Pharmacokinetics dose response with 2 compartment model - For GFR Identificaiton: (The data are from EI. Christina Excel)

$Xtime$	$Yconcentration$
7	375.97
10	296.1
15	219.73
20	188.4
25	169.52
30	149.8
45	124.76
60	110.36
90	93.29
120	78.47
150	67.42
180	62.52

Project parameters

Dose injection [mg] $D := 2500$

Duration_injection [min] $\tau := 3$

Initial Concentration

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

$c20 := 0$

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

$TOL := 10^{-9}$

Source: Eur J Clin Chem Clin Biochem 1995; 33 (no 4) pp. 201-209

$$con10 := c10 \quad con20 := c20 \quad Irate := \rho \quad Dosis := D \qquad \tau = 3$$

$$k01(vol1, clearance) := \frac{clearance}{vol1 \cdot 1000} \quad k21(t21) := \frac{\ln(2)}{t21}$$

$$k12(vol1, vol2, t21) := k21(t21) \cdot \frac{vol1}{vol2}$$

$$X10(vol1) := con10 \cdot vol1$$

$$X20(vol2) := con20 \cdot vol2$$

$$x1s(vol1, clearance) := \frac{\frac{Dosis}{\tau}}{k01(vol1, clearance)}$$

$$x2s(vol1, vol2, t21, clearance) := x1s(vol1, clearance) \cdot \frac{k21(t21)}{k12(vol1, vol2, t21)}$$

$$y1s(vol1, clearance) := \frac{Irate}{k01(vol1, clearance)}$$

$$y2s(vol1, vol2, t21, clearance) := y1s(vol1, clearance) \cdot \frac{k21(t21)}{k12(vol1, vol2, t21)}$$

$$ksum(vol1, vol2, t21, clearance) := k01(vol1, clearance) + k21(t21) + k12(vol1, vol2, t21)$$

$$diskrim(vol1, vol2, t21, clearance) := \sqrt{ksum(vol1, vol2, t21, clearance)^2 - 4 \cdot k01(vol1, clearance) \cdot k12(vol1, vol2, t21)}$$

$$\lambda1(vol1, vol2, t21, clearance) := -0.5 \cdot (ksum(vol1, vol2, t21, clearance) - diskrim(vol1, vol2, t21, clearance))$$

$$\lambda2(vol1, vol2, t21, clearance) := -0.5 \cdot (ksum(vol1, vol2, t21, clearance) + diskrim(vol1, vol2, t21, clearance))$$

$$a(vol1, vol2, t21, clearance) := \frac{k01(vol1, clearance) + k21(t21) + \lambda1(vol1, vol2, t21, clearance)}{k12(vol1, vol2, t21)}$$

$$b(vol1, vol2, t21, clearance) := \frac{k21(t21)}{k12(vol1, vol2, t21) + \lambda2(vol1, vol2, t21, clearance)}$$

$$M1(vol1, vol2, t21, clearance) := \frac{(X10(vol1) - x1s(vol1, clearance)) \cdot b(vol1, vol2, t21, clearance) - (X20(vol2) - x2s(vol1, vol2, t21, clearance))}{b(vol1, vol2, t21, clearance) - a(vol1, vol2, t21, clearance)}$$

$$M2(vol1, vol2, t21, clearance) := \frac{(X20(vol2) - x2s(vol1, vol2, t21, clearance)) - (X10(vol1) - x1s(vol1, clearance)) \cdot a(vol1, vol2, t21, clearance)}{b(vol1, vol2, t21, clearance) - a(vol1, vol2, t21, clearance)}$$

$$x1\tau(vol1, vol2, t21, clearance) := M1(vol1, vol2, t21, clearance) \cdot e^{\lambda1(vol1, vol2, t21, clearance) \cdot \tau} + M2(vol1, vol2, t21, clearance) \cdot e^{\lambda2(vol1, vol2, t21, clearance) \cdot \tau} + x1s(vol1, clearance)$$

$$x2\tau(vol1, vol2, t21, clearance) := M1(vol1, vol2, t21, clearance) \cdot a(vol1, vol2, t21, clearance) \cdot e^{\lambda1(vol1, vol2, t21, clearance) \cdot \tau} + M2(vol1, vol2, t21, clearance) \cdot b(vol1, vol2, t21, clearance) \cdot e^{\lambda2(vol1, vol2, t21, clearance) \cdot \tau} + x2s(vol1, vol2, t21, clearance)$$

$$N1(vol1, vol2, t21, clearance) := \frac{(x1\tau(vol1, vol2, t21, clearance) - y1s(vol1, clearance)) \cdot b(vol1, vol2, t21, clearance) - (x2\tau(vol1, vol2, t21, clearance) - y2s(vol1, vol2, t21, clearance))}{b(vol1, vol2, t21, clearance) - a(vol1, vol2, t21, clearance)}$$

$$N2(vol1, vol2, t21, clearance) := \frac{(x2\tau(vol1, vol2, t21, clearance) - y2s(vol1, vol2, t21, clearance)) - (x1\tau(vol1, vol2, t21, clearance) - y1s(vol1, clearance)) \cdot a(vol1, vol2, t21, clearance)}{b(vol1, vol2, t21, clearance) - a(vol1, vol2, t21, clearance)}$$

$$part1X1(t, vol1, vol2, t21, clearance) := M1(vol1, vol2, t21, clearance) \cdot e^{\lambda1(vol1, vol2, t21, clearance)(t)} + M2(vol1, vol2, t21, clearance) \cdot e^{\lambda2(vol1, vol2, t21, clearance)(t)} + x1s(vol1, clearance)$$

$$part2X1(t, vol1, vol2, t21, clearance) := N1(vol1, vol2, t21, clearance) \cdot e^{\lambda1(vol1, vol2, t21, clearance)(t-\tau)} + N2(vol1, vol2, t21, clearance) \cdot e^{\lambda2(vol1, vol2, t21, clearance)(t-\tau)} + y1s(vol1, clearance)$$

$$model\_analyX1(t, vol1, vol2, t21, clearance) := \frac{1}{vol1} \cdot \begin{cases} part1X1(t, vol1, vol2, t21, clearance) & \text{if } 0 \le t < \tau \\ part2X1(t, vol1, vol2, t21, clearance) & \text{else} \end{cases}$$

$$part1X2(t, vol1, vol2, t21, clearance) := M1(vol1, vol2, t21, clearance) \cdot a(vol1, vol2, t21, clearance) \cdot e^{\lambda1(vol1, vol2, t21, clearance)(t)} + M2(vol1, vol2, t21, clearance) \cdot b(vol1, vol2, t21, clearance) \cdot e^{\lambda2(vol1, vol2, t21, clearance)(t)} + x2s(vol1, vol2, t21, clearance)$$

$$part2X2(t, vol1, vol2, t21, clearance) := N1(vol1, vol2, t21, clearance) \cdot a(vol1, vol2, t21, clearance) \cdot e^{\lambda1(vol1, vol2, t21, clearance)(t-\tau)} + N2(vol1, vol2, t21, clearance) \cdot b(vol1, vol2, t21, clearance) \cdot e^{\lambda2(vol1, vol2, t21, clearance)(t-\tau)} + y2s(vol1, vol2, t21, clearance)$$

$$model\_analyX2(t, vol1, vol2, t21, clearance) := \frac{1}{vol2} \cdot \begin{cases} part1X2(t, vol1, vol2, t21, clearance) & \text{if } 0 \le t < \tau \\ part2X2(t, vol1, vol2, t21, clearance) & \text{else} \end{cases}$$

