Model Expression glucorticoid repectors

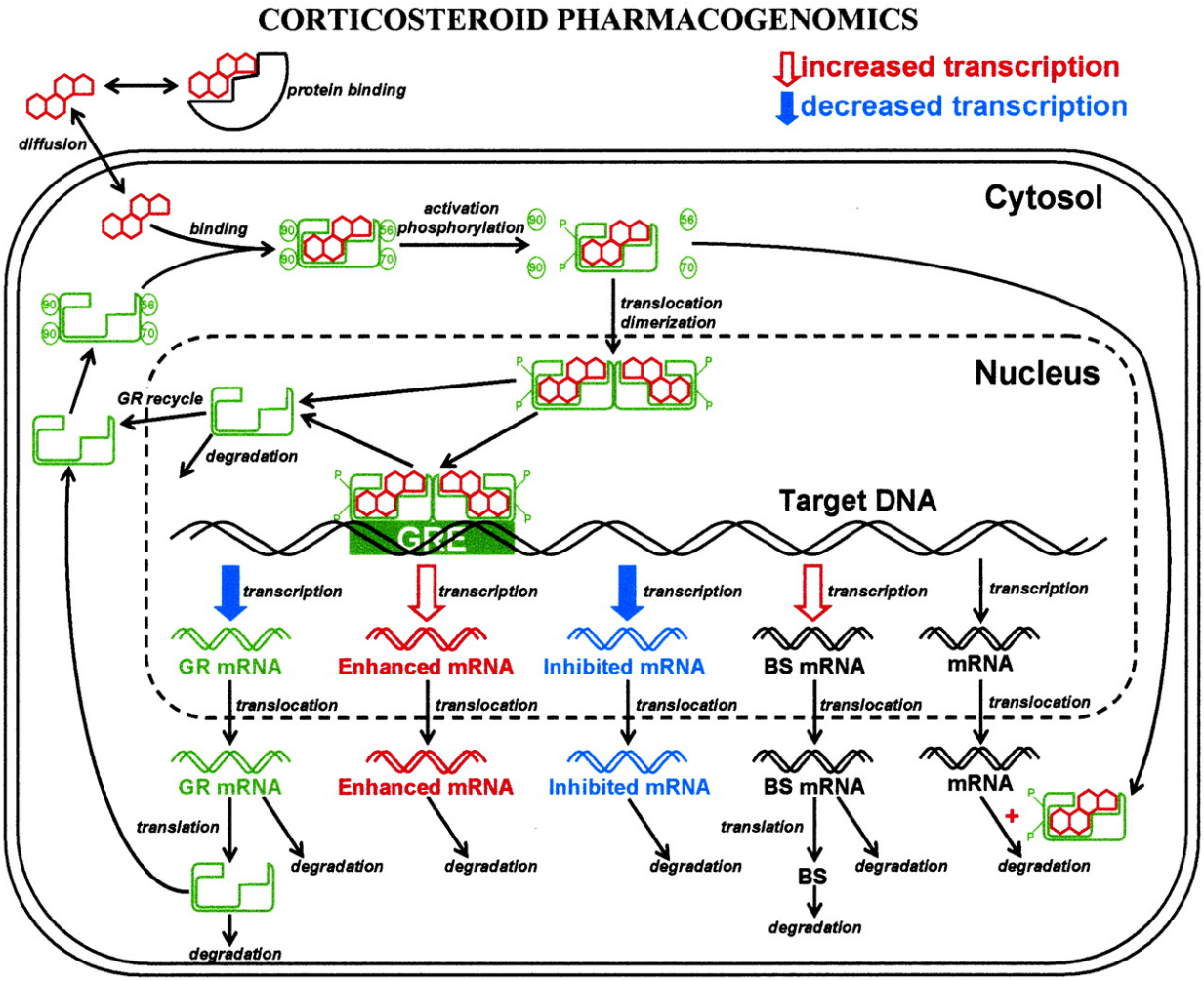

Figure 1: image

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Introduction

This project involves the validation and testing of a mathematical model regarding the expression of glucocorticoid receptors where the expression is regulated by corticosteroids. The corticosteroids regulate the transcription of inflammatory response genes, making them a great candidate for a possible drug.

Corticosteroids, also called adrenal cortex hormones, are steroids that are produced in the adrenal glands. The steroids are a derivative of the cholesterol molecules, are hydrophobic and typically remain in the cytosol. The corticosteroids are divisible in two groups:
Glucocorticoids and Mineralocorticoids. We will focus on the Glucocorticoids, these steroids regulate the metabolism of glucose. Besides promoting the synthesis of glucose the steroid also has other functions, including: * fat distribution * suppressing the immune response *suppressing inflammation* promoting the breakdown of proteins

The corticosteroid of choice is methylprednisolone(MPL), it is a widely used drug to treat inflammatory diseases such as asthma, rheumatism and lupus. MPL slows down the inflammatory response by binding to transcription factors that regulate transcription of genes involved in the inflammatory response. Besides that, they also slow down the synthesis of their own receptors by binding the steroid-receptor complex to the response elements.

