Dugga B 2020

TBMT37 / TBMT19

Please, write your Dugga-ID on all pages and your answers in Swedish or English. You need 12/15 points to pass.
Good luck! /Elin

1 Model parts

Consider the following model

$$d/dt(x1) = -k1*x1 - k2*x1 \qquad x1(0) = 1 \qquad \hat{y} = ky*x2$$
$$d/dt(x2) = -k3*x2 + k1*x1 + u \qquad x2(0) = 0$$

(a) List all model states! (1 point)

(b) List all model parameters! (1 point)

(c) What are the reactions? (1 point)

(d) What can be measured? Explain in words. (1 point)

2 Model simulation and cost function

Consider the following model

$$[\dot{A}] = -k1[A] + k2 \qquad [A](0) = 3 \qquad k1 = 2 \qquad k2 = 1$$

(a) Calculate $[A](0.1)$ with one step of Euler forward. (1 point)

(b) What is the input and output to a cost function? (1 point)

3 Model formulation

Consider the following reactions

$$A \rightarrow C \qquad (1)$$

$$A \rightarrow \varnothing \qquad (2)$$

$$C \rightarrow B \qquad (3)$$

(a) Write down the differential equations that corresponds to these reactions. Assume mass action kinetics for reaction 2-3 and assume that reaction 1 is saturated with respect to the concentration of A. Introduce parameters and initial conditions with values of your choice. (2 points)

(b) Add a measurement equation. You can measure something that is proportional to the sum of the concentrations of A and C. (1 point)

4 Statistical tests

(a) Formulate the null hypothesis underlying a whiteness test! (1 point)

(b) What do you conclude when you reject the null hypothesis in a $\chi 2$-test? (1 point)

(c) When do you want to use a likelihood ratio test? (1 point)

5 Predictions and experimental design

Describe all steps of a model based analysis ”the modeling cycle” and motivate each of the different steps: why are they there and what are they used for? Think about what you did in the computer exercise for example. Feel free to include drawings in your answer. (3 points)

Answers: Dugga B 2020

1

(a) $x1, x2$

(b) $k1, k2, k3, ky, x1(0), x2(0)$ (u is also ok to include in the answer)

(c) The reactions are
$x1 \rightarrow x2$
$x1 \rightarrow \varnothing$
$x2 \rightarrow \varnothing$
$\varnothing \rightarrow x2$

(d) The measurement equation, $\hat{y} = ky * x2$ shows that we can measure something that is proportional to $x2$.

2

(a) $[A](0.1) = [A](0) + [\dot{A}](0)\Delta t = 3 + (-2 * 3 + 1) * 0.1 = 2.5$

(b) A cost function could look like this $v(p) = \sum \frac{y(t) - \hat{y}(t,p)}{SEM(t)}$, where the sum is over all measured time points. The input to a cost function is the values of the parameters, p, and the output to a costfunction is the agreement between model simulations and data, $v(p)$, using these parameter values.

3

(a)

$$[\dot{A}] = -\frac{Vmax[A]}{(Km + [A])} - k1[A] \qquad [A](0) = 1$$
$$[\dot{B}] = k2[C] \qquad [B](0) = 2$$
$$[\dot{C}] = \frac{Vmax[A]}{(Km + [A])} - k2[C] \qquad [C](0) = 0$$
$$k1 = 3, k2 = 1, Km = 2, Vmax = 0.5$$

(b) $\hat{y} = ky([A] + [C])$

4

(a) The residuals are not correlated

(b) You conclude that the residuals are too large when you account for the data uncertainty and you therefore reject the null hypothesis (and the corresponding model structure)

(c) When you have two models that both are in agreement with data and you want to test if one of them is significantly better than the other at explaining data.

5

To start with, you need experimental data and biological knowledge to be able to formulate at least the first hypothesis. The hypothesis is formalized into ordinary differential equations, and the parameters of the model are estimated using a cost function and an optimization algorithm. From this step there are two different outcomes: 1) the model is not in agreement with data according to a statistical test, and the model must be rejected. In this case, we need to formulate a new hypothesis. 2) the model is in agreement with data and can thus not be rejected with a statistical test. In this case we collect an approximation of all parameters that give rise to model simulations that are in agreement with data and use for model predictions. These predictions are used to design new experiments to perform, and with the outcome of the experiment we see if the model can be validated (if the model prediction agrees with the new experiment) or has to be rejected.