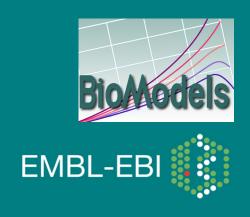
BioModels Database, a public model-sharing resource

Enabling Systems Biology University College London, UK. 11th - 14th, April 2011.

Vijayalakshmi Chelliah (viji@ebi.ac.uk)



Outline

BioModels Database:

- In general (Growth, Range of Models, Source of Models)
- SBML (Components, facilities etc..)
- Production Pipeline: Model
 - Submission
 - Curation
 - Annotation
 - Search
- Model components and Submodel creation.



In the beginning ...



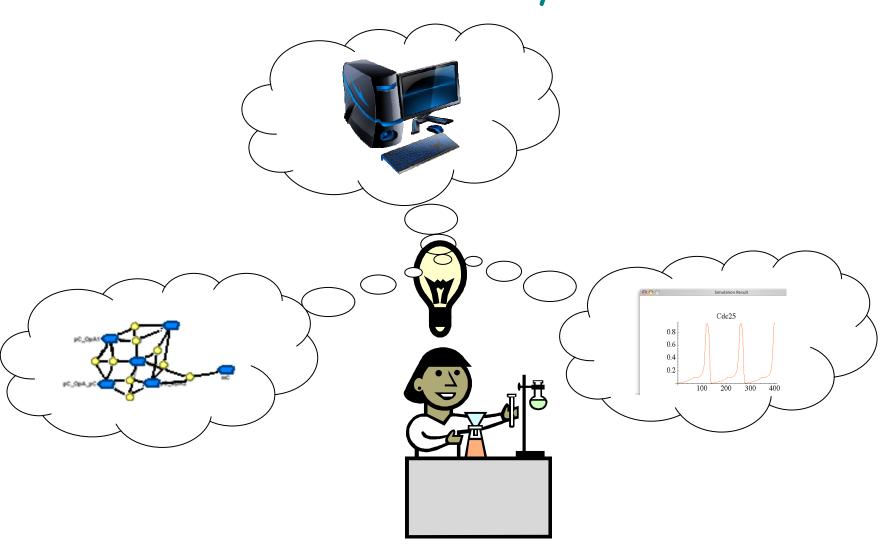




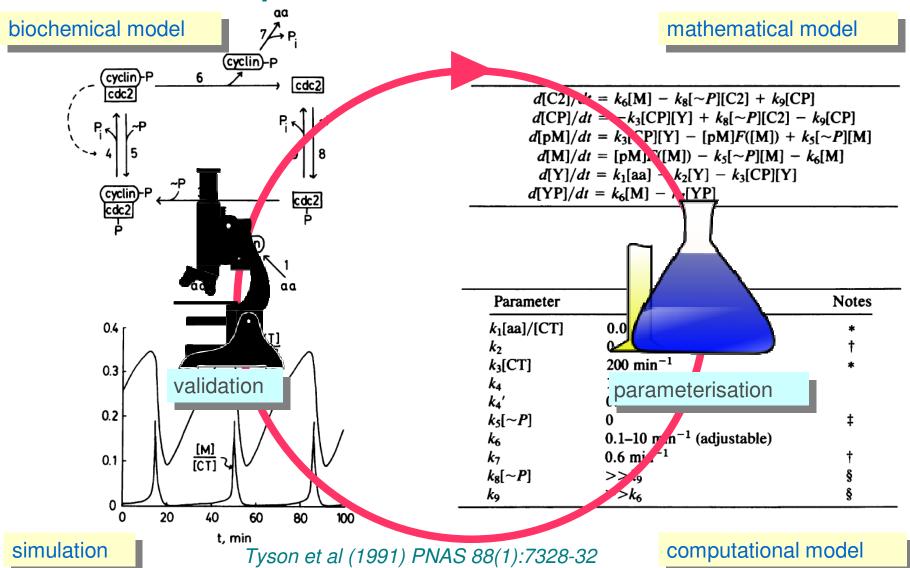
biologists worked in wet labs



then one day



Life cycle of a biochemical model



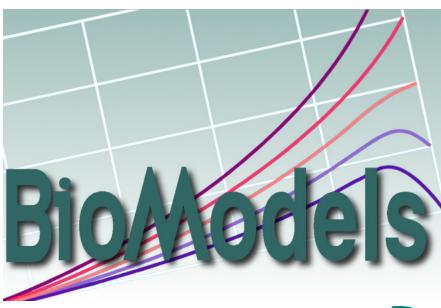
Repository of models: motivation & requirement

- both number and complexity of quantitative models in biology are increasing rapidly.
- modellers increasingly reuse and combine existing models. It often becomes impractical to reimplement models from literature.
- For easy and efficient use of the already published models, models
 - should be accessible.
 - source and detailed description of each model should be available and linked.
 - the modeller must be able to rely on the accuracy of the models.
 - the models should be available in common formats

```
(eg.:SBML (<a href="http://www.sbml.org">http://www.sbml.org</a>),
CellML (<a href="http://www.cellml.org">http://www.cellml.org</a>)
```

- should be searchable for different criteria.
- the structure and the components of the model should be browsable and identifiable.





- In General....



BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems

Le Novère N., Bornstein B., Broicher A., Courtot M., Donizelli M., Dharuri H., Li L., Sauro H., Schilstra M., Shapiro B., Snoep J.L., Hucka M. *Nucleic Acids Research*, (2006), 34: D689-D691

BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models.

Li C, Donizelli M, Rodriguez N, Dharuri H, Endler L, Chellian V, Li L, He E, Henry A, Stefan MI, Snoep JL, Hucka M, Le Novère N, Laibe C. BMC Syst Biol., (2010), Jun 29; 4:92.

BioModels

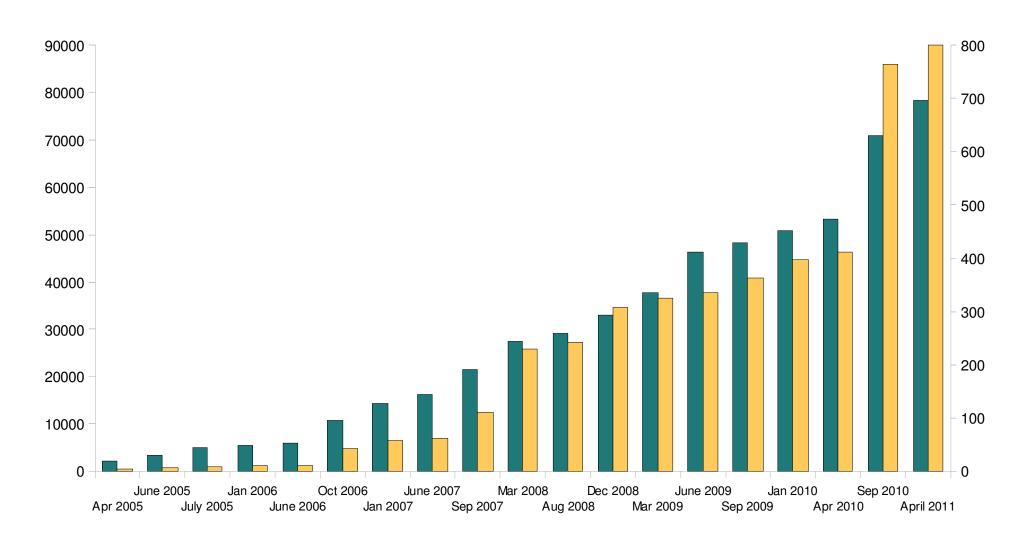
http://www.ebi.ac.uk/biomodels/

BioModels Database

- \$\footnote{\text{first launched on } 11\text{th } April 2005.}
- data resource that allows biologists to store and serve quantitative models of biomedical interest.
- stores only models described in the peer-reviewed scientific literature.
- Models are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, etc. to improve identification and retrieval.
- Models are accepted in several formats and served in several others.
- Partial/Sub models can be created and downloaded.
- online simulation available.

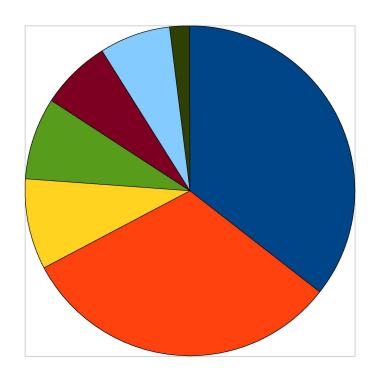


Database Growth





Types of Models in the BioModels Database



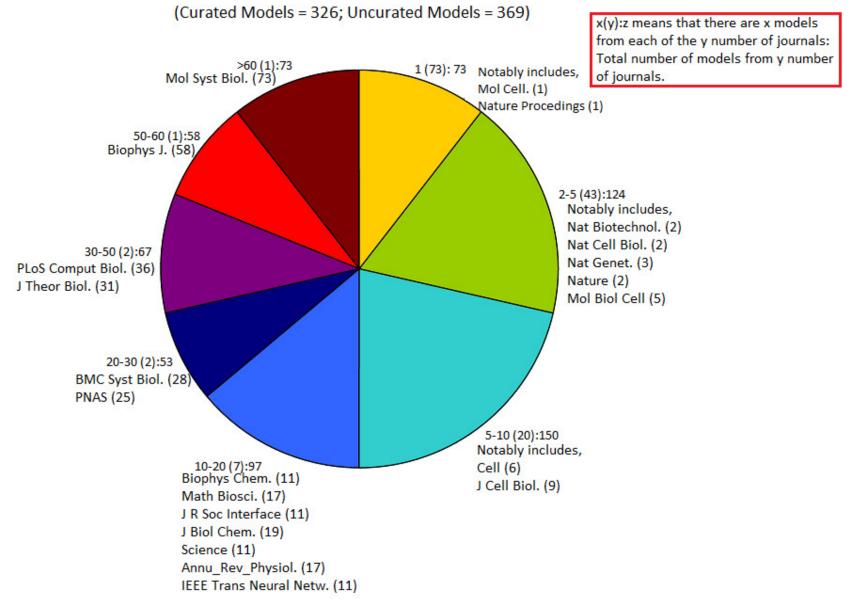
- cellular metabolic process (GO:0044237, wo. translation & transcription)
- signal transduction (GO:0007165)
- □ cell cycle (GO:0007049)
- circadian rhythm (GO:0007623)
- cytosolic calcium ion homeostasis (GO:0051480)
- transmission of nerve impulse (GO:0019226)
- cell differentiation (GO:0030154)

Where do models come from?

- submitted by curators
 - imported from other repositories (DOQCS, CelIML, JWS)
 - reimplemented from literature
 - imported from journals webpages
- · from authors before grant application or publication
 - some journals advocate submission to BioModels DB:
 - Molecular Systems Biology
 - PLoS journals
 - BioMedCentral journals
- various people who are interested.



The models in the BioModels Database come from 149 Journals. Plot made out of 695 models in the BioModels Database.



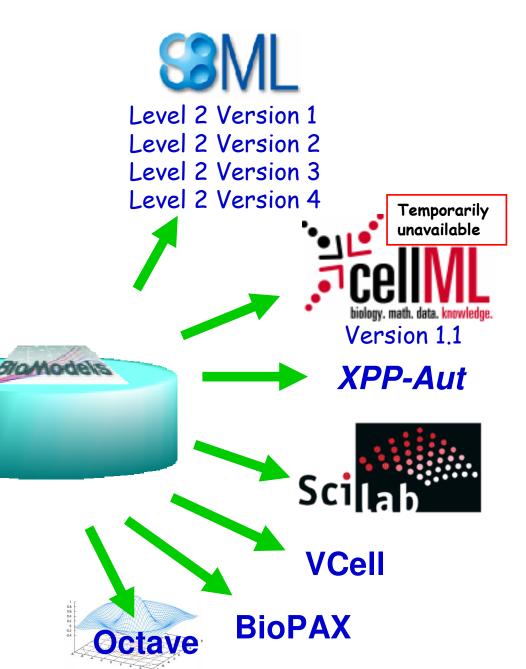
Model Format

SML

Level 1 Version 1 Level 1 Version 2 Level 2 Version 1 Level 2 Version 3 Level 2 Version 4



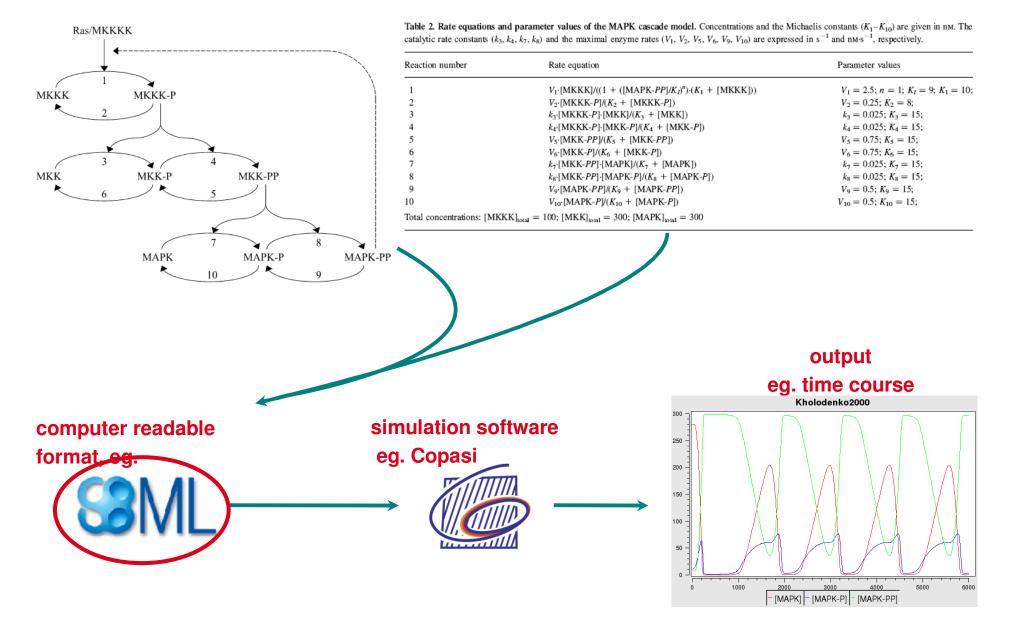
Version 1.0 Version 1.1





Encoding models using SBML





Kholodenko, Eur J Biochem (2000) 267: 1583-1588.





