Detailed Analysis

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```
packages <- c("deSolve", "ggplot2", "formatR", "scales")
invisible(lapply(packages, library, character.only = T))
```

```
MPL_data <- read.csv("MPL.csv", na.strings = "NA")

median_MPL_01 <- median(MPL_data$MPL_conc[MPL_data$dose==0.1], na.rm=T)
median_MPL_03 <- median(MPL_data$MPL_conc[MPL_data$dose==0.3], na.rm=T)

cat("Median of dose 0.1: ", median_MPL_01)
```

```
## Median of dose 0.1:  14.59
```

```
cat("Median of dose 0.3: ", median_MPL_03)
```

```
## Median of dose 0.3:  39.925
```

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

median_01 <- subset(medians, medians$dose == 0 | medians$dose == 0.1)
median_03 <- subset(medians, medians$dose == 0 | medians$dose == 0.3)

head(medians)
```

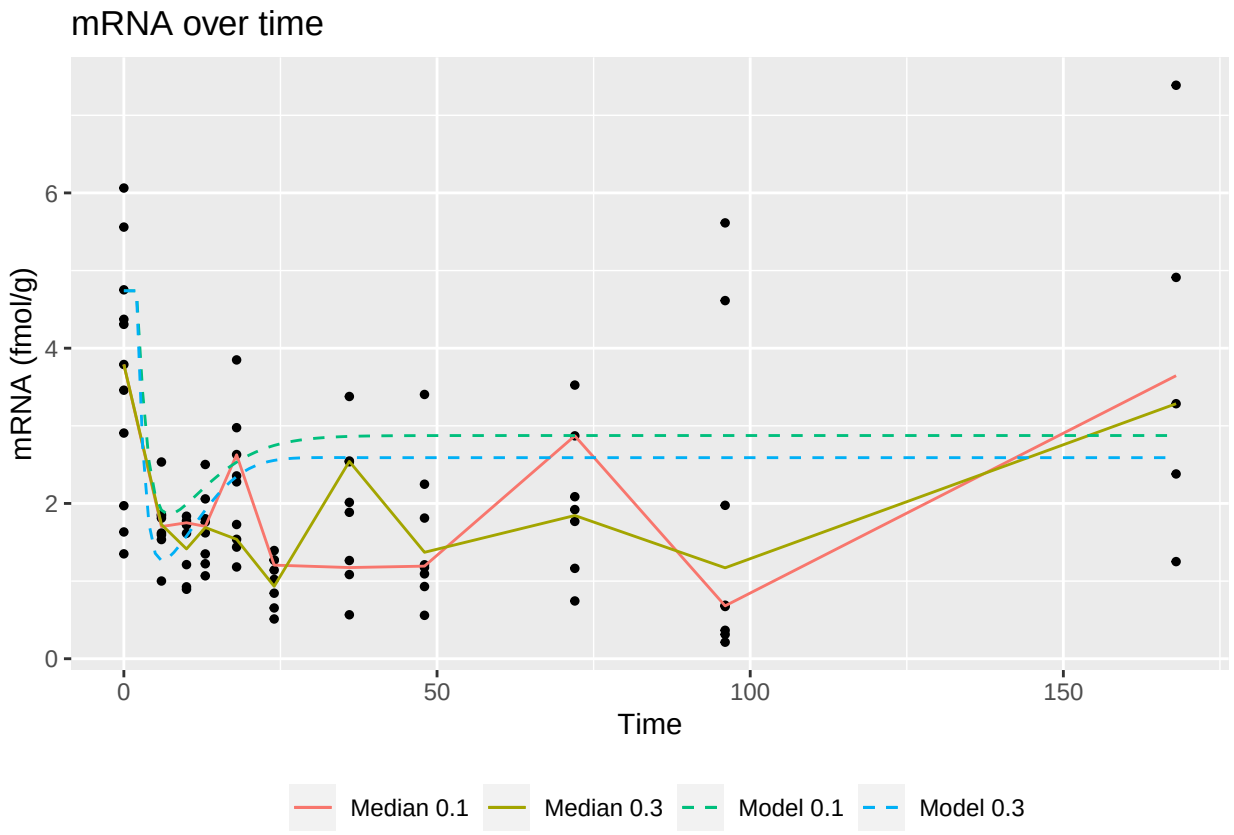
```
##   dose time MPL_conc   mRNA Free_receptor
## 1  0.0    0    0.000 3.7900        292.95
## 2  0.1    6   11.180 1.7025        124.70
## 3  0.3    6   31.295 1.7295         97.90
## 4  0.1   10   12.335 1.7515        157.80
## 5  0.3   10   36.960 1.4140         69.55
## 6  0.1   13   11.945 1.7045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

