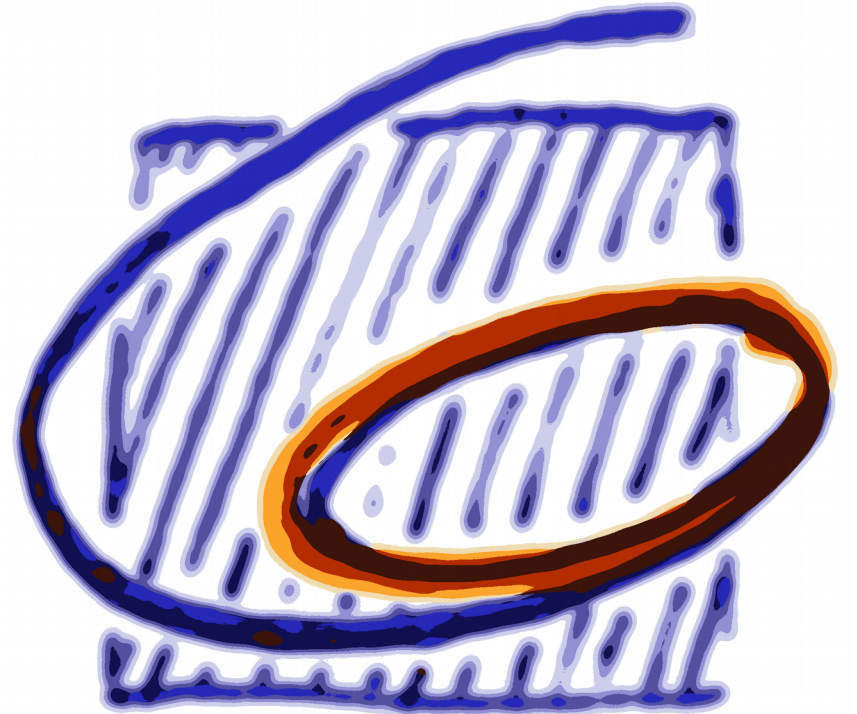


COPASI

Complex Pathway
Simulator



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Pedro Mendes, Jürgen Pahle

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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**](http://www.copasi.org)

