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1 Introduction

Introduction of the research and introduction research questions

The effect of plasma concentration should be related to the concentration of the test substance (so it implies the delayed ventricular regulation). The concentration of the test substance is highly effected by the extent of the delayed ventricular repolarization. Since the plasma concentration is most commonly used as the effective concentration. This research is interested in the mean concentration from drug where it meet cardiac ion channels within heart tissue.

Drug concentration in heart tissue should be of particular interest regarding all possible sites where the drug might meet cardiac ion channels.

1.1 Goal

- Describe Goal (not the educational goal but the research goal)
- Describe how you reach the goal (e.g. make model and figures, use different setting)
- formulate hypothesis

This research aims to give a good understanding of the drug concentration over time in different tissue types of the heart. A PBPK (physiologically-based pharmacokinetic) approach has hardly been used in the modeling of drug concentration in various locations within heart tissue so this might be a great opportunity to accelerate research into the role of drugs on many things heart related. In order to get a better understanding of this research, deSolve will be issued and model configurations should be set. In addition defined equatuions will be solved to enlarge the knowledge about the drug concentration. Therefore the Null-hypothesis; there is no significant difference between different sample groups, will be tested. If that's not the case then the alternative hypothesis is assumed to be true.

1.2 Theory

In order to understand the model, the concept of a PBPK model needs to be clear. Simpy put, PBPK is a computer modeling approach that incorporates blood flow and tissue composition of organs to define the pharmacokinetics (PK) of drugs. Alterations in PK properties, such as, absorption, distribution, metabolism, and excretion, can have a substantial impact on achieving the desired therapeutic concentration of a drug. PBPK is a very powerful tool, so a lot of computing power is necessary. The best use for a PBPK model is drug research, which is the reason this type of model will be used in this research. It can also be, for instance, used by the Pharmaceutical Industry. The essention of integral calculations results in surface area of the graph, which is a useful application for dynamic models like the PBPK model.

The equations which are part of the heart PBPK model are as follows:

(1)
- Vmax[mg/h] = Vmax_pmol x CYP x MPPGL x Wli x MW x 60 / 10^9

$$V_{maxpmol} * CYP * MPPGL * W_{li} * MW * 60/10^9$$

(2) • CLu int2C8 = Cl int2C8 x fumic x ISEF2C8

$$CLU_{int2C28} * FU_{mic} * ISEF_{2c8}$$

(3) •

$$\frac{\frac{fu_p}{BP} * CLu_{int} * Q_{he}}{Q_{he} + \frac{fu_p}{BP} * CLu_{int}}$$

For the Whole-body PBPK model the Michaelis-Menten enzyme kinetics served a great factor in the composition of the first equation. This equation calculates the values of the maximal rate of saturating substrate concentrations (Vmax) in [mg/h] for each CYPs isoform. CYPs are a group of enzymes that can break down foreign substances like drugs, that is also the reason why they are part of the equation. Some parameters were obtained by using another package called the simcyp simulator. The values gotten from that prediction will be used in equation 1.

The heart model contains two equations. Firstly, the intrinsic clearance for each enzyme based on unbound fraction of compound will be calculated using given parameter values. To clarify, intrinsic clearance is the ability of the liver to remove drug in the absence of flow limitations and binding to cells or proteins in the blood. This is pretty important information because this process wil impact the drug concentration over time. Secondly, The 3rd equation will calculate the total heart metabolic clearance. The importance of this value is also quite clear, because the metabolic clearance is recognized as one of the main determinants of the blood concentration as well as volume. This is therefore used to help predict toxicokinetics.

2 Methods

2.1 The software model

The tool used for this experiment is called deSolve. This is a R-package which can help solve ODE, or ordinary differential equations. A few parameters were gotten from another research which used a program called: "Simcyp Simulator" to create a PBPK model. This model can predict certain values for tissues like the Kp which is pretty useful in this case. The research talked about just now has also used a package called FME, which performs a model fit based on algorithms. Equation 4 also plays a crucial role in this step.

```r
knitr::include_graphics("derivative.png")
```

$$\frac{dA_{epi}}{dt} = Q_{he} \times (C_{ar} - \frac{C_{epi}}{Kp_{epi}} \times BP) - 1/3 \times CLm_{HT} \times C_{epi} \times fu_p - P \times (C_{epi} - fu_{pf} \times C_{pf})$$

$$\frac{dA_{mid}}{dt} = Q_{he} \times (\frac{C_{mid}}{Kp_{mid}} \times BP - \frac{C_{endo}}{Kp_{endo}} \times BP) - 1/3 \times CLm_{HT} \times C_{mid} \times fu_p$$

$$\frac{dA_{endo}}{dt} = Q_{he} \times (\frac{C_{mid}}{Kp_{mid}} \times BP - \frac{C_{endo}}{Kp_{endo}} \times BP) - 1/3 \times CLm_{HT} \times C_{mid} \times fu_p$$