Our main goal is to validate a mathematical model, we do this by running simulations in R using the desolve and rootsolve packages. These packages solve differential equations, so that way we can simulate and plot the model with various changes in parameters and states to compare them. The mathematical model describes the glucocorticoid receptor dynamics, including the synthesis of receptor mRNA, the vorming of the receptor-complex and its recycling, and ofcourse the influence of MPL concentrations. The model will be compared against real world experimental data to study its effectiveness.

The model

The model describes the interaction between MPL and the receptor, this can be written as four distinct ordinary differential equations (ODE's).

$$\frac{dmRNA_R}{dt} = k_{s\_Rm} \cdot \left(1 - \frac{DR(N)}{IC_{50\_Rm} + DR(N)}\right) - k_{d\_Rm} \cdot mRNA_R$$

$$\frac{dR}{dt} = k_{s\_R} \cdot mRNA_R + R_f \cdot k_{re} \cdot DR(N) - k_{on} \cdot D \cdot R - k_{d\_R} \cdot R$$

$$\frac{dDR}{dt} = k_{on} \cdot D \cdot R - k_T \cdot DR$$

$$\frac{dDR(N)}{dt} = k_T \cdot DR - k_{re} \cdot DR(N)$$

Figure 2: image

The first equation calculates the amount of receptor mRNA(mRNAr) by using the Ks_rm, the rate of mRNA synthesis. The amount of MPL-receptor complex in the nucleus, DR(N). IC50_rm, the concentration DR(N) where the synthesis of receptor mRNA decreases by 50 percent compared to base value. And finally Kd_rm, the rate of degradation of the mRNA receptor.

The second equation calculates the derivative of the density of the glucocorticoid receptor with which no complex has been formed. It does this by firstly multiplying the rate of receptor synthesis (Ks_r) by the amount of mRNAr. After which we add the Fraction of the free receptor that will be recycled multiplied by the recovery of the receptor from the nucleus to the cytosol (Kre) and finally multiplied by DR(N). And the third step is subtracting the concentration MPL (D) times the density of the glucocorticoid receptor (R) multiplied by Kon, the second order rate constant of MPL-complex synthesis. And finally we also subtract the rate of receptor degradation (Kd_r) times R.

The third formula calculates the new value for DR, the density of MPL receptor complex. It does this by multiplying Kon, D and R. And from that subtract Kt, the rate of translocation of the receptor complex from cytosol to the nucleus, times DR.

The final formula determines the derivative for DR(N) by multiplying Kt by DR and subtracting Kre times DR(N).

The timescale is in hours, so that means the unit of Kt, Kre and Kd_r is 1 over an hour. The unit of all the initial values except Rmo and IC50_rm, the starting level of mRNAr, are in fmol/mg protein. Rmo is in fmol / g, situated in the liver as is Ks_rm. The numerical values are shown in the table below, these are based upon experimental data from rats.

```
## [1] "values"
```

```
##         c(ks_Rm = 2.9, IC50_Rm = 26.2, kd_Rm = 0.612, ks_r = 3.22, Rf = 0.49, kre = 0.57, kon = 0.00
```