Model example: Glycolysis

$$glc' = v_{trans} - v_{hk}$$

$$g6p' = v_{hk} - v_{pgi}$$

$$f6p' = v_{pgi} - v_{pfk}$$

$$f16p' = v_{pfk} - v_{ald}$$

$$dhap' = v_{ald} - v_{ti}$$

$$gap' = v_{ald} + v_{ti} - v_{gpdh}$$

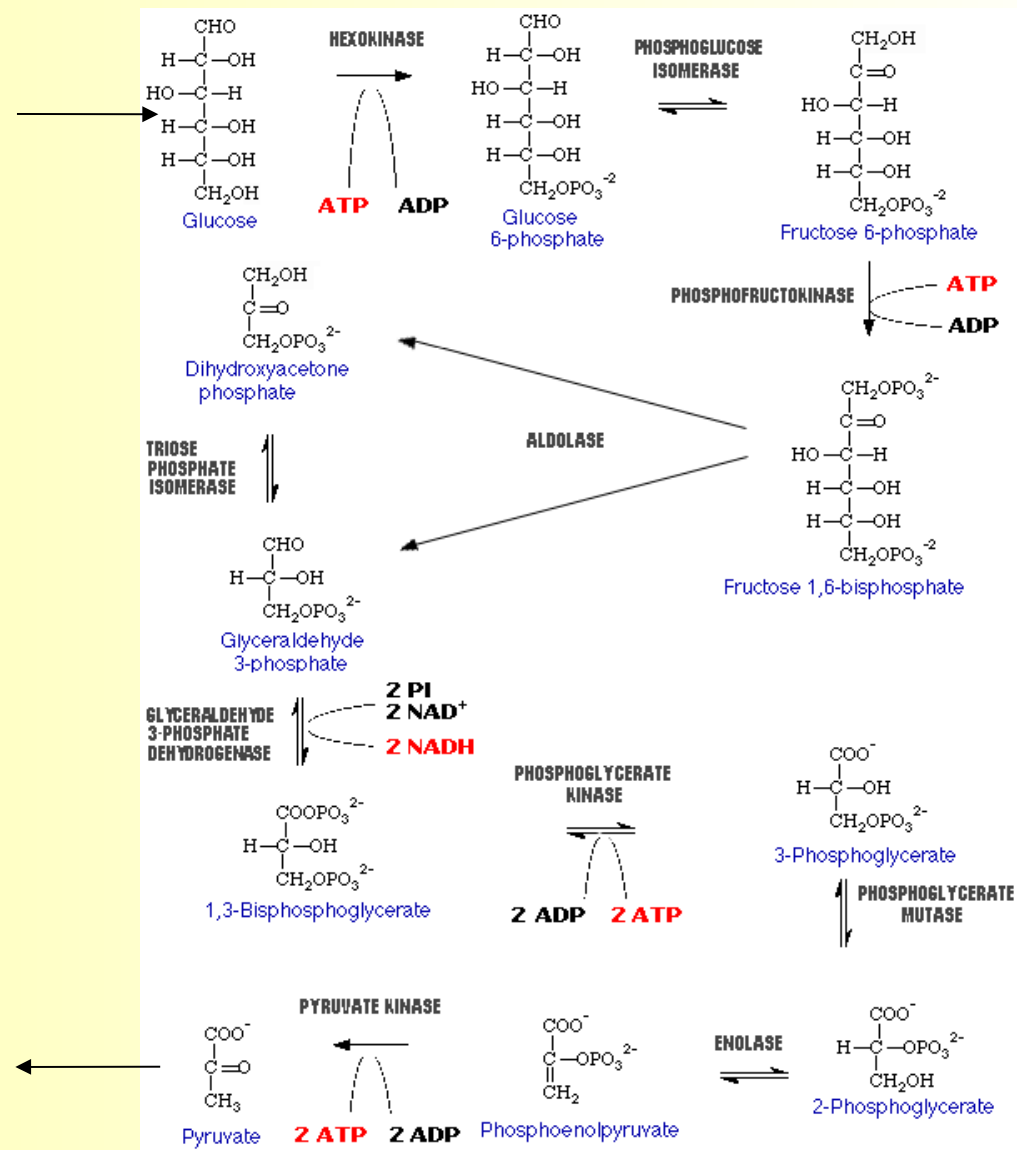
$$bpg' = v_{gpdh} - v_{pgk}$$

