

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

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

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

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](#)

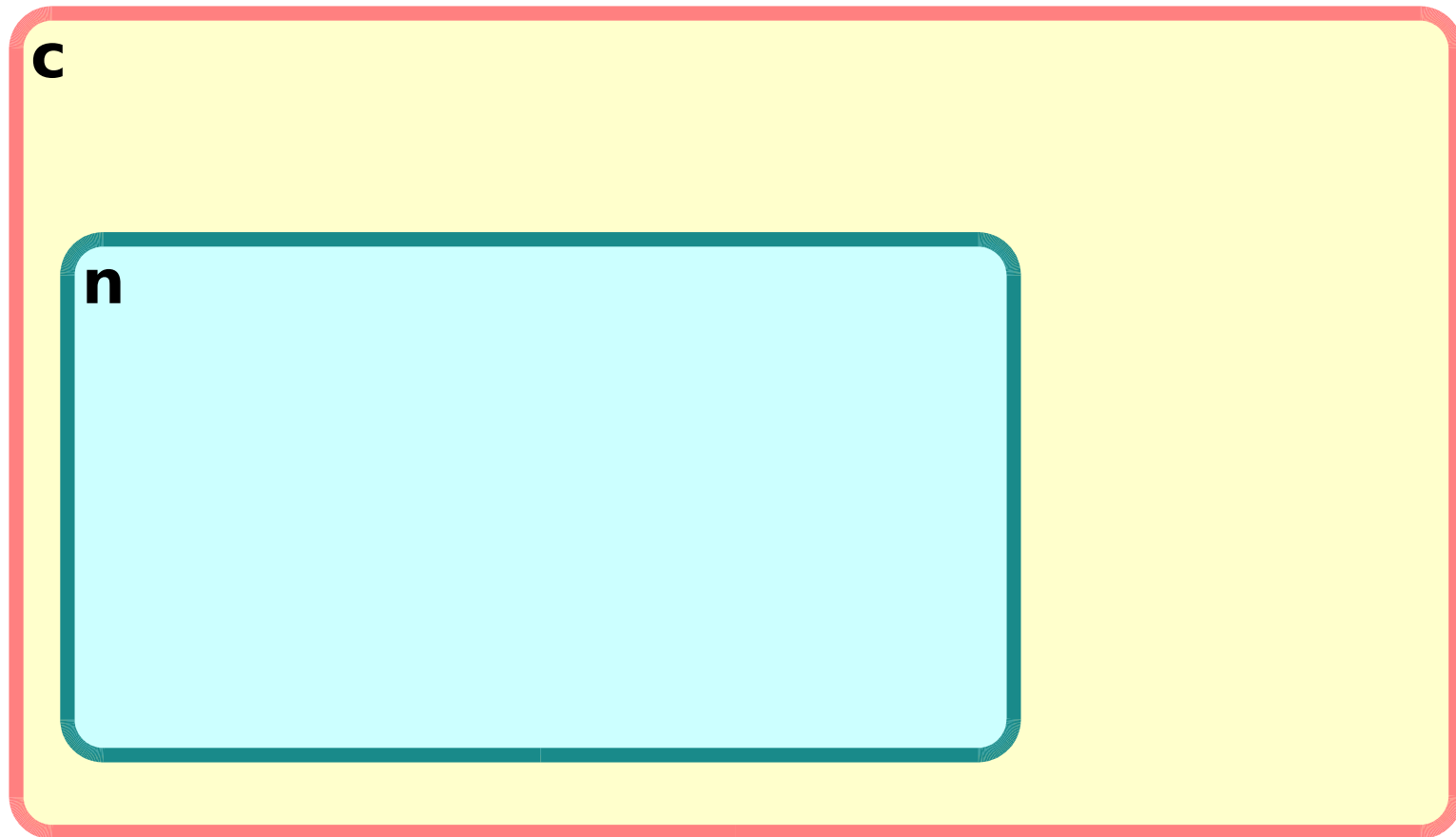
PROTON supports SBML

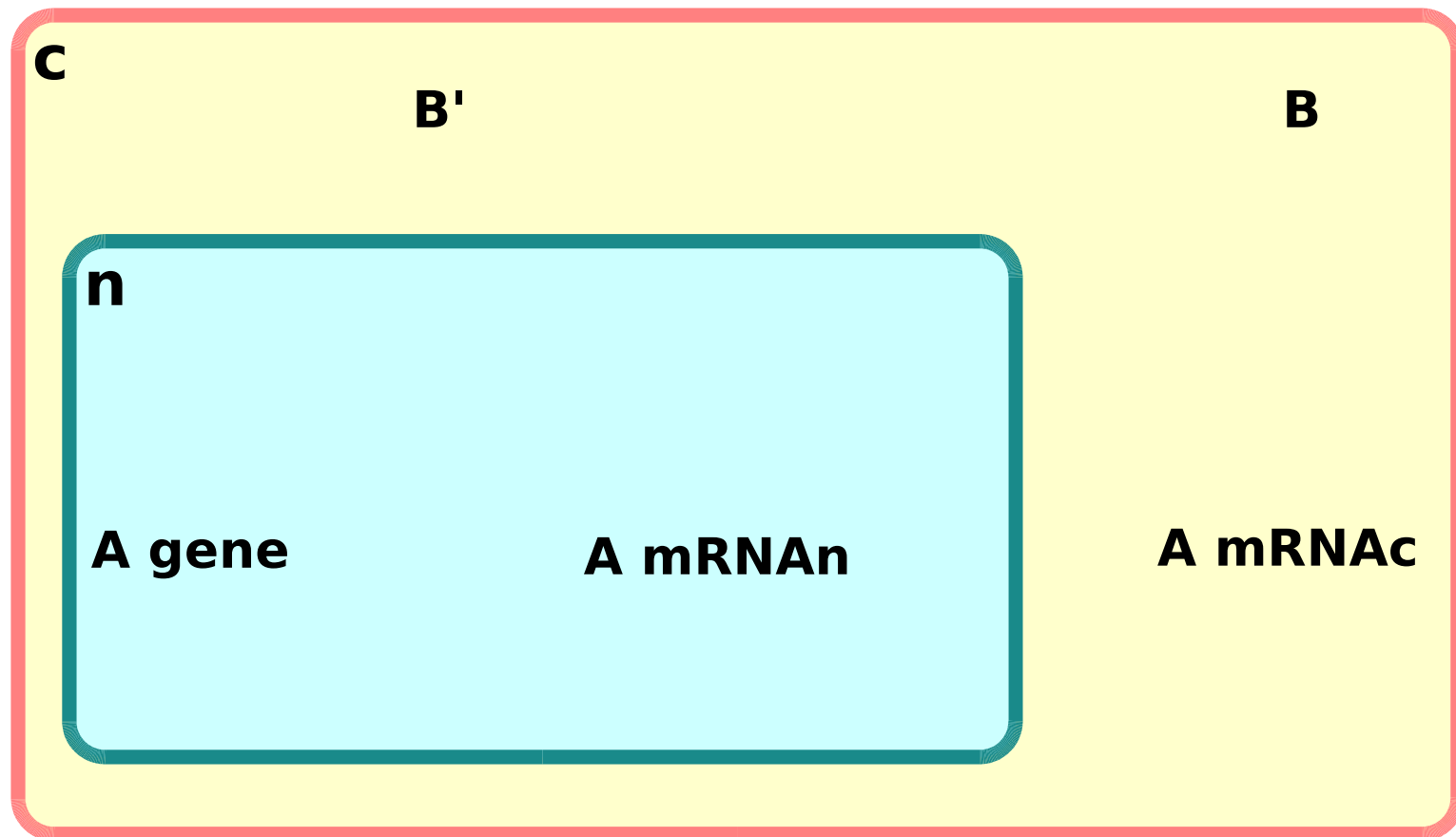
(June 23, 2005) **PROTON** is a tool to reconstruct user-specific models of biochemical networks from distributed databases. It supports SBML.

