



Metabolic {kinetic} model development with COPASI

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

Scope

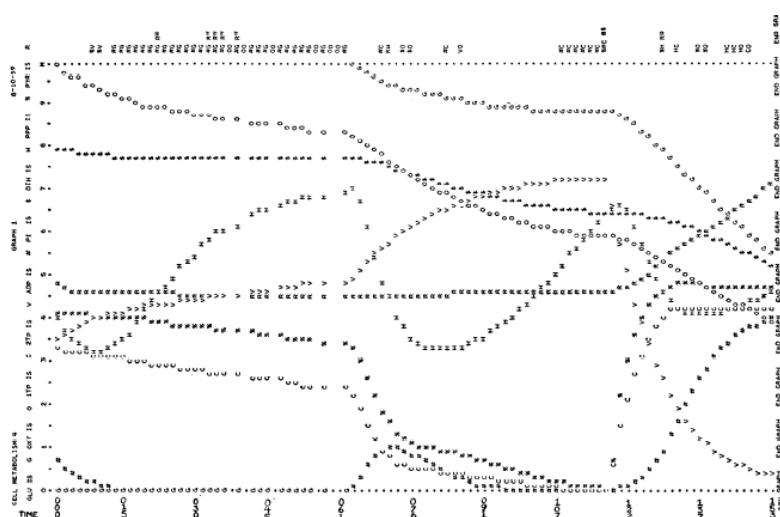
- A little bit of history...
- Overview of COPASI and its user ecosystem
- Simulation methods
- Analysis methods
- Reproducibility

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*

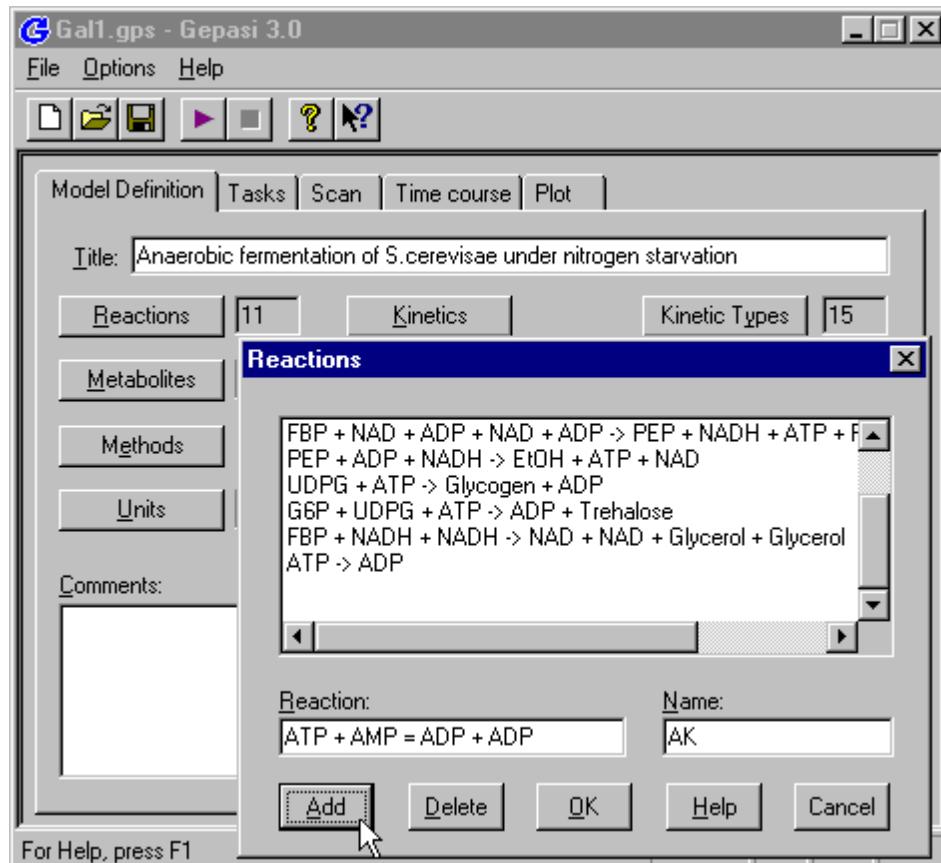
DAVID GARFINKEL

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 precuros towards reproducibility, where a model becomes independent from the source code that runs a simulation

