Curation, exchange annotation of kinetic models: The BioModels.net initiative

Nicolas Le Novère, EMBL-EBI

We need to reuse mathematical models

- Non-specialists need to use models relevant for their research with simulation software without messing with their structure.
- Modeling 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)

SBML Systems Biology Markup Language

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

Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is **supported by over 85 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
COPASI
Cytoscape
DBsolve*
Dizzy
E-CELL
ecellJ
ESS
FluxAnalyzer
Fluxor
Gepasi
INSILICO discovery
Jarnac
JDesigner
JigCell
JSIM
JWS Online
Karyote*
KEGG2SBML
Kinsolver*
libSBML
MATLAB SBToolbox
MathSBML
MesoRD
MetaboLogica
MetaFluxNet
MMT2
Modesto
Moleculizer
Monod
NetBuilder
PANTHER Pathway
PathArt
PathScout
Pathway Tools
PathwayBuilder
PaVESy
Reactome
ProcessDB*
PROTON
PySCeS*
runSBML
SBML ODE Solver
SBMLeditor
SBMLR
SBMLSim
SBMLToolbox
SBW
SCIpath
Sigmoid*
SigPath
SigTran
SIMBA
Simpathica
SimWiz
SmartCell
SRS Pathway Editor
StochSim
STOCKS
TERANODE Suite
Trelis
Virtual Cell
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, (2) enabling models to be shared and published in a form other researchers can use even in a different software environment, and (3) ensuring the survival of models (and the intellectual effort put into them) beyond the lifetime of the software used to create them.

SBMLSim Announced

(July 6, 2005) **SBMLSim** provides a MATLAB GUI that allows the user to import a SBML model, simulate it, and visualize the simulations.

read more

New SRS Pathway Editor

(July 5, 2005) LION bioscience AG has released **SRS Pathway Editor**, a system for constructing pathways from multiple data sources using Web Services.

read more

New SBML Integration Server

(June 28, 2005) An experimental new **SBML Integration Server** allows you to submit models for simulation and retrieve results later.

read more

New SBW Web service

(June 28, 2005) This experimental web service from the KGI group allows any SBW module to be turned into a web service.

read more

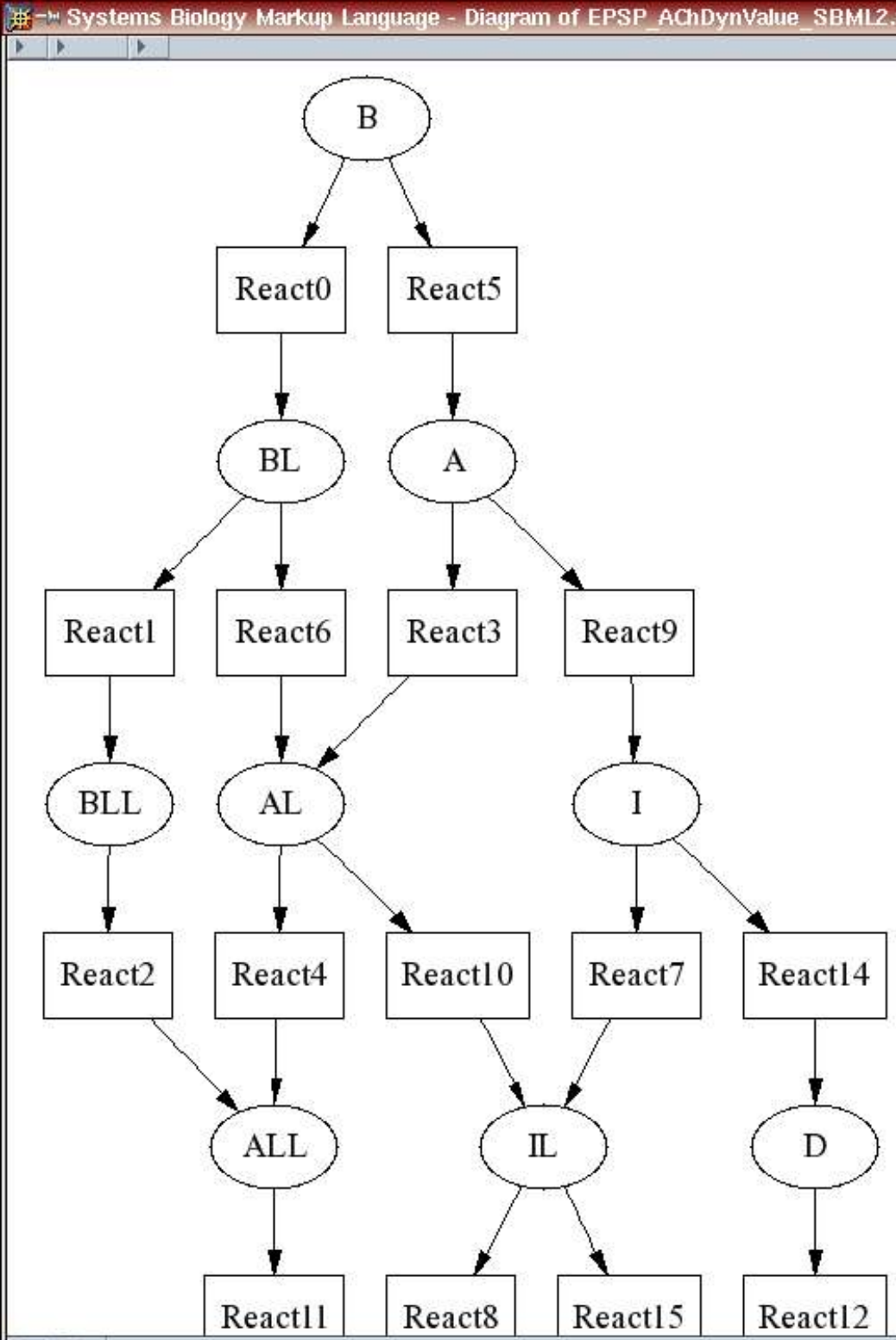
PROTON supports SBML

(June 23, 2005) **PROTON** is a tool to reconstruct user-specific models of biochemical networks from distributed databases. It supports SBML.

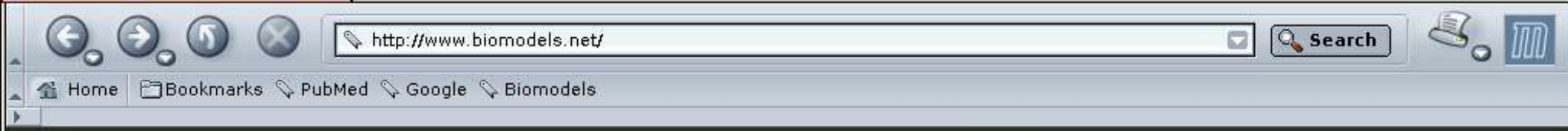
read more

See older news items.

```
<?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>
```


Systems Biology Markup Language - Diagram of EPSP_AChDynValue_SBML2.xml - Mozilla
B
React0
React5
BL
A
React1
React6
React3
React9
BLL
AL
I
React2
React4
React10
React7
React14
ALL
IL
D
React11
React8
React15
React12
http://sbml.org/documents

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.

