

Curation and exchange of kinetic models of biochemical pathways

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Ateliers génomique, 25 novembre 2005



One would like to be able to follow this more general process mathematically also. The difficulties are, however, such that one cannot hope to have any very embracing theory of such processes, beyond the statement of the equations. It might be possible, however, to treat a few particular cases in detail with the aid of a digital computer. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis.

A.M. Turing (1952). The chemical basis of morphogenesis. *Phyl Trans Roy Soc Lond B*237: 37-72

[About the development from one pattern to another, a non-linear process]



- Computational modelling in biology is a mature and complex field
 - Constellation of different approaches and algorithms signalling pathway:
 - graph/topology – flux analysis – kinetic simulation
 - discrete – continuous
 - ODE - PDE
 - Alternative models to describe the same phenomena
Bacterial chemotaxis, Cell cycle, MAPK, EGFR signalling,
 - Being not omniscient, one has to leverage on each other expertise
- Computational modelling at the core of modern biology
 - Rise of functional genomics and systems biology
Modern data are: high throughput, quantitative, quality-controlled
 - Number of models increasing exponentially
 - Size of the models is increasing with the data availability
 - “biologists” are more and more interested in challenging and using computer models

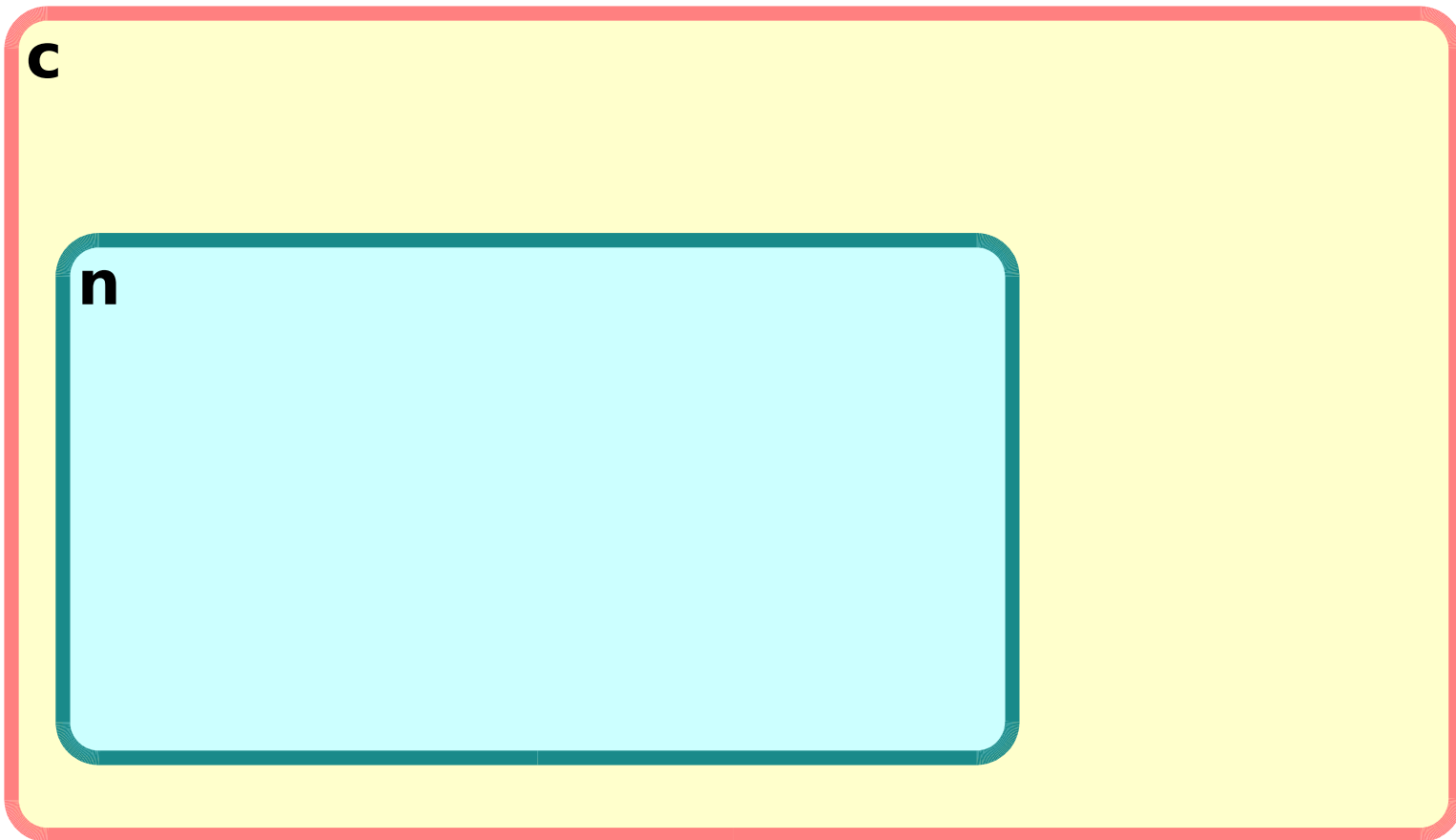


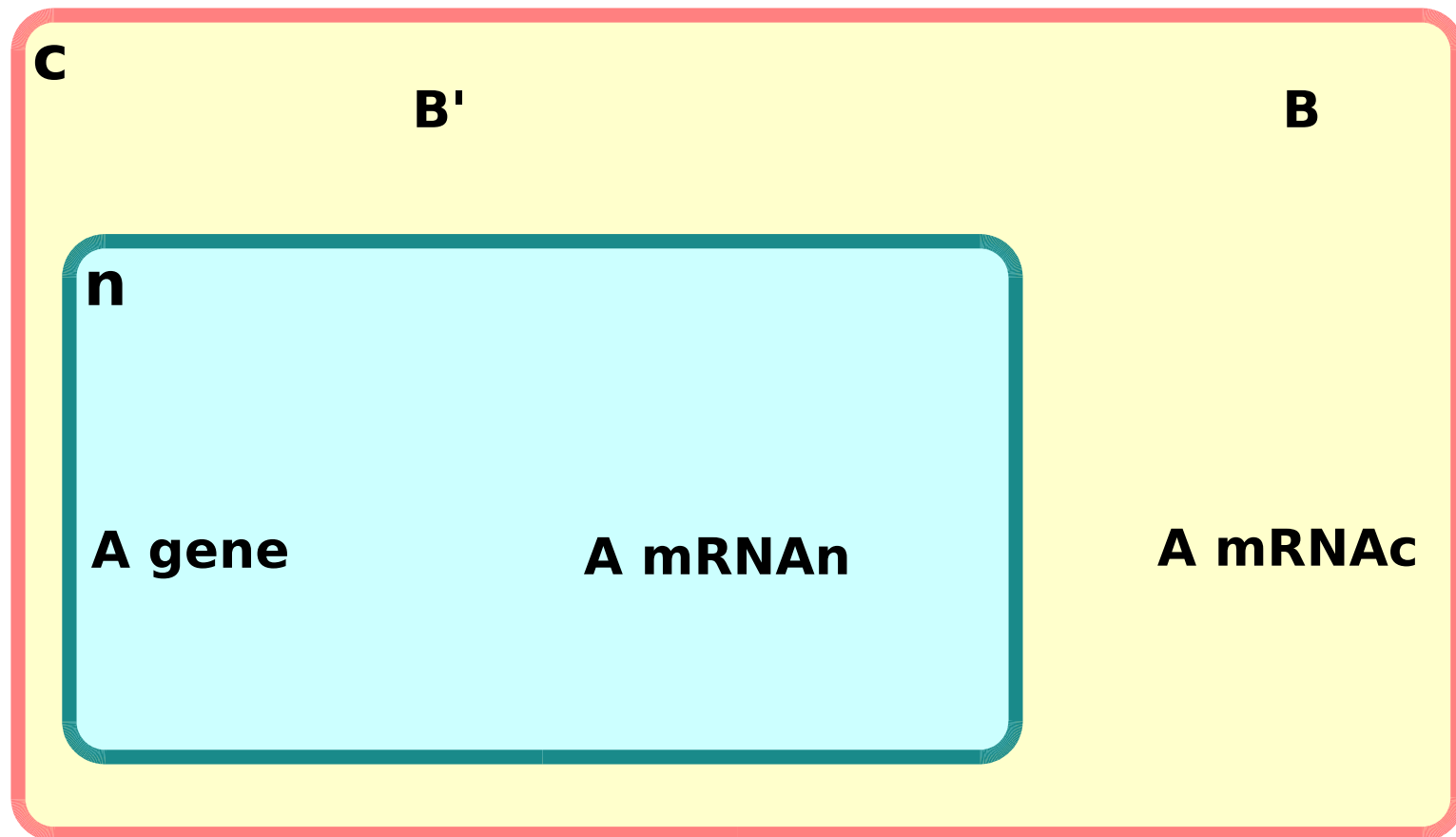
- Non-specialists need to use models relevant for their research with simulation software without messing with their structure.
 - Modelling literates need to reuse existing models rather than rewrite them from scratch.
 - Various software used during the modelling process, such as graphical designers, simulation engines and plotters or renderers, should be able to communicate.
-
- ➔ Systems Biology Markup Language (SBML): A community maintained open XML standard to encode quantitative models of biological systems.
 - ➔ MIME type application/sbml+xml
(RFC 3823 of the Internet Engineering Task Force)