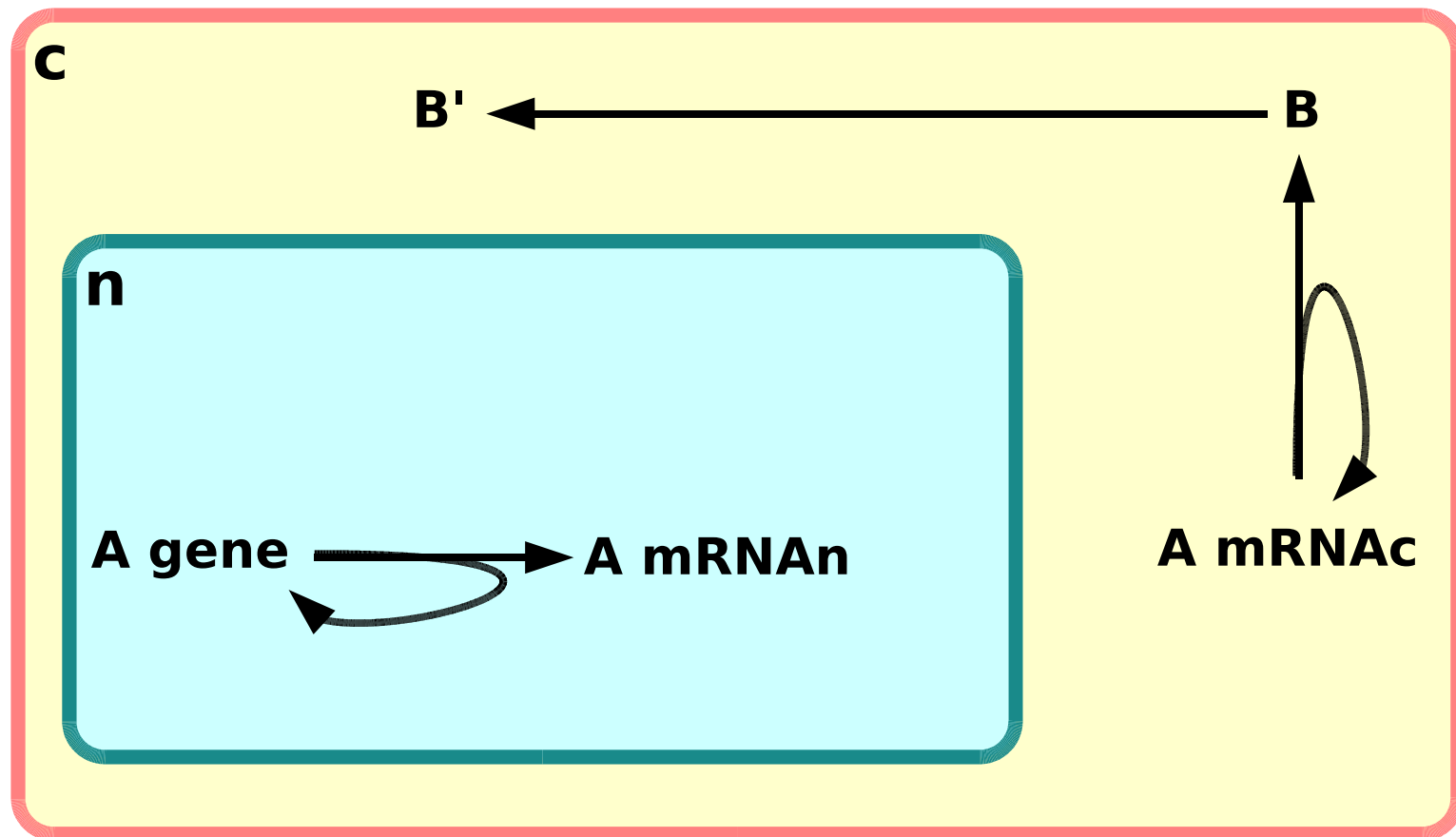
[read more](#)

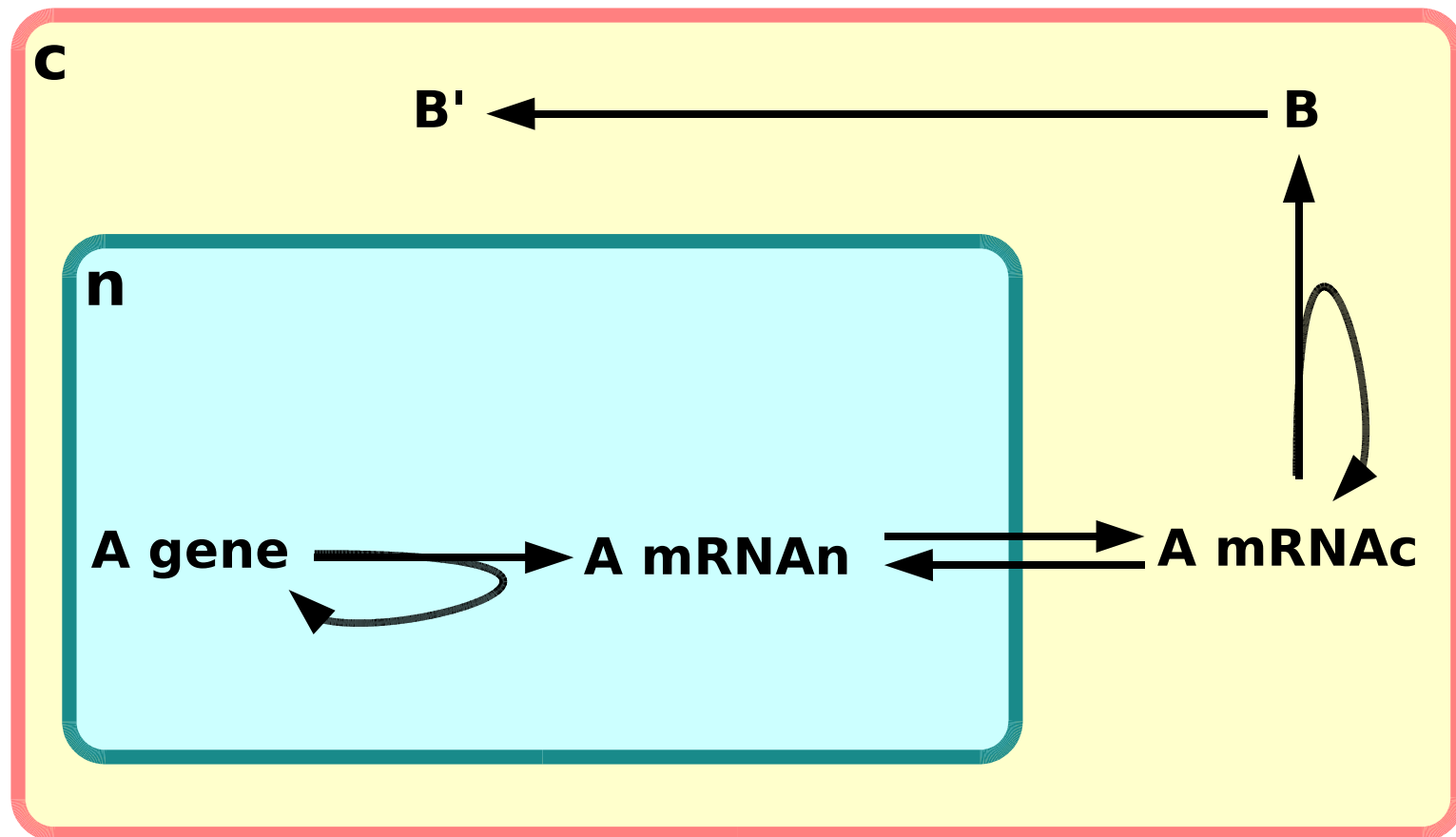
[See older news items.](#)

