EMBL-EBI

# BioModels Database, a curated resource of annotated published models

*Nicolas Le Novère, EMBL-EBI*

# What is a model? A simulation?

- A model is a mathematical description of the components of a system, their relationships, and the evolution of both.
  - ordinary differential equations (system evolution) $dX/dt = f(X)$
  - partial differential equation (system description) $\nabla X = g(X)$
  - algebraic equations (conservation laws) $h(X) = 0$
  - probability distributions $PX = i(X)$
  - master equation $dPX/dt = j(PX)$
  - cell automata/finite elements
  - ...

# What is a model? A simulation?

- A simulation is the instantiation of a model over time, using a given algorithmic approach, and a particular software: A model can generate simulations giving different results!
  - Logical (boolean or discrete) approach
  - Deterministic approach
  - Stochastic approach
  - Fixed timesteps
  - Adaptative timesteps
  - ...
- Plus ... range of simulations
  - parameter scan
  - parameter search/optimisation
  - phase-plane analysis
  - bifurcation analysis
  - ...

# SBML Systems Biology Markup Language





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

## Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is **supported by over 110 software systems**, including the following (where '*' indicates SBML support in development):

BALSA
BASIS
BIOCHAM
BioCharon
ByoDyn
BioCyc
BioGrid
BioModels
BioNetGen
BioPathwise
Bio Sketch Pad
BioSens
BioSPICE Dashboard
BioSpreadsheet
BioTapestry
BioUML
BSTLab
CADLIVE
CellDesigner
Cellerator
Cell Illustrator
CellML2SBML
Cellware
CL-SBML
CLEML
COPASI
Cyto-Sim
Cytoscape
DBsolve
Dizzy
E-CELL
ecellJ
ESS
FluxAnalyzer
Fluxor
Gepasi
Gillespie2
HSMB
HybridSBML
INSILICO discovery
JACOBIAN
Jarnac
JDesigner
JigCell
JSim
JWS Online
Karyote*
KEGG2SBML
Kineticon
Kinsolver*
libSBML
MathSBML
MesoRD
Meta-All
MetaFluxNet
MIRIAM
MMT2
Modesto
Moleculizer
Monod
Narrator
NetBuilder
Oscill8
PANTHER Pathway
PathArt
Pathway Analyser
PathwayLab
Pathway Tools
PathwayBuilder
PATIKAweb
PaVESy
PET
PNK
PottersWheel
ProcessDB
PROTON
pysbml
PySCeS
Reactome
RSBML
runSBML
SABIO-RK
SBML ODE Solver
SBML-PET
SBMLeditor
SBMLmerge
SBMLR
SBMLSim
SBMLToolbox
SBO
SBToolbox
SBW
SCIpath
Sigmoid*
SigPath
SigTran
SIMBA
SimBiology
Simpathica
SimPheny*
SimWiz
SloppyCell
SmartCell
SRS Pathway Editor
StochSim
StochKit
STOCKS
TERANODE Suite
Trelis
VANTED
Virtual Cell
WebCell
WinSCAMP
Xholon
XPPAUT

## A Free and Open Language

Advances in biotechnology are leading to larger, more complex quantitative models. The systems biology

### COPASI 4.1 Build 21 Released

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read more

See older news items.

# Systems Biology Markup Language

**Poster C112**
**BOF tuesday hall L**





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COPASI
Cyto-Sim
Cytoscape
DBsolve
Dizzy
E-CELL
ecellJ
ESS
FluxAnalyzer
Fluxor
Gepasi
Gillespie2
HSMB
HybridSBML
INSILICO discovery
JACOBIAN
Jarnac
JDesigner
JigCell
JSim
JWS Online
Karyote*
KEGG2SBML
Kineticon
Kinsolver*
libSBML
MathSBML
MesoRD
Meta-All
MetaFluxNet
MIRIAM
MMT2
Modesto
Moleculizer
Monod
Narrator
NetBuilder
Oscill8
PANTHER Pathway
PathArt
Pathway Analyser
PathwayLab
Pathway Tools
PathwayBuilder
PATIKAweb
PaVESy
PET
PNK
PottersWheel
ProcessDB
PROTON
pysbml
PySCeS
Reactome
RSBML
runSBML
SABIO-RK
SBML ODE Solver
SBML-PET
SBMLeditor
SBMLmerge
SBMLR
SBMLSim
SBMLToolbox
SBO
SBToolbox
SBW
SCIpath
Sigmoid*
SigPath
SigTran
SIMBA
SimBiology
Simpathica
SimPheny*
SimWiz
SloppyCell
SmartCell
SRS Pathway Editor
StochSim
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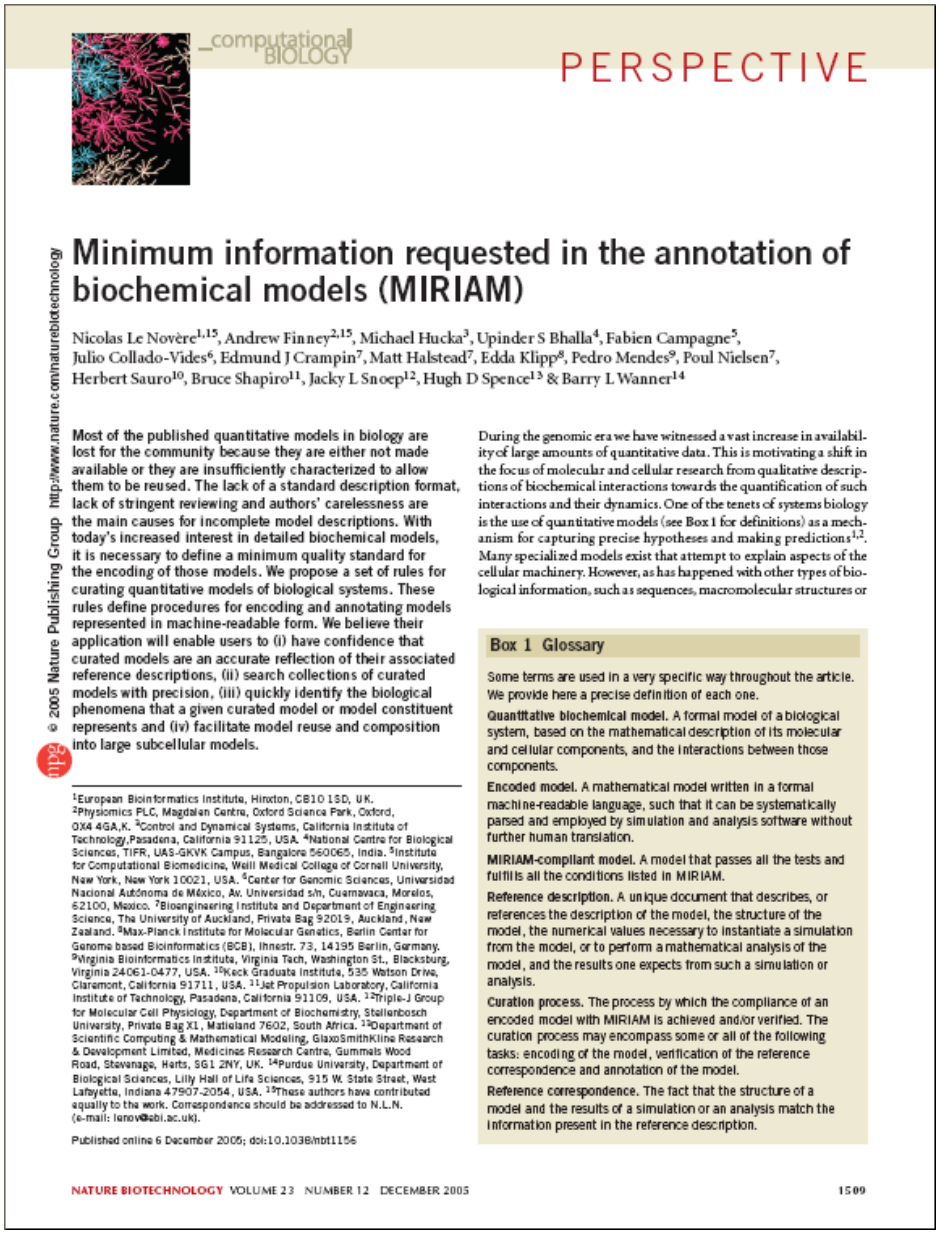
read more

See older news items.

- Proposed guidelines for curation of quantitative models
  - Specifically about encoding & annotation
  - Limited to models that can be simulated
- Effort arose from a meeting organized by Andrew Finney during ICSB 2004
- Not specific to SBML; applicable to any structured model format



_computational BIOLOGY

PERSPECTIVE

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

Nicolas Le Novère[1,15], Andrew Finney[2,15], Michael Hucka[3], Upinder S Bhalla[4], Fabien Campagne[5], Julio Collado-Vides[6], Edmund J Crampin[7], Matt Halstead[7], Edda Klipp[8], Pedro Mendes[9], Poul Nielsen[7], Herbert Sauro[10], Bruce Shapiro[11], Jacky L Snoep[12], Hugh D Spence[13] & Barry L Wanner[14]



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.

[1]European Bioinformatics Institute, Hinxton, CB10 1SD, UK. [2]Physiomics PLC, Magdalen Centre, Oxford Science Park, Oxford, OX4 4GA,K. [3]Control and Dynamical Systems, California Institute of Technology,Pasadena, California 91125, USA. [4]National Centre for Biological Sciences, TIFR, UAS-GKVK Campus, Bangalore 560065, India. [5]Institute for Computational Biomedicine, Weill Medical College of Cornell University, New York, New York 10021, USA. [6]Center for Genomic Sciences, Universidad Nacional Autónoma de México, Av. Universidad s/n, Cuernavaca, Morelos, 62100, Mexico. [7]Bioengineering Institute and Department of Engineering Science, The University of Auckland, Private Bag 92019, Auckland, New Zealand. [8]Max-Planck Institute for Molecular Genetics, Berlin Center for Genome based Bioinformatics (BCB), Ihnestr. 73, 14195 Berlin, Germany. [9]Virginia Bioinformatics Institute, Virginia Tech, Washington St., Blacksburg, Virginia 24061-0477, USA. [10]Keck Graduate Institute, 535 Watson Drive, Claremont, California 91711, USA. [11]Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California 91109, USA. [12]Triple-J Group for Molecular Cell Physiology, Department of Biochemistry, Stellenbosch University, Private Bag X1, Matieland 7602, South Africa. [13]Department of Scientific Computing & Mathematical Modeling, GlaxoSmithKline Research & Development Limited, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, UK. [14]Purdue University, Department of Biological Sciences, Lilly Hall of Life Sciences, 915 W. State Street, West Lafayette, Indiana 47907-2054, USA. [15]These authors have contributed equally to the work. Correspondence should be addressed to N.L.N. (e-mail: lenov@ebi.ac.uk).

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 tenets of systems biology is the use of quantitative models (see Box 1 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 components.

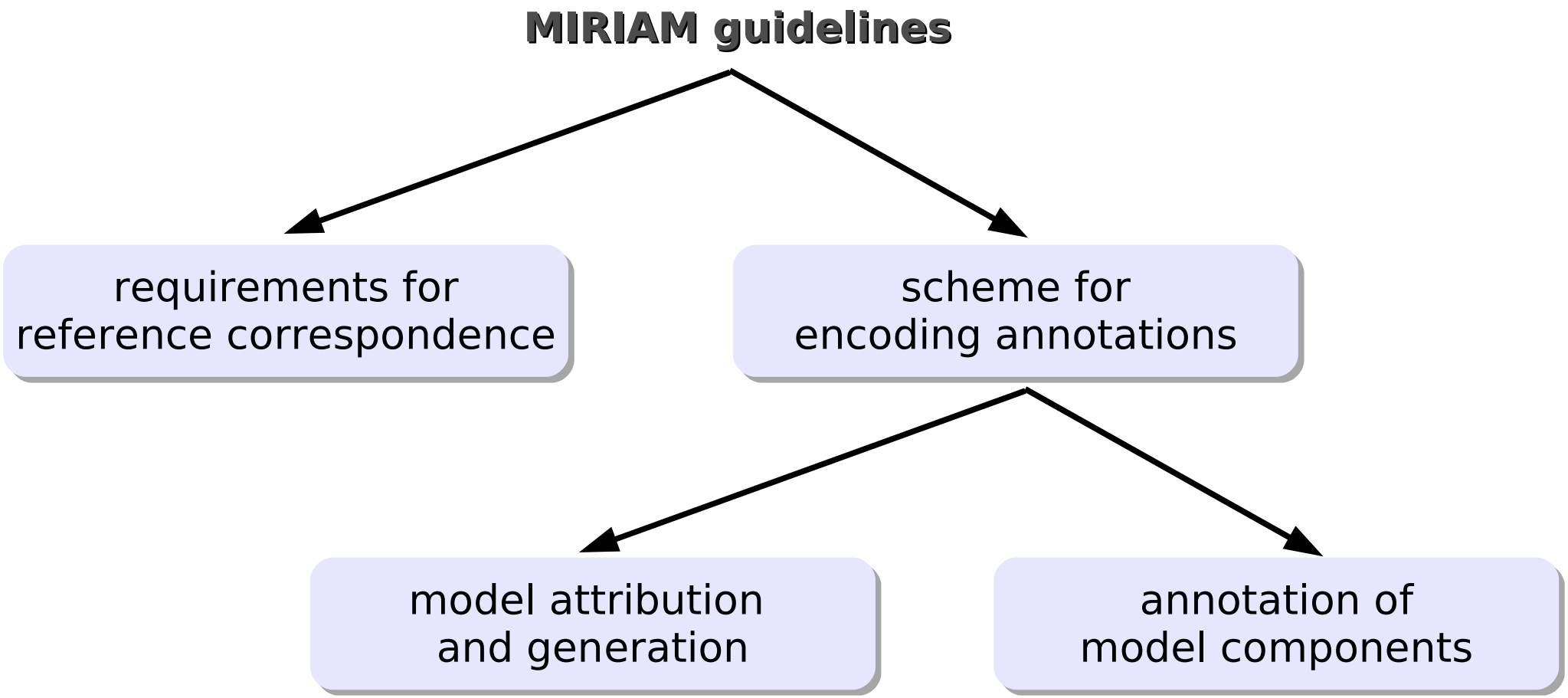
**Encoded model.** A mathematical model written in a formal machine-readable language, such that it can be systematically parsed and employed by simulation and analysis software without further human translation.