Search

RSS / Atom

Minimum Information Requested In the Annotation of Models

N Le Novère (BioModels DB)
A Finney, M Hucka, B Shapiro (SBML)
U Bhalla (DOQCS)
F Campagne (Sigpath)
J Collado-Vides (RegulonDB)
E Crampin, M Halstead, P Nielsen (CellML)
P Mendes (COPASI)
JL Snoep (JWS Online)
E Klipp, H Sauro, HD Spence, BL Wanner

accepted in *Nature Biotechnology*

- A Standard for reference correspondance
- An annotation scheme
  - Attribution of the model creation and curation
  - Relation wih external data resources

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.

Systems Biology Ontology

- 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.

Systems Biology Ontology

```
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
```

Hidden assumptions

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

  Henri-Michaelis-Menten (1913): $$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])} ; K_m = \frac{k_{-1}}{k_1}$$

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

  Van Slyke (1914): $$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])} ; K_m = \frac{k_p}{k_1}$$

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

  Briggs-Haldane (1925): $$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])} ; K_m = \frac{(k_{-1} + k_p)}{k_1}$$

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

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

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

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

Revealed assumptions

```
<reaction>
   <listOfReactants>
     <speciesReference species="S" />
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="P" />
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="E" />
   </listOfModifiers>
   <kineticLaw definitionURL="http://www.biomodels.net/SBO/#SBO:0000015">
     <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>
```

Complete description of a rate-law term

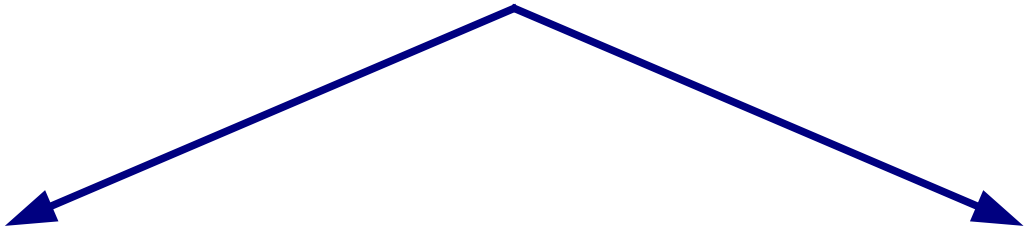
```
[Term]
id: SBO:0000015
name: Briggs-Haldane equation
def: "Rate-law presented in G. E. Briggs and J. B. S. Haldane (1925) A note on the
kinetics of enzyme action, Biochem. J., 19, 339-339. It is a general rate equation
that does not require the restriction of equilibrium of Michaelis-Menten or irreversible
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 Km 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">
      <lambda>
      <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000004">S</ci></bvar>
      <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>
      <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>
```

