Detailed Analysis

Lisa Hu, Niek Scholten

```
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)
```

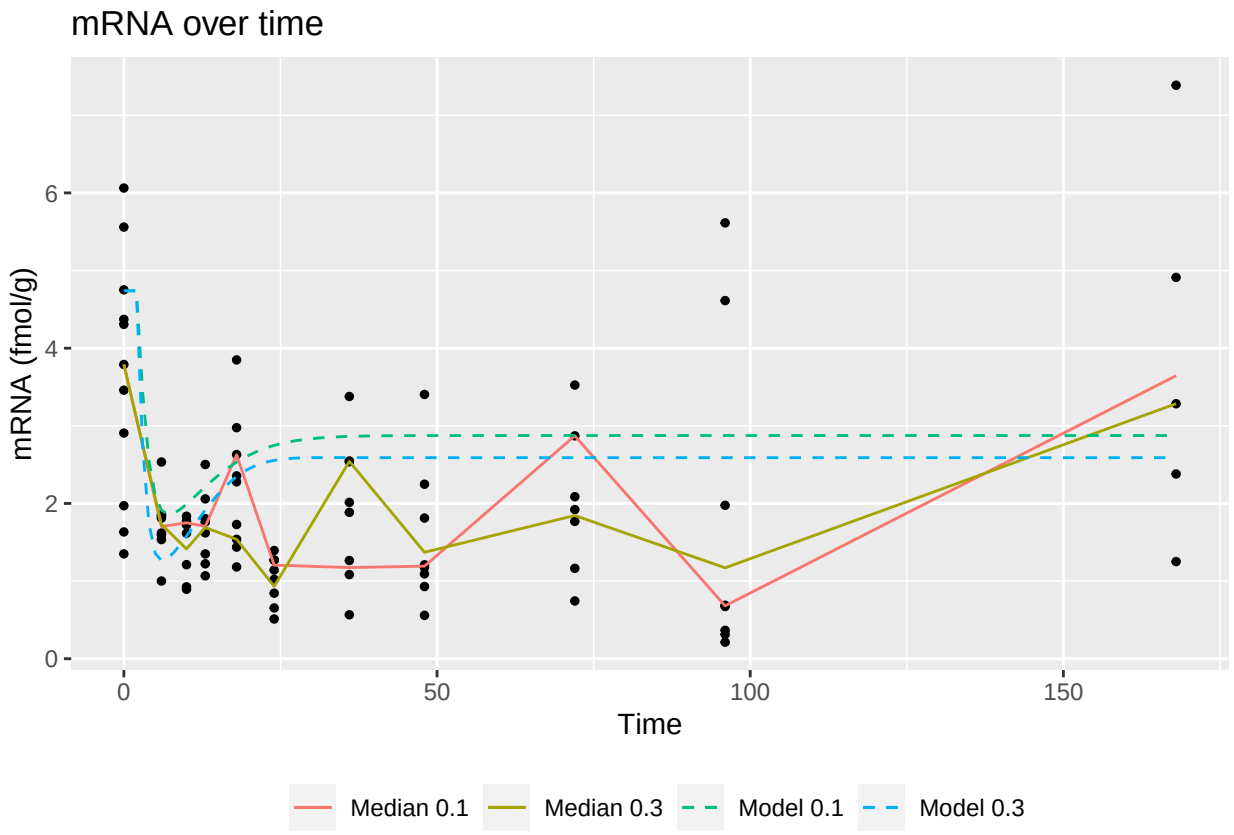
```
##   dose time MPL_conc   mRNA Free_receptor
## 1  0.0    0    0.000 3.7900        292.95
## 2  0.1    6   11.180 1.7025        124.70
## 3  0.3    6   31.295 1.7295         97.90
## 4  0.1   10   12.335 1.7515        157.80
## 5  0.3   10   36.960 1.4140         69.55
## 6  0.1   13   11.945 1.7045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

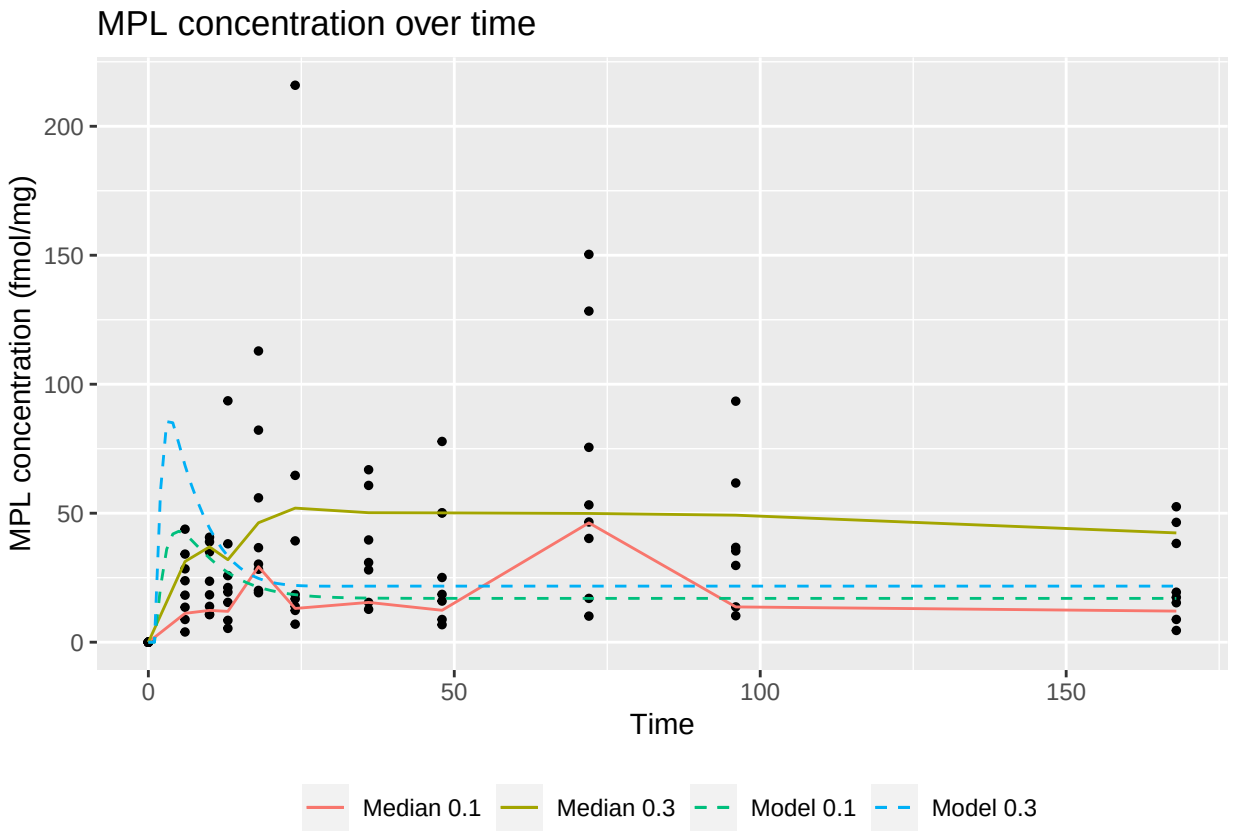
```
state <- c(
        mRNA = 4.74, # fmol / g liver, basisniveau concentratie receptor mRNA
        Free_receptor = 267, # fmol/mg protein, basisniveau concentratie vrije receptor
        DR = 0, # fmol/mg protein, dichtheid MPL
        MPL_conc = 0 # fmol/mg protein, hoeveelheid MPL
)