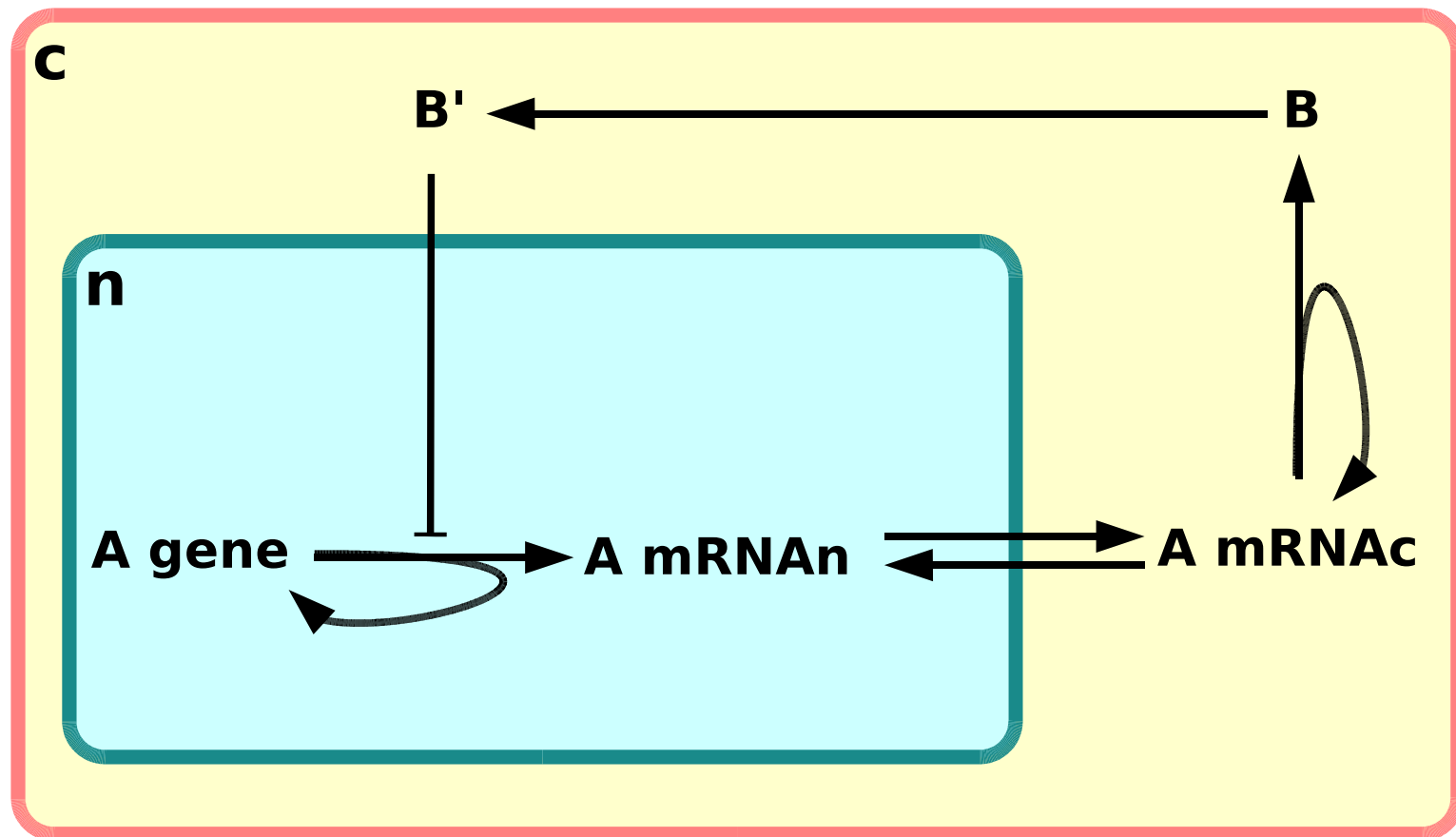
What can we encode in SBML?