$$\frac{dA_{pf}}{dt} = -P \times (fu_{pf} \times C_{pf} - C_{epi}) + Q_{pf} \times (C_{ar} - \frac{C_{pf}}{Kp_{pf}} \times BP)$$

```r
# Parameters to be used in the PBPK function
parameters <- c(CLuint = 4, CLmHT =  0, KPmid = 7.4, Qpf = 0.01, KPendo = 14.0, KPpf = 2.6, Car = 100 /


PBPK_func <- function(t, y, parms) {
    with(as.list(c(y, parms)),{

      CLmHT = (((fup / BP) * CLuint * Qhe) / Qhe + (fup / BP) * CLuint)

      dAepi_dt <- Qhe * (Car - (Cepi / KPepi) * BP) - 1/3 * CLmHT * Cepi * fup - P * (Cepi - fupf * Cpf)

      dAmid_dt <- Qhe * ((Cmid / KPmid) * BP - (Cendo / KPendo) * BP) - 1/3 * CLmHT * Cmid * fup

      dAendo_dt <- Qhe * ((Cmid / KPmid) * BP - (Cendo / KPendo) * BP) - 1/3 * CLmHT * Cmid * fup

      dApf_dt <- -P * (fup * Cpf - Cepi) + Qpf * (Car - (Cpf / KPpf) * BP)

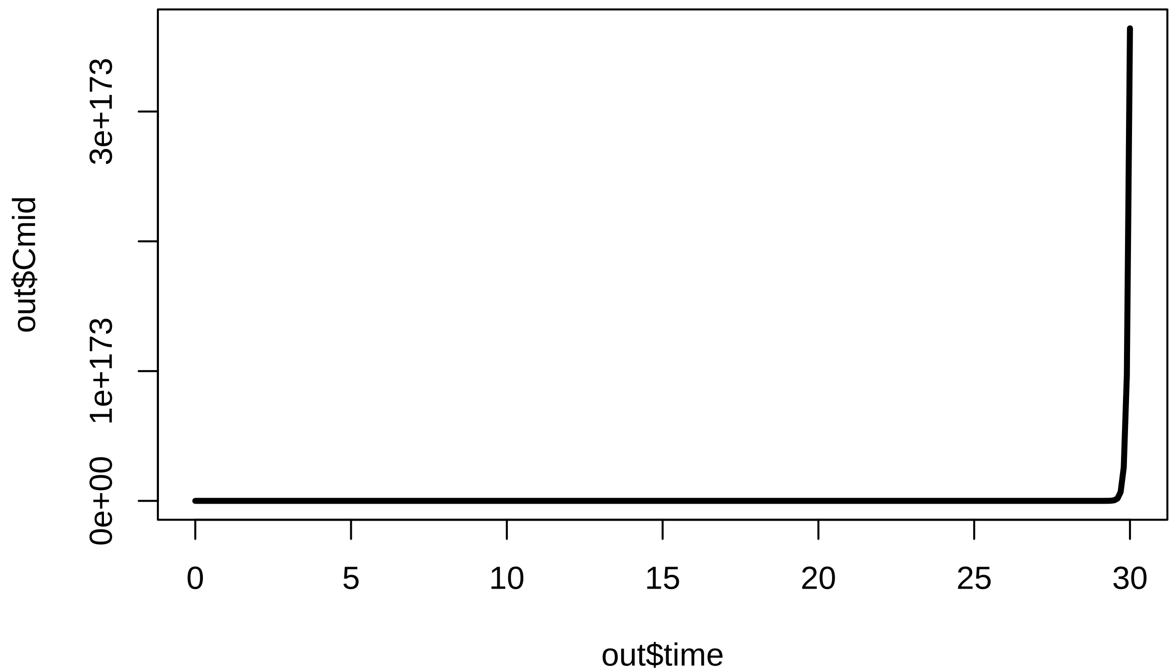


      return(list(c(dAepi_dt, dAmid_dt, dAendo_dt, dApf_dt)))
       }
       )
}

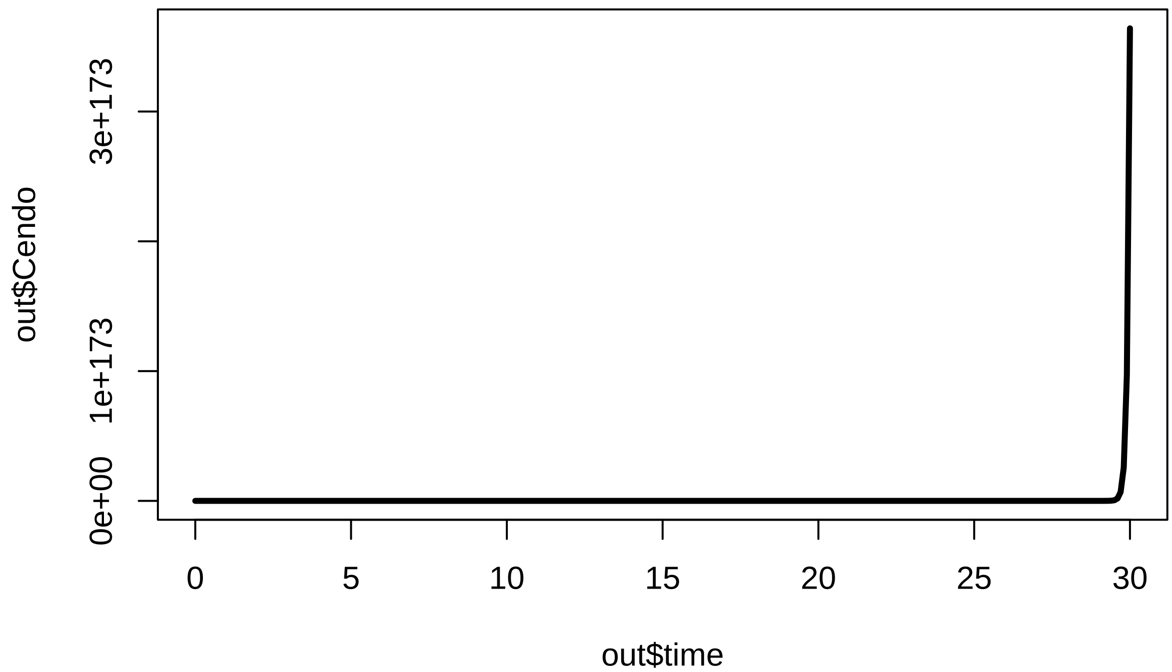
# Set initial values
state <- c(Cepi = 10, Cmid = 10, Cendo = 10, Cpf = 10)
t <- seq(0, 30, by = 0.1)

# Use the ode function from deSolve to create a line using our created function.
# We use the method: "lsode" to get a smooth curve.
out <- deSolve::ode(times = t, y = state, parms = parameters,
                    func = PBPK_func, method = "lsoda")

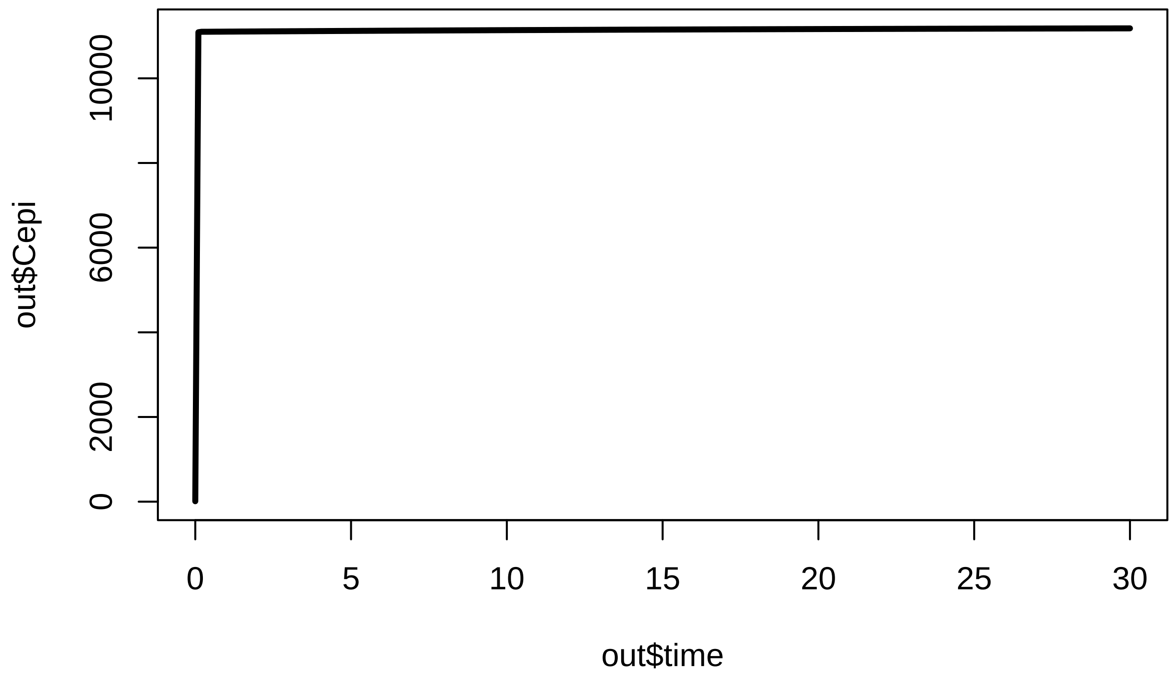
# Make a dataframe from the data of 'out'
out <- as.data.frame(out)
plot(out$time, out$Cmid, type = "l", lwd = 3)
```



