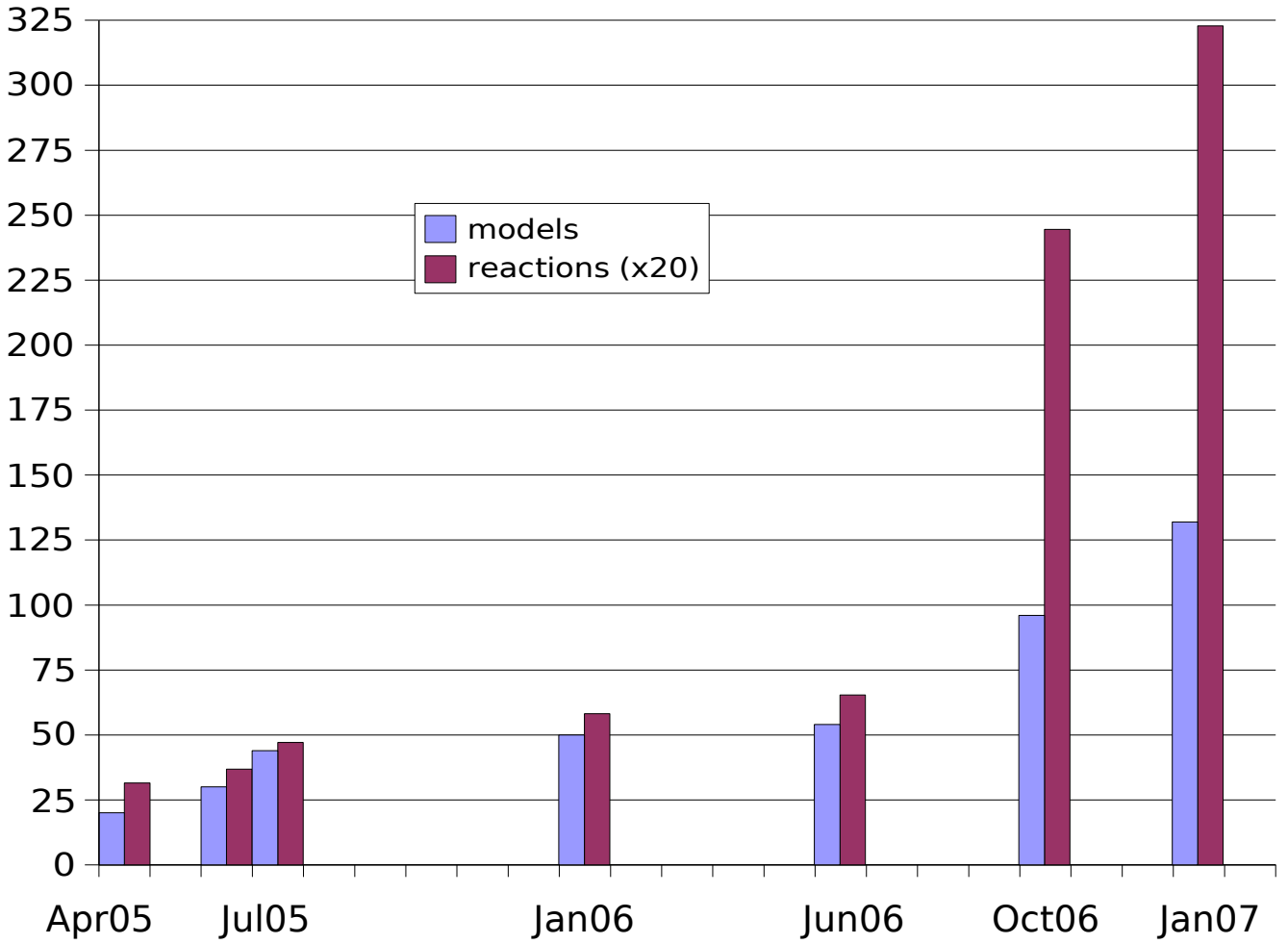
II) Individuals

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