Gepasi



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

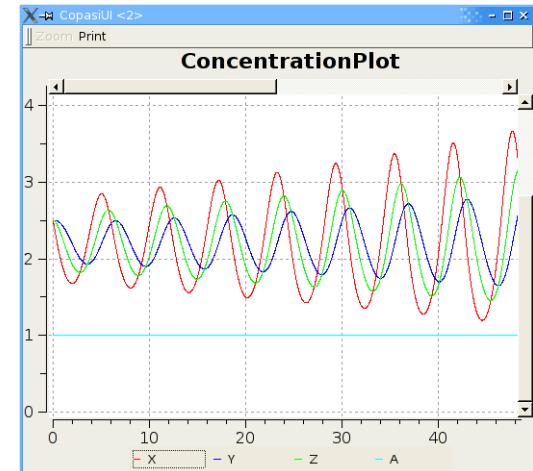
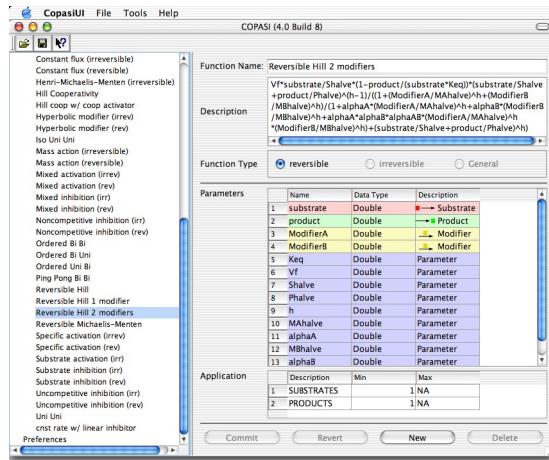
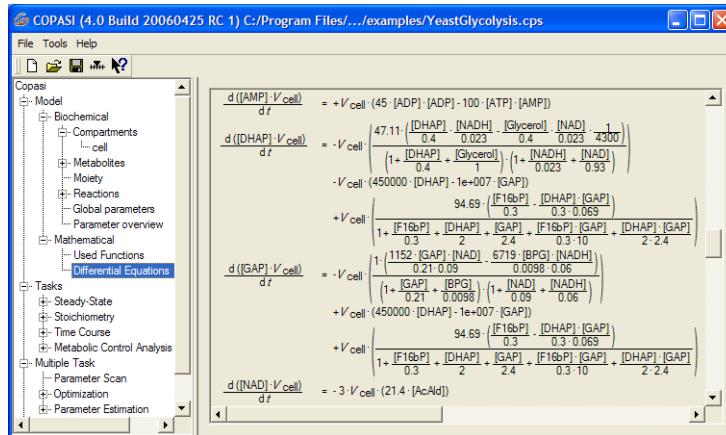
Mendes, P. (1997) *Trends Biochem. Sci.* **22**, 361-363.

