Week 4 assignments

Here is some help on how the assignments from week 4 should be approached.

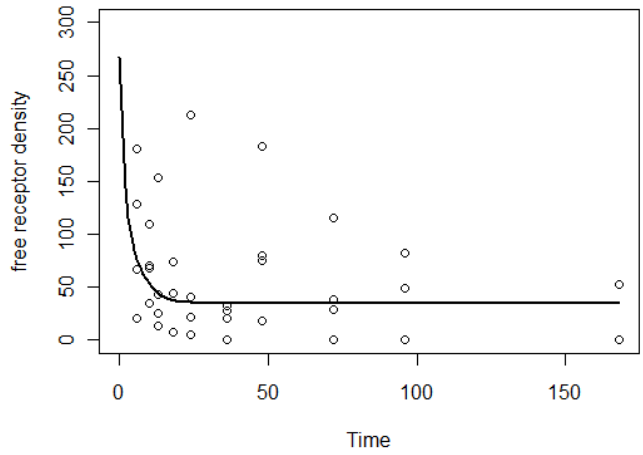
Part 1:

Median drug concentration for 0.1 dose is 14.59 ng/ml, this gives value of D = 14.59*1000/374.471= 39.0 nmol/L

Median drug concentration for 0.3 dose is 39.925 ng/ml, this gives value of D = 39.925*1000/374.471= 107 nmol/L

Simulate the dynamics of the system with these drug concentrations and add the data points to the graphs to compare the model predictions and experimental results.

You should have plots similar to this one (median from the experimental data could also be added to the plot):



Part 2:

Unless stated otherwise, in the simulations for the solutions to this part, the values of different parameters and initial conditions should be as in the table in the assignments document. Value of k_{d_Rm} should be 0.612, value of k_{s_r}=3.22, value of D=20*1000/374.471.

Include also a graph of the total receptor concentration!!!

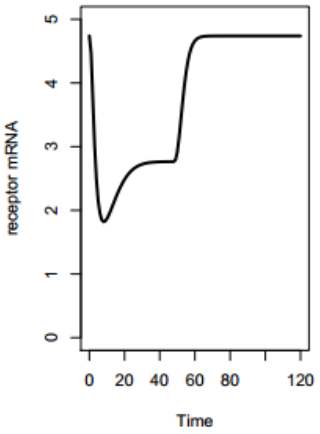
- what would be the time course concentration of the activated drug-receptor complex if there was no auto-regulation of glucocorticoid receptor?

Down-regulation of the receptor by the drug is through the reduction of the receptor mRNA synthesis rate by the activated drug-receptor complex. To remove this effect the equation 1 should be changed to

$$\frac{dmRNA_R}{dt} = k_{s\_Rm} - k_{d\_Rm} \cdot mRNA_R$$

- what is the time course of receptor and mRNA concentrations when the drug treatment is stopped?

After the steady state is reached with the drug, D should be set to zero and simulations run till the new steady state is reached. For example, the time course of the receptor mRNA concentration should look something like that:



- Different corticosteroids show different association rates from receptors (k_{on}) and different dissociation rates (in this model reflected by k_{re}). Assuming the same concentrations of the drug, what is the effect of different values of k_{on} and k_{re} (consider 2 and 5 times increase and decrease of both parameters separately) on the receptor and mRNA dynamics?

Simulations should be run for 4 new values of k_{on}: 0.00329/5, 0.00329/2, 0.00329*2 and 0.00329*5. The results should be compared to the basic scenario when k_{on}=0.00329

Separately, simulations should be run for 4 new values of k_{re}: 0.57/5, 0.57/2, 0.57*2 and 0.57*5. The results should be compared to the basic scenario when k_{on}= 0.57.

- What would happen if the synthesis of the receptor was completely blocked?

k_{s_r} should be set to zero.

- What is the dynamic of the system when the baseline rate of production of mRNA of the receptor is increased or decreased 2 or 5 fold (and degradation is also increased or decreased so that at the baseline (without the drug) mRNA levels are constant)?

k_{s_Rm} values should be changed, but we know that if without the drug the system is at steady-state then $k_{d\_Rm} = k_{s\_Rm}/R_{m0}$. Therefore if we change k_{s_Rm} we need to change k_{d_Rm} as well.

After we recalculate the value of k_{d_Rm} for the baseline conditions, the simulations should be run with drug present.

Simulations should be run for 4 different scenarios:

- k_{s_Rm} = 2.9/5 and k_{d_Rm}=2.9/5/4.74
- k_{s_Rm} = 2.9/2 and k_{d_Rm}=2.9/2/4.74
- k_{s_Rm} = 2.9*2 and k_{d_Rm}=2.9*2/4.74
- k_{s_Rm} = 2.9*5 and k_{d_Rm}=2.9*5/4.74

- Bonus question: Solve analytically the differential equations to obtain the steady state receptor densities and mRNA concentrations. Calculate and present graphically what is the effect of drug concentration (from 0 to 150 nM) on the equilibrium receptor densities and mRNA concentration. Describe your findings. What is approximately the drug concentration when the maximum response is reached?

All four equations should be set to zero. Since we want to study the effect of drug concentration, we need to find the steady state conditions with the drug, and not the baseline without the drug. The equations are quite complicated. If someone is interested they can come to me during the lesson.