```
params <- c(
        k.s_Rm = 2.90, # fmol/g liver/h, Oe k voor GR mRNA synthese
        IC.50_Rm = 26.2, # fmol/mg protein, concentratie DR(N) wat mRNAR inhibeert
        k.on = 0.00329, # L/nmol/h, 2e orde k voor vorming MPL-receptor complex
        k.T = 0.63, # 1/h, 1e orde k voor translocatie MPL-receptor complex naar nucleus
        k.re = 0.57, # 1/h, 1e orde k voor 'recovery' receptor (celkern -> cytosol)
        R.f = 0.49, # fractie vrije receptor die gerecycled wordt
        k.d_R = 0.0572, # 1/h, 1e orde k voor afbraak van de receptor
        k.d_Rm = 0.612, # 1e orde k voor GR mRNA afbraak
        k.s_R = 3.22, # 1e orde k voor aanmaak receptor
        D = (0 * 1000)/374.471 # nmol/L, als molgewicht[MPL] = 374.471 g/mol
)
```

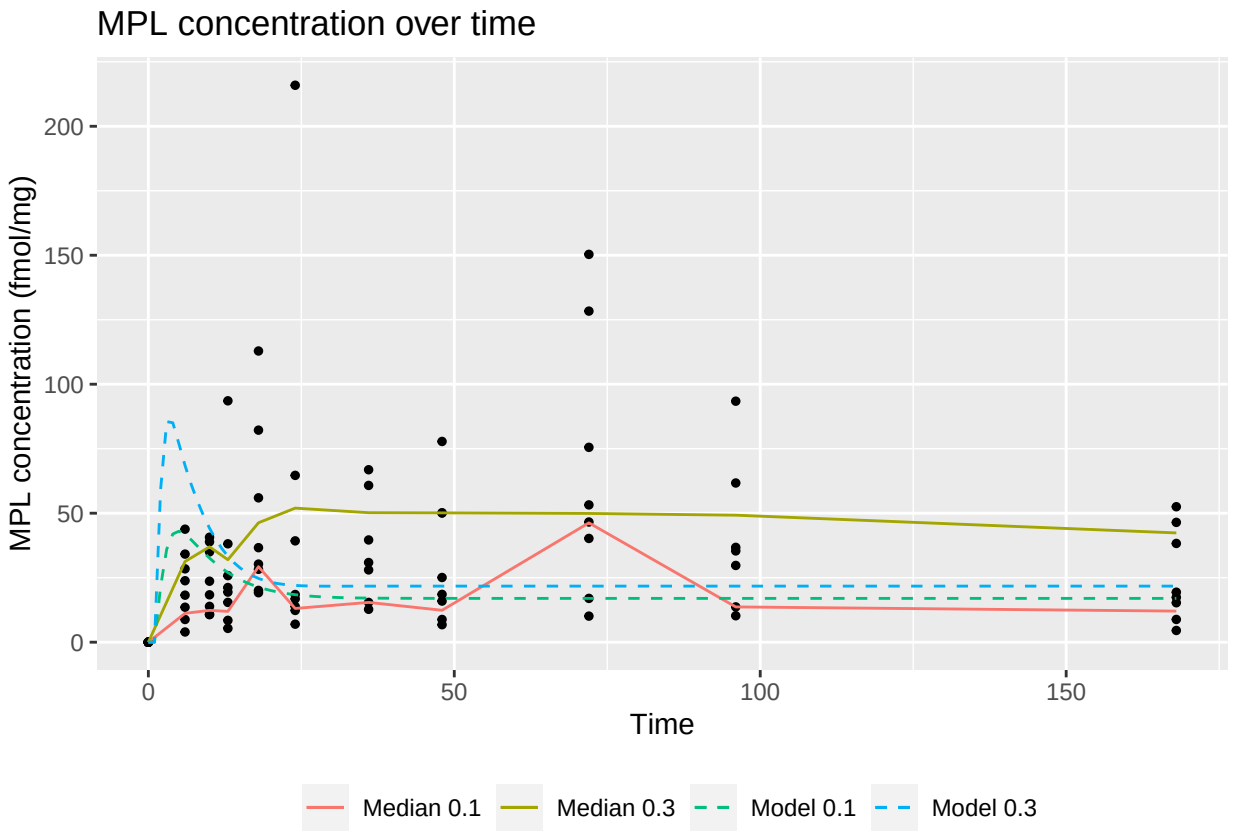
```
state <- c(
        mRNA = 4.74, # fmol / g liver, basisniveau concentratie receptor mRNA
        Free_receptor = 267, # fmol/mg protein, basisniveau concentratie vrije receptor
        DR = 0, # fmol/mg protein, dichtheid MPL
        MPL_conc = 0 # fmol/mg protein, hoeveelheid MPL
)

volume <- function(t, y, parms){
  with(as.list(c(parms, y)),{
    delta.mRNA_R <- k.s_Rm * (1 - ( MPL_conc / (IC.50_Rm + MPL_conc) ) ) - k.d_Rm * mRNA
    delta.R <- k.s_R * mRNA + R.f * k.re * MPL_conc -
            k.on * D * Free_receptor - k.d_R * Free_receptor
    delta.DR <- k.on * D * Free_receptor - k.T * DR
    delta.MPL_conc <- k.T * DR - k.re * MPL_conc
    return( list( c(delta.mRNA_R, delta.R, delta.DR, delta.MPL_conc ) ) )
  })
}

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

params$D <- (median_MPL_01 * 1000)/374.471
model_01 <- ode(times = times, y = state,
                parms = params, func = volume, method = "euler")
model_01 <- as.data.frame(model_01)