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

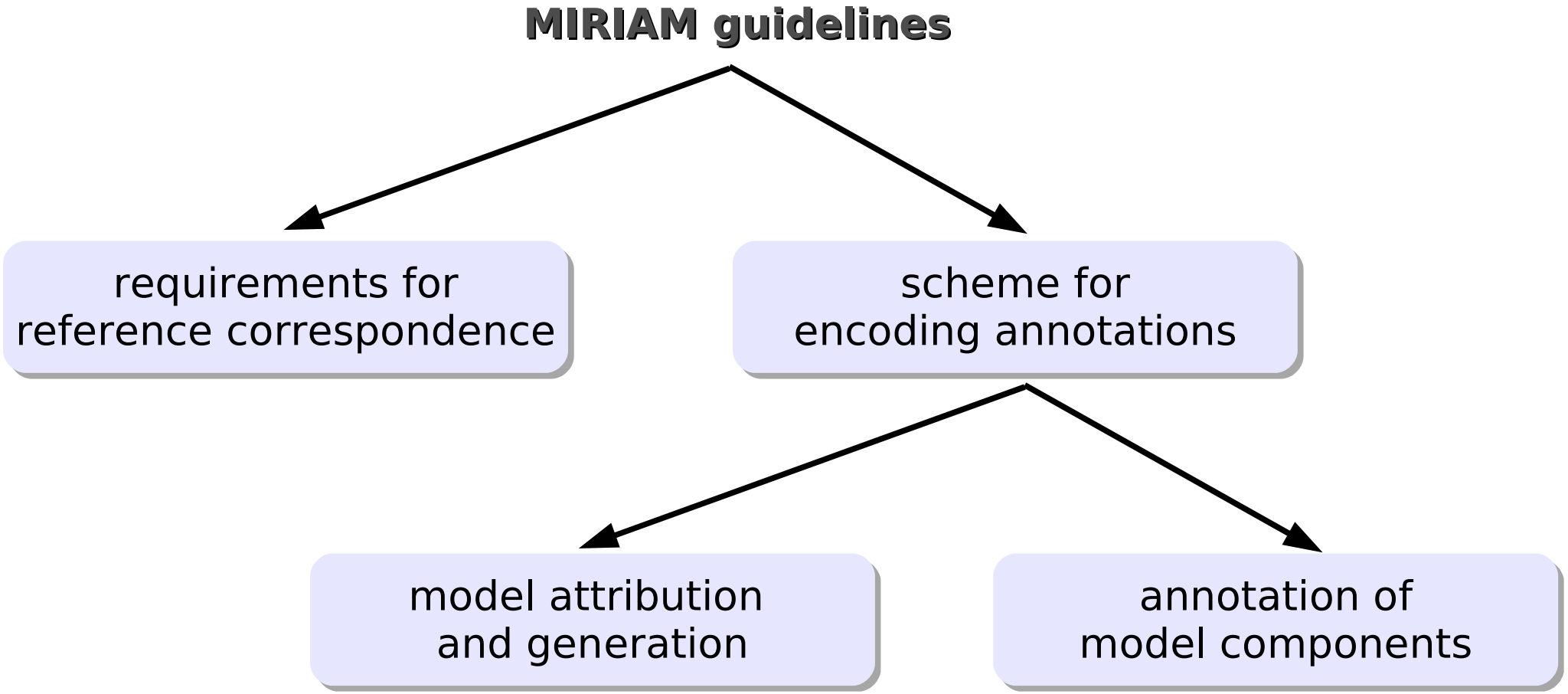
**Reference description.** A unique document that describes, or references the description of the model, the structure of the model, the numerical values necessary to instantiate a simulation from the model, or to perform a mathematical analysis of the model, and the results one expects from such a simulation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


MIRIAM guidelines
requirements for reference correspondence
scheme for encoding annotations
model attribution and generation
annotation of model components

# Poster C126


MIRIAM guidelines
requirements for reference correspondence
scheme for encoding annotations
model attribution and generation
annotation of model components

# BioModels Database

- Store and serve quantitative models of **biological** interest
- Only models described in the **peer-reviewed** scientific literature.
- Models are curated: computer software check the **syntax**, while human curators check the **semantics**.
- Models are **simulated** to check the reference correspondence
- Model components are **annotated**, to improve identification and retrieval.
- Models are accepted in several formats, and served in several others.
- Aims to be the “UniProt” of quantitative modelling.

nature

6 May 2005 Volume 435 Issue no 7038

# In pursuit of systems

**The study of functioning groups of molecules is an important frontier of biology at reductionist and holistic levels. Central to the long-term goals of scientific research, it brings its own challenges of infrastructure and evaluation.**

What is the difference between a live cat and a dead one? One scientific answer is 'systems biology'. A dead cat is a collection of its component parts. A live cat is the emergent behaviour of the system incorporating those parts. There is certainly a vast distance to go before we can fully encompass such a system within scientific description. So how is systems biology already moving us towards the fullest possible description of a live cat?

By focusing on the behaviour of individual proteins and other biomolecules, much of what gives life its unique properties can be missed. To a systems biologist, the network of interactions formed by these components is more important than the molecules themselves. Properties such as robustness and evolvability, essential characteristics of life, then emerge from the topology of biological networks, independent of the constituents from which they are built.

Such a holistic view may sound dangerously soft-edged. Far from it. Systems biology couples the acquisition of comprehensive, high-definition data sets to the construction of quantitative models and computer simulations. Indeed, it is an explicit aim of both the Kyoto Encyclopedia of Genes and Genomes and the Alliance for Cellular Signaling to construct a fully functioning computer model of a cell.

The present state of experimental systems biology is both tantalizing and frustrating. To provide the level of detail required for us to know what is going on in a cell, microarray technologies will need to be faster and require smaller samples; ways to label and follow more biological molecules within a cell must be discovered; new spectroscopic tools to non-invasively measure multiple metabolite levels will need to be developed, and so on. *Nature* is committed to publishing studies that push back the technological frontier of what it is possible to know about important biological systems.

But technical wizardry and large data sets are only part of the systems-biology approach — a system is not fully understood until a quantitative model can be built. The role of modelling in biological research is controversial and can spark heated debates. What is clear, though, is that the wealth of experimental data emerging from systems biology would be uninterpretable without detailed models against which they can be compared. Advances in modelling and simulation are thus no less important than data collection.

Every discipline generates community infrastructures, and systems biology is no exception. In the past five years, systems-biology institutes, departments and initiatives have been springing up across the globe. New journals have been launched, including The Institution of Electrical Engineers' *Systems Biology* and Nature Publishing Group's *Molecular Systems Biology*. The latter, an author-pays, online-only journal, is a joint venture with the European Molecular Biology Organization and went live last month.

The exchange of models between researchers is imperative, so a welcome development last month was the launch of BioModels (www.ebi.ac.uk/biomodels), a curated database for the deposition of biological models. BioModels has built on the success of Systems Biology Markup Language (SBML) in providing a format for the presentation of models, allowing them to be implemented on different software platforms. *Nature* journals and *Molecular Systems Biology* support submissions involving SBML.

It is hoped that BioModels will form the basis of a universally accepted repository that can do for systems biology what GenBank and the Protein Data Bank have done for genetics and structural biology. *Nature* applauds such efforts and will encourage authors of papers containing suitable models to contribute them to BioModels.

Systems biology presents an intellectual challenge to scientists and journal editors alike. Papers in this field document a highly multidisciplinary endeavour. Reviewers of such papers are very good at dissecting the aspects that fall within their sphere of expertise, but are less insightful beyond. So it falls to editors to weigh their frequently conflicting opinions in taking balanced and clear-sighted decisions. As a multidisciplinary journal, *Nature* welcomes the particular challenges that systems biology presents. ■

# Community support - Publishers

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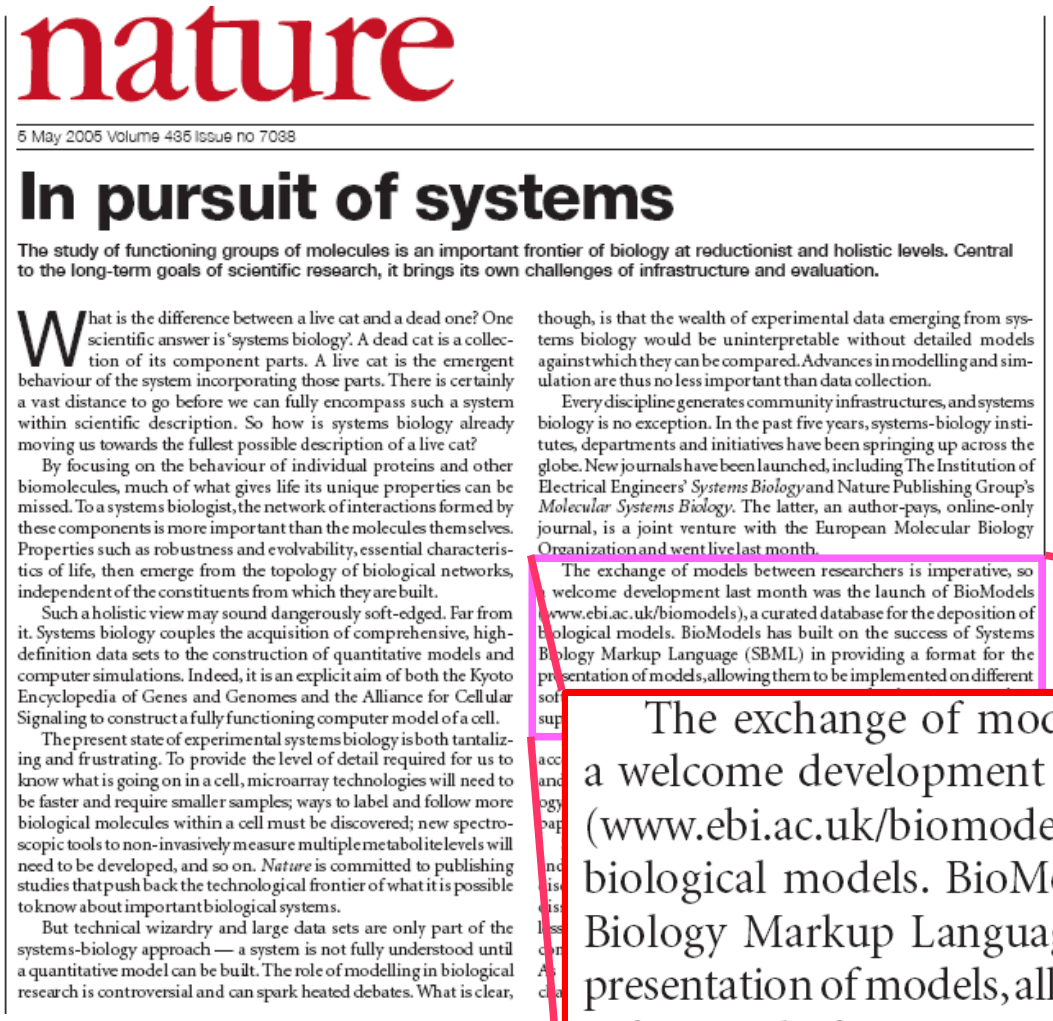

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- Deposition advised by
  - Molecular Systems Biology
  - all PLoS journals
  - all BMC Journals

## Correspondence

*Nature Biotechnology* **25**, 390 - 391 (2007)
doi:10.1038/nbt0407-390

### Systems biology standards—the community speaks

Edda Klipp[1], Wolfram Liebermeister[1], Anselm Helbig[1], Axel Kowald[1,2] & Jörg Schaber[1]

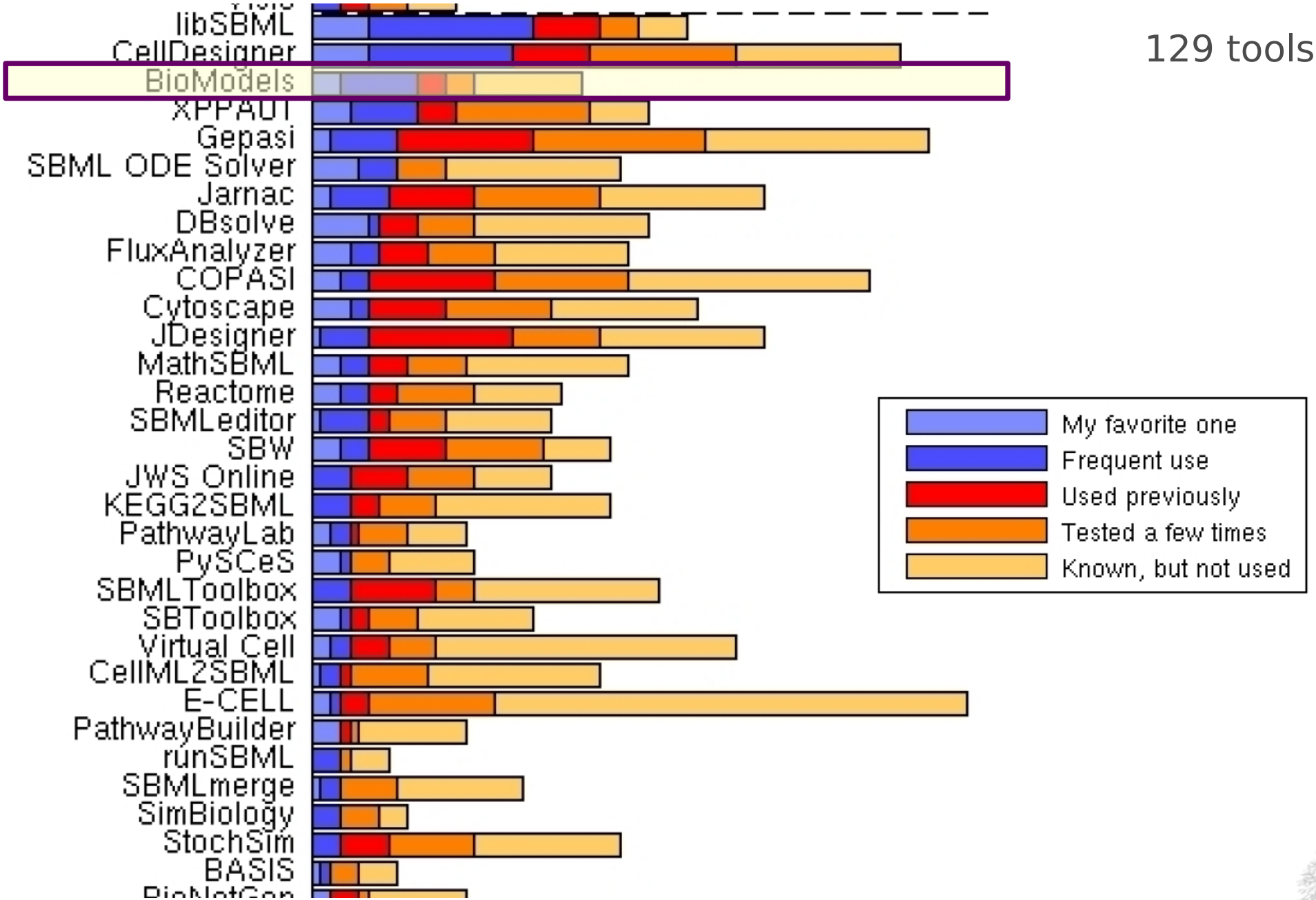
1. Max Planck Institute for Molecular Genetics, Otto Warburg Laboratory, Ihnestrasse 73, Berlin, 14195, Germany. e-mail: klipp@molgen.mpg.de
2. Ruhr University Bochum, Ruhr-University Bochum, Medical Proteom-Center, Universitaetsstrasse 150, Bochum, 44801 Germany.

**To the editor:**

Your editorial 'Standard operating procedures" in the November issue (*Nat. Biotechnol.* **24**, 1299, 2006) highlights the impetus for standards development in biology. Such standards are particularly important in the area of systems biology, which aims to build models and quantitative simulations of complex biological systems. In particular, standards concerning modeling workflows, data formats and model publication are needed to facilitate collaboration and communication between modelers and experimenters from diverse scientific backgrounds. Various aspects of standardization have already been addressed, such as minimal requirements in the annotation of biochemical models (MIRIAM[1]), compatibility of tools for kinetic modeling[2] and lessons that can be drawn from standards in high-throughput technologies[3]. Standardization is intensely debated in the systems biology community and plays a major role on the level of research politics: almost all systems biology projects that are currently funded by the European Commission (Brussels) promise to develop or define standards.

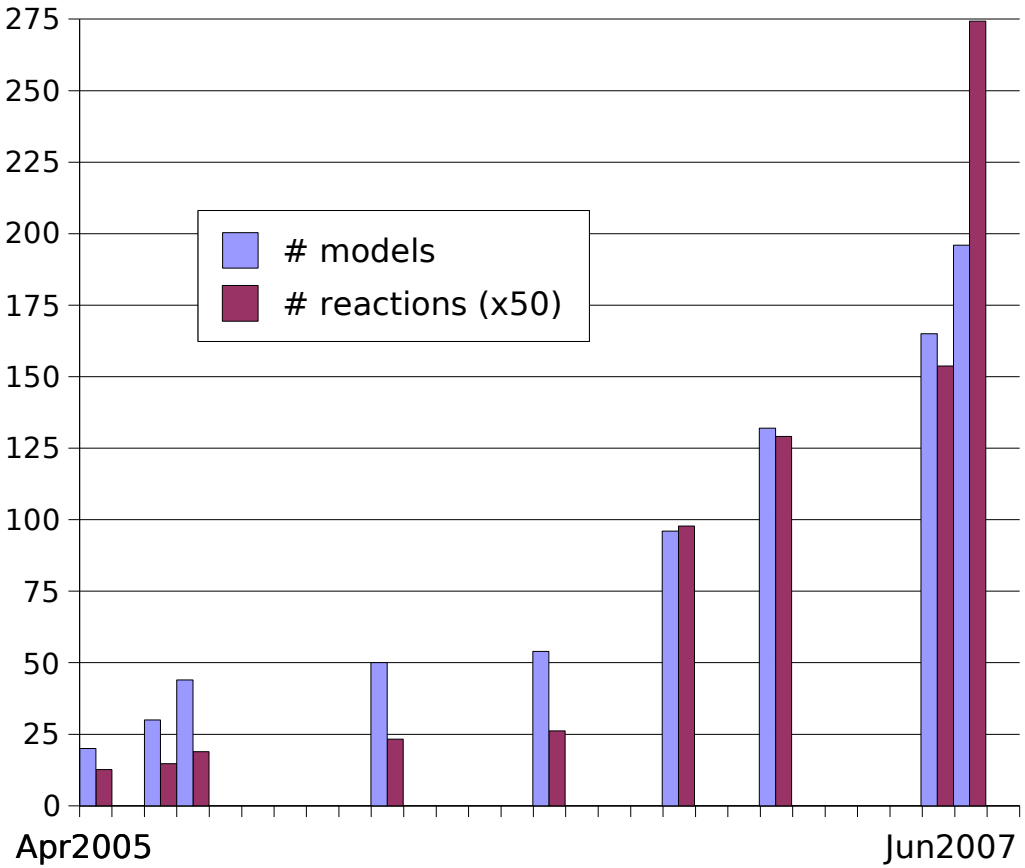
Here, we present the results of an online survey conducted to assess which *de facto* standards are already established in the community and whether scientists would appreciate the enforcement of further standards (Supplementary Results online). We