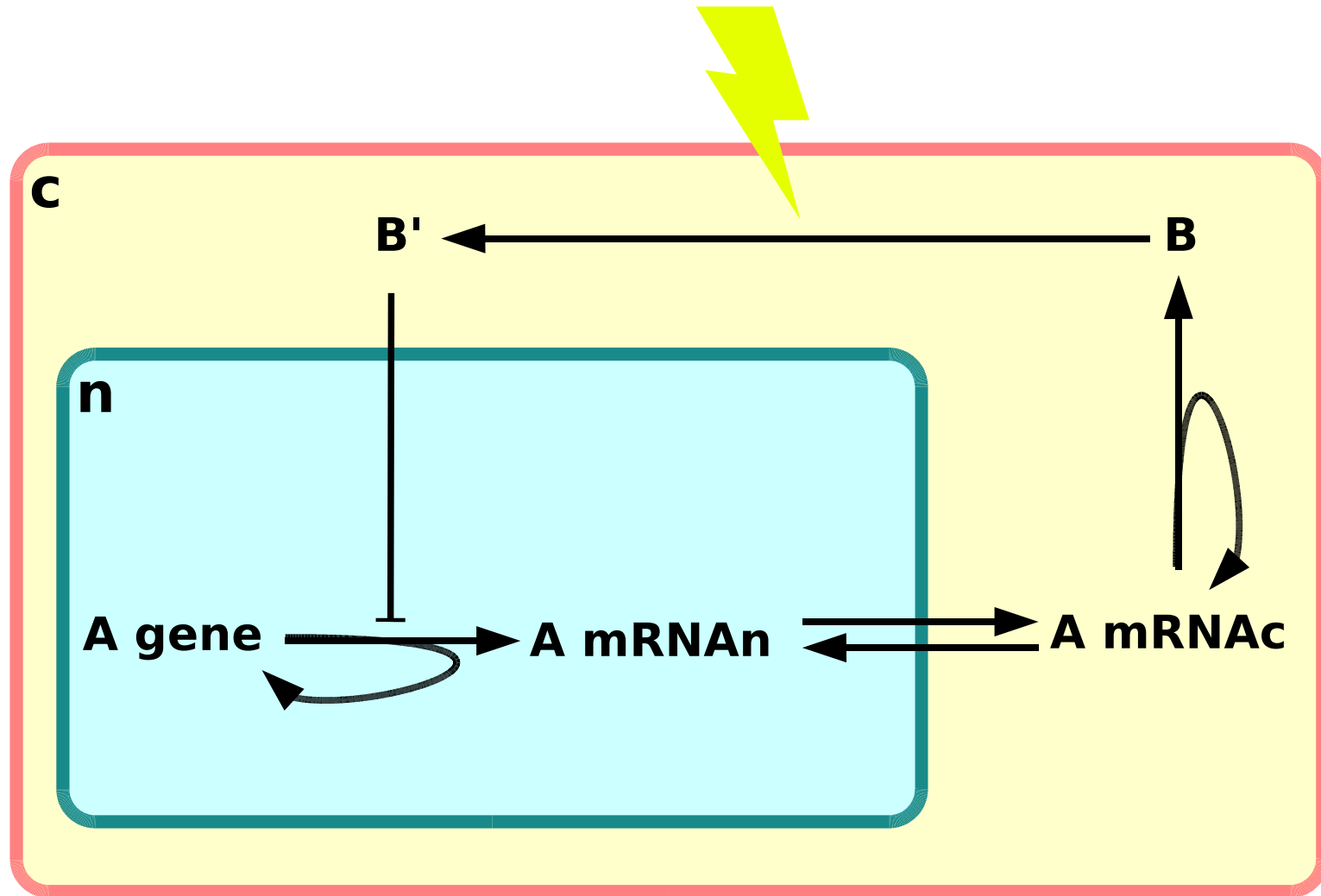


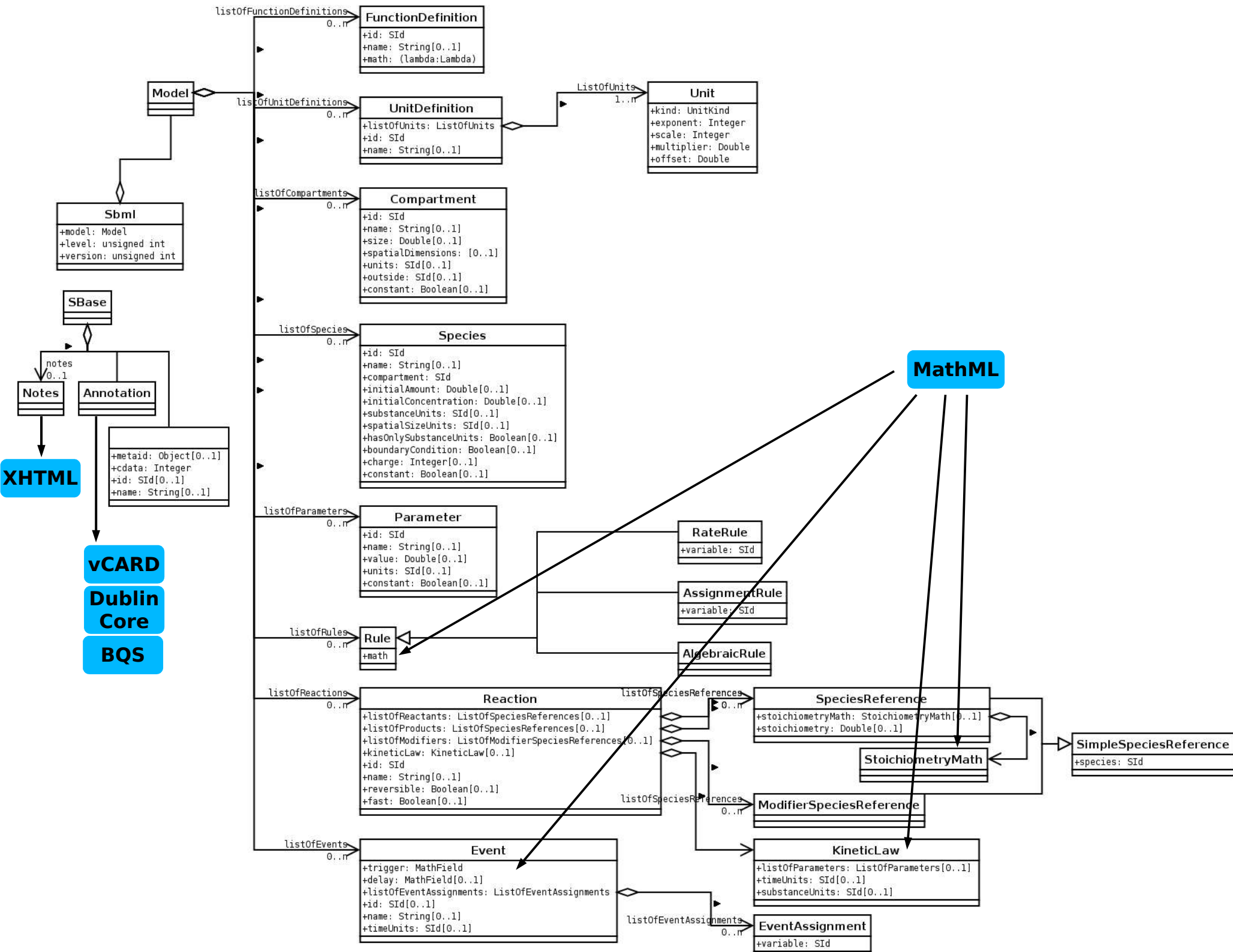












```
<?xml version="1.0" encoding="UTF-8"?>  
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
```

```
</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>
```

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<?xml version="1.0" encoding="UTF-8"?>
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  <model>
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    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
```

```
</model>
</sbml>
```

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<?xml version="1.0" encoding="UTF-8"?>
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    <listOfSpecies>
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      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
```

```
</model>
</sbml>
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<?xml version="1.0" encoding="UTF-8"?>
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    <listOfSpecies>
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      <species id="B" compartment="cell" initialConcentration="0"/>
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    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
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        </reaction>
      </listOfReactions>
    </model>
  </sbml>
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<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
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      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
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        </listOfReactants>

        </reaction>
      </listOfReactions>
    </model>
  </sbml>
```

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<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
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    </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>
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</sbml>
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<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
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      <species id="B" compartment="cell" initialConcentration="0"/>
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    </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>
```

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  id="A"
  name="a-tubulin"
  compartment="cell"
  initialAmount="1000"
  substanceUnits="item"
  hasOnlySubstanceUnits="true"
  boundaryCondition="true"
  constant="false"
  charge="0">
<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>
          <rdf:li rdf:resource="http://www.uniprot.org/#P68370"/>
          <rdf:li rdf:resource="http://www.geneontology.org/#0045298"/>
        </rdf:Bag>
      </dc:relation>
    </rdf:Description>
  </rdf:RDF>
</annotation>
</species>
```

- **Level 1 (March 2001)**

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

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

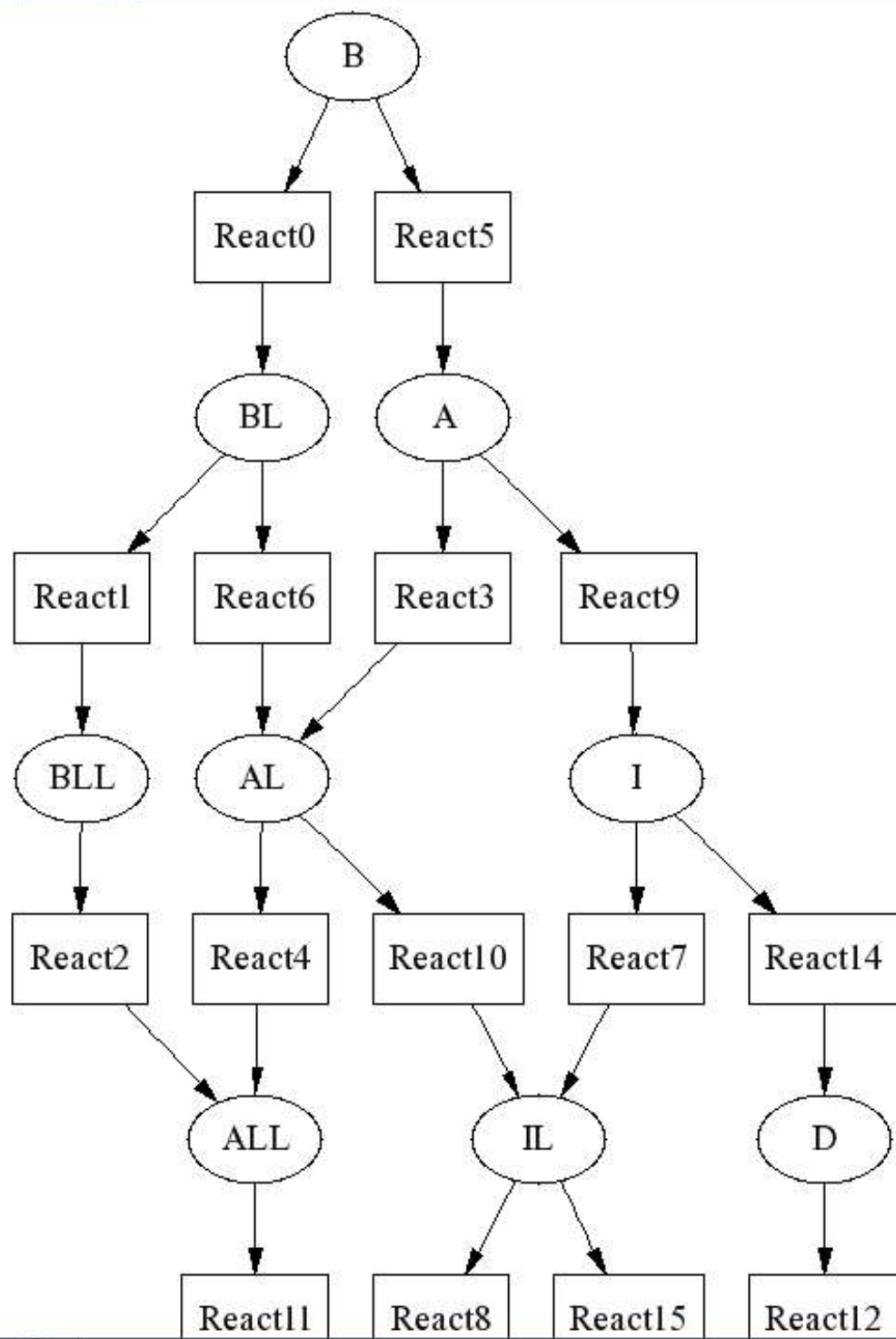
- **Level 2 (June 2003)**

- 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

No, it isn't!