Revealed assumptions

```
<reaction>
   <listOfReactants>
     <speciesReference species="S" definitionURL="http://www.biomodels.net/SBO/#SBO:0000004"/>
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="P" definitionURL="http://www.biomodels.net/SBO/#SBO:0000005"/>
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="E" definitionURL="http://www.biomodels.net/SBO/#SBO:0000006"/>
   </listOfModifiers>
   <kineticLaw definitionURL="http://www.biomodels.net/SBO/#SBO:0000015">
     <listOfParameters>
       <parameter id="Km"  definitionURL="http://www.biomodels.net/SBO/#SBO:0000008"/>
       <parameter id="kp" definitionURL="http://www.biomodels.net/SBO/#SBO:0000019"/>
     </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>
   <listOfReactants>
     <speciesReference species="A" definitionURL="http://www.biomodels.net/SBO/#SBO:0000004"/>
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="B" definitionURL="http://www.biomodels.net/SBO/#SBO:0000005"/>
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="C" definitionURL="http://www.biomodels.net/SBO/#SBO:0000006"/>
   </listOfModifiers>
   <kineticLaw definitionURL="http://www.biomodels.net/SBO/#SBO:0000015">
     <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

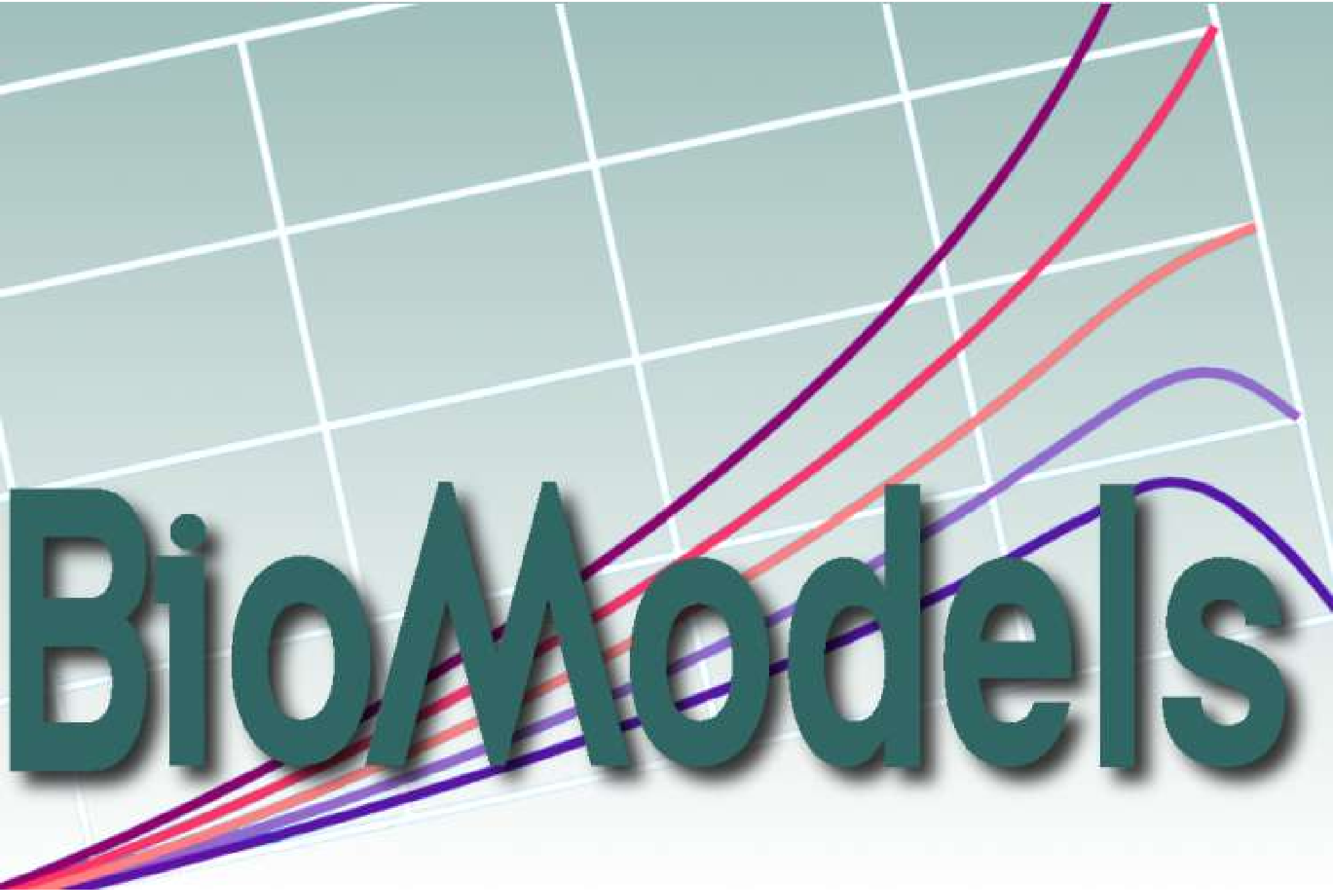
$$v = \frac{C \cdot V \cdot [A]}{(U + [A])}$$

discrete simulator

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

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

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

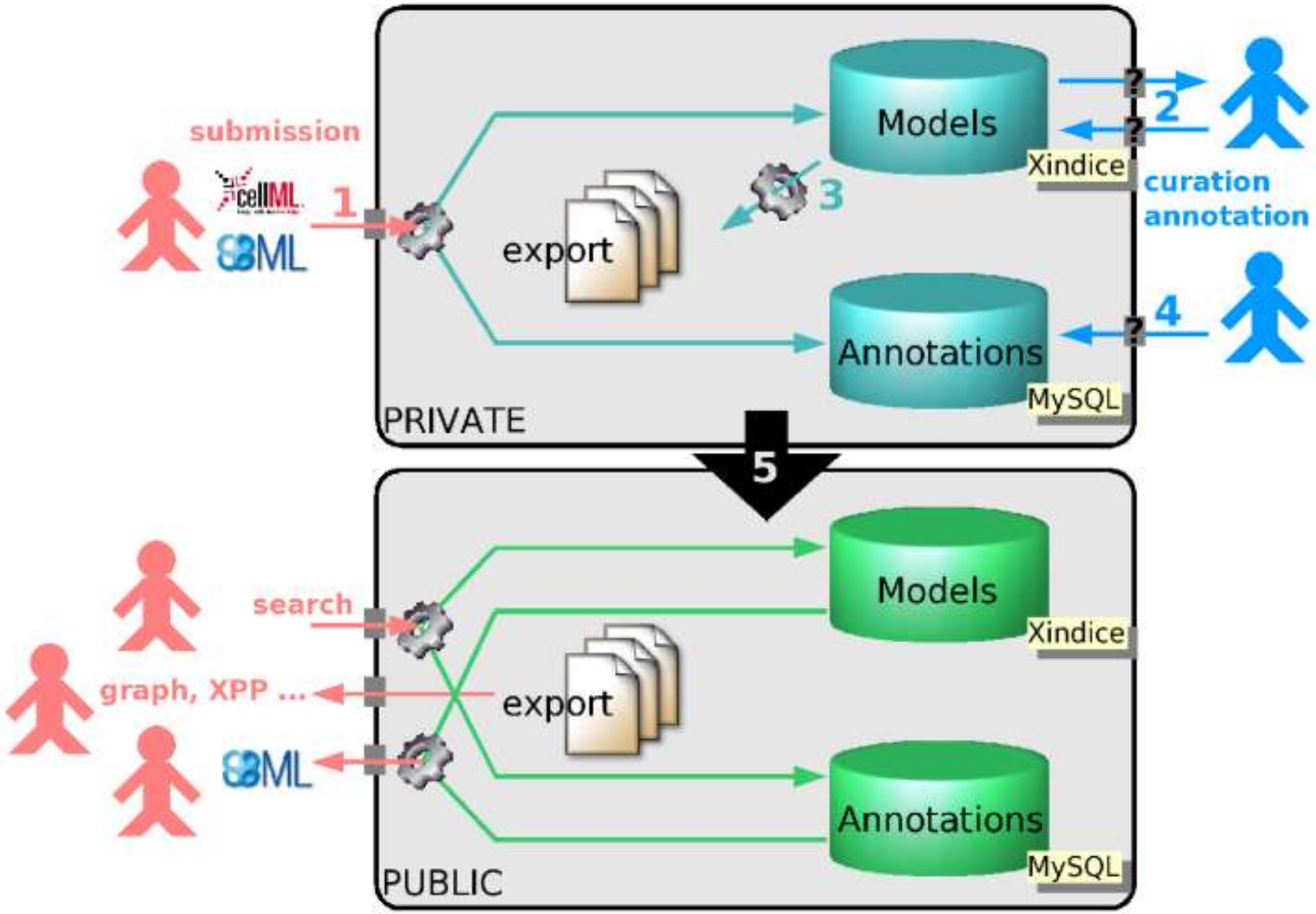

BioModels

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

Le Novère N, Bornstein B, Courtot C, Donizelli M, Dharuri H, Li L, Sauro H, Schilstra M, Shapiro B, Snoep JL, Hucka M. *Nucleic Acids Res.,* Submitted

Structure of BioModels Database



Model annotation

model	Submitter, Creators, publication, Gene Ontology, IC10, 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

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

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

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

Creators: Tomas Radivoyevitch
Nicolas Le Novere

Gene Ontology	GO:0046655
KEGG Pathway	map00670 map00790
Taxonomy	9606
ICD10	C50

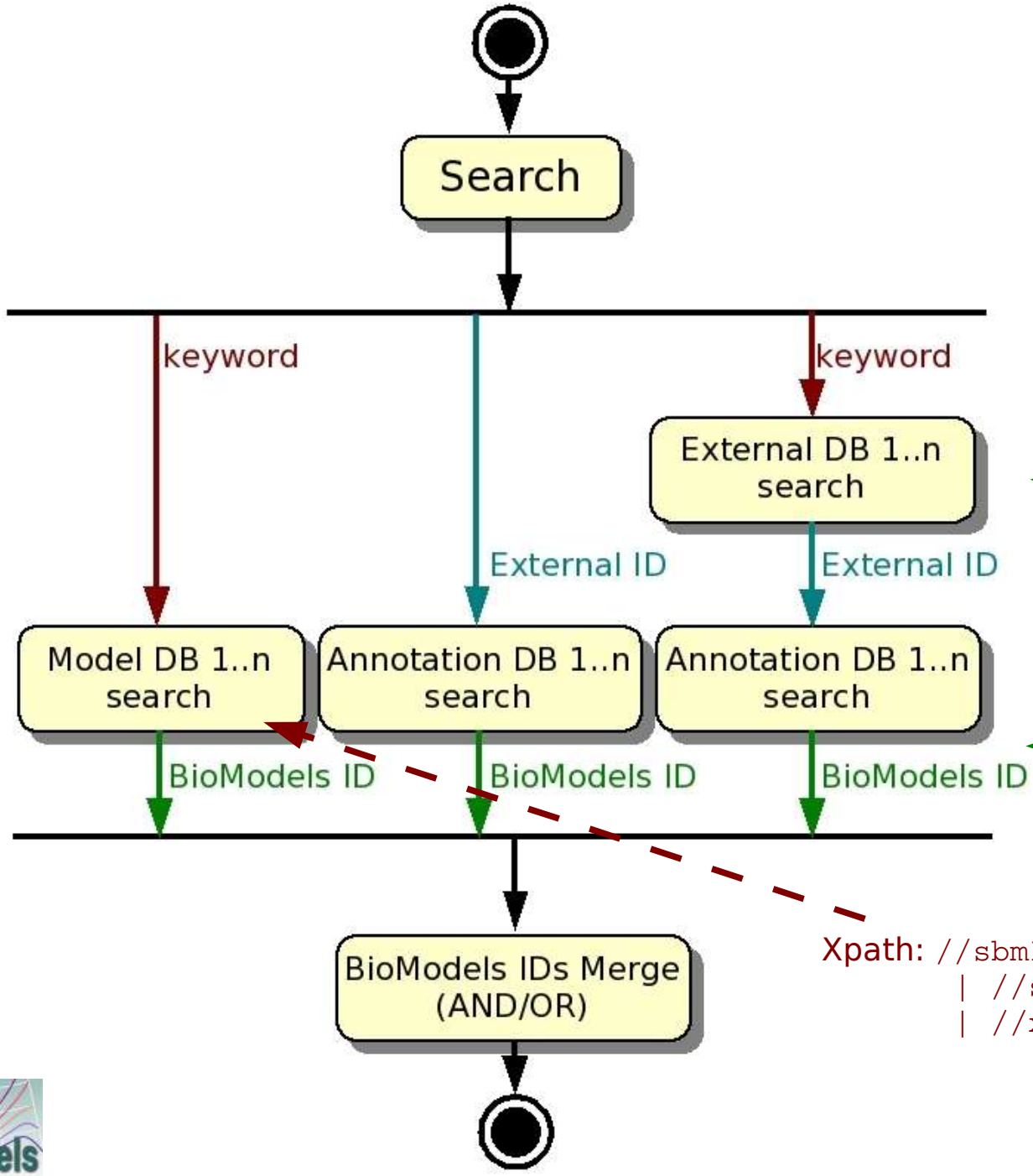
Compartments (2)

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

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')]
```