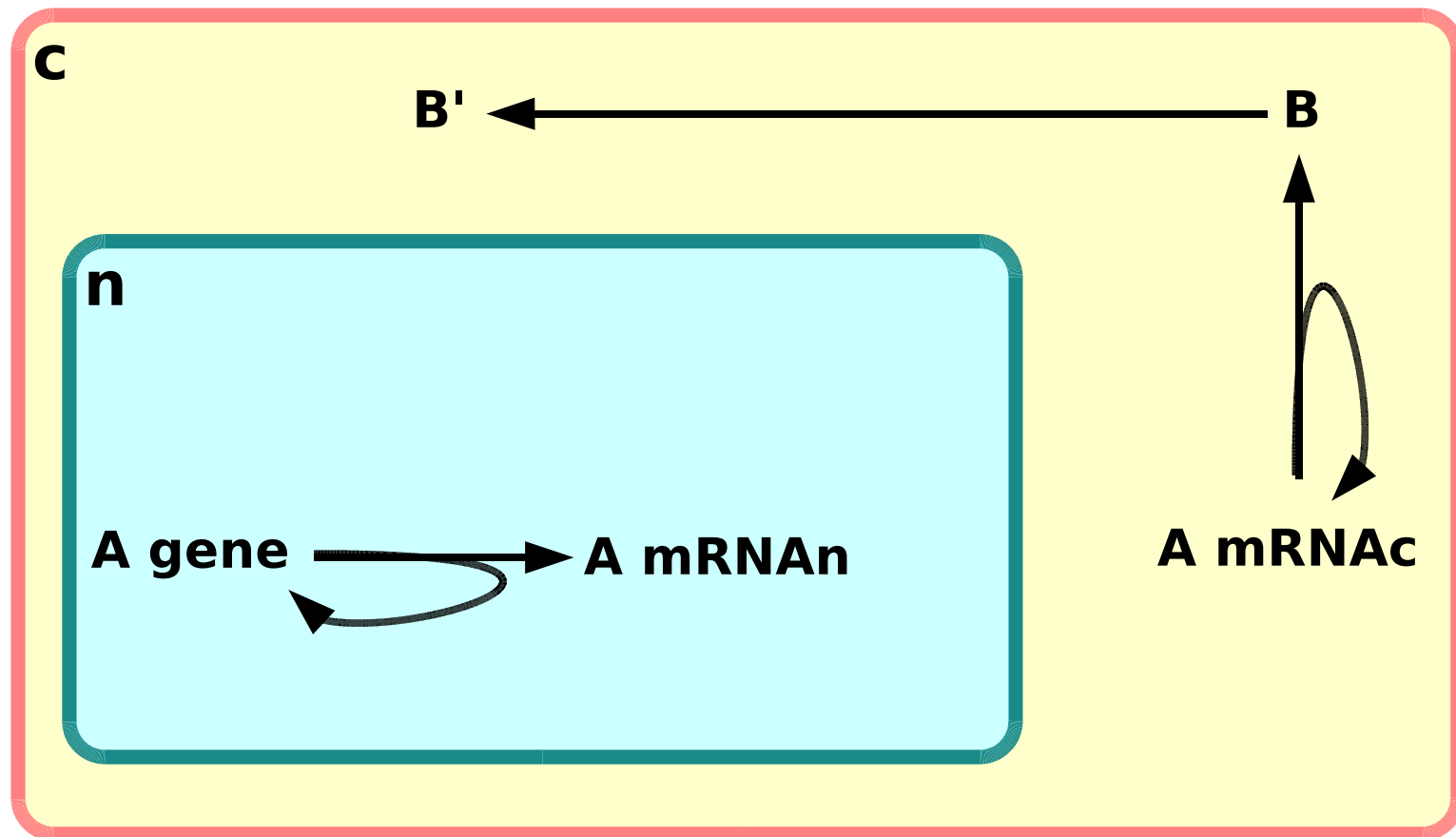


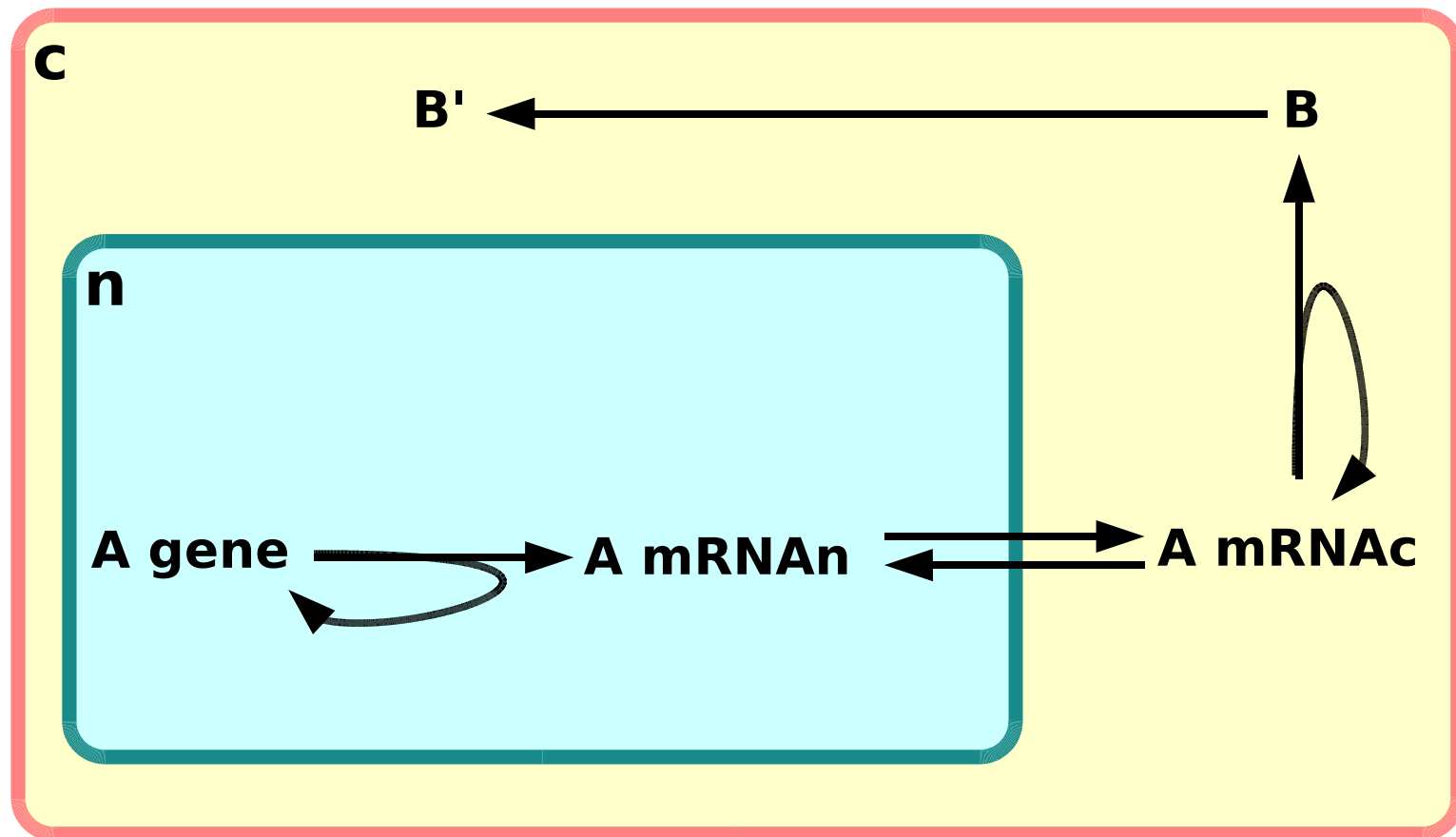
What can we encode in SBML?

