

BioModels Database: Curation and exchange of quantitative models

Nicolas Le Novère, EMBL-EBI, United-Kingdom



- We need to encode the models in a computer-edible way
 - Structured formats → easily “parsable”; mirror the model structure;
 - Public formats → Published specifications, freely re-usable
 - Community-developed formats ...





<http://www.cellml.org/>

Fixed specification; Based on modules;
scalable; ... complex



<http://www.neuroml.org/>

Flexible (expendable set of classes/schemas); scalable;

• **BrainML.org** <http://brainml.org/>

Models are XML-schemas

• **BioPAX** <http://www.biopax.org/>

No kinetics; deep semantics;



SBML Systems Biology Markup Language

Google

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

Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is **supported by over 90 software systems**, including the following (where "*" indicates SBML support in development):

BALSA	DBsolve	Molecularizer	SBMLR
BASIS	Dizzy	Monod	SBMLSim
BIOCHAM	E-CELL	Narrator	SBMLToolbox
BioCharon	ecellJ	NetBuilder	SBLiD
ByoDyn	ESS	Oscill8	SBToolbox
biocyc2SBML	FluxAnalyzer	PANTHER Pathway	SBW
BioGrid	Fluxor	PathArt	SClpath
BioModels	Gepasi	PathScout	Sigmoid*
BioNetGen	Gillespie2	PathwayLab	SigPath
BioPathway Explorer	INSILICO discovery	Pathway Tools	SigTran
Bio Sketch Pad	JACOBIAN	PathwayBuilder	SIMBA
BioSens	Jarnac	PATIKAwab	SimBiology
BioSPICE Dashboard	JDesigner	PaVESy	Simpathica
BioSpreadsheet	JigCell	PET	SimWiz
BioTapestry	JSim	PNK	SloppyCell
BioUML	JWS Online	Reactome	SmartCell
BSTLab	Karyote*	ProcessDB	SRS Pathway Editor
CADLIVE	KEGG2SBML	PROTON	StochSim
CellDesigner	Kinsolver*	pysbml	StochKit
Cellerator	libSBML	PySCeS	STOCKS
CellML2SBML	MathSBML	runSBML	TERANODE Suite
Cellware	MesoRD	SABIO-RK	Trelis
CL-SBML	MetaboLogica	SBML ODE Solver	Virtual Cell
CLEML	MetaFluxNet	SBML-PET	WebCell
COPASI	MMT2	SBMLEditor	WinSCAMP
Cytoscape	Modesto	SBMLmerge	XPPAUT

A Free and Open Language

SBML-PET Announced

(May 8, 2006) **SBML-PET** is a parameter estimation tool that uses SBML and can work with a variety of types of models.

[read more](#)

JSim supports SBML

(May 8, 2006) **JSim** is a Java-based simulation system for building and analyzing quantitative models.

[read more](#)

SBW 2.5.5 Released

(April 19, 2006) A new release of **SBW** (the Systems Biology Workbench) is now available. It features significant new capabilities and new modules.

[read more](#)

WebCell Supports SBML

(April 19, 2006) **WebCell** is a web-based simulation environment for biochemical networks. It supports exploration and analysis of steady-state and dynamic behaviors.

[read more](#)

SBML Hackathon 2006

(April 4, 2006) Visit the **SBML Hackathon 2006 page** for more info about the event happening this week in **Nové Hradý**, Czech Republic.

[read more](#)

- **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;
- A **species** is an entity participating to a reaction, not always a chemical entity:
 - It can be a receptor
 - It can be a neuron
 - It can be an functional assembly
 - It can be an organism

→ Systems Biology is scale-free!



- We need to encode the models in a computer-edible way
 - Structured formats → easily “parsable”; mirror the model structure;
 - Public formats → Published specifications, freely re-usable
 - Community-developed formats ...
- We need to make the content human-edible → semantics
 - Standards of content and annotation
 - Ontologies to relate model components and biological information



Minimum Information Requested In the Annotation of biochemical Models

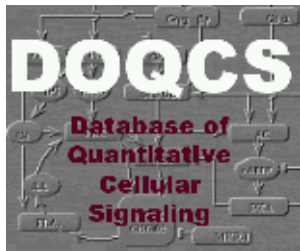
Le Novère N., Finney A., Hucka M., Bhalla U., Campagne F., Collado-Vides J.,
Crampin E., Halstead M., Klipp E., Mendes P., Nielsen P., Sauro H., Shapiro B.,
Snoep J.L., Spence H.D., Wanner B.L.
Nature Biotechnology (2005), 23: 1509-1515