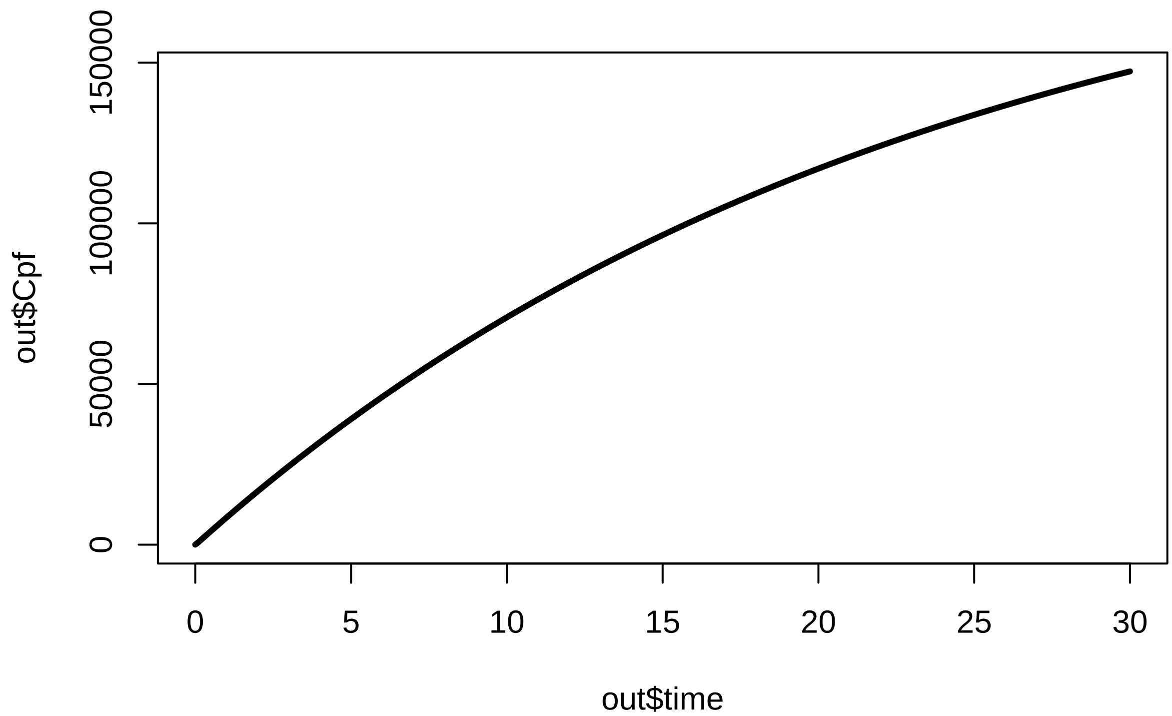

```
plot(out$time, out$Cendo, type = "l", lwd = 3)
```




```
plot(out$time, out$Cepi, type = "l", lwd = 3)
```




```
plot(out$time, out$Cpf, type = "l", lwd = 3)
```




```
out
```

```
##      time     Cepi         Cmid        Cendo        Cpf
## 1     0.0    10.00 1.000000e+01 1.000000e+01    10.0000
## 2     0.1 11088.66 3.760137e+01 3.760137e+01   754.8803
## 3     0.2 11099.13 1.413865e+02 1.413865e+02  1619.2685
## 4     0.3 11099.62 5.316330e+02 5.316330e+02  2480.0957
## 5     0.4 11100.09 1.999014e+03 1.999014e+03  3337.2666
## 6     0.5 11100.57 7.516577e+03 7.516577e+03  4190.7966
## 7     0.6 11101.04 2.826340e+04 2.826340e+04  5040.7013
## 8     0.7 11101.51 1.062744e+05 1.062744e+05  5886.9958
## 9     0.8 11101.98 3.996071e+05 3.996071e+05  6729.6958
## 10    0.9 11102.44 1.502580e+06 1.502580e+06  7568.8163
## 11    1.0 11102.92 5.649909e+06 5.649909e+06  8404.3726
## 12    1.1 11103.37 2.124448e+07 2.124448e+07  9236.3799
## 13    1.2 11103.83 7.988221e+07 7.988221e+07 10064.8532
## 14    1.3 11104.30 3.003684e+08 3.003684e+08 10889.8075
## 15    1.4 11104.75 1.129428e+09 1.129428e+09 11711.2577
## 16    1.5 11105.21 4.246810e+09 4.246810e+09 12529.2189
## 17    1.6 11105.66 1.596861e+10 1.596861e+10 13343.7057
## 18    1.7 11106.11 6.004421e+10 6.004421e+10 14154.7330
## 19    1.8 11106.56 2.257747e+11 2.257747e+11 14962.3153
## 20    1.9 11107.01 8.489451e+11 8.489451e+11 15766.4674
## 21    2.0 11107.45 3.192154e+12 3.192154e+12 16567.2038
## 22    2.1 11107.90 1.200295e+13 1.200295e+13 17364.5391
## 23    2.2 11108.34 4.513279e+13 4.513279e+13 18158.4877
## 24    2.3 11108.78 1.697057e+14 1.697057e+14 18949.0639
```

```
## 25   2.4 11109.22  6.381172e+14  6.381172e+14  19736.2821
## 26   2.5 11109.65  2.399412e+15  2.399412e+15  20520.1566
## 27   2.6 11110.09  9.022126e+15  9.022126e+15  21300.7015
## 28   2.7 11110.52  3.392446e+16  3.392446e+16  22077.9311
## 29   2.8 11110.95  1.275608e+17  1.275608e+17  22851.8593
## 30   2.9 11111.38  4.796467e+17  4.796467e+17  23622.5002
## 31   3.0 11111.80  1.803539e+18  1.803539e+18  24389.8678
## 32   3.1 11112.23  6.781563e+18  6.781563e+18  25153.9760
## 33   3.2 11112.66  2.549964e+19  2.549964e+19  25914.8385
## 34   3.3 11113.08  9.588225e+19  9.588225e+19  26672.4693
## 35   3.4 11113.50  3.605308e+20  3.605308e+20  27426.8820
## 36   3.5 11113.92  1.355647e+21  1.355647e+21  28178.0904
## 37   3.6 11114.33  5.097424e+21  5.097424e+21  28926.1079
## 38   3.7 11114.75  1.916703e+22  1.916703e+22  29670.9482
## 39   3.8 11115.16  7.207076e+22  7.207076e+22  30412.6247
## 40   3.9 11115.57  2.709963e+23  2.709963e+23  31151.1510
## 41   4.0 11115.98  1.018984e+24  1.018984e+24  31886.5403
## 42   4.1 11116.39  3.831525e+24  3.831525e+24  32618.8060
## 43   4.2 11116.79  1.440708e+25  1.440708e+25  33347.9614
## 44   4.3 11117.19  5.417265e+25  5.417265e+25  34074.0197
## 45   4.4 11117.60  2.036969e+26  2.036969e+26  34796.9939
## 46   4.5 11118.00  7.659288e+26  7.659288e+26  35516.8974
## 47   4.6 11118.41  2.880001e+27  2.880001e+27  36233.7429
## 48   4.7 11118.80  1.082921e+28  1.082921e+28  36947.5438
## 49   4.8 11119.19  4.071938e+28  4.071938e+28  37658.3127
## 50   4.9 11119.59  1.531106e+29  1.531106e+29  38366.0625
## 51   5.0 11119.98  5.757173e+29  5.757173e+29  39070.8062
## 52   5.1 11120.37  2.164779e+30  2.164779e+30  39772.5564
## 53   5.2 11120.76  8.139875e+30  8.139875e+30  40471.3259
## 54   5.3 11121.14  3.060707e+31  3.060707e+31  41167.1274
## 55   5.4 11121.53  1.150869e+32  1.150869e+32  41859.9734
## 56   5.5 11121.91  4.327433e+32  4.327433e+32  42549.8765
## 57   5.6 11122.29  1.627176e+33  1.627176e+33  43236.8493
## 58   5.7 11122.68  6.118414e+33  6.118414e+33  43920.9040
## 59   5.8 11123.06  2.300609e+34  2.300609e+34  44602.0532
## 60   5.9 11123.44  