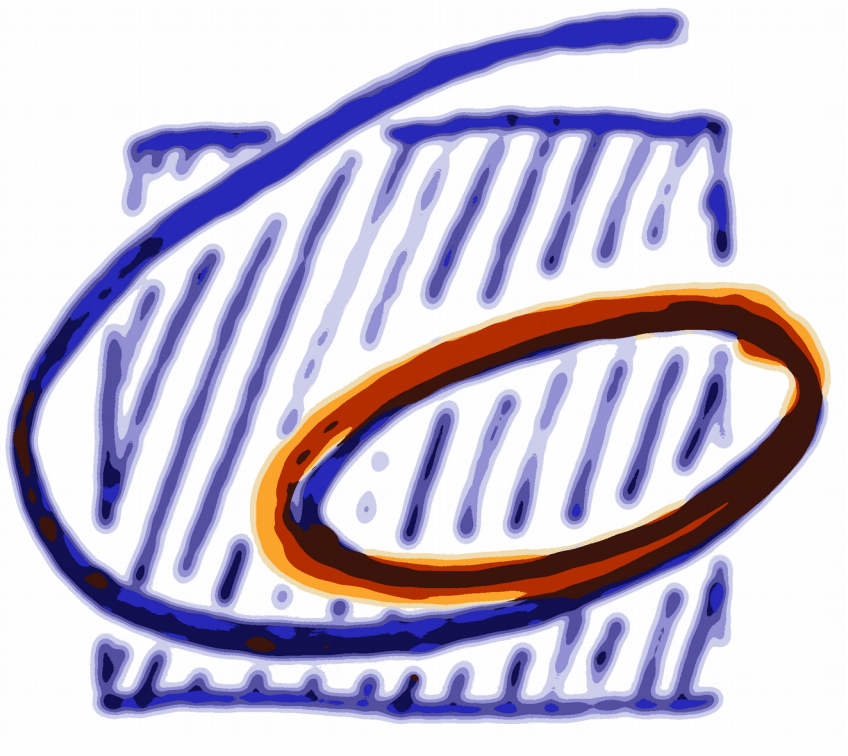
COPASI



Complex **Pa**thway
Simulator

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Pedro Mendes, Jürgen Pahle

Universities of Heidelberg, Connecticut and VT

General info about COPASI

COPASI is a software tool for editing, simulating, and analyzing quantitative models of biochemical reaction networks.

COPASI is available for all major platforms (**Linux, Windows, OS X**), easy to install

COPASI is free software and open source

General info (continued)

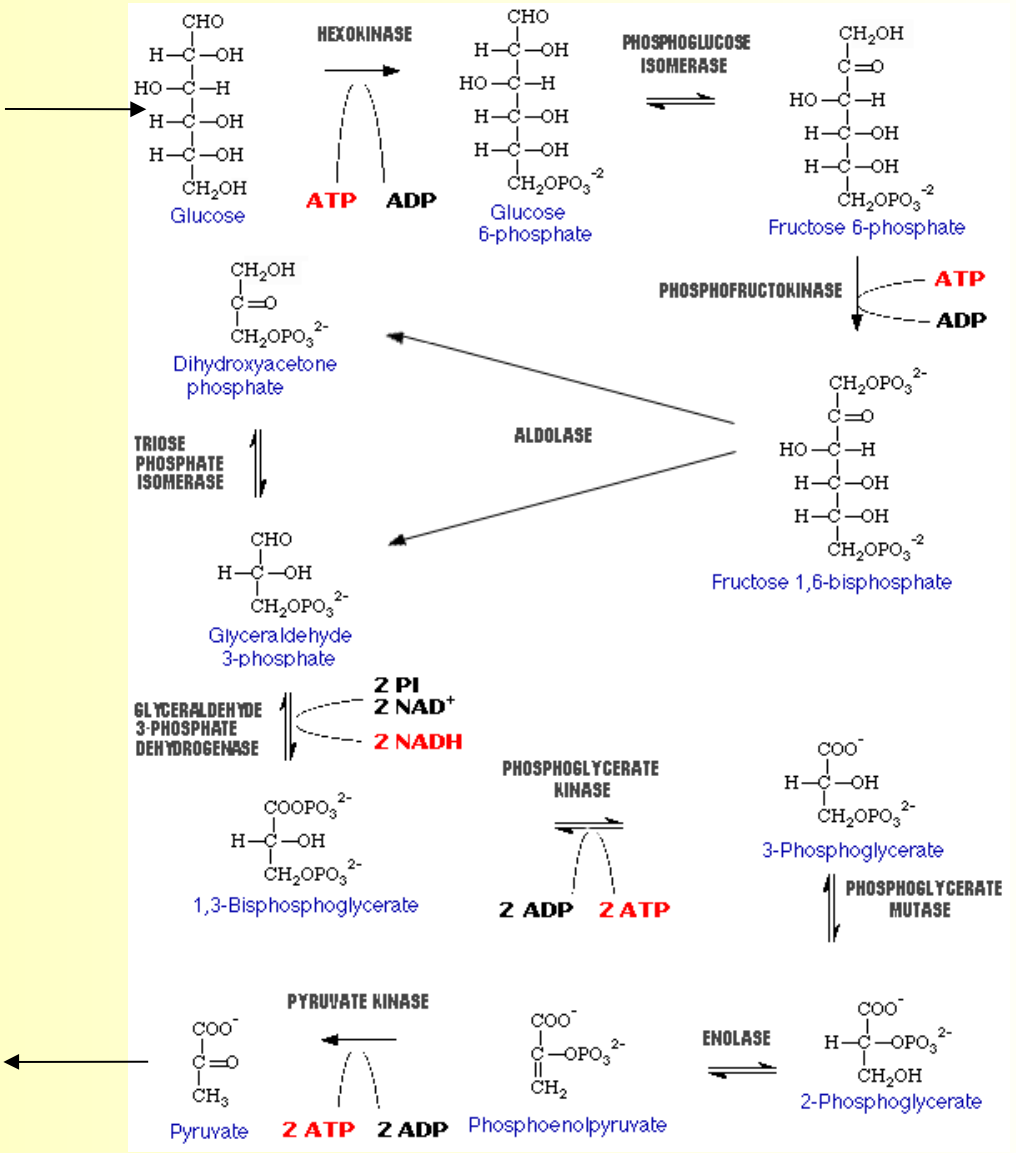
COPASI is a joint project of the groups of Ursula Kummer, Pedro Mendes, Stefan Hoops, Jurgen Pahle and Sven Sahle

