Importance of standards and model exchange for Systems Neurobiology

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We need to reuse mathematical models

- As such
  - Non-specialists need to use models relevant for their research, directly with their simulation software without messing with their structure.
  - Modelling literates need to reuse existing models rather than rewrite them from scratch.
  - Various software used during the modelling process, such as graphical designers, simulation engines and plotters or renderers, should be able to communicate.

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  - Various software used during the modelling process, such as graphical designers, simulation engines and plotters or renderers, should be able to communicate.
- For integration purpose
  - Different approaches: time-series (continuous, discrete), MCA, FBA, logical descriptions etc.
  - Different spatial scales: nanometer (channel) to meter (axon)
  - Different real time scales: microsecond (channel opening) to weeks (LTP)
  - (Different simulation time scale: single-particle tracking to ODE)

Standard languages and ontologies

- We need to encode the models in a computer-edible way
  - Structured formats ➔ easily “parsable”; mirror the model structure;
  - Public formats ➔ Published specifications, freely re-usable
  - Community-developed formats ...
- We need to make the content human-edible
  - Standards of content and annotation
  - Ontologies
- We need to make the models available
  - Personal websites
  - Publisher's websites
  - Curated repository/databases

Encode the models in a computer-edible way

- Systems Biology Markup Language (SBML): A community maintained open XML standard to encode quantitative models of biological systems.

  http://sbml.org

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

- MIME type application/sbml+xml
  (RFC 3823 of the Internet Engineering Task Force)

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 90 software systems**, including the following (where '*' indicates SBML support in development):

BALSA
BASIS
BIOCHAM
BioCharon
biocyc2SBML
BioGrid
BioModels
BioNetGen
BioPathway Explorer
Bio Sketch Pad
BioSens
BioSPICE Dashboard
BioSpreadsheet
BioTapestry
BioUML
BSTLab
CADLIVE
CellDesigner
Cellerator
CellML2SBML
Cellware
CL-SBML
CLEML
COPASI
Cytoscape
DBsolve
Dizzy
E-CELL
ecellJ
ESS
FluxAnalyzer
Fluxor
Gepasi
INSILICO discovery
JACOBIAN
Jarnac
JDesigner
JigCell
JWS Online
Karyote*
KEGG2SBML
Kinsolver*
libSBML
MathSBML
MesoRD
MetaboLogica
MetaFluxNet
MMT2
Modesto
Moleculizer
Monod
Narrator
NetBuilder
Oscill8
PANTHER Pathway
PathArt
PathScout
PathwayLab
Pathway Tools
PathwayBuilder
PATIKAweb
PaVESy
PET
PNK
Reactome
ProcessDB
PROTON
pysbml
PySCeS
runSBML
SABIO-RK
SBML ODE Solver
SBMLeditor
SBMLmerge
SBMLR
SBMLSim
SBMLToolbox
SBIiD
SBToolbox
SBW
SCIpath
Sigmoid*
SigPath
SigTran
SIMBA
SimBiology
Simpathica
SimWiz
SloppyCell
SmartCell
SRS Pathway Editor
StochSim
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 community needs information standards if models are to be shared, evaluated and developed cooperatively. SBML's widespread adoption **offers many benefits**, including: (1) enabling the use of multiple tools without rewriting models for each tool

SBW 2.5.5 Released

(April 19, 2006) A new release of **SBW** (the Systems Biology Workbench) is now available. It features significant new capabilities and new modules.

read more

WebCell Supports SBML

(April 19, 2006) **WebCell** is a web-based simulation environment for biochemical networks. It supports exploration and analysis of steady-state and dynamic behaviors.

read more

SBML Hackathon 2006

(April 4, 2006) Visit the **SBML Hackathon 2006 page** for more info about the event happening this week in Nové Hrady, Czech Republic.

read more

Introducing CLEML

(March 21, 2006) The Carbon Labeling Experiment Markup Language (**CLEML**) annotates SBML with formal descriptions of structure and states of systems in carbon labeling experiments. A software library, libCLEML, is available.

read more

New SBML Online Validator!

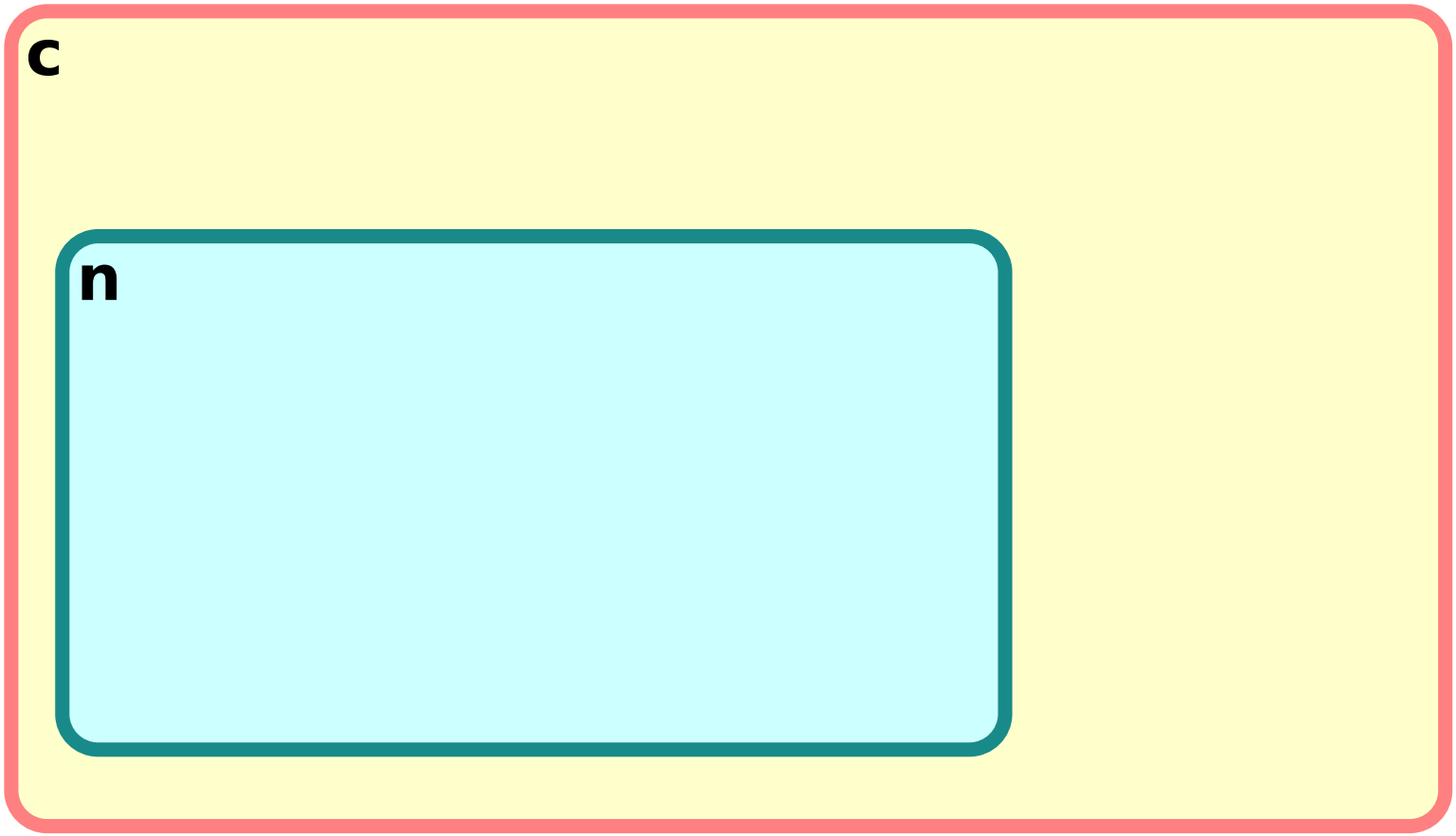
(March 6, 2006) SBML.org has a slick new online **SBML validator**, complete with remote API. Check it out!

read more

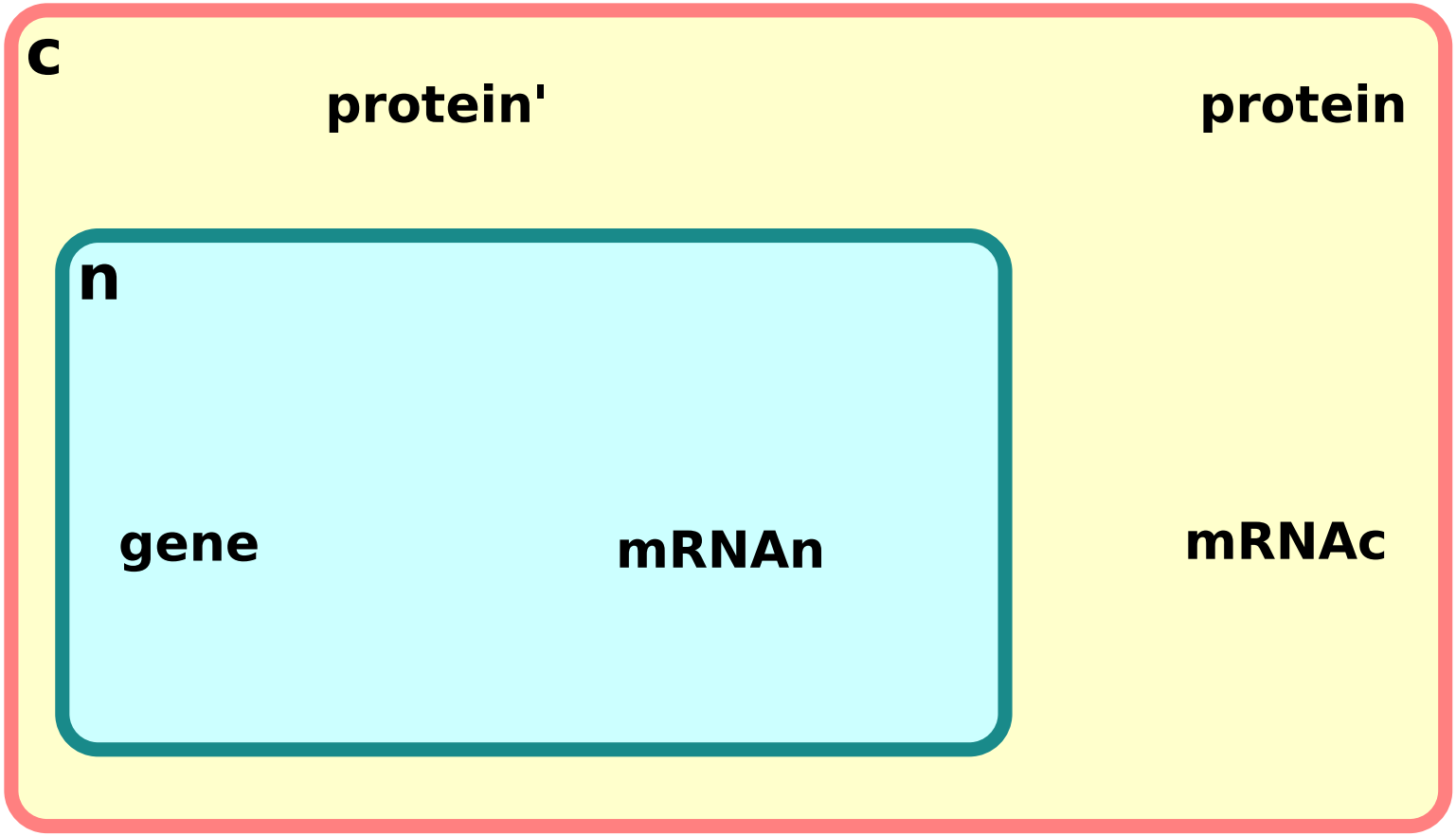
See older news items.

What can we encode in SBML?

