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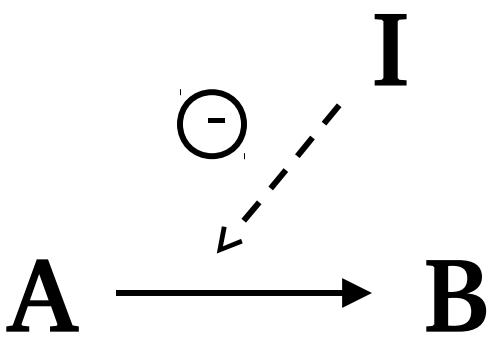
An introduction to modeling and simulation with COPASI

Pedro Mendes

http://www.comp-sys-bio.org

Reactions and kinetic functions



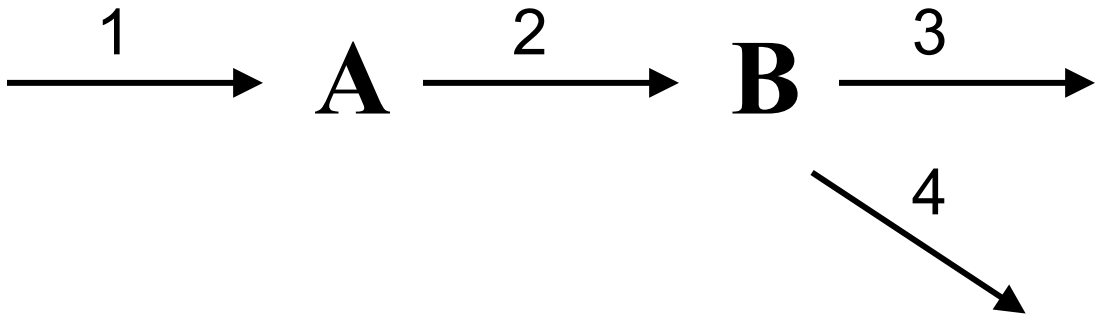
$$v = f\left(A, B, I; V, K_{ms}, K_{mp}, K_i\right)$$

$$v = \frac{\frac{A}{K_{ms}} \cdot V}{1 + \frac{A}{K_{ms}} + \frac{B}{K_{mp}} + \frac{I}{K_i}}$$

The rate of each reaction is a function of:

- concentration of the substrates
- concentration of the products
- concentration of the modifiers
- a set of constants

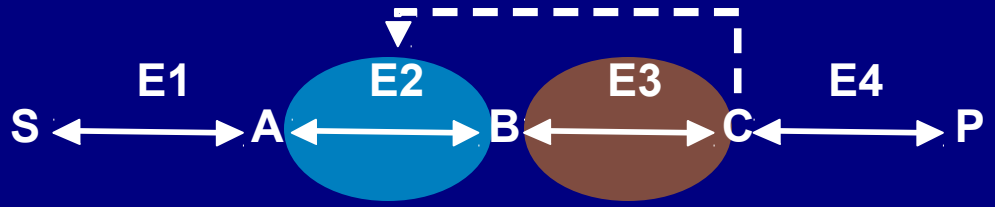
Species concentrations are represented by ODEs



$$\frac{dA}{dt} = v_1 - v_2 \qquad \frac{dB}{dt} = v_2 - v_3 - v_4$$

The rate of change of a species concentration is the algebraic sum of the rates producing it and the ones consuming it

An example

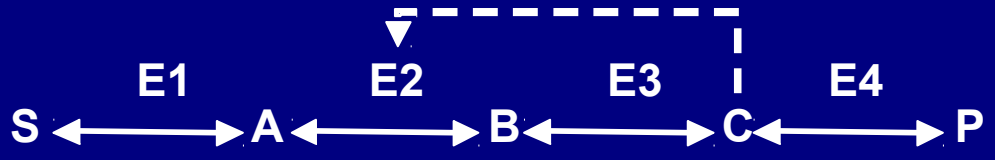


$$\frac{dA}{dt} = \frac{V_1^f \frac{S}{K_{1S}} - V_1^r \frac{A}{K_{1A}}}{1 + \frac{S}{K_{1S}} + \frac{A}{K_{1A}}} - \frac{\left(V_2^f \frac{A}{K_{2A}}\right)\left(1 - \frac{B}{S \cdot K_{2eq}}\right)\left(\frac{A}{K_{2A}} + \frac{B}{K_{2B}}\right)^{h-1}}{\left(\frac{A}{K_{2A}} + \frac{B}{K_{2B}}\right)^{h} + \frac{1 + \left(\frac{C}{K_{2C}}\right)^{h}}{1 + \alpha\left(\frac{C}{K_{2C}}\right)^{h}}}$$

$$\frac{dB}{dt} = \frac{\left(V_2^f \frac{A}{K_{2A}}\right)\left(1 - \frac{B}{S \cdot K_{2eq}}\right)\left(\frac{A}{K_{2A}} + \frac{B}{K_{2B}}\right)^{h-1}}{\left(\frac{A}{K_{2A}} + \frac{B}{K_{2B}}\right)^{h} + \frac{1 + \left(\frac{C}{K_{2C}}\right)^{h}}{1 + \alpha\left(\frac{C}{K_{2C}}\right)^{h}}} - \frac{V_3^f \frac{B}{K_{3B}} - V_3^r \frac{C}{K_{3C}}}{1 + \frac{B}{K_{3B}} + \frac{C}{K_{3C}}}$$

$$\frac{dC}{dt} = \frac{V_3^f \frac{B}{K_{3B}} - V_3^r \frac{C}{K_{3C}}}{1 + \frac{B}{K_{3B}} + \frac{C}{K_{3C}}} - \frac{V_4^f \frac{C}{K_{4C}} - V_4^r \frac{P}{K_{4P}}}{1 + \frac{C}{K_{4C}} + \frac{P}{K_{4P}}}$$

An example



$$\begin{bmatrix} \dot{A} \\ \dot{B} \\ \dot{C} \end{bmatrix} = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \dfrac{V_1^f \dfrac{S}{K_{1S}} - V_1^r \dfrac{A}{K_{1A}}}{1 + \dfrac{S}{K_{1S}} + \dfrac{A}{K_{1A}}} \\ \dfrac{\left(V_2^f \dfrac{A}{K_{2A}}\right)\left(1 - \dfrac{B}{S \cdot K_{2eq}}\right)\left(\dfrac{A}{K_{2A}} + \dfrac{B}{K_{2B}}\right)^{h-1}}{\left(\dfrac{A}{K_{2A}} + \dfrac{B}{K_{2B}}\right)^{h} + \dfrac{1 + \left(\dfrac{C}{K_{2C}}\right)^{h}}{1 + \alpha\left(\dfrac{C}{K_{2C}}\right)^{h}}} \\ \dfrac{V_3^f \dfrac{B}{K_{3B}} - V_3^r \dfrac{C}{K_{3C}}}{1 + \dfrac{B}{K_{3B}} + \dfrac{C}{K_{3C}}} \\ \dfrac{V_4^f \dfrac{C}{K_{4C}} - V_4^r \dfrac{P}{K_{4P}}}{1 + \dfrac{C}{K_{4C}} + \dfrac{P}{K_{4P}}} \end{bmatrix}$$

$$\dot{\mathbf{x}} = \mathbf{N} \cdot \mathbf{v}(\mathbf{x}, \mathbf{k})$$

COPASI simulation methods

COPASI allows simulations based on:

- ODEs
  - Built directly from reaction kinetics
  - Arbitrary ODEs
  - Compartment volumes can be variables (ODE)
- Stochastic kinetics based on Gillespie's SSA
- Models can have:
  - Algebraic assignments
  - Discrete events

Parameters and variables

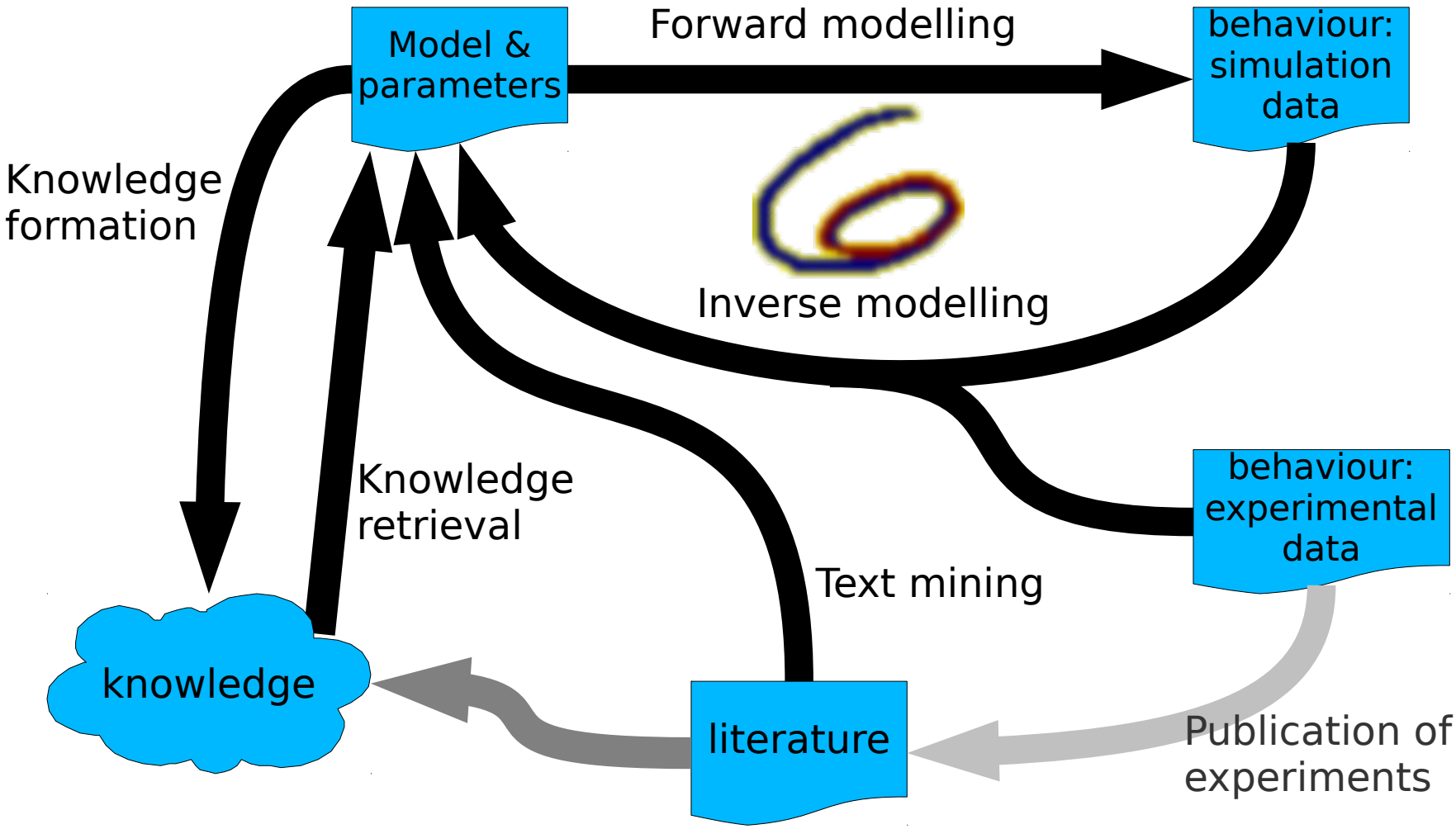
- **Parameters** are items that are independent of the system, *i.e.* are set by outside agents (*causes*).
- **Variables** are items of the system whose values are determined exclusively by the parameters (*effects*).
- **State** of the system is the set of all variables.
- One set of parameters determines unambiguously the variables.
- One set of variables can be caused by many parameter sets.

The central modelling question

- Given a model of a system: **how do the parameters affect the state of the system?**

- Answers explain:
  - which parameters have highest effect on desired outcomes (eg drug design)
  - what properties of the model are more fragile or robust
  - which parameters need accurate estimates (experimental design)

Modelling cycle



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Systems biology

COPASI—a COmplex PAthway SImulator

Stefan Hoops[1,†], Sven Sahle[2,†], Ralph Gauges[2], Christine Lee[1], Jürgen Pahle[2], Natalia Simus[2], Mudita Singhal[1], Liang Xu[1], Pedro Mendes[1,*] and Ursula Kummer[2]

[1]Virginia Bioinformatics Institute, Virginia Tech, Washington St. 0477, Blacksburg, VA 24061, USA and [2]Bioinformatics and Computational Biochemistry, EML Research, Schloss-Wolfsbrunnenweg 33, D-69118 Heidelberg, Germany

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ABSTRACT

Motivation: Simulation and modeling is becoming a standard approach to understand complex biochemical processes. Therefore, there is a big need for software tools that allow access to diverse simulation and modeling methods as well as support for the usage of these methods.
Results: Here, we present COPASI, a platform-independent and user-friendly biochemical simulator that offers several unique features. We discuss numerical issues with these features; in particular, the criteria to switch between stochastic and deterministic simulation methods, hybrid deterministic–stochastic methods, and the importance of random num-

and flux analysis (Klamt *et al.*, 2003). However, some tools contain whole suites of functionalities, e.g. simulation, flux and control analysis (Tomita *et al.*, 1999; Sauro *et al.*, 2003; Meng *et al.*, 2004).

In order to improve the compatibility of these tools, markup languages such as SBML (Hucka *et al.*, 2003) and CellML (Lloyd *et al.*, 2004) were created to allow model exchange. Many tools are now able to read and write models in these file formats.