Goal: reproducible and reusable models and simulations



Systems

Biology

Markup

Language





The Systems Biology Markup Language

👺 News Documents Downloads Forums Facilities Community Events About 🔝 📘

Q Google Site Search..

Welcome to the portal for the Systems Biology Markup Language (SBML), a free and open interchange format for computer models of biological processes. SBML is useful for models of metabolism, cell signaling, and more. It has been in development by an international community since the year 2000.



For the curious

What is SBML? Read our introduction, then perhaps browse the mailing lists to glim g with SBML today.



For modelers

Looking for software that supports SBML? Our software guide over 210 systems. Are you instead looking for models? Vis BioModels Database , where you can find hundreds!



For software developers

Interested in supporting SBML in your software? Read our basic introduction and then the SBML specifications to understand how to use SBML. After that, you may want to look at libSBML.

No matter how you use SBML, we invite you to sign up for news updates either through our RSS feed, our Twitter feed of, or one of the mailing lists, and get involved with community efforts to help keep improving SBML. You can also call attention to your project's support of SBML by displaying the SBML logo.

SBML would not have been possible without support from multiple agencies and organizations, as well as intellectual contributions from many motivated individuals, including the major contributors who are shaping SBML Level 3.



libSBML 4.3.1 released!

(29 Mar. 11) A minor update to eradicate a few bugs and compatibility

COMBINE 2011 set!

(29 Mar.'11) This year's COMBINE meeting will be held in Heidelberg, Germany, Sep 3-7.

Older news ...

Community News

SED-ML v1.1 released

(29 Mar. '11) The version 1.1 specification for SED-ML @ is now available!

ONDEX released

(21 Mar. '11) ONDEX P is a data integration platform enabling diverse data sets to be linked and visualized.

SBW 2.8.2 Released

(18 Mar. '11) SBW 🚱 has an updated JDesigner, improved SBML event handling, and SBGN-ML and SED-ML 1.1

Older news ...



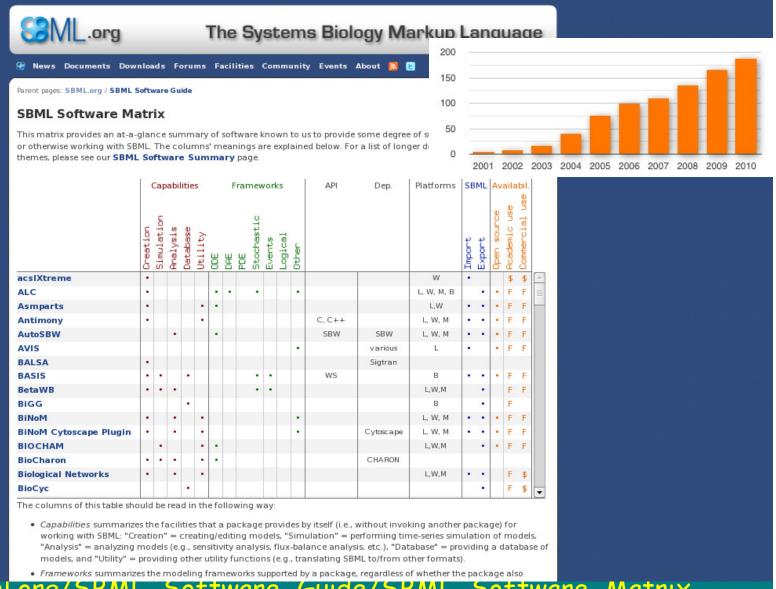
Please use our issue tracking system for any questions or suggestions about this website. This page was last modified 15:56, 14 December 2010.



Michael Hucka California Institute of Technology



213 tools support SBML upto now



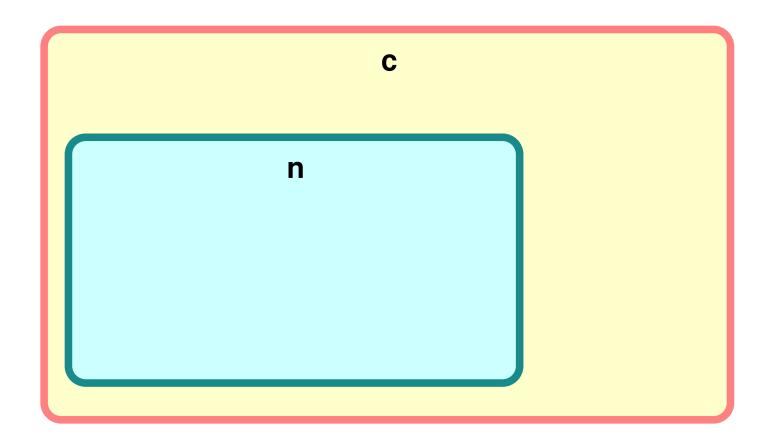
http://sbml.org/SBML_Software_Guide/SBML_Software_Matrix

What is SBML?

- a machine readable format for the representation of computational models of the biochemical reaction networks
- designed to be an exchange format for different tools => not dependent on a specific software
- it is **not**
 - a procedual or programming language
 - a format for configuration files for software tool
- SBML is encoded in XML
 - incorporates other standard formats like MathML, xHTML and RDF
- allows to integrate additional information in free form and standardized, machine readable formats (annotations)
- is developed by a large and active community and supported by more than hundred tools (see: http://sbml.org/SBML_Software_Guide/)

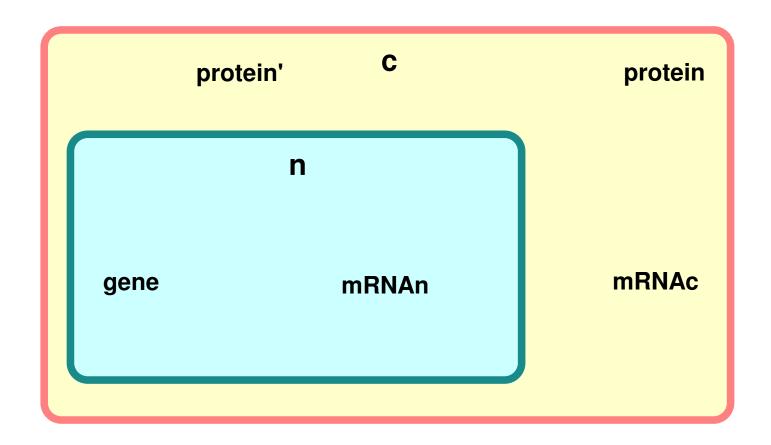


containers (compartments)



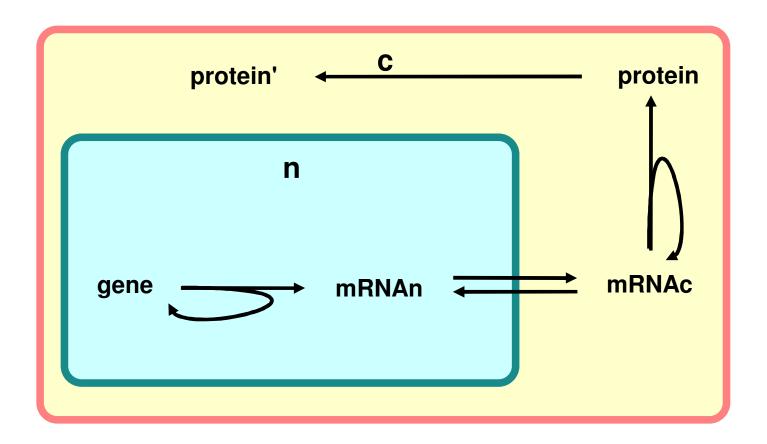


entity pools (species)



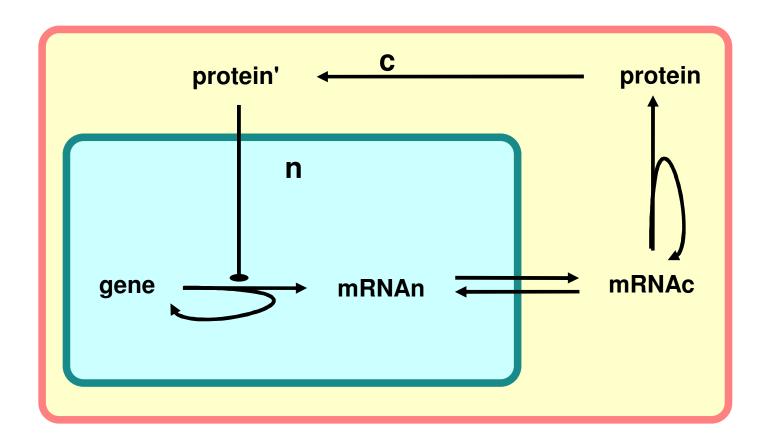


reactions



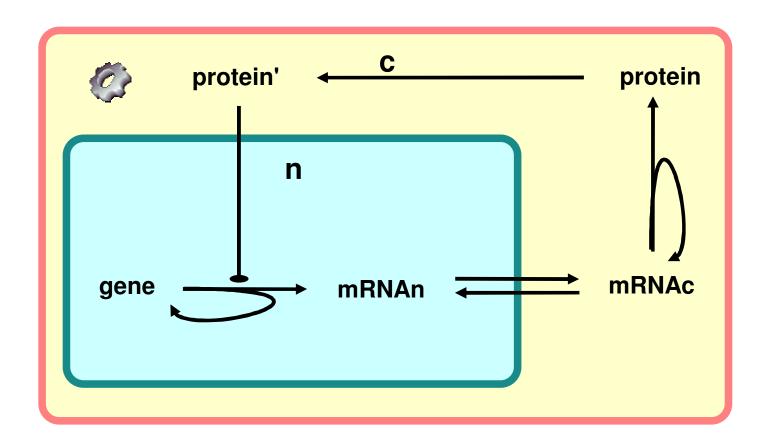


modulations

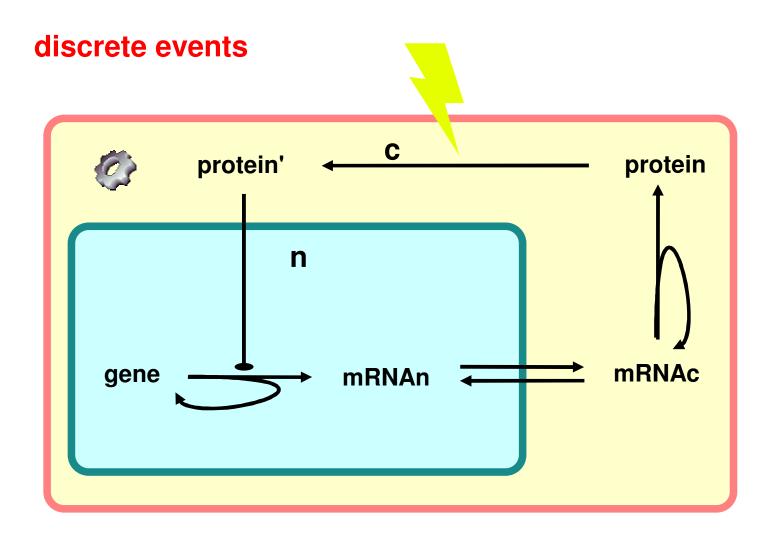




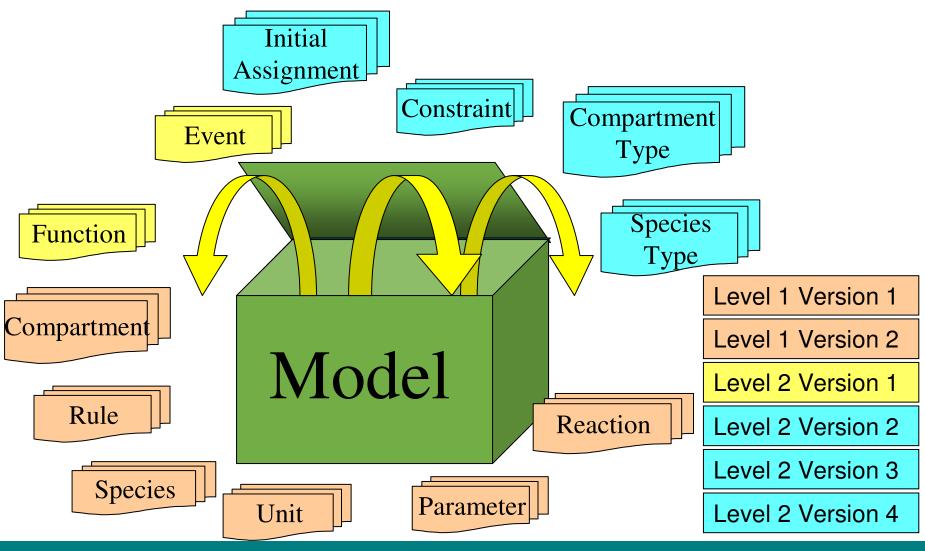
arbitratry rules







Main components of SBML





SBML components in detail

Function definition mathematical function that may be used throughout the rest of a model.

Unit definition new unit of measurement, or redefinition of an existing SBML default unit.

Compartment Type type of container

Species type type of entity that can participate in reactions.

Compartment well-stirred container of finite size where species may be located.

Species pool of entities of the same species type located in a specific compartment.

Parameter named quantity, whether constant or variable, global to the model

Initial Assignment mathematical expression to determine the initial conditions of a model.

