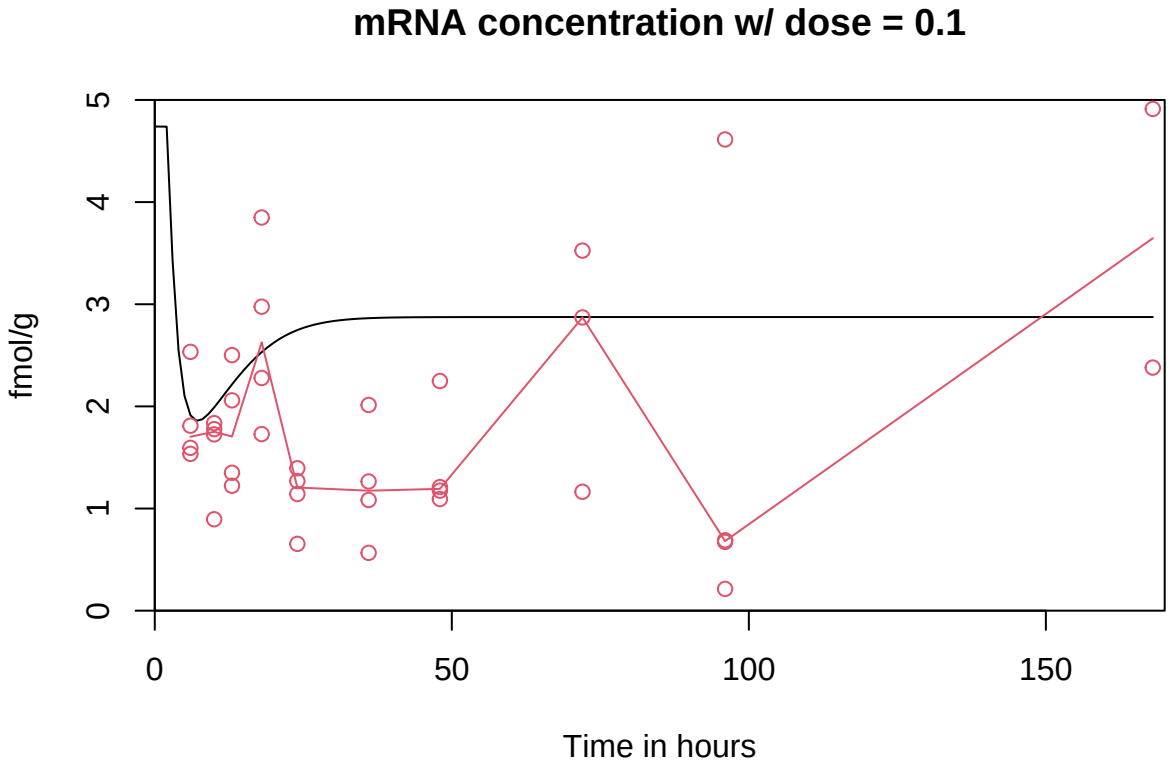
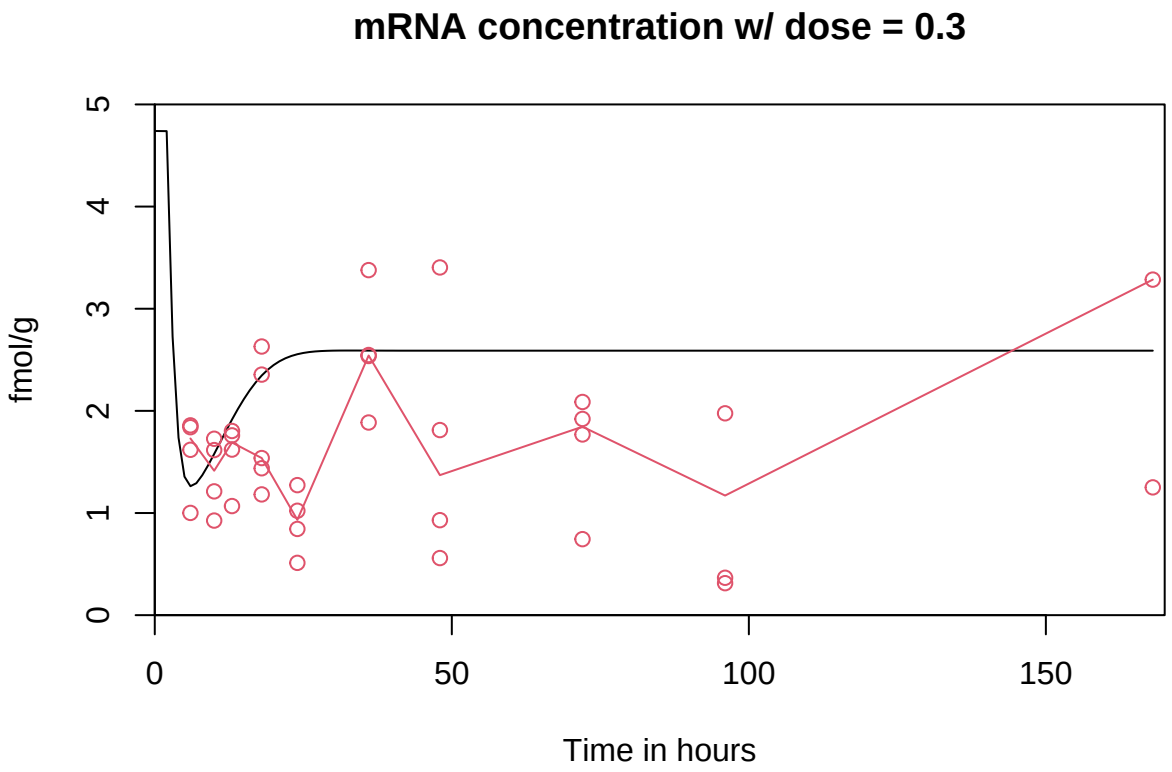
Week Three