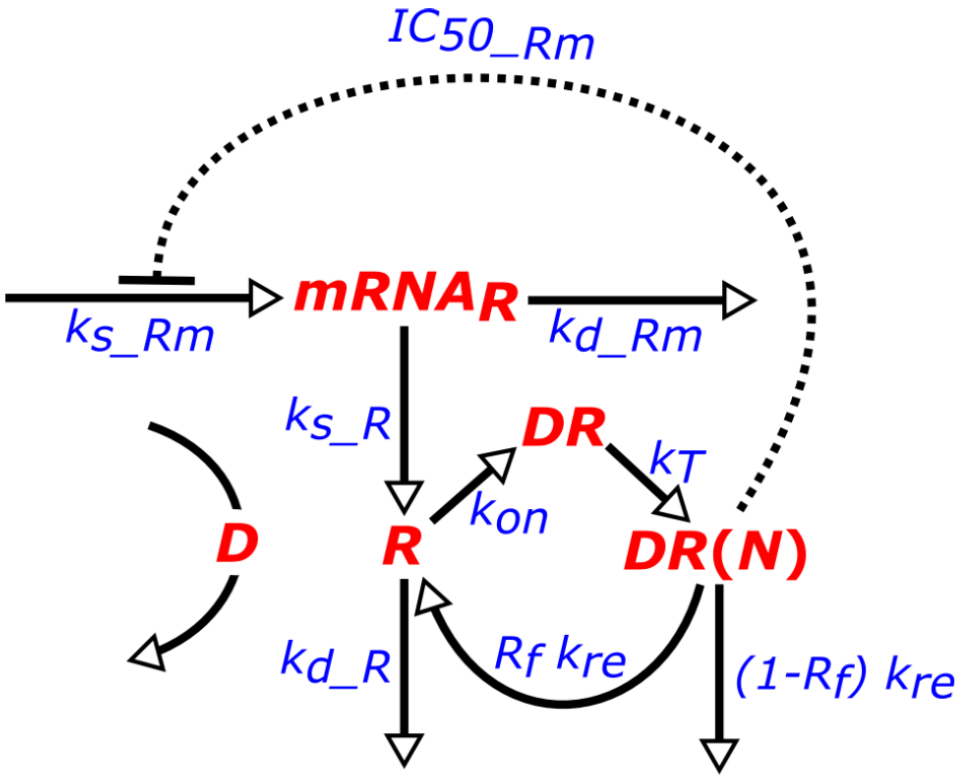


Figure 3: image

```
## ks_Rm
## IC50_Rm
## kd_Rm
## ks_r
## Rf
## kre
## kon
## kd_R
## kT
## D
```

```
## [1] "initial values"
```

```
##       c(mRNAr = 4.74, R = 267, DR = 0, DRN = 0)
## mRNAr                                      4.74
## R                                        267.00
## DR                                         0.00
## DRN                                        0.00
```

Results

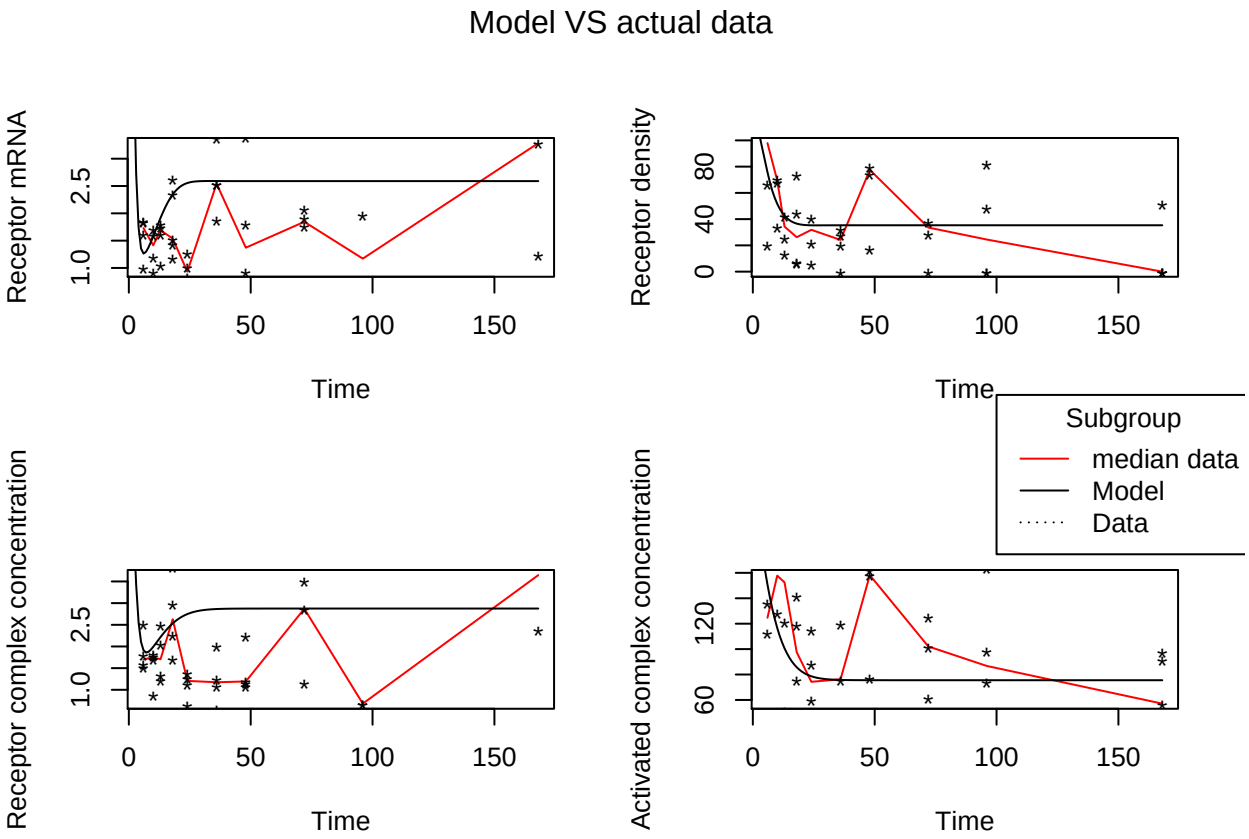


Fig 1; The results of the model are not in line with the data. The red line is going up and down. The general shape kind of follows the model though. An explanation for this could be that the glucose level in someone's body is constantly changing. Which could result in the lines shaking due to the glucose levels that are shaking too.

