Data and R code:

Pharmacological basis for abrogating myocardial reperfusion injury through a multi-target combined antioxidant therapy

I R code

R code utilized for calculations is explained here

For simulation equations presented here, $C(t)$ represents the function of plasmatic concentration over time, t the time instant, t_{Dn} and t_{Di} the time duration of the n-th and i-th infusion dose, R_n and R_i infusion rates of the n-th and i-th dose interval and CL the clearance of elimination. A, B, C are macro-constants, and k, α, β and γ are elimination rate micro-constants that can be calculated from the volume of distribution (V) for each compartment, and intercompartmental and elimination clearances (Q and CL, respectively) [1, 2]. Further detail about equations utilized in this article can be reviewed in Supplementary Materials.

Used libraries

```
library(dplyr)
library(ggplot2)
library(forcats)
```

Units of measure utilized here are as follow unless otherwise specified:

- mili mol (mmol) for quantities
- hours (h) for time
- kilograms (Kg) for mass

Abbreviation and simbols:

- `V`: Central compartment'svolume of distribution
- `V2`: Second compartment's volume of distribution
- `V3`: Third compartment's volume of distribution
- `CL`: Clearance of elimination
- `Q` or `Q2`: Inter-compartmental clearance between compartmentes 1 and 2
- `Q3`: Inter-compartmental clearance between compartmentes 1 and 3
- `R`: vector containing infusion rates
  - `R [i]`: infusion rate from `tD[i-1]` to `t[i]`
- `tD`: Vector containing end time of infusions:
  - `tD[i]`: time from beginning of simulation to end of infusion rate `R[i]`
- `td`: time duration of fast infusion rate
- `A, B, C`: first, second and third macroconstant

- `alpha, beta, gamma`: first, second and third microconstants
- `C`: Concentration
  - `Cph`: physiological concentration
  - `Css`: Steady state concentration

1 Functions definition

Units transformation, from mmol/h -> mmol/min:

```
trans <- function(x){
  x <- x/60
  return(x)
}
```

To simplify code comprehension, equations for each compartment model are presented before each R code function.

1.1 One compartment model

Simulation

Returns tibble with columns Time [min] from 0 to `tD[length(tD)]` and Plasmatic Concentration [mM]

$$k = \frac{CL}{V} \qquad \text{Eq. 1}$$

$$C(t) = \frac{R_n}{CL} \times \left(1 - e^{-k(t-t_{Dn-1})}\right) + \sum_{i=0}^{n-1} \frac{R_i}{CL} \times \left(1 - e^{-k(t_D-t_{Di-1})}\right) \times e^{-k(t-t_{Di})} \qquad \text{Eq. 2}$$

```
simul_1comp <- function(V, CL, tD, R, Cph=0){

  tD0 <- c(0,tD) #adding tD instant 0

  Tinf <- c(0) #infusion time
  pos0 <- 1
  time_tot <- tD [length(tD)]
  for(i in tD){
    Tinf [pos0] <- i - tD0[pos0]
    pos0 <- pos0 + 1
  }

  Ct <- tibble(Time=c(0:(time_tot*60)),
               Concentration=0) #defining output tibble in terms of time in
[min] and concentration [mM]
  # Parameters definition
  k <- CL/V
```

```
  # Decay Summation terms calculation
  summation <- tibble(Time = c(0:(time_tot*60)))
  pos1 <- 1
  tD_aux <- tD [-length(tD)]
  for (i in tD_aux) {
    summation <- summation %>%
      mutate(other=0)
    colnames(summation)[which(names(summation)=="other")] <-
      paste("decay_D", pos1, sep = ".")
    t1 <- i*60
    t1 <- trunc(t1)
    intervalo_ti.tn <- summation$Time[t1+1]:summation$Time[length(summation$T
ime)]
    for (j in intervalo_ti.tn) {
      t <- j/60
      summation[j+1, pos1+1] <- R[pos1]/CL * (1 - exp(-k*Tinf[pos1])) * exp(-
k*(t-i))
    }
    pos1 <- pos1 + 1
  }
  sigma <- summation %>%
    select(contains("decay_D")) %>%
    rowSums()
  summation <- summation %>%
    transmute(decay_accumulated=sigma)

  # final curve
  pos2 <- 1
  for (i in tD) {              # intervals according to end time tD[i] of inf
usion R[i]
    aux <- (tD0[pos2]*60):(i*60)

    for (j in aux) {            # j = time [min]
      t <- j/60               # t: time [h]
      taux <- tD0[pos2]       # taux: time since the end of previous infusion

      Ct$Concentration [j+1] <- (R[pos2]/CL) * (1-exp(-k*(t-taux)))+
        summation$decay_accumulated[j+1] + Cph

    }
    pos2 <- pos2 + 1
  }
  return(Ct)
}
```