COPASI is designed to be robust and user friendly, intended for general use not only by experts

Download from **www.copasi.org**

Model example: Glycolysis

$$glc' = v_{trans} - v_{hk}$$
$$g6p' = v_{hk} - v_{pgi}$$
$$f6p' = v_{pgi} - v_{pfk}$$
$$f16p' = v_{pfk} - v_{ald}$$
$$dhap' = v_{ald} - v_{ti}$$
$$gap' = v_{ald} + v_{ti} - v_{gpdh}$$
$$bpg' = v_{gpdh} - v_{pgk}$$
$$p3g' = v_{pgk} - v_{pgm}$$
$$p2g' = v_{pgm} - v_{eno}$$
$$pp' = v_{eno} - v_{pyk}$$
$$py' = v_{pyk} - v_{py}$$

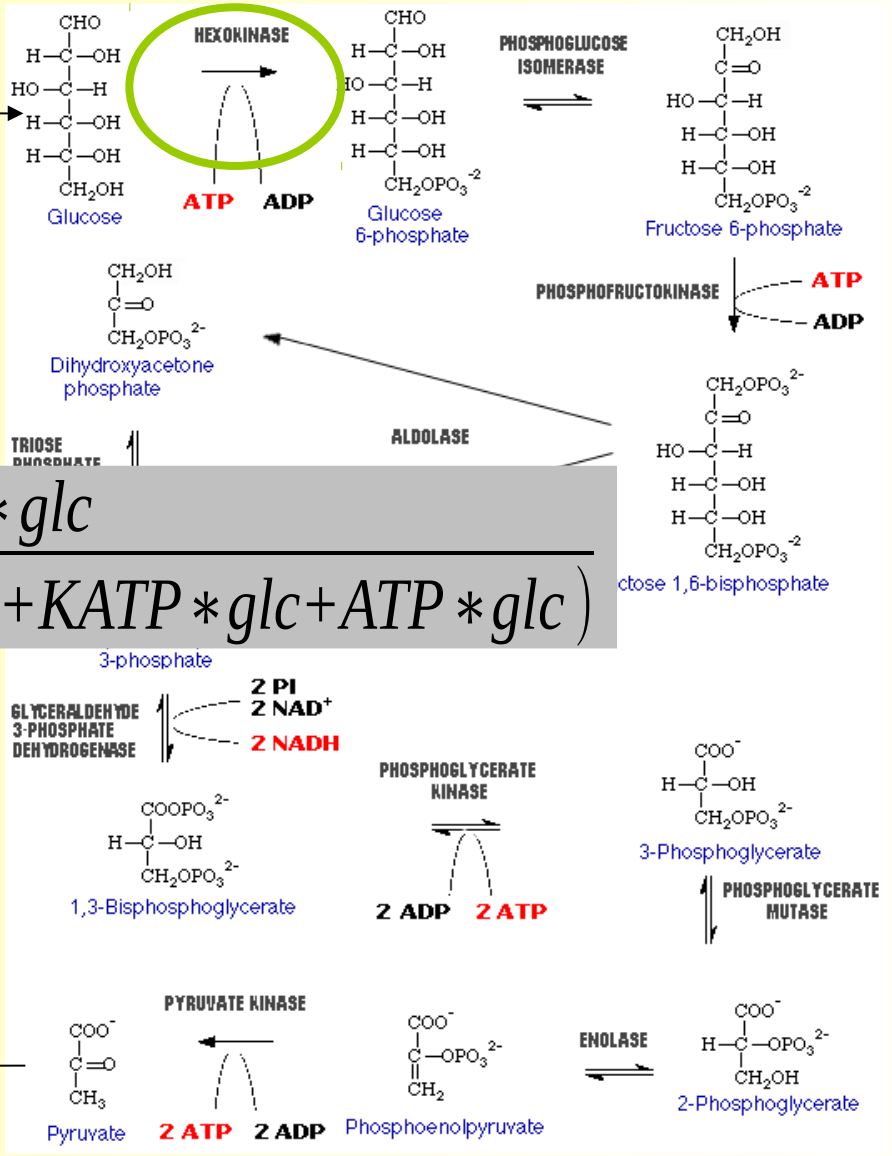


Model example: Glycolysis

V_{hk}

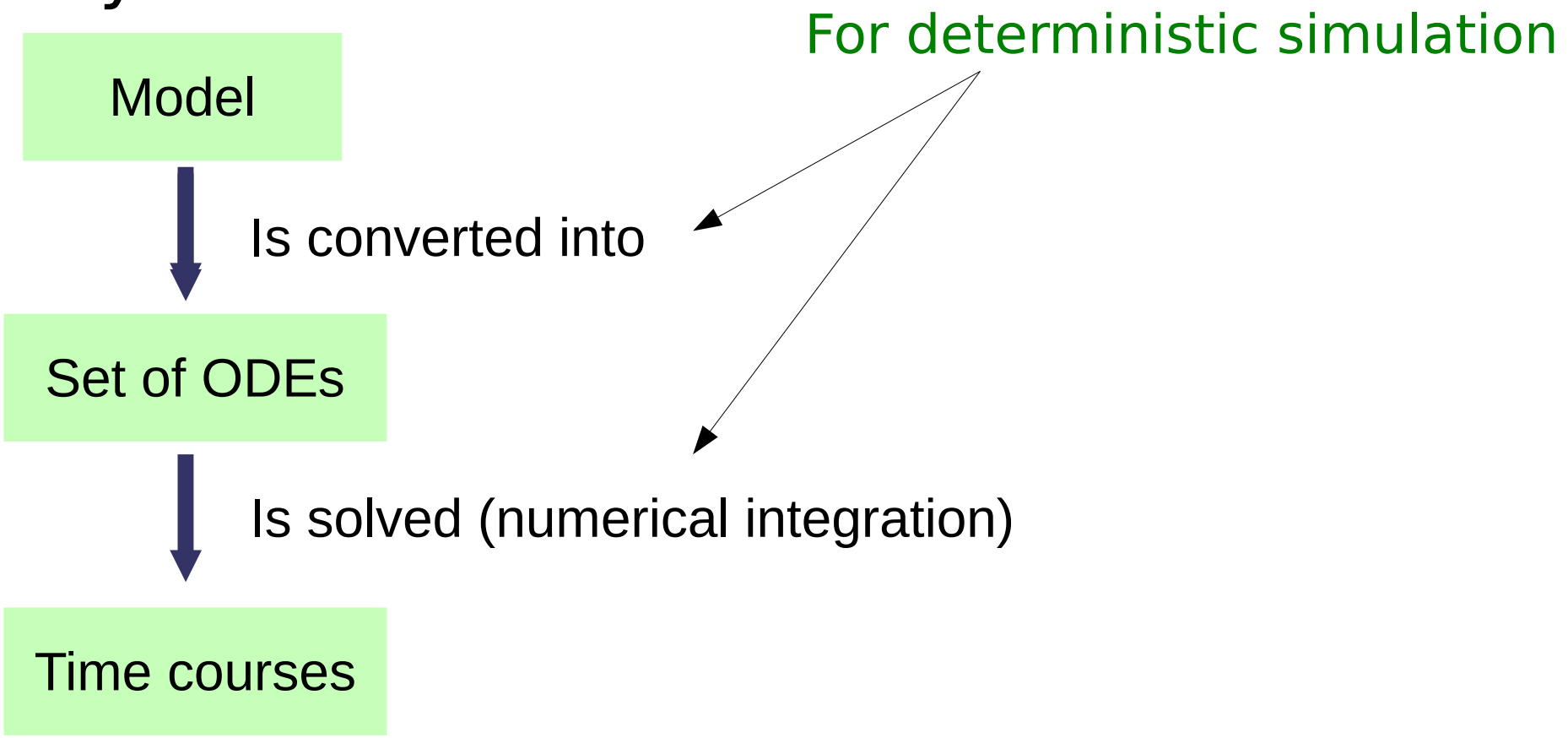
- MM for 2 non-competing substrates
- Often ATP as constant pool

$$vhk = Vhk * \frac{ATP * glc}{(KATP * Kglc + Kglc * ATP + KATP * glc + ATP * glc)}$$



Simulation

Simulation means the computer calculates the time course of the variables of the system



