Dugga A 2020

TBMT37 / TBMT19

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

1 Model formulation

Consider the following model

$$[\dot{A}] = -k1[A] - k2[A] \qquad [A](0) = 1 \qquad \hat{y} = ky \cdot ([A] + [B])$$
$$[\dot{B}] = -k3[B] + k1[A] \qquad [B](0) = 0$$

(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

$$[\dot{A}] = -k1[A] + k2 \qquad [A](0) = 5 \qquad k1 = 1 \qquad k2 = 3$$

(a) Calculate $[A](0.5)$ with one step of Euler forward. (1 point)

(b) What do you compute with a cost function? (1 point)

3 Model formulation

Consider the following reactions

$$A \rightarrow B \tag{1}$$
$$A \rightarrow \varnothing \tag{2}$$
$$B \rightarrow C \tag{3}$$

(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 concentration of A. (1 point)

4 Statistical tests

(a) Formulate the 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) What do you conclude when you cannot reject a whiteness test? (1 point)

5 Predictions and experimental design

You have two competing models, and none of them can be rejected with a $\chi 2$-test.

(a) Describe the steps of a core prediction analysis you would perform to be able to draw conclusions. (2 points)

(b) You convince an experimental collaborator to test the predictions from the core prediction analysis. Which are the different outcomes in terms of conclusions that are possible when you get the experimental data? (1 point)

Answers: Dugga A 2020

1

(a) $[A], [B]$

(b) $k1, k2, k3, ky, [A](0), [B](0)$

(c) The reactions are $A \rightarrow B$, $A \rightarrow \varnothing$ and $B \rightarrow \varnothing$

(d) The measurement equation, $\hat{y} = ky \cdot ([A] + [B])$ shows that we can measure something that is proportional to the sum of the concentrations of A and B.

2

(a) $[A](0.5) = [A](0) + [\dot{A}](0)\Delta t = 5 + (-1 \cdot 5 + 3) \cdot 0.5 = 4$

(b) You compute the agreement between model simulations and experimental data. A cost function could look like this:

$$V(p) = \sum \frac{(y(t) - \hat{y}(t,p))^2}{SEM(t)^2}$$

where the sum is over all measured time points

3

(a)

$$[\dot{A}] = -\frac{Vmax[A]}{(Km + [A])} - k1[A] \qquad [A](0) = 1$$
$$[\dot{B}] = \frac{Vmax[A]}{(Km + [A])} - k2[B] \qquad [B](0) = 2$$
$$[\dot{C}] = k2[B] \qquad [C](0) = 0$$
$$k1 = 3, k2 = 1, Km = 2, Vmax = 0.1$$

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

4

(a) There is no difference between the models abilities to explain data
or
The added complexity did not improve the fit with data (if you compared a simpler and a more complex model)

(b) You conclude that the residuals are large compare to the data uncertainty and you therefore reject the null hypothesis (and the corresponding model structure)

(c) No conclusion

5

(a) You simulate an approximation of all acceptable parameters for both models and look for predictions that differ between the models. Predictions can be for example for unmeasured states, for other inputs (stronger/weaker/multiple etc), or for longer times. You discuss with an experimental collaborator if the core predictions are feasible to measure experimentally.

(b) You reject either one of the models or both models. The experimental data cannot be in agreement with more than one of the models, since the core predictions are different for the two models.

Common errors

1. Model formulation
   (a) **Missing states.** Don't forget to give the ODEs for all states in the model.
   (b) **Defining reaction rates but not using them.** This is not wrong, but if you define reaction rates (e.g. v1 = k1*A), then you can/should them in the ODE. For example d/dt(A) = -v1 instead of d/dt(A) = -k1*A.
2. Cost function
   (a) **Average/mean vs sum.** We do not take the average of the residuals; we take the sum.
   (b) **Only answering "agreement to data".** You should also say what is in agreement with data. E.g. "the cost is the agreement between the model and the data".
3. Statistics
   (a) **Likelihood ratio test, not defining what the models are equally good at.** "The null hypothesis is that the models are equally good at explaining data.
4. Core predictions / core prediction analysis
   (a) **Not knowing the definition.** A core prediction is a model prediction that is well defined, i.e. that has low uncertainty.
   (b) **Thinking that core-predictions always occur when t-¿ ∞.** This is not true. Core predictions does not have anything to do with when they occur, only with the uncertainty. Furthermore, in many cases, simulations tend to diverge at large time points.
   (c) **Not saying anything about uncertainty.** A key point of core predictions is that the prediction uncertainty is small. How do you get this uncertainty? At least say that the uncertainty is estimated, e.g. by using a sample of all acceptable parameters.
   (d) **Not saying anything about differences in predictions.** In order to use core predictions ideally when comparing two models, the predictions should behave differently for the models. Otherwise we may not be able to reject at least one model.
   (e) **Not saying anything about how the predictions can be obtained.** Say something about what you can change: timescales, input strength, input complexity, different inputs.
   (f) **Not saying anything on how they can be tested.** You should say something along the line that the prediction must be tested experimentally.