

Week_Opdracht3

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Week Opdracht 3

Assignment 1

Code

```
library(deSolve)
library(ggplot2)

data <- read.csv("data/MPL.csv", na.strings = "NA")
median_MPL_01 <- median(data$MPL_conc[data$dose==0.1], na.rm=T)
median_MPL_03 <- median(data$MPL_conc[data$dose==0.3], na.rm=T)

# Define the parameters
volume_D <- median_MPL_03
nmol <- volume_D * 1000 * (1 / 374.477)
parameters <- c(Kd_Rm = 0.612, Kre = 0.57, Ks_Rm = 2.90, IC50_Rm = 26.2,
                Kd_R = 0.0572, Rf = 0.49, Kon= 0.00329,
                Kt = 0.63, D=nmol, Ks_r = 3.22)

# The model we will use
model <- function(t, y, parms){
  with(as.list(c(y, parms)),{
    # Concentratie Receptor mRNA
    dmRNA.R_dt <- Ks_Rm * (1 - (DRN/(IC50_Rm+DRN))) - Kd_Rm * mRNA.R

    # Het basisniveau van de concentratie vrije receptor
    dR_dt <- Ks_r* mRNA.R + Rf * Kre * DRN - Kon * D * R - Kd_R * R

    # De dichtheid van het MPL-receptor complex
    dDR_dt <- Kon * D * R - Kt * DR

    # De hoeveelheid MPL-receptor complex in de celkern
    dDRN_dt <- Kt * DR - Kre * DRN

    return(list(c(dmRNA.R_dt, dR_dt, dDR_dt, dDRN_dt)))
  })
}
```

```

# Initial values
state <- c(mRNA.R = 4.74,
          R = 267,
          DR = 0,
          DRN = 0)

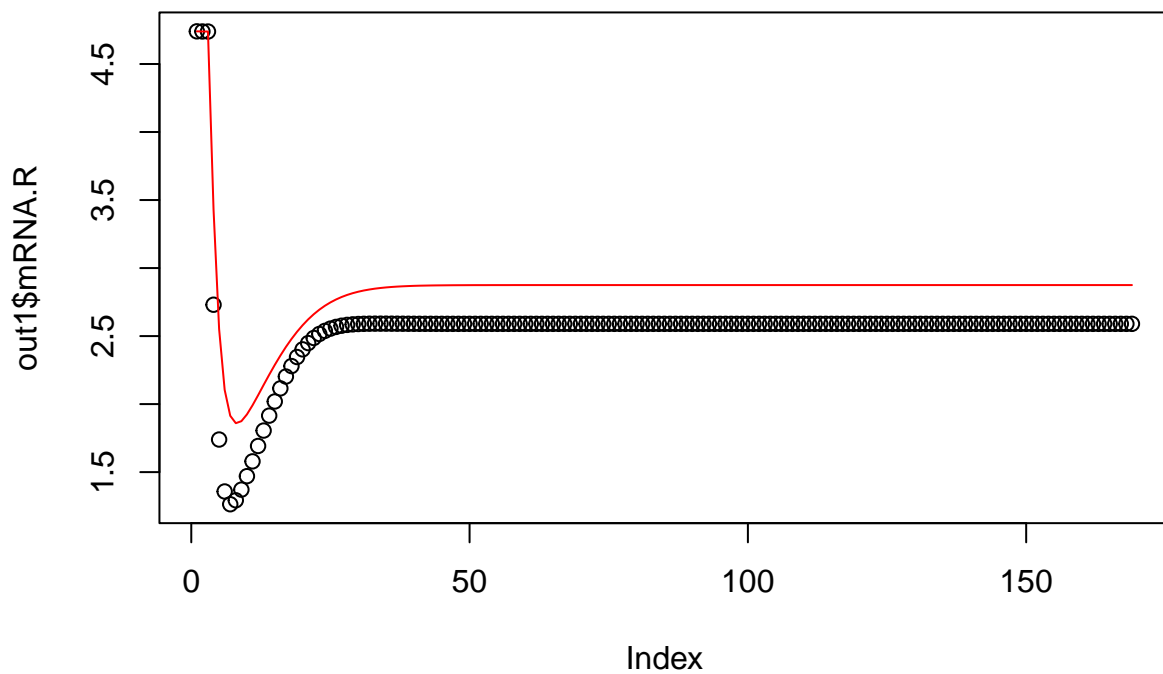
times <- seq(0,
            168,
            by = 1)

# Using the model with our parameters and initial values
out <- ode(times = times,
          y = state,
          parms = parameters,
          func = model,
          method = "euler")
out1 <- data.frame(out)

volume_D <- median_MPL_01
nmol <- volume_D * 1000 * (1 / 374.477)
parameters <- c(Kd_Rm = 0.612, Kre = 0.57, Ks_Rm = 2.90, IC50_Rm = 26.2,
               Kd_R = 0.0572, Rf = 0.49, Kon= 0.00329,
               Kt = 0.63, D=nmol, Ks_r = 3.22)

# Using the model with our parameters and initial values
out <- ode(times = times,
          y = state,
          parms = parameters,
          func = model,
          method = "euler")
out <- data.frame(out)
plot(out1$mRNA.R)
lines(out$mRNA.R, col="red")

```



```

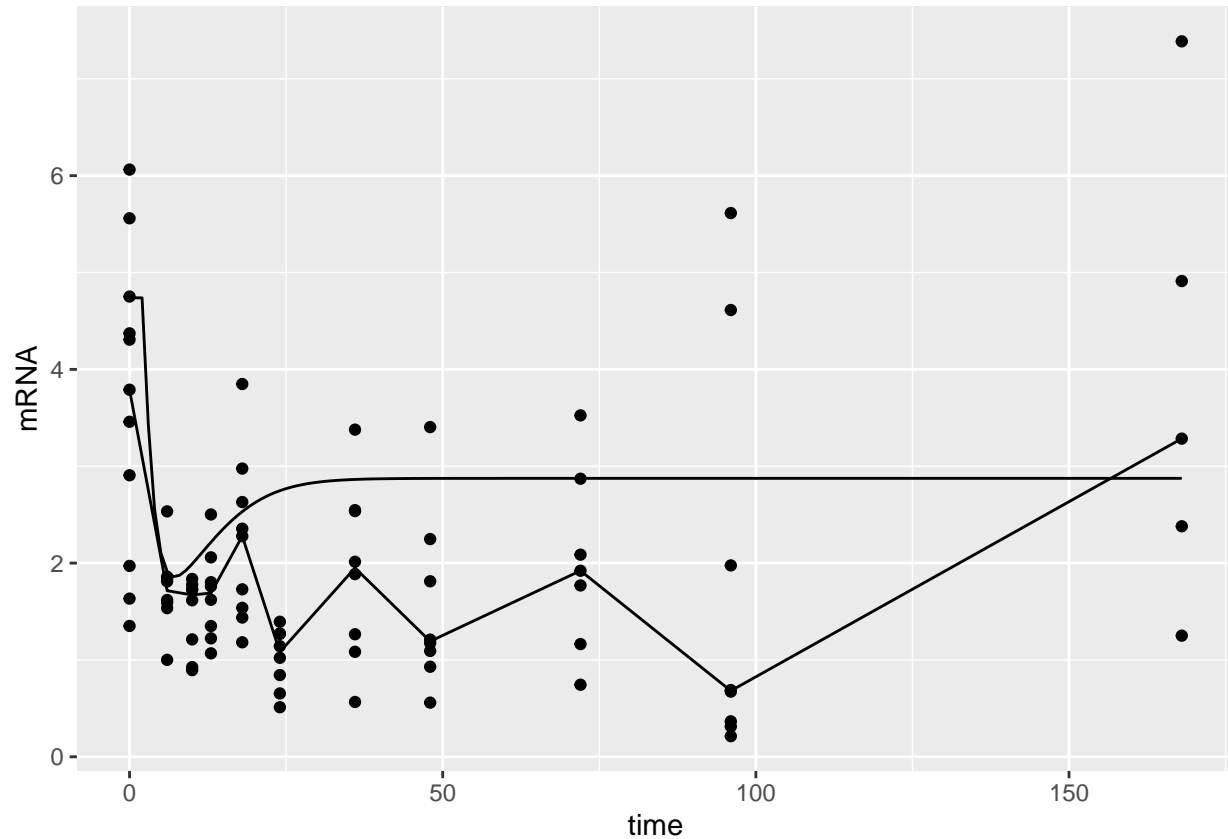
medians <- aggregate(data[,c("MPL_conc", "mRNA", "Free_receptor")], list(data$dose, data$time), median, na.rm=T)
names(medians)[1:2] <- c("dose", "time")

md <- aggregate(data$mRNA, list(data$time), median, na.rm=T)
names(md)[1:2] <- c("time", "median")

ggplot() + geom_point(data, mapping=aes(x=time, y=mRNA)) + geom_line(out, mapping=aes(x=time, y=mRNA.R))

## Warning: Removed 6 rows containing missing values (geom_point).

