Detailed Analysis

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Assignment 1

Data loading

```
## Read the data
MPL_data <- read.csv("MPL.csv", na.strings = "NA")
names(MPL_data)[4:5] <- c("R.m0", "R.0")

## Subset per dose
data_01 <- subset(MPL_data, MPL_data$dose == 0 | MPL_data$dose == 0.1)
data_03 <- subset(MPL_data, MPL_data$dose == 0 | MPL_data$dose == 0.3)

## Create the medians subsets
medians <- aggregate(MPL_data[,c("MPL_conc","R.m0","R.0")],
                     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)

## Function that calculates D
calc.D <- function(dose){
  return( (dose * 1000)/374.471 )
}
```

Implement the model

Following experiments with methylprednisolone in rats, a set of values for the model is defined:

Table 1: Parameter values for MPL

Parameter	Value	Unit	Explanation
k_{s_Rm}	2.90	fmol/g	Zero-order rate constant: GR mRNA synthesis
IC_{50_Rm}	26.2	fmol/mg	Concentration DR(N) that inhibits mRNA synthesis (50%)
k_{on}	0.00329	L/nmol/h	Second-order rate constant: forming MPL-receptor complex
k_T	0.63	1/h	First-order rate constant: translocation of receptor (cytosol -> nucleus)
k~re	0.57	1/h	First-order rate constant: recovery of receptor (nucleus -> cytosol)
R_f	0.49	-	Fraction free receptor that gets recycled
k_{d_R}	0.0572	1/h	First-order rate constant: breakdown of receptor
k_{d_Rm}	0.612	-	First-order rate constant: breakdown of GR mRNA
k_{s_R}	3.22	-	First-order rate constant: production of receptor
D	~	nmol/L	Concentration MPL (Calculated with molecular weight = 374.471

Table 2: Initial values for MPL

Parameter	Value	Unit	Explanation
R_{m0} (mRNA)	4.74	fmol/g	Concentration $mRNA_R$
R_0 (Free_receptor)	267	fmol/mg	Concentration free receptors
DR	0	fmol/mg	MPL in the cytosol
DR(N)	0	fmol/mg	MPL in the nucleus

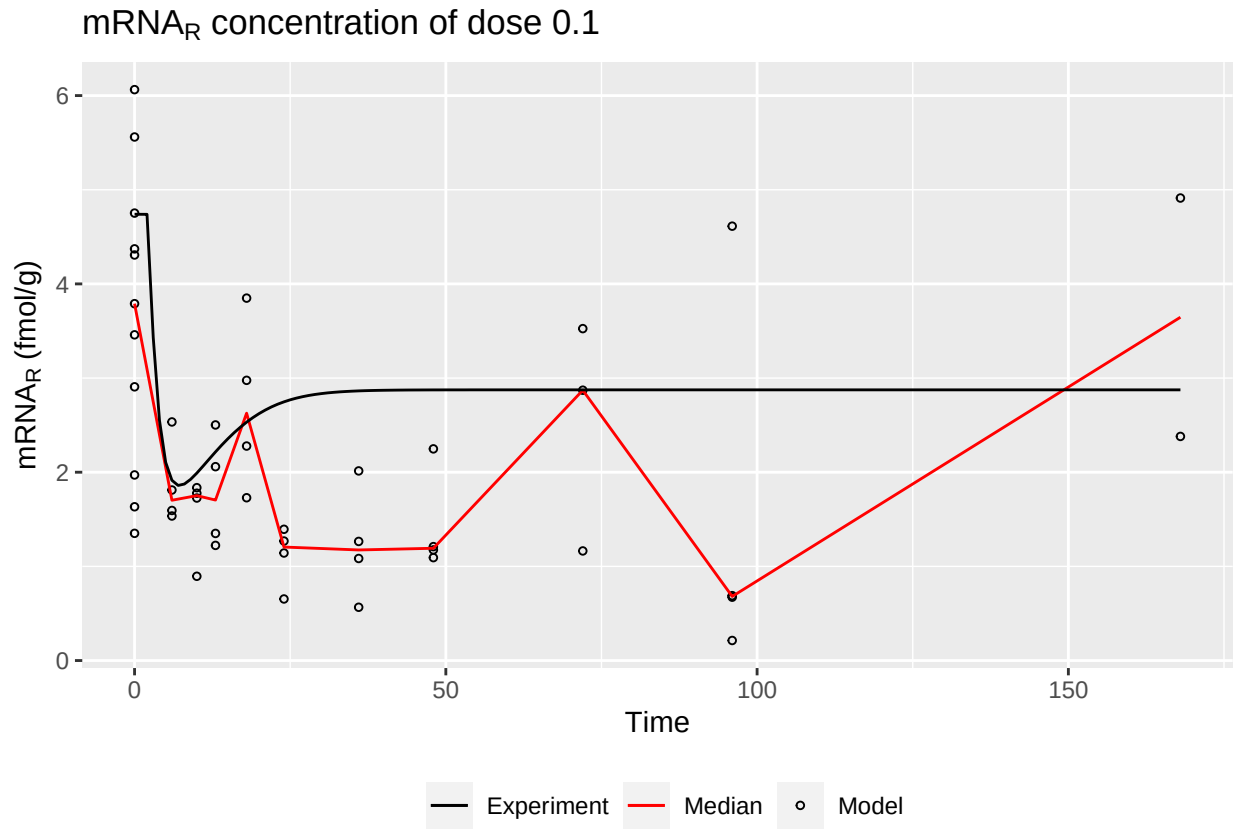
The experiment followed rats for 7 days under constant infusion of the drug: 0.1 or 0.3 $mg_{drug}/kg_{rat}/h$. With this information, models can be created:

```
## Set the model data
params <- c(
        k.s_Rm = 2.90,
        IC.50_Rm = 26.2,
        k.on = 0.00329,
        k.T = 0.63,
        k.re = 0.57,
        R.f = 0.49,
        k.d_R = 0.0572,
        k.d_Rm = 0.612,
        k.s_R = 3.22,
        D = 0
)

state <- c(
        R.m0 = 4.74,
        R.0 = 267,
        DR = 0,
        DRN = 0
)

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

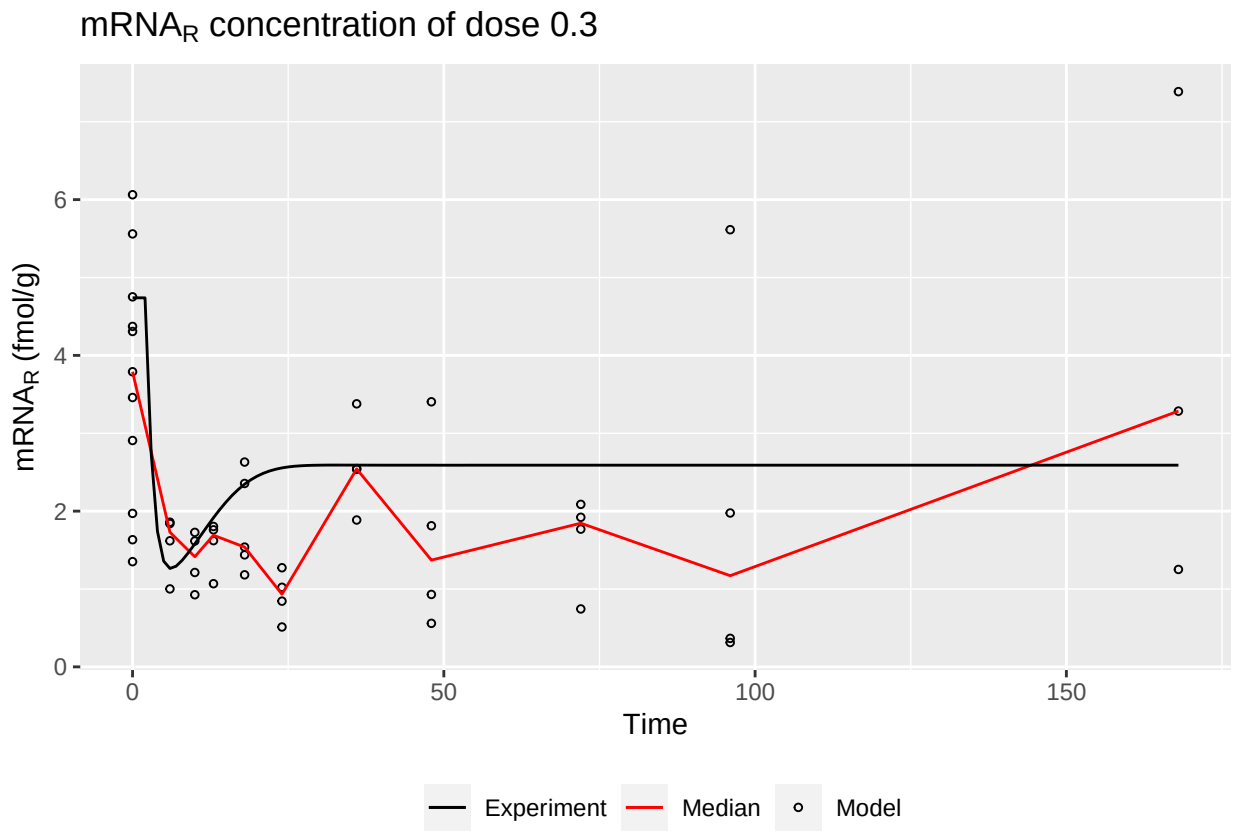
```
## Model function
grd_model <- function(t, y, parms){
  with(as.list(c(parms, y)),{
    delta.mRNA_R <- k.s_Rm * (1 - ( DRN / (IC.50_Rm + DRN) ) ) - k.d_Rm * R.m0
    delta.R <- k.s_R * R.m0 + R.f * k.re * DRN - k.on * D * R.0 - k.d_R * R.0
    delta.DR <- k.on * D * R.0 - k.T * DR
    delta.DRN <- k.T * DR - k.re * DRN
    return( list( c(delta.mRNA_R, delta.R, delta.DR, delta.DRN ) ) )
  })
}

