

Lecture: Computational Systems Biology
Universität des Saarlandes, SS 2012

**06 Parameter scanning, parameter sampling,
discrete events, rules**

Dr. Jürgen Pahle

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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

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

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

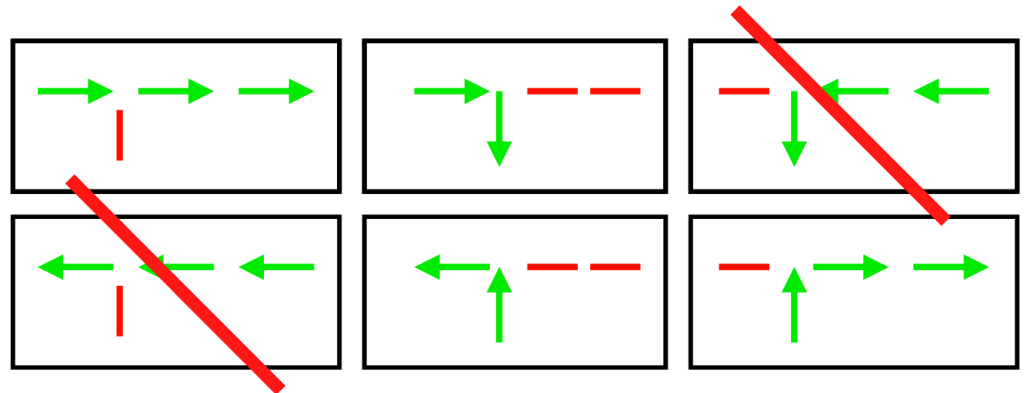
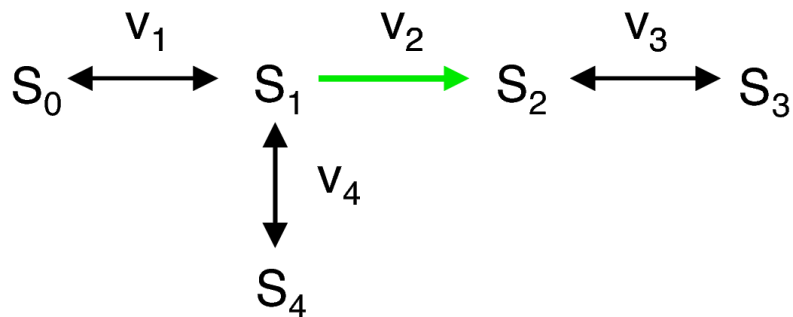
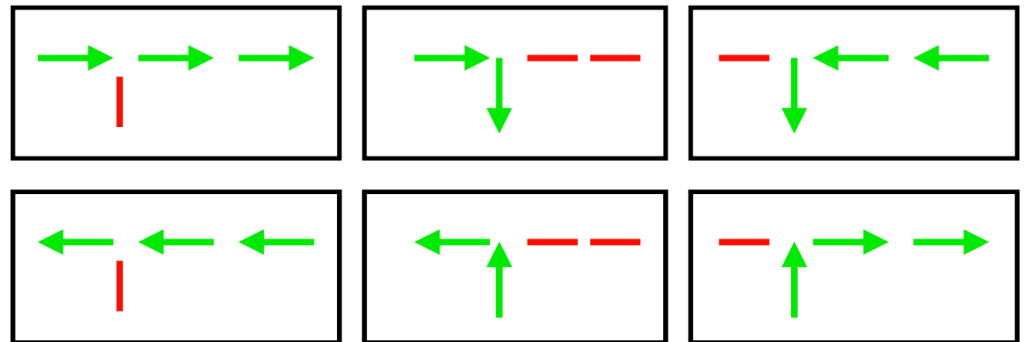
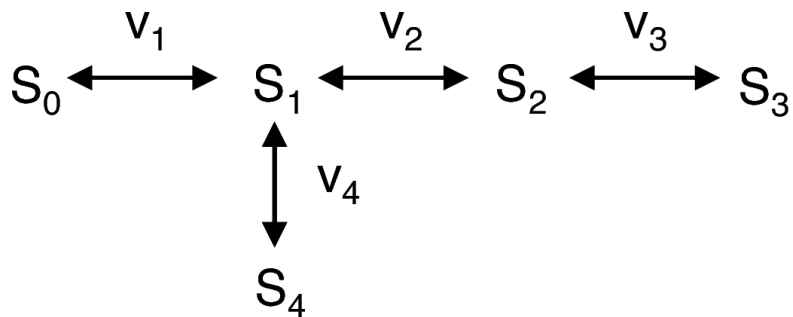
- it corresponds to a steady state
 - all sign restrictions (irreversible reactions) are fulfilled
-
- Can be calculated using COPASI or specialised software, such as Metatool