BIOMODELS.NET

BioModels Database
- Browse
- Search

Submit Your Model

Curators Sign In

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

New Search

BIOMODELS.NET

BioModels Database

Submit Your Model

BioModels Annotation

- Browse
- Search
- Submit
- Replace
- Annotate

Terms of Use

Contact

Computational Neurobiology

BIOMD0000000007 Novak1997_CellCycle_13var

Download SBML

Reference Publication

PubMed ID: 9256450

Proc Natl Acad Sci U S A. 1997 Aug 19;94(17):9147-52.
Modeling the control of DNA replication in fission yeast.
Novak B, Tyson JJ.

Model

Submitter: Nicolas Le Novère

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

Last Modification Date: 2005-04-01T23:58:07

Creators: Bruce Shapiro

Gene Ontology	GO:0000278 GO:0007049
KEGG Pathway	sce04110
Taxonomy	4896
Reactome	69278

Compartments (1)

Species (14)

Reactions (33)

Reaction1
Reactants: EmptySet
Products: mass
Modifiers:

Reaction2
Reactants: EmptySet
Products: G2K
Modifiers:

Reactome	68910 69282

Reaction3
Reactants: G2K
Products: EmptySet

Gene Ontology	GO:0008054

1: Proc Natl Acad Sci U S A. 1997 Aug 19;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.

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), cdc13Delta and rum1(OP) (endoreplication), and wee1(-) rum1Delta (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]

BIOMODELS.NET

BioModels Database

Submit Your Model

BioModels Annotation

- Browse
- Search
- Submit
- Replace
- Annotate

Terms of Use

Contact

Computational Neurobiology

BIOMD0000000007 **Novak1997_CellCycle_13var**

Download SBML

Reference Publication

PubMed ID: 9256450

Proc Natl Acad Sci U S A. 1997 Aug 19;94(17):9147-52.
Modeling the control of DNA replication in fission yeast.
Novak B, Tyson JJ.

Model

Submitter: Nicolas Le Novère

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

Last Modification Date: 2005-04-01T23:58:07

Creators: Bruce Shapiro

Gene Ontology	GO:0000278 GO:0007049
KEGG Pathway	sce04110
Taxonomy	4896
Reactome	69278

Compartments (1)

Species (14)

Reactions (33)

Reaction1
Reactants: EmptySet
Products: mass
Modifiers:

Reaction2
Reactants: EmptySet
Products: G2K
Modifiers:

Reactome	68910 69282

Reaction3
Reactants: G2K
Products: EmptySet

Gene Ontology	GO:0008054

Novak and Tyson Cell Cycle Model (1997)

Citation

Novak B, tyson JJ (1997) Modeling the control of DNA replication in fission yeast, PNAS, USA, 94:9147-9152. http://www.pnas.org/cgi/content/abstract/ 94/17/9147

Description

A cell cycle model with 13 dynamic variables (Cdc25,G1K,G1R=[Cig2/Cdc2/Rum1],G2K=[Cdc13/Cdc2],G2R=[Cdc13/Cdc2/Rum1],IE=[Intermediary enzyme],mass,PG2=[Cdc13/P-Cdc2],PG2R=[Cdc13/P-Cdc2/Rum1],R=[Rum1],UbE,UbE2, Wee1} and two auxilllary variables MPF = G2K+ beta*PG2, SPF=MPF+alpha*G1K+Cig1, (alpha, beta, Cig1 constants) . NOTE: The following switches in the published model are NOT described by the SBML: "Switches(i) When SPF crosses 0.1 from below, S phase is initiated (Start).(ii) When UbE crosses 0.1 from above, the cell divides functionally (mass->mass/2), although visible cytokinesis may be delayed.(iii) 60 min after Start,kp is divided by 2, and at cell division kp is multiplied by 2." (from Table 1 of the cited reference).

Rate constant	Reaction
0	G1R -> R
0.00175	EmptySet -> G1K
0.00495*mass[t]	EmptySet -> mass
0.0075*(1 - UbE[t]) + 0.25*UbE[t]	G2K -> EmptySet
0.0075*(1 - UbE[t]) + 0.25*UbE[t]	PG2 -> EmptySet
0.015	EmptySet -> G2K
0.025*(1 - Cdc25[t]) + 0.5*Cdc25[t]	PG2 -> G2K
0.035*(1 - Wee1[t]) + 0.35*Wee1[t]	G2K -> PG2
0.0375*(1 - UbE2[t]) + 7.5*UbE2[t]	G1K -> EmptySet
0.05 + 0.0075*(1 - UbE[t]) + 0.25*UbE[t]	G2R -> R
0.05 + 0.0075*(1 - UbE[t]) + 0.25*UbE[t]	PG2R -> R
0.09375	EmptySet -> R
0.1	G1R -> G1K + R
0.1	G2R -> G2K + R
0.1	PG2R -> PG2 + R
0.1875	G1R -> G1K

BIOMODELS.NET

BioModels Database
- Browse
- Search

Submit Your Model

Curators Sign In

FAQ

Terms of Use

Contact

BIOMD0000000007 Novak1997_CellCycle

- Download SBML
- View Model Graph
- Submit Model Issue

Reference Publication

PubMed ID: 9256450

Proc Natl Acad Sci U S A. 1997 Aug 19;94(17):9147-52.
Modeling the control of DNA replication in fission yeast.
Novak B, Tyson JJ.