$$p3g' = v_{pgk} - v_{pgm}$$

$$p2g' = v_{pgm} - v_{eno}$$

$$pp' = v_{eno} - v_{pyk}$$

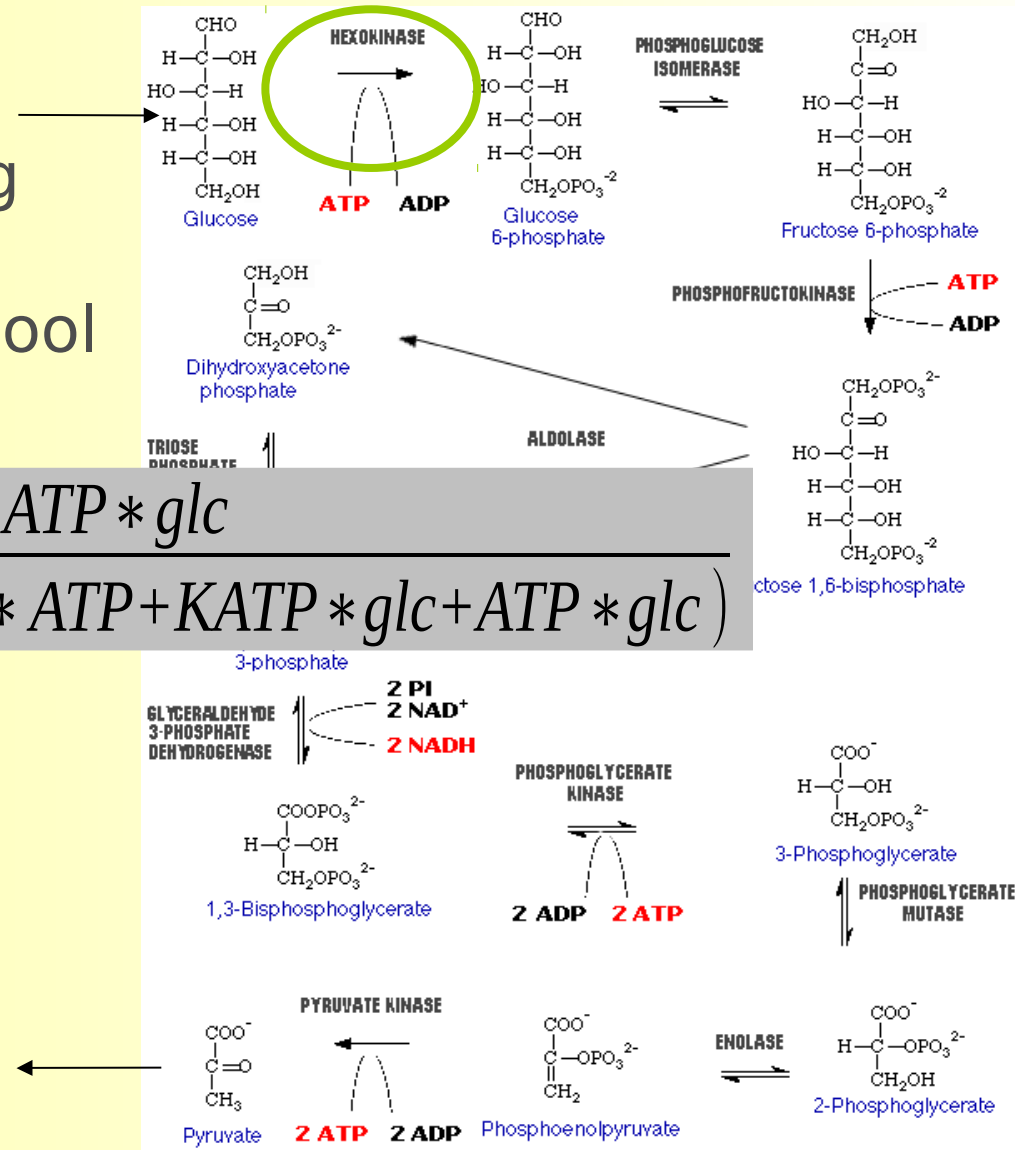
$$py' = v_{pyk} - v_{py}$$



Model example: Glycolysis

V_{hk}

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

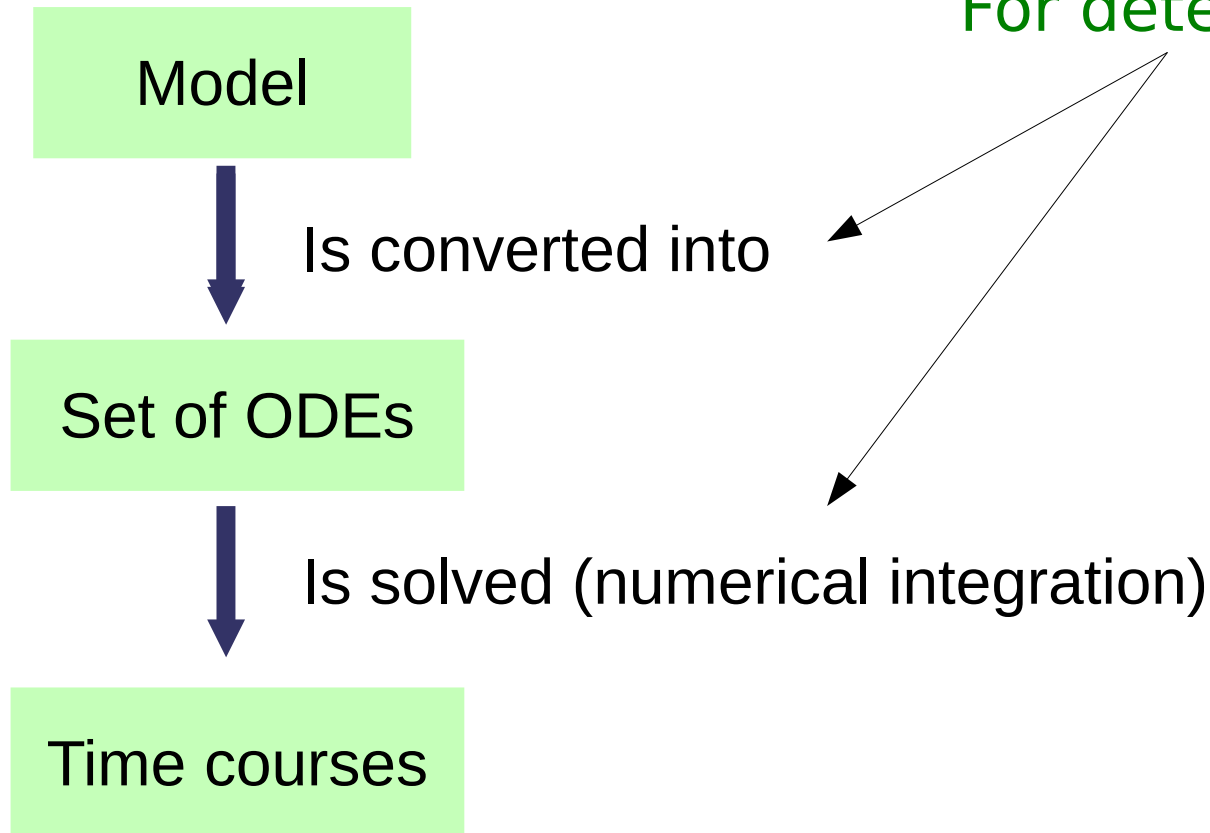