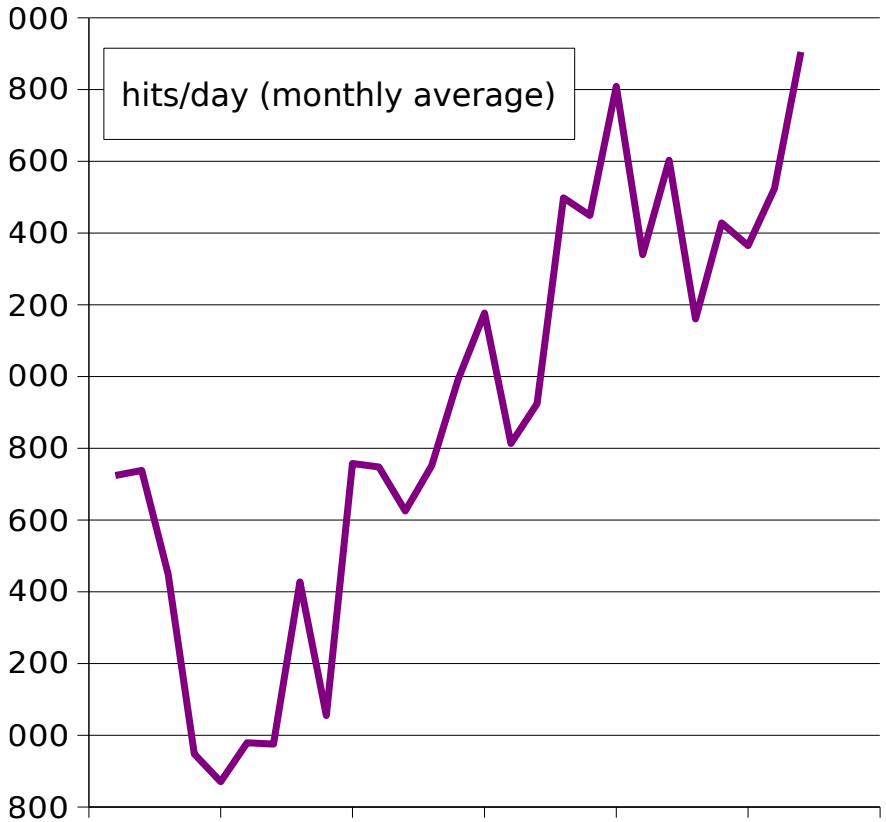
# Community support - Scientists




129 tools

# Steady-increase of BioModels DB

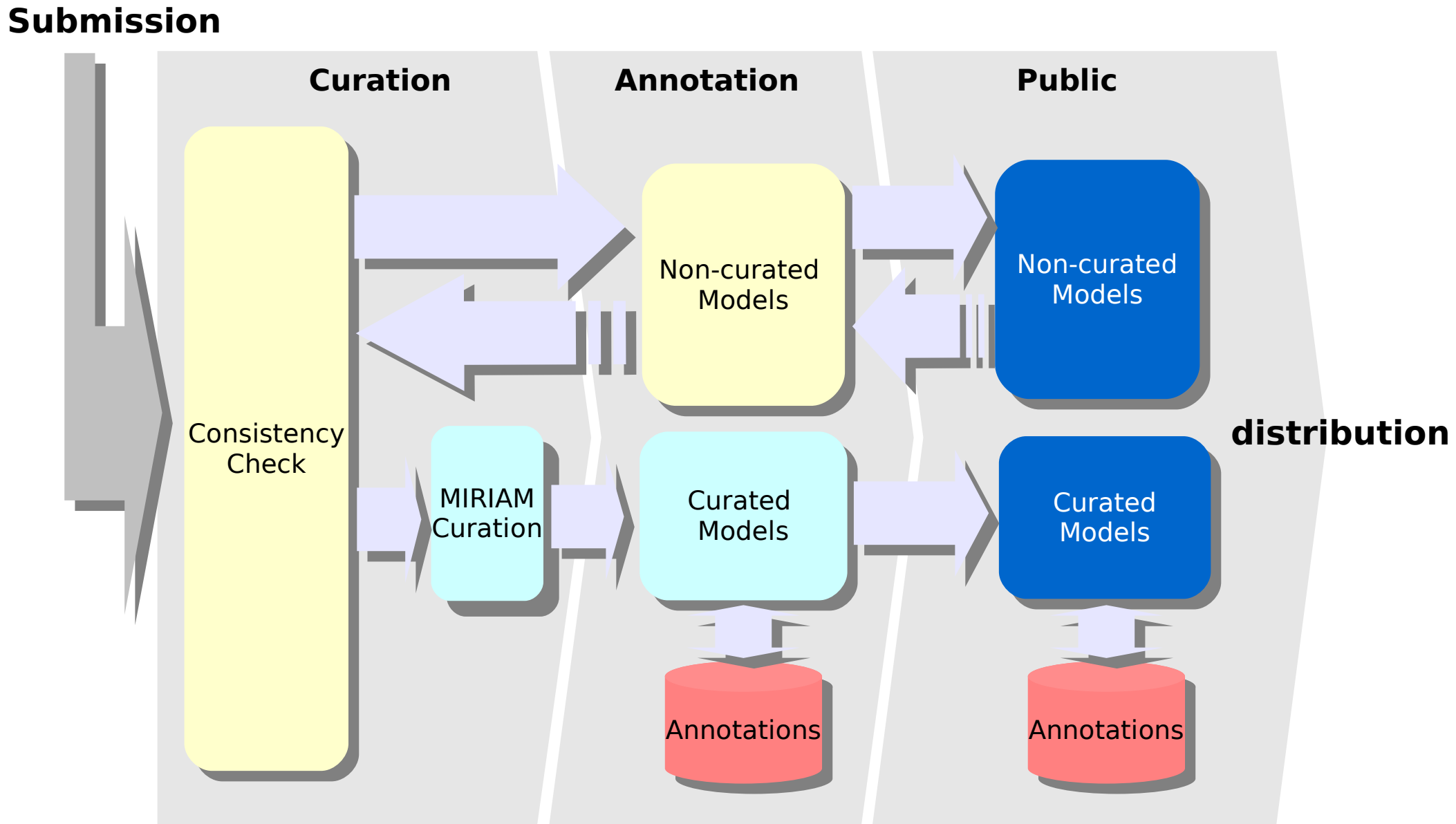


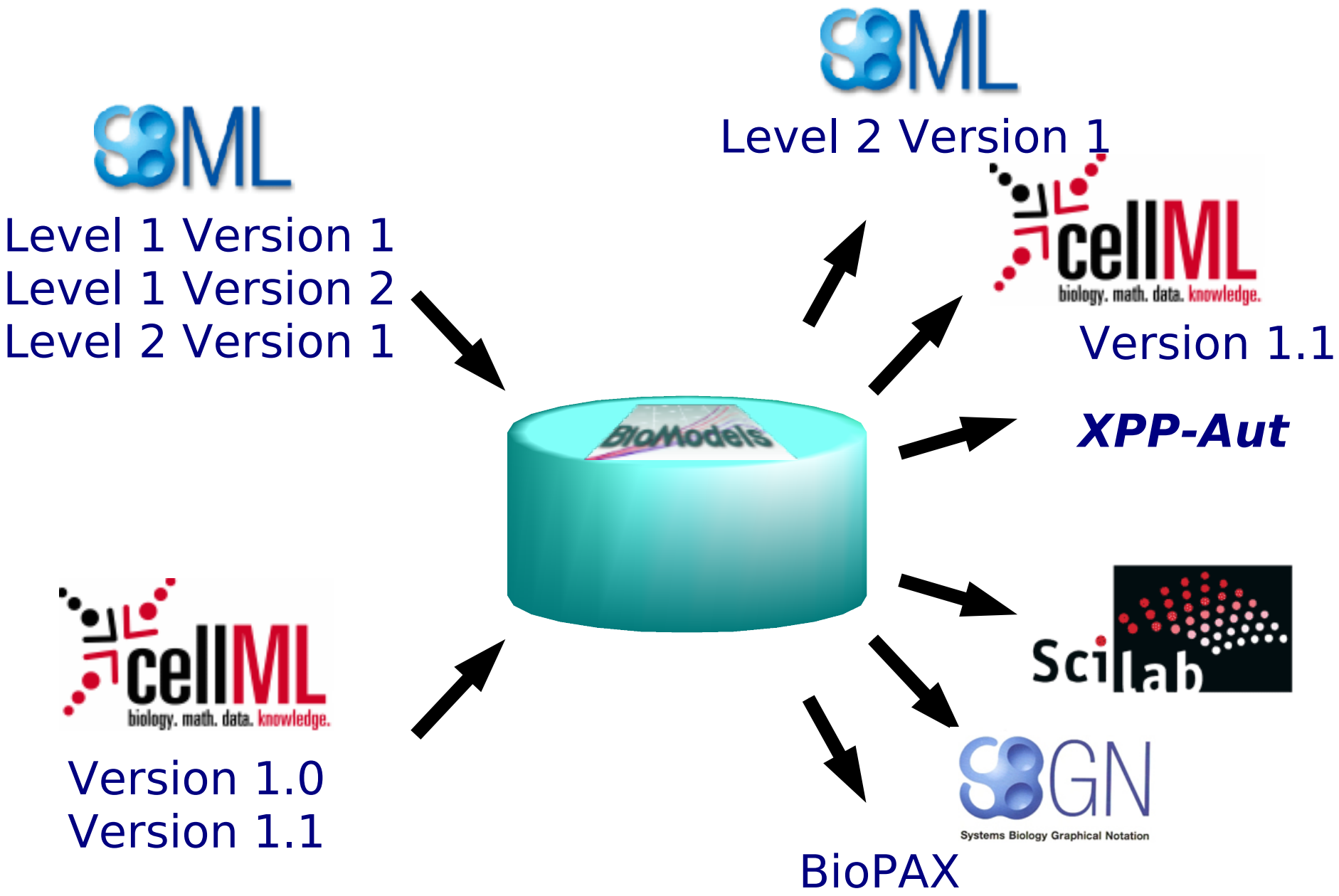
# The "mirrors"

- CellDesigner (Japan)
  http://www.celldesigner.org/
- CSML (Japan)
  http://www.csml.org/models/imported-models/models-imported-from-biomodels/
- Jsim (USA)
  http://www.physiome.org/jsim/models/biomodels/
- SIGMOID (USA)
  http://www.sigmoid.org/models/ModelBrowse.do
- WebCell (Korea)
  http://webcell.org/
- ...

# Production pipeline



# BioModels DB and interoperability in CSB



BioModels

- Curated Models
- Non-curated Models
- Search
- Simulate in JWS

- Submit Your Model

- Sign-in

- News
- Model of the Month
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## BioModels Database

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

# A Database of Annotated Published Models

BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, controlled vocabularies, etc.

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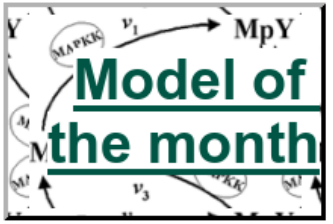


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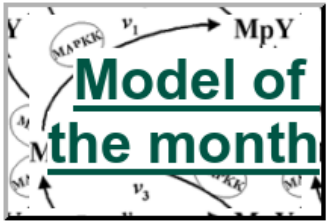


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**17194217**

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.

PLoS Comput Biol 2006 Dec;2(12):e176.

# DARPP-32 Is a Robust Integrator of Dopamine and Glutamate Signals.

**Fernandez E, Schiappa R, Girault JA, Nov?re NL.**

Integration of neurotransmitter and neuromodulator signals in the striatum plays a central role in the functions and dysfunctions of the basal ganglia. DARPP-32 is a key actor of this integration in the GABAergic medium-size spiny neurons, in particular in response to dopamine and glutamate. When phosphorylated by cAMP-dependent protein kinase (PKA), DARPP-32 inhibits protein phosphatase-1 (PP1), whereas when phosphorylated by cyclin-dependent kinase 5 (CDK5) it inhibits PKA. DARPP-32 is also regulated by casein kinases and by several protein phosphatases. These complex and intricate regulations make simple predictions of DARPP-32 dynamic behaviour virtually impossible. We used detailed quantitative modelling of the regulation of DARPP-32 phosphorylation to improve our understanding of its function. The models included all the combinations of the three best-characterized phosphorylation sites of DARPP-32, their regulation by kinases and phosphatases, and the regulation of those enzymes by cAMP and Ca(2+) signals. Dynamic simulations allowed us to observe the temporal relationships between cAMP and Ca(2+) signals. We confirmed that the proposed regulation of protein phosphatase-2A (PP2A) by calcium can account for the observed decrease of Threonine 75 phosphorylation upon glutamate receptor activation. DARPP-32 is not simply a switch between PP1-inhibiting and PKA-inhibiting states. Sensitivity analysis showed that CDK5 activity is a major regulator of the response, as previously suggested. Conversely, the strength of the regulation of PP2A by PKA or by calcium had little effect on the PP1-inhibiting function of DARPP-32 in these conditions. The simulations showed that DARPP-32 is not only a robust signal integrator, but that its response also depends on the delay between cAMP and calcium signals affecting the response to the latter. This integration did not depend on the concentration of DARPP-32, while the absolute effect on PP1 varied linearly. In silico mutants showed that Ser137 phosphorylation affects the influence of the delay between dopamine and glutamate, and that constitutive phosphorylation in Ser137 transforms DARPP-32 in a quasi-irreversible switch. This work is a first attempt to better understand the complex interactions between cAMP and Ca(2+) regulation of DARPP-32. Progressive inclusion of additional components should lead to a realistic model of signalling networks underlying the function of striatal neurons.

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**Publication ID:** 371/journal.pcbi.0020176 **PubMed** (Search Medline) **DOI** (Resolve a DOI) **URL** **Unpublished**

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10.1371/journal.pcbi.0020176

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Click *Cancel* to return to the models submission page.

| | |
|---|---|
| **Journal:** | PLoS Comput Biol 2(12): e176. Dec 22, 2006 |
| **Title:** | DARPP-32 Is a Robust Integrator of Dopamine and Glutamate Signals |
| **Authors:** | Éric Fernandez, Renaud Schiappa, Jean-Antoine Girault, Nicolas Le Novère. |
| **Affiliation:** | EMBL-EBI, Wellcome-Trust Genome Campus, Hinxton, United Kingdom |
| **Abstract:** | Integration of neurotransmitter and neuromodulator signals in the striatum plays a central role in the functions and dysfunctions of the basal ganglia. DARPP-32 is a key actor of this integration in the GABAergic medium-size spiny neurons, in particular in response to dopamine and glutamate. When phosphorylated by cAMP-dependent protein kinase (PKA), DARPP-32 inhibits protein phosphatase-1 (PP1), whereas when phosphorylated by cyclin-dependent kinase 5 (CDK5) it inhibits PKA. DARPP-32 is also regulated by casein kinases and by several protein phosphatases. These |

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- 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 your personal details and any comment useful for thecuration step (underlined fields are required), and then click *Submit*.

**First name:** Nicolas

**Last name:** Le Novère

**Organisation:** EMBL-EBI

**Email:** lenov@ebi.ac.uk

**Comment:**
```
This is a deterministic discrete model generated with
E-Cell3 and SBMLeditor. It containst assignmentRules and
events.
```

**Original model:** http://compbiol.plosjournals.org/archive/1553-7358/2/12/supinfo/Fernandez2006.eml

**Model file:** /home/lenov/MEETINGS/ISMB2007/Fernandez2006.xml Browse...

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## Submit - Step 4

Your request to submit the model contained within the file:

**Fernandez2006.xml**

and with name:

**Fernandez2006_ModelB**

has been successfully completed.