```



Questions

[1] Why is it best practice to plot the median for the experimental data? Explain in your report

In experimentele data kunnen snel uitschieters voorkomen. Als je het gemiddelde zal pakken dan zal dit verder uitwijken. daarom is het meer betrouwbaar om het mediaan te pakken.

[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 dosis D and plot these to find the answer.

Wanneer de dosis hogere(0.3) is wordt de mrna transcriptie meer geremd dan met een lagere dosis. Het aantal vrije receptoren neemt sneller af met een hogere dosis.

[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).

Ja, Dat is te herleiden uit het figuur. Daar is te zien dat de waarden gegroepeerd dalen via dezelfde tijdseenheid als bij het model.

Assignment 2

Code

```
# Paramaters
parameters <- c(Kd_Rm = 0.612, Kre = 0.57, Ks_Rm = 2.90, IC50_Rm = 26.2,
                Kd_R = 0.0572, Rf = 0.49, Kon= 0.00329,
                Kt = 0.63, D=20*1000/374.471, Ks_r = 3.22)

# Initial values
state <- c(mRNA.R = 4.74,
           R = 267,
           DR = 0,
           DRN = 0)

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

Questions

[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 not effect of 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.

```
# The model we will use
model <- function(t, y, parms){
  with(as.list(c(y, parms)),{
    # Concentratie Receptor mRNA
    dmRNA.R_dt <- Ks_Rm - Kd_Rm * mRNA.R

    # Het basisniveau van de concentratie vrije receptor
    dR_dt <- Ks_r* mRNA.R + Rf * Kre * DRN - Kon * D * R - Kd_R * R

    # De dichtheid van het MPL-receptor complex
    dDR_dt <- Kon * D * R - Kt * DR

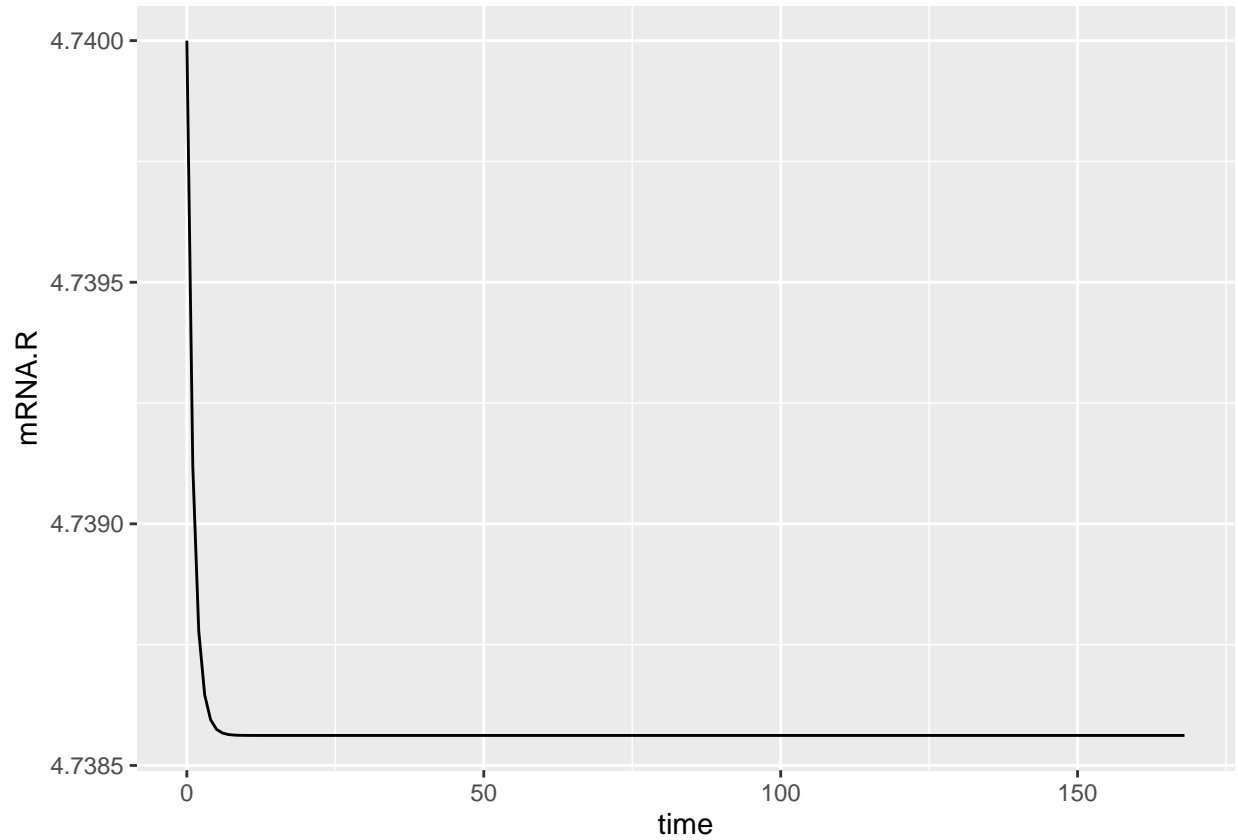
    # De hoeveelheid MPL-receptor complex in de celkern
    dDRN_dt <- Kt * DR - Kre * DRN

    return(list(c(dmRNA.R_dt, dR_dt, dDR_dt, dDRN_dt)))
  })
}

output <- ode(times = times,
              y = state,
              parms = parameters,
              func = model,
              method = "euler")
```

```
output <- data.frame(output)

# Data plotting
ggplot() +
  geom_line(output, mapping = aes(x=time, y=mRNA.R))
```



Als er geen auto regulatie zou zijn zal betegenen dat de aanmaak van mrna constant zou zijn. Door de in

1.

$$\frac{dmRNA_R}{dt} = k_{s_Rm} \left(1 - \frac{DR(N)}{IC_{50_Rm} + DR(N)} \right) - k_{d_Rm} * mRNA_R$$

2.

$$\left(1 - \frac{DR(N)}{IC_{50_Rm} + DR(N)} \right)$$

3.

$$\frac{dmRNA_R}{dt} = k_{s_Rm} - k_{d_Rm} * mRNA_R$$

[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). Run the simulations and plot the results from t = 0 till t_steady_second.

