**Lesson 7**

**Task 1: Understanding the Emax function**

The aim of this task is for you to study the behaviour of the Emax function described in the lecture notes by using excel. First, you need to download the excel file "**Emax function.xlsx**".

**Information about the excel file**

When you open the excel file, you will notice that is has 3 sheets: EMAX-SHIFT, EC50-SHIFT and GAMMA-SHIFT. Within each sheet, there are three pre-defined parameters values for Emax, EC50, and Gamma in cells A2, B2 and C2 respectively. Do not change any of these values. These values are used to generate a reference plot for the Emax function. Once you start changing a parameter of the Emax model, you will notice that there are two curves on the plot. One line will remain at the same position and the other will shift depending on the value of the parameter you are changing in cell "A6". If you click in cell "A6", a small box with a triangle will appear to the right of the cell. Click the box, to see a list of numbers that you can use as input to the Emax function.

a) Open the "EMAX-SHIFT" sheet then start changing the value in cell "A6" and observe change to the plot each time you select a different value.
b) Repeat the same using the EC50-SHIFT and GAMMA-SHIFT sheets.

**Questions**

1. Describe what happens to the **response** when you change the value of
    a) Emax,
    b) EC50 and
    c) Gamma?

**Task 2: Implementation of the direct effect model in Berkeley Madonna**

In this task, we will use the Berkeley Madonna to implement a direct effect PK/PD model.

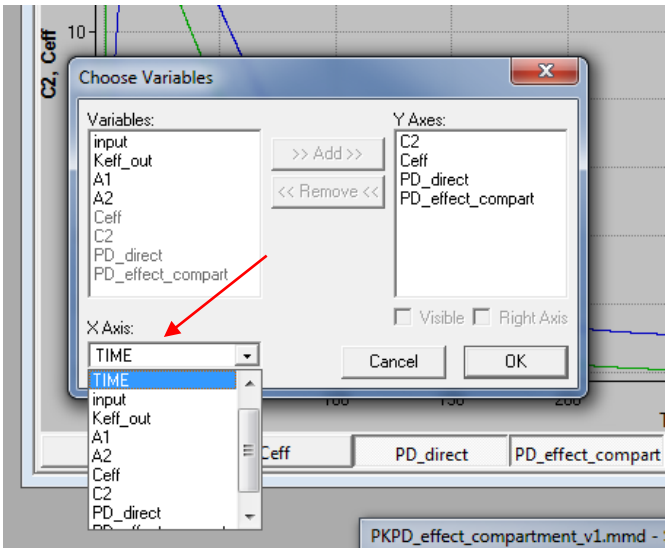
The Emax function you explored in task 1 has been incorporated into the model. First open the Berkeley Madonna file "**PKPD_direct-effect.mmd**"

***Part 1***

a) From the model file, identify the dose and dosing interval.

b) First display on the same graph, the PD and CONC on the vertical axis and TIME on the horizontal axis. Observe and describe the trend in PD in response to CONC?

c) Now create a plot of PD vs. CONC and describe the relationship (you can create this plot by clicking the left button of the mouse twice in the middle of the plot and choosing CONC from the drop down menu in the left corner of the window that pops up, see the figure below). Can you recognize the Emax function from task 1? Hint: Check the scale of the axis




***Part 2***

Using the model file from part 1 above, we would like to determine an appropriate dosing strategy for the drug described in the model file. We want to make sure that drug concentrations remain below 9 mg/L, whilst achieving a drug effect target of at least 15.

a) Use the sliders to determine an appropriate dose and dose schedule assuming that each tablet strength is 100 mg. How long does it take to attain the PD target required?
b) If you would like to include a loading dose (an extra amount on the first dose), how would the strategy change? How long does it take to attain the PD target required?

**Task 3 – Delayed response though an effect compartment**

In this task we're looking at an example of delayed response, which is caused by the drug having to distribute to the target site, e.g. the receptor itself is not in the plasma itself but in a different tissue.

Using Berkeley Madonna open model **PKPD_effect_compartment_v1.mmd**. Inspect the code before running the model – can you see any differences comparing the previous model? How many differential equations can you see?

Run the model. In order to help you compare this effect to a direct one we repeated in the model a case of a direct PD response (PK_direct, driven by concentration in central compartment – C2) and added the aforementioned case of delayed PD response (PD_effect_compartment, driven by the concentration in the effect compartment - Ceff).

a) What can you say about the generated plots in regards to the concentrations and the response (direct vs indirect model)?

b) Using sliders explore the effect of changing Keff_in between 0 and 1 (it might be useful to keep the overlay function on).
    i) What can you say about changes to Cmax, Tmax and AUC of the concentration in the effect compartment?
    ii) What can you say about changes to the strength and the time of onset of the indirect effect?

c) How does changing the dose affect parameters explored in point b)?

d) Change the X-axis of the plot from TIME to C2 (you can do that by clicking the left button of the mouse twice in the middle of the plot and choosing C2 from the drop down menu in the left corner of the window that pops up) – what can you say about plots describing PD_direct and PD_effect_compart?
   This type of plot is called hysteresis loop.

e) Change X-axis to Ceff – what can you say about plots describing PD_direct and PD_effect_compart?

**Task 4 – Indirect effect model with inhibition of input**

In this task we're looking at an example where the drug concentration is acting on (inhibiting) the input of an effect compartment, e.g. the drug is blocking a metabolic pathway by inhibiting an enzyme production.

Using Berkeley Madonna, open model **PKPD_indirect_inputINH_v1.mmd** Inspect the code before running the model.

a) Bring up sliders and move them to explore the effect of changing values for Imax. Can Imax have a value greater than 1?

b) After setting Imax back to 1, explore the effect of changing the dose on the PK: Cmax, Tmax and AUC.

c) How does the dose change the PD response? And its timing?