The model has been assigned the temporary ID:

**MODEL4792426675**

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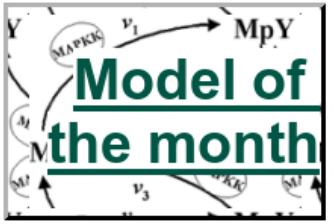


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**Text:** map kinase

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Show 10 Only

**31** Curated Models returned.

| BioModels ID | Name | Publication ID | Last Modified |
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| BIOMD0000000003 | Goldbeter1991_MinMitOscil | 1833774 | 2007-04-30T21:35:17 |
| BIOMD0000000004 | Goldbeter1991_MinMitOscil_ExplInact | 1833774 | 2007-05-14T23:01:13 |
| BIOMD0000000005 | Tyson1991_CellCycle_6var | 1831270 | 2007-05-15T18:24:25 |
| BIOMD0000000008 | Gardner1998_CellCycle_Goldbeter | 9826676 | 2007-01-05T10:37:30 |
| BIOMD0000000009 | Huang1996_MAPK_ultrasens | 8816754 | 2006-12-29T00:54:48 |
| BIOMD0000000010 | Kholodenko2000_MAPK_feedback | 10712587 | 2007-01-10T10:35:07 |
| BIOMD0000000011 | Levchenko2000_MAPK_noScaffold | 10823939 | 2007-01-10T10:22:40 |
| BIOMD0000000014 | Levchenko2000_MAPK_Scaffold | 10823939 | 2007-01-26T22:30:39 |
| BIOMD0000000026 | Markevich2004_MAPK_orderedElementary | 14744999 | 2006-12-29T00:28:06 |
| BIOMD0000000027 | Markevich2004_MAPK_orderedMM | 14744999 | 2006-12-29T00:28:55 |
| BIOMD0000000028 | Markevich2004_MAPK_phosphoRandomElementary | 14744999 | 2006-12-29T00:39:36 |
| BIOMD0000000029 | Markevich2004_MAPK_phosphoRandomMM | 14744999 | 2006-12-29T00:43:12 |
| BIOMD0000000030 | Markevich2005_MAPK_AllRandomElementary | 14744999 | 2006-12-29T01:03:25 |
| BIOMD0000000031 | Markevich2004_MAPK_orderedMM2kinases | 14744999 | 2006-12-29T21:41:12 |
| BIOMD0000000032 | Kofahl2004_pheromone | 15300679 | 2007-02-19T09:32:27 |
| BIOMD0000000033 | Brown2004_NGF_EGF_signaling | 14525003 | 2006-12-29T23:16:17 |
| BIOMD0000000049 | Sasagawa2005_MAPK | 15793571 | 2007-03-02T23:37:04 |
| BIOMD0000000051 | Chassagnole2002_Carbon_Metabolism | 10.1002/bit.10288... | 2007-04-29T23:11:28 |
| BIOMD0000000061 | Hynne2001 Glycolysis | 11744196 | 2007-02-22T23:03:18 |
| BIOMD0000000063 | Galazzo1990_pathway_kinetics | 10.1016/0141-0229(90... | 2007-02-23T22:50:44 |
| BIOMD0000000064 | Teusink2000_Glycolysis | 10951190 | 2007-02-23T23:13:15 |
| BIOMD0000000066 | Chassagnole2001_Threonine Synthesis | 11368770 | 2007-04-29T22:37:37 |

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- *Person* → Search BioModels Database for model submitter and/or creator(s) names, or model reference publication author(s) names (for example *Nicolas Le Novère*, *Nicolas*, *Bruce Shapiro* or *Shapiro*, *Edelstein* or *Novak*).
- *SBML Elements* → Search BioModels Database using the content of either "name" or "*notes*" SBML elements (for example *Edelstein* or *nicotinic*). Select the checkbox behind, if you want to find documents which matches the exact phrase; otherwise, all words will be searched as default.
- *Resource* → Search BioModels Database for related information found in the models reference publication or third-party resources, by either publication/resource identifier or text (for example *9256450* or *cyclin* for publication, *GO:0007049* or *cell cycle* for Gene Ontology, *P04551* or *cell division* for UniProt).
- *Resource ID* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for InterPro, *hsa04080* for KEGG Pathway, *68910* for Reactome).

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

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

**BioModels ID:**

**Person:**

**SBML Elements:** ☐ match the **exact phrase**

**Resource:** Gene Ontology — map kinase

**Resource:**

**Resource:**

Publication
ChEBI
Gene Ontology
Taxonomy
UniProt

**Resource ID:**

**Resource ID:** BIND

**Resource ID:** BIND

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## Search - Models

The search totally returned **15** models.

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**15** Curated Models returned.

| BioModels ID | Name | Publication ID | Last Modified |
|---|---|---|---|
| BIOMD0000000009 | Huang1996_MAPK_ultrasens | 8816754 | 2006-12-29T00:54:48 |
| BIOMD0000000010 | Kholodenko2000_MAPK_feedback | 10712587 | 2007-01-10T10:35:07 |
| BIOMD0000000011 | Levchenko2000_MAPK_noScaffold | 10823939 | 2007-01-10T10:22:40 |
| BIOMD0000000014 | Levchenko2000_MAPK_Scaffold | 10823939 | 2007-01-26T22:30:39 |
| BIOMD0000000026 | Markevich2004_MAPK_orderedElementary | 14744999 | 2006-12-29T00:28:06 |
| BIOMD0000000027 | Markevich2004_MAPK_orderedMM | 14744999 | 2006-12-29T00:28:55 |
| BIOMD0000000028 | Markevich2004_MAPK_phosphoRandomElementary | 14744999 | 2006-12-29T00:39:36 |
| BIOMD0000000029 | Markevich2004_MAPK_phosphoRandomMM | 14744999 | 2006-12-29T00:43:12 |
| BIOMD0000000030 | Markevich2005_MAPK_AllRandomElementary | 14744999 | 2006-12-29T01:03:25 |
| BIOMD0000000031 | Markevich2004_MAPK_orderedMM2kinases | 14744999 | 2006-12-29T21:41:12 |
| BIOMD0000000032 | Kofahl2004_pheromone | 15300679 | 2007-02-19T09:32:27 |
| BIOMD0000000033 | Brown2004_NGF_EGF_signaling | 14525003 | 2006-12-29T23:16:17 |
| BIOMD0000000049 | Sasagawa2005_MAPK | 15793571 | 2007-03-02T23:37:04 |
| BIOMD0000000084 | Hornberg2005_ERKcascade | 15634347 | 2007-01-03T05:59:37 |
| BIOMD0000000099 | Laub1998_SpontaneousOscillations | 9843585 | 2007-04-30T21:59:10 |

New Search

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Computational Neurobiology | SBML | DOQCS Database of Quantitative Cellular Signaling | SBW | SBI | JWS online

# Search - Models

Text Search

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

- *BioModels ID* → Search BioModels Database for *exact* BioModels identifiers (for example *BIOMD0000000001* or *BIOMD0000000022*).
- *Person* → Search BioModels Database for model submitter and/or creator(s) names, or model reference publication author(s) names (for example *Nicolas Le Novère*, *Nicolas*, *Bruce Shapiro* or *Shapiro*, *Edelstein* or *Novak*).
- *SBML Elements* → Search BioModels Database using the content of either "name" or "*notes*" SBML elements (for example *Edelstein* or *nicotinic*). Select the checkbox behind, if you want to find documents which matches the exact phrase; otherwise, all words will be searched as default.
- *Resource* → Search BioModels Database for related information found in the models reference publication or third-party resources, by either publication/resource identifier or text (for example *9256450* or *cyclin* for publication, *GO:0007049* or *cell cycle* for Gene Ontology, *P04551* or *cell division* for UniProt).
- *Resource ID* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for InterPro, *hsa04080* for KEGG Pathway, *68910* for Reactome).

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

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

**BioModels ID:**

**Person:**

**SBML Elements:** ☐ match the **exact phrase**

**Resource:** Taxonomy — mammalia

**Resource:**

**Resource:**

Publication
ChEBI
Gene Ontology
Taxonomy
UniProt

**Resource ID:**

**Resource ID:** BIND

**Resource ID:** BIND

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## Search - Models

The search totally returned **26** models.

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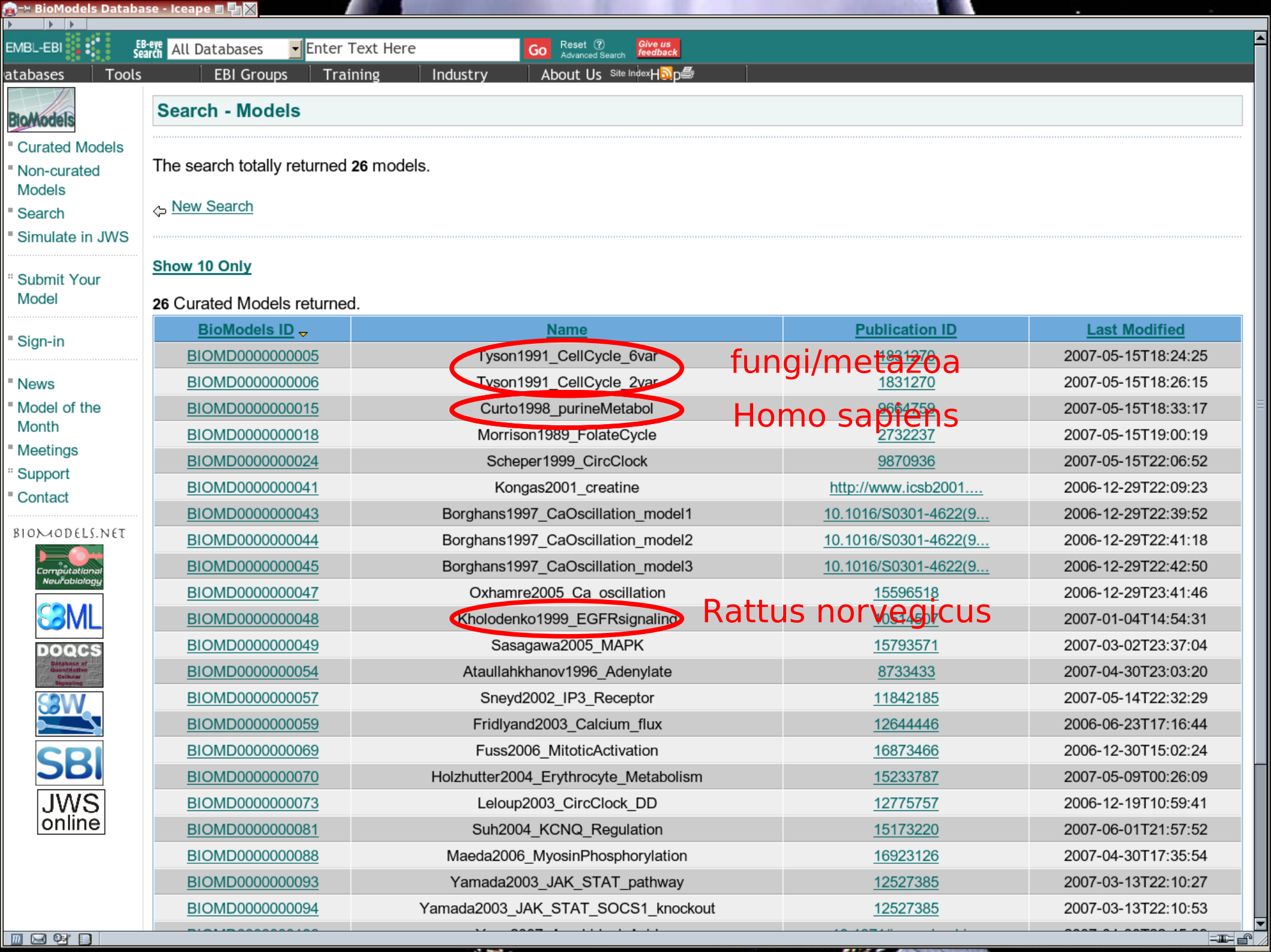
**26** Curated Models returned.

| BioModels ID | Name | Publication ID | Last Modified |
|---|---|---|---|
| BIOMD0000000005 | Tyson1991_CellCycle_6var | 1831270 | 2007-05-15T18:24:25 |
| BIOMD0000000006 | Tyson1991_CellCycle_2var | 1831270 | 2007-05-15T18:26:15 |
| BIOMD0000000015 | Curto1998_purineMetabol | 9664759 | 2007-05-15T18:33:17 |
| BIOMD0000000018 | Morrison1989_FolateCycle | 2732237 | 2007-05-15T19:00:19 |
| BIOMD0000000024 | Scheper1999_CircClock | 9870936 | 2007-05-15T22:06:52 |
| BIOMD0000000041 | Kongas2001_creatine | http://www.icsb2001.... | 2006-12-29T22:09:23 |
| BIOMD0000000043 | Borghans1997_CaOscillation_model1 | 10.1016/S0301-4622(9... | 2006-12-29T22:39:52 |
| BIOMD0000000044 | Borghans1997_CaOscillation_model2 | 10.1016/S0301-4622(9... | 2006-12-29T22:41:18 |
| BIOMD0000000045 | Borghans1997_CaOscillation_model3 | 10.1016/S0301-4622(9... | 2006-12-29T22:42:50 |
| BIOMD0000000047 | Oxhamre2005_Ca_oscillation | 15596518 | 2006-12-29T23:41:46 |
| BIOMD0000000048 | Kholodenko1999_EGFRsignaling | 10514507 | 2007-01-04T14:54:31 |
| BIOMD0000000049 | Sasagawa2005_MAPK | 15793571 | 2007-03-02T23:37:04 |
| BIOMD0000000054 | Ataullahkhanov1996_Adenylate | 8733433 | 2007-04-30T23:03:20 |
| BIOMD0000000057 | Sneyd2002_IP3_Receptor | 11842185 | 2007-05-14T22:32:29 |
| BIOMD0000000059 | Fridlyand2003_Calcium_flux | 12644446 | 2006-06-23T17:16:44 |
| BIOMD0000000069 | Fuss2006_MitoticActivation | 16873466 | 2006-12-30T15:02:24 |
| BIOMD0000000070 | Holzhutter2004_Erythrocyte_Metabolism | 15233787 | 2007-05-09T00:26:09 |
| BIOMD0000000073 | Leloup2003_CircClock_DD | 12775757 | 2006-12-19T10:59:41 |
| BIOMD0000000081 | Suh2004_KCNQ_Regulation | 15173220 | 2007-06-01T21:57:52 |
| BIOMD0000000088 | Maeda2006_MyosinPhosphorylation | 16923126 | 2007-04-30T17:35:54 |
| BIOMD0000000093 | Yamada2003_JAK_STAT_pathway | 12527385 | 2007-03-13T22:10:27 |
| BIOMD0000000094 | Yamada2003_JAK_STAT_SOCS1_knockout | 12527385 | 2007-03-13T22:10:53 |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BioModels ID
Name
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BIOMD0000000005 Tyson1991_CellCycle_6var 1831270 2007-05-15T18:24:25
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BIOMD0000000044 Borghans1997_CaOscillation_model2 10.1016/S0301-4622(9... 2006-12-29T22:41:18
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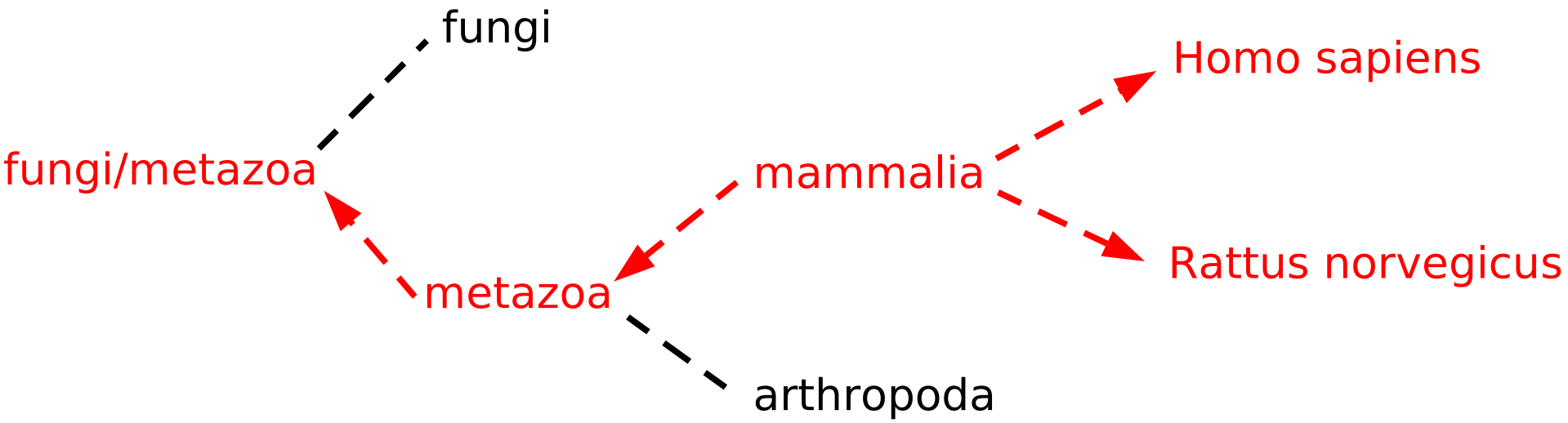
BIOMD0000000088 Maeda2006_MyosinPhosphorylation 16923126 2007-04-30T17:35:54
BIOMD0000000093 Yamada2003_JAK_STAT_pathway 12527385 2007-03-13T22:10:27
BIOMD0000000094 Yamada2003_JAK_STAT_SOCS1_knockout 12527385 2007-03-13T22:10:53
fungi/metazoa
Homo sapiens
Rattus norvegicus


fungi
fungi/metazoa
Homo sapiens
mammalia
Rattus norvegicus
metazoa
arthropoda

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| BIOMD0000000010 | Kholodenko2000_MAPK_feedback | 10712587 | 2007-01-10T10:35:07 |
| BIOMD0000000011 | Levchenko2000_MAPK_noScaffold | 10823939 | 2007-01-10T10:22:40 |
| BIOMD0000000014 | Levchenko2000_MAPK_Scaffold | 10823939 | 2007-01-26T22:30:39 |
| BIOMD0000000026 | Markevich2004_MAPK_orderedElementary | 14744999 | 2006-12-29T00:28:06 |
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| BIOMD0000000028 | Markevich2004_MAPK_phosphoRandomElementary | 14744999 | 2006-12-29T00:39:36 |
| BIOMD0000000029 | Markevich2004_MAPK_phosphoRandomMM | 14744999 | 2006-12-29T00:43:12 |
| BIOMD0000000030 | Markevich2005_MAPK_AllRandomElementary | 14744999 | 2006-12-29T01:03:25 |
| BIOMD0000000031 | Markevich2004_MAPK_orderedMM2kinases | 14744999 | 2006-12-29T21:41:12 |
| BIOMD0000000032 | Kofahl2004_pheromone | 15300679 | 2007-06-08T11:42:52 |
| BIOMD0000000033 | Brown2004_NGF_EGF_signaling | 14525003 | 2006-12-29T23:16:17 |
| BIOMD0000000049 | Sasagawa2005_MAPK | 15793571 | 2007-03-02T23:37:04 |
| BIOMD0000000084 | Hornberg2005_ERKcascade | 15634347 | 2007-01-03T05:59:37 |
| BIOMD0000000099 | Laub1998_SpontaneousOscillations | 9843585 | 2007-04-30T21:59:10 |

