The Pharmacokinetics dose response with 3 compartment model:
(The data are from the EXCEL FILE delieved by Dr Zitta)

$$XY := \begin{bmatrix} 7 & 394.63 \\ 10 & 318.63 \\ 15 & 243.34 \\ 20 & 209.04 \\ 25 & 187.74 \\ 30 & 176.31 \\ 45 & 137.89 \\ 60 & 114.73 \\ 90 & 87.22 \\ 120 & 74.01 \\ 150 & 61.61 \\ 180 & 60.25 \end{bmatrix}$$

$$\begin{bmatrix} Xtime & Yconcentration \end{bmatrix} := \begin{bmatrix} XY^{\langle 0 \rangle} & XY^{\langle 1 \rangle} \end{bmatrix}$$

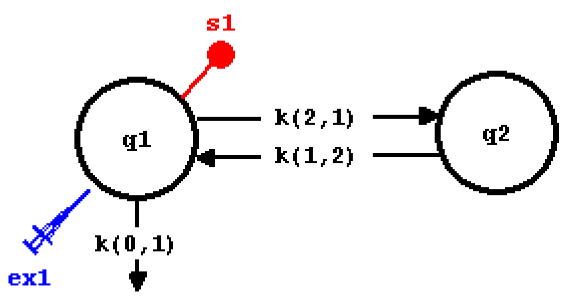


Fig1. 2-compartment model

Project parameters

Dose injection [mg] $D := 2500$

Duration_injection [min] $\tau := 3$

Initial Concentration

in Central comp't [mg/l] $c10 := 0$

in Peripheral coomp't [mg/l] $c20 := 0$

Infusionrate: (for an infusion pump) $\rho := 0$

Measurement Variance: $\sigma_M := 7.8188$

Auxilliary parameters in the system

$$f(time) := \begin{cases} \dfrac{D}{\tau} & \text{if } 0 \le time < \tau \\ \rho & \text{else} \end{cases}$$

$Number\_of\_Artificial\_Protocols := 2$

$\mathbf{TOL} := 10^{-9}$

$end := 500$ Integration t (in minutes)

Here the solution of the ODE is done with Laplace Transform:

$\mathbf{clear}_{\mathbf{sym}}(D)$ $\mathbf{clear}_{\mathbf{sym}}(time)$

$\mathbf{clear}_{\mathbf{sym}}(\rho)$ $\mathbf{clear}_{\mathbf{sym}}(c10)$

$\mathbf{clear}_{\mathbf{sym}}(\tau)$ $\mathbf{clear}_{\mathbf{sym}}(c20)$

The f(Xtime) can also be written with the Heaviside Function:

$$f(time) := \frac{D}{\tau} \cdot \Phi(time) + \left(\rho - \frac{D}{\tau}\right) \cdot \Phi(time - \tau)$$

for simplification the calculation starts for f(t) where t=τ

$$\frac{D}{\tau} \xrightarrow{laplace} \frac{D}{s \cdot \tau}$$

Here for simplification, the x1(0) = DOSE and the transformed ODE looks like this:

$$\varepsilon(s) := -\left(k_{01} + k_{21}\right) \cdot Lx1 + k_{12} \cdot Lx2 \rightarrow Lx2 \cdot k_{12} - Lx1 \cdot \left(k_{01} + k_{21}\right)$$

$$\zeta(s) := k_{21} \cdot Lx1 - k_{12} \cdot Lx2 \rightarrow Lx1 \cdot k_{21} - Lx2 \cdot k_{12}$$