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

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

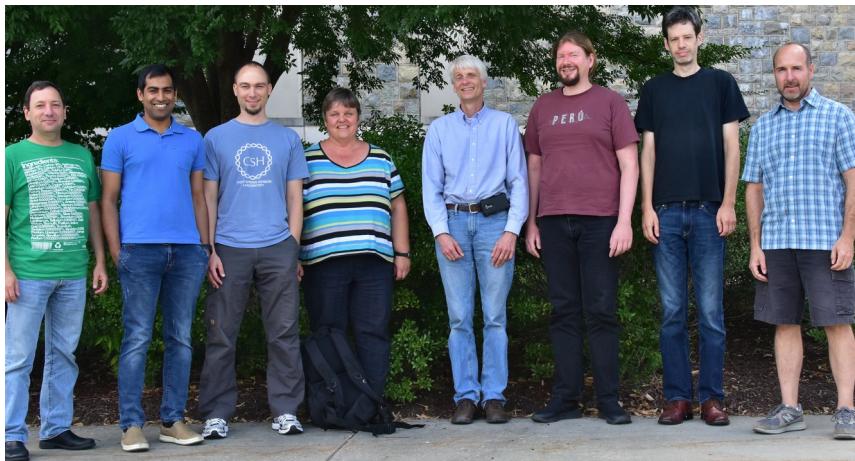


- ODE, SDE, or SSA
- Discrete events
- Steady states
- Stability analysis
- Parameter scans
- Sensitivity analysis
- Metabolic Control Analysis
- Time scale separation analysis
- Optimisation,
- Parameter estimation
- Cross-sections
- Lyapunov exponents
- Network diagrams
- 2D and surface plots
- GUI and command line versions
- Reads/writes SBML



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



National Institute of
General Medical Sciences

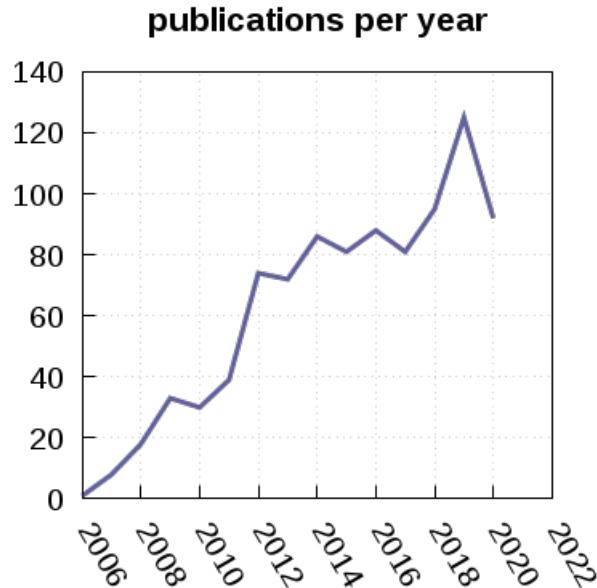
R24 GM137787 Mechanistic Modeling of Cellular Systems