Model

Submitter: Nicolas Le Novère

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

Last Modification Date: 2005-06-27T16:56:33

Creators: Bruce Shapiro

Gene Ontology	GO:0000278
KEGG Pathway	sce04110
Taxonomy	4896
Reactome	69278

Compartments (1)

Species (22)

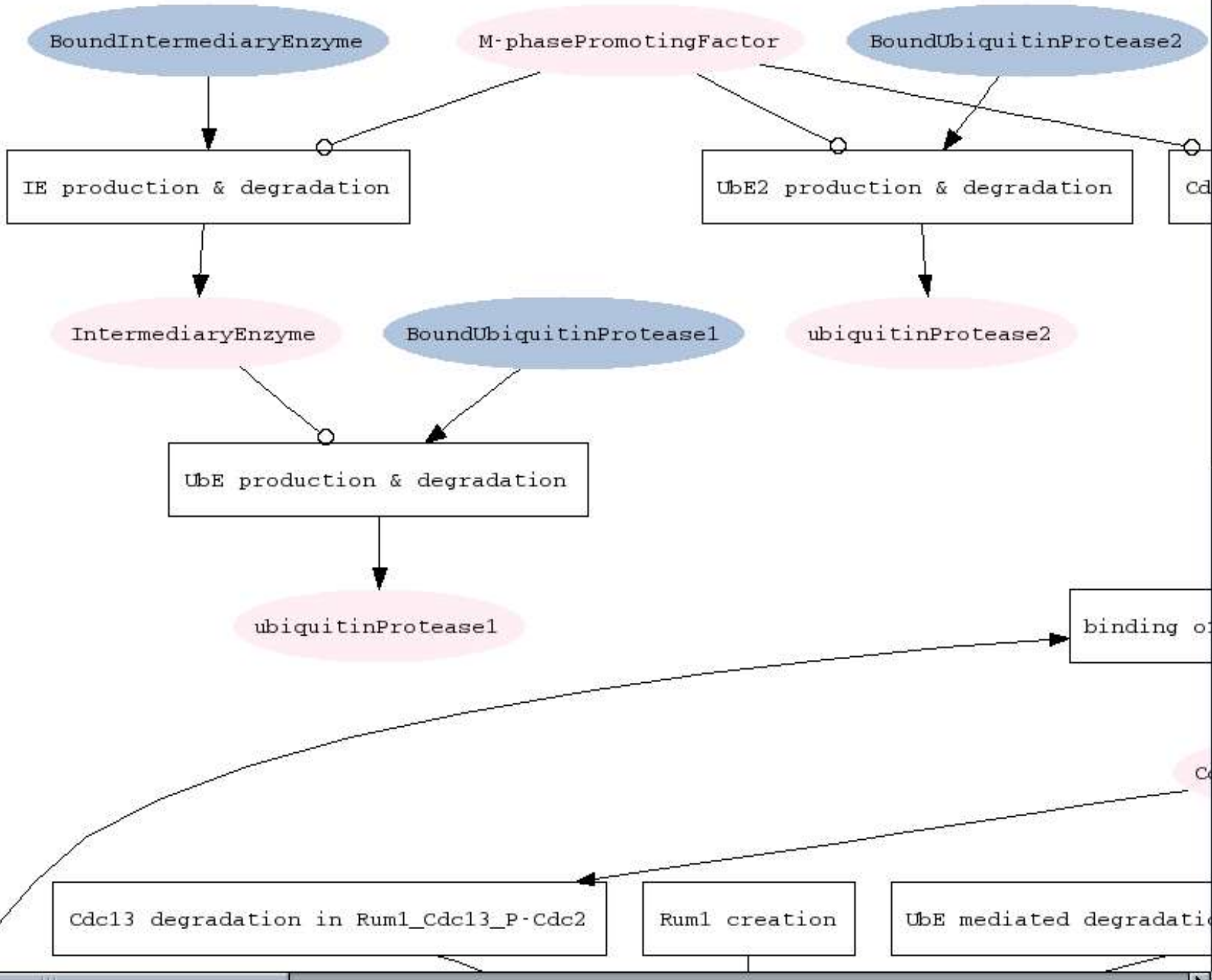
Reactions (25)

Cdc13_Cdc2 creation
Reactants:
Products: Cdc13_Cdc2
Modifiers:

Reactome	68910 69282

Cig2_Cdc2 creation
Reactants:
Products: Cig2_Cdc2

BIOMD0000000007 Novak1997_CellCycle



BIOMODELS.NET

BioModels Database
- Browse
- Search

Submit Your Model

Curators Sign In

FAQ

Terms of Use

Contact

BIOMD0000000007 Novak1997_CellCycle

- Download SBML
- View Model Graph
- Submit Model Issue

Reference Publication

PubMed ID: 9256450

Proc Natl Acad Sci U S A. 1997 Aug 19;94(17):9147-52.
Modeling the control of DNA replication in fission yeast.
Novak B, Tyson JJ.

Model

Submitter: Nicolas Le Novère

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

Last Modification Date: 2005-06-27T16:56:33

Creators: Bruce Shapiro

Gene Ontology	GO:0000278
KEGG Pathway	sce04110
Taxonomy	4896
Reactome	69278

Compartments (1)

Species (22)

Reactions (25)

Cdc13_Cdc2 creation
Reactants:
Products: Cdc13_Cdc2
Modifiers:

Reactome 68910 69282

Cig2_Cdc2 creation
Reactants:
Products: Cig2_Cdc2

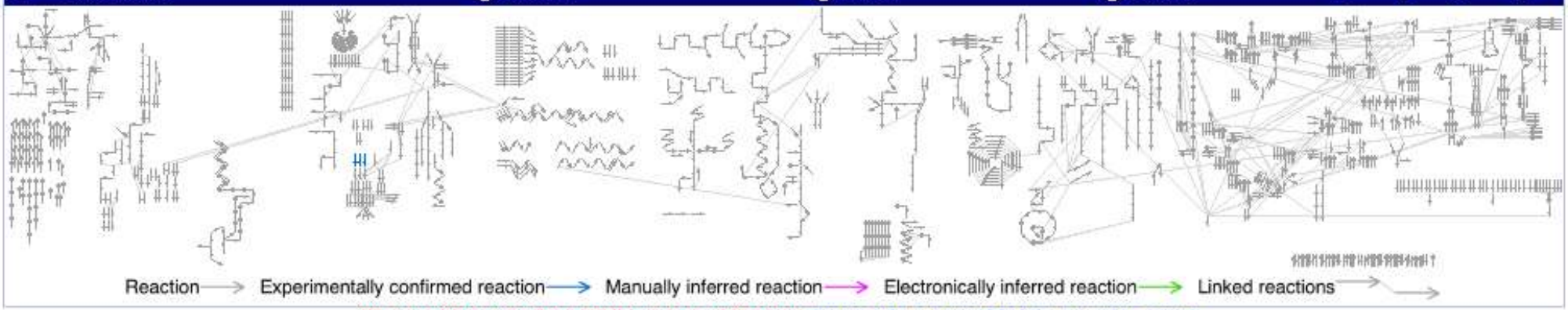
Reactome: Formation of Cyclin A/B1:Cdc2 complexes - Mozilla

BioModels Database - Mozilla

Home | About | TOC | User Guide | Data Model | Schema | Extended search | PathFinder | SkyPainter | Download | Linking | Citing

Find everything with ALL of the words in Homo sapiens Go!