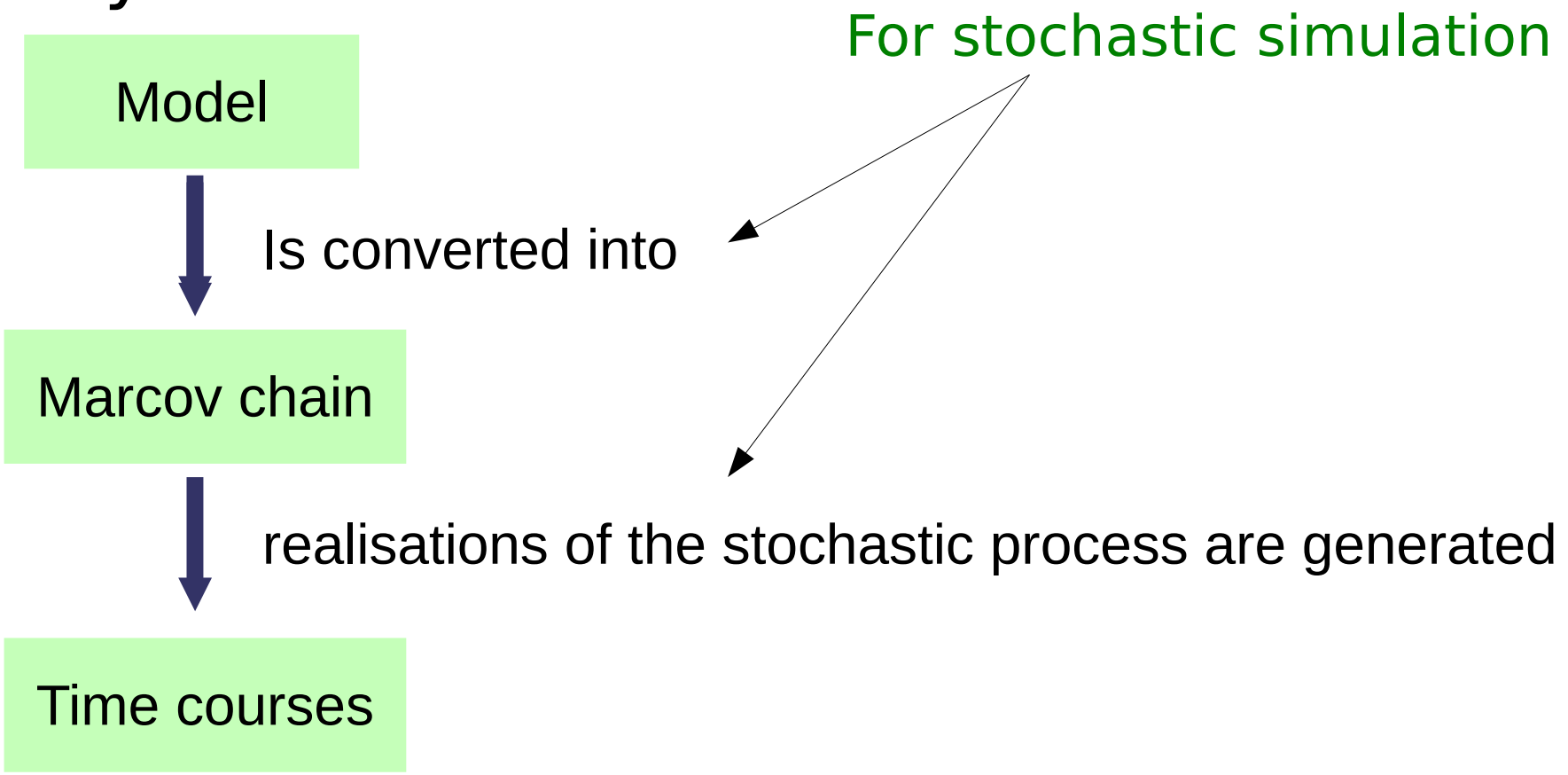
different mathematical interpretations of a model

A key feature of COPASI is the ability to switch transparently between a deterministic and a stochastic model interpretation

- Deterministic: ODEs are automatically generated and solved using LSODA
- Stochastic: Reaction rates are converted to reaction probabilities. Exact simulation with Gibson/Bruck or hybrid simulation

Stochastic Simulation

Simulation means the computer calculates the time course of the variables of the system



Steady State analysis

- Robust algorithm to find steady states
- Stability analysis (eigenvalues of jacobian)
- Metabolic control analysis / MCA (control coefficients)

Sensitivities

In general, a sensitivity can be described as the partial derivative of some system property with respect to some parameter, scaled to relative values:

$$S_p^X = \frac{p}{X}\frac{\partial X}{\partial p} = \frac{\partial \ln X}{\partial \ln p}$$

Metabolic Control Analysis

MCA is a specific kind of sensitivity analysis for steady states

- For a deterministic model of species and reactions, translated into an ODE.
- The control coefficients are the dependency of the steady state concentration/fluxes on the rate of a the different reactions.
- There are robust algorithms to calculate the control coefficients from properties of the single reactions.