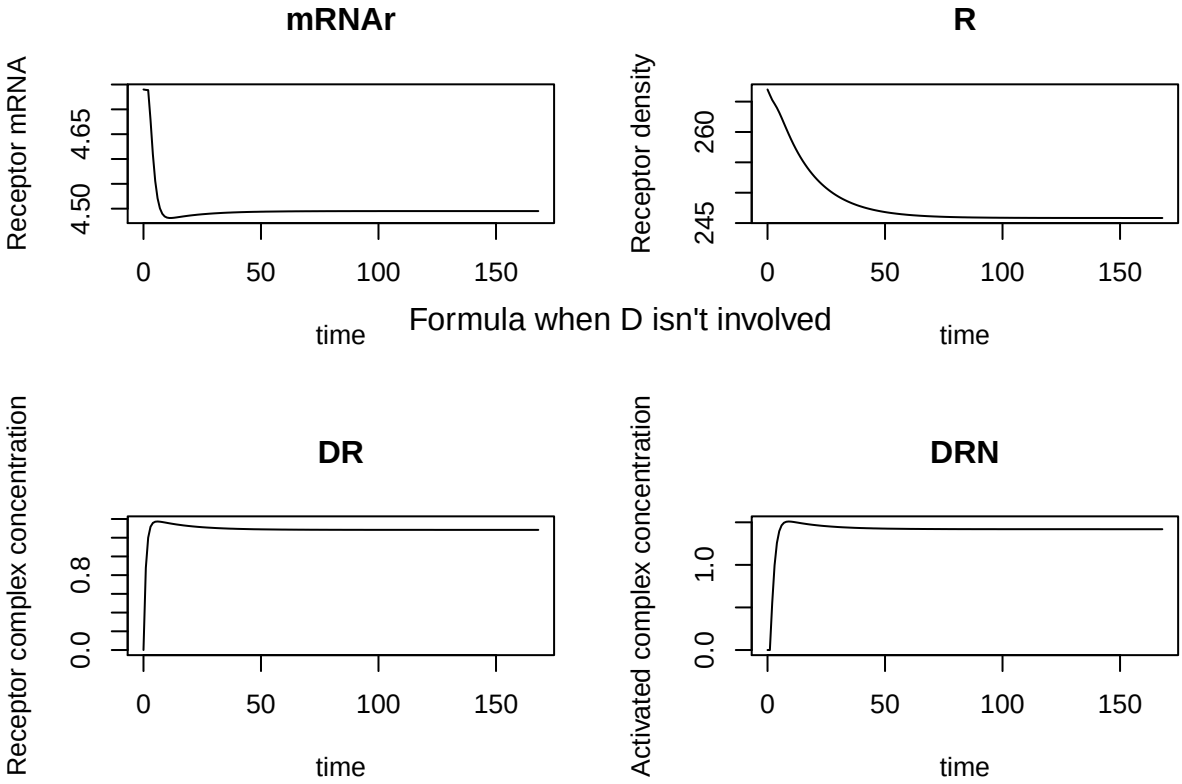


Fig 2; If the drug has no influence on the synthesis of mRNA this would be expected. The main differences are the levels of the Receptor mRNA and the receptor density which are now higher, the Receptor complex concentration and the Activated complex concentration are now lower aswell.