Click on the map: shifts focus zooms in zooms out



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]**

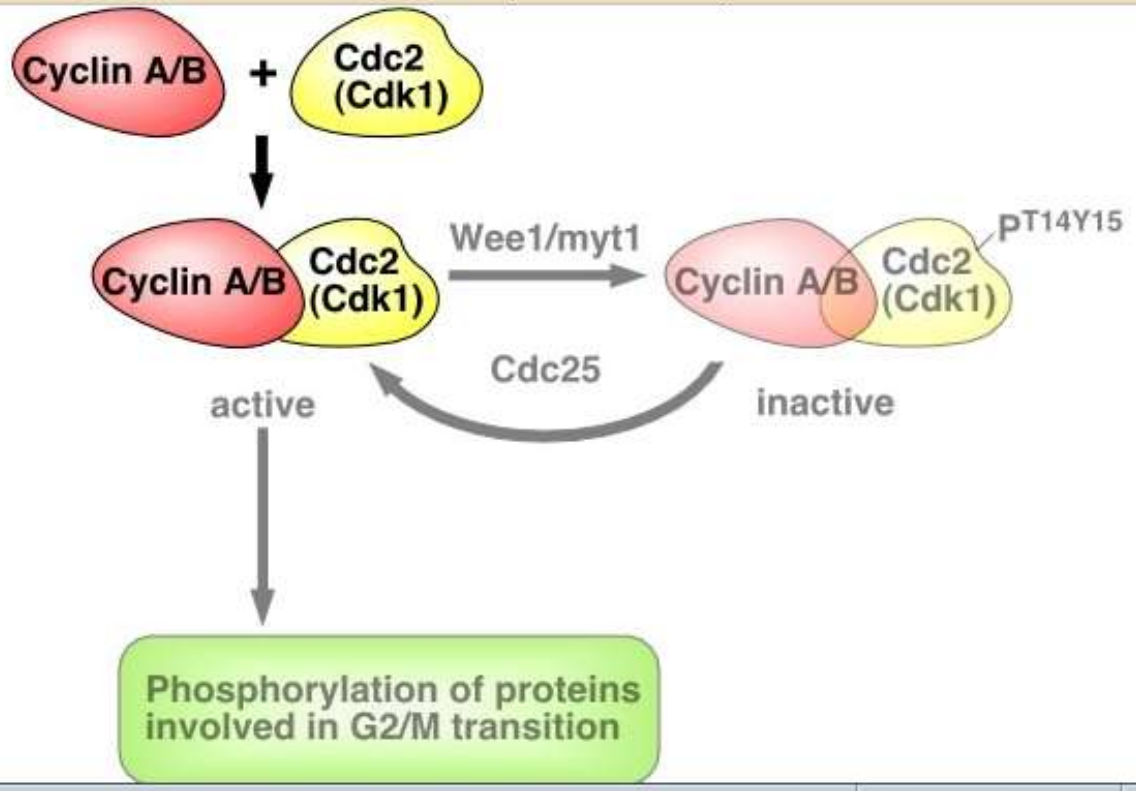
Formation of Cyclin A1:Cdc2 complexes

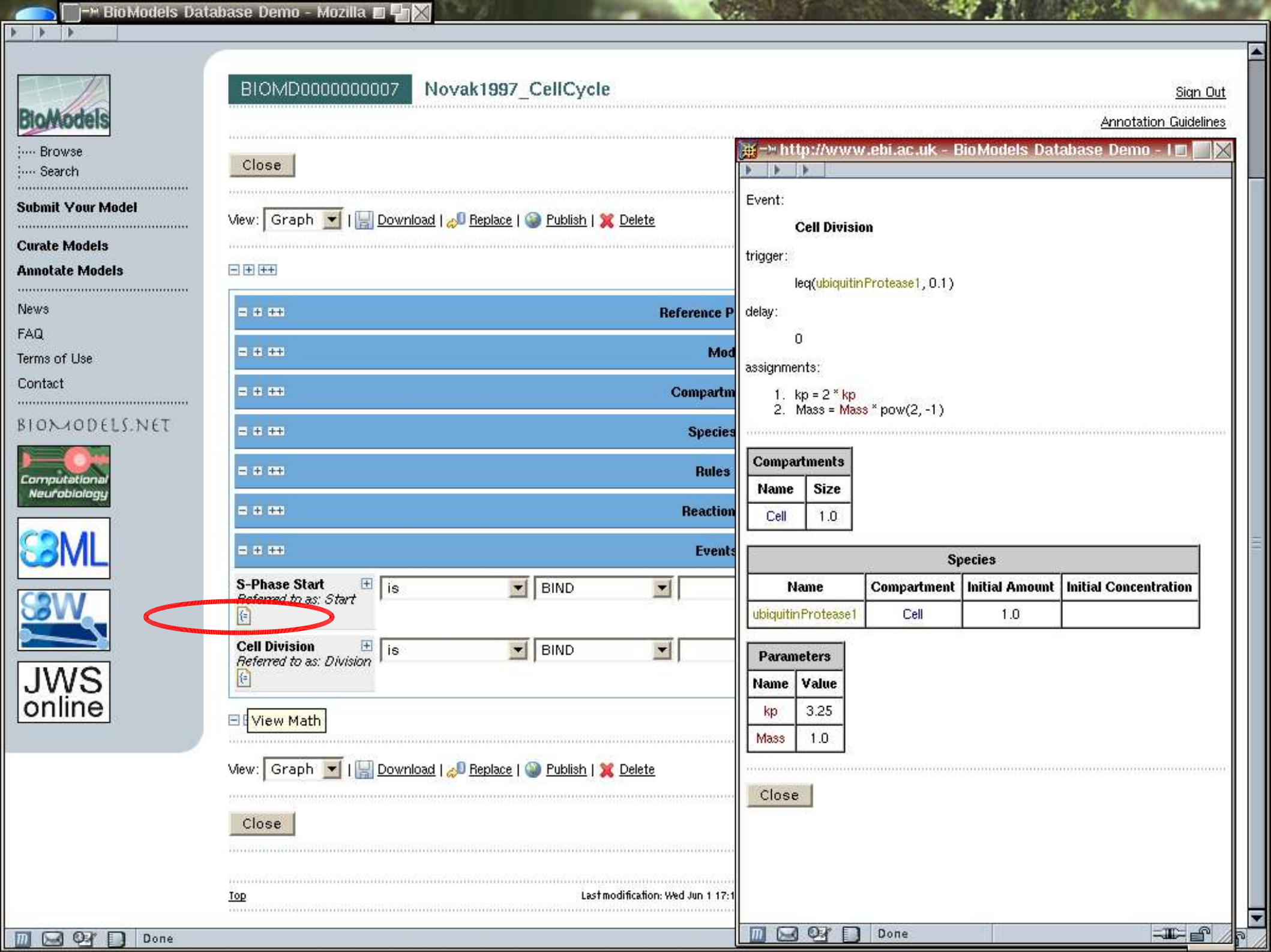
Formation of Cyclin A2:Cdc2 complexes

Formation of Cyclin B1:Cdc2 complexes

Show hierarchy types

Formation of Cyclin A/B1:Cdc2 complexes




BioModels Database Demo - Mozilla
BioModels
Browse
Search
Submit Your Model
Curate Models
Annotate Models
News
FAQ
Terms of Use
Contact
BIOMODELS.NET
Computational Neurobiology
SBML
SBW
JWS online
BIOMD0000000007
Novak1997_CellCycle
Sign Out
Annotation Guidelines
Close
View: Graph | Download | Replace | Publish | Delete
Reference P
Mod
Compartm
Species
Rules
Reaction
Events
S-Phase Start
Referred to as: Start
is
BIND
Cell Division
Referred to as: Division
is
BIND
View Math
View: Graph | Download | Replace | Publish | Delete
Close
Top
Last modification: Wed Jun 1 17:1
Done
http://www.ebi.ac.uk - BioModels Database Demo - I
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
Close
Done