1.2 Two Compartments model

Parameters

$$\beta = \frac{1}{2} \times \left(\frac{Q}{V} + \frac{Q}{V_2} + \frac{CL}{V} - \sqrt{\left(\frac{Q}{V} + \frac{Q}{V_2} + \frac{CL}{V} \right)^2 - 4 \times \frac{Q}{V_2} \times \frac{CL}{V}} \right) \quad \text{Eq. 3}$$

$$\alpha = \frac{\frac{Q}{V_2} \times \frac{CL}{V}}{\beta} \quad \text{Eq. 4}$$

$$A = \frac{\frac{1}{V} \times \left(\alpha - \frac{Q}{V_2} \right)}{(\alpha - \beta)} \quad \text{Eq. 5}$$

$$B = \frac{\frac{1}{V} \times \left(\beta - \frac{Q}{V_2} \right)}{(\beta - \alpha)} \quad \text{Eq. 6}$$

Simulation

$$C(t) = R_n \times \left(\frac{A}{\alpha} \left(1 - e^{-\alpha (t - t_{Dn-1})} \right) + \frac{B}{\beta} \left(1 - e^{-\beta (t - t_{Dn-1})} \right) \right) + \sum_{i=0}^{n-1} R_i \times \left(\begin{array}{l} \frac{A}{\alpha} \left(1 - e^{-\alpha (t_{Di} - t_{Di-1})} \right) e^{-\alpha (t - t_{Di})} + \\ \frac{B}{\beta} \left(1 - e^{-\beta (t_{Di} - t_{Di-1})} \right) e^{-\beta (t - t_{Di})} \end{array} \right) \quad \text{Eq. 7}$$

```
simul_2comp <- function(V, V2, CL, Q, tD, R, Cph=0){

  tD0 <- c(0,tD)

  Tinf <- c(0)
  pos0 <- 1
  time_tot <- tD [length(tD)]
  for(i in tD){
    Tinf [pos0] <- i - tD0[pos0]
    pos0 <- pos0 + 1
  }
```

```
  Ct <- tibble(Time=c(0:(time_tot*60)),
                   Concentration=0)

  # Parameters definition
  terms <- (Q/V) + (Q/V2) + (CL/V)
  beta <- 0.5 * (terms - sqrt(terms^2 - 4*(Q/V2)*(CL/V)))
  alpha <- ((Q/V2)*(CL/V))/beta
  A <- (1/V) * (alpha - (Q/V2))/(alpha-beta)
  B <- (1/V) * ((beta - Q/V2)/(beta-alpha))

  summation <- tibble(Time = c(0:(time_tot*60)))
  pos1 <- 1
  tD_aux <- tD [-length(tD)]
  for (i in tD_aux) {
    summation <- summation %>%
      mutate(other=0)

    colnames(summation)[which(names(summation)=="other")] <-
      paste("decay_D", pos1, sep = ".")
    t1 <- i*60
    t1 <- trunc(t1)
    intervalo_ti.tn <- summation$Time[t1+1]:summation$Time[length(summation$T
ime)]
    for (j in intervalo_ti.tn) {
      t <- j/60
      summation[j+1, pos1+1] <- R[pos1] * (
        (A/alpha) * (1 - exp(-alpha*Tinf[pos1])) * exp(-alpha*(t-i)) +
          (B/beta) * (1 - exp(-beta*Tinf[pos1])) * exp(-beta*(t-i)))
    }
    pos1 <- pos1 + 1
  }
  sigma <- summation %>%
    select(contains("decay_D")) %>%
    rowSums()
  summation <- summation %>%
    transmute(decay_accumulated=sigma)

  pos2 <- 1
  for (i in tD) {
    aux <- (tD0[pos2]*60):(i*60)

    for (j in aux) {
      t <- j/60
      taux <- tD0[pos2]
      Ct$Concentration [j+1] <- R[pos2] *
        ((A/alpha) * (1-exp(-alpha*(t-taux))) +
           (B/beta) * (1-exp(-beta*(t-taux)))) +
        summation$decay_accumulated[j+1] +
```

```
        Cph
    }
    pos2 <- pos2 + 1
  }
  return(Ct)
}
```

