**Dugga 2016-02-16, TBMT19 and TBMT37**

*Write Dugga-id on all pages. If you are doing this as an omdugga from previous years, Dugga 1 corresponds to questions 1-3, Dugga 2, to questions 3-5. If you take the course 2016, do all questions. G starts at 12/15 (omdugga-G at 7/9). 3 points per question. Answer in Swedish or English.*

1. Consider the following model, in reaction form

(R1) x1 => x2 v1 = k1\*x1

(R2) x2 => v2 = Vmax\*x2/(Km + x2)

(x1(0) , x2(0)) = (2 , 3)   
k1 = 1   
yhat = ky\*x2  
ky = 1  
Vmax = 2  
Km = 1

* 1. What are the states?
  2. What are the parameters?
  3. What can be measured? (describe it in words)

ANSWER: a) the amount or concentration of x1 and x2,

b) k1, Vmax, Km, x1(0), x2(0), ky

c) You can measure (the concentration or amount of) x2 times a scaling constant ky

1. Consider the following set of reactions:

(R1) A => B

(R2) B => C

(R3) B + C => A

* 1. What are the differential equations? Assume mass action kinetics for R1 and R3, and Michaelis-Menten kinetics for R2. Don’t forget to specify the initial conditions. Specify some values for any parameters you might introduce.
  2. Add a measurement equation saying that you can measure something that is proportional to the sum of A and B.

ANSWER:

a) x1 = [A], x2 = [B], x3 = [C] , v1 = k1\*x1, v2 = Vmax\*x2/(Km + x2), v3 = k3\*x2\*x3

d/dt(x1) = -v1 + v3, d/dt(x2) = v1 – v2 – v3, d/dt(x3) = v2 – v3,

x1(0) = 1, x2(0) = x3(0) = 0, k1 = 3, Vmax = Km = 4.5, k3 = 8

b) yhat = ky\*(x1 + x2), ky = 84

1. Fitting the model to data
   1. What is the input and output of a cost function?
   2. What are the residuals, and how do they relate to the cost function?
   3. What is the principle behind numerical simulations of ordinary differential equations?

ANSWER:

a) Input: Parameters, Output: Cost, i.e. agreement with data

b) the residuals are the differences between individual data points and simulations. The cost function is the total difference, usually obtained by normalization, squaring, and finally summation of the residuals

c) “Go with the flow”, i.e. take a step in the direction of the gradient, recalculate the gradient, etc

1. Statistical tests
   1. Name one benefit of using independent validation data
   2. What is the null hypothesis of a whiteness test?
   3. What happens if you do not reject a chi-square test?

ANSWER:

a) One benefit: that you can easier detect overfitting. Another benefit: that don’t have to compensate for the number of fitted parameters in the statistical tests. The easiest to understand benefit: that you can see if the model is able to describe something it hasn’t seen before

b) that the residuals are uncorrelated

c) nothing, the model is still a working hypothesis

1. Closing the loop
   1. A core prediction has been tested experimentally, and the experiment shows that a value outside the predicted interval has been obtained. What can we then conclude? How would that be different if the prediction was not known to be a core prediction?

ANSWER: You reject the biological hypothesis implemented in the model structure (i.e. the equations). Otherwise you only reject a particular set of parameters for those equations.

* 1. You have two models that are acceptable given the current data. How can you use predictions to design an experiment that ensures that a new experiment will be able to distinguish between the models?

ANSWER: Find core predictions that are more different than the uncertainty in the data.

* 1. Is it better to have a well-determined or an undetermined prediction when trying to convince a biologist to collect experimental measurements of that prediction? Motivate your answer.

ANSWER: It depends. For instance, if the biologist wants to test the accuracy of the model or a stated conclusion (a necessary consequence of the model and the data), he should test a well-determined prediction. Alternatively, if one wishes to determine parameters in the model, it is better to measure a poorly determined prediction.