

SBML and related resources for computational systems biology

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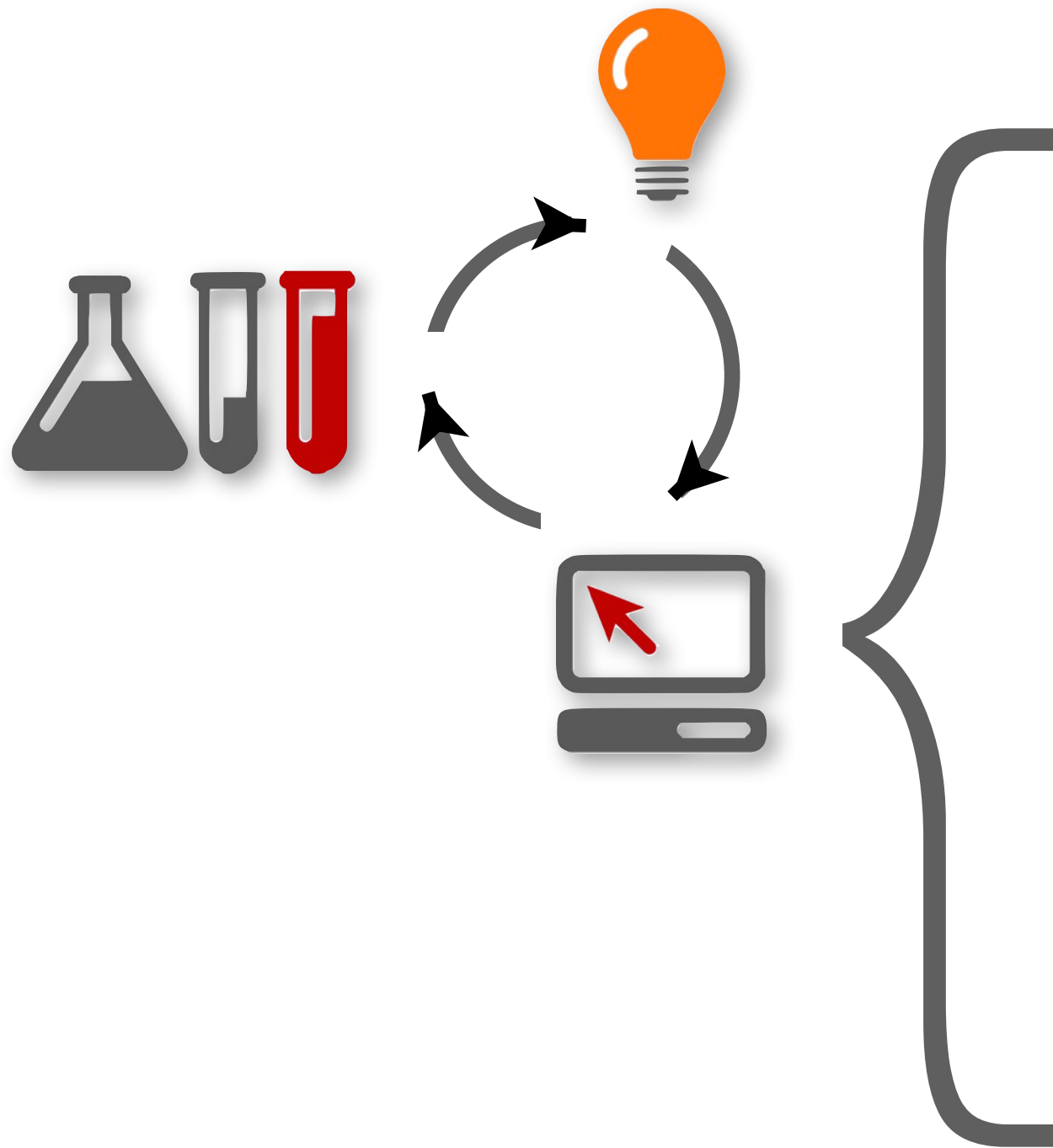
Twitter: [@mhucka](https://twitter.com/mhucka)

Outline

- SBML (Systems Biology Markup Language)
- A sample of SBML software resources
- A sample of related resources and efforts
- COMBINE
- Acknowledgments

Introduction to SBML

Background context: formal models

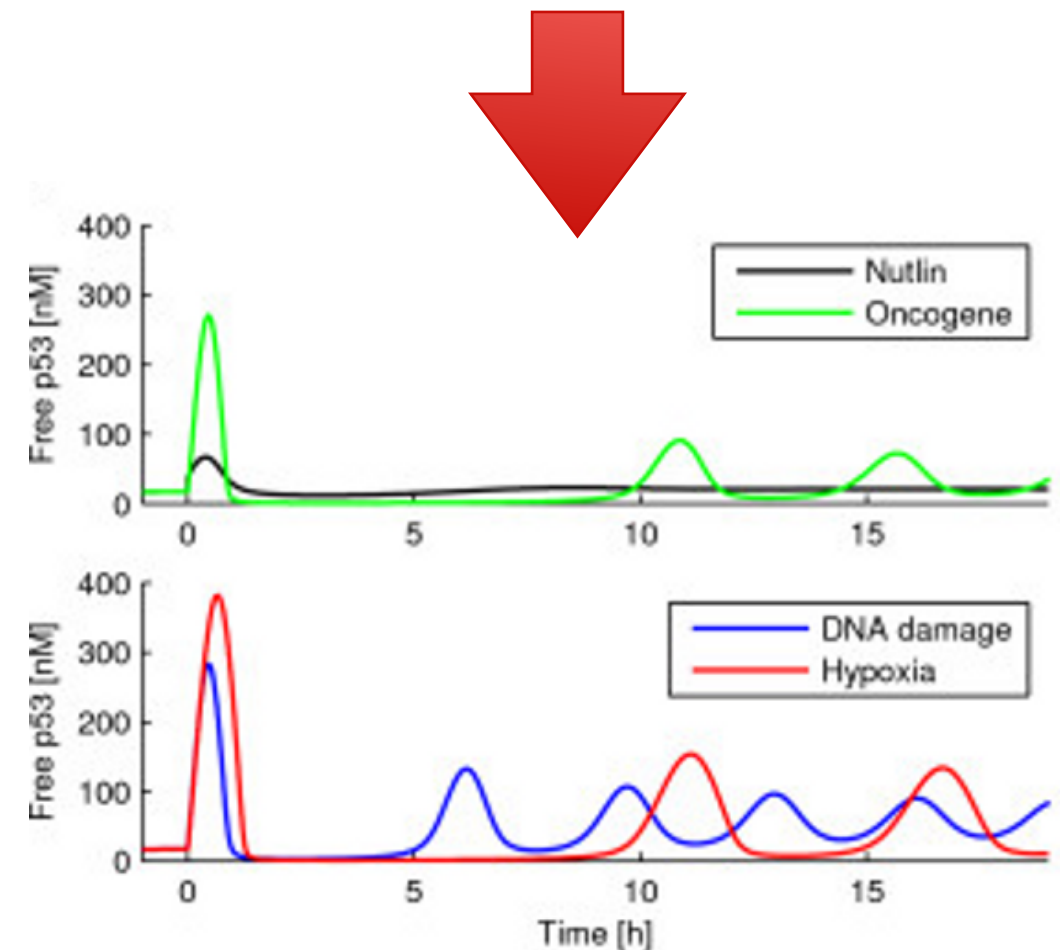


$$\frac{d[p]}{dt} = \sigma - \alpha[p] - k_f[m][p] + k_b[c] + \gamma[c]$$

$$\frac{d[m_m]}{dt} = k_t[p]^2 - \beta m_m$$

$$\frac{d[m]}{dt} = k_{tl}[m_m] - k_f[p][m] + k_b[c] + \delta[c] - \gamma[m]$$

$$\frac{d[c]}{dt} = k_f[p][m] - k_b[c] - \delta[c] - \gamma[c]$$



ABC–SysBio	CellNetAnalyzer	Karyote*	PaVESy	SBW: Auto Layout
acslXtreme	CellNOpt	KEGGconverter	PAYAO	sbw: javasim
ALC	Cellware	KEGGtranslator	PET	sbw: stochastic simulator
AMIGO	CLEML	Kineticon	PhysioLab Modeler	SCIpath
Antimony	CL–SBML	Kinsolver	PINT	SED–ML Web Tools
APMonitor	COBRA	libAnnotationSBML	PK–Sim / MoBi	semanticSBML
Arcadia	CompuCell3D	libRoadRunner	PNK	SensSB
Asmparts	ConsensusPathDB	libSBML	PottersWheel	SGMP
Athena	COPASI	libSBMLSim	PRISM	Sigmoid*
AutoSBW	CRdata	libStruct	ProcessDB	SIGNALIGN
AVIS	CycSim	MASS Toolbox	ProMoT	Signalink
BALSA	CySBML	MatCont	PROTON	SigPath
BASIS	Cytoscape	MathSBML	pybrn	SigTran
BetaWB	Cyto–Sim	Medicel	PyDSTool	SIMBA
Bifurcation Discovery Tool	DBSolve	MEMOSys	PySB	SimBiology
BiGG	DEDiscover	MesoRD	PySCeS	Simpathica
BiNoM	Dizzy	Meta–All	RANGE	SimPheny*
BiNoM Cytoscape Plugin	DOTcvpSB	Metaboflux	RAVEN	Simulate3D
Bio Sketch Pad	E–CELL	MetaCrop	Reactome	Simulation Core Library
BioBayes	ecellJ	MetaFluxNet	ReMatch	Simulation Tool
BIOCHAM	EPE	Metannogen	RMBNToolbox	SimWiz
BioCharon	ESS	Metatool	roadRunner	SloppyCell
BioCyc	Facile	MetExplore	RSBML	SmartCell
BioGRID	FAME	MetNetMaker	SABIO–RK	Snoopy
Biological Networks	FASIMU	MIRIAM Resources	Saint	SOSlib
BioMet Toolbox	FBASBW	MMT2	SBFC	SPDBS
BioModels Database	FERN	modelMaGe	SBML Harvester	SRS
BioModels Importer	FluxBalance	ModeRator	SBML Layout	STEPS
BioNessie	Fluxor	Modesto	SBML Reaction Finder	StochKit
BioNetGen	Genetdes	Moleculizer	SBML Translators	StochPy
BioPARKIN	Genetic Network Analyzer	MonaLisa	SBML2APM	StochSim
BioPathwise	Gepasi	Monod	SBML2BioPax	STOCKS
BioPAX2SBML	Gillespie2	MOOSE	SBML2LaTeX	SurreyFBA
BioRica	GINsim	MuVal (Multi–valued logic)	SBML2NEURON	SyBiL
BioSens	GNAT	Narrator	SBML2Octave	SYCAMORE
BioSPICE Dashboard	GNU MCSim	nemo	SBML2SMW	SynBioSS
BioSpreadsheet	GRENDEL	NetBuilder'	SBML2TikZ	Systrip
BioSyS	HSMB	NetPath	SBML2XPP	TERANODE Suite
BioTapestry	HybridSBML	NetPro	SBMLEditor	The Cell Collective
BioUML	iBioSim	Odefy	SBML–PET–MPI	Tide
BoolNet	IBRENA	Omix	SBMLR	TinkerCell
braincirc	Insilico Discovery	ONDEX	SBML–SAT	Trelis
BRENDA	insilicoIDE	optflux	SBML–shorthand	UTKornTools
BSTLab	iPathways	Oscill8	SBMLSim	VANTED
ByoDyn	JACOBIAN	PANTHER Pathway	SBMLsqueezer	Vcell
CADLIVE	Jacobian Viewer	PathArt	sbmltidy	WebCell
Cain	Jarnac	Pathway Access	SBMLToolbox	WinSCAMP
CARMEN	JarnacLite	Pathway Analyser	SBMM assistant	Wolfram SystemModeler
Cell Illustrator	CellML2SBML	Pathway Editor	SBML2CellML	xCellerator
CellDesigner	CellML2SBML	Pathway Editor	SBML2CellML	Xholon
Cellerator	CellML2SBML	Pathway Editor	SBML2CellML	XPPAUT
CellMC	CellML2SBML	Pathway Editor	SBML2CellML	
CellML2SBML	CellML2SBML	Pathway Editor	SBML2CellML	