BioModels
Browse
Search

Submit Your Model

Curate Models

Annotate Models

News
FAQ
Terms of Use
Contact

BIOMODELS.NET

Computational Neurobiology

SBML

SBW

JWS online

BIOMD0000000007 **Novak1997_CellCycle**

Sign Out

Annotation Guidelines

Close

View: Graph | Download | Replace | Publish | Delete

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

is set #1

Gene Ontology mitotic cell cycle Remove

KEGG Pathway sce04110 Remove

Reactome 69278 Remove

Taxonomy 4896 Remove

Gene Ontology | GO: | Add

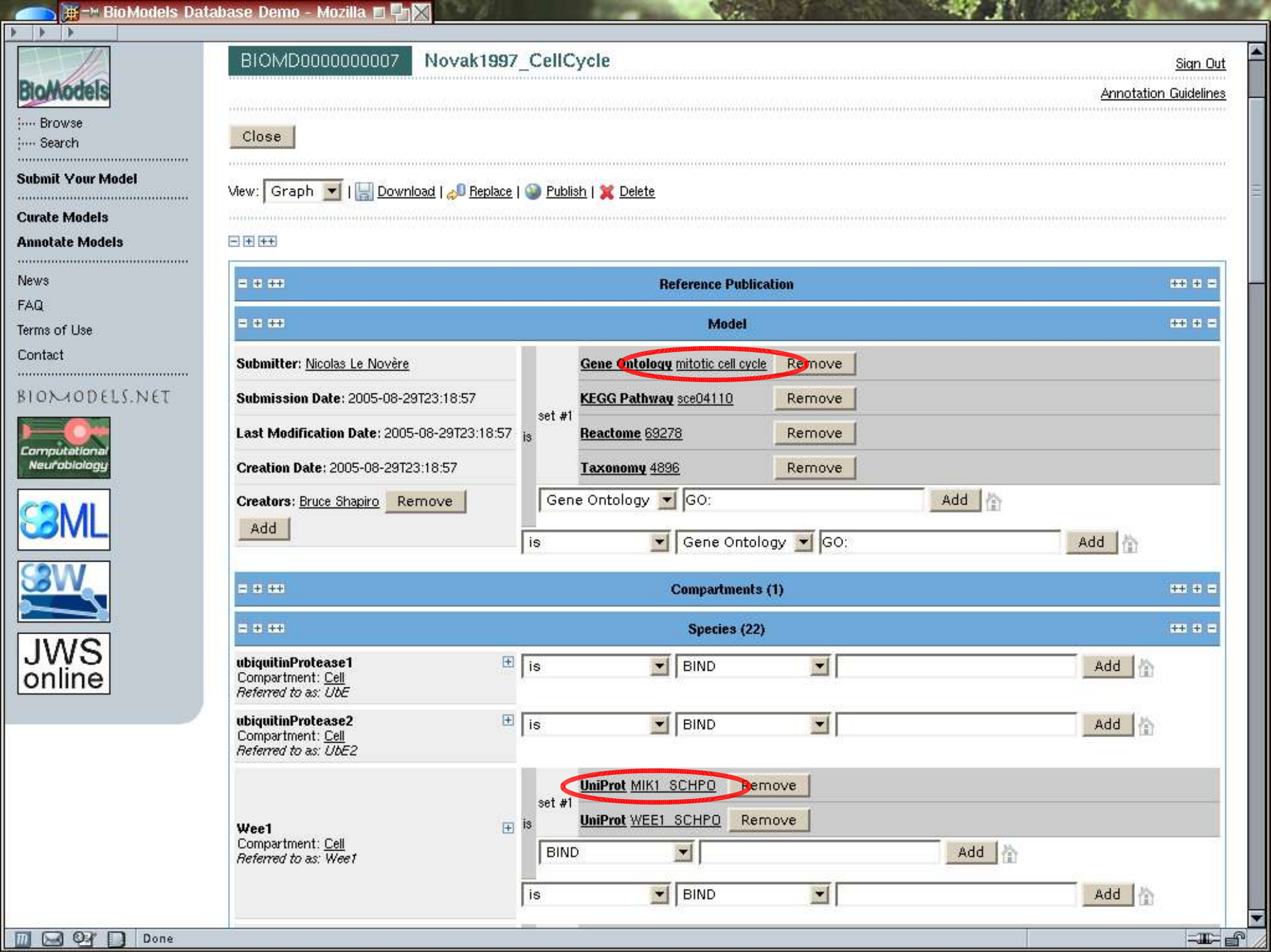
is | Gene Ontology | GO: | Add

is
has part
is part of
is version of
has version
is referenced by

Compartments (1)

Species (22)

Rules (15)


BioModels Database Demo - Mozilla
BioModels
Browse
Search
Submit Your Model
Curate Models
Annotate Models
News
FAQ
Terms of Use
Contact
BIOMODELS.NET
Computational Neurobiology
SBML
SBW
JWS online
BIOMD0000000007
Novak1997_CellCycle
Sign Out
Annotation Guidelines
Close
View: Graph | Download | Replace | Publish | Delete
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
set #1
is
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
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
set #1
is
UniProt MIK1_SCHPO Remove
UniProt WEE1_SCHPO Remove
BIND Add
is BIND Add
Done

Browse
Search

Submit Your Model

Curate Models

Annotate Models

News
FAQ
Terms of Use
Contact

BIOMODELS.NET

BIOMD0000000007 Novak1997_CellCycle

Sign Out

Annotation Guidelines

Close

View: Graph | Download | Replace | Publish | Delete

Graph
XPP

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

Compartments (1)

Species (22)

Rules (15)

Reactions (25)

Events (2)

View: Graph | Download | Replace | Publish | Delete

Close

BIOMODELS.NET

BioModels Database
- Browse
- Search

Submit Your Model

Curators Sign In

FAQ

Terms of Use

Contact

BIOMD0000000007 Novak1997_CellCycle

- Download SBML
- View Model Graph
- Submit Model Issue

Reference Publication

PubMed ID: 9256450

Proc Natl Acad Sci U S A. 1997 Aug 19;94(17):9147-52.
Modeling the control of DNA replication in fission yeast.
Novak B, Tyson JJ.

