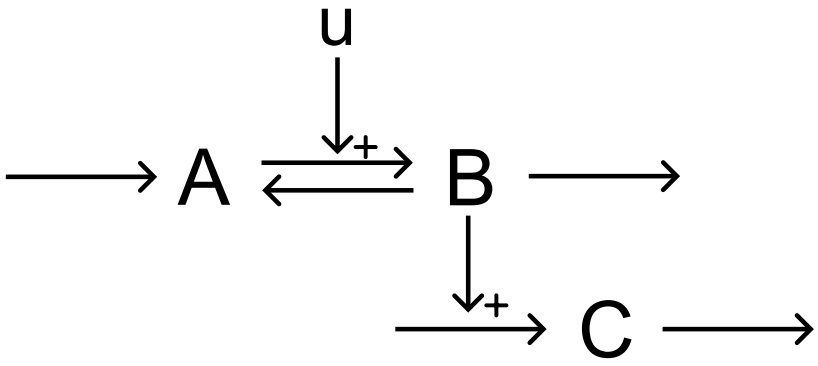
Dugga 2025-02-26

TBMT19 / TBMT37

Write your Dugga-ID on all pages and your answers in Swedish or English. There are in total 5 questions, each worth 3 points. You need at least 10 points with 2 points per question, or 12 points in total to pass. Good luck! /William

1 Model formulation and model parts

(a) For the following interaction graph, give the model equations. Introduce and assign values to model parameters as needed. Clearly mark the model parameters (and optionally the initial conditions). Assume mass-action kinetics. (2 point)



(b) Update one of the reaction rates to be *saturated*, in other words change from mass-action to Michaelis-Menten kinetics. (1 point)

2 Model simulation

(a) Use the Euler forward method to simulate the following model with step-length $\Delta t = 1$. What are the values in t = 1, and t = 2? (1 point)

$$d/dt(X) = v1 - v2, \qquad v1 = k1, \qquad v2 = k2 \cdot X$$

$$k1 = 2, \quad k2 = 1, \quad X(0) = 100$$

(b) If we simulate the model for a long time, what value will X go towards? (1 point)

(c) Why do we need to numerically simulate systems biology models? (1 point)

3 Parameter estimation

(a) You have a model simulation ($\hat{y}$) of four different time-points for a given parameter set (θ):

$$\hat{y}(\theta) = [1,2,3,4]$$

You also have corresponding experimental data (y) with measurement uncertainties (SEM):

$$y = [2,3,4,5], \qquad SEM = [1,1,1,2]$$

What is the cost for the parameter set θ? (1 points)

(b) Why do we normalize the residuals with the data uncertainty (SEM)? (1 point)

(c) Are *global* optimization algorithms guaranteed to find the optimal solution? (1 point)

4 Statistical tests

Assume that we again have the same model simulation and data as in question 3 above.

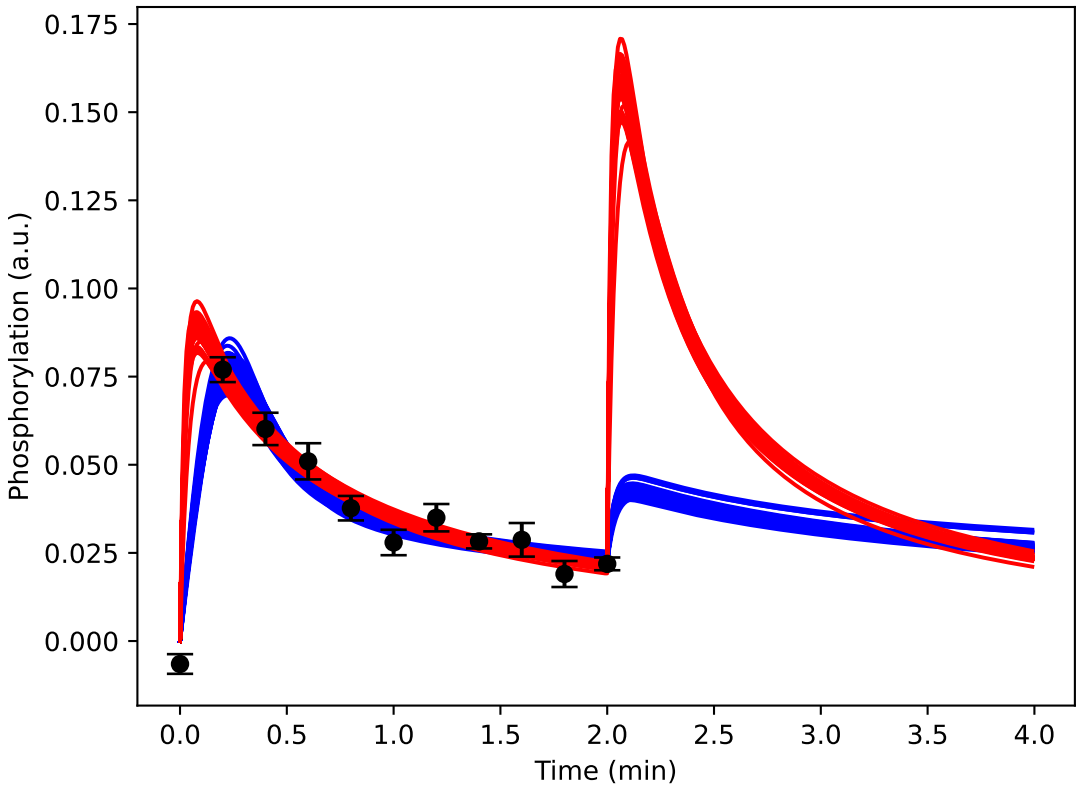
(a) If the χ^2-limit is 2.4, should you reject the model simulation given the parameter set θ? What is the conclusion of the test? (1 point)
If you did not calculate the cost in 3(a), assume that the cost is 3.3.