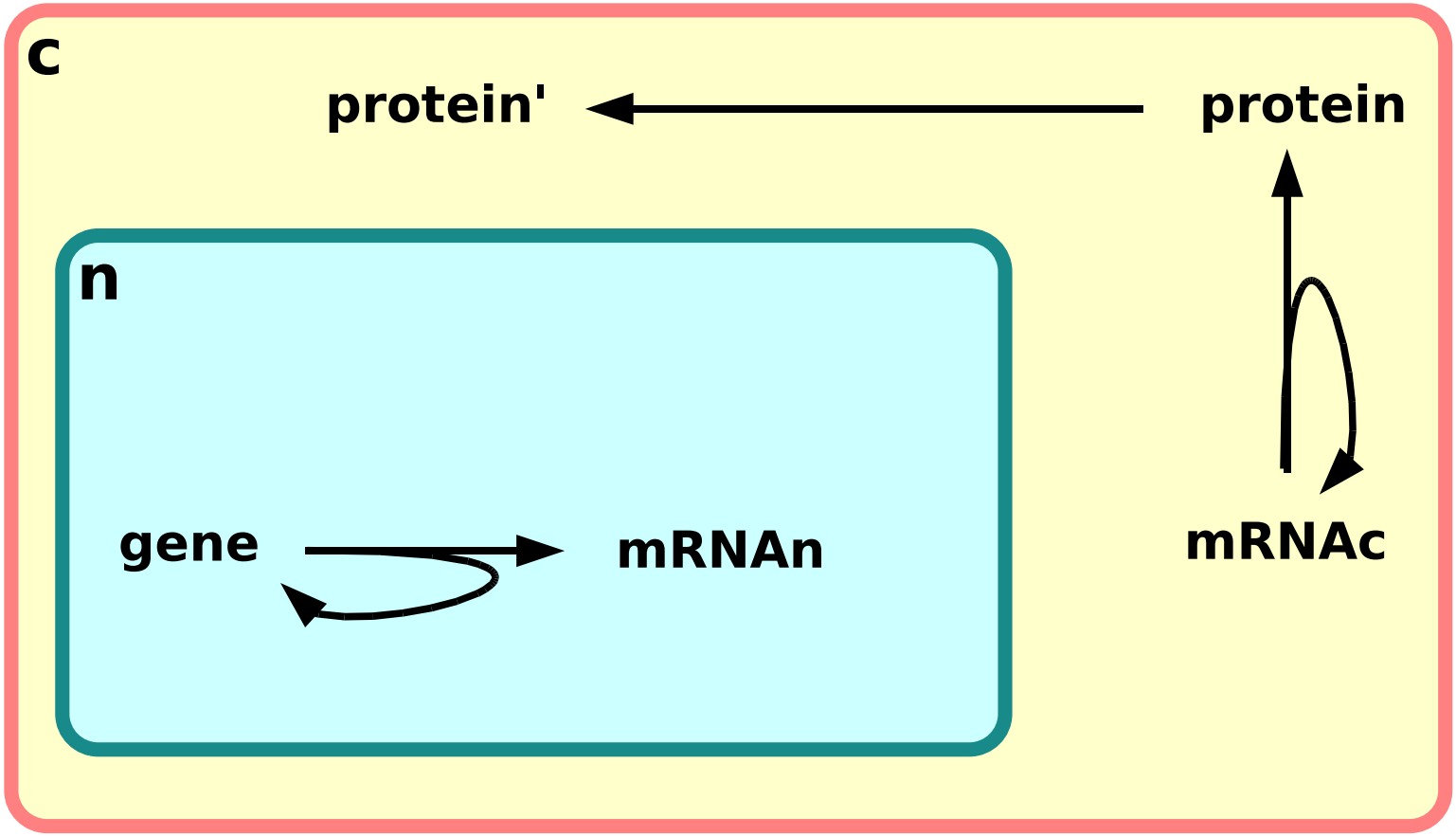
What can we encode in SBML?



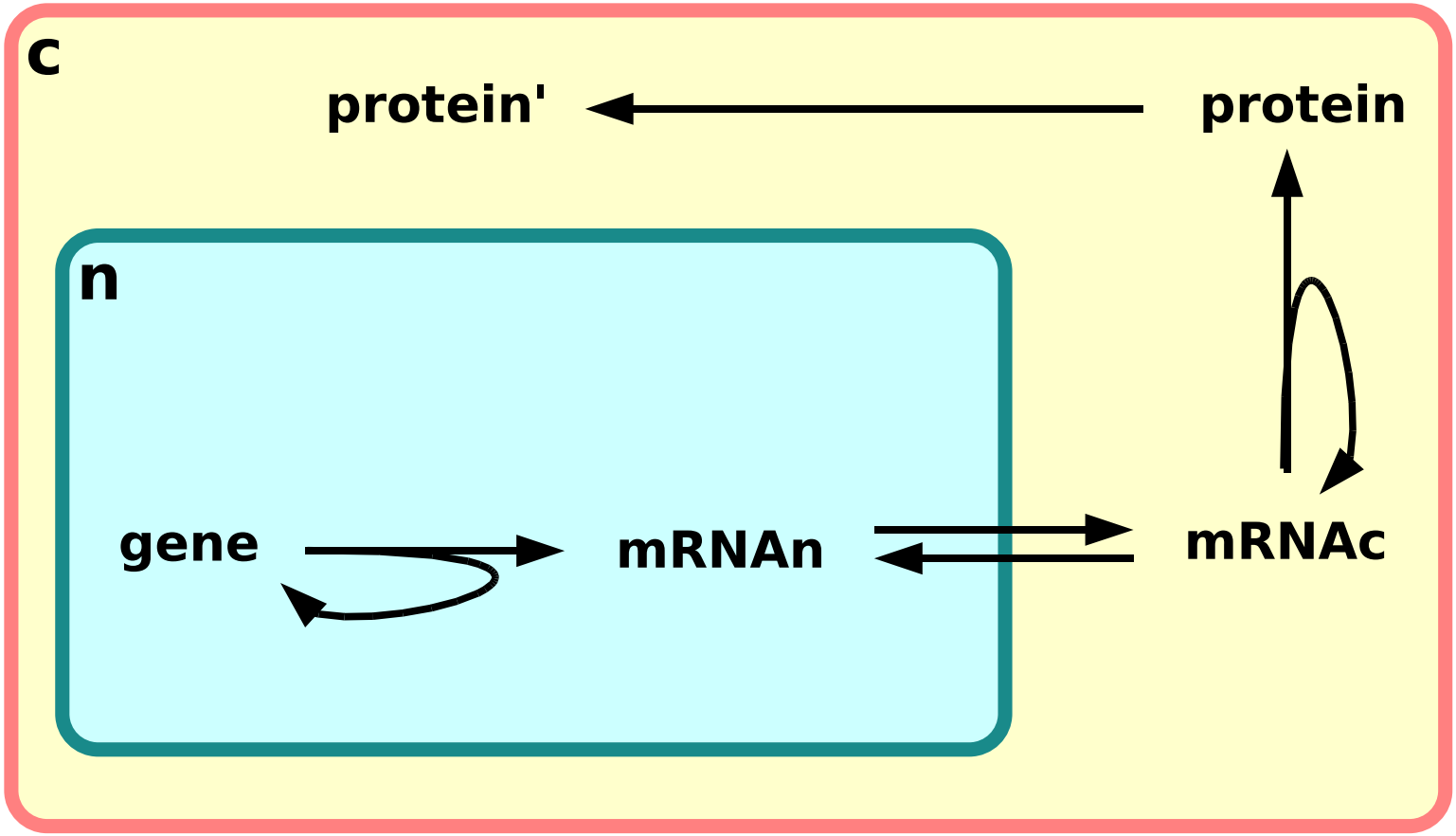
What can we encode in SBML?



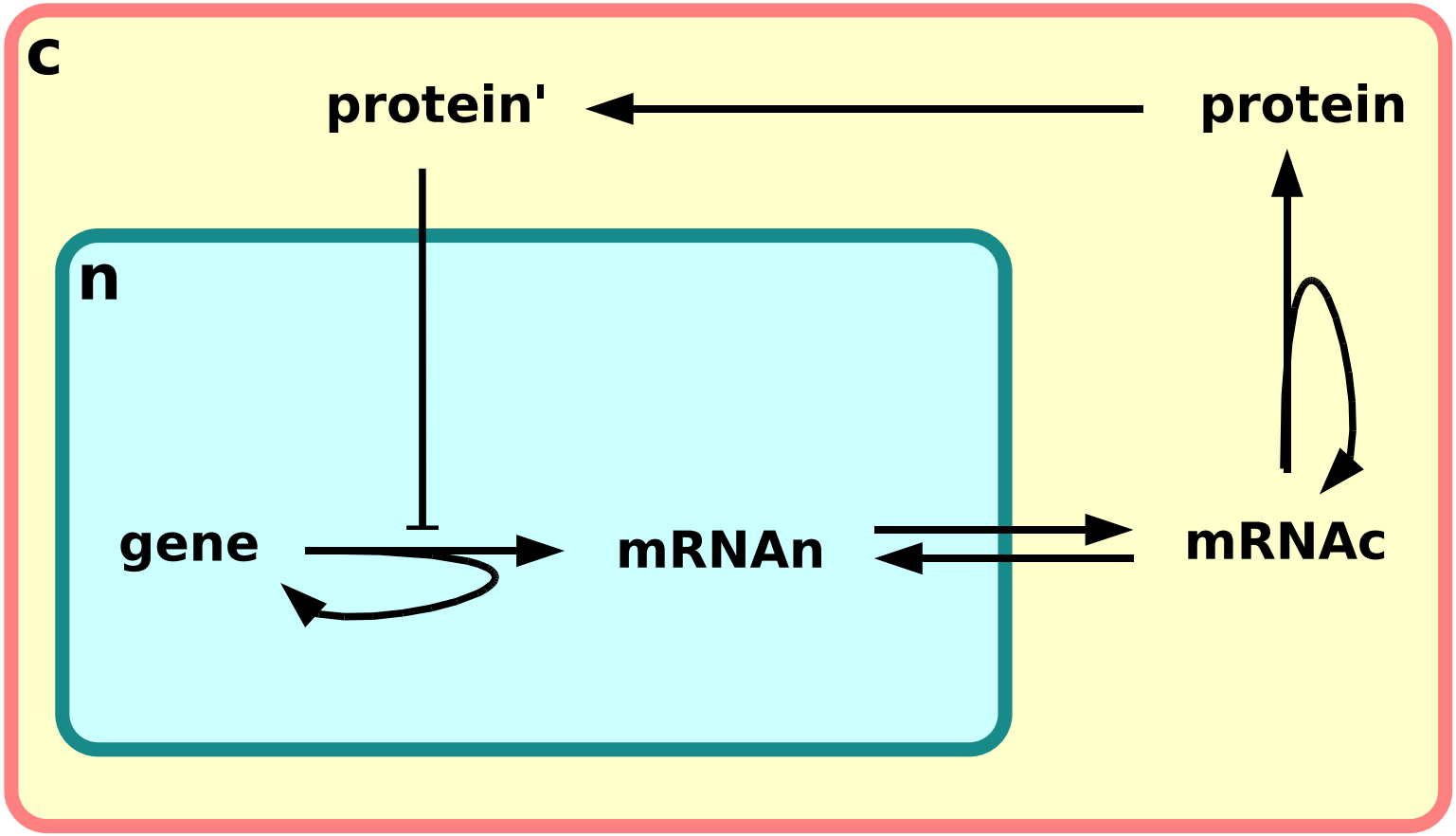
What can we encode in SBML?