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

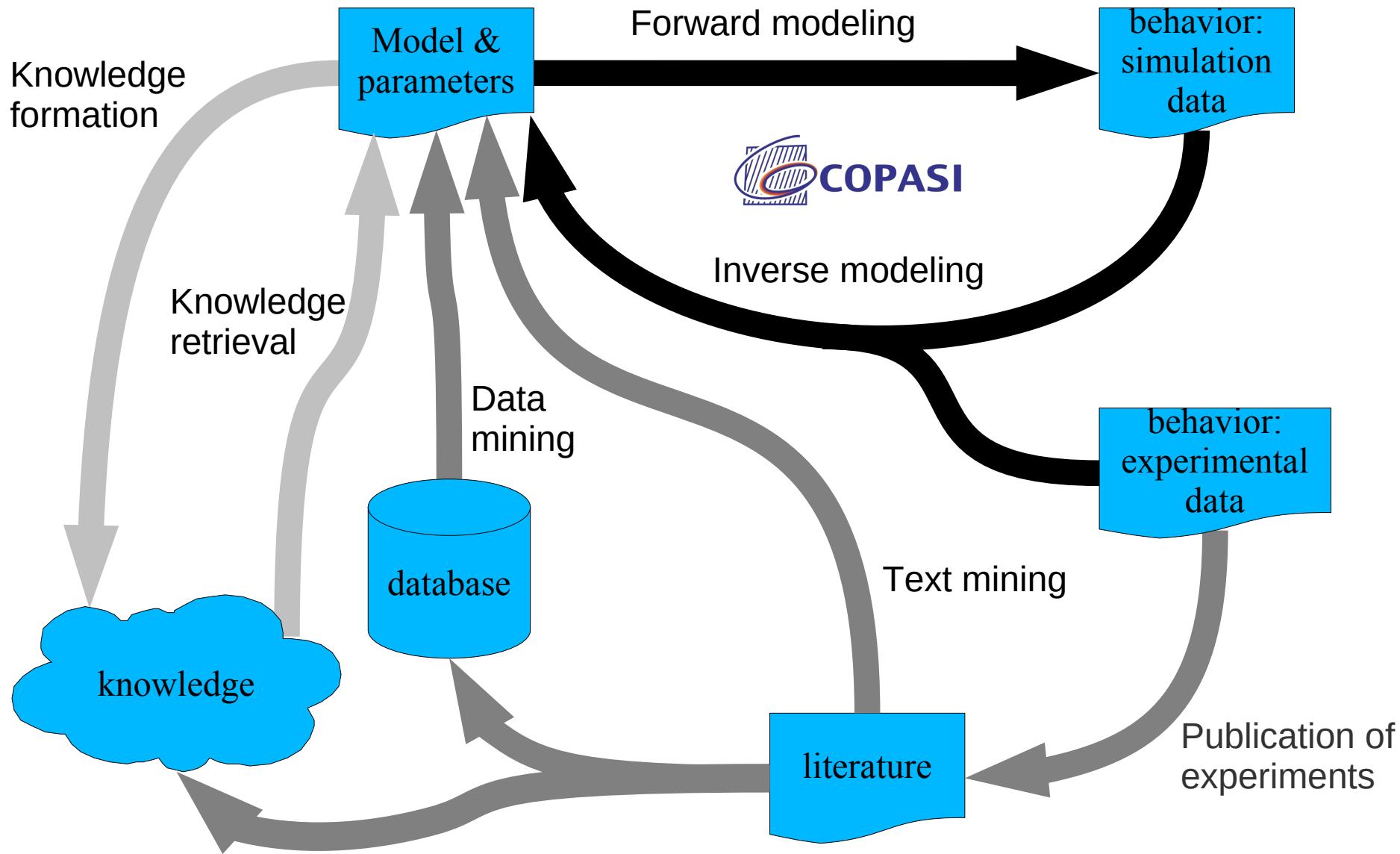


<http://copasi.org/Research>

Citation analysis

• 854 journal articles	• PLOS One	44	• Chemistry	204
• 91 theses	• J. Am. Chem. Soc.	38	• Signaling	168
• 33 conf. procs.	• BMC Sys. Bio.	30	• Metabolism	140
• 16 book chapters	• PLOS Comp. Bio.	28	• Biochemistry	64
• 16 preprints	• Scientific Reports	21	• Microbiology	63
	• J. Biol. Chem.	15	• Enzymology	59
	• PNAS	15	• Macromol. Biochem.	57
	• FEBS J.	12	• Cell Biology	56
	• ACS Catalysis	12	• Physiology	53
	• Organometallics	11	• Immunology	51
	• Bioinformatics	11	• Synthetic Biology	38
	• Comput. Method	148	• Biotechnology	29
	• Software	38	• Pharmacology	24
	• Lab. Method	23	• Genetics	24
	• Theory	18	• Biophysics	17
	• Education	6	• Genomics	16
			• Toxicology	13
			• Epidemiology	6
			• Whole-Cell Models	5
			• Parasitology	5