Many software tools for modeling
and simulation are available



**Research often involves the
use of more than one tool**



**Need flexible way to exchange results
between tools (and researchers)**

EMBL-EBI BioModels Database

Enter Text Here

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BioModels Home Models Submit Support About BioModels


BioModels Database - A Database of Annotated Published Models

BioModels Database is a repository of peer-reviewed, published, computational models. These mathematical models are primarily from the field of systems biology, but more generally are those of biological interest. This resource allows biologists to store, search and retrieve published mathematical models. In addition, models in the database can be used to generate sub-models, can be simulated online, and can be converted between different representational formats. This resource also features programmatic access via Web Services.

All unmodified models in the database are available freely for use and distribution, to all users. This resource is developed and maintained by the [BioModels.net](http://www.biomodels.net) initiative. More information about BioModels Database can be found in the [Frequently Asked Questions](#).

COPASI 4.8 (Build 35)

Concentrations

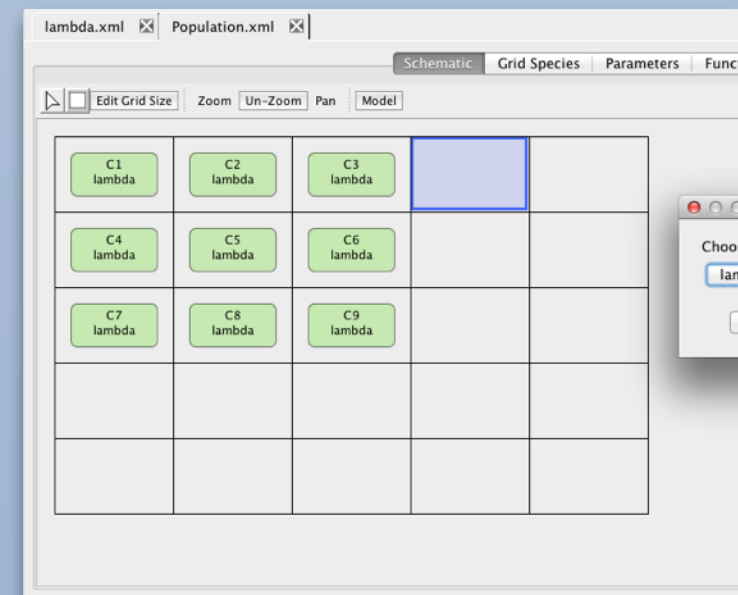
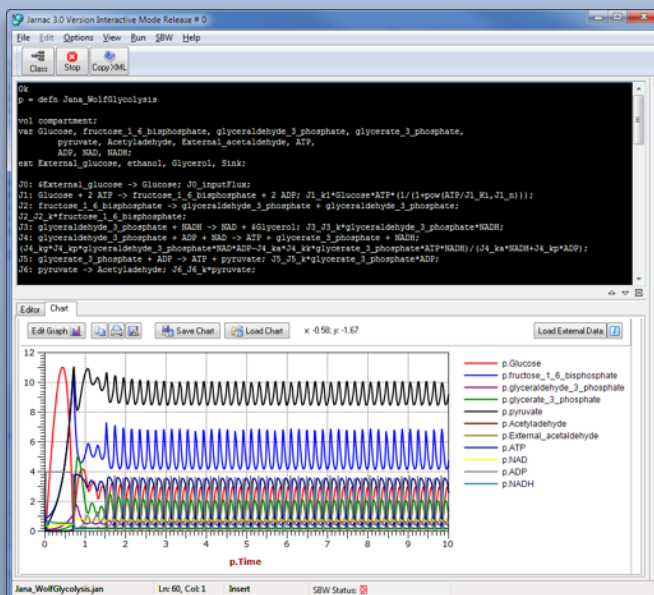
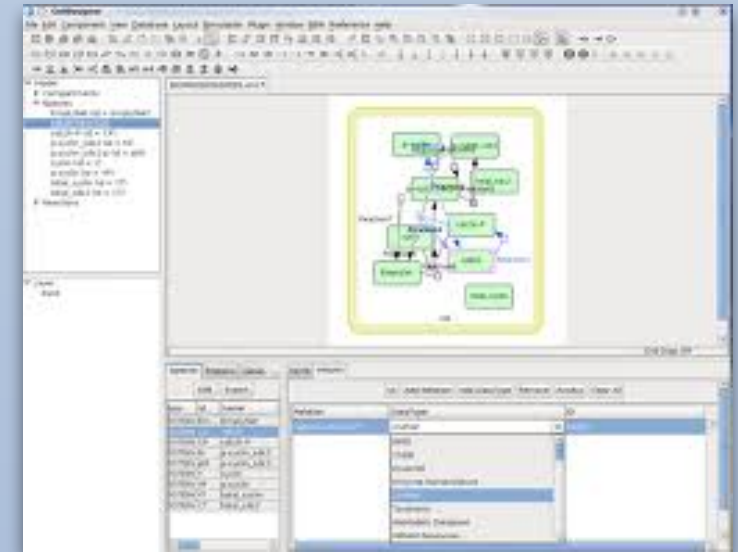


COPASI

Version 4.8 (Build 35)

The use of this software indicates the acceptance of the attached license. [View License](#)

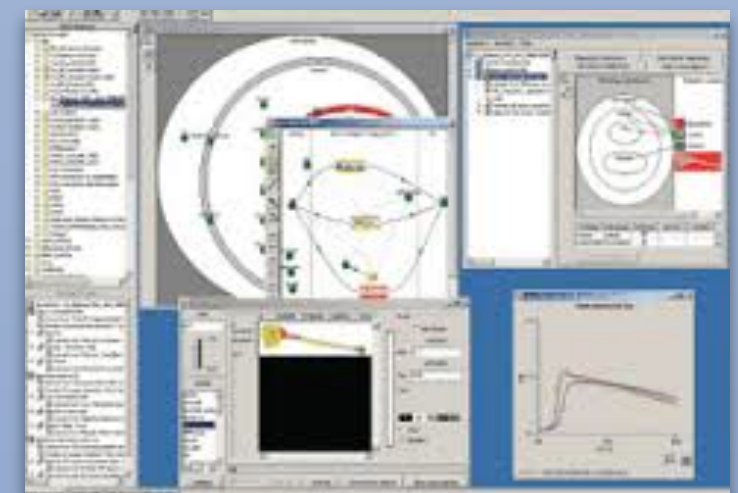
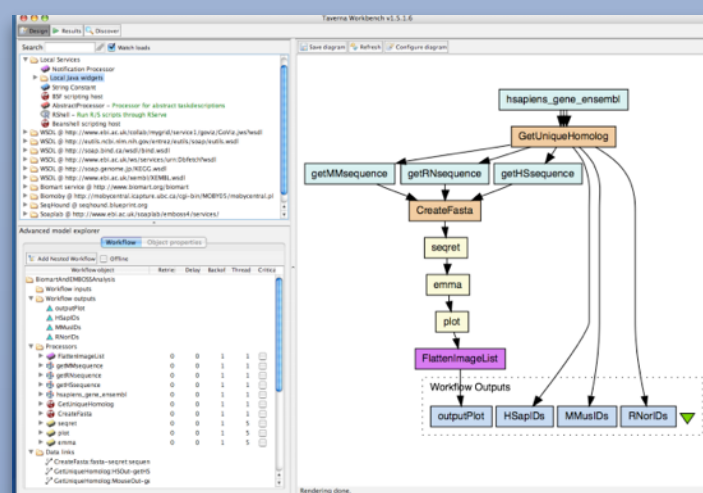
- Model
 - Biochemical
 - Compartments (0)
 - Species (0)
 - Reactions (0)
 - Global Quantities (0)
 - Events (0)
 - Parameter Overview
 - Mathematical Diagrams
- Tasks
 - Steady-State
 - Stoichiometric Analysis
 - Time Course
 - Metabolic Control Analysis
 - Lyapunov Exponents
 - Time Scale Separation Analysis
 - Parameter Scan
 - Optimization
 - Parameter Estimation
 - Sensitivities
 - Output Specifications
 - Functions (40)



SABIO Biochemical Reaction Kin

Welcome!

SABIO-RK is a curated database that contains information about biochemical reactions, their kinetic rate equations with parameters and experimental conditions.



SBML = Systems Biology Markup Language

Format for **representing** models of biological processes

- Data structures + principles + serialization to XML
- (Mostly) Declarative, not procedural—not a scripting language
- For **software** to read/write, **not humans**

(Mostly) **neutral** with respect to modeling framework

- E.g., ODE, stochastic systems, etc.