(b) Would you reject the model simulation with a whiteness test? Why/why not? (1 point)

(c) Based on your conclusion from 4(a), should you reject the *model* if the parameter set θ is the optimal parameter set? (1 point)

5 Predictions and experimental design

Assume that you have the following model predictions from two different models: a *red* model and a *blue* model. The predictions correspond to the phosphorylation of a protein over time.



(a) If you could measure at one time-point, where would you measure? Why? (1 point)

(b) Why is it important that we quantify the model uncertainty correctly? (1 point)

(c) If one of the models is able to predict the new experiment/data correctly, what would you do next? (1 point)

Answers: Dugga 2025-02-26 (revised: February 27, 2025)

1 Model formulation and model parts

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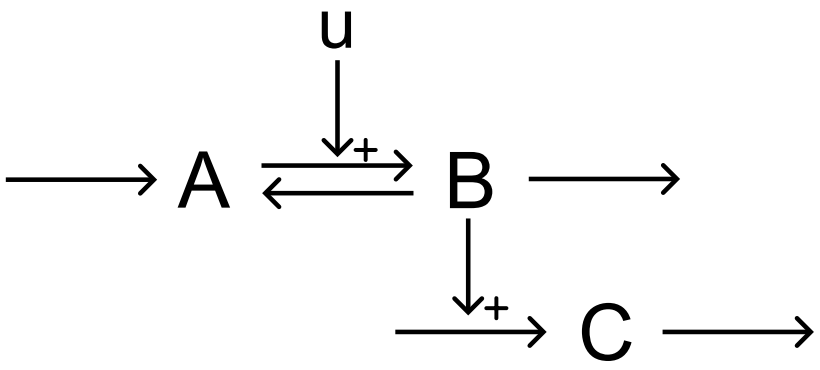


Answer:
The model equation can be like this:

$$\frac{dA}{dt} = v1 - v2 + v3 \qquad v1 = k1 \qquad v2 = k2 \cdot A \cdot u$$

$$\frac{dB}{dt} = v2 - v3 - v4 \qquad v3 = k3 \cdot B \qquad v4 = k4 \cdot B$$

$$\frac{dC}{dt} = v5 - v6 \qquad v5 = k5 \cdot B \qquad v6 = k6 \cdot C$$

$[k1, k2, k3, k4, k5, k6] = [1, 1, 2, 2, 3, 3]$ $\leftarrow$ parameters

$[A(0), B(0), C(0)] = [1, 0, 0]$ $\leftarrow$ initial conditions

$u1 = 2$ $\leftarrow$ input (not necessary for the answer)

(b) Update one of the reaction rates to be *saturated*, in other words change from mass-action to Michaelis-Menten kinetics. (1 point)

Answer:
I update the reaction $\rightarrow C$ (with input from B), corresponding to the reaction rate v5.

To make $v5$ be saturated with respect to B update the reaction rate to:

$$v5 = Vmax \cdot \frac{B}{kM + B}$$

Value for the new introduced parameter (made up): $Vmax = 3$, $kM = 1$.