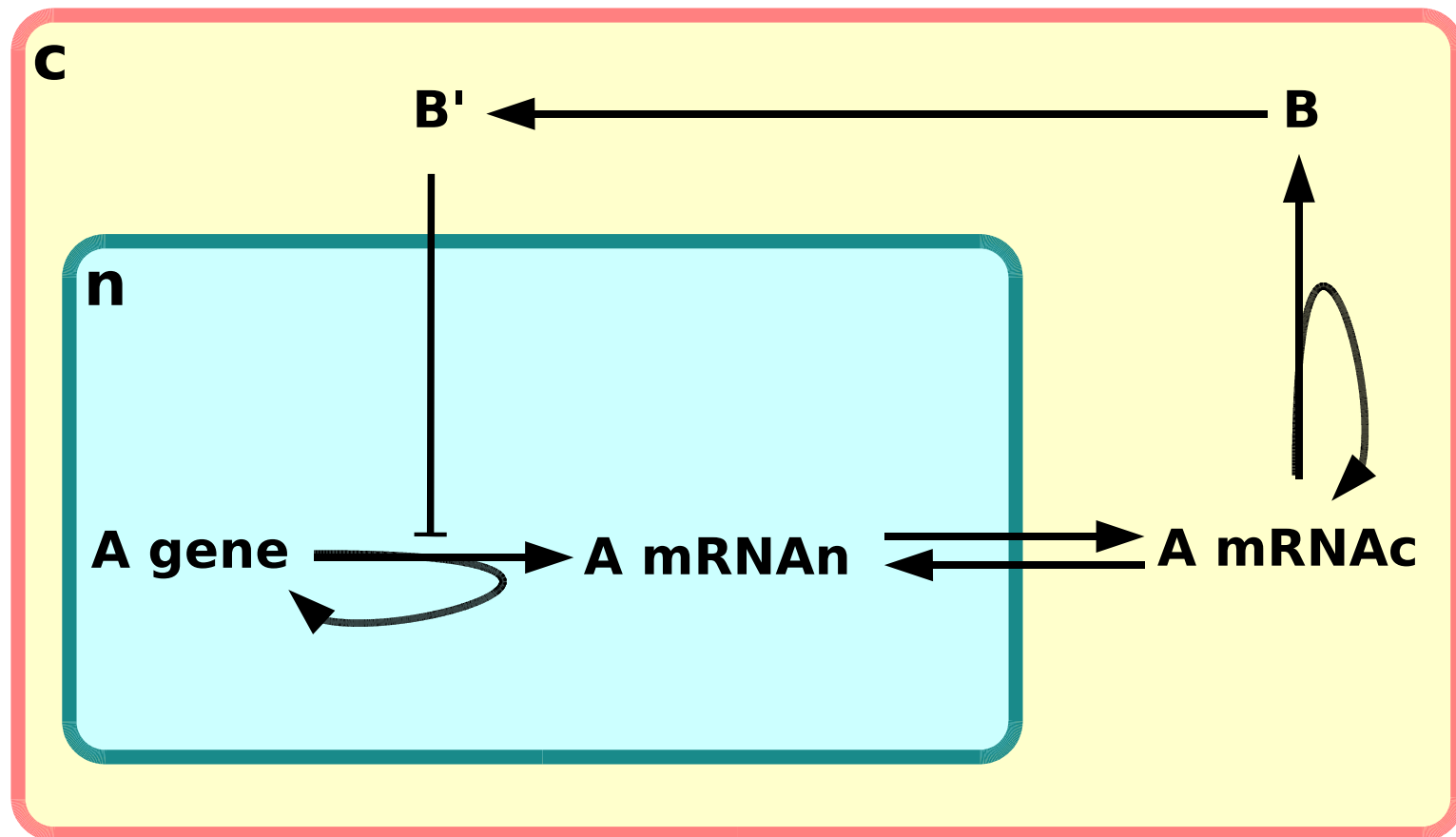


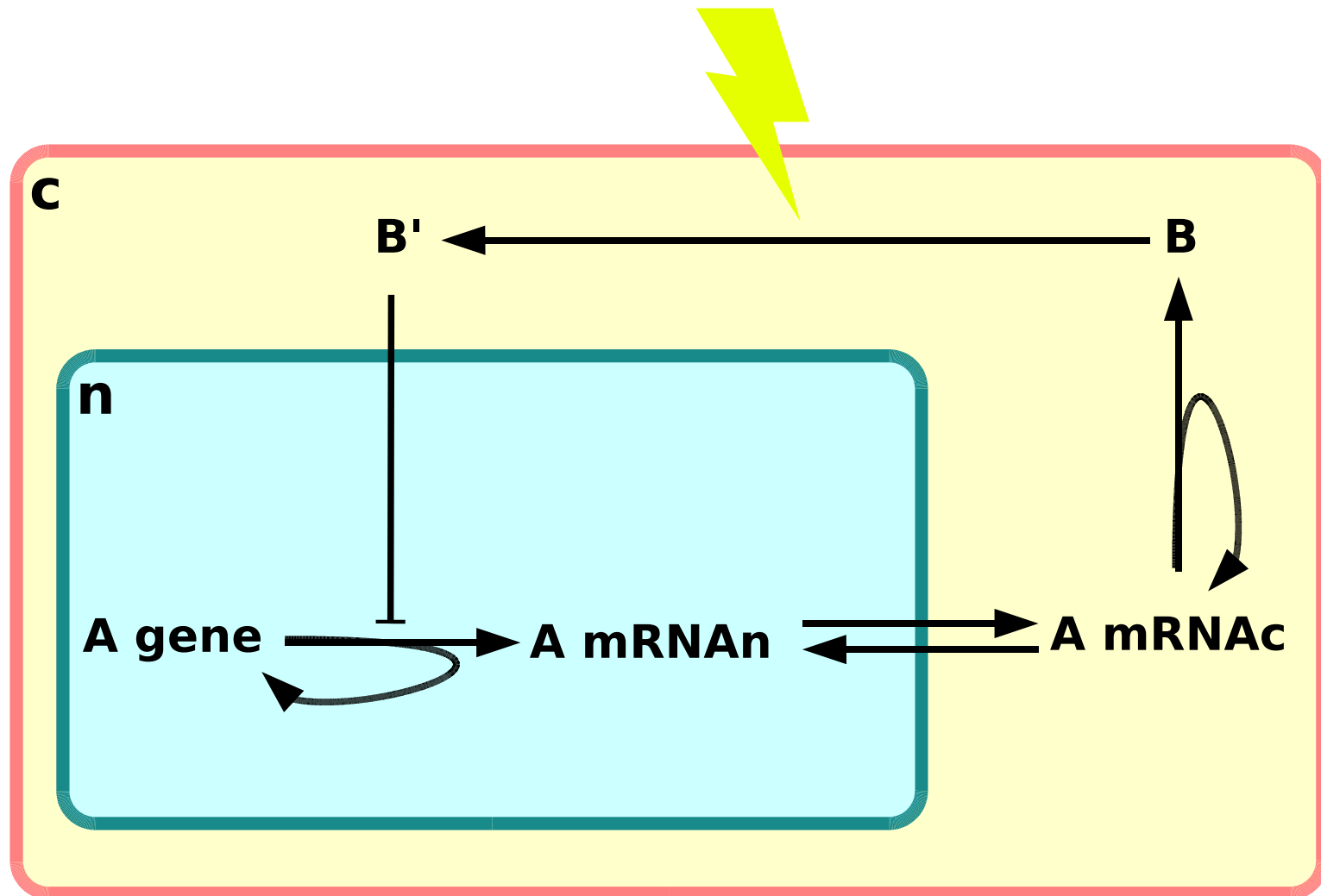












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</sbml>
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</sbml>
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    <listOfParameters>
      <parameter id="kon" value="1"/>
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    <listOfReactions>
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        </listOfReactants>

        </reaction>
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              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```



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  compartment="cell"
  initialAmount="1000"
  substanceUnits="item"
  hasOnlySubstanceUnits="true"
  boundaryCondition="true"
  constant="false"
  charge="0"
  metaid="PX" >
<notes>
  <body xmlns="http://www.w3.org/1999/xhtml">
    <p>One of the components of microtubule</p>
  </body>
</notes>
<annotation>
  <rdf:RDF
    xmlns:dc="http://purl.org/dc/elements/1.1/"
    xmlns:dcterms="http://purl.org/dc/terms/"
    xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#PX">
      <dc:relation>
        <rdf:Bag>
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```