```

# The model we will use
model <- function(t, y, parms){
  with(as.list(c(y, parms)),{
    # Concentratie Receptor mRNA
    dmRNA.R_dt <- Ks_Rm * (1 - (DRN/(IC50_Rm+DRN))) - Kd_Rm * mRNA.R

    # Het basisniveau van de concentratie vrije receptor
    dR_dt <- Ks_r* mRNA.R + Rf * Kre * DRN - Kon * D * R - Kd_R * R

    # De dichtheid van het MPL-receptor complex
    dDR_dt <- Kon * D * R - Kt * DR

    # De hoeveelheid MPL-receptor complex in de celkern
    dDRN_dt <- Kt * DR - Kre * DRN

    return(list(c(dmRNA.R_dt, dR_dt, dDR_dt, dDRN_dt)))
  })
}

# Initial Values
parameters_1 <- c(Kd_Rm = 0.612, Kre = 0.57, Ks_Rm = 2.90, IC50_Rm = 26.2,
                  Kd_R = 0.0572, Rf = 0.49, Kon= 0.00329,
                  Kt = 0.63, D=20*1000/374.471, Ks_r = 3.22)

state_1 <- c(mRNA.R = 4.74,
            R = 267,
            DR = 0,
            DRN = 0)

times_1 <- seq(0,
              66,
              by = 1)

output <- data.frame(ode(times = times_1,
                        y = state_1,
                        parms = parameters_1,
                        func = model,
                        method = "euler"))

# Second Values
parameters_2 <- c(Kd_Rm = 0.612, Kre = 0.57, Ks_Rm = 2.90, IC50_Rm = 26.2,
                  Kd_R = 0.0572, Rf = 0.49, Kon= 0.00329,
                  Kt = 0.63, D=0, Ks_r = 3.22)

times_2 <- seq(66,
              168,
              by = 1)

t_steady1 <- c(output[67,])

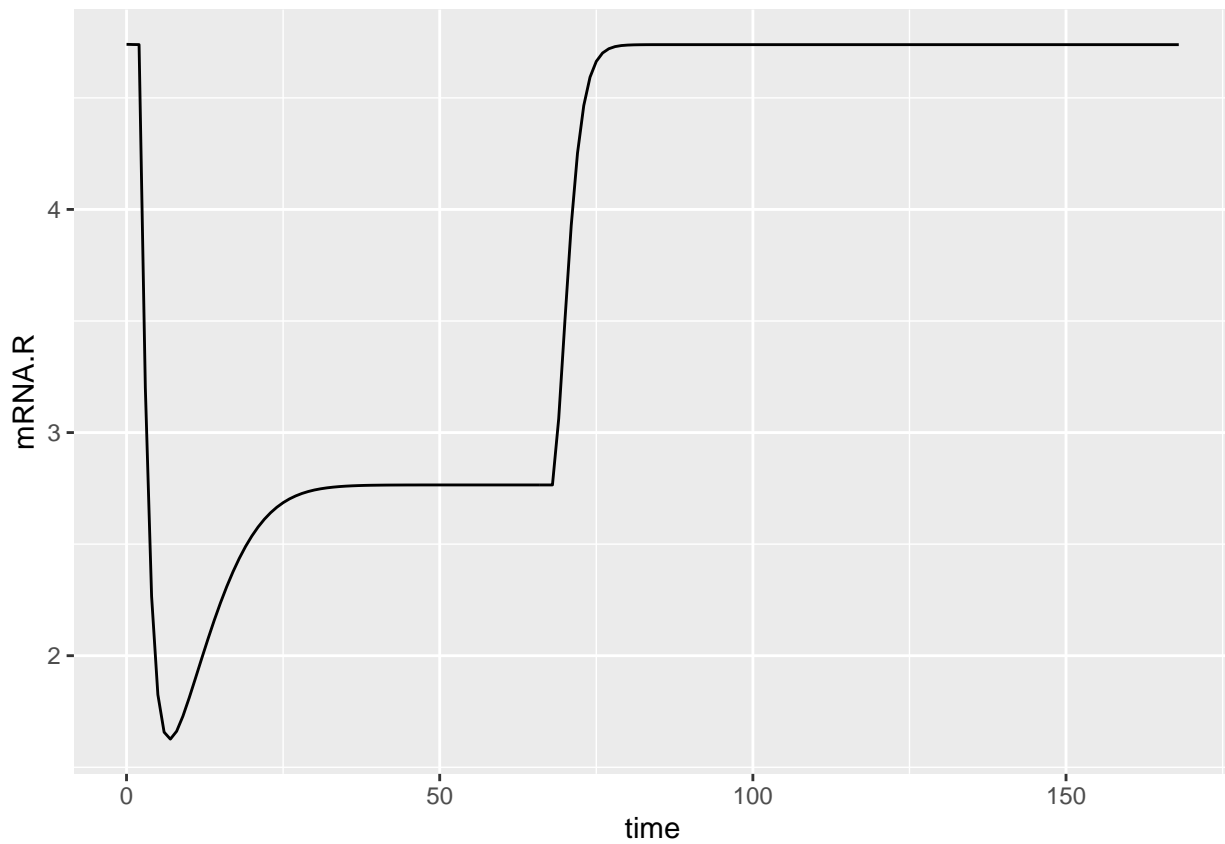
```

```

state_2 <- c(mRNA.R = t_steady1$mRNA.R,
             R = t_steady1$R,
             DR = t_steady1$DR,
             DRN = t_steady1$DRN)
# Second Run
output_2 <- data.frame(ode(times = times_2,
                           y = state_2,
                           parms = parameters_2,
                           func = model,
                           method = "euler"))

# Data plotting
ggplot() +
  geom_line(output, mapping = aes(x=time, y=mRNA.R)) +
  geom_line(output_2, mapping = aes(x=time, y=mRNA.R))