Here we present a new program—COPASI (COmplex PAthway SImulator)—which combines all of the above standards and some unique methods for the simulation and analysis of biochemical

Hoops *et al.* (2006) *Bioinformatics* **22**, 3067-3074

Frequent releases...

COPASI 4.8 (Build 35) Released

By: Stefan Hoops on: Tue 20 of Dec., 2011 17:21 GMT (3836 Reads)

The COPASI team announces the immediate availability of the stable release COPASI 4.8 (Build 35).

Read More (1251 bytes)

New Language Bindings for COPASI 4.7 (Build 34)

By: gauges on: Sat 13 of Aug., 2011 12:24 GMT (2128 Reads)

New versions of the COPASI language bindings based on the latest COPASI 4.7 (Build 34) have been released.

Read More (678 bytes)

COPASI 4.7 (Build 34) Released

By: Stefan Hoops on: Thu 14 of July, 2011 01:57 GMT (3203 Reads)

The COPASI team announces the immediate availability of the stable release COPASI 4.7 (Build 34).

Read More (2218 bytes)

Documentation and support

Several sources available at www.copasi.org:

- User manual
- FAQ
- User forum
- Issue tracker
- Technical documentation:
  - File format specification (including schema)
  - Documentation of API

Latest Versions

Stable:

COPASI 4.8 (Build 35)

Development:

COPASI 4.6.33 (development)

Menu

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User Support Forum

We have limited posting to this forum to registered users to prevent spamming. However, the registration is open to everyone. If you need any help regarding COPASI we kindly ask you to register.

Forums > User Support Forum

New Topic Forum List Edit Forum Manage Reported Messages (1)

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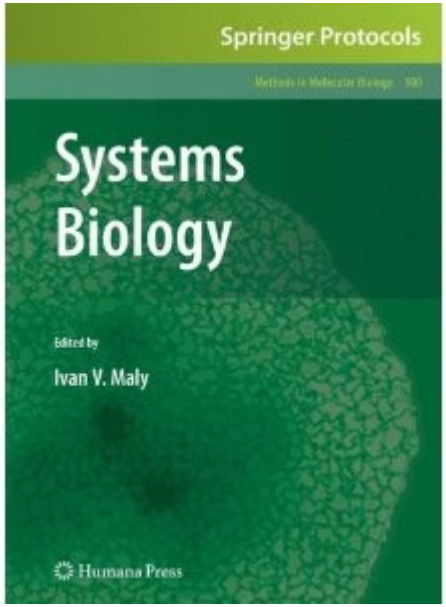
	Type	Title	Replies	Reads	Last Post	Author
		Running several simulations with different parameter values	1	8463	Tue 04 of Dec., 2012 17:00 GMT *Re: Running several simulations with different parameter values* by shoops	tschirmer
		reaction without species???	9	28118	Tue 11 of Dec., 2012 14:54 GMT *Re: Re: reaction without species???* by shoops	Max
		global fitting of model to experimental data acquired at varying conditions	9	23989	Tue 27 of Nov., 2012 00:39 GMT *Re: global fitting of model to experimental data acquired at varying conditions* by Holmes	tschirmer
		What does "An equilibrium steady state (zero flux)" mean?	2	3269	Sat 24 of Nov., 2012 01:27 GMT *Re: What does "An equilibrium steady state (zero flux)" mean?* by Holmes	Holmes
		overlay of curves from different runs	3	4535	Sat 24 of Nov., 2012 11:46 GMT *Re: overlay of curves from different runs* by tschirmer	tschirmer
		Stochastic simulations not working	3	5747	Mon 26 of Nov., 2012 02:36 GMT *Re: Stochastic simulations not working* by bp	bp
		time dependent reaction rates for stochastic simulation	3	9925	Mon 26 of Nov., 2012 10:31 GMT *Re: time dependent reaction rates for stochastic simulation* by sven	anzezupanic
		Modeling lysis-lysogeny decision circuit in Lambda phage	1	11783	Mon 26 of Nov., 2012 15:48 GMT *Re: Modeling lysis-lysogeny decision circuit in Lambda phage* by shoops	shawon
		Modeling Protein degradation	1	8039	Tue 13 of Nov., 2012 12:52 GMT *Re: Modeling Protein degradation* by shoops	zoltuz
		Residence time	2	9718	Mon 26 of Nov., 2012 10:40 GMT	Aman



Mendes, P, Hoops, S, Sahle, S, Gauges, R, Dada, J, Kummer, U (2009) Computational Modeling of Biochemical Networks Using COPASI. Methods Mol. Biol. 500, 17-59.

Chapter 2

Computational Modeling of Biochemical Networks Using COPASI

Pedro Mendes, Stefan Hoops, Sven Sahle, Ralph Gauges, Joseph Dada, and Ursula Kummer

Summary

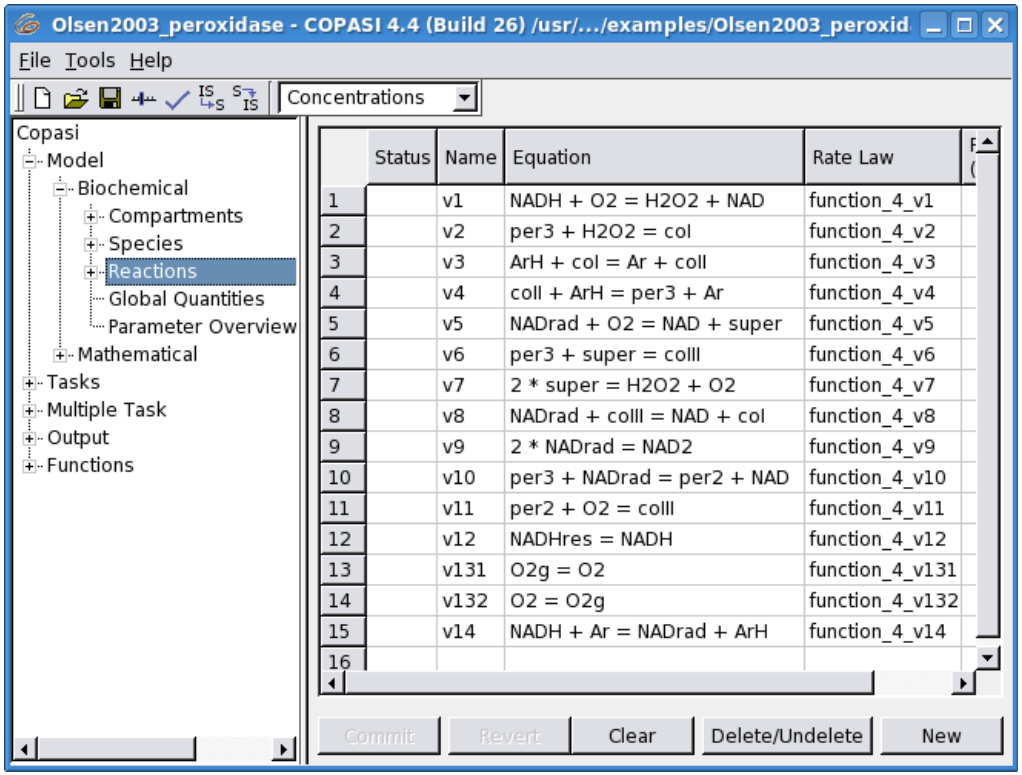
Computational modeling and simulation of biochemical networks is at the core of systems biology and this includes many types of analyses that can aid understanding of how these systems work. COPASI is a generic software package for modeling and simulation of biochemical networks which provides many of these analyses in convenient ways that do not require the user to program or to have deep knowledge of the numerical algorithms. Here we provide a description of how these modeling techniques can be applied to biochemical models using COPASI. The focus is both on practical aspects of software usage as well as on the utility of these analyses in aiding biological understanding. Practical examples are described for steady-state and time-course simulations, stoichiometric analyses, parameter scanning, sensitivity analysis (including metabolic control analysis), global optimization, parameter estimation, and stochastic simulation. The examples used are all published models that are available in the BioModels database in SBML format.

Systems Biology Markup Language

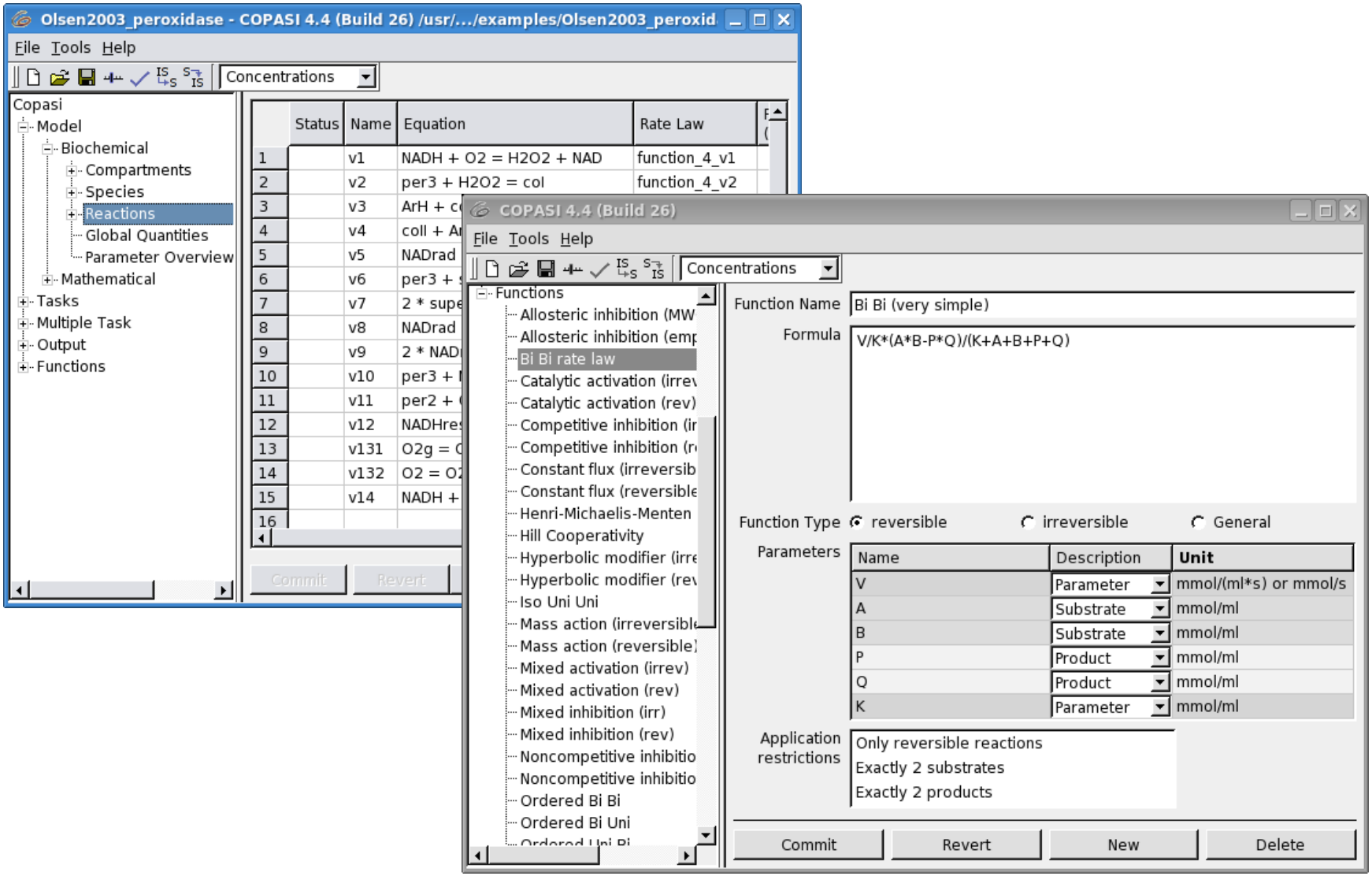
- Exchange medium for systems biology models, based on XML (used by >100 programs)
- Specifies models based on the biology, not on the maths
- Software interpret the models and translate them into mathematical/computational representations
- Allows ODEs, assignment rules, and events