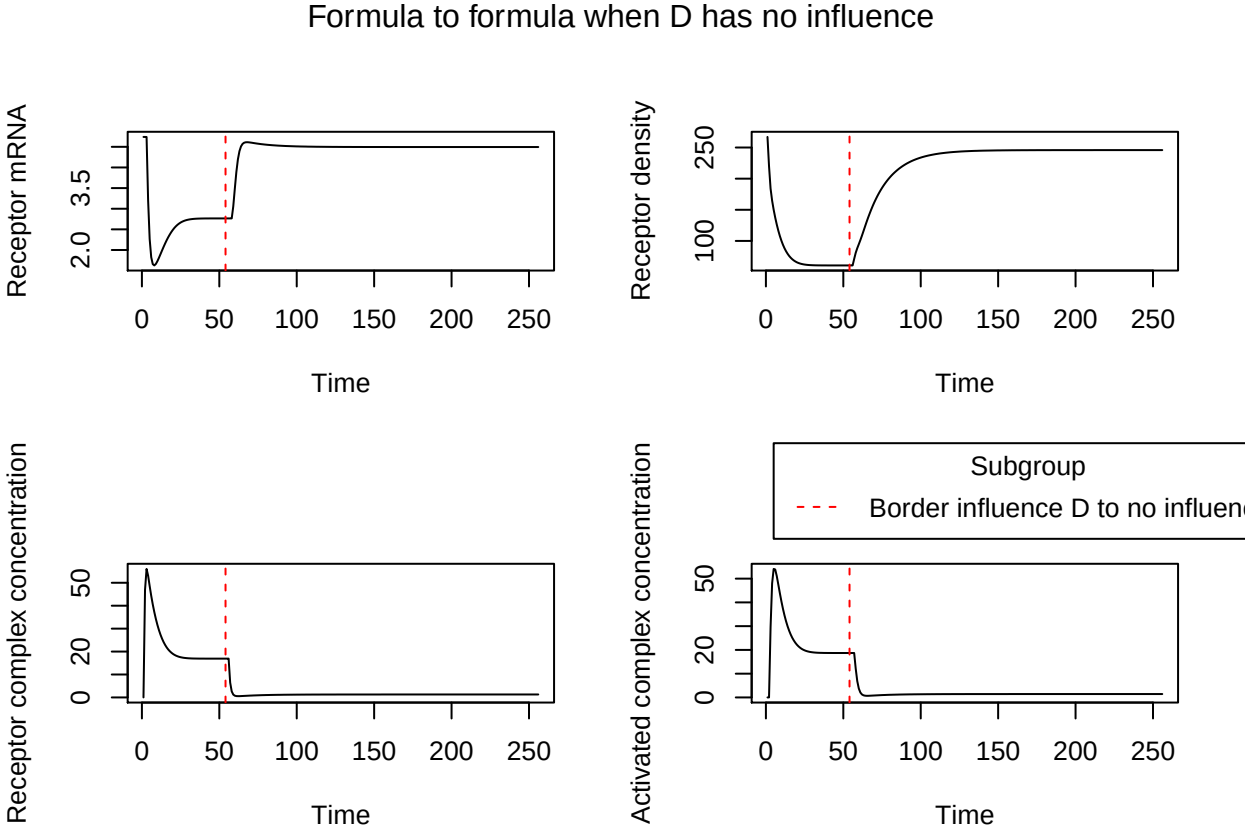


Fig 3; This plot shows the normal process until the steady state is reached. When it's reached the formula will run with the end values. Except for the D that will now be 0. The formula will run from there until a new steady state is reached. Something that stands out is that all the values end around the value that they started with.

```
## Warning in par(xpd = xpd): NAs introduced by coercion
```

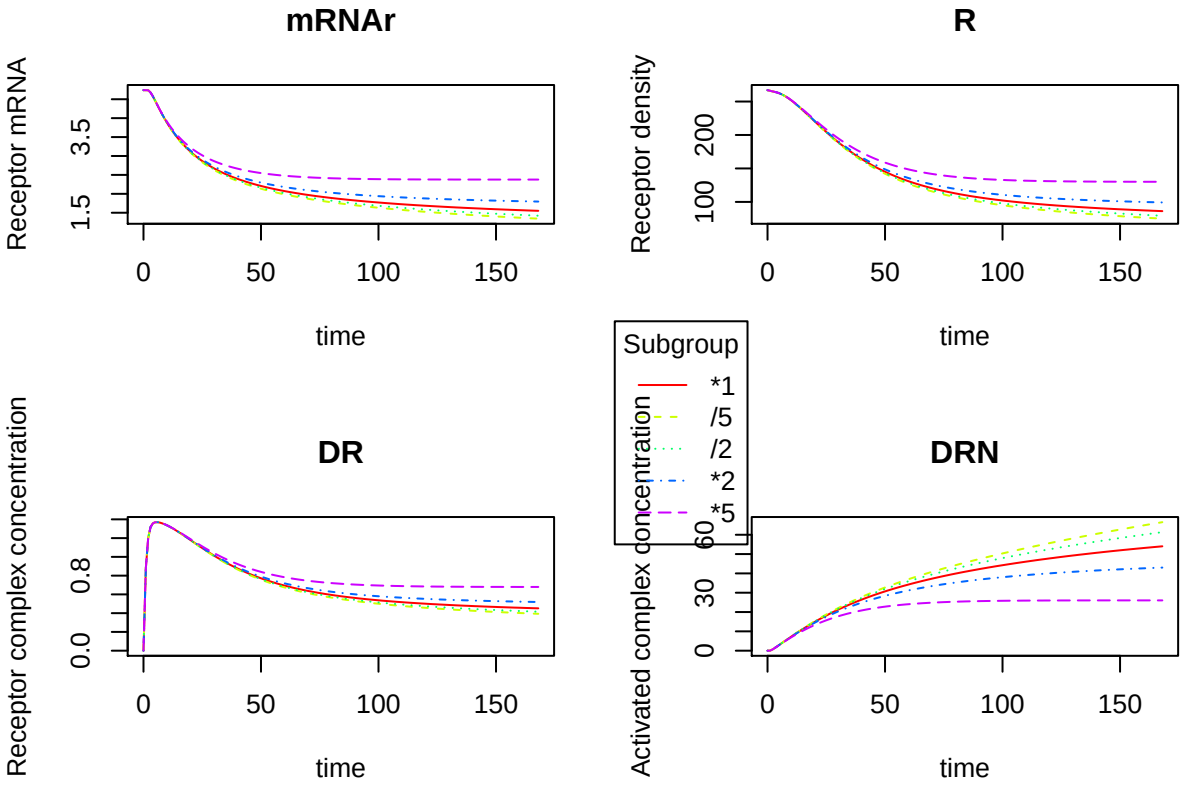


Fig 4; This plot shows the change of results whenever the kre variable changes. The receptor mRNA, Receptor density and the Receptor complex concentration will lower more slowly whenever the value is higher. The Activated complex concentration however lowers faster the higher the value is.