1.3 Three compartments model

Parameters

$$a_0 = kk_{21}k_{31} = \frac{Cl}{V_1}\frac{Q_2}{V_2}\frac{Q_3}{V_3}$$

$$a_1 = \begin{cases} kk_{31} + k_{21}k_{31} + k_{21}k_{13} + kk_{21} + k_{31}k_{12} \\ \frac{Cl}{V_1}\frac{Q_3}{V_3} + \frac{Q_2}{V_2}\frac{Q_3}{V_3} + \frac{Q_2}{V_2}\frac{Q_3}{V_1} + \frac{Cl}{V_1}\frac{Q_2}{V_2} + \frac{Q_3}{V_3}\frac{Q_2}{V_1} \end{cases}$$

$$a_2 = \begin{cases} k + k_{12} + k_{13} + k_{21} + k_{31} \\ \frac{Cl}{V_1} + \frac{Q_2}{V_1} + \frac{Q_3}{V_1} + \frac{Q_2}{V_2} + \frac{Q_3}{V_3} \end{cases}$$

$$p = a_1 - a_2^2/3$$

$$q = 2a_2^3/27 - a_1a_2/3 + a_0$$

$$r_1 = \sqrt{-(p^3/27)}$$

$$r_2 = 2r_1^{1/3}$$

$$\phi = \arccos\left(-\frac{q}{2r_1}\right)/3$$

$$\alpha = -\left(\cos(\phi)\, r_2 - a_2/3\right)$$

$$\beta = -\left(\cos\left(\phi + \frac{2\pi}{3}\right) r_2 - a_2/3\right)$$

$$\gamma = -\left(\cos\left(\phi + \frac{4\pi}{3}\right) r_2 - a_2/3\right)$$

$$A = \frac{1}{V}\frac{k_{21}-\alpha}{\alpha-\beta}\frac{k_{31}-\alpha}{\alpha-\gamma} = \frac{1}{V_1}\frac{\frac{Q_2}{V_2}-\alpha}{\alpha-\beta}\frac{\frac{Q_3}{V_3}-\alpha}{\alpha-\gamma}$$

$$B = \frac{1}{V}\frac{k_{21}-\beta}{\beta-\alpha}\frac{k_{31}-\beta}{\beta-\gamma} = \frac{1}{V_1}\frac{\frac{Q_2}{V_2}-\beta}{\beta-\alpha}\frac{\frac{Q_3}{V_3}-\beta}{\beta-\gamma}$$

$$C = \frac{1}{V}\frac{k_{21}-\gamma}{\gamma-\beta}\frac{k_{31}-\gamma}{\gamma-\alpha} = \frac{1}{V_1}\frac{\frac{Q_2}{V_2}-\gamma}{\gamma-\beta}\frac{\frac{Q_3}{V_3}-\gamma}{\gamma-\alpha}$$