http://www.sbml.org

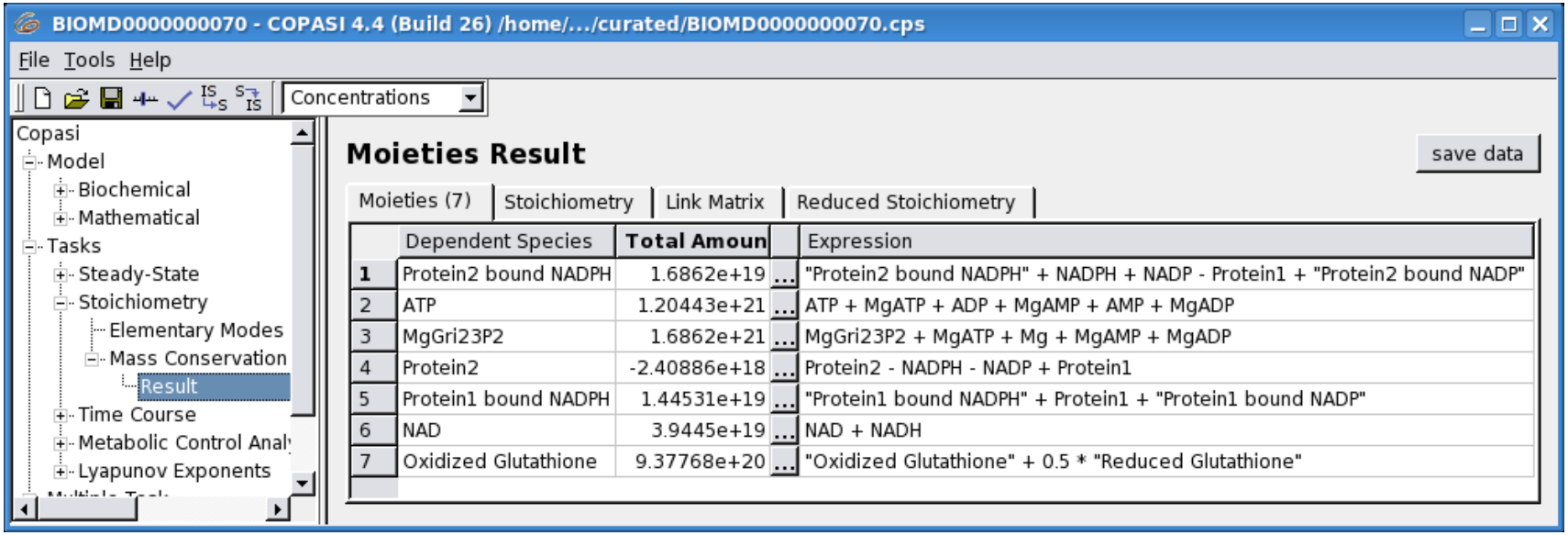
Model Definition



Model Definition

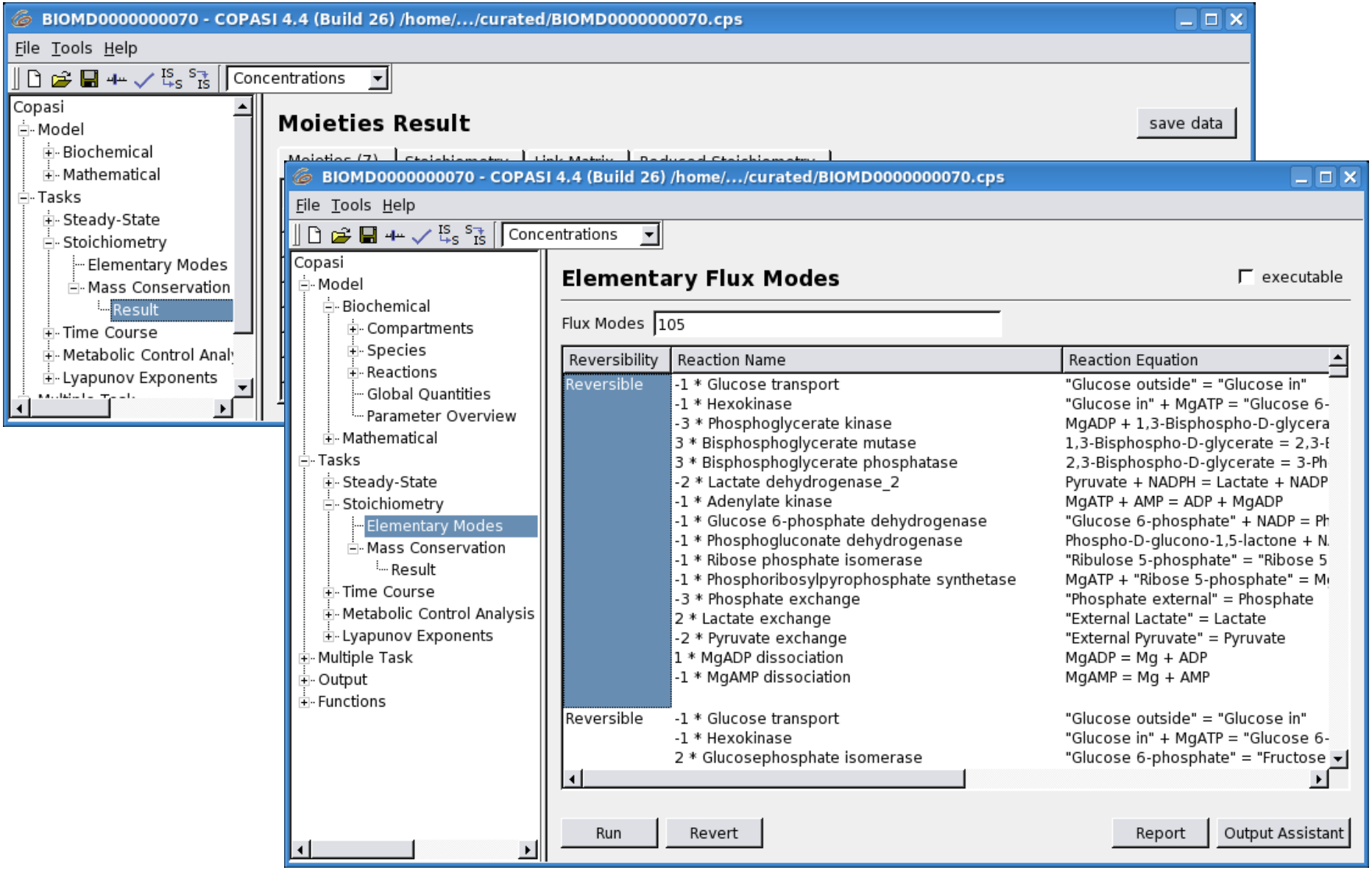


Stoichiometric analyses

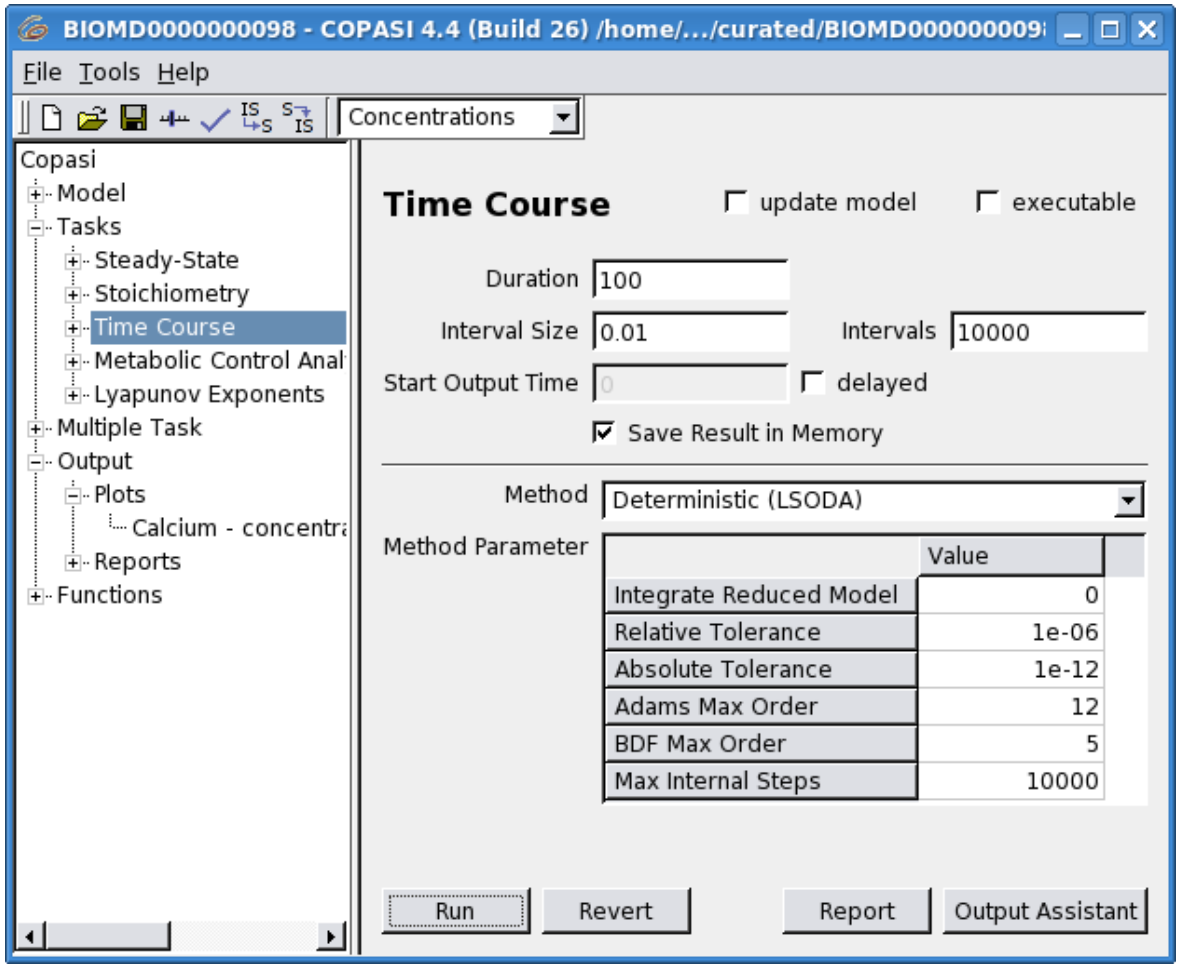


	Dependent Species	Total Amoun		Expression
1	Protein2 bound NADPH	1.6862e+19	...	"Protein2 bound NADPH" + NADPH + NADP - Protein1 + "Protein2 bound NADP"
2	ATP	1.20443e+21	...	ATP + MgATP + ADP + MgAMP + AMP + MgADP
3	MgGri23P2	1.6862e+21	...	MgGri23P2 + MgATP + Mg + MgAMP + MgADP
4	Protein2	-2.40886e+18	...	Protein2 - NADPH - NADP + Protein1
5	Protein1 bound NADPH	1.44531e+19	...	"Protein1 bound NADPH" + Protein1 + "Protein1 bound NADP"
6	NAD	3.9445e+19	...	NAD + NADH
7	Oxidized Glutathione	9.37768e+20	...	"Oxidized Glutathione" + 0.5 * "Reduced Glutathione"