## Create the models with the different medians
params$D <- calc.D( median(MPL_data$MPL_conc[MPL_data$dose==0.1], na.rm=T) )
model_01 <- ode(times = times, y = state,
                parms = params, func = grd_model, method = "euler")
model_01 <- as.data.frame(model_01)

params$D <- calc.D( median(MPL_data$MPL_conc[MPL_data$dose==0.3], na.rm=T) )
model_03 <- ode(times = times, y = state,
                parms = params, func = grd_model, method = "euler")
model_03 <- as.data.frame(model_03)
```

Visualizing these models give the following:

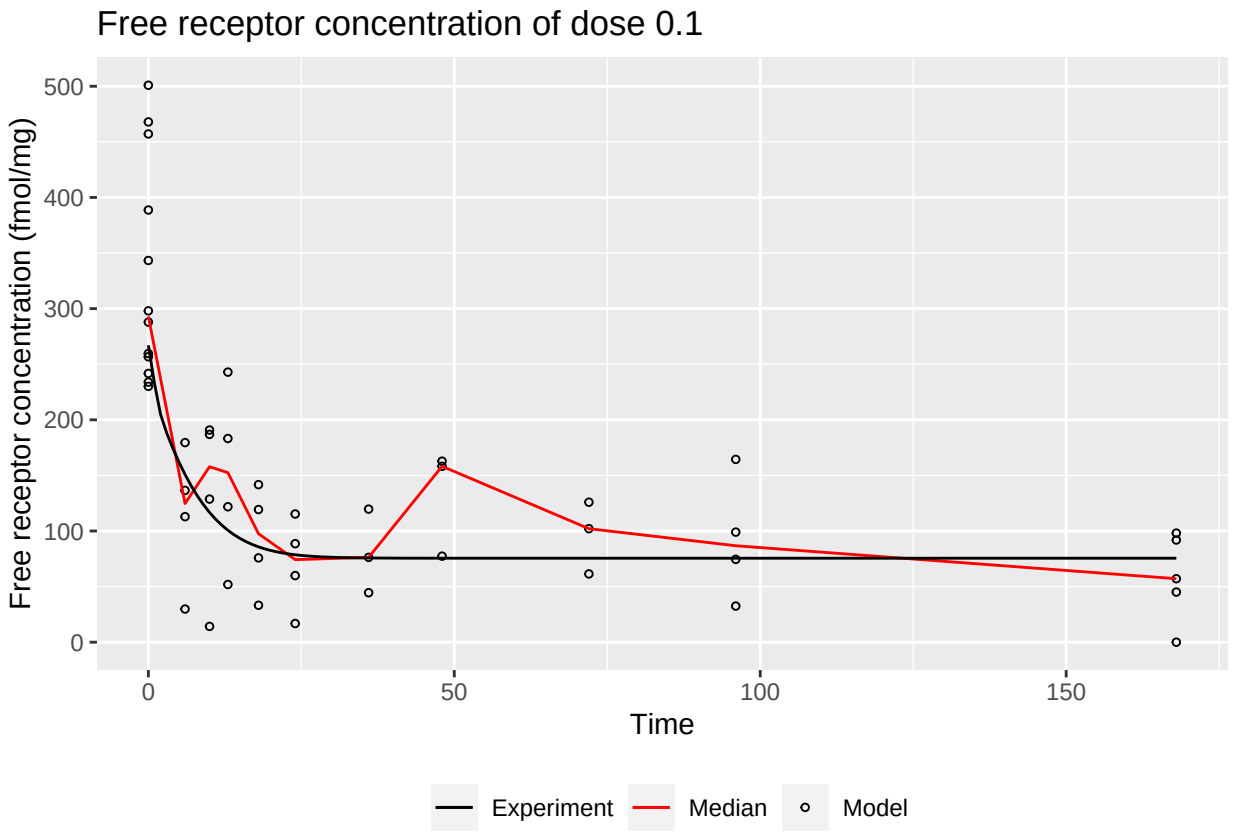
```
ggplot(data = data_01, mapping = aes(x = time, y = R.m0)) +
       geom_point(size = 1, shape = 1, aes(color = "Experiment") ) +
       geom_line(data = median_01, aes(color = "Median")) +
       geom_line(data = model_01, aes(color = "Model")) +
labs(x = "Time", y = expression("mRNA"["R"]*" (fmol/g)"),
            title = expression("mRNA"["R"]*" concentration of dose 0.1") ) +
       theme(legend.position = "bottom") +
       scale_colour_manual(values = c("black", "red", "black"),
                           limits = c("Experiment", "Median", "Model") ) +
       guides(color = guide_legend(title = "",
                                   override.aes = list(linetype = c(1, 1, NA),
                                                       shape = c(NA, NA, 1)) ) )
```



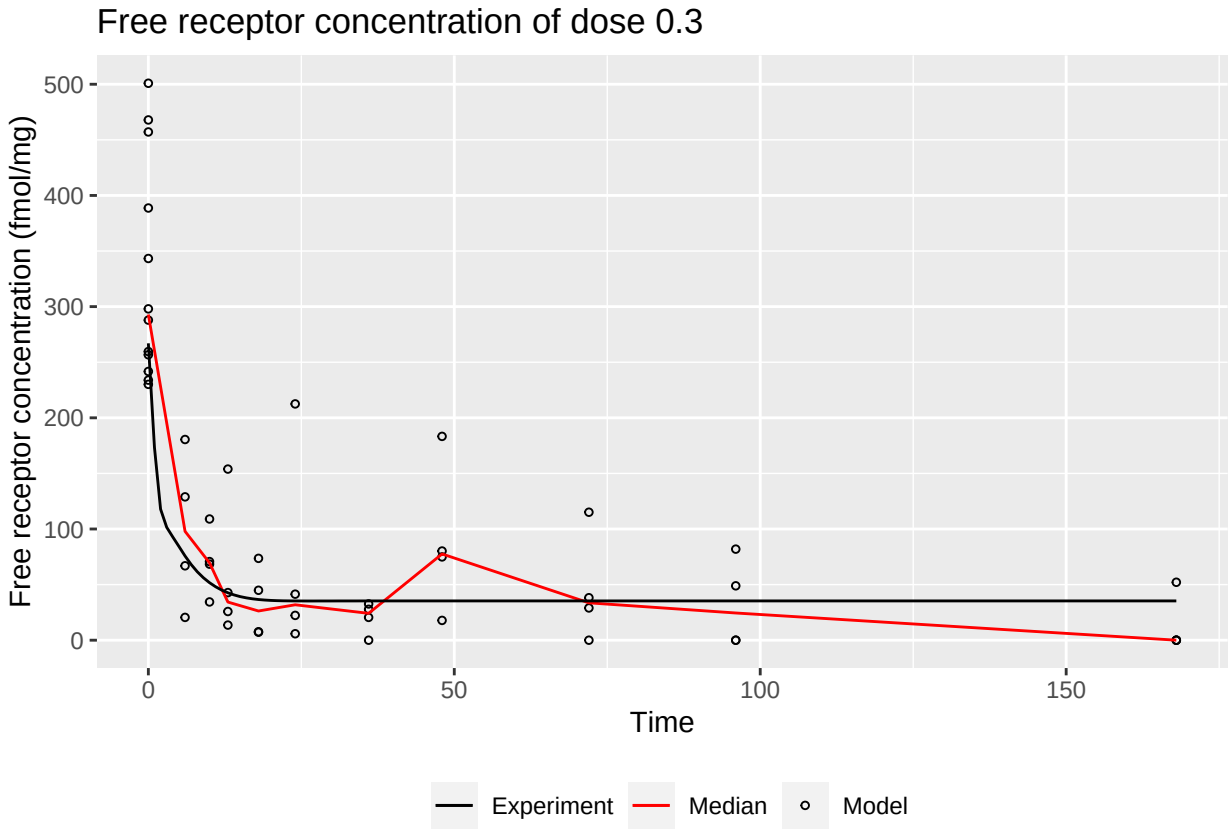

