UCONN HEALTH

Metabolic {kinetic} model development with COPASI

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

Scope

- A little bit of history...
- Overview of COPASI and its user ecosystem
- Simulation methods
- Analysis methods
- Reproducibility

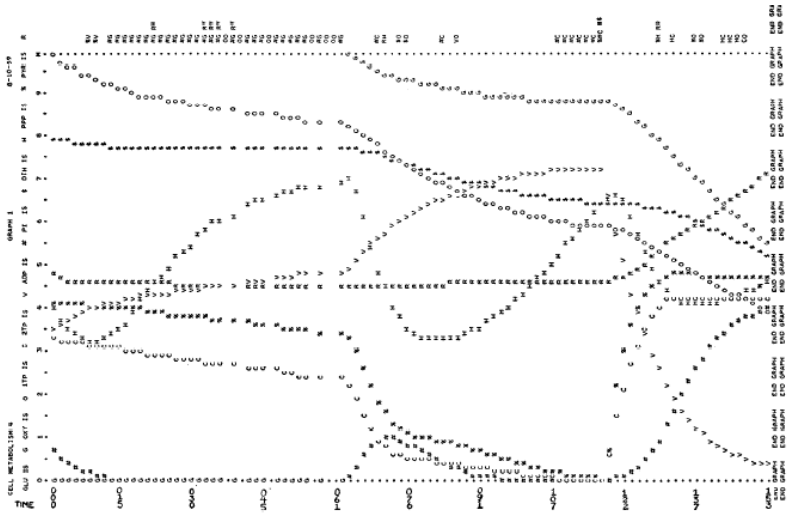
THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 235, No. 8, August 1960
Printed in U.S.A.

Metabolic Control Mechanisms

V. A SOLUTION FOR THE EQUATIONS REPRESENTING INTERACTION BETWEEN GLYCOLYSIS AND RESPIRATION IN ASCITES TUMOR CELLS*†

BRITTON CHANCE, DAVID GARFINKEL,‡ JOSEPH HIGGINS,§ AND BENNO HESS¶

- 500 hours of UNIVAC I time
- Euler method for integration, 12-digit numbers
- Many failures of model against experiment but an exemplary application of model-based reasoning



BIOSSIM – A generic “biosimulator”

COMPUTERS AND BIOMEDICAL RESEARCH 2, 31–44 (1968)

A Machine-Independent Language for the Simulation of Complex Chemical and Biochemical Systems*

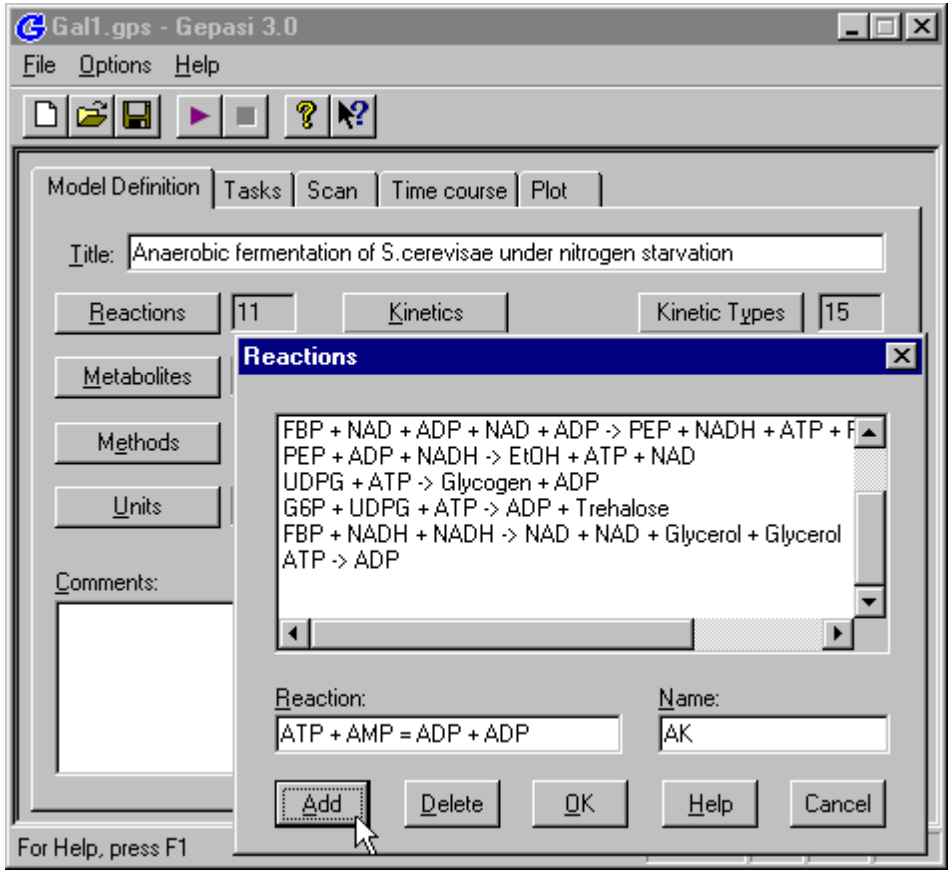
DAVID GARFINKEL

Johnson Research Foundation, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received April 6, 1968

- Model specification and simulation without need for programming
- Models can be easily manipulated without having to understand specific code
- This is a precursos towards reproducibility, where a model becomes independent from the source code that runs a simulation

Gepasi



http://www.gepasi.org/

Mendes, P. (1993) *Comput. Applic. Biosci.* **9**, 563-571.