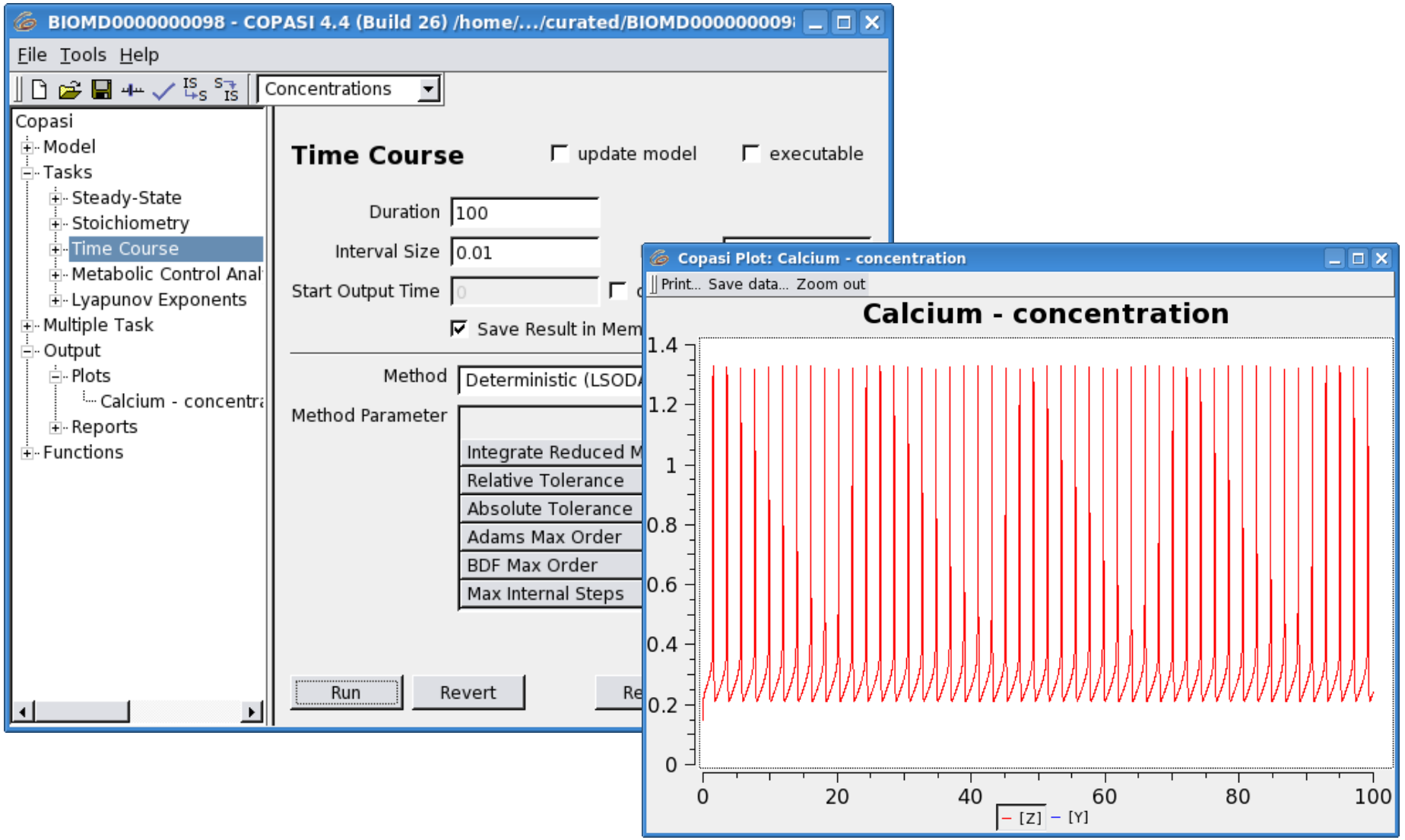
Stoichiometric analyses



Deterministic time course simulations



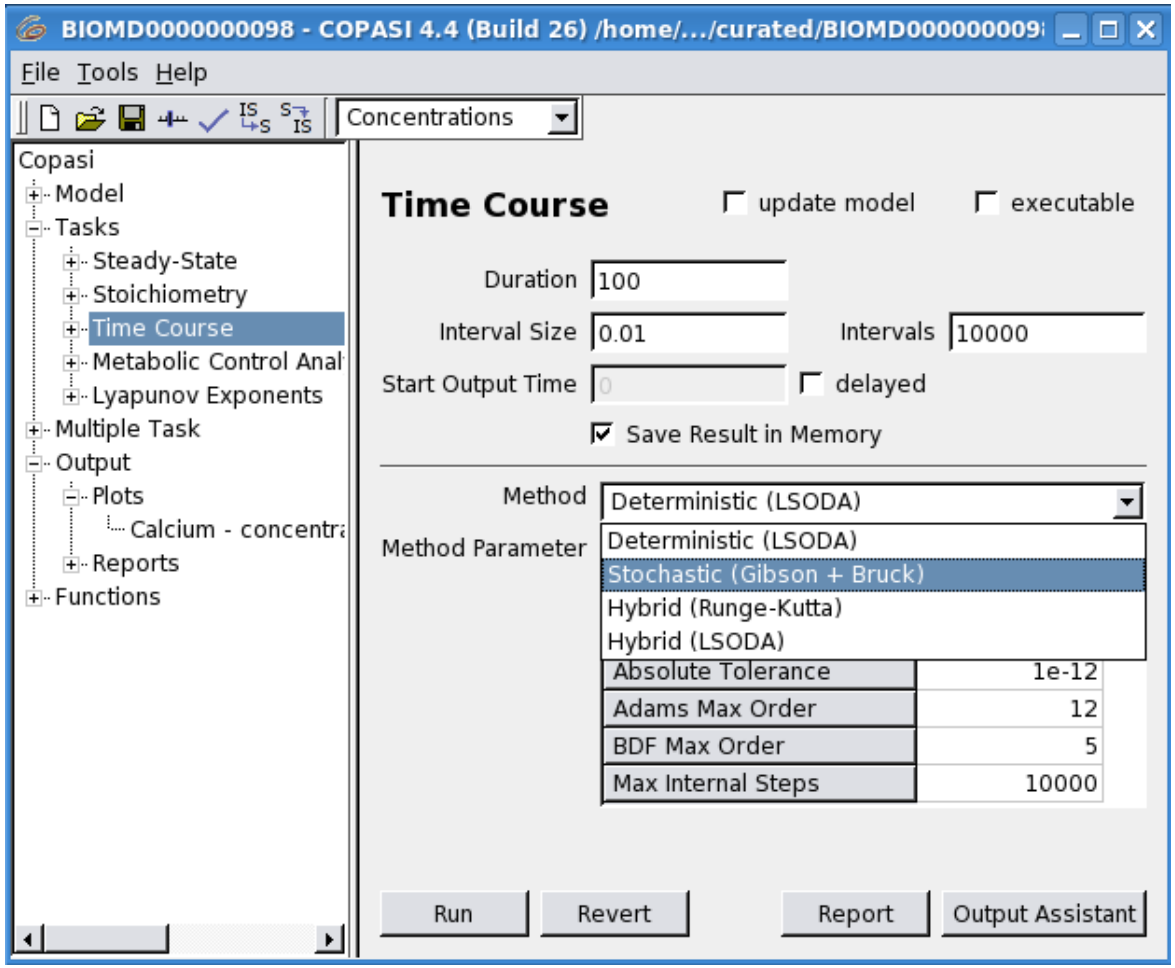
Deterministic time course simulations



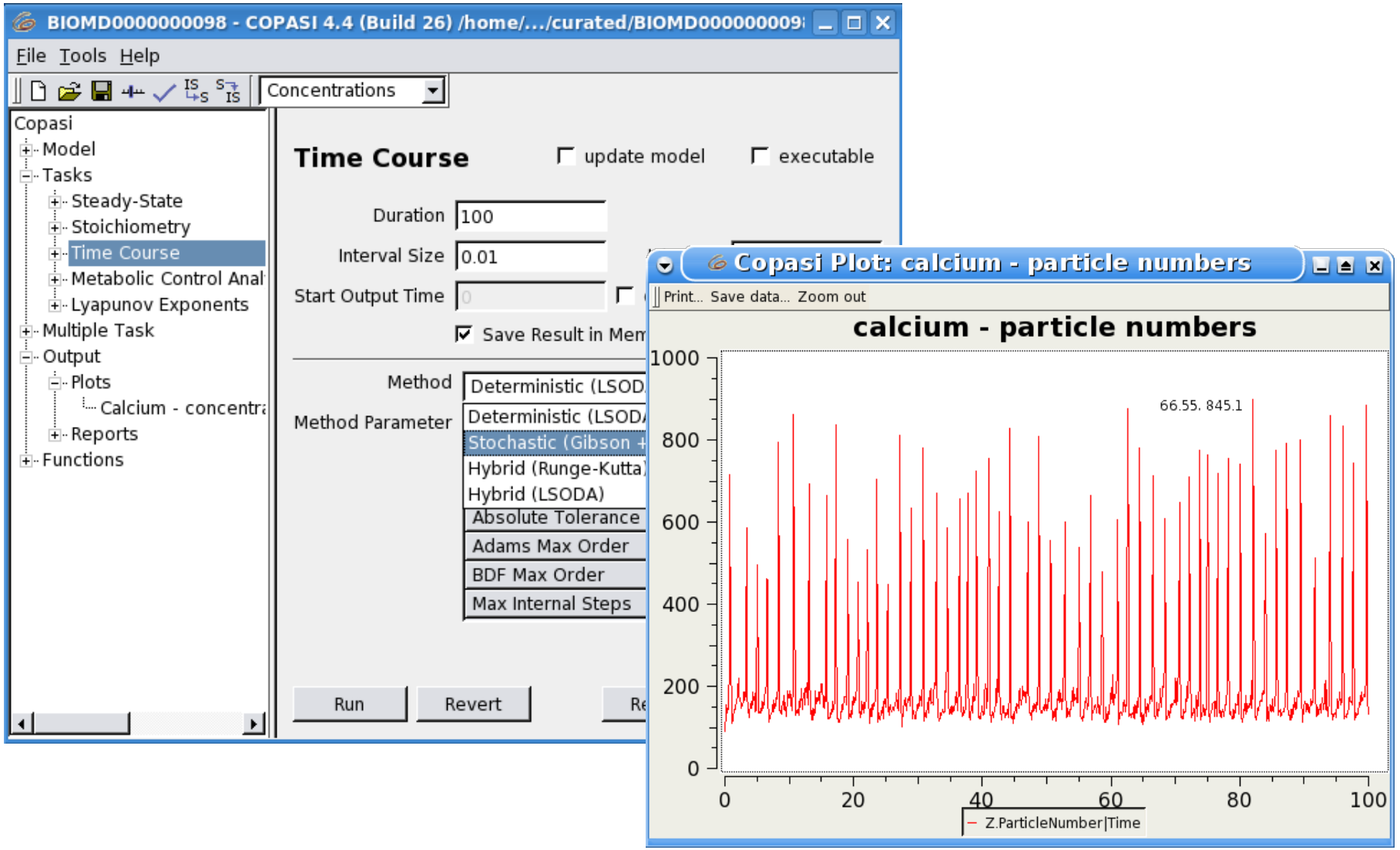
Hybrid ODE-discrete event

- System of ODEs is associated with events
- An event (conditional state transition) consist of:
  - a trigger (Boolean expression)
  - at least one assignment
  - a delay (optional)
- When trigger expression changes from FALSE to TRUE, the even triggers and causes the assignments. If there is a delay, the trigger will only be that time after the trigger

