Lecture: Computational Systems Biology
Universität des Saarlandes, SS 2012

06 Parameter scanning, parameter sampling, discrete events, rules

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Recap

- Stoichiometry, (ir-)reversibility
- Information contained in the stoichiometric matrix ***N***
- Kernel matrix ***K***
- Pathways: **Elementary flux modes**
- **Conservation relations** (matrix ***G***), conserved moieties

Flux modes (recap)

- Definition

$$\boldsymbol{M} = \{ \boldsymbol{v} \in R^r | \boldsymbol{v} = \lambda \cdot \hat{\boldsymbol{v}}, \lambda > 0 \}$$

with $\hat{\boldsymbol{v}}$ an *r*-dimensional vector (not the null vector) such that

  - it corresponds to a steady state
  - all sign restrictions (irreversible reactions) are fullfilled

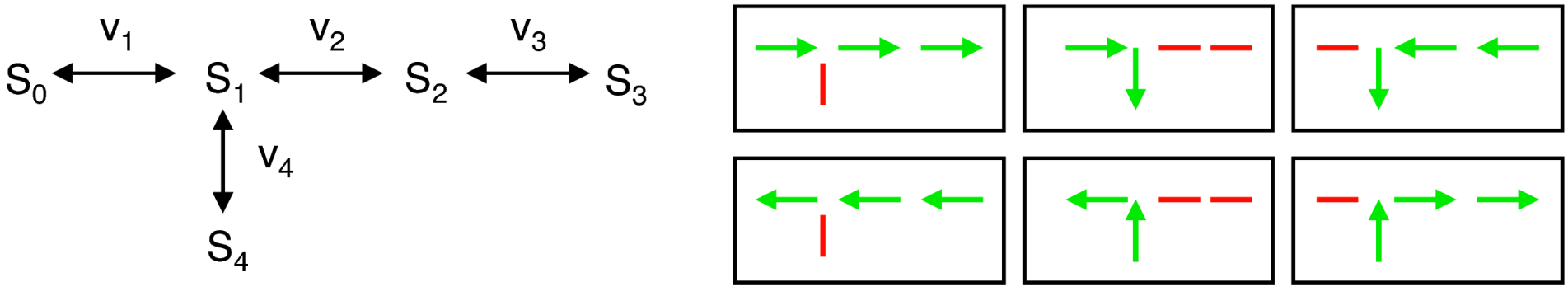
- Can be calculated using COPASI or specialised software, such as Metatool

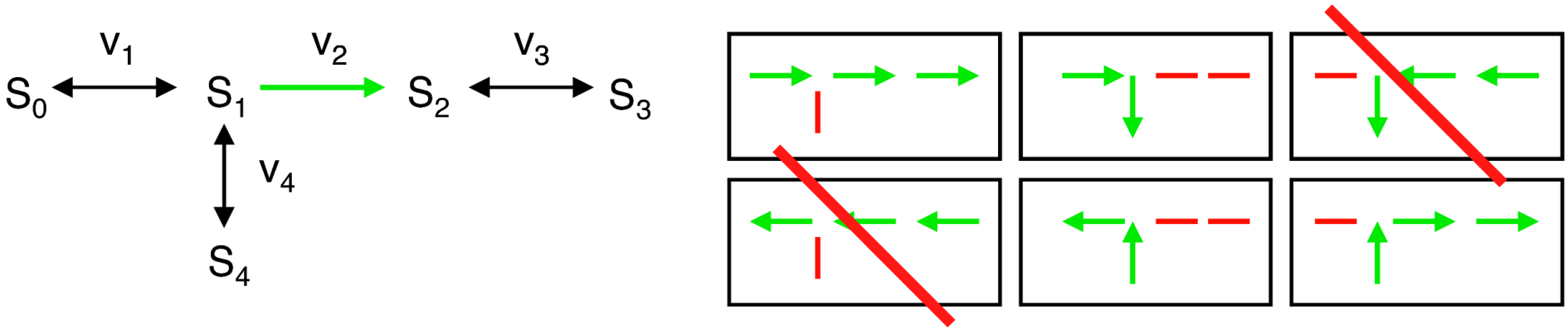
Elementary flux modes (recap)

- **Minimal** sets of reactions that allow steady state dynamics
- All steady state fluxes are linear combinations of elementary flux modes
- Calculation only requires structural information (stoichiometry matrix)

Examples (recap)

Elementary Flux Modes





Klipp - Systems Biology
ISBN: 978-3-527-31874-2 fig-02-06

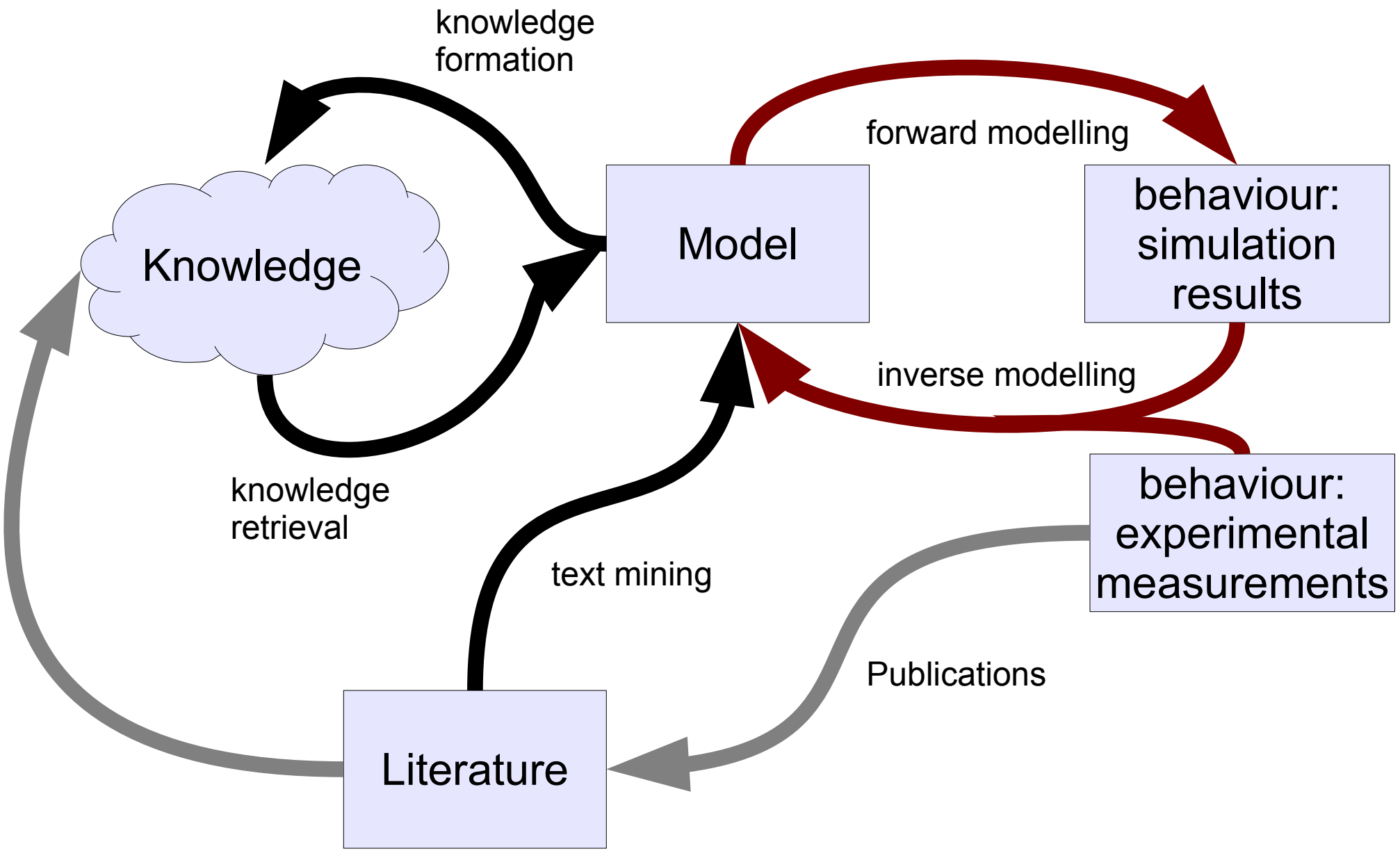
Conservation relations (recap)