Does **not** store experimental data

Does **not** store simulation descriptions

Does define how annotations may be written within an SBML file

SBML is a file format based on XML

```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialAmount="0"      name="ES"/>
  <species compartment="cytosol" id="P"   initialAmount="0"      name="P"/>
  <species compartment="cytosol" id="S"   initialAmount="1e-20"   name="S"/>
  <species compartment="cytosol" id="E"   initialAmount="5e-21"   name="E"/>
</listOfSpecies>
<listOfReactions>
  <reaction id="veq">
    <listOfReactants>
      <speciesReference species="E"/>
      <speciesReference species="S"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES"/>
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>
          <times/>
          <ci>cytosol</ci>
          <apply>
            <minus/>
            <apply>
              <times/>
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
            <apply>
              <times/>
              <ci>koff</ci>
              <ci>ES</ci>
            </apply>
          </apply>
        </math>
      </kineticLaw>
    </reaction>
  </listOfReactions>
```


SBML is a file format based on XML

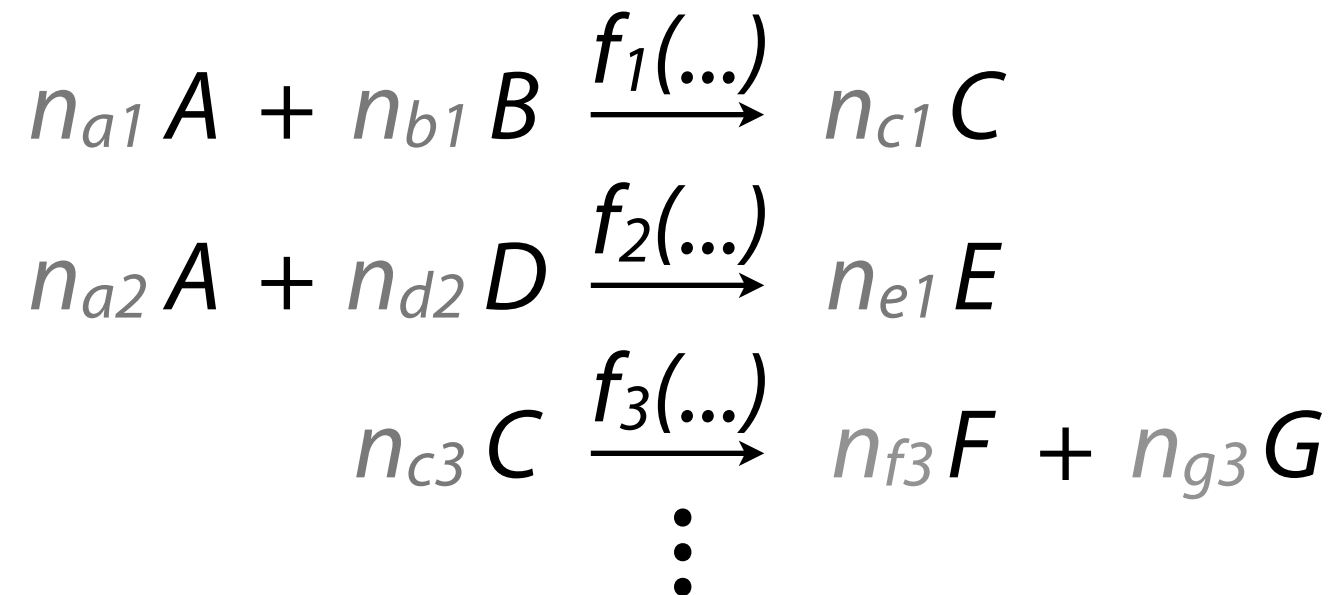
```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialAmount="0" name="ES"/>
  <species compartment="cytosol" id="P" initialAmount="0" name="P"/>
  <species compartment="cytosol" id="S" initialAmount="1e-20" name="S"/>
  <species compartment="cytosol" id="E" initialAmount="5e-21" name="E"/>
</listOfSpecies>
<listOfReactions>
  <reaction id="veq">
    <listOfReactants>
      <speciesReference species="E"/>
      <speciesReference species="S"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES"/>
    </listOfProducts>
```

Don't work with it directly! Let software do it.

```
<kineticLaw>
  <math xmlns="http://www.w3.org/1998/Math/ML">
    <apply>
      <times/>
      <ci>cytosol</ci>
      <apply>
        <minus/>
        <apply>
          <times/>
          <ci>kon</ci>
          <ci>E</ci>
          <ci>S</ci>
        </apply>
        <apply>
          <times/>
          <ci>koff</ci>
          <ci>ES</ci>
        </apply>
      </apply>
    </math>
  </kineticLaw>
```


The *process* is central

- Literally called “**reaction**” (not necessarily biochemical)
- Participants are pools of entities of the same kind (“**species**”)



- Species are located in containers (“**compartments**”)
 - Core SBML assumes well-mixed compartments (but see Level 3)

Models can further include:

- Explicit math expressions
- Discontinuous **events**
- Unit definitions
- **Annotations**
- Other constants & variables

Core SBML concepts are fairly simple

Example of model type

Typical ODE models (e.g., cell differentiation)

Conductance-based models (e.g., Hodgkin-Huxley)

*Typically do not use SBML “reaction” construct,
but instead use “rate rules” construct*

Neural models (e.g., spiking neurons)

Typically use “events” for discontinuous changes

Pharmacokinetic/dynamics models

“Species” are not required to be biochemical entities

Infectious diseases

Example model

BioModels Database model
#BIOMD0000000451

BioModels Database model
#BIOMD0000000020

BioModels Database model
#BIOMD0000000127

BioModels Database model
#BIOMD0000000234

BioModels Database model
#MODEL1008060001

List originally by Nicolas Le Novère

Core SBML constructs support many types of models

A community-driven global reconstruction of human metabolism

Ines Thiele^{1,2,37}, Neil Swainston^{3,4,37},
Maike K Aurich¹, Hulda Haraldsdottir¹,
Stefan G Thorleifsson¹, Rasmus Agreus¹,
Paul Dobson¹², Warwick B Dunn^{3,13},
Daniel Jameson^{3,4}, Neema Jamshidi⁷,
Nicolas Le Novère^{17,18}, Naglis Malys³,
Evgeni Selkov, Sr²³, Martin I Sigurdsson¹,
Anatoly Sorokin^{21,27}, Johannes H G M
Hans V Westerhoff^{3,28,33,34}, Daniel
Dunn^{3,13}

arXiv.org > q-bio > arXiv:1311.5696

Quantitative Biology > Molecular Networks

Striking a balance with Recon 2.1

Kieran Smallbone

(Submitted on 22 Nov 2013)

Recon 2 is a highly curated reconstruction of the human metabolic network. Whilst the network is state of the art, it has shortcomings, including the presence of unbalanced reactions involving generic metabolites. By replacing these generic molecules with each of their specific instances, we can ensure full elemental balancing, in turn allowing constraint-based analyses to be performed. The resultant model, called Recon 2.1, is an order of magnitude larger than the original.

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A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology

Markus J Herrgård^{1,19,20}, Neil Swainston^{2,3,20}, Paul Dobson^{3,4}, Warwick B Dunn^{3,4}, K Yalçın Arga⁵, Mikko Arvas⁶,
Nils Blüthgen^{3,7}, Simon Borger⁸, Roeland Costenoble⁹, Matthias Heinemann⁹, Michael Hucka¹⁰,
Niels de Vries¹¹, Peter D. Wolf¹², Peter J. Stange¹³, Michael J. Bennett¹⁴, Michael J. Bennett¹⁴,
Stephen Pettifer^{2,5}, Evangelos Simionidis^{5,7}, Kieran Smallbone^{3,15}, Irena Spasic^{4,5}, Dieter Weichart^{3,4},
Roger Brent¹⁴, David S Broomhead^{3,13}, Hans V Westerhoff^{3,7,15}, Betül Kirdar⁵, Maria Penttilä⁶, Edda Klipp⁸

SBML enables large, collaborative, model-building efforts

Accepted by dozens of journals *

100's of software tools available today

- 260+ listed in SBML Software Guide †

1000's of models available

- ... in public databases
- ... as supplementary data to papers
- ... in private repositories

* http://sbml.org/Documents/Publications_known_to_accept_submissions_in_SBML_format

† http://sbml.org/SBML_Software_Guide



Many models and software resources are available today

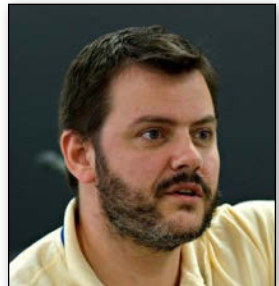
SBML Editors



Andreas Dräger



Sarah Keating
Coordinator



Nicolas Le Novère



Brett Olivier



Lucian Smith
Secretary



Dagmar Waltemath

Current

Past

Frank Bergmann

Hamid Bolouri

Andrew Finney

Stefan Hoops

Michael Hucka

Chris Myers

Sven Sahle

Herbert Sauro

James Schaff

Dagmar Waltemath

Darren Wilkinson

SBML Level 1	SBML Level 2	SBML Level 3
predefined math functions	user-defined functions	user-defined functions
text-string math notation	MathML subset	MathML subset
reserved namespaces for annotations	no reserved namespaces for annotations	no reserved namespaces for annotations
no controlled annotation scheme	RDF-based controlled annotation scheme	RDF-based controlled annotation scheme
no discrete events	discrete events	discrete events
default values defined	default values defined	no default values
monolithic	monolithic	modular & extensible

**Level 3 packages add constructs
on top of SBML Level 3 Core**



Level 3 package	What it supports	Status
Hierarchical model composition	Models composed from other models/parts	✓
Flux balance constraints	Constraint-based (a.k.a. steady-state) models	✓
Qualitative models	Petri net, Boolean, and similar model types	✓
Graph layout	Storing layouts of network diagrams	✓
Groups	Grouping elements for conceptual purposes	✓
Arrays	Arrays of components	⌚
Distributions	Statistical distributions of values	⌚
Multicomponent/state species	Rule-based descriptions of entities with features	⌚
Spatial	Nonhomogeneous spatial models	⌚
Graph rendering	Storing graphical symbols used in Layout diagrams	⌚
Dynamic structures	Creation/destruction of entities during simulation	⌚
Extended Math	Additional MathML constructs	⌚

Level 3 package	What it supports	Status
-----------------	------------------	--------

Hierarchical model composition	Models composed from other models/parts	✓
Flux balance constraints	Constraint-based (a.k.a. steady-state) models	✓
Qualitative models	Petri net, Boolean, and similar model types	✓
Graph layout	Storing layouts of network diagrams	✓
Groups	Grouping elements for conceptual purposes	✓
Arrays	Arrays of components	Implementations being tested
Distributions	Statistical distributions	Implementations being tested
Multicomponent/state species	Rule-based descriptions	Implementations being tested
Spatial	Nonhomogeneous systems	Implementations being tested
Graph rendering	Storing graphical systems	Implementations being tested
Dynamic structures	Creation/destruction of entities during simulation	🕒
Extended Math	Additional MathML constructs	🕒

SBML Level 3 package: Spatial Processes (“spatial”)

Main components:

- Coordinate systems
- Patches of spatial geometries, called **domains**
- Mapping of SBML compartments, species, & parameters to domains
- Definition of **molecular transport** mechanisms (advection, diffusion, boundary conditions)
- Mapping of molecular transport mechanisms to domains

Developed mostly by Jim Schaff & Anu Lakshminarayana (VCell), with recent input and involvement from Devin Sullivan (U. Pittsburgh), Lucian Smith and Frank Bergmann

- Beta implementation for libSBML available today

http://sbml.org/Documents/Specifications/SBML_Level_3/Packages/spatial

Draft implementations available in several tools already

SBML Level 3 Package Specification

Spatial Processes

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Farmington, Connecticut, US

Anu Lakshminarayana
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Lucian P. Smith
lpsmith@u.washington.edu
Computing and Mathematical Sciences
California Institute of Technology
Seattle, Washington, US

Version 1, Release 0.88 (Draft)