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          <ci>blood</ci>
        </apply>
      </math>
    </kineticLaw>
  </reaction>
</listOfReactions>
```



- **Level 1 (March 2001)**

- Predefined kinetics functions
- One type of reactive substance
- ISO646 encoding

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

- **Level 2 (June 2003)**

- Function definitions
- Modifier species
- Events
- All math in MathML
- Unicode encoding

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

- **Level 3 (?)**

- Modular SBML (“packages”)
- Graph layout
- Multi-component species
- Model composition
- Arrays of elements



SBML Systems Biology Markup Language

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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	Cytoscape	MMT2	SBMLR
BASIS	DBsolve	Modesto	SBMLSim
BIOCHAM	Dizzy	Molecularizer	SBMLToolbox
BioCharon	E-CELL	Monod	SBToolbox
biocyc2SBML	ecellJ	Narrator	SBW
BioGrid	ESS	NetBuilder	SCIpath
BioModels	FluxAnalyzer	PANTHER Pathway	Sigmoid*
BioNetGen	Fluxor	PathArt	SigPath
BioPathway Explorer	Gepasi	PathScout	SigTran
Bio Sketch Pad	INSIICO discovery	PathwayLab	SIMBA
BioSens	JACOBIAN	Pathway Tools	SimBiology
BioSPICE Dashboard	Jarnac	PathwayBuilder	Simpathica
BioSpreadsheet	JDesigner	PaVESy	SimWiz
BioTapestry	JigCell	PNK	SmartCell
BioUML	JWS Online	Reactome	SRS Pathway Editor
BSTLab	Karyote*	ProcessDB	StochSim
CADLIVE	KEGG2SBML	PROTON	STOCKS
CellDesigner	Kinsolver*	pysbml	TERANODE Suite
Cellerator	libSBML	PySCeS	Trelis
CellML2SBML	MathSBML	runSBML	Virtual Cell
Cellware	MesoRD	SBML ODE Solver	WinSCAMP
CL-SBML	MetaboLogica	SBMLeditor	XPPAUT
COPASI	MetaFluxNet	SBMLmerge	

MathWorks SimBiology Released

(November 12, 2005) **SimBiology**, the systems biology toolkit from the makers of MATLAB, is now available.

[read more](#)

Database Curator Sought

(November 11, 2005) The Caltech group is looking for a full-time postdoc to perform database curation for BioModels Database.

[read more](#)

Nanator supports SBML

(November 9, 2005) **Nanator** is a graphical modeling tool for biological processes, integrating an intuitive overview of the system being modeled with an underlying ODE interpretation.

[read more](#)

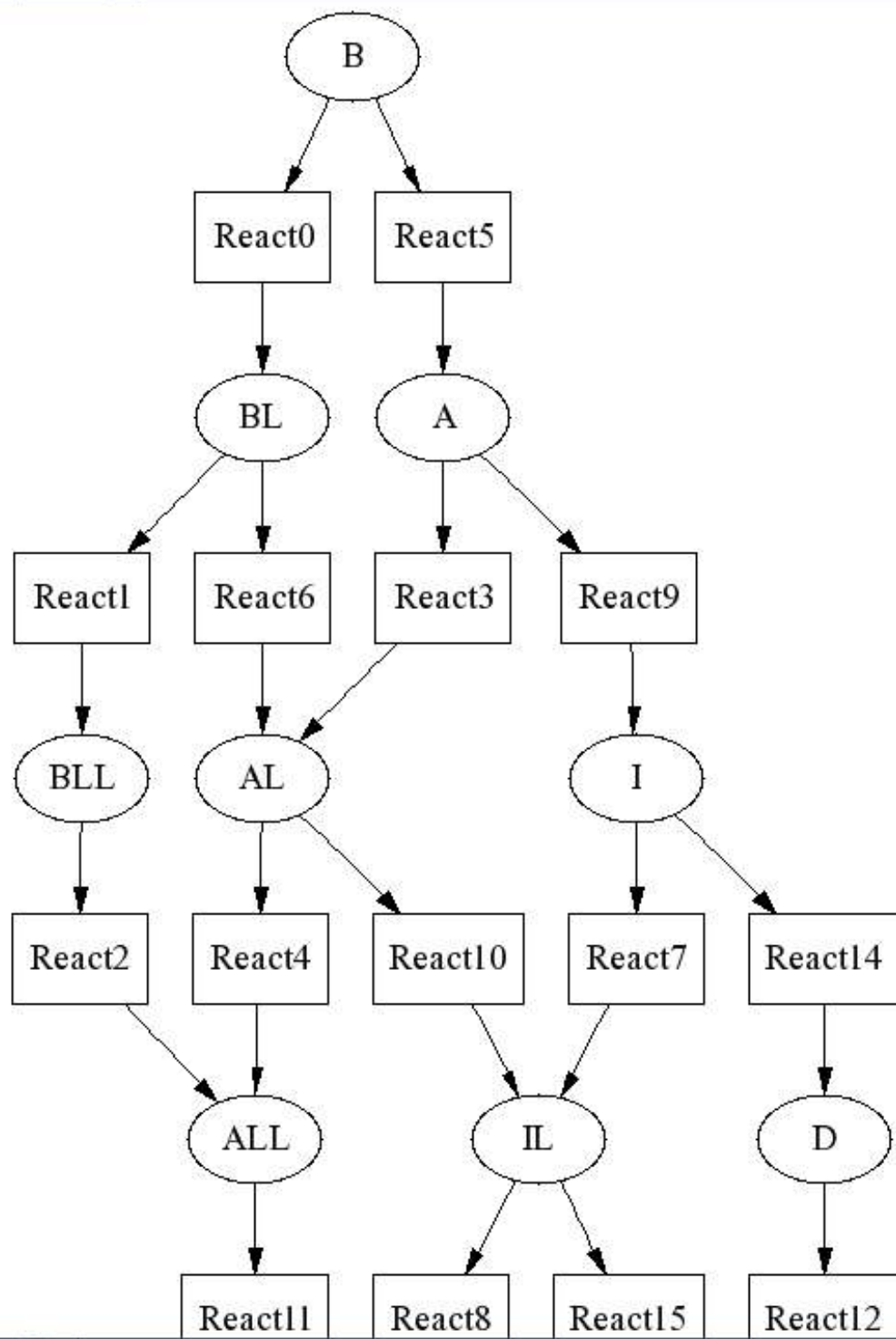
SBToolbox v1.5

(November 7, 2005) Version 1.5 of the **Systems Biology Toolbox** for MATLAB, by Henning Schmidt, features many enhancements, fixes, and new detailed tutorials.

[read more](#)

JACOBIAN Supports SBML

(October 25, 2005) Numerica Technology's **JACOBIAN** is a dynamic modeling and optimization software with support for model

No, it isn't!

BIO MODELS.NET

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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.

Search

[RSS](#) / [Atom](#)

Minimum Information Requested In the Annotation of biochemical Models (MIRIAM)

**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: in the press**



- 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)

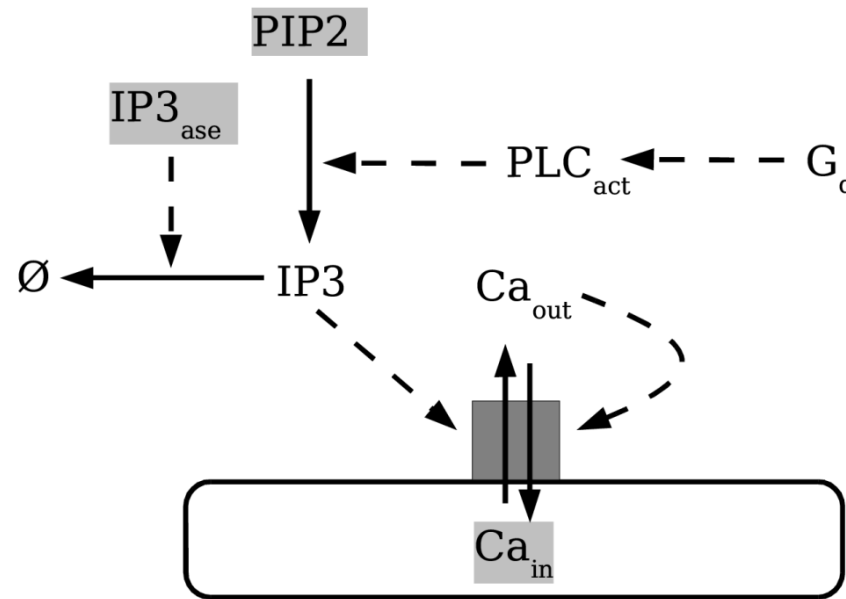


- The model has to be named.
- A citation of the reference description must be joined (complete citation, unique identifier, unambiguous URL). The citation should permit to identify the *authors* of the model.
- The name and contact of model *creators* must be joined.
- The date and time of creation 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”.



- 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 constituent 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.





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

$$Km_1 = 10^{-7} \text{ M}, Km_2 = 10^{-8}, Km_3 = 2 \cdot 10^{-6} \text{ M}$$

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

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

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

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

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

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



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/ http://www.ncbi.nlm.nih.gov/Taxonomy/ http://www.geneontology.org/ http://www.geneontology.org/ http://www.genome.jp/kegg/pathway/ http://www.genome.jp/kegg/pathway/	0000000 9606 GO:0007204 GO:0051279 hsa04020 hsa04070	 IsVersionOf IsVersionOf IsPartOf IsPartOf	 <i>Homo sapiens</i> <i>positive regulation of cytosolic [ca²⁺]</i> <i>regulation of release of sequestered ca²⁺ into cytop</i> <i>Calcium signaling pathway - H sapiens</i> <i>Phosphatidylinositol signaling system - H sapiens</i>
compartment ER	http://www.geneontology.org/	GO:0005790		<i>smooth endoplasmic reticulum</i>
reactant Ca _{in}	http://www.ebi.ac.uk/chebi/	CHEBI:29108		<i>calcium(2+)</i>
cytoplasm	http://www.geneontology.org/	GO:0005737		<i>cytoplasm</i>
reactant Ca _{out}	http://www.ebi.ac.uk/chebi/	CHEBI:29108		<i>calcium(2+)</i>
reactant IP3	http://www.ebi.ac.uk/chebi/	CHEBI:16595		<i>1D-myo-inositol 1,4,5-tris(dihydrogen phosphate)</i>
reactant PIP2	http://www.ebi.ac.uk/chebi/	CHEBI:18348		<i>1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate</i>
reactant IP3R	http://www.uniprot.org/ http://www.uniprot.org/ http://www.uniprot.org/	Q14643 Q14571 Q14573	HasVersion HasVersion HasVersion	<i>Inositol 1,4,5-trisphosphate receptor type 1</i> <i>Inositol 1,4,5-trisphosphate receptor type 2</i> <i>Inositol 1,4,5-trisphosphate receptor type 3</i>
reactant PLC _{act}	http://www.uniprot.org/	Q9NQ66	IsVersionOf	<i>PIP2 phosphodiesterase β1</i>
reactant PLC _{tot}	http://www.uniprot.org/	Q9NQ66		<i>PIP2 phosphodiesterase β1</i>
reactant IP3 _{ase}	http://www.uniprot.org/	Q14642		<i>Type I inositol-1,4,5-trisphosphate 5-phosphatase</i>
reactant G _q	http://www.uniprot.org/	Q6NT27		<i>Guanine nucleotide binding protein Gq</i>
reaction Ca _{release}	http://www.geneontology.org/ http://www.geneontology.org/	GO:0005220 GO:0008095	 IsVersionOf	<i>IP3-sensitive calcium-release channel activity</i> <i>IP3 receptor activity</i>
reaction IP3 _{production}	http://www.geneontology.org/ http://www.ebi.ac.uk/intenz/	GO:0004435 3.1.4.11	IsVersionOf IsVersionOf	<i>phosphoinositide phospholipase C activity</i> <i>phosphoinositide phospholipase C</i>
reaction IP3 _{degradation}	http://www.ebi.ac.uk/intenz/	3.1.3.56	IsVersionOf	<i>inositol-polyphosphate 5-phosphatase</i>
reaction PLC _{activation}	http://www.geneontology.org/	GO:0007200		<i>G-protein signaling coupled to IP3 2nd messenger</i>

The Systems Biology Ontology

**Le Novère N., Hucka M., Finney A., Cox C.D., McCollum J.M., Wilkinson D.,
Courtot M., ... Yourself**



- 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>
- “An indexed dictionary”. *Nicolas Le Novère. This presentation.*
- “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*

- 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.



- 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.



- A taxonomy of the roles of reaction participants, including the following potential terms: “**substrate**”, “**catalyst**”, “**inhibitor**”, “**competitive inhibitor**”, “**non-competitive inhibitor**” etc.
- A CV for parameter roles in quantitative models. This CV will include terms like “**Hill coefficient**”, “**Michaelis constant**” etc.
- A classification of rate laws. This CV is a taxonomy of kinetic rate equations. Examples of potential terms in this CV are “**Mass action**”, “**Henri-Michaelis-Menten**”, “**Hill**” etc. Each term contains a precise mathematical expression stored as a MathML lambda function. The variable will refer to the CVs described above.
- A list of modelling framework to precise how to interpret the rate-law. E.g. “**continuous mass-action kinetics**”, “**discrete mass-action kinetics**”, etc.



```
SBO:0000000 ; Systems Biology Ontology
% SBO:0000001 ; rate law
  % SBO:0000007 ; mass-action kinetics
  % SBO:0000011 ; kinetics of unireactant enzymes
    % SBO:0000012 ; Henri equation
    % SBO:0000013 ; Henri-Michaelis-Menten equation
    % SBO:0000014 ; Van Slyke equation
    % SBO:0000015 ; Briggs-Haldane equation
% SBO:0000002 ; quantitative parameter
  % SBO:0000018 ; kinetic constant
    % SBO:0000019 ; catalytic constant
    % SBO:0000008 ; Michaelis constant
% SBO:0000003 ; species role
  % SBO:0000004 ; reactant
  % SBO:0000005 ; product
  % SBO:0000006 ; modifier
    % SBO:0000016 ; activator
    % SBO:0000017 ; inhibitor
```





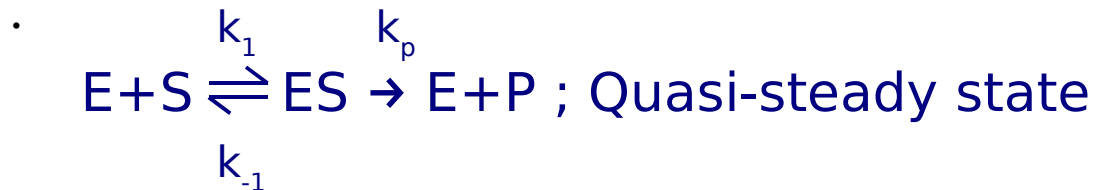
Henri-Michaelis-Menten:

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



Van Slyke:

$$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])} ; K_m = \frac{k_p}{k_1}$$



Briggs-Haldane:

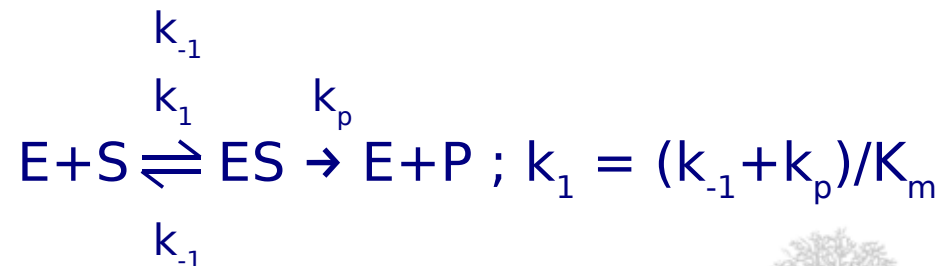
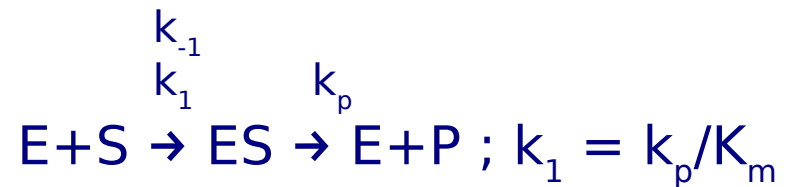
$$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])} ; K_m = \frac{(k_{-1} + k_p)}{k_1}$$