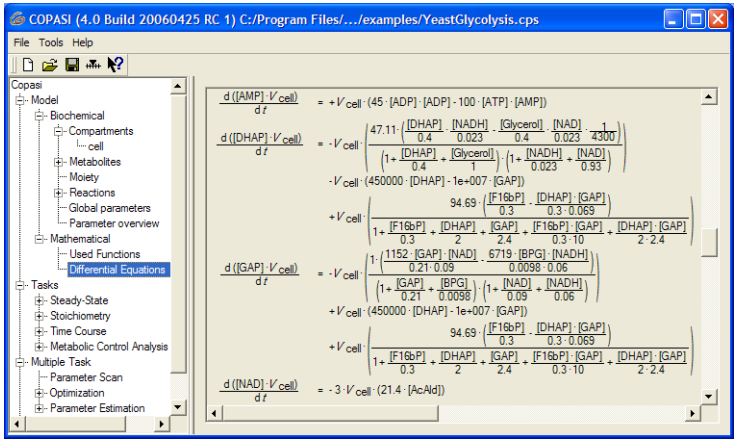
Mendes, P. (1997) *Trends Biochem. Sci.* **22**, 361-363.

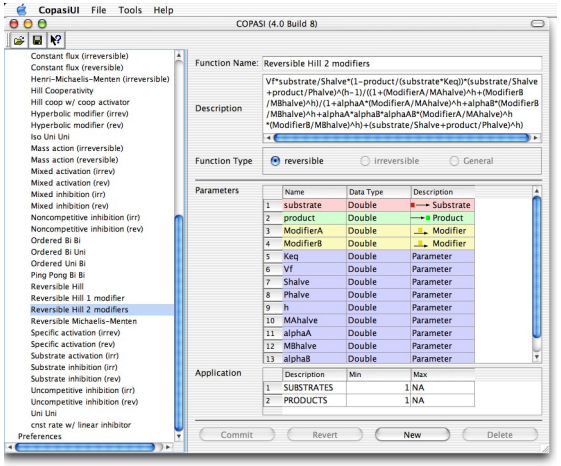
Mendes, P. & Kell, D. B. (1998) *Bioinformatics* **14**, 869-883

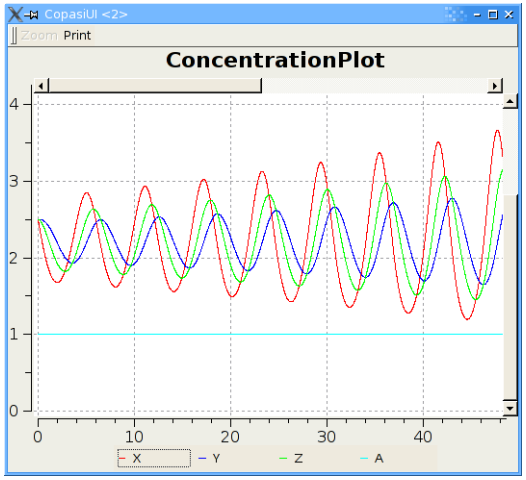
COPASI

- ODE, SDE, or SSA
- Discrete events
- Steady states
- Stability analysis
- Parameter scans
- Sensitivity analysis
- Metabolic Control Analysis
- Time scale separation analysis

- Optimisation,
- Parameter estimation
- Cross-sections
- Lyapunov exponents
- Network diagrams
- 2D and surface plots
- GUI and command line versions
- Reads/writes SBML



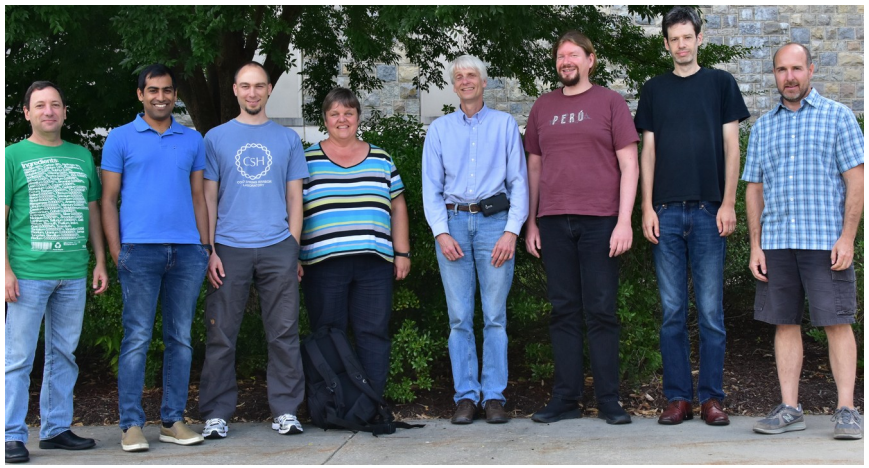




http://www.copasi.org **@COPASI_software**

COPASI development

- Collaboration with Ursula Kummer since 1999
- New GUI, combined Gepasi back-end w/ Kummer's STODE for stochastic simulation
- First public release of COPASI in 2006



Mendes group
Connecticut, USA
UCONN SCHOOL OF MEDICINE

Kummer, Sahle, & Pahle groups
Heidelberg, Germany

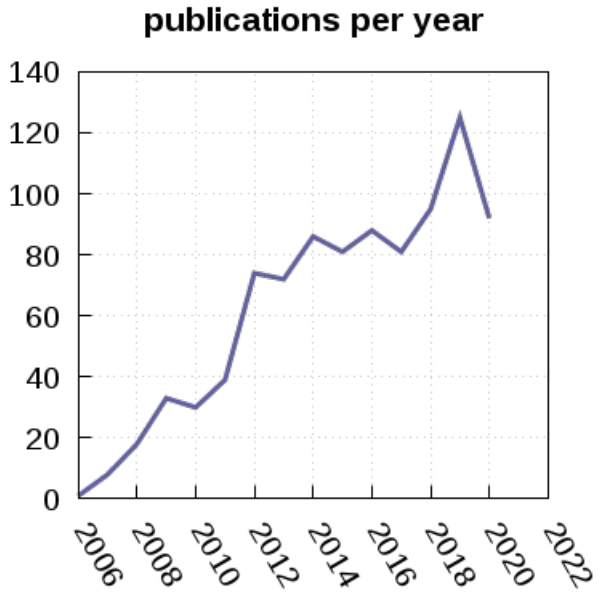
Hoops group
Virginia, USA
University of Virginia