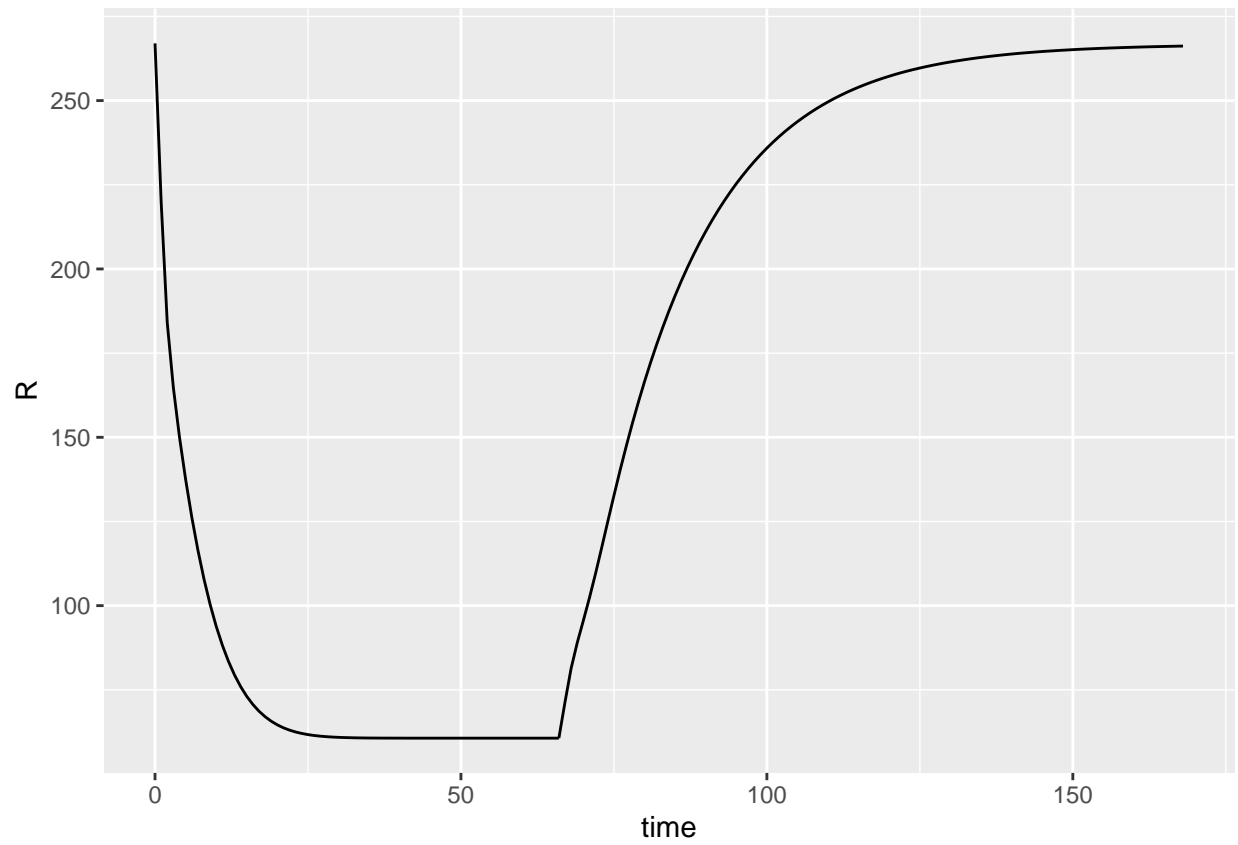
```



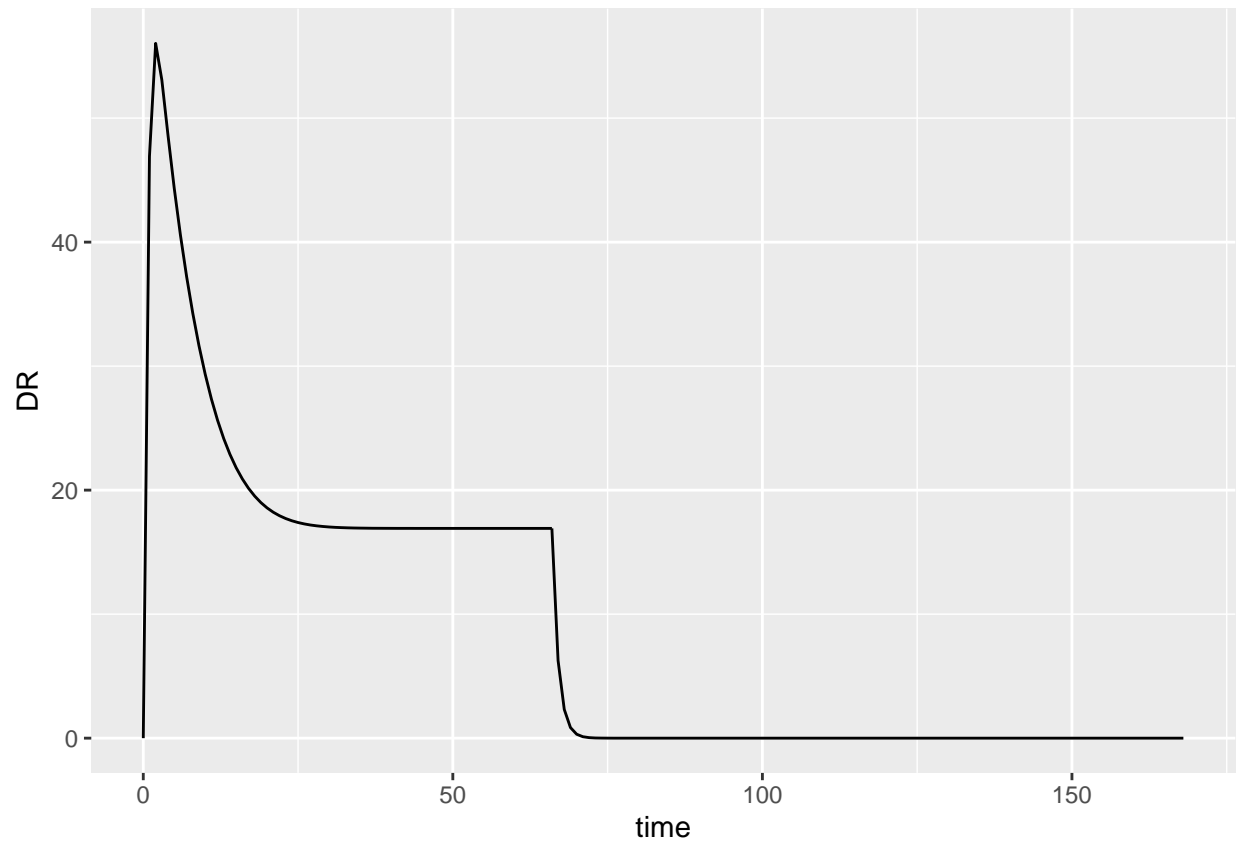
```

ggplot() +
  geom_line(output, mapping = aes(x=time, y=R)) +
  geom_line(output_2, mapping = aes(x=time, y=R))

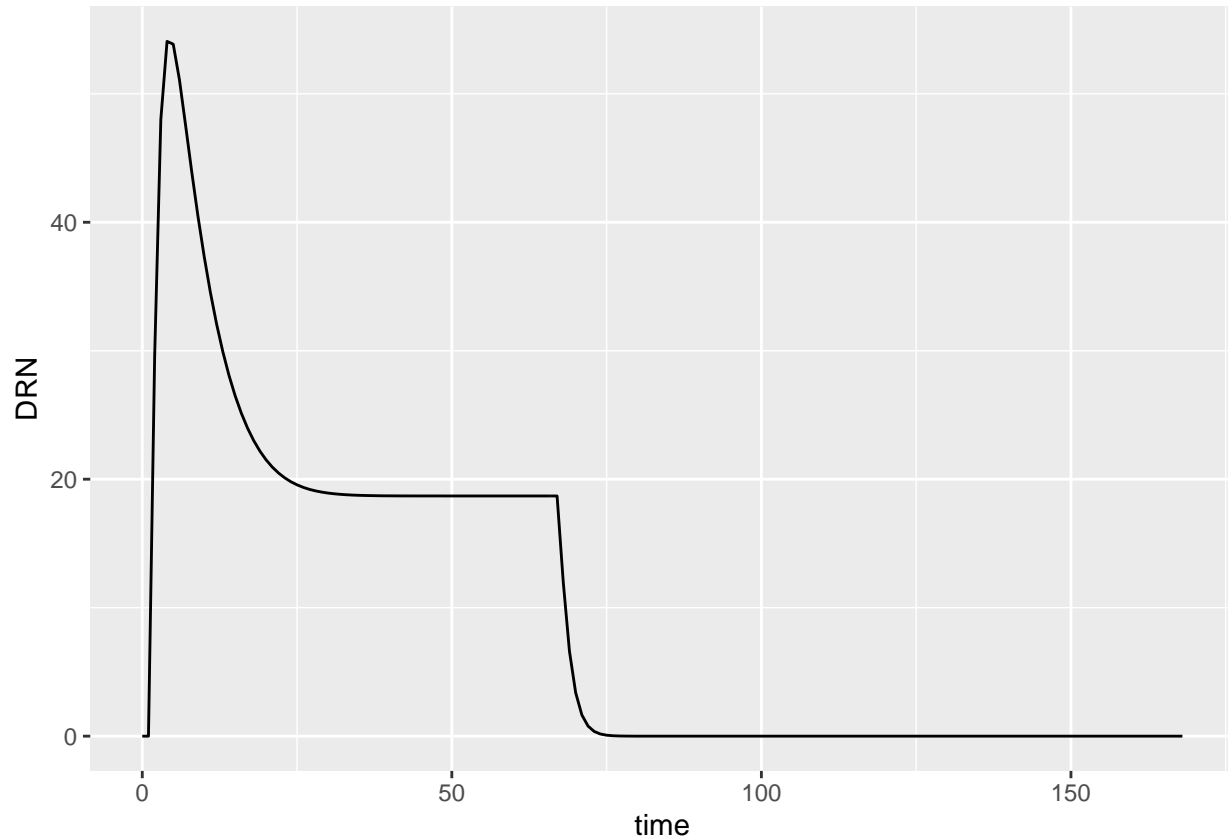
```

```
ggplot() +  
  geom_line(output, mapping = aes(x=time, y=DR)) +  
  geom_line(output_2, mapping = aes(x=time, y=DR))
```