Note: the symbolic substitution does only work with the legacy symbolic processor (muPAD) in Prime 6.0

$$partk1X1(t, vol1, kk01, kk12, kk21) := part1X1(t, vol1, vol2, t21, clearance) \xrightarrow{substitute, clearance = kk01 \cdot 1000 \cdot vol1, t21 = \frac{ln(2)}{kk21}, vol2 = vol1 \cdot \frac{kk21}{kk12}}$$

$$partk1X1(1, 2, 3, 4, 5) = 203.309$$

$$partk2X1(t, vol1, kk01, kk12, kk21) := part2X1(t, vol1, vol2, t21, clearance) \xrightarrow{substitute, clearance = kk01 \cdot 1000 \cdot vol1, t21 = \frac{ln(2)}{kk21}, vol2 = vol1 \cdot \frac{kk21}{kk12}}$$

$$partk1X2(t, vol1, kk01, kk12, kk21) := part1X2(t, vol1, vol2, t21, clearance) \xrightarrow{substitute, clearance = kk01 \cdot 1000 \cdot vol1, t21 = \frac{ln(2)}{kk21}, vol2 = vol1 \cdot \frac{kk21}{kk12}}$$

$$partk2X2(t, vol1, kk01, kk12, kk21) := part2X2(t, vol1, vol2, t21, clearance) \xrightarrow{substitute, clearance = kk01 \cdot 1000 \cdot vol1, t21 = \frac{ln(2)}{kk21}, vol2 = vol1 \cdot \frac{kk21}{kk12}}$$

Final model with the kk-Values:

$$model\_analykX1(t, kk01, kk12, kk21, vol1) := \frac{1}{vol1} \cdot \begin{cases} partk1X1(t, vol1, kk01, kk12, kk21) & \text{if } 0 \le t < \tau \\ partk2X1(t, vol1, kk01, kk12, kk21) & \text{else} \end{cases}$$

$$model\_analykX2(t, kk01, kk12, kk21, vol1) := \frac{kk12}{kk21 \cdot vol1} \cdot \begin{cases} partk1X2(t, vol1, kk01, kk12, kk21) & \text{if } 0 \le t < \tau \\ partk2X2(t, vol1, kk01, kk12, kk21) & \text{else} \end{cases}$$

Residuals- Function with vol1, vol2, t21 and clearance:

$$resid(vol1, vol2, t21, clearance) := Yconcentration - \overrightarrow{model\_analyX1(Xtime, vol1, vol2, t21, clearance)}$$

$est\_V1 := 5 \quad est\_V2 := 4.1 \quad est\_t21 := 8.9 \quad est\_cl := 51$

Schätzwerte

$$\begin{bmatrix} est\_cl \\ est\_V1 \\ est\_V2 \\ est\_t21 \end{bmatrix} := \begin{bmatrix} 50 \\ 5 \\ 4.1 \\ 8.9 \end{bmatrix}$$

Nebenbedingungen

$$0 = resid(est\_V1, est\_V2, est\_t21, est\_cl)$$

Gleichungslöser

$$\begin{bmatrix} anak\_vol1 \\ anak\_vol2 \\ anak\_t21 \\ anak\_clearance \end{bmatrix} := \mathbf{minerr}(est\_V1, est\_V2, est\_t21, \mathbf{est\_cl})$$

$$SSE(vol1, vol2, t21, clearance) := \sum resid(vol1, vol2, t21, clearance)^2$$

$$\frac{SSE(anak\_vol1, anak\_vol2, anak\_t21, anak\_clearance)}{8} = 26.635$$

$$\begin{bmatrix} anak\_clearance \\ anak\_vol1 \\ anak\_vol2 \\ anak\_t21 \end{bmatrix} = \begin{bmatrix} 81.199 \\ 4.136 \\ 8.131 \\ 8.864 \end{bmatrix}$$

Pragmatical relationships:

$$k_{01} := \frac{anak\_clearance}{1000 \cdot anak\_vol1} \quad k_{21} := \frac{\ln(2)}{anak\_t21} \quad k_{12} := anak\_vol1 \cdot \frac{k_{21}}{anak\_vol2}$$

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ anak\_vol1 \end{bmatrix} = \begin{bmatrix} 0.02 \\ 0.04 \\ 0.078 \\ 4.136 \end{bmatrix}$$

Residuals- Function with k-values:

$$residk(k01, k12, k21, vol1) := Yconcentration - \overrightarrow{model\_analykX1(Xtime, k01, k12, k21, vol1)}$$

Schätzwerte

$$\begin{bmatrix} est\_vol1 \\ est\_k01 \\ est\_k12 \\ est\_k21 \end{bmatrix} := \begin{bmatrix} 5 \\ 0.04 \\ 0.04 \\ 0.09 \end{bmatrix}$$

Nebenbedingungen

$$0 = residk(est\_k01, est\_k12, est\_k21, est\_vol1)$$

Gleichungslöser

$$\begin{bmatrix} ana\_k01 \\ ana\_k12 \\ ana\_k21 \\ ana\_vol1 \end{bmatrix} := \mathbf{minerr}(est\_k01, est\_k12, est\_k21, est\_vol1)$$

Pragmatical relationships:

$$clearance := ana\_k01 \cdot 1000 \cdot ana\_vol1$$

$$t21 := \frac{\ln(2)}{ana\_k21}$$

$$vol2 := ana\_vol1 \cdot \frac{ana\_k21}{ana\_k12}$$

$$\begin{bmatrix} ana\_k01 \\ ana\_k12 \\ ana\_k21 \\ ana\_vol1 \end{bmatrix} = \begin{bmatrix} 0.02 \\ 0.04 \\ 0.078 \\ 4.136 \end{bmatrix}$$

$$SSE(vol1, vol2, t21, clearance) := \sum resid(vol1, vol2, t21, clearance)^2$$

$$\frac{SSE(ana\_vol1, vol2, t21, clearance)}{8} = 26.635$$

$$\begin{bmatrix} clearance \\ ana\_vol1 \\ vol2 \\ t21 \end{bmatrix} = \begin{bmatrix} 81.199 \\ 4.136 \\ 8.131 \\ 8.864 \end{bmatrix}$$

The following terms are manuelly substituted

$k01(vol1, clearance) := \frac{clearance}{vol1 \cdot 1000}$ $k21(t21) := \frac{\ln(2)}{t21}$ $k12(vol1, vol2, t21) := k21(t21) \cdot \frac{vol1}{vol2}$ $X10k(vol1) := con10 \cdot vol1$ $X20(vol2) := con20 \cdot vol2$

$$X20k(kk12, kk21, vol1) := \frac{con20 \cdot kk21 \cdot vol1}{kk12}$$

$$x1sk(kk01) := \frac{Dosis}{\tau \cdot kk01}$$

$$x2sk(kk01, kk12, kk21) := \frac{Dosis \cdot kk21}{\tau \cdot kk01 \cdot kk12}$$

$$y1sk(kk01) := \frac{Irate}{kk01}$$

$$y2sk(kk01, kk12, kk21) := \frac{kk21}{kk01 \cdot kk12}$$

$$ksumk(kk01, kk12, kk21) := kk01 + kk21 + kk12$$

$$diskrimk(kk01, kk12, kk21) := \sqrt{ksumk(kk01, kk12, kk21)^2 - 4 \cdot kk01 \cdot kk12}$$

$$\lambda k1(kk01, kk12, kk21) := -0.5 \cdot (ksumk(kk01, kk12, kk21) - diskrimk(kk01, kk12, kk21))$$
$$\lambda k2(kk01, kk12, kk21) := -0.5 \cdot (ksumk(kk01, kk12, kk21) + diskrimk(kk01, kk12, kk21))$$

$$ak(kk01, kk12, kk21) := \frac{kk01 + kk21 + \lambda k1(kk01, kk12, kk21)}{kk12}$$

