Lecture: Computational Systems Biology
Universität des Saarlandes, SS 2012

12 Wrap-up, questions & answers

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Recap

- Particle swarm optimisation
- No free lunch-theorems of optimisation
- Practical tips on using optimisation techniques
- Parameter estimation/fitting:
  - How to get parameters that produce desired behaviour?
  - Objective function is implicitly given by the (experimental) data
  - Scaling of residuals
  - Identifiability (structural ↔ practical)
  - Overfitting
  - Examples (Kholodenko 2000 and Brusselator)

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- Ralph Gauges (Sigmaringen) and Ursula Kummer's group (Heidelberg), and
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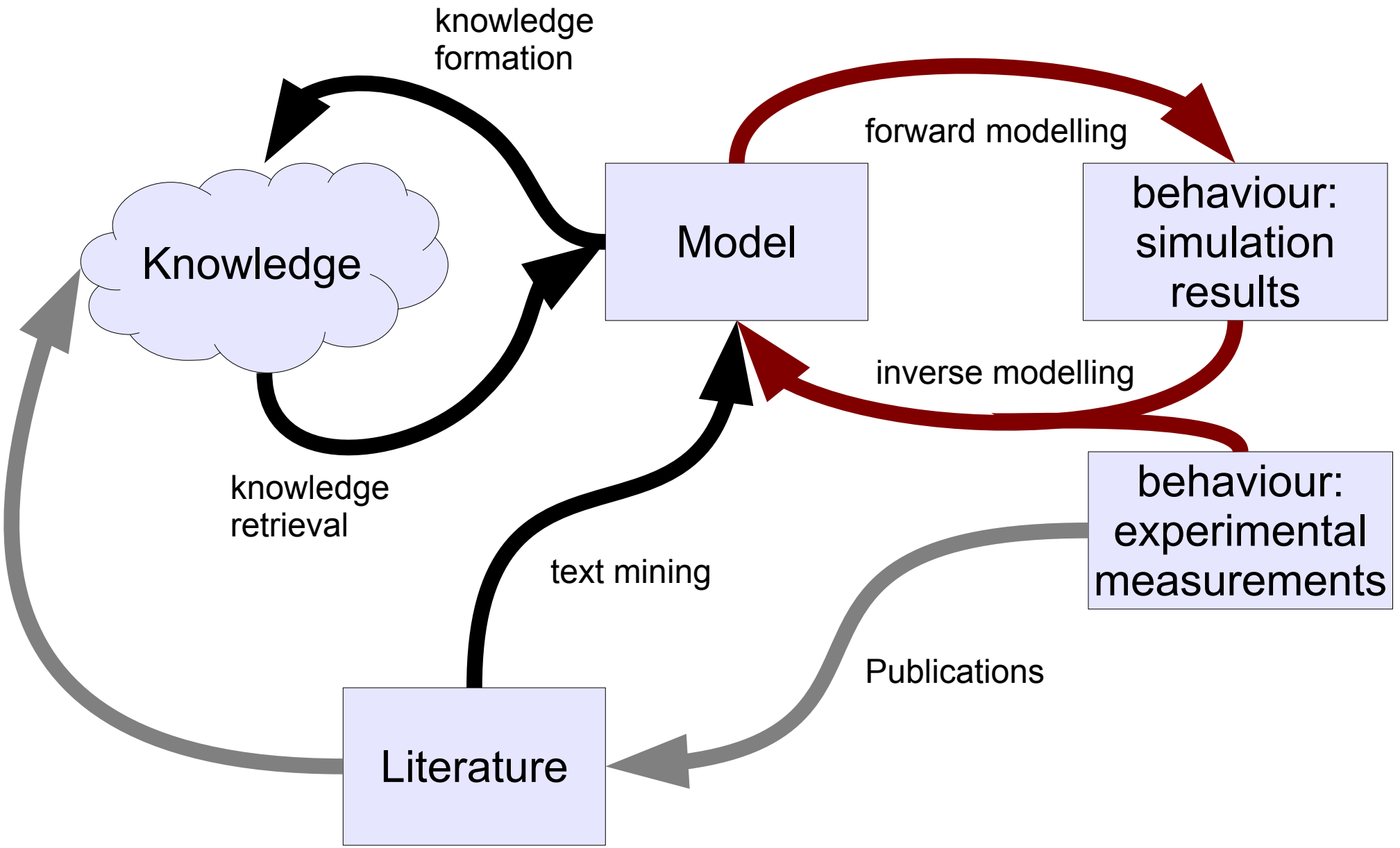
for some of the lecture slides and examples.