Rule mathematical expression added to the set of equations constructed based

on the reactions

Constraint means of detecting out-of-bounds conditions during a dynamical simulation

Reaction statement describing some transformation, transport or binding process

that can change the amount of one or more species

Event statement describing an instantaneous change in a set of variables



<?xml version="1.0" encoding="UTF-8"?>



</sbml>



```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4/"</pre>
      level="2"
      version="4">
  <model ...>
  </model>
</sbml>
```



```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4/"</pre>
      level="2"
      version="4">
  <model ...>
   <listOfXYZ>
  </model>
</sbml>
```



```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4/"</pre>
       level="2"
       version="4">
  <model ...>
   <listOfSpecies>
     <species ...</pre>
   </listOfSpecies>
  </model>
</sbml>
```

Compartment

a container of finite size for well-stirred substances

Species

a pool of a chemical substance



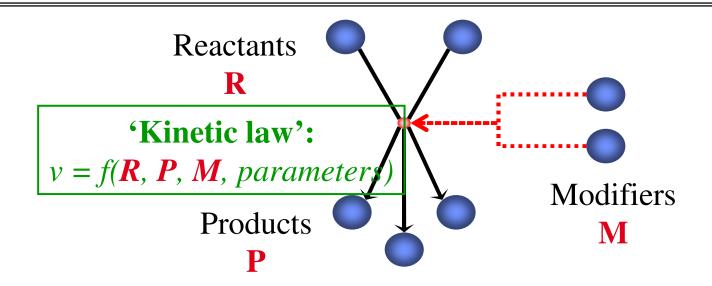
Parameter

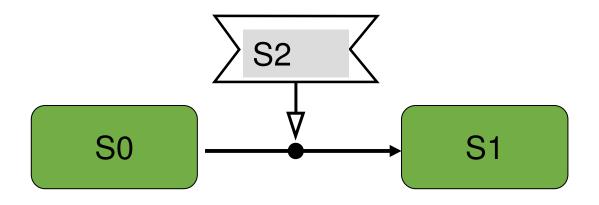
a quantity of whatever type is appropriate



Reaction

a statement describing some transformation, transport or binding process that can change one or more species





rate law: k * S0 * S2





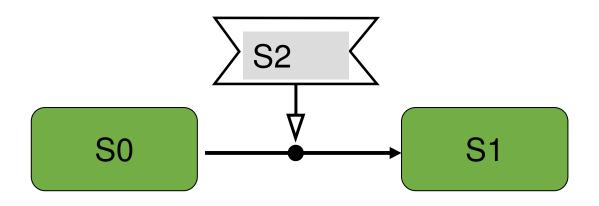
```
<listOfSpecies>
 <species id="S0"</pre>
                    compartment="comp1" initialAmount="1.66057788110262e-21/>
 <species id="S1"
                    compartment="comp1" initialAmount="0"/>
 <species id="S2"</pre>
                    compartment="comp1" initialAmount="2e-21"/>
</listOfSpecies>
<listOfReactions>
 <reaction>
  <listOfReactants>
    <speciesReference species="S0"/</pre>
  IstOfReactants>
  <listOfProducts>
    <speciesReference species="S1"/>
  /listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="S2"/>
```





```
<kineticLaw>
 <math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
    <times/>
      <ci> comp1 </ci>
      <ci> k </ci>
      <ci> S0 </ci>
      <ci> S2 </ci>
     </apply>
  <listOfLocalParameters>
    <localParameter id="k" value="2"/>
  IstOfLocalParameters>
</kineticLaw>
```





rate law: k * S0 * S2

dS0/dt = - k * S0 * S2 * comp

dS1/dt = + k * S0 * S2 * comp



Rule

a mathematical expression that is added to the model equations

assignmentRule x = f(y)

rateRule dx/dt = f(y)

algebraicRule f(x,y) = 0

SBML is not limited to biochemistry!

- Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage;
- Events can describe any discontinuous change, e.g. neurotransmitter release or repolarisation;
- A species is an entity participating to a reaction, not always a chemical entity:
 - It can be a molecule
 - It can be a cell
 - It can be an organ
 - It can be an organism
- Systems Biology is scale-free!

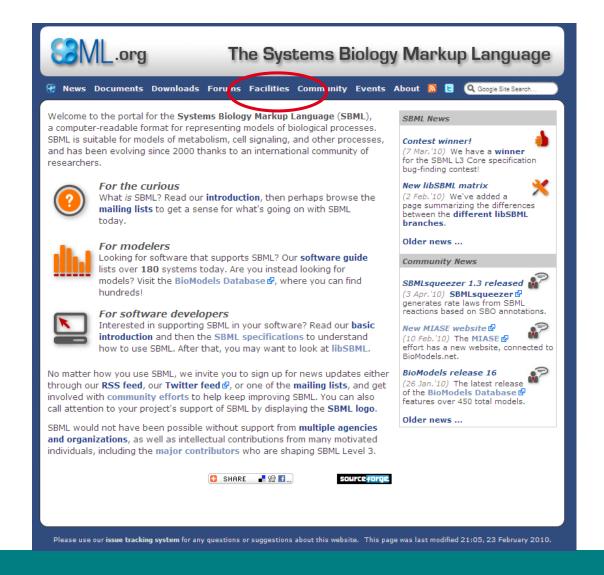


Event

a set of mathematical formulas evaluated at specified moments in the time evolution of the system

event
$$\begin{cases} flag = 0 \\ flag = 1 \text{ when } t > 30 \end{cases}$$

SBML Resources



SBML Resources

Online validator



Parent pages: SBML.org / Facilities

Online SBML Validator

Last Updated: 2010-01-21



You can upload (or access at a URL) a file in SBML format and have its syntax and internal consistency tested. All specifications of SBML are supported, including **Level 2 Version 4 Release 1**. Passing this validator doesn't guarantee the file is 100% correctly formatted SBML, but it's the best automated assessment available.

In the form below, select an SBML file on your computer, or type the URL of an SBML file located on another computer. The file can be uncompressed, or compressed using zip, gzip or bzip2.

Upload File Submit URL			
Browse	Validate		
e.g. C\:Program Files\SBML\MyModels\I2v1-branch.xml			
Options:			
Check consistency of measurement units associated with quantities (SBML L2V4 rules 105nn)			
☑ Check correctness and consistency of identifiers used for model entities (SBML L2V4 rules 103)	3nn)		
✓ Check syntax of MathML mathematical expressions (SBML L2V4 rules 102nn)			
Check validity of SBO identifiers (if any) used in the model (SBML L2V4 rules 107nn)			
Perform static analysis of whether the model is overdetermined			



SBML Resources

Results:

This document is not valid SBML!

1 Error

1. Error Line 8 Column 40: (SBML Validation Rule #20601) The value of 'compartment' in a <species> definition must be the identifier of an existing <compartment> defined in the model. (References: L2V1 Section 4.6.2; L2V2 Section 4.8.3; L2V3 Section 4.8.3; L2V4 Section 4.8.3) Compartment 'a' is undefined.

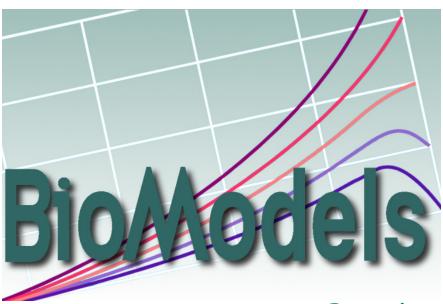
```
<species id="s" compartment="a"/>
```

Document Listing

```
1. <?xml version="1.0" encoding="UTF-8"?>
2. <sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
3. <model>
4. st0fCompartments>
5. <compartment id="c"/>
6. </list0fCompartments>
7. st0fSpecies>
8. <species id="s" compartment="a"/>
9. </list0fSpecies>
10. </model>
11. </sbml>
```





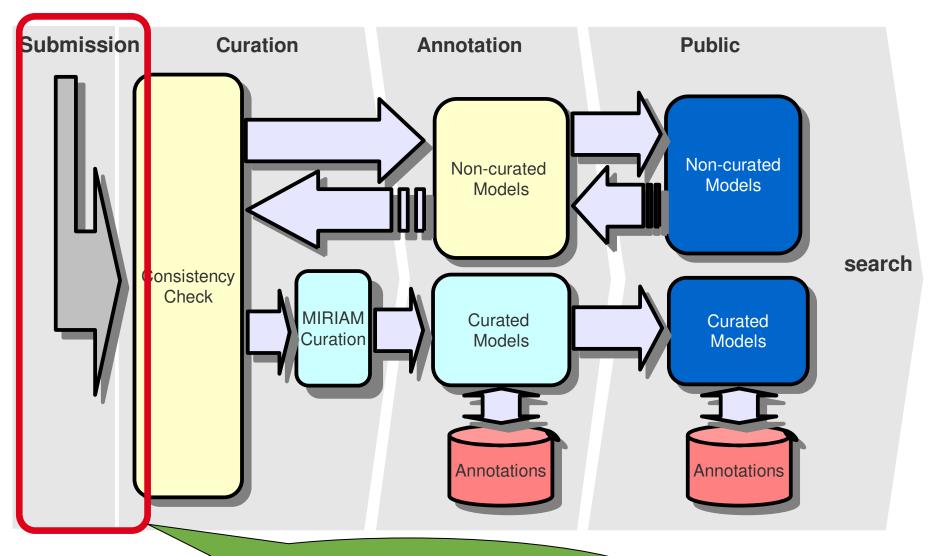


-Production Pipeline.....

Submission Curation Annotation Search



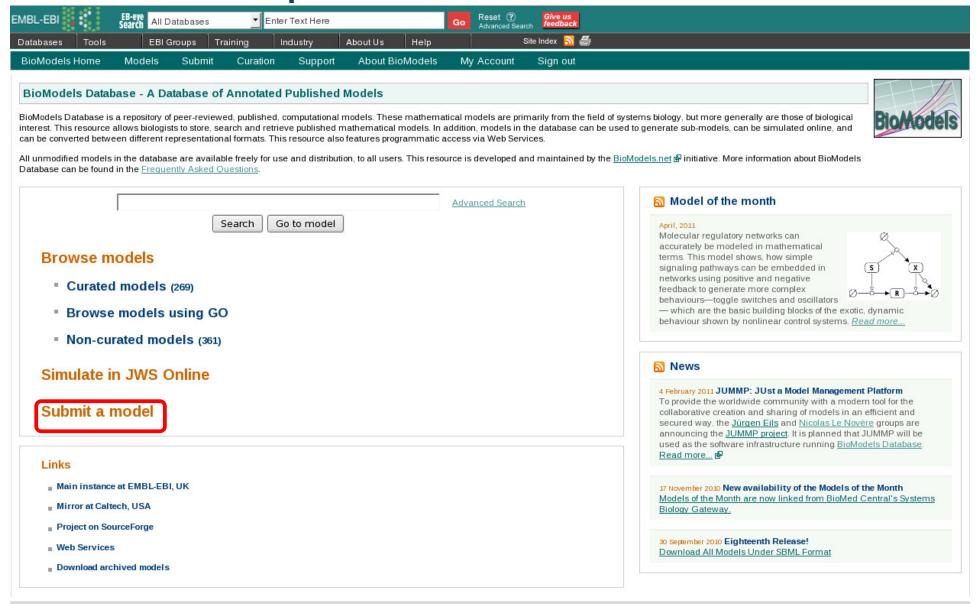
Production pipeline



Model source and Format (eg. SBML), Submission steps



http://www.ebi.ac.uk/biomodels/





You can submit here models to be included in the BioModels Database. The following formats are currently accepted:

- SBML Level 2 Version 3
- SBML Level 2 Version 2
- SBML Level 2 Version 1
- SBML Level 1 Version 2
- SBML Level 1 Version 1
- CellML 1.1
- CelIML 1.0

If you wish to submit a model under a different format, please contact us.

The submitted models will not be incorporated into the BioModels Database straightaway, since they have to undergo a curation phase before. During this curation phase, the models will be first converted to the SBML Level 2 Version 3 format in case they were submitted under a different format, and then tested to verify that they both are consistent and reproduce the results published in the respective reference publication. To actually facilitate this curation phase, prior to submitting a model, please do the following:

- Enter all the relevant information you believe is necessary for the curation (Relation between the model and publication, modifications or clarifications of the model, etc.) either directly into the model file if possible (for example using the notes elements if your model is under one of the SBML formats), or into the Curation comment text field provided by the form in step 3.
- If you created the model, or collaborated to its creation, and you are not an author of the reference publication, add to the model element a descreator annotation containing your data (first and last name, organisation, email), so that your contribution can be acknowledged. Click here to view an example of a descreator annotation which you can re-use (skip blue part if already present).
- Choose a meaningful value for the attribute name of the model element. Examples of good model names are NameAuthorYear_Topic_Method, Levchenko2000_MAPK_noScaffold or Edelstein1996_EPSP_AChEvent.
- Check the validity of the model (for example by using this online validator if your model is under one of the SBML formats). All the models undergo a primary XML validity check upon submission anyway, and, as mentioned before, a more thorough testing during the curation phase, but an already valid model is of great help nevertheless!

Thanks a lot for your contribution to the BioModels Database!

•				
Please enter the ID of the reference publication associated with the model, and then click Continue, if unpublished the ID is optional.				
Publication ID: 1831270 • PubMed (Search Medline) • DOI (Resolve a DOI) • URL • Unpublished Continue Reset				
Developed by Pistadels Team of Computational Neuropialsey Croup in European Riginformatics Institute Torms of the Contact the				





Below is the summary for the publication with PubMed ID:

1831270

If the publication summary is not what you expected, click Back to enter a different PubMed ID.

Otherwise click Continue to go on submitting the model to the curation phase.

Click Cancel to return to the models submission page.

Proc Natl Acad Sci U S A 1991 Aug;88(16):7328-32.

Modeling the cell division cycle: cdc2 and cyclin interactions.

Tyson JJ.

Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg 24061.

The proteins cdc2 and cyclin form a heterodimer (maturation promoting factor) that controls the major events of the cell cycle. A mathematical model for the interactions of cdc2 and cyclin is constructed. Simulation and analysis of the model show that the control system can operate in three modes: as a steady state with high maturation promoting factor activity, as a spontaneous oscillator, or as an excitable switch. We associate the steady state with metaphase arrest in unfertilized eggs, the spontaneous oscillations with rapid division cycles in early embryos, and the excitable switch with growth-controlled division cycles typical of nonembryonic cells.

Back Continue Cancel





You can submit here models to be included in the BioModels Database. The following formats are currently accepted:

- SBML Level 2 Version 3
- SBML Level 2 Version 2
- SBML Level 2 Version 1
- SBML Level 1 Version 2
- SBML Level 1 Version 1
- CellML 1.1
- CellML 1.0

If you wish to submit a model under a different format, please contact us.

