Dugga B 2022

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

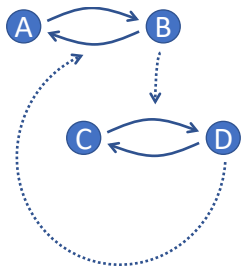
$$
\begin{aligned}
d/dt(x1) &= -k1 \cdot x1 + k2 \cdot x3 & x1(0) &= 0 & \hat{y} &= ky \cdot x1 \\
d/dt(x2) &= -Vmax \cdot x2/(Km + x2) + k1 \cdot x1 & x2(0) &= 1 & & \\
d/dt(x3) &= -k2 \cdot x3 + Vmax \cdot x2/(Km + x2) & x3(0) &= 0 & &
\end{aligned}
$$

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

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

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

2 Model formulation



Consider the interaction graph. The concentrations of B has a positive impact on the reaction rate in the reaction from C to D, but B is not consumed in that reaction. The concentration of D

has a positive impact on the reaction rate in the reaction from B to A, but D is not consumed in that reaction.

Use the information to write down the ordinary differential equations that corresponds to the interaction graph. Assume that we can measure something proportional to the concentration of D. Make necessary assumptions and include in the answer. Introduce parameters with values of your choice. Make sure your suggested model is complete. (3 points)

3 Simulation and optimization

(a) Why do we use numerical simulation in systems biology? (1 point)

(b) Give example of a cost function and explain around this function (1 point)

(c) What is an optimization algorithm? (1 point)

4 Statistical tests

(a) Formulate a null hypothesis underlying a likelihood ratio test! (1 point)

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

(c) Give example of a situation when you would use cross validation! (1 point)

5 Predictions and experimental design

(a) What is a core prediction? (1 point)

(b) How would you convince an experimental collaborator that core predictions that separate between two hypotheses is useful in the design of a new experiment? (2 points)

Answers: Dugga B 2022

1

(a) States: $x1, x2, x3$ and Model parameters: $k1, k2, Vmax, Km, ky, x1(0), x2(0), x3(0)$

(b) The reactions are
$x1 \rightarrow x2$
$x2 \rightarrow x3$
$x3 \rightarrow x1$

(c) The measurement equation, $\hat{y} = ky * x1$ shows that we can measure something that is proportional to $x1$.

2

1. Identify model states:

$$x1 = [A]$$
$$x2 = [B]$$
$$x3 = [C]$$
$$x4 = [D]$$

2. Identify reaction rates, including what we know about parameters:

$$v1 = k1 \cdot x1$$
$$v2 = k2 \cdot x2 \cdot x4$$
$$v3 = k3 \cdot x3 \cdot x2$$
$$v4 = k4 \cdot x4$$

Assumtions: mass-action kinetics, no input

3. Formulate ODEs:

$$d/dt(x1) = -v1 + v2$$
$$d/dt(x2) = v1 - v2$$
$$d/dt(x3) = -v3 + v4$$
$$d/dt(x4) = v3 - v4$$

4. What is measured?

$$\hat{y} = ky \cdot x4$$

5. Parameters and their values:
   $k1 = 3$, $k2 = 1$, $k3 = 2$, $k4 = 4$, $ky = 1$
   $x1(0) = 200$, $x2(0) = 0$, $x3(0) = 0$, $x4(0) = 5$
   All parameter values are made up.

3

(a) We use numerical simulation since most models are complex and thus the ordinary differential equations does not have analytical solutions.

(b) A cost function could look like this $v(p) = \sum \frac{y(t) - \hat{y}(t,p)}{SEM(t)}$, where y(t) and SEM(t) are the measured mean and standard error of the mean values, $\hat{y}(t,p)$ is the corresponding model simulation, and 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, $v(p)$.

(c) We use optimization methods (global and local) to find the optimal parameters, i.e. model parameters that give the best possible agreement between model simulations and data. The input to an optimization algorithm is a start guess of the parameters, and the output is the best found agreement.

4

(a) There is no difference between the models' agreement with data

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

(c) When you have a model that is in agreement with data and you want to control for over-fitting and test if the model has the right level of complexity.

5

(a) A core prediction is a model-based prediction with smalland well-defined uncertainty of a model property that can be tested experimentally.

(b) When we have such a core prediction analysis, we know that the new experiment will always provide new knowledge. Regardless of the outcome of the experiment, we will be able to draw at least one of these conclusions: to reject the first hypothesis, to reject the second hypothesis, or to reject both hypotheses.