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# BIOMD0000000010 - Kholodenko2000_MAPK_feedback

**SBML L2 V1** | CellML | SciLab | XPP | BioPAX

Simulation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Online

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## Reference Publication

| | |
|---|---|
| **Publication ID:** 10712587 | Eur J Biochem 2000 Mar;267(6):1583-8.<br>Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades.<br>Kholodenko BN.<br>Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA 19107, USA.<br>Boris.Kholodenko@mail.tju.edu [more] |

## Model

## Compartments (1)

## Species (8)

## Rules (0)

## Reactions (10)

## Events (0)

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Simulation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Online

**SBML L2 V1** | CellML | SciLab | XPP | BioPAX

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| | |
|---|---|
| **Pubmed id** | 10712587 |
| **Title** | **Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades.** |
| **Authors** | Kholodenko BN |
| **Affiliation** | Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu |
| **Language** | English |
| **Journal** | Eur. J. Biochem. (ISSN: 0014-2956) (ESSN: 1432-1033) [2000 Mar; Volume: 267 (Issue: 6 )] Page info: 1583-8 |
| **Publication type** | Journal Article; Research Support, U.S. Gov't, P.H.S.; |
| **Full text article** | ABS ABS |
| **XML** | XML |

**Abstract**

Functional organization of signal transduction into protein phosphorylation cascades, such as the mitogen-activated protein kinase (MAPK) cascades, greatly enhances the sensitivity of cellular targets to external stimuli. The sensitivity increases multiplicatively with the number of cascade levels, so that a tiny change in a stimulus results in a large change in the response, the phenomenon referred to as ultrasensitivity. In a variety of cell types, the MAPK cascades are imbedded in long feedback loops, positive or negative, depending on whether the terminal kinase stimulates or inhibits the activation of the initial level. Here we demonstrate that a negative feedback loop combined with intrinsic ultrasensitivity of the MAPK cascade can bring about sustained oscillations in MAPK phosphorylation. Based on recent kinetic data on the MAPK cascades, we predict that the period of oscillations can range from minutes to hours. The phosphorylation level can vary between the base level and almost 100% of the total protein. The oscillations of the phosphorylation cascades and slow protein diffusion in the cytoplasm can lead to intracellular waves of phospho-proteins.

**Keywords (Mesh)**



tivated protein kinase cascades.

Philadelphia, PA 19107, USA.

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# BIOMD0000000010 - Kholodenko2000_MAPK_feedback

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Kholodenko BN.
Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu [more]

## Model

**Original Model:** *Unspecified*

**Submitter:** Nicolas Le Novere

**Submission Date:** 2005-09-13T13:39:02

**Last Modification Date:** 2007-01-10T10:35:07

**Creation Date:** 2005-02-12T00:18:12

**Creators:** Herbert Sauro

| | | | |
|---|---|---|---|
| bqbiol:is | set #1 | **Taxonomy** | Xenopus laevis |
| bqbiol:isVersionOf | set #1 | **Gene Ontology** | MAPKKK cascade |
| bqbiol:isHomologTo | set #1 | **Reactome** | REACT_634 |

## Compartments (1)

## Species (8)

## Rules (0)

## Reactions (10)

## Events (0)

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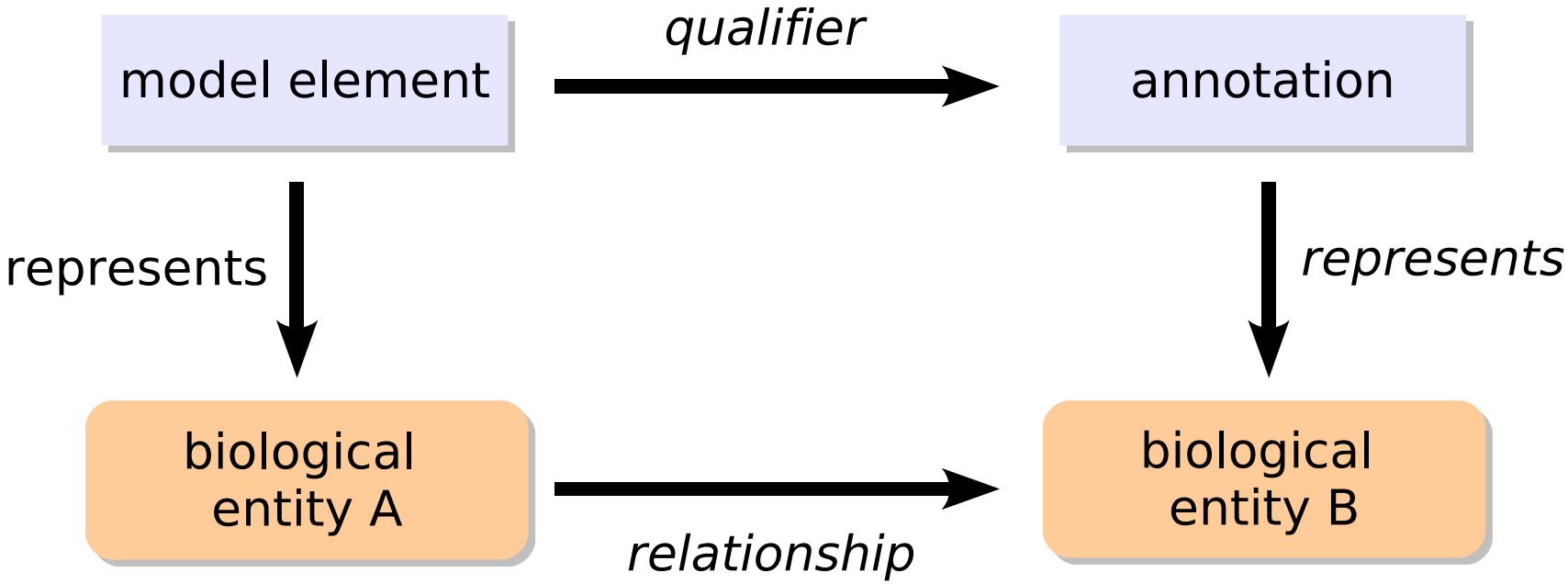
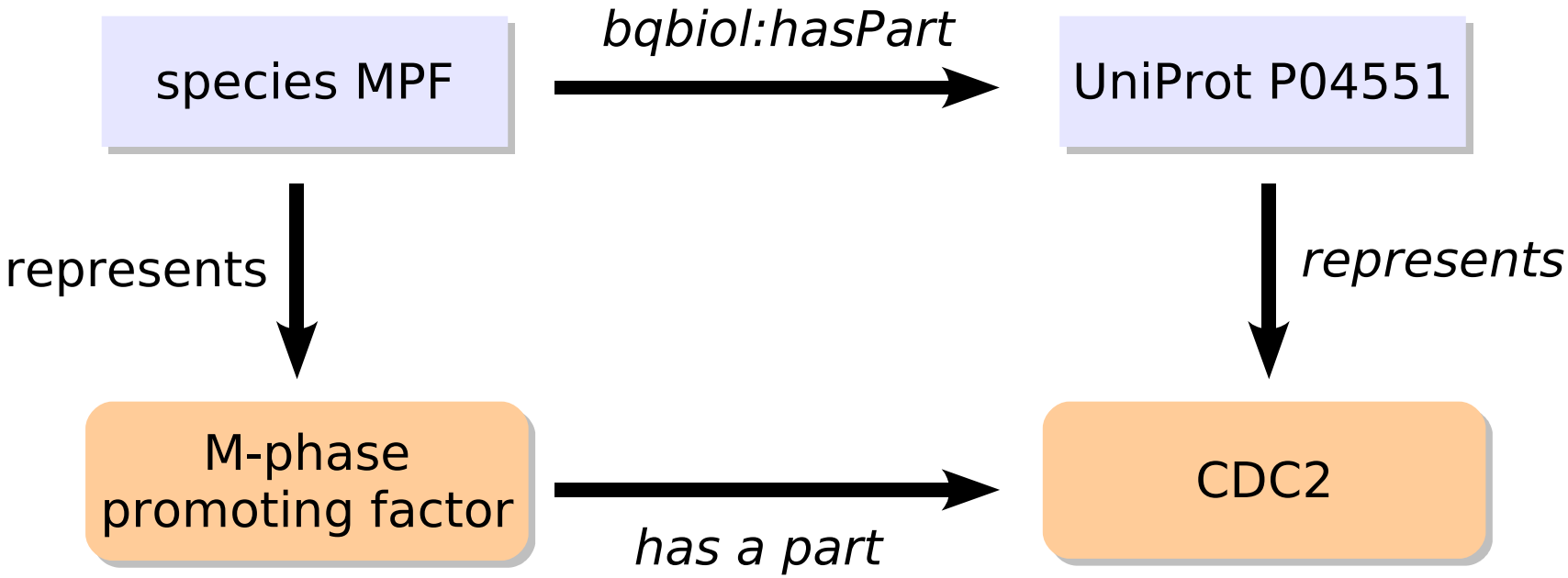
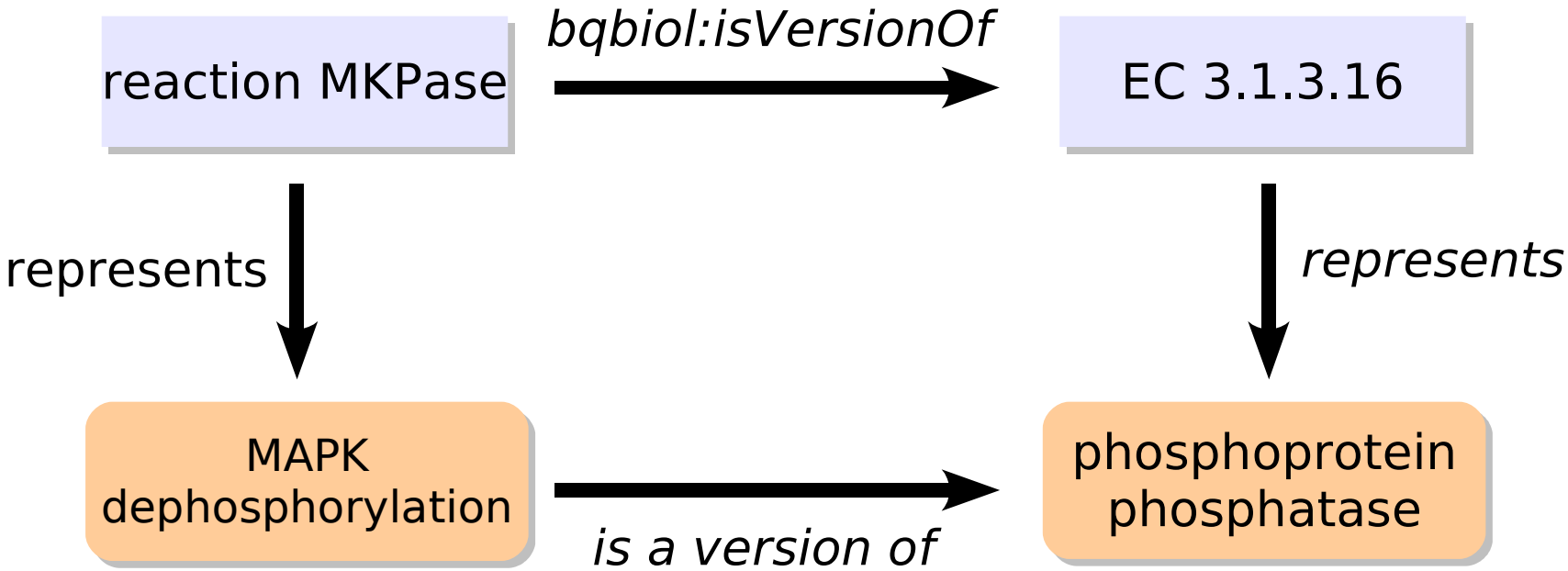
# Qualification of annotation



# Qualification of annotation



# Qualification of annotation



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| **MekInactive**<br>Compartment: cell<br>*Referred to as: MekInactive* | bqbiol:isVersionOf | set #1 | **UniProt** MP2K1_RAT<br>**UniProt** MP2K2_RAT |
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| **C3GInactive**<br>Compartment: cell<br>*Referred to as: C3GInactive* | bqbiol:isVersionOf | set #1 | **UniProt** Q9QYV3_RAT |
| **C3GActive**<br>Compartment: cell<br>*Referred to as: C3GActive* | bqbiol:isVersionOf | set #1 | **UniProt** Q9QYV3_RAT |
| **Rap1Inactive**<br>Compartment: cell<br>*Referred to as: Rap1Inactive* | bqbiol:hasVersion | set #1 | **UniProt** #RAPA_HUMAN<br>**UniProt** RAP1B_RAT |
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| **RapGapActive**<br>Compartment: cell | bqbiol:is | set #1 | **UniProt** RGP2_HUMAN |

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# BIOMD0000000010 - Kholodenko2000_MAPK_feedback

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Simulation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Online

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## Reference Publication

## Model

## Compartments (1)

## Species (8)

## Rules (0)

## Reactions (10)

**MAPKKK activation**
Reactants: MAPKKK
Products: MAPKKK-P
Modifiers: MAPK-PP
*Referred to as: J0*

| | | |
|---|---|---|
| bqbiol:isVersionOf | set #1 | Enzyme Nomenclature 2.7.11.1<br>Gene Ontology activation of MAPKKK activity<br>Gene Ontology MAP kinase kinase kinase kinase activity |
| bqbiol:isHomologTo | set #1 | Reactome REACT_525 |