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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](#)

- Bench biologists need to find models relevant for their research.
- Modellers need to reuse existing models, or portions of models, rather than rewrite them from scratch. Model composition on a large scale will be possible only if we have such a model “shopping cart”.
- But ...
 - No true database of models, only repositories, sometimes with side information.
 - Poor quality control on the models available online (JWS excepted).
 - No annotation of models: reactants are A,B,C, reactions 1, 2, 3 etc.
 - Lack of standards on production, curation and annotation of models.
- ⇒ Biomodels.net: collaboration between Caltech, EMBL-EBI, SBI, JWS etc. etc.
 - MIRIAM:
Minimum Information Requested In the Annotation of Models
 - Systems Biology Ontology:
 - Species-roles: “substrate”, “competitive inhibitor” etc.
 - Parameters: K_d , K_a , K_p , IC_{50} ARE DIFFERENT!
 - Rate-laws: “Michaelis-Menten”, “Mass Action Law” etc.
 - BioModels Database, a database of “Systems Biology Models”

Minimal 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)

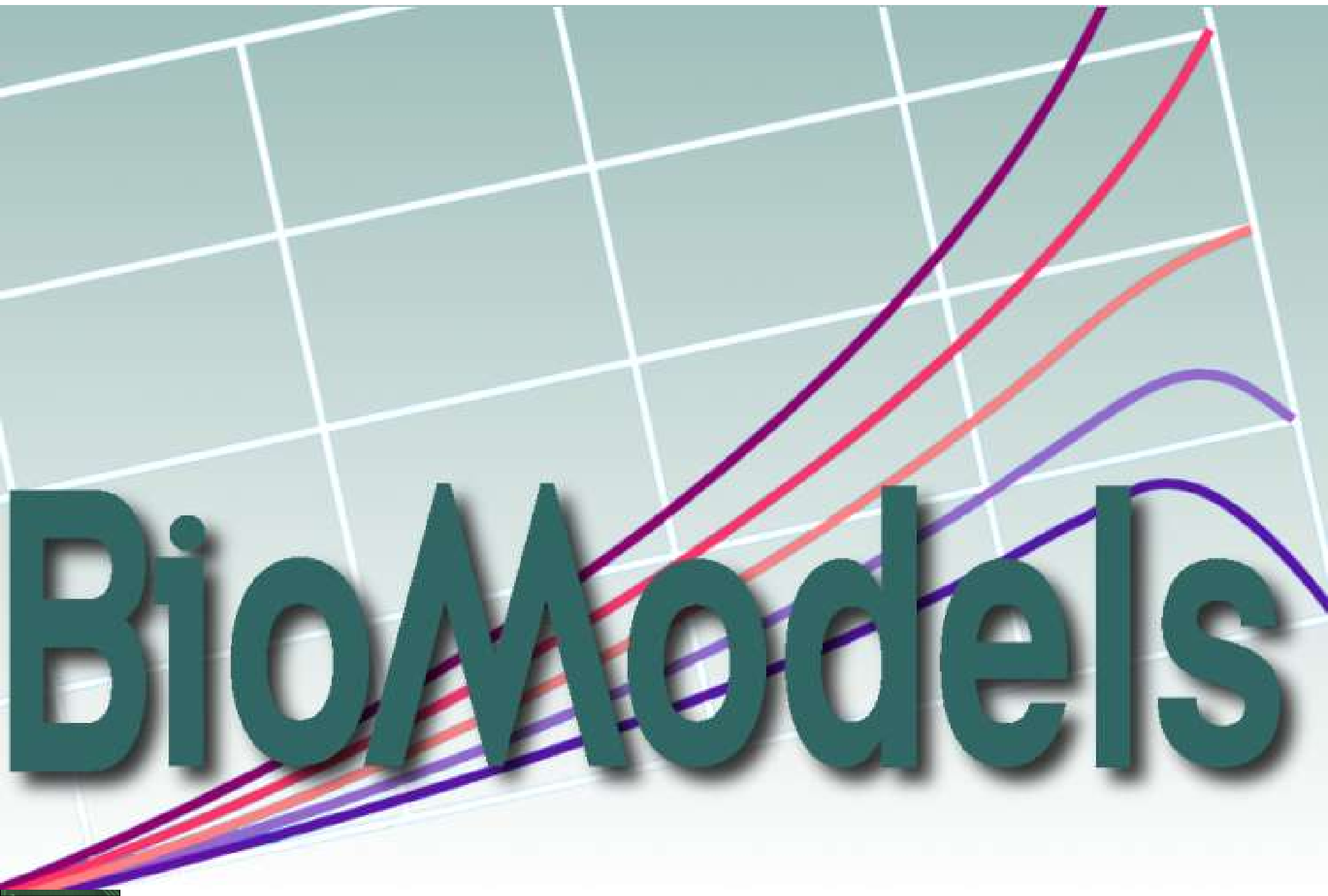
E Klipp, H Sauro, HD Spence, BL Wanner

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

- 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)

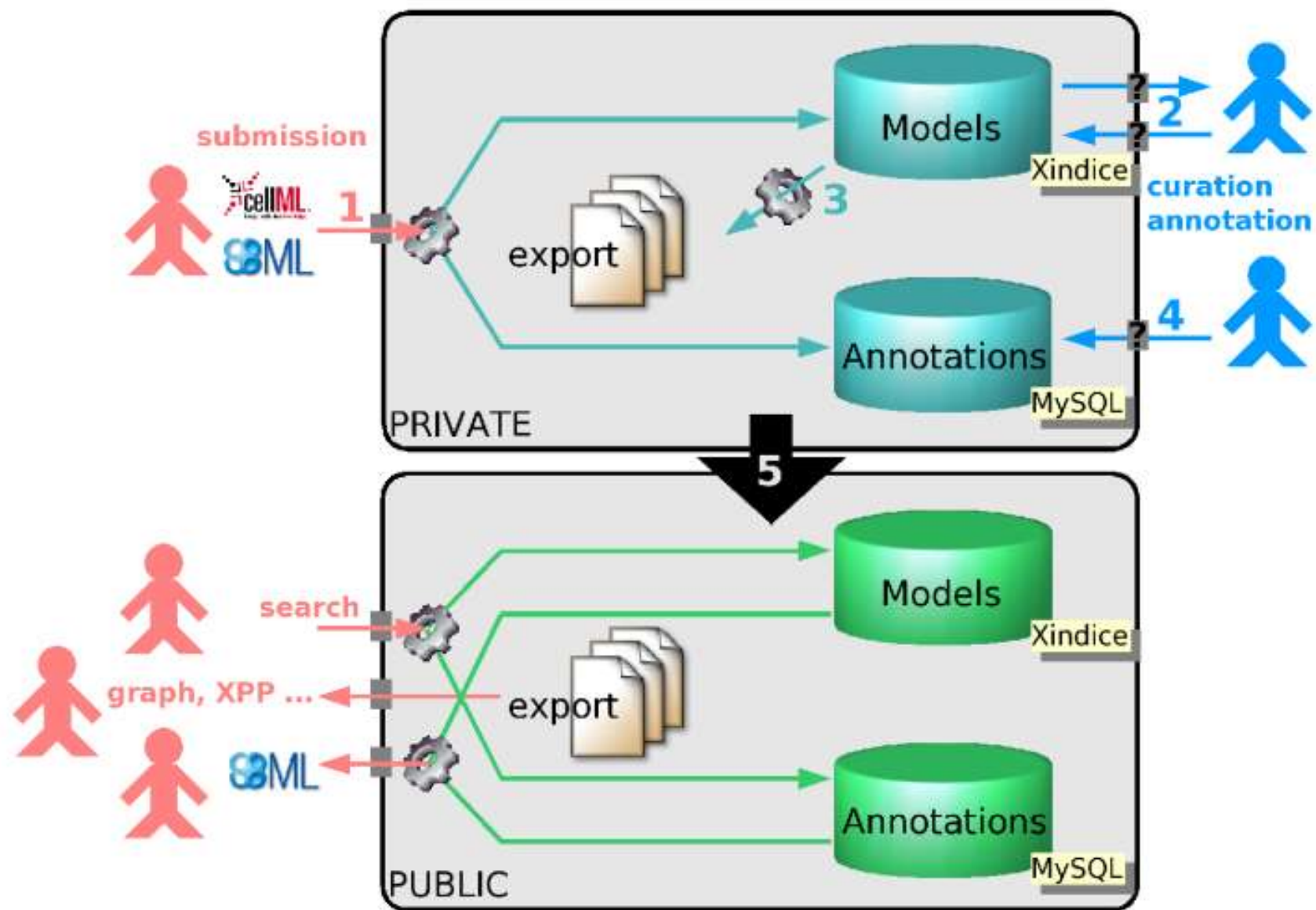
- The model has to be named.
- A citation of the reference description must be joined (complete citation, unique identifier, unambiguous URL). The citation should permit to identify the *authors* of the model.
- The name and contact of model *creators* must be joined.
- The date and time of creation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



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.