$$bk(kk01, kk12, kk21) := \frac{kk21}{kk12 + \lambda k2(kk01, kk12, kk21)}$$

$$M1k(kk01,kk12,kk21,vol1) := \frac{(X10k(vol1) - x1sk(kk01)) \cdot bk(kk01,kk12,kk21) - (X20k(kk12,kk21,vol1) - x2sk(kk01,kk12,kk21))}{bk(kk01,kk12,kk21) - ak(kk01,kk12,kk21)}$$

$$M2k(kk01,kk12,kk21,vol1) := \frac{(X20k(kk12,kk21,vol1) - x2sk(kk01,kk12,kk21)) - (X10k(vol1) - x1sk(kk01)) \cdot ak(kk01,kk12,kk21)}{bk(kk01,kk12,kk21) - ak(kk01,kk12,kk21)}$$

$$x1\tau k(kk01,kk12,kk21,vol1) := M1k(kk01,kk12,kk21,vol1) \cdot e^{\lambda k1(kk01,kk12,kk21) \cdot \tau} + M2k(kk01,kk12,kk21,vol1) \cdot e^{\lambda k2(kk01,kk12,kk21) \cdot \tau} + x1sk(kk01)$$

$$x2\tau k(kk01,kk12,kk21,vol1) := M1k(kk01,kk12,kk21,vol1) \cdot ak(kk01,kk12,kk21) \cdot e^{\lambda k1(kk01,kk12,kk21) \cdot \tau} + M2k(kk01,kk12,kk21,vol1) \cdot bk(kk01,kk12,kk21) \cdot e^{\lambda k2(kk01,kk12,kk21) \cdot \tau} + x2sk(kk01,kk12,kk21)$$

$$N1k(kk01,kk12,kk21,vol1) := \frac{(x1\tau k(kk01,kk12,kk21,vol1) - y1sk(kk01)) \cdot bk(kk01,kk12,kk21) - (x2\tau k(kk01,kk12,kk21,vol1) - y2sk(kk01,kk12,kk21))}{bk(kk01,kk12,kk21) - ak(kk01,kk12,kk21)}$$

$$N2k(kk01,kk12,kk21,vol1) := \frac{(x2\tau k(kk01,kk12,kk21,vol1) - y2sk(kk01,kk12,kk21)) - (x1\tau k(kk01,kk12,kk21,vol1) - y1sk(kk01)) \cdot ak(kk01,kk12,kk21)}{bk(kk01,kk12,kk21) - ak(kk01,kk12,kk21)}$$

$$model\_analykX1(t,kk01,kk12,kk21,vol1) := \frac{1}{vol1} \cdot \begin{cases} M1k(kk01,kk12,kk21,vol1) \cdot e^{\lambda k1(kk01,kk12,kk21)(t)} + M2k(kk01,kk12,kk21,vol1) \cdot e^{\lambda k2(kk01,kk12,kk21)(t)} + x1sk(kk01) & \text{if } 0 \le t < \tau \\ N1k(kk01,kk12,kk21,vol1) \cdot e^{\lambda k1(kk01,kk12,kk21)(t-\tau)} + N2k(kk01,kk12,kk21,vol1) \cdot e^{\lambda k2(kk01,kk12,kk21)(t-\tau)} + y1sk(kk01) & \text{else} \end{cases}$$

$$model\_analykX2(t,kk01,kk12,kk21,vol1) := \frac{1}{vol1 \cdot \frac{kk21}{kk12}} \cdot \begin{cases} M1k(kk01,kk12,kk21,vol1) \cdot ak(kk01,kk12,kk21) \cdot e^{\lambda k1(kk01,kk12,kk21)(t)} + M2k(kk01,kk12,kk21,vol1) \cdot bk(kk01,kk12,kk21) \cdot e^{\lambda k2(kk01,kk12,kk21)(t)} + x2sk(kk01,kk12,kk21) & \text{if } 0 \le t < \tau \\ N1k(kk01,kk12,kk21,vol1) \cdot ak(kk01,kk12,kk21) \cdot e^{\lambda k1(kk01,kk12,kk21)(t-\tau)} + N2k(kk01,kk12,kk21,vol1) \cdot bk(kk01,kk12,kk21) \cdot e^{\lambda k2(kk01,kk12,kk21)(t-\tau)} + y2sk(kk01,kk12,kk21) & \text{else} \end{cases}$$

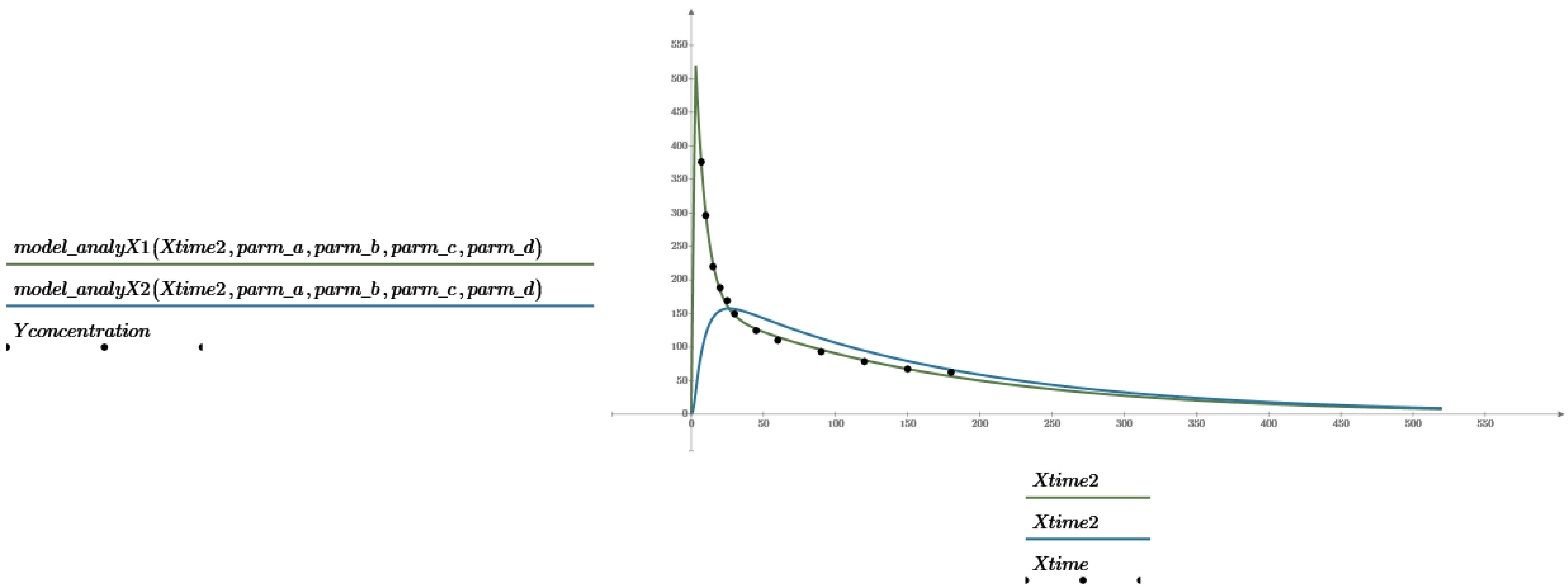
$end := 500$

$model\_analykX1(Xtime2, parm\_a, parm\_b, parm\_c, parm\_d)$

$$\begin{bmatrix} parm\_a \\ parm\_b \\ parm\_c \\ parm\_d \end{bmatrix} := \begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ anak\_vol1 \end{bmatrix} = \begin{bmatrix} 0.02 \\ 0.04 \\ 0.078 \\ 4.136 \end{bmatrix}$$