Parameter Fitting / Optimization

Many powerful algorithms

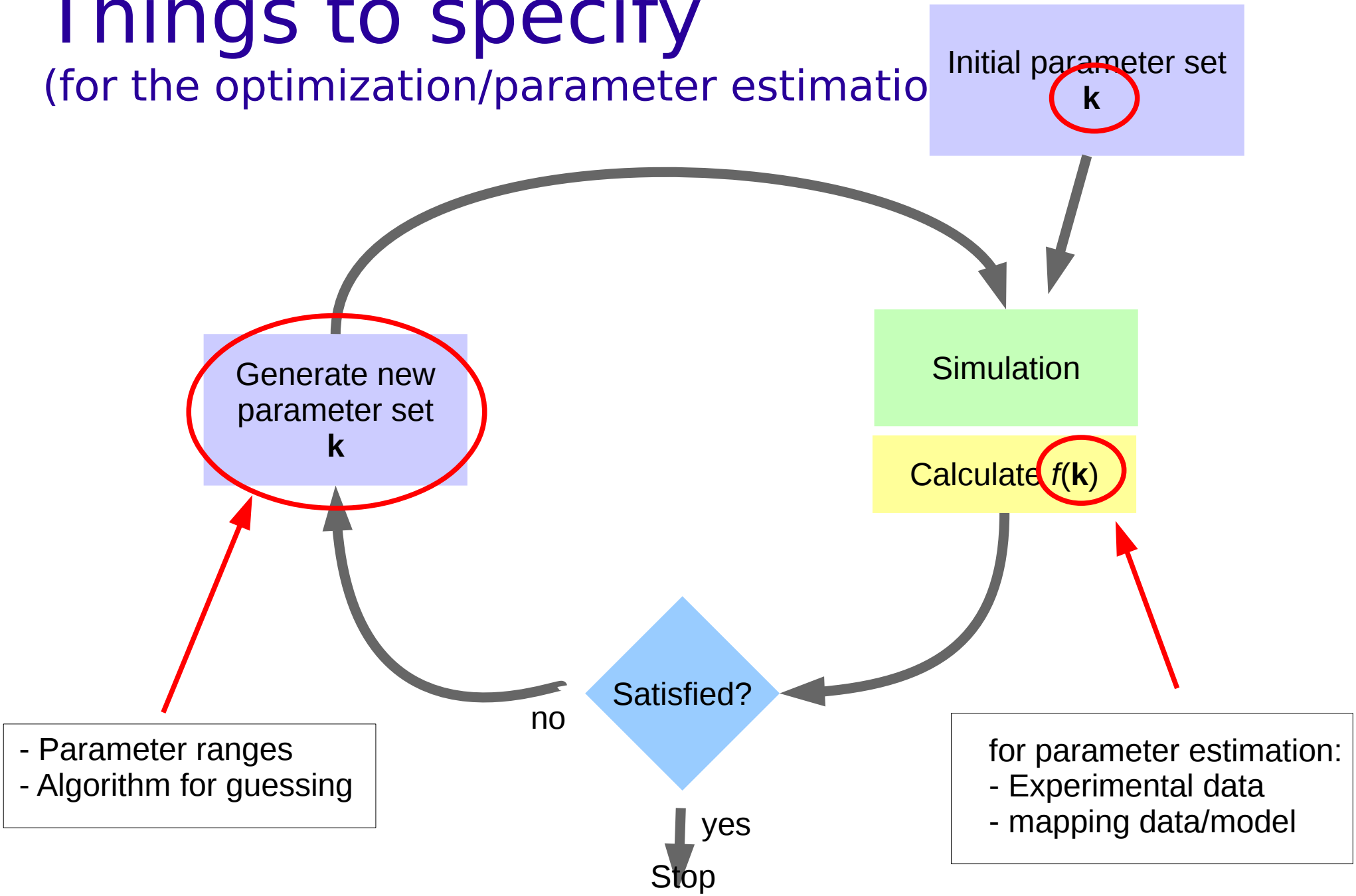
- Gradient based
  - Steepest Descent
  - Levenberg Marquardt
- direct deterministic
  - Hooke-Jeeves
  - Nelder-Mead (simplex)
- direct random
  - random search
  - simulated annealing
  - Evolutionary programming
  - Genetic Algorithm
  - SRES (stochastic ranking evolutionary)
  - Particle Swarm

Parameter fitting

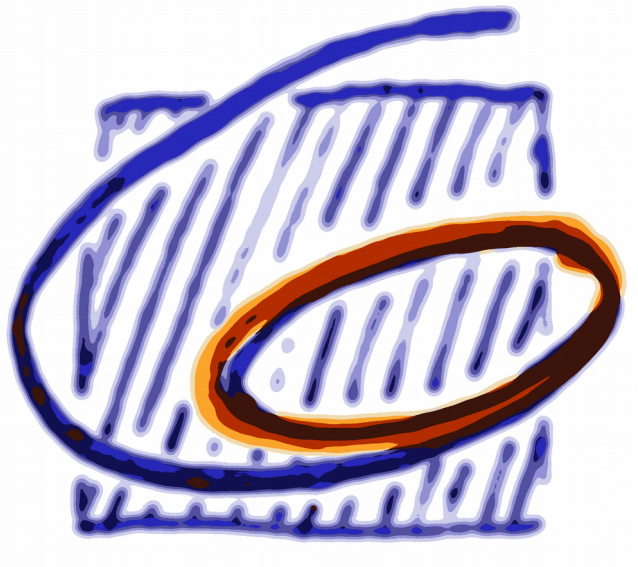
- flexible input of experimental data
- arbitrary number of experiments
- simultaneously fitting of steady state and time course data
- potentially large number of parameters
  (takes a long time -> use command line version of COPASI)