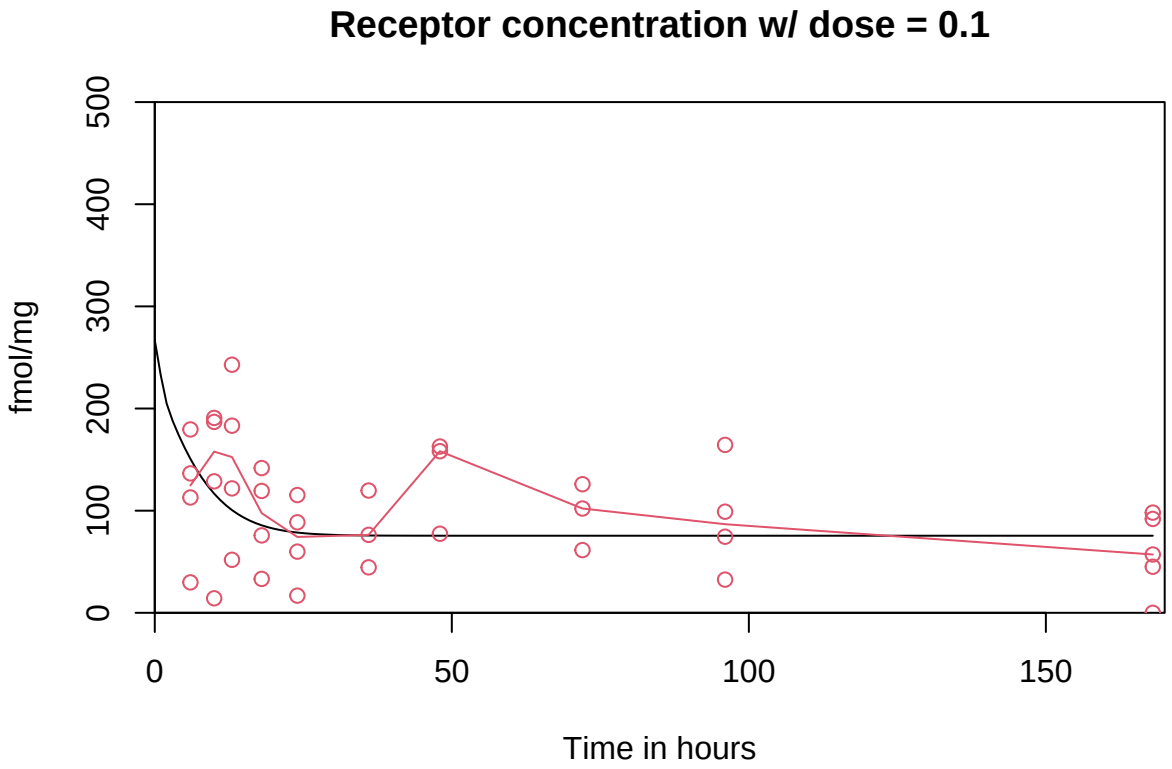
Eline Smit

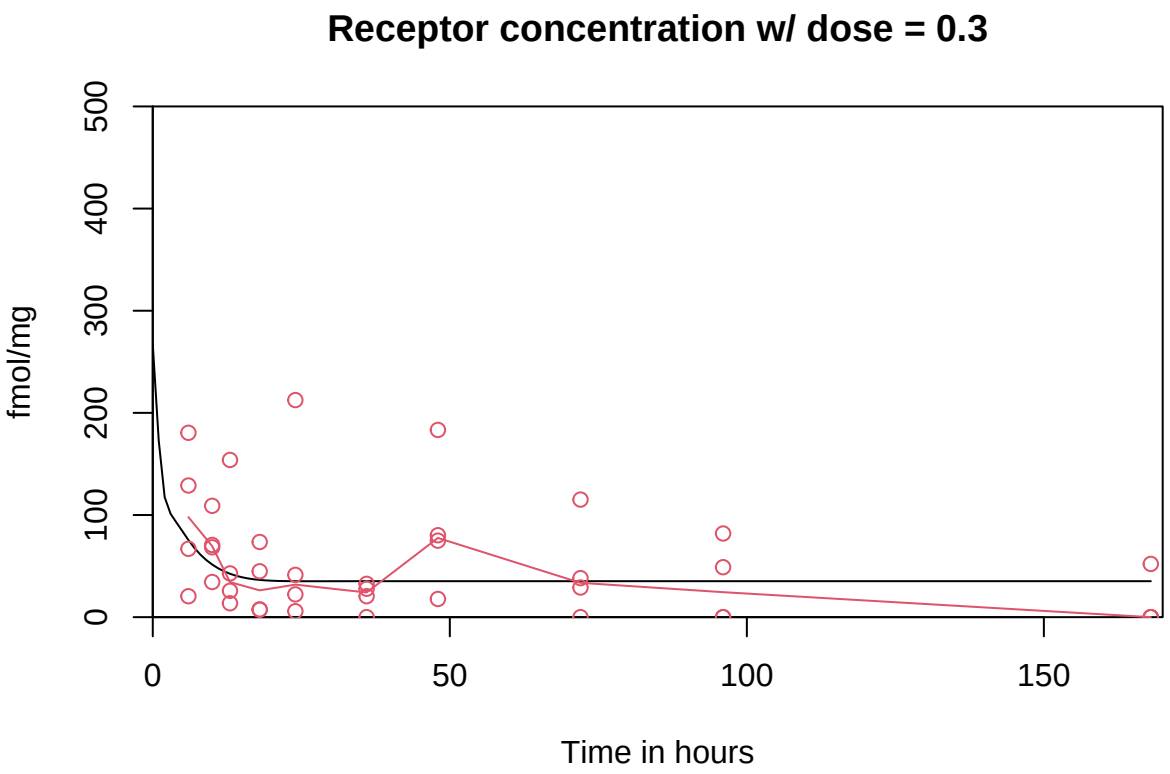
5/16/2022

In this case we use the median, as using the mean will cause outliers to influence the data more easily. Using the median




mRNA concentration w/ dose = 0.3
fmol/g
0
1
2
3
4
5
0
50
100
150
Time in hours

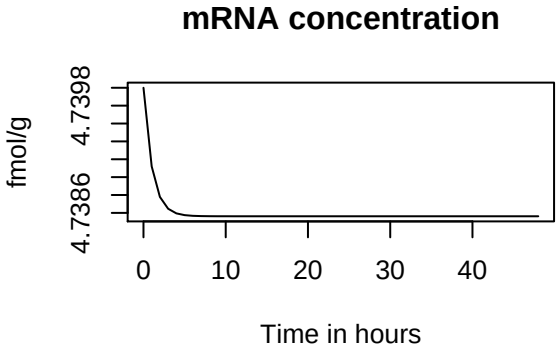

Receptor concentration w/ dose = 0.1
fmol/mg
0
100
200
300
400
500
0
50
100
150
Time in hours

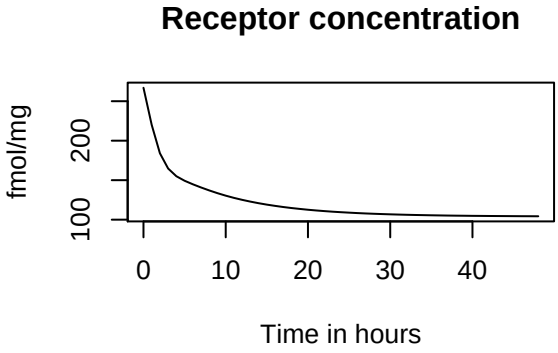


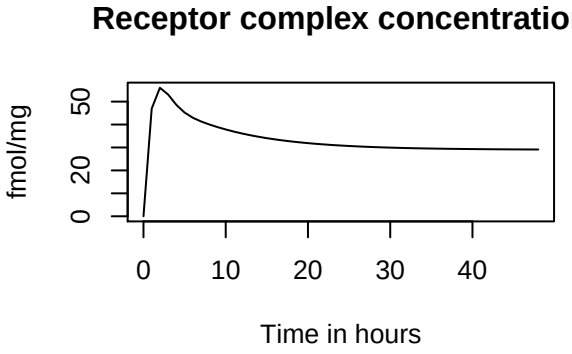
The simulation from the model does not seem to match the experimental data very well when it comes to the mRNA concentration, while it does seem to match the model pretty well for the concentration of the free receptor, this difference between the experiment and the model could be caused by differences in parameters in the experimental data. The kd_Rm and the ks_Rm parameters seem the most likely to be affecting this difference.

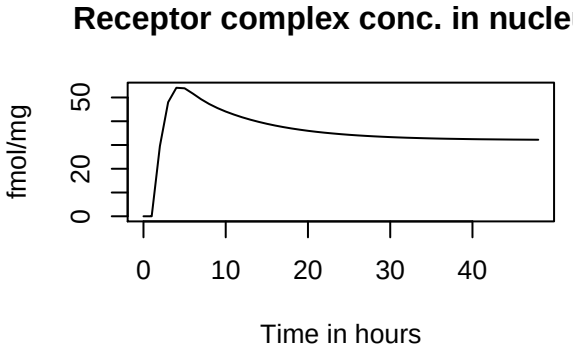
Assignment 2

[1] To remove the effect from the medicine on the rate of synthesis of mRNA, the formula $k_{s\_rm} \cdot (1 - \frac{DR(N)}{IC_{50\_Rm}+DR(N)}) - k_{d\_Rm} \cdot mRNA_r$ needs to be changed to only $k_{s\_rm} - k_{d\_Rm} \cdot mRNA_r$.