Model

Submitter: Nicolas Le Novère

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

Last Modification Date: 2005-06-27T16:56:33

Creators: Bruce Shapiro

Gene Ontology	GO:0000278
KEGG Pathway	sce04110
Taxonomy	4896
Reactome	69278

Compartments (1)

Species (22)

Reactions (25)

Cdc13_Cdc2 creation
Reactants:
Products: Cdc13_Cdc2
Modifiers:

Reactome	68910 69282

Cig2_Cdc2 creation
Reactants:
Products: Cig2_Cdc2

COPASI (4.0 Build 12 test version)

rxvt <2>

File Tools Help

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

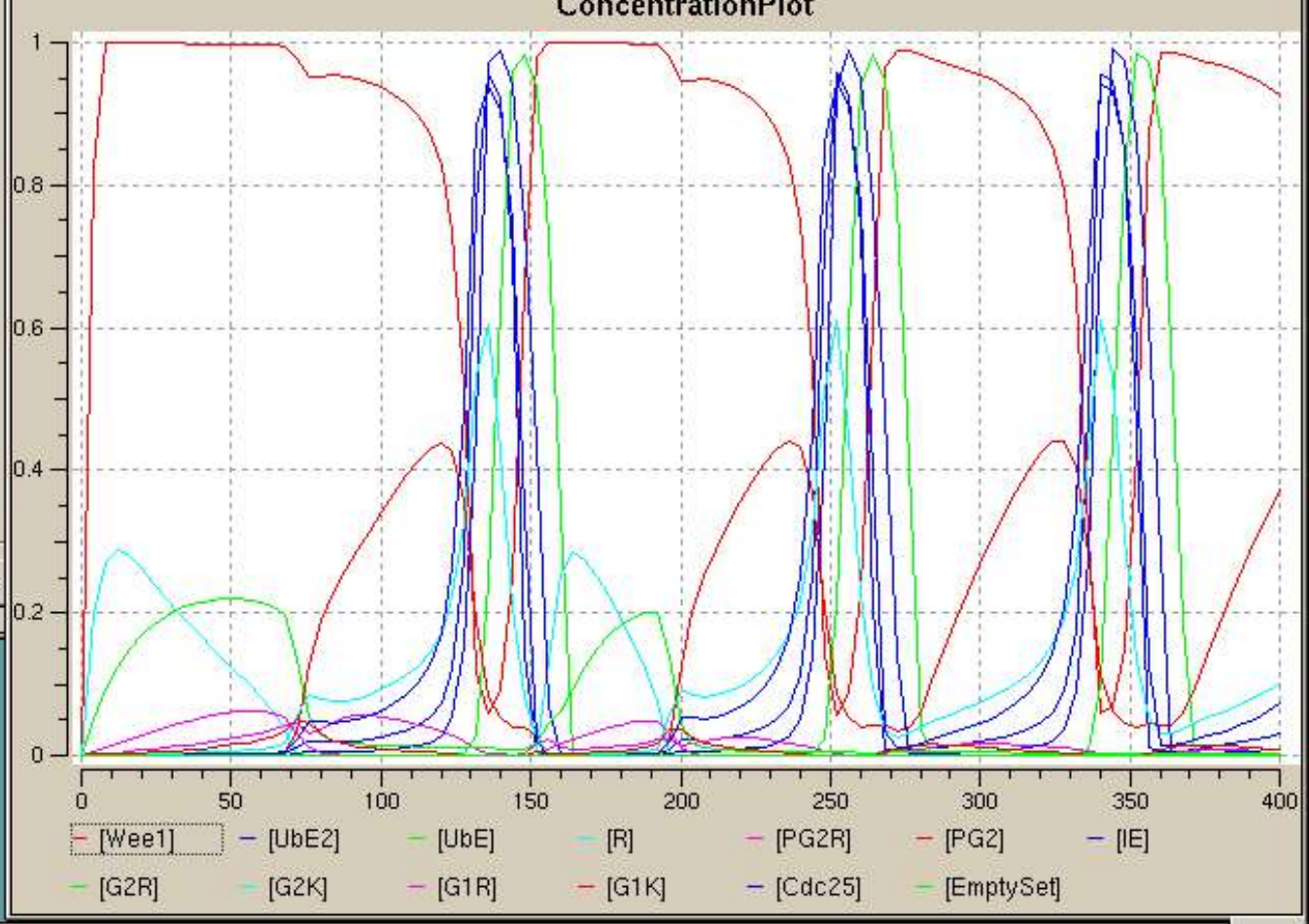
	Value
LSODA.RelativeTolerance	1e-06

Run

```
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
```

Copasi Plot: ConcentrationPlot

Zoom Print



Bottleneck: Few models are directly usable

- syntactically wrong (incorrect SBML)
  - typos in the elements and attributes
  - invalid default: e.g. “constant” parameter fixed by a rule
- semantically wrong (correct SBML but make no sense)
  - wrong species: misunderstanding of “constant” and “boundaryCondition”
  - wrong initialconditions: everything zeroed, would not start
  - wrong reaction: the rate law produces concentrations rather than amounts
- bad correspondence with the article
  - wrong units: built-in are not redefined, resulting in M instead of μM
  - wrong compartments: only one compartment represents nucleus+cytoplasm
  - wrong formalism: Michaelis-Menten instead of elementary reactions
  - everything is fine but does not produce the same results than in paper ...

Steady increase

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

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

An international collaboration

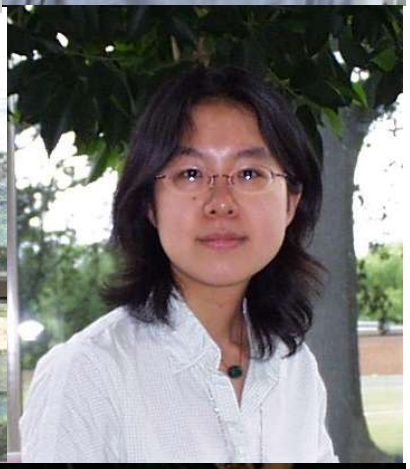
- EBI
  - Nicolas Le Novère
  - Marco Donizelli
  - Mélanie Courtot
  - Lu Li
  - Alexander Broicher
- SBML team
  - Michael Hucka
  - Andrew Finney
  - Bruce Shapiro
  - Benjamin Borstein
  - Maria Schilstra
  - Sarah Keating
- Keck Graduate Institute
  - Herbert Sauro
  - Harish Dharuri
- Systems Biology Institute
  - Hiroaki Kitano
  - Akira Funahashi
- Stellenbosh University
  - Jacky Snoep
- External contributors
  - Upinder Bhalla
  - Christoph Flamm
  - Ryan Gutenkunst
  - Adam Halasz
  - Rainer Machné
  - Marc Poolman
  - Tomas Radivoyevitch
  - Oleg Sokolsy
  - Joanne Matthews
  - Les Grivell
  - Boris Kholodenko
  - Tjeerd olde Scheper
  - Paul Smolen
  - Yukiko Matsuoka
- Programs used for curation
  - COPASI
  - SBMLodeSolver
  - Jarnac

The EBI team









```
<compneur>
  <member name="Nicolas Le Novère" role="leader"/>
  <member name="Alexander Broicher" role="alumni"/>
  <member name="Mélanie Courtot" role="developer"/>
  <member name="Marie-Ange Djite" role="alumni"/>
  <member name="Marco Donizelli" role="developer">
  <member name="Éric Fernandez" role="alumni"/>
  <member name="Lu Li" role="trainee"/>
  <member name="Nicolas Rodriguez" role="developer"/>"
  <member name="Dominic Tölle" role="PhD student"/>
</compneur>
```