params$D <- (median_MPL_03 * 1000)/374.471
model_03 <- ode(times = times, y = state,
                parms = params, func = volume, method = "euler")
model_03 <- as.data.frame(model_03)
```

Assignment 1

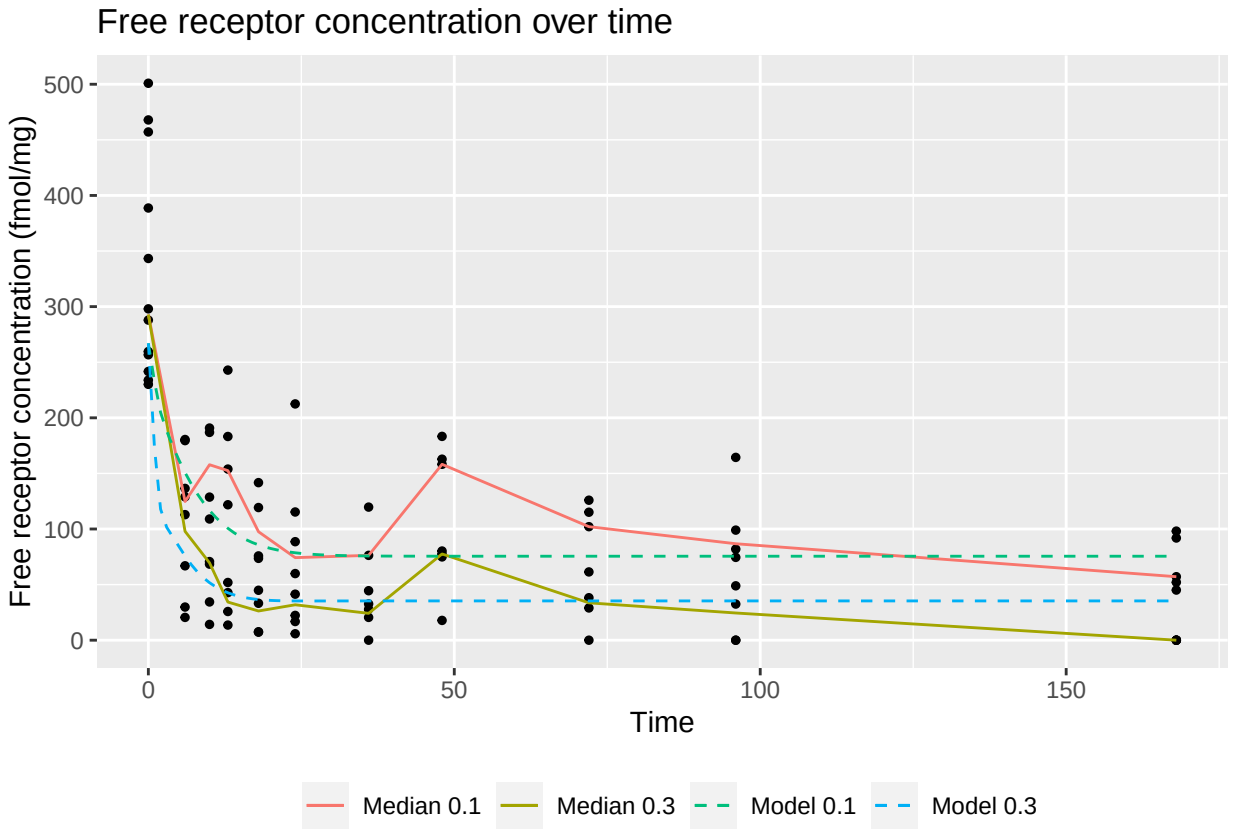
```
## Create the colours
group.cols <- hue_pal()(5)
## Assign each colour for legibility
colours <- c("Median 0.1" = group.cols[1], "Median 0.3" = group.cols[2],
             "Model 0.1" = group.cols[3], "Model 0.3" = group.cols[4],
             "Model 20" = group.cols[5])
ggplot(data = MPL_data, mapping = aes(x = time, y = mRNA)) +
        geom_point(size = 1) +
        geom_line(data = median_01, aes(color ="Median 0.1")) +
        geom_line(data = median_03, aes(color = "Median 0.3")) +
        geom_line(data = model_01, linetype = "dashed", aes(color = "Model 0.1")) +
        geom_line(data = model_03, linetype = "dashed", aes(color = "Model 0.3")) +
        labs(x = "Time", y = "mRNA (fmol/g)", title = "mRNA over time") +
        theme(legend.position = "bottom") +
        scale_colour_manual(values = group.cols[1:4],