Linear combinations of species whose overall concentration stays constant

Might not be obvious from visual inspection of the network diagram only

Important for reducing the system (→ link matrix)

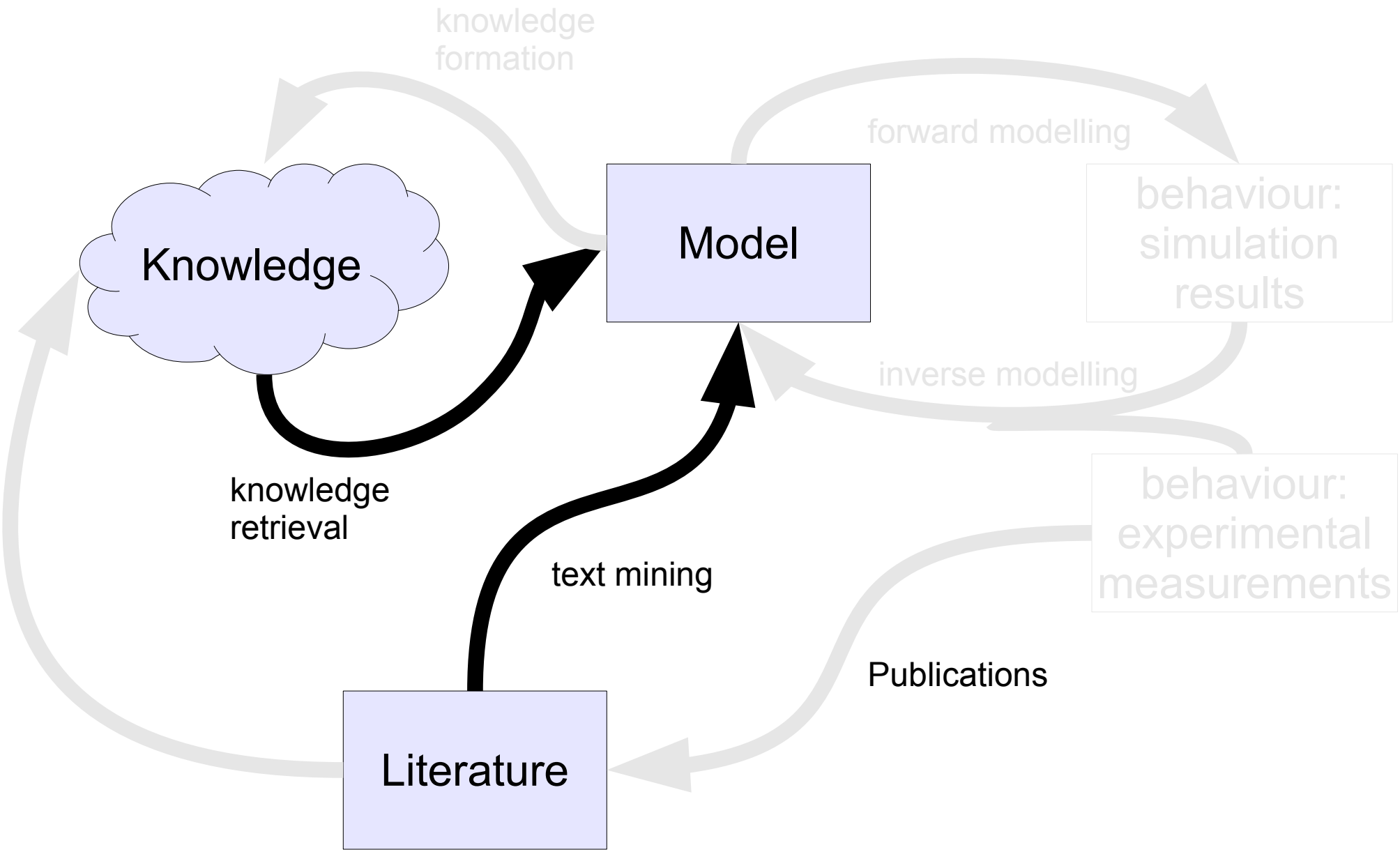
Iterative modelling cycle



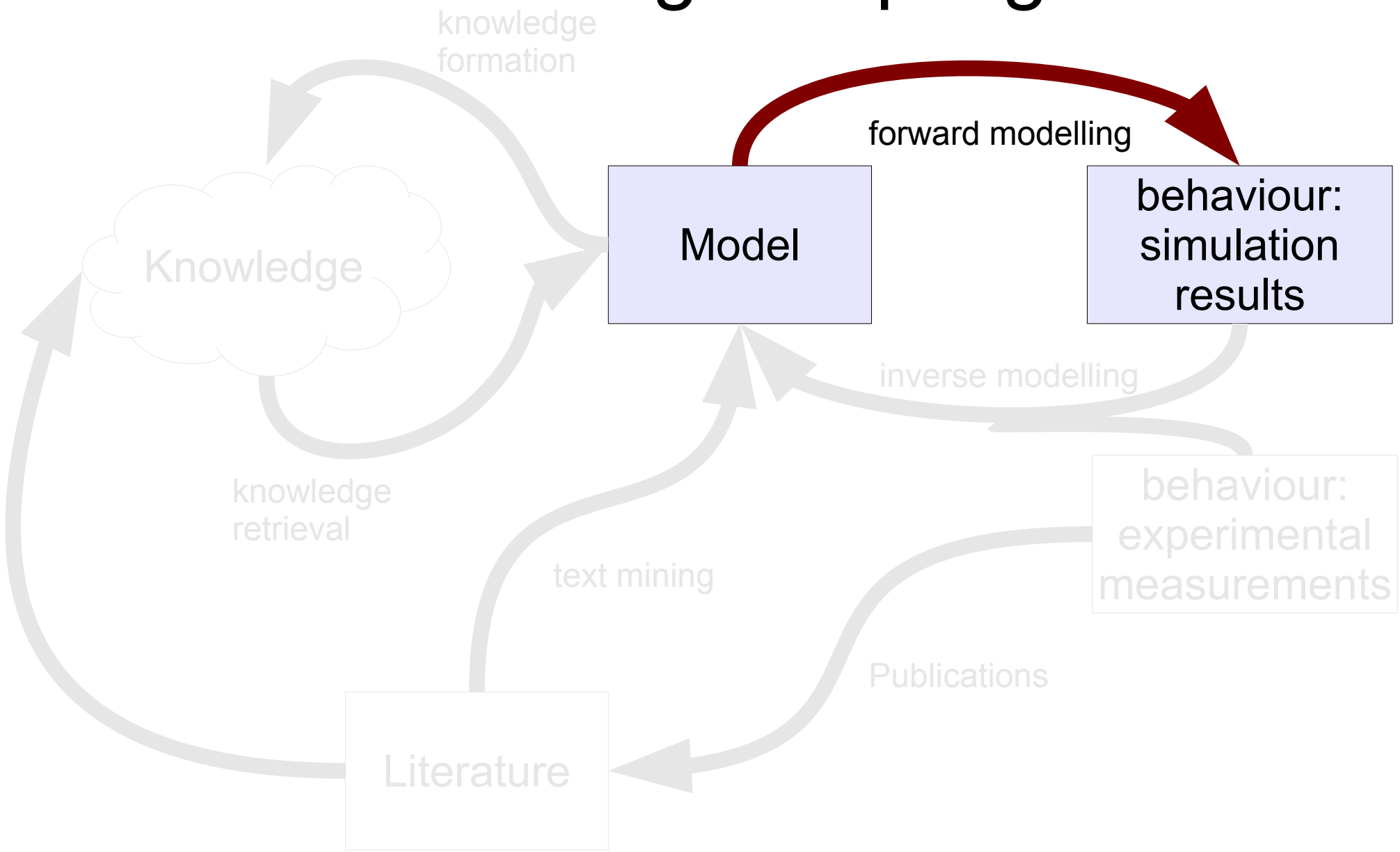
The central modelling question

- Given a model of a system: **how does the model behaviour depend on the parameters of the system?**
- Answers explain:
  - which parameters have the highest effect on desired outcomes (e.g. drug design)
  - what properties of the model are more fragile or robust
  - which parameters need accurate estimates (experimental design)
  - etc.