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



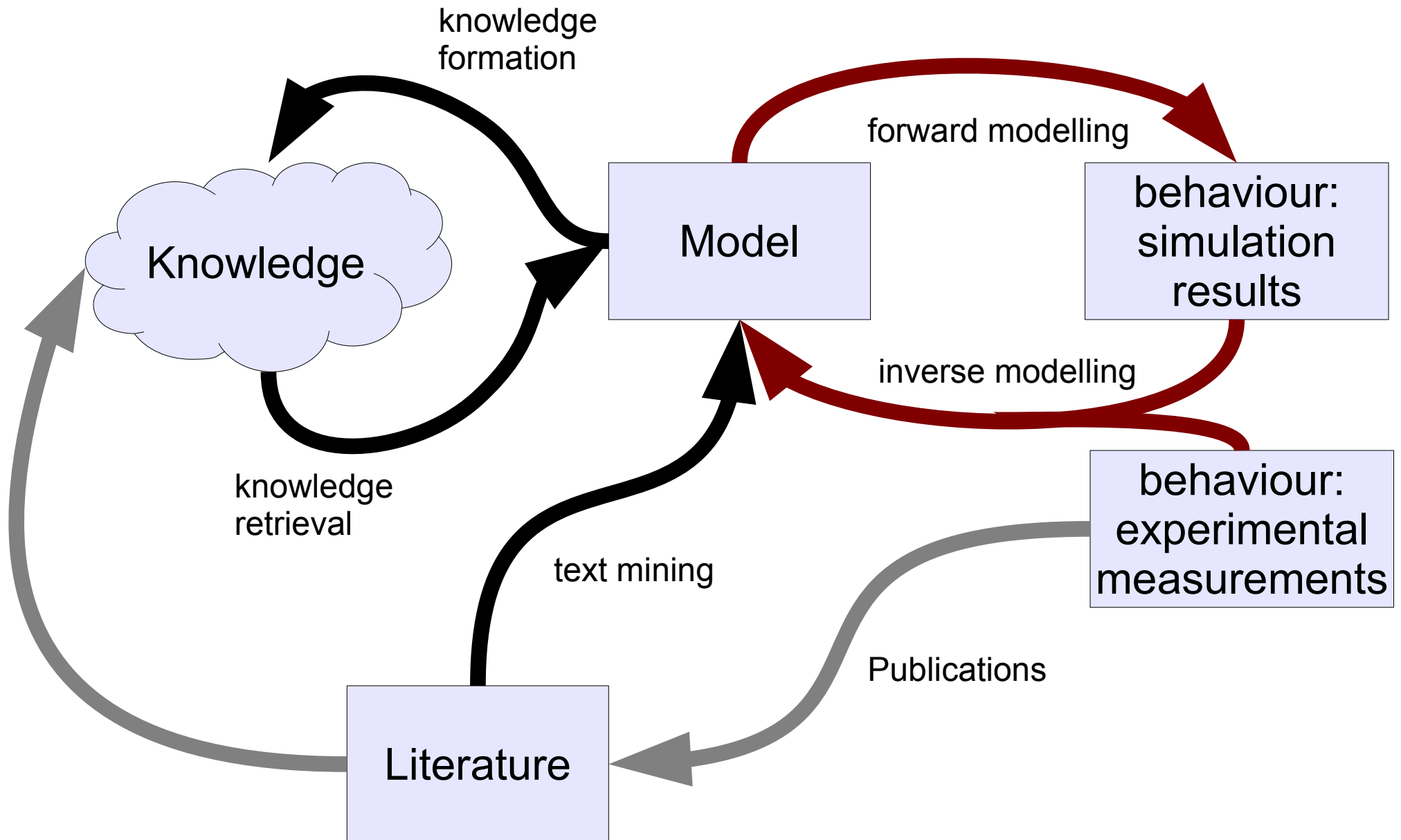
Conservation relations (recap)

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 (\rightarrow link matrix)

