Worksheet: OPTIMISATION (3. July 2012)
Lecture "Computational Systems Biology", Dr. Jürgen Pahle

1) Comprehension questions
a) What is an objective function?
b) What does the general scheme of operation of most optimisation methods look like?
c) What elements do you have to provide when you are formulating an optimisation problem? What should you consider when setting up constraints?
d) What is the difference between global and local optimisation methods? In what circumstances should you use local methods? When should you use global methods?
e) What are the advantages of stochastic and evolutionary optimisation methods?
f) What are the problems of grid-based exhaustive searches of the permissible parameter space to find optima?
g) What is the metropolis algorithm? How can it be used for optimisation (simulated annealing)?
h) What happens if you make variation (mutation, cross-over) too strong compared to selection in evolutionary algorithms? What happens if you make it too weak?
i) You are optimising a biotechnological process and the optimisation results tell you to increase the V_{max} of one of the enzymatic reactions. What could you do to realise this in the original system? What if you need to decrease a K_m parameter value?

2) In the following we will use model number 23 by Rohwer and Botha (2011) in the Biomodels.net database. We have studied this model already in the exercise on sensitivities and metabolic control analysis, and you can actually compare your optimisation results with the ones you got from MCA. This model describes the accumulation of sugar in sugar cane. In the model, flux J_{11} describes the accumulation of sugar in the vacuole and flux J_9 describes the hydrolysis of sugar. If you want to optimise the accumulation of sugar you could therefore try to minimize the ratio J_9/J_{11}. Let us assume that we could manipulate the total levels of the enzymes catalyzing reactions *v1*, *v2*, *v3*, *v4*, and *v5* (e.g., by overexpression or by

interfering with the upstream regulatory sequences of their genes). The question then becomes what would be the best combination of the levels of these enzymes to achieve the lowest possible ratio J_9/J_{11}. Remember that the level of enzymes correspond to the V_{max} parameter values. Assume that you could change them between 50% to 400% of their original values.

a) Set up this optimisation problem in COPASI

b) Use the Truncated Newton method to optimise

c) Go to the results section and find out what changes are suggested by the optimisation method to achieve the optimisation task (minimising the objective function)

d) You will probably encounter the situation that in the optimised system the levels of Fructose and Glucose will be unrealistically high (*e.g.* 1 molar in the case of Fructose). Therefore, add constraints such that the concentrations of Fructose and Glucose are not allowed to increase above 100 mM.

e) Now repeat the optimisation, this time using a different optimisation algorithm, *e.g.* Particle Swarm, with a maximal number of iterations of 50. How long does it take compared to the derivative-based method used before? What results do you get?

f) Rerun the optimisation a few times and observe that you will get different results each time. Also try out different optimisation algorithms, *e.g.* Genetic Algorithm.