Model creation / refinement



Simulation, analysis, parameter scanning/sampling



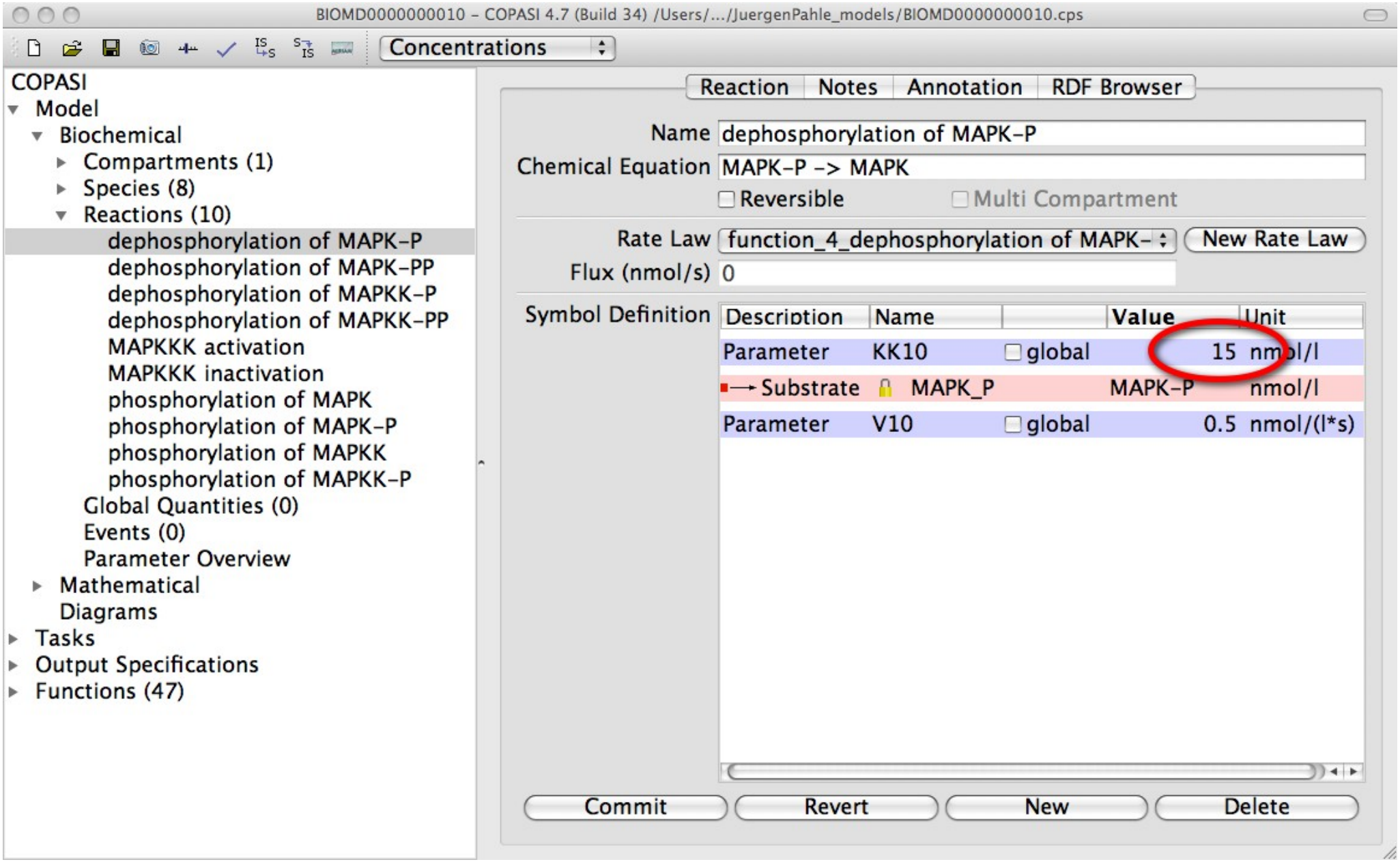
Find out the effect of parameters

(manually)

1. set a specific value for the parameter
2. run the simulation (or other calculation)
3. record the results (sheet of paper, Excel,...)
4. set another value
5. run the simulation again
6. record the results
7. ....

Changing parameters in COPASI

(reaction window → kinetic parameters)



Changing parameters in COPASI

(species window → initial concentrations)

BIOMD0000000010 – COPASI 4.7 (Build 34) /Users/.../JuergenPahle_models/BIOMD0000000010.cps

Concentrations

- COPASI
  - Model
    - Biochemical
      - Compartments (1)
      - Species (8)
        - MAPK
        - MAPK-P
        - MAPK-PP
        - MAPKK
        - MAPKK-P
        - MAPKK-PP
        - MAPKKK
        - MAPKKK-P
      - Reactions (10)
        - dephosphorylation of MAPK-P
        - dephosphorylation of MAPK-PP
        - dephosphorylation of MAPKK-P
        - dephosphorylation of MAPKK-PP
        - MAPKKK activation
        - MAPKKK inactivation
        - phosphorylation of MAPK
        - phosphorylation of MAPK-P
        - phosphorylation of MAPKK
        - phosphorylation of MAPKK-P
      - Global Quantities (0)
      - Events (0)
      - Parameter Overview
    - Mathematical
    - Diagrams