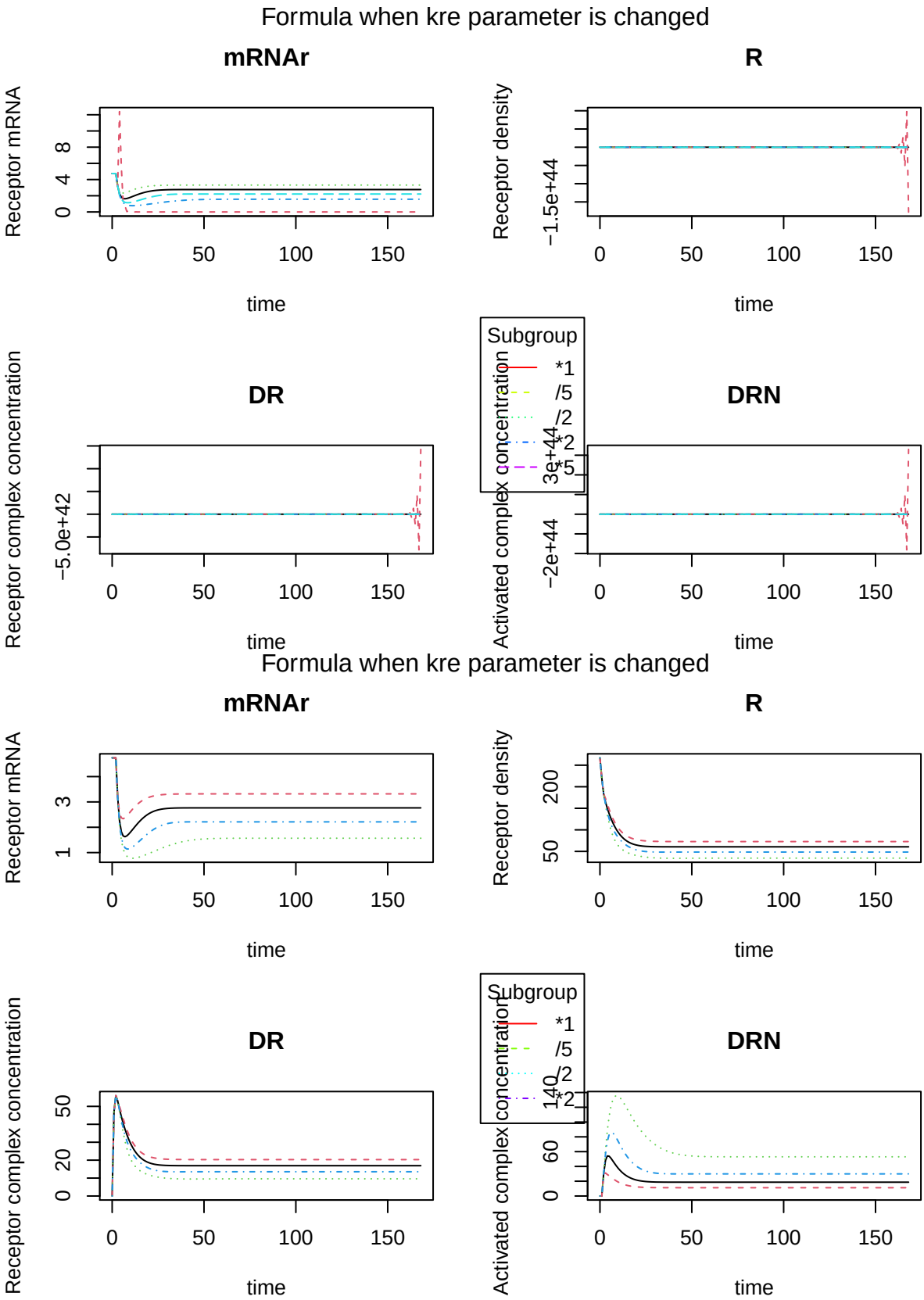


Fig 5; These plots show what happens when the kre parameter becomes different. The *5 values really mess up the plot which is why there is another plot without the* 5 values.