September 2014

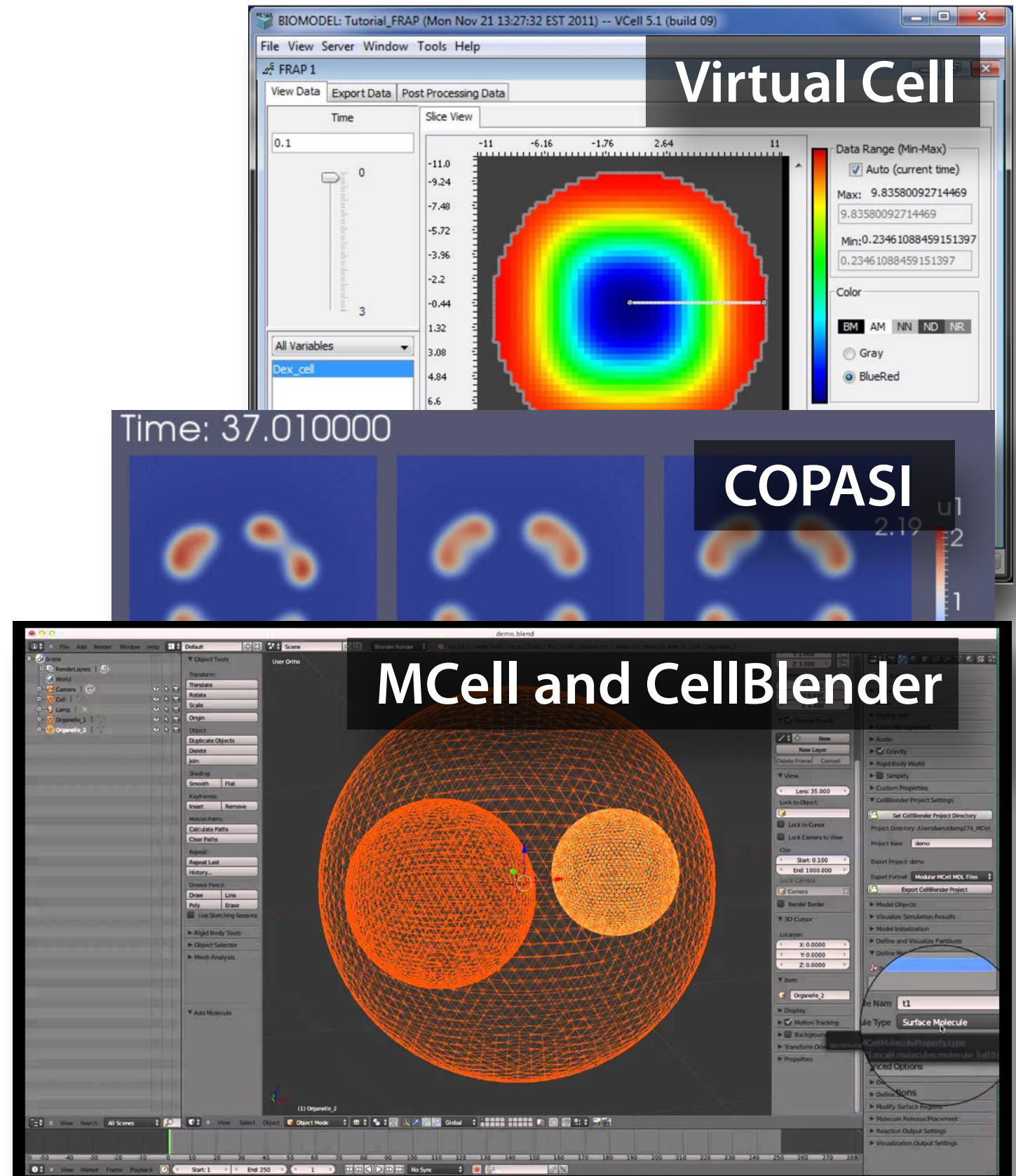
This is a draft specification for the SBML Level 3 package called "spatial". It is not a normative document. Please send feedback to the Package Working Group mailing list at sbml-spatial@lists.sourceforge.net.

The latest release, past releases, and other materials related to this specification are available at http://sbml.org/Documents/Specifications/SBML_Level_3/Packages/spatial

This release of the specification is available at
TBD



SBML Level 3 *Spatial* package
draft specification



The image displays three software interfaces used for simulating spatial processes:

- Virtual Cell:** A screenshot of the Virtual Cell software interface showing a 2D spatial simulation of a cell. The interface includes a menu bar (File, View, Server, Window, Tools, Help), a toolbar, and a main window displaying a color-coded spatial distribution of a variable. A "Data Range (Min-Max)" panel on the right shows values: Max: 9.83580092714469, Min: 0.23461088459151397. The "Color" panel shows "BlueRed" selected.
- COPASI:** A screenshot of the COPASI software interface showing a 2D spatial simulation of a cell. The interface includes a menu bar (File, Edit, View, Tools, Help), a toolbar, and a main window displaying a color-coded spatial distribution of a variable. A "Data Range (Min-Max)" panel on the right shows values: Max: 9.83580092714469, Min: 0.23461088459151397. The "Color" panel shows "BlueRed" selected.
- MCell and CellBlender:** A screenshot of the MCell and CellBlender software interface showing a 3D spatial simulation of a cell. The interface includes a menu bar (File, Edit, View, Tools, Help), a toolbar, and a main window displaying a 3D model of a cell. The "Properties" panel on the right shows "Surface Molecule" selected.

SBML & JSBML Team: Mike Hucka, Sarah Keating, Frank Bergmann, Lucian Smith, Andrew Finney, Herbert Sauro, Hamid Bolouri, Ben Bornstein, Maria Schilstra, Jo Matthews, Bruce Shapiro, Linda Taddeo, Akira Funahashi, Akiya Juraku, Ben Kovitz, Nicolas Rodriguez, Andreas Dräger, Alex Thomas

SBML Editors: Mike Hucka, Frank Bergmann, Andreas Dräger, Sarah Keating, Nicolas Le Novère, Chris Myers, Lucian Smith, Stefan Hoops, Brett Olivier, Sven Sahle, James Schaff, Dagmar Waltemath, Darren Wilkinson

SBML Package authors (so far): Duncan Berenguier, Frank Bergmann, Claudine Chaouiya, Andreas Dräger, Andrew Finney, Ralph Gauges, Colin Gillespie, Martin Ginkel, Tomás Helikar, Stefan Hoops, Sarah Keating, Anu Lakshminarayana, Nicolas Le Novère, Wolfram Liebermeister, Martin Meier-Schellersheim, Stuart Moodie, Ion Moraru, Chris Myers, Aurélien Naldi, Brett Olivier, Ursula Rost, Lucian Smith, Sven Sahle, James Schaff, Devin P. Sullivan, Denis Thieffry, Martijn P. van Iersel, Leandro Watanabe, Katja Wengler, Darren Wilkinson, Maciej Swat (EBI), Fengkai Zhang

Many people contributed to the development of SBML

Outline

- SBML (Systems Biology Markup Language)
- A sample of SBML software resources
- A sample of related resources and efforts
- COMBINE
- Acknowledgments

API libraries for supporting SBML

libSBML

- Written in portable C++
 - Linux, Mac, Windows
- APIs for C, C++, C#, Java, JavaScript, MATLAB, Octave, Perl, PHP, Python, R, Ruby
- Reads, writes, validates SBML
- Many other features: e.g., unit checking & conversion

JSBML

- Pure Java
- API very similar to libSBML, but more Java-ish
- Reads, writes, manipulates SBML
- Additional Java-relevant APIs such as listeners

Both are free, open-source under LGPL

<http://sbml.org/Software/libSBML>

<http://sbml.org/Software/JSBML>

The Online SBML Validator checks SBML files

Reports whether an SBML file conforms to the SBML specifications

- Helpful when 3rd-party software complains, or fails to load a file

Offers browser-based user interface *and* RESTful network API


Recent changes:

- Support for **draft SBML Level 3 packages**
 - Traditionally used libSBML for officially released packages
 - Now *also* uses separate **RELAX NG schemas** for *draft* packages
- Offers to send files to **other services** for additional analyses
- Moved to faster hardware

Software updates by Frank Bergmann; RNG schemas by Sarah Keating

sbml.org/Facilities/Validator/index.js

1 pkt 2 wos 3 website 5 pt 4 saf 6 jrns 7 lastmod 8 permalink 9 g Clip to OneNote E-M1 tools \$\$ >> +



The Systems Biology Markup Language

News Documents Downloads Forums Facilities Community Events About

Parent pages: [SBML.org](#) / [Facilities](#) / [Online SBML Validator](#)

This tests the syntax and internal consistency of an SBML file. Passing this validator does not *guarantee* correctness, but it's the best automated assessment available.

Use the form below to upload your SBML content. You can also access this service via a [network API](#). By using any part of this service, you agree to the terms of the [privacy notice](#).

[Sign in](#) or [Register](#) with this service.

You can retrieve the result of a previously-scheduled validation run by entering its key here:

 [Submit](#)
 (E.g., 7bf66904-7d67-49bb-9127-bee77a8f96ba)

[Upload File](#)
[Submit URL](#)
[Paste SBML](#)

[Browse](#)
[Clear Queue](#)


Select an SBML file located on your computer. The file can be uncompressed, or compressed using **zip**, **gzip** or **bzip2**.

[Validate now](#)
[Schedule for Validation](#)

<http://sbml.org/Facilities/Validator>

sbml.org/Facilities/Validator/index.js

1 pkt 2 wos 3 website 5 pt 4 saf 6 jrns 7 lastmod 8 permalink 9 g Clip to OneNote E-M1 tools \$\$ >> +



The Systems Biology Markup Language

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This tests the syntax and internal consistency of an SBML file. Passing this validator does not *guarantee* correctness, but it's the best automated assessment available.

Use the form below to upload your SBML content. You can also access this service via a [network API](#). By using any part of this service, you agree to the terms of the [privacy notice](#).

[Sign in](#) or [Register](#) with this service.

You can retrieve the result of a previously-scheduled validation run by entering its key here:

(E.g., 7bf66904-7d67-49bb-9127-bee77a8f96ba)

Upload File

Submit URL

Paste SBML

Select an SBML file located on your computer. The file can be uncompressed, or compressed using **zip**, **gzip** or **bzip2**.