$$v_{hk} = V_{hk} * \frac{ATP * glc}{(K_{ATP} * K_{glc} + K_{glc} * ATP + K_{ATP} * glc + ATP * glc)}$$

Simulation

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

For deterministic simulation



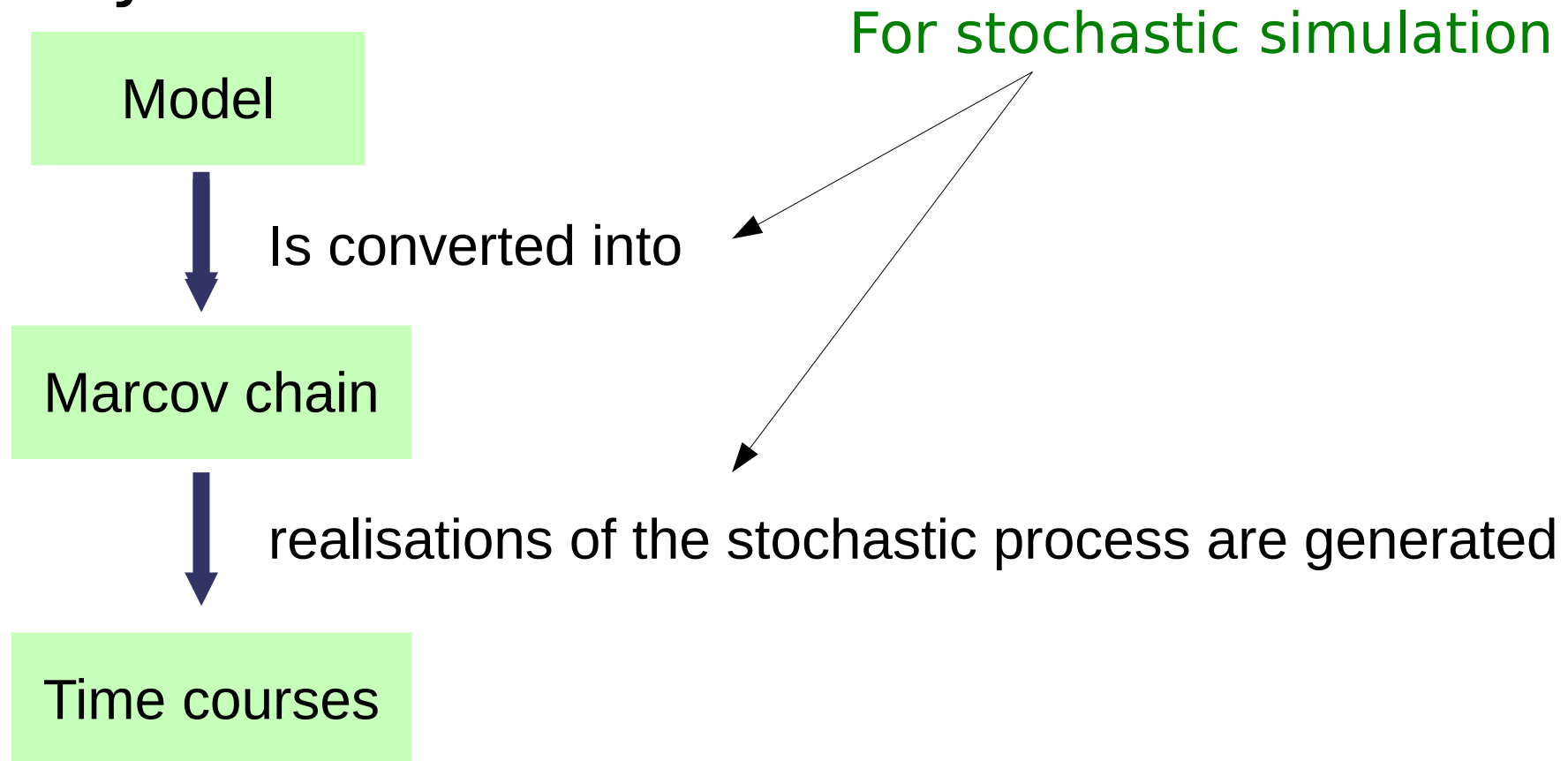
different mathematical interpretations of a model

