Omdugga2, Juni 2015

Omdugga 1, questions 1-3. Omdugga 2, questions 3-5. Omdugga both, questions 1-5.

Good luck! ☺

1 Consider the following little system:

d/dt(x1) = -k1*x1 + k2*x2 + k3
d/dt(x2) = k1*x1 - k2*x2
yhat = x1 + x2 + kmeas
x1(0) = 0.5, x2(0) = 0.6
k1 = 1, k2 = 2, k3 = 3
kmeas = 5

a) Which are the states in this system?
b) Which are the reaction rates?
c) Are any of the reactions reversible/irreversible? Why/why not?

ANSWER:

a) x1, x2, b) k1*x1, k2*x2, k3, c) the k1 and k2-reactions together can be considered as reversible. It is because they together describe the reaction A ⇔ B, where x1 = [A], x2 = [B]

2 Cost functions and optimization

a) What is the input and output of a cost function? What does it do?
b) What are the residuals? Both give a formula, and say in words what they "do".
c) What is the difference between a local and global optimization function?

ANSWER:

a) input: parameters, output: cost. The cost function calculates the cost for the given parameters, i.e. the agreement with the data. High cost = poor agreement with data

b) The residuals are the distances between the simulations and the data, r = y – yhat

c) A local optimization function only goes down-hill, and cannot go further away than the closest local optimum. In contrast, a global optimization function can search beyond the nearest local optimum and thus try to find the global optimum, which may be further away.

3 Consider the following system:

d/dt(x1) = -k1*x1
d/dt(x2) = k1*x1 - k2

yhat = (x1)*kmeas
x1(0) = 0.5, x2(0) = 0.6
k1 = 1, k2 = 2
kmeas = 5

a) Assume that the k1-reaction is saturated, with a Michaelis-Menten expression. What changes in the model?

ANSWER: The ODEs become:

d/dt(x1) = -k1*x1/(Km + x1)
d/dt(x2) = k1*x1/(Km + x1) - k2
and you need values for the new parameters Km ,e.g. Km = 9

b) What is the residual at time t=0, if the measurement is y(0) = 4

ANSWER: r = y – yhat = 4 - 0.5*5 = 4-2.5 = 1.5

c) What are the reactions in the following model?

d/dt([A]) = k1 - Vmax*[A]/(Km + [A]) + k2*[B]
d/dt([B]) = + Vmax*[A]/(Km + [A]) - k2*[B] - k3*[B]
yhat = ky*[A]

ANSWER: => A <=> B =>

4 Statistical tests:

a) What do you conclude if you reject a whiteness test?
b) What is the null hypothesis of a chi-square test?
c) Assume that you have two acceptable models, but where one of them has a slightly lower cost than the other. How can you test whether this difference is significant? What is the test, and what should happen (reject/not reject)?

ANSWERS:

a) that the residuals are correlated and that you should reject the model

b) that the residuals are small, i.e. in the same order of magnitude as the measurement uncertainty

c) If you reject a likelihood ratio test the difference is significant

5 Closing the loop, predictions and experimental tests.

a) What is the problem with parameters in biological models describing complex systems? How does this affect the quality of the predictions, compared to e.g. the situation in physics?
b) Name one type of conclusion that you can draw using a model. How can that conclusion be stronger because of the model, compared to if you didn't have it, and just looked at the data?
c) You have two hypotheses that can explain all available data. How can you use modelling to design an experiment that ensures that no matter what the outcome of the experiment is, you will be able to reject at least one of the models?

ANSWER: a) the parameters are typically much more uncertain in biology, meaning that the predictions will be uncertain as well. Also the data is more uncertain in biology.
b) You can reject an hypothesis, i.e. a proposed mechanistic explanation for the data. This can be done more securely using the model, because of the complexity in biological systems and data
c) You can ensure that an experiment will distinguish between two model structures if the predictions of the model structures for that experimental design is more different – even when taking the uncertainties into account – than the measurement uncertainty