The submitted models will not be incorporated into the BioModels Database straightaway, since they have to undergo a curation phase before. During this curation phase, the models will be first converted to the SBML Level 2 Version 3 format in case they were submitted under a different format, and then tested to verify that they both are gone stent and reproduce the results published in the respective reference publication. To actually facilitate this curation phase, prior to submitting a model, please do the following:

- Enter all the relevant information you believe is necessary for the curation (reference publication, modifications or clarifications of the model, etc.) either directly into the model file if allowed (for example using the notes elements if your model is under one of the SBML formats), or into the Curation comment text field provided by the form below.
- If you created the model, or collaborated to its creation, and you are not an author of the reference publication, add to the model element a discreator annotation containing your data (first and last name, organisation, email), so that your contribution can be acknowledged. Click here to view an example of a discreator annotation which you can re-use (skip blue part if already present).
- Choose a meaningful value for the attribute name of the model element. Examples of good model names are NameAuthorYear. Topic, Method, Levchenko2000. MAPK. noScaffold or Edebtein 1996. EPSP. AChEvent.
- Check the validity of the model (for example by using this online validator if your model is under one of the SBML formats). All the models undergo a primary XML validity check upon submission anyway, and, as mentioned before, a more thorough testing during the curation phase, but an already valid model is of great help nevertheless!
- If the model was not created directly in SBML, or if it requires a specific software to be simulated adequately, please enter in the Original Model form a URL pointing to the model in the original repository. Refrain from entering a generic URL to the repository itself.

Please enter yo	our personal details and any comment useful for thecuration step (underlined fields are required), and then click Submit.	
First name:	Vijayalakshmi	
Lest neme:	Chelliah	
Organisation:	EBI-EMBL	
Email:	viji@ebi.ac.uk	
Comment:	Cell division cycle xxxxxxx	
Original model		
Model file:	/automount/nas10b_vol-vol1-homes/viji/work_viji/biomodels/model5/cellcycle.xml	Browse
Submit	Reset	





Dear Vijayalakshmi, your request to submit the model contained within the file

cellcycle.xml

and with name:

Tyson1991_CellCycle_6variable

has been successfully completed.

The model has been assigned the unique ID

MODEL8232600906

Submit Another Model

model accession ID is unique and perennial and can be used as a reference in publications and for searching and retrieving the model

■ Subject: BioModels Database - Notification of New Model Submission

From: biomodels-database-mailer@ebi.ac.uk

Date: 09:30

To: viji@ebi.ac.uk

PLEASE DO NOT REPLY TO THIS EMAIL

Dear submitter,

Thank you for submitting the model Tyson1991 CellCycle 6variable, published in

Proc Natl Acad Sci U S A 1991 Aug;88(16):7328-32. Modeling the cell division cycle: cdc2 and cyclin interactions. Tyann JJ

The model is now in the process pipeline with the unique accession MODEL8232600906 This identifier is unique and can be used, for instance in scientific publications or grant applications. Our team of curators will now verify the syntax and the semantic of the model. You will be notified when this is done and the model enters the annotation phase.

We welcome any updates, comments, or other notices about this or any other models. Please feel free to contact us at:

The BioModels Database team Computational Neurobiology EMBL-EBI Wellcome-Trust Genome Campus Hinxton Cambridge CB10 ISD United-Kingdom

E-mail: biomodels-cura AT ebi.ac.uk

Tel: +44 (0)1223 494521 Fax: +44 (0)1223 494468

Thank you,

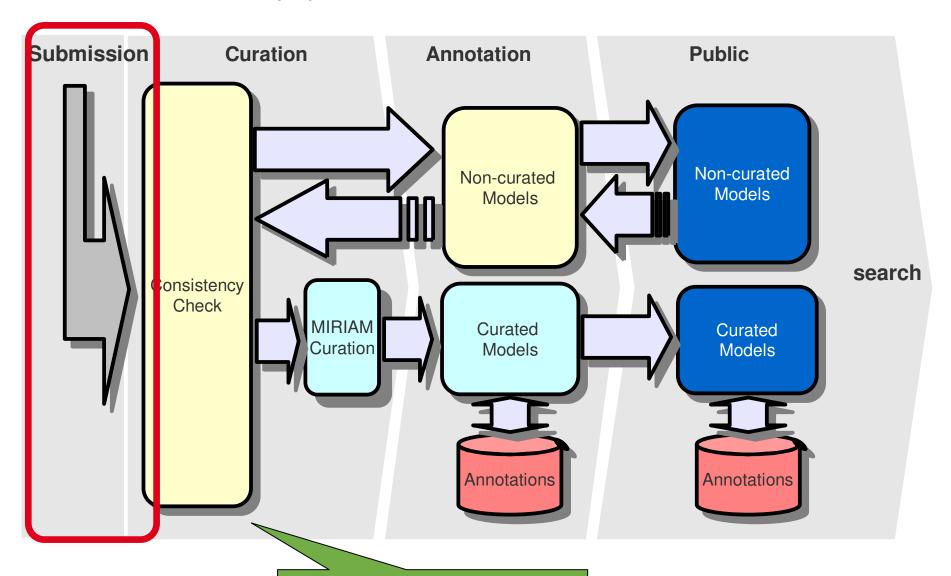
The BioModels Database Team

BioModels Database is developed in collaboration by the teams of Nicolas Le Novère (EMBL-EBI, United-Kingdom), Michael Hucka (SBML Team, Caltech, USA), Herbert Sauro (Keck Graduate Institute, USA) and Jacky Snoep (JWS Online, Stellenbosch University, ZA), as part of the BioModels net initiative. BioModels Database development is funded by the European Molecular Biology Laboratory and the National Institute of General Medical Sciences.

Please quote the reference publication associated with the model, when quoting a model present in the BioModels Database.



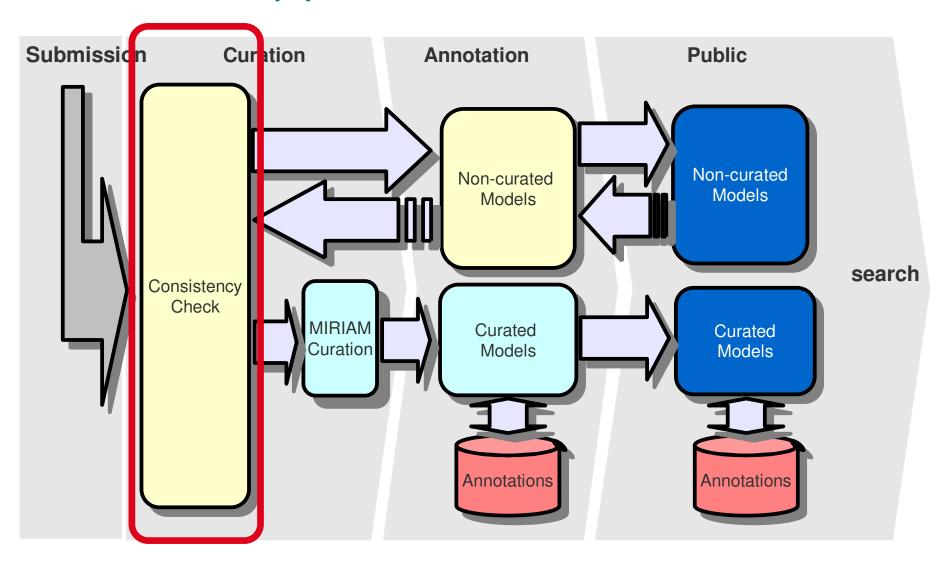
Production pipeline



computer software checks the SBML syntax.



Production pipeline





MIRIAM guidelines

- Reporting guidelines for curation of quantitative models
 - Specifically about encoding & annotating models.
 - Limited for the moment to models that can be numerically evaluated.
- Not specific to SBML; applicable to any structured model format.



computationa

PERSPECTIVE

Minimum information requested in the annotation of biochemical models (MIRIAM)

Nicolas Le Novère^{1,15}, Andrew Finney^{2,15}, Michael Hucka³, Upinder S Bhalla⁴, Fabien Campagne⁵, Julio Collado-Vides⁶, Edmund J Crampin⁷, Matt Halstead⁷, Edda Klipp⁸, Pedro Mendes⁸, Poul Nielsen⁷, Herbert Sauro¹⁰, Bruce Shapiro¹¹, Jacky L Snoep¹², Hugh D Spence¹³ & Barry L Wanner¹⁴

Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main causes for incomplete model descriptions. With today's increased interest in detailed biochemical models, it is necessary to define a minimum quality standard for the encoding of those models. We propose a set of rules for curating quantitative models of biological systems. These rules define procedures for encoding and annotating models represented in machine-readable form. We believe their application will enable users to (i) have confidence that curated models are an accurate reflection of their associated reference descriptions, (ii) search collections of curated models with precision, (iii) quickly identify the biological phenomena that a given curated model or model constituent represents and (iv) facilitate model reuse and composition into large subcellular models.



European Bioinformatics Institute, Hinston, CB10 150, UK
"Physimione FJR, Wagdalen Centre, Ondred Science Park, Oxford,
OX4 40A,K. "Sciential and Dynamical Systems, California Institute of
Technology, Pasadean, California 19125, USA. "National Centre for Biological
Sciences, TIFR, UAS, GARVK Campus, Bangalore 560065, India: "Institute
of Computational Biomedicine, Well Medical College of Cornell University,
New York, New York, 10021, USA. "Centre for Genomic Sciences, Universidad
62100, Messic, "Placengineering institute and Department of Engineering
Science, The University of AuxStand, Private Bag 92019, AuxStand, New
2cland, Muss, "Placengineering institute and Department of Engineering
Science, The University of AuxStand, Private Bag 92019, AuxStand, New
Yelgand Silonformatics (BDD), Intent. 73, 14195 Berlin, Germany,
Virginia 2closi-Lod 77, USA. "Neck, Graduate Institute, 535 Waston Drive,
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Published online 6 December 2005; doi:10.1038/nbt1156

During the genomic era we have witnessed a vast increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their dynamics. One of the tenest of systems biology is the use of quantitative models (see Box1 for definitions) as a mechanism for capturing precise hypotheses and making predictions^{1,2}. Many specialized models exist that attempt to explain aspects of the cellular machinery. However, as has happened with other types of biological information, such as sequences, macromolecular structures or

Box 1 Glossary

Some terms are used in a very specific way throughout the article. We provide here a precise definition of each one.

Quantitative biochemical model. A formal model of a biological system, based on the mathematical description of its molecular and cellular components, and the interactions between those

Encoded model. A mathematical model written in a formal machine-readable language, such that it can be systematically parsed and employed by simulation and analysis software without further human translation.

MIRIAM-compliant model. A model that passes all the tests and fulfills all the conditions listed in MIRIAM.

Reference description. A unique document that describes, or references the description of the model, the structure of the model, the numerical values necessary to instantiate a simulation from the model, or to perform a mathematical analysis of the model, and the results one expects from such a simulation or analysis.

Curation process. The process by which the compliance of an encoded model with MIRIAM is achieved and/or verified. The curation process may encompass some or all of the following tasks: encoding of the model, verification of the reference correspondence and annotation of the model.

Reference correspondence. The fact that the structure of a model and the results of a simulation or an analysis match the information present in the reference description.

NATURE BIOTECHNOLOGY VOLUME 23 NUMBER 12 DECEMBER 2005

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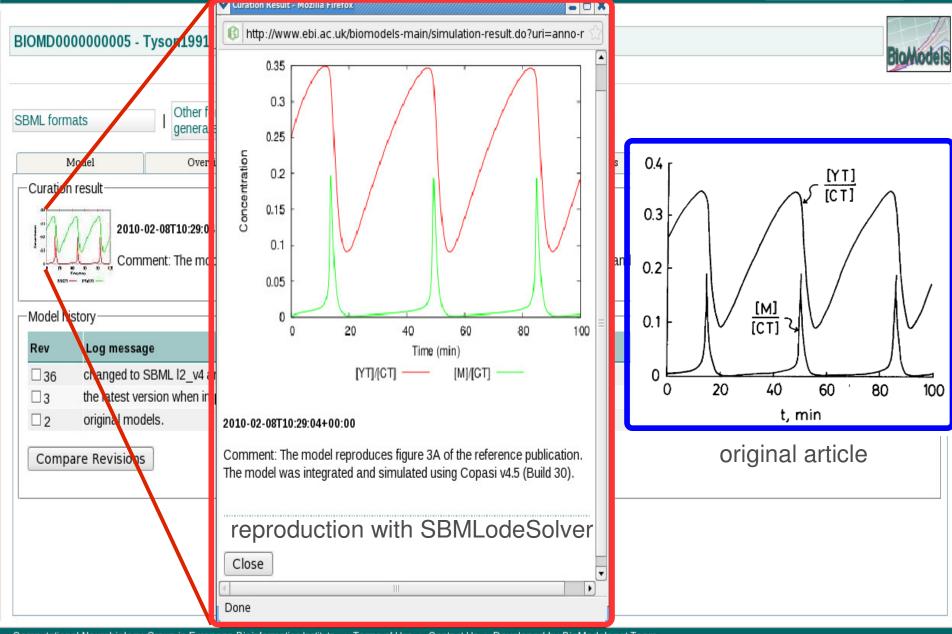
MIRIAM compliance

Minimum Information Requested In the Annotation of Models Le Novère N. et al. *Nature Biotechnology* (2005), 23: 1509-1515

model must:

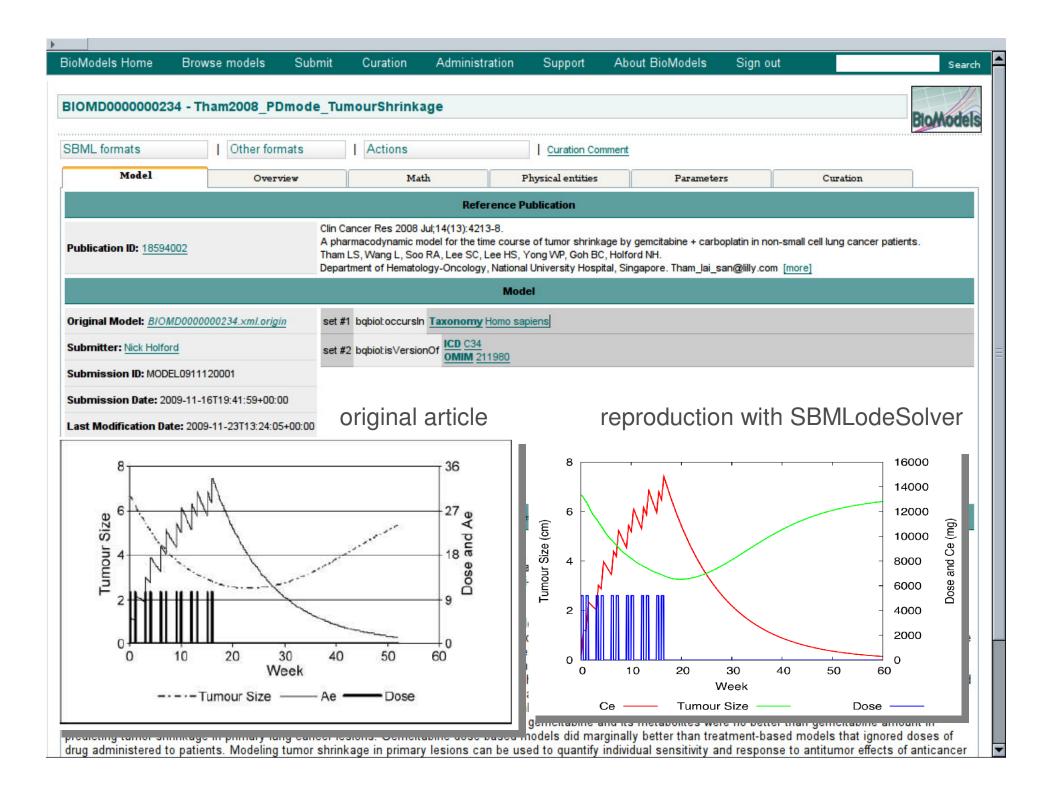
- be encoded in a standard format (CellML, SBML)
- contain link to a single reference description (peer reviewed for BioMdDB)
- reflect the structure of the biological processes described in the reference paper
- be able to reproduce the results given in the reference paper (all quantitative attributes should be defined)
- contain creator's contact details.



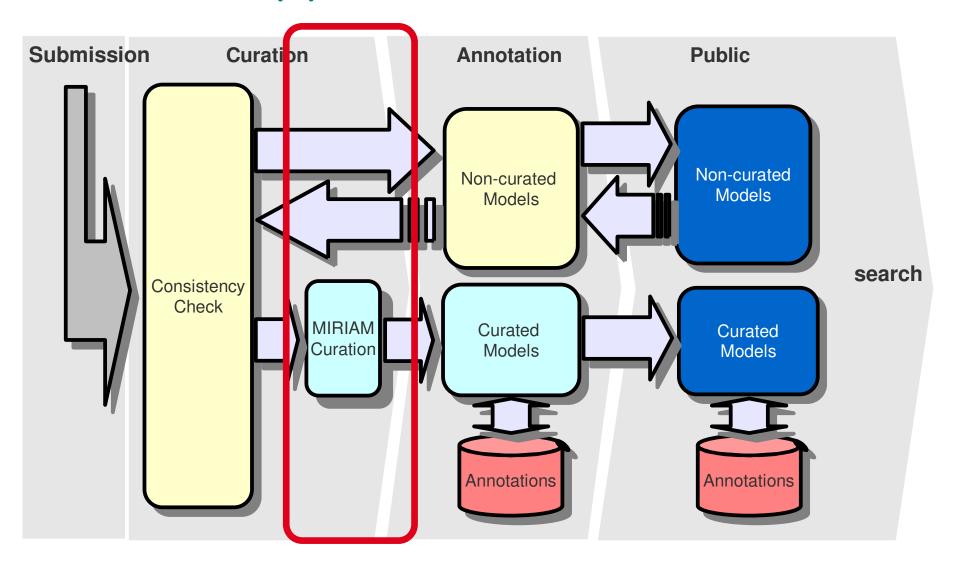


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Production pipeline





Curated and Non-curated Models

Curated models - MIRIAM compliance successfully checked

Non-Curated models - valid SBML, not curated or annotated by the curators.

- not MIRIAM compliant
 - can not reproduce results published in the paper.
 - differ in model structure
 - non kinetic models (eg. FBA, stoichiometric maps)
- MIRIAM compliant
 - models contain kinetics that we cannot curate up to now.
 - will be moved into curated branch as soon as possible (model being checked by curators).



Why are annotations important?

Annotation of model components are essential to:

- · unambiguously identify model components
 - · improve understanding the structure of the model
 - · allow easier comparison of different models
 - ease the integration of models
- · allow efficient search strategies
- add a semantic layer to the model
 - improve understanding the biology behind the model
 - allow conversion and reuse of the model
 - ease the integration of model and biological knowledge



Why annotation?

но-р-он

1,3-Bisphosphoglycerate

- Synonyms
 - e.g.: Glyceric Acid 1,3 bisphosphate 3-phospho-D-glyceroyl phosphate
- Identifiers used in models in BioModels Database: BPG, BPG13, Gri13P2, DPG, pgp, PGAP ...
- => annotations can help to find models containing BPG for example searching using KEGG ID (CO0236) or CHEBI ID (CHEBI:16001)



MIRIAM Annotations

Each model element is linked to the external data resource. This

enhances model quality

- Taxonamy, Gene Ontology, ChEBI, UniPROT,
- is essential for search criteria. KEGG, Reactome, Enzyme Nomenclature, etc.

MIRIAM Annotations are represented as a triplet which consists of:

- resource (eg. Enzyme Nomenclature)
- identifier (eg. EC 3.1.3.16 = phosphoprotein phosphatase)
- qualifier (eg. is Version of)

Resource and identifier together, are in the form of **URI** (*Uniform Resource Identifier*):

urn:miriam:ec-code:3.1.3.16

these are resolved to a **URL** using MIRIAM Resources (http://www.ebi.ac.uk/miriam/)

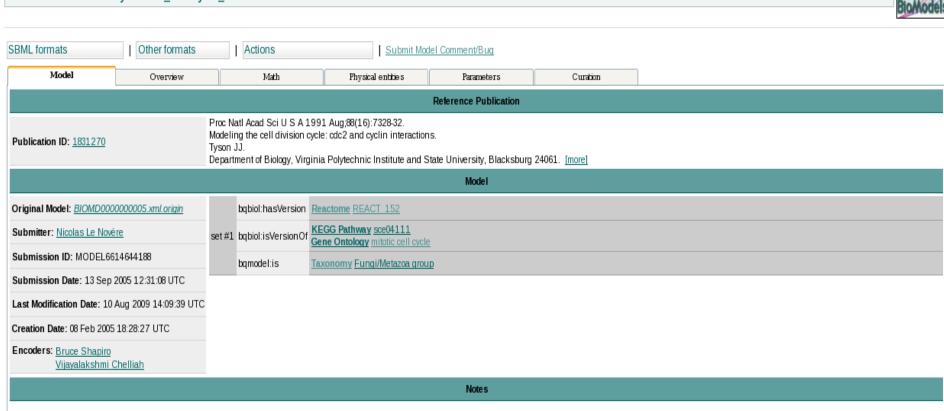




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BIOMD000000005 - Tyson1991_CellCycle_6var





This a model from the article:

Modeling the cell division cycle: cdc2 and cyclin interactions.

Tyson JJ Proc. Natl. Acad. Sci. U.S.A.1991; 88(16); 7328-32 1831270,

Abstract:

The proteins cdc2 and cyclin form a heterodimer (maturation promoting factor) that controls the major events of the cell cycle. A mathematical model for the interactions of cdc2 and cyclin is constructed. Simulation and analysis of the model show that the control system can operate in three modes: as a steady state with high maturation promoting factor activity, as a spontaneous oscillator, or as an excitable switch. We associate the steady state with metaphase arrest in unfertilized eggs, the spontaneous oscillations with rapid division cycles in early embryos, and the excitable switch with growth-controlled division cycles typical of nonembryonic cells.

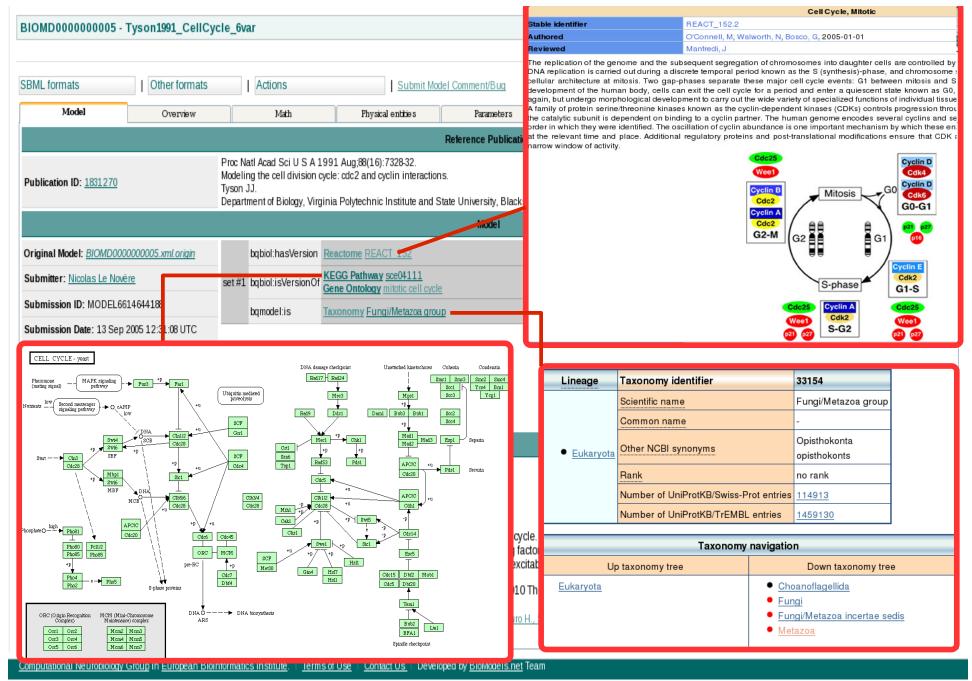
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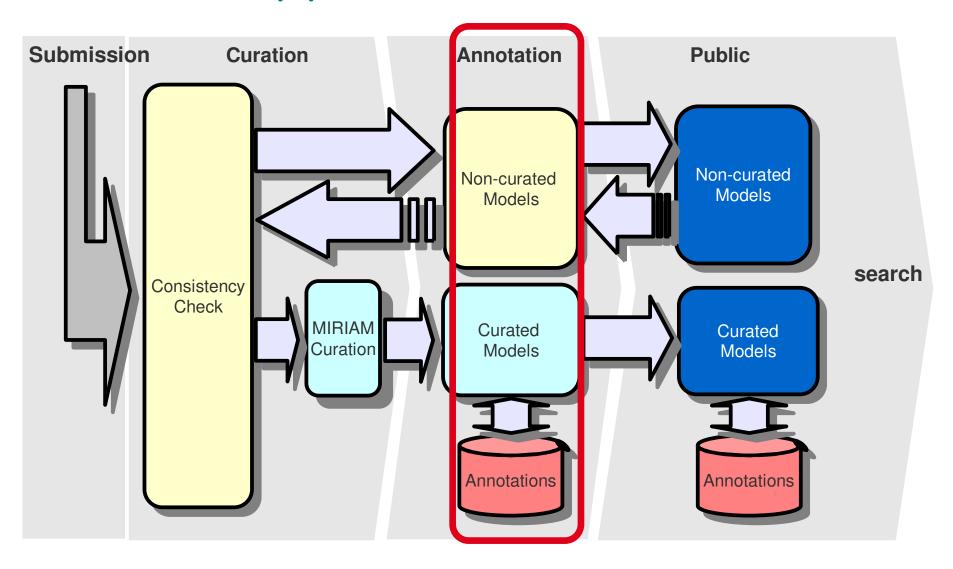
To cite BioModels Database, please use Le Novère N., Bornstein B., Broicher A., Courtot M., Donizelli M., Dharuri H., Li L., Sauro H., Schilstra M., Shapiro B., Snoep J.L., Hucka M. (2006) BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems Nucleic Acids Res., 34: D689-D691.

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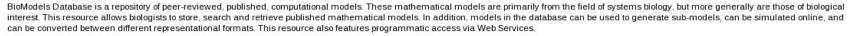
Production pipeline







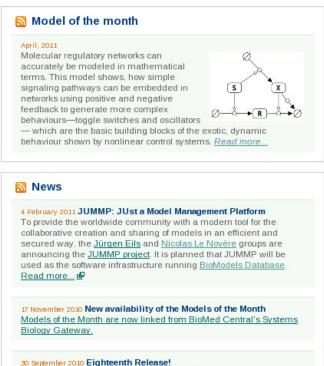
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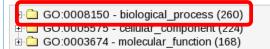
Download All Models Under SBML Format



Browse - Curated models



This is a tree view of the models in BioModels Database based on Gene Ontology. To browse the models, please click 🗈 to expand the branch, or click 🖯 to collapse the branch. By double clicking the Gene Ontology term, the detail of the term will be displayed in a new window. By double clicking the BioModels Model ID, this page will be forwarded to the detail of selected model.



BioModels ID: Unspecified

Name: N/A Publication ID: N/A

Last Modified: N/A

The relationships between terms are represented by different icons.