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

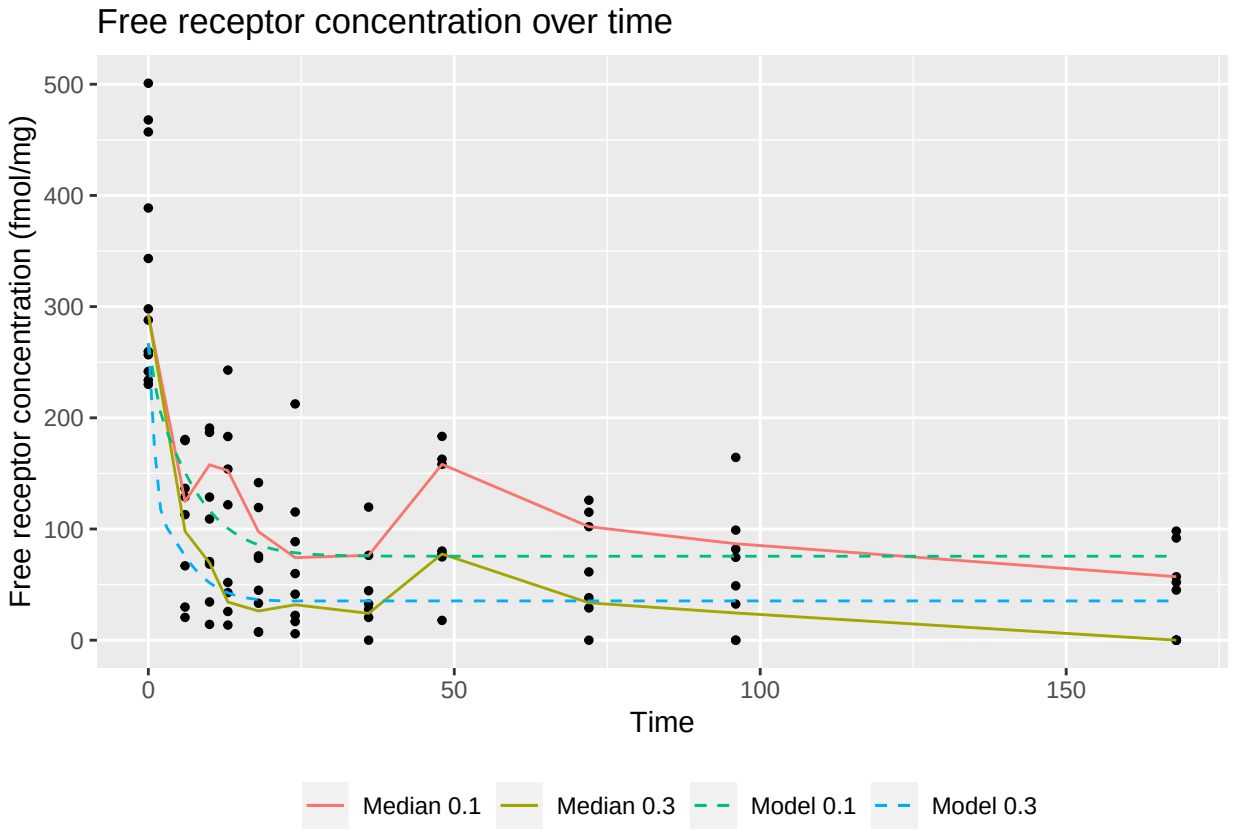
```
## Create the colours
group.cols <- hue_pal()(5)
## Assign each colour for legibility
colours <- c("Median 0.1" = group.cols[1], "Median 0.3" = group.cols[2],
             "Model 0.1" = group.cols[3], "Model 0.3" = group.cols[4],
             "Model 20" = group.cols[5])
ggplot(data = MPL_data, mapping = 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) ) ) )
```



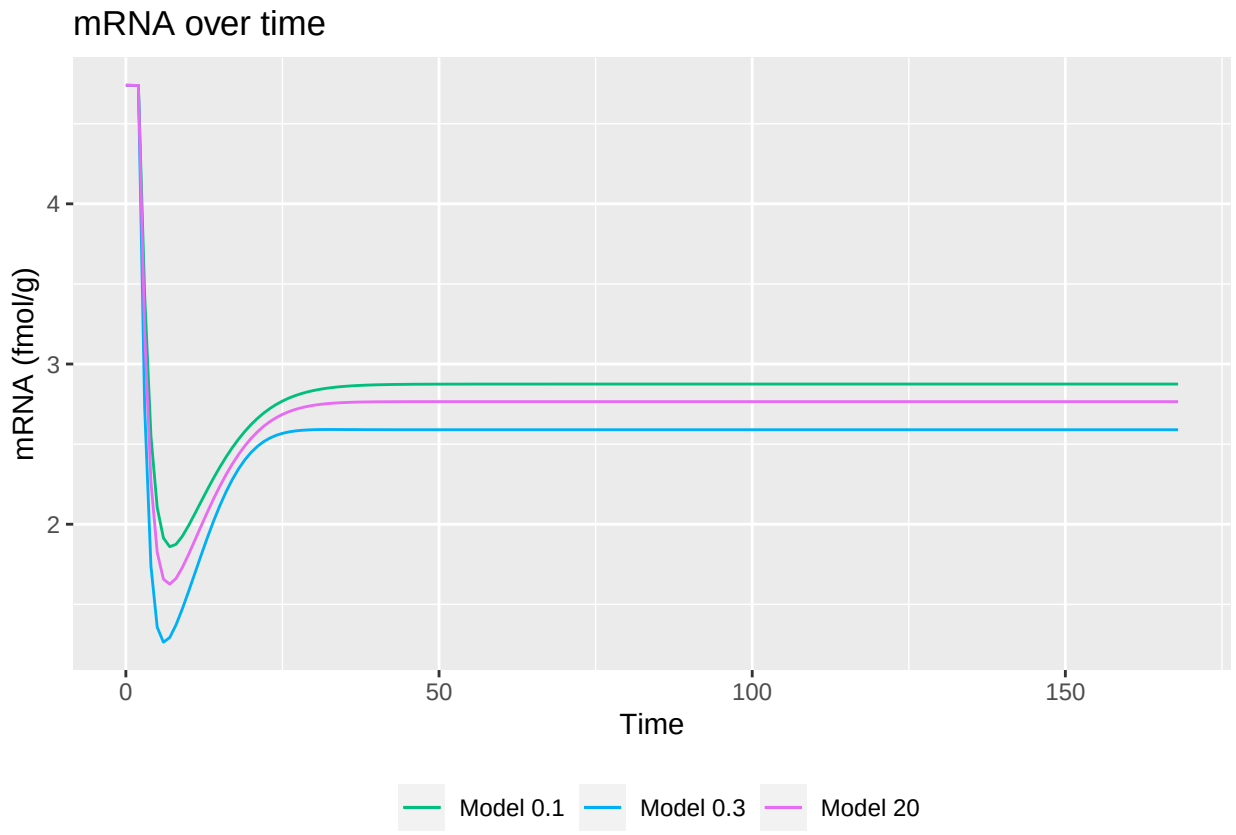

```
ggplot(data = MPL_data, mapping = aes(x = time, y = Free_receptor)) +
        geom_point(size = 1) +
        geom_line(data = median_01, aes(color ="Median 0.1")) +
        geom_line(data = median_03, aes(color = "Median 0.3")) +
        geom_line(data = model_01, linetype = "dashed", aes(color = "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) ) ) )
```



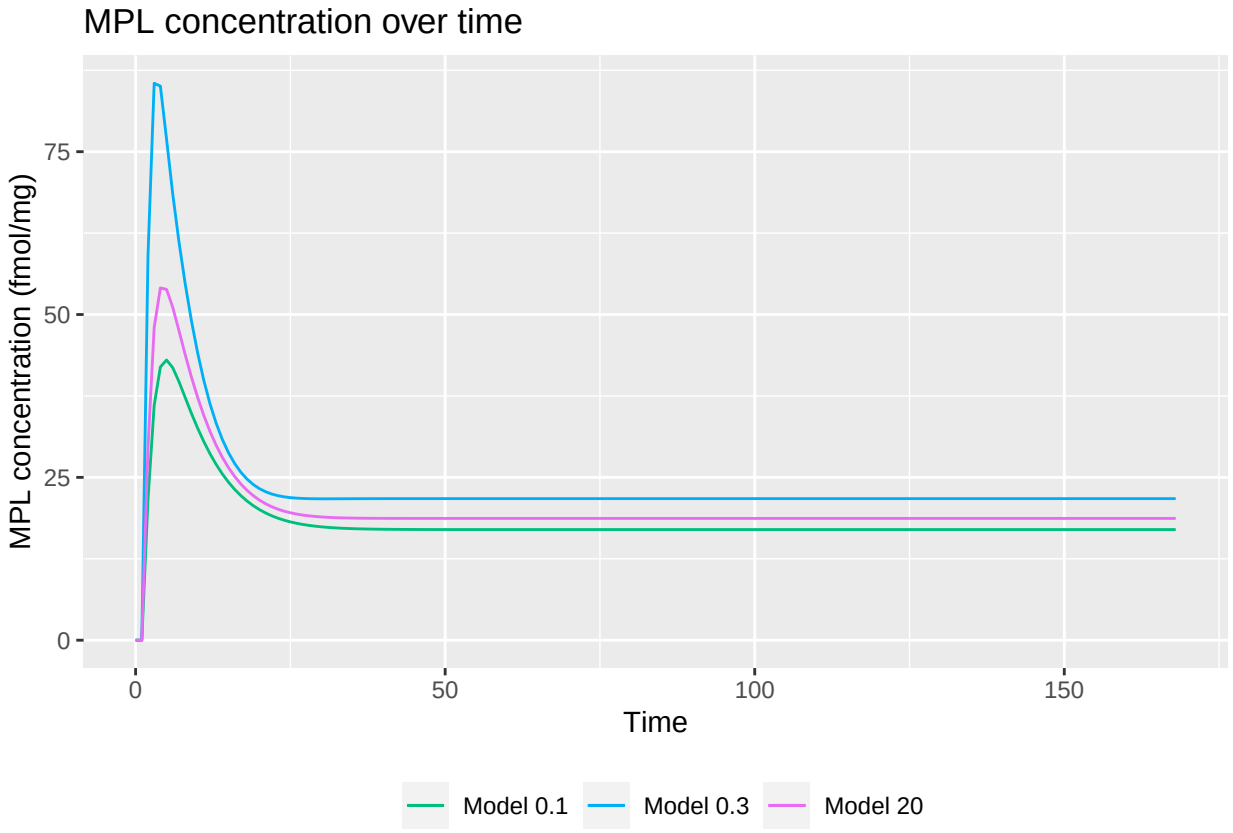
- [1] Why is it best practice to plot the median for the experimental data?168 >The median does not change with huge outliers, so the data is more reliable. If there is a significant difference, it will show.
- [2] How do the results of the simulations depend on the dose and concentration of the drug? >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