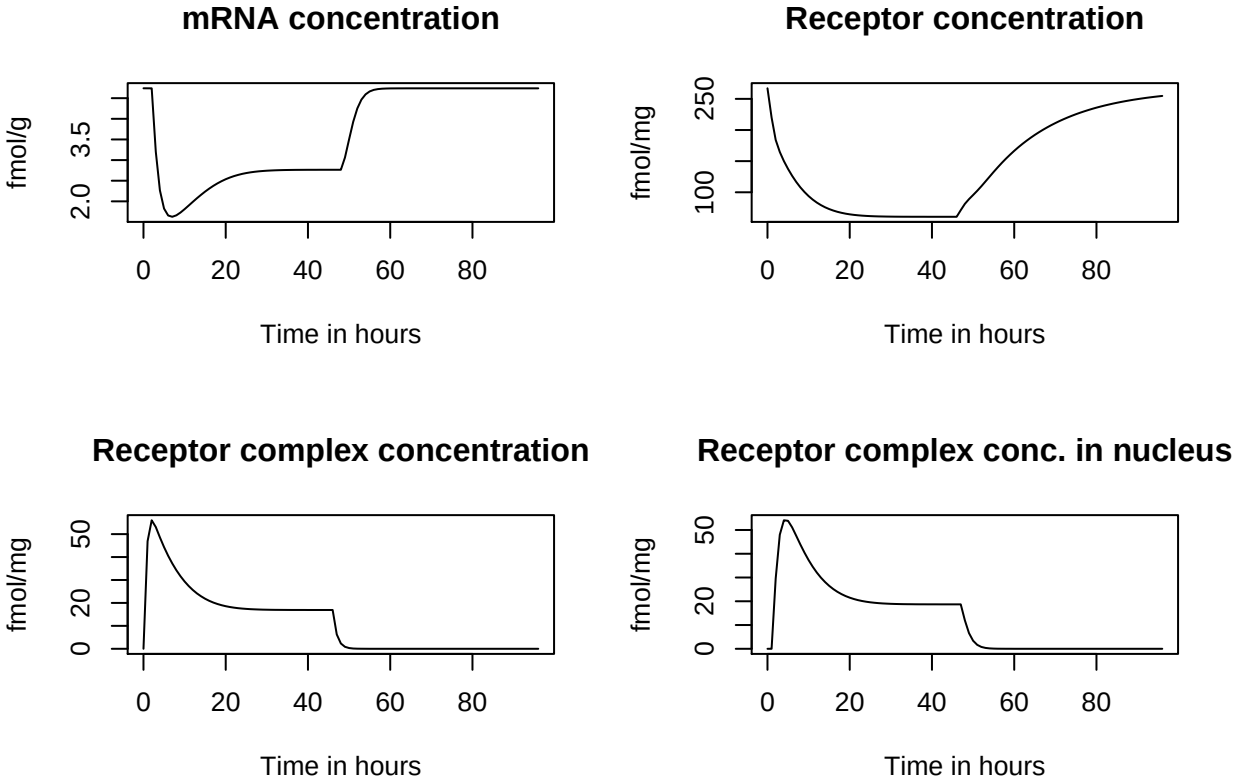




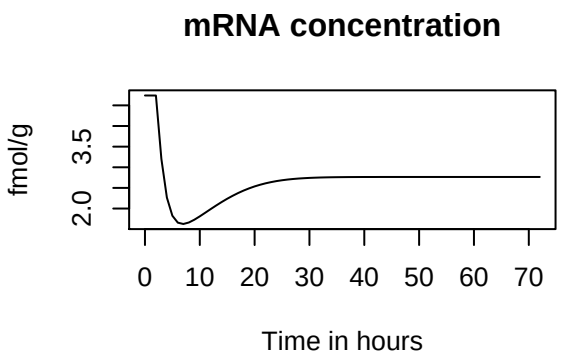


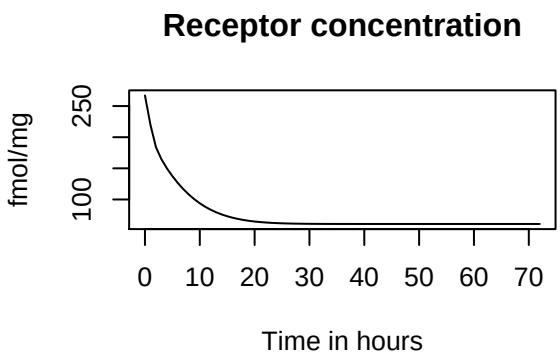


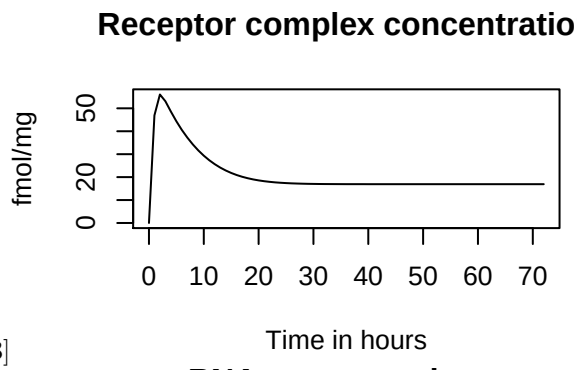
[2]

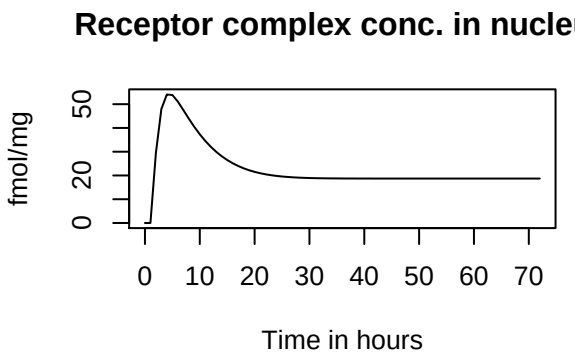


after stopping the treatment with the medicine, following the model, the numbers seem to go back to the initial levels. the receptor concentration taking the longest time to get back to base levels