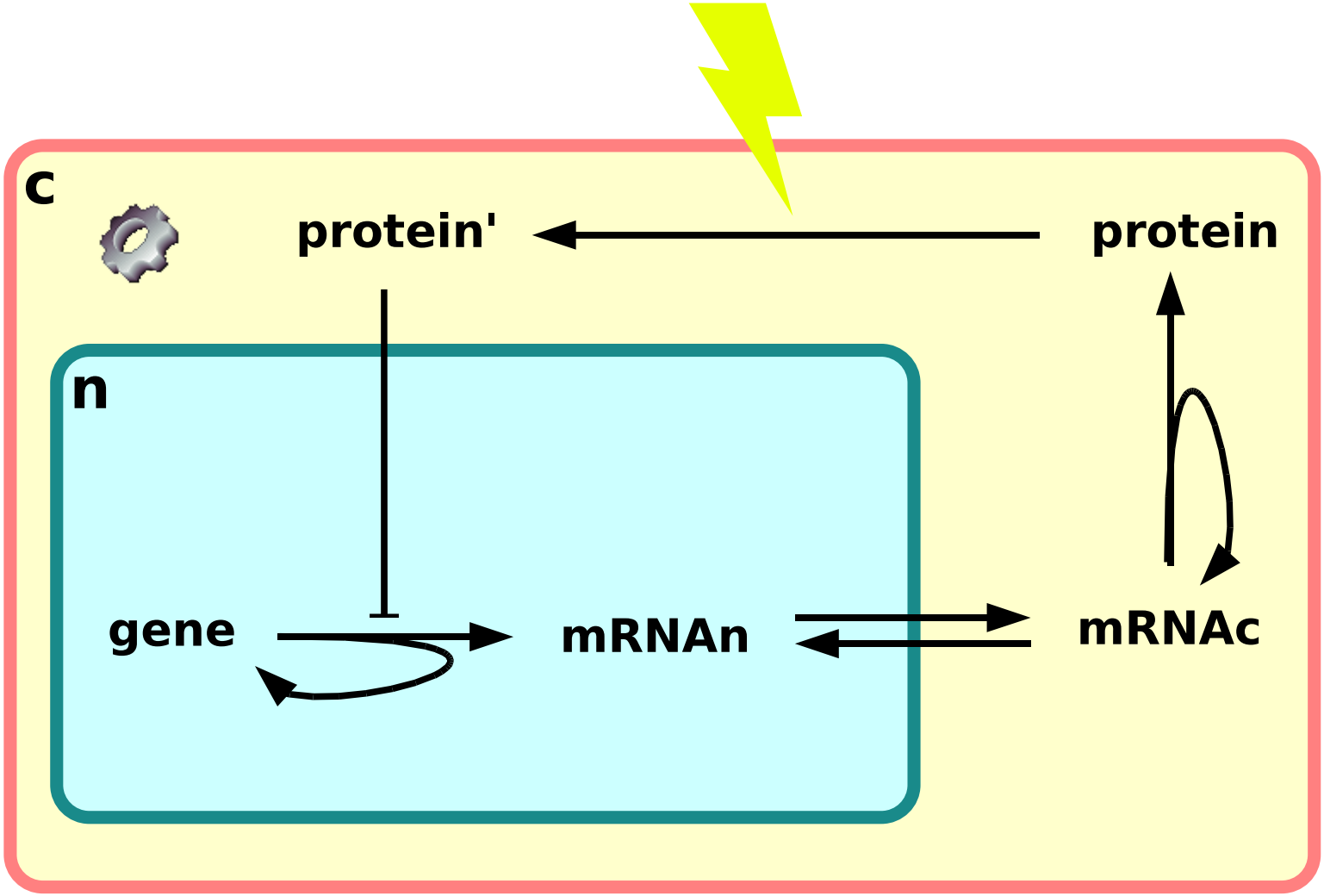
What can we encode in SBML?



What can we encode in SBML?



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>









  </model>
</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>




  </model>
</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>









  </model>
</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>









      </reaction>
    </listOfReactions>
  </model>
</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>









      </reaction>
    </listOfReactions>
  </model>
</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 a chemical species:
  - It can be a cell
  - It can be an organ
  - It can be an organism

➔ Systems Biology is scale-free!

SBML Level 2 Version 2

- Finalised on April 8th 2006
- Simpler and cleaner (units ...)
- Generics (compartmentType, speciesType)
  ➔ path to generalised reactions
- Constraints and initialAssignments
- Backward compatible with Level 2 Version 1
- More detailed and bug-free specification ... 128 pages

SBML Level 3

- Modular SBML, with core + optional packages (Not certain, but necessary IMHO)
- Generalised reactions
- Graph Layout (certain; already in use in Level 2 as annotation, shared by several software)
- Model composition (probable)
- Complex species (probable)
- Arrays or sets (maybe)
- Geometry (maybe)
- ???

Related efforts

- 

http://www.cellml.orl/

  Fixed specification; Based on modules; scalable; ... complex

- 

http://www.neuroml.org/

  Flexible (expendable set of schemas); scalable;

- BrainML.org http://brainml.org/

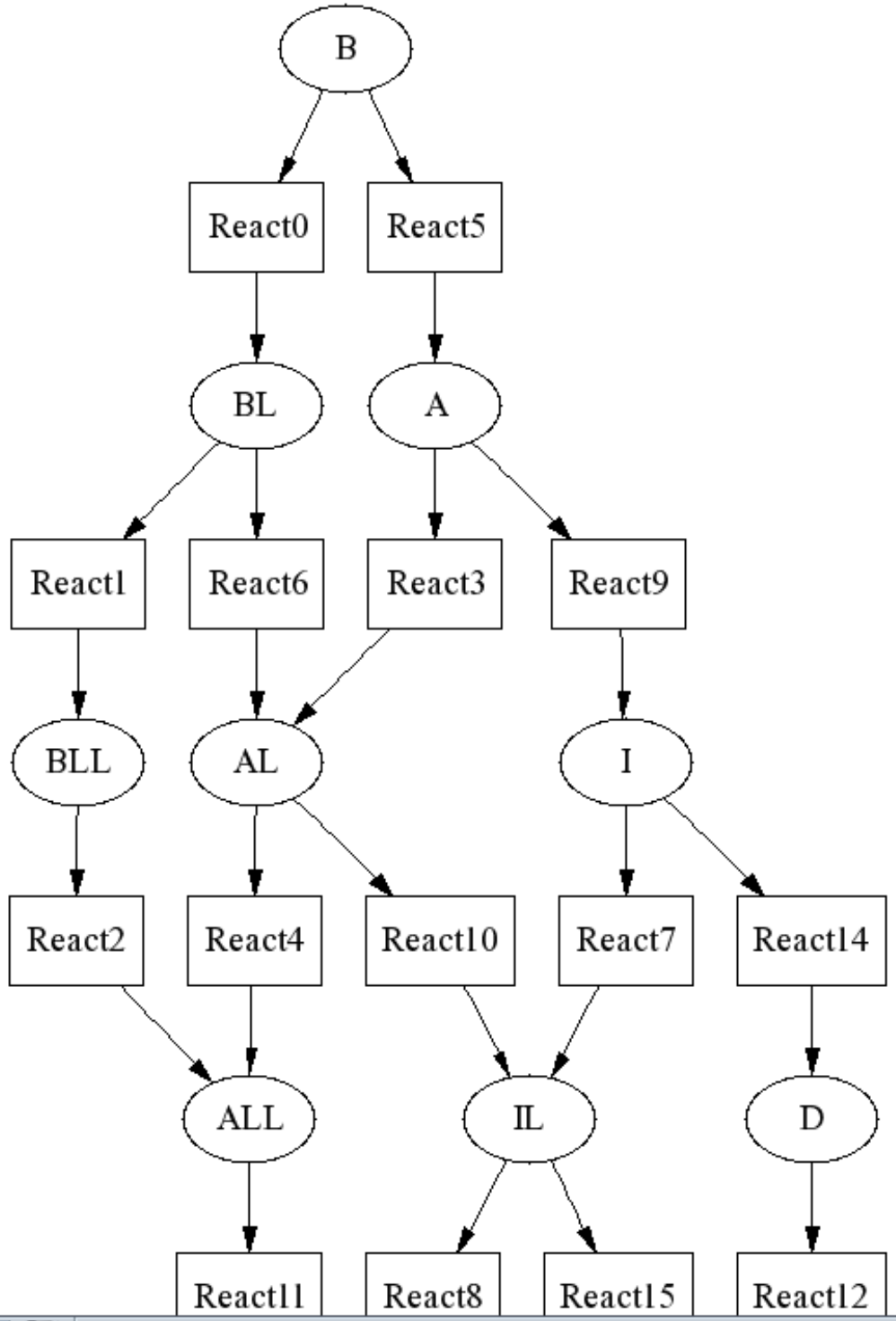
  Models are XML-schemas

- BioPAX http://www.biopax.org/

  No kinetics; deep semantics;

Systems Biology Markup Language - Diagram of EPSP_AChDynValue_SBML2.xml - Mozilla

No, it isn't!



BIOMODELS.NET

The Next Step After Standard Formats

For computational modeling to become more widely used in biological research, researchers must be able to exchange and share their results. The development and broad acceptance of common model representation formats such as **SBML** is a crucial step in that direction, allowing researchers to exchange and build upon each other's work with greater ease and accuracy.

The BioModels.net project is another step: an international effort to (1) define agreed-upon standards for model curation, (2) define agreed-upon vocabularies for annotating models with connections to biological data resources, and (3) provide a free, centralized, publicly-accessible database of annotated, computational models in SBML and other structured formats.

Helping to Define Community Standards

To facilitate assembling useful collections of quantitative models of biological phenomena, it is crucial to establish standards for the vocabularies used in model annotations as well as criteria for minimum quality levels of those models. The BioModels.net project aims to bring together a community of interested researchers to address these issues. We are working towards defining these standards through white papers and process definitions. All of the products of our efforts are open and freely available through this site.

Standards and Processes Developed Hand-in-Hand with a New Database

The database component of BioModels.net is especially designed for working with *annotated* computational models: each model is carefully reviewed and augmented by human annotators on the BioModels.net team to add metadata linking the model elements to other biological databases and resources. The **BioModels database at the EBI** system goes far beyond other collections of models by being a *true* database, featuring browsing, cross-referencing, searching, and (coming soon) facilities for visualization, exporting models in different formats, and remote API access.

EMBL-EBI

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)

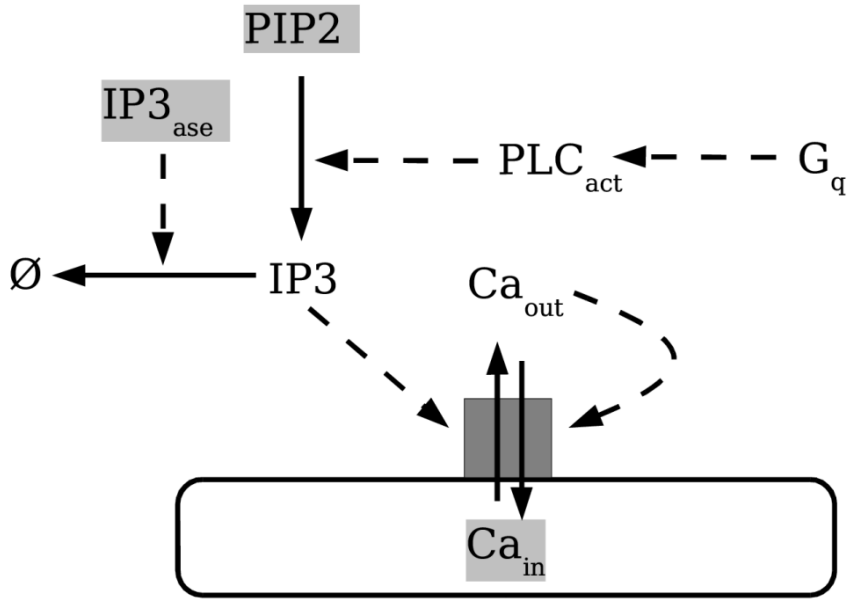
Attribution annotation

- 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 data-type should be written as a Unique Resource Identifier (URI). Either a URL (webpage) or a URN (e.g. LSID). Not necessarily a physical location.
  - The identifier is analysed by the software within the framework of the data-type.
  - Data-type and Identifier can be combined in a single URI
    http://www.myResource.org/#myIdentifier
    urn:lsid:myResource.org:myIdentifier
  - Qualifiers (optional) should refine the link between the model constitutent and the piece of knowledge: “has a”, “is version of”, “is homolog to” etc.
- The community will have to agree on a set of standard valid URIs. A database and the associated API (WebServices) are currently in development at the EBI.