Validation 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 103nn](#))
- ☒ 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**
- ☒ Perform additional checks for recommended good **modeling practices**
- ☒ Perform all other general SBML consistency checks ([SBML L2V4 rules 2nnnn](#); **highly recommended**)
- ☐ Ignore SBML Level 3 packages that are not officially finalized

This validator supports all specifications of SBML through **Level 3 Version 1 Core** (Release 1), as well as all **Level 3 packages** for which specifications exist. **Limitations:** (1) For SBML Level 3 packages that have not been finalized, validation is limited to XML syntax *only*; consequently, a model may have other errors in its use of Level 3 package constructs yet still pass this validator. (2) SBML `<annotation>` element content is always only checked for proper XML syntax: the *content* of annotations is *not* validated: consequently, a model may have errors in its annotations yet still pass

<http://sbml.org/Facilities/Validator>

MOCCASIN is a MATLAB converter

Model ODE Converter for Creating Automated SBML INteroperability

Converts certain basic forms of MATLAB ODE models into SBML form

Written in Python – does **not** need or rely on MATLAB

- Parses MATLAB into abstract syntax tree using custom parser
- Uses heuristics to resolve ambiguous constructs (arrays vs functions)
- **Infers reactions** from ODEs using algorithm by Fages, Gay & Soliman
 - “Inferring reaction systems from ordinary differential equations”, *Theoretical Computer Science*, 599:64–78, 2015
 - Uses BIOCHAM web service

Developed by Michael Hucka, Sarah Keating, Harold Gómez

NIH funding via Mount Sinai School of Medicine thanks to Stuart Sealfon

Simple example

```
% Various parameter settings. The specifics here are unimportant; this  
% is just an example of a real input file.
```

```
%
```

```
tspan   = [0 300];  
xinit   = [0; 0];  
a       = 0.01 * 60;  
b       = 0.0058 * 60;  
c       = 0.006 * 60;  
d       = 0.000192 * 60;
```

```
% A call to a MATLAB ODE solver
```

```
%
```

```
[t, x] = ode45(@f, tspan, xinit);
```

```
% A function that defines the ODEs of the model.
```

```
%
```

```
function dx = f(t, x)  
    dx = [a - b * x(1); c * x(1) - d * x(2)];  
end
```


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%
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Currently ignored

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Used for initial values

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SBML parameters & initial assignments

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```
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```

Currently ignored

Used for initial values

SBML parameters & initial assignments

Used to name the SBML species

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% A call to
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```
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Used to name the SBML species

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```

```
end
```

ODEs for the species – used to infer reaction equations

Upcoming for MOCCASIN

Provide way for users to identify—

- Compartments
- Preferred names for species/parameters/compartments
- Units

Interpret and support more MATLAB constructs

- E.g.: if/then/else, load, switch, reshape, linspace, etc.
- Deconstruct arrays so can convert to core SBML
 - Idea: translate to Numpy, then use Numpy functions to simplify

Support models split across multiple files

Implement the Fages et al. algorithm in MOCCASIN itself

<http://sbml.org/Software/MOCCASIN>

Discussion groups, Twitter feed, G+, RSS – see SBML.org

Main Page – SBML.caltech.edu

sbml.org/Main_Page

Reader

SBML.org

The Systems Biology Markup Language

News Documents Downloads Forums Facilities Community Events About

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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 **continues to be evolved and expanded** by an international community.

For the curious
What *is* SBML? Read our [introduction](#), then perhaps browse the [mailing lists](#), the [FAQ](#), and the [SBML Level 3 package activities](#) to glimpse what's happening with SBML today.

For modelers
Looking for software that supports SBML? Our [software guide](#) lists over **250** systems. Are you instead looking for models? Visit [BioModels Database](#), where you can find hundreds!

For software developers
Want to support SBML in your software? Read our [intro](#) and then the [specifications](#) to understand SBML in depth, then check our [libraries](#), [test resources](#), and also [3rd-party software](#).

No matter how you use SBML, we invite you to sign up for news updates either through our [RSS feed](#), our [Twitter feed](#), or one of the [mailing lists](#), and get involved with [community efforts](#) to help improve 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.

SBML News

libSBML 5.10.2 released!
(17 Jul.'14) The new version fixes many bugs and updates SBML L3 package support.

COMBINE 2014
(27 Apr.'14) Registration for the August event in Los Angeles is now open.

libSBML 5.10.0
(10 Apr.'14) The new version of [libSBML](#) improves math handling, L3 packages, and more.

[Older news ...](#)

Community News

Tellerium 1.1.3 released
(24 Jul.'14) New features and updated libraries in this Python-based modeling environment.

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(22 Jul.'14) New features and bug fixes in the pure Java simulation library.

libRoadRunner 1.2.3 released
(22 Jul.'14) Updates and bug fixes for this fast SBML simulation library.

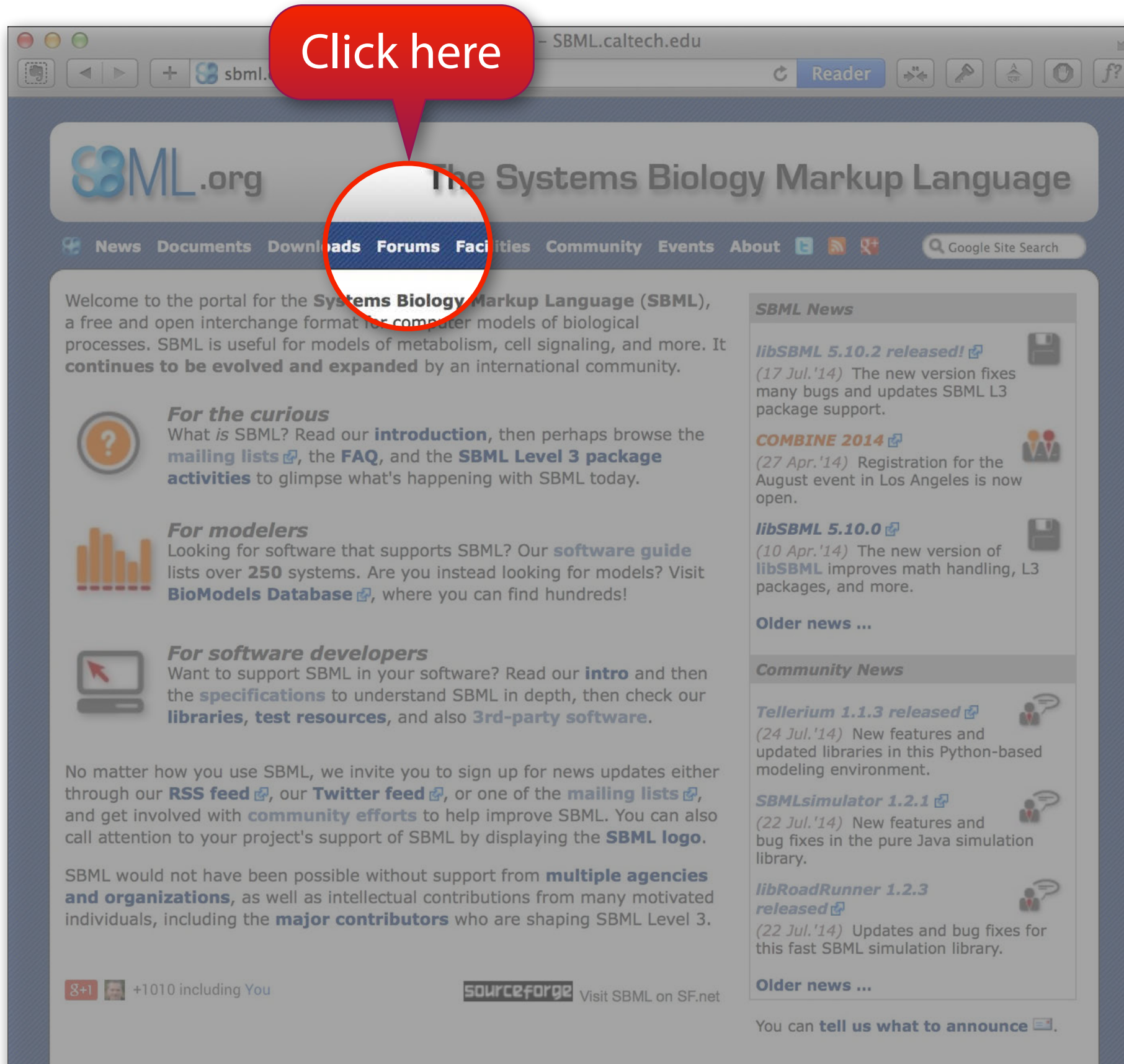
[Older news ...](#)

You can [tell us what to announce](#).

g+1 +1010 including You

sourceforge Visit SBML on SF.net

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SBML.org The Systems Biology Markup Language

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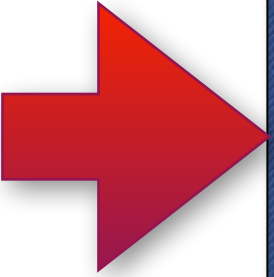
Older news ...

You can **tell us what to announce**.

g+1 +1010 including You

sourceforge Visit SBML on SF.net

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Parent pages: [SBML.org](#)

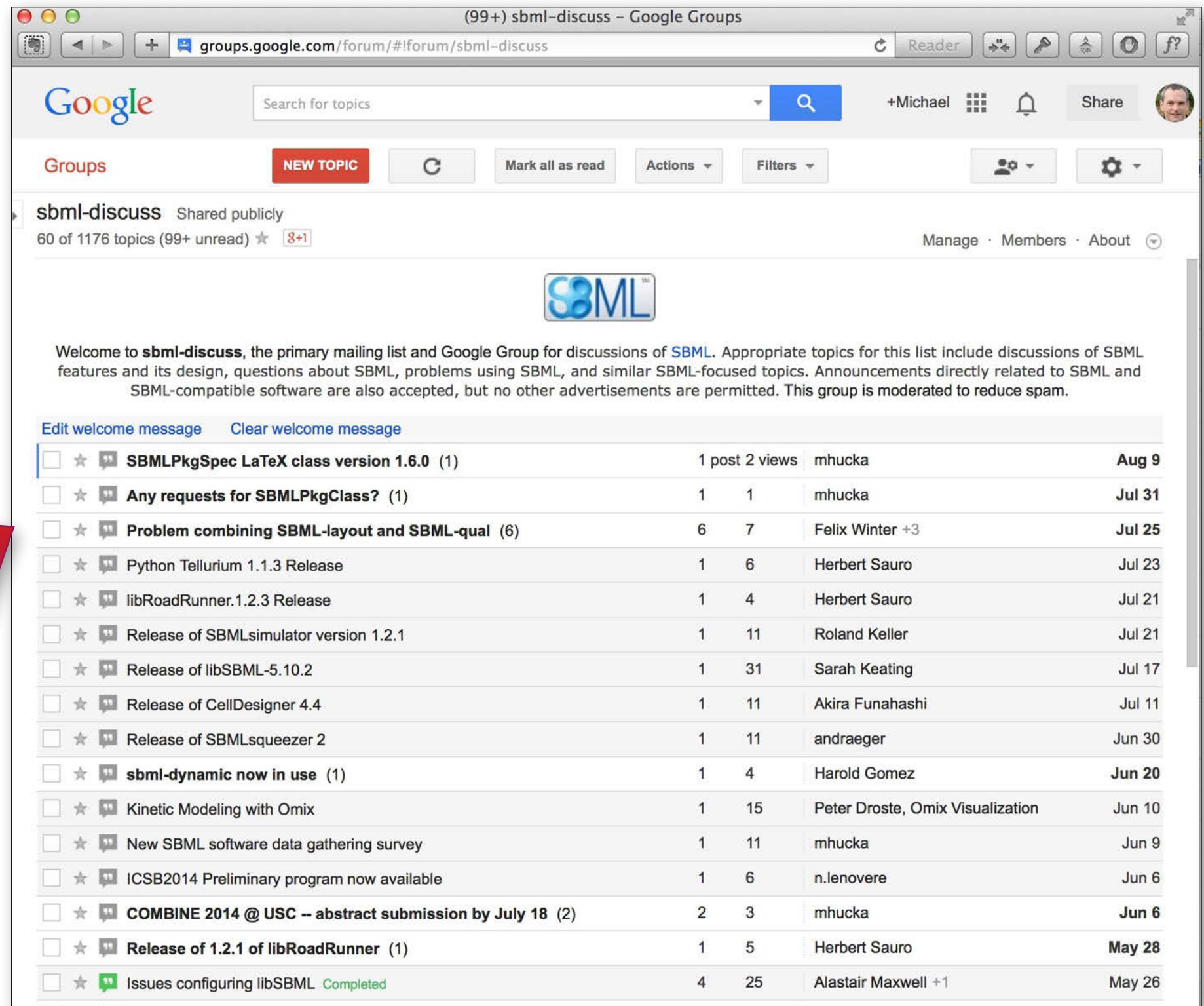
Forums

Discussions about SBML and related topics takes place over several mailing lists implemented as Google Groups. Please see the table below for more information about the different lists/groups available. **Note:** clicking on the links will take you away from SBML.org and to pages at Google.com. SBML.org is not affiliated with Google in any way.