$model\_analyX1(Xtime2, parm\_a, parm\_b, parm\_c, parm\_d)$

$$\begin{bmatrix} parm\_a \\ parm\_b \\ parm\_c \\ parm\_d \end{bmatrix} := \begin{bmatrix} ana\_vol1 \\ vol2 \\ t21 \\ clearance \end{bmatrix} = \begin{bmatrix} 4.136 \\ 8.131 \\ 8.864 \\ 81.199 \end{bmatrix}$$



Solution of the ODE by numerical solution

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

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

Solving the ODE according Adaptive

Nebenbedingungen / Schätzwerte

$$x1(0) = c10 \cdot V_1$$

$$x2(0) = c20 \cdot V_1 \cdot \left(\frac{k_{21}}{k_{12}}\right)$$

$$x1'(Xtime) = \left(f(Xtime) - (k_{01} + k_{21}) \cdot x1(Xtime) + k_{12} \cdot x2(Xtime)\right)$$

$$x2'(Xtime) = \left(k_{21} \cdot x1(Xtime) - k_{12} \cdot x2(Xtime)\right)$$

Gleichungslöser

$$Sol(k_{01}, k_{12}, k_{21}, V_1) := \text{odesolve}\left(\begin{bmatrix} x1(Xtime) \\ x2(Xtime) \end{bmatrix}, end\right)$$

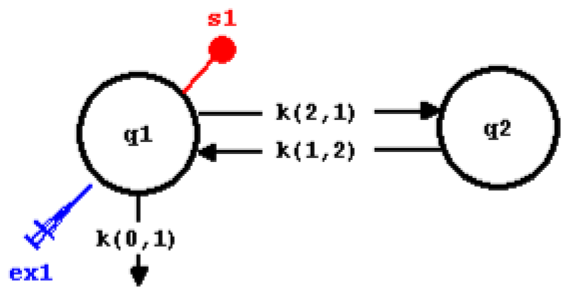
Guesses for minerr

$$\begin{bmatrix} k_{01} & k_{12} & k_{21} & V_1 \end{bmatrix} := \begin{bmatrix} 0.086 & 0.04 & 0.08 & 0.32 \end{bmatrix}$$

Nebenbedingungen / Schätzwerte

Rather than residuals, calculate the predicted values and equate those to the input values.

$$\left\| \begin{array}{l} \begin{bmatrix} X1 \\ X2 \end{bmatrix} \leftarrow Sol(k_{01}, k_{12}, k_{21}, V_1) \\ Xt \leftarrow Xtime \\ \dfrac{\overrightarrow{X1(Xt)}}{V_1} \end{array} \right. = Yconcentration$$



Gleichungslöser

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix} := \text{Minerr}(k_{01}, k_{12}, k_{21}, V_1)$$

$$\begin{bmatrix} X1 \\ X2 \end{bmatrix} := Sol(k_{01}, k_{12}, k_{21}, V_1)$$

Residuals comparition of numerical & analytical solutions

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix} = \begin{bmatrix} 0.02 \\ 0.04 \\ 0.078 \\ 4.136 \end{bmatrix}$$

Pragmatical relationships:

$$V_2 := V_1 \cdot \left(\frac{k_{21}}{k_{12}}\right) \qquad Clearance := k_{01} \cdot 1000 \cdot V_1 \qquad t21 := \frac{\ln(2)}{k_{21}}$$

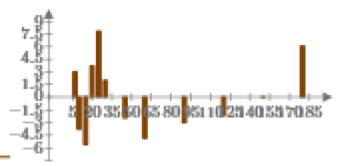
$$\begin{bmatrix} Clearance \\ V_1 \\ V_2 \\ t21 \end{bmatrix} = \begin{bmatrix} 81.199 \\ 4.136 \\ 8.131 \\ 8.864 \end{bmatrix}$$

$Xtime2 := 0 .. end$

$i := 0 .. \mathrm{last}(Xtime)$

$$ery\_ana := resid(anak\_vol1, anak\_vol2, anak\_t21, anak\_clearance)$$

$$\overrightarrow{\left(Yconcentration - \frac{X1(Xtime)}{V_1}\right)}$$



$Xtime$

$$ery_i := Yconcentration_i - \frac{X1(Xtime_i)}{V_1}$$

$$ery = \begin{bmatrix} 3.011 \\ -3.762 \\ -5.6 \\ 3.702 \\ 7.845 \\ 1.974 \\ -2.392 \\ -4.847 \\ -2.975 \\ -2.102 \\ -0.02 \\ 6.072 \end{bmatrix} \qquad ery\_ana = \begin{bmatrix} 3.011 \\ -3.763 \\ -5.601 \\ 3.702 \\ 7.845 \\ 1.974 \\ -2.392 \\ -4.846 \\ -2.975 \\ -2.102 \\ -0.02 \\ 6.072 \end{bmatrix}$$

$|ery| = 14.597$

$SSEnum := \sum ery^2$

$$\begin{bmatrix} aV1 \\ aV2 \\ at21 \\ aCl \end{bmatrix} := \begin{bmatrix} anak\_vol1 \\ anak\_vol2 \\ anak\_t21 \\ anak\_clearance \end{bmatrix} \qquad \begin{bmatrix} aV1 \\ aV2 \\ at21 \\ aCl \end{bmatrix} := \begin{bmatrix} V_1 \\ V_2 \\ t21 \\ Clearance \end{bmatrix}$$

$$\frac{SSEnum}{8} = 26.635$$

Evaluation of the convergence by truncating the endpoint from 50 min to the end

For convergence check the data should be analysed with the endpoint where the time >= 60 min.

$begintime := 60$

$analyseend := 7$

$$beginanalyse := \left\| \begin{array}{l} ba \leftarrow \text{last}(Xtime) \\ \text{for } z \in \text{last}(Xtime)..0 \\ \quad \left\| \begin{array}{l} \text{if } Xtime_z \geq begintime \\ \quad \| ba \leftarrow z \end{array} \right. \\ ba \end{array} \right.$$

$$trunca(M, e) := \text{submatrix}(M, 0, e, 0, \text{cols}(M) - 1)$$

$$inputDATA := \text{augment}(Xtime, Yconcentration)$$

$$inputDATA = \begin{bmatrix} 7 & 375.97 \\ 10 & 296.1 \\ 15 & 219.73 \\ 20 & 188.4 \\ 25 & 169.52 \\ 30 & 149.8 \\ 45 & 124.76 \\ 60 & 110.36 \\ 90 & 93.29 \\ 120 & 78.47 \\ 150 & 67.42 \\ 180 & 62.52 \end{bmatrix}$$

$$a := \text{WRITEEXCEL}(\text{“DATA\_Prime.xlsx”}, inputDATA)$$

Measurement Variance: $\sigma_M := 4.38612$

if the σ_M is not known, then set it to 1

Auxilliary parameters in the system

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

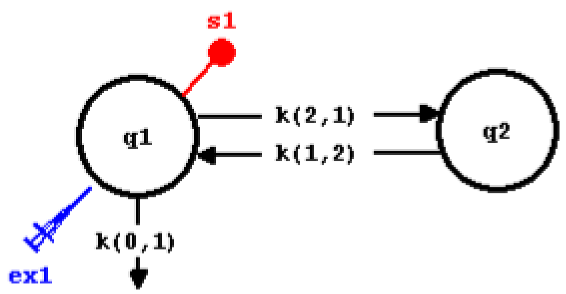
$$\begin{bmatrix} k_{01} & k_{12} & k_{21} & V_1 \end{bmatrix} := \begin{bmatrix} 0.016 & 0.04 & 0.03 & 6 \end{bmatrix}$$

Guesses for minerr

Nebenbedingungen Schätzwerte

Rather than residuals, calculate the predicted values and equate those to the input values.

$$\left\| \begin{array}{l} \begin{bmatrix} X1 \\ X2 \end{bmatrix} \leftarrow Sol(k_{01}, k_{12}, k_{21}, V_1) \\ Xt \leftarrow trunca(Xtime, endpoint) \\ \dfrac{\overrightarrow{X1(Xt)}}{V_1} \end{array} \right. = trunca(Yconcentration, endpoint)$$