Simulation

$$C(t) = R_n \times \left(\frac{A}{\alpha}\left(1-e^{-\alpha(t-t_{Dn-1})}\right)+\frac{B}{\beta}\left(1-e^{-\beta(t-t_{Dn-1})}\right)+\frac{C}{\gamma}\left(1-e^{-\gamma(t-t_{Dn-1})}\right)\right)$$

$$+\sum_{i=0}^{n-1} R_i \times \left(\begin{array}{l}\frac{A}{\alpha}\left(1-e^{-\alpha(t_{Di}-t_{Di-1})}\right)e^{-\alpha(t-t_{Di})}+\\ \frac{B}{\beta}\left(1-e^{-\beta(t_{Di}-t_{Di-1})}\right)e^{-\beta(t-t_{Di})}+\\ \frac{C}{\gamma}\left(1-e^{-\gamma(t_{Di}-t_{Di-1})}\right)e^{-\gamma(t-t_{Di})}\end{array}\right) \quad \text{Eq. 8}$$

```
simul_3comp <- function(V1, V2, V3, CL, Q2, Q3, tD, R, Cph=0){
  tD0 <- c(0,tD)

  Tinf <- c(0)
  pos0 <- 1
  time_tot <- tD [length(tD)]
  for(i in tD){
    Tinf [pos0] <- i - tD0[pos0]
    pos0 <- pos0 + 1
  }

  Ct <- tibble(Time=c(0:(time_tot*60)),
                    Concentration=0)

  # Parameters definition
  a0 <- (CL*Q2*Q3)/(V1*V2*V3)
  a1 <- (CL*Q3)/(V1*V3) + (Q2*Q3)/(V2*V3) + (Q2*Q3)/(V2*V1) +
    (CL*Q2)/(V1*V2) + (Q3*Q2)/(V3*V1)
  a2 <- CL/V1 + Q2/V1 + Q3/V1 + Q2/V2 + Q3/V3

  p <- a1 - (a2^2)/3
  q <- 2*(a2^3)/27 - a1*a2/3 + a0
  r1 <- sqrt(-(p^3)/27)
  r2 <- 2*r1^(1/3)
  phi <- acos(-q/(2*r1))/3
```

```
  alpha <- -(cos(phi)*r2 - a2/3)
  beta <- -(cos(phi + 2*pi/3)*r2 - a2/3)
  gamma <- -(cos(phi + 4*pi/3)*r2 - a2/3)


  A <- 1/V1 * (Q2/V2 - alpha)/(alpha-beta) * (Q3/V3 - alpha)/(alpha-gamma)
  B <- 1/V1 * (Q2/V2 - beta)/(beta-alpha) * (Q3/V3 - beta)/(beta-gamma)
  C <- 1/V1 * (Q2/V2 - gamma)/(gamma-beta) * (Q3/V3 - gamma)/(gamma-alpha)

  summation <- tibble(Time = c(0:(time_tot*60)))
  pos1 <- 1
  tD_aux <- tD [-length(tD)]
  for (i in tD_aux) {
    summation <- summation %>%
      mutate(other=0)
    colnames(summation)[which(names(summation)=="other")] <-
      paste("decay_D", pos1, sep = ".")
    t1 <- i*60
    t1 <- trunc(t1)
    intervalo_ti.tn <- summation$Time[t1+1]:summation$Time[length(summation$T
ime)]
    for (j in intervalo_ti.tn) {
      t <- j/60
      summation[j+1, pos1+1] <- R[pos1] *
        ((A/alpha)*(1 - exp(-alpha*Tinf[pos1]))*exp(-alpha*(t-i))+
           (B/beta)*(1 - exp(-beta*Tinf[pos1]))*exp(-beta*(t-i))+
           (C/gamma)*(1 - exp(-gamma*Tinf[pos1]))*exp(-gamma*(t-i)))
    }
    pos1 <- pos1 + 1
  }
  sigma <- summation %>%
    select(contains("decay_D")) %>%
    rowSums()
  summation <- summation %>%
    transmute(decay_accumulated=sigma)

  pos2 <- 1
  for (i in tD) {
    aux <- (tD0[pos2]*60):(i*60)

    for (j in aux) {
      t <- j/60
      taux <- tD0[pos2]
      Ct$Concentration [j+1] <- R[pos2] *
        ((A/alpha) * (1-exp(-alpha*(t-taux))) +
           (B/beta) * (1-exp(-beta*(t-taux))) +
           (C/gamma) * (1-exp(-gamma*(t-taux)))) +
        summation$decay_accumulated[j+1] + Cph
```

```
    }
    pos2 <- pos2 + 1
  }

  return(Ct)
}
```