Lecture content overview

- Basics of modelling, models, stoichiometry, (enzyme) rate laws, ODEs, steady states, simulation
- Software, databases, standards
- Elementary flux modes, conservation relations
- Parameter scanning/sampling, discrete events
- Sensitivities, metabolic control analysis
- Case studies
- Stochastic modelling and simulation
- Optimisation
- Parameter estimation

Iterative modelling cycle



Introduction

- In Systems Biology we, *inter alia*, represent processes in living systems using models
- Models can be of various types and use different mathematical formalisms
- Modelling is an iterative process including literature and database search, experimental measurements, simulations, model refinement, etc.
- Models can be used to predict and also to study and understand biological processes (exploratory/explanatory models)

Modelling [part 1]

- Some biochemistry basics: chemical reactions, equilibrium, biochemical pathways,
  genes → mRNA → proteins
- Stoichiometry (-ic matrix)
- Kinetic functions: mass action, Michaelis-Menten (enzymatic reactions)
- How to transform a reaction system into a quantitative model, e.g. ordinary differential equation system (ODE)
- Simulation: numerical integration of (stiff) ODEs
- COPASI (exercise)

Modelling [part 2]

- Equilibrium constant K_{eq} (remember: enzymes don't change K_{eq})
- Enzyme kinetic laws
  - Michaelis-Menten (irreversible, reversible)
  - Competitive, uncompetitive, noncompetitive, substrate inhibition, and others
  - Hill equation, Monod-Wyman-Changeux model
  - Other kinetic frameworks (generalised mass action, lin-log, convenience kinetics)
- Dynamical systems
  - Steady states, stability (local/global), Jacobian matrix, how to find steady states (integration, Newton method), attractors, bifurcations, limit cycles

Standards, software, databases

- Standards
  - Systems Biology Markup Language (SBML)
  - Systems Biology Graphical Notation (SBGN)
  - Minimal information required in the annotation of models (MIRIAM)
- Software
  - COPASI, CellDesigner, etc.
- Databases
  - Pathway databases (KEGG, Reactome, ...)
  - Databases providing kinetic parameters (BRENDA, Sabio-RK)
  - Model databases (Biomodels, JWS)

Structural analysis

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

Parameter scanning/sampling, discrete events, rules

- Studying the **effect of parameters on the system's behaviour**:
  - Manual changes and recalculation of quantities of interest
  - Sliders (in COPASI)
  - Parameter scanning (systematic sweep of parameter space)
  - Parameter sampling (randomly exploring parameter space)
- **Discrete events** (discrete changes in systems, described by triple [trigger condition, target, expression])
- **Rules** (describe the behaviour of additional variables in the system with algebraic expressions or ODEs)

Sensitivities, metabolic control analysis

- Rate limiting step?
- How to quantify control?
- Sensitivity analysis → sensitivity coefficients
  - Normalisation factor
- Metabolic control analysis
  - (local) ε- and π-elasticity coefficients
  - (global) flux and concentration control coefficients
- Summation theorems / distribution of control
- Connectivity theorems

Case studies

- General workflow of modelling biochemical networks
- Different types of biochemical networks → different experimental data and computational analysis methods
- Main types of systems:
  - Metabolism, e.g. glycolysis (catabolic) or amino acid synthesis (anabolic)
  - Signal transduction pathways, e.g. MAPK cascades, NF-κB or Calcium signalling
  - Gene expression networks, e.g. cell cycle

Stochastic modelling and simulation

- Biochemical systems show **(intrinsic) random fluctuations** in molecular numbers due to **stochastic timings** of **discrete** reactive events in the system ("firings of reactions")
- This can lead to **quantitative and qualitative different behaviour in stochastic models** (continuous-time Markov process described by a chemical master equation) compared to deterministic models → stochastic effects
- There exist several **exact stochastic simulation algorithms** (SSA, e.g. Gillespie's Direct Method) to capture these effects but they can be computationally demanding
- Therefore **approximate stochastic simulation algorithms**, such as τ-Leaping, are being developed (trade-off between accuracy and run time)
- **Hybrid algorithms**, seem particularly promising because they integrate different mathematical frameworks and can deal with the multi-scale nature of biochemical systems

Optimisation

- "How to change parameters in a model to achieve a desired behaviour?" → **optimisation**
- **Objective function**, parameters to change (and, possibly, constraints)
- **Iterative scheme**: 1) generate par. values, 2) evaluate obj. function
- **Local methods** ↔ **global methods**
- Different **families of optimisation methods**:
  - gradient-based (e.g. steepest descent, Newton, Levenberg-Marquardt)
  - direct (e.g. grid search, simplex method of Nelder and Mead)
  - evolutionary (genetic algorithms, evolutionary programming)
  - other stochastic (e.g. multistart, particle swarm, simulated annealing)
- **Variation** ↔ **selection** in population-based methods
- **Termination criteria?**

Optimisation / Parameter estimation

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  - Examples (Kholodenko 2000 and Brusselator)

Topics for further study

- Bifurcation analysis, Lyapunov exponents
- Time scale separation
- Flux balance analysis
- and many others ...

Exam

When? 31. July 2012, 10-12am

Where? HS001, E1 3

Scope? Everything that we covered in the lectures AND the exercises. There will be no questions on things that are in the textbook but that we did not discuss in the lecture.

Tools? Pen

Question types? Multiple choice, brief explanations, drawing reaction networks, setting up simple ODEs, some maths (calculating the rank of matrizes, simple derivatives, roots of functions, etc.) → see worksheets!

Re-exam? oral, dates in Sep. to be agreed on

Exam (cont.)

Registration! (HISPOS)

Please check the **course webpage** for last minute information (*e.g.* on Friday and Monday)!

If anything is still unclear

→ email (juergen@pahle.de) or personally (room 303, E1 3)

Questions

... and answers