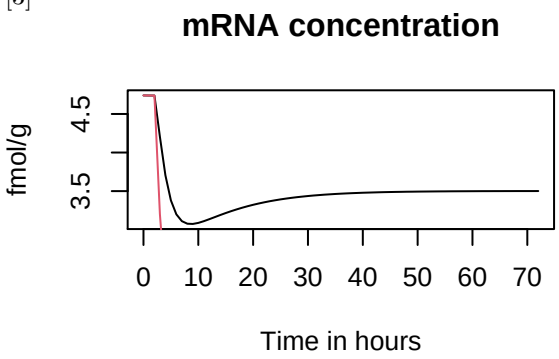

mRNA concentration
fmol/g
2.0
3.5
0
10
20
30
40
50
60
70
Time in hours

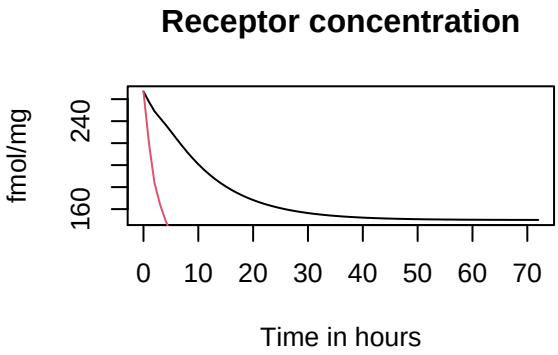

Receptor concentration
fmol/mg
100
250
0
10
20
30
40
50
60
70
Time in hours

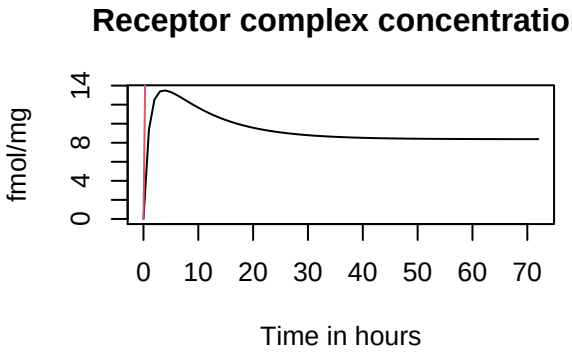

Receptor complex concentration
fmol/mg
0
20
50
0
10
20
30
40
50
60
70
Time in hours

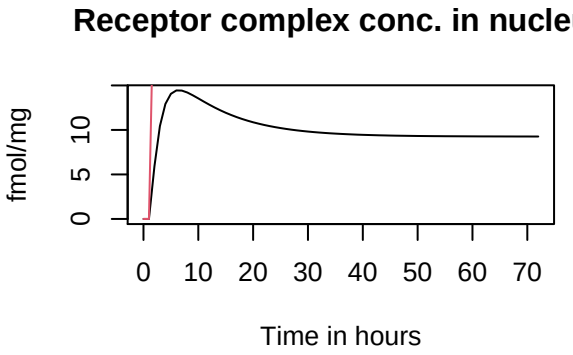

Receptor complex conc. in nucleus
fmol/mg
0
20
50
0
10
20
30
40
50
60
70
Time in hours

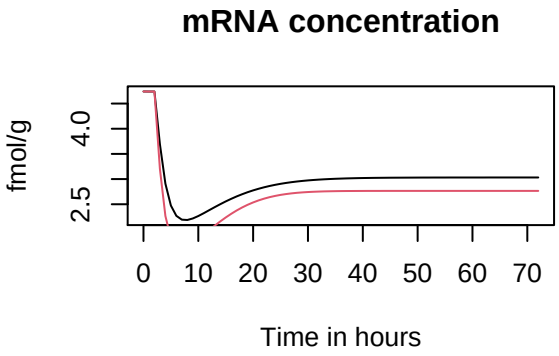
[3]

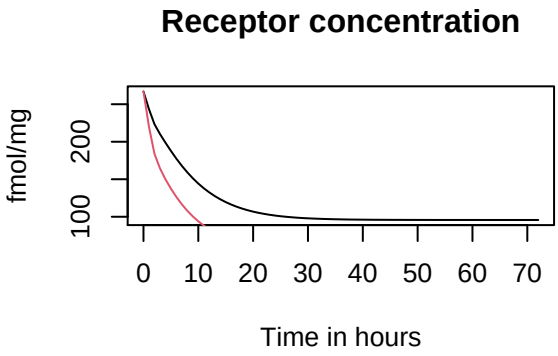

mRNA concentration
fmol/g
3.5
4.5
0
10
20
30
40
50
60
70
Time in hours

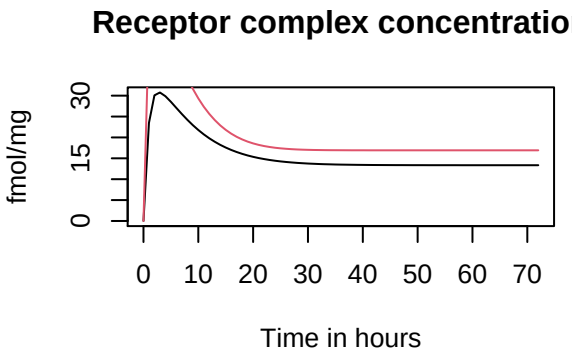

Receptor concentration
fmol/mg
160
240
0
10
20
30
40
50
60
70
Time in hours

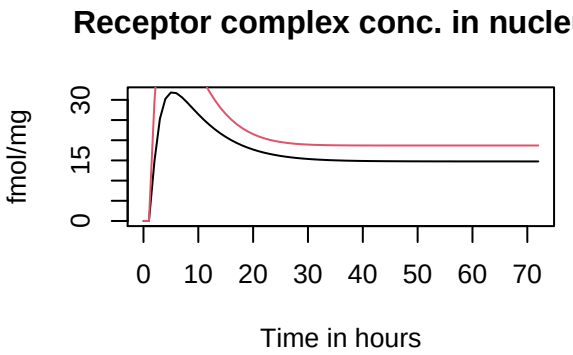

Receptor complex concentration
fmol/mg
0
4
8
14
0
10
20
30
40
50
60
70
Time in hours

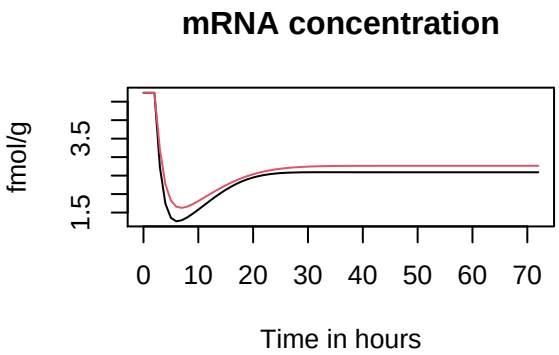

Receptor complex conc. in nucleus
fmol/mg
0
5
10
0
10
20
30
40
50
60
70
Time in hours

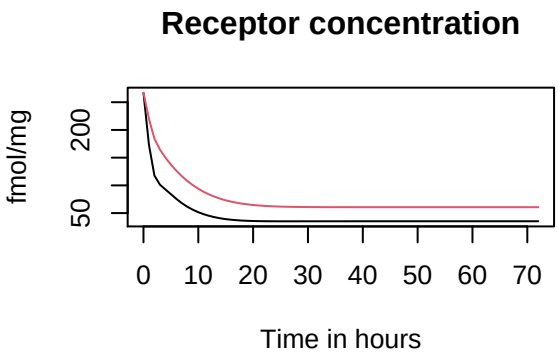

mRNA concentration
fmol/g
2.5
4.0
0
10
20
30
40
50
60
70
Time in hours

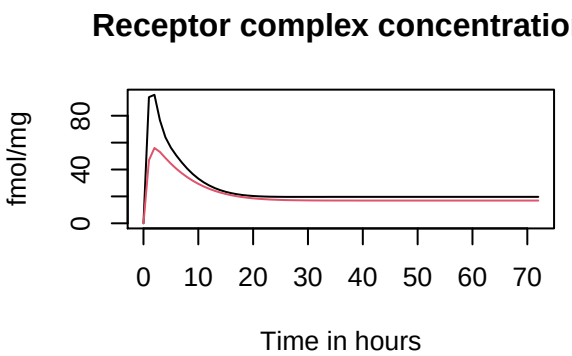

Receptor concentration
fmol/mg
100
200
0
10
20
30
40
50
60
70
Time in hours

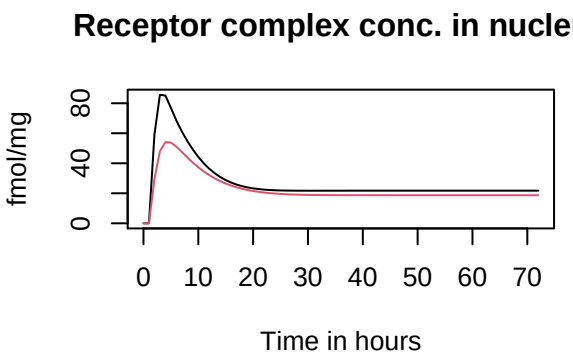

Receptor complex concentration
fmol/mg
0
15
30
0
10
20
30
40
50
60
70
Time in hours