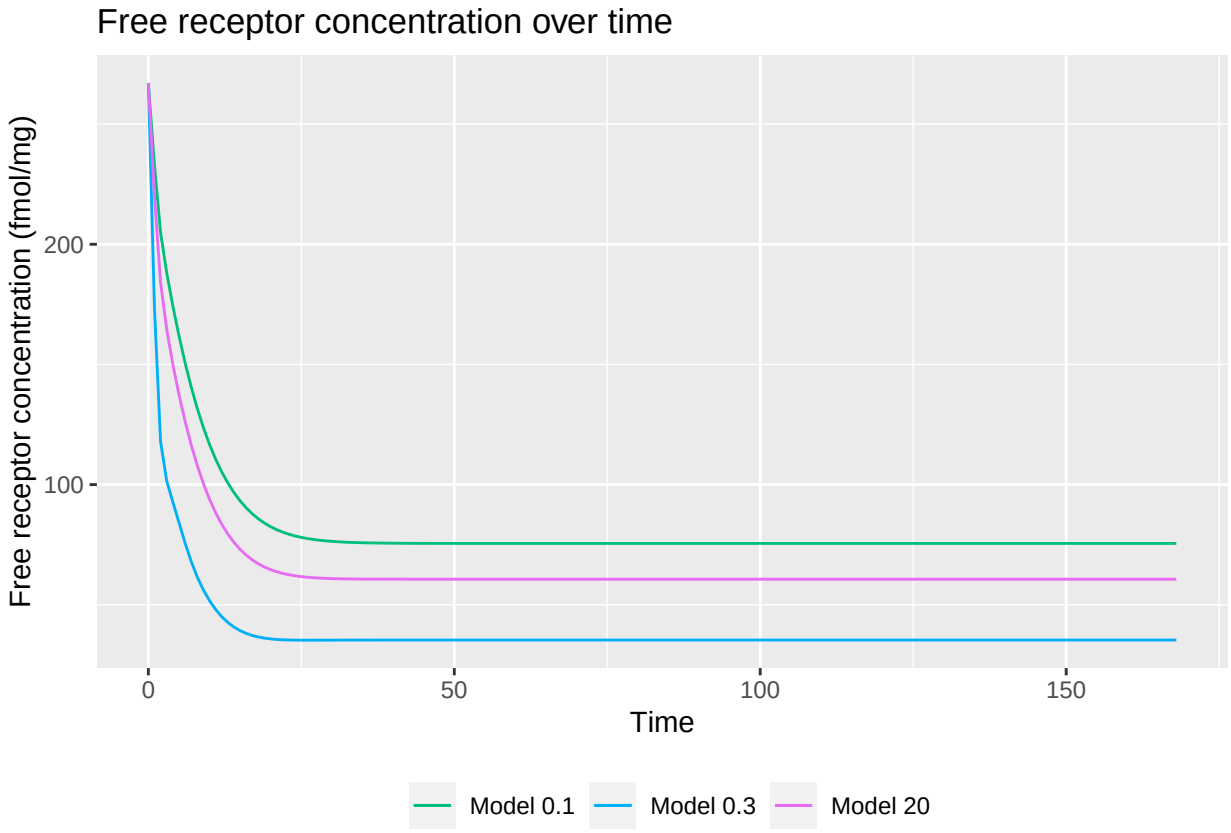
```
params$D <- (20 * 1000)/374.471
model_20 <- ode(times = times, y = state,
                parms = params, func = volume, method = "euler")
model_20 <- as.data.frame(model_20)

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"))
```

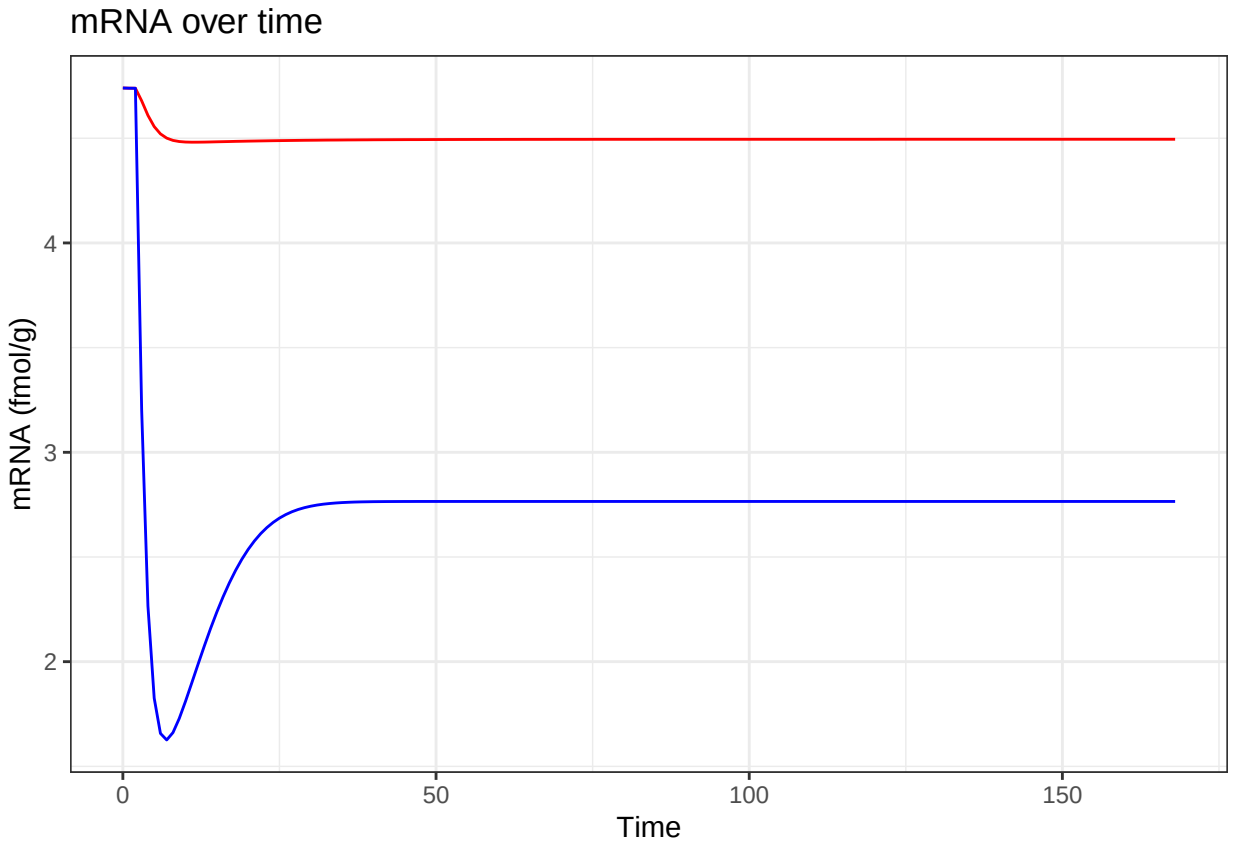



```
ggplot(data = MPL_data, mapping = aes(x = time, y = Free_receptor)) +
        geom_line(data = model_01, aes(color = "Model 0.1")) +
        geom_line(data = model_03, aes(color = "Model 0.3")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "Time", y = "Free receptor 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()
```