Model example



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

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

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

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

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

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

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

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

creators	Joe User (juser@eden.com), Anne Other (aother@eden.com)
creation date	01 January 0000
last modification	31 May 2005

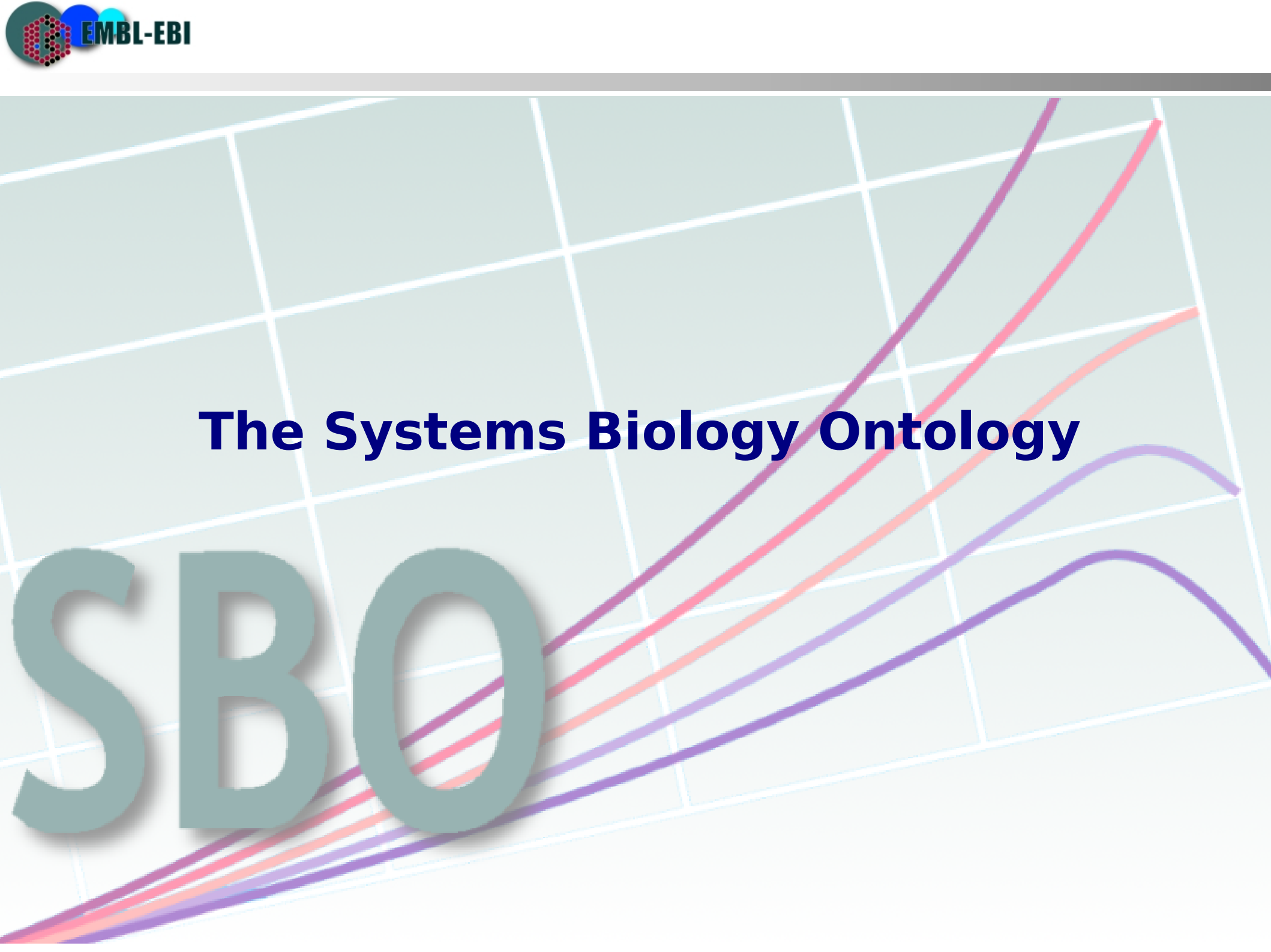
Constituent	Data Type	Identifier	Qualifier	Meaning
model	http://www.pubmed.gov/	0000000		
	http://www.ncbi.nlm.nih.gov/Taxonomy/	9606		*Homo sapiens*
	http://www.geneontology.org/	GO:0007204	IsVersionOf	*positive regulation of cytosolic [ca^{2+}]*
	http://www.geneontology.org/	GO:0051279	IsVersionOf	*regulation of release of sequestered ca^{2+} 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+)*
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.ebi.ac.uk/intenz/	3.1.4.11	IsVersionOf	*phosphoinositide phospholipase C*
reaction $IP3_{degradation}$	http://www.ebi.ac.uk/intenz/	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*

creators	Joe User (juser@eden.com), Anne Other (aother@eden.com)
creation date	01 January 0000
last modification	31 May 2005

What is common?

Constituent	Data Type	Identifier	Qualifier	Meaning
model	http://www.pubmed.gov/	0000000		
	http://www.ncbi.nlm.nih.gov/Taxonomy/	9606		*Homo sapiens*
	http://www.geneontology.org/	GO:0007204	IsVersionOf	*positive regulation of cytosolic [ca^{2+}]*
	http://www.geneontology.org/	GO:0051279	IsVersionOf	*regulation of release of sequestered ca^{2+} 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+)*
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.ebi.ac.uk/intenz/	3.1.4.11	IsVersionOf	*phosphoinositide phospholipase C*
reaction $IP3_{degradation}$	http://www.ebi.ac.uk/intenz/	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*

The Systems Biology Ontology



Hidden assumptions

- $E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_p} E+P$; Rapid equilibrium

  Henri-Michaelis-Menten: $$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])} ; K_m = \frac{k_{-1}}{k_1}$$

- $E+S \xrightarrow{k_1} ES \xrightarrow{k_p} E+P$; Total duration equal sum of duration

  Van Slyke-Cullen: $$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])} ; K_m = \frac{k_p}{k_1}$$

- $E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_p} E+P$; Quasi-steady state

  Briggs-Haldane: $$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])} ; K_m = \frac{(k_{-1} + k_p)}{k_1}$$

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>
```

$$E+S \rightarrow E+P$$

Import in a discrete simulator

?

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

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

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

Some definitions

- ## Controlled Vocabularies

- "Organized lists of words and phrases, or notation systems, that are used to initially tag content, and then to find it through navigation or search." *Amy J. Warner. A Taxonomy Primer.* `http://www.lexonomy.com/publications/aTaxonomyPrimer.html`

- "A set of codes, managed by some authority (eg a person or an organisation), employing some mechanism". Misha Wolf on *IPTC internal developer forum for the News Metadata Framework WG*

- "An indexed dictionary". *Nicolas Le Novère. This presentation.*

- ## Ontology

- "(Computers) A systematic arrangement of all of the important categories of objects or concepts which exist in some field of discourse, showing the relations between them. When complete, an ontology is a categorization of all of the concepts in some field of knowledge, including the objects and all of the properties, relations, and functions needed to define the objects and specify their actions. A simplified ontology may contain only a **hierarchical** classification (a **taxonomy**)" *The Collaborative International Dictionary of English v.0.48*

- A set of controlled vocabularies with defined relationships between terms. *Nicolas Le Novère. This presentation.*

Classifications Vs. Ontologies

- Each term is associated to a perennial identifier. Once created a term is never destroyed. It can be merged with other, 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

- A taxonomy of the roles of reaction participants, including the following terms: “substrate”, “catalyst” etc.

- A CV for parameter roles in quantitative models. This CV includes terms like “Michaelis constant” , “forward unimolecular rate constant”etc.

- A classification of rate laws. This CV is a taxonomy of kinetic rate equations. Examples of terms in this CV 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.

- A list of modelling framework to precise how to interpret the rate-law. E.g. “continuous modelling”, “discrete modelling” etc.

SBO term

id	SBO:\d{7}	minOccurs=1	maxOccurs=1
name	unicode string	minOccurs=1	maxOccurs=1
def	unicode string	minOccurs=0	maxOccurs=1
is_a	SBO:\d{7}	minOccurs=0	minOccurs=n
part_of	SBO:\d{7}	minOccurs=0	maxOccurs=1
synonyms	unicode string	minOccurs=0	minOccurs=n
mathml	MathML lambda function	minOccurs=0	maxOccurs=1

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Computational Neurobiology

SBO Ontology Browser

SBO::Systems Biology Ontology

- sbo
  - rate law
    - mass action kinetics
    - kinetics of unireactant enzymes
      - Henri-Michelis Menten equation
      - Van Slyke-Cullen equation
      - Briggs-Haldane equation
    - obsolete rate law
  - quantitative parameter
    - kinetic constant
    - Michaelis constant
    - obsolete parameter
  - participant role
    - reactant
    - product
    - modifier
    - obsolete species role
  - modelling framework
    - continuous framework
    - discrete framework
    - obsolete modelling framework

SBO:0000029 Henri-Michelis Menten equation

Definition

First general rate equation for reactions involving enzymes, it was presented in "V. Henri. Lois Générales de l'Action des Diastases. Paris, Hermann, 1903.". The reaction is assumed to be made of a reversible of the binding of the substrate to the enzyme, followed by the breakdown of the complex generating the product. Ten years after Henri, Michaelis and Menten presented a variant of his equation, based on the hypothesis that the dissociation rate of the substrate was much larger than the rate of the product generation. Leonor Michaelis, Maud Menten (1913). Die Kinetik der

MathML

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
   <lambda>
     <bvar><ci
definitionURL="http://biomodels.net/SBO/SBO:0000025">kcat</ci></bvar>
     <bvar><ci
definitionURL="http://biomodels.net/SBO/SBO:0000014">Et</ci></bvar>
     <bvar><ci
definitionURL="http://biomodels.net/SBO/SBO:0000015">S</ci></bvar>
```

Comment

Parent(s)

SBO:0000028 kinetics of unireactant enzymes (is a)

Complete description of a rate-law term

```
[Term]
id: SBO:0000031
name: Briggs-Haldane equation
def: "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.
is_a: SBO:0000011 ; kinetics of unireactant enzymes
MathML: <math xmlns="http://www.w3.org/1998/Math/MathML">
      <lambda>
      <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000015">S</ci></bvar>
      <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000014">E</ci></bvar>
      <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000025">kp</ci></bvar>
      <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000008">Km</ci></bvar>
         <apply>
           <divide/>
           <apply>
             <times/><ci>E</ci><ci>kp</ci><ci>S</ci>
           </apply>
           <apply>
             <plus/><ci>Km</ci><ci>S</ci>
           </apply>
         </apply>
       </lambda>
    </math>
```

New SBML attribute: sboTerm

- syntax: <elementX sboTerm=”SBO:ddddddd” >
- present in:
  - model
  - initialAssignment (new element of L2V2)
  - rule
  - constraint (new element of L2V2)
  - reaction
  - speciesReference and modifierSpeciesReference
  - kineticLaw
  - parameter

Revealed assumptions

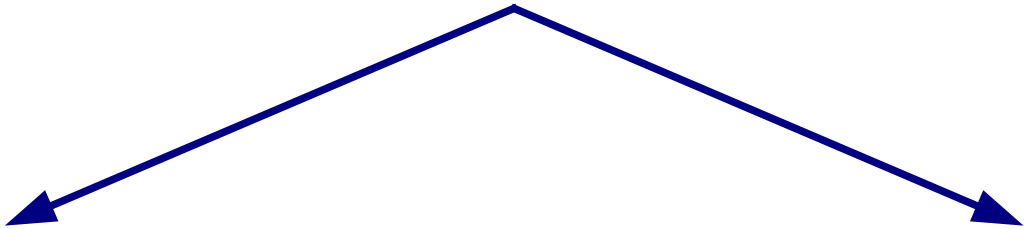
```
<reaction>
   <listOfReactants>
     <speciesReference species="S" />
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="P" />
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="E" />
   </listOfModifiers>
   <kineticLaw sboTerm="SBO:0000031">
     <listOfParameters>
       <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>
```

Revealed assumptions

```
<reaction sboTerm="SBO:0000062">
   <listOfReactants>
     <speciesReference species="S" sboTerm="SBO:0000015"/>
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="P" sboTerm="SBO:0000011"/>
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="E" sboTerm="SBO:0000014"/>
   </listOfModifiers>
   <kineticLaw sboTerm="SBO:0000031">
     <listOfParameters>
       <parameter id="Km" sboTerm="SBO:0000008"/>
       <parameter id="kp" sboTerm="SBO:0000025"/>
     </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>
```