```
ggplot(data = data_03, mapping = aes(x = time, y = R.m0)) +
        geom_point(size = 1, shape = 1, aes(color = "Experiment") ) +
        geom_line(data = median_03, aes(color = "Median")) +
        geom_line(data = model_03, aes(color = "Model")) +
labs(x = "Time", y = expression("mRNA"["R"]*" (fmol/g)"),
             title = expression("mRNA"["R"]*" concentration of dose 0.3") ) +
        theme(legend.position = "bottom") +
        scale_colour_manual(values = c("black", "red", "black"),
                            limits = c("Experiment", "Median", "Model") ) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(1, 1, NA),
                                                        shape = c(NA, NA, 1)) ) )
```




```
ggplot(data = data_01, mapping = aes(x = time, y = R.0)) +
        geom_point(size = 1, shape = 1, aes(color = "Experiment") ) +
        geom_line(data = median_01, aes(color = "Median")) +
        geom_line(data = model_01, aes(color = "Model")) +
        labs(x = "Time", y = "Free receptor concentration (fmol/mg)",
             title = "Free receptor concentration of dose 0.1") +
        theme(legend.position = "bottom") +
        scale_colour_manual(values = c("black", "red", "black"),
                            limits = c("Experiment", "Median", "Model") ) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(1, 1, NA),
                                                        shape = c(NA, NA, 1)) ) )
```




```
ggplot(data = data_03, mapping = aes(x = time, y = R.0)) +
        geom_point(size = 1, shape = 1, aes(color = "Experiment") ) +
        geom_line(data = median_03, aes(color = "Median")) +
        geom_line(data = model_03, aes(color = "Model")) +
        labs(x = "Time", y = "Free receptor concentration (fmol/mg)",
             title = "Free receptor concentration of dose 0.3") +
        theme(legend.position = "bottom") +
        scale_colour_manual(values = c("black", "red", "black"),
                            limits = c("Experiment", "Median", "Model") ) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(1, 1, NA),
                                                        shape = c(NA, NA, 1)) ) )
```



Questions

- [1] Why is it best practice to plot the median for the experimental data?

  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 can influence the steady state of the different concentrations. The shape of the median lines is generally unaffected.

- [3] Are the results of the model in line with experimental data?

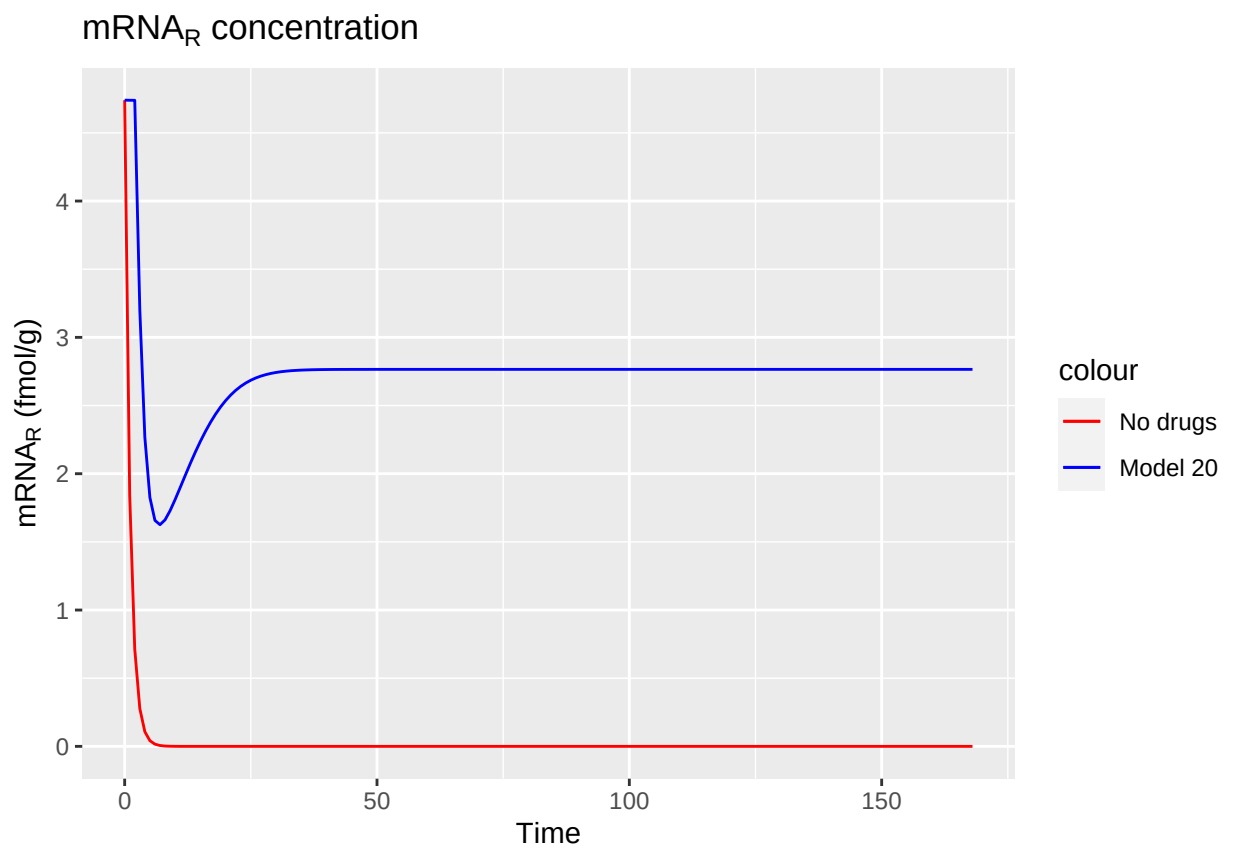
  Yes, to some extent. The values that the experiment and the model end on is similar, but the values between the start and the end fluctuate a bit. The graphs of the free receptor concentration show that the experimental data conform with the model. In the mRNA graphs, there are some deviations from the model around Time = 25.

Assignment 2

No Auto-Regulation Glucocorticoid Receptor

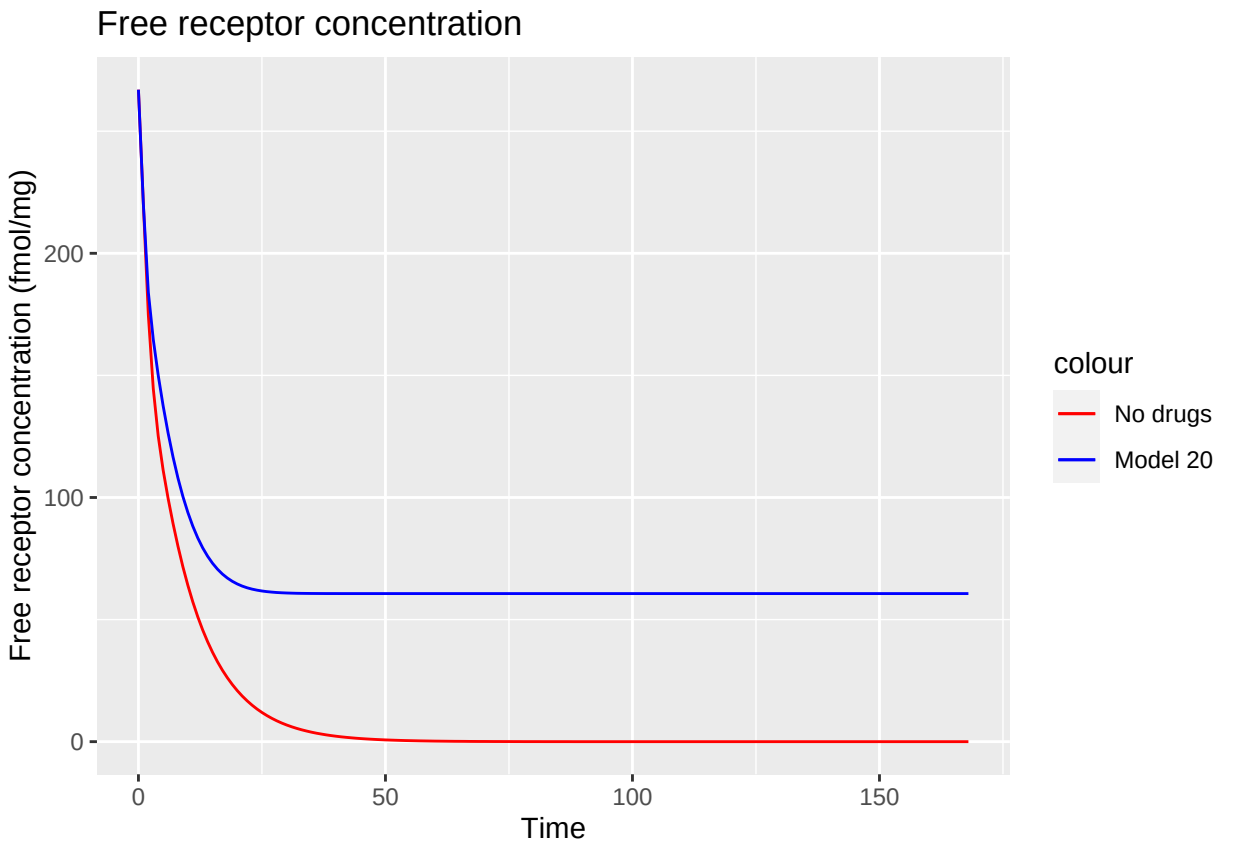
```
## Create function for no drugs
receptor_noDrugs <- function(t, y, parms){
  with(as.list(c(parms, y)),{
    delta.R.m0 <- -k.d_Rm * R.m0
    delta.R <- k.s_R * R.m0 + R.f * k.re * DRN - k.on * D * R.0 - k.d_R * R.0
    delta.DR <- k.on * D * R.0 - k.T * DR
```