- BioModels qualifiers:
 - bqbiol:is
 - bqbiol:isVersionOf ⊎ bqbiol:hasPart
- · Gene Ontology relationships:
 - 📄 is a part of
 - develops from
 - other

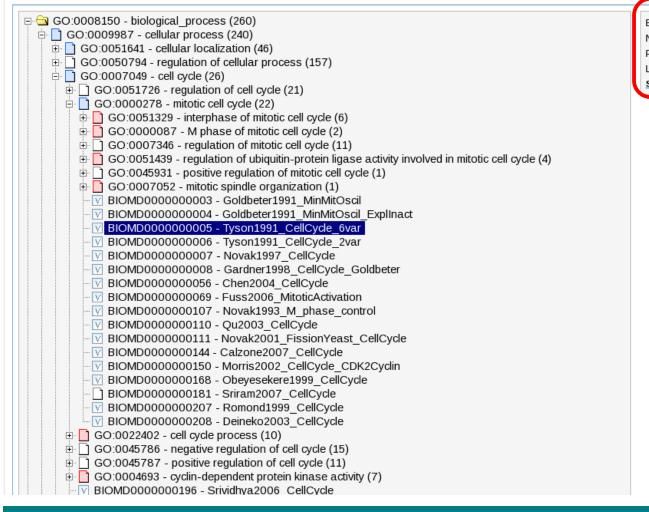
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BioModels ID: <u>BIOMD000000005</u>

Name: Tyson1991_CellCycle_6var

Publication ID: <u>1831270</u>

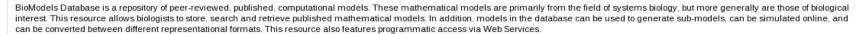
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<u>SBML L2 V4</u>



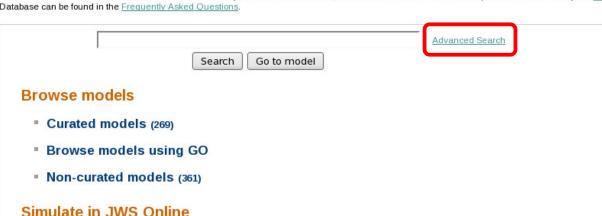


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Model of the month

April, 2011

Molecular regulatory networks can accurately be modeled in mathematical terms. This model shows, how simple signaling pathways can be embedded in networks using positive and negative feedback to generate more complex behaviours—toggle switches and oscillators



— which are the basic building blocks of the exotic, dynamic behaviour shown by nonlinear control systems. Read more...

Submit a model

Links

- Main instance at EMBL-EBI, UK
- Mirror at Caltech, USA
- Project on SourceForge
- Web Services
- Download archived models

News

4 February 2011 JUMMP: JUst a Model Management Platform

To provide the worldwide community with a modern tool for the collaborative creation and sharing of models in an efficient and secured way, the <u>Jürgen Eils</u> and <u>Nicolas Le Novère</u> groups are announcing the <u>JUMMP project</u>. It is planned that JUMMP will be used as the software infrastructure running <u>BioModels Database</u>. Read more...

17 November 2010 New availability of the Models of the Month Models of the Month are now linked from BioMed Central's Systems Biology Gateway.

30 September 2010 Eighteenth Release!

Download All Models Under SBML Format

Tarme of Llea 👉 ERI Funding 👉 Contact ERI 👉 🖱 Furnician Richinformatics Institute 2011 - ERI is an Outstation of the Furnician Malecular Richard Laboratory



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- 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:0000278 or cell cycle for Gene Ontology, P04551 or cell division for UniProt).
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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. 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.

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Resource ID:	Enzyme Nomenclature	企	Gene Ontology: <i>GO:0000278 or cell cycle</i>
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Search - Models

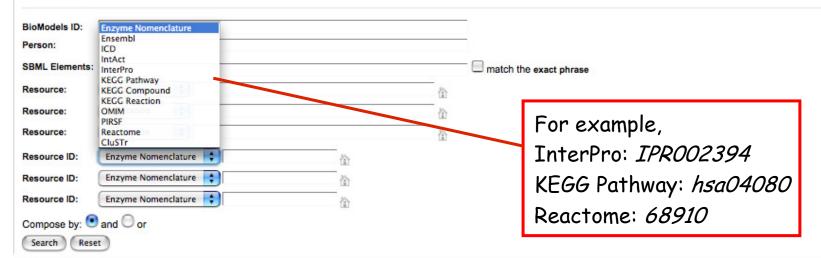


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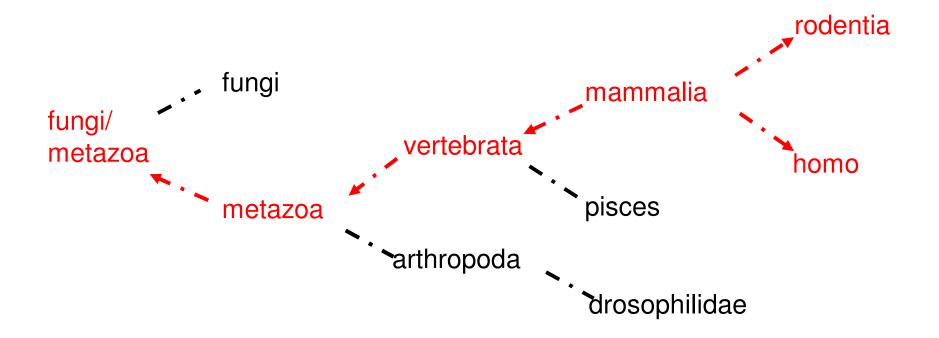


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Taxonomic Searches

linking to hierarchical controlled vocabularies allows for more elaborate searching:

e.g.: searching BioModels DataBase for all models fitting mammals

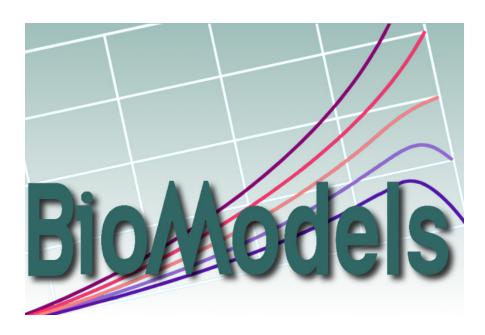






■ 26 Curated Models returned.

BioModels ID ▽	<u>Name</u>	Publication ID	Last Modified
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BIOMD000000006	Tyson1991_CellCycle_2var	- metazoa/fungi	2009-02-25T14:41:44+00:00
BIOMDOCCCCCCC24 hams	Scheper1999_CiroClock	<u>9870936</u>	2008-08-21T11:46:43+00:00
BIOMD000000043	Borghans1997_CaOscillation_model1	17029867	2009-04-21T12:52:44+00:00
BIOMD000000044	Borghans1997_CaOscillation_model2	<u>17029867</u>	2008-08-21T11:53:55+00:00
BIOMD000000045	Borghans1997_CaOscillation_model3	- rattus 17029867	2008-08-21T11:54:12+00:00
BIOMD000000047	Oxhamre2005_Ca_oscillation	15596518	2008-08-21T11:54:50+00:00
BIOMD000000057	Sneyd2002_IP3_Receptor	11842185	2008-08-21T11:58:43+00:00
BIOMD000000059	Fridlyand2003_Calcium_flux	<u>12644446</u>	2008-10-01T17:23:42+00:00
BIOMD000000073	Leloup2003_CircClock_DD	12775757	2008-08-21T12:04:54+00:00
BIOMD0000000114	Somogyi1990_CaOscillations	<u>1904060</u>	2008-08-21T12:20:25+00:00
BIOMD0000000115	Somogyi1990_CaOscillations_SingleCaSpike	<u>1904060</u>	2008-08-21T12:20:44+00:00
BIOMD000000124	Wu2006_K+Channel	16375866	2007-09-25T10:20:25+00:00
BIOMD000000154	Zatorsky2006_p53_Model3	16773083	2008-01-14T21:29:55+00:00
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BIOMD000000157	Zatorsky2006_p53_Model4	- homo sapie <u>ns</u>	2008-01-14T21:39:09+00:00
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BIOMD000000181	Sriram2007_CellCycle	18203579	2009-04-22T10:19:56+00:00
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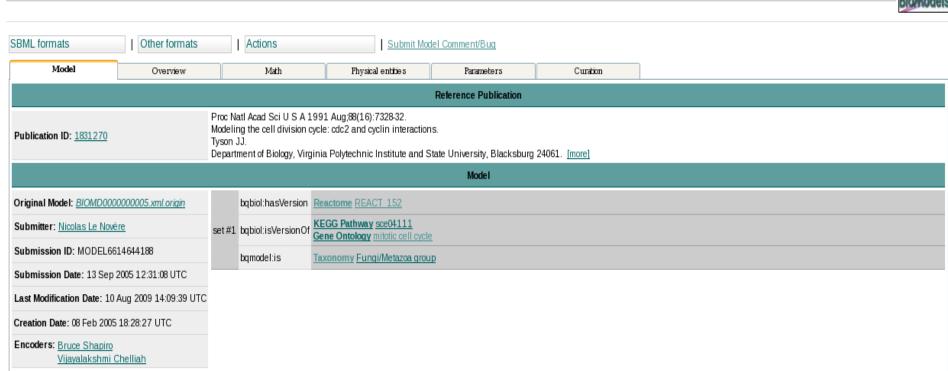
Model components & Sub-model creation



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BIOMD000000005 - Tyson1991_CellCycle_6var





This a model from the article:

Modeling the cell division cycle: cdc2 and cyclin interactions.

Tyson JJ Proc. Natl. Acad. Sci. U.S.A.1991; 88(16); 7328-32 1831270.

Abstract:

The proteins cdc2 and cyclin form a heterodimer (maturation promoting factor) that controls the major events of the cell cycle. A mathematical model for the interactions of cdc2 and cyclin is constructed. Simulation and analysis of the model show that the control system can operate in three modes: as a steady state with high maturation promoting factor activity, as a spontaneous oscillator, or as an excitable switch. We associate the steady state with metaphase arrest in unfertilized eggs, the spontaneous oscillations with rapid division cycles in early embryos, and the excitable switch with growth-controlled division cycles typical of nonembryonic cells.

Notes

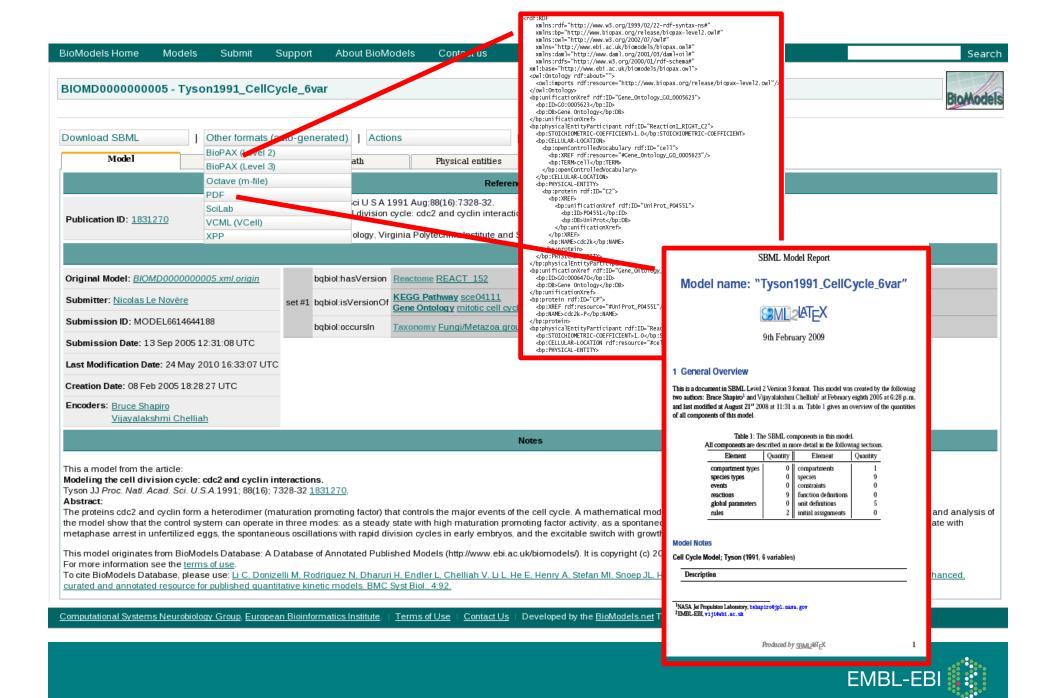
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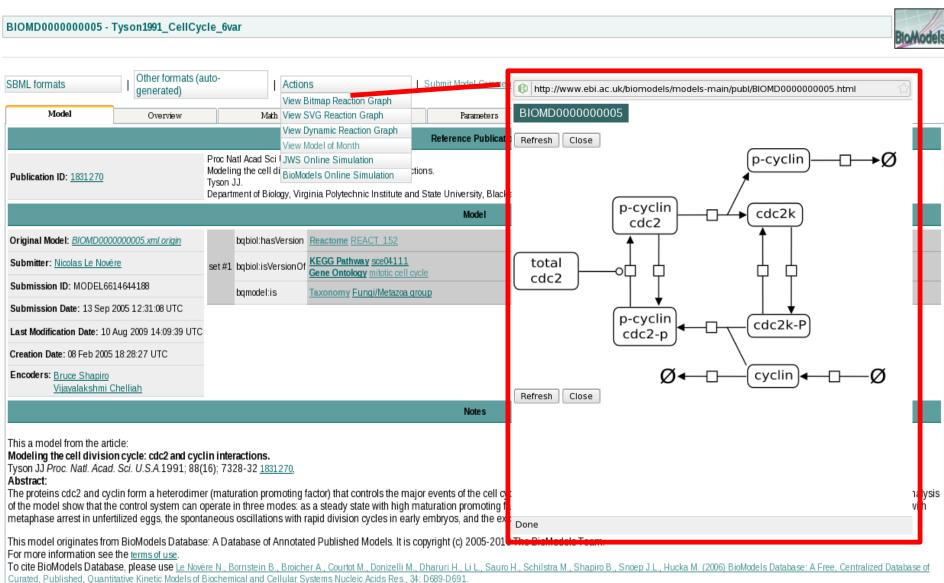
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EMBL-EBI





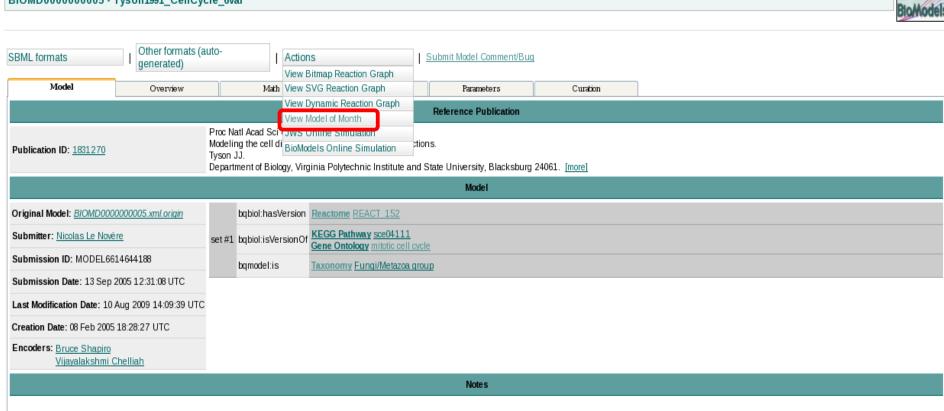


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BIOMD000000005 - Tyson (1991), modelling cell division

by Nicolas Le Novère

One of the characteristics of <u>life</u> is <u>autopoiesis</u>, that is the auto-production. The biological cell is the archetypal example of an autopoietic systems. One of the key events of cell reproduction is the <u>division of a cell</u> into two descendants. In population formed of unicellular organisms, but also in many tissues of pluricellular organisms, this processus is a periodic one, called cell cycle. The mechanisms underlying <u>eukaryotic cell</u> cycle have been extensively studied, and have been found remarkably conserved throughout evolution. Their elucidation has been awarded the <u>Nobel prize of physiology and medecine in 2001</u>. Cell division is not only the basic mechanism by which a human is built from the egg, when altered it also triggers diseases such as cancers.