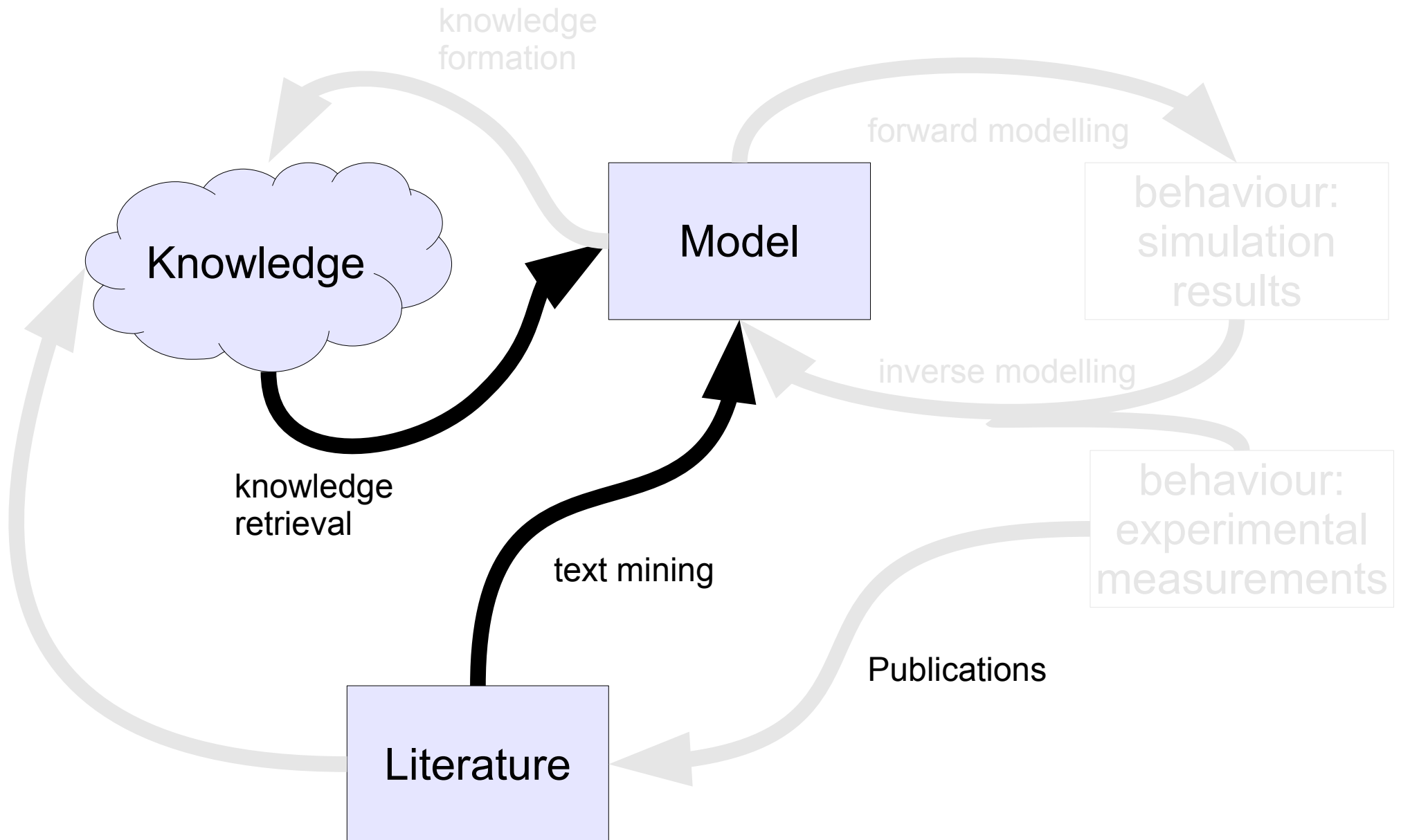
Iterative modelling cycle



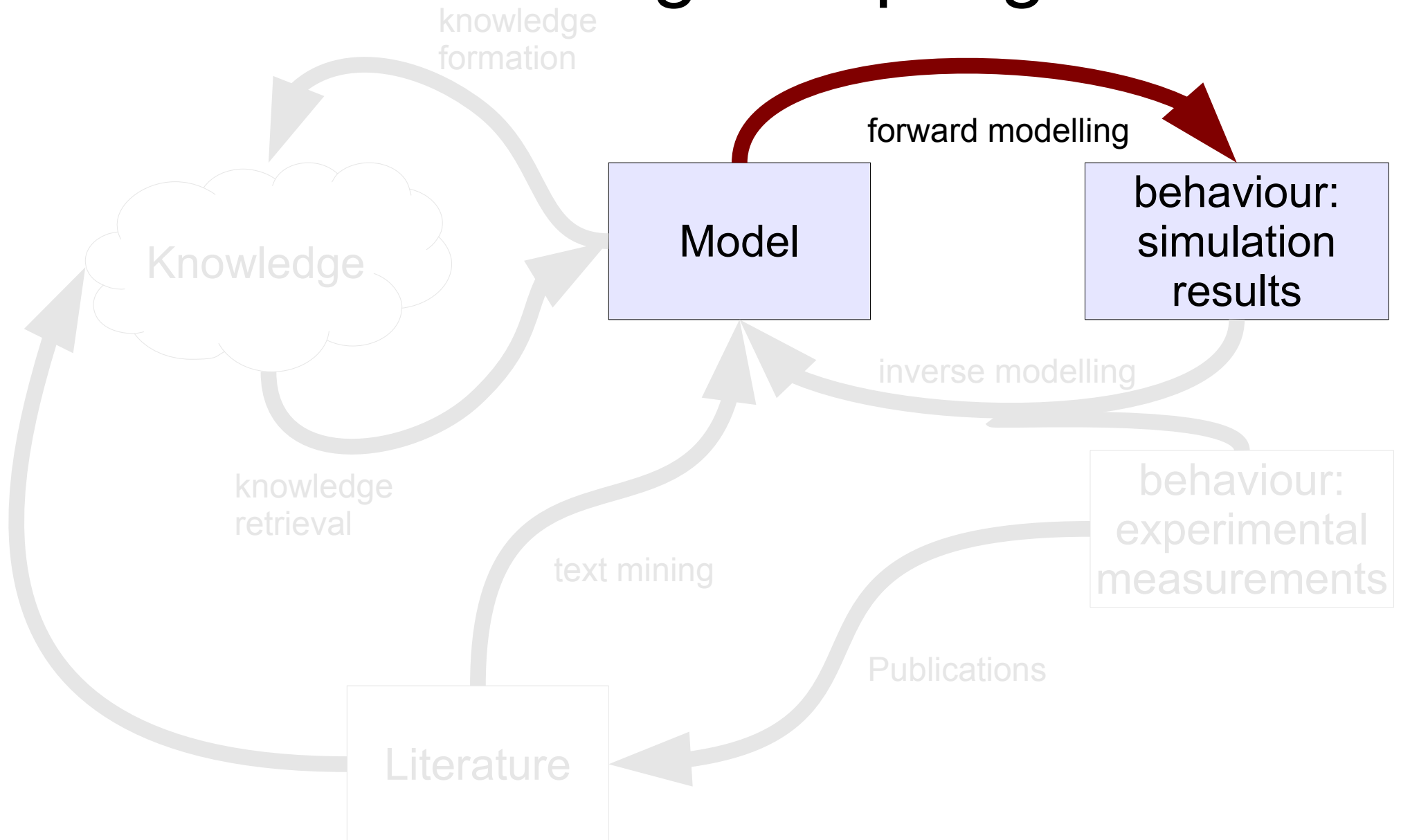
The central modelling question

- 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)

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

Concentrations

COPASI

- Model
 - Biochemical
 - Compartments (1)
 - Species (8)
 - 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
 - Tasks
 - Output Specifications
 - Functions (47)

Reaction Notes Annotation RDF Browser

Name dephosphorylation of MAPK-P

Chemical Equation MAPK-P -> MAPK

☐ Reversible ☐ Multi Compartment

Rate Law function_4_dephosphorylation of MAPK- New Rate Law

Flux (nmol/s) 0

Symbol Definition

	Description	Name		Value	Unit
Parameter		KK10	<input type="checkbox"/> global	15	nmol/l
→ Substrate		MAPK_P	<input type="checkbox"/> global	MAPK-P	nmol/l
Parameter		V10	<input type="checkbox"/> global	0.5	nmol/(l*s)

Commit Revert New Delete

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
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 - dephosphorylation of MAPKK-P
 - dephosphorylation of MAPKK-PP
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 - MAPKKK inactivation
 - phosphorylation of MAPK
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 - phosphorylation of MAPKK
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 - 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-P → MAPK
dephosphorylation of MAPK-P: MAPK-P → MAPK

Commit Revert New Delete

Changing parameters in COPASI

(compartment window → initial volumes)

The screenshot displays the COPASI 4.7 (Build 34) interface. The title bar indicates the file path: BIOMD0000000010 - COPASI 4.7 (Build 34) /Users/.../JuergenPahle_models/BIOMD0000000010.cps. The left sidebar shows a hierarchical tree of the model structure:

- COPASI
 - Model
 - Biochemical
 - Compartments (1)
 - uVol**
 - Species (8)
 - 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
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The main window is titled 'Concentrations' and features tabs for 'Compartment', 'Notes', 'Annotation', and 'RDF Browser'. The 'Compartment' tab is active, showing the following fields for the selected compartment 'uVol':