2 Model simulation

(a) Use the Euler forward method to simulate the following model with step-length $\Delta t = 1$. What are the values in t = 1, and t = 2? (1 point)

$$d/dt(X) = v1 - v2 \qquad v1 = k1, \qquad v2 = k2 \cdot X$$

$$k1 = 2, \quad k2 = 1, \quad X(0) = 100$$

Answer:
In the Euler forward method, we start with the initial values of the states and calculate the values of the ODEs at the initial time-point. We then take a small step in the direction of the ODEs, and use the new values to calculate the ODEs at the next time-point. This is repeated until the time-frame asked for by the user has been simulated.

The Euler forward method can be written as:

$$x(t + \Delta t) = x(t) + d/dt(x(t)) \cdot \Delta t$$

For this model, to calculate the values of X in t = 1, and t = 2 we start by calculating the values for t = 1 using the following steps:

$$v1(0) = k1 = 2$$

$$v2(0) = k2 \cdot X(0) = 1 \cdot 100 = 100$$

$$d/dt(X(0)) = v1(0) - v2(0) = 2 - 100 = -98$$

$$X(1) = X(0) + d/dt(X(0)) \cdot \Delta t = 100 - 98 \cdot 1 = 2$$

Then we calculate the values for t = 2 using the following steps:

$$v1(1) = k1 = 2$$

$$v2(1) = k2 \cdot X(1) = 1 \cdot 2 = 2$$

$$d/dt(X(1)) = v1(1) - v2(1) = 2 - 2 = 0$$

$$X(2) = X(1) + d/dt(X(1)) \cdot \Delta t = 2 + 0 \cdot 1 = 2$$

So, the values of X in t = 1, and t = 2 are:

$$X(1) = 2, \quad X(2) = 2$$

(b) If we simulate the model for a long time, what values will X go towards? (1 point)

Answer:
We know that $d/dt(X(1)) = 0$, which means that the value of X will not change if we take a further step. Since X then does not change, all future values of X will be the same as $X(1) = 2$. So, X will go towards 2.

Alternative answer if you did not calculate the derivatives: Since X has both a positive and a negative reaction, it will go towards a value that is not 0 nor ∞. It will change in the first time points to then settle at a non-zero, non-infinite value.

Alternative answer, assuming you remember how to calculate stable points from a previous course: The steady state (final) value of the system can be calculated by setting the derivative to 0. In this case, $d/dt(X) = 0 = v1 - v2 = k1 - k2 \cdot X$. This gives $X = k1/k2 = 2/1 = 2$.

(c) Why do we need to numerically simulate systems biology models? (1 point)

Answer:
In systems biology, we often have complex models with many states and reactions, and it is often not feasible to solve these models analytically. Therefore, we need to use numerical simulation to solve the models and obtain the model simulations.

3 Parameter estimation

(a) You have a model simulation ($\hat{y}$) of four different time-points for a given parameter set (θ):

$$\hat{y}(\theta) = [1,2,3,4]$$

You also have corresponding experimental data (y) with measurement uncertainties (SEM):

$$y = [2,3,4,5], \qquad SEM = [1,1,1,2]$$

What is the cost for the parameter set θ? (1 points)

Answer:
The cost for the parameter set θ is calculated as follows:

$$\text{residuals} = y - \hat{y} = [2,3,4,5] - [1,2,3,4] = [1,1,1,1]$$

$$v(\theta) = \sum_{t=1}^{N} \frac{(y(t) - \hat{y}(t,\theta))^2}{SEM(t)^2} = \frac{1^2}{1^2} + \frac{1^2}{1^2} + \frac{1^2}{1^2} + \frac{1^2}{2^2}$$

$$= \frac{1}{1} + \frac{1}{1} + \frac{1}{1} + \frac{1}{4} = 3 + \frac{1}{4} = 3.25$$

(b) Why do we normalize the residuals with the data uncertainty (SEM)? (1 point)

Answer:
To put more focus on the certain points (low SEM) and less focus on uncertain points (high SEM).

(c) Are *global* optimization algorithms guaranteed to find the optimal solution? (1 point)

Answer:
No, neither global nor local optimization algorithms are guaranteed to find the optimal solution. It is possible that global optimization algorithms might find the optimal solution, but it is not guaranteed.

4 Statistical tests

Assume that we again have the same model simulation and data as in question 3 above.

(a) If the χ^2-limit is 2.4, should you reject the model simulation given the parameter set θ? What is the conclusion of the test? (1 point)
If you did not calculate the cost in 3(a), assume that the cost is 3.3.