```
    delta.DRN <- k.T * DR - k.re * DRN
    return( list( c(delta.R.m0, delta.R, delta.DR, delta.DRN ) ) )
  })
}

## The model with a dose of 20
params$D <- calc.D(20)
model_20 <- ode(times = times, y = state,
                parms = params, func = grd_model, method = "euler")
model_20 <- as.data.frame(model_20)

## The model without drug influence
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 = R.m0)) +
        geom_line(data = model_noDrugs, linetype = "solid", aes(color = "No drugs")) +
        geom_line(data = model_20, linetype = "solid", aes(color = "Model 20")) +
        labs(x = "Time", y = expression("mRNA"["R"]*" (fmol/g)"),
             title = expression("mRNA"["R"]*" concentration") ) +
        scale_colour_manual(values = c("red", "blue"), limits = c("No drugs", "Model 20"))
```




```
ggplot(data = MPL_data, mapping = aes(x = time, y = R.0)) +
        geom_line(data = model_noDrugs, linetype = "solid", aes(color = "No drugs")) +
        geom_line(data = model_20, linetype = "solid", aes(color = "Model 20")) +
        labs(x = "Time", y = "Free receptor concentration (fmol/mg)",
             title = "Free receptor concentration") +
```

```
        scale_colour_manual(values = c("red", "blue"), limits = c("No drugs", "Model 20"))
```



When the DR(N) has no influence on the mRNA_R synthesis, a big part of the first equation disappears: $k_{s_{Rm}} \cdot (1 - \frac{DR(N)}{IC_{50_{Rm}} + DR(N)})$ The figures show, when DR(N) has no influence on the mRNA_R synthesis, the mRNA_R concentration drops to zero fairly quickly and stays zero due to no mRNA_R synthesis. The blue line details the normal scenario in which the drug is working correctly with a dose of 20.

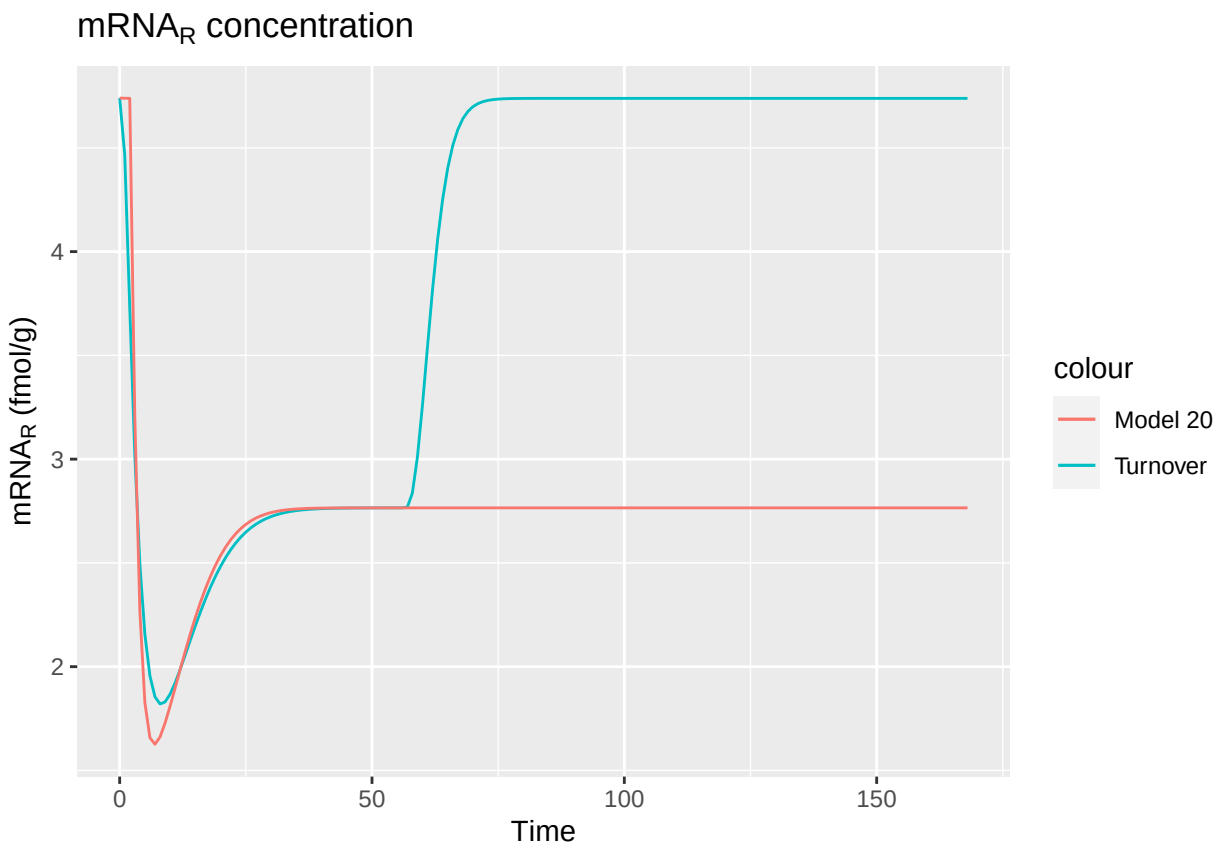
Stopping drug treatment at Steady State

```
## Define new model
steady_model <- function(t, y, parms){
  with(as.list(c(parms, y)),{
    delta.mRNA_R <- k.s_Rm * (1 - ( DRN / (IC.50_Rm + DRN) ) ) - k.d_Rm * R.m0
    delta.R <- k.s_R * R.m0 + R.f * k.re * DRN - k.on * D * R.0 - k.d_R * R.0
    delta.DR <- k.on * D * R.0 - k.T * DR
    delta.DRN <- k.T * DR - k.re * DRN
    delta.D <- 0
    return( list( c(delta.mRNA_R, delta.R, delta.DR, delta.DRN, delta.D) ) )
  })
}