Gleichungslöser

$$Params(endpoint) := \textbf{Minerr}(k_{01}, k_{12}, k_{21}, V_1)$$

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix} := Params(\text{last}(Xtime))$$

Pragmatical relationships:

$$V_2 := V_1 \cdot \left(\frac{k_{21}}{k_{12}}\right) \quad Clearance := k_{01} \cdot 1000 \cdot V_1 \quad t21 := \frac{\ln(2)}{k_{21}}$$

$$\begin{bmatrix} Clearance \\ V_1 \\ V_2 \\ t21 \end{bmatrix} = \begin{bmatrix} 81.199 \\ 4.136 \\ 8.131 \\ 8.864 \end{bmatrix}$$

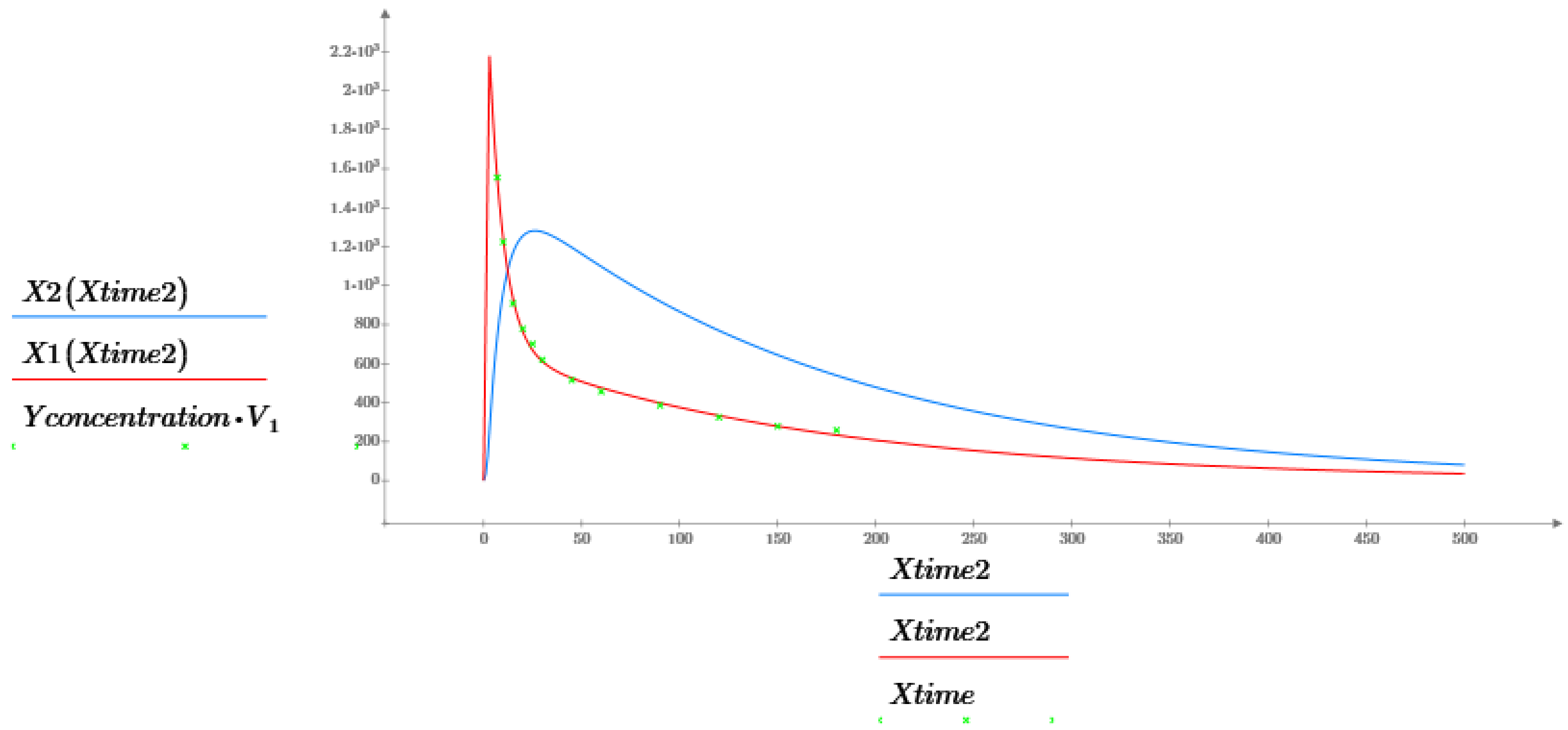
Results from SAAM II accoring Tutorial.

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix} = \begin{bmatrix} 0.02 \\ 0.04 \\ 0.078 \\ 4.136 \end{bmatrix}$$

$Model-Definitions$

$$model_a(k_{01}, k_{12}, k_{21}, V_1, myTime) := \left\| \begin{array}{l} \begin{bmatrix} X1 \\ X2 \end{bmatrix} \leftarrow Sol(k_{01}, k_{12}, k_{21}, V_1) \\ \dfrac{X1(myTime)}{V_1} \end{array} \right.$$

$$\begin{bmatrix} X1 \\ X2 \end{bmatrix} := Sol(k_{01}, k_{12}, k_{21}, V_1) \qquad Xtime2 := 0..500$$


X2(Xtime2)
X1(Xtime2)
Ycentration·V1
2.2·10^3
2·10^3
1.8·10^3
1.6·10^3
1.4·10^3
1.2·10^3
1·10^3
800
600
400
200
0
0
50
100
150
200
250
300
350
400
450
500
Xtime2
Xtime2
Xtime

Calculation of the standard deviation with the Fisher's Info Matrix:

$diff := 0.000001$

Calculate the Products of the
Sensi-Matrice

$$Adj(diff, i, n) := \left\| \begin{array}{l} a \leftarrow 0 \\ a_{n-1} \leftarrow 0 \\ a \leftarrow a+1 \\ a_i \leftarrow a_i + diff \\ a \end{array} \right.$$

To use this for different analyses, you need to porivde the endpoint and also parameterize the parameter values (rather than use the current worksheet values).

$$Derivs(pars, diff, endpoint) := \left\| \begin{array}{l} \text{for } i \in 0..3 \\ \quad \left\| \begin{array}{l} \begin{bmatrix} Ak_{01} \\ Ak_{12} \\ Ak_{21} \\ AV_1 \end{bmatrix} \leftarrow \overrightarrow{(pars \cdot Adj(diff, i, 4))} \\ X11(myTime) \leftarrow model_a(Ak_{01}, Ak_{12}, Ak_{21}, AV_1, myTime) \\ \begin{bmatrix} Ak_{01} \\ Ak_{12} \\ Ak_{21} \\ AV_1 \end{bmatrix} \leftarrow \overrightarrow{(pars \cdot Adj(-diff, i, 4))} \\ X12(myTime) \leftarrow model_a(Ak_{01}, Ak_{12}, Ak_{21}, AV_1, myTime) \\ Xt \leftarrow trunca(Xtime, endpoint) \\ D^{\langle i \rangle} \leftarrow \dfrac{\overrightarrow{X11(Xt) - X12(Xt)}}{2 \cdot diff \cdot pars_i} \end{array} \right. \\ D \end{array} \right.$$

$$DerivM := Derivs\left(\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix}, diff, \text{last}(Xtime)\right)$$

$$SSE(endpoint, V_1) := \sum_{i=0}^{endpoint} \left(\left(Yconcentration_i - \frac{X1\left(Xtime_i\right)}{V_1}\right)^2\right)$$