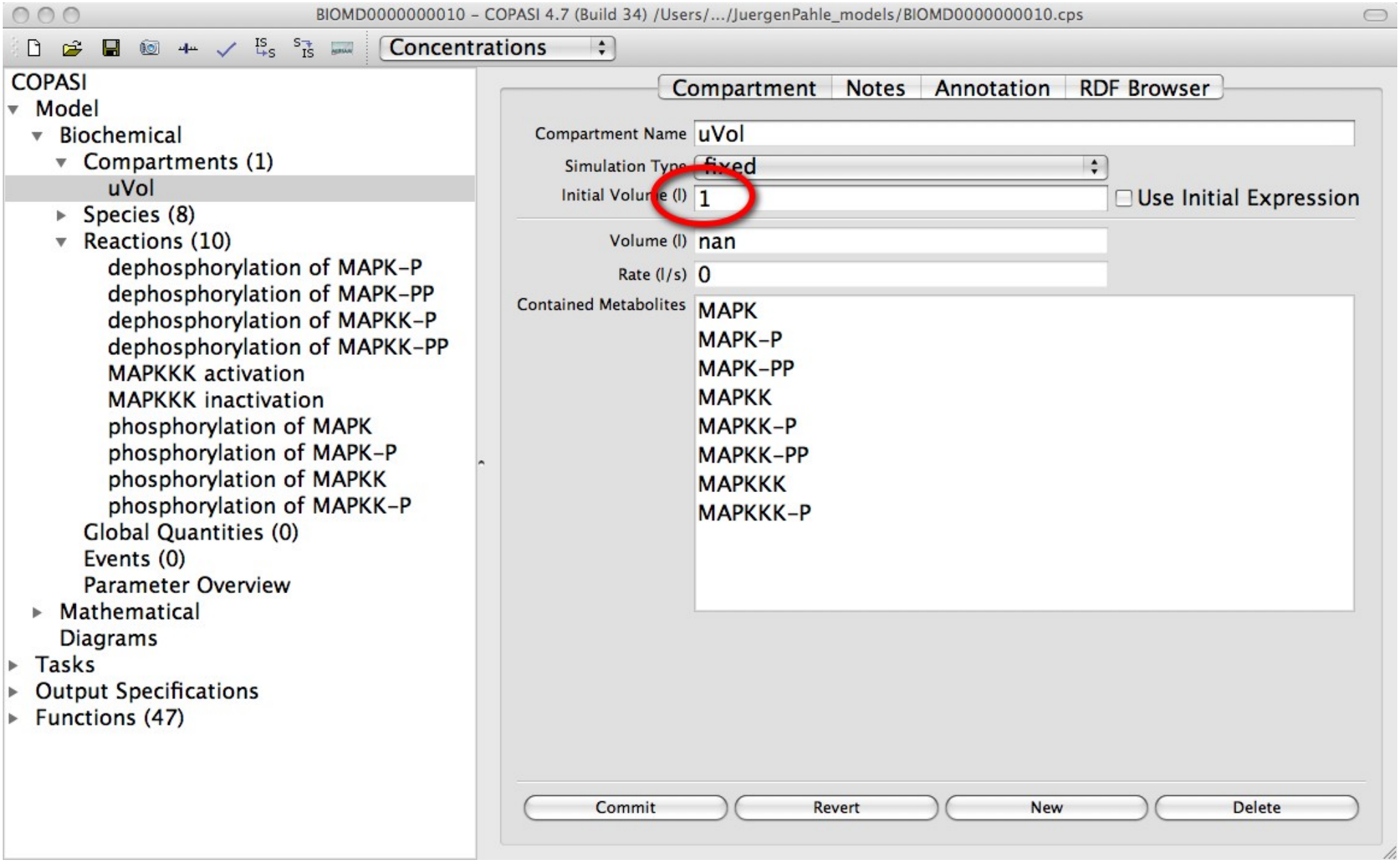
Species | Notes | Annotation | RDF Browser

Name	MAPK
Compartment	uVol
Simulation Type	reactions
Initial Concentration (nmol/l)	280
Use Initial Expression	
Concentration (nmol/l)	nan
Rate (nmol/(l*s))	nan
Transition Time (s)	0
Involved in Reactions	phosphorylation of MAPK: MAPK -> MAPK-P; MAPKK-PP dephosphorylation of MAPK-P: MAPK-P -> MAPK

Commit | Revert | New | Delete

Changing parameters in COPASI

(compartment window → initial volumes)



Changing parameters in COPASI

(parameter overview)

BIOMD0000000010 – COPASI 4.7 (Build 34) /Users/.../JuergenPahle_models/BIOMD0000000010.cps

Concentrations

- COPASI
  - Model
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        - dephosphorylation of MAPK-P
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        - phosphorylation of MAPK-P
        - phosphorylation of MAPKK
        - phosphorylation of MAPKK-P
      - Global Quantities (0)
      - Events (0)
      - Parameter Overview
    - Mathematical
    - Diagrams
  - Tasks
  - Output Specifications
  - Functions (47)

Model parameters

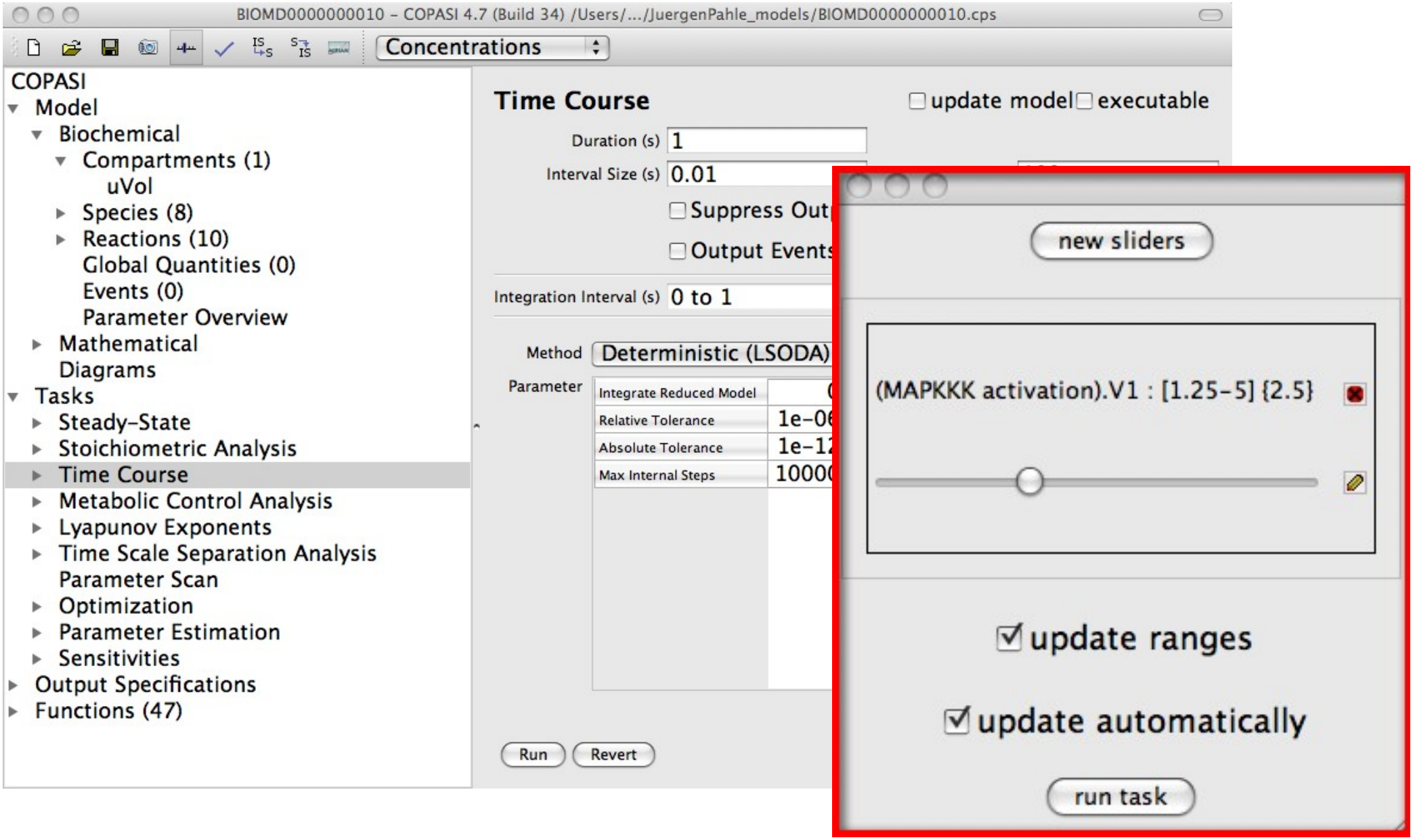
Save data...