## Parameters for the steady state model
params_steady <- c(
        k.s_Rm = 2.90,
        IC.50_Rm = 26.2,
        k.on = 0.00329,
        k.T = 0.63,
```

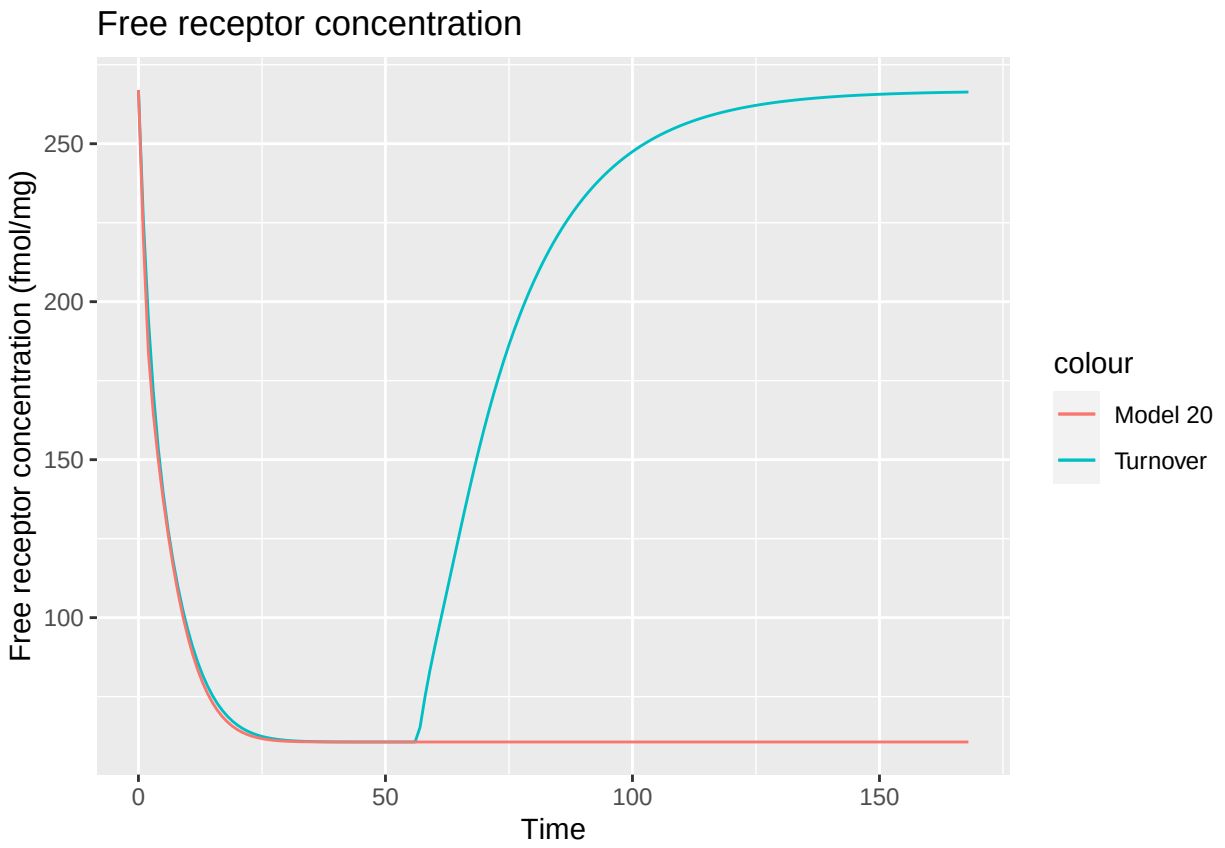
```
        k.re = 0.57,
        R.f = 0.49,
        k.d_R = 0.0572,
        k.d_Rm = 0.612,
        k.s_R = 3.22
)

## State parameters for steady state model
state_steady <- c(
        R.m0 = 4.74,
        R.0 = 267,
        DR = 0,
        DRN = 0,
        D = calc.D(20)
)

## Create the event for the model (this will happen when steady state is found
trigger <- function(t, y, params){
  y["D"] <- 0
  return(y)
}

## Check when the steady state is found
root <- function (t, y, params){
  x <- unlist(grd_model(t, y, params))
  numb1 <- sum(abs(x)) - 1e-4
  numb2 <- numb1 + y["D"]

  return(c(numb1, numb2))
}

## Create the model with the turnover
steadys <- ode( times = times, y = state_steady, parms = params_steady,
                func = steady_model, rootfun = root,
                events = list(func = trigger, root = TRUE, terminalroot = 2) )

## The step where steady state was found
cat("Steady state at:", attributes(steadys)$troot)
```

```
## Steady state at: 56.55569
```

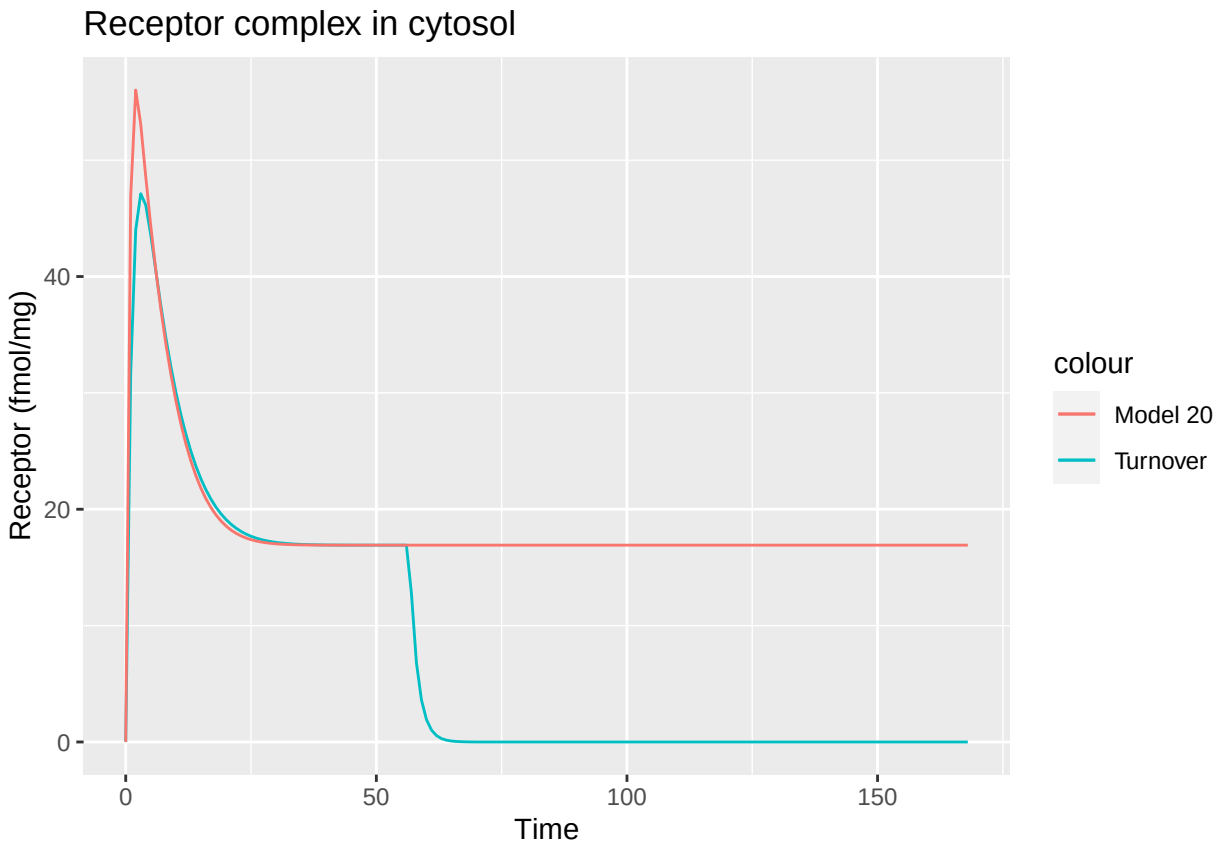
```
steadys <- as.data.frame(steadys)

## Create plots
ggplot(data = steadys, mapping = aes(x = time, y = R.m0)) +
        geom_line(aes(color = "Turnover")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "Time", y = expression("mRNA"["R"]*" (fmol/g)"),
             title = expression("mRNA"["R"]*" concentration") )
```



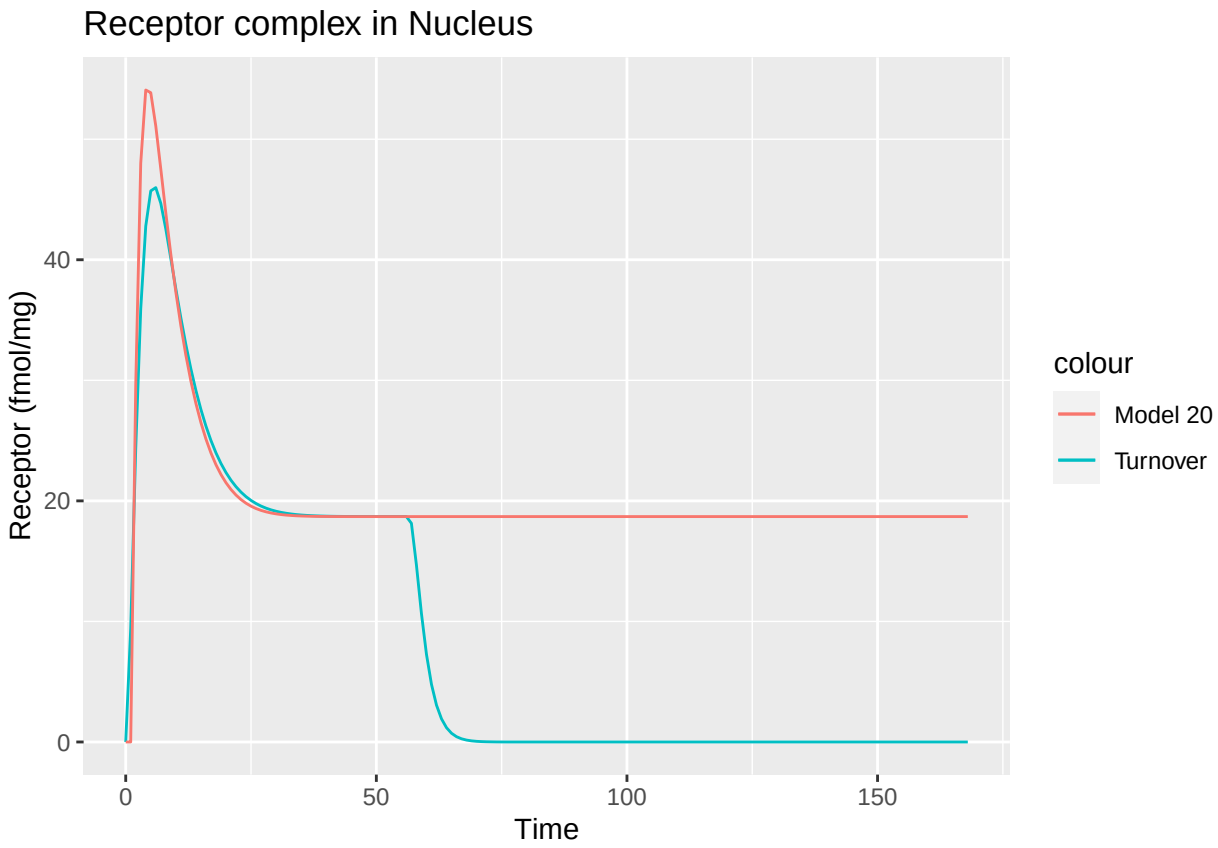

