

Omdugga 2012

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

Good luck! ☺

- 1 Consider the following little system:

$$d/dt(x_1) = -k_1 \cdot x_1 + k_2 \cdot x_2$$

$$d/dt(x_2) = k_1 \cdot x_1 - k_2 \cdot x_2 - k_3$$

$$y_{\text{hat}} = x_1 + x_2 + k_{\text{meas}}$$

$$x_1(0) = 0.5, x_2(0) = 0.6$$

$$k_1 = 1, k_2 = 2, k_3 = 3$$

$$k_{\text{meas}} = 5$$

- a) Which are the states in this system?

ANSWER: x_1 and x_2

- b) Which are the reaction rates?

ANSWER: $v_1 = k_1 \cdot x_1$, $v_2 = k_2 \cdot x_2$, $v_3 = k_3$

- c) Are any of the reactions reversible/irreversible? Why/why not?

ANSWER: As considered above, R1, R2 and R3 (corresponding to v_1, v_2, v_3 , respectively), are irreversible. However, R2 goes in the opposite direction of R1, and you could therefore consider the reaction R1 and R2 together as a single reversible reaction.

- 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 input and output of an optimization algorithm? What does it do?

ANSWER:

- a) Parameters are input, cost is output. The cost evaluates the agreement between the model simulations and the experimental data
b) Residuals, $r(t)$, are the differences between individual data points $y(t)$ and the corresponding simulated values $y_{\text{hat}}(t, p)$, i.e. $r(t) = y(t) - y_{\text{hat}}(t, p)$
c) Input is startguess and cost function, output is estimated parameters. The optimization algorithm searches the parameter space for the parameters that gives the lowest cost.

3 Consider the following system:

$$\begin{aligned}d/dt(x_1) &= -k_1*x_1 + u \\d/dt(x_2) &= k_1*x_1 - k_2 \\yhat &= (x_1 + x_2)*kmeas \\x_1(0) &= 0.5, x_2(0) = 0.6 \\k_1 &= 1, k_2 = 2 \\kmeas &= 5\end{aligned}$$

a) Assume that the k_1 -reaction is saturated, with a Michaelis-Menten expression. What changes in the model?

ANSWER:

$$\begin{aligned}d/dt(x_1) &= -V_{max}*x_1/(K_m+x_1) + u \\d/dt(x_2) &= V_{max}*x_1/(K_m+x_1) - k_2\end{aligned}$$

Also: k_1 disappears, and V_{max} and K_m appear as parameters, which need values.

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

ANSWER:

$$yhat(0,p) = kmeas*(x_1(0) + x_2(0)) = 5*(0.5+0.6) = 5*1.1 = 5.5$$

$$r(0) = y(0)-yhat(0,p) = 4-5.5 = -1.5$$

c) What are the reactions in the following model?

$$\begin{aligned}d/dt([A]) &= k_1 - V_{max}*[A]/(K_m + [A]) + k_2*[B] \\d/dt([B]) &= + V_{max}*[A]/(K_m + [A]) - k_2*[B] - k_3*[B] \\yhat &= k_y*[A]\end{aligned}$$

ANSWER:

R1: $\Rightarrow A$ (the k_1 reaction)

R_MM: $A \Rightarrow B$ (the V_{max} -reaction)

R2: $B \Rightarrow A$ (the k_2 reaction)

R3: $B \Rightarrow$ (the k_3 reaction)

4 Statistical tests:

- a) What do you conclude if you do not 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) Nothing (or that the residuals are not clearly correlated)
- b) That the residuals are small, i.e. as large the measurement noise (i.e. they have the same sigma, and are normally distributed)
- c) You use e.g. a likelihood ratio test, and if it is rejected, you rejected the model with the higher cost

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?

ANSWER: The problem is that the parameters in biology are typically not known, and only seldom can be uniquely estimated. This means that predictions will be equally uncertain (beach statements) unless you do a core prediction analysis, and look at the behavior for all acceptable parameters.

- 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?

ANSWER:

You can e.g. conclude that a mechanistic hypothesis is not a satisfactory mechanistic explanation to some given data, but that some fundamental/important component is missing. You can also conclude that a certain prediction has to be fulfilled if the given hypothesis should be able to explain the data. Neither of these two types of conclusions are as reliable as mere verbal reasoning, because biological systems are complex and reasoning often leads you wrong.

c) You are sitting at the table at the end of the project, discussing with the customer. Your analysis of the model(s) have shown that a certain experiment would be a good idea; e.g. measuring the amount of a protein after 10 minutes. What could be a possible reason for doing that measurement? Also specify what the corresponding model prediction would be to that argument; is it a core prediction?

ANSWER:

There are three possible and qualitatively different reasons:

- a) That that amount is a well-determined prediction (a core prediction) of one of the models, that hence can be tested
- b) That that amount has two different well-determined predictions (core predictions) for two different models, which thus through the experiment can be distinguished
- c) That that amount is extremely poorly determined in one of the models, which thus through this particular experiment can become much better determined (here the prediction is not a core prediction, but the opposite, a beach statement=a very poorly determined prediction)