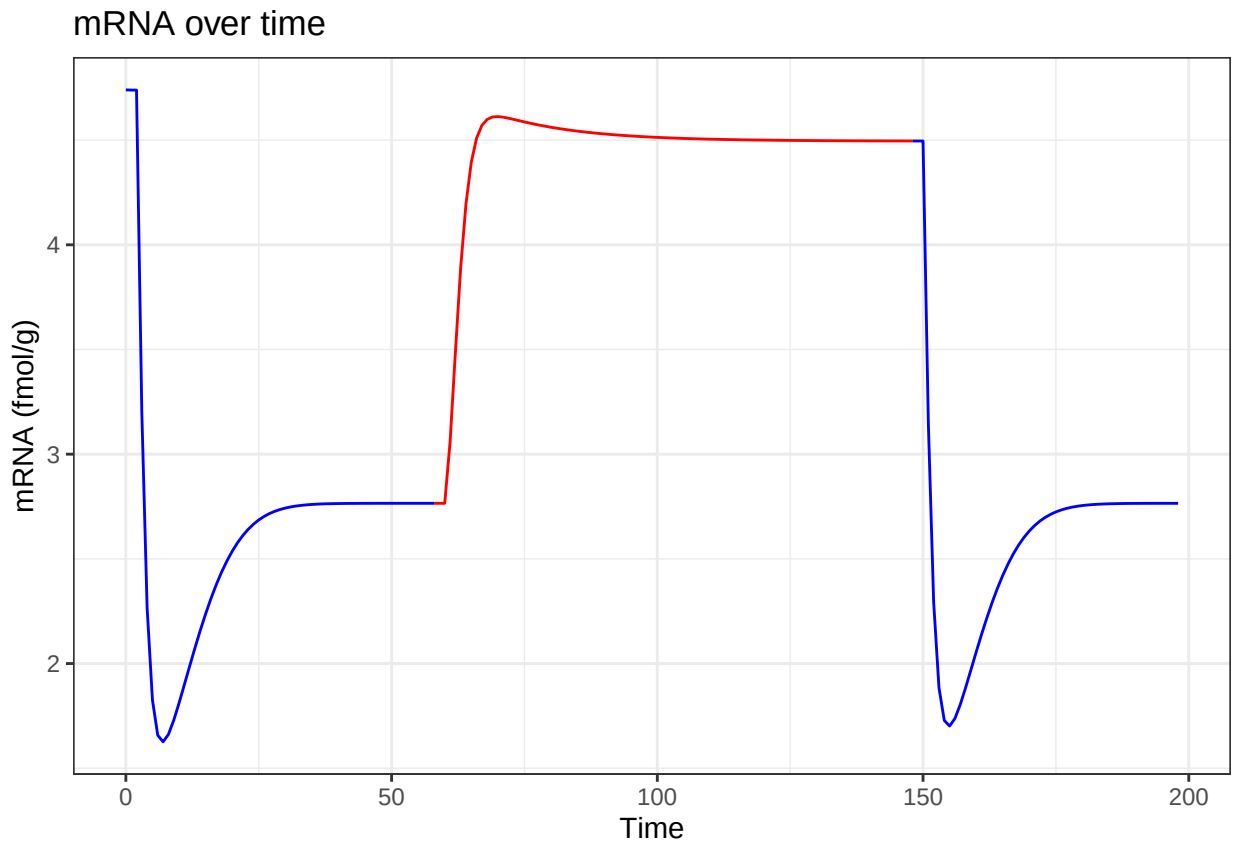


The figure above shows that when D is taken out of the equation, the mRNA concentration drops a bit and stays steady in that state. This line is shown in red. The blue line details the normal scenario in which the drug is working correctly with a dose of 20.

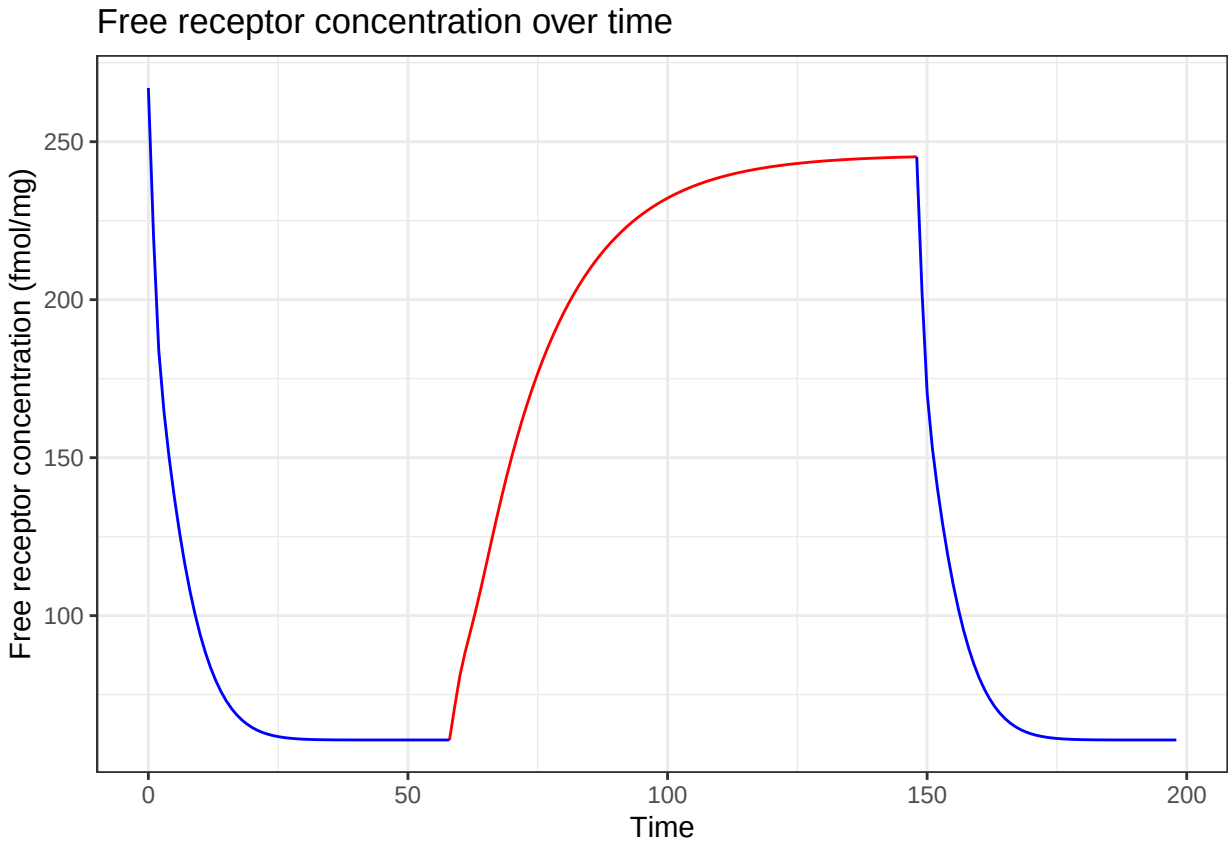
- [2] What is the time course of receptor and mRNA concentrations when the drug treatment is stopped? So after the steady state is reached (at time t_steady), D should be set to zero and the simulation should continue from time t_steady till the new steady state is reached (t_steady_second).

```
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 = "Free receptor concentration (fmol/mg)", title = "Free receptor concentrati
        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 (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, 0.003292 *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

$$k_{re}$$

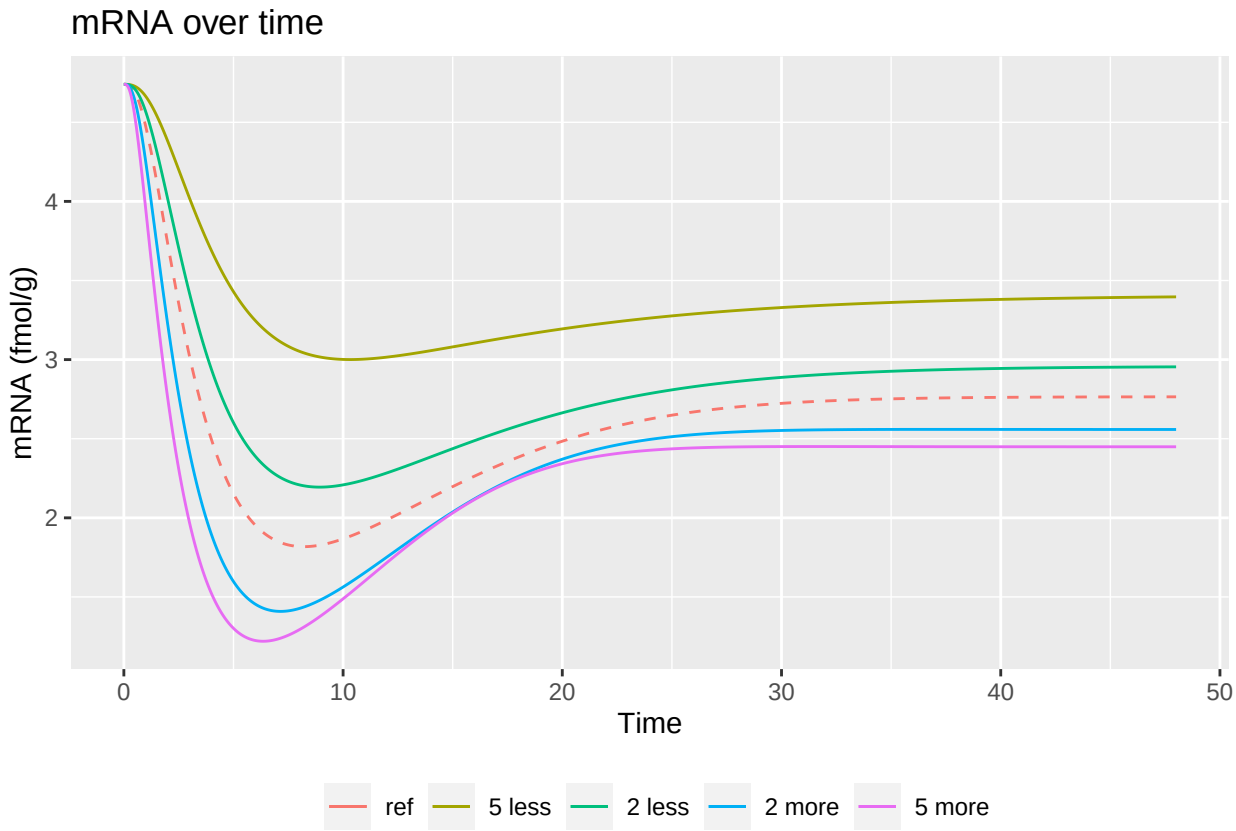
: 0.57/5, 0.57/2, 0.57*2 and 0.575*. The results should be compared to the basic scenario when

$$k_{re}$$

= 0.57.