- Compartment Name: uVol
- Simulation Type: fixed
- Initial Volume (l): 1 (highlighted with a red circle)
- Use Initial Expression: ☐
- Volume (l): nan
- Rate (l/s): 0
- Contained Metabolites: MAPK, MAPK-P, MAPK-PP, MAPKK, MAPKK-P, MAPKK-PP, MAPKKK, MAPKKK-P

At the bottom of the window, there are four buttons: Commit, Revert, New, and Delete.

Changing parameters in COPASI

(parameter overview)

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

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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)

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

Concentrations

COPASI

- Model
 - Biochemical
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 - uVol
 - Species (8)
 - Reactions (10)
 - 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
 - Sensitivities
 - Output Specifications
 - Functions (47)

Time Course ☐ update model ☐ executable

Duration (s) 1

Interval Size (s) 0.01

☐ Suppress Output

☐ Output Events

Integration Interval (s) 0 to 1

Method **Deterministic (LSODA)**

Parameter

Integrate Reduced Model	
Relative Tolerance	1e-06
Absolute Tolerance	1e-12
Max Internal Steps	10000

new sliders

(MAPKKK activation).V1 : [1.25-5] {2.5}

☐ update ranges

☒ update automatically

run task

Run Revert

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

The screenshot shows the COPASI 4.7 (Build 34) interface. The title bar indicates the file path: BIOMD0000000010 - COPASI 4.7 (Build 34) /Users/.../JuergenPahle_models/BIOMD0000000010.cps. The main window is titled "Concentrations". On the left, a sidebar lists various tasks, with "Parameter Scan" highlighted. The "Parameter Scan" dialog box is open, showing a "Scan" section with a red border. The "Parameter" field is set to "(MAPKKK activation).V1". The "Intervals" section shows a "min" value of 0.5 and a "max" value of 2, with a "10" value in the "Intervals" field. The "logarithmic scan" checkbox is unchecked. Below the "Scan" section, the "Task" is set to "Steady State", and the "always use initial conditions" checkbox is checked. The "output during subtask execution" checkbox is unchecked. At the bottom, there are buttons for "Run", "Revert", "Report", and "Output Assistant".