$$num\_of\_Params := 4$$

$$degree\_of\_freedom(endpoint) := endpoint + 1 - num\_of\_Params$$

$$C_M := \text{identity}(\text{rows}(Xtime)) \cdot \sigma_M^2$$

$$\sqrt{\frac{SSE(\text{last}(Xtime), V_1)}{degree\_of\_freedom(\text{last}(Xtime))}} = 5.161$$

$$FisherInfoMat := DerivM^T \cdot C_M^{-1} \cdot DerivM$$

$$\text{last}(Xtime) = 11$$

$$degree\_of\_freedom(\text{last}(Xtime)) = 8$$

$$FisherInfoMat := DerivM^T \cdot DerivM \cdot \left(\frac{degree\_of\_freedom(\text{last}(Xtime))}{SSE(\text{last}(Xtime), V_1)}\right)$$

$$FisherInfoMat = \begin{bmatrix} 4.012 \cdot 10^6 & -1.472 \cdot 10^6 & 1.113 \cdot 10^6 & 4.755 \cdot 10^4 \\ -1.472 \cdot 10^6 & 7.724 \cdot 10^5 & -5.57 \cdot 10^5 & -2.006 \cdot 10^4 \\ 1.113 \cdot 10^6 & -5.57 \cdot 10^5 & 6.269 \cdot 10^5 & 2.284 \cdot 10^4 \\ 4.755 \cdot 10^4 & -2.006 \cdot 10^4 & 2.284 \cdot 10^4 & 910.227 \end{bmatrix}$$

$$VAR\_KOV_{Parm} := FisherInfoMat^{-1}$$

$$VAR\_KOV_{Parm} = \begin{bmatrix} 2.039 \cdot 10^{-6} & 3.715 \cdot 10^{-6} & 6.741 \cdot 10^{-6} & -1.938 \cdot 10^{-4} \\ 3.715 \cdot 10^{-6} & 1.038 \cdot 10^{-5} & 1.589 \cdot 10^{-5} & -3.64 \cdot 10^{-4} \\ 6.741 \cdot 10^{-6} & 1.589 \cdot 10^{-5} & 4.444 \cdot 10^{-5} & -0.001 \\ -1.938 \cdot 10^{-4} & -3.64 \cdot 10^{-4} & -0.001 & 0.031 \end{bmatrix}$$

$$SSE(\text{last}(Xtime), V_1) = 213.081$$

$$\begin{bmatrix} \sigma k_{01} \\ \sigma k_{12} \\ \sigma k_{21} \\ \sigma V_1 \end{bmatrix} := \sqrt{\text{diag}(FisherInfoMat^{-1})}$$

RESULTS of system parameters with standard deviations (central differences):
--> When the σ_M is not known!! σ_M^2 is estimed as SSE/degree_of_freedom

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix} = \begin{bmatrix} 0.02 \\ 0.04 \\ 0.078 \\ 4.136 \end{bmatrix} \qquad \begin{bmatrix} \sigma k_{01} \\ \sigma k_{12} \\ \sigma k_{21} \\ \sigma V_1 \end{bmatrix} = \begin{bmatrix} 1.42798E-003 \\ \vdots \end{bmatrix}$$

$$\begin{bmatrix} \sigma k_{01} \\ \sigma k_{12} \\ \sigma k_{21} \\ \sigma V_1 \end{bmatrix} := \sqrt{\text{diag}(FisherInfoMat^{-1})}$$

RESULTS calculated in SAAM II with its std dev of the parameters: (When σ_M is known)

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix} = \begin{bmatrix} 0.02 \\ 0.04 \\ 0.078 \\ 4.136 \end{bmatrix} \qquad \begin{bmatrix} \sigma k_{01} \\ \sigma k_{12} \\ \sigma k_{21} \\ \sigma V_1 \end{bmatrix} = \begin{bmatrix} 1.42798E-003 \\ \vdots \end{bmatrix}$$

95% Confidence Intervall:

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix} - \text{qt}(0.975, degree\_of\_freedom(\text{last}(Xtime))) \cdot \begin{bmatrix} \sigma k_{01} \\ \sigma k_{12} \\ \sigma k_{21} \\ \sigma V_1 \end{bmatrix} = \begin{bmatrix} 0.016 \\ 0.032 \\ 0.063 \\ 3.729 \end{bmatrix}$$

$$\begin{bmatrix} k_{01} \\ k_{12} \\ k_{21} \\ V_1 \end{bmatrix} + \text{qt}(0.975, degree\_of\_freedom(\text{last}(Xtime))) \cdot \begin{bmatrix} \sigma k_{01} \\ \sigma k_{12} \\ \sigma k_{21} \\ \sigma V_1 \end{bmatrix} = \begin{bmatrix} 0.023 \\ 0.047 \\ 0.094 \\ 4.544 \end{bmatrix}$$

Calculation of the Variance / Std Dev of the Clearance with Fisher

$$clearance := 1000 \cdot V_1 \cdot k_{01}$$

$$clearance = 81.199$$

Arrange the matrix, so that 1st paramter is V_1 and second k_{01}

$$Variance\_dx := \begin{bmatrix} VAR\_KOV_{Parm_{3,3}} & VAR\_KOV_{Parm_{0,3}} \\ VAR\_KOV_{Parm_{0,3}} & VAR\_KOV_{Parm_{0,0}} \end{bmatrix}$$

$$Jacob\left(1000 \cdot V_1 \cdot k_{01}, \begin{bmatrix} V_1 \\ k_{01} \end{bmatrix}\right) = \begin{bmatrix} 19.63 & 4.136 \cdot 10^3 \end{bmatrix}$$

$$\begin{bmatrix} 1000 \cdot k_{01} & 1000 \cdot V_1 \end{bmatrix} = \begin{bmatrix} 19.63 & 4.136 \cdot 10^3 \end{bmatrix}$$

$$FIM := \left(\begin{bmatrix} 1000 \cdot k_{01} & 1000 \cdot V_1 \end{bmatrix} \cdot Variance\_dx \cdot \begin{bmatrix} 1000 \cdot k_{01} & 1000 \cdot V_1 \end{bmatrix}^T\right)$$

$$Var\_Cl := FIM$$

$$Var\_Cl = 15.453$$

$$\sigma_{Clearance} := \sqrt{Var\_Cl}$$

$$\sigma_{Clearance} = 3.931$$

```
Email from Brad Bell:
Suppose that we have a derived function
    h(x)
then
    h + dh ~= h(x) + h'(x) * dx
so
    Variance(h) = E[ h'(x) * dx * dx^T * h'(x)^T ]
                = h'(x) * Variance(dx) * h'(x)^T

For your case below
    x = ( V1, k01 )^T

h(x)  = 1000 * x1 * x2
h'(x) = 1000 * [ x2 , x1 ]

Variance(dx)  =  [ C11 , C12 ]
                 [ C21 , C22 ]
```

```
AllResult := for i ∈ beginanalyse .. last(Xtime)
               [k01; k12; k21; V1] ← Params(i)
               [X1; X2] ← Sol(k01, k12, k21, V1)
               Clearance_(i−beginanalyse) ← 1000·V1·k01
               SSE ← Σ_(k=0)^i ((Yconcentration_k − X1(Xtime_k)/V1)^2)
               DerivMat ← Derivs([k01; k12; k21; V1], diff, i)
               FIM ← DerivMat^T · DerivMat · (degree_of_freedom(i)/SSE)
               VAR_KOV_Parm ← FIM^−1
               VAR_dx ← [VAR_KOV_Parm_(3,3)  VAR_KOV_Parm_(0,3); VAR_KOV_Parm_(0,3)  VAR_KOV_Parm_(0,0)]
               σ_Clearance_(i−beginanalyse) ← sqrt(([1000·k01  1000·V1] · VAR_dx · [1000·k01  1000·V1]^T))
               EXL ← if i > beginanalyse
                        stack(EXL, [Xtime_i  Clearance_(i−beginanalyse)  σ_Clearance_(i−beginanalyse)])
                     else
                        ([Xtime_i  Clearance_(i−beginanalyse)  σ_Clearance_(i−beginanalyse)])
               D^⟨i−beginanalyse⟩ ← [Clearance_(i−beginanalyse); σ_Clearance_(i−beginanalyse); sqrt(SSE/degree_of_freedom(i)); Xtime_i]
             [D  EXL]
```