Google Group & archive	Purpose of this group/ mailing list	RSS feeds info page
sbml-announce	Low-volume, broadcast-only list for announcements of importance to the SBML community, such as new releases of SBML specifications and upcoming events.	RSS feeds info
sbml-discuss	Main list for SBML development and community interaction. Announcements related to SBML-compatible software are accepted, but no other advertisements are permitted.	RSS feeds info
sbml-interoperability	Discussions of use and interoperability of all software that supports SBML. LibSBML questions and other topics are perfectly acceptable here.	RSS feeds info
libsbml-development	Technical discussions specifically about libSBML and its development, including requests for new features and questions about its operation.	RSS feeds info
jsbml-development	Technical discussions specifically about JSBML (a pure Java SBML library) and its development.	RSS feeds info

The various SBML mailing lists were previously implemented as Mailman lists. In February 2014, they were recreated as Google Groups.

Discussion groups, Twitter feed, G+, RSS – see SBML.org



(99+) sbml-discuss – Google Groups

groups.google.com/forum/#!forum/sbml-discuss


Google Search for topics

+Michael

Share

















Groups NEW TOPIC Mark all as read Actions Filters

sbml-discuss Shared publicly
60 of 1176 topics (99+ unread) 8+1 Manage · Members · About



Welcome to **sbml-discuss**, the primary mailing list and Google Group for discussions of **SBML**. Appropriate topics for this list include discussions of SBML features and its design, questions about SBML, problems using SBML, and similar SBML-focused topics. Announcements directly related to SBML and SBML-compatible software are also accepted, but no other advertisements are permitted. This group is moderated to reduce spam.

[Edit welcome message](#) [Clear welcome message](#)

<input type="checkbox"/>	★		SBMLPkgSpec LaTeX class version 1.6.0 (1)	1 post 2 views	mhucka	Aug 9
<input type="checkbox"/>	★		Any requests for SBMLPkgClass? (1)	1 1	mhucka	Jul 31
<input type="checkbox"/>	★		Problem combining SBML-layout and SBML-qual (6)	6 7	Felix Winter +3	Jul 25
<input type="checkbox"/>	★		Python Tellurium 1.1.3 Release	1 6	Herbert Sauro	Jul 23
<input type="checkbox"/>	★		libRoadRunner.1.2.3 Release	1 4	Herbert Sauro	Jul 21
<input type="checkbox"/>	★		Release of SBMLsimulator version 1.2.1	1 11	Roland Keller	Jul 21
<input type="checkbox"/>	★		Release of libSBML-5.10.2	1 31	Sarah Keating	Jul 17
<input type="checkbox"/>	★		Release of CellDesigner 4.4	1 11	Akira Funahashi	Jul 11
<input type="checkbox"/>	★		Release of SBMLsqueezer 2	1 11	andraeger	Jun 30
<input type="checkbox"/>	★		sbml-dynamic now in use (1)	1 4	Harold Gomez	Jun 20
<input type="checkbox"/>	★		Kinetic Modeling with Omix	1 15	Peter Droste, Omix Visualization	Jun 10
<input type="checkbox"/>	★		New SBML software data gathering survey	1 11	mhucka	Jun 9
<input type="checkbox"/>	★		ICSB2014 Preliminary program now available	1 6	n.lenovere	Jun 6
<input type="checkbox"/>	★		COMBINE 2014 @ USC -- abstract submission by July 18 (2)	2 3	mhucka	Jun 6
<input type="checkbox"/>	★		Release of 1.2.1 of libRoadRunner (1)	1 5	Herbert Sauro	May 28
<input type="checkbox"/>	★		Issues configuring libSBML Completed	4 25	Alastair Maxwell +1	May 26

Outline

- SBML (Systems Biology Markup Language)
- A sample of SBML software resources
- A sample of related resources and efforts
- COMBINE
- Acknowledgments

BioModels Database

BioModels Database

Stores & serves quantitative models of biological interest

- **Free**, public resource
- Models must be described in **peer-reviewed publication(s)**

Hundreds of models are **curated by hand**

Imports & exports models in several formats

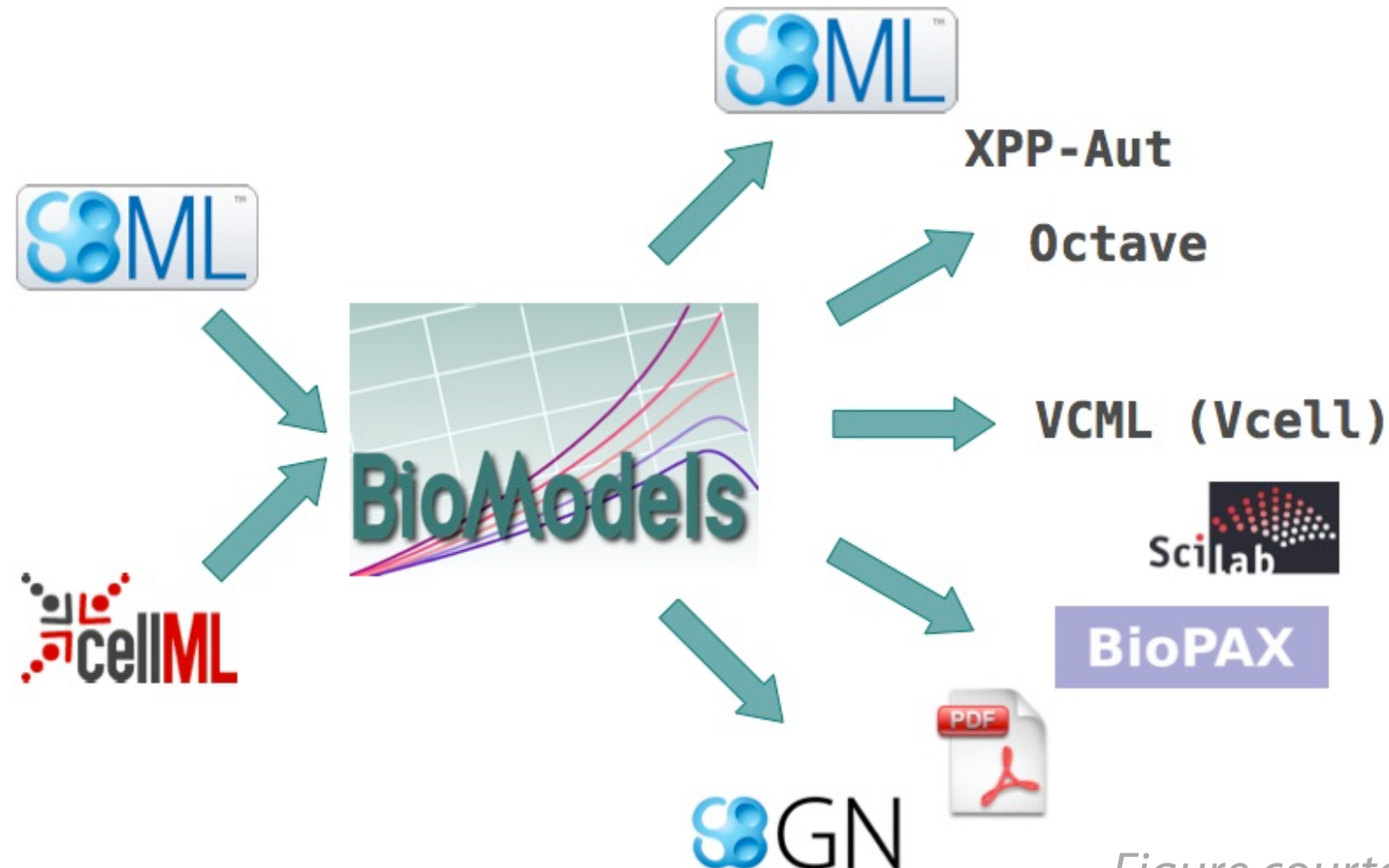


Figure courtesy of Camille Laibe

BioModels Database models are annotated by humans

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BIOMD0000000030 - Markevich2004_MAPK_AllRandomElementary

[SBML formats](#)[Other formats](#)[Actions](#)[Submit Model Comment/Bug](#)[Model](#)[Overview](#)[Math](#)[Physical entities](#)[Parameters](#)

Reactions (20)

☒ binding MAPKK on Tyr site of MAPK
$$[\text{MAPK}] + [\text{MAPKK}] \leftrightarrow [\text{MAPK_MAPKK_Y}];$$
Math:
$$\text{cell} \times (k_1 \times M \times \text{MAPKK} - (k_{-1} \times M_{\text{MAPKK_Y}})) \quad (\text{Detail: } \img alt="document icon" data-bbox="838 545 858 565"/>$$
Annotations:

set #1


bqbiol:isVersionOf

[Gene Ontology mitogen-activated protein kinase kinase binding](#)
[Gene Ontology mitogen-activated protein kinase binding](#)


bqbiol:isHomologTo

[Reactome REACT_1780](#)
[Reactome REACT_495](#)☒ tyr phosphorylation of MAPK
$$[\text{MAPK_MAPKK_Y}] \rightarrow [\text{MAPK-PY}] + [\text{MAPKK}];$$
☒ binding of MAPKK on MAPK-PY
$$[\text{MAPK-PY}] + [\text{MAPKK}] \leftrightarrow [\text{MAPK-PY_MAPKK}];$$
☒ thr phosphorylation of MAPK
$$[\text{MAPK-PY_MAPKK}] \rightarrow [\text{MAPK-PP}] + [\text{MAPKK}];$$
☒ binding of MAPKK on Thr site of MAPK
$$[\text{MAPK}] + [\text{MAPKK}] \leftrightarrow [\text{MAPK_MAPKK_T}];$$

Visit <http://biomodels.net> and submit your models!