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

Concentrations

COPASI

- Model
- Tasks
 - Steady-State
 - Stoichiometric Analysis
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 - Metabolic Control Analysis
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 - Parameter Scan**
 - Optimization
 - Parameter Estimation
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- 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

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

Scan

Parameter [MAPK-P]_0

Intervals min max

10 5 20

☐ logarithmic scan

Task Steady State

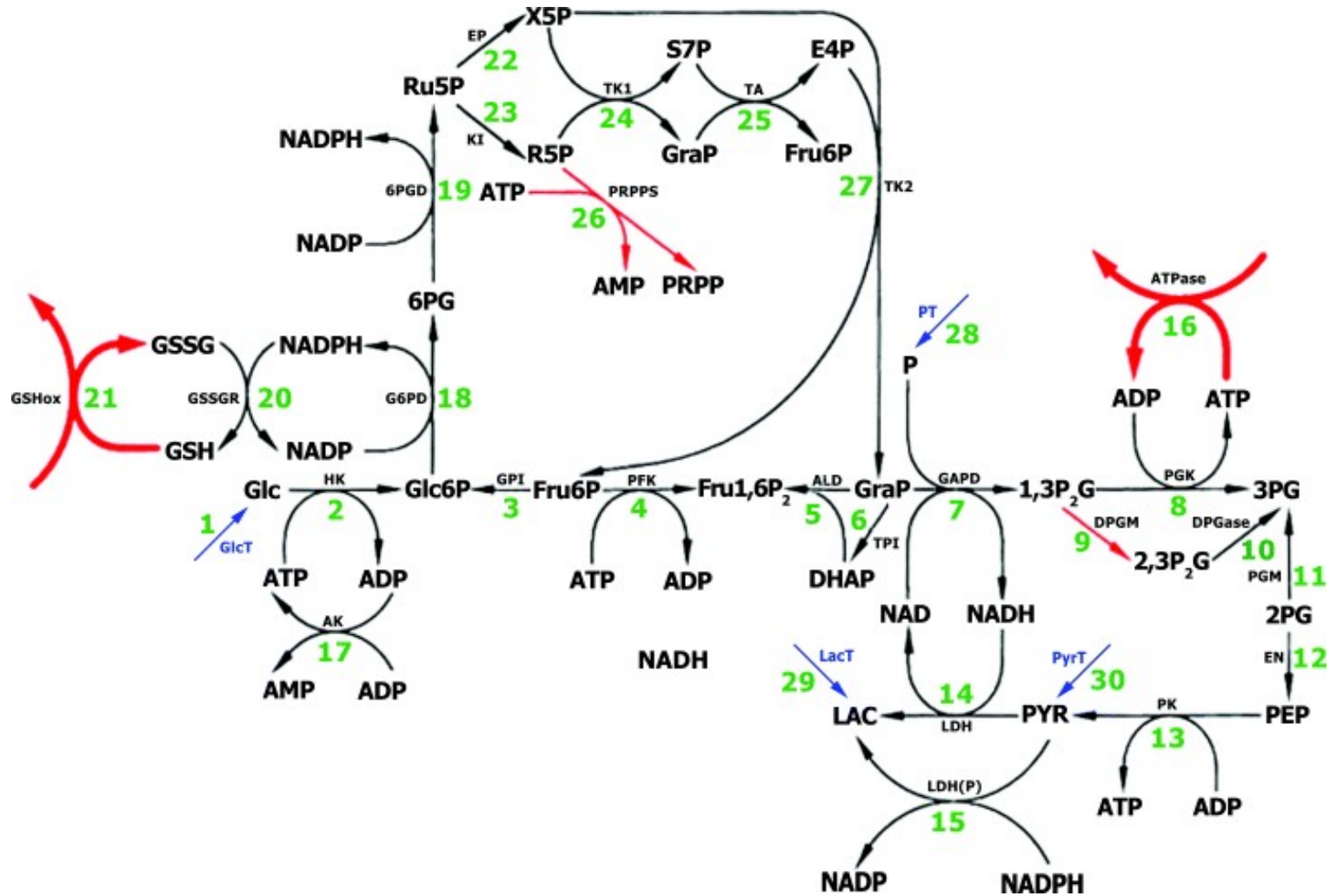
☒ always use initial conditions ☐ output during subtask execution