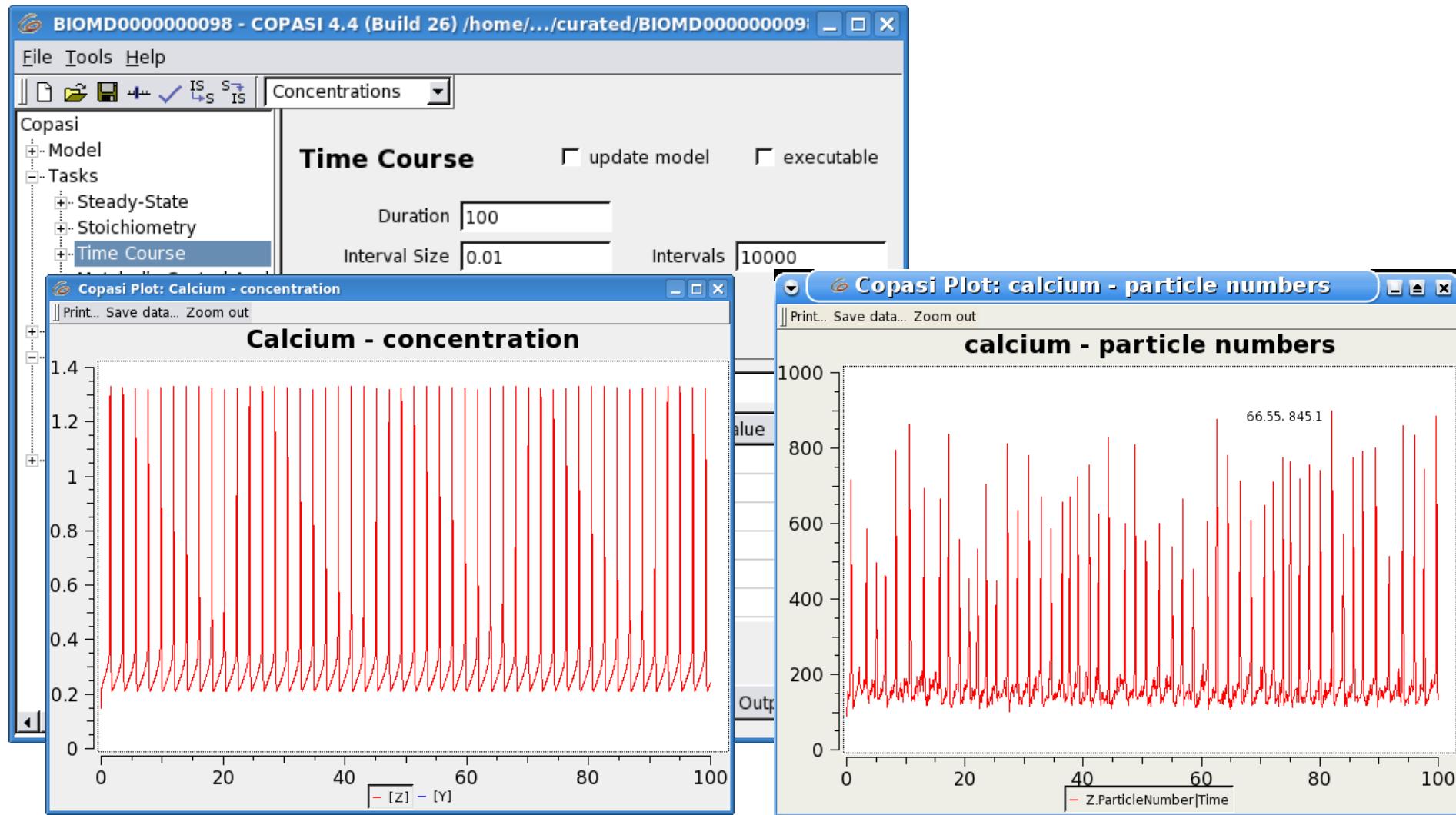
Modeling cycle



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	FDP + HCO3 = OAA + P- ACCOA CIT FDP F1U		