With his model published in 1991 [1], John Tyson played a pioneer role in what would become one of the most prolific fields of quantitative modeling in cell biology. One of the crucial events deciding the cell division is the formation of the Maturation Promoting Factor (MPF), from oscillating proteins called cyclin and specific protein kinases. With only 6 reacting species and 9 reactions (figure 1), Tyson built a mechanistic model explaining a very complex cellular behaviour from simple molecular events. The model is based on the creation and degradation of cyclin, its binding to and dissociation from cyclin dependent kinase CDC2, and the phosphorylation of both proteins. Although his model was primarily devoted to explain yeast cell cycle, its explanatory power covered the whole metazoa/fungi group.

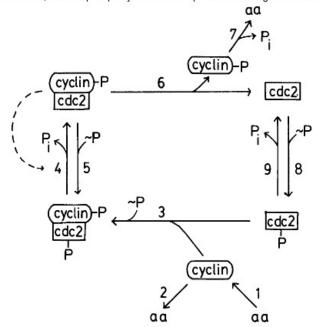


Figure 1: Reaction graph of the model from Tyson 1991.

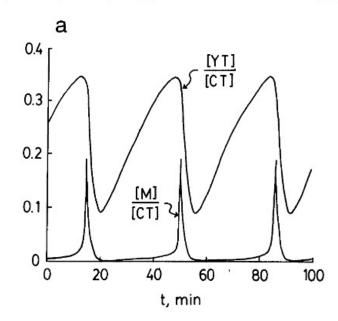


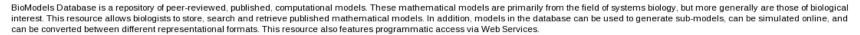
Figure 2: Oscillations of the total cyclin (YT) and the total MPF, relative to the total cyclin dependent kinase CDC2.





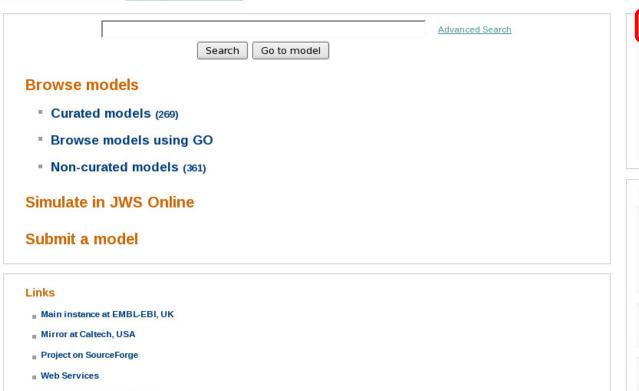
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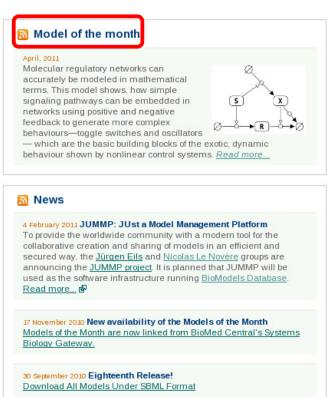
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View - Models of the month

Each "Model of the Month" is an article which explores the biological significance of a particular model from BioModels Database. Every article includes elements such as:

- the description of the model itself and its results
- . the biological background of the model
- a brief description of the biological processes that are encoded as a mathematical model
- · the biological role of each of the model elements
- . the diseases that are caused due to the malfunction of these elements
- the presenters own view on the model

Direct access to the models of the month for a given year: 2006 | 2007 | 2008 | 2009 | 2010 | 2011

2011

- April: BIOMD0000000306, BIOMD0000000307, BIOMD000000308, BIOMD0000000309, BIOMD0000000310, BIOMD0000000311, BIOMD0000000312
 Tyson et al., (2003). Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell., by Lukas Endler
- March:

BIOMD0000000129, BIOMD0000000131, BIOMD0000000132, BIOMD0000000133, BIOMD0000000134, BIOMD0000000135, BIOMD0000000136, BIOMD0000000141, BIOMD0 bikevich EM (2004), Which model to use for cortical spiking neurons?, by Junmei Zhu

- February: BIOMD0000000270
- Schilling et al. (2009), Theoretical and experimental analysis links isoform-specific ERK signalling to cell fate decisions., by Benedetta Frida Baldi
- January: BIOMD0000000215
- Schulz et al., (2009), Sequential polarization and imprinting of type 1T helper lymphocytes by interferon-gamma and interleukin-12., by Christine Hoyer

2010

- December: BIOMD0000000258
- Ortega et al. (2006), Bistability from double phosphorylation in signal transduction. Kinetic and structural requirements., by Massimo Lai
- November: BIOMD0000000249
- Restif and Grenfell (2006), Integrating life history and cross-immunity into the evolutionary dynamics of pathogens, by Lukas Endler
- August: BIOMD000000178, BIOMD000000267
- Lebeda et. al. (2008), Onset dynamics of type A botulinum neurotoxin-induced paralysis, by Vijayalakshmi Chelliah
- July: BIOMD0000000139, BIOMD000000140
- Hoffmann et. al. (2002), The IkB-NF-kB Signaling Module: Temporal Control and Selective Gene Activation, by Lu Li
- June: BIOMD0000000209, BIOMD0000000210
- Chickarmane and Peterson (2008), A computational model for understanding stem cell, trophectoderm and endoderm lineage determination, by Nick Juty
- May: BIOMD0000000127
- Izhikevich EM (2003), Simple model of spiking neurons, by Michele Mattioni
- April: BIOMD0000000166
- Zhu et al. (2007), A theoretical study on activation of transcription factor modulated by intracellular Ca2+ oscillations, by Benedetta Frida Baldi



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Tham et al. (2008). A Pharmacodynamic Model for the Time Course of Tumour Shrinkage by Gemcitabine + Carboplatin in Non-Small Cell Lung Cancer Patients

January 2010, model of the month by Vijayalakshmi Chelliah Original model: BIOM D0000000234

The drug development process is greatly benefited by the advancement in the PharmacoKinetic (PK) / PharmacoKinetic (PK) / PharmacoKinetic (PK) (III), research and modelling techniques. PharmacoKinetic (simply referred as, what the body does to the body in the body in the pharmacoKinetic (PK) (III), research and modelling techniques. PharmacoKinetic (simply referred as, what a drug does to the body), describes the relationship between the drug effect on the body over time. A range of factor, including age, body weight, sex, renal function, liver function, genetic factor, disease status, drug - interaction, absorbtion, distribution and clearance, and various other factors can influence the pharmacoKinetic of a drug, and consequently the pharmacoKinetic (i.e. the patients response to the drug therapy). Therefore, drug dosage adjustments are often required to ensure that the patients achieves an adequate dose without risk in toxicidy, and this is where the PK/PD modelling studies played potential role.

The model by Tham et al., 2008 (gg, BIOM 000000000234), describes the PD model of Genetations in combination with Carboptein for the treatment of Non-small cellung cancer, and study the drug effect on the turnour size in relation to the dosage.

Gemcitabine (Figure 1, figure taken from __nem), a synthetic pyrimidine nucleoside antimetabolite anticancer agent with complex metabolic pathways, is a group of chemotherapy drug. Initially, cytidine deaminase deactivates the parent compound - an inactive prodrug and its major inactive metabolite 2,2-diffuorordeoxyluridine (dFdU) is formed. Extracellularly, a small fraction is also catabolized via a pathway mediated by pyrimidine nucleoside phosphorylase. The remaining gemcitabine and dFdU are then transported into the cell and activated intracellularly through progressive phosphorylations by deoxycytidine kinase. The metabolites produced through this process of phosphorylation are the monophosphate, diphosphate, and triphosphate (dFdCTP) forms of gemcitabine, the latter being its active metabolite.

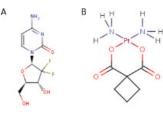


Figure 1: Chemical Structure of the Chemotherapy Drugs A) Gemotabline and B) Carboplatin. Figures taken from CHEBI:179801 and CHEBI:31365.

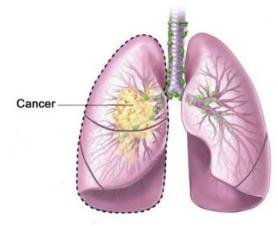


Figure 2: Non-small cell lung cancer. Figure taken from here

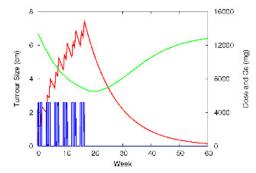
It arrests cell cycle in two ways. 1) As with fluorouracil and other analogues of pyrimidines, the triphosphate analogue of gemcitabine replaces one of the building blocks of nucleic acids, in this case cytidine, during DNA replication. The process arrests tumor growth, as new nucleosides cannot be attached to the "faulty" nucleoside, resulting in apoptosis. 2) Another target of gemcitabine is the enzy me ribonucleoside reductase (RNR). The diphosphate analogue binds to RNR active site and inactivates the enzy me irreversibly. Once RNR is inhibited, the cell cannot produce the deoxy ribonucleotides required for DNA replication and repair, and cell apoptosis is induced.

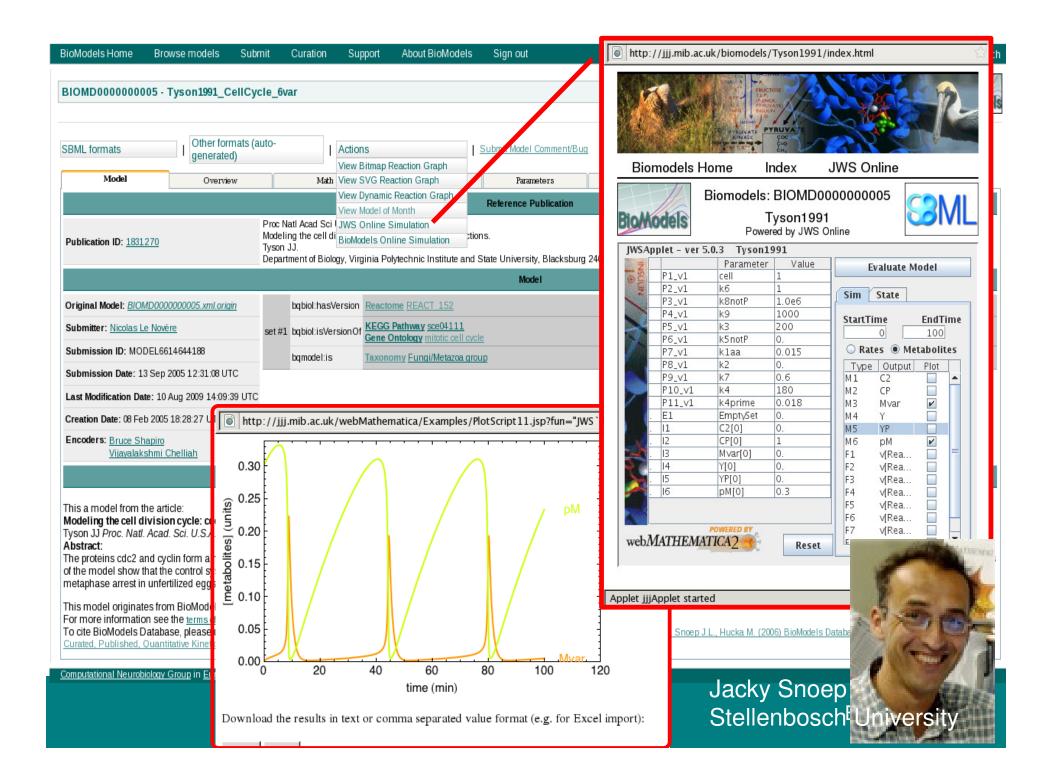
Gemcitabine is widely used in the treatment of cancers and has shown activity against a variety of solid tumours, including pancreatic, breast, bladder, ovarion and non-small cell lung cancer. Notable effect of the treatment is observed when Gemcitabine is used in combination with Carboplatin (Figure 1, taken from <a href="https://exempt.com/englists/e