2 Utilized pharmacokinetics data

```
PKdata <- tibble(read.csv2("PKdata (with reduced NAC).csv"))
PKdataVC <- tibble(read.csv2("PK VitaminC.csv"))
knitr::kable(PKdata)
```

Drug	MM	V1	V2	V3	CL	Q	Q3	Reference
Vitamin C	198.11	15.20	NA	NA	6.84	NA	NA	Nielsen et al. 2015
N-acetylcysteine	163.20	4.48	8.75	9.8	40.6	70.7	4.41	Brown et al. 2004
Deferoxamine	560.68	77.40	238.0	NA	19.30	17.60	NA	Bellanti et al. 2016

Drug	C_ph_min	C_ph_max
Vitamin C	0.05	0.07
N-acetylcysteine	0.00	NA
Deferoxamine	0.00	NA

```
knitr::kable(PKdataVC)
```

Drug	Autor	Modelo	MM	V1	V2	CL	Q
Vitamin C	Grooth	2comp	176.12	31.6	39.6	4.27	5.21
Vitamin C	NielsenHighDose	1comp	176.12	15.2	NA	5.92	NA
Vitamin C	NielsenLowDose	1comp	176.12	15.2	NA	6.84	NA

Drug	C_ph_min	C_ph_max
Vitamin C	0.05	0.07
Vitamin C	0.05	0.07
Vitamin C	0.05	0.07

3 VC 1 compartment vs 2 compartment model comparison

```
Ramossimul1comp <- simul_1comp(PKdataVC$V1[2], PKdataVC$CL[2],
                    tD= c(1, 3,24),
                    R= c(0.32*10*60, 0.32*3*60, 0),
                    0.06)
Ramossimul2comp <- simul_2comp(PKdataVC$V1[1], PKdataVC$V2[1],
```

```
                          PKdataVC$CL[1], PKdataVC$Q[1],
                          tD= c(1, 3,24),
                          R= c(0.32*10*60, 0.32*3*60, 0),
                          0.06)
VC_compartments <- bind_rows("One compartment" = Ramossimul1comp,
                             "Two compartments"= Ramossimul2comp,
                             .id = "Studies")
Ramos <- tibble (read.csv2("RamosVC.csv"))
knitr::kable(Ramos)
```

Time.min	Time.h	M_conc.mM	Qmin.mM	Qmax.mM	Dose.mmol.min
0	0	0.04	0.02	0.09	0.00
60	1	NA	NA	NA	3.20
120	2	NA	NA	NA	0.96
180	3	9.63	6.26	11.64	0.96
420	7	0.72	0.23	2.43	0.00
1440	24	0.02	0.01	0.05	0.00

```
ggplot()+
  geom_line(data=VC_compartments, aes(x=Time, y=Concentration, col=Studies),
            size = 1 )+
  scale_color_manual(values = c(rgb(1,0.5,0.5), rgb(1,0.8,0.9)))+
  geom_errorbar(data=Ramos, aes(x=Time.min, y=M_conc.mM,
                                ymin=Qmin.mM, ymax=Qmax.mM),
                col="black", size=1)+
  geom_point(data=Ramos, aes(x=Time.min, y=M_conc.mM), na.rm = T, col="black"
, size=4, shape="square")+
  scale_x_continuous(breaks=seq(from=0,to=1440, by=240), label = seq(from=0,
to=24, by=4))+
  labs(x="Time [h]", y="Concentration [mM]")+
  theme_classic()+
  theme(legend.position = "bottom" )+
  guides(title=NULL,col = guide_legend(nrow = 2))+
  theme(legend.position = c(0.7,0.7), legend.title = element_blank(),
        legend.text = element_text(size=8),
        axis.text = element_text(size = 8),
        axis.title = element_text(size=8))

ggsave("ComparisonVC_2vs1.pdf", width = 6, height = 6, units = c("cm"))
```