Name	Status	Value	Unit
Global Quantities			
Initial Concentrations			
MAPK	indep	280	nmol/l
MAPK-P	indep	10	nmol/l
MAPK-PP	dep	10	nmol/l
MAPKK	indep	280	nmol/l
MAPKK-P	indep	10	nmol/l
MAPKK-PP	dep	10	nmol/l
MAPKKK	indep	90	nmol/l
MAPKKK-P	dep	10	nmol/l
Initial Time			
Model		0	s
Initial Volumes			
uVol	fixed	1	l
Kinetic Parameters			
dephosphorylation of MAPK-P			
KK10		15	nmol/l
V10		0.5	nmol/(l*s)
dephosphorylation of MAPK-PP			
KK9		15	nmol/l
V9		0.5	nmol/(l*s)
dephosphorylation of MAPKK-P			
KK6		15	nmol/l
V6		0.75	nmol/(l*s)

Commit Revert

Changing parameters in COPASI

(sliders: parameter change and automatic calculations)



Sliders

- Parameter change plus automatic calculation
- Can be defined via menu *Tools* → *Show sliders* or with the corresponding button in COPASI
- Only active in some tasks within COPASI (steady state, time course, metabolic control analysis, parameter scan)
- Convenient for **manually exploring model behaviour** and adjusting parameters in a quick way

Parameter scanning

- Systematic change of parameter(s) within a given interval

  e.g. "change parameter k_1 from 0.5 to 2.0 in steps of 0.5 and calculate a steady state for each value"

- Automated repetitive calculation of tasks in COPASI
- Sometimes also called "parameter sweep"

Parameter scanning in COPASI

BIOMD0000000010 – COPASI 4.7 (Build 34) /Users/.../JuergenPahle_models/BIOMD0000000010.cps

Concentrations

COPASI
- Model
- Tasks
  - Steady-State
  - Stoichiometric Analysis
  - Time Course
  - Metabolic Control Analysis
  - Lyapunov Exponents
  - Time Scale Separation Analysis
  - Parameter Scan
  - Optimization
  - Parameter Estimation
  - Sensitivities
- Output Specifications
- Functions (47)

Parameter Scan

☐ update model ☐ executable

New scan item: Parameter Scan ... Create!

Scan

Parameter (MAPKKK activation).V1

Intervals	min	max
10	0.5	2

☐ logarithmic scan

Task Steady State

☑ always use initial conditions ☐ output during subtask execution

Run Revert Report Output Assistant

Calculations on regular parameter grids

- Parameter scans can be stacked on top of each other → simple loop "programs" in COPASI

- CAUTION: the order matters

Parameter scanning (2-D) in COPASI

BIOMD0000000010 – COPASI 4.7 (Build 34) /Users/.../JuergenPahle_models/BIOMD0000000010.cps

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Parameter Scan

☐ update model ☐ executable

New scan item: Parameter Scan ... Create!

Scan

Parameter (MAPKKK activation).V1

Intervals	min	max
10	0.5	2

☐ logarithmic scan

Scan

Parameter [MAPK-P]_0

Intervals	min	max
10	5	20

☐ logarithmic scan

Task Steady State

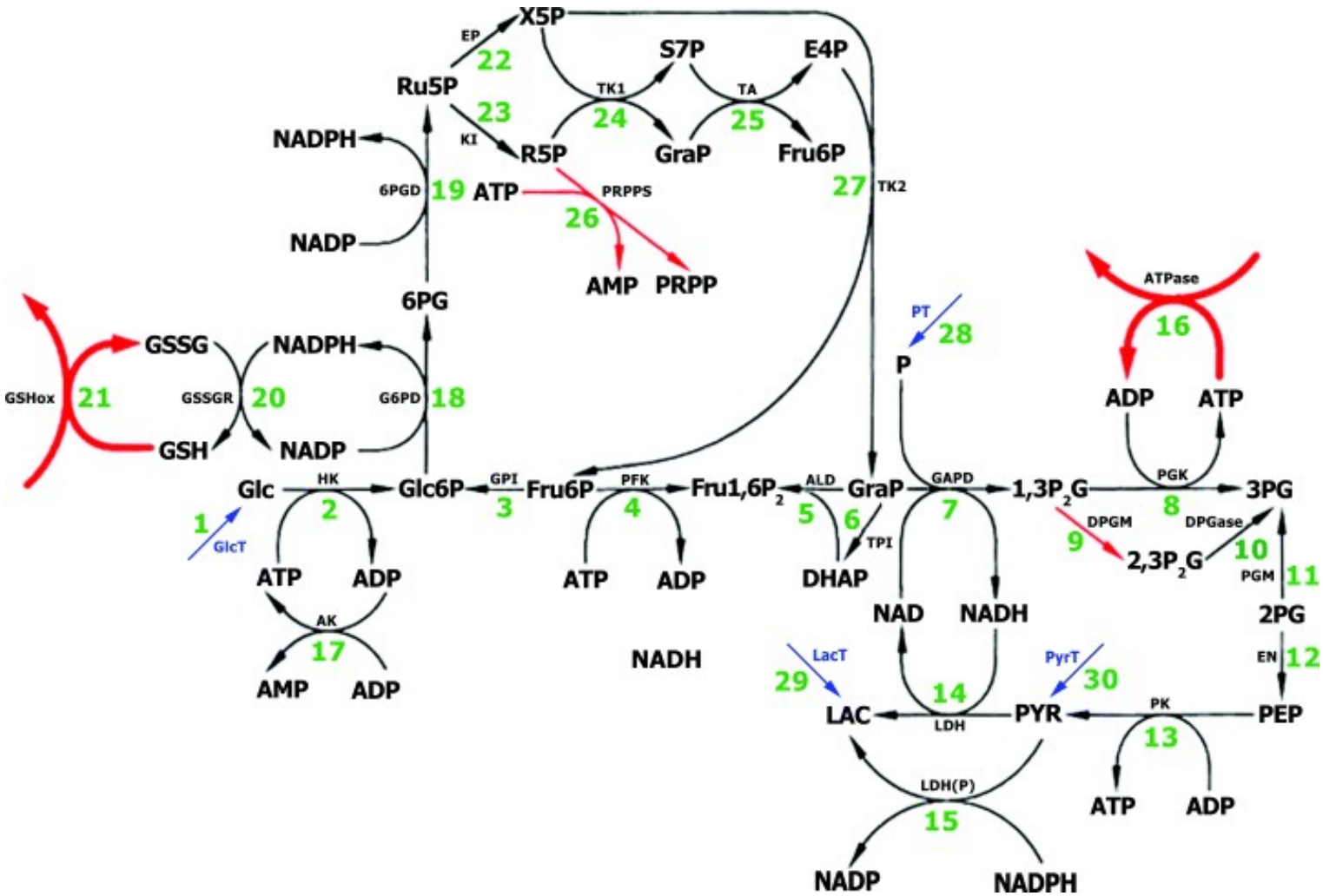
☑ always use initial conditions ☐ output during subtask execution