```
ggplot(data = steadys, mapping = aes(x = time, y = R.0)) +
       geom_line(aes(color = "Turnover")) +
       geom_line(data = model_20, aes(color = "Model 20")) +
       labs(x = "Time", y = "Free receptor concentration (fmol/mg)",
            title = "Free receptor concentration")
```




```
ggplot(data = steadys, mapping = aes(x = time, y = DR)) +
        geom_line(aes(color = "Turnover")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "Time", y = "Receptor (fmol/mg)",
             title = "Receptor complex in cytosol")
```



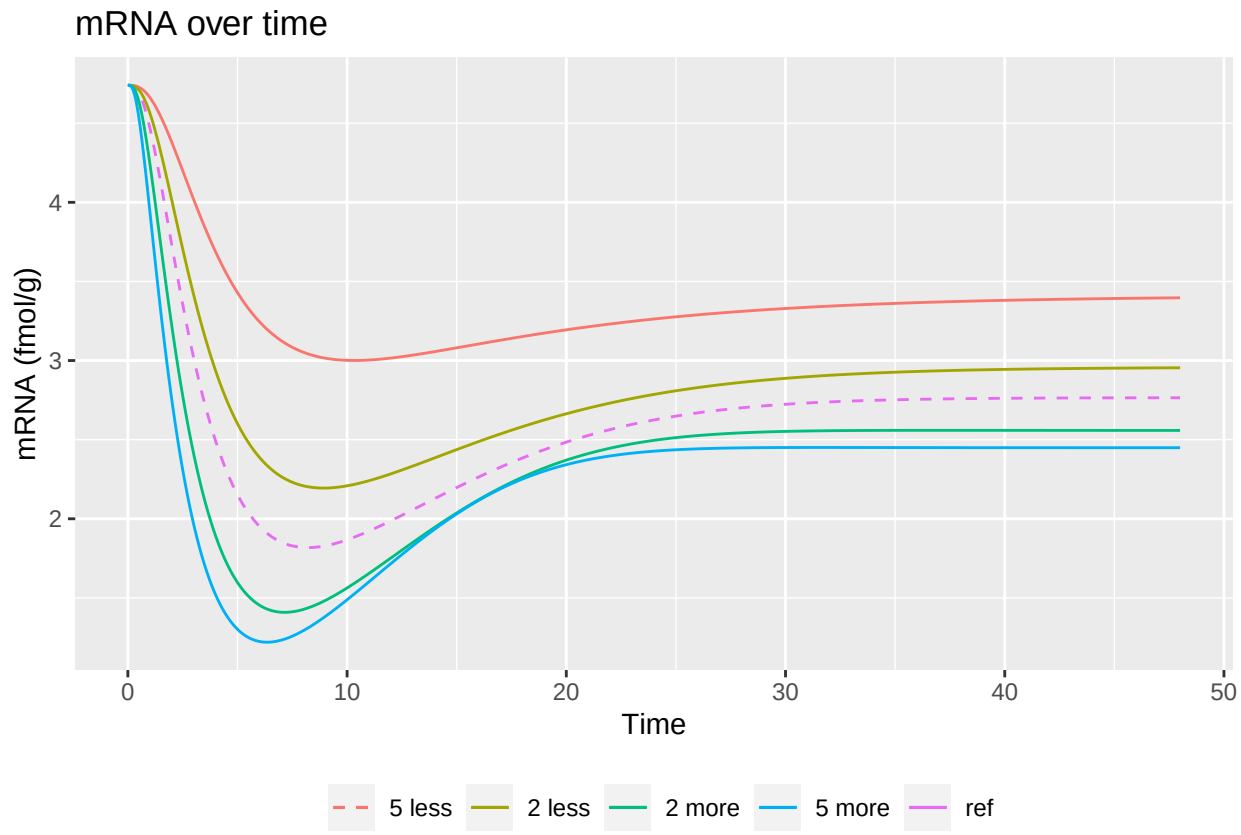

```
ggplot(data = steadys, mapping = aes(x = time, y = DRN)) +
        geom_line(aes(color = "Turnover")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "Time", y = "Receptor (fmol/mg)",
             title = "Receptor complex in Nucleus")
```



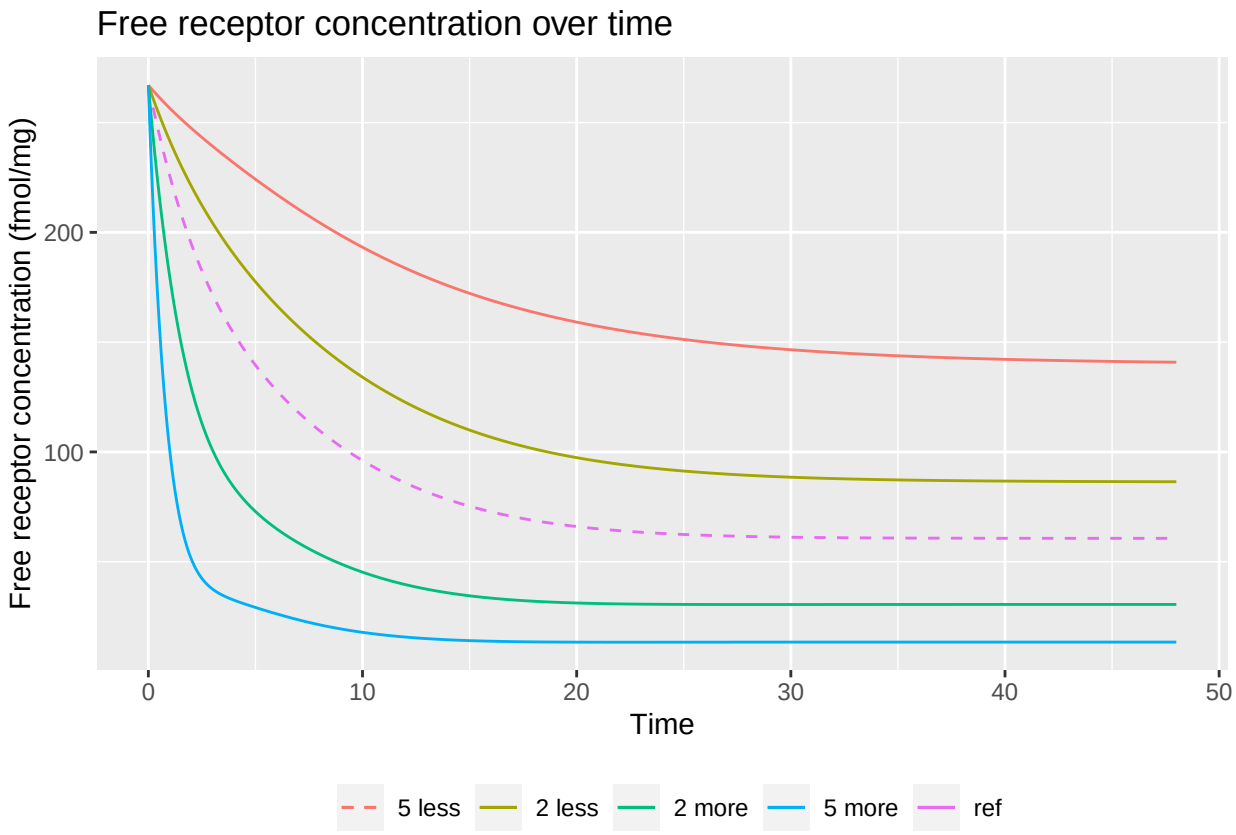
Changes in k_{on} and k_{re}