**MAPKKK inactivation**
Reactants: MAPKKK-P
Products: MAPKKK
Modifiers:
*Referred to as: J1*

| | | |
|---|---|---|
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**phosphorylation of MAPKK**
Reactants: MAPKK
Products: MAPKK-P
Modifiers: MAPKKK-P
*Referred to as: J2*

| | | |
|---|---|---|
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**phosphorylation of MAPKK-P**
Reactants: MAPKK-P

| | | |
|---|---|---|
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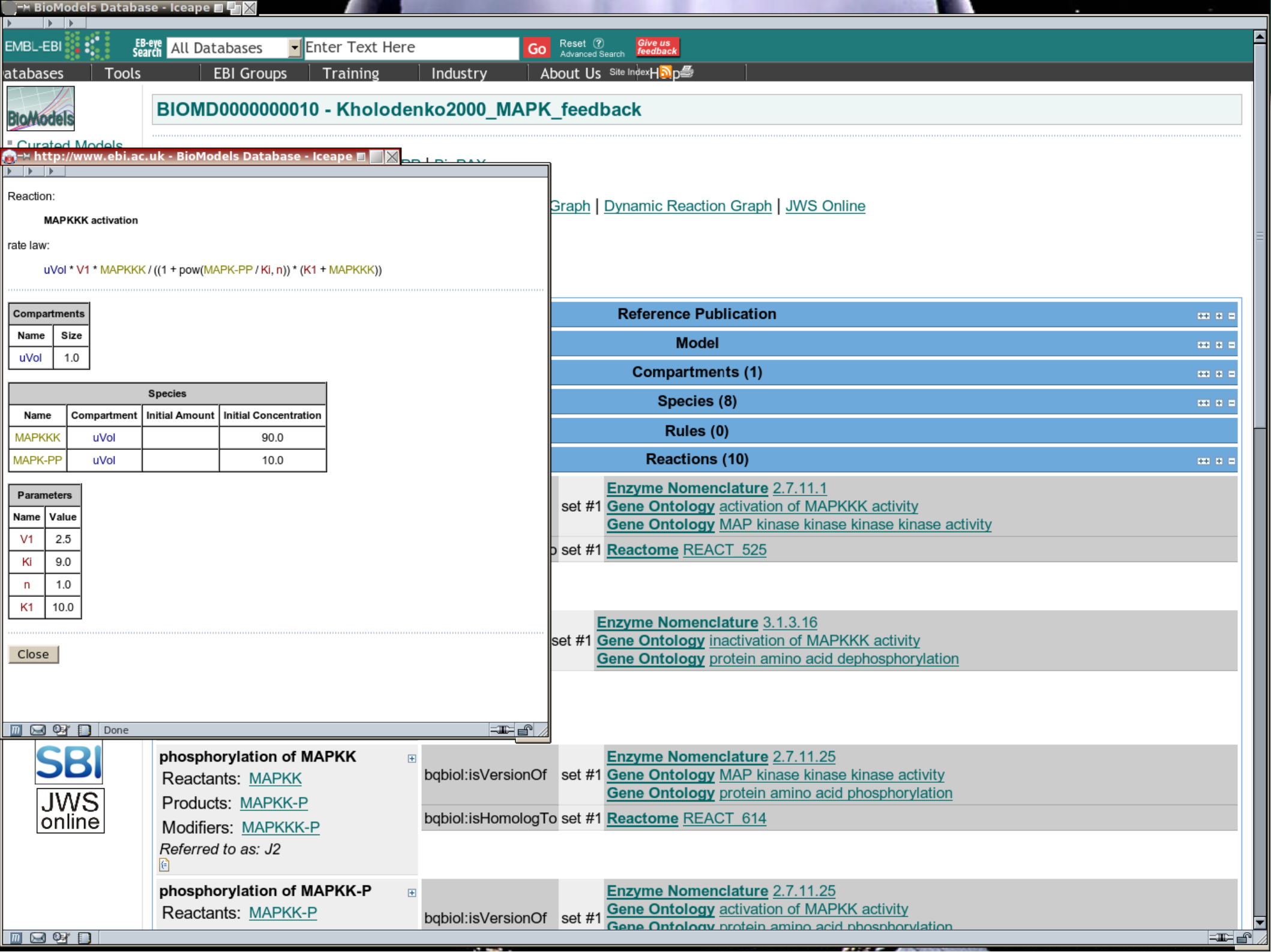
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BIOMD0000000010 - Kholodenko2000_MAPK_feedback
http://www.ebi.ac.uk - BioModels Database - Iceape
Reaction:
MAPKKK activation
rate law:
uVol * V1 * MAPKKK / ((1 + pow(MAPK-PP / Ki, n)) * (K1 + MAPKKK))
Compartments
Name
Size
uVol
1.0
Species
Name
Compartment
Initial Amount
Initial Concentration
MAPKKK
uVol
90.0
MAPK-PP
uVol
10.0
Parameters
Name
Value
V1
2.5
Ki
9.0
n
1.0
K1
10.0
Close
Done
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Species (8)
Rules (0)
Reactions (10)
set #1
Enzyme Nomenclature 2.7.11.1
Gene Ontology activation of MAPKKK activity
Gene Ontology MAP kinase kinase kinase kinase activity
set #1
Reactome REACT_525
set #1
Enzyme Nomenclature 3.1.3.16
Gene Ontology inactivation of MAPKKK activity
Gene Ontology protein amino acid dephosphorylation
SBI
JWS online
phosphorylation of MAPKK
Reactants: MAPKK
Products: MAPKK-P
Modifiers: MAPKKK-P
Referred to as: J2
bqbiol:isVersionOf
set #1
Enzyme Nomenclature 2.7.11.25
Gene Ontology MAP kinase kinase kinase activity
Gene Ontology protein amino acid phosphorylation
bqbiol:isHomologTo
set #1
Reactome REACT_614
phosphorylation of MAPKK-P
Reactants: MAPKK-P
bqbiol:isVersionOf
set #1
Enzyme Nomenclature 2.7.11.25
Gene Ontology activation of MAPKK activity

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## Species (8)

## Rules (0)

## Reactions (10)

**MAPKKK activation**
Reactants: MAPKKK
Products: MAPKKK-P
Modifiers: MAPK-PP
*Referred to as: J0*

| | | |
|---|---|---|
| bqbiol:isVersionOf | set #1 | Enzyme Nomenclature 2.7.11.1<br>Gene Ontology activation of MAPKKK activity<br>Gene Ontology MAP kinase kinase kinase kinase activity |
| bqbiol:isHomologTo | set #1 | Reactome REACT_525 |

**MAPKKK inactivation**
Reactants: MAPKKK-P
Products: MAPKKK
Modifiers:
*Referred to as: J1*

| | | |
|---|---|---|
| bqbiol:isVersionOf | set #1 | Enzyme Nomenclature 3.1.3.16<br>Gene Ontology inactivation of MAPKKK activity<br>Gene Ontology protein amino acid dephosphorylation |

**phosphorylation of MAPKK**
Reactants: MAPKK
Products: MAPKK-P
Modifiers: MAPKKK-P
*Referred to as: J2*

| | | |
|---|---|---|
| bqbiol:isVersionOf | set #1 | Enzyme Nomenclature 2.7.11.25<br>Gene Ontology MAP kinase kinase kinase activity<br>Gene Ontology protein amino acid phosphorylation |
| bqbiol:isHomologTo | set #1 | Reactome REACT_614 |

**phosphorylation of MAPKK-P**
Reactants: MAPKK-P

| | | |
|---|---|---|
| bqbiol:isVersionOf | set #1 | Enzyme Nomenclature 2.7.11.25<br>Gene Ontology activation of MAPKK activity<br>Gene Ontology protein amino acid phosphorylation |

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Fill the form below (all fields are required), and then click *Submit*.

Click *Cancel* to return to the model page.

Cancel

BioModels ID: BIOMD0000000010

Name: Kholodenko2000_MAPK_feedback

About: General comment about the model

- General comment about the model
- Bug in the model
- General comment about the model annotations
- Bug in the model annotations

Description:

Reply to:

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# BIOMD0000000010 - Kholodenko2000_MAPK_feedback

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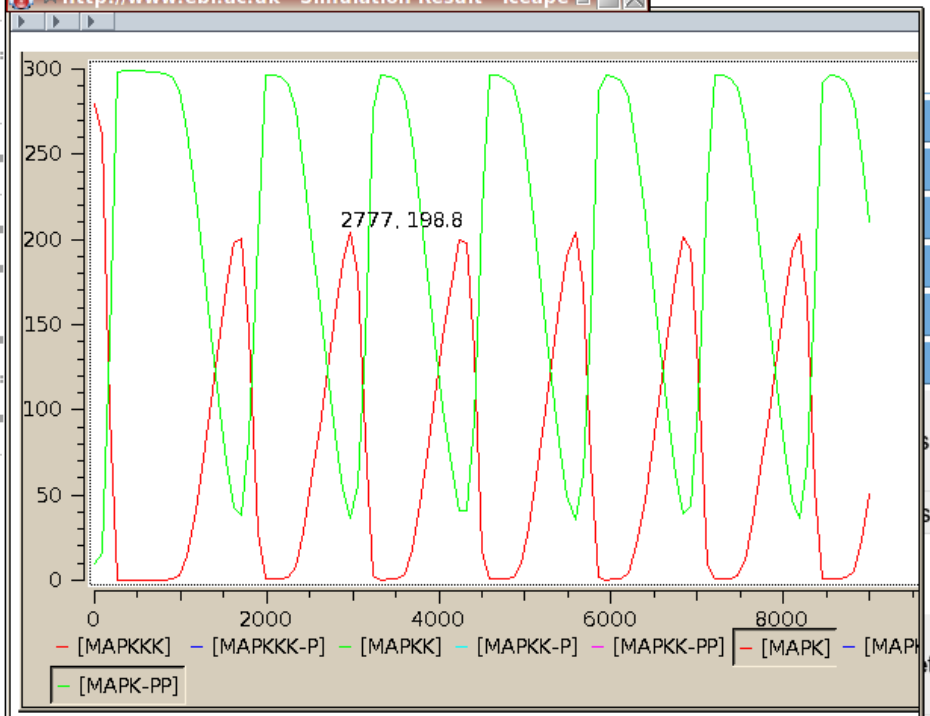


**2006-09-30T23:27:45**

Comment: Reproduction of figure 2a in COPASI 4.0 build 18

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Done

**Reference Publication**

**Model**

**Compartments (1)**

**Species (8)**

**Rules (0)**

**Reactions (10)**

set #1 Enzyme Nomenclature 2.7.11.1
Gene Ontology activation of MAPKKK activity
Gene Ontology MAP kinase kinase kinase activity

set #1 Reactome REACT_525

t #1 Enzyme Nomenclature 3.1.3.16
Gene Ontology inactivation of MAPKKK activity
Gene Ontology protein amino acid dephosphorylation

set #1 Enzyme Nomenclature 2.7.11.25
Gene Ontology MAP kinase kinase kinase activity
Gene Ontology protein amino acid phosphorylation

set #1 Reactome REACT_614

Modifiers: MAPKKK-P
*Referred to as: J2*

**phosphorylation of MAPKK-P**
Reactants: MAPKK-P

bqbiol:isVersionOf set #1 Enzyme Nomenclature 2.7.11.25
Gene Ontology activation of MAPKK activity
Gene Ontology protein amino acid phosphorylation

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BIOMD0000000010 Kholodenko2000_MAPK_feedback

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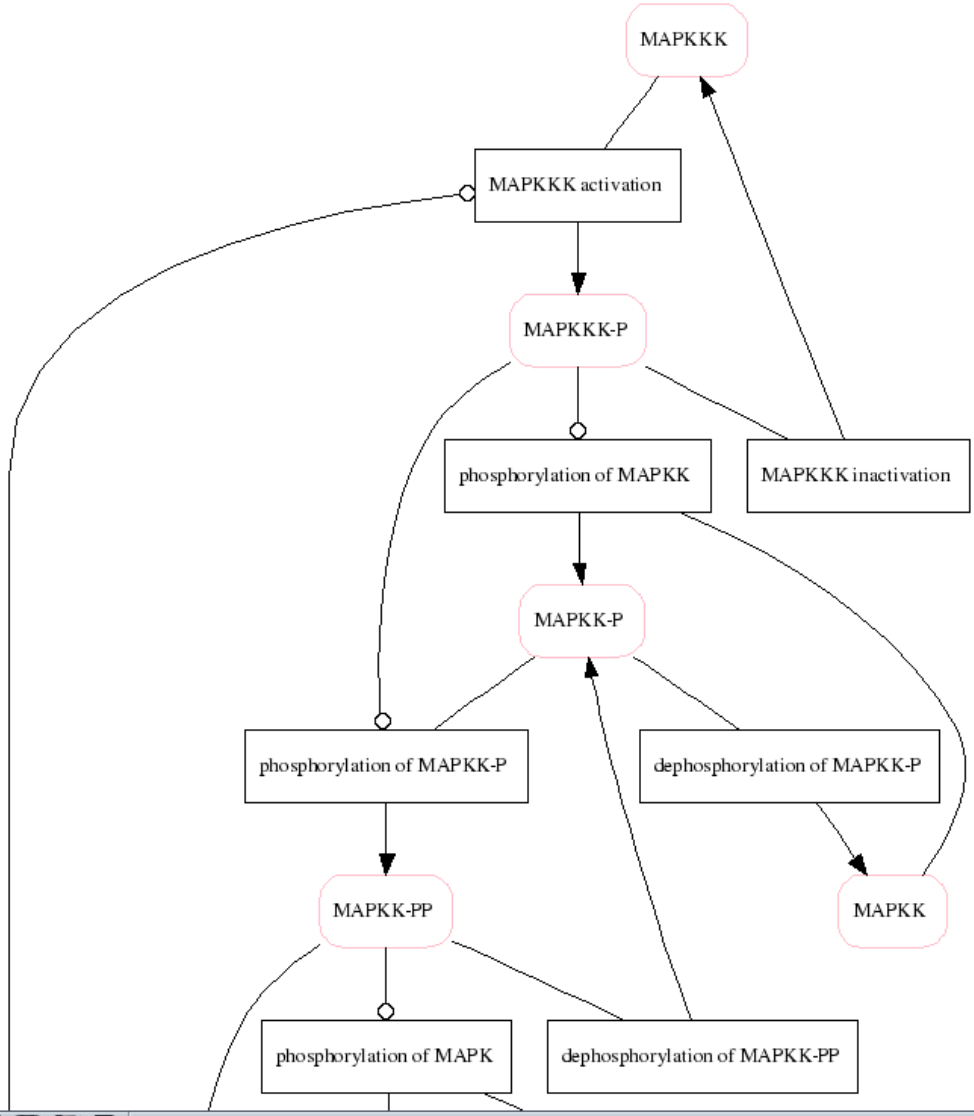


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25

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ure 2.7.11.25
kinase kinase kinase activity
ein amino acid phosphorylation
14

ure 2.7.11.25
ation of MAPKK activity
ein amino acid phosphorylation

javascript:window.name='biomodels';open_popup('http://www.ebi.ac.uk/compneur-srv/biomodels/models-main/publ/BIOMD0000000010.html');

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Please click here for legend of graph.

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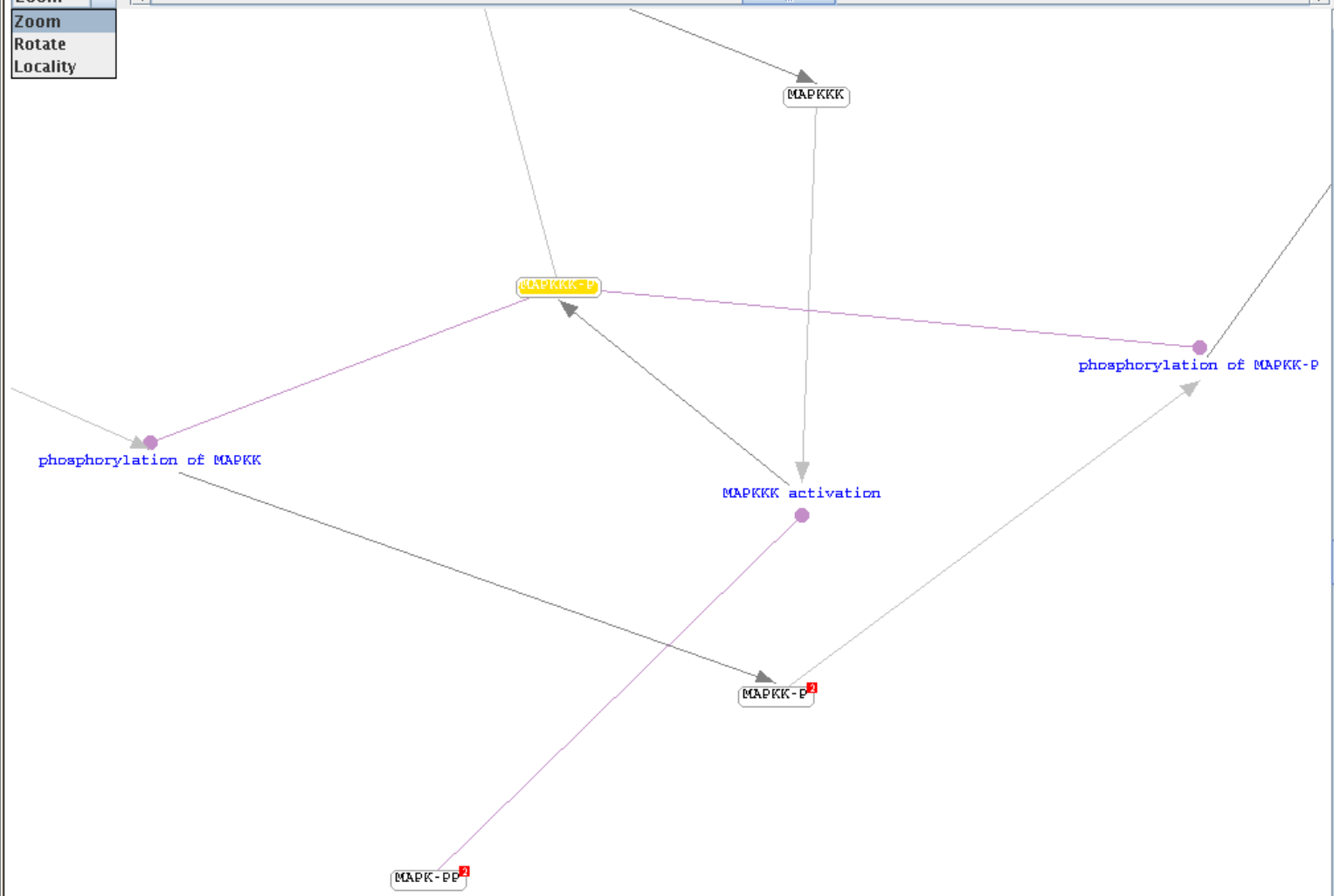
Zoom
Rotate
Locality