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

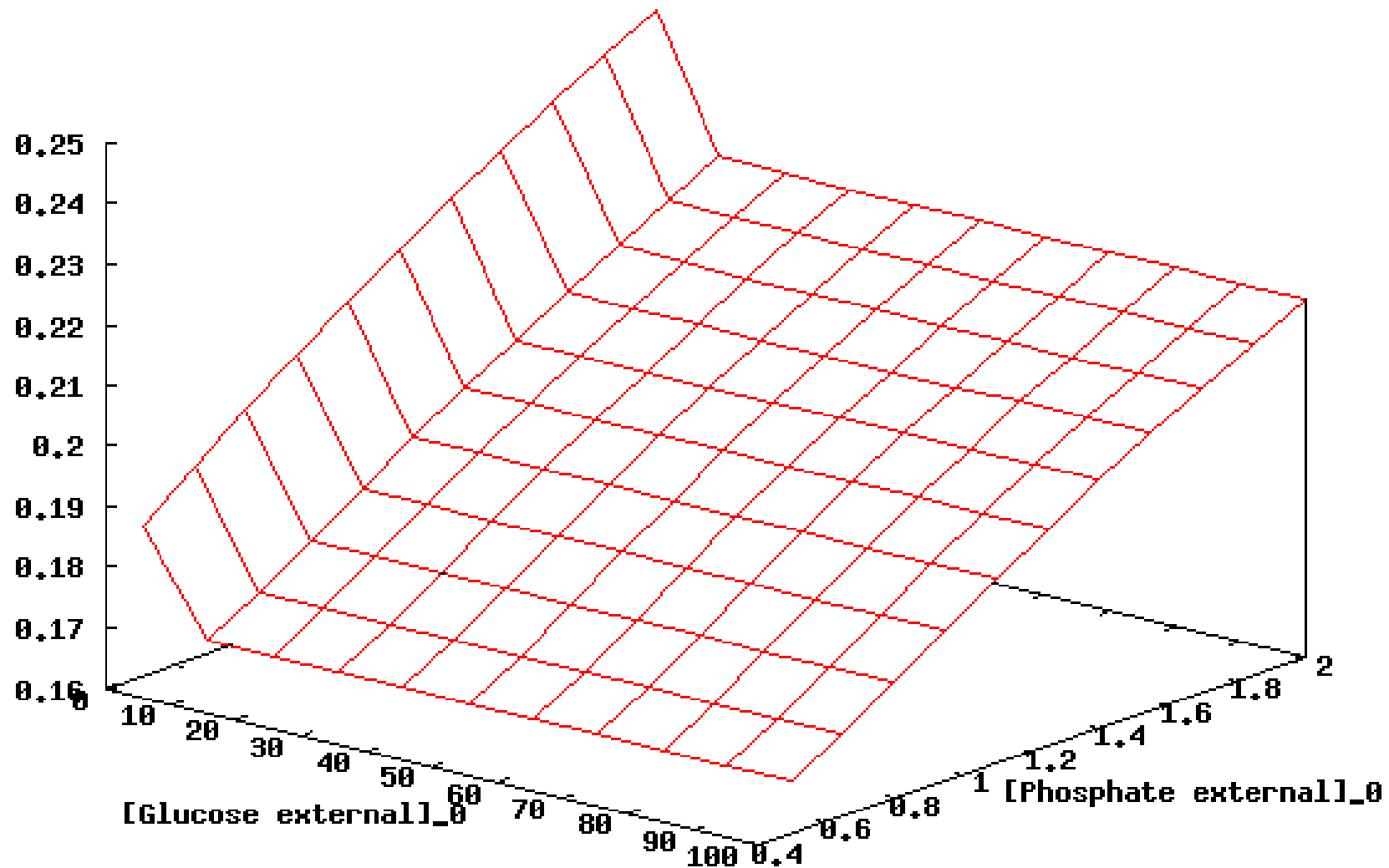
Biomodels 70



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

ADP —



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

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: 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