EMBL-EBI 

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BioModels Database

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Advanced

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BioModels Database is a repository of computational models of biological processes. Models described from literature are manually curated and enriched with cross-references. All models are provided in the Public Domain. More information about BioModels Database can be found in the [FAQ](#).

Models published in the literature

[Browse](#)



[Manually curated](#)
(613 models)



[Non curated](#)
(903 models)

Alternative access



[Gene
Ontology
classification](#)



[Gene
Ontology tree](#)



[Advanced
search](#)

Models automatically generated from pathway resources (Path2Models)

[Browse](#)



[Metabolic](#) (112,898 models)

[Non-metabolic](#) (27,531 models)

[Whole genome metabolism](#) (2,641 models)

Alternative access



[Taxonomy](#)



[Dedicated search](#)

[Contact us](#) | [Main instance at EMBL-EBI, UK](#) | [Mirror at Caltech, USA](#) | [Model archives](#) | [Web Services](#)

[Acknowledgements:](#)



Model of the month

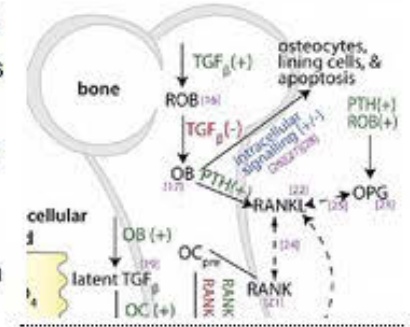
July, 2016

A milestone QSP model on calcium homeostasis and bone remodelling.

This model by Peterson and Riggs., (2010)

analyses the effects of parathyroid hormone on calcium and bone

systems. The model examines hypoparathyroidism and has been used to further the clinical application of recombinant PTH administration.



[Access this model of the month.](#)

News

1 July 2016 [New Models in BioModels](#)

BioModels now provides 1516 literature-based models.

Live now - an [interactive map](#) of molecular processes described by mechanistic models of neurodegenerative diseases.

10 May 2016 [30th BioModels Release](#)

We are extremely happy to announce the 30th release of BioModels, which now provides access to 1483 literature-based models and 143,070 models automatically generated from pathway resources, with additional and updated features.

04 May 2016 [BBSRC BBR Grant](#)

The proposal we submitted to BBSRC (BBR fund) for

SED-ML


```

<sbml xmlns="http://www.sbml.org/sbml/level2/version4" xmlns:rdf="http://www.w3.org/
biomodels.net/biology-qualifiers/" xmlns:bqmodel="http://biomodels.net/model-qualifi
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  </compartment>
</listOfCompartments>
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  <species metaid="_462448" id="beta" name="beta" compartment="cell" initialConcen
  <species metaid="_462451" id="gamma" name="gamma" compartment="cell" initialConc
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  <reaction metaid="_462452" id="r1" reversible="false" sboTerm="SBO:0000176">
    <listOfProducts>
      <speciesReference species="alpha"/>
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> v_Km1 </ci>
      </math>
      <listOfParameters>
        <parameter metaid="_462462" id="v_Km1" value="0.45" units="per_sec" sboTer
      </listOfParameters>
    </kineticLaw>
  </reaction>
  <reaction metaid="_462455" id="r2" reversible="false" sboTerm="SBO:0000176">
    <listOfReactants>
      <speciesReference species="alpha"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="beta" stoichiometry="50"/>
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>

```

BIOMD0000000319 in BioModels Database

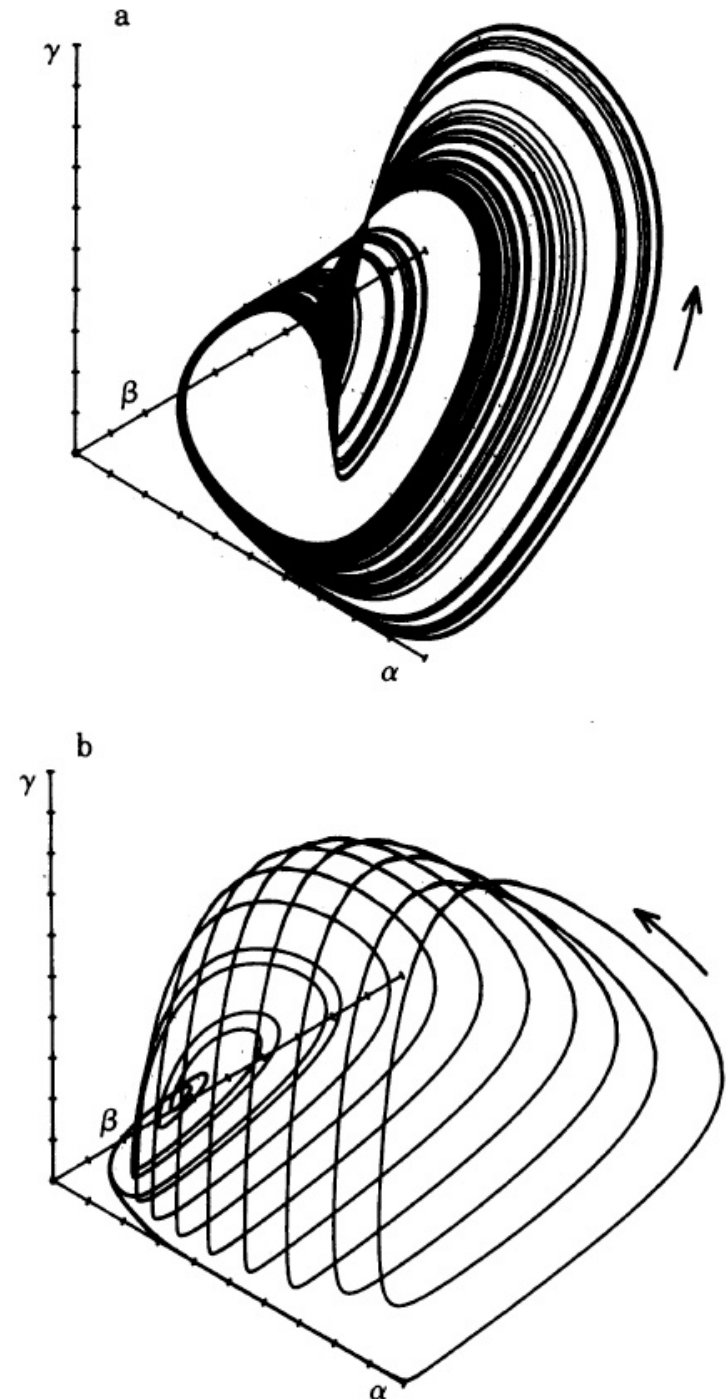
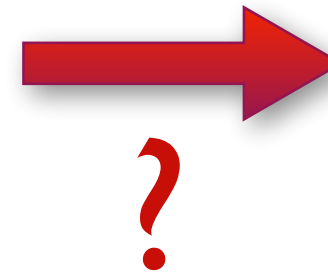


FIG. 4. Trajectories in the phase space (α , β , γ) associated with chaos (a) and with complex periodic behavior (b). The curves correspond to the substrate evolution depicted in Fig. 2 c and d, respectively, and have been obtained by integration of the kinetic equations from $t = 0-5,000$ sec. The ranges of variation of α , β , and γ in a are $\alpha = 28.44-50.6$, $\beta = 50.05-351.1$, and $\gamma = 0.05-2.28$ and in b are $\alpha = 28.18-190.5$, $\beta = 0.14-604.0$, and $\gamma = 0.00014-8.8$.

Another problem: software can't read figure legends

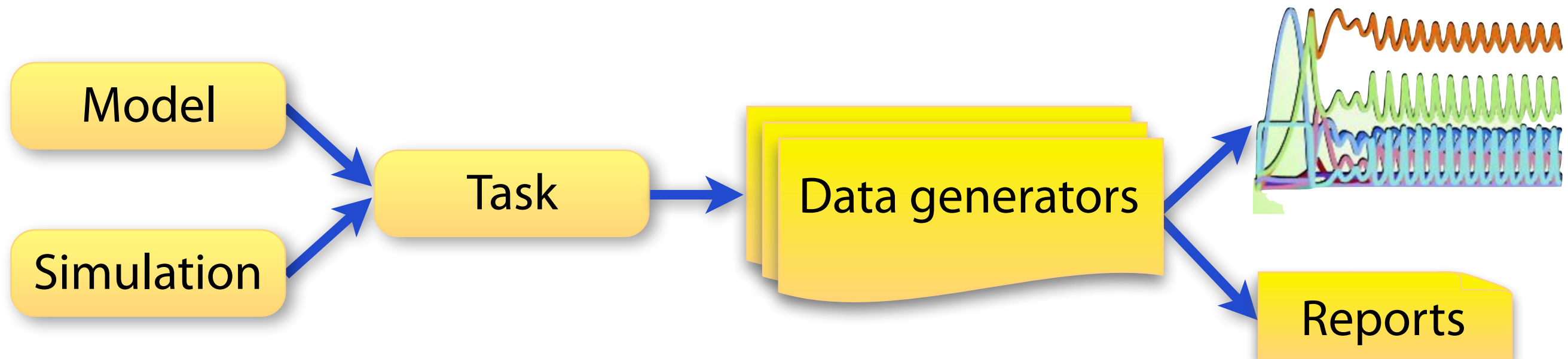
SED-ML = Simulation Experiment Description ML