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## Reference Publication

## Model

## Compartments (1)

## Species (8)

## Rules (0)

## Reactions (10)

**MAPKKK activation**
Reactants: MAPKKK
Products: MAPKKK-P
Modifiers: MAPK-PP
*Referred to as: J0*

| | | |
|---|---|---|
| bqbiol:isVersionOf | set #1 | Enzyme Nomenclature 2.7.11.1<br>Gene Ontology activation of MAPKKK activity<br>Gene Ontology MAP kinase kinase kinase kinase activity |
| bqbiol:isHomologTo | set #1 | Reactome REACT_525 |

**MAPKKK inactivation**
Reactants: MAPKKK-P
Products: MAPKKK
Modifiers:
*Referred to as: J1*

| | | |
|---|---|---|
| bqbiol:isVersionOf | set #1 | Enzyme Nomenclature 3.1.3.16<br>Gene Ontology inactivation of MAPKKK activity<br>Gene Ontology protein amino acid dephosphorylation |

**phosphorylation of MAPKK**
Reactants: MAPKK
Products: MAPK-P
Modifiers: MAPKKK-P
*Referred to as: J2*

| | | |
|---|---|---|
| bqbiol:isVersionOf | set #1 | Enzyme Nomenclature 2.7.11.25<br>Gene Ontology MAP kinase kinase kinase activity<br>Gene Ontology protein amino acid phosphorylation |
| bqbiol:isHomologTo | set #1 | Reactome REACT_614 |

**phosphorylation of MAPKK-P**
Reactants: MAPKK-P

| | | |
|---|---|---|
| bqbiol:isVersionOf | set #1 | Enzyme Nomenclature 2.7.11.25<br>Gene Ontology activation of MAPKK activity<br>Gene Ontology protein amino acid phosphorylation |

Cytoscape Desktop (Session: BIOMD0000000010.owl) | BioModels Database - Iceape

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BioPAX v 0_5 Search:

CytoPanel 1

work | Editor | BioPAX Extension

Visual Legend | About

Node Details

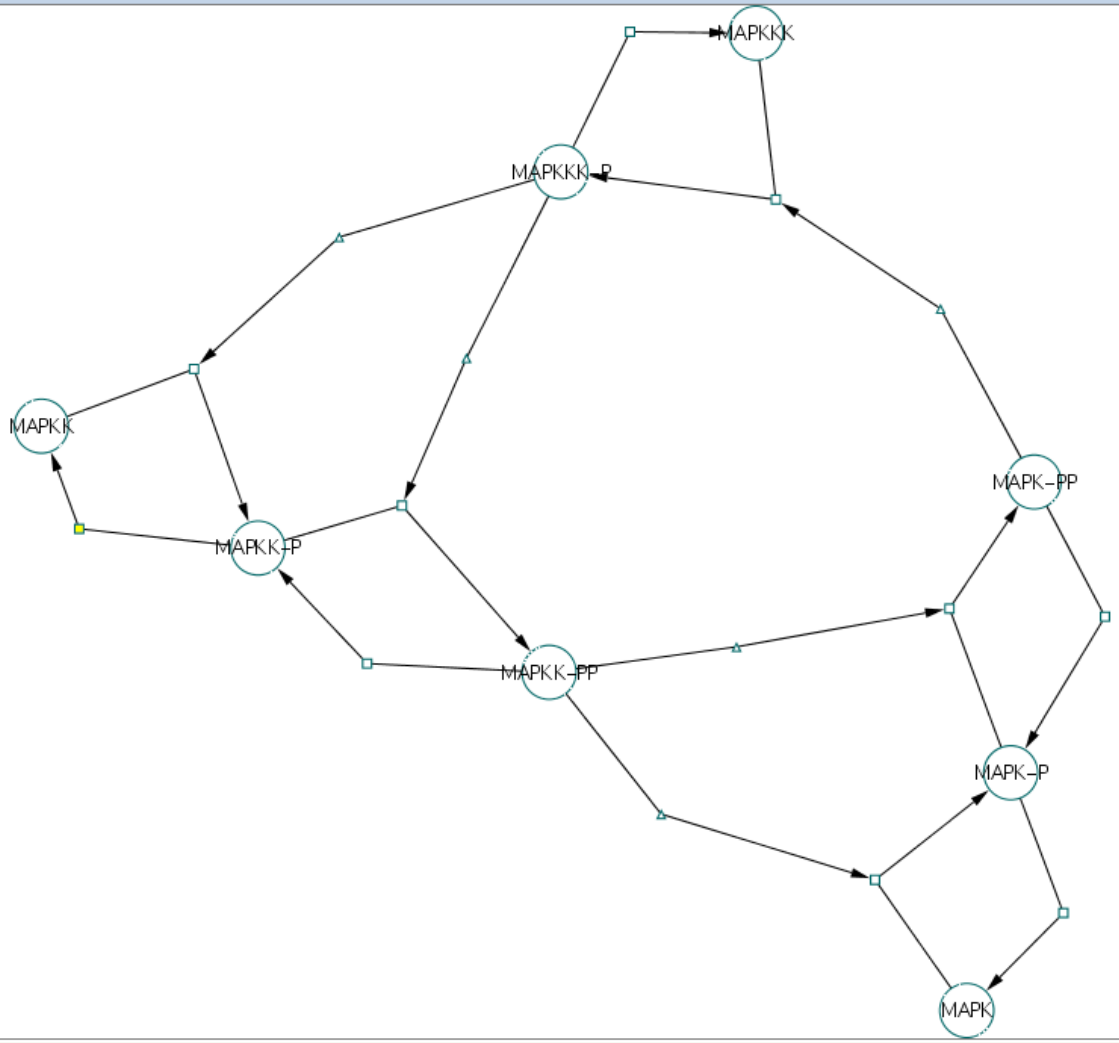
Type

Conversion

Name

dephosphorylation of MAPKK-P

MAPKKK




CytoPanel 2

| ID |
| --- |
| conversion_J5 |

Node Attribute Browser | Edge Attribute Browser | Network Attribute Browser

Welcome to Cytoscape 2.4.1 Right-click + drag to ZOOM Middle-click + drag to PAN

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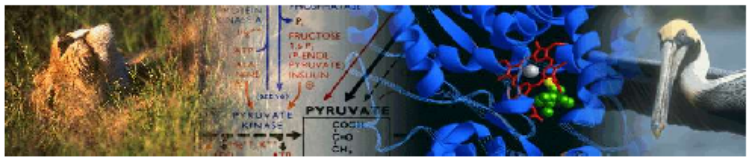


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BioModels

Biomodels: BIOMD0000000010
noname8

Powered by JWS Online

SBML

JWSApplet - ver 4.1.1 noname8

| | Parameter | Value |
|---|---|---|
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| P2_v1 | J0V1 | 2.5 |
| P3_v1 | J0Ki | 9 |
| P4_v1 | J0n | 1 |
| P5_v1 | J0K1 | 10 |
| P6_v1 | J1V2 | 0.25 |
| P7_v1 | J1KK2 | 8 |
| P8_v1 | J2k3 | 0.025 |
| P9_v1 | J2KK3 | 15 |
| P10_v1 | J3k4 | 0.025 |
| P11_v1 | J3KK4 | 15 |
| P12_v1 | J4V5 | 0.75 |
| P13_v1 | J4KK5 | 15 |
| P14_v1 | J5V6 | 0.75 |
| P15_v1 | J5KK6 | 15 |
| P16_v1 | J6k7 | 0.025 |
| P17_v1 | J6KK7 | 15 |
| P18_v1 | J7k8 | 0.025 |
| P19_v1 | J7KK8 | 15 |
| P20_v1 | J8V9 | 0.5 |

Evaluate Model

Sim | State | MCA

StartTime 0 EndTime 6000

Rates Metabolites

| Type | Output | Plot |
|---|---|---|
| M1 | MAPK | ☑ |
| M2 | MAPKP | ☑ |
| M3 | MKK | ☑ |
| M4 | MKKK | ☑ |
| M5 | MKKP | ☑ |
| M6 | MAPK... | ☑ |
| M7 | MKKKP | ☑ |
| M8 | MKKPP | ☑ |
| F1 | v[J0] | ☑ |
| F2 | v[J1] | ☑ |
| F3 | v[J2] | ☑ |
| F4 | v[J3] | ☑ |
| F5 | v[J4] | ☑ |

Applet jjjApplet started

Graph | Dynamic Reaction Graph | JWS Online

**Reference Publication**

**Model**

**Compartments (1)**

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**Rules (0)**

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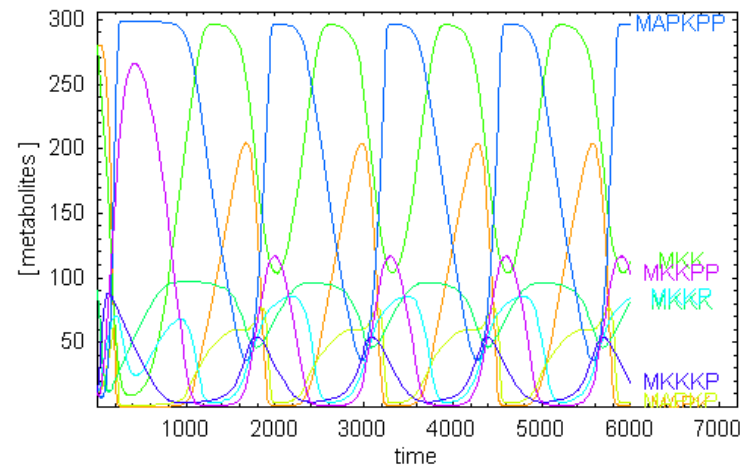