NIH National Institute of General Medical Sciences R24 GM137787 Mechanistic Modeling of Cellular Systems

BBSRC bioscience for the future
EPSRC
Bundesministerium für Bildung und Forschung
Virginia Bioinformatics Institute at Virginia Tech
KTF

COPASI

- Has now a well-established worldwide user-base
- > 1000 publications that use COPASI
- Around 100 papers published yearly that use COPASI
- Over 10,000 downloads per year



http://copasi.org/Research

Citation analysis

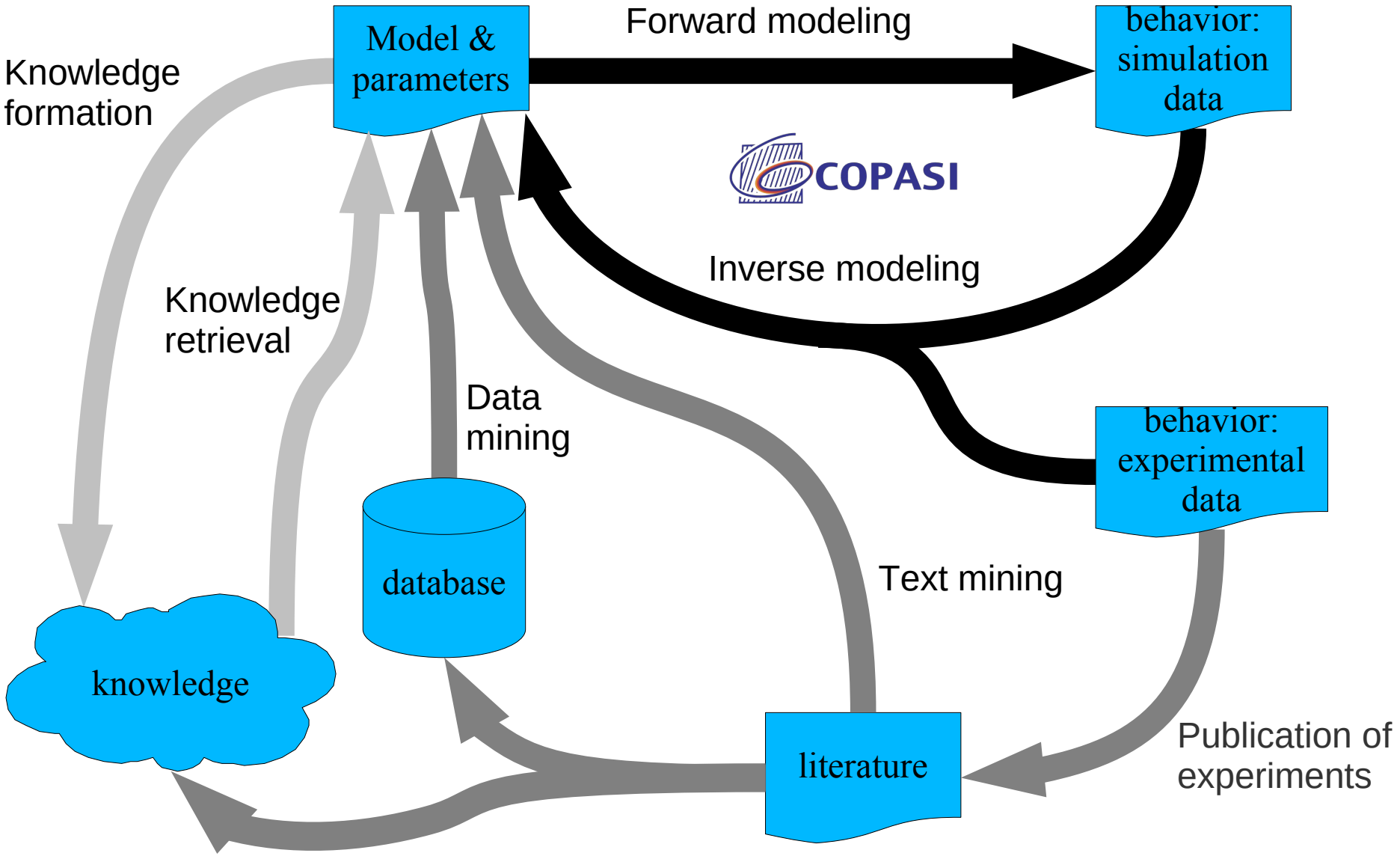
- 854 journal articles
- 91 theses
- 33 conf. procs.
- 16 book chapters
- 16 preprints

• PLOS One	44
• J. Am. Chem. Soc.	38
• BMC Sys. Bio.	30
• PLOS Comp. Bio.	28
• Scientific Reports	21
• J. Biol. Chem.	15
• PNAS	15
• FEBS J.	12
• ACS Catalysis	12
• Organometallics	11
• Bioinformatics	11

• Comput. Method	148
• Software	38
• Lab. Method	23
• Theory	18
• Education	6

• Chemistry	204
• Signaling	168
• **Metabolism**	**140**
• Biochemistry	64
• **Microbiology**	**63**
• Enzymology	59
• Macromol. Biochem.	57
• Cell Biology	56
• Physiology	53
• Immunology	51
• Synthetic Biology	38
• **Biotechnology**	**29**
• Pharmacology	24
• Genetics	24
• Biophysics	17
• Genomics	16
• Toxicology	13
• Epidemiology	6
• **Whole-Cell Models**	**5**
• Parasitology	5