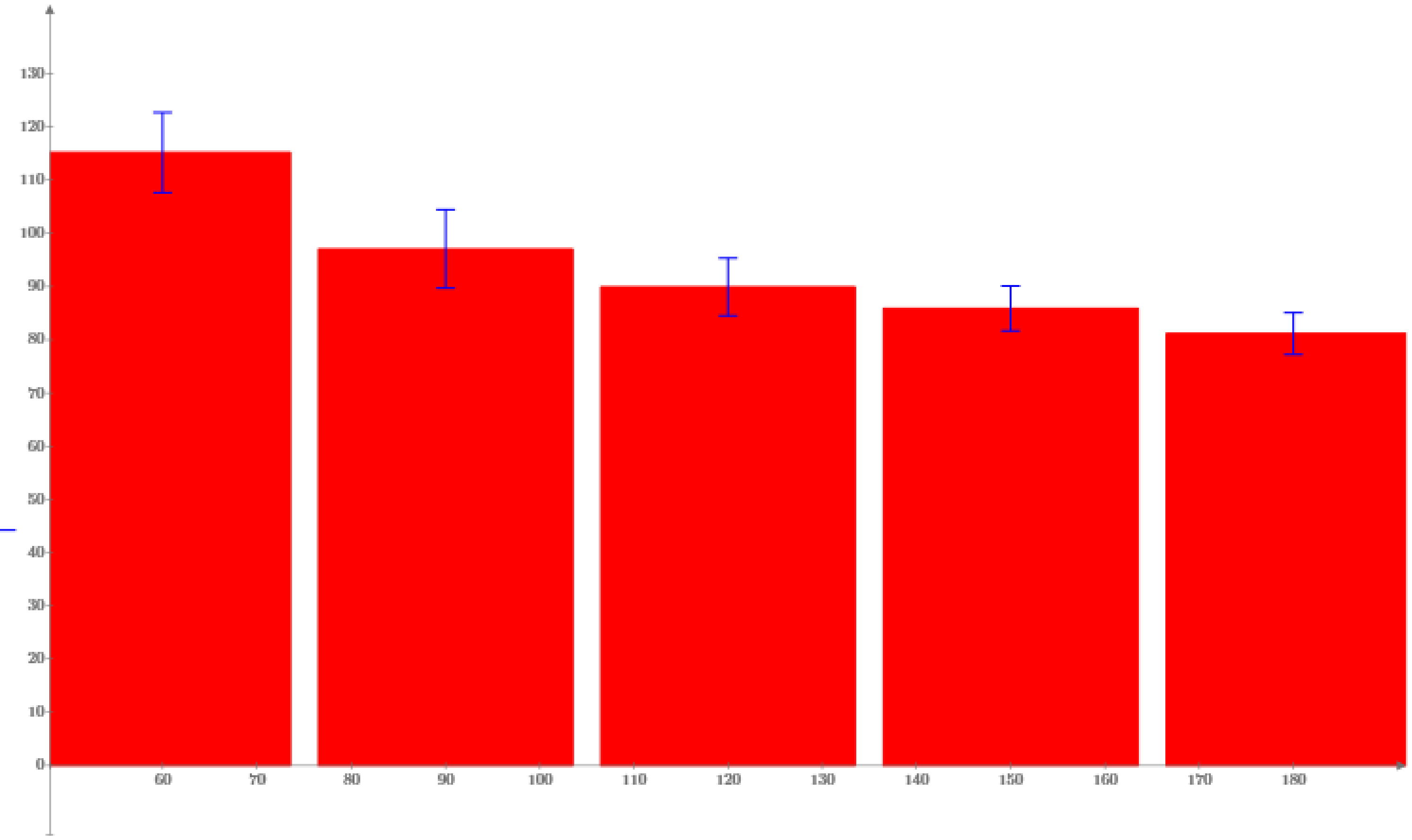
$Result := (AllResult)^{\langle 0 \rangle}$ $\quad Result := Result_{0,0}$ $\quad EXLResult := AllResult^{\langle 1 \rangle}$ $\quad EXLResult := EXLResult_{0,0}$

$$Result = \begin{bmatrix} 115.174 & 97.086 & 89.962 & 85.901 & 81.199 \\ 7.536 & 7.356 & 5.415 & 4.225 & 3.931 \\ 3.369 & 4.573 & 4.665 & 4.67 & 5.161 \\ 60 & 90 & 120 & 150 & 180 \end{bmatrix}$$

$$EXLResult=\begin{bmatrix} 60 & 115.174 & 7.536 \\ 90 & 97.086 & 7.356 \\ 120 & 89.962 & 5.415 \\ 150 & 85.901 & 4.225 \\ 180 & 81.199 & 3.931 \end{bmatrix}$$

$\left(Result^{T}\right)^{\langle 0\rangle}$

$\text{augment}\left(\left(\left(Result^{T}\right)^{\langle 0\rangle}\right)+\left(Result^{T}\right)^{\langle 1\rangle},\left(Result^{T}\right)^{\langle 0\rangle}-\left(Result^{T}\right)^{\langle 1\rangle}\right)$



$\left(Result^{T}\right)^{\langle 3\rangle}$

$EXLResult:=\text{WRITEEXCEL}(\text{“CL\_EXCEL.xls”},EXLResult,1,1,\text{“,”})$

Analyse of the Calculation method used in SAAM

$$\frac{4.40726 - V_1}{-\sigma V_1} = -1.532$$ this is z for the SAAM results

this is z according Wikibooks.org

$$z\left(1 - \frac{\alpha}{2}\right) := 1.96$$

$$\text{qnorm}(0.975, 0, 1) = 1.96$$

$$\alpha := 0.05$$

$$P\left(\overline{X} - z\left(1 - \frac{\alpha}{2}\right) \cdot \frac{\sigma}{\sqrt{n}} \leq \mu \leq \overline{X} + z\left(1 - \frac{\alpha}{2}\right) \cdot \frac{\sigma}{\sqrt{n}}\right) = 1 - \alpha \,.$$

SOLUTION: in SAAM the T-Distribution is used:

$$\text{qt}(0.975, degree\_of\_freedom(\text{last}(Xtime))) = 2.306$$

This is the t-Distribution for α/2 and dfreedom

Source:

http://de.wikipedia.org/wiki/Studentsche_t-Verteilung

Beispielsweise gilt für die Schätzung des Erwartungswertes einer normalverteilten Grundgesamtheit: Wenn die unabhängigen Zufallsvariablen $X_1, X_2, \ldots, X_n$ identisch normalverteilt sind mit den Parametern μ und σ, dann unterliegt die stetige Zufallsgröße

$$t_{n-1} = \frac{\bar{X} - \mu}{S}\sqrt{n}$$

worin

$$S^2 = \frac{1}{n-1}\sum_{i=1}^{n}(X_i - \bar{X})^2$$

die Stichprobenvarianz ist, einer Studentschen t-Verteilung mit $(n-1)$ Freiheitsgraden.