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

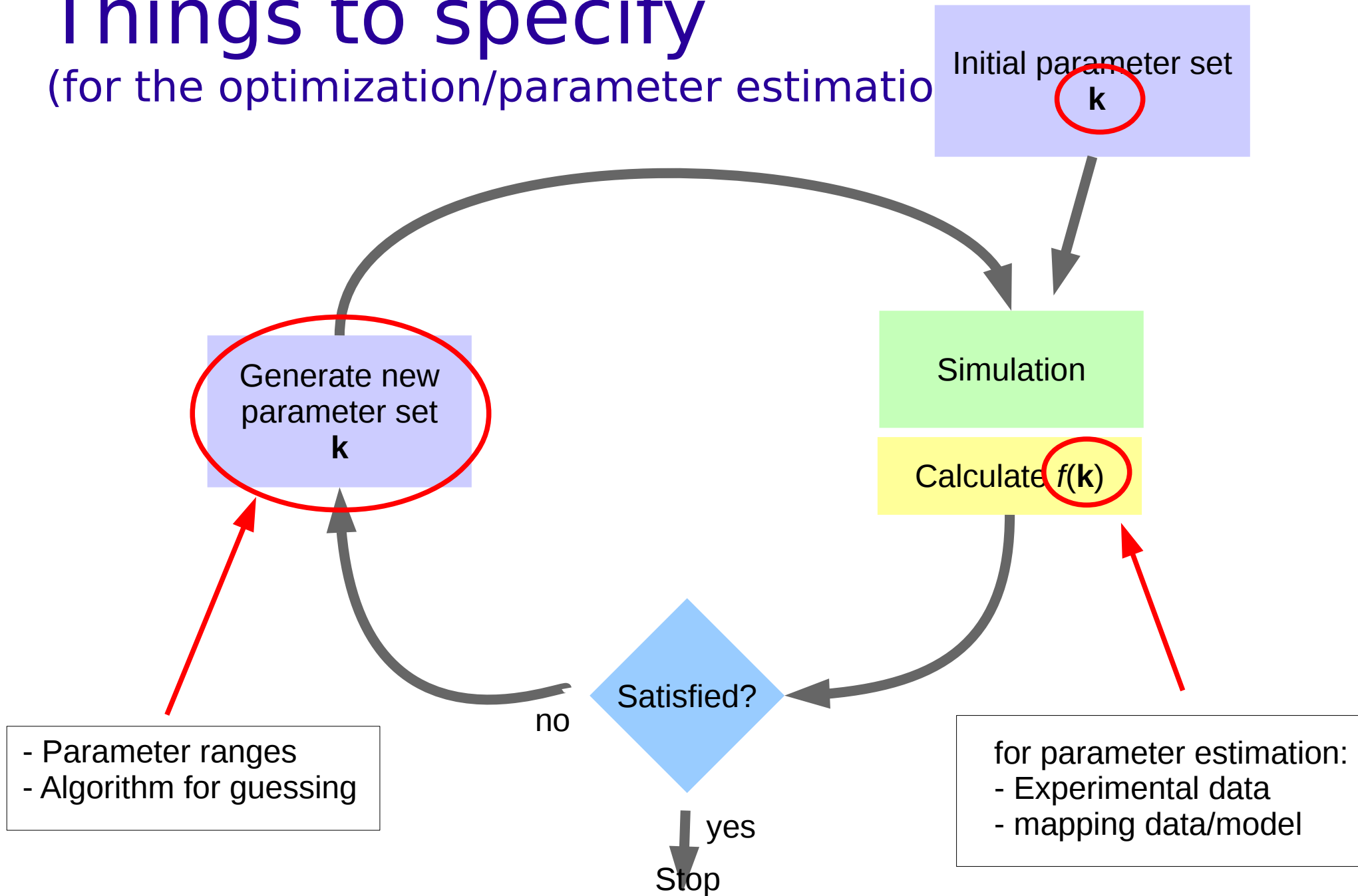
- Gradient based
 - Steepest Descent
 - Levenberg Marquardt
- direct deterministic
 - Hooke-Jeeves
 - Nelder-Mead (simplex)
- direct random
 - random search
 - simulated annealing
 - Evolutionary programming
 - Genetic Algorithm
 - SRES (stochastic ranking evolutionary)
 - Particle Swarm

