Week 3: Detailed analysis of the model.

This assignment you will be doing in **couples**. This week you will analyse the model in details and compare the simulation results to the experimental data.

Comparing simulation data with experimental data for two dosis

In the file `MPL.csv` you will find results of the experiments in rats. In the experiments the methylprednisolone was administered for 7 days under constant infusion of 0.1 or 0.3 mg drug/kg rat/h. Concentration of the drug was measured (in ng/mL), of the receptor mRNA (in fmol/g liver) and of the free receptor (in fmol/mg protein). Time is given in hours.

```
##    dose time MPL_conc  mRNA Free_receptor
## 89  0.3   96    93.43 0.366             0
## 90  0.3   96    61.71 1.976          48.9
## 91  0.3  168    17.38    NA             0
## 92  0.3  168    38.28 7.387             0
## 93  0.3  168    46.45 1.251          52.1
## 94  0.3  168    52.51 3.285             0
```

To calculate D we need the median MPL_concentration per dose (ng/ml) as a base.

```
data <- read.csv("MPL.csv", na.strings = "NA")
median_MPL_01 <- median(data$MPL_conc[data$dose==0.1], na.rm=TRUE)
median_MPL_01
```

```
## [1] 14.59
```

So the 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. The variability in plasma drug concentration is high but you can assume that it is constant over time.

Assignment 1: assess model validity

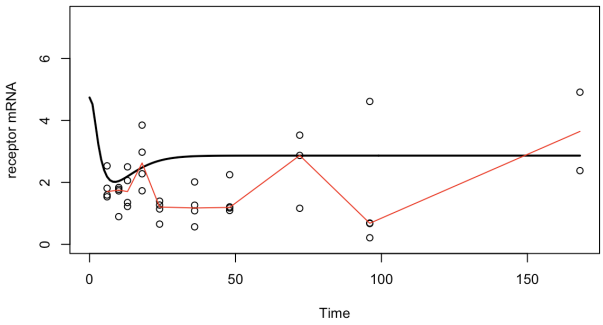
You have to compare the data from the experiment with the simulation data, to assess the model validity. The best way to do this is plotting the model results and the experimental results in one graph. The model results have one value per time unit, the experimental results have multiple values per time unit. Either plot all data points of the experimental data using a scatterplot or calculate the median results for each time unit and plot a line of these median points. You can do this for instance with the function `aggregate`.

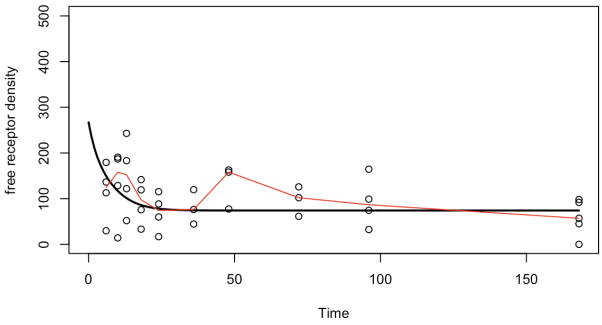
```
medians <- aggregate(data[,c("MPL_conc","mRNA","Free_receptor")],
                     list(data$dose,data$time),
                     median, na.rm=TRUE)
names(medians)[1:2] <- c("dose","time")
head(medians)
```

```
##   dose time MPL_conc   mRNA Free_receptor
## 1  0.0    0    0.000 3.7900        292.95
## 2  0.1    6   11.180 1.7025        124.70
## 3  0.3    6   31.295 1.7295         97.90
## 4  0.1   10   12.335 1.7515        157.80
## 5  0.3   10   36.960 1.4140         69.55
## 6  0.1   13   11.945 1.7045        152.50
```

The results of the entire experiment can be found in `MPL.csv`, the results of the model is to be calculated with the model you programmed in the previous assignment. Make sure you calculate the right dose concentration parameter (D) for the model corresponding with the dose 0.1 and 0.3.

An example of a the mRNA plot with the model(black line), the experiment(datapoints) and the median of the experimental data(red line) you find below (this is just an example, parameter values might be different!)





Questions

1. Why is it best practice to plot the median for the experimental data? Explain in your report
2. How do the results of the simulations depend on the dose and concentration of the drug? Compare the model variables $mRNA$, R with the experimental data by running the simulations adjusting dose D and plot these to find the answer.
3. Are the results of the model in line with experimental data? If not, what could be the reason? Think of at least one explanation. Try to test it with simulations (you will get bonus points for that, your explanation does not need to be correct, but should be logical).

Assignment 2: simulate scenario's

You are going to check what happens if you change the model and model parameters and compare the results to the basic scenario (from week 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. The value of $k_{d\_Rm} = 0.612$, value of $k_{s\_r} = 3.22$, value of $D = 20 * 1000/374.471$.

Questions

1. What would be the time dependent concentration of the activated drug-receptor complex if there was no auto-regulation of glucocorticoid receptor, i.e. if there was no effect of the drug on the synthesis of the receptor mRNA? What formula needs to be changed? Adjust the model, run the simulation and plot the results to find out.

2. What is the time dependence of receptor and mRNA concentrations when the drug treatment is stopped? So after the steady state is reached (at time $t = t_{steady}$), D should be set to zero and the simulation should continue from time $t = t_{steady}$ till a new steady state is reached (t_{steady_second}). Run the simulations and plot the results from $t = 0$ till t_{steady_second}.

3. 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? Adjust k_{on} and k_{re} as below and plot the results of the simulation for each change. Note: 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 $k_{re} = 0.57$.

4. What would happen if the synthesis of the receptor was completely blocked? Which parameter needs to be put to zero? Adjust the parameter, run the simulations and plot the results.

5. What are the dynamics of the system when the baseline rate of production of mRNA of the receptor is increased or decreased 2 or 5 fold (recalculate the rate of mRNA degradation so that the steady-state assumption at baseline (without the drug) is still valid, i.e. mRNA levels are constant when there is no drug)? Mind you: k_{s_Rm} values should be changed, but we know that if without the drug the system is at steady-state then $k_{d\_Rm} = \frac{k_{s\_Rm}}{R_{m0}}$. Therefore if we change k_{s_Rm} we need to change k_{d_Rm} as well. Also 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?

Write a Markdown report according the report styleguide constaining:

- answers of assignment 1
- answers of assignment 2
- graphs with informative legends below the figures – be efficient, do not produce too many separate figures and make it easy to compare new results with basic scenario
- the R scripts