Things to specify

(for the optimization/parameter estimatio



The COPASI Team



Blacksburg: Stefan Hoops, Brian Klahn

Farmington: Pedro Mendes, Abhishekh Gupta

Heidelberg: Frank Bergmann, Ursula Kummer, Sven Sahle, Jürgen Pahle

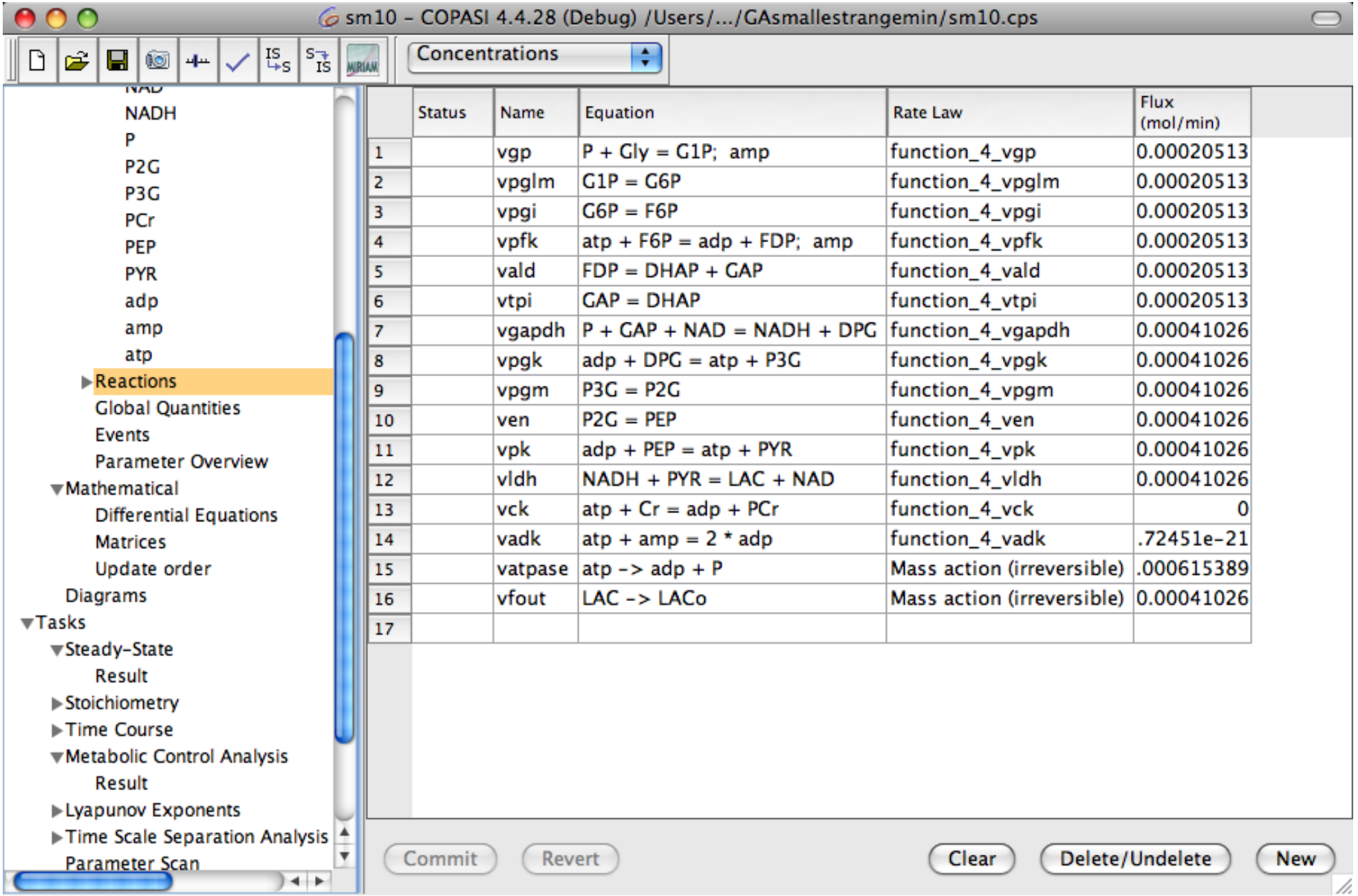
For support: **User forum at www.copasi.org**

de NBI
GERMAN NETWORK FOR BIOINFORMATICS INFRASTRUCTURE

We would like to thank the Klaus Tschira Foundation, the BMBF and the NIH for funding.