MIRIAM

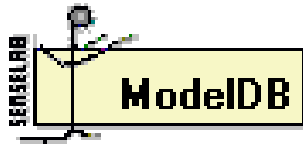
<http://www.ebi.ac.uk/compneur-srv/miriam/>

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 - Structured formats → easily “parsable”; mirror the model structure;
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 - Standards of content and annotation
 - Ontologies to relate model components and biological information
- We need to make the models available
 - Personal websites
 - Publisher's websites
 - Curated repository/databases





- [\[GENESIS\]](#)[\[curation\]](#)[\[search\]](#)



- of SenseLab [\[NEURON, GENESIS\]](#)[\[search\]](#)



- models repository [\[CellML\]](#)[\[curation...\]](#)[\[search\]](#)

- JWS online [\[SBML, Pysces\]](#)[\[curation\]](#)



- Developer Network [\[E-Cell, SBML\]](#)

- + ...



- Neither focussed on a particular biological substrate or process, nor specialised on a given modelling approach
- Real “searchable” database rather than mere repository
- Models thoroughly verified, structure and results, and annotated
- International collaboration rather than a one-group effort
- Long-term commitment and secure funding
- Freely available and reusable



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

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



- Neither focussed on a particular biological substrate or process, nor specialised on a given modelling approach
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- Long-term commitment and secure funding
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- Store and serve quantitative models of biomedical 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 “Swiss-Prot” of quantitative modelling.



I) Repositories

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

II) Individuals

- Members of the SBML community (developers+modellers)
- Authors (prior to grant application, before publication etc.)

III) Supported by Nature Publishing Group. MSB advises deposition, and forward supplementary material

IV) BioModels DB curators encode new models from literature



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 for SBML elements by either name or *notes* content (for example *Edelstein* or *nicotinic*).
- *Resource* → Search BioModels Database for related information found in the models reference publication or third-party resources, by either publication/resource identifier or text (for example *9256450* or *cyclin* for publication, *GO:0007049* or *cell cycle* for *Gene Ontology*, *P04551* or *cell division* for *UniProt*).
- *Resource ID* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for *InterPro*, *hsa04080* for *KEGG Pathway*, *68910* for *Reactome*).

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

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

BioModels ID:	
Person:	
SBML Elements:	
Resource:	Gene Ontology Publication ChEBI Gene Ontology Taxonomy UniProt
Resource ID:	MAPK
Resource ID:	MAPK
Resource ID:	MAPK
Resource ID:	MAPK
Resource ID:	MAPK
Resource ID:	MAPK

Compose by: ☒ and ☐ or

Search Reset

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Last modification: Fri May 28 02:36:06 BST 2006

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http://www.ebi.ac.uk/compneur-srv/biomodels-main/search-models.do?cmd=ADVANCED:SEARCH

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compneur

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PubMed

SBO::Systems ...

European Bioinformatics Institute

EBI Home

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BIOMODELS.NET

JWS online

Search

Models

The search returned 13 models.

[↶ New Search](#)

Show 10 Only

BioModels ID	Name	Publication ID	Last Modified	
BIOMD0000000009	Huang1996_MAPK_ultrasens	8816754	2006-06-13T23:09:10	SBML L2 V1
BIOMD0000000010	Kholodenko2000_MAPK_feedback	10712587	2006-04-07T22:02:49	SBML L2 V1
BIOMD0000000011	Levchenko2000_MAPK_noScaffold	10823939	2006-01-31T10:04:06	SBML L2 V1
BIOMD0000000014	Levchenko2000_MAPK_Scaffold	10823939	2006-01-31T10:08:46	SBML L2 V1
BIOMD0000000026	Markevich2004_MAPK_orderedElementary	14744999	2006-04-02T18:50:28	SBML L2 V1
BIOMD0000000027	Markevich2004_MAPK_orderedMM	14744999	2006-01-31T10:12:00	SBML L2 V1
BIOMD0000000028	Markevich2004_MAPK_phosphoRandomElementary	14744999	2006-04-02T18:53:13	SBML L2 V1
BIOMD0000000029	Markevich2004_MAPK_phosphoRandomMM	14744999	2006-04-02T18:55:05	SBML L2 V1
BIOMD0000000030	Markevich2005_MAPK_AIRandomElementary	14744999	2006-04-02T18:57:56	SBML L2 V1
BIOMD0000000031	Markevich2004_MAPK_orderedMM2kinases	14744999	2006-04-02T18:58:15	SBML L2 V1
BIOMD0000000032	Kofahl2004_pheromone	15300679	2006-03-24T13:34:26	SBML L2 V1
BIOMD0000000033	Brown2004_NGF_EGF_signaling	14525003	2006-05-03T13:02:33	SBML L2 V1
BIOMD0000000049	Sasagawa2005_MAPK	15793571	2006-03-07T11:36:34	SBML L2 V1