Parameter fitting

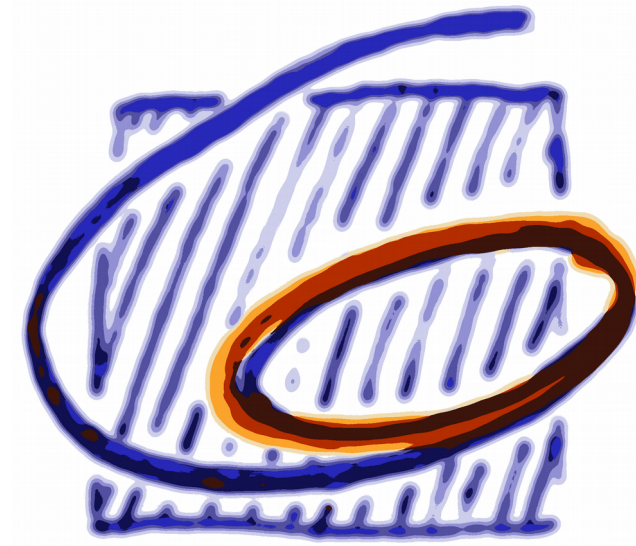
- flexible input of experimental data
- arbitrary number of experiments
- simultaneously fitting of steady state and time course data
- potentially large number of parameters
(takes a long time -> use command line version of COPASI)

Things to specify

(for the optimization/parameter estimation)



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



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The model in COPASI

Screenshots

sm10 - COPASI 4.4.28 (Debug) /Users/.../GAsmallestrangemin/sm10.cps

Concentrations

	Status	Name	Equation	Rate Law	Flux (mol/min)
1		vgp	$P + Gly = G1P; \text{ amp}$	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	$atp + F6P = adp + FDP; \text{ amp}$	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	$atp \rightarrow adp + P$	Mass action (irreversible)	.000615389
16		vfout	$LAC \rightarrow LACo$	Mass action (irreversible)	0.00041026
17					

Commit Revert Clear Delete/Undelete New

A reaction in COPASI

sm10 - COPASI 4.4.28 (Debug) /Users/.../GAsmallestrangemin/sm10.cps

Concentrations

Reaction Annotation RDF Browser

Name:

Chemical Equation:

☒ Reversible ☐ Multi Compartment

Rate Law:

Flux (mol/min):

Symbol Definition

Description	Name	Value	Unit
→ Substrate	F6P	F6P	mol/l
→ Product	FDP	FDP	mol/l
Parameter	KpfkadpT_4	0.00271	mol/l
Parameter	Kpfkadp_4	0.00271	mol/l
Parameter	Kpfkamp_4	6e-05	mol/l
Parameter	KpfkatpT_4	0.00025	mol/l
Parameter	Kpfkatp_4	8e-05	mol/l
Parameter	Kpfkf6pT_4	0.02	mol/l

