

Assignment week 2  
Glucocorticoid receptor dynamica



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# 1 Introduction

Glucocorticoids are a subclass of corticosteroids, which are a class of steroid hormones produced in the adrenal cortex of vertebrates. Glucocorticoids and mineralocorticoids, another subclass of corticosteroids, are of great importance because they're involved in a wide range of physiological processes, such as stress response, immune response, regulation of inflammation and more.

## 1.1 About corticosteroids

## 1.2 How they work and when they are used

## 1.3 Effect of medicine on receptor production

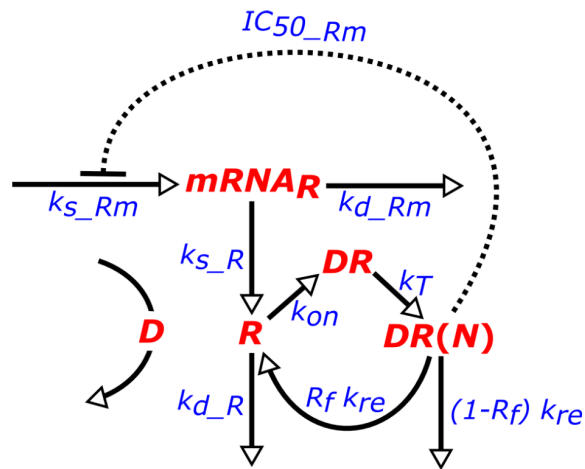


Figure 1: flowdiagram glucocorticoide receptor dynamica

## 2 Model for Glucocorticoids Receptor Dynamics (GRD)

### 2.1 Differential equations

$$\begin{aligned}\frac{\Delta mRNA_R}{\Delta t} &= k_{s\_Rm} * (1 - \frac{DR(N)}{IC_{50\_Rm} + DR(N)}) - k_{d\_Rm} * mRNA_R \\ \frac{\Delta R}{\Delta t} &= k_{s\_R} * mRNA_R + R_f * K_{re} * DR(N) - K_{on} * D * R - k_{d\_R} * R \\ \frac{\Delta DR}{\Delta t} &= k_{on} * D * R - k_T * DR \\ \frac{\Delta DR(N)}{\Delta t} &= k_T * DR - k_{re} * DR(N)\end{aligned}$$

### 2.2 Creating an R function of the GRD model

```
# Create function of GRD model
model <- function(time, cur.state, parameters) {
  # Unpack the current state and the parameters for instant access
  with(as.list(c(cur.state, parameters)), {
    # Calculate delta for each equation
    delta.Rm <- k.s_Rm * ( 1 - DR_N / ( IC.50_Rm + DR_N )) - k.d_Rm * Rm
    delta.R <- k.s_R * Rm + R.f * k.re * DR_N - k.on * D * R - k.d_R * R
    delta.DR <- k.on * D * R - k.T * DR
    delta.DR_N <- k.T * DR - k.re * DR_N
    # Return delta's in a list for `ode` function to use
    return(list(c(delta.Rm, delta.R, delta.DR, delta.DR_N)))
  })
}
```

### 2.3 Simulating the model for MPL using given values

For this assignment the corticosteroid that is used is methylprednisolone (MPL).

Parameters for MPL in a GRD model are already given, their values were previously determined by performing experiments on rats.

Table 1: Initial Values for MPL

| Parameter | Value | Unit                   | Explanation                                  |
|-----------|-------|------------------------|--|
| Rm        | 4.74  | <i>fmol/g liver</i>    | concentration of receptor mRNA               |
| R         | 267   | <i>fmol/mg protein</i> | concentration of free receptor in cytosol    |
| DR        | 0     | <i>fmol/mg protein</i> | concentration of receptor complex in cytosol |
| DR_N      | 0     | <i>fmol/mg protein</i> | concentration of receptor complex in nucleus |

The plasma concentration of corticosteroid is constant and thus is a parameter. It is given in 20 ng/mL but needs to be converted to nmol/L, this is done by multiplying by a thousand (1000) and then dividing by the molecular weight of the molecule. For this experiment MPL is used and it's molecular weight is 374.471. Because of the required conversion, D's value is not included in the table below.