[↶ New Search](#)

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Last modification: Fri May 28 02:36:06 BST 2006

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BioModels

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- Curation tips
- Annotation tips

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- Related Software
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- Quote

BIOMODELS.NET

Computational Neurobiology

SBML

SBW

JWS online

BIOMD0000000009 Huang1996_MAPK_ultrasens

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

View Model Graph | View Model SVG

Submit Model Comment/Bug

□ □ □

Reference Publication	
Publication ID: 8816754	Proc Natl Acad Sci U S A 1996 Sep;93(19):10078-83. Ultrasensitivity in the mitogen-activated protein kinase cascade. Huang CY, Ferrell JE. Department of Molecular Pharmacology, Stanford University School of Medicine, CA 94305-5332, USA.

Model	
Submitter: Nicolas Le Novère	bqbiol:is set #1 Gene Ontology MAPKKK cascade Taxonomy Xenopus laevis
Submission Date: 2005-09-13T13:37:52	
Last Modification Date: 2006-06-13T23:09:10	
Creation Date: 2005-02-10T23:39:30	
Creators: Rainer Machne	

Compartments (1)	
compartment +	
Referred to as: compartment	

Species (22)	
MAPKKK activator +	bqbiol:isVersionOf set #1 InterPro IPR003577
Compartment: compartment Referred to as: E1	
MAPKKK inactivator +	
Compartment: compartment Referred to as: E2	
MAPKKK +	bqbiol:isVersionOf set #1 UniProt MOS_XENLA
Compartment: compartment Referred to as: KKK	
P-MAPKKK +	bqbiol:isVersionOf set #1 UniProt MOS_XENLA
Compartment: compartment Referred to as: P_KKK	
MAPKK +	bqbiol:isVersionOf set #1 UniProt MP2K1_XENLA
Compartment: compartment Referred to as: KK	
P-MAPKK +	bqbiol:isVersionOf set #1 UniProt MP2K1_XENLA
Compartment: compartment Referred to as: P_KK	
PP-MAPKK +	bqbiol:isVersionOf set #1 UniProt MP2K1_XENLA
Compartment: compartment Referred to as: PP_KK	