```
times <- seq(0, 48, by=0.01)

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
)

params <- c(
        k.s_Rm = 2.90, # fmol/g liver/h, 0e 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 = (20 * 1000)/374.471 # nmol/L, als molgewicht[MPL] = 374.471 g/mol
)

## Create the colours

## Assign each colour for legibility
colours <- c("5 less" = group.cols[1], "2 less" = group.cols[2],
             "2 more" = group.cols[3], "5 more" = group.cols[4],
             "ref" = group.cols[5])

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

params$k.on <- 0.0039/5

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(mapping = aes(x = time, y = mRNA)) +
        geom_line(data = model_k.on_ref, linetype = "dashed", aes(color = "ref")) +
        geom_line(data = model_k.on_min5, aes(color = "5 less")) +
        geom_line(data = model_k.on_min2, aes(color = "2 less")) +
        geom_line(data = model_k.on_plus2, aes(color = "2 more")) +
        geom_line(data = model_k.on_plus5, aes(color = "5 more")) +
        labs(x = "Time", y = "mRNA (fmol/g)", title = "mRNA over time") +
        theme(legend.position = "bottom") +
        scale_colour_manual(name = "", values = group.cols,
                            limits = c("ref", "5 less", "2 less", "2 more", "5 more"))
```



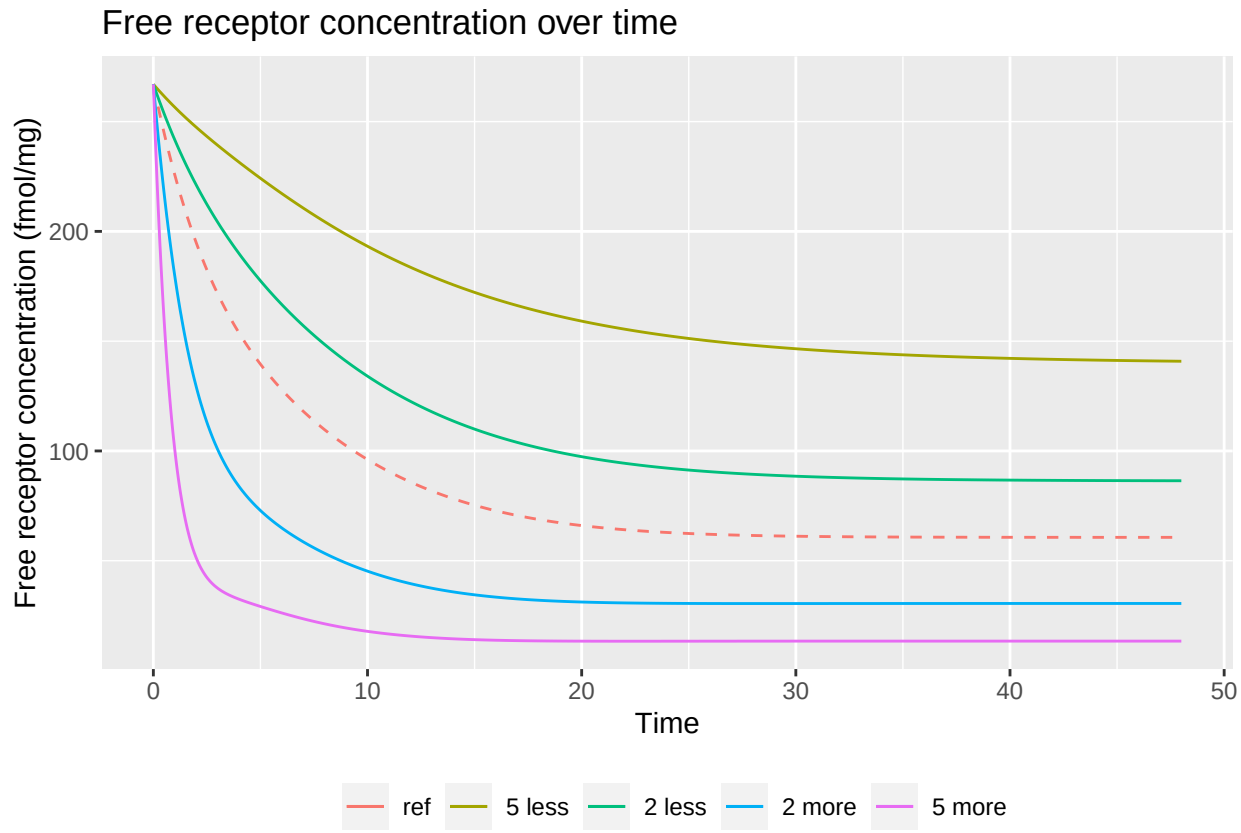

```
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(2, 1, 1, 1, 1) ) ) )
```

```
## $colour
## $title
## [1] ""
##
## $title.position
## NULL
##
## $title.theme
```

```
## NULL
##
## $title.hjust
## NULL
##
## $title.vjust
## NULL
##
## $label
## [1] TRUE
##
## $label.position
## NULL
##
## $label.theme
## NULL
##
## $label.hjust
## NULL
##
## $label.vjust
## NULL
##
## $keywidth
## NULL
##
## $keyheight
## NULL
##
## $direction
## NULL
##
## $override.aes
## $override.aes$linetype
## [1] 2 1 1 1 1
##
##
## $nrow
## NULL
##
## $ncol
## NULL
##
## $byrow
## [1] FALSE
##
## $reverse
## [1] FALSE
##
## $order
## [1] 0
##
## $available_aes
## [1] "any"
```

```
##
## $name
## [1] "legend"
##
## attr(,"class")
## [1] "guide"  "legend"
##
## attr(,"class")
## [1] "guides"
```