                            limits = c("Median 0.1", "Median 0.3",
                                       "Model 0.1", "Model 0.3") ) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(1, 1, 2, 2) ) ) )
```




```
ggplot(data = MPL_data, mapping = aes(x = time, y = MPL_conc)) +
        geom_point(size = 1) +
        geom_line(data = median_01, aes(color ="Median 0.1")) +
        geom_line(data = median_03, aes(color = "Median 0.3")) +
        geom_line(data = model_01, linetype = "dashed", aes(color = "Model 0.1")) +
        geom_line(data = model_03, linetype = "dashed", aes(color = "Model 0.3")) +
        labs(x = "Time", y = "MPL concentration (fmol/mg)",
             title = "MPL concentration over time") +
        theme(legend.position = "bottom") +
        scale_colour_manual(values = group.cols[1:4],
                            limits = c("Median 0.1", "Median 0.3",
                                       "Model 0.1", "Model 0.3") ) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(1, 1, 2, 2) ) ) )
```



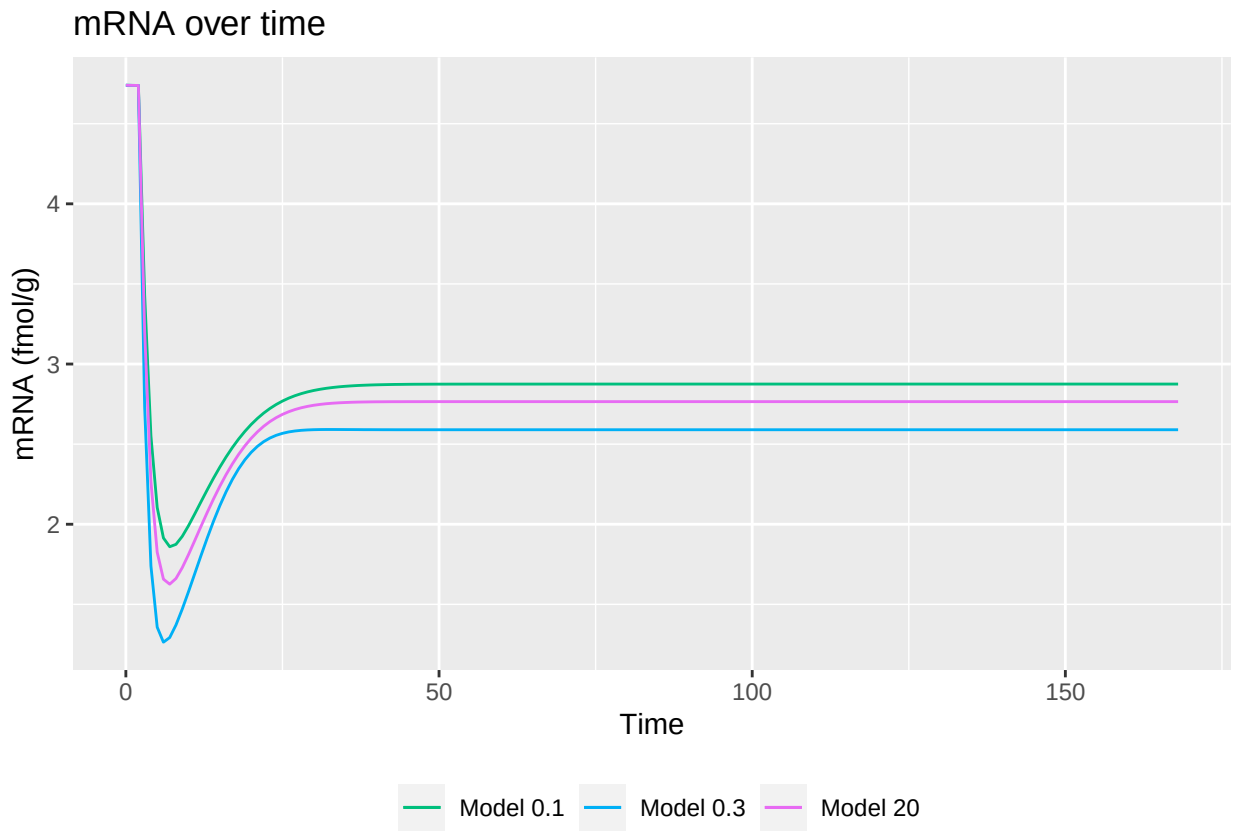