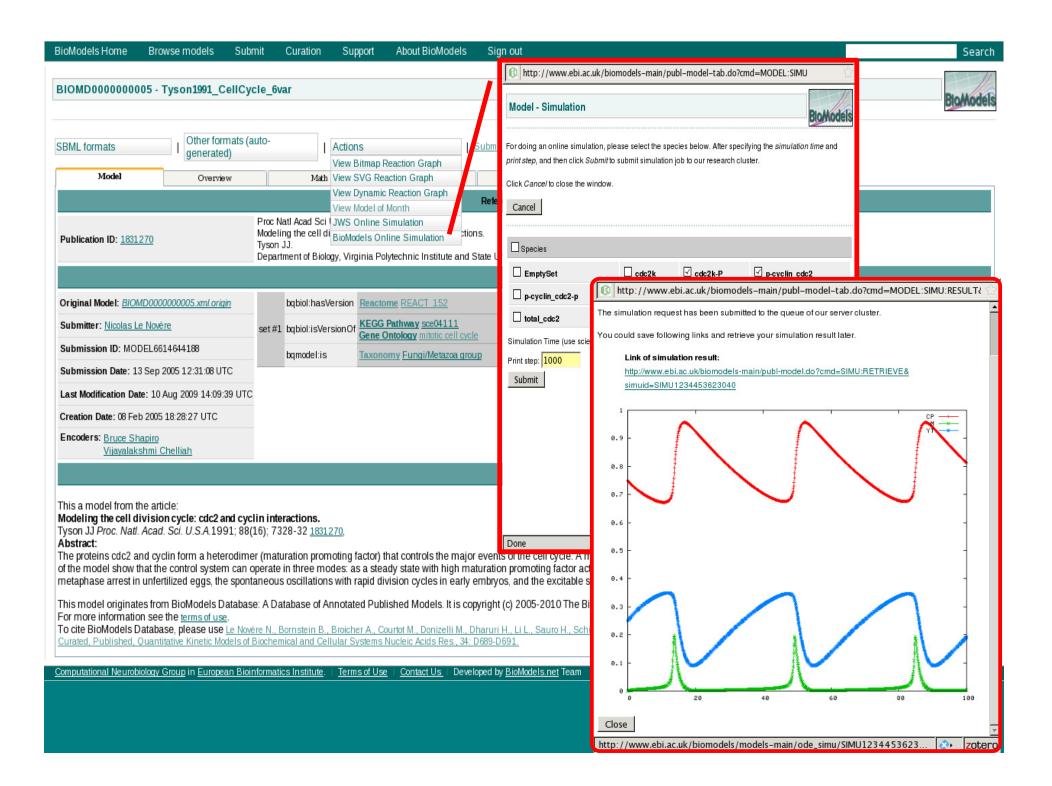
This paper investigates a longitudinal turnour response model to describe and predict the response of the primary lesion in non-small cell lung cancer (Figure 2, taken from here) to gerncitatine (with carboplatin) chemotherapy.

A total of 202 tumour size measurements from 56 patients were used to establish the pharmacodynamic model for tumour response. Gemcitabine was infused at either a fixed dose rate of 750mg/m2 over 75 mins or 1000mg/m2 over 30 mins on days 1 and 8 every 3 week in stage IIIB or IV non-small cell lung cancer patients. Cartoplatin dose was administered as a 1 hour infusion just before gemcitabine on day 1 of every cycle to patients. The pharmacokinetic exposure variables are the Gemcitabine dose and the AUCs (concentration-time curve) corresponding to each dose given, over the entire duration of treatment. Serial measurements of the largest dimension of the primary tumour were done on radiological images using electronic callipers at baseline after cycles 2, 4 and 6 and timonthly thereafter for at least 4 months after tratment. The tumour size measurement (sum of the longest unidimensional measurement) were used as the drug response measure for the pharmacodynamic model. Figure 3 shows a comparison of drug dose, effective exposure and tumour size change over time. A Gemcitabine amount in the body of 10,600mg is required to achieve a 5046 reduction in tumour growth rate (baseline tumour size being 6.66cm). The reduce in tumour size indicate the rate of cancerous cells killed due to the effect of drug.

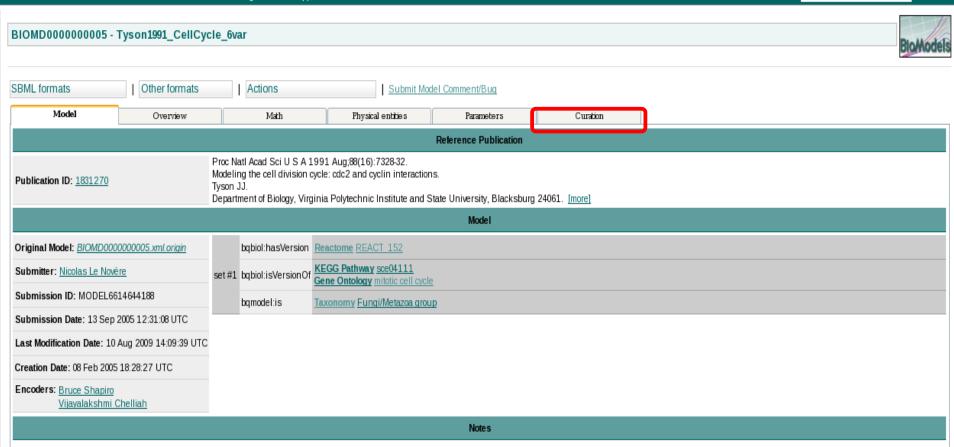
The pharmacodynamic model deducing the potency and time course of the anticancer agent in shrinking the primary turnours can have potential role to decide dosage and treatment duration. As these examinations can be routinely done during early phase of clinical trials, this could give further insights in the drug development process and also gives improved understanding of the clinical actions of drugs that are already marketed.







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This a model from the article:

Modeling the cell division cycle: cdc2 and cyclin interactions.

Tyson JJ Proc. Natl. Acad. Sci. U.S.A.1991; 88(16); 7328-32 1831270,

Abstract:

The proteins cdc2 and cyclin form a heterodimer (maturation promoting factor) that controls the major events of the cell cycle. A mathematical model for the interactions of cdc2 and cyclin is constructed. Simulation and analysis of the model show that the control system can operate in three modes: as a steady state with high maturation promoting factor activity, as a spontaneous oscillator, or as an excitable switch. We associate the steady state with metaphase arrest in unfertilized eggs, the spontaneous oscillations with rapid division cycles in early embryos, and the excitable switch with growth-controlled division cycles typical of nonembryonic cells.

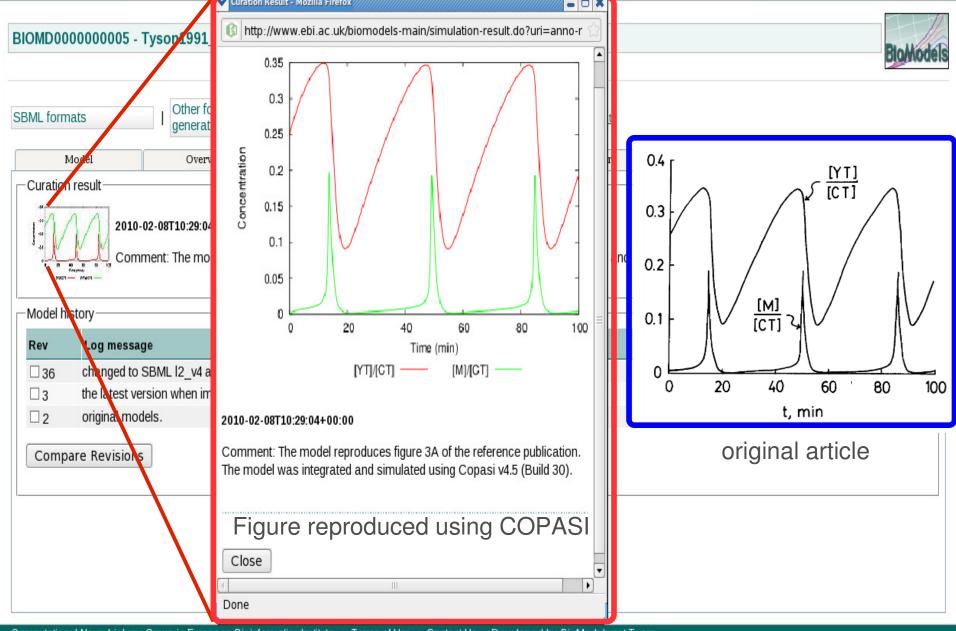
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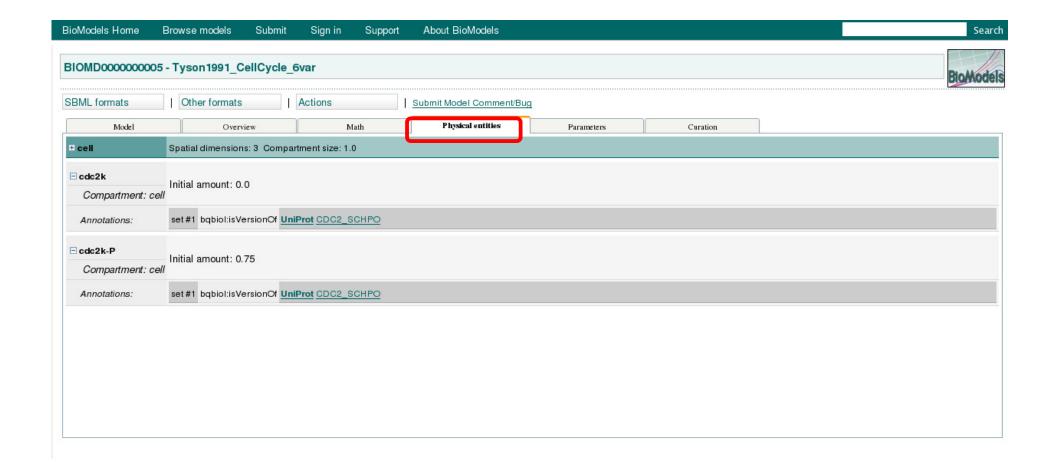




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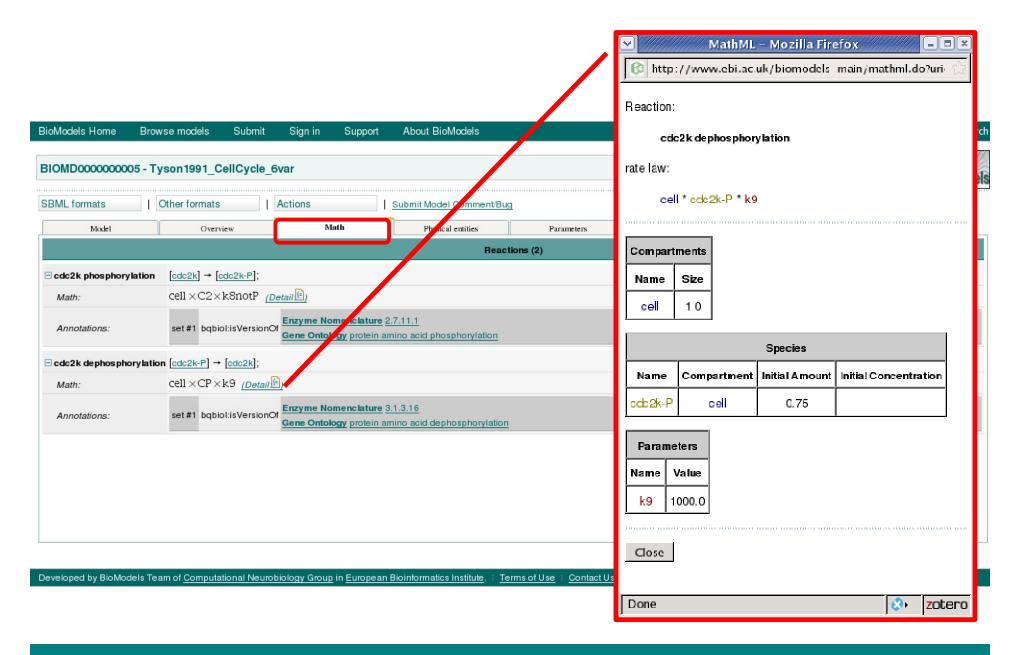


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BioModels Web Services

Available features

With BioModels Web Services, users can access the up-to-date resources in BioModels Database without installing a local copy of the database. There are a range of available features for searching and retrieving models. Furthermore, some features can help users to extract interesting parts from a large model and construct them into a submodel. For any comments or new feature enquiries, please feel free to contact us.

- Available features
- javadoc
- WSDL

The WSDL (Web Services Description Language) defines and describes the available features in an XML format file. This enables third-party sofware to automate parsing all available features of BioModels Web Services. Comparing with WSDL, Javadoc is API documentation which provides more information to the developers.

Download

According to different cases, we provide two kinds of libraries for using BioModels Web Services. For downloading, please right click on the link and "Save Target As" or "Save Link As".

Description	Size	Link
Standalone and includes all external dependencies and ready for use	1.9M	biomodelswslib-standalone-1.11.jar
Light-weight, but needs other dependencies to work together	6.4K	biomodelswslib-single-1.11.jar

These are the dependencies only needed by light-weight library.

- axis.jar
- jaxrpc.jar
- · commons-logging-1.1.jar
- · commons-discovery-0.2.jar
- saai.iai
- wsdl4j-1.5.1.jar

Basics - Getting Started

Firstly, download the library we provided. I guess you already done it.

Assuming that you downloaded the biomodelswslib-standalone.jar, let's write a simple HelloBioModels.java to test if it works on your environment.

```
import uk.ac.ebi.bicmodels.*;

public class HelloBicModels
{
   public static void main(String args[]) throws Exception
   {
      BicModelsWSClient client = new BicModelsWSClient();

      /* uncomment when a proxy is needed
      client.setProperty("http.proxyHost", "your.http.proxy.host");
      client.setProperty("http.proxyPort", "yourHttpProxyPort");
      client.setProperty("socks.proxyHost", "your.socks.proxy.host");
      client.setProperty("socks.proxyPort", "yourSocksProxyPort");
      */
```



BioModels Database: widely used

- For benchmarking the modeling and simulation tools.
- Models are downloaded by researches to generate more elaborate models (i.e. including more reactions, etc.).
- Clustering and Merging models using annotations.

and many more....



BioModels Team at EBI

Nicolas Le Novère



Camille Laibe



Nicolas Rodriguez



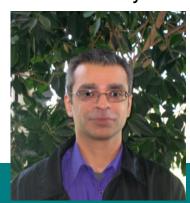
Sarah Keating



Lukas Endler



Nick Juty



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