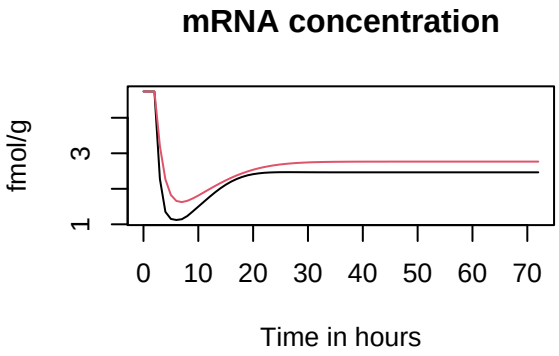

Receptor complex conc. in nucleus
fmol/mg
0
15
30
0
10
20
30
40
50
60
70
Time in hours

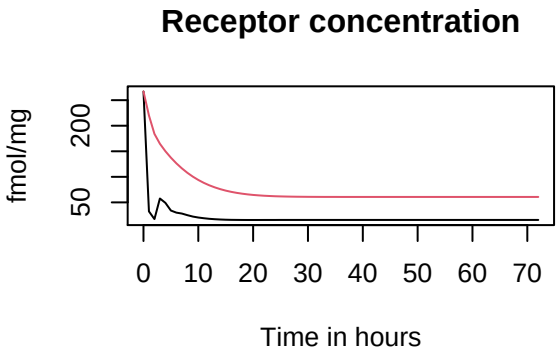

mRNA concentration
fmol/g
1.5
3.5
0
10
20
30
40
50
60
70
Time in hours

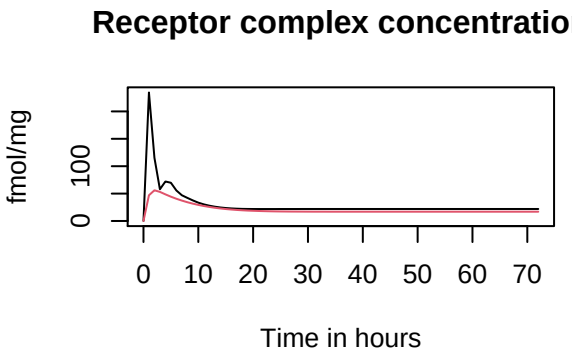

Receptor concentration
fmol/mg
50
200
0
10
20
30
40
50
60
70
Time in hours

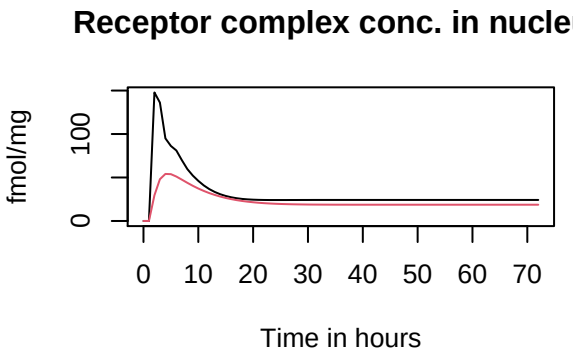

Receptor complex concentration
fmol/mg
0
40
80
0
10
20
30
40
50
60
70
Time in hours

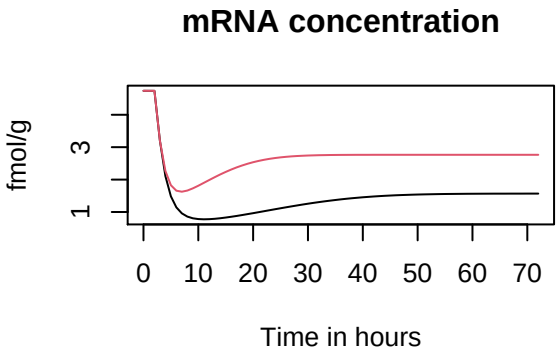

Receptor complex conc. in nucleus
fmol/mg
0
40
80
0
10
20
30
40
50
60
70
Time in hours

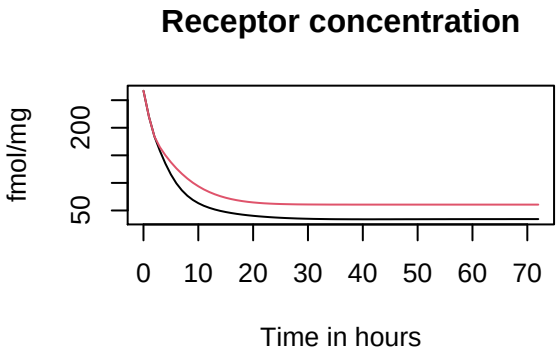

mRNA concentration
fmol/g
1
3
0 10 20 30 40 50 60 70
Time in hours

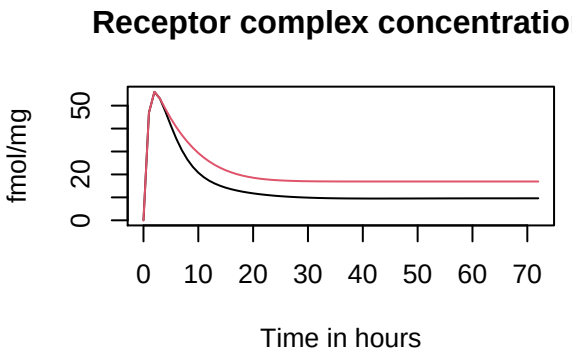

Receptor concentration
fmol/mg
50
200
0 10 20 30 40 50 60 70
Time in hours

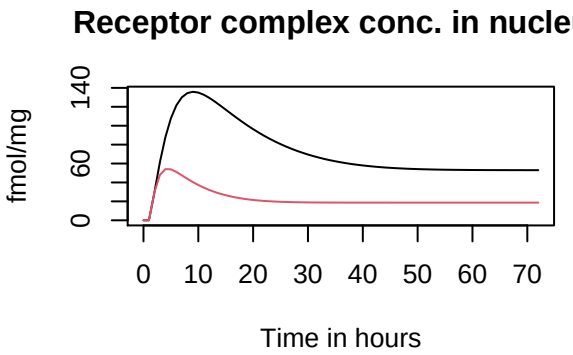

Receptor complex concentration
fmol/mg
0
100
0 10 20 30 40 50 60 70
Time in hours

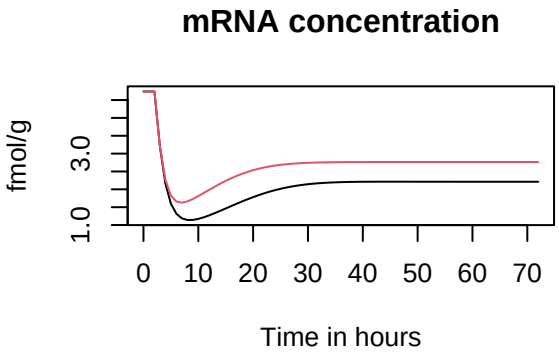

Receptor complex conc. in nucleus
fmol/mg
0
100
0 10 20 30 40 50 60 70
Time in hours