```
ggplot(mapping = aes(x = time, y = Free_receptor)) +
        geom_line(data = model_k.on_ref, linetype = "dashed", aes(color = "ref")) +
        geom_line(data = model_k.on_min5, aes(color = "5 less")) +
        geom_line(data = model_k.on_min2, aes(color = "2 less")) +
        geom_line(data = model_k.on_plus2, aes(color = "2 more")) +
        geom_line(data = model_k.on_plus5, aes(color = "5 more")) +
        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,
                            limits = c("ref", "5 less", "2 less", "2 more", "5 more"))
```




```
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(2, 1, 1, 1, 1) ) ) )
```

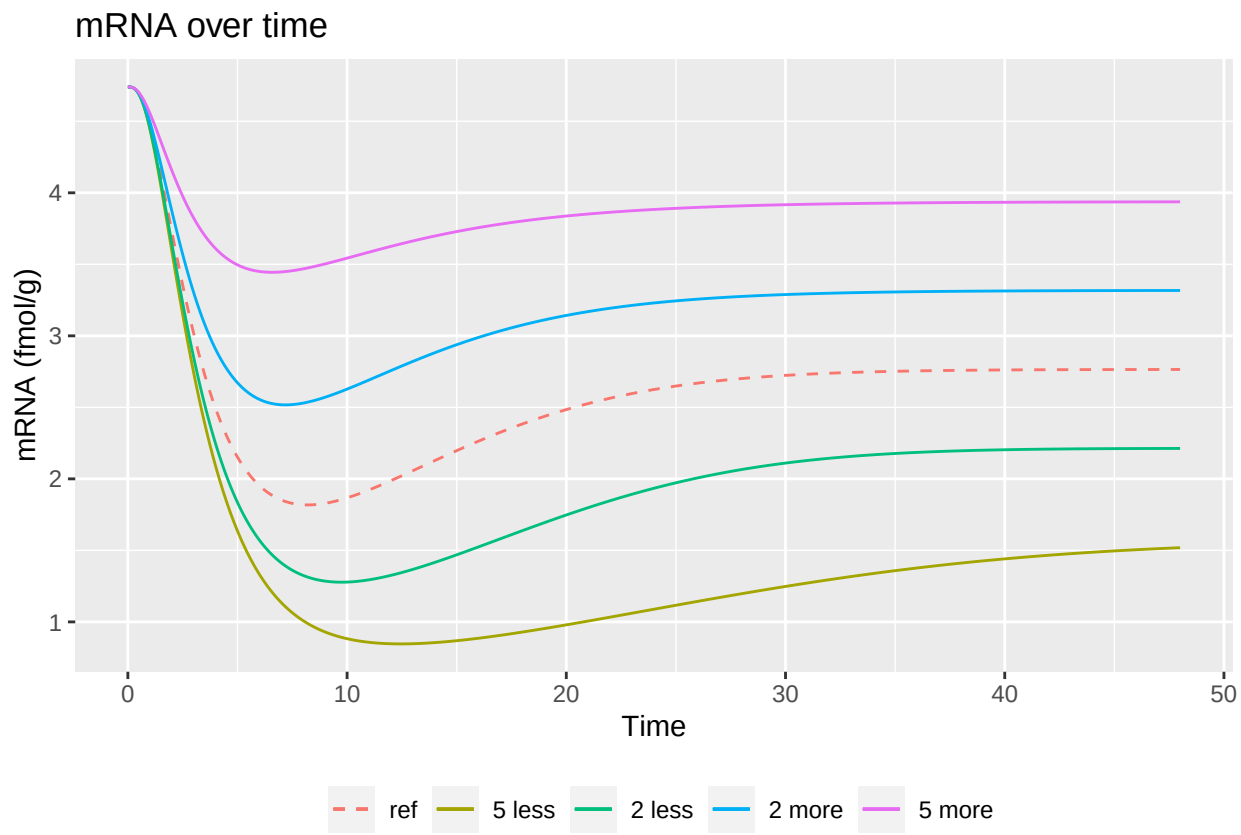
```
## $colour
## $title
## [1] ""
```

```
##
## $title.position
## NULL
##
## $title.theme
## NULL
##
## $title.hjust
## NULL
##
## $title.vjust
## NULL
##
## $label
## [1] TRUE
##
## $label.position
## NULL
##
## $label.theme
## NULL
##
## $label.hjust
## NULL
##
## $label.vjust
## NULL
##
## $keywidth
## NULL
##
## $keyheight
## NULL
##
## $direction
## NULL
##
## $override.aes
## $override.aes$linetype
## [1] 2 1 1 1 1
##
##
## $nrow
## NULL
##
## $ncol
## NULL
##
## $byrow
## [1] FALSE
##
## $reverse
## [1] FALSE
##
```

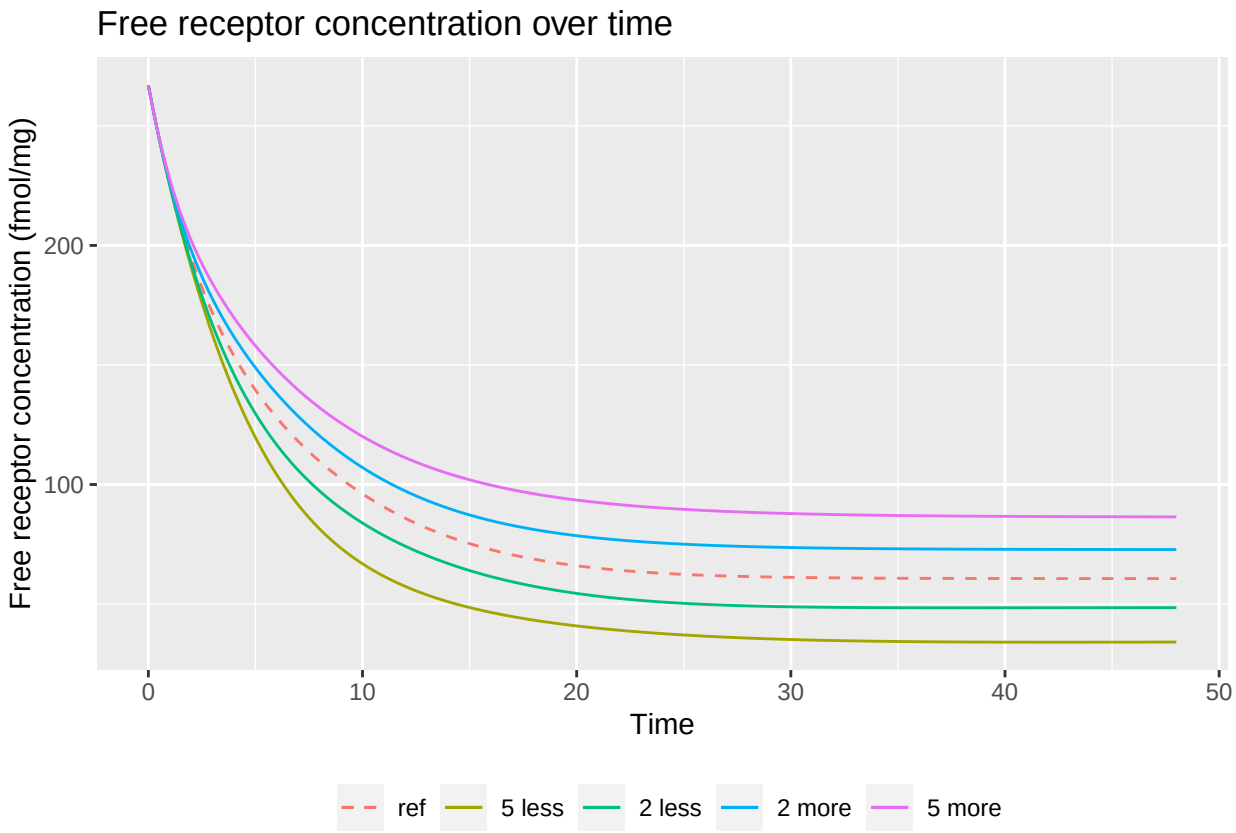
```
## $order
## [1] 0
##
## $available_aes
## [1] "any"
##
## $name
## [1] "legend"
##
## attr(,"class")
## [1] "guide"  "legend"
##
## attr(,"class")
## [1] "guides"
```

```
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 = (20 * 1000)/374.471 # nmol/L, als molgewicht[MPL] = 374.471 g/mol
)

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

params$k.re <- 0.57/5

model_k.re_min5 <- as.data.frame(ode(times = times, y = state,
                parms = params, func = volume, method = "euler"))

params$k.re <- 0.57/2

model_k.re_min2 <- as.data.frame(ode(times = times, y = state,
                parms = params, func = volume, method = "euler"))

params$k.re <- 0.57*2

model_k.re_plus2 <- as.data.frame(ode(times = times, y = state,
                parms = params, func = volume, method = "euler"))

params$k.re <- 0.57*5

model_k.re_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.re_ref, linetype = "dashed", aes(color = "ref")) +
        geom_line(data = model_k.re_min5, aes(color = "5 less")) +
```