8.650617e+34  8.650617e+34  45280.3092
## 61   6.0 11123.81  3.252754e+35  3.252754e+35  45955.6843
## 62   6.1 11124.18  1.223082e+36  1.223082e+36  46628.1908
## 63   6.2 11124.56  4.598960e+36  4.598960e+36  47297.8406
## 64   6.3 11124.93  1.729273e+37  1.729273e+37  47964.6462
## 65   6.4 11125.30  6.502314e+37  6.502314e+37  48628.6194
## 66   6.5 11125.66  2.444962e+38  2.444962e+38  49289.7725
## 67   6.6 11126.03  9.193403e+38  9.193403e+38  49948.1172
## 68   6.7 11126.40  3.456850e+39  3.456850e+39  50603.6655
## 69   6.8 11126.76  1.299825e+40  1.299825e+40  51256.4294
## 70   6.9 11127.12  4.887524e+40  4.887524e+40  51906.4207
## 71   7.0 11127.48  1.837778e+41  1.837778e+41  52553.6511
## 72   7.1 11127.84  6.910307e+41  6.910307e+41  53198.1323
## 73   7.2 11128.20  2.598373e+42  2.598373e+42  53839.8761
## 74   7.3 11128.55  9.770249e+42  9.770249e+42  54478.8941
## 75   7.4 11128.91  3.673754e+43  3.673754e+43  55115.1978
## 76   7.5 11129.26  1.381383e+44  1.381383e+44  55748.7987
## 77   7.6 11129.61  5.194193e+44  5.194193e+44  56379.7084
## 78   7.7 11129.96  1.953090e+45  1.953090e+45  57007.9383
```

```
## 79   7.8 11130.31  7.343897e+45  7.343897e+45  57633.4998
## 80   7.9 11130.66  2.761409e+46  2.761409e+46  58256.4042
## 81   8.0 11131.00  1.038329e+47  1.038329e+47  58876.6627
## 82   8.1 11131.34  3.904263e+47  3.904263e+47  59494.2867
## 83   8.2 11131.69  1.468058e+48  1.468058e+48  60109.2873
## 84   8.3 11132.03  5.520107e+48  5.520107e+48  60721.6757
## 85   8.4 11132.37  2.075639e+49  2.075639e+49  61331.4629
## 86   8.5 11132.70  7.804695e+49  7.804695e+49  61938.6600
## 87   8.6 11133.04  2.934675e+50  2.934675e+50  62543.2780
## 88   8.7 11133.38  1.103480e+51  1.103480e+51  63145.3278
## 89   8.8 11133.71  4.149239e+51  4.149239e+51  63744.8205
## 90   8.9 11134.04  1.560172e+52  1.560172e+52  64341.7667
## 91   9.0 11134.37  5.866469e+52  5.866469e+52  64936.1774
## 92   9.1 11134.70  2.205876e+53  2.205876e+53  65528.0634
## 93   9.2 11135.03  8.294404e+53  8.294404e+53  66117.4352
## 94   9.3 11135.36  3.118815e+54  3.118815e+54  66704.3037
## 95   9.4 11135.68  1.172718e+55  1.172718e+55  67288.6794
## 96   9.5 11136.01  4.409586e+55  4.409586e+55  67870.5729
## 97   9.6 11136.33  1.658066e+56  1.658066e+56  68449.9949
## 98   9.7 11136.65  6.234568e+56  6.234568e+56  69026.9558
## 99   9.8 11136.97  2.344285e+57  2.344285e+57  69601.4660
## 100  9.9 11137.29  8.814840e+57  8.814840e+57  70173.5358
## 101 10.0 11137.60  3.314505e+58  3.314505e+58  70743.1758
## 102 10.1 11137.92  1.246301e+59  1.246301e+59  71310.3963
## 103 10.2 11138.23  4.686266e+59  4.686266e+59  71875.2074
## 104 10.3 11138.55  1.762103e+60  1.762103e+60  72437.6195
## 105 10.4 11138.86  6.625756e+60  6.625756e+60  72997.6427
## 106 10.5 11139.17  2.491378e+61  2.491378e+61  73555.2871
## 107 10.6 11139.48  9.367936e+61  9.367936e+61  74110.5631
## 108 10.7 11139.79  3.522476e+62  3.522476e+62  74663.4804
## 109 10.8 11140.10  1.324501e+63  1.324501e+63  75214.0491
## 110 10.9 11140.40  4.980309e+63  4.980309e+63  75762.2794
## 111 11.0 11140.70  1.872668e+64  1.872668e+64  76308.1809
## 112 11.1 11141.00  7.041493e+64  7.041493e+64  76851.7638
## 113 11.2 11141.30  2.647700e+65  2.647700e+65  77393.0377
## 114 11.3 11141.60  9.955730e+65  9.955730e+65  77932.0126
## 115 11.4 11141.90  3.743495e+66  3.743495e+66  78468.6981
## 116 11.5 11142.20  1.407607e+67  1.407607e+67  79003.1040
## 117 11.6 11142.50  5.292802e+67  5.292802e+67  79535.2401
## 118 11.7 11142.79  1.990168e+68  1.990168e+68  80065.1158
## 119 11.8 11143.09  7.483315e+68  7.483315e+68  80592.7409
## 120 11.9 11143.38  2.813832e+69  2.813832e+69  81118.1249
## 121 12.0 11143.67  1.058041e+70  1.058041e+70  81641.2773
## 122 12.1 11143.96  3.978383e+70  3.978383e+70  82162.2075
## 123 12.2 11144.25  1.495928e+71  1.495928e+71  82680.9251
## 124 12.3 11144.54  5.624903e+71  5.624903e+71  83197.4394
## 125 12.4 11144.82  2.115043e+72  2.115043e+72  83711.7599
## 126 12.5 11145.11  7.952858e+72  7.952858e+72  84223.8956
## 127 12.6 11145.39  2.990388e+73  2.990388e+73  84733.8561
## 128 12.7 11145.67  1.124428e+74  1.124428e+74  85241.6505
## 129 12.8 11145.96  4.228009e+74  4.228009e+74  85747.2880
## 130 12.9 11146.23  1.589792e+75  1.589792e+75  86250.7779
## 131 13.0 11146.51  5.977839e+75  5.977839e+75  86752.1291
## 132 13.1 11146.78  2.247752e+76  2.247752e+76  87251.3509
```