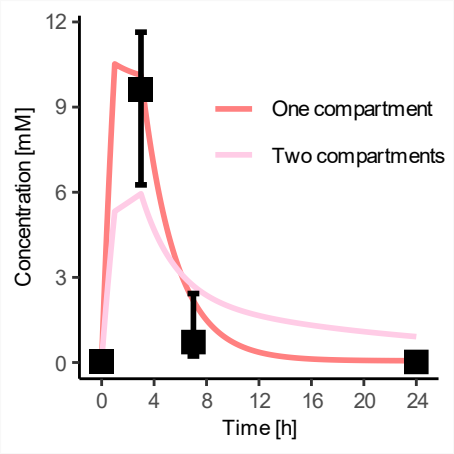


Fig. 2 One compartment vs two compartment model comparison for VC AMI setting. Curves represent simulations of concentration-time curves for reported administration scheme by Ramos et al. [20]. Black boxes and error bars respectively represent median and interquarti le range values for VC concentration measured by Ramos et al. 2017 [20].

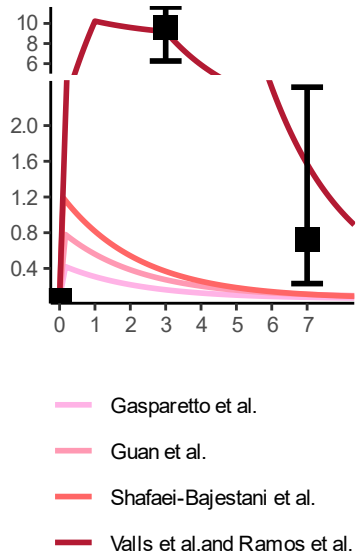
4 Clinical trials comparison

It should be noted that code presented here was slightly modified to make the figures more readable by separating the curves in more than one graph or changing the colors.

Vitamin C

```
Ramos <- tibble (read.csv2("RamosVC.csv"))
Guan <- simul_1comp(PKdata$V1[1], PKdata$CL[1],
                    tD= c(1/6, 24),
                    R= c((2000/PKdata$MM[1])*6, (20/PKdata$MM[1])),
                    0.06)
Gasparetto <- simul_1comp(PKdata$V1[1], PKdata$CL[1],
                          tD=c(1/6, 24),
                          R= c(1000/PKdata$MM[1]*6, 0),
                          0.06)

Valls_Ramos <- simul_1comp(PKdata$V1[1], PKdata$CL[1],
                           tD= c(1, 3, 24),
                           R= c(0.32*10*60, 0.32*3*60, 0),
                           0.06)

Shafaei <- simul_1comp(PKdata$V1[1], PKdata$CL[1],
                    tD= c(0.1, 0.1+(1/60), 12),
                    R= c(500*60/PKdata$MM[1], 100/PKdata$MM[1]*60, 0),
                    0.06)

ComparisonVC <- bind_rows("Shafaei-Bajestani et al."=Shafaei,
                          "Valls et al.and Ramos et al."=Valls_Ramos,
                          "Gasparetto et al."=Gasparetto,
                          "Guan et al." =Guan,
```

```
                          .id = "Studies")

  ggplot()+
    geom_line(data=ComparisonVC, aes(x=Time, y=Concentration, col=Studies),
              size = 1)+
    scale_color_manual(values = c(rgb(1,0.7,0.9), rgb(1,0.6,0.7),rgb(1,0.4,0.
4), rgb(0.7,0.1,0.2)))+
    geom_errorbar(data=Ramos, aes(x=Time.min, y=M_conc.mM,
                                  ymin=Qmin.mM, ymax=Qmax.mM),
                  col="black", size=1)+
    geom_point(data=Ramos, aes(x=Time.min, y=M_conc.mM), na.rm = T, col="blac
k", size=4, shape="square")+
    scale_y_break(breaks=c(2.5,5), scales=c(.3))+
    scale_x_continuous(breaks = seq(0,420,60), limits = c(-15, 500), labels =
seq(0,7,1))+

    scale_y_continuous(n.breaks = 3, breaks = c(seq(from=0,to=2, by=0.4),6,8,
10))+
    labs(x=NULL, y=NULL)+
    theme_classic()+
    guides(title=NULL,col = guide_legend(ncol = 1))+
    theme(legend.position = "bottom", legend.title = element_blank(),
          legend.text = element_text(size=8),
          axis.text = element_text(size = 8))
```