```
ggplot(data = MPL_data, mapping = aes(x = time, y = Free_receptor)) +
        geom_point(size = 1) +
        geom_line(data = median_01, aes(color ="Median 0.1")) +
        geom_line(data = median_03, aes(color = "Median 0.3")) +
        geom_line(data = model_01, linetype = "dashed", aes(color = "Model 0.1")) +
        geom_line(data = model_03, linetype = "dashed", aes(color = "Model 0.3")) +
        labs(x = "Time", y = "Free receptor concentration (fmol/mg)",
             title = "Free receptor concentration over time") +
       theme(legend.position = "bottom") +
        scale_colour_manual(values = group.cols[1:4],
                            limits = c("Median 0.1", "Median 0.3",
                                       "Model 0.1", "Model 0.3") ) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(1, 1, 2, 2) ) ) )
```



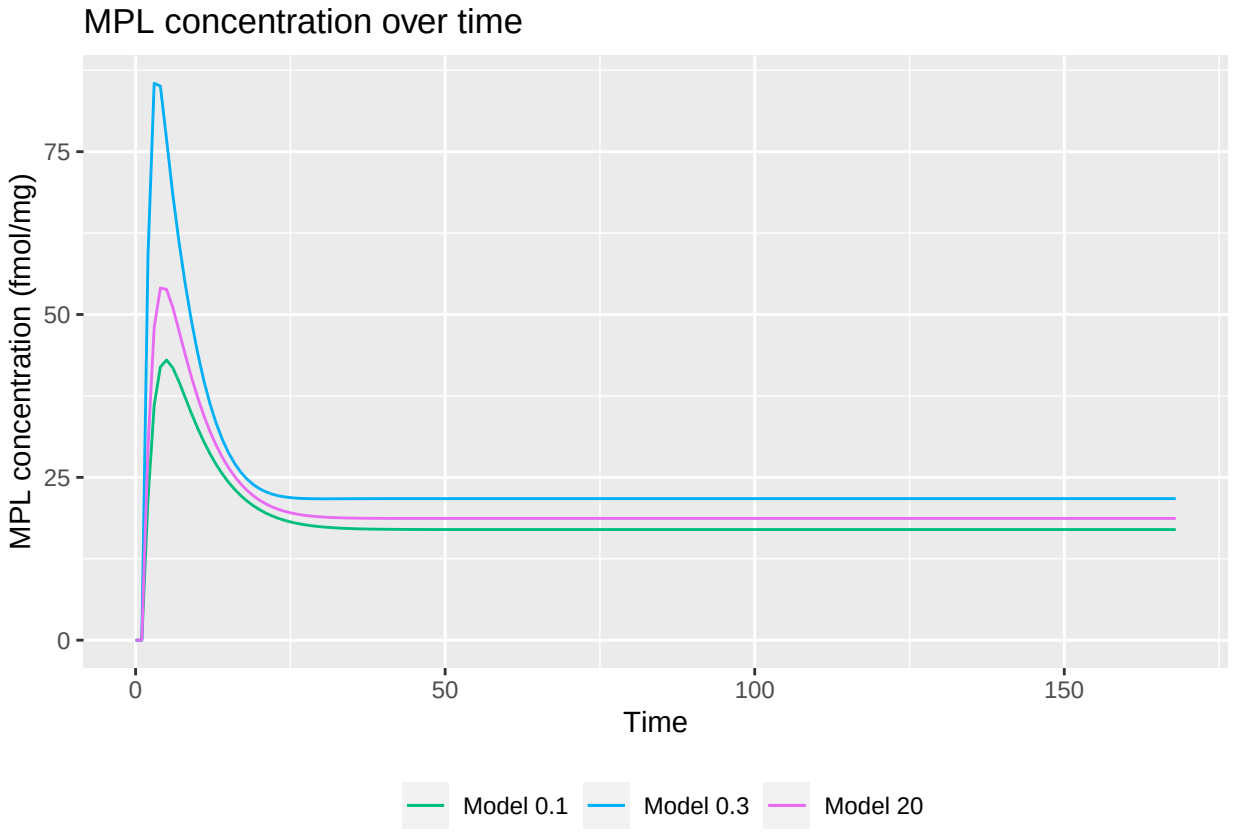
- [1] Why is it best practice to plot the median for the experimental data?168 >The median does not change with huge outliers, so the data is more reliable. If there is a significant difference, it will show.
- [2] How do the results of the simulations depend on the dose and concentration of the drug? >The dose is very important in determining how low the graph will go. The shape of the median lines is generally unaffected.
- [3] Are the results of the model in line with experimental data? >Yes, to some extent. The values that the experiment and the model end on is similar. But the values between the start and the end fluctuate a bit.

Assignment 2

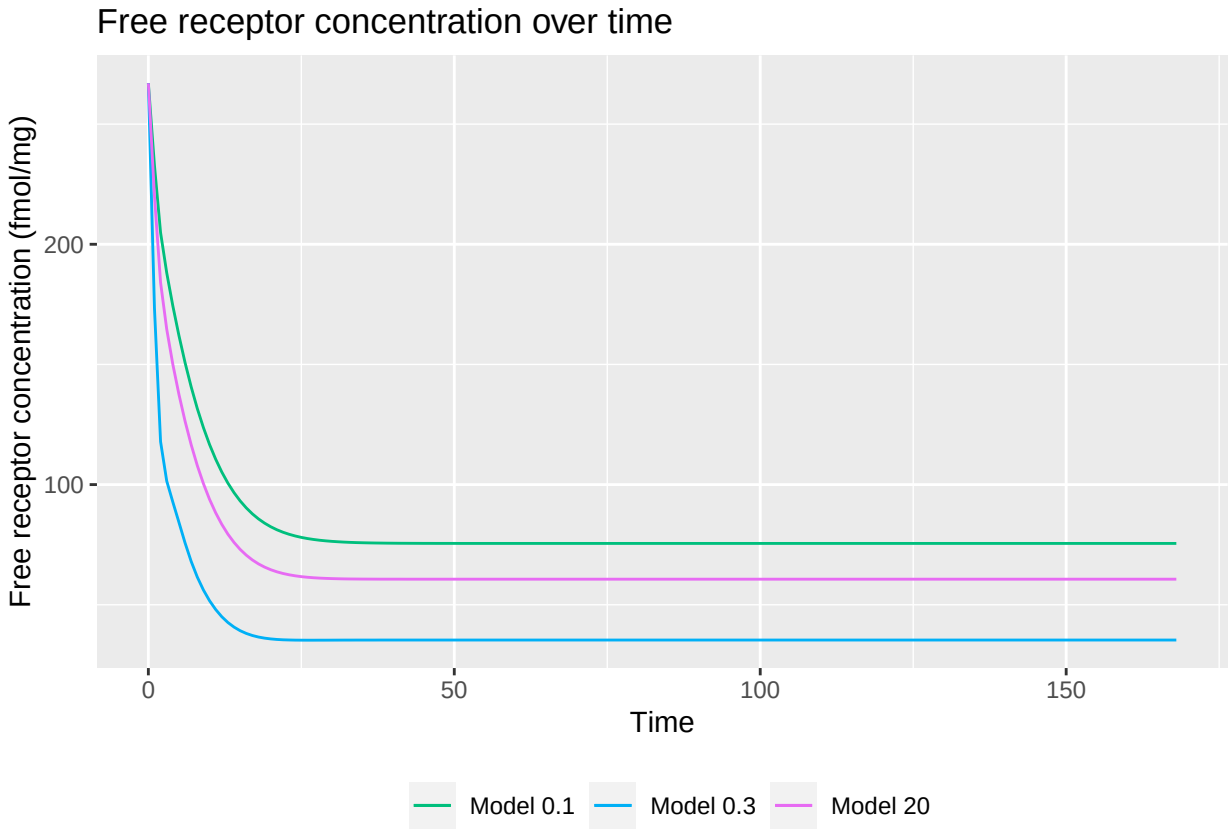
```
params$D <- (20 * 1000)/374.471
model_20 <- ode(times = times, y = state,
                parms = params, func = volume, method = "euler")
model_20 <- as.data.frame(model_20)