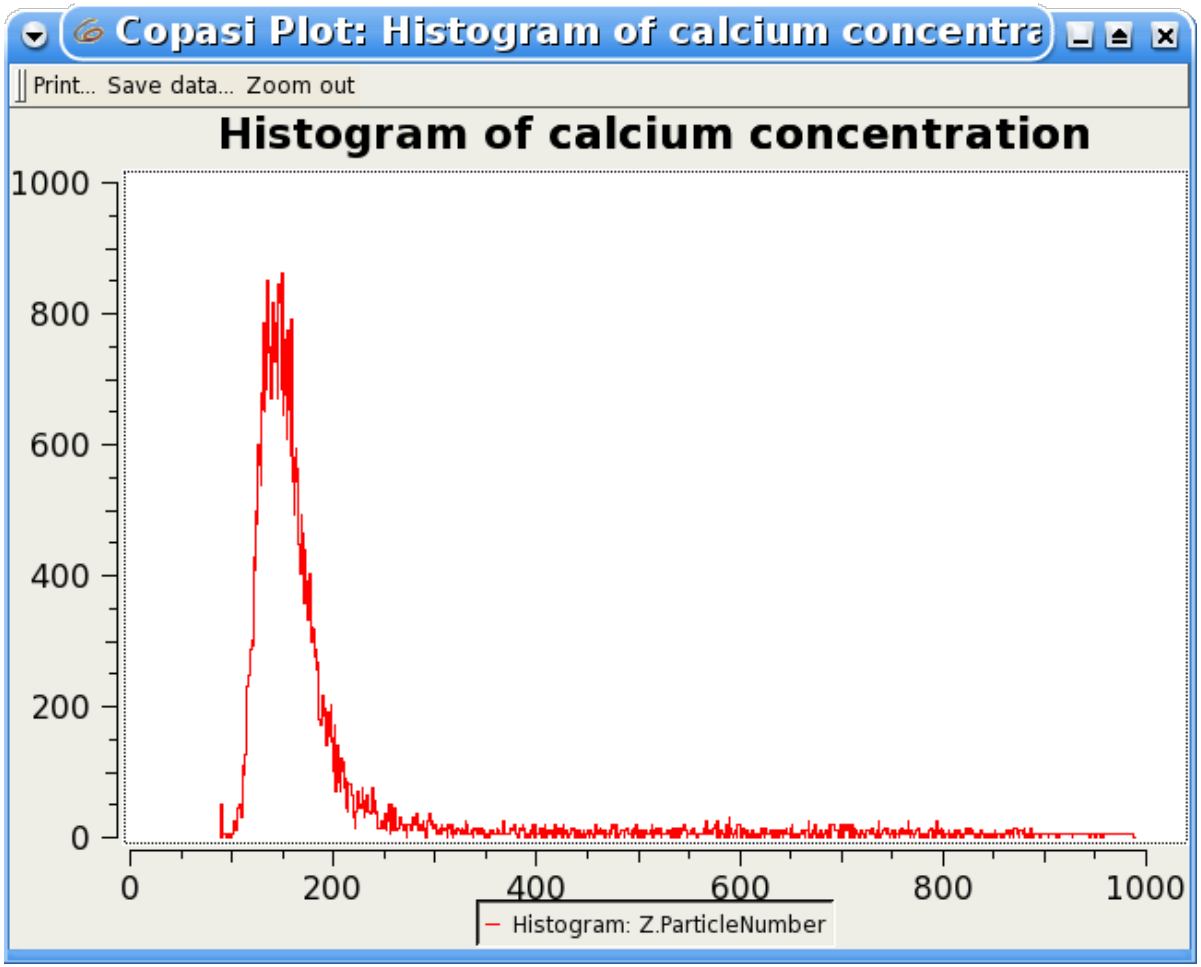
Stochastic time course simulations



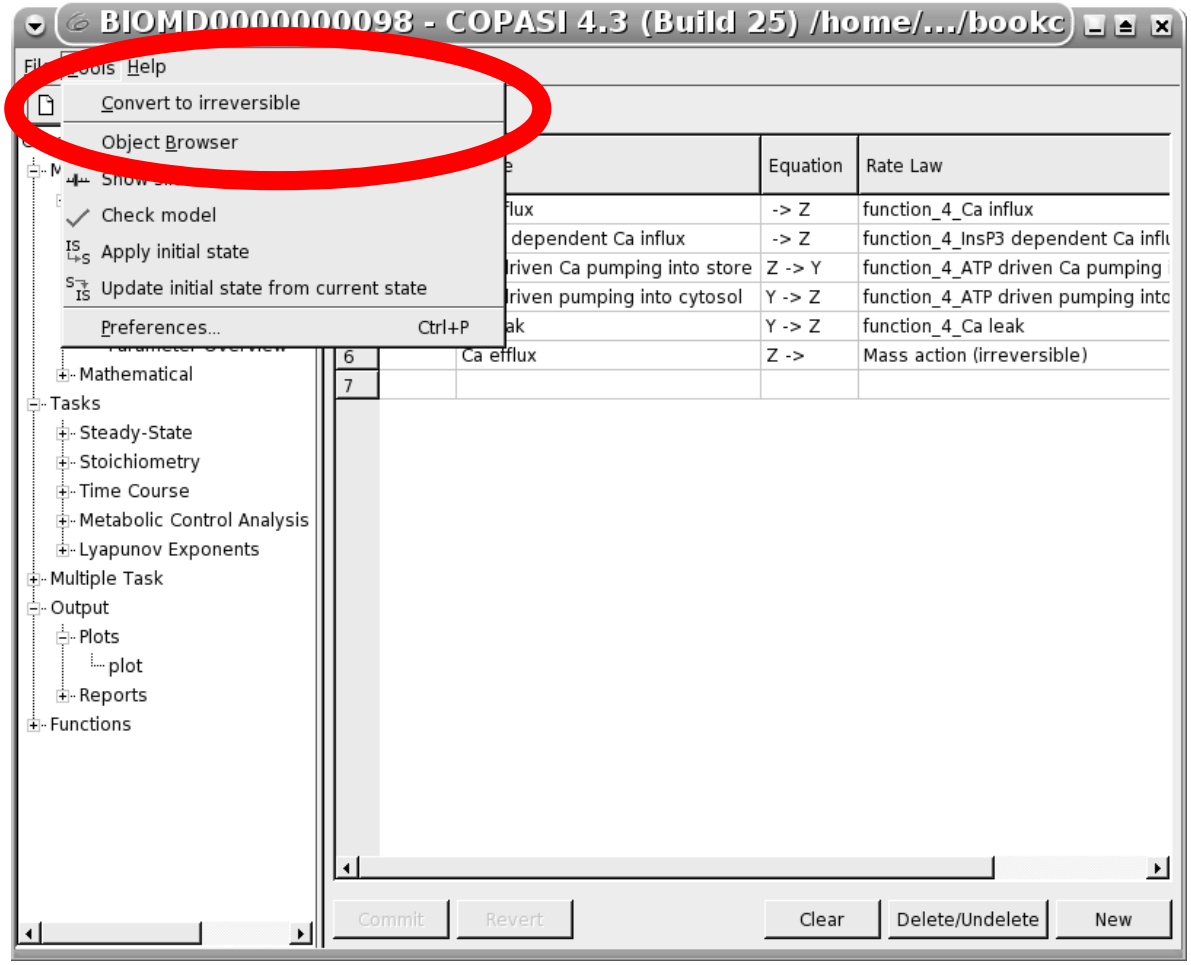
Stochastic time course simulations



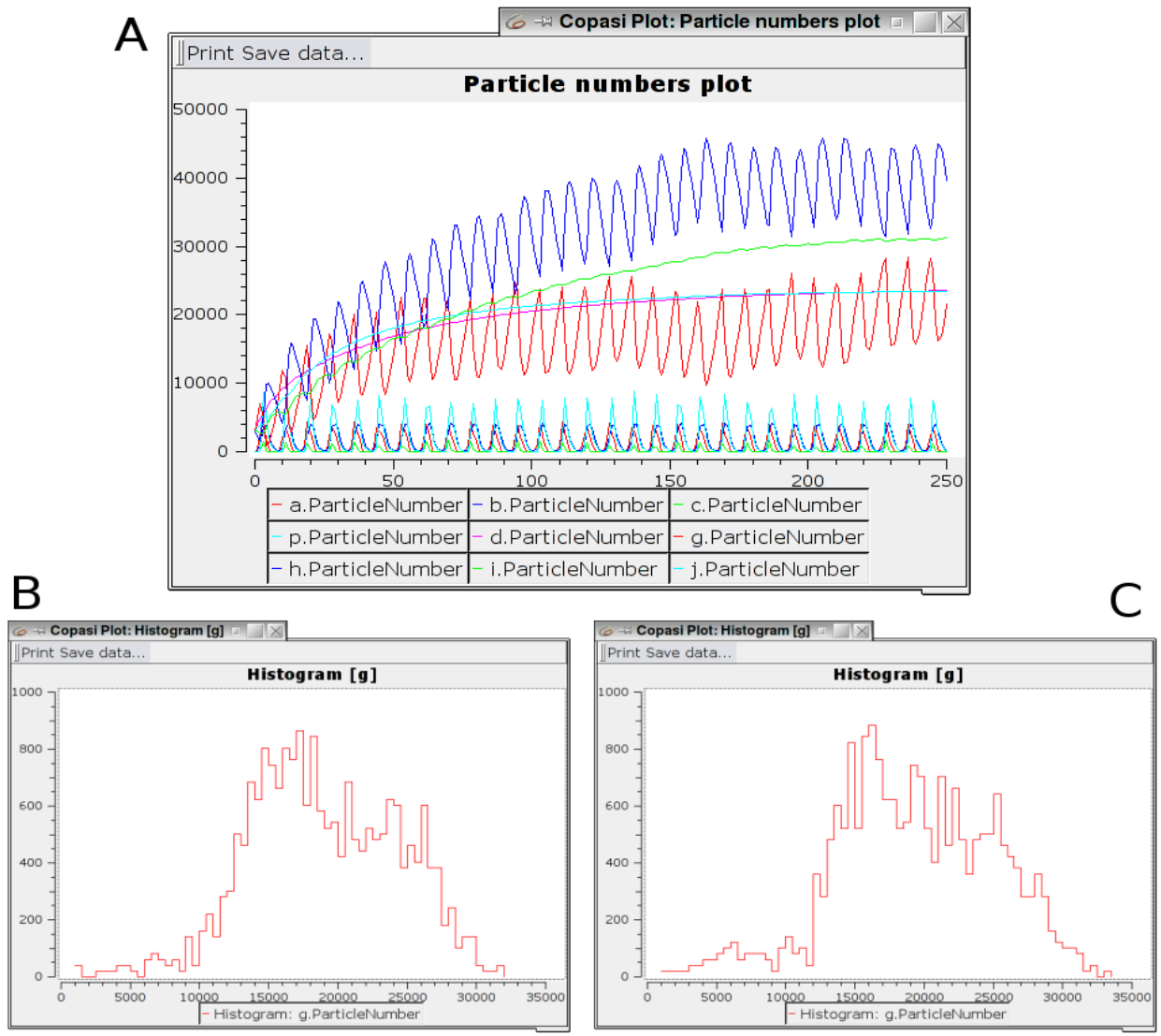
Histograms


Copasi Plot: Histogram of calcium concentra
Print... Save data... Zoom out
Histogram of calcium concentration
1000
800
600
400
200
0
0
200
400
600
800
1000
Histogram: Z.ParticleNumber

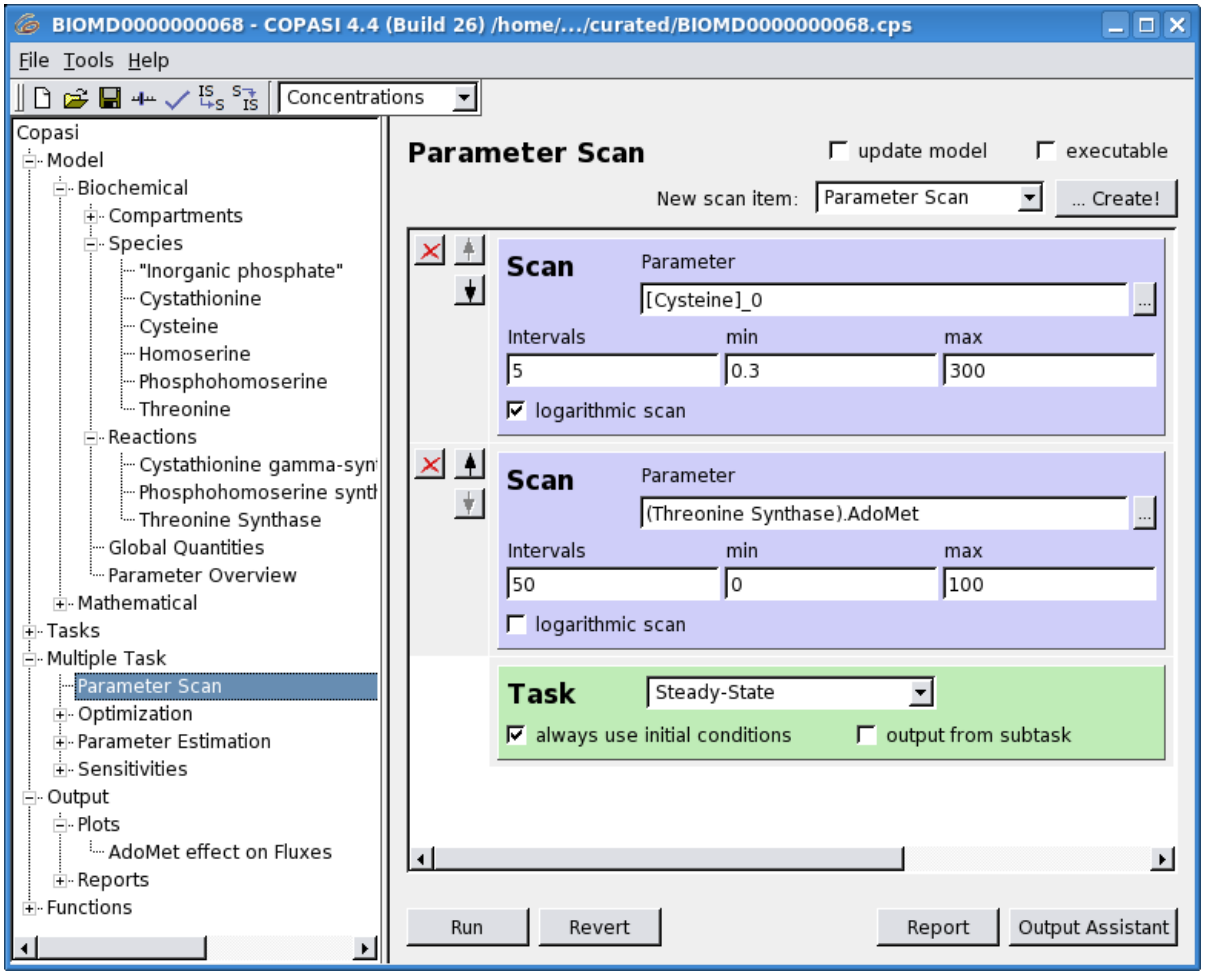
Automatic conversion to irreversible reactions