Table 2: Parameter Values for MPL

| Parameter | Value   | Unit                   | Explanation  |
|-----------|---------|------------------------|--|
| k.s_Rm    | 2.9     | <i>fmol/g liver/h</i>  | zero-order rate constant of receptor mRNA synthesis                            |
| k.d_Rm    | 0.612   | -                      | first-order rate constant receptor mRNA degradation                            |
| IC.50_Rm  | 26.2    | <i>fmol/mg protein</i> | concentration of DR_N where receptor mRNA synthesis drops to 50% of base value |
| k.on      | 0.00329 | <i>L/nmol/h</i>        | second-order rate constant of receptor complex formation                       |
| k.T       | 0.63    | <i>1/h</i>             | first-order rate constant of translocation of receptor complex to nucleus      |
| k.re      | 0.57    | <i>1/h</i>             | first-order rate constant of receptor 'recovery' from nucleus to cytosol       |
| R.f       | 0.49    | -                      | fraction of receptor being recycled from complexes                             |
| k.s_R     | 3.22    | -                      | first-order rate constant of receptor synthesis                                |
| k.d_R     | 0.0572  | <i>1/h</i>             | first-order rate constant of receptor degradation                              |
| D         | -       | <i>nmol/L</i>          | plasma concentration of corticosteroid   |

```
# Initial values and time frame
initial.values <- c(Rm = 4.74, R = 267, DR = 0, DR_N = 0)
times <- seq(0, 48, by = 1)

## Convert concentration of MPL from ng/mL to nmol/L
D <- 20 * 1000 / 374.471
# Define parameters determined for methylprednisolone (MPL)
parameters <- c(k.s_Rm = 2.9, k.d_Rm = 0.612, IC.50_Rm = 26.2, k.on = 0.00329,
                k.T = 0.63, k.re = 0.57, R.f = 0.49, k.s_R = 3.22, k.d_R = 0.0572, D = D)

# Perform ODE function using the model with the given values for MPL
out <- ode(times = times, y = initial.values, parms = parameters,
           func = model, method = "euler")
plot(out)
```

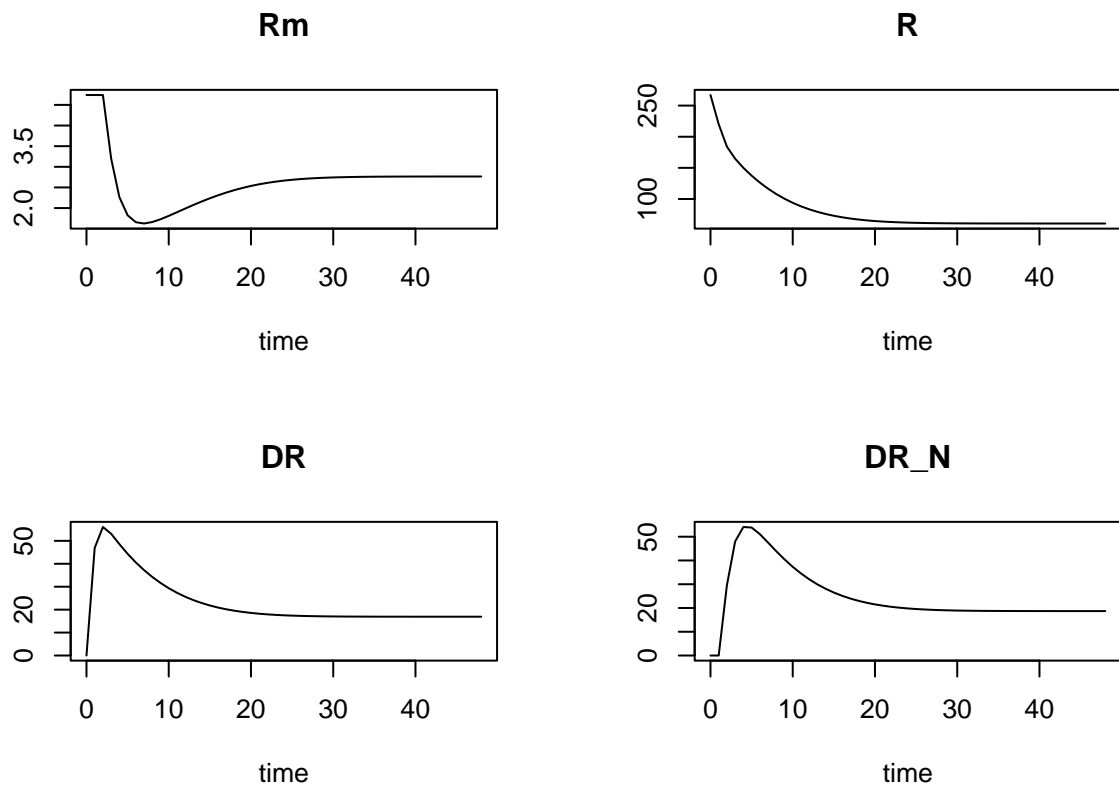


Figure 2: plot of glucocorticoids receptor dynamics simulation with given determined parameter values

## 3 Results

### 3.1 Concentration changes

- Concentration of receptor mRNA ( $\Delta mRNA_R$ )
- Concentration of free receptor ( $R$ )
- Concentration of MPL-receptor complex in cytosol ( $DR$ )
- Concentration of activated MPL-receptor complex ( $DR(N)$ )
- Total receptor concentration

## 4 Discussion and Conclusion

Changes over time explained by interactions between variables.



## References

- [1] Barnes, P.J. (2011), *Glucocorticosteroids: current and future directions*, British Journal of Pharmacology, 163: 29-43, <https://doi.org/10.1111/j.1476-5381.2010.01199.x> (accessed May 11, 2022).