Run Revert Report Output Assistant

Example Parameter scanning

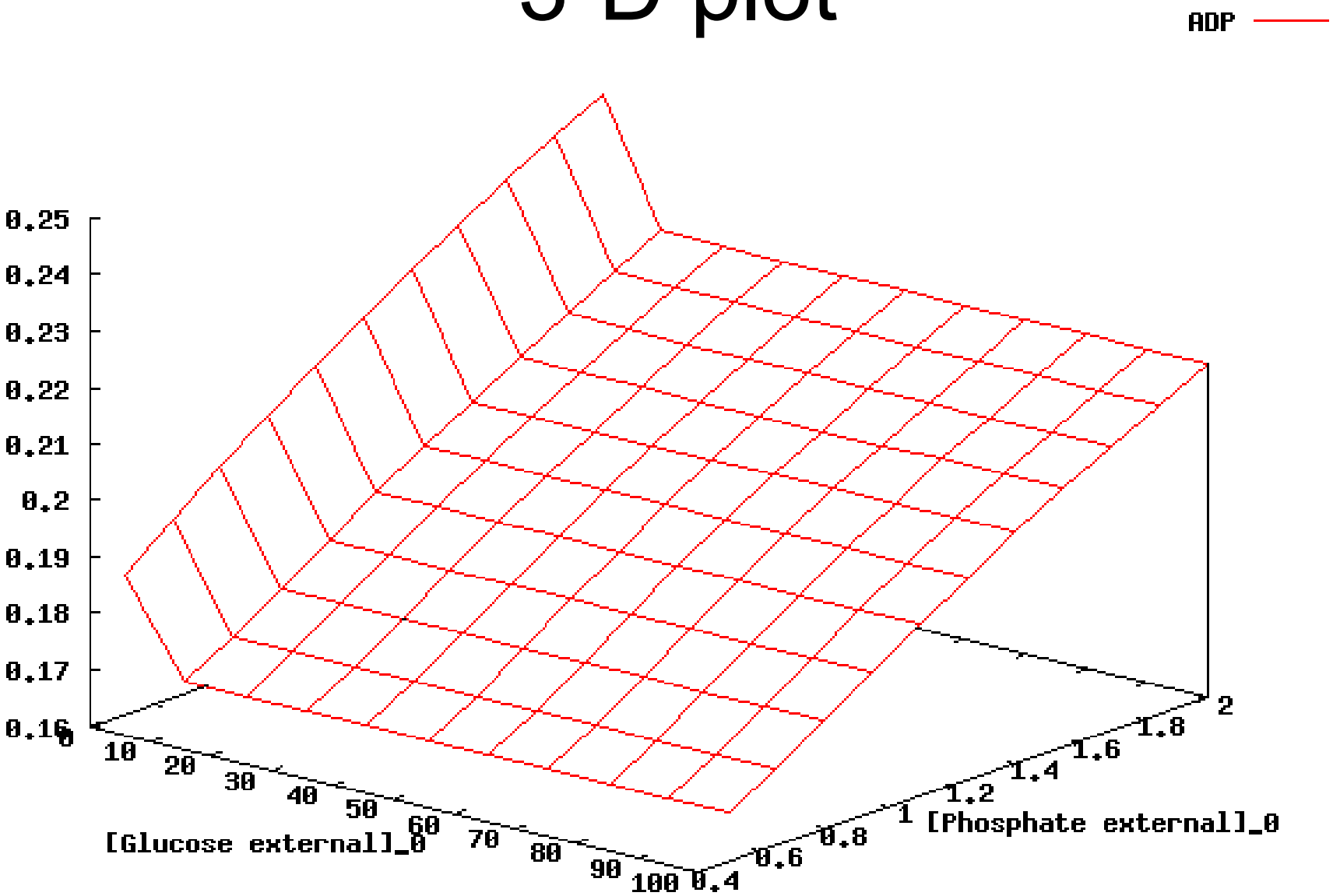
- Erythrocyte model by Holzhütter (biomodel 70)
- Scan over *[Glucose outside](0)* with SS task
- Create plot of, e.g., flux of hexokinase or concentration of Fructose 1,6-bisphosphate
- 2-D scan, add scan for *[Phosphate external](0)*
- Create a plot for ADP and AMP concentrations

Biomodels 70



Holzhütter HG. (2004) The principle of flux minimization and its application to estimate stationary fluxes in metabolic networks. *Eur J Biochem.* 271(14):2905-22

3-D plot



not yet supported in COPASI → define report, write out data to file, use specialised plotting software (e.g. Gnuplot) to generate plot

Parameter scanning

- CAUTION: Calculation/run time **scales exponentially with the number of parameters** (or stacked parameter scans), e.g. with 6 parameters and only 10 different values each we will already end up with 1 million single calculations!

- Also, visualising data in more than 3 dimensions in any useful way is difficult

Parameter sampling

- Don't calculate for each set of parameters on a regular grid. Instead, draw a fixed number of parameter sets randomly within given intervals and do the calculations for these only
- Advantage: all parameters can change simultaneously; do calculations for fewer points in parameter space

- Result: **Sampling of the space of possible results**. Exploring the space of possible solutions

BIOMD0000000010 – COPASI 4.7 (Build 34) /Users/.../JuergenPahle_models/BIOMD0000000010.cps

Concentrations

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Parameter Scan

☐ update model ☐ executable

New scan item: Random distribution ... Create!

Repeat Number of iterations 10

Random Distribution

Parameter (MAPKKK activation).V1

Type	min	max
Uniform distribution	1.25	5

☐ logarithmic

Random Distribution

Parameter [MAPK-P]_0

Type	min	max
Uniform distribution	5	20

☐ logarithmic

Task Steady State

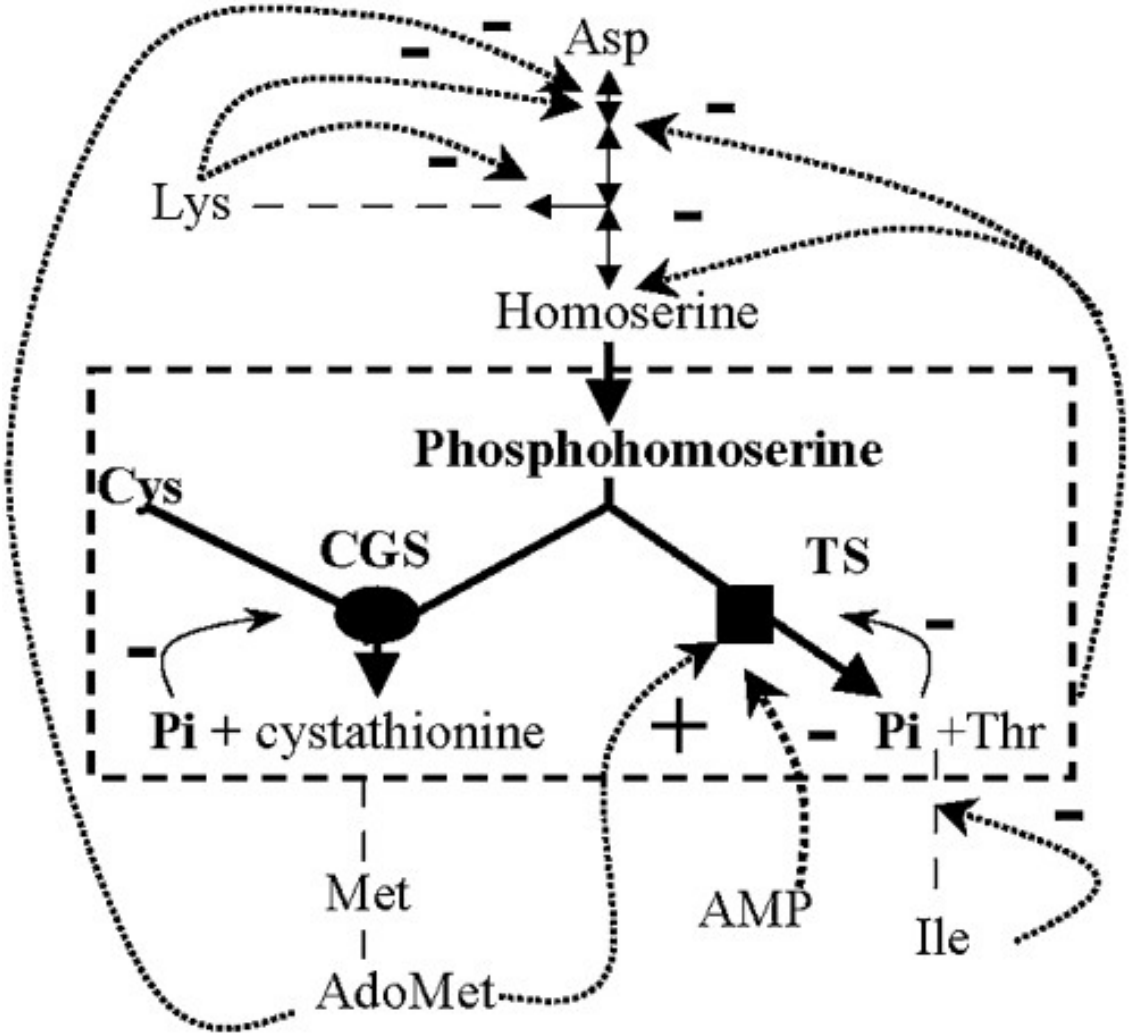
☑ always use initial conditions ☐ output during subtask execution