ggplot(data = MPL_data, mapping = aes(x = time, y = mRNA)) +
        geom_line(data = model_01, aes(color = "Model 0.1")) +
        geom_line(data = model_03, aes(color = "Model 0.3")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "Time", y = "mRNA (fmol/g)", title = "mRNA over time") +
        theme(legend.position = "bottom") +
        scale_colour_manual(name = "", values = group.cols[3:5],
                            limits = c("Model 0.1", "Model 0.3", "Model 20"))
```




```
ggplot(data = MPL_data, mapping = aes(x = time, y = MPL_conc)) +
        geom_line(data = model_01, aes(color = "Model 0.1")) +
        geom_line(data = model_03, aes(color = "Model 0.3")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "Time", y = "MPL concentration (fmol/mg)",
             title = "MPL concentration over time") +
        theme(legend.position = "bottom") +
        scale_colour_manual(name = "", values = group.cols[3:5],
                            limits = c("Model 0.1", "Model 0.3", "Model 20"))
```

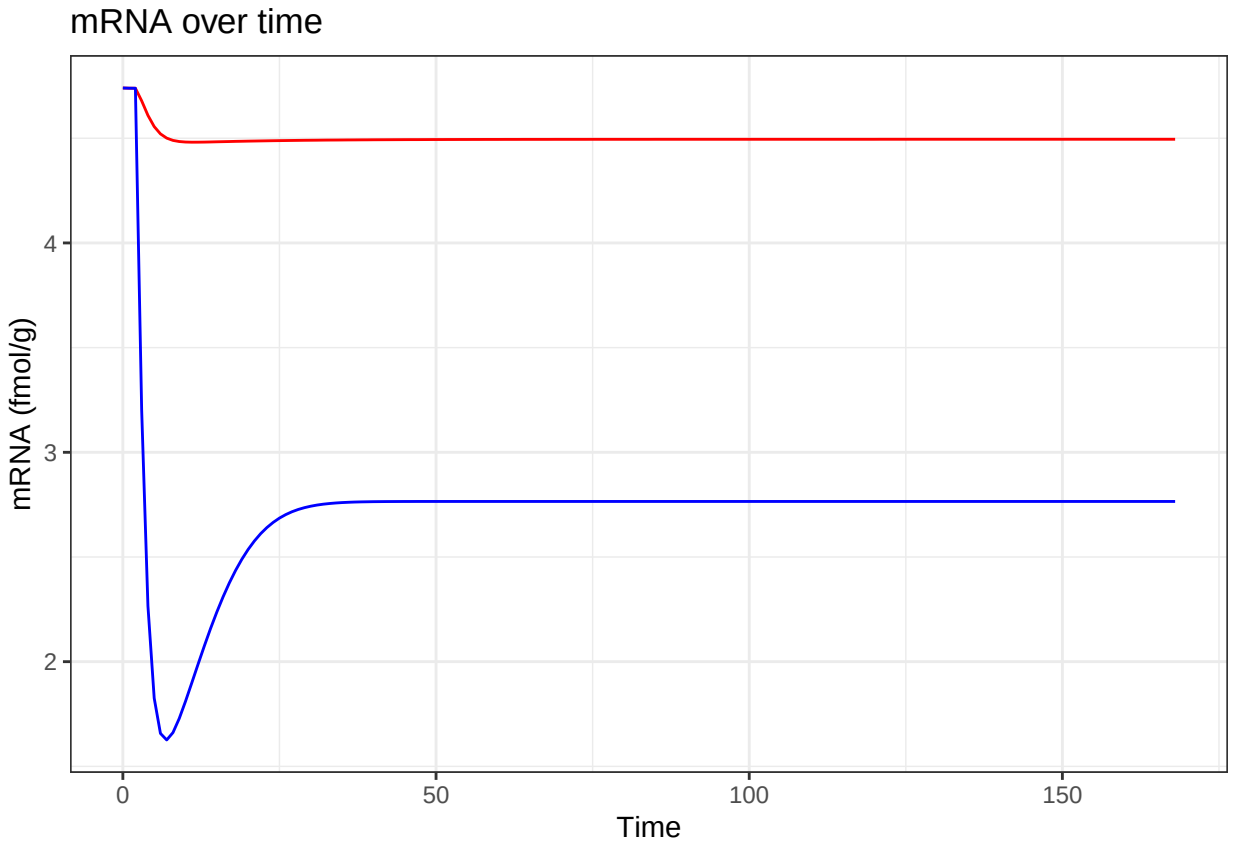



```
ggplot(data = MPL_data, mapping = aes(x = time, y = Free_receptor)) +
        geom_line(data = model_01, aes(color = "Model 0.1")) +
        geom_line(data = model_03, aes(color = "Model 0.3")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "Time", y = "Free receptor concentration (fmol/mg)",
             title = "Free receptor concentration over time") +
        theme(legend.position = "bottom") +
        scale_colour_manual(name = "", values = group.cols[3:5],
                            limits = c("Model 0.1", "Model 0.3", "Model 20"))
```



- [1] What would be the time course concentration of the activated drug-receptor complex if there was no auto-regulation of glucocorticoid receptor, i.e. if there was no effect of drug on the synthesis of the receptor mRNA? What formula needs to be changed?

```
receptor_noDrugs <- function(t, y, parms){
  with(as.list(c(parms, y)),{
    delta.mRNA_R <- k.s_Rm * (1 - ( MPL_conc / (IC.50_Rm + MPL_conc) ) ) - k.d_Rm * mRNA
    delta.R <- k.s_R * mRNA + R.f * k.re * MPL_conc -
            k.on  * Free_receptor - k.d_R * Free_receptor
    delta.DR <- k.on * Free_receptor - k.T * DR
    delta.MPL_conc <- k.T * DR - k.re * MPL_conc
    return( list( c(delta.mRNA_R, delta.R, delta.DR, delta.MPL_conc ) ) )
  })
}

model_noDrugs <- as.data.frame(ode(times = times, y = state,
                 parms = params, func = receptor_noDrugs, method = "euler"))