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



Level 2 Version 1

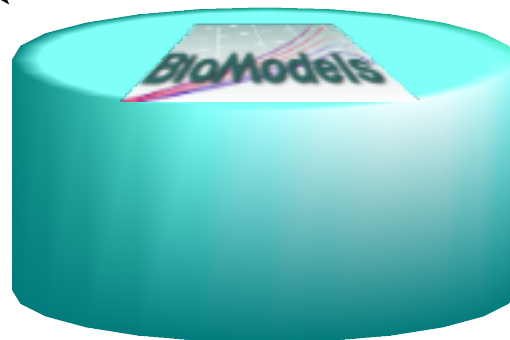


Version 1.1

XPP-Aut

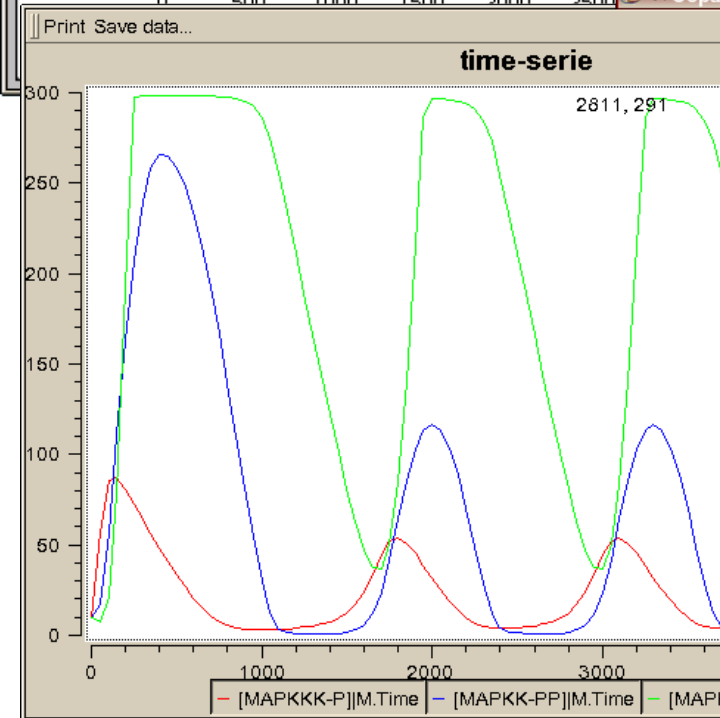
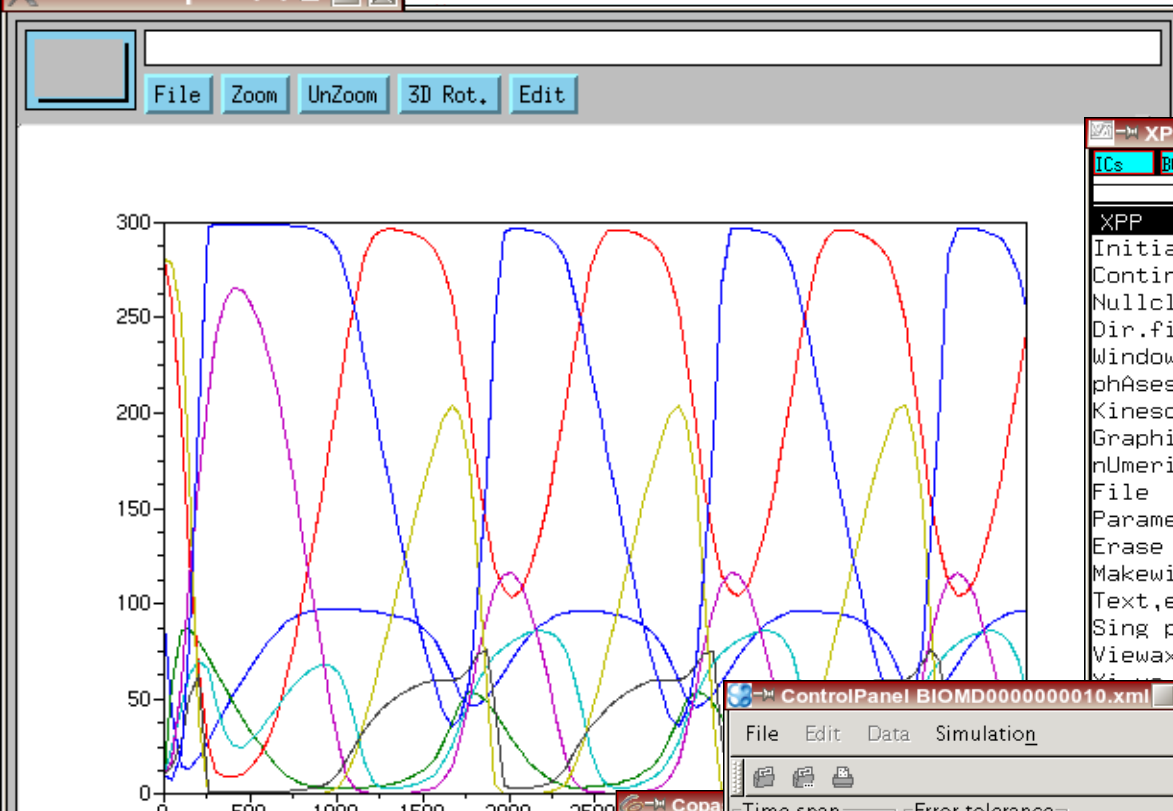