- **Step Two:** Apply linear property to get a system of equations for $\widehat{x}(s)$ and $\widehat{y}(s)$, due to $\mathcal{L}(x') = s\widehat{x}(s) - x(0)$ and $\mathcal{L}(y') = s\widehat{y}(s) - y(0)$,

$$s \cdot Lx - x(0) = \varepsilon(s) \rightarrow ?$$

$$\left(s \cdot Ly - y(0) = \zeta(s)\right) \rightarrow ?$$

$$s \cdot Lx1 - D = \varepsilon(s) \xrightarrow{solve, Lx1} \frac{D + Lx2 \cdot k_{12}}{s + k_{01} + k_{21}}$$

$$s \cdot Lx2 - 0 = \zeta(s) \xrightarrow{solve, Lx2} \frac{Lx1 \cdot k_{21}}{s + k_{12}}$$

$$lapsys := \begin{bmatrix} s \cdot Lx1 - D = \varepsilon(s) \\ s \cdot Lx2 - 0 = \zeta(s) \end{bmatrix}$$

$$lapsys \xrightarrow[]{\substack{solve\,,Lx1\,,Lx2\\ simplify}} \begin{bmatrix} \dfrac{D \cdot (s + k_{12})}{s^2 + s \cdot k_{01} + s \cdot k_{12} + s \cdot k_{21} + k_{01} \cdot k_{12}} & \dfrac{D \cdot k_{21}}{s^2 + s \cdot k_{01} + s \cdot k_{12} + s \cdot k_{21} + k_{01} \cdot k_{12}} \end{bmatrix}$$

$$sol(V_1, k_{01}, k_{12}, k_{21}, D, \tau, \rho, c10, c20, t) := lapsys \xrightarrow[]{\substack{solve\,,Lx1\,,Lx2\\ simplify\\ invlaplace}} \left[\frac{D \cdot e^{-\frac{t \cdot (k_{01}+k_{12}+k_{21})}{2}} \cdot \left(\cosh\left(\frac{t \cdot \sqrt{4 \cdot \left(\frac{k_{01}}{2} + \frac{k_{12}}{2} + \frac{k_{21}}{2}\right)^2 - 4 \cdot k_{01} \cdot k_{12}}}{2} \right) \cdot \sqrt{4 \cdot \left(\frac{k_{01}}{2} + \frac{k_{12}}{2} + \frac{k_{21}}{2}\right)^2 - 4 \cdot k_{01} \cdot k_{12}} - k_{01} \cdot \sinh\left(\frac{t \cdot \sqrt{4 \cdot \left(\frac{k_{01}}{2} + \frac{k_{12}}{2} + \frac{k_{21}}{2}\right)^2 - 4 \cdot k_{01} \cdot k_{12}}}{2} \right) + k_{12} \cdot \sinh\left(\frac{t \cdot \sqrt{4 \cdot \left(\frac{k_{01}}{2} + \frac{k_{12}}{2} + \frac{k_{21}}{2} \right.}}{2} \right. \right.}{\sqrt{4 \cdot \left(\frac{k_{01}}{2} + \frac{k_{12}}{2} + \frac{k_{21}}{2}\right)^2 - 4 \cdot k_{01} \cdot k_{12}}} \right.$$

Project parameters

Dose injection [mg] $D := 2500$

Duration_injection [min] $\tau := 3$

$\rho := 0$

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix} := \begin{bmatrix} 0.01972 \\ 0.04048 \\ 0.06134 \\ 4.28619 \end{bmatrix} \qquad \begin{bmatrix} Clearance \\ V_1 \\ V_2 \\ t21 \end{bmatrix} := \begin{bmatrix} 84.50884 \\ 4.28619 \\ 6.49569 \\ 11.29983 \end{bmatrix}$$