The model in COPASI

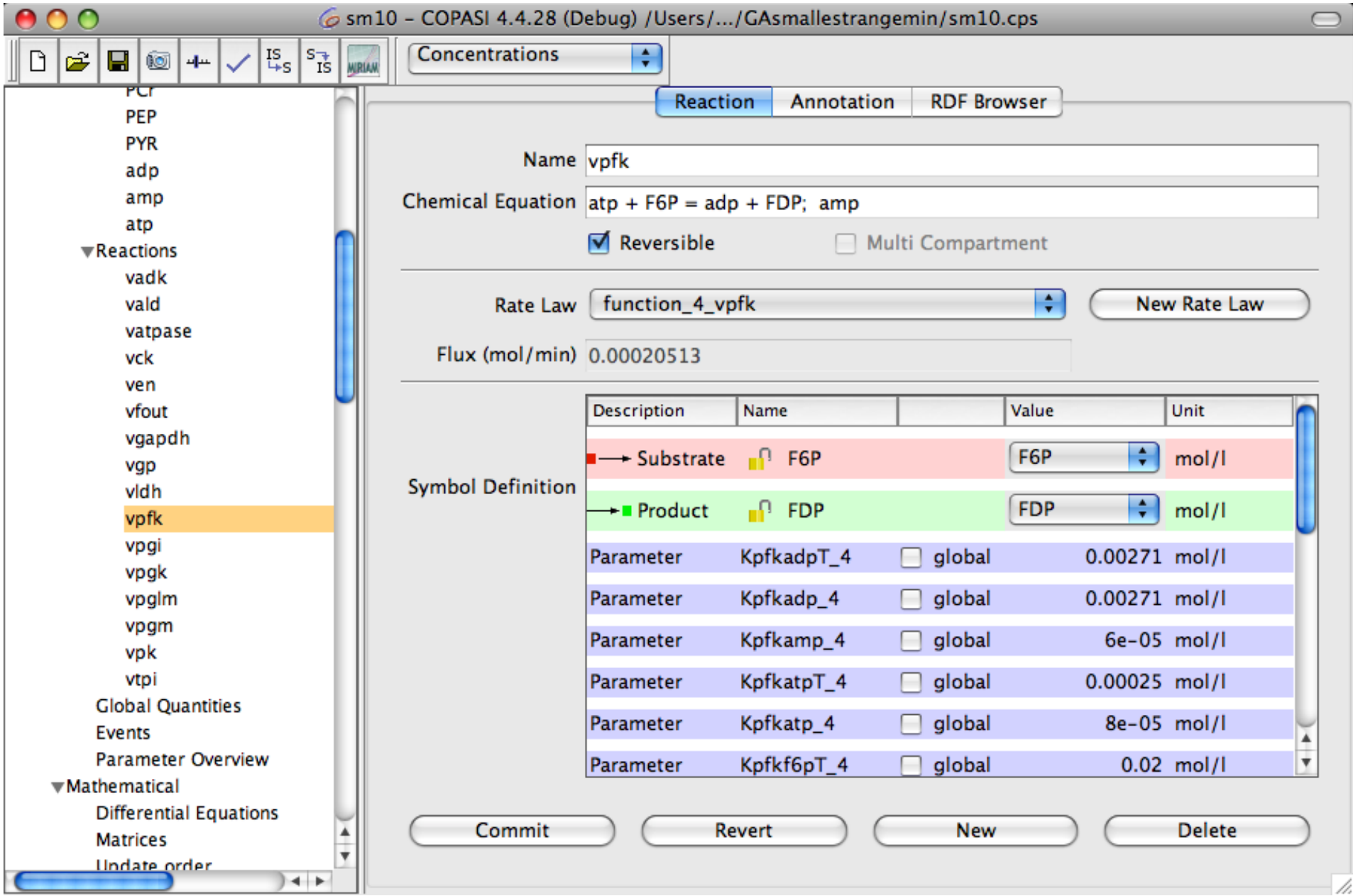
Screenshots



	Status	Name	Equation	Rate Law	Flux (mol/min)
1		vgp	P + Gly = G1P; amp	function_4_vgp	0.00020513
2		vpglm	G1P = G6P	function_4_vpglm	0.00020513
3		vpgi	G6P = F6P	function_4_vpgi	0.00020513
4		vpfk	atp + F6P = adp + FDP; amp	function_4_vpfk	0.00020513
5		vald	FDP = DHAP + GAP	function_4_vald	0.00020513
6		vtpi	GAP = DHAP	function_4_vtpi	0.00020513
7		vgapdh	P + GAP + NAD = NADH + DPG	function_4_vgapdh	0.00041026
8		vpgk	adp + DPG = atp + P3G	function_4_vpgk	0.00041026