```
ggplot() +  
  geom_line(output, mapping = aes(x=time, y=DRN)) +  
  geom_line(output_2, mapping = aes(x=time, y=DRN))
```



[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} : $0.00329/5$, $0.00329/2$, $0.00329 \cdot 2$ and $0.00329 \cdot 5$. 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} : $0.57/5$, $0.57/2$, $0.57 \cdot 2$ and $0.57 \cdot 5$. The results should be compared to the basic scenario when $k_{re}=0.57$.

```
# Initial values
state <- c(mRNA.R = 4.74,
          R = 267,
          DR = 0,
          DRN = 0)

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

kon_var <- c(0.00329/5,
            0.00329/2,
            0.00329*2,
            0.00329*5)

plot_series <- function(y_kon=0.00329){
```

```

parameters <- c(Kd_Rm = 0.612, Kre = 0.57, Ks_Rm = 2.90, IC50_Rm = 26.2,
  Kd_R = 0.0572, Rf = 0.49, Kon= y_kon,
  Kt = 0.63, D=20*1000/374.471, Ks_r = 3.22)

output <- data.frame(ode(times = times,
  y = state,
  parms = parameters,
  func = model,
  method = "euler"))

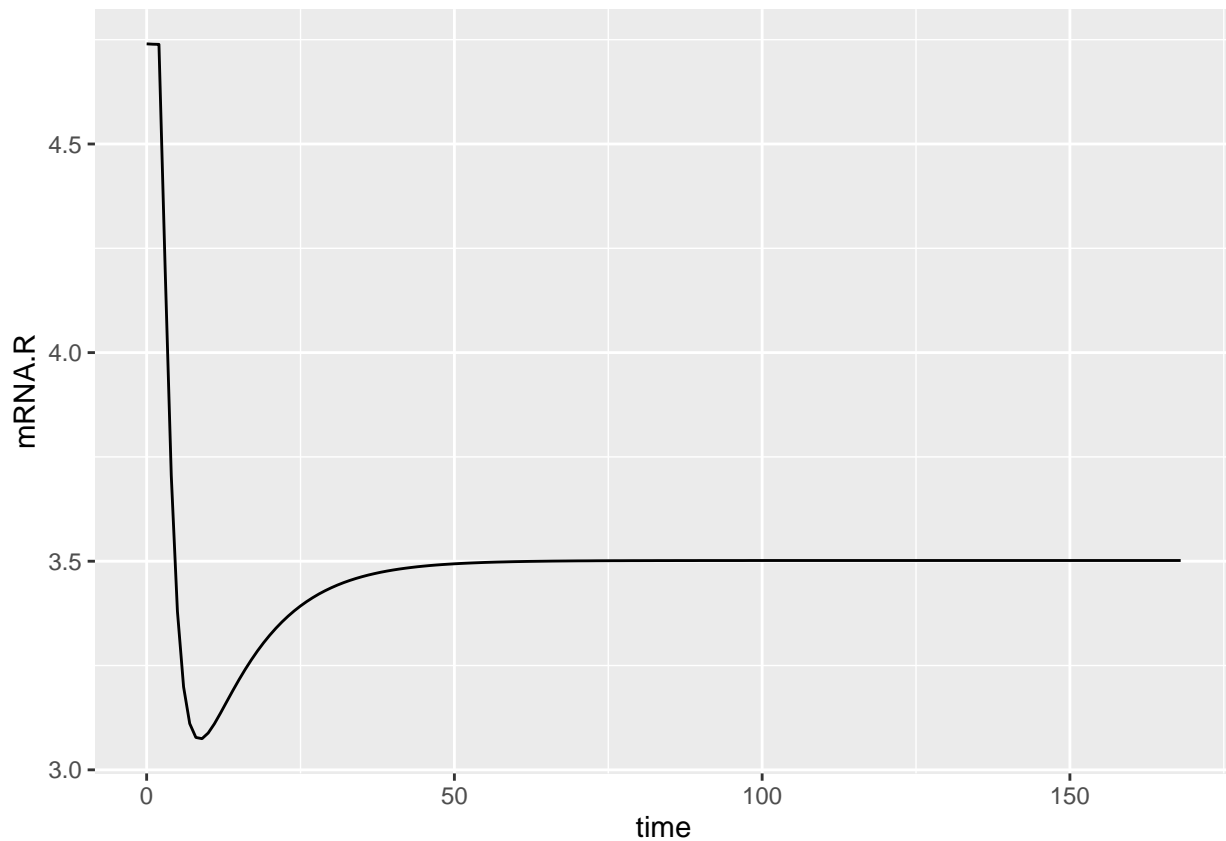
print(y_kon)
# Data plotting
print(ggplot() +
  geom_line(output, mapping = aes(x=time, y=mRNA.R)))