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

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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](#)

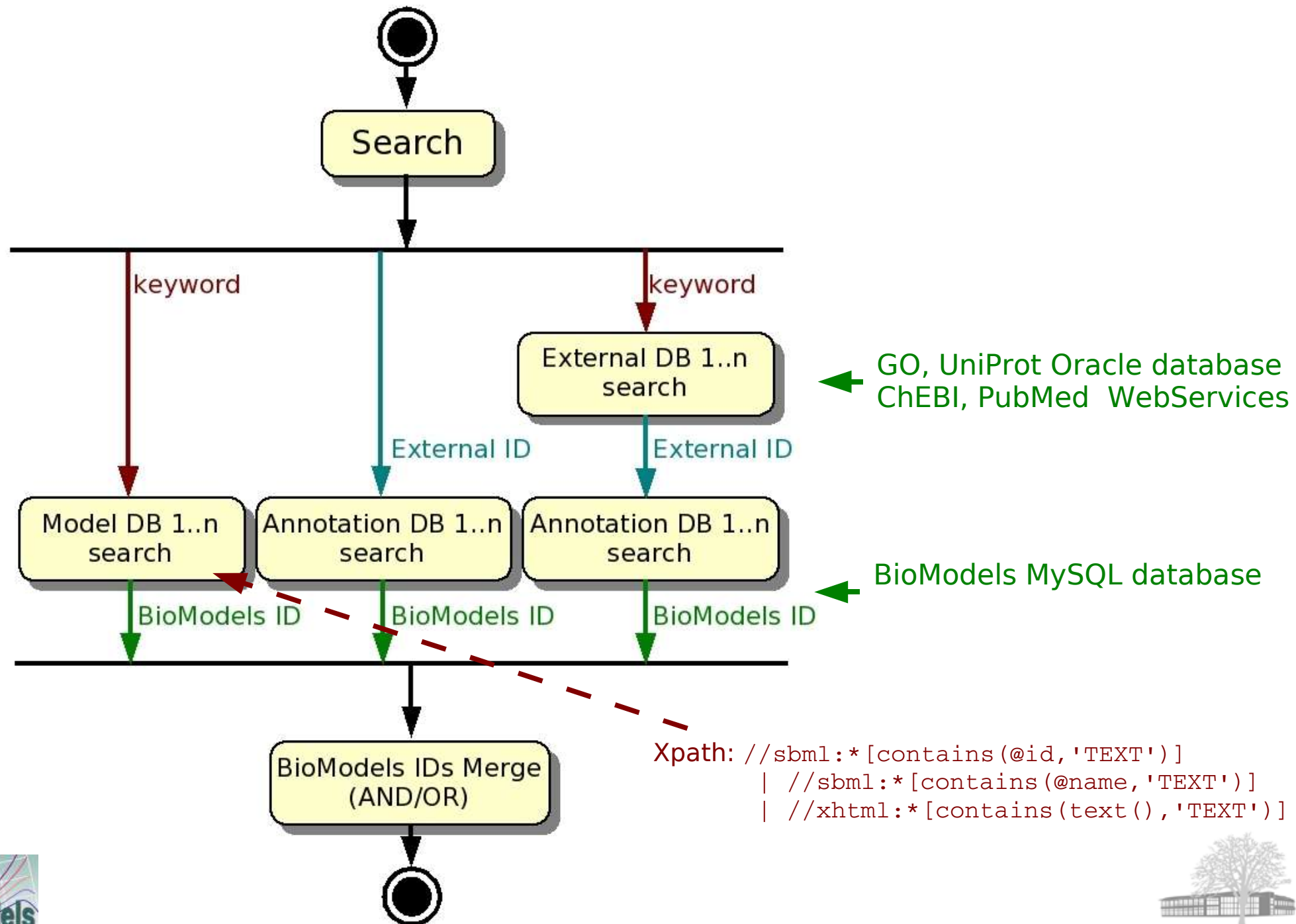
KEGG Compound [C00101](#)

5,10-methylene-tetrahydrofolate

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

ChEBI [CHEBI:15636](#)

KEGG Compound [C00143](#)



BIOMODELS.NET

BioModels Database

- Browse
- Search

Submit Your Model

Curators Sign In

FAQ

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Search Models

You can search BioModels Database for models using one or more of the following criteria:

- *BioModels ID* → Search BioModels Database for BioModels identifiers, for example *BIOMD0000000003*, *00003* or *3*.
- *Person* → Search BioModels Database for submitter and/or creator names, for example *Nicolas Le Novère*, *Nicolas*, *Bruce Shapiro* or *Shapiro*.
- *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 third-party resources by either resource identifier or text, for example *9256450* or *cyclin* for [PubMed](#), *GO:0007049* or *cell cycle* for [Gene Ontology](#).
- *Resource ID* → Search BioModels Database for annotations with third-party resource identifiers, for example *CHEBI:15422* or *15422* for [ChEBI](#), *68910* or *69278* for [Reactome](#), *P04551* or *4551* for [UniProt](#).

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

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

BioModels ID:

Person:

SBML Elements:

Resource:

Gene Ontology

Resource:

PubMed

Resource:

PubMed

Resource ID:

BIND

Resource ID:

BIND

Resource ID:

BIND

 Compose by: ☒ and ☐ or

[Top](#)

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

[Contact](#)

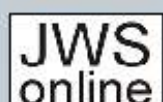
BIOMODELS.NET

BioModels Database

- Browse
- Search

Submit Your Model

Curators Sign In

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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](#)[Top](#)

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

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BioModels Database

Submit Your Model

BioModels Annotation

- Browse
- Search
- Submit
- Replace
- Annotate

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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](#)**Gene Ontology** [GO:0000278](#) [GO:0007049](#)**Submission Date:** 2005-02-09T13:27:02**KEGG Pathway** [sce04110](#)**Last Modification Date:** 2005-04-01T23:58:07**Taxonomy** [4896](#)**Creators:** [Bruce Shapiro](#)**Reactome** [69278](#)**Compartments (1)****Species (14)****Reactions (33)****Reaction1**Reactants: [EmptySet](#)Products: [mass](#)

Modifiers:

Reaction2Reactants: [EmptySet](#)Products: [G2K](#)

Modifiers:

Reactome [68910](#) [69282](#)**Reaction3**Reactants: [G2K](#)Products: [EmptySet](#)**Gene Ontology** [GO:0008054](#)

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All: 1 Review: 0

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PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
LinkOut
My NCBI (Cubby)
Related Resources
Order Documents
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

☐ 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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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](#)**Gene Ontology** [GO:0000278](#) [GO:0007049](#)**Submission Date:** 2005-02-09T13:27:02**KEGG Pathway** [sce04110](#)**Last Modification Date:** 2005-04-01T23:58:07**Taxonomy** [4896](#)**Creators:** [Bruce Shapiro](#)**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 auxillary 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: "(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

0
0.00175
0.00495*mass[t]
0.0075*(1 - UbE[t]) + 0.25*UbE[t]
0.0075*(1 - UbE[t]) + 0.25*UbE[t]
0.015
0.025*(1 - Cdc25[t]) + 0.5*Cdc25[t]
0.035*(1 - Wee1[t]) + 0.35*Wee1[t]
0.0375*(1 - UbE2[t]) + 7.5*UbE2[t]
0.05 + 0.0075*(1 - UbE[t]) + 0.25*UbE[t]
0.05 + 0.0075*(1 - UbE[t]) + 0.25*UbE[t]
0.09375
0.1
0.1
0.1

Reaction

G1R -> R
EmptySet -> G1K
EmptySet -> mass
G2K -> EmptySet
PG2 -> EmptySet
EmptySet -> G2K
PG2 -> G2K
G2K -> PG2
G1K -> EmptySet
G2R -> R
PG2R -> R
EmptySet -> R
G1R -> G1K + R
G2R -> G2K + R
PG2R -> PG2 + R
G1R -> G1K

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Model

Submitter: [Nicolas Le Novère](#)

Gene Ontology [GO:0000278](#)

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

KEGG Pathway [sce04110](#)

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

Taxonomy [4896](#)

Creators: [Bruce Shapiro](#)

Reactome [69278](#)

Compartments (1)

Species (22)

Reactions (25)