Modeling cycle

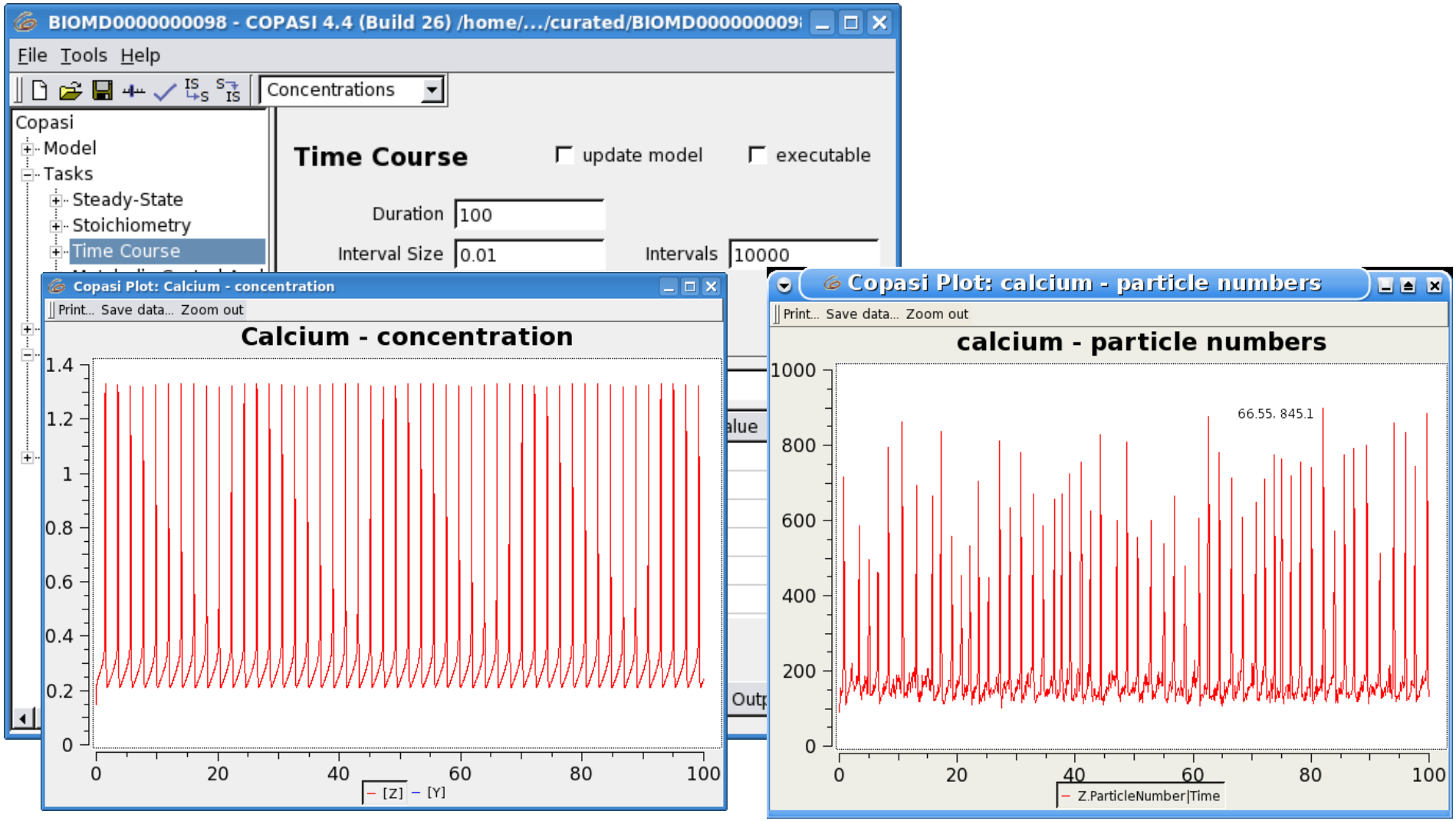


Simulation methods available in COPASI

- ODE-based
- Stochastic differential equations (SDE)
- Steady-state analysis
- Linear noise approximation
- Gillespie exact methods
- Gillespie approximate methods
- Hybrid ODE-Gillespie methods

- Arbitrary number of compartments
- Compartment sizes can be dynamic (variables)
- Discrete events possible in most simulations

Deterministic and stochastic time course simulations



Steady state solutions

Steady State Result

Update Model | Save to File

A steady state with given resolution was found.

Species | Compartments | Model Quantities | Reactions | Stability | Jacobian (Complete) | Jacobi...

	Name	Type	Concentration [mmol/l]	Rate [mmol/(l*s)]	Transition Time [s]
1	ACCOA	reactions	0.154743	-1.67319e-15	0.386001
2	ACO	reactions	0.0321499	8.18909e-15	0.142034
3	ACP	reactions	0.0143909	2.35334e-15	0.785229
4	AKG	reactions	0.597871	-5.56708e-15	4.65494
5	BPG	reactions	0.0654104	7.27768e-13	0.168473
6	CIT	reactions	0.0895308	-7.4001e-15	0.395534
7	DAP	reactions	0.437094	-6.97569e-14	2.3739
8	E4P	reactions	0.1313	7.48172e-17	11.6509
9	F6P	reactions	0.261766	-5.27483e-15	1.41235
10	FDP	reactions	0.281808	2.12146e-14	1.52957
11	FUM	reactions	0.213115	1.46914e-15	1.01694
12	G6P	reactions	0.861128	7.32784e-15	3.74403
13	GAP	reactions	0.117183	3.61337e-14	0.291839
14	GL6P	reactions	0.00326164	2.87716e-15	0.0557485
15	GLX	reactions	0.00881041	1.21068e-15	0.0899794
16	ICIT	reactions	0.105783	-1.68679e-15	0.467333
17	KDPG	reactions	0.0868177	1.32631e-16	5.30709
18	MAL	reactions	1.03215	5.0182e-14	0.366193
19	NAD	reactions	1.41154	1.18164e-13	1.47068
20	NADH	reactions	0.158456	-1.18164e-13	0.165096
21	NADP	reactions	0.167837	-1.33311e-14	0.5997

Steady State Result

Update Model | Save to File

A steady state with given resolution was found.