```
## 133 13.2 11147.07  8.451867e+76  8.451867e+76  87748.4520
## 134 13.3 11147.34  3.178023e+77  3.178023e+77  88243.4418
## 135 13.4 11147.62  1.194981e+78  1.194981e+78  88736.3291
## 136 13.5 11147.89  4.493297e+78  4.493297e+78  89227.1228
## 137 13.6 11148.16  1.689543e+79  1.689543e+79  89715.8318
## 138 13.7 11148.43  6.352923e+79  6.352923e+79  90202.4651
## 139 13.8 11148.70  2.388788e+80  2.388788e+80  90687.0313
## 140 13.9 11148.97  8.982184e+80  8.982184e+80  91169.5394
## 141 14.0 11149.24  3.377429e+81  3.377429e+81  91649.9979
## 142 14.1 11149.51  1.269961e+82  1.269961e+82  92128.4156
## 143 14.2 11149.77  4.775234e+82  4.775234e+82  92604.8014
## 144 14.3 11150.03  1.795555e+83  1.795555e+83  93079.1636
## 145 14.4 11150.29  6.751541e+83  6.751541e+83  93551.5111
## 146 14.5 11150.56  2.538675e+84  2.538675e+84  94021.8520
## 147 14.6 11150.82  9.545782e+84  9.545782e+84  94490.1952
## 148 14.7 11151.08  3.589347e+85  3.589347e+85  94956.5491
## 149 14.8 11151.34  1.349645e+86  1.349645e+86  95420.9222
## 150 14.9 11151.60  5.074857e+86  5.074857e+86  95883.3228
## 151 15.0 11151.85  1.908218e+87  1.908218e+87  96343.7593
## 152 15.1 11152.11  7.175168e+87  7.175168e+87  96802.2402
## 153 15.2 11152.36  2.697965e+88  2.697965e+88  97258.7736
## 154 15.3 11152.61  1.014473e+89  1.014473e+89  97713.3678
## 155 15.4 11152.87  3.814563e+89  3.814563e+89  98166.0311
## 156 15.5 11153.12  1.434329e+90  1.434329e+90  98616.7718
## 157 15.6 11153.37  5.393282e+90  5.393282e+90  99065.5980
## 158 15.7 11153.61  2.027950e+91  2.027950e+91  99512.5177
## 159 15.8 11153.86  7.625379e+91  7.625379e+91  99957.5390
## 160 15.9 11154.11  2.867252e+92  2.867252e+92 100400.6702
## 161 16.0 11154.35  1.078127e+93  1.078127e+93 100841.9191
## 162 16.1 11154.60  4.053908e+93  4.053908e+93 101281.2938
## 163 16.2 11154.84  1.524327e+94  1.524327e+94 101718.8022
## 164 16.3 11155.09  5.731686e+94  5.731686e+94 102154.4523
## 165 16.4 11155.33  2.155195e+95  2.155195e+95 102588.2519
## 166 16.5 11155.57  8.103838e+95  8.103838e+95 103020.2090
## 167 16.6 11155.81  3.047158e+96  3.047158e+96 103450.3313
## 168 16.7 11156.05  1.145775e+97  1.145775e+97 103878.6267
## 169 16.8 11156.28  4.308274e+97  4.308274e+97 104305.1028
## 170 16.9 11156.52  1.619972e+98  1.619972e+98 104729.7675
## 171 17.0 11156.75  6.091325e+98  6.091325e+98 105152.6284
## 172 17.1 11156.99  2.290424e+99  2.290424e+99 105573.6931
## 173 17.2 11157.22  8.612319e+99  8.612319e+99 105992.9694
## 174 17.3 11157.45 3.238354e+100 3.238354e+100 106410.4648
## 175 17.4 11157.68 1.217666e+101 1.217666e+101 106826.1869
## 176 17.5 11157.92 4.578599e+101 4.578599e+101 107240.1431
## 177 17.6 11158.15 1.721618e+102 1.721618e+102 107652.3410
## 178 17.7 11158.37 6.473528e+102 6.473528e+102 108062.7882
## 179 17.8 11158.60 2.434138e+103 2.434138e+103 108471.4919
## 180 17.9 11158.83 9.152703e+103 9.152703e+103 108878.4596
## 181 18.0 11159.05 3.441546e+104 3.441546e+104 109283.6988
## 182 18.1 11159.28 1.294070e+105 1.294070e+105 109687.2166
## 183 18.2 11159.50 4.865889e+105 4.865889e+105 110089.0205
## 184 18.3 11159.73 1.829642e+106 1.829642e+106 110489.1177
## 185 18.4 11159.95 6.879712e+106 6.879712e+106 110887.5155
## 186 18.5 11160.17 2.586869e+107 2.586869e+107 111284.2211
```