Answer:
The χ^2-limit is 2.4, and the cost is 3.25 (or 3.3). Since the cost is larger than the χ^2-limit, we should reject the model simulation given the parameter set θ. The conclusion of the test is that we reject the model given the parameter set θ.

(b) Would you reject the model simulation with a whiteness test? Why/why not? (1 point)

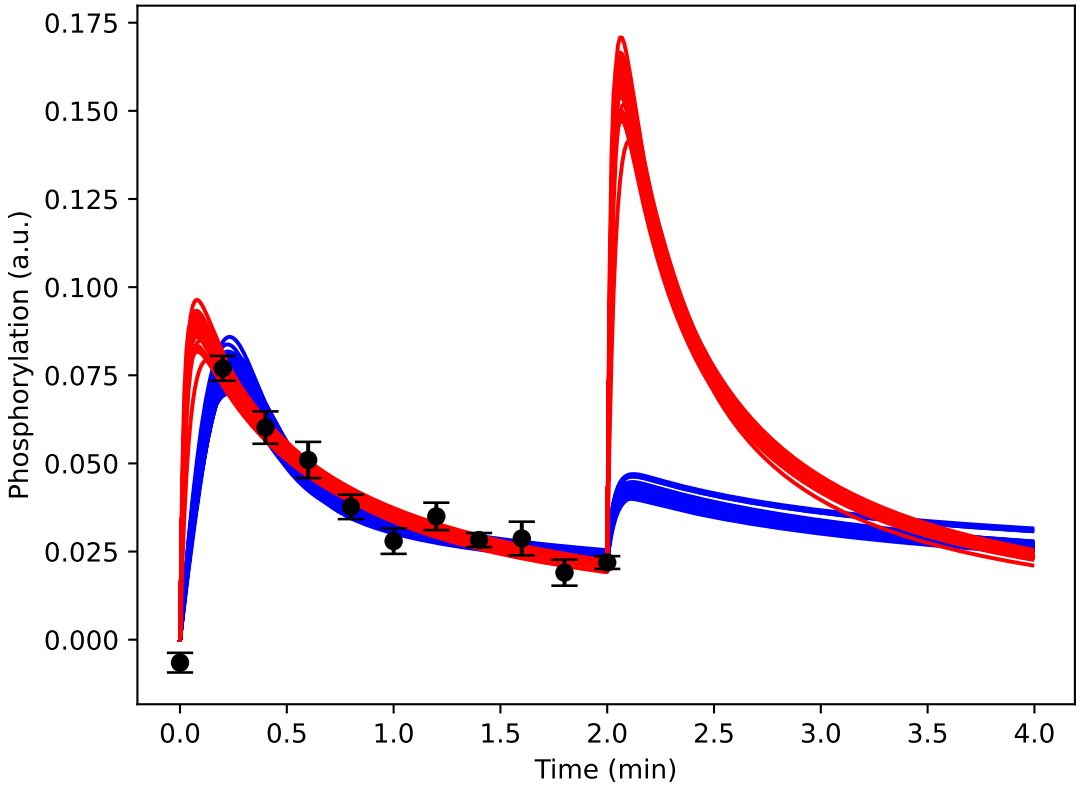
Answer:
The residuals are correlated (since the model simulation value is smaller than the data at all time-points), and therefore we would reject the model simulation with a whiteness test (the residuals are too correlated).

(c) Based on your conclusion from 4(a), should you reject the *model* if the parameter set θ is the optimal parameter set? (1 point)

Answer:
Yes, since the parameter set θ is the optimal parameter set, no other better parameter set exist. Therefore, if the model with θ is rejected, no other parameter values can give a better agreement to data, and thus the model (structure/equations) must be rejected.

5 Predictions and experimental design

Assume that you have the following model predictions from two different models: a *red* model and a *blue* model. The predictions correspond to the phosphorylation of a protein over time.



(a) If you could measure at one time-point, where would you measure? Why? (1 point)

Answer:
I would measure one point, around t=2.25, since this is where the models differ the most and the uncertainty is low. If the experimental data has a reasonable uncertainty, we will be able to reject at least one of the models.

(b) Why is it important that we quantify the model uncertainty correctly? (1 point)

Answer:
If we did not quantify the uncertainty correctly, we could draw the wrong conclusions from the data. For example, if the uncertainty is underestimated, we might reject a model that is actually correct. If it is overestimated then we might accept a model that is incorrect.

(c) If one of the models is able to predict the new experiment/data correctly, what would you do next? (1 point)

Answer:
I would continue with the model that was not rejected and continue validating the model by making additional predictions and experiments.