Species | Compartments | Model Quantities | Reactions | Stability | Jacobian (Complete) | Jacobi...

	Name	Flux (extensive) [mmol/s]	Flux (intensive) [mmol/(l*s)]	Reaction
1	PGI	0.168301	0.168301	G6P = F6P; PEP PGN
2	PFK	0.18424	0.18424	ATP + F6P = ADP + FDP; PEP MgADP MgATP
3	FBA	0.184125	0.184125	FDP = DAP + GAP; PEP
4	TPI	0.184125	0.184125	DAP = GAP
5	GDH	0.388254	0.388254	GAP + NAD + P = BPG + NADH
6	PGK	0.388254	0.388254	ADP + BPG = ATP + PGA3; MgADP MgATP
7	GPM	0.364998	0.364998	PGA3 = PGA2
8	ENO	0.364998	0.364998	PGA2 = PEP
9	PYK	0.158113	0.158113	ADP + PEP -> ATP + PYR; FDP G6P GL6P ...
10	ZWF	0.0585065	0.0585065	G6P + NADP = GL6P + NADPH
11	PGL	0.0585064	0.0585064	GL6P = PGN; G6P
12	GND	0.0421477	0.0421477	NADP + PGN = NADPH + RU5P + HCO3; AT...
13	RPE	0.0169246	0.0169246	RU5P = X5P
14	RPI	0.025223	0.025223	RU5P = R5P; E4P
15	X5P_GAP_TKT	0.0169246	0.0169246	tkt + X5P = GAP + tktC2
16	F6P_E4P_TKT	0.00565509	0.00565509	E4P + tktC2 = F6P + tkt
17	S7P_R5P_TKT	0.0112695	0.0112695	R5P + tktC2 = S7P + tkt
18	F6P_GAP_TAL	0.0112695	0.0112695	GAP + talC3 = F6P + tal
19	S7P_E4P_TAL	0.0112695	0.0112695	S7P + tal = E4P + talC3
20	FBP	0.000115429	0.000115429	FDP -> F6P + P; AMP MG MgFDP
21	PPC	0.079423	0.079423	PEP + HCO3 = OAA + P; ACCOA CIT FDP FU...

The central modeling question

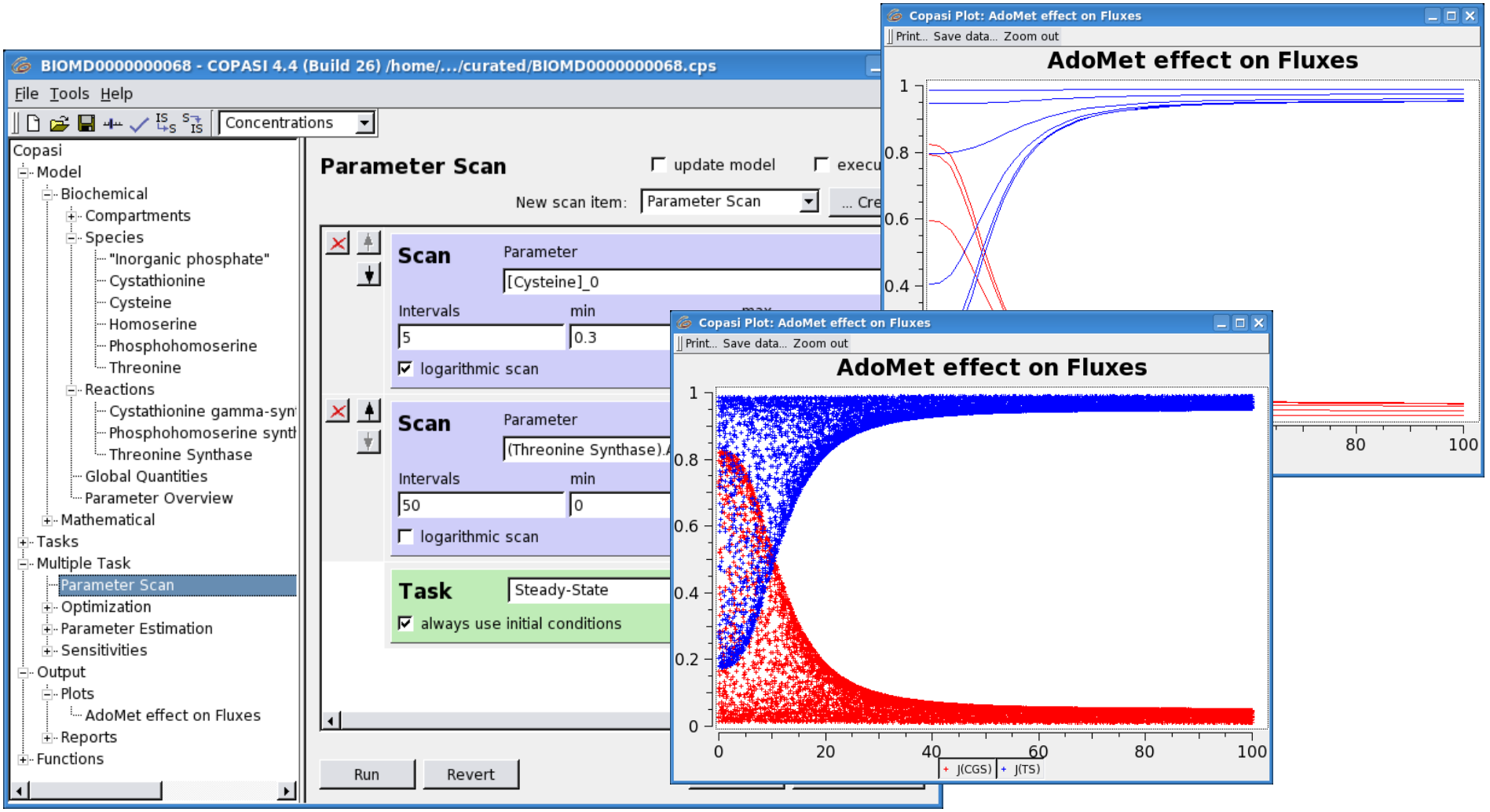
- Given a model of a system:
  how do the parameters affect the state of the system?