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Done

SBI

JWS online

**phosphorylation of MAPKK**

Reactants: MAPKK

Products: MAPKK-P

Modifiers: MAPKKK-P

*Referred to as: J2*

bqbiol:isVersionOf

bqbiol:isHomologT

**phosphorylation of MAPKK-P**

Reactants: MAPKK-P

bqbiol:isVersionOf set #1

Enzyme Nomenclature 2.7.11.25

Gene Ontology activation of MAPKK activity

Gene Ontology protein amino acid phosphorylation

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File Edit View Window Help

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        <annotation>
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                <times/>
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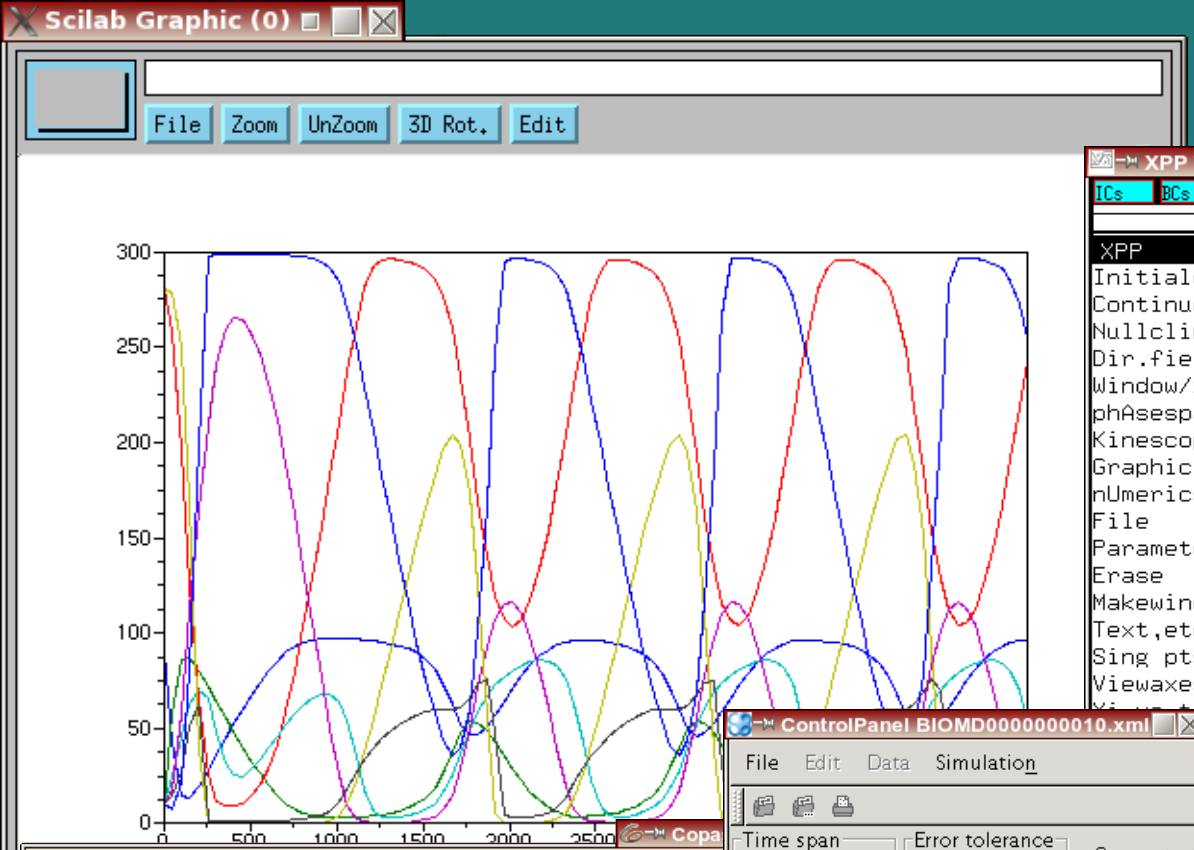
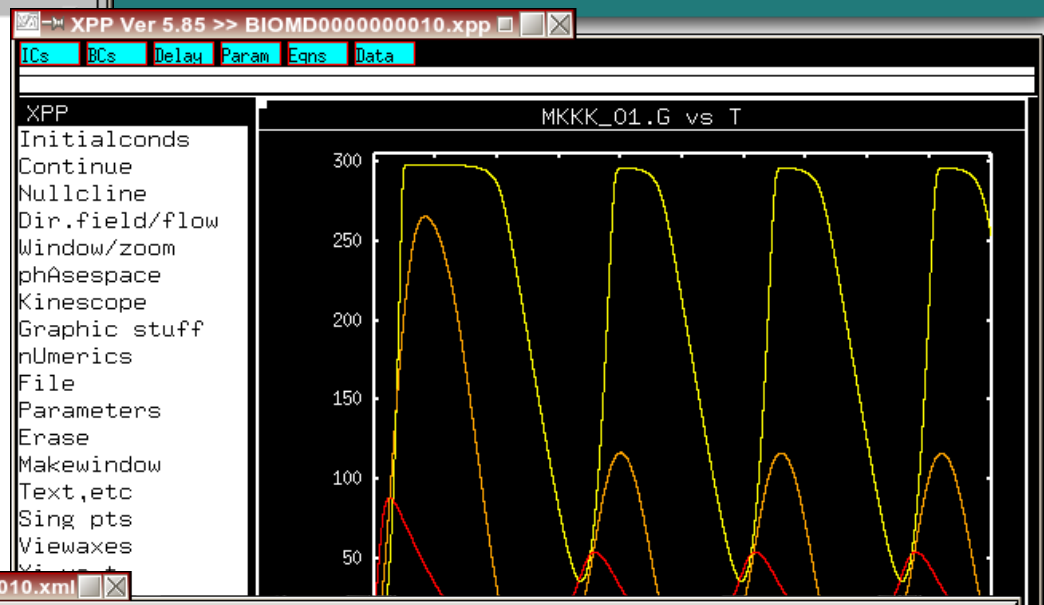
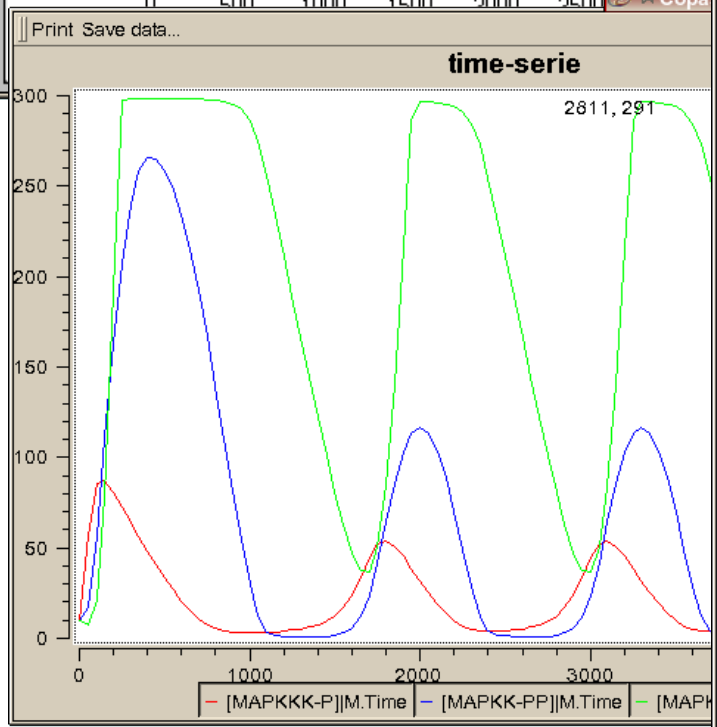
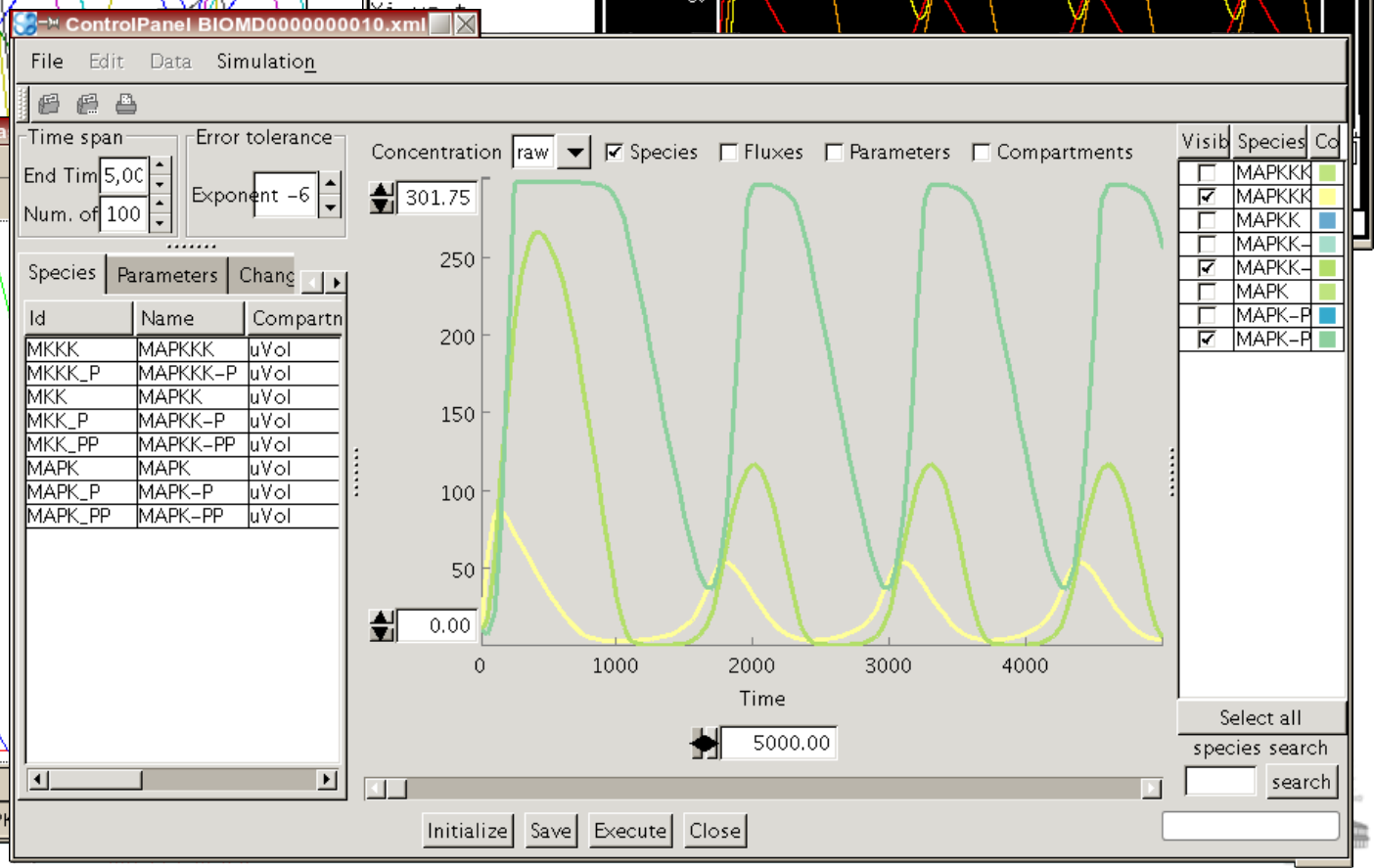
                  <apply>
                    <power/>
                    <apply>
                      <divide/>
                      <ci> MAPK_PP </ci>
                      <ci> Ki </ci>
                    </apply>
                    <ci> n </ci>
                  </apply>
```

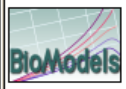
# Kholodenko 2000





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- June 2007 - BIOMD0000000026-31: **Markevich et al. (2004), MAPK** *by Lu Li* [More]
- May 2007 - BIOMD0000000017: **Hoefnagel et al. (2002), Metabolic Control Analysis** *by Dominic P. Tolle* [More]
- April 2007 - BIOMD0000000058: **Bindschadler and Sneyd (2001), Coupled Calcium Oscillators** *by Melanie Stefan* [More]
- March 2007 - BIOMD0000000001: **Edelstein (1996), Nicotinic Receptor** *by Nicolas Le Novère* [More]
- February 2007 - BIOMD0000000049: **Sasagawa (2005), MAPK** *by Lu Li* [More]
- January 2007 - BIOMD0000000064: **Teusink (2000), Glycolysis** *by Dominic P. Tolle* [More]
- December 2006 - BIOMD0000000065: **Yildirim (2003), lac Operon** *by Melanie Stefan* [More]
- November 2006 - BIOMD0000000025: **Smolen (2002), Circadian Oscillator** *by Enuo He* [More]
- October 2006 - BIOMD0000000005: **Tyson (1991), Modelling Cell Division** *by Nicolas Le Novère* [More]
- September 2006 - BIOMD0000000020: **Hodgkin and Huxley (1952), Membrane Current in the Giant Squid Axon** *by Melanie Stefan* [More]
- August 2006 - BIOMD0000000048: **Kholodenko (1999), Epidermal Growth Factor Receptor signalling** *by Renaud Schiappa* [More]
- July 2006 - BIOMD0000000012: **Elowitz and Leibler (2000), The Repressilator** *by Dominic P. Tolle* [More]
- June 2006 - BIOMD0000000009: **Huang and Ferrell (1996), MAPK ultrasensitivity** *by Nicolas Le Novère* [More]

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# BIOMD0000000020 - Hodgkin and Huxley (1952), Membrane Current in the Giant Squid Axon

*by Melanie Stefan*

The mechanisms and rules that govern nervous impulses have been the focus of research and speculation throughout the centuries [1]. In the 1930, Alan Hodgkin and Andrew Huxley started a series of experiments and modelling to elucidate the flow of electric current through an axonal membrane. This lead to the formulation of the Hodgkin-Huxley model in 1952 [2], which has had a lasting influence on our understanding of neuronal function. Both were awarded the Nobel Prize in Physiology or Medicine in 1963.

Hodgkin and Huxley chose the giant squid axon as a model system for their experiments, since it is unusually large (around 0.5 mm in diameter) and therefore quite suitable for electrophysiological experiments [1]. In particular, it was possible to insert a micropipette into the axon and perform voltage-clamp experiments, a technique that had been devised in the 1930s by Cole and Curtis [3]. The experiments were combined with detailed quantitative modelling, which involved a considerable amount of work: Since the university computer in Cambridge was on a six-month downtime in 1951, the calculations were performed on a hand-operated machine [4]. The outcome was a sound mathematical description of the system's behaviour, now known as the Hodgkin-Huxley equations [2].

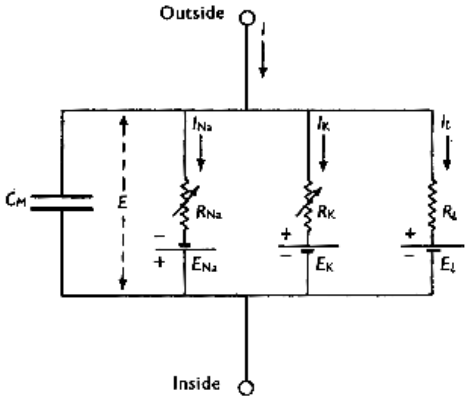
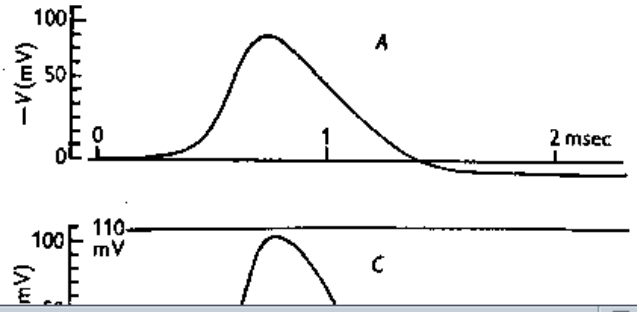



Figure 1: The membrane as an electrical circuit (from [2])

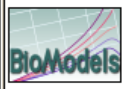
In the Hodgkin-Huxley model, the membrane can be represented as an electrical circuit, as shown in figure 1. Ionic current through the membrane can be divided into three components: potassium current ($I_K$), sodium current ($I_{Na}$), and a small leakage current ($I_l$) caused by other ions [2]. Each component can be expressed in terms of the cell's resting potential (E), the respective equilibrium potential for each component ($E_K$, $E_{Na}$, and $E_l$), constants reflecting the conductance of each component ($G_K$, $G_{Na}$, and $G_l$) and additional variables representing the activation of potassium transport (n), or the activation (m) or non-inhibition (h) of sodium transport. The equation for the total ionic current thus reads:

$$I = G_K n^4(E-E_K) + G_{Na} m^3 h(E-E_{Na}) + G_l(E-E_l)$$

The model thus related changes in membrane potentials to conductance changes. It proved to be very powerful in describing, amongst other things, the form and amplitude of propagated action potentials, the total inward movement of sodium ions and the total outward movement of potassium ions associated with an impulse, the threshold and response during the refractory period following an axion potential and the form of subthreshold responses [2].




An example for the fit between calculated and observed action potentials is shown in figure



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"Model Creators"

The individuals who wrote the model present in the BioModels Database, based on the reference publication. Model creators are listed within the model.

"Complete Dataset"

The entire content of the BioModels Database, including the models and their annotations.

1. The copyright on the encoded form of a model distributed by BioModels Database does not imply any copyright of the model characteristics, whether interaction graph, mathematical description or simulation results, as they are described in the original publication. Each individual model retains the copyright assigned by the author(s) of the reference publication."

2. You may distribute verbatim copies of the complete dataset or a subset of the models, provided that you duplicate this copyright notice and the disclaimers shown below.

3. You may otherwise modify your copy of any of the models in any way, provided that you also do at least ONE of the following:

a. Use the modified model only within your organization.
b. Contact BioModels team to include your modifications in the standard version of the model.
c. Rename the modified model, and remove both the BioModels Database identifier and any mention of the model creators.

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# Related Software

The following software was developed for BioModels Database purposes. However, since it relates to SBML, we feel it could be used by others. All our software is distributed under the General Public License.

To edit the models, BioModels Database team uses the SBML editor.

In order to provide a variety of export formats, we developed convertion tools. This software uses the Extensible Stylesheet Language. We use them in conjunction with Xalan Java. Because some of our XSL stylesheets use the extension exsl, they could cause problems with other XSLT engines not supporting it.

## SBML to XPP-Aut

XPP-Aut is a numerical analysis software. It permits to solve differential equations, difference equations, delay equations, functional equations, boundary value problems, and stochastic equations. Its graphical capabilities are quite user-friendly.

The conversion is performed in one XSLT pass, but using five stylesheets:

1. sbml_xpp16.xsl
2. xpp_math16.xsl
3. xpp_test16.xsl
4. xpp_variable16.xsl
5. bounds16.xsl

To generate an XPP-Aut ode file from a SBML model, run:

```
Xalan MyModel_sbml.xml sbml_xpp16.xsl > MyModel.xpp
```

## SBML to SciLab

SciLab is a scientific software package for numerical computations providing a powerful open computing environment for engineering and scientific applications.

The conversion is performed in one XSLT pass, but using four stylesheets:

1. sbml_to_scilab.xsl
2. scilab_math.xsl
3. scilab_test.xsl
4. scilab_variable.xsl

To generate an SciLab file from a SBML model, run:

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# BioModels Web Services

## Available features

Following are the currently available features in BioModels Web Services. In order to make using data in BioModels Database more conveniently, we will consider all requirements about new features.

- String helloBioModels()
- String[] getAllModelsId()
- String getModelById(String id)
- String getModelNameById(String id)
- String[] getModelsIdByName(String modelName)
- String[] getModelsIdByPublication(String publicationIdOrText)
- String[] getModelsIdByPerson(String personName)

For more detail, please see javadoc or WSDL.

## 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*".

| Name | Description | Size | Link |
|---|---|---|---|
| biomodelswslib-standalone.jar | standalone and includes all external dependencies and ready for use; | 1.8M | http://www.ebi.ac.uk/compneur-srv/biomodels/softwares/biomodelswslib-standalone.jar |
| biomodelswslib.jar | light-weight, but needs other dependencies to work togeter. | 2.1K | http://www.ebi.ac.uk/compneur-srv/biomodels/softwares/biomodelswslib.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
- saaj.jar
- wsdl4j-1.5.1.jar

# Future of BioModels DB

- Uncoupling user's view and curator's view
  - Following biological processes structure and not SBML structure
  - Different views of the same model
  - Use of JSF and AJAX
- Enlargind BioModels DB coverage
  - Steady-state (FBA, MCA)
  - Multi-scale, multi-components, multi-states
  - Spatial models (finite elements, PDE)
  - Physiological models (not molecule-based)

# The BioModels Database team

Nicolas Le Novère

Michael Hucka

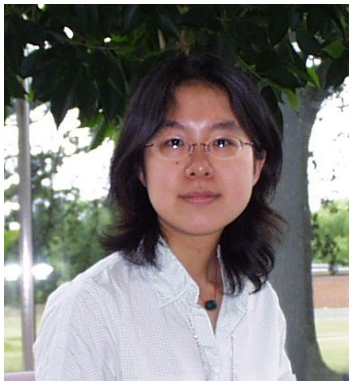
## Development

Marco Donizelli

Chen Li

Arnaud Henry

Lu Li



## Curation

Harish Dharuri

Enuo He

Bruce Shapiro

Rainer Machne

# An international collaboration

- EBI
  - **Nicolas Le Novère**
  - Mélanie Courtot
  - Marco Donizelli
  - Arnaud Henry
  - Christian Knuepfer
  - Chen Li
  - Lu Li
  - Camille Laibe
  - Nicolas Rodriguez
  - Alexander Broicher
- SBML team (Caltech)
  - **Michael Hucka**
  - **Andrew Finney**
  - Benjamin Borstein
  - Harish Dharuri
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- Vienna TBI
  - Rainer Machne
  - Christof Flamm
  - James Lu
- Systems Biology Institute (Tokyo)
  - Hiroaki Kitano
  - Akira Funahashi
- JWS Online (Stellenbosh+Amsterdam)
  - Jacky Snoep
  - Hans Westerhoff
- Journals supporting BioModels Database
  - Molecular Systems Biology
  - All PLoS Journals
  - All BioMedCentral Journals
- Programs used for curation
  - CellDesigner/SBMLodeSolver
  - COPASI
  - Jarnac/JDesigner
  - MathSBML
  - RoadRunner
  - SBMLeditor
  - XPP-Aut

The community of Systems Biology for their contributions of models and comments.