ggplot(data = MPL_data, mapping = aes(x = time, y = mRNA)) +
        geom_line(data = model_noDrugs, linetype = "solid", color = "red") +
        geom_line(data = model_20, linetype = "solid", color = "blue") +
        labs(x = "Time", y = "mRNA (fmol/g)", title = "mRNA over time") +
        theme_bw()
```

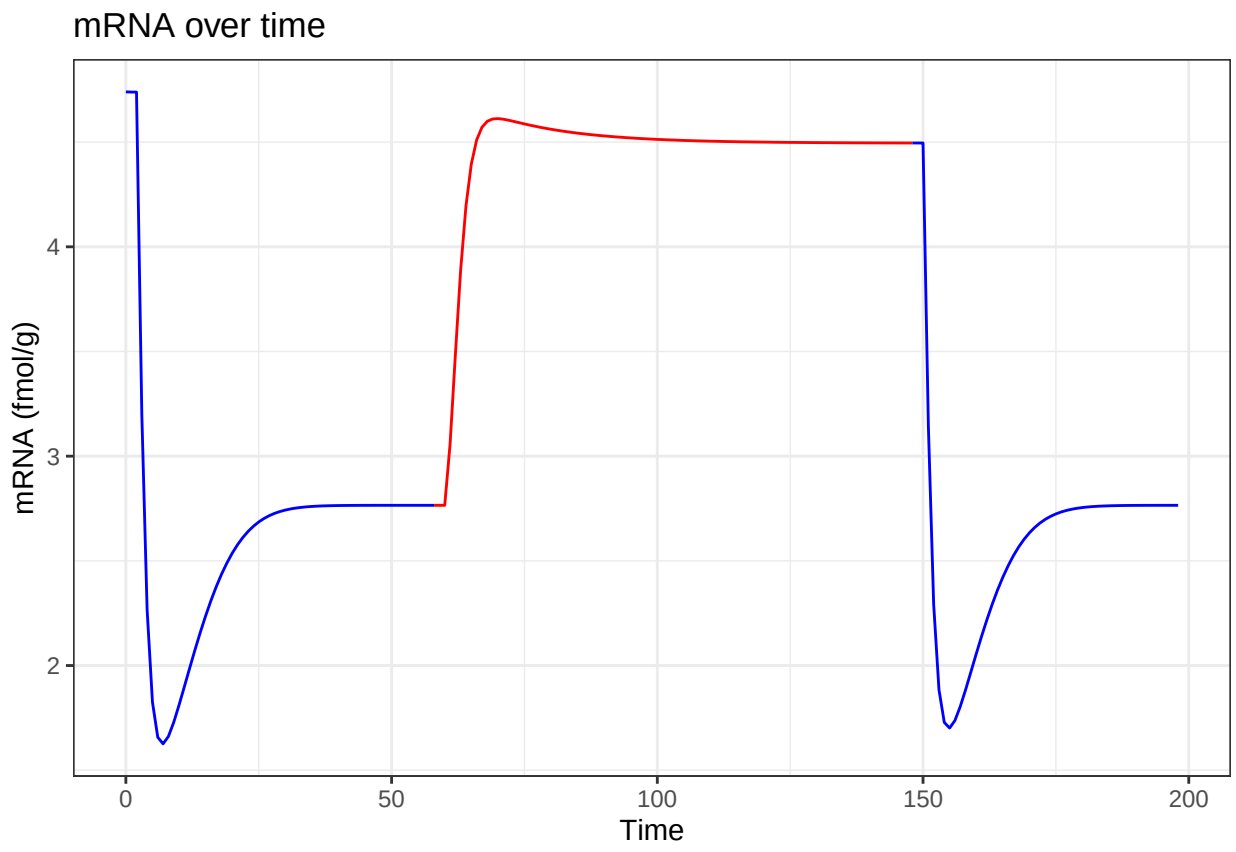


The figure above shows that when D is taken out of the equation, the mRNA concentration drops a bit and stays steady in that state. This line is shown in red. The blue line details the normal scenario in which the drug is working correctly with a dose of 20.

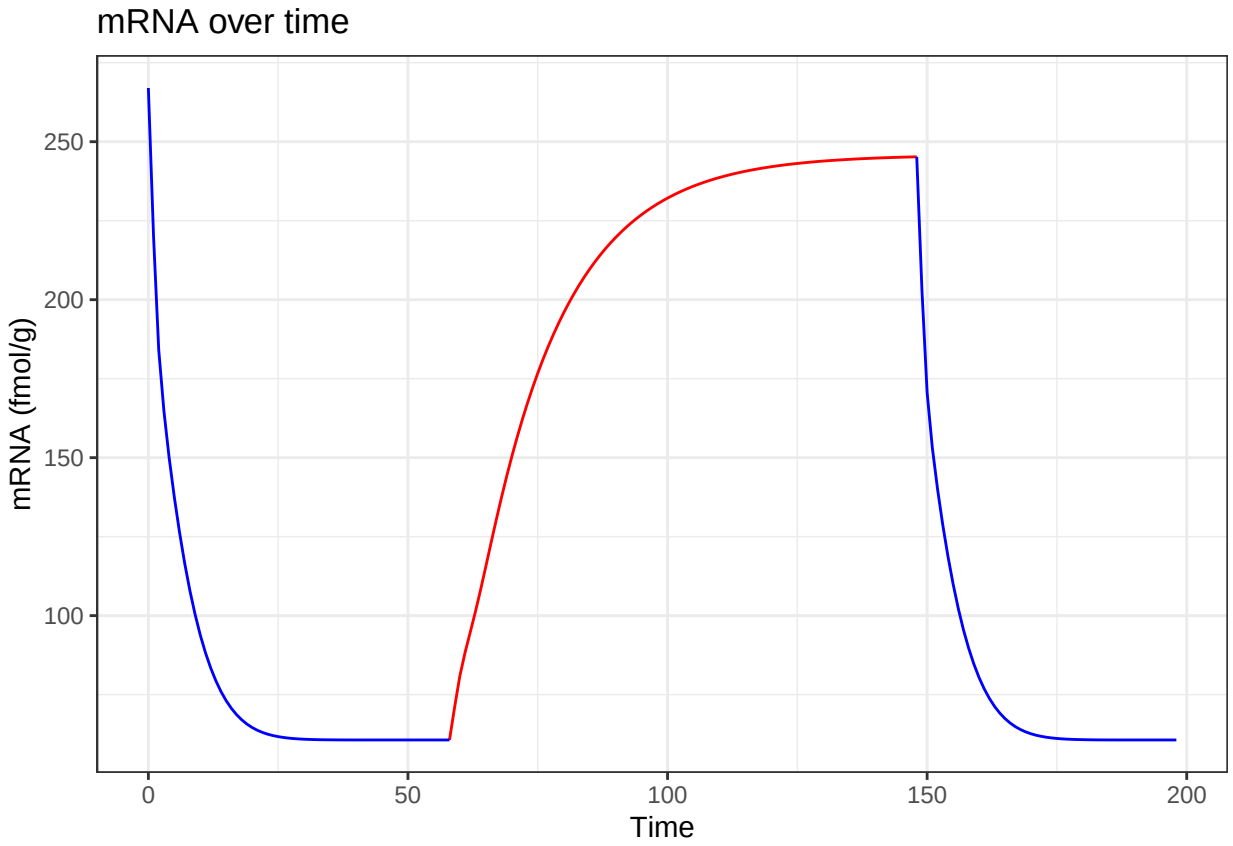
- [2] What is the time course of receptor and mRNA concentrations when the drug treatment is stopped? So after the steady state is reached (at time t_steady), D should be set to zero and the simulation should continue from time t_steady till the new steady state is reached (t_steady_second).