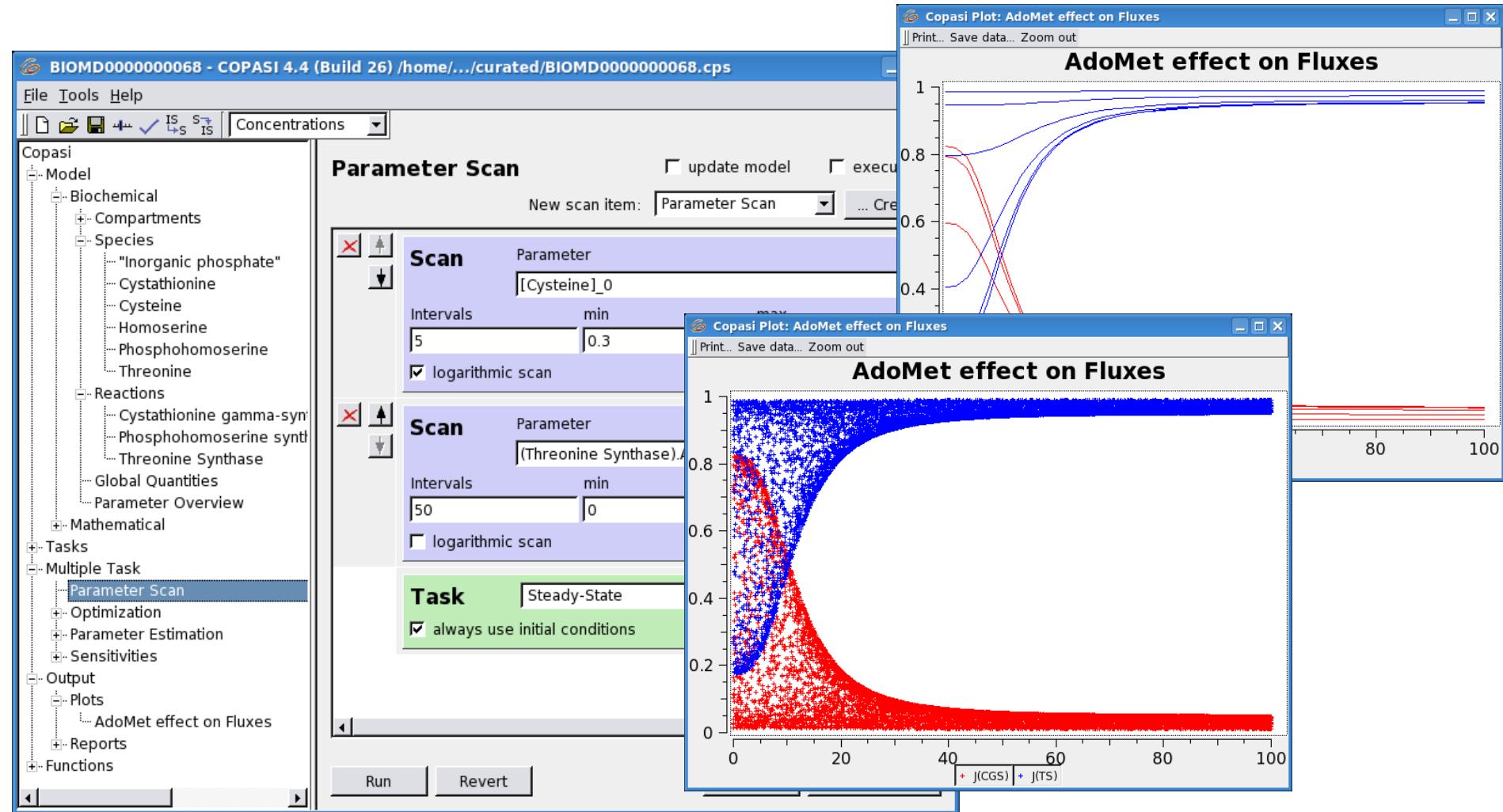
The central modeling question

- 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

BIOMD0000000023 - COPASI 4.4 (Build 26) /Users/.../Documents/BIOMD0000000023.cps

Copasi

Model

- Biochemical
 - Compartments
 - Species
 - Reactions
 - Global Quantities
 - Parameter Overview
- Mathematical

Tasks

- Steady-State
- Stoichiometry
- Time Course
- Metabolic Control Analysis
 - Result
- Lyapunov Exponents

Multiple Task

Output

Functions

Concentrations

Steady State found. All coefficients available.

scaled

	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

YeastGlycolysis - COPASI 4.8 (Build 35) /home/.../ICSB07/YeastGlycolysis.cps

File Tools Help

Concentrations

COPASI

Model

- Biochemical
 - Compartments (1)
 - Species (25)
 - Reactions (19)
 - 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
 - Result
 - Sensitivities
- Output Specifications
- Functions (90)

Optimization

Expression: "(ADH).Flux"

minimize (radio button)

maximize (radio button)