```
<reaction>
  <listOfReactants>
    <speciesReference species="S" />
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="P" />
  </listOfProducts>
  <listOfModifiers>
    <speciesReference species="E" />
  </listOfModifiers>
  <kineticLaw>
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      <parameter id="kp"/>
    </listOfParameters>
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        <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>
```



Import in a discrete simulator



```
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  </listOfReactants>
  <listOfProducts>
    <speciesReference species="P" />
  </listOfProducts>
  <listOfModifiers>
    <speciesReference species="E" />
  </listOfModifiers>
  <kineticLaw definitionURL="http://www.biomodels.net/SBO/#SBO:0000015">
    <listOfParameters>
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      <parameter id="kp"/>
    </listOfParameters>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
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          <ci>S</ci>
        </apply>
        <apply>
          <plus/><ci>Km</ci>
          <ci>S</ci>
        </apply>
      </apply>
    </math>
  </kineticLaw>
</reaction>
```



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  </listOfReactants>
  <listOfProducts>
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  </listOfProducts>
  <listOfModifiers>
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  </listOfModifiers>
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    <listOfParameters>
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      <parameter id="kp" definitionURL="http://www.biomodels.net/SBO/#SBO:0000019"/>
    </listOfParameters>
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        <divide/><apply>
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        <apply>
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    </math>
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</reaction>

```



[Term]
id: SBO:0000015
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 Michaelis-Menten or irreversible reactions of Van Slyke, but instead make the hypothesis that the complex enzyme-substrate is in steady-state. Although of the same form than the Henri-Michaelis-Menten equation, it is semantically different since K_m now represents a pseudo-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
math: <math xmlns="http://www.w3.org/1998/Math/MathML">
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 <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000006">E</ci></bvar>
 <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000019">kp</ci></bvar>
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 <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>