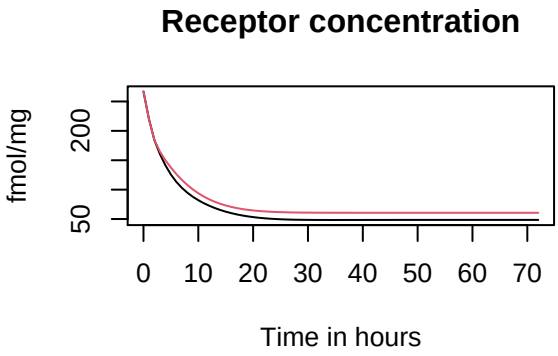

mRNA concentration
fmol/g
1
3
0 10 20 30 40 50 60 70
Time in hours

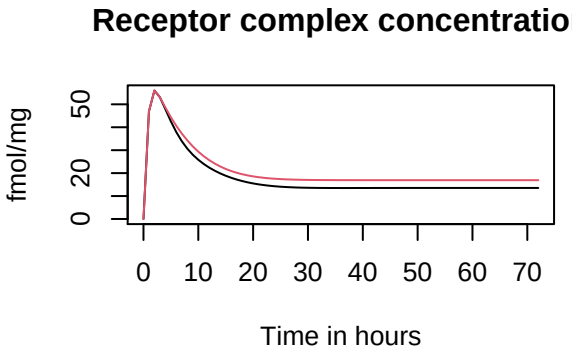

Receptor concentration
fmol/mg
50
200
0 10 20 30 40 50 60 70
Time in hours

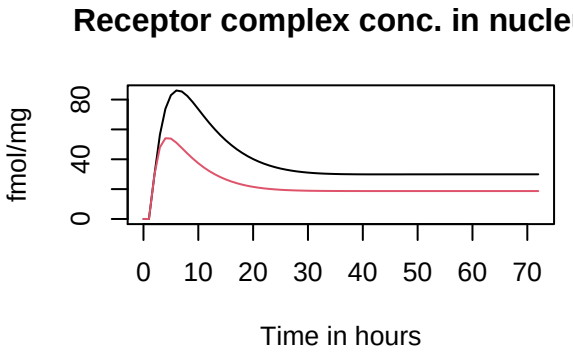

Receptor complex concentration
fmol/mg
0
20
50
0 10 20 30 40 50 60 70
Time in hours

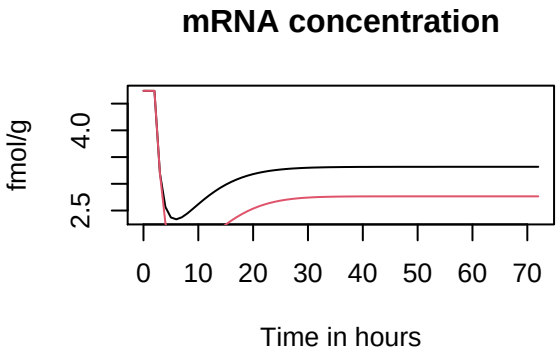

Receptor complex conc. in nucleus
fmol/mg
0
60
140
0 10 20 30 40 50 60 70
Time in hours

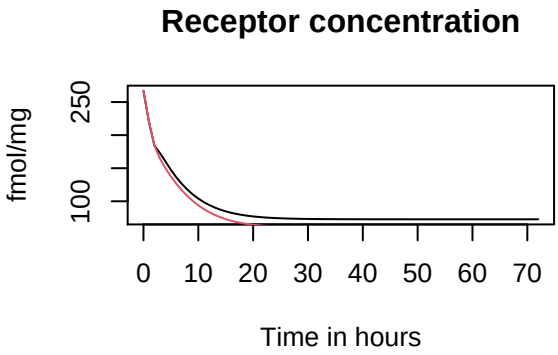

mRNA concentration
fmol/g
1.0
3.0
0
10
20
30
40
50
60
70
Time in hours

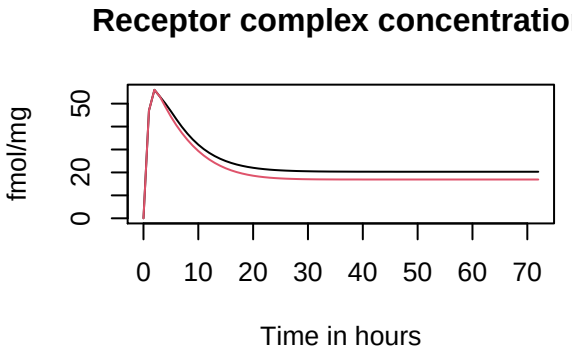

Receptor concentration
fmol/mg
50
200
0
10
20
30
40
50
60
70
Time in hours

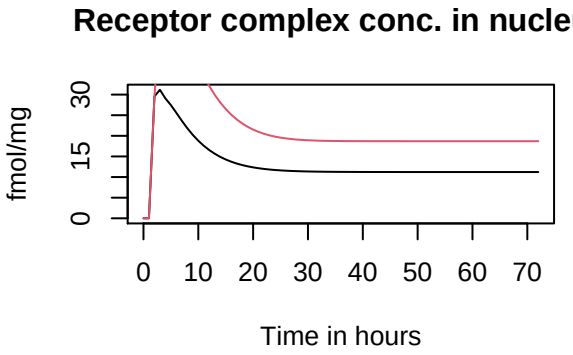

Receptor complex concentration
fmol/mg
0
20
50
0
10
20
30
40
50
60
70
Time in hours

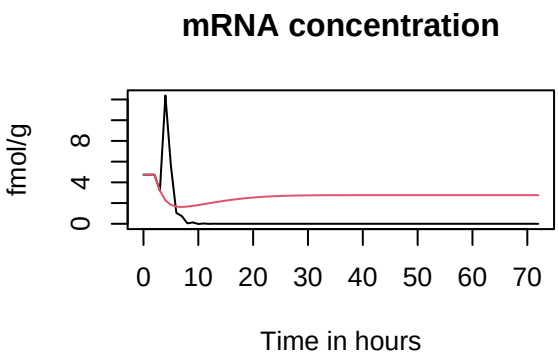

Receptor complex conc. in nucleus
fmol/mg
0
40
80
0
10
20
30
40
50
60
70
Time in hours