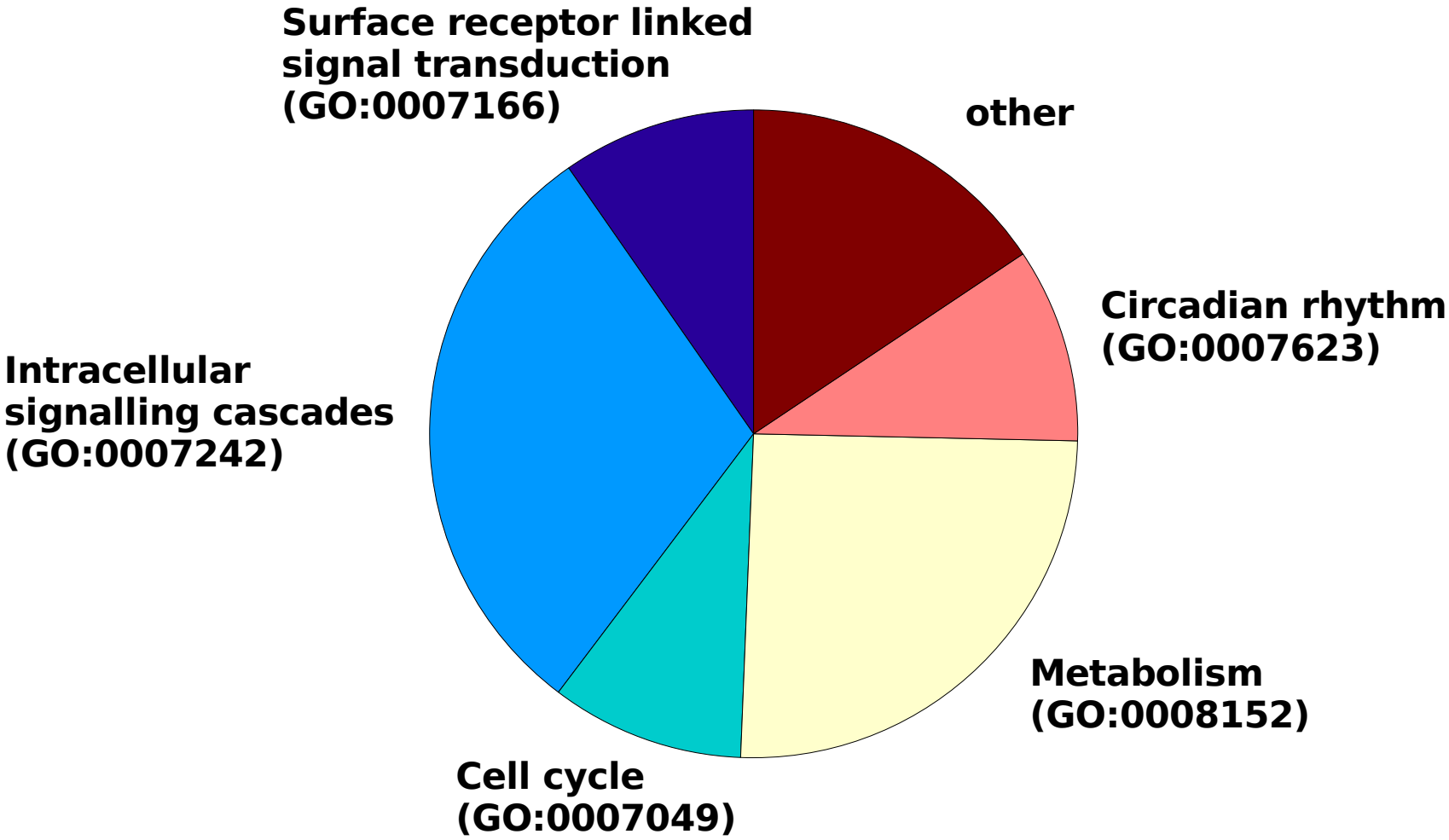
III) Journals (Molecular Systems Biology and PloS Computational Biology advise deposition)