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  </listOfModifiers>
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    <listOfParameters>
      <parameter id="U" definitionURL="http://www.biomodels.net/SBO/#SBO:0000008"/>
      <parameter id="V" definitionURL="http://www.biomodels.net/SBO/#SBO:0000019"/>
    </listOfParameters>
  </kineticLaw>
</reaction>
```

continuous simulator

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

discrete simulator

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

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

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



[Term]
id: SBO:0000015
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 Michaelis-Menten or irreversible reactions of Van Slyke, but instead make the hypothesis that the complex enzyme-substrate is in steady-state. Although of the same form than the Henri-Michaelis-Menten equation, it is semantically different since K_m now represents a pseudo-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
math: <math xmlns="http://www.w3.org/1998/Math/MathML">
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 <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000004">S</ci></bvar>
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 <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000019">kp</ci></bvar>
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 </apply>
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</math>



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: in the press**

BioModels



- 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 format, and served in several others.
- Aims to be the Swiss-Prot of quantitative modelling.



I) Repositories

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

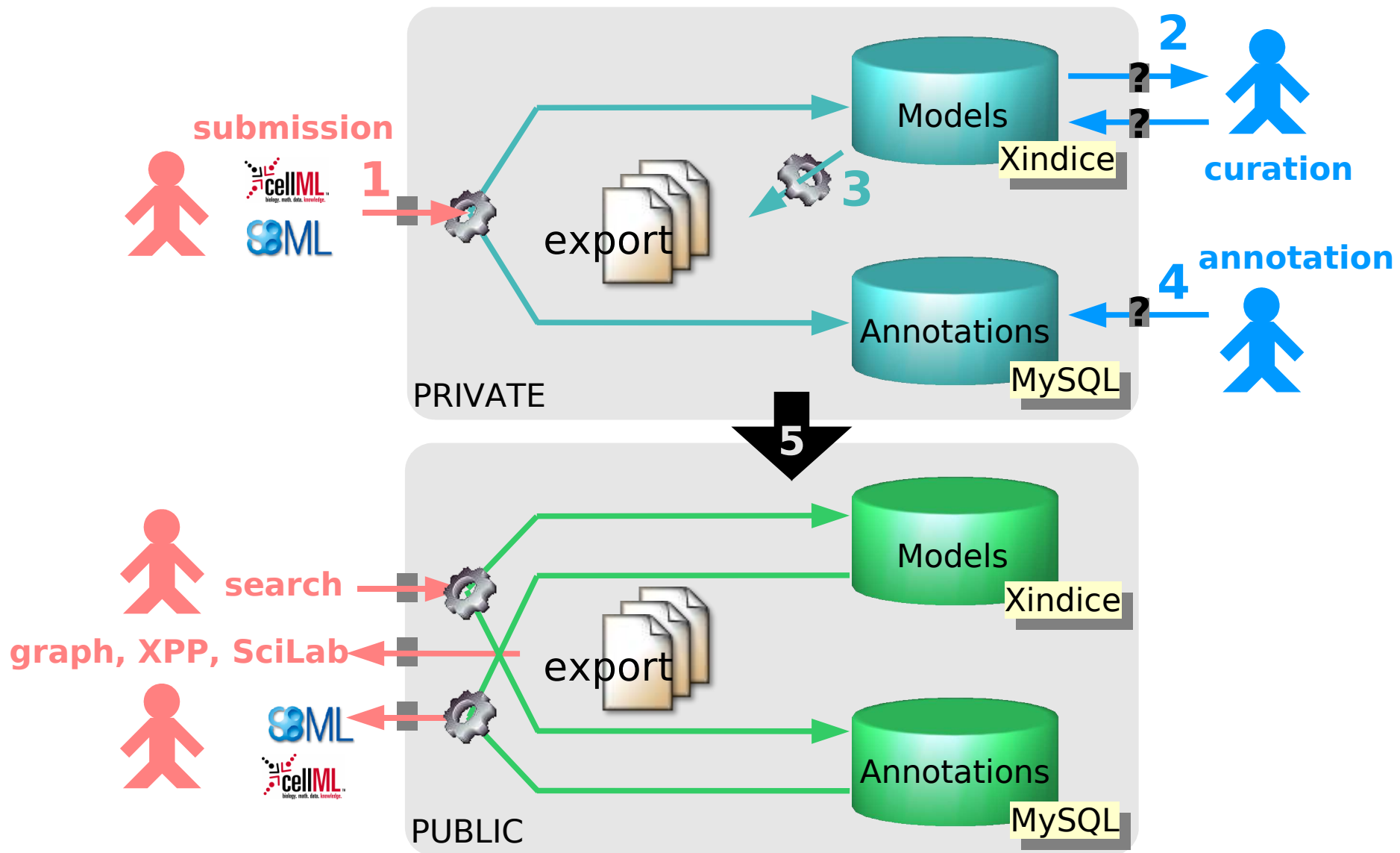
II) Individuals

- Members of the SBML community (developers+modelers)
- Authors

III) Journals (NPG/EMBO MSB; cf JWS)

IV) BioModels Database curators





- 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
 - SBML annotation in the RDF format proposed by Le Novère and Finney is recognised and reused!



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

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Reference Publication

PubMed ID: [2732237](#)

J Biol Chem. 1989 Jun 25;264(18):10552-66.
Folate cycle kinetics in human breast cancer cells.
Morrison PF, Allegra CJ.

Model

Submitter: [Nicolas Le Novère](#)

Gene Ontology [GO:0046855](#)

Submission Date: 2005-03-09T00:38:18

KEGG Pathway [map00670](#) [map00790](#)

Last Modification Date: 2005-06-29T11:23:01

Taxonomy [9606](#)

Creators: [Tomas Radivoyevitch](#)
[Nicolas Le Novère](#)

ICD10 [C50](#)



Compartments (2)

cell

Gene Ontology [GO:0005623](#)

ext

Gene Ontology [GO:0005615](#)

Species (33)

dihydrofolate free

Compartment: [cell](#)
Initial Concentration: 0.0012

ChEBI [CHEBI:15633](#)

KEGG Compound [C00415](#)

dihydrofolate bound

Compartment: [cell](#)
Initial Concentration: 0.0024

ChEBI [CHEBI:15633](#)

KEGG Compound [C00415](#)

dihydrofolate reductase free

Compartment: [cell](#)
Initial Concentration: 0.64

UniProt [P00374](#)

dihydrofolate reductase total

Compartment: [cell](#)
Initial Concentration: 0.64

UniProt [P00374](#)

tetrahydrofolate

Compartment: [cell](#)
Initial Concentration: 0.46

ChEBI [CHEBI:20506](#)

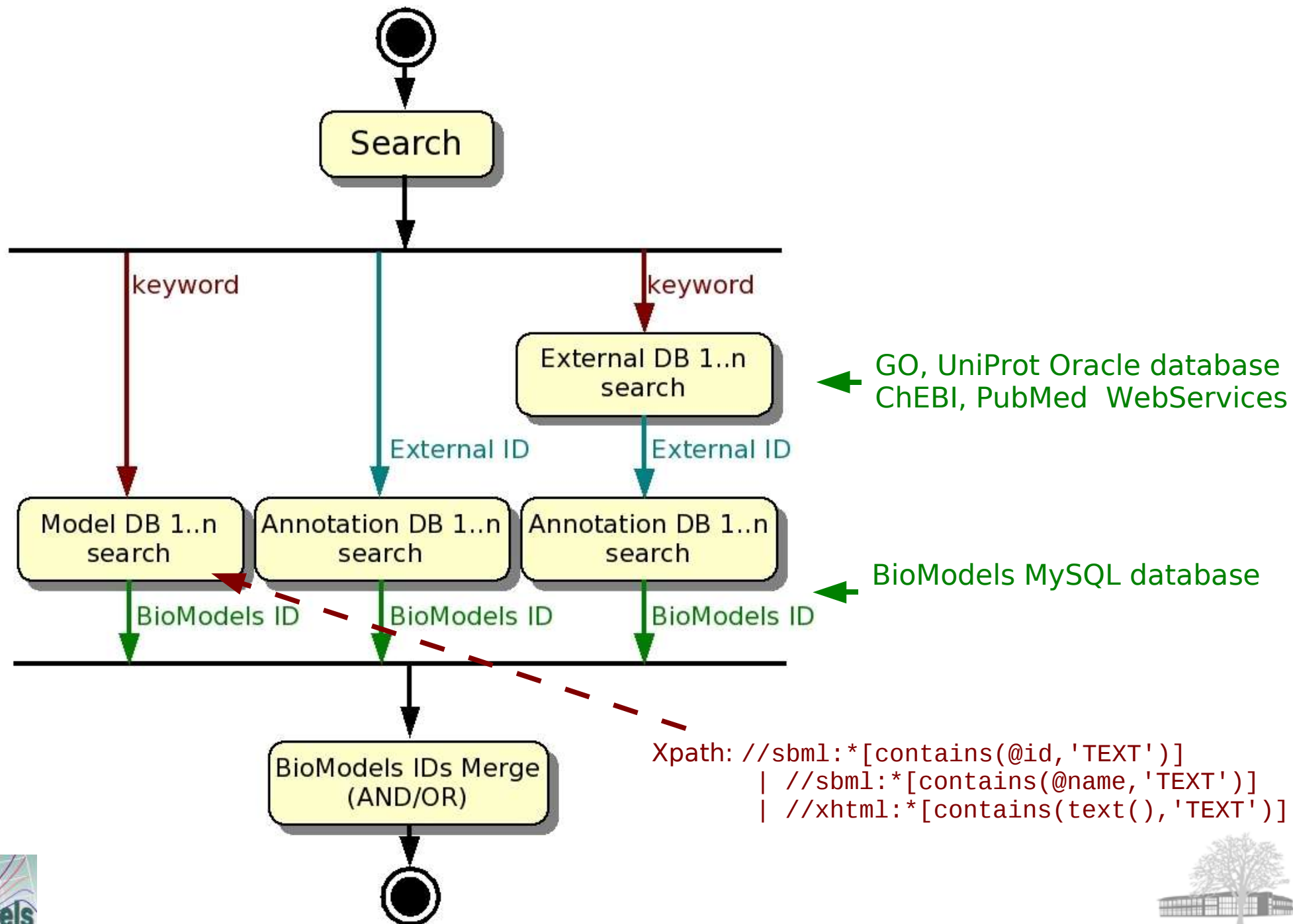
KEGG Compound [C00101](#)

5,10-methylene-tetrahydrofolate

Compartment: [cell](#)
Initial Concentration: 0.26

ChEBI [CHEBI:15636](#)

KEGG Compound [C00143](#)



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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
Resource ID:	Gene Ontology
	UniProt
Resource ID:	BIND
Resource ID:	BIND

Compose by: ☒ and ☐ or

[Top](#)

Last modification: Sun Sep 18 17:09:04 BST 2005

[Contact](#)

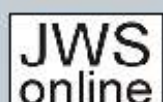
BIOMODELS.NET

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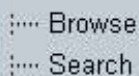
[FAQ](#)[Terms of Use](#)[Contact](#)[Search](#) [Models](#)The search returned **6** models.[New Search](#)

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

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Last modification: Thu Apr 7 12:31:47 BST 2005

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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.

+++ + -

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

++ + -

+++ + -

++ + -

++ + -

++ + -

– + ++

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☐ 1: Proc Natl Acad Sci U S A. 1997 Aug 19;94(17):9147-52. [Related Articles, Links](#)

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www.pnas.org

FREE full text article
in PubMed Central

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.

A central event in the eukaryotic cell cycle is the decision to commence DNA replication (S phase). Strict controls normally operate to prevent repeated rounds of DNA replication without intervening mitoses ("endoreplication") or initiation of mitosis before DNA is fully replicated ("mitotic catastrophe"). Some of the genetic interactions involved in these controls have recently been identified in yeast. From this evidence we propose a molecular mechanism of "Start" control in *Schizosaccharomyces pombe*. Using established principles of biochemical kinetics, we compare the properties of this model in detail with the observed behavior of various mutant strains of fission yeast: *wee1*(-) (size control at Start), *cdc13*Δ and *rum1*(OP) (endoreplication), and *wee1*(-) *rum1*Δ (rapid division cycles of diminishing cell size). We discuss essential features of the mechanism that are responsible for characteristic properties of Start control in fission yeast, to expose our proposal to crucial experimental tests.