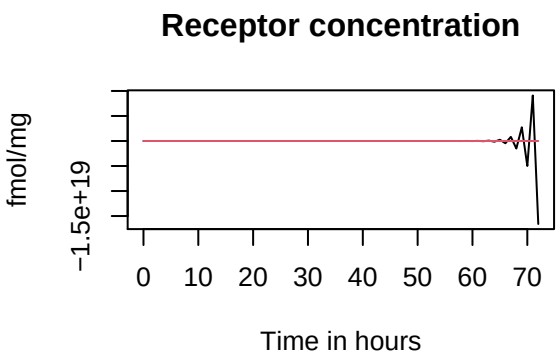

mRNA concentration
fmol/g
2.5
4.0
0
10
20
30
40
50
60
70
Time in hours

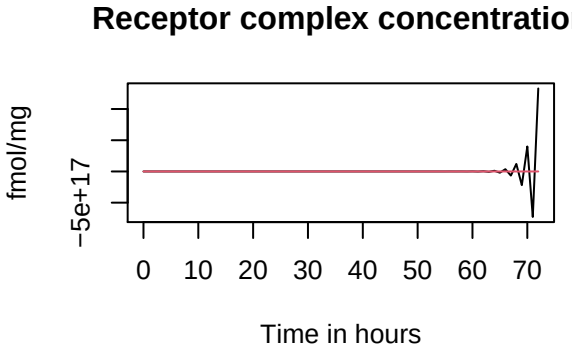

Receptor concentration
fmol/mg
100
250
0
10
20
30
40
50
60
70
Time in hours

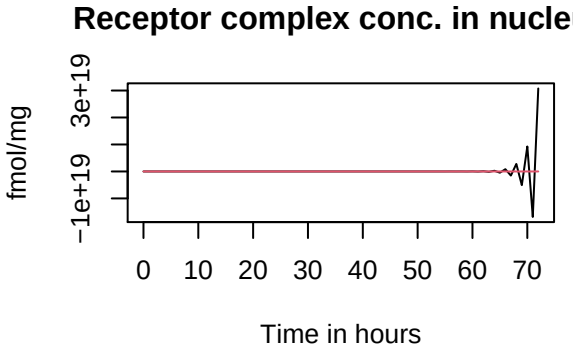

Receptor complex concentration
fmol/mg
0
20
50
0
10
20
30
40
50
60
70
Time in hours


Receptor complex conc. in nucleus
fmol/mg
0
15
30
0
10
20
30
40
50
60
70
Time in hours

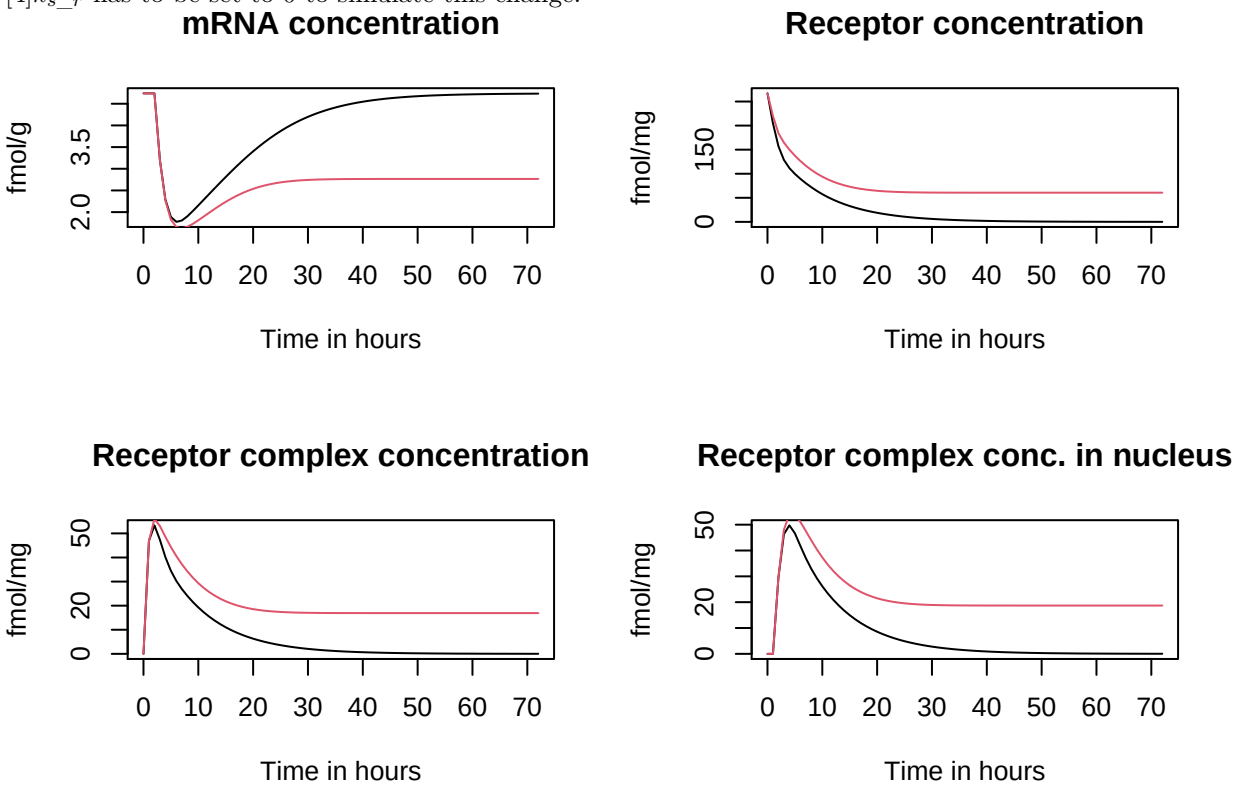

mRNA concentration
fmol/g
0 4 8
0 10 20 30 40 50 60 70
Time in hours


Receptor concentration
fmol/mg
−1.5e+19
0 10 20 30 40 50 60 70
Time in hours


Receptor complex concentration
fmol/mg
−5e+17
0 10 20 30 40 50 60 70
Time in hours


Receptor complex conc. in nucleus
fmol/mg
3e+19
−1e+19
0 10 20 30 40 50 60 70
Time in hours

[4]k_{s_r} has to be set to 0 to simulate this change.



The red lines in these graphs are the original lines, where the receptor synthesis is still active. Without receptor synthesis, all concentrations return to their original values except the receptor concentration, which will reach 0 and stay there. It also takes longer for it to return to a steady state.

[5]