Automatic conversion

```
<reaction sboTerm="SBO:0000062">
   <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>
```



continuous simulator

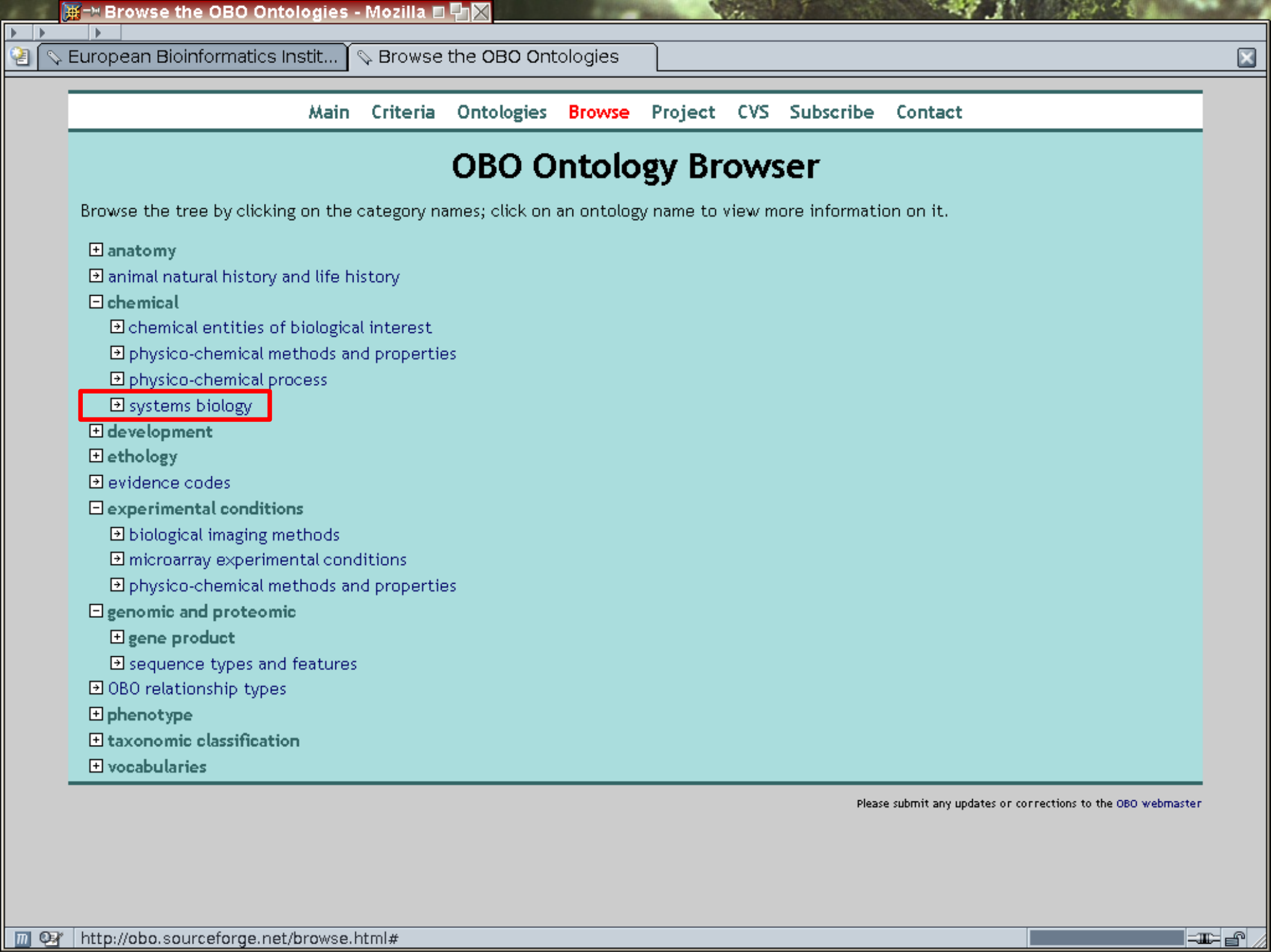
$$v = \frac{C \cdot V \cdot [A]}{(U + [A])}$$

discrete simulator

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

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

$$v3 = V \cdot [D]$$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Browse the OBO Ontologies
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OBO Ontology Browser
Browse the tree by clicking on the category names; click on an ontology name to view more information on it.
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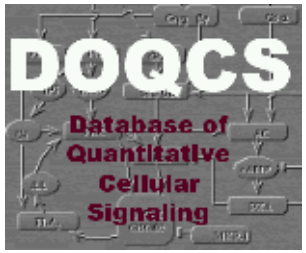
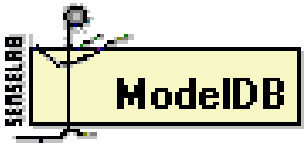
animal natural history and life history
chemical
chemical entities of biological interest
physico-chemical methods and properties
physico-chemical process
systems biology
development
ethology
evidence codes
experimental conditions
biological imaging methods
microarray experimental conditions
physico-chemical methods and properties
genomic and proteomic
gene product
sequence types and features
OBO relationship types
phenotype
taxonomic classification
vocabularies
Please submit any updates or corrections to the OBO webmaster
http://obo.sourceforge.net/browse.html#

Models repositories for modelling neurons

- 

[GENESIS][curation][search]
- 

models repository [CellML][curation...][search]
- JWS online [SBML, Pysces][curation]
- 

of SenseLab [NEURON, GENESIS]
- 

Developer Network [E-Cell, SBML]
- **+ ...**

Requirements for a unified model resource

- Not focussed on a particular biological substrate or process nor specialised on a given modelling approach
- Real database rather than repository
- Thoroughly curated and annotated
- International collaboration rather than a one-group effort
- Long-term commitment and 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

What is BioModels Database

- Store and serve quantitative models of biomedical interest
- BioModels Database goes further than MIRIAM: 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.

Where are the models coming from

I) Repositories

- SBML repository
- JWS Online
- E-Cell Developer Network
- CellML repository

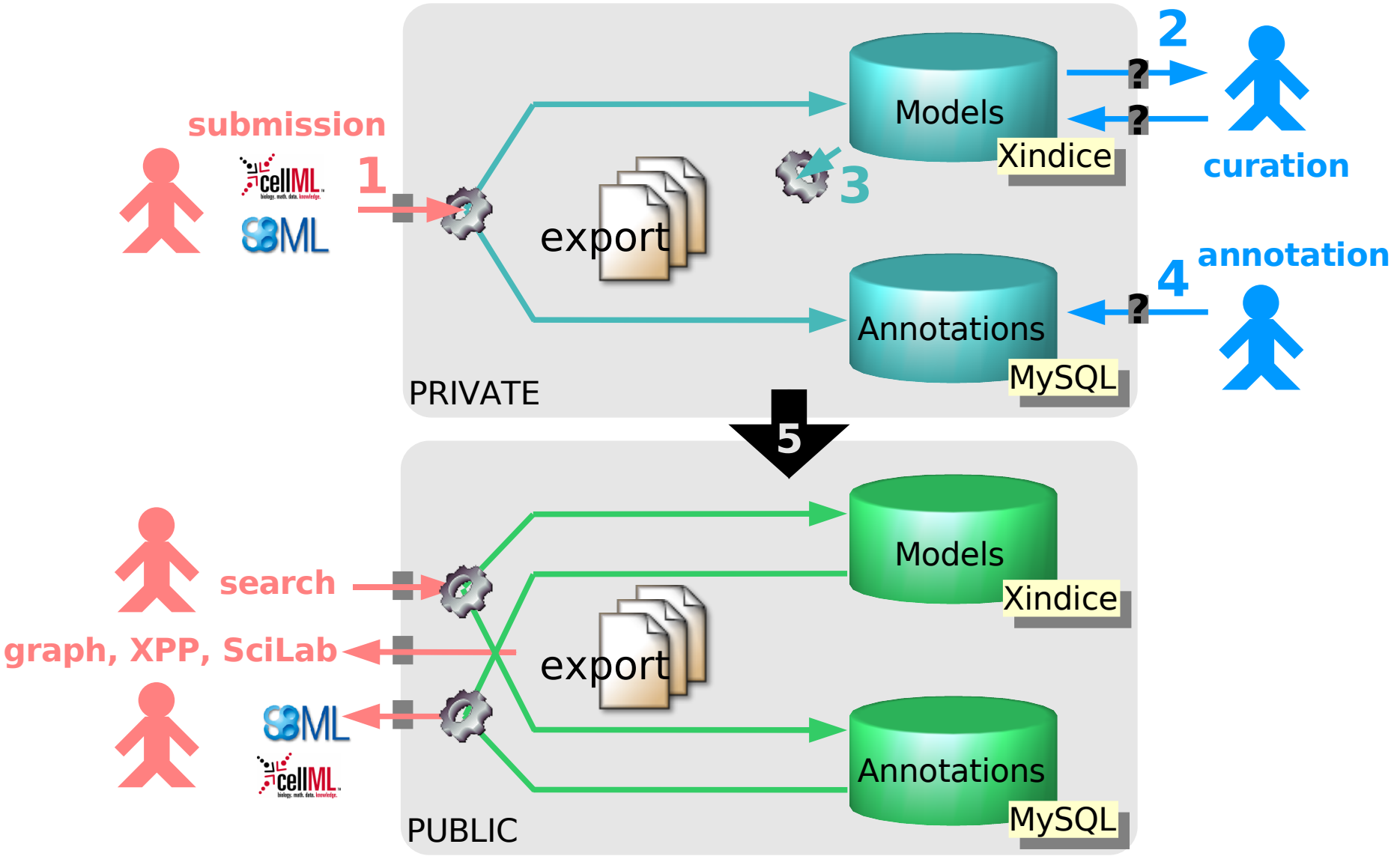
II) Individuals

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

III) Supported by Nature Publishing Group. MSB advices deposition, and forward supplementary material

IV) BioModels DB curators encode new models from literature

Structure of BioModels Database



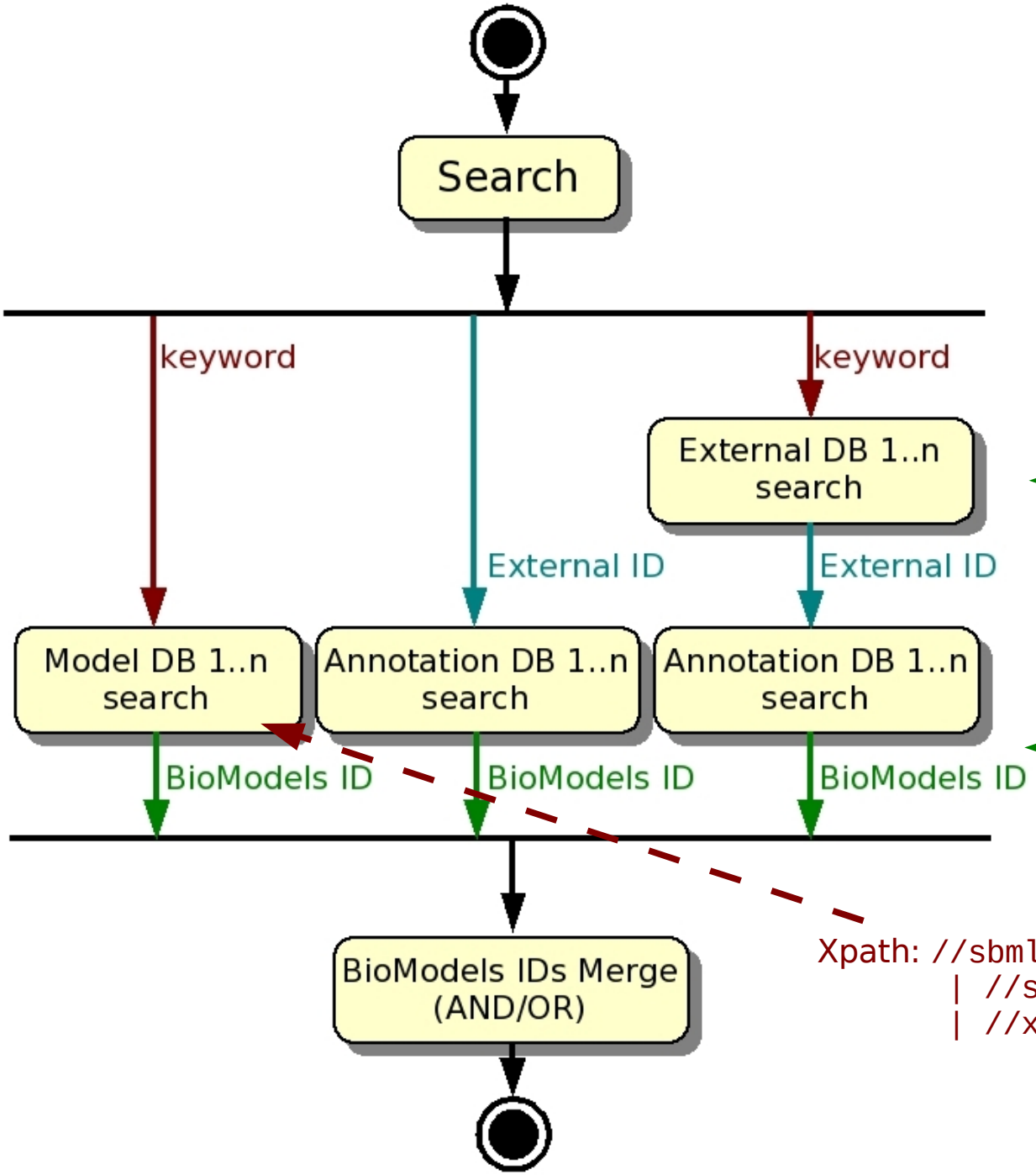
Detailed pipeline

1) Non-authenticated submission: SBML or CellML
   - Annotation in the model (<notes>, <annotation>)
   - Annotation entered through submission form
2) [Transformation into SBML Level 2 Version 1]
3) XML schema validation
4) Consistency check
5) Generation of export formats (SBML, CellML, SciLab, XPP, dot)
6) Authenticated semantic curation (correspondence with paper)
7) 3 to 5 again
8) Authenticated annotation