PMID: 9256450 [PubMed - indexed for MEDLINE]

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Gardner1998_CellCycle_Goldbeter

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Publication ID: 9826676

Submitter: Nicolas Le Novère

Submission Date: 2005-09-13T13:36:21

Last Modification Date: 2005-09-13T13:36:21

Creation Date: 2005-01-30T13:02:57

Creators: Bruce Shapiro



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

Minimal Mitotic Oscillator with Inhibitor

Citation

Gardner TS, Dolnik M, Collins JJ (1998) A theory for controlling cell cycle dynamics using a reversibly binding inhibitor. PNAS 95: 14190-14195 <http://www.pnas.org/cgi/content/abstract/95/24/14190>

Description

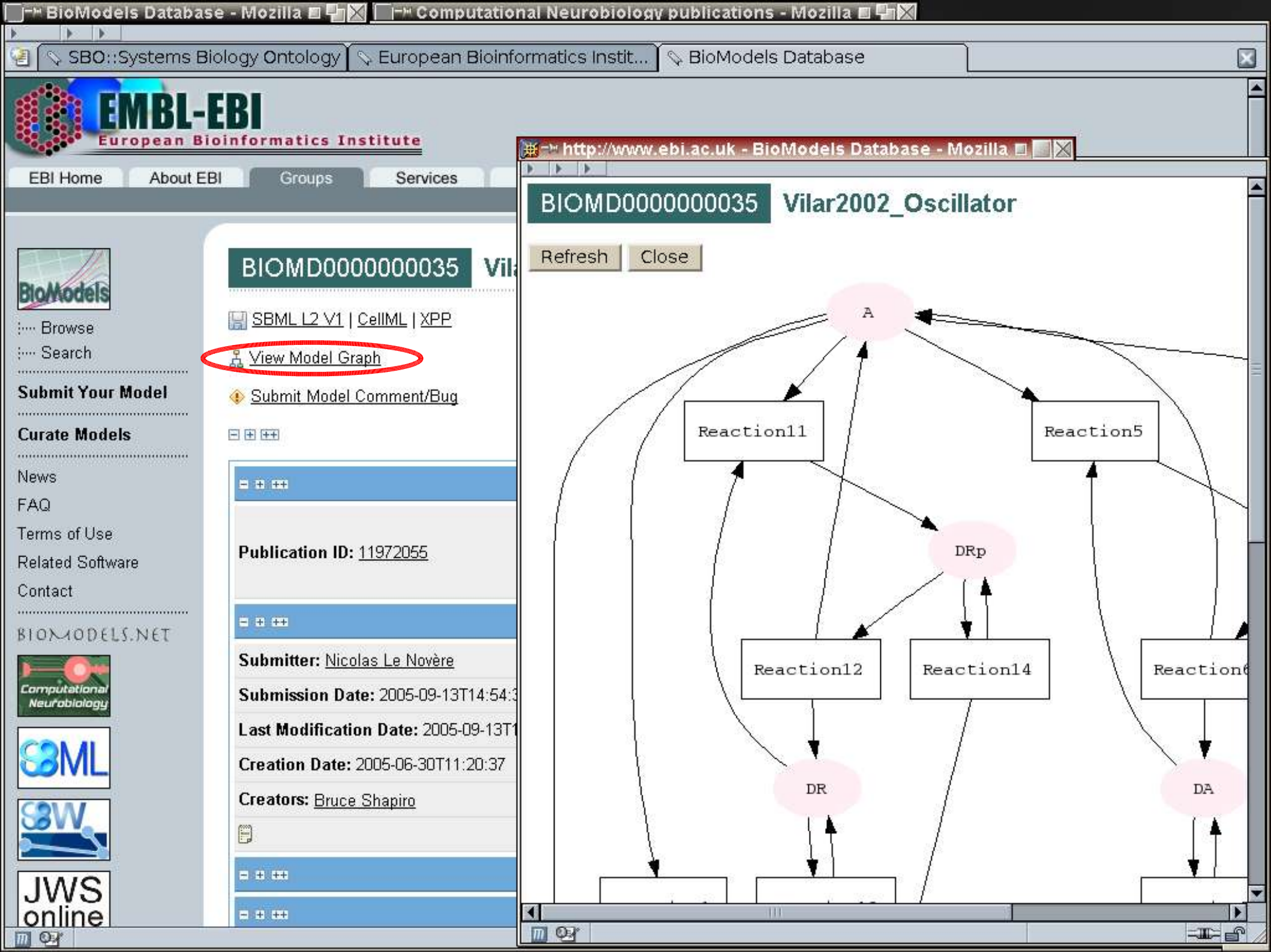
This is a modification of the widely cited (Goldbeter 1991) minimal (3-variable) model for a mitotic oscillator. The three variables represent Cyclin (C), inactive cdc-2 Kinase (M) and an active cdc-2 Kinase (X). Two additional variables Y, Z control the dynamics of the inhibitor.

Generated by Cellerator Version 1.0 update 3.0217 using Mathematica 4.2 for Mac OS X (June 4, 2002), February 19, 2003 10:40:59, using (PowerMac,PowerPC, Mac OS X,MacOSX,Darwin)

author=B.E.Shapiro

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BIOMD0000000007 Novak1997_CellCycle

SBML L2 V1 | CellML | XPP

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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)

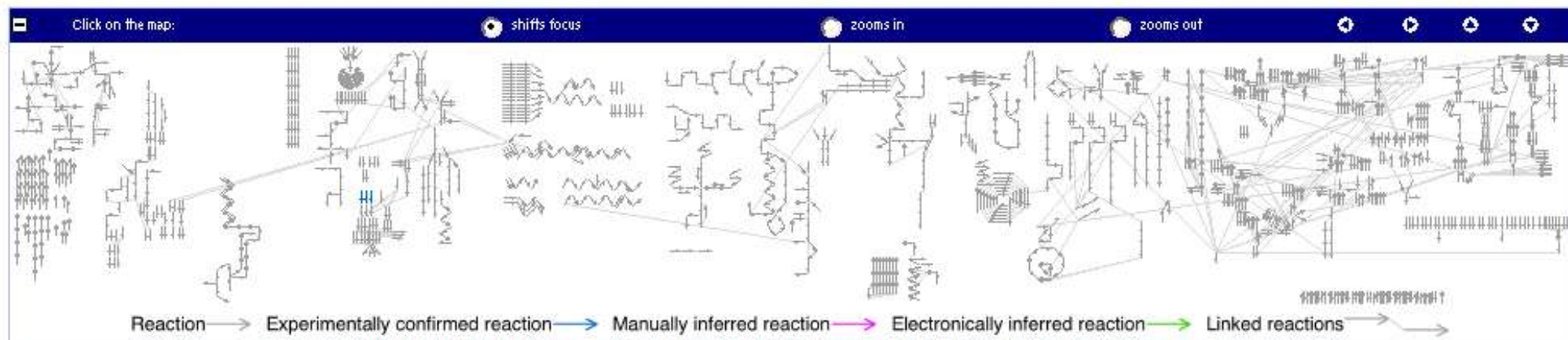
Reactions (25)

Cdc13_Cdc2 creation

Reactants:

Products: [Cdc13_Cdc2](#)

[Reactome 68910](#)
[Reactome 69282](#)

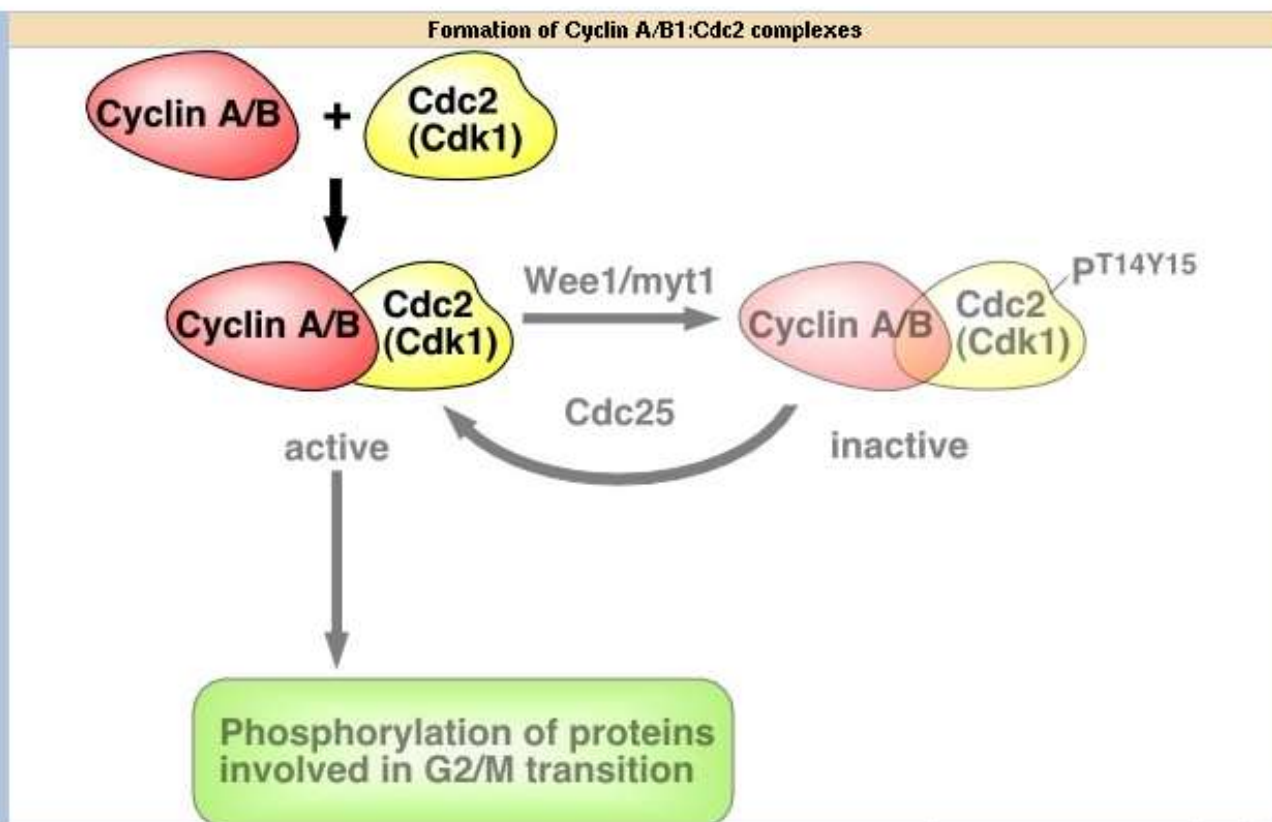


We appreciate your feedback and thoughts about Reactome. Please take a moment to take our online survey.

[Reactome Home]

- + Cell Cycle, Mitotic
 - + G2/M Transition
 - + Cyclin A/B1 associated events during G2/M transition
 - Formation of Cyclin A/B1:Cdc2 complexes [Homo sapiens]
 - Formation of Cyclin A1:Cdc2 complexes
 - Formation of Cyclin A2:Cdc2 complexes
 - Formation of Cyclin B1:Cdc2 complexes

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	Reference P
	Mod
	Compartment
	Species
	Rules
	Reaction
	Events

S-Phase Start is is BIND

Referred to as: Start

Cell Division is is BIND

Referred to as: Division

View Math

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Last modification: Wed Jun 1 17:1

Event:

Cell Division

trigger:

leq(ubiquitinProtease1, 0.1)

delay:

0

assignments:

- 1. $kp = 2 * kp$
- 2. $Mass = Mass * pow(2, -1)$

Compartments

Name	Size
Cell	1.0

Species

Name	Compartment	Initial Amount	Initial Concentration
ubiquitinProtease1	Cell	1.0	

Parameters

Name	Value
kp	3.25
Mass	1.0

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Novak1997_CellCycle

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Reference Publication

Publication ID: [9256450](#) [Edit](#)

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: 2005-08-29T23:18:57

Last Modification Date: 2005-08-29T23:18:57

Creation Date: 2005-08-29T23:18:57

Creators: [Bruce Shapiro](#) [Remove](#)[Add](#)[Gene Ontology](#) mitotic cell cycle [Remove](#)[KEGG Pathway](#) sce04110 [Remove](#)[Reactome](#) 69278 [Remove](#)[Taxonomy](#) 4896 [Remove](#)[Gene Ontology](#) [GO:](#) [Add](#)[is](#) [Gene Ontology](#) [GO:](#) [Add](#)[is](#)
[has part](#)
[is part of](#)
[is version of](#)
[has version](#)
[is referenced by](#)

Compartments (1)

Species (22)

Rules (15)

BIOMD0000000007

Novak1997_CellCycle

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[Annotation Guidelines](#)

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- + ++

- + ++

Reference Publication

++ + -

- + ++

Model

++ + -

Submitter: [Nicolas Le Novère](#)

Submission Date: 2005-08-29T23:18:57

Last Modification Date: 2005-08-29T23:18:57

Creation Date: 2005-08-29T23:18:57

Creators: [Bruce Shapiro](#) Remove

Add

Gene [ontology mitotic cell cycle](#) Remove

KEGG Pathway [sce04110](#) Remove

Reactome [69278](#) Remove

Taxonomy [4896](#) Remove

set #1

is

Gene Ontology

GO:

Add



is

Gene Ontology

GO:

Add



- + ++

Compartments (1)

++ + -

- + ++

Species (22)

++ + -

ubiquitinProtease1

Compartment: [Cell](#)

Referred to as: *Ube*

+

is

BIND

Add



ubiquitinProtease2

Compartment: [Cell](#)

Referred to as: *Ube2*

+

is

BIND

Add



Wee1

Compartment: [Cell](#)

Referred to as: *Wee1*

+

is

UniProt [MIK1_SCHPO](#) Remove

set #1

UniProt [WEE1_SCHPO](#) Remove

BIND

Add



is

BIND

Add



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BIOMD0000000007 Novak1997_CellCycle

[SBML L2 V1](#) | [CellML](#) | [XPP](#)

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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)

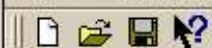
Reactions (25)

Cdc13_Cdc2 creation

Reactants:

Products: [Cdc13_Cdc2](#)

[Reactome 68910](#)
[Reactome 69282](#)



Copasi

Model

Tasks

Steady-State

Stoichiometry

Time Course

Result

Metabolic Control Analysis

Output

Plots

ConcentrationPlot

Reports

Functions

Task Name

Trajectory Task

☐ Task Executable

Start Time

0

End Time

400

Interval size

4

Intervals

100

☒ store time series in memory

Method

Deterministic (LSODA)

Parameter value

Value

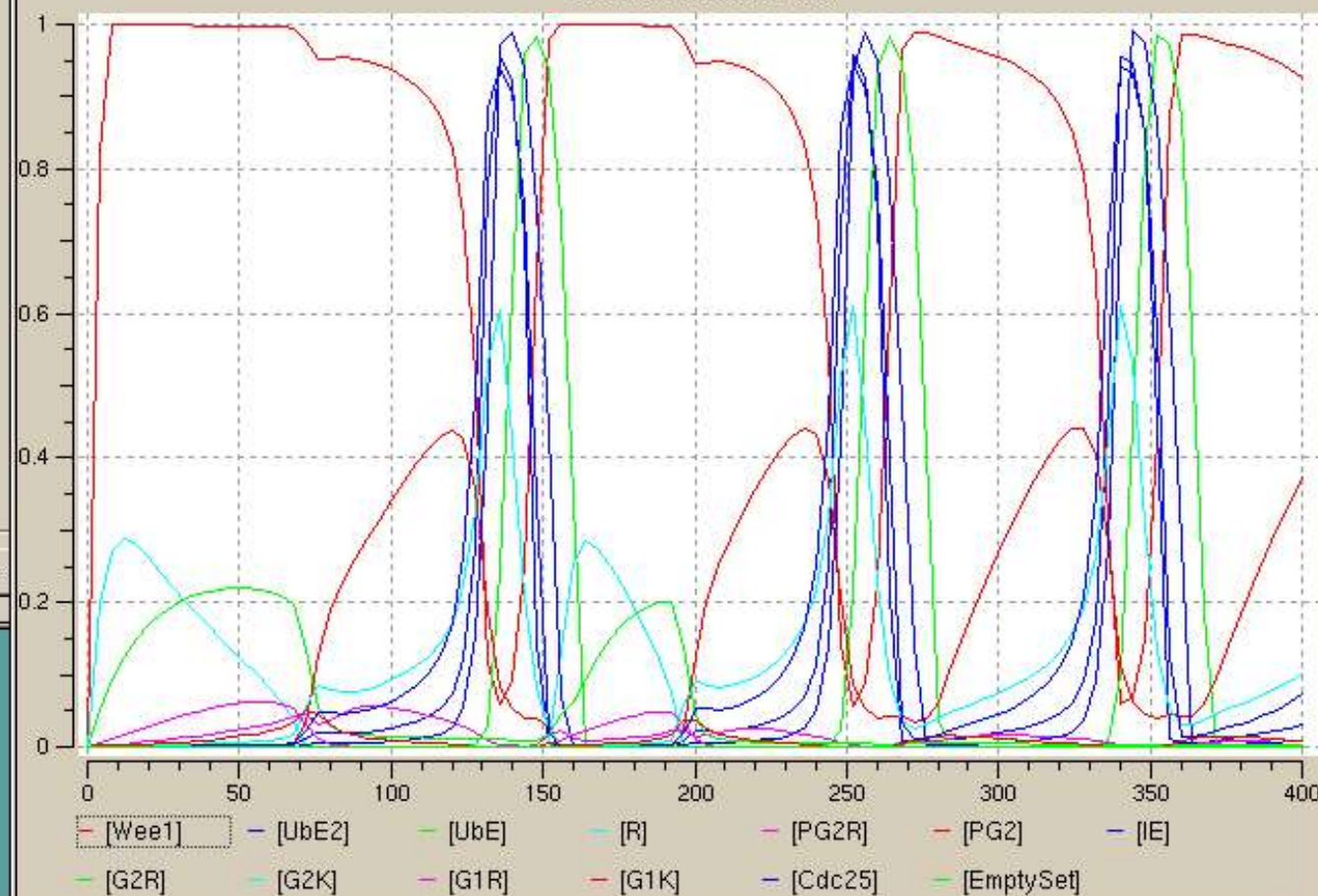
LSODA.RelativeTolerance

1e-06

COPASI Plot: ConcentrationPlot

Zoom Print

ConcentrationPlot