```
state <- c(
        mRNA = model_20$mRNA[model_20$time == 58],
        Free_receptor = model_20$Free_receptor[model_20$time == 58],
        DR = model_20$DR[model_20$time == 58],
        MPL_conc = model_20$MPL_conc[model_20$time == 58]
)

times <- seq(58, 148, by = 1)

model_noDrugs_fromSteady <- as.data.frame(ode(times = times, y = state,
                 parms = params, func = receptor_noDrugs, method = "euler"))

state <- c(
        mRNA = model_noDrugs_fromSteady$mRNA[model_noDrugs_fromSteady$time == 148],
        Free_receptor = model_noDrugs_fromSteady$Free_receptor[model_noDrugs_fromSteady$time == 148],
        DR = model_noDrugs_fromSteady$DR[model_noDrugs_fromSteady$time == 148],
        MPL_conc = model_noDrugs_fromSteady$MPL_conc[model_noDrugs_fromSteady$time == 148]
)

times <- seq(148, 198, by = 1)
```

```
model_Drugs_fromSteady <- as.data.frame(ode(times = times, y = state,
                 parms = params, func = volume, method = "euler"))

ggplot(data = MPL_data, mapping = aes(x = time, y = mRNA)) +
        geom_line(data = model_noDrugs_fromSteady, linetype = "solid", color = "red") +
        geom_line(data = model_Drugs_fromSteady, linetype = "solid", color = "blue") +
        geom_line(data = model_20[0:59,], linetype = "solid", color = "blue") +
        labs(x = "Time", y = "mRNA (fmol/g)", title = "mRNA over time") +
        theme_bw()
```




```
ggplot(data = MPL_data, mapping = aes(x = time, y = Free_receptor)) +
        geom_line(data = model_noDrugs_fromSteady, linetype = "solid", color = "red") +
        geom_line(data = model_Drugs_fromSteady, linetype = "solid", color = "blue") +
        geom_line(data = model_20[0:59,], linetype = "solid", color = "blue") +
        labs(x = "Time", y = "mRNA (fmol/g)", title = "mRNA over time") +
        theme_bw()
```



The red part of the line indicates the period where there is no drug present in the system. The blue parts indicate an administration of a single dose of 20 ng/ml.

- [3] Different corticosteroids show different association rates from receptors (kon) 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 kon and kre (consider 2 and 5 times increase and decrease of both parameters separately) on the receptor and mRNA dynamics? Adjust kon and kre 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, 0.003292 *and 0.003295*. 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, 0.572 *and 0.575*. The results should be compared to the basic scenario when kre= 0.57.

```
times <- seq(0, 200, by = 1)

state <- c(
        mRNA = 4.74, # fmol / g liver, basisniveau concentratie receptor mRNA
        Free_receptor = 267, # fmol/mg protein, basisniveau concentratie vrije receptor
        DR = 0, # fmol/mg protein, dichtheid MPL
        MPL_conc = 0 # fmol/mg protein, hoeveelheid MPL
)

## Create the colours
group.cols <- hue_pal()(4)
## Assign each colour for legibility
colours <- c("Median 0.1" = group.cols[1], "Median 0.3" = group.cols[2],
             "Model 0.1" = group.cols[3], "Model 0.3" = group.cols[4])

params$k.on <- 0.0039/5
```

```r
model_k.on_min5 <- as.data.frame(ode(times = times, y = state,
                  parms = params, func = volume, method = "euler"))

params$k.on <- 0.0039/2

model_k.on_min2 <- as.data.frame(ode(times = times, y = state,
                  parms = params, func = volume, method = "euler"))

params$k.on <- 0.0039*2

model_k.on_plus2 <- as.data.frame(ode(times = times, y = state,
                  parms = params, func = volume, method = "euler"))

params$k.on <- 0.0039*5

model_k.on_plus5 <- as.data.frame(ode(times = times, y = state,
                  parms = params, func = volume, method = "euler"))

ggplot(data = MPL_data, mapping = aes(x = time, y = mRNA)) +
        geom_line(data = model_k.on_min5, aes(color = "Model 0.1")) +
        geom_line(data = model_k.on_min2, aes(color = "Model 0.3")) +
        geom_line(data = model_k.on_plus2, aes(color = "Model 20")) +
        geom_line(data = model_k.on_plus5, aes(color = "Model 20")) +
        labs(x = "Time", y = "mRNA (fmol/g)", title = "mRNA over time") +
        theme(legend.position = "bottom") +
        scale_colour_manual(name = "", values = group.cols[3:5],
                            limits = c("Model 0.1", "Model 0.3", "Model 20"))
```