ggplot() +
  geom_line(output, mapping = aes(x=time, y=R))
}

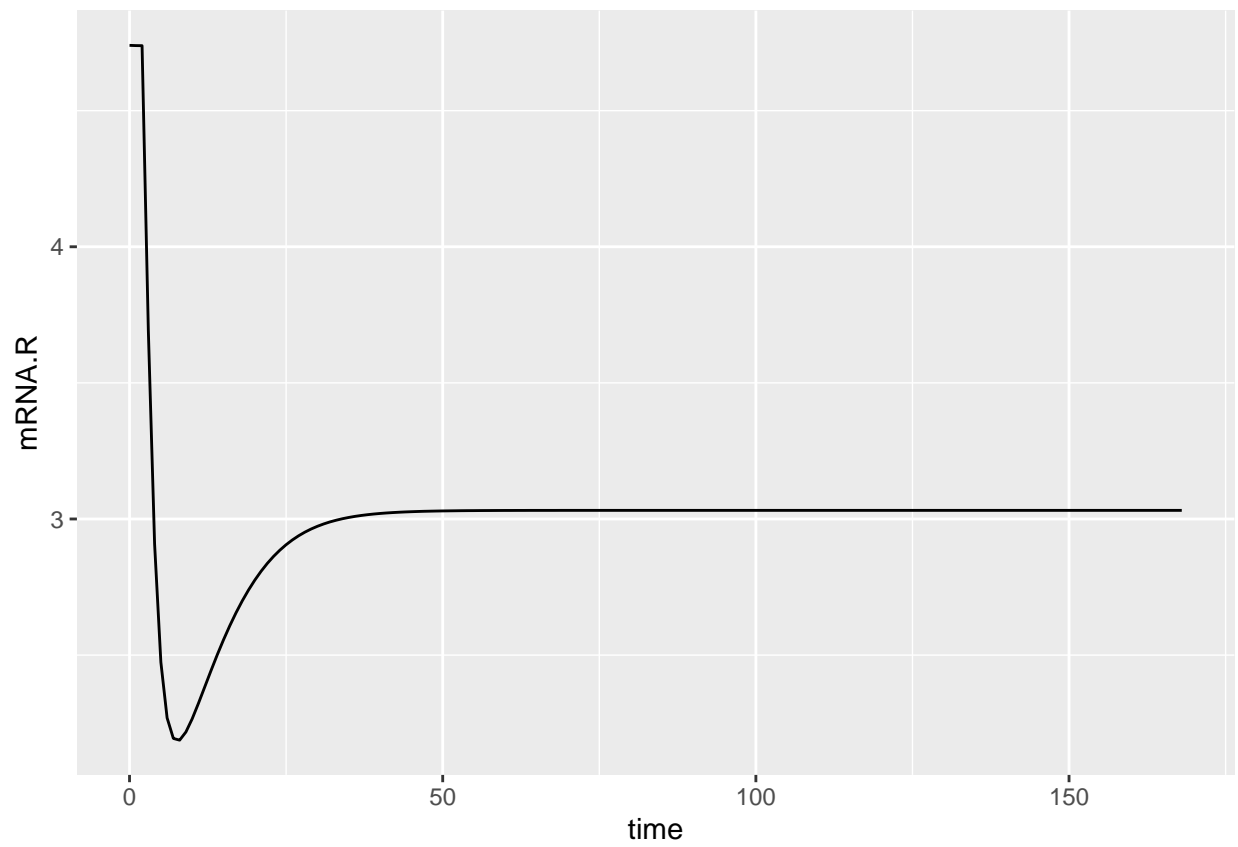
lapply(kon_var, plot_series)

```

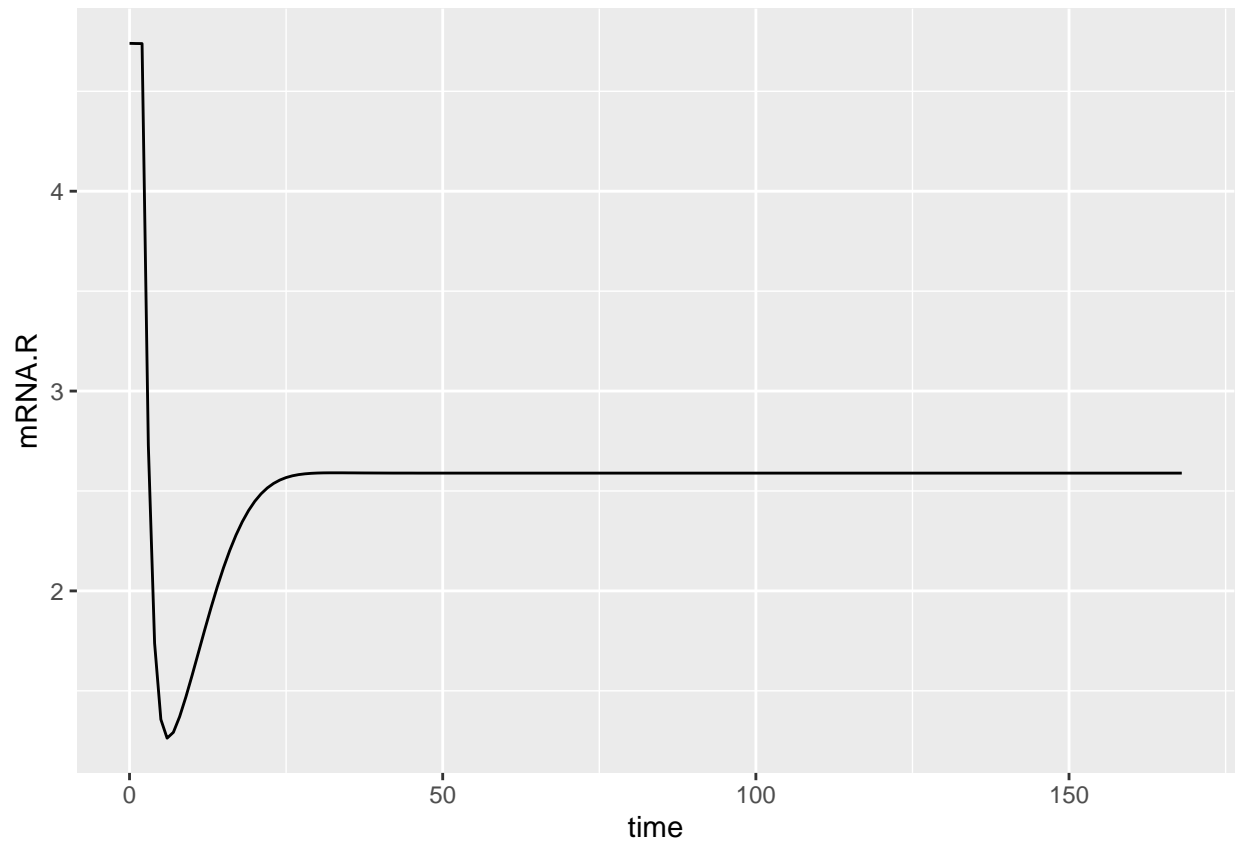
```
## [1] 0.000658
```



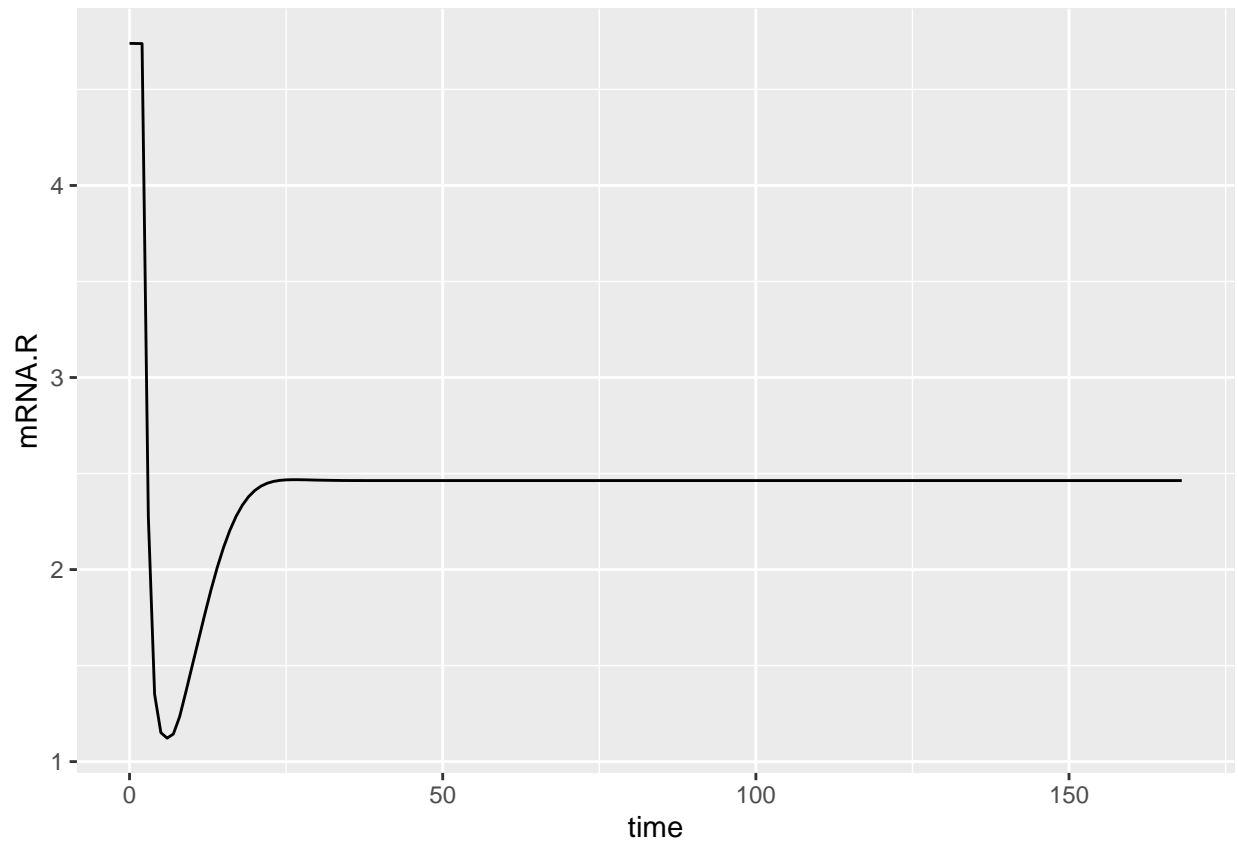
```
## [1] 0.001645
```



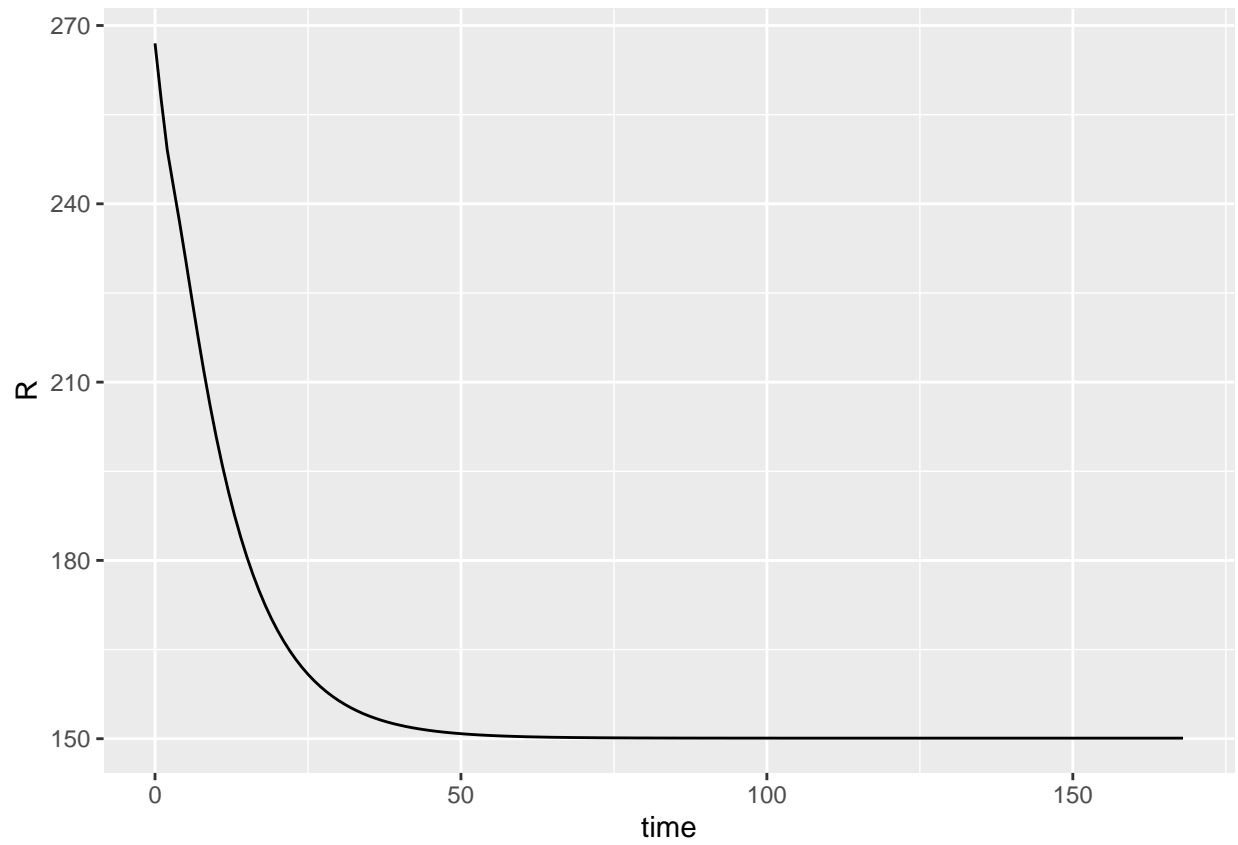
```
## [1] 0.00658
```



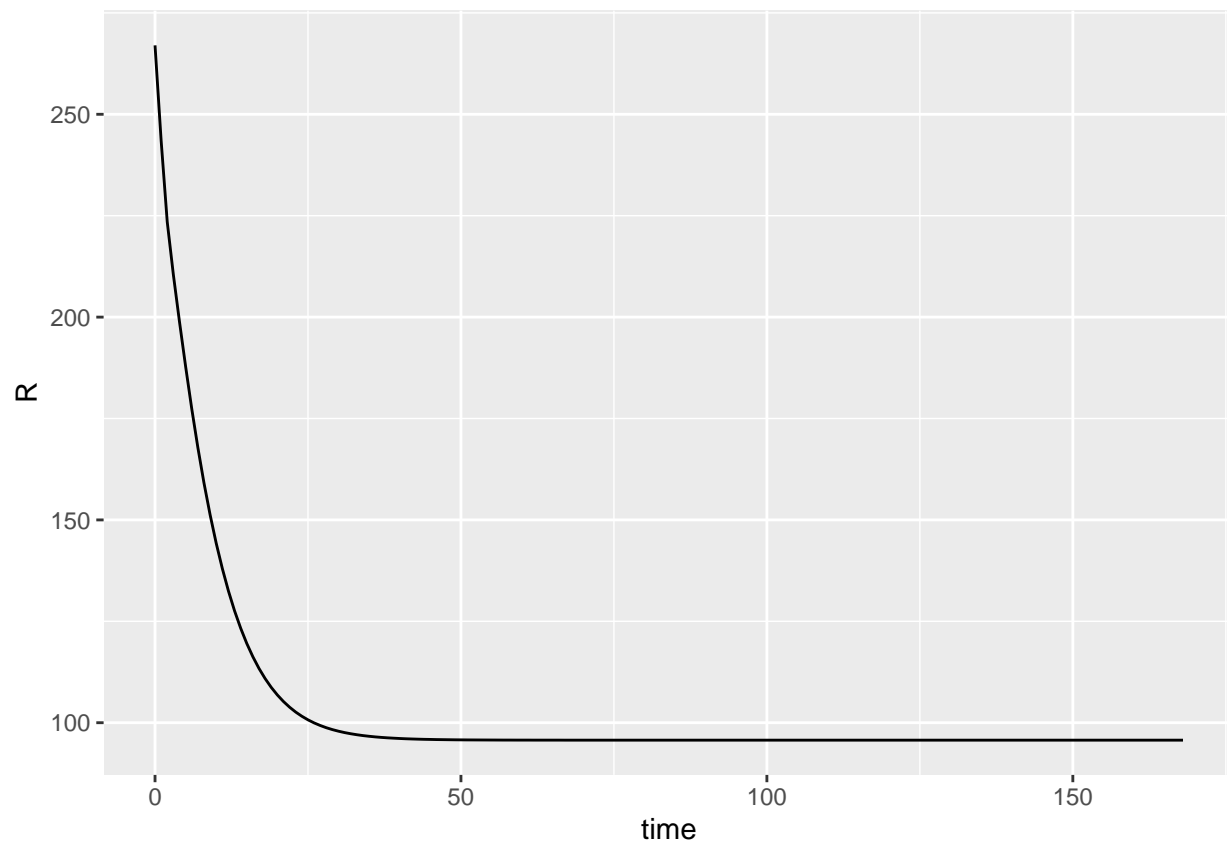
```
## [1] 0.01645
```