```
        geom_line(data = model_k.re_min2, aes(color = "2 less")) +
        geom_line(data = model_k.re_plus2, aes(color = "2 more")) +
        geom_line(data = model_k.re_plus5, aes(color = "5 more")) +
        labs(x = "Time", y = "mRNA (fmol/g)", title = "mRNA over time") +
        theme(legend.position = "bottom") +
        scale_colour_manual(name = "", values = group.cols,
                            limits = c("ref", "5 less", "2 less", "2 more", "5 more")) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(2, 1, 1, 1, 1) ) ) )
```




```
ggplot(data = MPL_data, mapping = aes(x = time, y = Free_receptor)) +
        geom_line(data = model_k.re_ref, linetype = "dashed", aes(color = "ref")) +
        geom_line(data = model_k.re_min5, aes(color = "5 less")) +
        geom_line(data = model_k.re_min2, aes(color = "2 less")) +
        geom_line(data = model_k.re_plus2, aes(color = "2 more")) +
        geom_line(data = model_k.re_plus5, aes(color = "5 more")) +
        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,
                            limits = c("ref", "5 less", "2 less", "2 more", "5 more")) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(2, 1, 1, 1, 1) ) ) )
```



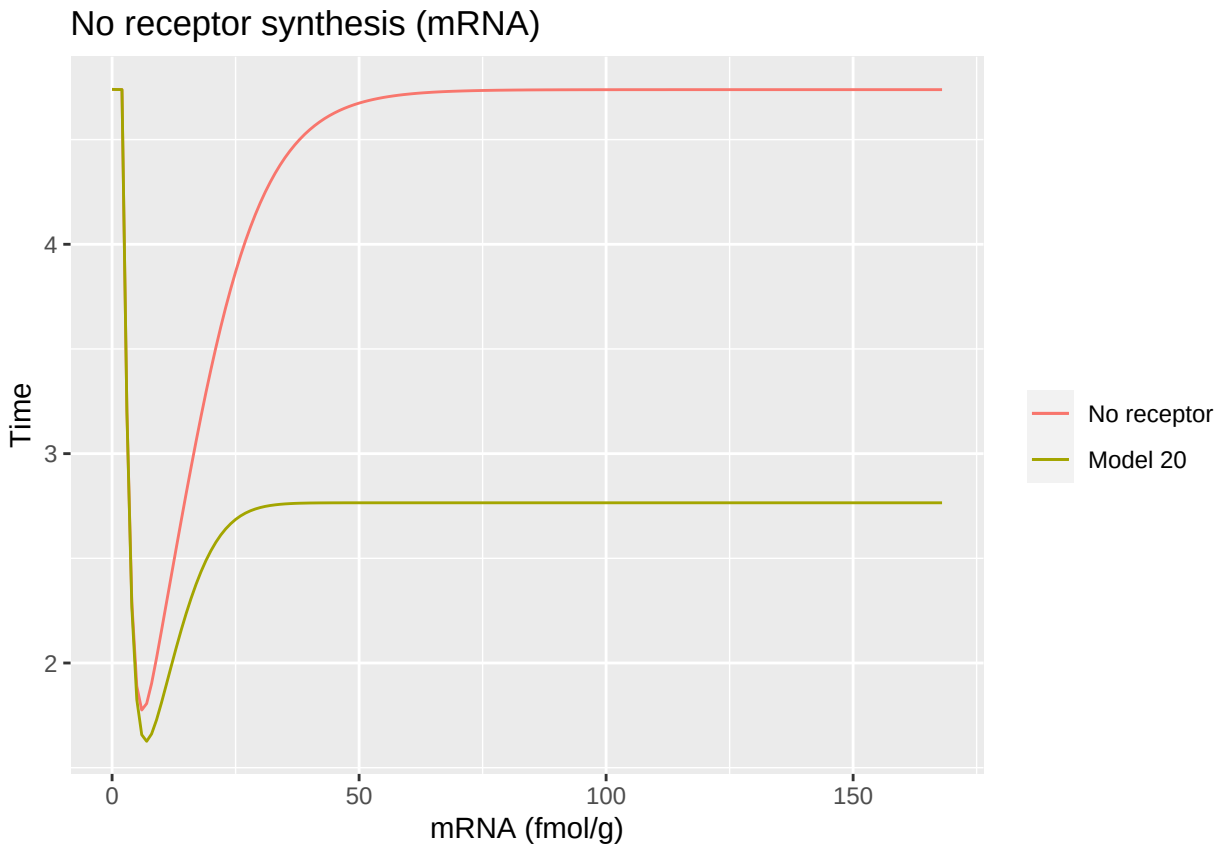
- [4] What would happen if the synthesis of the receptor was completely blocked? To simulate this situation,

$$k_{s_R}$$

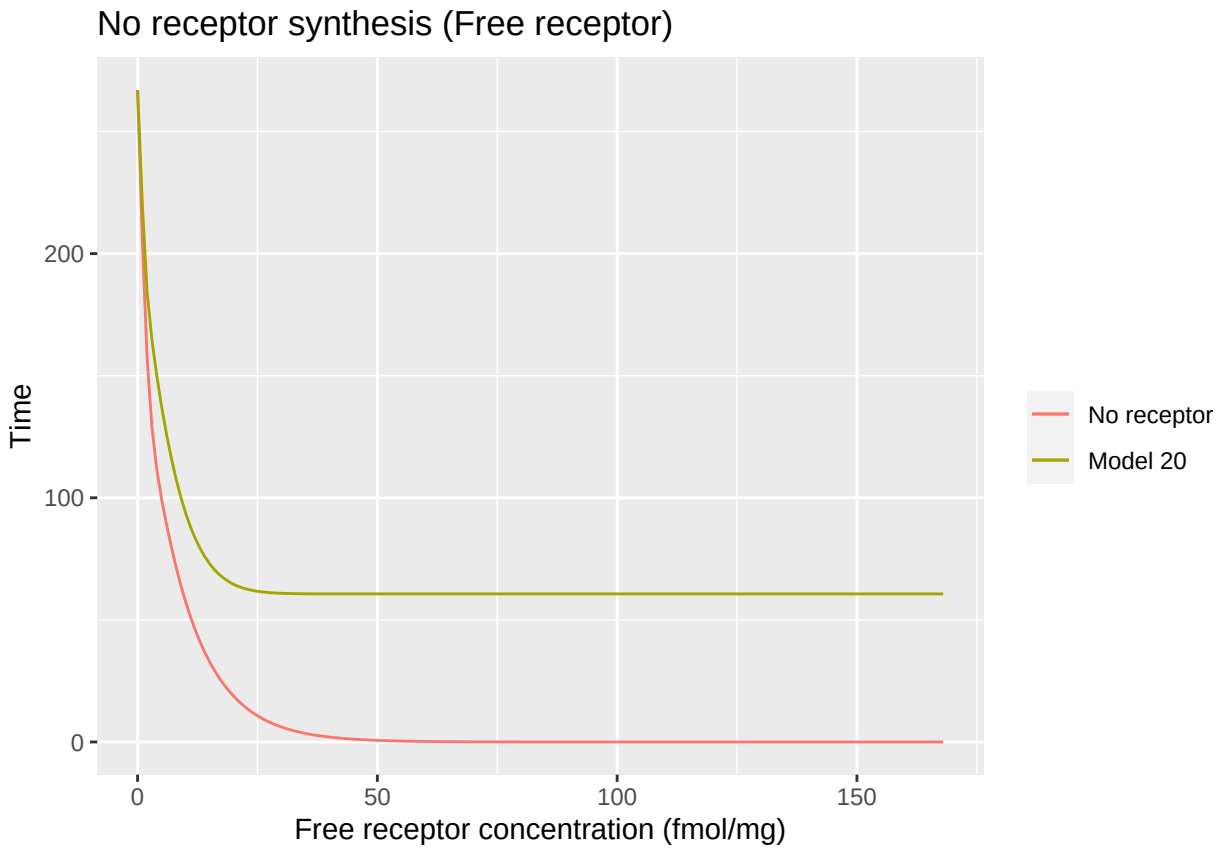
needs to be put to zero.