Run Revert Report Output Assistant

Example: Parameter sampling

- Model of threonine/methionine biosynthesis by Curien *et al.* (biomodels 68)
- Effect of Cysteine (Cys) and S-Adenosylmethionine (AdoMet) on the partition of the output fluxes
- Scan/sample over initial concentration of AdoMet (50 intervals, 0-100), and Cys (5 intervals, 0.3-300, logarithmic scan)
- plot fluxes of Cystathionine gamma-synthase and Threonine Synthase
- sample the system 10000 times using the same parameters (change plot from "Type: lines" to "Type" symbols")

Biomodels 68



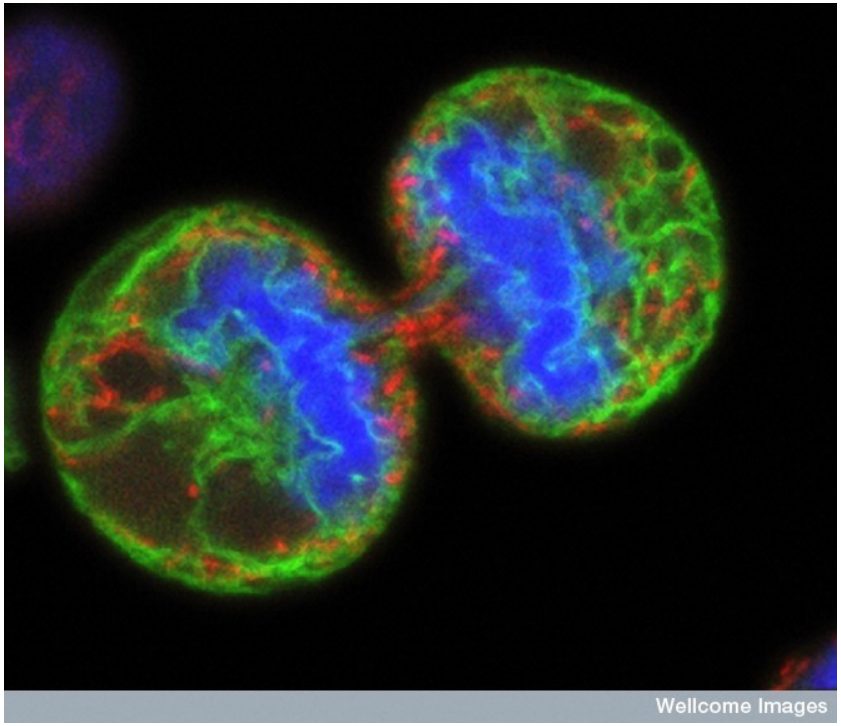
Curien G, Ravanel S, Dumas R. (2003) A kinetic model of the branch-point between the methionine and threonine biosynthesis pathways in *Arabidopsis thaliana*. Eur J Biochem. 270(23):4615-27

Parameter sampling

- CAUTION: sampling of results space is dependent on distributions assumed for the parameters!
  Therefore, distribution of results does not necessarily reflect the distribution of behaviours seen in the real system

- CAUTION: some results might occur only rarely or not at all in the sample. Nevertheless, they might be the ones realised in nature

Discrete events → continuous/discrete systems



Cell division

Discrete changes of the environment:
Lab experiments, manual intervention, discrete control in (bio-)chemical reactors

On-/Off-states of genes, etc.