Left sidebar contents:

- PCR
- PEP
- PYR
- adp
- amp
- atp
- ▼ Reactions
 - vadk
 - vald
 - vatpase
 - vck
 - ven
 - vfout
 - vgapdh
 - vgp
 - vidh
 - vpfk**
 - vpgi
 - vpgk
 - vpglm
 - vpgm
 - vpk
 - vtpi
- Global Quantities
- Events
- Parameter Overview
- ▼ Mathematical
 - Differential Equations
 - Matrices
 - Update order

ODEs generated from the reaction network Example
(continued)

Example (continued)

Concentrations

Copasi

- Model
 - Biochemical
 - Compartments
 - Species
 - Reactions
 - Global Quantities
 - Events
 - Parameter Overview
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 - Differential Equations**
 - Matrices
 - Update order
 - Diagrams
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 - Steady-State
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 - Time Course
 - Metabolic Control Analysis
 - Result
 - Lyapunov Exponents
 - Time Scale Separation Analysis
 - Parameter Scan
 - Optimization
 - Parameter Estimation
 - Sensitivities
 - Output
 - Functions
 - Allosteric inhibition (MWC)
 - Allosteric inhibition (empirical)
 - Catalytic activation (irrev)
 - Catalytic activation (rev)
 - Competitive inhibition (irr)
 - Competitive inhibition (rev)
 - Constant flux (irreversible)
 - Constant flux (reversible)
 - Henri-Michaelis-Menten (irreversible)
 - Hill Cooperativity
 - Hyperbolic modifier (irrev)

local parameters

functions

Save Formula to Disk

$$\frac{d([DHAP] \cdot V_{uVol})}{dt} = - V_{uVol} \cdot \left(1 + \frac{[FDP]}{Kaldfdp_5} + \frac{[GAP]}{Kaldgap_5} + \frac{[DHAP]}{Kalddhap_5} \right) \cdot \frac{Vfald_5 \cdot Kaldgap_5 \cdot Kalddhap_5}{Kaldfdp_5 \cdot 9.5e-05} \cdot [DHAP] \cdot [GAP] - V_{uVol} \cdot \frac{Vftpi_6 \cdot Ktpidhap_6}{Ktpigap_6 \cdot Ktpidhap_6} \cdot [DHAP] \cdot [GAP] + V_{uVol} \cdot \left(1 + \frac{[GAP]}{Ktpigap_6} + \frac{[DHAP]}{Ktpidhap_6} \right) \cdot \frac{Vfald_5 \cdot Kaldgap_5 \cdot Kalddhap_5}{Kaldfdp_5 \cdot 9.5e-05} \cdot [DHAP] \cdot [GAP] - V_{uVol} \cdot \frac{Vftpi_6 \cdot Ktpidhap_6}{Ktpigap_6 \cdot Ktpidhap_6}$$

$$\frac{d([GAP] \cdot V_{uVol})}{dt} = + V_{uVol} \cdot \left(1 + \frac{[FDP]}{Kaldfdp_5} + \frac{[GAP]}{Kaldgap_5} + \frac{[DHAP]}{Kalddhap_5} \right) \cdot \frac{Vfald_5 \cdot Kaldgap_5 \cdot Kalddhap_5}{Kaldfdp_5 \cdot 9.5e-05} \cdot [DHAP] \cdot [GAP] - V_{uVol} \cdot \frac{Vftpi_6 \cdot Ktpidhap_6}{Ktpigap_6 \cdot Ktpidhap_6} \cdot [DHAP] \cdot [GAP] + V_{uVol} \cdot \left(1 + \frac{[GAP]}{Ktpigap_6} + \frac{[DHAP]}{Ktpidhap_6} \right) \cdot \frac{Vfald_5 \cdot Kaldgap_5 \cdot Kalddhap_5}{Kaldfdp_5 \cdot 9.5e-05} \cdot [DHAP] \cdot [GAP] - V_{uVol} \cdot \frac{Vftpi_6 \cdot Ktpidhap_6}{Ktpigap_6 \cdot Ktpidhap_6}$$

MCA results

Example
(continued)

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