```
## Different times values due to conflict in results
times <- seq(0, 48, by=0.01)

state <- c(
        R.m0 = 4.74,
        R.0 = 267,
        DR = 0,
        DRN = 0
)

params <- c(
        k.s_Rm = 2.90,
        IC.50_Rm = 26.2,
        k.on = 0.00329,
        k.T = 0.63,
        k.re = 0.57,
        R.f = 0.49,
        k.d_R = 0.0572,
        k.d_Rm = 0.612,
        k.s_R = 3.22,
        D = calc.D(20)
)

group.cols <- hue_pal()(5)
```

```r
## 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 = grd_model, method = "euler"))

params$k.on <- 0.0039/5

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

params$k.on <- 0.0039/2

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

params$k.on <- 0.0039*2

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

params$k.on <- 0.0039*5

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

ggplot(mapping = aes(x = time, y = R.m0)) +
        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 = names(colours)) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(2, 1, 1, 1, 1) ) ) )
```




```
ggplot(mapping = aes(x = time, y = R.0)) +
        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 = names(colours)) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(2, 1, 1, 1, 1) ) ) )
```




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

params$k.re <- 0.57/5

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

params$k.re <- 0.57/2

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

params$k.re <- 0.57*2

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

params$k.re <- 0.57*5

model_k.re_plus5 <- as.data.frame(ode(times = times, y = state,
                 parms = params, func = grd_model, method = "euler"))

ggplot(data = model_k.re_ref, mapping = aes(x = time, y = R.m0)) +
        geom_line(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")) +
```

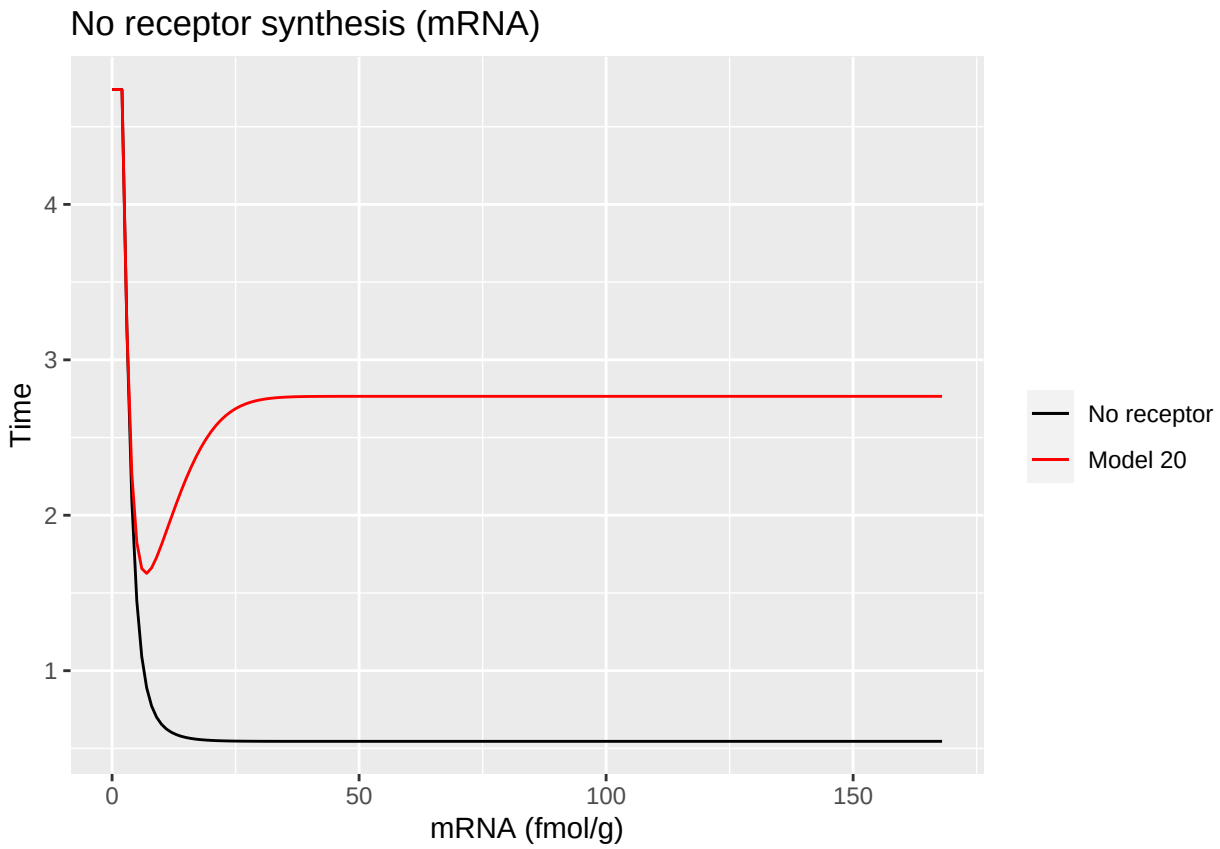
```
        geom_line(data = model_k.re_plus2, aes(color = "2 more")) +
        geom_line(data = model_k.re_plus5, aes(color = "5 more")) +
        labs(x = "Time", y = "mRNA (fmol/g)", title = "mRNA over time") +
        theme(legend.position = "bottom") +
        scale_colour_manual(name = "", values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

ggplot(data = model_k.re_ref, mapping = aes(x = time, y = R.0)) +
        geom_line(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 = names(colours)) +
        guides(color = guide_legend(title = "",
                                    override.aes = list(linetype = c(2, 1, 1, 1, 1) ) ) )
```

Block Synthesis of Receptor

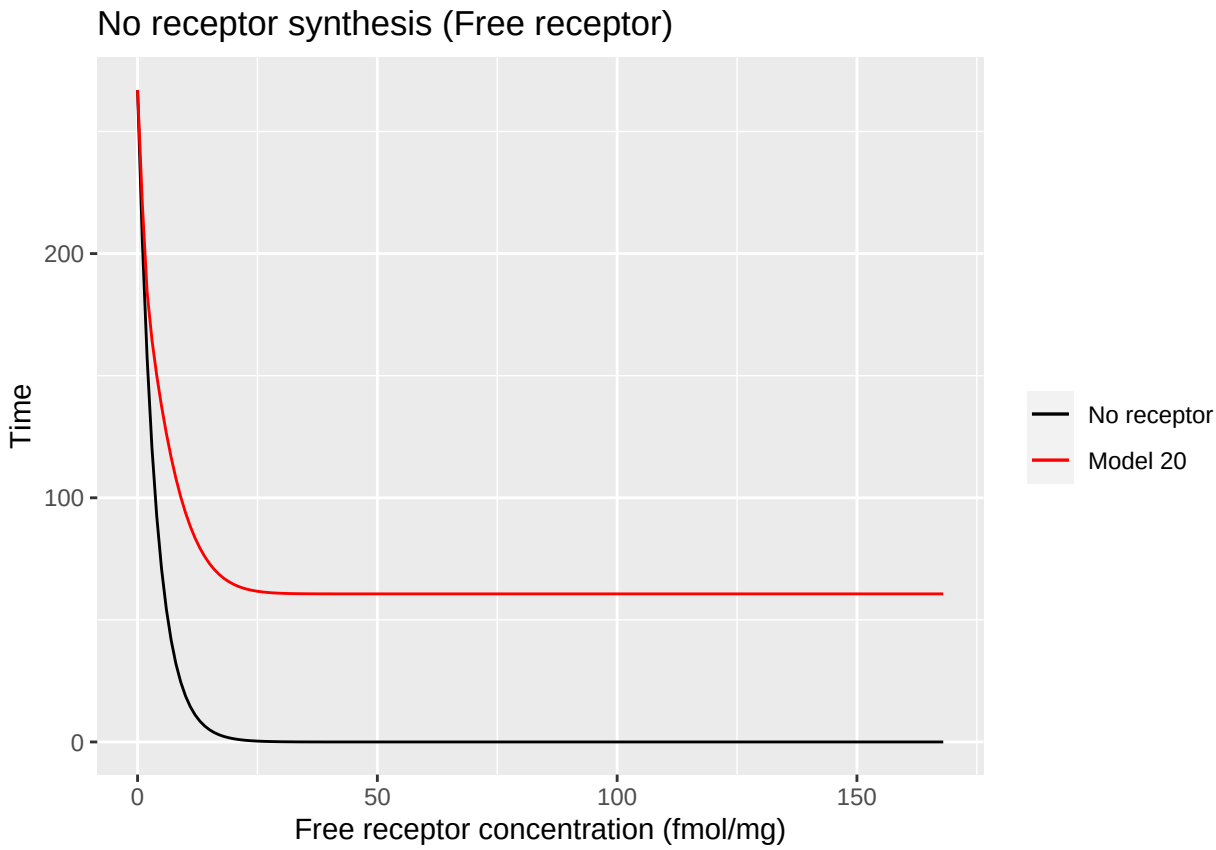
To simulate this situation, k_{s_R}, R_f and k_{re} need to be put to zero.

```
params <- c(
        k.s_Rm = 2.90,
        IC.50_Rm = 26.2,
        k.on = 0.00329,
        k.T = 0.63,
        k.re = 0,
        R.f = 0,
        k.d_R = 0.0572,
        k.d_Rm = 0.612,
        k.s_R = 0,
        D = calc.D(20)
)

state <- c(
        R.m0 = 4.74,
        R.0 = 267,
        DR = 0,
        DRN = 0
)
times <- seq(0, 168, by = 1)
no.Receptor <- as.data.frame(ode(times = times, y = state, parms = params,
                                 func = grd_model, method = "euler"))

ggplot(data = no.Receptor, mapping = aes(x = time, y = R.m0)) +
        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)") +
```