IV) BioModels DB curators encode new models from literature

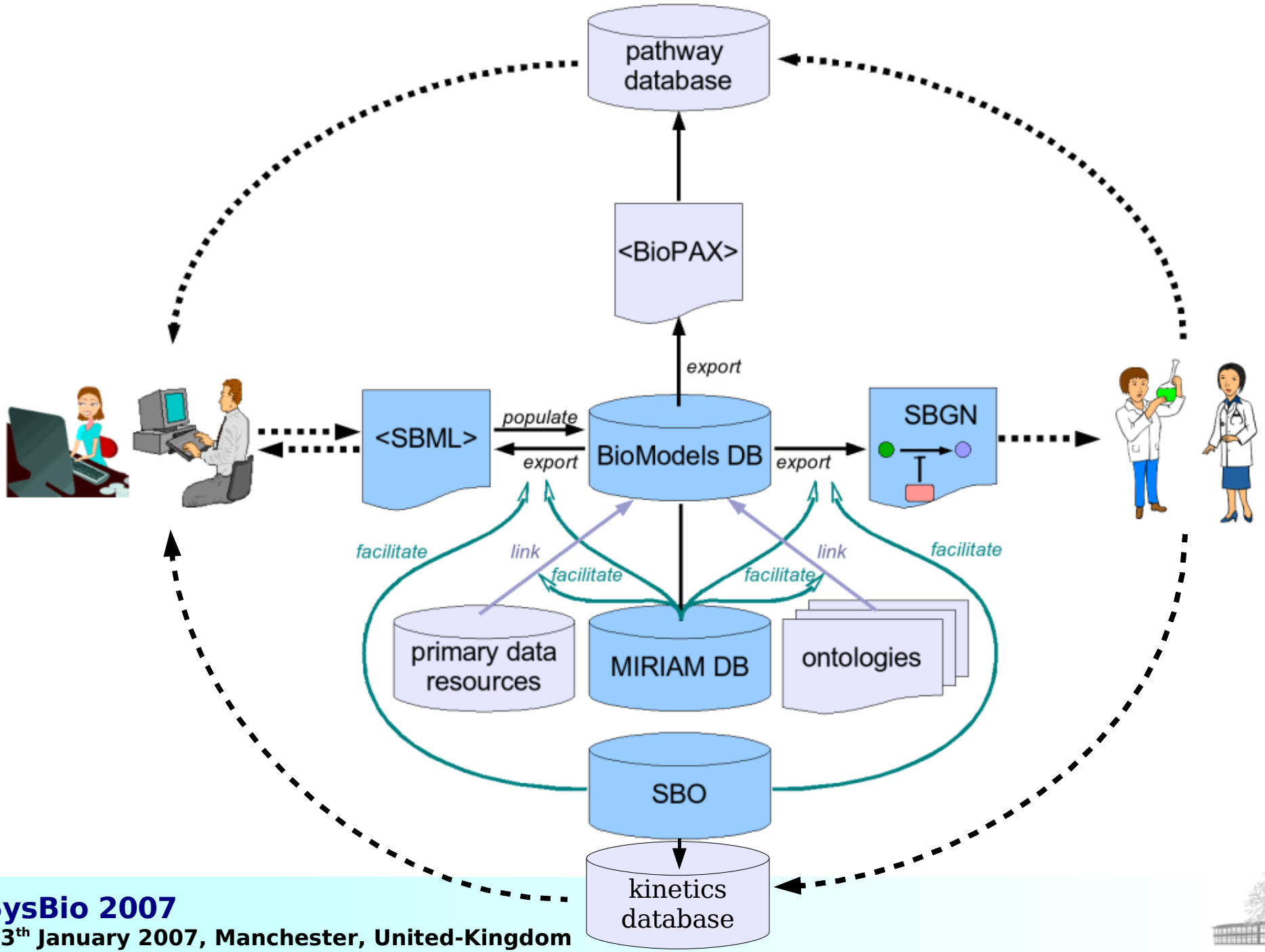
Steady increase



Topical repartition



Is the mosaic complete?



The BioModels.net team

Enuo He

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Harish Dharuri

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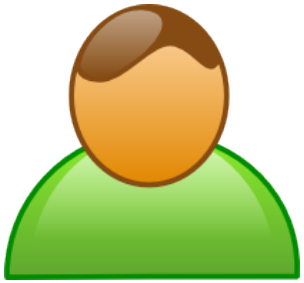
Chen Li

Rainer Machne



Camille Laibe

Melanie Courtot

Arnaud Henry

Nicolas Le Novère

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
  - Michael Hucka
  - Andrew Finney
  - Bruce Shapiro
  - Benjamin Borstein
  - Maria Schilstra
  - Sarah Keating
  - Harish Dharuri
- NCBS
  - Upinder Bhalla
  - 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.