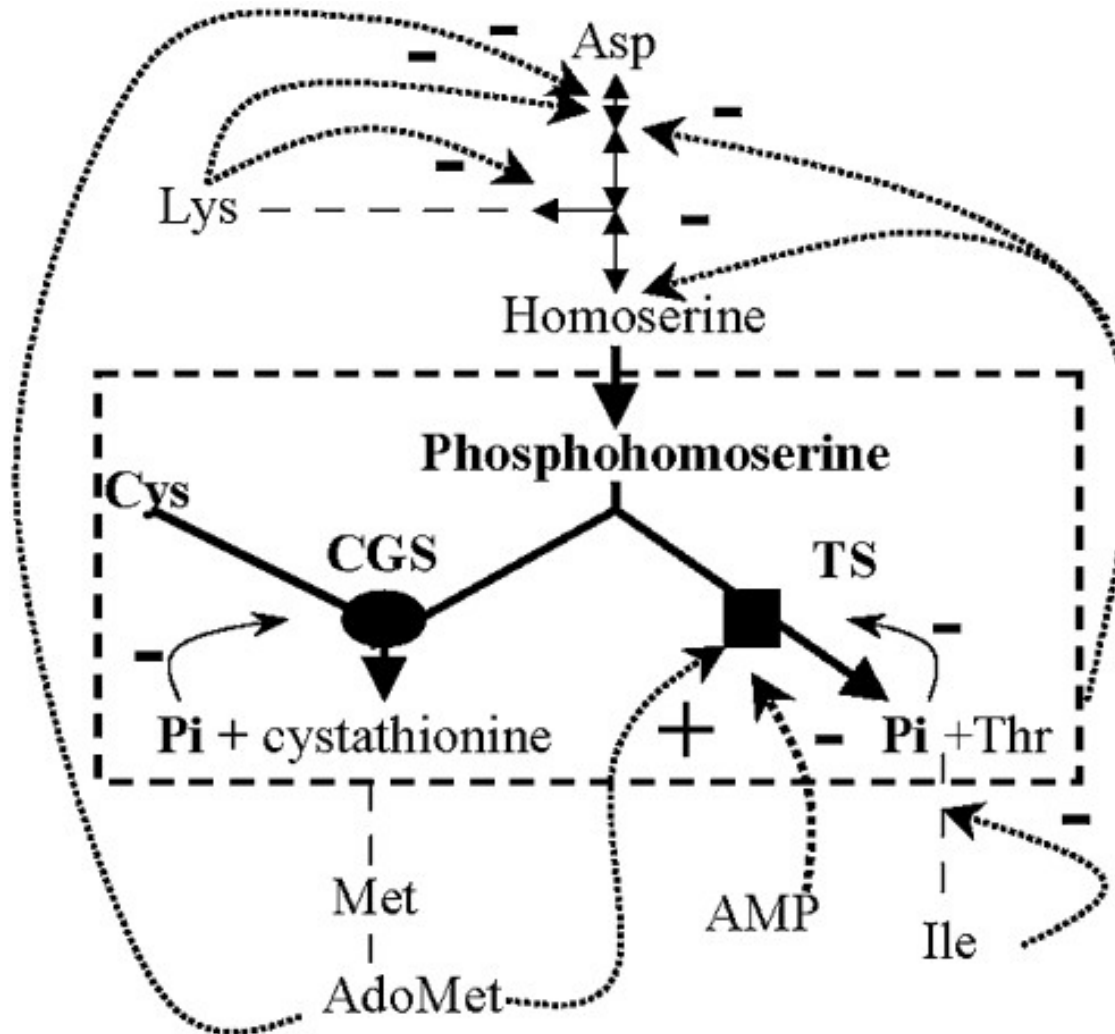
Report

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

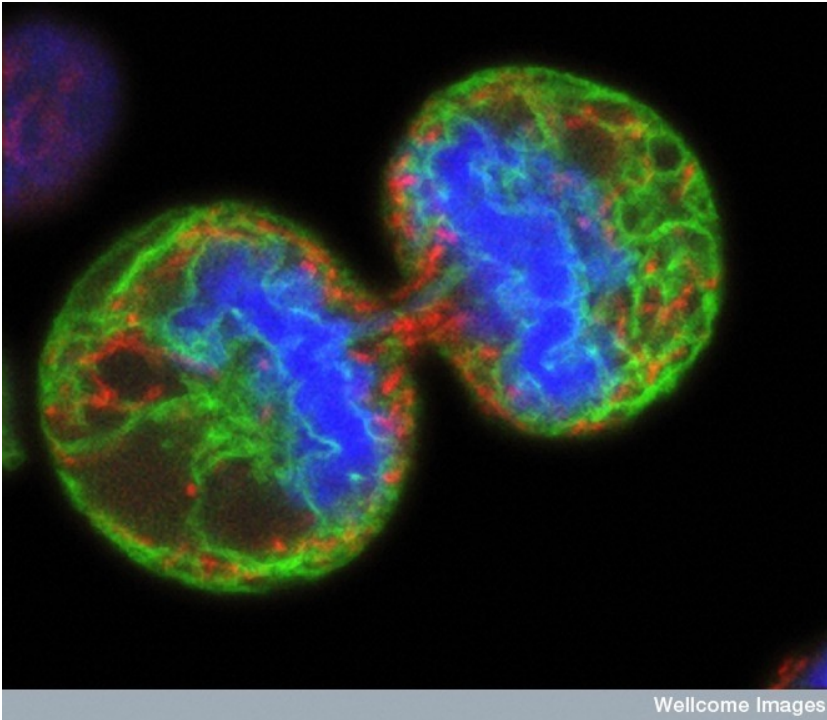


Curien G, Ravanel S, Dumas R. (2003) A kinetic model of the branch-point between the methionine and threonine biosynthesis pathways in *Arabidopsis thaliana*. Eur J Biochem. 270(23):4615-27

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

On-/Off-states
of genes, etc.



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

Discrete events

- Represented by triples
(Trigger condition, Target, Expression)
- Root finding → LSODAR ("g-stop" feature)
- examples in COPASI
 - Ashall 2009, NF- κ B model where stimulus (TNF) is added in a pulsed fashion
 - Novak 1997 (Biomodels.net 7), cell division

Discrete events in COPASI

ashall2009_60min - COPASI 4.7 (Build 34) /Users/.../JuergenPahle_models/ashall2009_60min.cps

Concentrations

COPASI

- ▼ Model
 - ▼ Biochemical
 - Compartments (2)
 - Species (14)
 - Reactions (27)
 - Global Quantities (5)
 - ▼ Events (6)
 - 1pulse_a
 - 1pulse_b
 - 2pulse_a
 - 2pulse_b
 - 3pulse_a
 - 3pulse_b
 - Parameter Overview
 - Mathematical Diagrams
 - Tasks
 - Output Specifications
 - Functions (51)