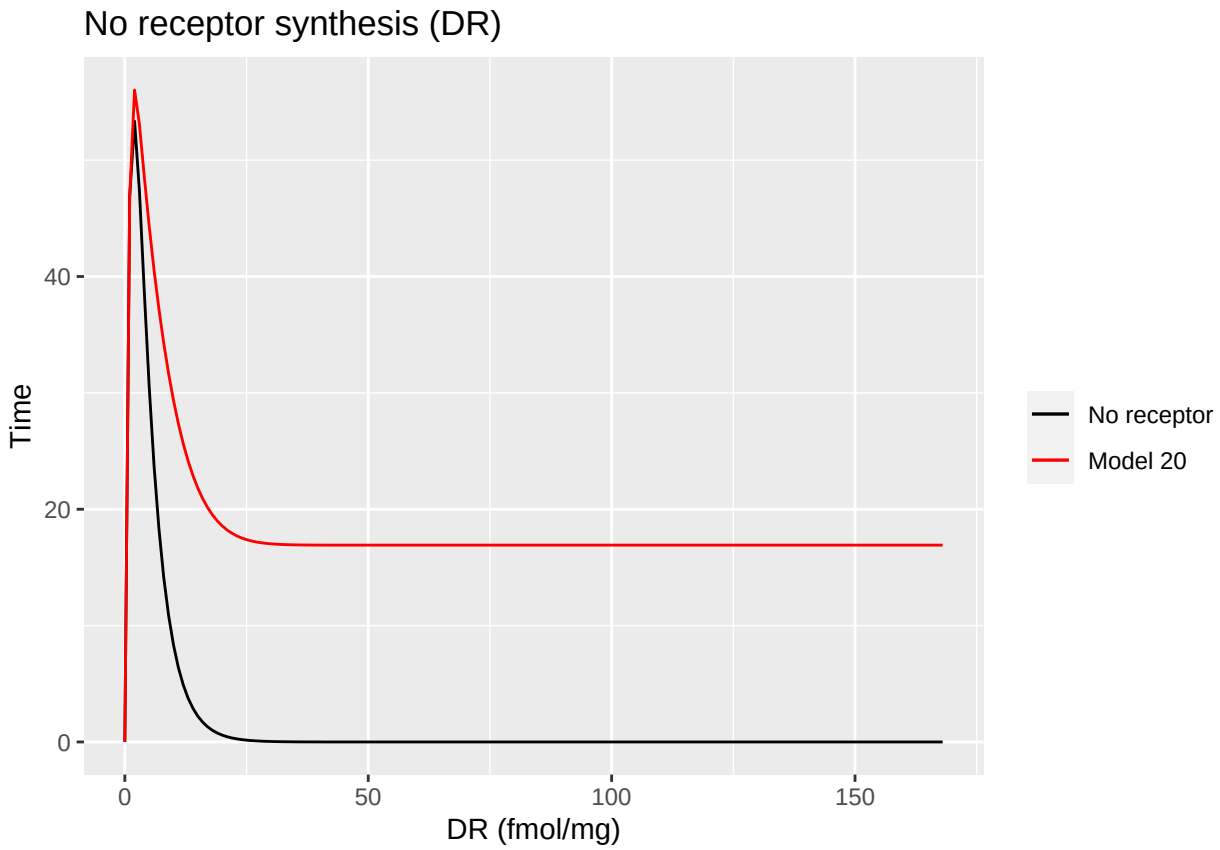
```
        scale_colour_manual(name = "", values = c("black", "red"),
                            limits = c("No receptor", "Model 20"))
```



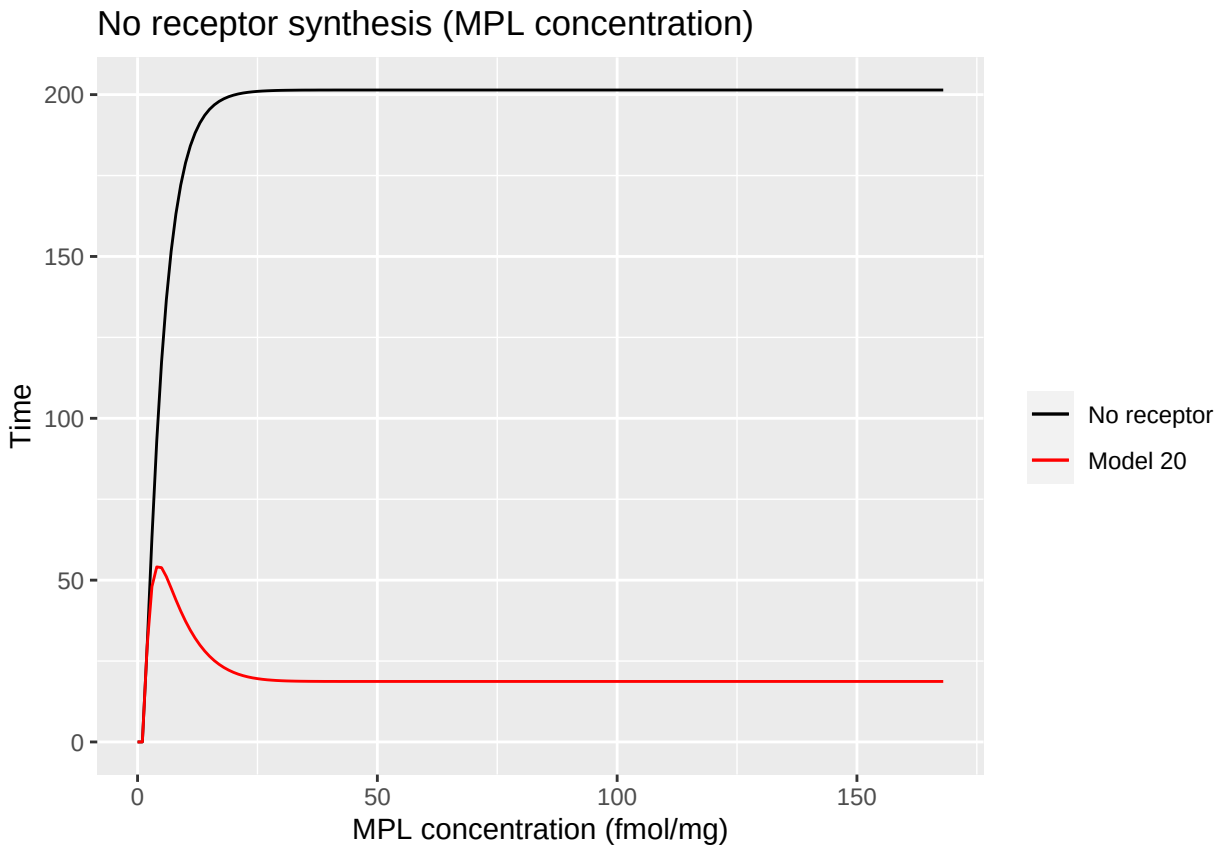

```
ggplot(data = no.Receptor, mapping = aes(x = time, y = R.0)) +
        geom_line(aes(color = "No receptor")) +
        geom_line(data = model_20, aes(color = "Model 20")) +
        labs(x = "Free receptor concentration (fmol/mg)", y = "Time",
             title = "No receptor synthesis (Free receptor)") +
        scale_colour_manual(name = "", values = c("black", "red"),
                            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 = c("black", "red"),
                            limits = c("No receptor", "Model 20"))
```




```
ggplot(data = no.Receptor, mapping = aes(x = time, y = DRN)) +
        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 = c("black", "red"),
                            limits = c("No receptor", "Model 20"))
```


No receptor synthesis (MPL concentration)
Time
200
150
100
50
0
0
50
100
150
MPL concentration (fmol/mg)
No receptor
Model 20