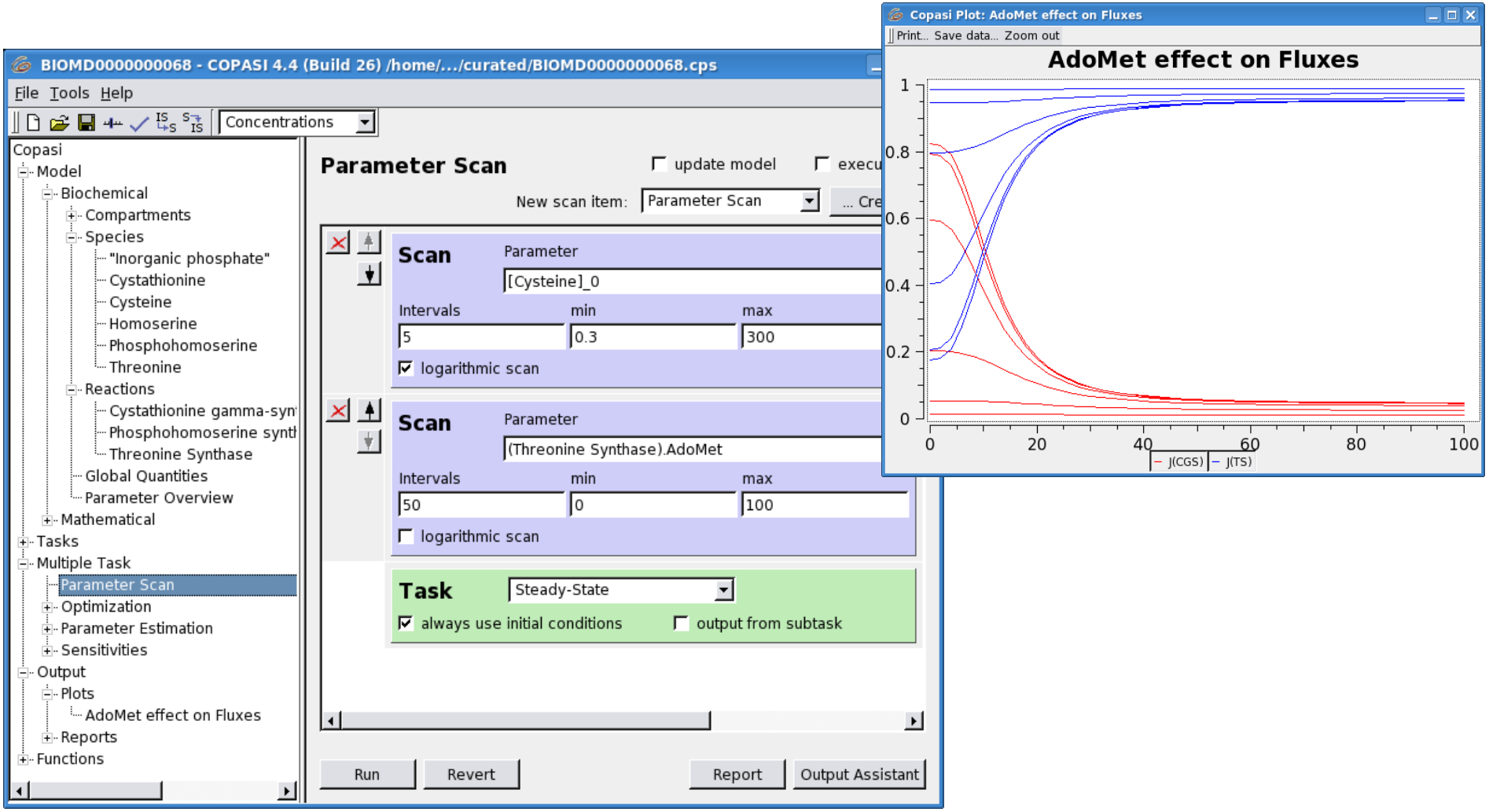
Hybrid ODE-stochastic



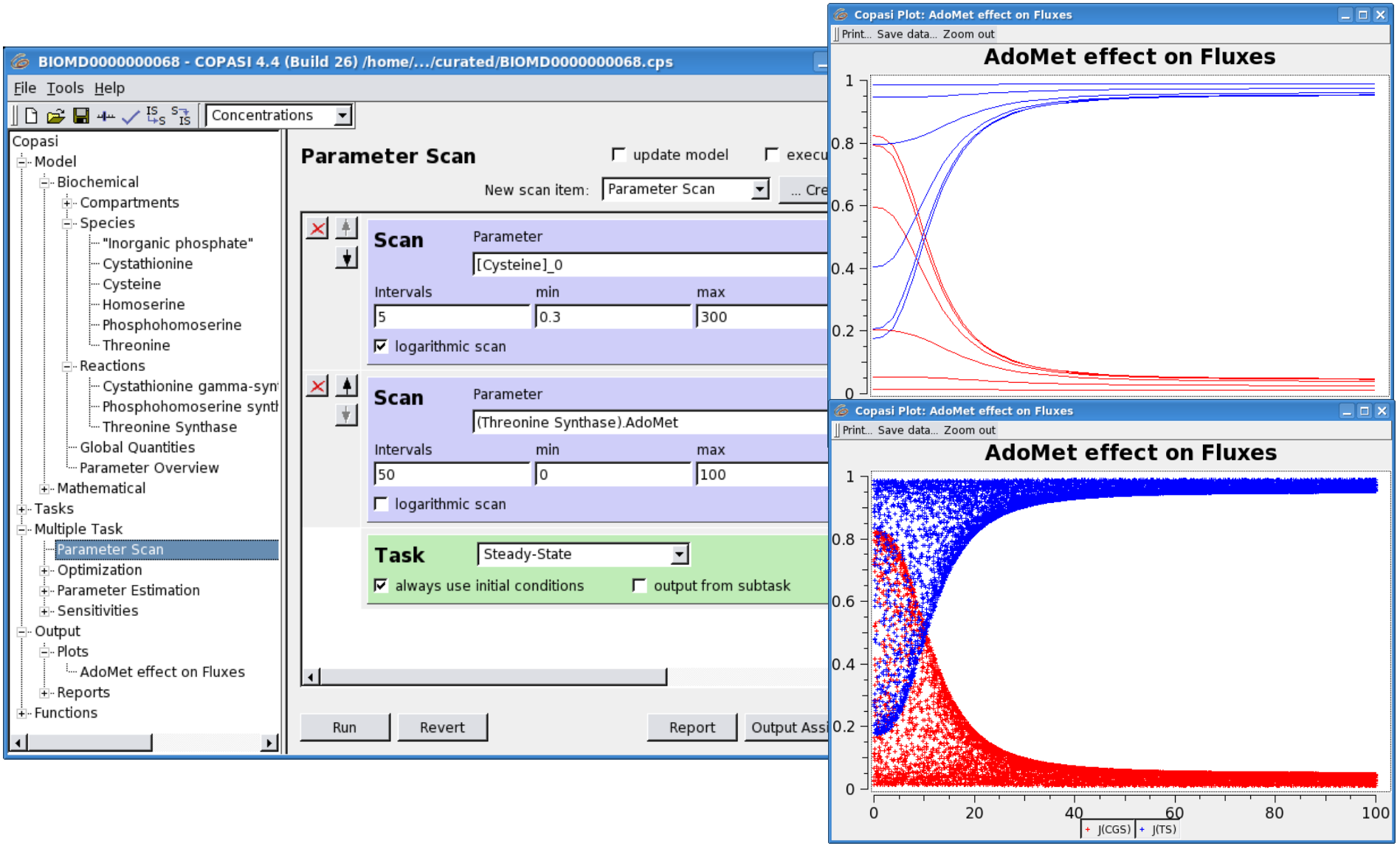
Parameter scanning & sampling



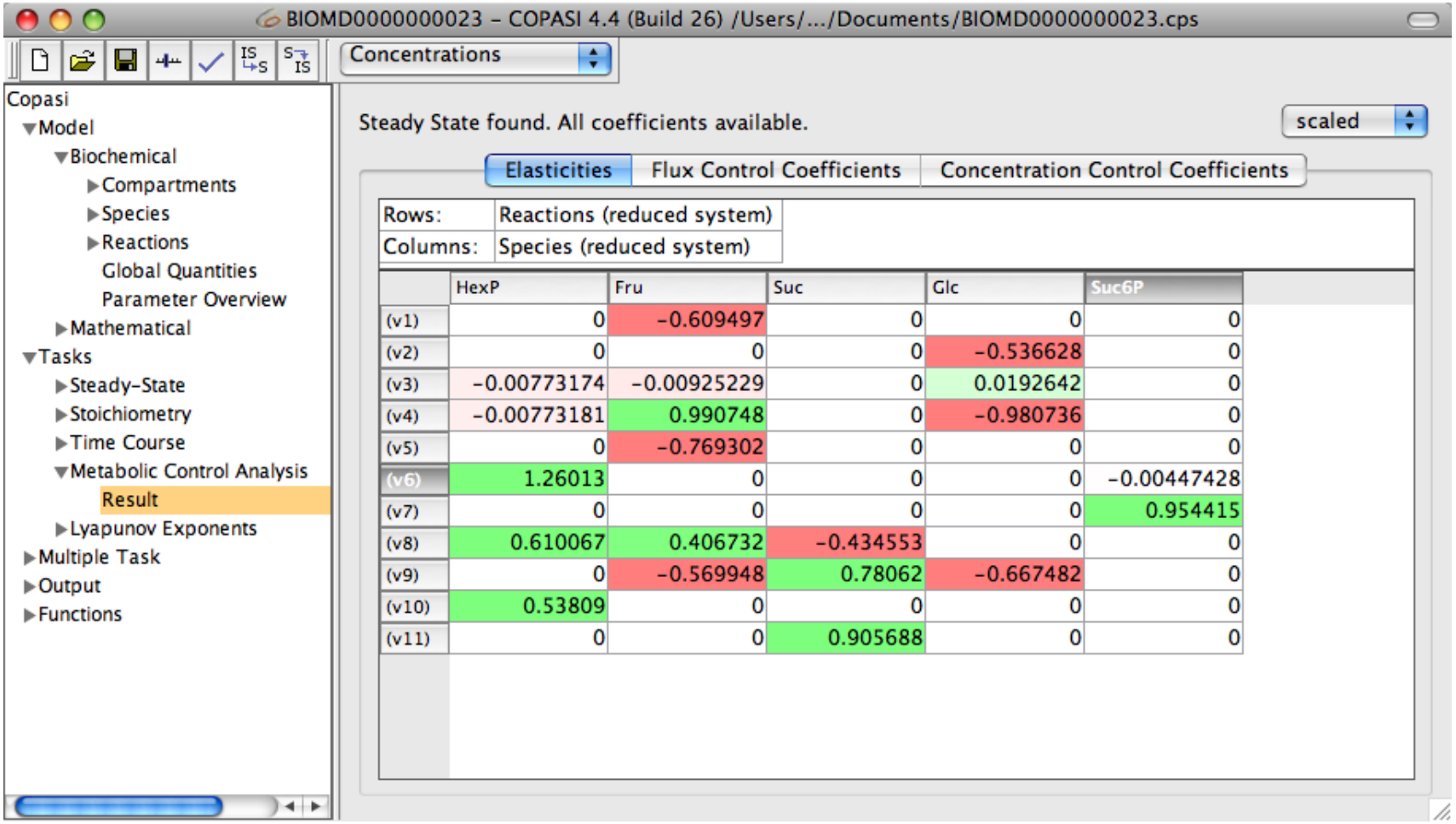
Parameter scanning & sampling



Parameter scanning & sampling

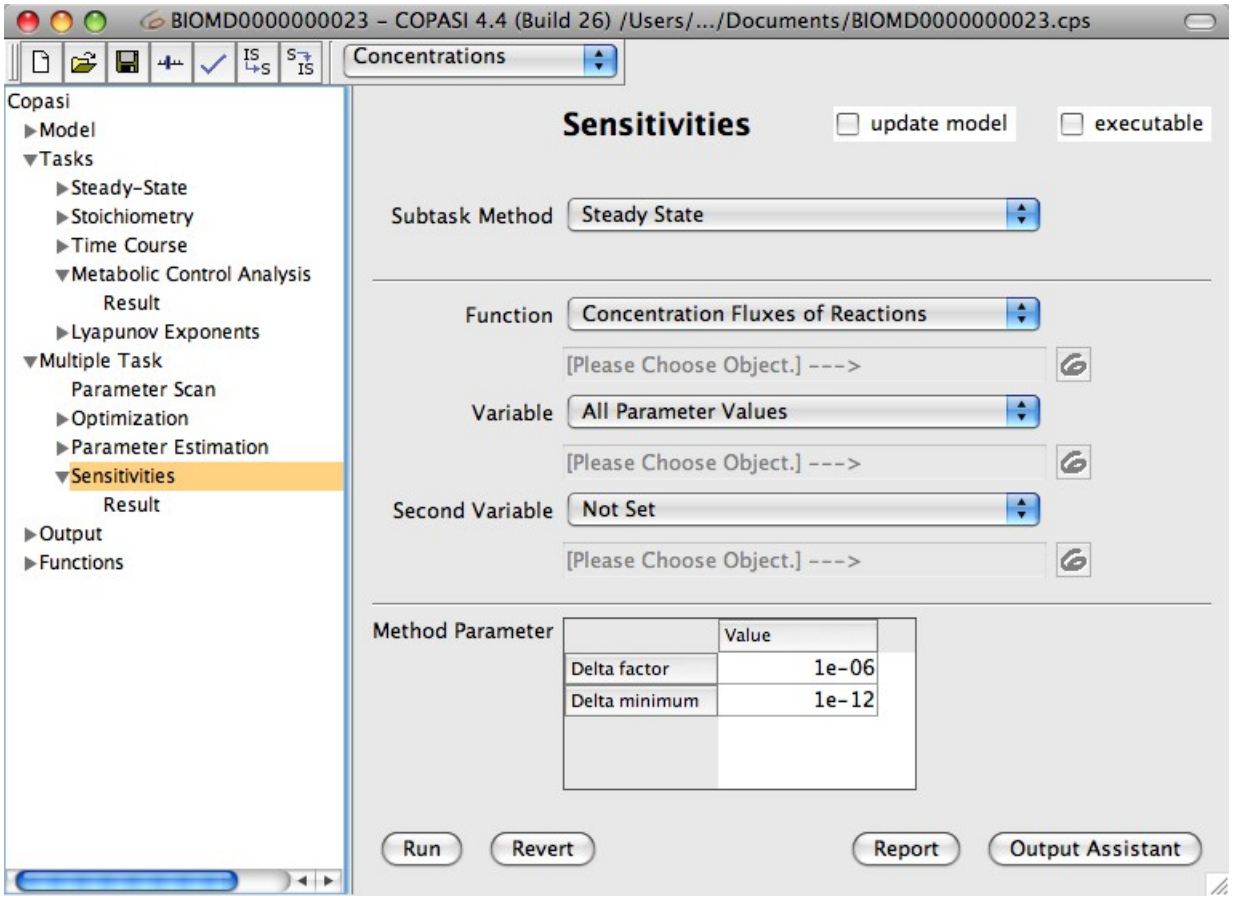


Sensitivity analysis (MCA)

