Dugga A 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

$$
\begin{aligned}
d/dt(x1) &= -k1 \cdot x1 - k2 \cdot x1 & x1(0) &= 1 & \hat{y} &= ky \cdot x3 \\
d/dt(x2) &= -Vmax \cdot x2/(Km + x2) + k1 \cdot x1 & x2(0) &= 0 \\
d/dt(x3) &= -k3 \cdot x3 + Vmax \cdot x2/(Km + x2) & x3(0) &= 0
\end{aligned}
$$

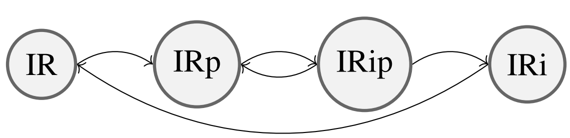
(a) List all model states and parameters! (1 point)

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

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

2 Model formulation

Consider the following interaction graph for the insulin receptor (IR).



The receptor becomes phosphorylated (p), internalized (i), and dephosphorylated before returning to the plasma membrane.

Use the information to write down the ordinary differential equations that corresponds to the interaction graph. Assume that we have measured the total amount of phosphorylated receptors. 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) Explain the Euler forward method. (1 point)

(b) How do we know if the agreement between model simulations and data is poor? What can we do to get a better agreement? (2 point)

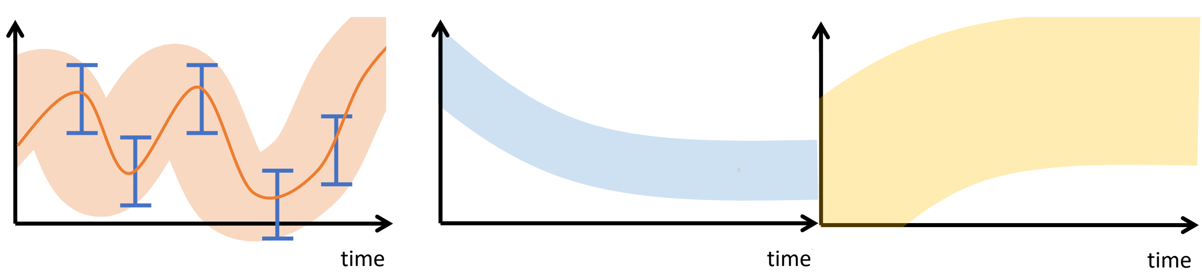
4 Statistical tests

(a) Formulate a null hypothesis underlying a $\chi 2$-test! (1 point)

(b) What do you conclude when you reject the null hypothesis in a whiteness-test? (1 point)

(c) Give example of a situation when you would use a likelihood ratio test! (1 point)

5 Predictions and experimental design



Here you see results from a model based analysis. To the left is data (blue), best model simulation (orange), and an approximation of all acceptable parameters (light orange). In the middle and to the right you see two different model-based predictions of two different, potentially interesting properties. Explain the results to experimental collaborators and tell them which experiment you would like them to perform. Include a motivation. What possible conclusions can you draw after the experiment? (3 points)

Answers: Dugga A 2022

1

(a) States: $x1, x2, x3$ and Model parameters: $k1, k2, k3, Vmax, Km, ky, x1(0), x2(0), x3(0)$

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

(c) The measurement equation, $\hat{y} = ky * x3$ shows that we can measure something that is proportional to $x3$.

2

1. Identify model states:

$$
\begin{aligned}
x1 &= \#IR \\
x2 &= \#IRp \\
x3 &= \#IRip \\
x4 &= \#IRi
\end{aligned}
$$

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

$$
\begin{aligned}
v1 &= k1 \cdot x1 \\
v2 &= k2 \cdot x2 \\
v3 &= k3 \cdot x3 \\
v4 &= k4 \cdot x3 \\
v5 &= k5 \cdot x4
\end{aligned}
$$

Assumtions: mass-action kinetics

3. Formulate ODEs:

$$
\begin{aligned}
d/dt(x1) &= -v1 + v5 \\
d/dt(x2) &= v1 - v2 + v3 \\
d/dt(x3) &= v2 - v3 - v4 \\
d/dt(x4) &= v4 - v5
\end{aligned}
$$

4. What is measured?

$$\hat{y} = (x2 + x3)$$

5. Parameters and their values:
   $k1 = 3$, $k2 = 1$, $k3 = 2$, $k4 = 4$, $k5 = 1$
   $x1(0) = 200$, $x2(0) = 0$, $x3(0) = 0$, $x4(0) = 5$
   All parameter values are made up.

3

(a) In the Forward Euler method we take small time steps in the direction of the flow. We use numerical simulation since most models are complex and thus the ordinary differential equations does not have analytical solutions.

(b) To evaluate the agreement, we use both visual inspection and a cost function that 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, $v(p)$. We can use optimization methods (global and local) to find a better agreement between model simulations and data.

4

(a) The residuals are small

(b) You conclude that the residuals are too correlated 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 (according to a $\chi 2$-test) and you want to test if one of them is significantly better than the other at explaining data.

5

I have analyzed the biological system with the model that we agreed upon. The model can explain data and I therefore used the model to design new experiments. To do so I have performed a core prediction analysis, where I first collected an approximation of all acceptable parameters, to get model predictions with uncertainty. I have made two simulations of potentially interesting properties. One of the simulations (middle) has a rather well-defined uncertainty, so if this is a property of the system that is possible to test experimentally, this is a core prediction that would lead to a conclusion. Possible conclusions are either 1) the new data is in agreement with the model prediction - we have validated the model 2) the data is not in agreement with the model prediction - we reject the model. From both conclusions we learn new things about the biological systems. The other simulation (right) has a rather large uncertainty, meaning that it would be hard to use that predictions to draw conclusions even if we did the corresponding measurement.