```
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 = 0, # 1e orde k voor aanmaak receptor
        D = (20 * 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
)
times <- seq(0, 168, by = 1)
no.Receptor <- as.data.frame(ode(times = times, y = state, parms = params,
                                 func = volume, method = "euler"))
```

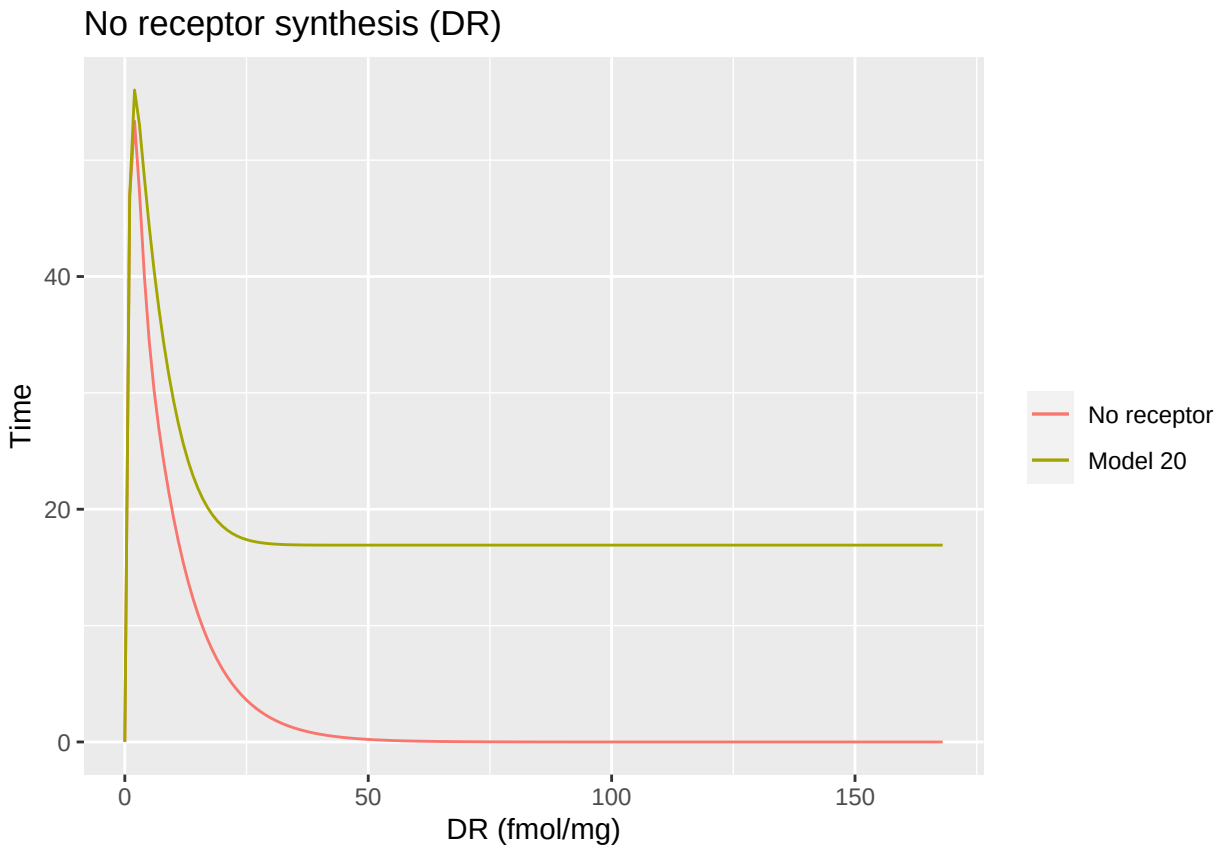
```
ggplot(data = no.Receptor, mapping = aes(x = time, y = mRNA)) +
        geom_line(aes(color = "No receptor")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "mRNA (fmol/g)", y = "Time", title = "No receptor synthesis (mRNA)") +
        scale_colour_manual(name = "", values = group.cols[1:2],
                            limits = c("No receptor", "Model 20"))
```



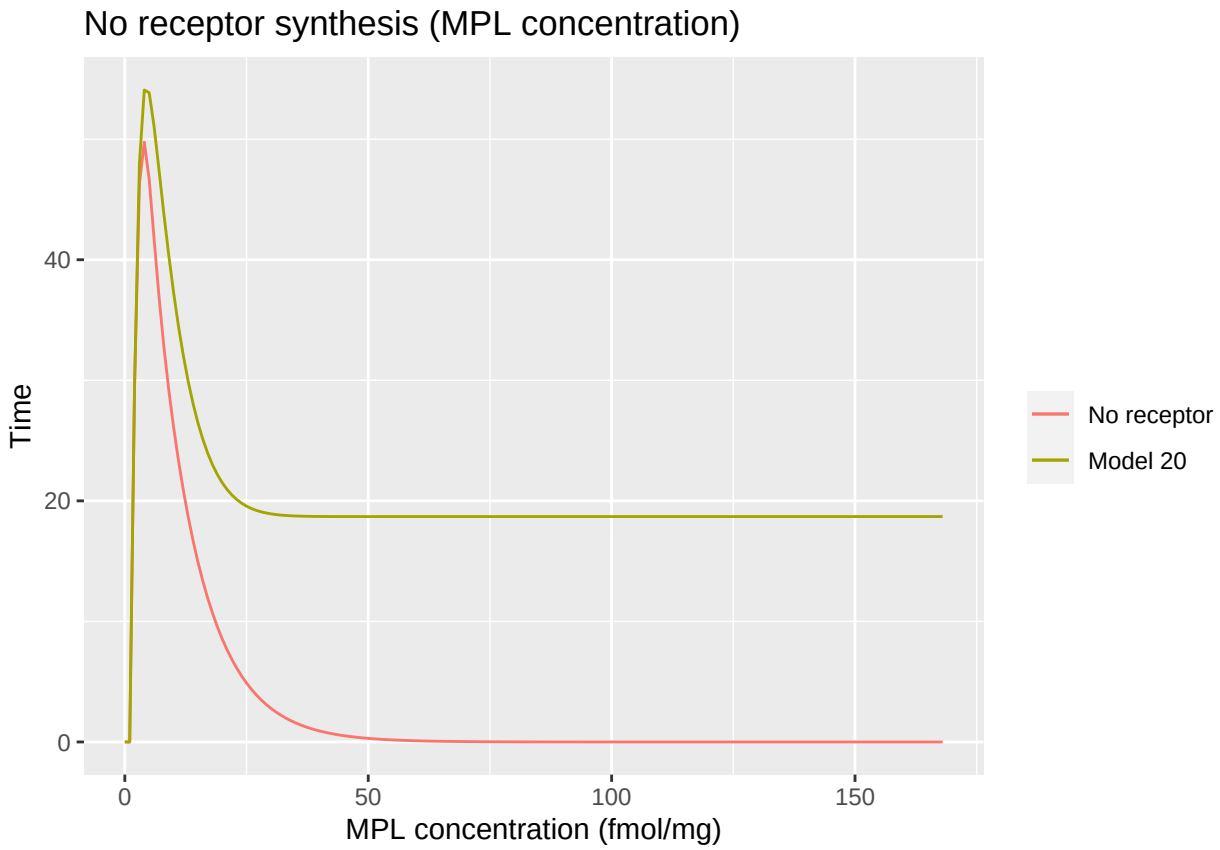

```
ggplot(data = no.Receptor, mapping = aes(x = time, y = Free_receptor)) +
        geom_line(aes(color = "No receptor")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "Free receptor concentration (fmol/mg)", y = "Time",
             title = "No receptor synthesis (Free receptor)") +
        scale_colour_manual(name = "", values = group.cols[1:2],
                            limits = c("No receptor", "Model 20"))
```




```
ggplot(data = no.Receptor, mapping = aes(x = time, y = DR)) +
        geom_line(aes(color = "No receptor")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "DR (fmol/mg)", y = "Time", title = "No receptor synthesis (DR)") +
        scale_colour_manual(name = "", values = group.cols[1:2],
                            limits = c("No receptor", "Model 20"))
```




```
ggplot(data = no.Receptor, mapping = aes(x = time, y = MPL_conc)) +
        geom_line(aes(color = "No receptor")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "MPL concentration (fmol/mg)", y = "Time",
             title = "No receptor synthesis (MPL concentration)") +
        scale_colour_manual(name = "", values = group.cols[1:2],
                            limits = c("No receptor", "Model 20"))
```


No receptor synthesis (MPL concentration)
Time
40
20
0
0
50
100
150
MPL concentration (fmol/mg)
No receptor
Model 20