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## 187 18.6 11160.39 9.726996e+107 9.726996e+107 111679.2417
## 188 18.7 11160.60 3.657487e+108 3.657487e+108 112072.5844
## 189 18.8 11160.82 1.375267e+109 1.375267e+109 112464.2563
## 190 18.9 11161.04 5.171199e+109 5.171199e+109 112854.2646
## 191 19.0 11161.26 1.944444e+110 1.944444e+110 113242.6163
## 192 19.1 11161.47 7.311388e+110 7.311388e+110 113629.3185
## 193 19.2 11161.69 2.749184e+111 2.749184e+111 114014.3782
## 194 19.3 11161.89 1.033732e+112 1.033732e+112 114397.8023
## 195 19.4 11162.11 3.886979e+112 3.886979e+112 114779.5977
## 196 19.5 11162.32 1.461560e+113 1.461560e+113 115159.7715
## 197 19.6 11162.54 5.495669e+113 5.495669e+113 115538.3305
## 198 19.7 11162.74 2.066449e+114 2.066449e+114 115915.2815
## 199 19.8 11162.95 7.770141e+114 7.770141e+114 116290.6315
## 200 19.9 11163.16 2.921683e+115 2.921683e+115 116664.3870
## 201 20.0 11163.37 1.098594e+116 1.098594e+116 117036.5551
## 202 20.1 11163.57 4.130869e+116 4.130869e+116 117407.1424
## 203 20.2 11163.78 1.553266e+117 1.553266e+117 117776.1556
## 204 20.3 11163.98 5.840499e+117 5.840499e+117 118143.6014
## 205 20.4 11164.19 2.196110e+118 2.196110e+118 118509.4864
## 206 20.5 11164.39 8.257684e+118 8.257684e+118 118873.8173
## 207 20.6 11164.59 3.105006e+119 3.105006e+119 119236.6007
## 208 20.7 11164.79 1.167526e+120 1.167526e+120 119597.8432
## 209 20.8 11164.99 4.390065e+120 4.390065e+120 119957.5512
## 210 20.9 11165.20 1.650726e+121 1.650726e+121 120315.7314
## 211 21.0 11165.39 6.206962e+121 6.206962e+121 120672.3902
## 212 21.1 11165.59 2.333906e+122 2.333906e+122 121027.5341
## 213 21.2 11165.79 8.775817e+122 8.775817e+122 121381.1695
## 214 21.3 11165.98 3.299831e+123 3.299831e+123 121733.3029
## 215 21.4 11166.18 1.240783e+124 1.240783e+124 122083.9405
## 216 21.5 11166.37 4.665520e+124 4.665520e+124 122433.0887
## 217 21.6 11166.56 1.754302e+125 1.754302e+125 122780.7540
## 218 21.7 11166.76 6.596423e+125 6.596423e+125 123126.9425
## 219 21.8 11166.95 2.480349e+126 2.480349e+126 123471.6606
## 220 21.9 11167.14 9.326461e+126 9.326461e+126 123814.9144
## 221 22.0 11167.33 3.506880e+127 3.506880e+127 124156.7103
## 222 22.1 11167.52 1.318637e+128 1.318637e+128 124497.0544
## 223 22.2 11167.71 4.958261e+128 4.958261e+128 124835.9529
## 224 22.3 11167.90 1.864376e+129 1.864376e+129 125173.4118
## 225 22.4 11168.08 7.010319e+129 7.010319e+129 125509.4374
## 226 22.5 11168.27 2.635979e+130 2.635979e+130 125844.0357
## 227 22.6 11168.45 9.911654e+130 9.911654e+130 126177.2129
## 228 22.7 11168.64 3.726923e+131 3.726923e+131 126508.9748
## 229 22.8 11168.82 1.401375e+132 1.401375e+132 126839.3275
## 230 22.9 11169.01 5.269370e+132 5.269370e+132 127168.2770
## 231 23.0 11169.19 1.981358e+133 1.981358e+133 127495.8294
## 232 23.1 11169.37 7.450189e+133 7.450189e+133 127821.9904
## 233 23.2 11169.55 2.801375e+134 2.801375e+134 128146.7660
## 234 23.3 11169.73 1.053356e+135 1.053356e+135 128470.1622
## 235 23.4 11169.91 3.960770e+135 3.960770e+135 128792.1847
## 236 23.5 11170.09 1.489306e+136 1.489306e+136 129112.8394
## 237 23.6 11170.27 5.599999e+136 5.599999e+136 129432.1321
## 238 23.7 11170.44 2.105679e+137 2.105679e+137 129750.0686
## 239 23.8 11170.62 7.917652e+137 7.917652e+137 130066.6546
## 240 23.9 11170.78 2.977149e+138 2.977149e+138 130381.8961
```