9		vpgm	P3G = P2G	function_4_vpgm	0.00041026
10		ven	P2G = PEP	function_4_ven	0.00041026
11		vpk	adp + PEP = atp + PYR	function_4_vpk	0.00041026
12		vldh	NADH + PYR = LAC + NAD	function_4_vldh	0.00041026
13		vck	atp + Cr = adp + PCr	function_4_vck	0
14		vadk	atp + amp = 2 * adp	function_4_vadk	.72451e-21
15		vatpase	atp -> adp + P	Mass action (irreversible)	.000615389
16		vfout	LAC -> LACo	Mass action (irreversible)	0.00041026
17					

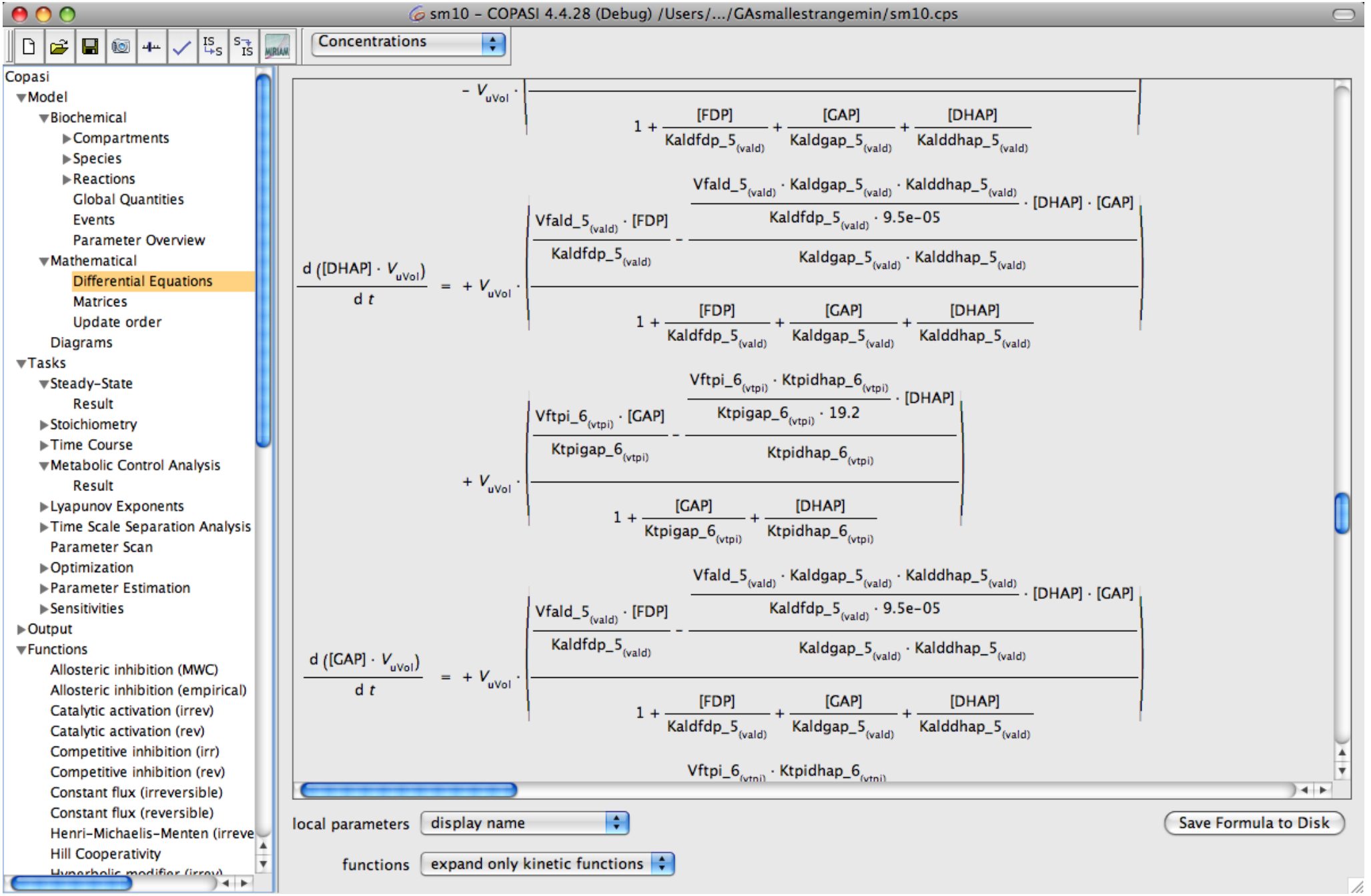
Example
(continued)