```
PlotItem_0
** compiling a CModel is requested.
PlotItem_0
** compiling a CModel is requested.
PlotItem_0
** compiling a CModel is requested.
PlotItem_0
** compiling a CModel is requested.
PlotItem_0
```

Release	# models	# reactions	# annotations
11 April 2005	20	631	1084
01 June 2005	30	736	1609
28 July 2005	44	943	2373
?? Decemberish	~75		

- Still important legacy from JWS Online, DOQCS, CellML Repo
- Supported by Nature Publishing Group and BioMedCentral. MSB advises deposition, and forward supplementary material
- Curation teams encode new models from literature



Level 1 Version 1
Level 1 Version 2
Level 2 Version 1



Level 2 Version 1



Version 1.1
XPP-Aut



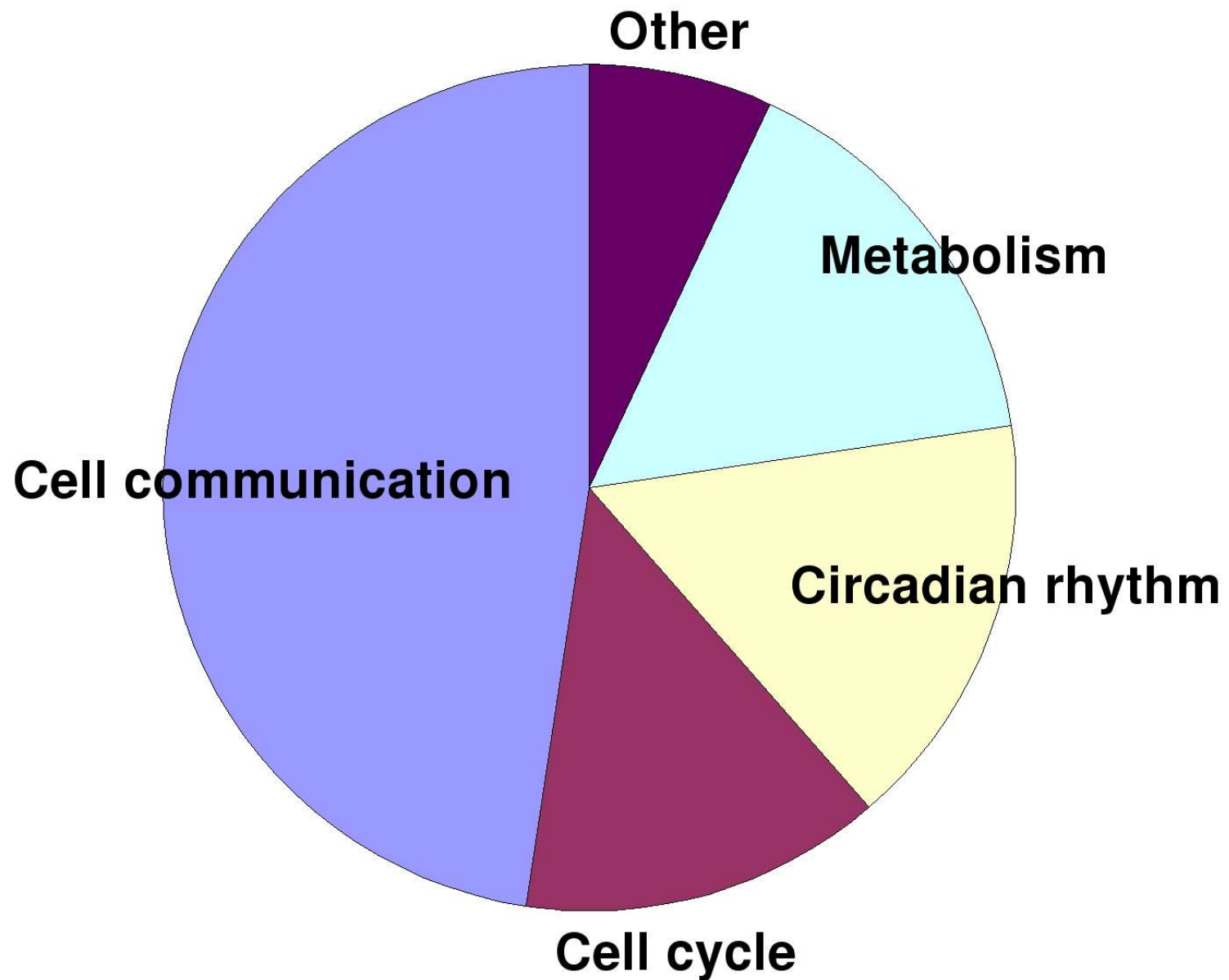
Version 1.0
Version 1.1



Graphs (SBGN?)

BioPAX?



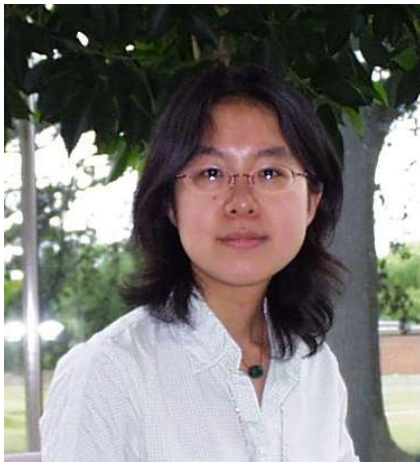




Marco Donizelli, Chen Li: Tomcat/Xindice/Web interface



Melanie Courtot: MySQL



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



Curation



External contributors

EBI

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- Marco Donizelli
- Mélanie Courtot
- Chen Li
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- Nicolas Rodriguez
- Alexander Broicher

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Programs used for curation

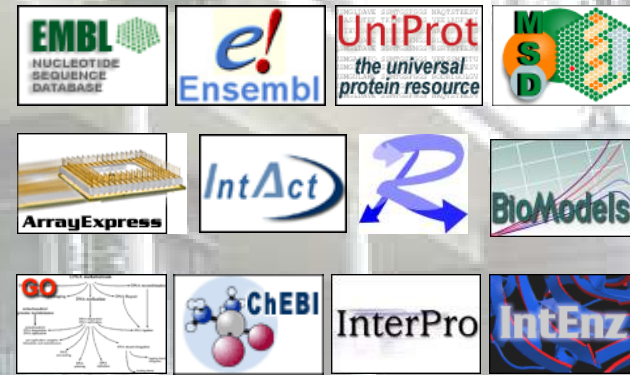
- COPASI
- SBMLodeSolver
- Jarnac/JDesigner
- XPP-Aut



British outstation of the European Molecular Biology Laboratory

- Data resources

- Sequences, structures
- Transcriptomics, Proteomics pathways, models
- Controlled vocabularies and dictionaries
- + ~200 other resources



- Research groups

- Comparative genomics (Ouzounis)
Structural Genomics (Thornton)
Molecular Evolution (Goldman)
- Text-Mining (Rebholz-Schumman)
Computational Systems Biology (Le Novère)
Statistical array analysis (Huber)
Genomic analysis of regulatory systems (Luscombe)

Marie Curie Training site Fellowships: 3-6 months. Fully funded.