Model annotation

model	Submitter, Creators, publication, Gene Ontology, ICD10, KEGG pathway, OMIM, Reactome, Taxonomy
compartment	Gene Ontology
species	BIND complex, ChEBI, Ensembl, Gene Ontology, InterPro, KEGG compound, OMIM, Taxonomy, UniProt
rule	BIND interaction, EC code, Gene Ontology, IntAct, KEGG pathway, KEGG Reaction, Reactome
reaction	BIND interaction, EC code, Gene Ontology, IntAct, KEGG pathway, KEGG Reaction, Reactome
event	BIND interaction, EC code, Gene Ontology, IntAct, KEGG pathway, KEGG Reaction, Reactome

Search strategy



GO, UniProt Oracle database
ChEBI, PubMed WebServices

BioModels MySQL database

Xpath:
```
//sbml:*[contains(@id,'TEXT')]
| //sbml:*[contains(@name,'TEXT')]
| //xhtml:*[contains(text(),'TEXT')]
```

Curate Models

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- *BioModels ID* → Search BioModels Database for *exact* BioModels identifiers (for example *BIOMD0000000007* or *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: Publication

Resource: Gene Ontology — cell cycle

Resource:

Publication
ChEBI
Gene Ontology
UniProt

Resource ID:

Resource ID: BIND

Resource ID: BIND

Compose by: and or

Search Reset

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Search Models

The search returned **6** models.

New Search

BioModels ID	Name	PubMed Id	Last Modified	
BIOMD0000000003	Goldbeter1991_MinMitOscil	1833774	2005-06-27T16:53:31	SBML
BIOMD0000000004	Goldbeter1991_MinMitOscil_ExplInact	1833774	2005-06-27T16:53:42	SBML
BIOMD0000000005	Tyson1991_CellCycle_6var	1831270	2005-06-27T16:54:42	SBML
BIOMD0000000006	Tyson1991_CellCycle_2var	1831270	2005-06-27T16:54:55	SBML
BIOMD0000000007	Novak1997_CellCycle	9256450	2005-06-27T16:56:33	SBML
BIOMD0000000008	Gardner1998_CellCycle_Goldbeter	9826676	2005-06-27T16:56:45	SBML

New Search

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BIOMD0000000005 Tyson1991_CellCycle_6var

SBML L2 V1 | CellML | SciLab | XPP

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Publication ID: 1831270

Submitter: Nicolas Le Novere

Submission Date: 2005-09-13T13:31:0

Last Modification Date: 2005-09-13T1

Creation Date: 2005-02-08T18:28:27

Creators: Bruce Shapiro

Cell Cycle Model; Tyson (1991, 6 variables)

Citation

Tyson JJ, (1991). Modeling the cell division cycle: cdc2 and cyclin interactions. PNAS, 88: 7328-7332. http://www.pnas.org/cgi/content/abstract/88/16/7328

Description

A model of the cell cycle based on the interactions between cdc2 and cyclin. The model has six dynamic variables: C2 (cdc2); CP (cdc2-P complex); pM (P-cyclin-cdc2-P complex); M (active MPF, P-cyclin-cdc2 complex); Y (cyclin); and YP (cyclin-P). Total cyclin concentration (YT) is the sum YT=Y+YP+pM+M4

Rate constant	Reaction
k1aa = 0.015	EmptySet -> Y
k2 = 0	Y -> EmptySet
k3 = 200	CP + Y -> pM
k4prime + k4*M[t]^2	pM -> M
k5notP = 0	M -> pM
k6 = 1	M -> C2 + YP
k7 = 0.6	YP -> EmptySet
k8notP = 1000000	C2 -> CP
k9 = 1000	CP -> C2

Variable	IC	ODE
C2	0	C2'[t] == -(k8notP*C2[t]) + k9*CP[t] + k6*M[t]
CP	1	CP'[t] == k8notP*C2[t] - k9*CP[t] - k3*CP[t]*Y[t]
M	0	M'[t] == -(k5notP*M[t]) - k6*M[t] + (k4prime + k4*M[t]^2)*pM[t]
pM	0.3	pM'[t] == k5notP*M[t] - (k4prime + k4*M[t]^2)*pM[t] + k3*CP[t]*Y[t]

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SBML L2 V1 | Cel

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Submit Model Cor

Publication ID: 183

Submitter: Nicolas

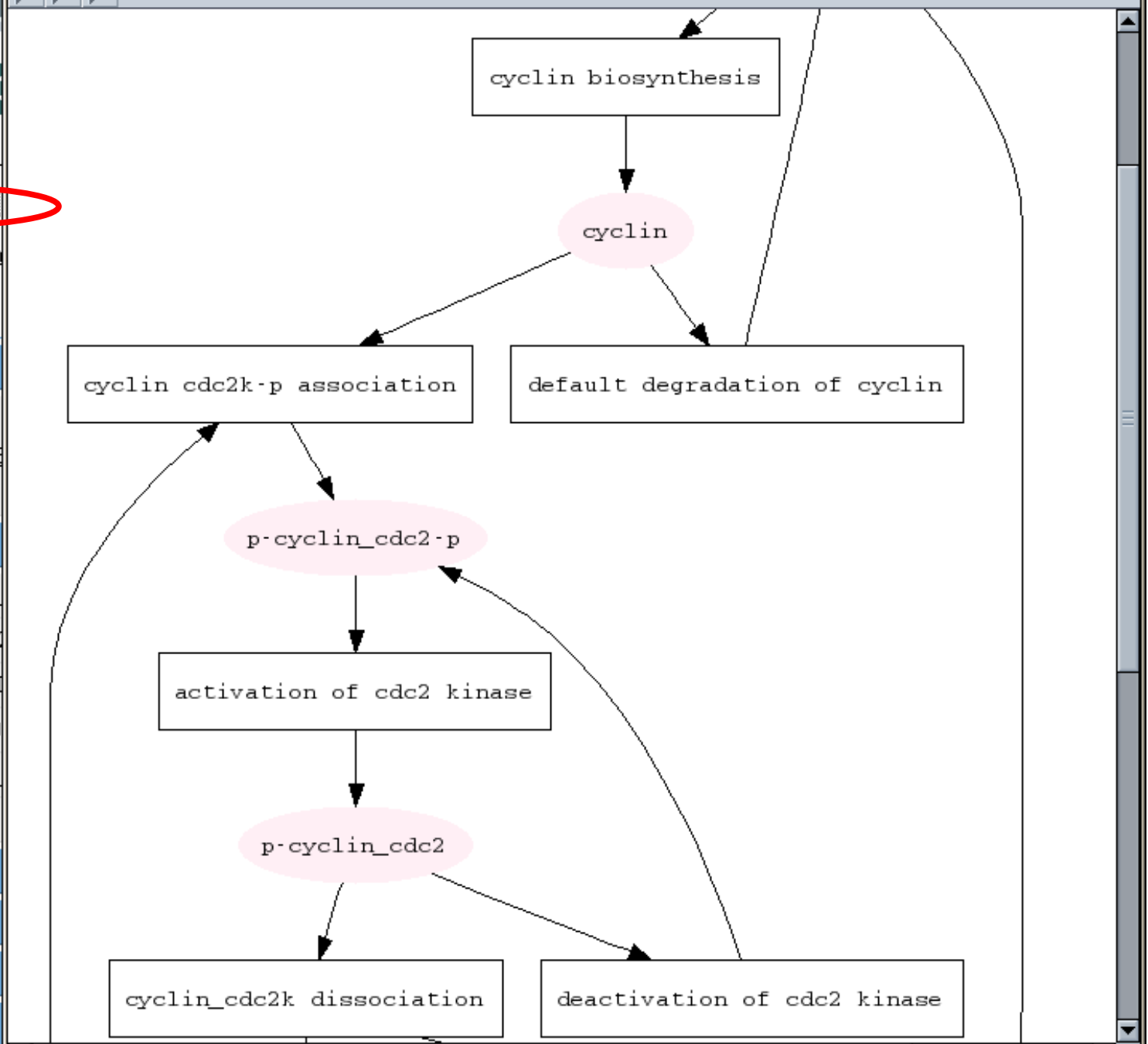
Submission Date:

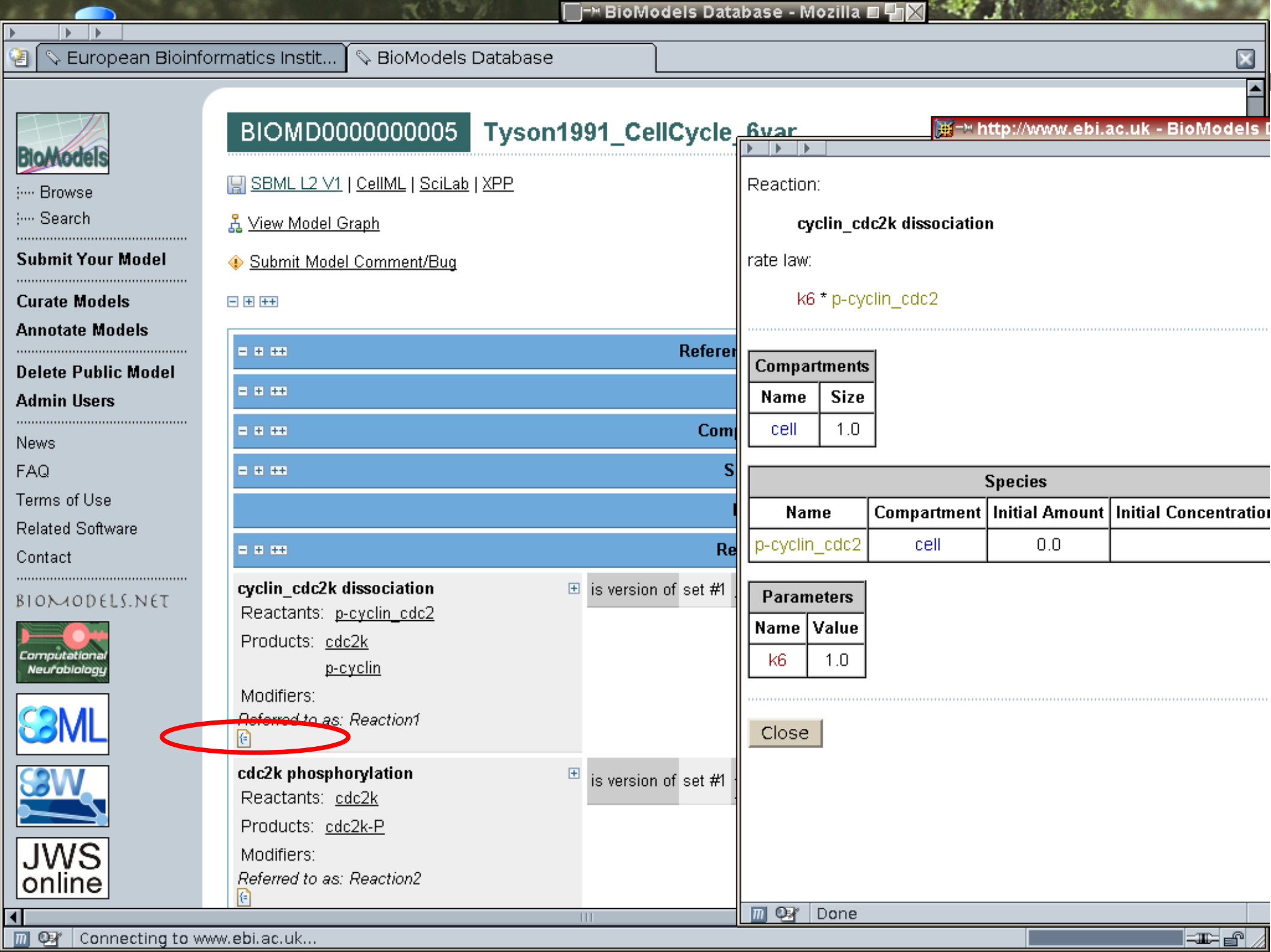
Last Modification

Creation Date: 200

Creators: Bruce Sh

http://www.ebi.ac.uk - BioModels Database - Mozilla

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cyclin_cdc2k dissociation
is version of set #1
Reactants: p-cyclin_cdc2
Products: cdc2k
p-cyclin
Modifiers:
Referred to as: Reaction1
cdc2k phosphorylation
is version of set #1
Reactants: cdc2k
Products: cdc2k-P
Modifiers:
Referred to as: Reaction2
http://www.ebi.ac.uk - BioModels
Reaction:
cyclin_cdc2k dissociation
rate law:
k6 * p-cyclin_cdc2
Compartments
Name
Size
cell
1.0
Species
Name
Compartment
Initial Amount
Initial Concentration
p-cyclin_cdc2
cell
0.0
Parameters
Name
Value
k6
1.0
Close
Done
Connecting to www.ebi.ac.uk...

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BIOMD0000000007 Novak1997_CellCycle

SBML L2 V1 | CellML | XPP

View Model Graph

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Reference Publication

Publication ID: 9256450

Proc Natl Acad Sci U S A 1997 Aug;94(17):9147-52.
Modeling the control of DNA replication in fission yeast.
Novak B, Tyson JJ.
Department of Agricultural Chemical Technology, Technical University of Budapest, 1521 Budapest, St. Gellert ter 4, Hungary.

Model

Submitter: Nicolas Le Novère

Submission Date: 2005-09-13T13:33:30

Last Modification Date: 2005-09-13T13:33:30

Creation Date: 2005-02-09T13:27:02

Creators: Bruce Shapiro

Gene Ontology mitotic cell cycle
KEGG Pathway sce04110
Reactome 69278
Taxonomy 4896

Compartments (1)

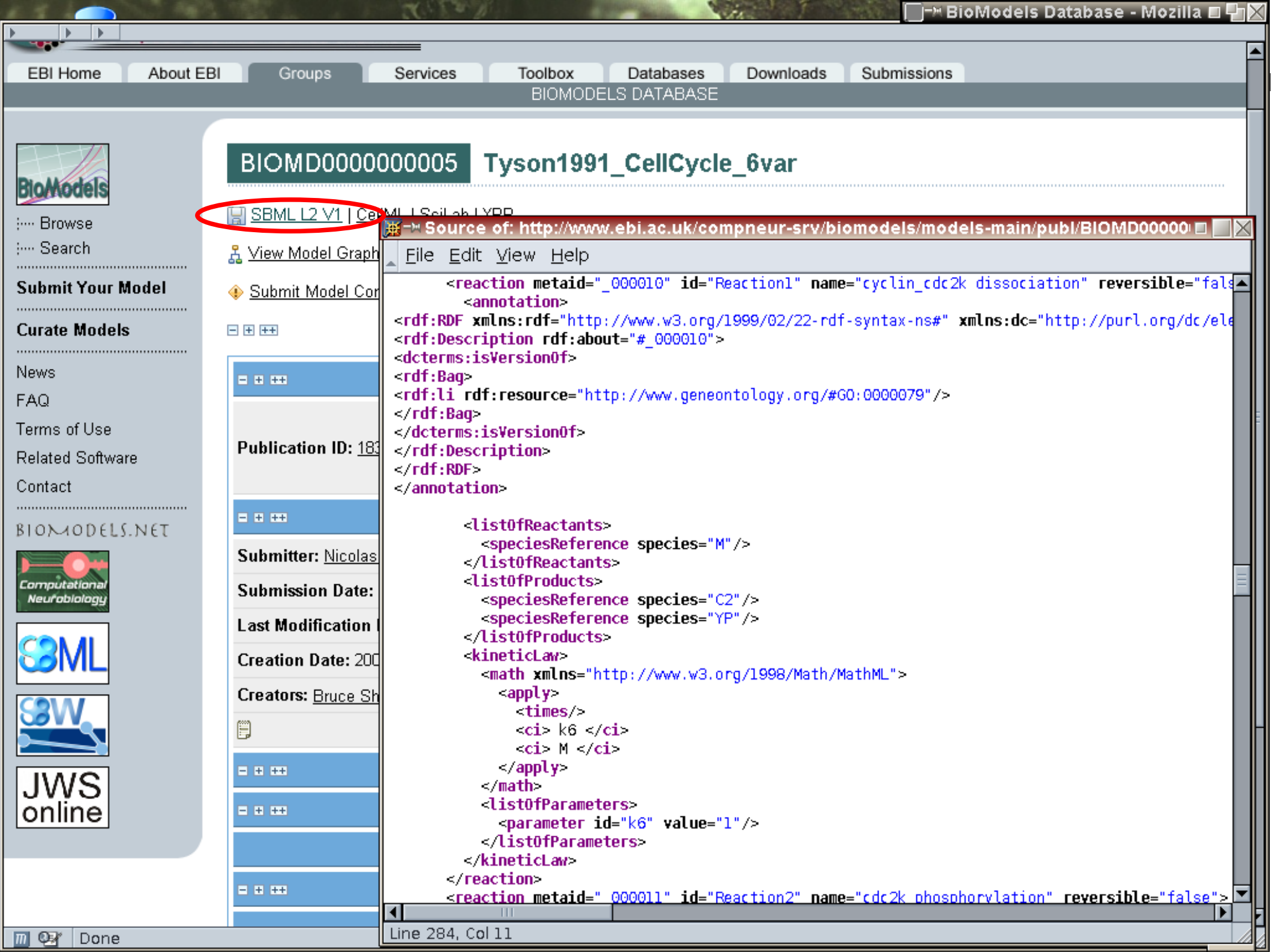
Species (22)

Rules (15)

Reactions (25)

Cdc13_Cdc2 creation
Reactants:
Products: Cdc13_Cdc2

Reactome 68910
Reactome 69282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Publication ID: 183
Submitter: Nicolas
Submission Date:
Last Modification
Creation Date: 200
Creators: Bruce Sh
Source of: http://www.ebi.ac.uk/compneur-srv/biomodels/models-main/publ/BIOMD00000
File Edit View Help
<reaction metaid="_000010" id="Reaction1" name="cyclin_cdc2k dissociation" reversible="fals
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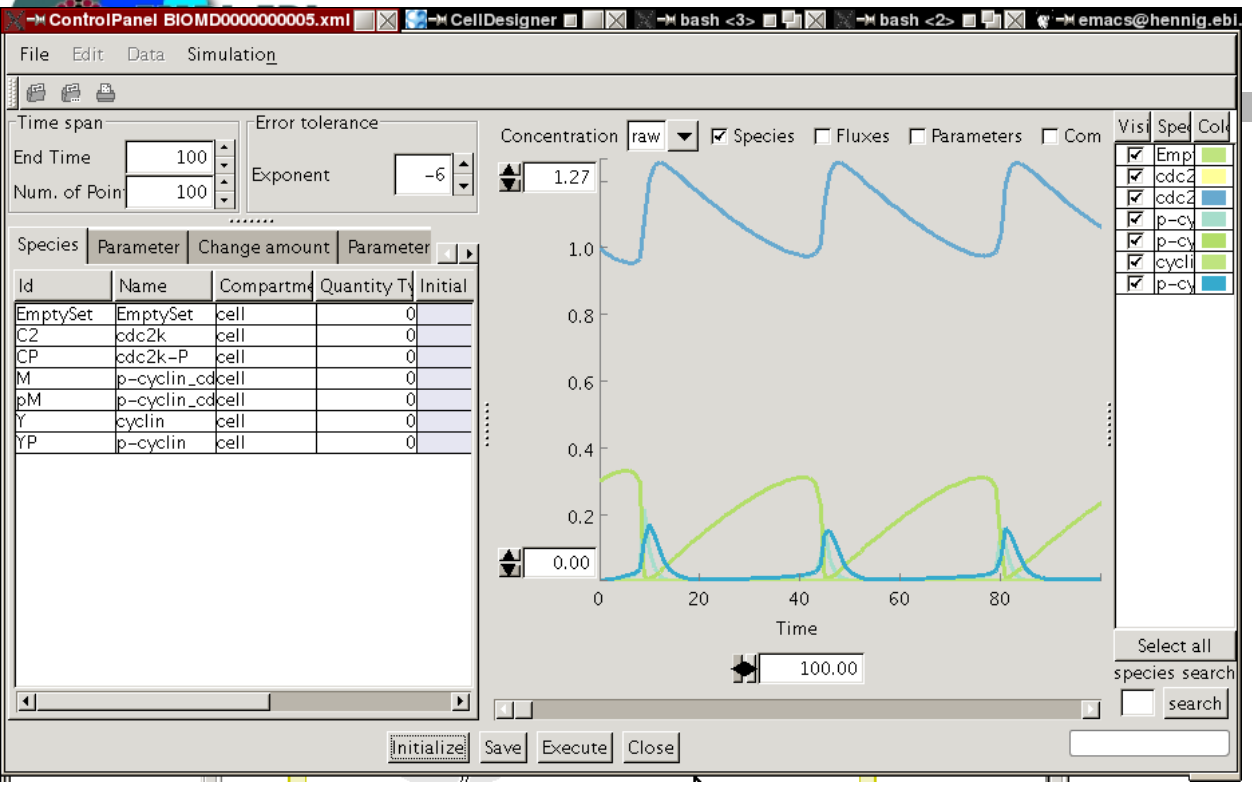
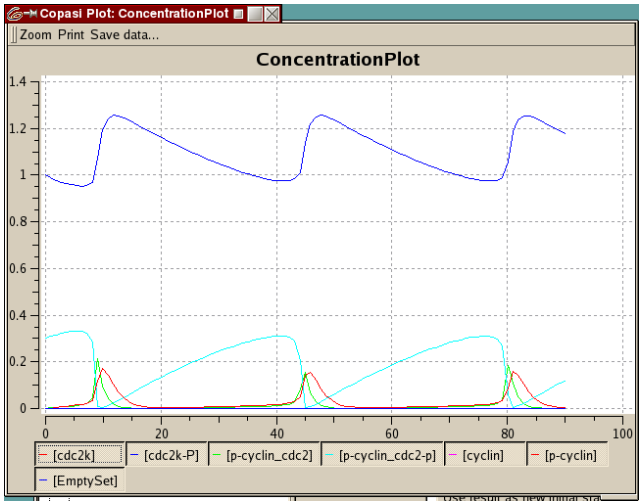
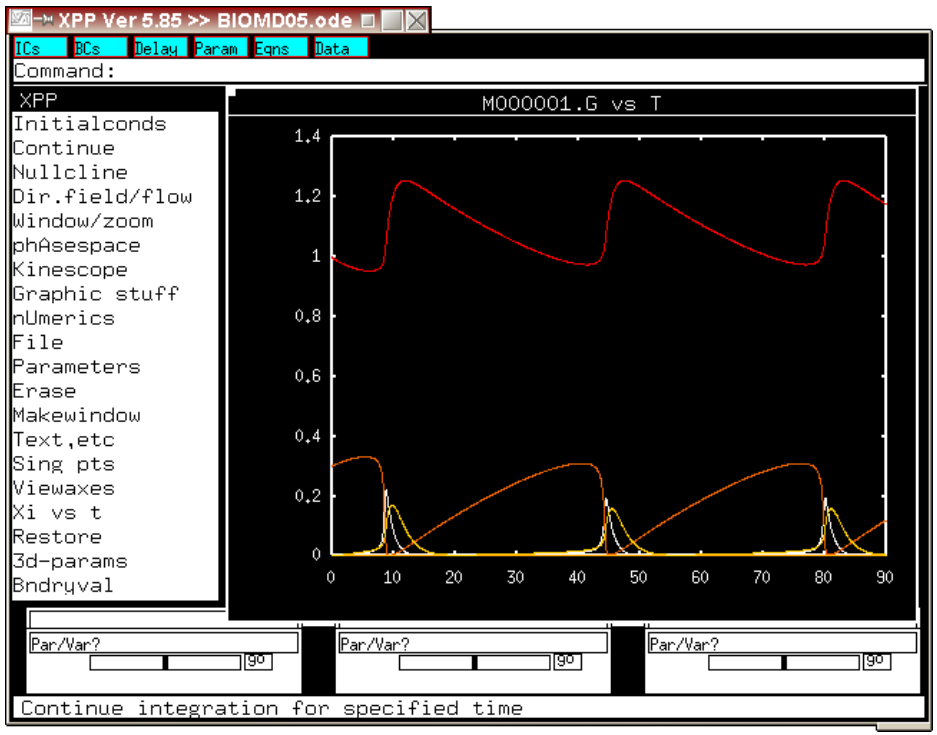
Line 284, Col 11
Done