A reaction in COPASI



ODEs generated from the reaction network

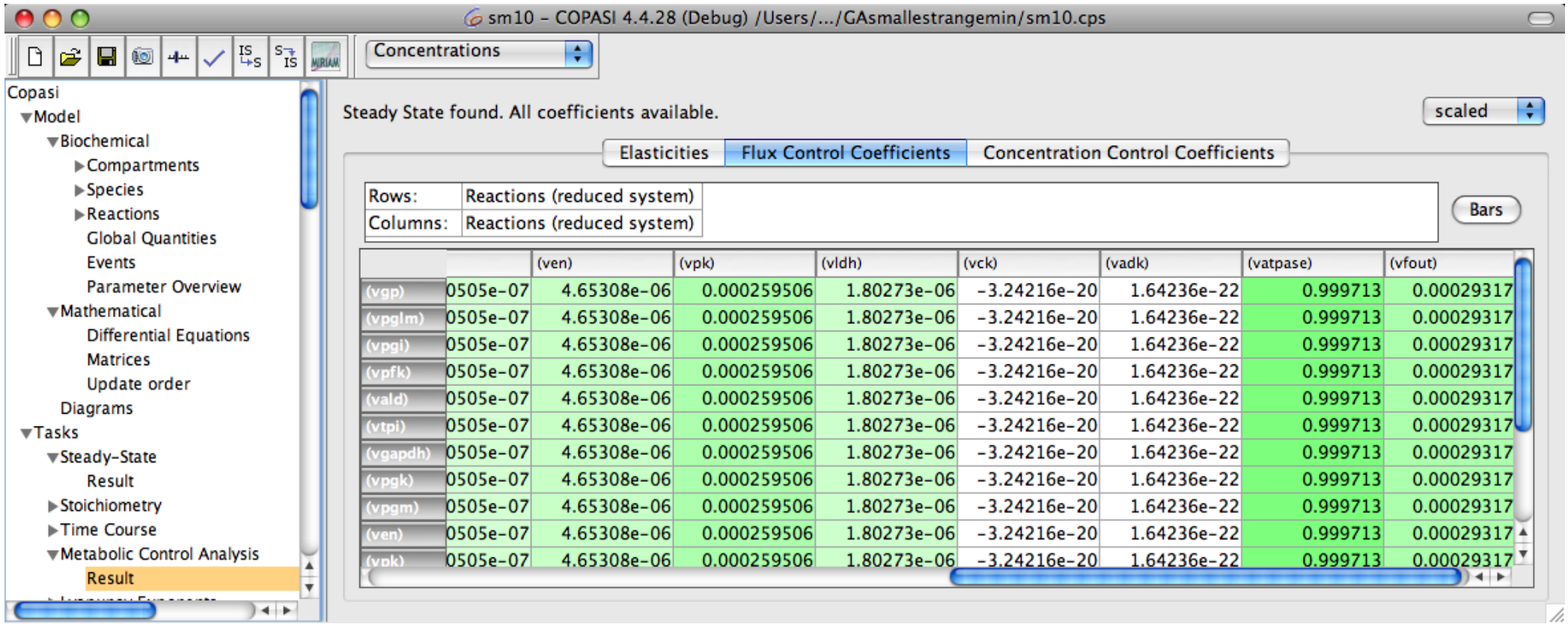
Example (continued)



MCA results

Example
(continued)

- For the given parameters the steady state is almost completely controled by the ATPase.



		(ven)	(vpk)	(vldh)	(vck)	(vadk)	(vatpase)	(vfout)
(vgp)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(vpglm)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(vpgi)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(vpfk)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(vald)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(vtpi)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(vgapdh)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(vpgk)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(vpgm)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(ven)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317
(vpk)	0505e-07	4.65308e-06	0.000259506	1.80273e-06	-3.24216e-20	1.64236e-22	0.999713	0.00029317