Subtask: Steady-State

Randomize Start Values Calculate Statistics

Parameters (3) Constraints (0)

1	$1 \leq (\text{Glycogen Branch}).\text{KGLYCOGEN} \leq 8$; Start Value = 0
2	$1 \leq (\text{Trehalose Branch}).\text{Ktrehalose} \leq 5$; Start Value = 0
3	$1 \leq (\text{Succinate Branch}).k \leq 25$; Start Value = 0

Object: Genetic Algorithm

Lower Bound: 1

Upper Bound: 25

Start Value: 1

Method: Genetic Algorithm

Parameter: 100

Run

Current Solution Statistics

Genetic Algorithm SR

Hooke & Jeeves

Levenberg - Marquardt

Evolutionary Programming

Random Search

Nelder - Mead

Particle Swarm

Praxis

Truncated Newton

Simulated Annealing

Evolution Strategy (SRES)

Steepest Descent

Report Output Assistant

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

BrusselatorFit - COPASI 4.8 (Build 35) /home/.../Barcelona2012Workshop/Brusselat

File Tools Help

IS IS Concentrations

COPASI

- Model
 - Biochemical
 - Compartments (1)
 - Species (6)
 - Reactions (4)
 - Global Quantities (0)
 - Events (0)
 - Parameter Overview
- Mathematical Diagrams
- Tasks
 - Steady-State
 - Stoichiometric Analysis
 - Time Course
 - Metabolic Control Analysis
 - Lyapunov Exponents
 - Time Scale Separation Anal...
 - Parameter Scan
 - Optimization
- Parameter Estimation
 - Result
 - Sensitivities
- Output Specifications
- Functions (38)

Parameter Estimation update model executable

Randomize Start Values Calculate Statistics

Parameters (4) Constraints (0)

1	$0.001 \leq (R1).k1 \leq 1000$; Start Value = 387.439
2	$0.001 \leq (R2).k1 \leq 1000$; Start Value = 189.856
3	$0.001 \leq (R3).k1 \leq 1000$; Start Value = 133.852
4	$0.001 \leq (R4).k1 \leq 1000$; Start Value = 1.16966

Object: (R1).k1
Lower Bound: -Infinity 0.001
Upper Bound: +Infinity 1000
Start Value: 387.439
Affected Experiments: all

Duplicate for each Experiment

Method: Particle Swarm

Parameter

- Iteration Limit: 2000
- Swarm Size: 50
- Std. Deviation: 1e-06

Run Revert Report Output Assistant

Copasi Plot: Progress of Fit

Print Save Image Save Data Zoom out Show All Hide All

Progress of Fit

1e+07
1e+06
100,000
10,000
1,000
100
10

0 20,000 40,000 60,000 80,000 100,000

— sum of squares

Copasi Plot: [Y]

Print Save Image Save Data Zoom out Show All Hide All

[Y]

Experiment(Measured Value) Experiment(Fitted Value)
Experiment(Weighted Error)

The screenshot shows the COPASI software interface for parameter estimation. On the left, the 'Parameter Estimation' section is selected in the tree view. It displays four parameters being estimated, each with a range constraint and a start value. Below this, there are fields for setting the method (Particle Swarm), iteration limit (2000), swarm size (50), and standard deviation (1e-06). At the bottom, buttons for 'Run', 'Revert', 'Report', and 'Output Assistant' are visible.

On the right, two plots are shown. The top plot, titled 'Copasi Plot: Progress of Fit', shows the 'sum of squares' error over 100,000 iterations, starting at 1e+07 and rapidly decreasing to around 10. The bottom plot, titled 'Copasi Plot: [Y]', compares experimental measured values (red '+' markers) with fitted values (blue line) for a variable 'Y' across a range from 0 to 20. A legend indicates the red '+' markers represent 'Experiment(Measured Value)' and the blue line represents 'Experiment(Fitted Value)'. A green '+' marker also appears in the legend, likely representing 'Experiment(Weighted Error)'.

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

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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:

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Sahle

VCELL collaborators:

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