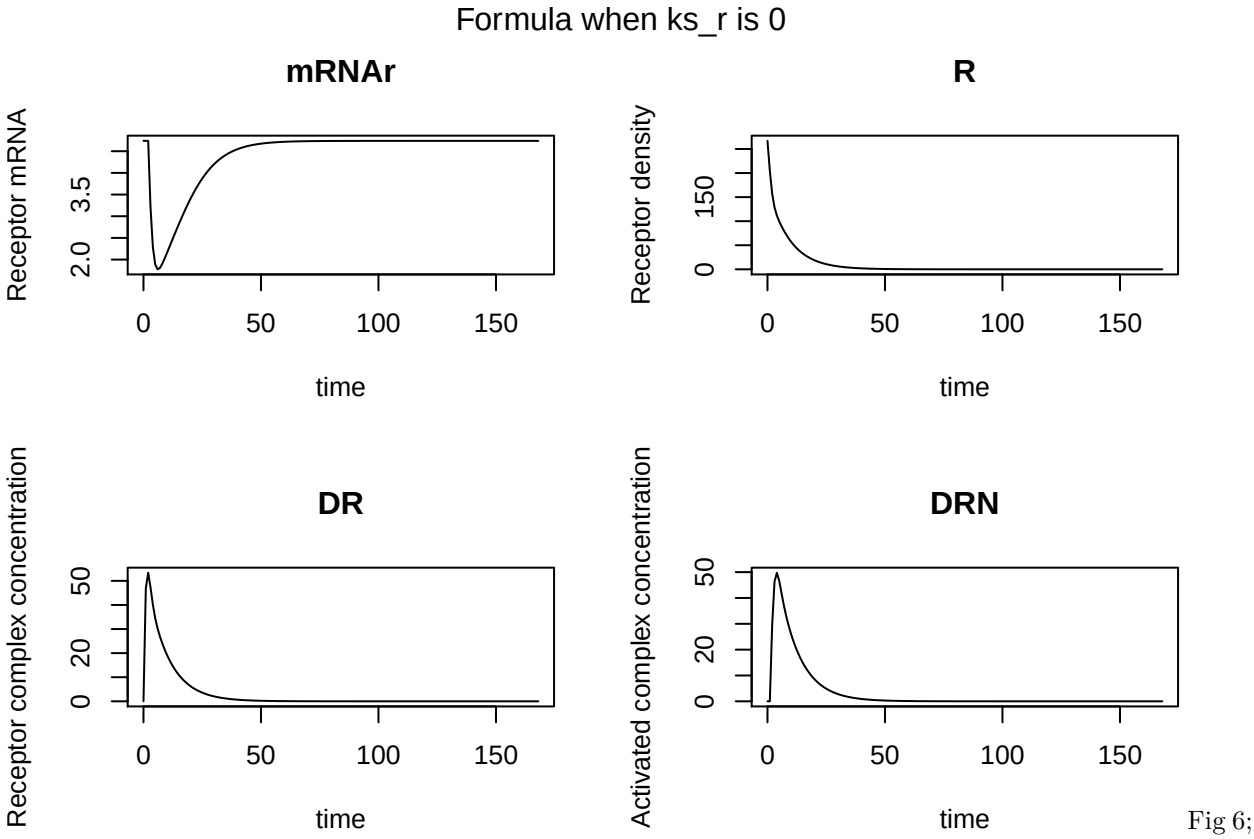
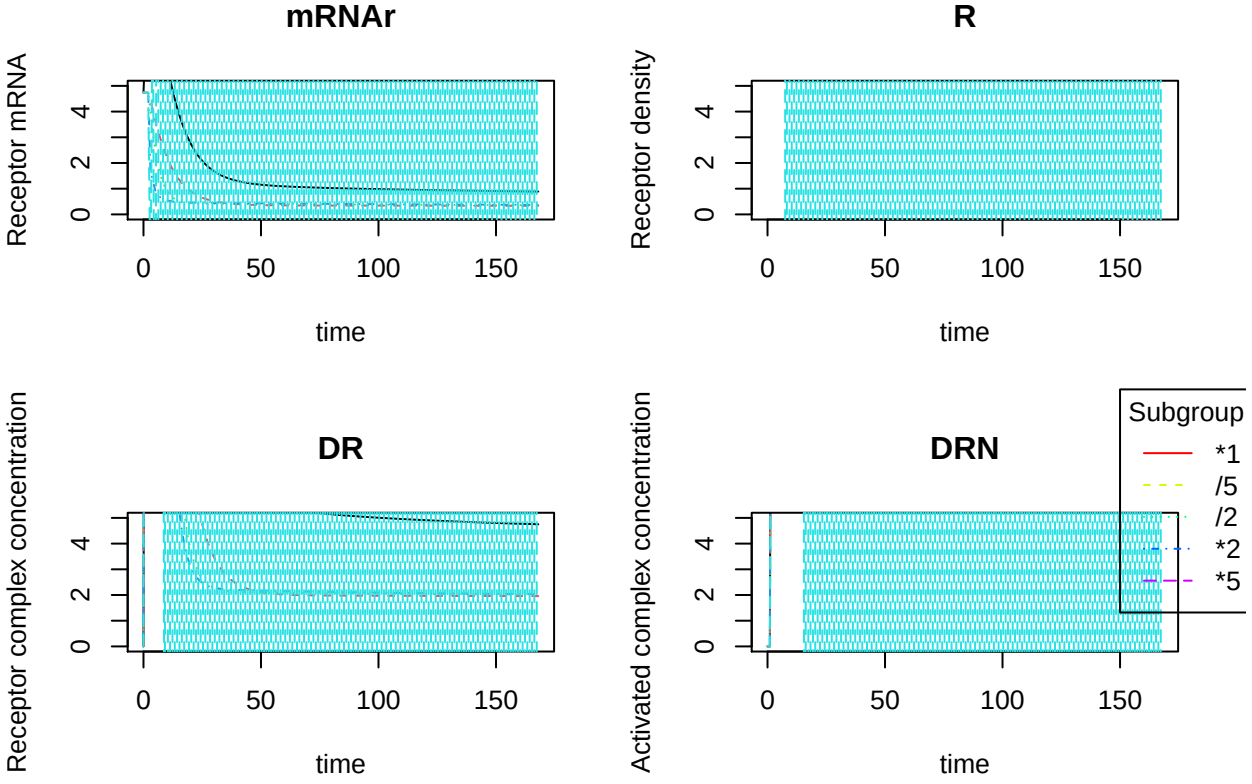


Fig 6; This plot shows the model with the ks_r parameter being 0. This parameter is the speedconstant of the GR mRNA synthese. The main thing that changes is that the values get higher and lower faster and more extreme. For example the Receptor mRNA gets to 0.1 instead of 1.1.