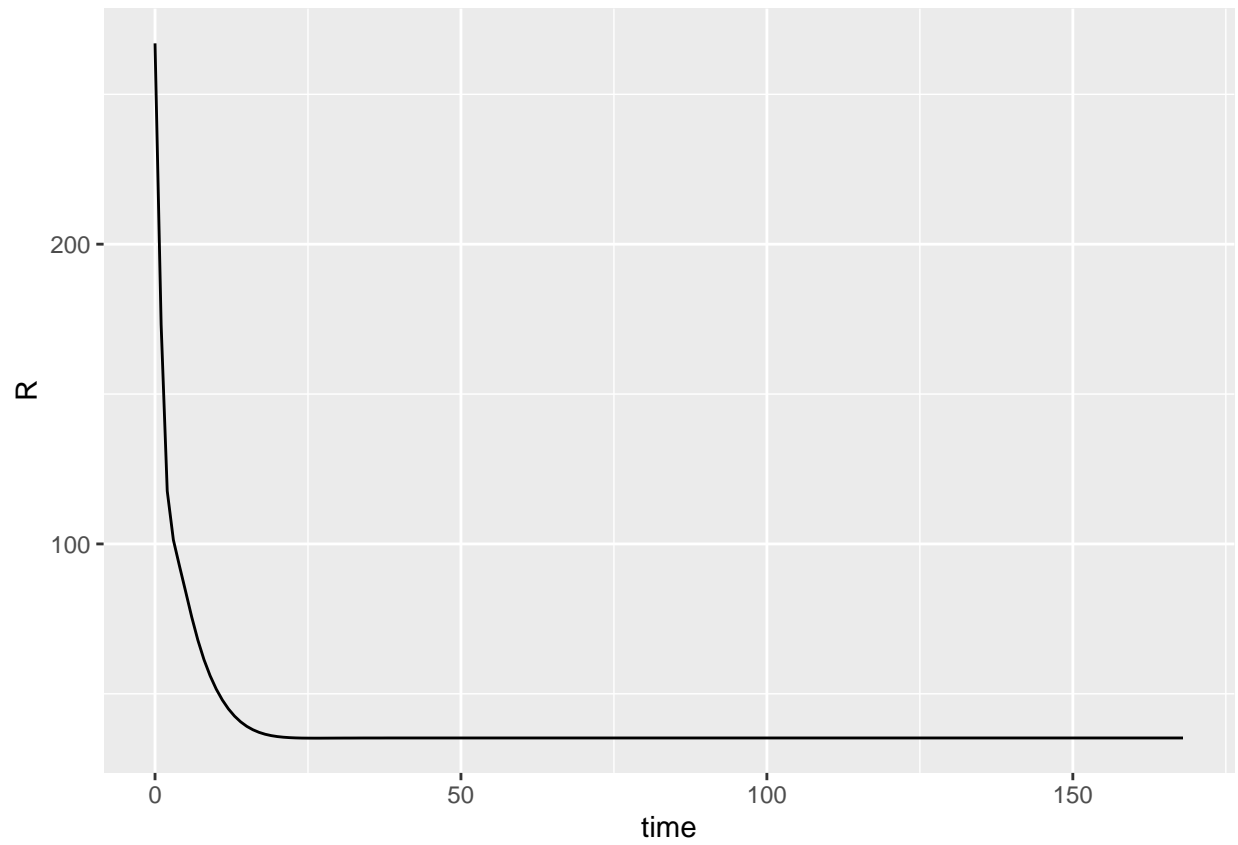
[[1]]



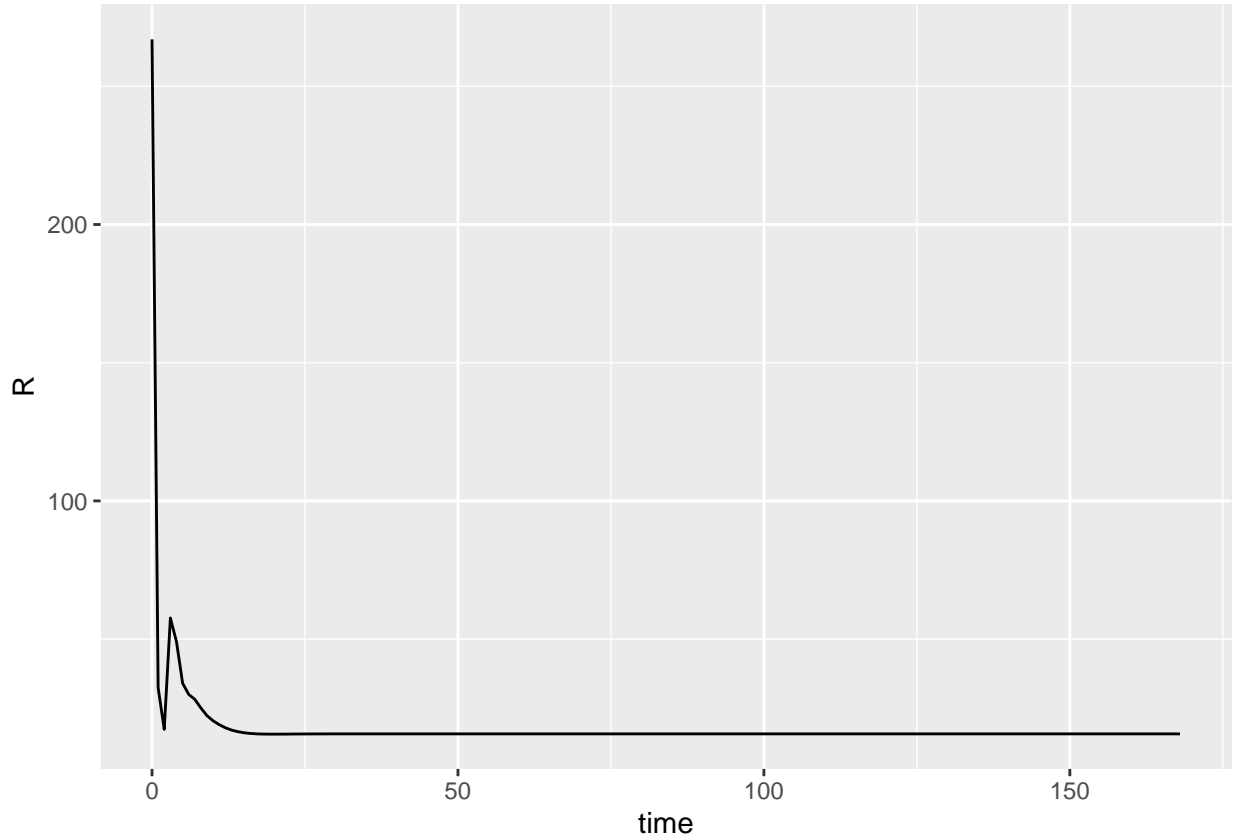
```
##  
## [[2]]
```

```
##  
## [[3]]
```



```
##  
## [[4]]
```



[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 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 (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 not drug)? Mind you: ks_Rm values should be changed, but we know that if without the drug the system is at steady-state then $kd_Rm = ks_Rm/Rm0$. Therefore if we change ks_Rm we need to change kd_Rm as well. Also after we recalculate the value of kd_Rm for the baseline conditions, the simulations should be run with drug present. Simulations should be run for 4 different scenarios:

- $ks_Rm = 2.9/5$ and $kd_Rm=2.9/5/4.74$
- $ks_Rm = 2.9/2$ and $kd_Rm=2.9/2/4.74$
- $ks_Rm = 2.92$ and $kd_Rm=2.92/4.74$
- $ks_Rm = 2.95$ and $kd_Rm=2.95/4.74$