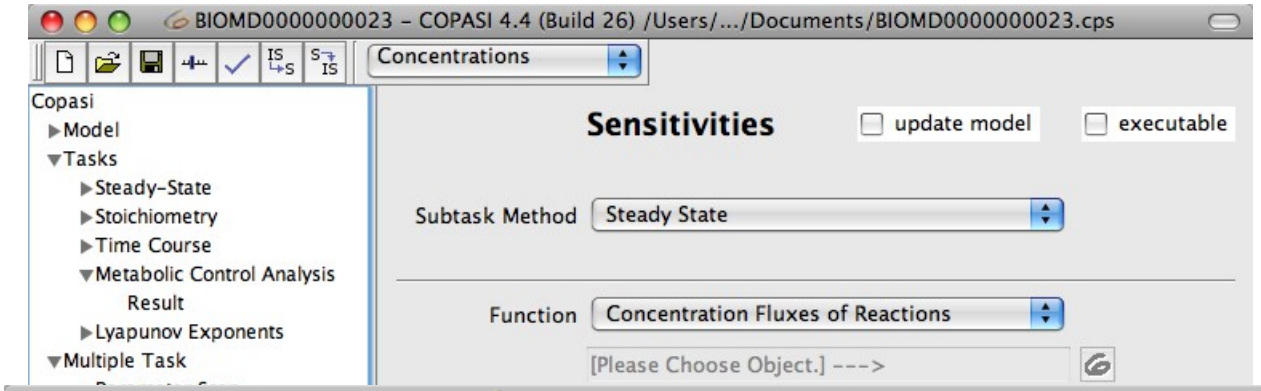


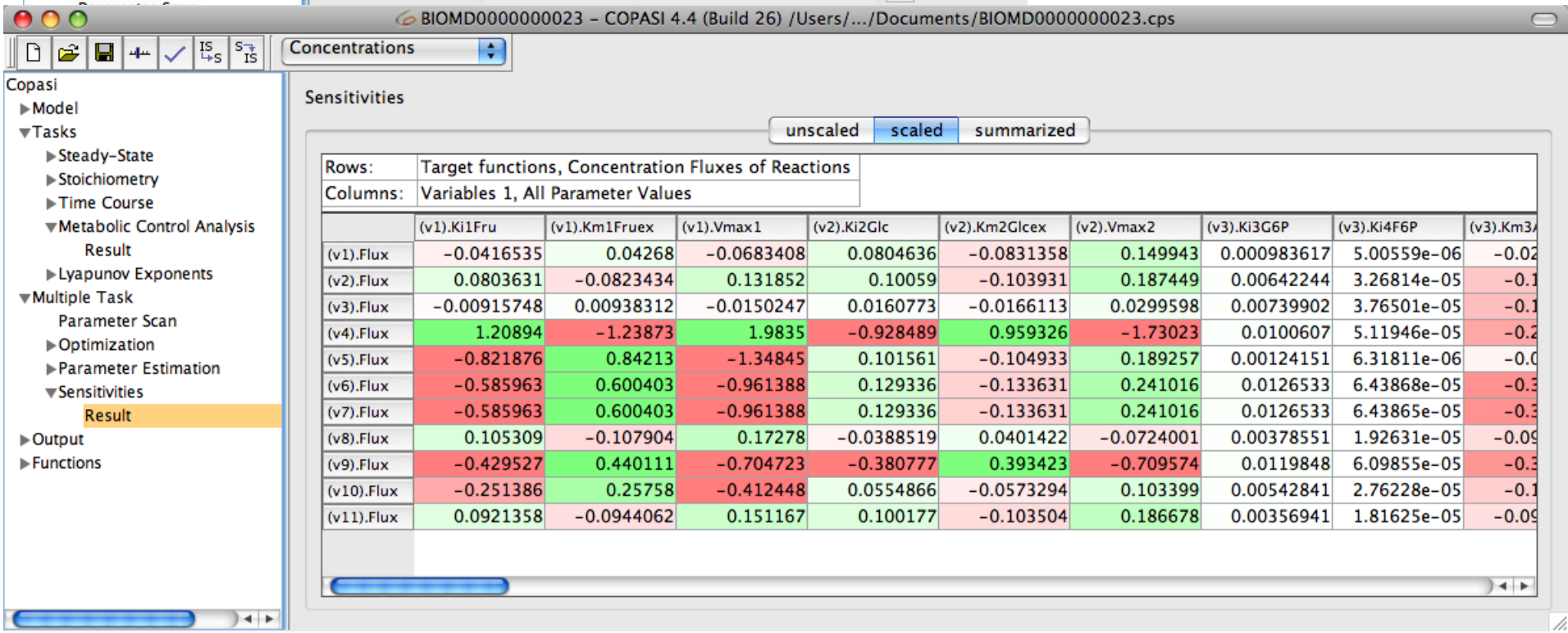
	HexP	Fru	Suc	Glc	Suc6P
(v1)	0	-0.609497	0	0	0
(v2)	0	0	0	-0.536628	0
(v3)	-0.00773174	-0.00925229	0	0.0192642	0
(v4)	-0.00773181	0.990748	0	-0.980736	0
(v5)	0	-0.769302	0	0	0
(v6)	1.26013	0	0	0	-0.00447428
(v7)	0	0	0	0	0.954415
(v8)	0.610067	0.406732	-0.434553	0	0
(v9)	0	-0.569948	0.78062	-0.667482	0
(v10)	0.53809	0	0	0	0
(v11)	0	0	0.905688	0	0

Sensitivity analysis (general)



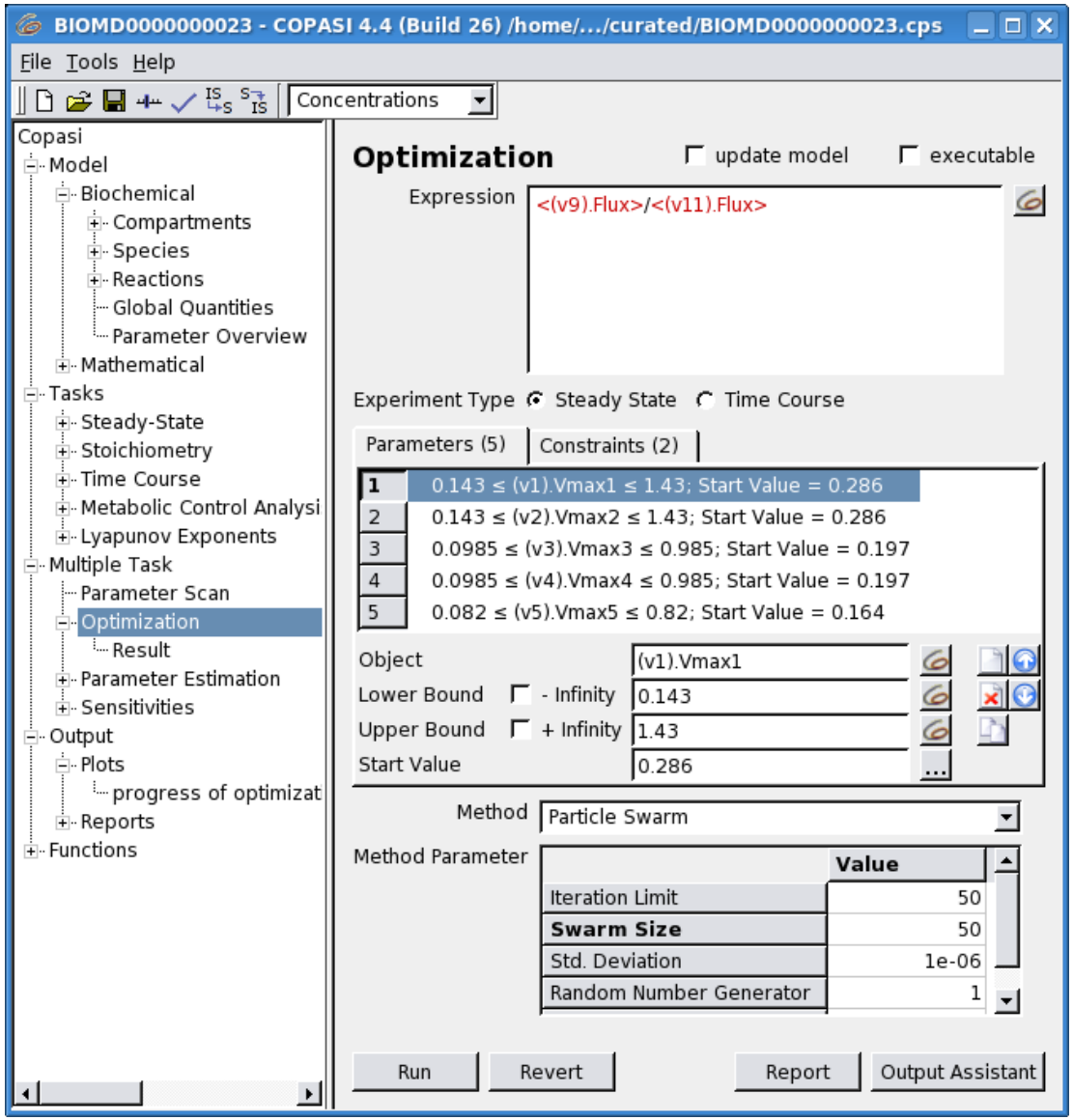
Sensitivity analysis (general)