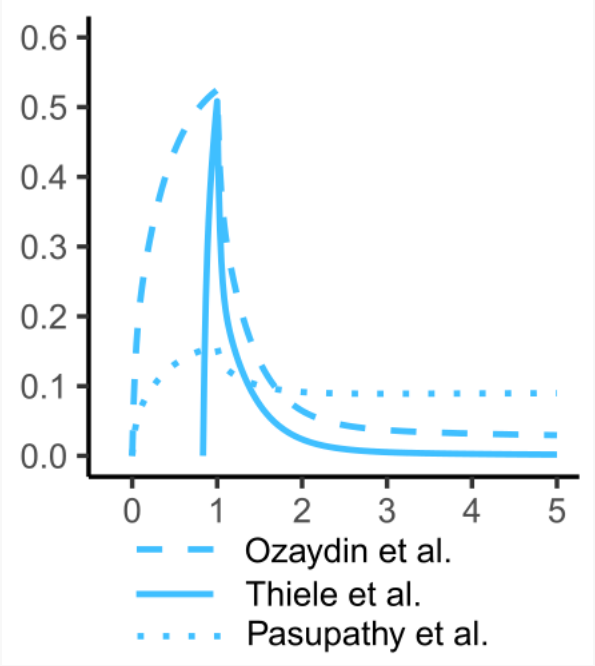


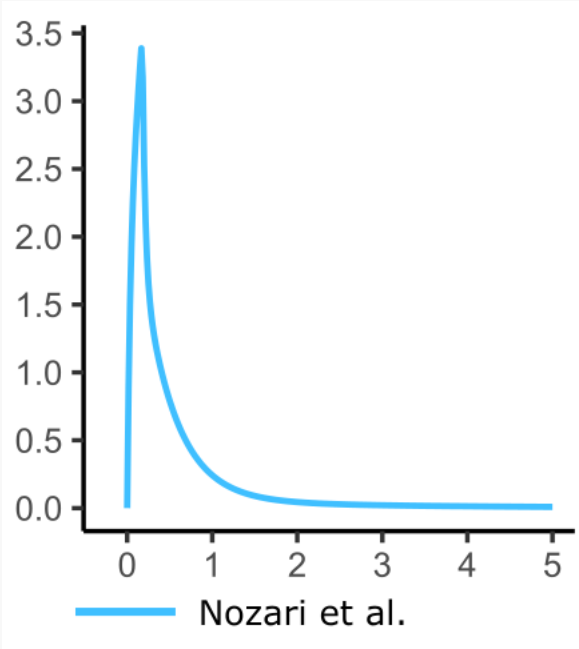

```
  ggsave("ComparisonVC.pdf", width = 5, height = 8, units = c("cm"))
```

N-acetylcysteine

```
naciam <- simul_3comp(PKdata$V1[2], PKdata$V2[2], PKdata$V3[2],
                      PKdata$CL[2], PKdata$Q[2],PKdata$Q3[2],
                    tD= c(1, 48),
```