- 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)

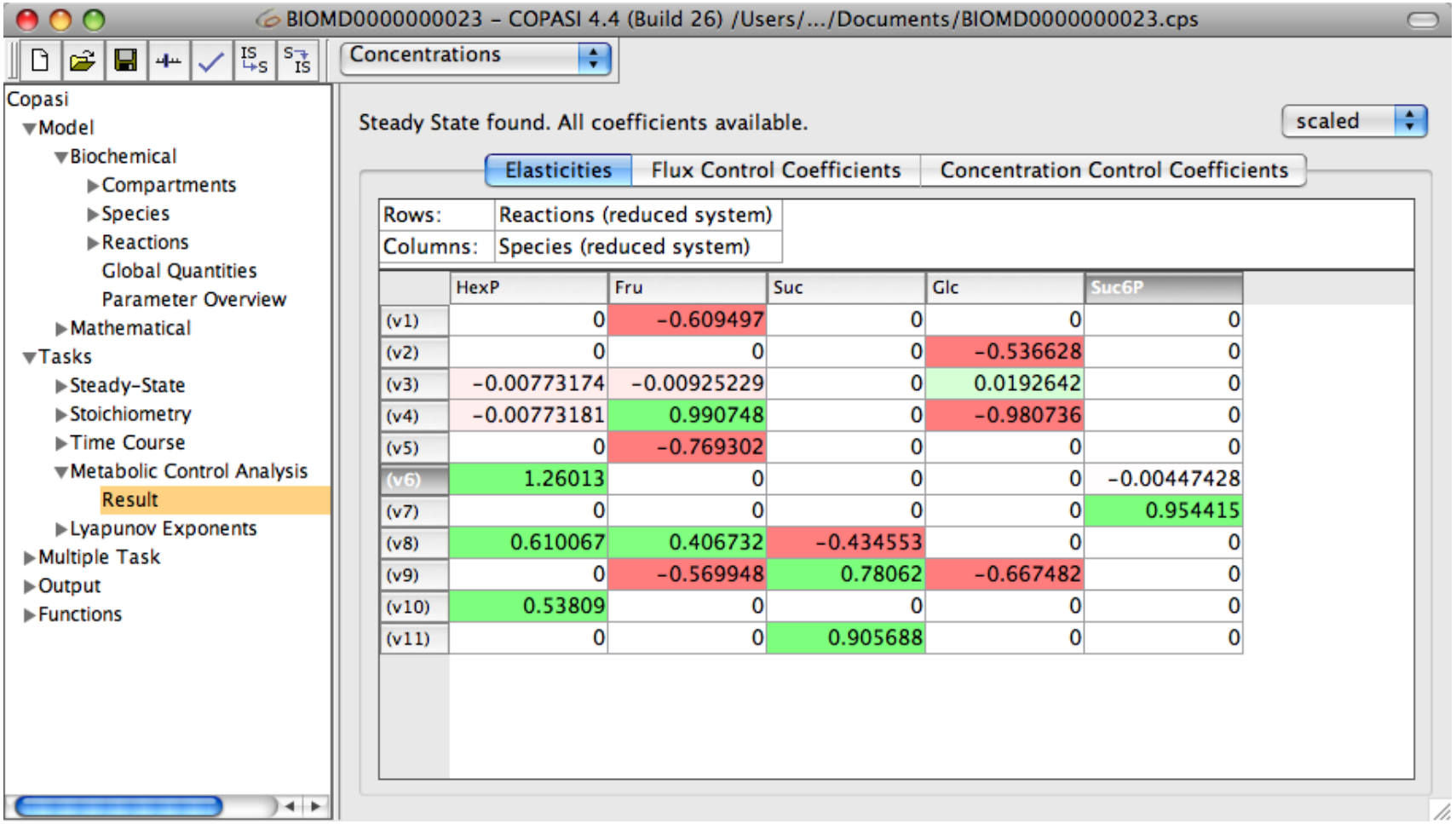
Analyses of dynamic simulations

- ***Stability analysis***: evaluate if steady state is stable
- ***Sensitivity analysis***: measures how much a parameter affects a variable (linearization)
- ***Parameter scanning***: perform several simulations at different values of one (or more) parameter(s)
- ***Optimization***: find parameter values for optimal states of the system (optimal means the maximum or minimum of some function of interest)
- ***Time scale analyses***: identify the distribution of time scales in the system
- ***Periodicity analysis***: identify periods/frequencies of oscillations

