Worksheet: MODELS OF BIOCHEMICAL SYSTEMS (part 2]
(15. May 2012)
Lecture "Computational Systems Biology", Dr. Jürgen Pahle

1) Comprehension questions:

a) What is a state space (also called phase space)?

b) What is the difference between a trajectory and an attractor?

c) Can two trajectories cross in phase space?

d) We learned that a system can have more than one steady state (right hand side of ODE equals zero) with the same parameter set. Can a system have a steady state and a limit cycle at the same time?

e) How would a system behave if it was started (initial condition) exactly on an unstable steady state? What happens if you simulate such a system?

f) How does a system evolve if you start it close to a stable limit cycle?

g) Are all globally stable steady states also locally stable?

2) Open and closed systems

Create a model in COPASI for a closed system that converts 2,3-Bisphosphoglycerate to 1,3-Bisphosphoglycerate (normally catalyzed by 2,3-Bisphosphoglycerate-mutase). Model the system once by using a single reaction with a reversible mass action kinetic and once by using two reactions each using an irreversible mass action kinetics. Start with a reaction rate constant k_f for the forward reaction of 5.0 and k_r for the backward reaction of 2.0. As well as initial values for *[2,3-Bisphosphoglycerate]* of 200.0 and 0.0 for *[1,3-Bisphosphoglycerate]*.

a) What is the difference between the model with one reaction and the model that uses two reactions?

b) What is the equilibrium constant here? How much of each substance do you get if you simulate long enough?

c) How does the ratio of the two substance concentrations change if you change the initial values?

d) How does the ratio of the two substrate concentrations change if you change the rate constants?

e) Change the system to an open system with influx of 2,3-Bisphosphoglycerate and eflux of 1,3-Bisphosphoglycerate. What would be appropriate rate laws/kinetic functions for the in- and eflux? Play around with the parameters in the simulation and see how this changes the behaviour of the model.

3) Find out how you can specify new kinetic functions/rate laws (user-defined functions) in COPASI. Then implement a simple model with only one reaction A → B, the four species A, B, I (inhibitor) and J (activator), and the hypothetical rate law

$$\frac{V \cdot substrate \cdot activator}{(Km + substrate) \cdot (1 + \frac{inhibitor}{Ki})}$$

For this you have to define the different roles of all the symbols in the user-defined kinetic function (parameter, modifier, etc.), and then (in the reaction window) map the symbols to actual entities in your model (species, constants, etc.)

Simulate the system with different (initial) concentrations of A that are kept constant during the course of each simulation (fixed) and see how the flux of the reaction changes.

4) The Jacobian $\boldsymbol{A}_a$ of the following ODE system depends on the parameter a:

$$\frac{d}{dt}\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 0 & -1 \\ 10+a & a \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix}$$

a) To every choice of parameter a belongs a point $(Tr\ \boldsymbol{A}_a,\ Det\ \boldsymbol{A}_a)$ in the plane spanned by trace and determinant of $\boldsymbol{A}_a$. Draw the curve $(Tr\ \boldsymbol{A}_a,\ Det\ \boldsymbol{A}_a)$ in this space for a as a changing parameter.

b) For which values of a is $(x,y) = (0,0)$ a saddle point, node or focus? (see lecture slides)