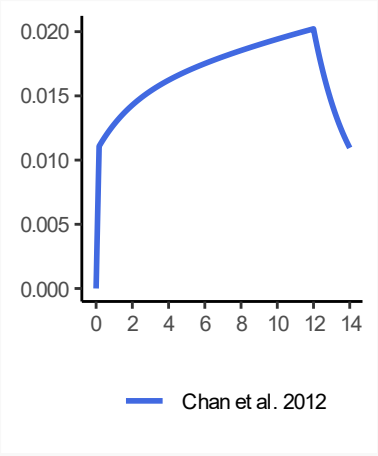
```
                      R= c((20/PKdata$MM[2])*60, (10/PKdata$MM[2])*60))
  lipsia <- simul_3comp(PKdata$V1[2], PKdata$V2[2], PKdata$V3[2],
                        PKdata$CL[2], PKdata$Q[2],PKdata$Q3[2],
                        tD= c(1/6, 12, 24, 36),
                        R= c((1200/PKdata$MM[2])*6, 0, (1200/PKdata$MM[2])*6,
0))
  Nozari <- simul_3comp(PKdata$V1[2], PKdata$V2[2], PKdata$V3[2],
                        PKdata$CL[2], PKdata$Q[2],PKdata$Q3[2],
                        tD= c(1/6, 1/6 + 1/60, 12, 12+1/6,24),
                        R= c((100*80/PKdata$MM[2])*6,
                             (480/PKdata$MM[2])*60, 0,
                             (10*80/PKdata$MM[2])*6,0))
  Ozaydin <- simul_3comp(PKdata$V1[2], PKdata$V2[2], PKdata$V3[2],
                        PKdata$CL[2], PKdata$Q[2],PKdata$Q3[2],
                        tD= c(1, 49),
                        R= c((50*80/PKdata$MM[2]),
                             (50*80/(24*PKdata$MM[2]))))

  ComparisonNAC <- bind_rows("NACIAM"=naciam,
                             "LIPSIA"=lipsia,
                             "Nozari et al."=Nozari,
                             "Ozaydin et al."=Ozaydin,
                             .id = "Studies")

  ggplot()+
    geom_line(data=ComparisonNAC, aes(x=Time, y=Concentration, col=Studies),
              size = 1)+
    scale_color_manual(values = c("red", "blue","yellow", "orange"))+
    scale_x_continuous(breaks = seq(0,420,60), limits = c(-5, 300), labels =
seq(0,7,1))+
    labs(x=NULL, y=NULL)+
    theme_classic()+
    guides(title=NULL,col = guide_legend(nrow = 4))+
    theme(legend.position = "bottom", legend.title = element_blank(),
          legend.text = element_text(size = 8),
          axis.text = element_text(size = 8))

  ggsave("ComparisonNAC.pdf", width = 5, height = 8, units = c("cm"))
```





Deferoxamine

```
Chan_DFO <- tibble(Units=c("mg  (/h)", "mmol  (/h)"),
                   Bolus=c(500, 500/PKdata$MM[3]),
                   Infusion=c(50*80/12, 50*80/(12*PKdata$MM[3])))

simul_DFO.Chan <- simul_2comp(V=PKdata$V1[3], V2=PKdata$V2[3],
                              CL=PKdata$CL[3], Q=PKdata$Q[3],
                              tD=c(1/6,12,24),
                              R=c(Chan_DFO$Bolus[2]*6, Chan_DFO$Infusion[2],0
))
ggplot()+
  geom_line(data = simul_DFO.Chan, aes(x=Time, y=Concentration, col="Chan et
al. 2012"),
            size = 1)+
  scale_color_manual(values = "royal blue")+
  scale_x_continuous(breaks = seq(0,1500,120), limits = c(-5, 840), labels =
seq(0,24,2))+
  labs(x=NULL, y=NULL)+
  theme_classic()+
  guides(title=NULL)+
  theme(legend.position = "bottom", legend.title = element_blank(),
        legend.text = element_text(size=8),
        axis.text = element_text(size = 8))

ggsave("ComparisonDFO.pdf", width = 5, height = 6, units = c("cm"))
```


0.020
0.015
0.010
0.005
0.000
0
2
4
6
8
10
12
14
Chan et al. 2012