Cdc13_Cdc2 creation

Reactants:

Products: [Cdc13](#) [Cdc2](#)

Modifiers:

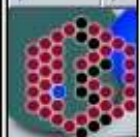
Reactome [68910](#) [69282](#)

Cig2_Cdc2 creation

Reactants:

Products: [Cig2](#) [Cdc2](#)

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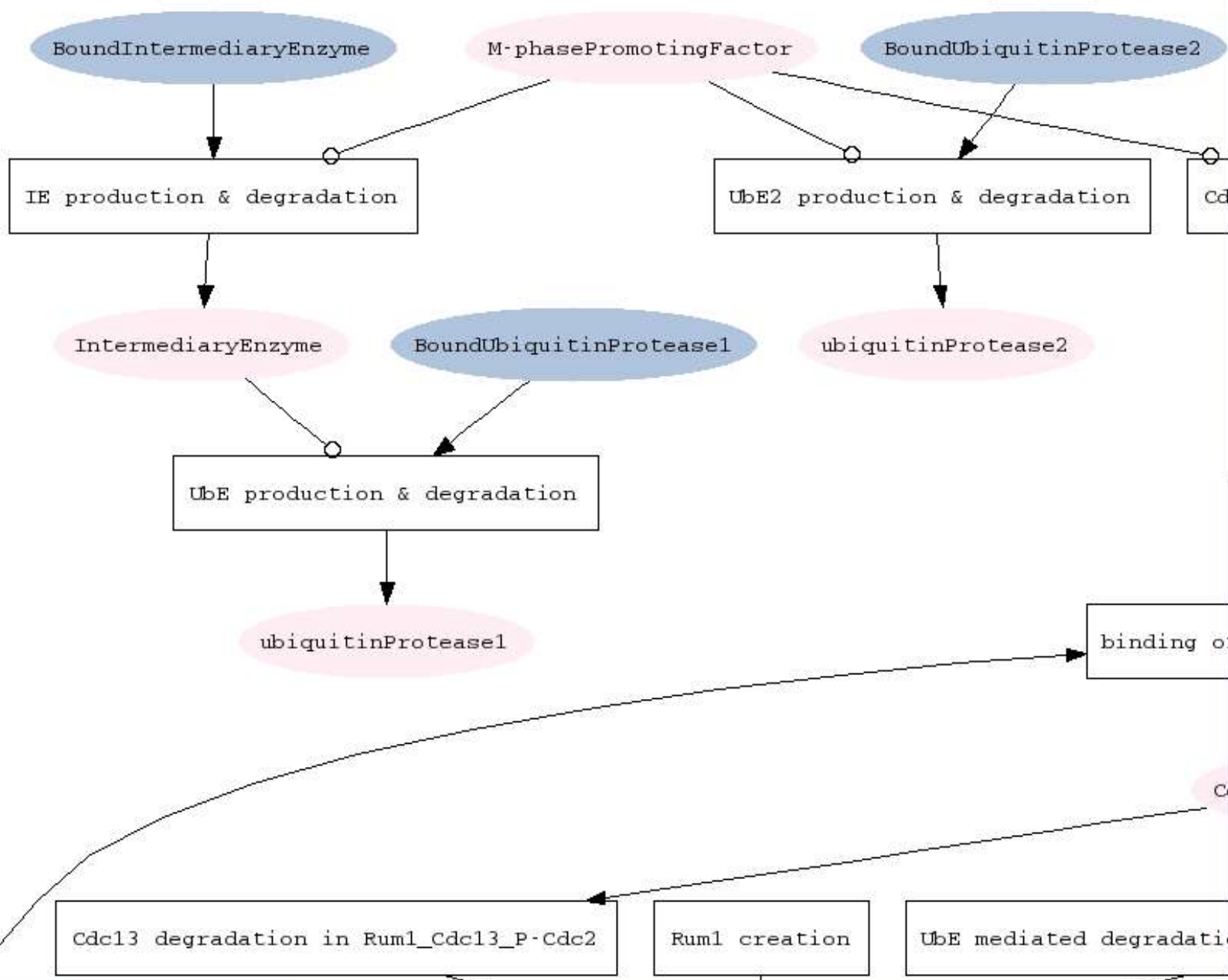
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Taxonomy [4896](#)Creators: [Bruce Shapiro](#)Reactome [69278](#)

Compartments (1)

Species (22)

Reactions (25)

Cdc13_Cdc2 creation

Reactants:

Products: [Cdc13_Cdc2](#)

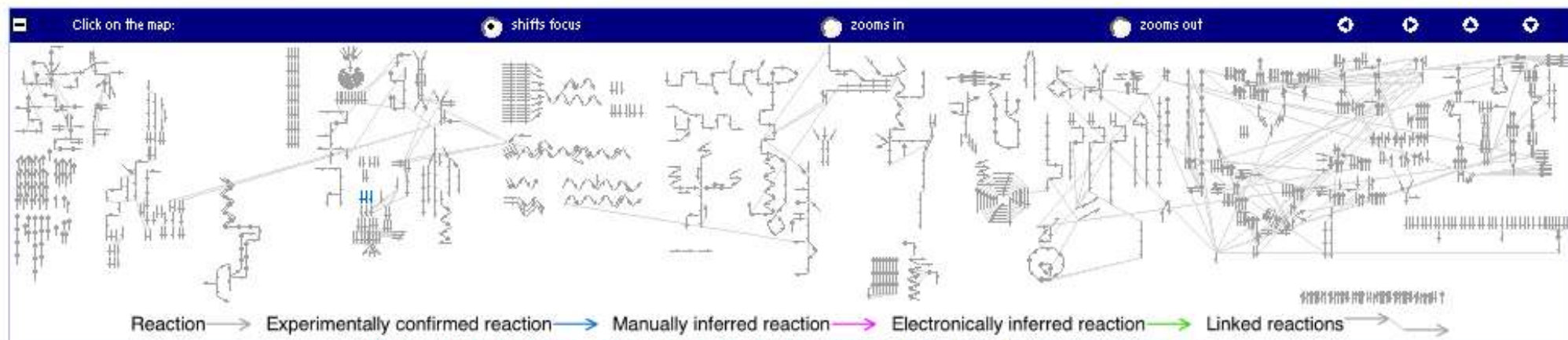
Modifiers:

Reactome [68910 69282](#)

Cig2_Cdc2 creation

Reactants:

Products: [Cig2_Cdc2](#)