```
## 241 24.0 11170.97 1.119451e+139 1.119451e+139 130695.7983
## 242 24.1 11171.14 4.209291e+139 4.209291e+139 131008.3673
## 243 24.2 11171.32 1.582753e+140 1.582753e+140 131319.6086
## 244 24.3 11171.49 5.951375e+140 5.951375e+140 131629.5281
## 245 24.4 11171.66 2.237803e+141 2.237803e+141 131938.1310
## 246 24.5 11171.83 8.414450e+141 8.414450e+141 132245.4232
## 247 24.6 11172.00 3.163951e+142 3.163951e+142 132551.4101
## 248 24.7 11172.17 1.189691e+143 1.189691e+143 132856.0973
## 249 24.8 11172.34 4.473405e+143 4.473405e+143 133159.4904
## 250 24.9 11172.51 1.682063e+144 1.682063e+144 133461.5948
## 251 25.0 11172.68 6.324797e+144 6.324797e+144 133762.4159
## 252 25.1 11172.84 2.378213e+145 2.378213e+145 134061.9594
## 253 25.2 11173.01 8.942420e+145 8.942420e+145 134360.2305
## 254 25.3 11173.17 3.362476e+146 3.362476e+146 134657.2346
## 255 25.4 11173.34 1.264339e+147 1.264339e+147 134952.9773
## 256 25.5 11173.51 4.754092e+147 4.754092e+147 135247.4637
## 257 25.6 11173.67 1.787606e+148 1.787606e+148 135540.6994
## 258 25.7 11173.83 6.721654e+148 6.721654e+148 135832.6895
## 259 25.8 11173.99 2.527436e+149 2.527436e+149 136123.4393
## 260 25.9 11174.15 9.503513e+149 9.503513e+149 136412.9542
## 261 26.0 11174.31 3.573456e+150 3.573456e+150 136701.2393
## 262 26.1 11174.47 1.343670e+151 1.343670e+151 136988.3000
## 263 26.2 11174.63 5.052390e+151 5.052390e+151 137274.1413
## 264 26.3 11174.79 1.899770e+152 1.899770e+152 137558.7685
## 265 26.4 11174.95 7.143404e+152 7.143404e+152 137842.1868
## 266 26.5 11175.11 2.686021e+153 2.686021e+153 138124.4011
## 267 26.6 11175.26 1.009982e+154 1.009982e+154 138405.4169
## 268 26.7 11175.42 3.797676e+154 3.797676e+154 138685.2390
## 269 26.8 11175.57 1.427980e+155 1.427980e+155 138963.8725
## 270 26.9 11175.73 5.369404e+155 5.369404e+155 139241.3225
## 271 27.0 11175.88 2.018972e+156 2.018972e+156 139517.5940
## 272 27.1 11176.03 7.591622e+156 7.591622e+156 139792.6921
## 273 27.2 11176.19 2.854556e+157 2.854556e+157 140066.6216
## 274 27.3 11176.34 1.073354e+158 1.073354e+158 140339.3877
## 275 27.4 11176.49 4.035962e+158 4.035962e+158 140610.9951
## 276 27.5 11176.64 1.517579e+159 1.517579e+159 140881.4489
## 277 27.6 11176.79 5.706314e+159 5.706314e+159 141150.7539
## 278 27.7 11176.94 2.145654e+160 2.145654e+160 141418.9150
## 279 27.8 11177.09 8.067963e+160 8.067963e+160 141685.9371
## 280 27.9 11177.23 3.033668e+161 3.033668e+161 141951.8251
## 281 28.0 11177.38 1.140703e+162 1.140703e+162 142216.5836
## 282 28.1 11177.53 4.289201e+162 4.289201e+162 142480.2176
## 283 28.2 11177.67 1.612800e+163 1.612800e+163 142742.7318
## 284 28.3 11177.82 6.064357e+163 6.064357e+163 143004.1309
## 285 28.4 11177.96 2.280284e+164 2.280284e+164 143264.4197
## 286 28.5 11178.11 8.574189e+164 8.574189e+164 143523.6030
## 287 28.6 11178.25 3.224017e+165 3.224017e+165 143781.6853
## 288 28.7 11178.40 1.212276e+166 1.212276e+166 144038.6715
## 289 28.8 11178.54 4.558330e+166 4.558330e+166 144294.5660
## 290 28.9 11178.68 1.713997e+167 1.713997e+167 144549.3737
## 291 29.0 11178.82 6.444869e+167 6.444869e+167 144803.0990
## 292 29.1 11178.97 2.423362e+168 2.423362e+168 145055.7466
## 293 29.2 11179.10 9.112183e+168 9.112183e+168 145307.3212
## 294 29.3 11179.24 3.426312e+169 3.426312e+169 145557.8271
```