Das 95%-Konfidenzintervall für den Mittelwert μ wäre dann

$$\overline{x} - t \cdot \sqrt{\frac{\sum_{i=1}^{n}(X_i - \bar{X})^2}{n(n-1)}} \leq \mu \leq \overline{x} + t \cdot \sqrt{\frac{\sum_{i=1}^{n}(X_i - \bar{X})^2}{n(n-1)}},$$

wobei t durch $F(t \mid n-1) = 0{,}975$ bestimmt ist. Dieses Intervall ist etwas größer als dasjenige, welches sich mit bekanntem σ aus der Verteilungsfunktion der Normalverteilung bei gleichem Konfidenzniveau ergeben hätte $\left(\mu \in (\overline{x} \pm 1{,}96 \cdot \frac{\sigma}{\sqrt{n}})\right)$.

Appendix: From Dissertation von Veronika Boltz:

This last calculations lead to the following approximation for the desired covariance matrix:

$$\mathbf{V}(\hat{\mathbf{p}}) \;=\; [\mathbf{J}^T\,\mathbf{R}^{-1}\,\mathbf{J}]^{-1}.$$

where the Jacobi matrix $\mathbf{J}$ is evaluated at $\mathbf{p} = \hat{\mathbf{p}}$.

So, what does this mean for our model?
As we only have one measurement series per patient we don't know the required error variances $\sigma^2(t_l)$. But we can estimate the value of σ^2 through the variance of the residuals

$$s^2 \;=\; \frac{Q(\hat{\mathbf{p}})}{n-m} \tag{7.8}$$

which is the residual sum of squares $Q(\hat{\mathbf{p}})$ divided by the degrees of freedom (number of measurements minus the number of parameters).

We therefore arrive at the following approximation for the covariance matrix of the parameter estimates:

$$\mathbf{V}(\hat{\mathbf{p}}) \;=\; [\mathbf{J}^T\mathbf{J}]\,\frac{n-m}{Q(\hat{\mathbf{p}})}$$

Having estimated $\mathbf{V}(\hat{\mathbf{p}})$ the diagonal elements $v_{ii}(\hat{p}_i)$ of $\mathbf{V}(\hat{\mathbf{p}})$ provide the desired variances of the parameter estimates, so that the accuracy with which the parameter p_i can be estimated may be expressed in terms of its standard deviation by

$$\hat{p}_i \,\pm\, \sqrt{v_{ii}(\hat{p}_i)}$$

The FisherInfoMatrix is:

$$f_{ij} \;=\; \sum_{l=1}^{N} \frac{1}{\sigma^2(t_l)}\,\frac{\partial\, y(t_l)}{\partial\, p_i}\,\frac{\partial\, y(t_l)}{\partial\, p_j} \tag{7.7}$$

The calculation with SAAM II is as follows:

1) Define SD = 1 in the DATA WINDOW for the DATA
2) RUN the calculation and export t,plasma and s1_res as TABLE in the TABLE WINDOW
3) Import the TABLE into EXCEL and calculate SSE = s1_res*s1_res and sigma (see the formular below at the red arrow Note: 6 is the actual number of parameters HERE: must be 4)
4) SET SD = sigma and calculate the model once more to get the proper parameter standard deviations

t	plasma	s1_res	SSE	sigma	
0	-		0,000000000		
5	-		0,000000000		
5	-		0,000000000		
7	893	-1,40E+00	1,965744203		
10	708	3,275	10,725625000		
15,25	514	-1,46E+00	2,143559528		
20,25	419	-1,44E+00	2,068821956		
25	361	-4,57E+00	20,876766192		
30,08	332	6,486	42,068196000		
45	253	1,016	1,032256000		
60,33	203	-5,74E-01	0,330049101		
75,33	167,6	-1,78E+00	3,160715066		
90	141,9	-2,17E+00	4,702478990		
105	-		0,000000000		
120	108,7	0,934	0,872356000		
135	-		0,000000000		
150	88,2	4,689	21,986721000		
165	-		0,000000000		
180	63,6	-2,39E+00	5,718172213		
205	-		0,000000000		
222,5	-		0,000000000		
240	41	-1,29E+00	1,672417968		
265	-		0,000000000		
282,5	-		0,000000000		
300	28,4	0,962	0,925444000		
325	-		0,000000000		
342,5	-		0,000000000		
360	17,4	-4,57E-01	0,208946809		
385	-		0,000000000		
410	-		0,000000000		
435	-		0,000000000		WURZEL(((ABS(SUMME(E:E))))/(ANZAHL(D:D)-6))
457,5	-		0,000000000		
480	7,3	-2,77E-01	0,076868117		
500	-		0,000000000		
500	-		0,000000000		
				3,3102477	

Appendix: Equations from Source: Eur J Clin Chem Clin Biochem 1995; 33 (no 4) pp. 201-209

$$\lambda_1 = -\tfrac{1}{2}((k_{01} + k_{21} + k_{12}) - ((k_{01} + k_{21} + k_{12})^2 - 4k_{01}k_{12})^{1/2}) \quad \text{(Eq. 9)}$$

$$\lambda_2 = -\tfrac{1}{2}((k_{01} + k_{21} + k_{12}) + ((k_{01} + k_{21} + k_{12})^2 - 4k_{01}k_{12})^{1/2}) \quad \text{(Eq. 10)}$$

$$a = (k_{01} + k_{21} + \lambda_1)/k_{12} \quad \text{(Eq. 11)}$$

$$b = k_{21}/(k_{12} + \lambda_2) \quad \text{(Eq. 12)}$$

$$x_{1s} = (D/\tau)/k_{01} \quad \text{(Eq. 13)}$$

$$x_{2s} = x_{1s}(k_{21}/k_{12}) \quad \text{(Eq. 14)}$$

$$y_{1s} = \rho/k_{01} \quad \text{(Eq. 15)}$$

$$y_{2s} = y_{1s}(k_{21}/k_{12}) \quad \text{(Eq. 16)}$$

$$M_1 = ((x_{10} - x_{1s})b - (x_{20} - x_{2s}))/(b - a) \quad \text{(Eq. 17)}$$

$$M_2 = ((x_{20} - x_{2s}) - (x_{10} - x_{1s})a)/(b - a) \quad \text{(Eq. 18)}$$

$$x_{1\tau} = M_1 \exp(\lambda_1 t) + M_2 \exp(\lambda_2 t) + x_{1s} \quad \text{(Eq. 19)}$$

$$x_{2\tau} = M_1 a \exp(\lambda_1 \tau) + M_2 b \exp(\lambda_2 \tau) + x_{2s} \quad \text{(Eq. 20)}$$

$$N_1 = ((x_{1\tau} - y_{1s})b - (x_{2\tau} - y_{2s}))/(b - a) \quad \text{(Eq. 21)}$$

$$N_2 = ((x_{2\tau} - y_{2s}) - (x_{1\tau} - y_{1s})a)/(b - a) \quad \text{(Eq. 22)}$$

If $0 \leq t < \tau$:

$$x_1(t) = M_1 \exp(\lambda_1 t) + M_2 \exp(\lambda_2 t) + x_{1s} \quad \text{(Eq. 23)}$$

$$x_2(t) = M_1 a \exp(\lambda_1 t) + M_2 b \exp(\lambda_2 t) + x_{2s} \quad \text{(Eq. 24)}$$

If $\tau \leq t < T_c$:

$$x_1(t) = N_1 \exp(\lambda_1(t - \tau)) + N_2 \exp(\lambda_2(t - \tau)) + y_{1s} \quad \text{(Eq. 25)}$$

$$x_2(t) = N_1 a \exp(\lambda_1(t - \tau)) + N_2 b \exp(\lambda_2(t - \tau)) + y_{2s} \quad \text{(Eq. 26)}$$

The temporal profiles of the concentrations $c_1(t)$ and $c_2(t)$ in their respective compartments are defined by Eqs. 27 and 28:

$$c_1(t) = x_1(t)/V_1 \quad \text{(Eq. 27)}$$

$$c_2(t) = x_2(t)/V_2 \quad \text{(Eq. 28)}$$