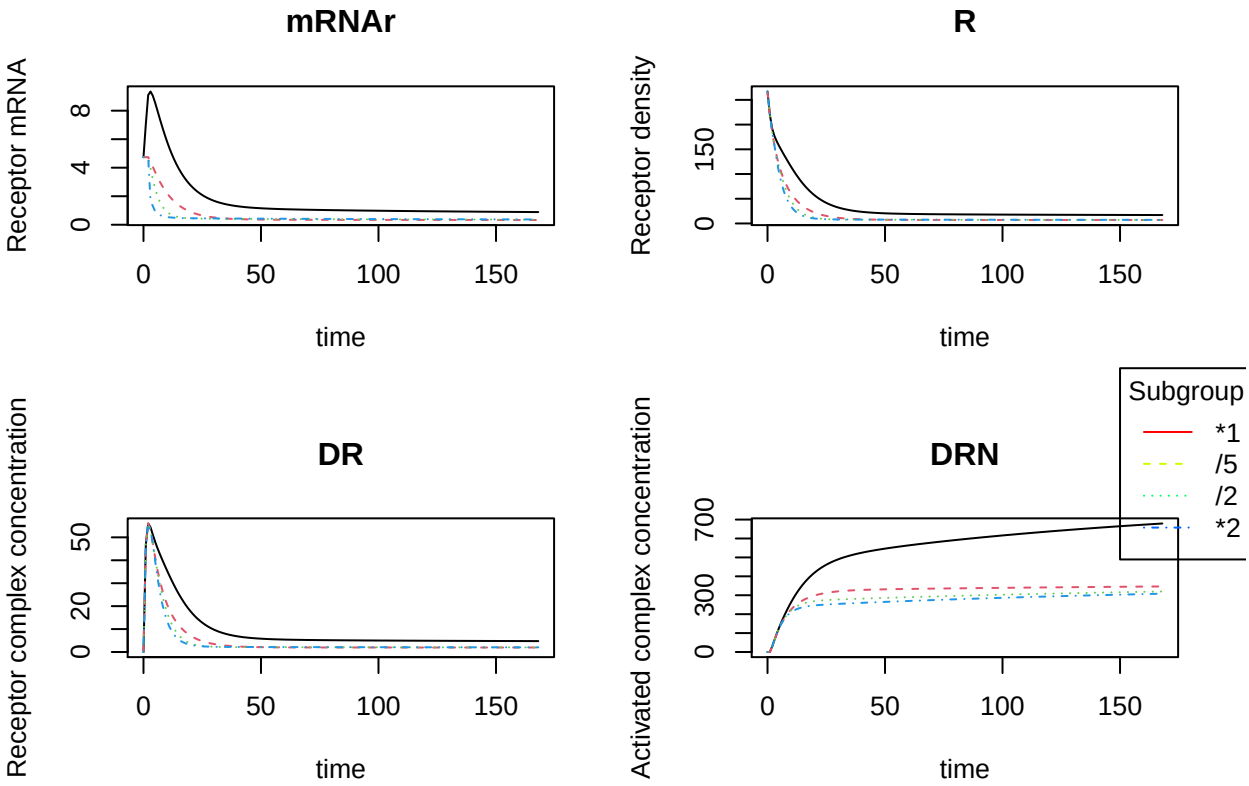


Fig 7; Like figure 5, the *5 value destroys the formula. Which is why there's a second plot as well. The plot does not look like expected. The black like is not in between the others. Which is weird because the values are below and above it. Meaning something strange is happening.

Discussion

In general, the results confirm that the model do kind of align with the actual data meaning that the model is valid. Something that directly stands out is the values in figure 4 being the same value after being in the steady-state as the start values. This clearly shows its a cycle and is interesting to see.
Another interesting thing to see is the model after the ks_r parameter becomes 0. The results have a really fascinating effect. The values become more extreme, which makes sense. Something else that stands out is the *5 lines in figure 5 and 7. For some reason high values like that break the formula. It is no coincidence this happens, the explanation is just not found yet. This is something the model could be improved on. Something else the model could improve on is implementing the values going up and down (fig 1). This would be hard to implement due to the glucose levels being inconsistent, but it would be good for a future research. Another thing would be the* 5 lines being extremely different than the others. The reason for this is unclear yet and could be researched on.