BIOMD0000000005

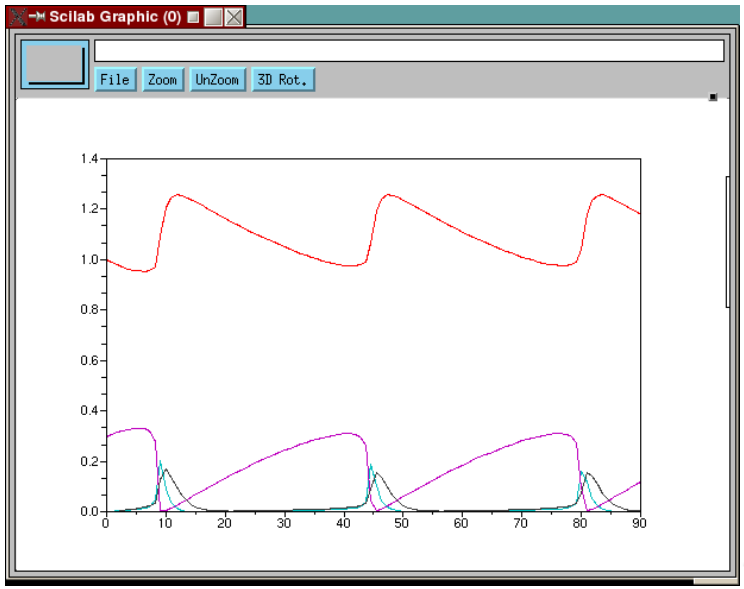




SBML import



export in proprietary formats

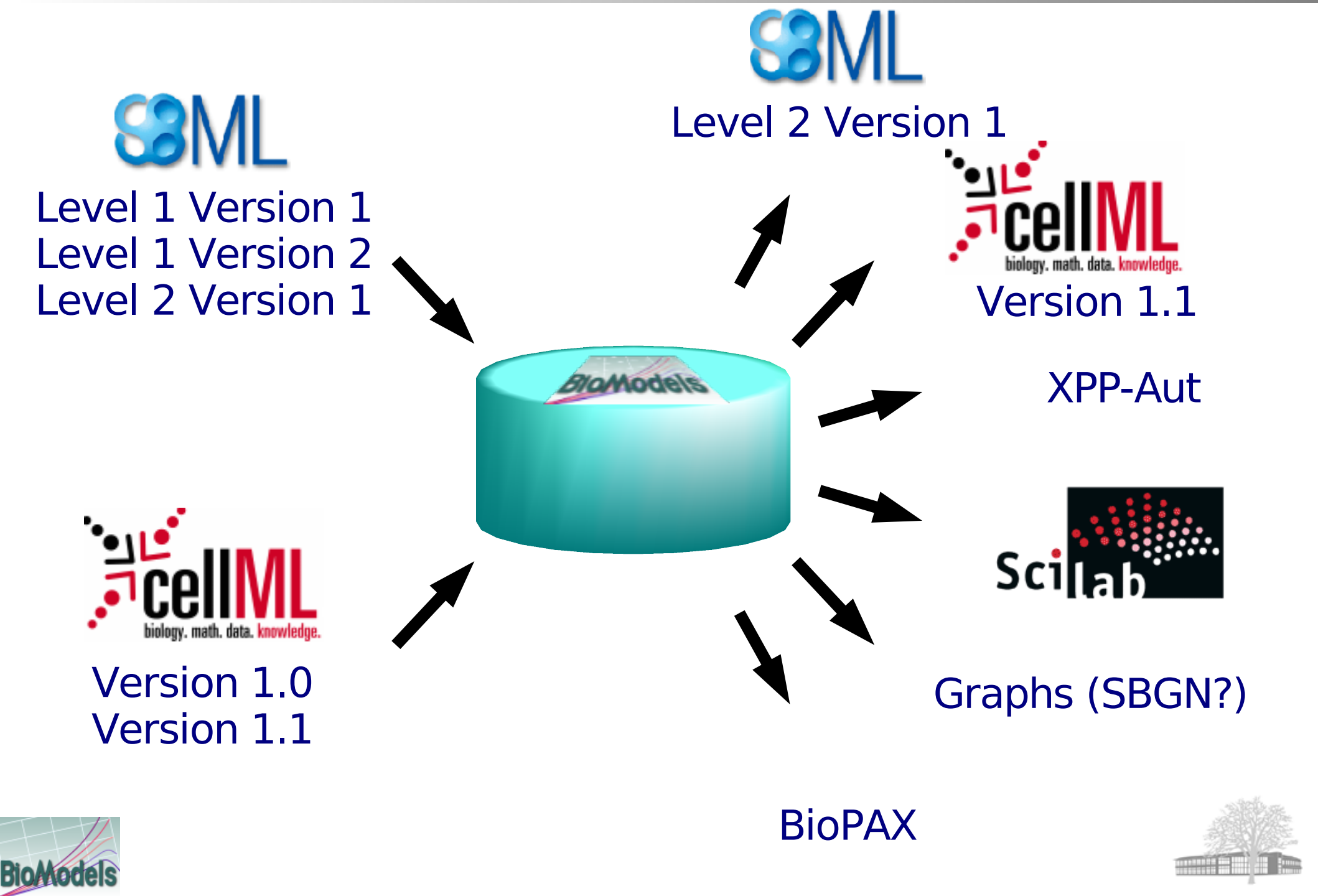


Steady increase

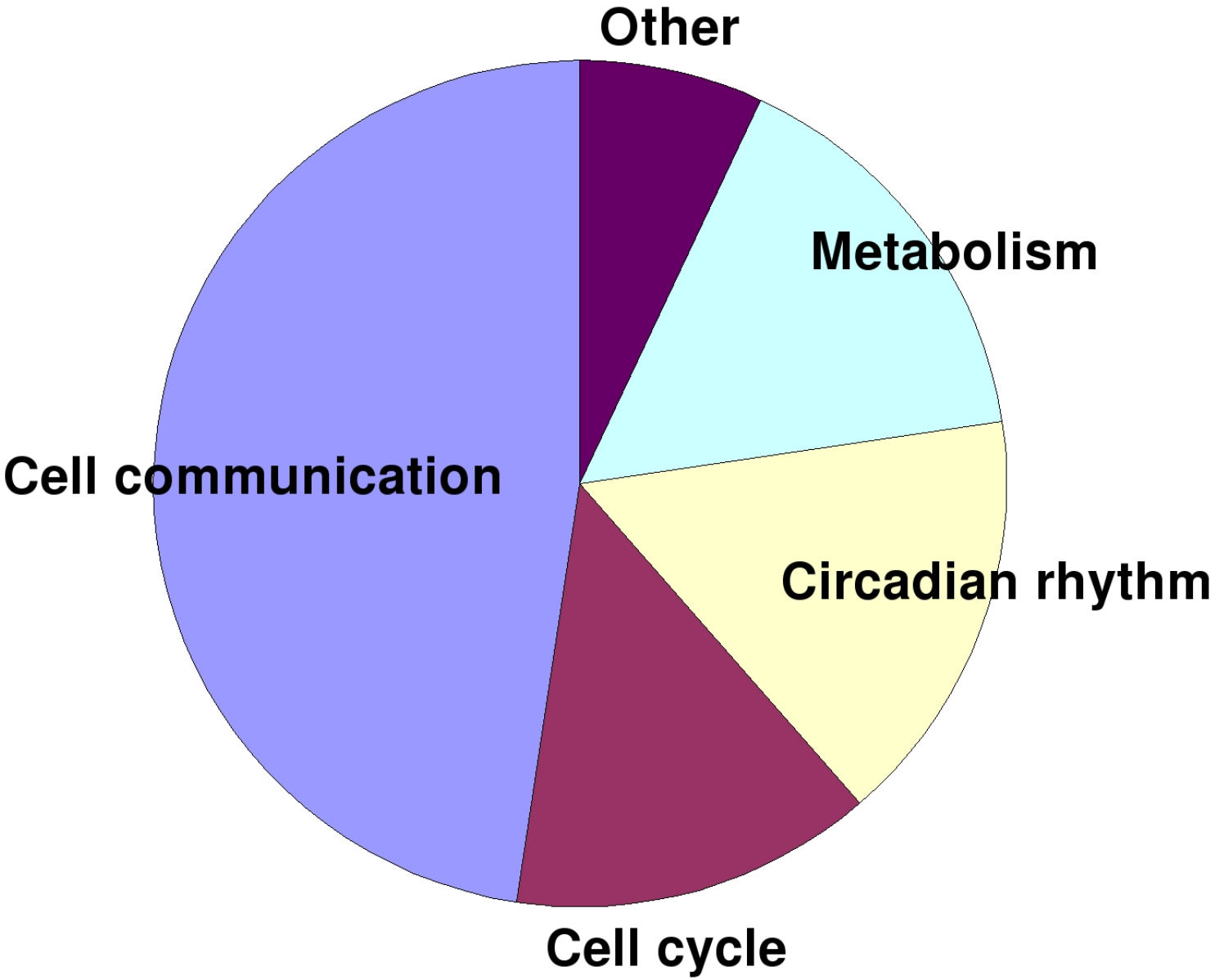
Release	# models	# reactions	#annotations
11 April 2005	20	631	1084
01 June 2005	30	736	1609
28 July 2005	44	943	2373
30 January 2006	50	1163	3126

- Around 30 models in the curation pipeline
- Still important legacy from JWS Online and CellML Repository (DOCQS)?
- Non time-series: Ex Palsson models
- Spatial models: e.g. VCell, SmartCell, MesoRD

Compatibility



Topical repartition



Neurobiology-related: 1, 2 (channel conformation), 20 (HH), 33 (EGF/NGF)
+ circadian rhythms?

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Melanie Courtot:
MySQL/Tomcat

Camille Laibe
WebServices

Lu Li:
Graph, CellML, XPP,
SciLab exports and curation

Arnaud Henry:
BioPAX export

Nicolas Le Novère:
Design and curation

An international collaboration

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  - Mélanie Courtot
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  - Henning Schmidt
  - Paul Smolen
  - Darren Wilkinson
  - Molecular Systems Biology
- Programs used for curation
  - CellDesigner
  - COPASI
  - Jarnac/JDesigner
  - SBMLodeSolver
  - XPP-Aut