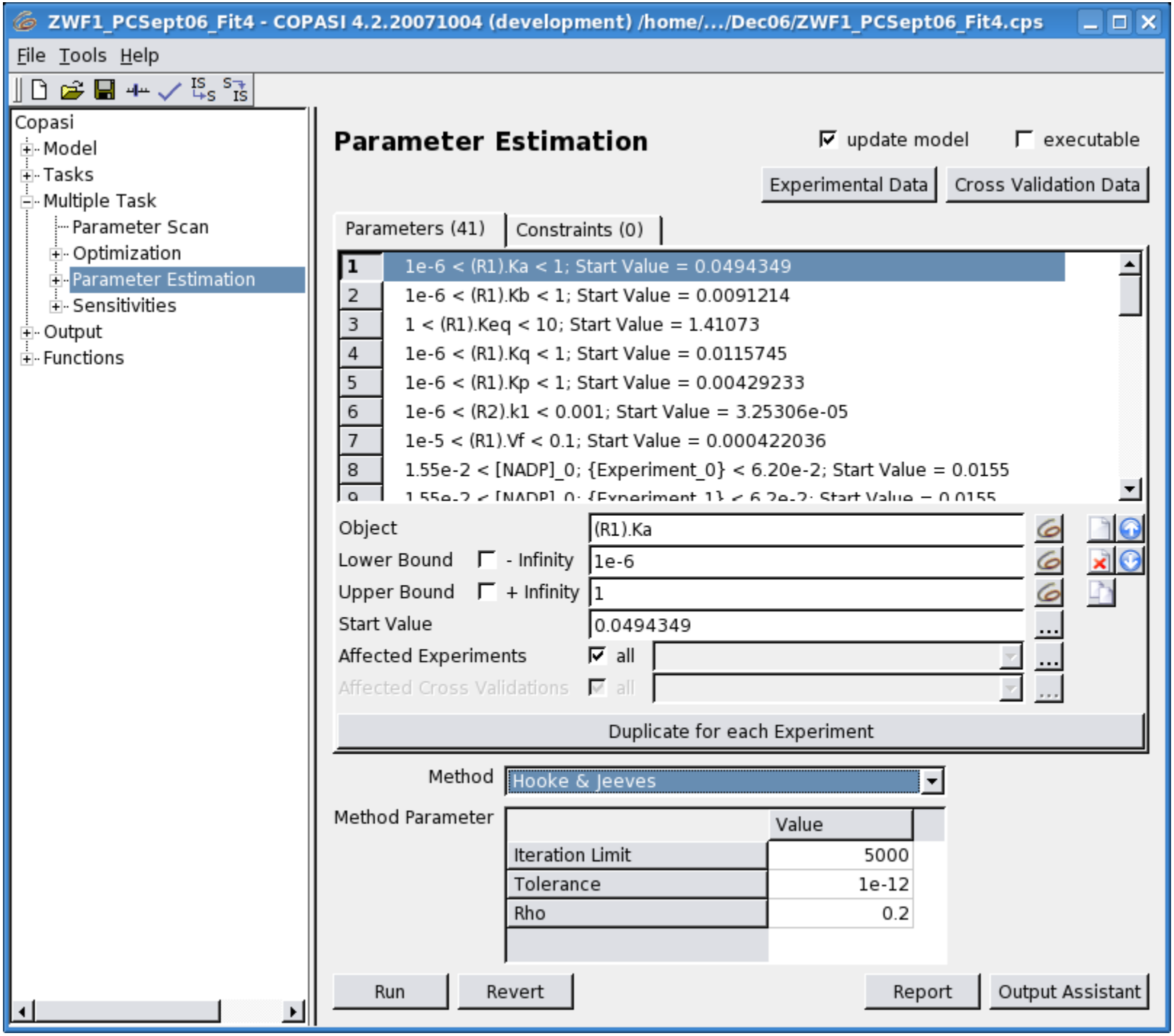


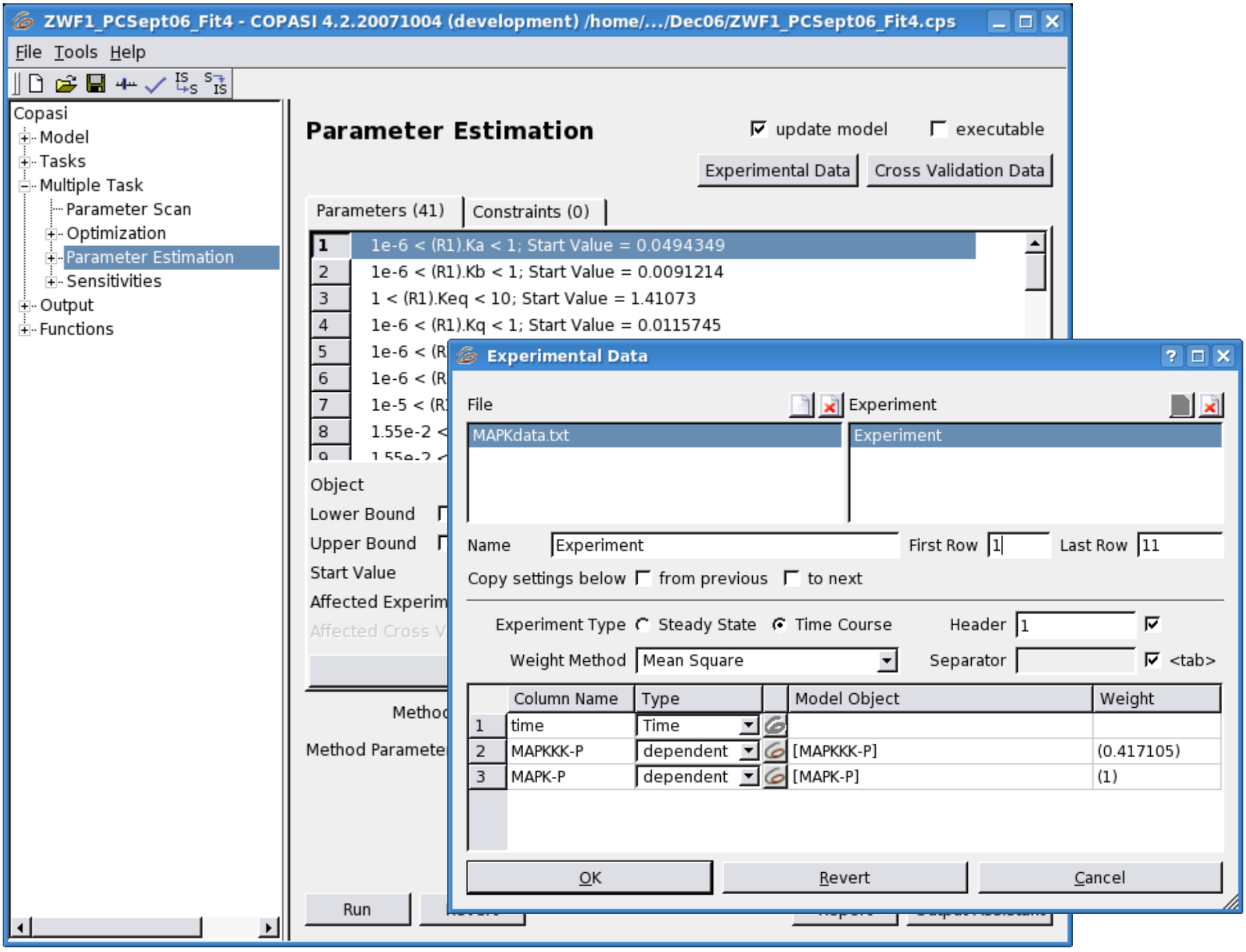


	(v1).Ki1Fru	(v1).Km1Fruex	(v1).Vmax1	(v2).Ki2Glc	(v2).Km2Glcex	(v2).Vmax2	(v3).Ki3G6P	(v3).Ki4F6P	(v3).Km3A
(v1).Flux	-0.0416535	0.04268	-0.0683408	0.0804636	-0.0831358	0.149943	0.000983617	5.00559e-06	-0.02
(v2).Flux	0.0803631	-0.0823434	0.131852	0.10059	-0.103931	0.187449	0.00642244	3.26814e-05	-0.1
(v3).Flux	-0.00915748	0.00938312	-0.0150247	0.0160773	-0.0166113	0.0299598	0.00739902	3.76501e-05	-0.1
(v4).Flux	1.20894	-1.23873	1.9835	-0.928489	0.959326	-1.73023	0.0100607	5.11946e-05	-0.2
(v5).Flux	-0.821876	0.84213	-1.34845	0.101561	-0.104933	0.189257	0.00124151	6.31811e-06	-0.0
(v6).Flux	-0.585963	0.600403	-0.961388	0.129336	-0.133631	0.241016	0.0126533	6.43868e-05	-0.3
(v7).Flux	-0.585963	0.600403	-0.961388	0.129336	-0.133631	0.241016	0.0126533	6.43865e-05	-0.3
(v8).Flux	0.105309	-0.107904	0.17278	-0.0388519	0.0401422	-0.0724001	0.00378551	1.92631e-05	-0.09
(v9).Flux	-0.429527	0.440111	-0.704723	-0.380777	0.393423	-0.709574	0.0119848	6.09855e-05	-0.3
(v10).Flux	-0.251386	0.25758	-0.412448	0.0554866	-0.0573294	0.103399	0.00542841	2.76228e-05	-0.1
(v11).Flux	0.0921358	-0.0944062	0.151167	0.100177	-0.103504	0.186678	0.00356941	1.81625e-05	-0.09

Global optimisation




ZWF1_PCSept06_Fit4 - COPASI 4.2.20071004 (development) /home/.../Dec06/ZWF1_PCSept06_Fit4.cps
File Tools Help
Copasi
Model
Tasks
Multiple Task
Parameter Scan
Optimization
Parameter Estimation
Sensitivities
Output
Functions
Parameter Estimation
update model
executable
Experimental Data
Cross Validation Data
Parameters (41)
Constraints (0)
1 1e-6 < (R1).Ka < 1; Start Value = 0.0494349
2 1e-6 < (R1).Kb < 1; Start Value = 0.0091214
3 1 < (R1).Keq < 10; Start Value = 1.41073
4 1e-6 < (R1).Kq < 1; Start Value = 0.0115745
5 1e-6 < (R1).Kp < 1; Start Value = 0.00429233
6 1e-6 < (R2).k1 < 0.001; Start Value = 3.25306e-05
7 1e-5 < (R1).Vf < 0.1; Start Value = 0.000422036
8 1.55e-2 < [NADP]_0; {Experiment_0} < 6.20e-2; Start Value = 0.0155
Object
(R1).Ka
Lower Bound
- Infinity
1e-6
Upper Bound
+ Infinity
1
Start Value
0.0494349
Affected Experiments
all
Affected Cross Validations
all
Duplicate for each Experiment
Method
Hooke & Jeeves
Method Parameter
Value
Iteration Limit
5000
Tolerance
1e-12
Rho
0.2
Run
Revert
Report
Output Assistant


ZWF1_PCSept06_Fit4 - COPASI 4.2.20071004 (development) /home/.../Dec06/ZWF1_PCSept06_Fit4.cps
File Tools Help
Copasi
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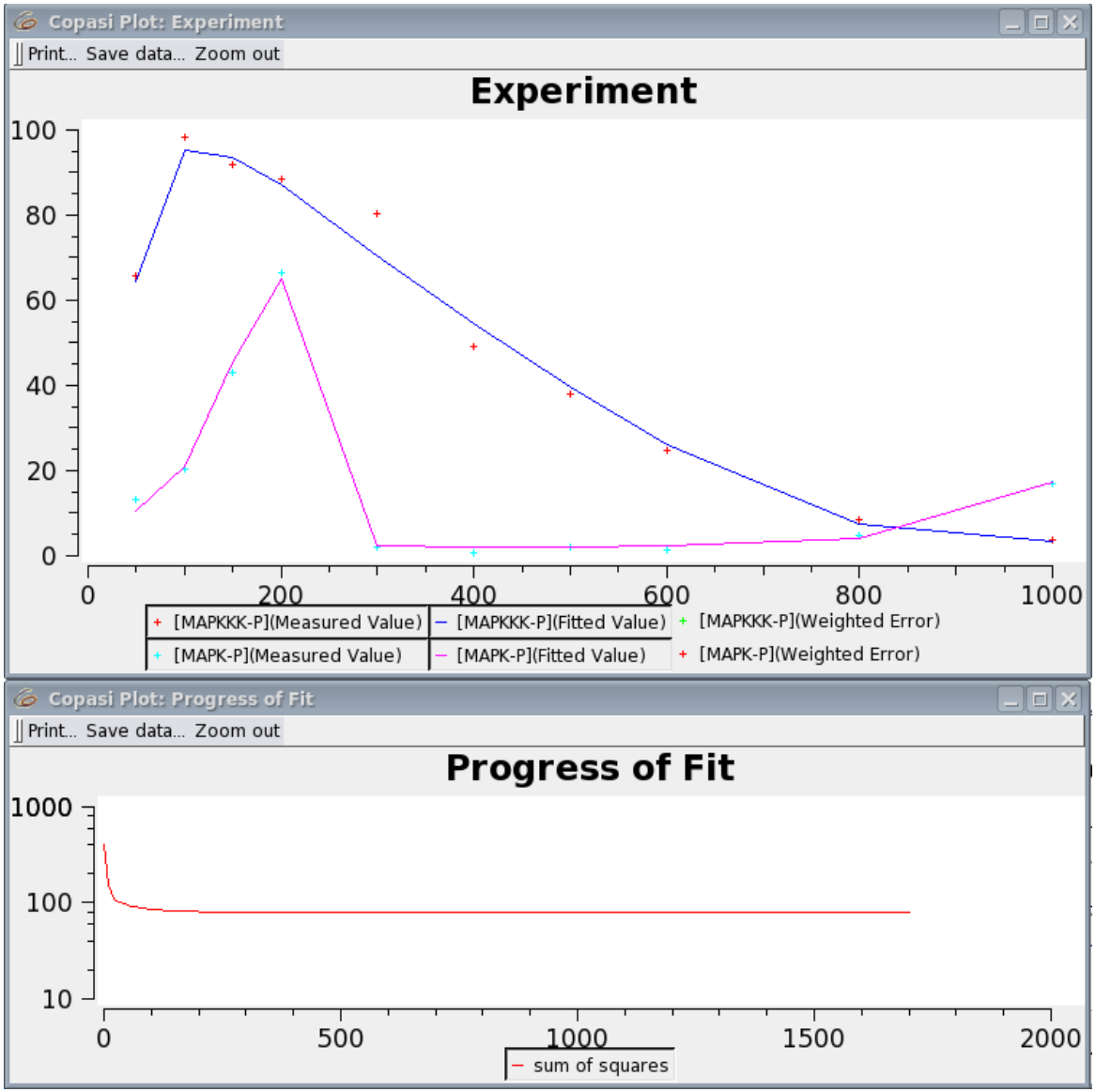
4 1e-6 < (R1).Kq < 1; Start Value = 0.0115745
Object
Lower Bound
Upper Bound
Start Value
Affected Experim
Method
Method Paramete
Run
Experimental Data
File
Experiment
MAPKdata.txt
Experiment
Name
Experiment
First Row
1
Last Row
11
Copy settings below
from previous
to next
Experiment Type
Steady State
Time Course
Header
1
Weight Method
Mean Square
Separator
<tab>
Column Name
Type
Model Object
Weight
1 time Time
2 MAPKKK-P dependent [MAPKKK-P] (0.417105)
3 MAPK-P dependent [MAPK-P] (1)
OK
Revert
Cancel

Parameter estimation



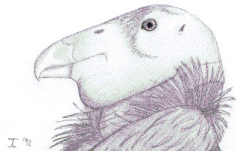
Command line version

- **CopasiSE**

  All model relevant information is contained in .cps file (COPASIML, an XML schema)

```
Usage: CopasiSE [options] [file]
  --configdir string              The configuration directory for copasi.
                                  The default is .copasi in the home
                                  directory.
  --configfile string             The configuration file for copasi. The
                                  default is copasi in the ConfigDir.
  --exportBerkeleyMadonna string  The Berkeley Madonna file to export.
  --exportC string                The C code file to export.
  --home string                   Your home directory.
  --license                       Display the license.
  --verbose                       Enable output of messages during runtime
                                  to std::error.
  -c, --copasidir string          The COPASI installation directory.
  -e, --exportSBML string         The SBML file to export.
  -i, --importSBML string         A SBML file to import.
  -s, --save string               The file the model is saved to after work.
  -t, --tmp string                The temp directory used for autosave.
```

Condor-COPASI high-throughput computing



Condor-COPASI Web Frontend - Stochastic Simulation - Mozilla Firefox

File Edit View History Bookmarks Tools Help

Condor-COPASI Web Frontend - Stochas...

Condor-COPASI

Welcome **mendes** | Administration | Logout

Home >> Tasks >> Stochastic Simulation >>

- Home
- My Account
- Tasks
  - Sensitivity Optimization
  - Stochastic Simulation
  - Scan in Parallel
  - Optimization Repeat
  - Parameter Estimation Repeat
  - Optimization Repeat (Different Algorithms)
- Help

Stochastic Simulation

Select the COPASI model to submit. Before submitting, ensure the model has been correctly configured:

- **Time Course task:**
  - The Time Course should be set up as if a single run were to take place on the local machine
  - An appropriate stochastic method must be selected

Condor-COPASI will automatically generate an appropriate report; no report needs to be set for the Time Course task.

Please note - it is very important that the COPASI file is saved using a supported version of COPASI. At present, only Build 33 (version 4.6.33) and Build 34 (version 4.6.34) are supported.

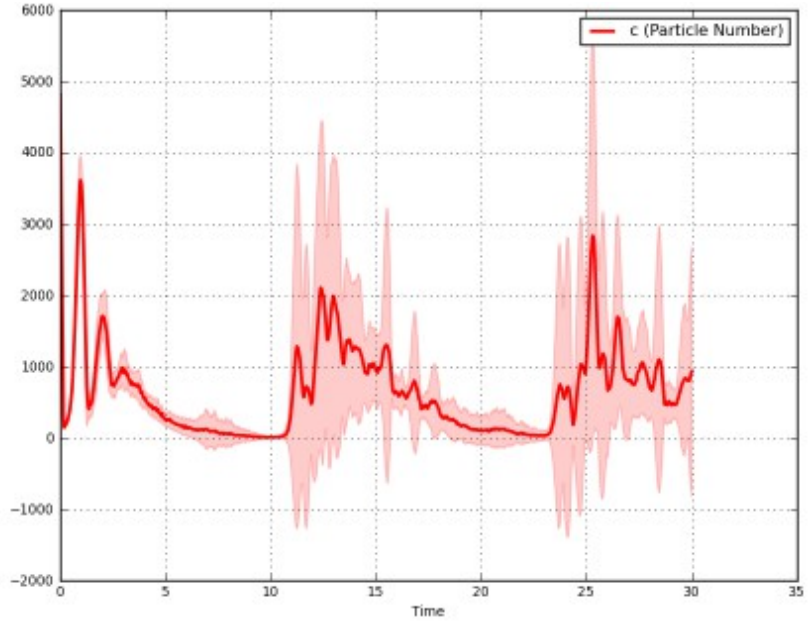
Model file: Browse...

Job Name: For your reference, enter a name for this job

Skip load balancing step: Select this to skip the automatic load balancing step, and make the run time of each parallel job as short as possible. **Use with caution! This has the potential to overload the Condor system with huge numbers of parallel jobs.** Not applicable for some job types - see documentation for further details.

Repeats: The number of repeats to perform

Submit



Compare Global Sensitivity Job Output