```
## 295 29.4 11179.38 1.288341e+170 1.288341e+170 145807.2690
## 296 29.5 11179.52 4.844343e+170 4.844343e+170 146055.6514
## 297 29.6 11179.66 1.821542e+171 1.821542e+171 146302.9787
## 298 29.7 11179.79 6.849256e+171 6.849256e+171 146549.2556
## 299 29.8 11179.93 2.575417e+172 2.575417e+172 146794.4863
## 300 29.9 11180.06 9.683932e+172 9.683932e+172 147038.6755
## 301 30.0 11180.20 3.641295e+173 3.641295e+173 147281.8274
```

```r
x <- c(1,2,3,4,5)
```

2.2 Model configuration

Chosen parameter- and initial values can be found in the tables below. Do please note that each table corresponds to their own model respectively.

... This part is work in progress...

3 Results

The structure representing the simulation of the PBPK model is shown here.

```r
print("Hier komt die code!")
```

```
## [1] "Hier komt die code!"
```

```r
#plot(out)
#code to generate figures with title, subscripts, legenda etc
```

- Describe what can be seen in such way that it leads to an answer to your research questions
- Give your figures a number and a descriptive title.
- Provide correct axis labels (unit and quantity), legend and caption.
- Always refer to and discuss your figures and tables in the text - they never stand alone.

4 Discussion and Conclusion

4.1 Discussion

- Compare your results with what is expecting from the literature and discuss differences with them.
- Discuss striking and surprising results.
- Discuss weaknesses in your research and how they could be addressed.

4.2 General conclusion and perspective

Discuss what your goal was, what the end result is and how you could continue working from here.

References

[1] Soetaert, K., Petzoldt, T., and Woodrow Setzer, R.: *Solving differential equations in R: package deSolve*, J. Stat. Softw., 33, 1-25, 2010.