Application-independent format

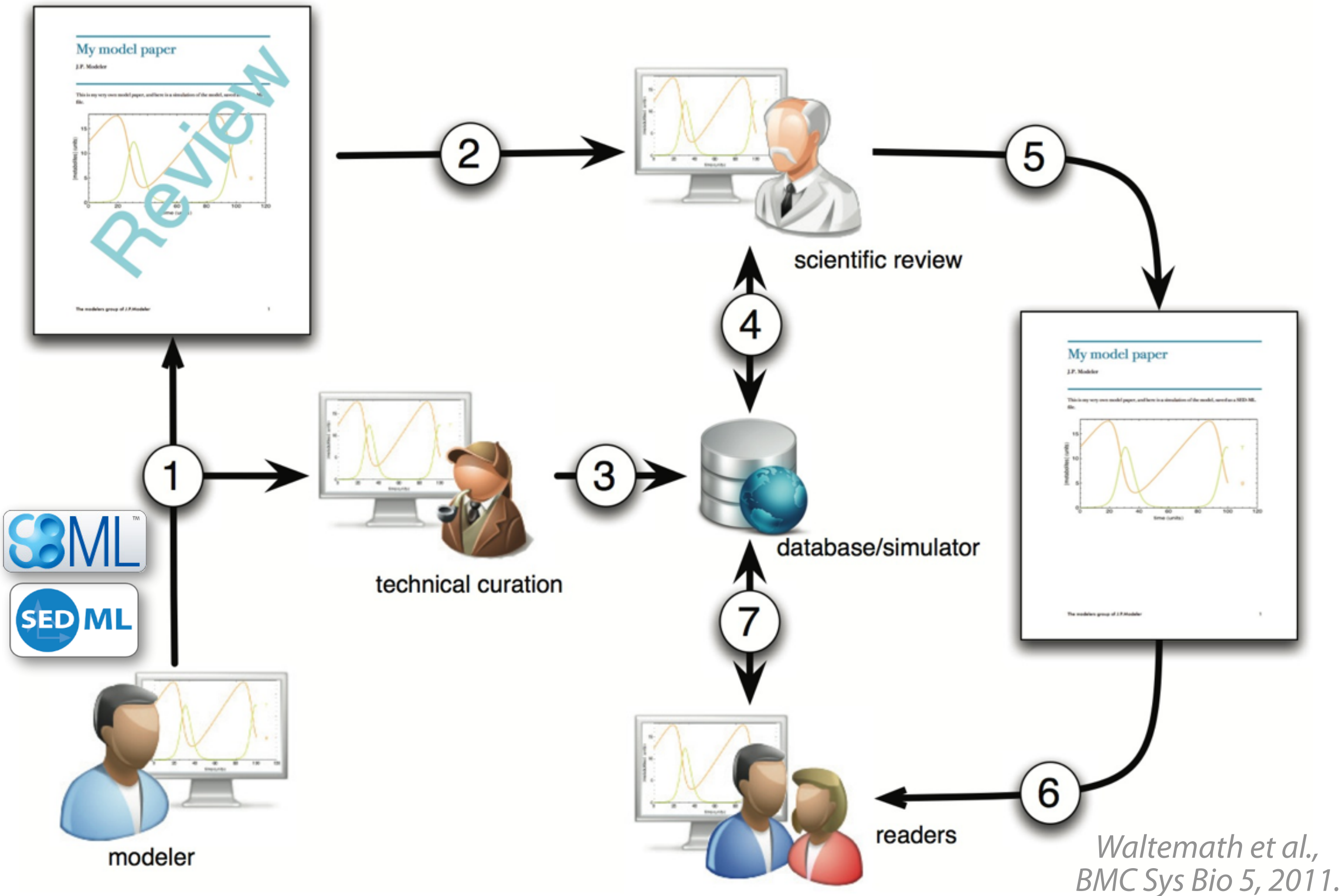
- Captures procedures, algorithms, parameter values

Can be used for

- Simulation experiments encoding parametrizations & perturbations
- Simulations using more than one model and/or method
- Data manipulations to produce plot(s)



<http://sedml.org>



SED-ML improves reproducibility

COMBINE Archive

The problem

Multiple files usually comprise a single simulation experiment

- Model(s) file(s), possibly in multiple formats
- Simulation set-up (e.g., in SED-ML format)
- Parameter settings data files
- Diagrams (e.g., in SBGN format)
- Other files...

All the files need to be communicated together

- Opportunity to lose or mix up files during exchange & sharing

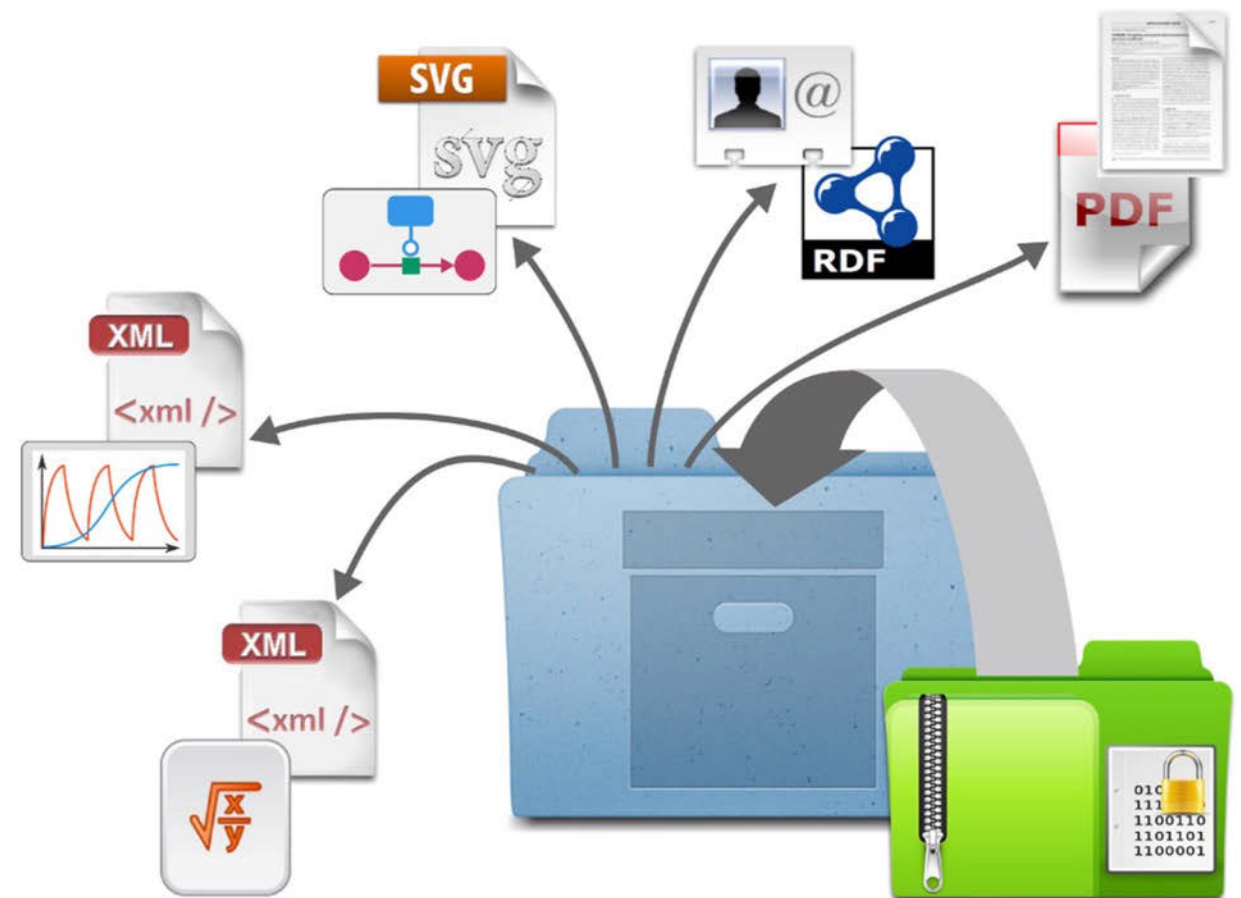
Open Modeling EXchange format (OMEX)

COMBINE Archive format = single file that supports exchange of all information necessary for any modeling and simulation experiment

- Not SBML-specific at all
- Not programming-language specific
- Not domain specific

OMEX = file format for COMBINE Archive

- ZIP file containing manifest file (in XML form) + other files
- Use of ZIP leverages many existing programming libraries



<http://co.mbine.org/documents/archive>

Outline

- SBML (Systems Biology Markup Language)
- A sample of SBML software resources
- A sample of related resources and efforts
- **COMBINE**
- Acknowledgments

Motivations for the creation of COMBINE

Realizations about the state of affairs in late-2000's

- Many efforts overlapped, but lacked coordination
- Invented their own processes from scratch
- Many separate meetings meant more travel for many people
- Limited and fragile funding didn't support solid base

COMBINE = Computational Modeling in Biology Network

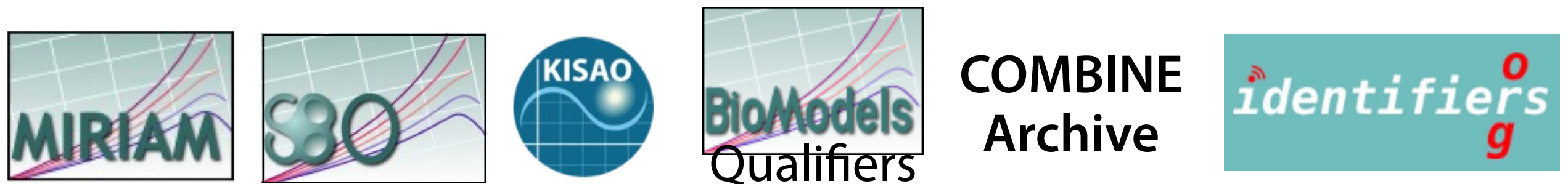
- Coordinate meetings
- Coordinate standards development
- Develop common procedures & tools
- Provide a recognized voice



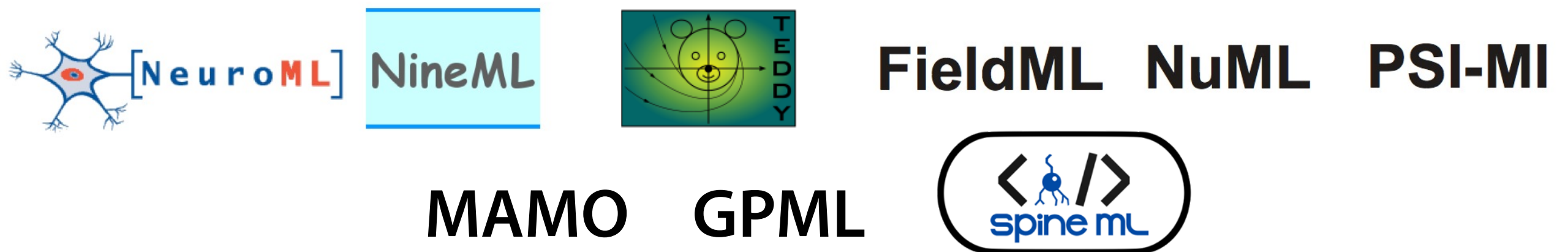
COMBINE Standards



Associated Standardization Efforts



Related Standardization Efforts



Standardization efforts represented in COMBINE today

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Software described

National Institutes of Health (USA):

- **Core SBML resources:** NIGMS R01GM070923
- **MOCCASIN** initial funding: Modeling Immunity for Biodefense contract HHSN266200500021C (PI: Stuart Sealfon)

Google Summer of Code

Overall SBML support

NIH NIGMS (USA)

BBSRC (UK)

Google Summer of Code (USA)

Virtual Liver Network (BMBF, Germany)

MedSys project Spher4Sys (BMBF, Germany)

ELIXIR (EU)

Keio University (Japan)

Drug Disease Model Resources (EU-EFPIA)

National Science Foundation (USA)

Japanese Ministry of Agriculture

Japanese Ministry of Educ., Culture, Sports, Science & Tech.

DARPA IPTO Bio-SPICE Bio-Computation Program (USA)

Air Force Office of Scientific Research (USA)

STRI, University of Hertfordshire (UK)

Molecular Sciences Institute (USA)

JST ERATO Kitano Symbiotic Systems Project (Japan)

JST ERATO-SORST Program (Japan)

International Joint Research Program of NEDO (Japan)

Institutional support

California Institute of Technology (USA)

Babraham Institute (UK)

EMBL-EBI (UK)

University of Tuebingen (Germany)

University of Heidelberg (Germany)

Funding and support



Attendees of COMBINE 2014, Los Angeles, California, USA

Huge thanks to everyone in the COMBINE community



Attendees of COMBINE 2015, Salt Lake City

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