Appendix: All code for this report

```
knitr::opts_chunk$set(echo = FALSE)
library(deSolve)

setwd("/homes/kbsmit/Documents/project8/SystemsBiologyProject8/Data/")
expdata = read.csv("MPL.csv")

medians <- aggregate(expdata[,c("MPL_conc","mRNA","Free_receptor")],list(expdata$dose,expdata$time), me
names(medians)[1:2] <- c("dose","time")

#set the initial states, timeframe, and parameters, and create a function for the formulas
state <- c(rm0 = 4.74,
           r0 = 267,
           dr = 0,
           drn = 0)

timeframe <- seq(0, 168, by = 1)

parmezan <- c(ksrm = 2.90,
            ic50rm = 26.2,
            kon = 0.00329,
            kt = 0.63,
            kre = 0.57,
            Rf = 0.49,
            kdr = 0.0572,
            kdrm = 0.612,
            ksr = 3.22,
            D = 39)

formulas <- function(t, y, parameters){
  with(as.list(c(y, parameters)), {
    dmRNAr <- ksrm * (1 - (drn) / (ic50rm + drn)) - kdrm * rm0
    dR <- ksr * rm0 + Rf * kre * drn - kon * D * r0 - kdr * r0
    dDR <-kon * D * r0 - kt * dr
    dDRN <- kt * dr - kre * drn

    return(list(c(dmRNAr, dR, dDR, dDRN)))
    }
  )
}

# generate output from using all the data given, then adjust D for the 2nd concentration and generate a
out  <- ode(times = timeframe, y = state,   parms = parmezan, func = formulas, method = "euler")

parmezan["D"] <- 107

out2  <- ode(times = timeframe, y = state,   parms = parmezan, func = formulas, method = "euler")

# Plot the graphs for mRNA with the first concentration first
par(yaxs = "i", xaxs = "i")
plot(out[,c("time", "rm0")],
     type="l", xlab = "Time in hours",
```

```
     ylab = "fmol/g",
     main = "mRNA concentration w/ dose = 0.1",
     xlim = c(0, 170),
     ylim = c(0,5))
lines(medians[medians$dose == 0.1, c("time", "mRNA")], col=2)
lines(expdata[expdata$dose == 0.1, c("time", "mRNA")], col=2, type = "p")

# Plot the graphs for mRNA with the second concentration
par(yaxs = "i", xaxs = "i")
plot(out2[,c("time", "rm0")],
     type="l",
     xlab = "Time in hours",
     ylab = "fmol/g",
     main = "mRNA concentration w/ dose = 0.3",
     xlim = c(0, 170),
     ylim = c(0,5))
lines(medians[medians$dose == 0.3, c("time", "mRNA")], col=2)
lines(expdata[expdata$dose == 0.3, c("time", "mRNA")], col=2, type = "p")

# Now do the same for the receptor concentrations
par(yaxs = "i", xaxs = "i")
plot(out[,c("time", "r0")],
     type="l",
     xlab = "Time in hours",
     ylab = "fmol/mg",
     main = "Receptor concentration w/ dose = 0.1",
     xlim = c(0, 170),
     ylim = c(0,500))
lines(medians[medians$dose == 0.1, c("time", "Free_receptor")], col=2)
lines(expdata[expdata$dose == 0.1, c("time", "Free_receptor")], col=2, type = "p")

par(yaxs = "i", xaxs = "i")
plot(out2[,c("time", "r0")],
     type="l",
     xlab = "Time in hours",
     ylab = "fmol/mg",
     main = "Receptor concentration w/ dose = 0.3",
     xlim = c(0, 170),
     ylim = c(0,500))
lines(medians[medians$dose == 0.3, c("time", "Free_receptor")], col=2)
lines(expdata[expdata$dose == 0.3, c("time", "Free_receptor")], col=2, type = "p")

#Set D back to the base we use for the remaining exercises and set a timeframe
parmezan["D"] <- 20*1000/374.471
timeframe <- seq(0, 48, by = 1)

#Create a function for the edited formulas
edited_formulas_one <- function(t, y, parameters){
  with(as.list(c(y, parameters)), {
    dmRNAr <- ksrm - kdrm * rm0
    dR <- ksr * rm0 + Rf * kre * drn - kon * D * r0 - kdr * r0
    dDR <-kon * D * r0 - kt * dr
    dDRN <- kt * dr - kre * drn
```

```
    return(list(c(dmRNAr, dR, dDR, dDRN)))
    }
  )
}

#Plot the new graphs with the edited formula
out_syntheffect  <- ode(times = timeframe, y = state,   parms = parmezan, func = edited_formulas_one, m
plot(out_syntheffect,
     lty = 1,
     main = c("mRNA concentration", "Receptor concentration", "Receptor complex concentration", "Recept
     xlab = "Time in hours",
     ylab = c("fmol/g", "fmol/mg", "fmol/mg", "fmol/mg"))

# Set a timeframe for this exercise
timeframe <- seq(0, 96, by = 1)

# Make an edited formula function where D is set to 0 at a point where the model is in a steady state
formula_stopmed <- function(t, y, parameters){
  if(t>45){
    parameters["D"]=0
  }
  with(as.list(c(y, parameters)), {
    dmRNAr <- ksrm * (1 - (drn) / (ic50rm + drn)) - kdrm * rm0
    dR <- ksr * rm0 + Rf * kre * drn - kon * D * r0 - kdr * r0
    dDR <-kon * D * r0 - kt * dr
    dDRN <- kt * dr - kre * drn

    return(list(c(dmRNAr, dR, dDR, dDRN)))
    }
  )
}
out_stopmed  <- ode(times = timeframe, y = state,   parms = parmezan, func = formula_stopmed, method =
plot(out_stopmed,
     lty = 1,
     main = c("mRNA concentration", "Receptor concentration", "Receptor complex concentration", "Recept
     xlab = "Time in hours",
     ylab = c("fmol/g", "fmol/mg", "fmol/mg", "fmol/mg"))
#function to plot comparisons on all 4 graphs generated by the model
compare_plots <- function(base, changed){
  par(mfrow=c(2,2))
  plot(changed[,c("time", "rm0")],
       type = "l",
       lty = 1,
       main = "mRNA concentration",
       xlab = "Time in hours",
       ylab = "fmol/g")
  lines(base[,c("time", "rm0")], col=2)

  plot(changed[,c("time", "r0")],
       type = "l",
       lty = 1,
       main = "Receptor concentration",
       xlab = "Time in hours",
```

```
      ylab = "fmol/mg")
  lines(base[,c("time", "r0")], col=2)

  plot(changed[,c("time", "dr")],
      type = "l",
      lty = 1,
      main = "Receptor complex concentration",
      xlab = "Time in hours",
      ylab = "fmol/mg")
  lines(base[,c("time", "dr")], col=2)

  plot(changed[,c("time", "drn")],
      type = "l",
      lty = 1,
      main = "Receptor complex conc. in nucleus",
      xlab = "Time in hours",
      ylab = "fmol/mg")
  lines(base[,c("time", "drn")], col=2)
}



timeframe <- seq(0, 72, by = 1)
parmezan["D"] <- 20*1000/374.471
kon = c(0.00329/5, 0.00329/2, 0.00329*2, 0.00329*5)
kre = c(0.57/5, 0.57/2, 0.57*2, 0.57*5)

out_base <- ode(times = timeframe, y = state,   parms = parmezan, func = formulas, method = "euler")
plot(out_base,
     lty = 1,
     main = c("mRNA concentration", "Receptor concentration", "Receptor complex concentration", "Recept
     xlab = "Time in hours",
     ylab = c("fmol/g", "fmol/mg", "fmol/mg", "fmol/mg"))

for(x in kon){
    parmezan["kon"] <- x
    out_kon <- ode(times = timeframe, y = state,   parms = parmezan, func = formulas, method = "euler")
    compare_plots(out_base, out_kon)
  }
parmezan["kon"] <- 0.00329

for(x in kre){
    parmezan["kre"] <- x
    out_kre <- ode(times = timeframe, y = state,   parms = parmezan, func = formulas, method = "euler")
#  plot(out_kre,
#       lty = 1,
#       main = c("mRNA concentration", "Receptor concentration", "Receptor complex concentration", "Rec
#       xlab = "Time in hours",
#       ylab = c("fmol/g", "fmol/mg", "fmol/mg", "fmol/mg"))
    compare_plots(out_base, out_kre)
  }
parmezan["kre"] <- 0.57
```

```
out_withksr <- ode(times = timeframe, y = state,   parms = parmezan, func = formulas, method = "euler")
parmezan["ksr"] <- 0
out_noksr <- ode(times = timeframe, y = state,   parms = parmezan, func = formulas, method = "euler")

par(mfrow=c(2,2))
plot(out_noksr[,c("time", "rm0")],
     type = "l",
     lty = 1,
     main = "mRNA concentration",
     xlab = "Time in hours",
     ylab = "fmol/g")
lines(out_withksr[,c("time", "rm0")], col=2)

plot(out_noksr[,c("time", "r0")],
     type = "l",
     lty = 1,
     main = "Receptor concentration",
     xlab = "Time in hours",
     ylab = "fmol/mg")
lines(out_withksr[,c("time", "r0")], col=2)

plot(out_noksr[,c("time", "dr")],
     type = "l",
     lty = 1,
     main = "Receptor complex concentration",
     xlab = "Time in hours",
     ylab = "fmol/mg")
lines(out_withksr[,c("time", "dr")], col=2)

plot(out_noksr[,c("time", "drn")],
     type = "l",
     lty = 1,
     main = "Receptor complex conc. in nucleus",
     xlab = "Time in hours",
     ylab = "fmol/mg")
lines(out_withksr[,c("time", "drn")], col=2)
```