Event Notes Annotation RDF Browser

Name 1pulse_a Order 1

Trigger Expression Time > 240000

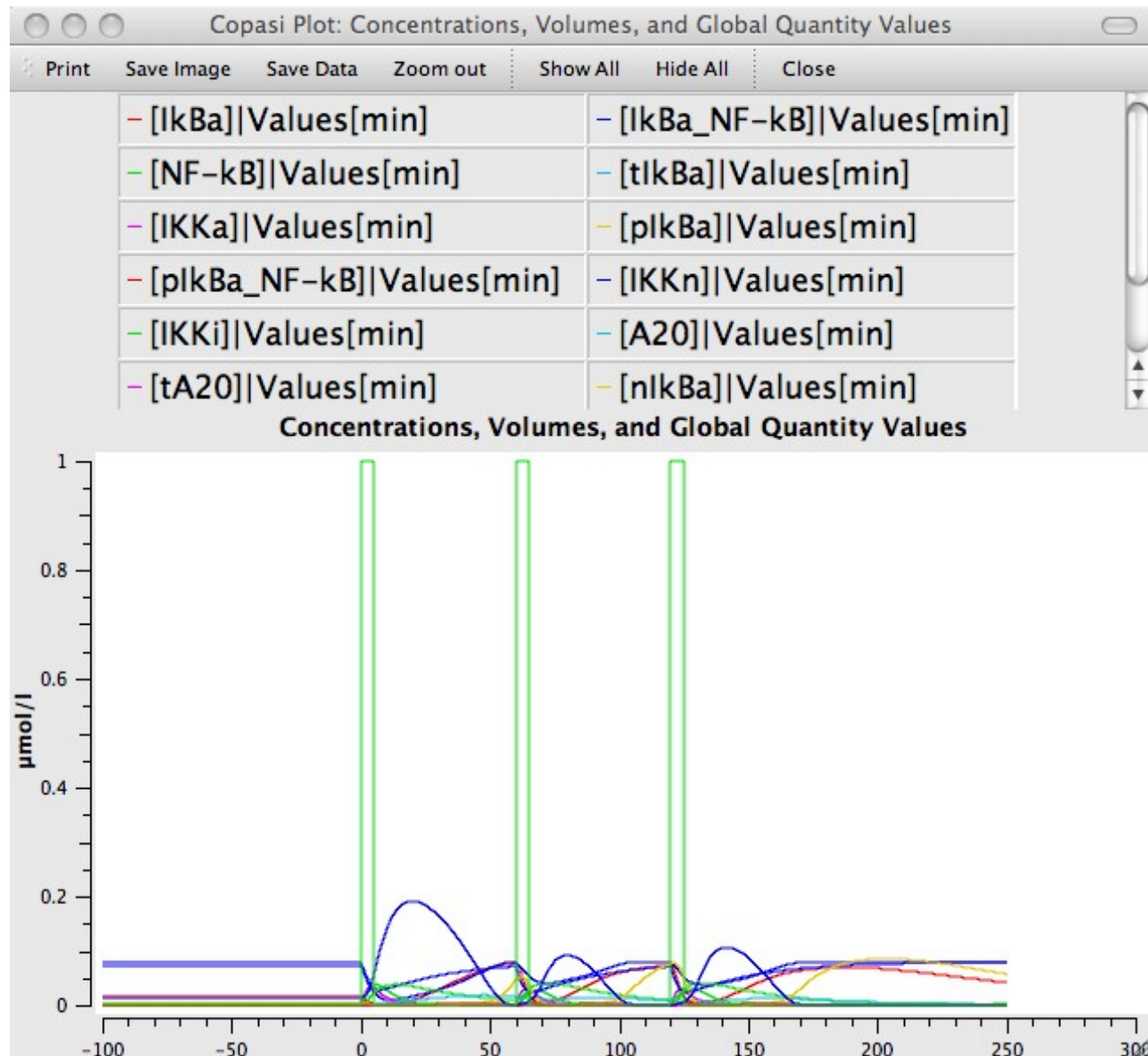
☐ Delay

Target Values[TNFa]

Expression 1

Commit Revert New Delete

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)

The screenshot displays the COPASI 4.7 (Build 34) interface. The title bar indicates the file path: `ashall2009_60min - COPASI 4.7 (Build 34) /Users/.../JuergenPahle_models/ashall2009_60min.cps`. The left sidebar shows the model hierarchy: **COPASI** > **Model** > **Biochemical** > **Species (14)** > **N:C_Nf-kB**. The main window is titled **Concentrations** and contains the following fields:

- Name:** `N:C_Nf-kB`
- Simulation Type:** `assignment`
- Expression:**
`"nNF-kB.ParticleNumber" + "nlkBa_nNF-kB.ParticleNumber"`
`"NF-kB.ParticleNumber" + "lkBa_NF-kB.ParticleNumber" + "plkBa_NF-kB.ParticleNumber"`
- Initial Value:** `0` (with a checkbox for **Use Initial Expression**)
- Value:** `0.003635227467`
- Rate:** `nan`

At the bottom of the window are four buttons: **Commit**, **Revert**, **New**, and **Delete**.

Example: Rules

(ratios of species concentrations in different compartments)