Version 1.0
Version 1.1



Graphs

BioPAX

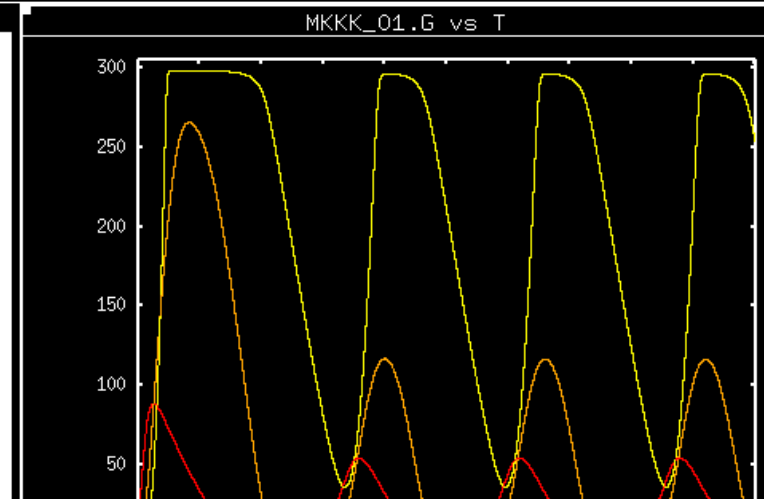


XPP Ver 5.85 >> BIOMD0000000010.xpp

ICs BCs Delay Param Eqns Data

XPP

- Initialconds
- Continue
- Nullcline
- Dir.field/flow
- Window/zoom
- phAsespace
- Kinescope
- Graphic stuff
- nUmeric
- File
- Parameters
- Erase
- Makewindow
- Text,etc
- Sing pts
- Viewaxes



ControlPanel BIOMD0000000010.xml

File Edit Data Simulation

Time span

End Tim 5,00

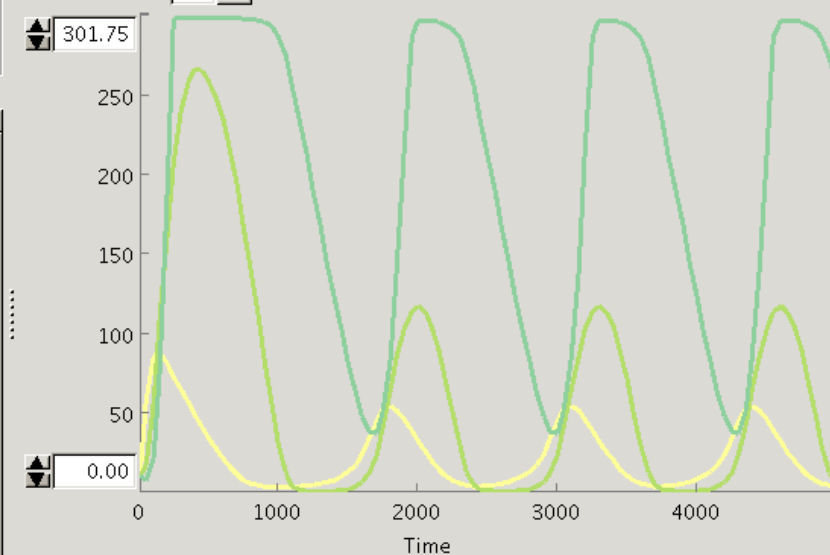
Num. of 100

Error tolerance

Exponent -6

Species Parameters Change

Id	Name	Compartment
MKKK	MAPKKK	uVol
MKKK_P	MAPKKK-P	uVol
MKK	MAPKK	uVol
MKK_P	MAPKK-P	uVol
MKK_PP	MAPKK-PP	uVol
MAPK	MAPK	uVol
MAPK_P	MAPK-P	uVol
MAPK_PP	MAPK-PP	uVol

Concentration raw ☒ Species ☐ Fluxes ☐ Parameters ☐ Compartments

Visib	Species	Co
☐	MAPKKK	
☒	MAPKKK	
☐	MAPKK	
☐	MAPKK-	
☒	MAPKK-	
☐	MAPK	
☐	MAPK-P	
☒	MAPK-P	

Select all

species search

search

Initialize Save Execute Close

- CellDesigner:
<http://www.systems-biology.org/cd/features/BioModelsNet.html>
- SIGMOID:
<http://www.sigmoid.org/models/ModelBrowse.do>
- JSIM:
<http://nsr.bioeng.washington.edu/cgi-bin/butterw/jquery.cgi?d=biomodels>

We are happy about that! Feel-free to do the same!





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



Melanie Courtot:
MySQL/Tomcat



Camille Laibe
WebServices



Lu Li:
Curation plus Graph, CellML,
XPP and SciLab exports



Arnaud Henry:
BioPAX export



Nicolas Le Novère:
Design and curation



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- Lu Li
- Chen Li
- Nicolas Rodriguez
- Alexander Broicher
- Arnaud Henry
- Camille Laibe

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- Birgit Schoeberl
- Henning Schmidt
- Paul Smolen
- Darren Wilkinson
- Molecular Systems Biology

Programs used for curation

- CellDesigner
- COPASI
- Jarnac/JDesigner
- MathSBML
- SBMLeditor
- SBMLodeSolver
- XPP-Aut