Parameter scanning & sampling

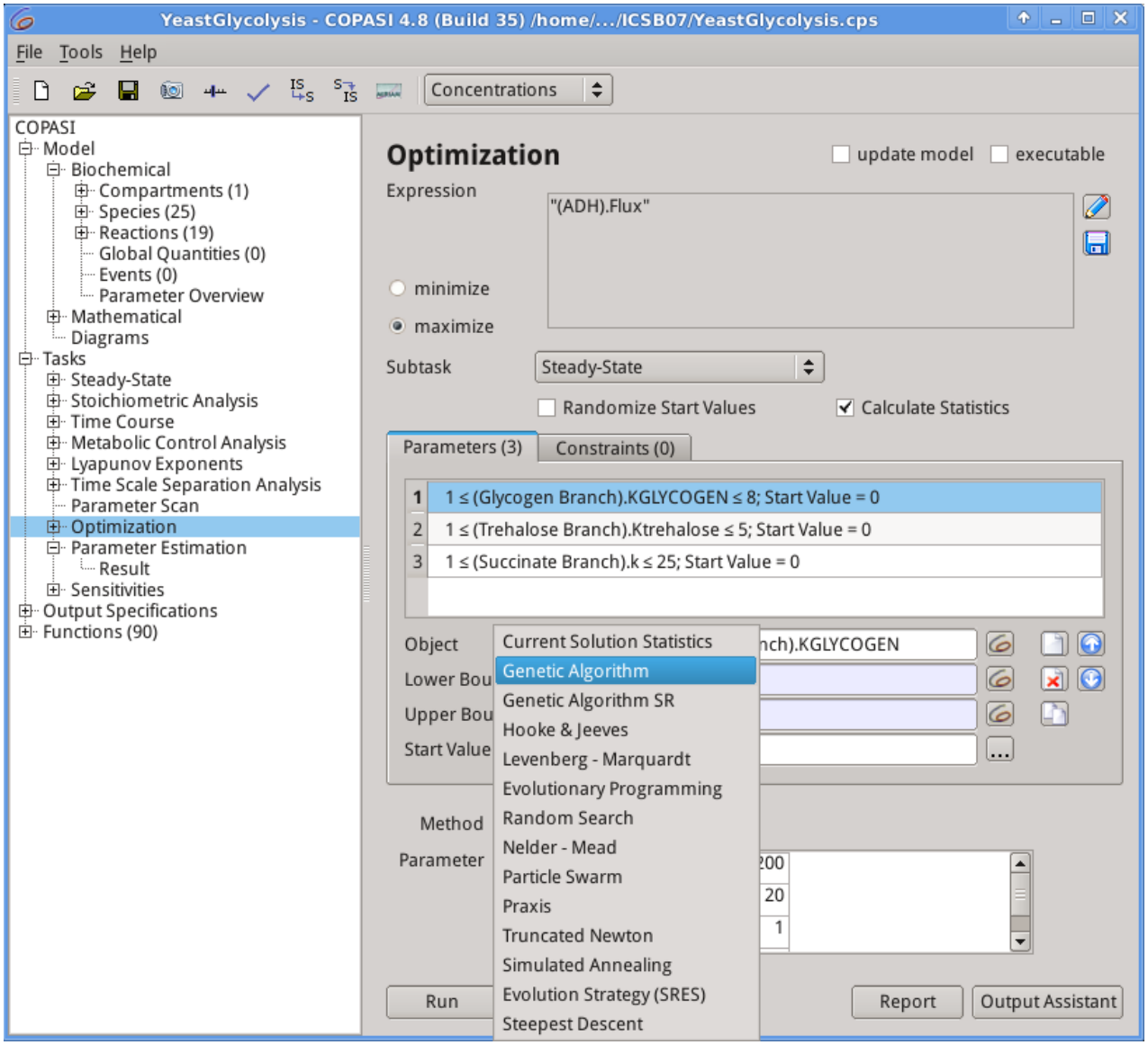


Sensitivity analysis & MCA



	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

COPASI – Optimisation



Optimization methods

Based on derivatives:

- Levenberg-Marquardt
- Steepest descent
- Truncated Newton

Direct search:

- Hooke & Jeeves
- Nelder & Mead
- Praxis

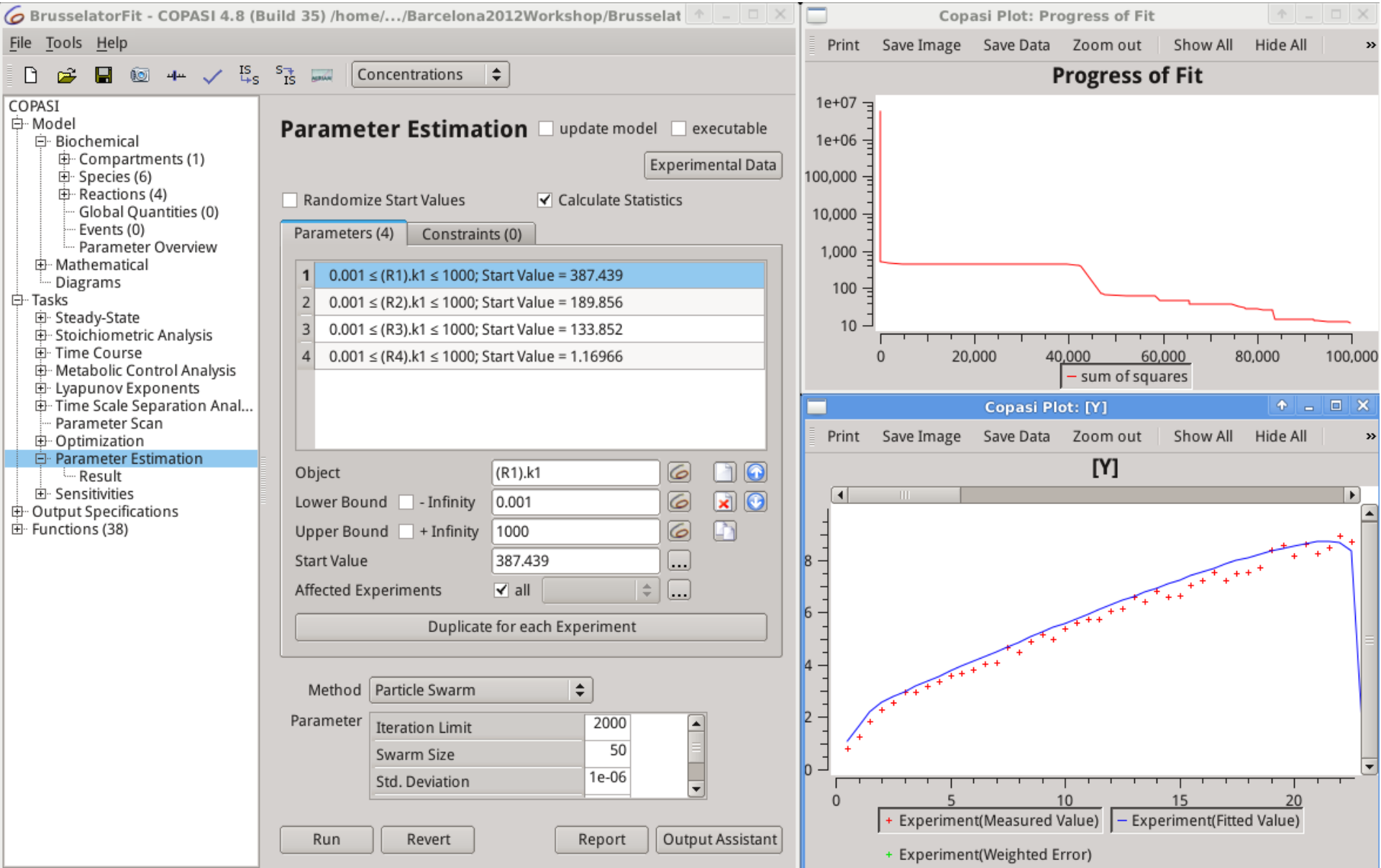
Evolutionary:

- Genetic algorithm
- GA w/ stochastic ranking
- Evolutionary programming
- Evolution strategy w/ stochastic ranking

Other stochastic:

- Simulated annealing
- Particle swarm
- Random search

COPASI – Parameter estimation



Programming with COPASI

- Command line simulation engine (CopasiSE)

- Low-level API native C++ w/ bindings for Python, Java, R, etc...
  - Downloadable from main webpage
  - Used by Virtual Cell, Cell Designer, PyCoTools, SBpipe, etc.

- **CoRC** – accessing COPASI through R
  - https://jpahle.github.io/CoRC/
- **BasiCO** – accessing COPASI through python
  - https://github.com/copasi/basico

Reproducibility in modeling metabolism

- SBML – allows models to be described in a program-independent way. Models written with older software can still be easily run with modern software.
- MIRIAM – describes level of annotation that would allow a model and its parts to be easily interpretable
- SED-ML – allows describing model simulations and associated output, independently of software
- OMEX – file format that can include SBML, SED-ML, data sources, metadata, etc. in a single container
- Biosimulators.org and Biosimulations.org make use of these technologies to allow a standard interface to simulate the same models across a range of software

COPASI publications

- Hoops S, Sahle S, Gauges R, Lee C, Pahle J, Simus N, Singhal M, Xu L, Mendes P & Kummer U (2006) COPASI: a COmplex PAthway SImulator. *Bioinformatics* 22: 3067-74**.**
- Bergmann FT, Hoops S, Klahn B, Kummer U, Mendes P, Pahle J, Sahle S (2017) COPASI and its applications in biotechnology. *J. Biotechnology* 261:215–220
- Mendes P, Hoops S, Sahle S, Gauges R, Dada JO & Kummer U (2009) Computational Modeling of Biochemical Networks Using COPASI. *Methods Mol. Biology*, Humana Press. 500: 17-59.
- Challenger JD, McKane AJ & Pahle J (2012). Multi-compartment linear noise approximation. *J. Stat. Mech.* P11010.
- Pahle J, Challenger JD, Mendes P & McKane AJ (2012) Biochemical fluctuations, optimisation and the linear noise approximation. *BMC Systems Biology* 6: 86
- Surovtsova I, Simus N, Lorenz T, König A, Sahle S & Kummer U (2009) Accessible methods for the dynamic time-scale decomposition of biochemical systems. *Bioinformatics* 25: 2816-23.
- Dada, J.O. and Mendes, P. (2009). Design and Architecture of Web Services for Simulation of Biochemical Systems. *Lecture Notes in Computer Science*, Springer 5647: 182-195.
- Kent E, Hoops S, Mendes P (2012) Condor-COPASI: High-Throughput Computing for Biochemical Networks. *BMC Systems Biology* 6:91

Acknowledgments

Mendes group (throughout 2000-2022):

Postdocs:

J. Dada, H. Baig, A. Gupta, A. Kamal, E. Murabito, J. Pahle, P. Zarrineh

PhD students:

E. Kent

Ms students:

Y. He, M. Kulkarni, C. Lee, R. Luktuke, G. Singh, M. Singhal, A. Srivastava, W. Sun, S. Tupe, L. Xu

Undergraduates:

A. Riley, M. Kaszuba

COPASI collaborators:

F. Bergmann, S. Hoops, B. Klahn, U. Kummer, J. Pahle, N. Paton, S. Sahle

VCELL collaborators:

M. Blinov, A. Cowan, L. Loew, I. Moraru, B. Slepchenko