$c10 := 0$ $c20 := 0$

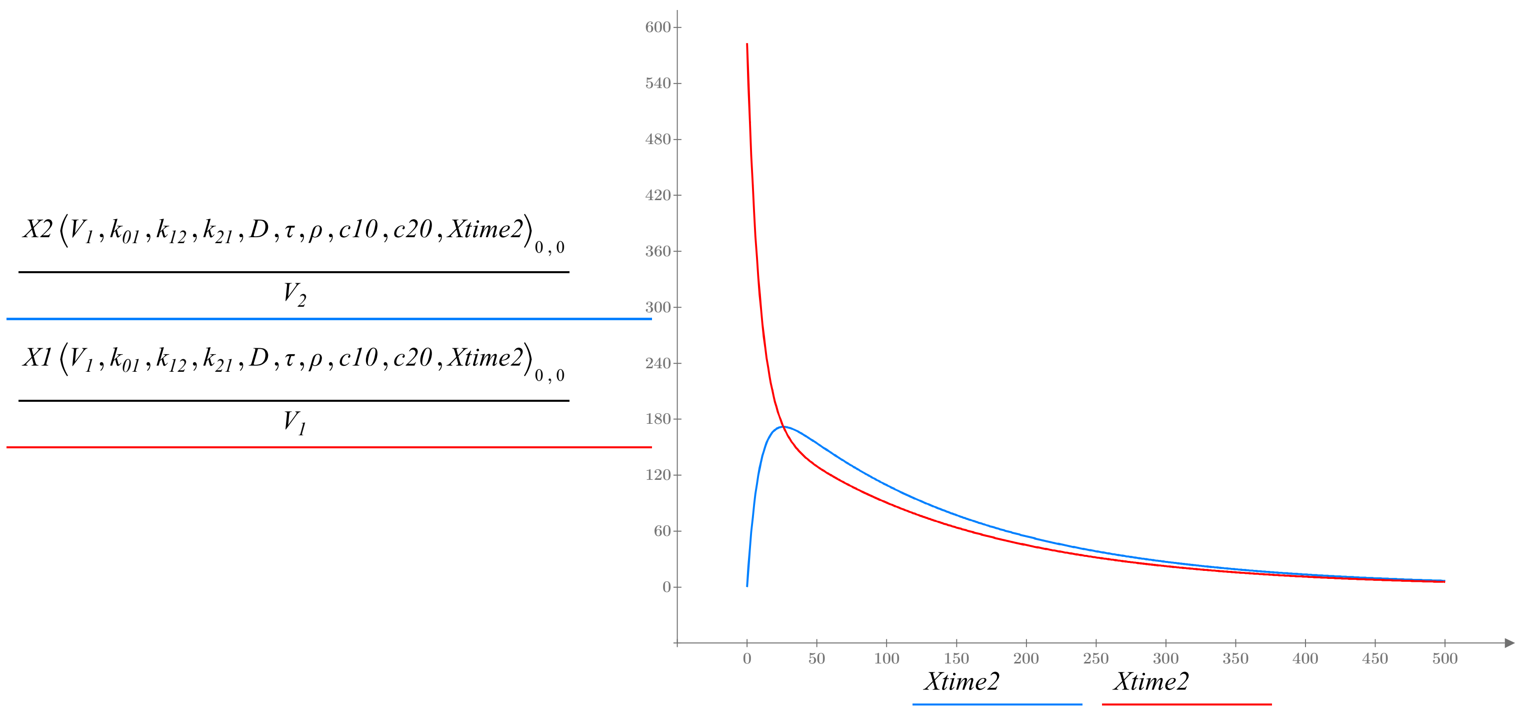
$$sol(V_1, k_{01}, k_{12}, k_{21}, D, \tau, \rho, c10, c20, 3) = [1983.18944 \quad 385.04627]$$

$$X1(V_1, k_{01}, k_{12}, k_{21}, D, \tau, \rho, c10, c20, tonne) := sol(V_1, k_{01}, k_{12}, k_{21}, D, \tau, \rho, c10, c20, tonne)^{\langle 0 \rangle}$$

$$X2(V_1, k_{01}, k_{12}, k_{21}, D, \tau, \rho, c10, c20, tonne) := sol(V_1, k_{01}, k_{12}, k_{21}, D, \tau, \rho, c10, c20, tonne)^{\langle 1 \rangle}$$

$j := 0 .. 400$

$Xtime2 := 0 .. 500$


X2(V1, k01, k12, k21, D, τ, ρ, c10, c20, Xtime2)0,0 / V2
X1(V1, k01, k12, k21, D, τ, ρ, c10, c20, Xtime2)0,0 / V1
600
540
480
420
360
300
240
180
120
60
0
0
50
100
150
200
250
300
350
400
450
500
Xtime2
Xtime2