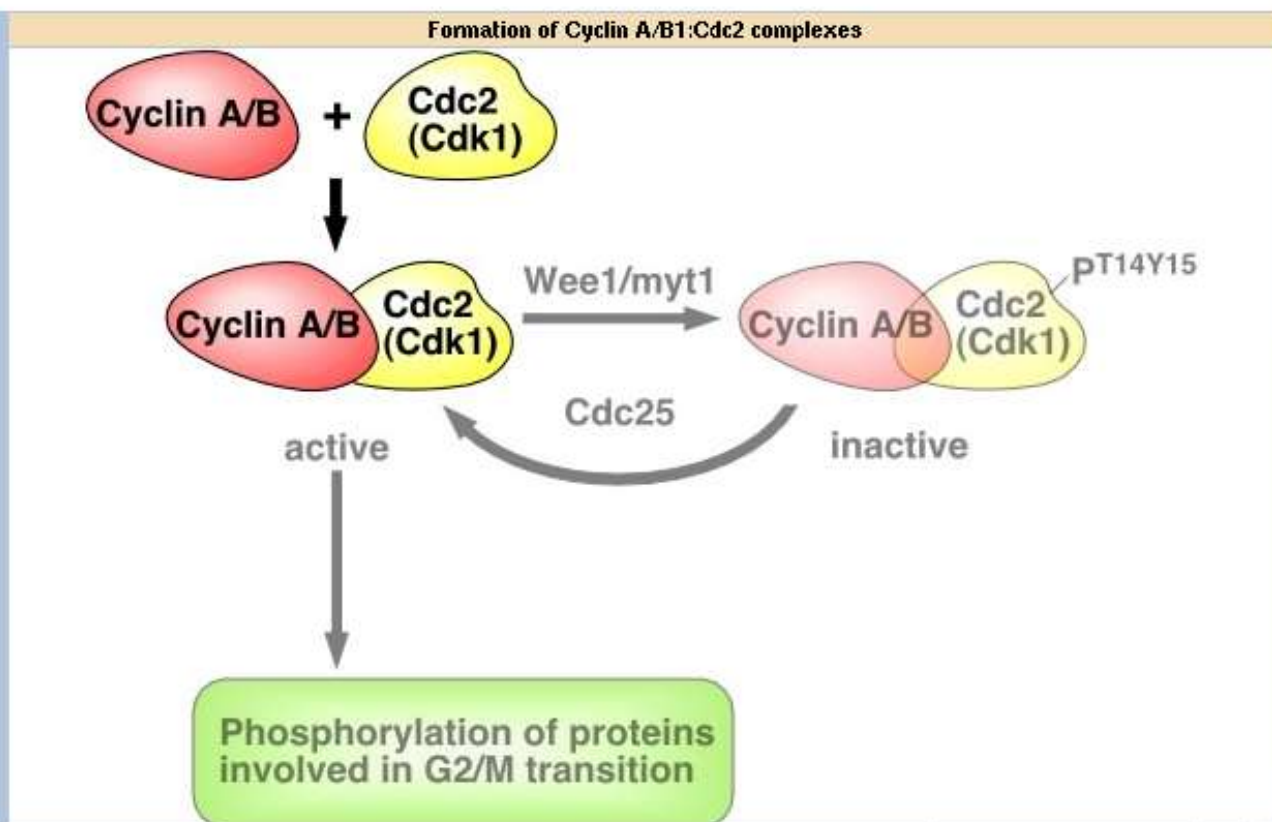


We appreciate your feedback and thoughts about Reactome. Please take a moment to take our online survey.

[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





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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

Close



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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](#)

Gene Ontology [mitotic cell cycle](#)

KEGG Pathway [sce04110](#)

Reactome [69278](#)

Taxonomy [4896](#)

is

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

Compartments (1)

Species (22)

Rules (15)

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- + ++

Reference Publication

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- + ++

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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 Home

is Gene Ontology GO: Add Home

- + ++

Compartments (1)

++ + -

- + ++

Species (22)

++ + -

ubiquitinProtease1

Compartment: [Cell](#)

Referred to as: *Ube*

+ is BIND Add Home

ubiquitinProtease2

Compartment: [Cell](#)

Referred to as: *Ube2*

+ is BIND Add Home

Wee1

Compartment: [Cell](#)

Referred to as: *Wee1*

+ is BIND Add Home

UniProt [MIK1_SCHPO](#) Remove

UniProt [WEE1_SCHPO](#) Remove

set #1
is

BIND Add Home

is BIND Add Home



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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		++ +- -
Compartments (1)		++ +- -
Species (22)		++ +- -
Rules (15)		++ +- -
Reactions (25)		++ +- -
Events (2)		++ +- -

+- ++

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Reactants:

Products: [Cdc13](#) [Cdc2](#)

Modifiers:

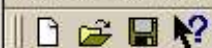
Reactome [68910](#) [69282](#)

Cig2_Cdc2 creation

Reactants:

Products: [Cig2](#) [Cdc2](#)


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</reaction>
<reaction fast="false" id="G2R_Creation" metaid="metaid_0000094" name="binding of Rum1 with Cdc13_Cdc2" reversible="false">
  <listOfReactants>
    <speciesReference species="G2K"/>
    <speciesReference species="R"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="G2R"/>
  </listOfProducts>
  <!-- <listOfModifiers/> -->
  <kineticLaw substanceUnits="substance" timeUnits="time">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <plus/>
        <apply>
          <times/>
          <ci>G2K</ci>
          <ci>k7</ci>
          <ci>R</ci>
        </apply>
        <apply>
          <times/>
          <cn type="integer">-1</cn>
          <apply>
            <times/>
            <ci>G2R</ci>
            <ci>k7r</ci>
          </apply>
        </apply>
      </math>
    <!-- <listOfParameters/> -->
  </kineticLaw>
</reaction>
<reaction fast="false" id="PG2R_Creation" metaid="metaid_0000095" name="binding of Rum1 with Cdc13_P-Cdc2" reversible="false">
  <listOfReactants>
    <speciesReference species="PG2"/>
    <speciesReference species="R"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="PG2R"/>
  </listOfProducts>
  <!-- <listOfModifiers/> -->
  <kineticLaw substanceUnits="substance" timeUnits="time">
```



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

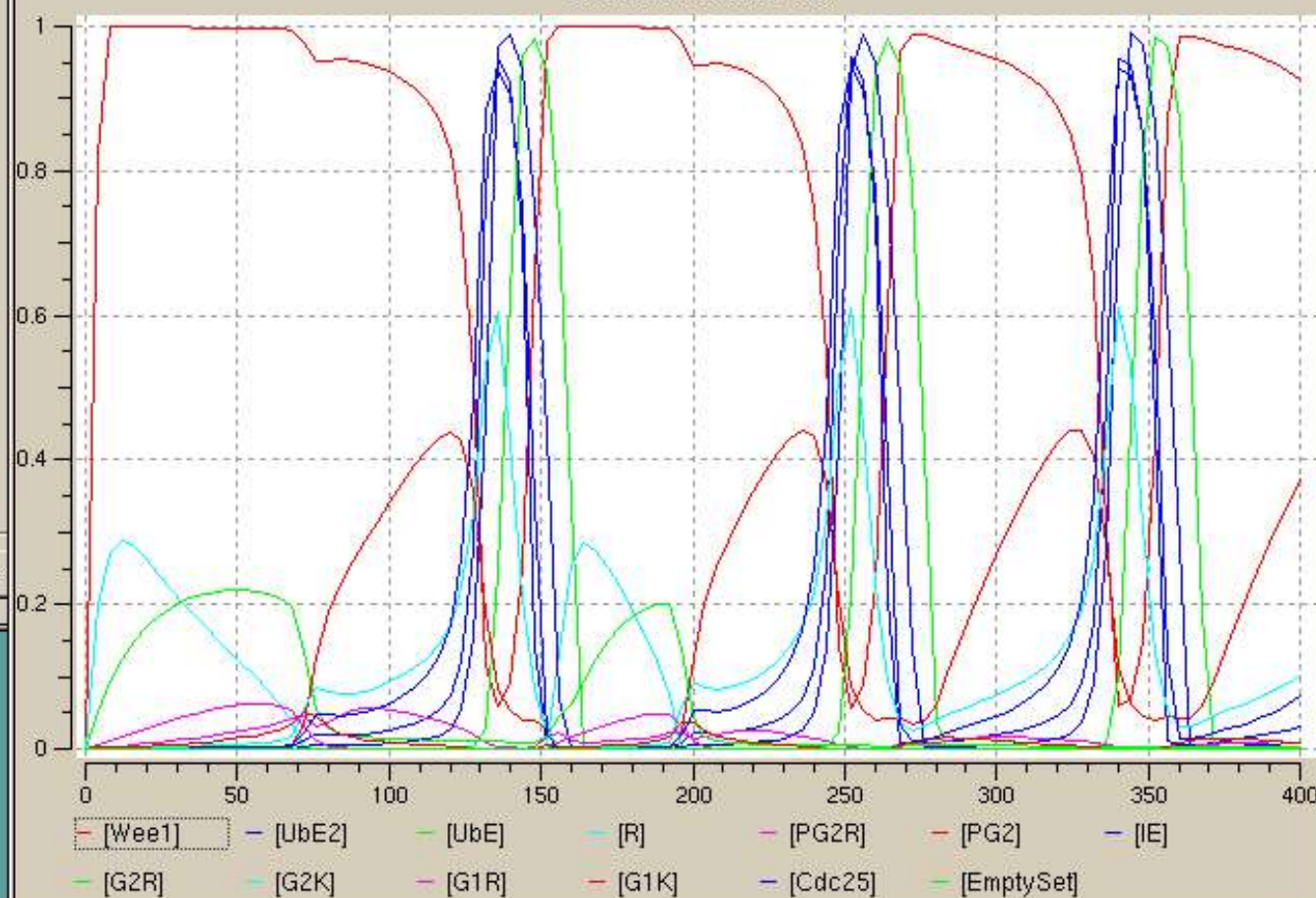
LSODA.RelativeTolerance

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
```


- 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 ...

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 advises deposition, and forward supplementary material
- Curation teams encode new models from literature