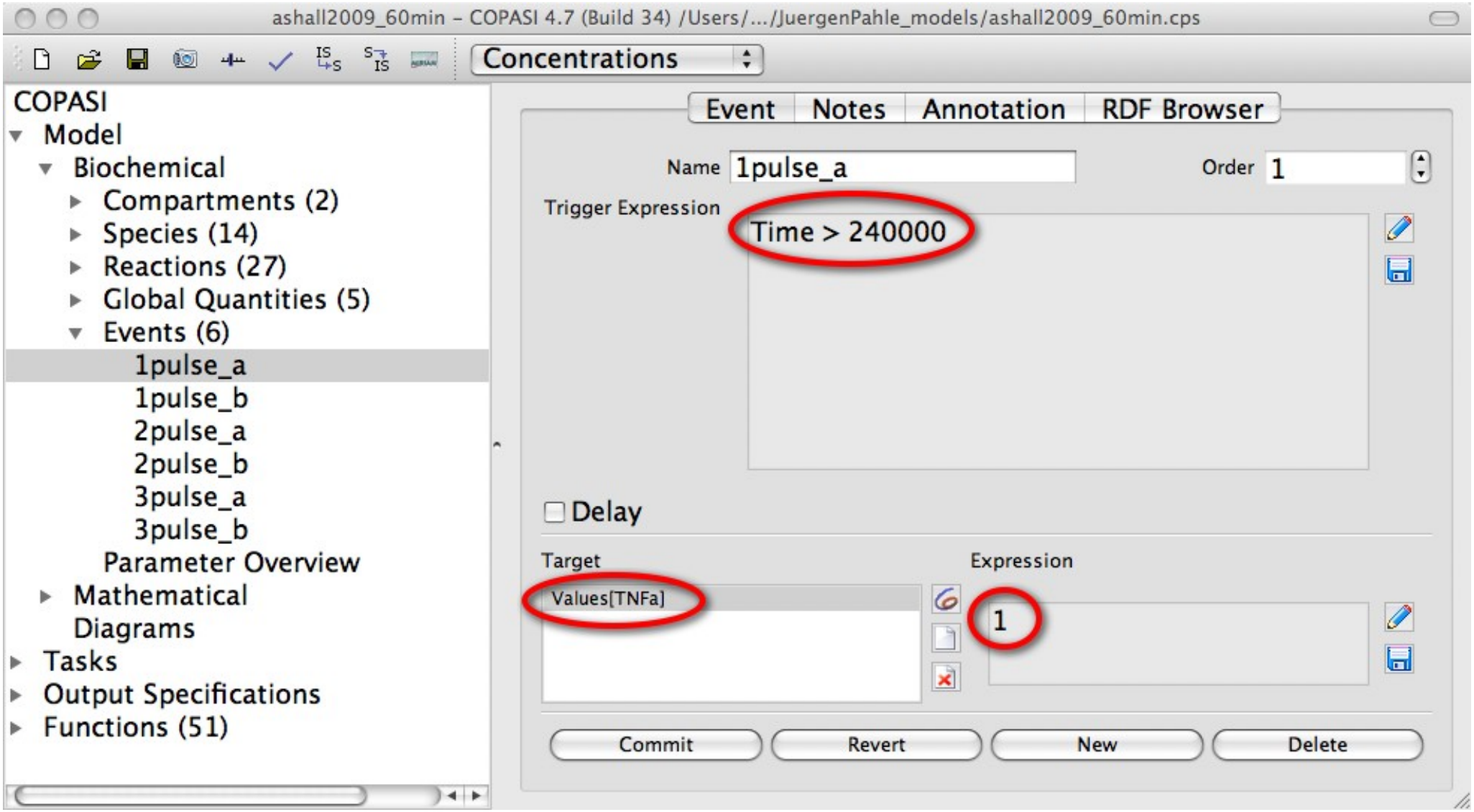
Discrete events

- Represented by triples

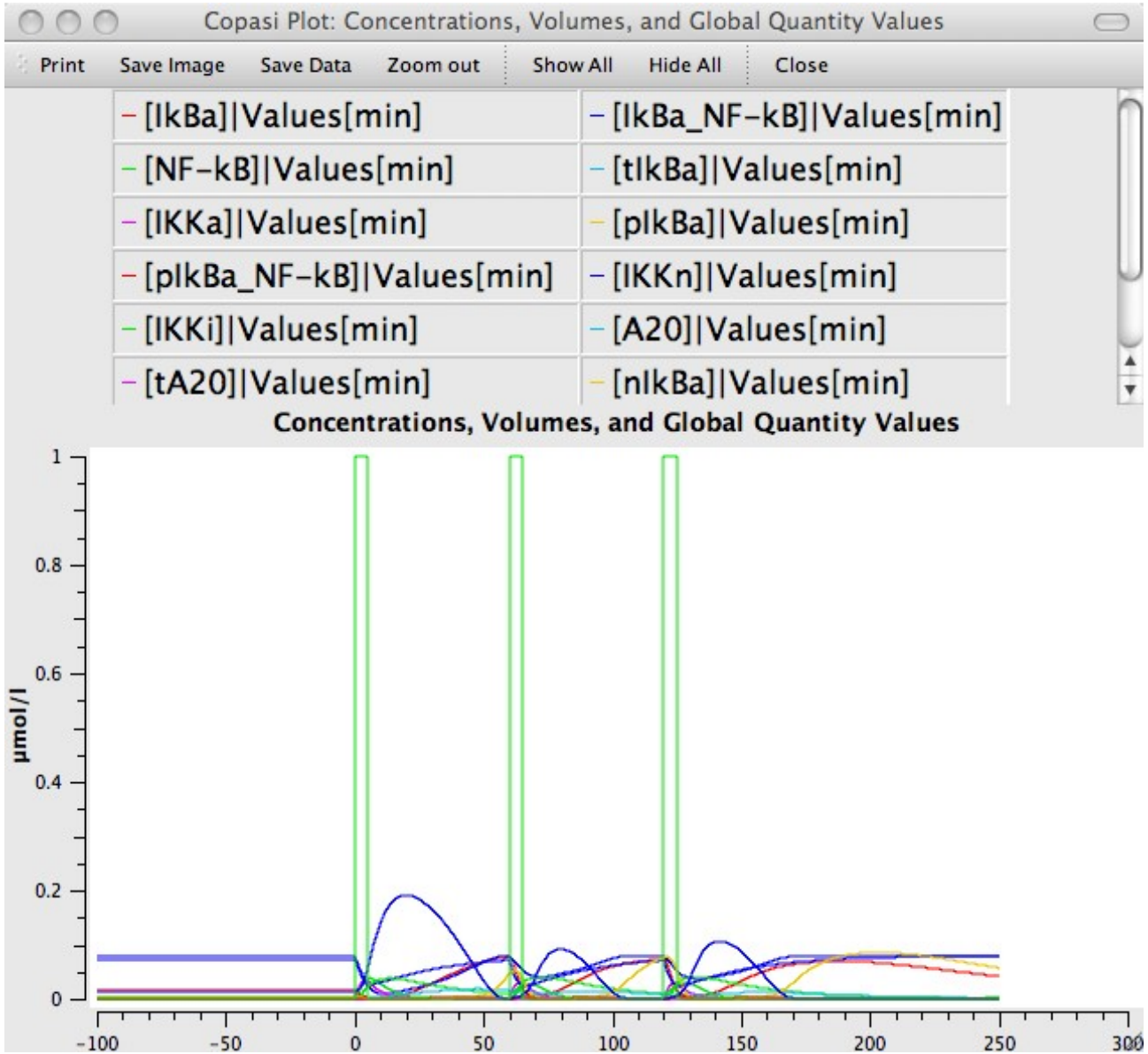
  (Trigger condition, Target, Expression)

- Root finding → LSODAR ("g-stop" feature)
- examples in COPASI
  - Ashall 2009, NF-κB model where stimulus (TNF) is added in a pulsed fashion
  - Novak 1997 (Biomodels.net 7), cell division

Discrete events in COPASI



Example: Discrete events (pulsed changes of concentrations in medium)



Discrete events

Events consist of:

1) **trigger**: logical expression that changes from FALSE to TRUE
2) **effects**: target variables that are assigned the value of an algebraic expression
3) **(optional) time delay**: time between trigger and effects

Discrete events can be used to **cause jump-like changes** in the model or to **record values** at specific discrete points in time

Rules

- In COPASI (and other SBML-compliant software) the system equations are constructed from the reaction system specified
- Rules allow further **algebraic expressions or differential equations** to be added to the system equations that describe additional variables ("Global quantities” in COPASI-speak) in the model
  - algebraic expressions/assignments: how one variable is calculated from other variables
  - "ODE rules": describe the rate of change of a variable

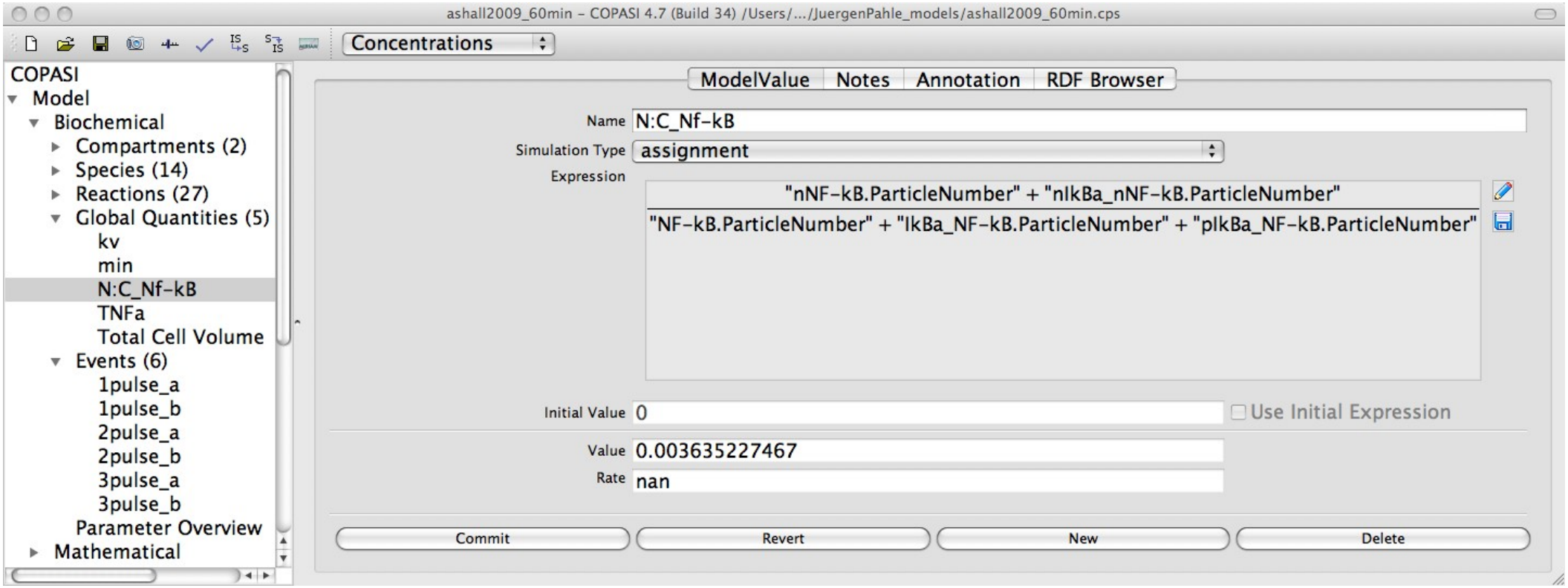
Rules (use cases)

- Variables that are neither species concentrations nor reaction fluxes, e.g. "biomass", pH, temperature, etc.
- Combinations of variables in the model that one wants to study, e.g. sums of concentrations, quotient of fluxes, etc.

Note: These additional variables can be plotted but they can also be used in kinetic functions just like species concentrations

Example: Rules

(ratios of species concentrations in different compartments)



Example: Rules

(ratios of species concentrations in different compartments)