LUND
UNIVERSITY

Department of
AUTOMATIC CONTROL

Exam FRTF01 - Physiological Models and Computation

January 12 2015, 8-13

Points and grades

All answers must include a clear motivation. The total number of points is 25. The maximum number of points is specified for each subproblem. Preliminary grades:

Grade 3: 12–16.5 points
4: 17 –21.5 points
5: 22 –25 points

Accepted aid

Lecture slides, any books (without relevant exercises with solutions), standard mathematical tables and “Formelsamling i reglerteknik”. Calculator.

Results

The result of the exam will be posted in LADOK no later than February 9. Information on when the corrected exam papers will be shown, will be given on the course homepage.

1. The half life of a drug solution is 6 days. Assume it is eliminated from plasma as a linear process after it has been injected to plasma.

a. You are given some measurements of the concentration of the drug at some time and the corresponding velocity at that same time, see Tab. 1 below. Use the least squares method to determine the rate constant for the process.

Table 1: Drug data for problem 1

Concentration [units]	Velocity [units/days]
0.9	-0.12
2.0	-0.27
3.3	-0.33
4.1	-0.58

(1 p)

b. Determine the rate constant from the half life instead. Compare the result with subproblem **a.** and mention one fact that could account for the difference in the result.

(1.5 p)

c. If injected with the drug solution, how long will it take for the concentration in plasma to be lowered by 30 %, of the initial concentration? Use either of the k-values determined in the previous subproblems.

(0.5 p)

d. Assume instead the drug is taken orally. Draw a sketch of the different compartments you think are necessary for a model of the drug's way through the body as well as the measurements taken from plasma. See Tab. 2 below for some important rate constants.

Table 2: Compartment data for problem 1

Parameter	Description
k_{GB}	Kinetic coefficient Gut-to-blood $[s^{-1}]$
k_{BL}	Kinetic coefficient blood-to-liver $[s^{-1}]$
k_{LB}	Kinetic coefficient liver-to-blood $[s^{-1}]$
k_{KB}	Kinetic coefficient kidneys-to-blood $[s^{-1}]$
k_{BK}	Kinetic coefficient blood-to-kidneys $[s^{-1}]$
$k_{e,G}$	Elimination constant, gut $[s^{-1}]$
$k_{e,B}$	Elimination constant, blood $[s^{-1}]$
$k_{e,L}$	Elimination constant, liver $[s^{-1}]$
$k_{e,K}$	Elimination constant, kidneys $[s^{-1}]$

(1 p)

Solution

a. The process is $y = dC/dt = -kC$ and we have values on y and C and want to determine k. Let the regressor matrix be

$$\Phi = \begin{pmatrix} -C_1 \\ -C_2 \\ -C_3 \\ -C_4 \end{pmatrix} = \begin{pmatrix} -0.9 \\ -2.0 \\ -3.3 \\ -4.1 \end{pmatrix}$$

where C_i is the i-th value of $[C]$ in Table 1 given in the problem text. The least-squares solution is then

$$\hat{k} = \left(\Phi^T \Phi\right)^{-1} \Phi^T y = 0.1266 \text{ days}^{-1}$$

where $y = \begin{pmatrix} -0.12 & -0.27 & -0.33 & -0.58 \end{pmatrix}^T$.

b. Set $C(t)$ to be the concentration at time t. The initial condition and balance equation of the system are the following

$$C(0) = C_0 \text{ [units/volume]}$$

The solution of the differential equation is

$$C(t) = C_0 e^{-kt}$$

After 6 days, the concentration is halved. Therefore, if the half-life is stated as $t_{1/2} = 6$, the concentration at $t_{1/2}$ is given by

$$C(t_{1/2}) = \frac{C_0}{2} = C_0 e^{-kt_{1/2}}$$

Thus k is,

$$k = \frac{\ln(2)}{t_{1/2}} = \frac{0.6931}{6} = 0.1155 \text{ days}^{-1}$$

The values of k are somewhat different. This could be due to poor measurements of either the concentration and/or velocity or the half life.

c. When the concentration is lowered 30 % of the ititial concentration, 70 % of the initial concentration is left. Set up the following equation do determine the time it takes,

$$0.7C_0 = C_0 e^{-kt}$$

This can be rewritten as follows,

$$\ln\left(\frac{0.7C_0}{C_0}\right) = -kt$$

and further as,

$$t = -\frac{1}{k}\ln\left(\frac{0.7C_0}{C_0}\right).$$

The minus sign swaps the numerator and denominator in the natural logarithm. Therefore, the equation can be written as,

$$t = \frac{1}{k} \cdot \ln\left(\frac{C_0}{0.7 \cdot C_0}\right)$$

With $k = 0.1155$, $t = \frac{1}{0.1155}\ln(1/0.7) = 3.09$. Hence, it takes approximately 3 days for the inital concentration to be lowered by 30 %.

d. In the figure below, one proposal of the sketch of the model is shown.

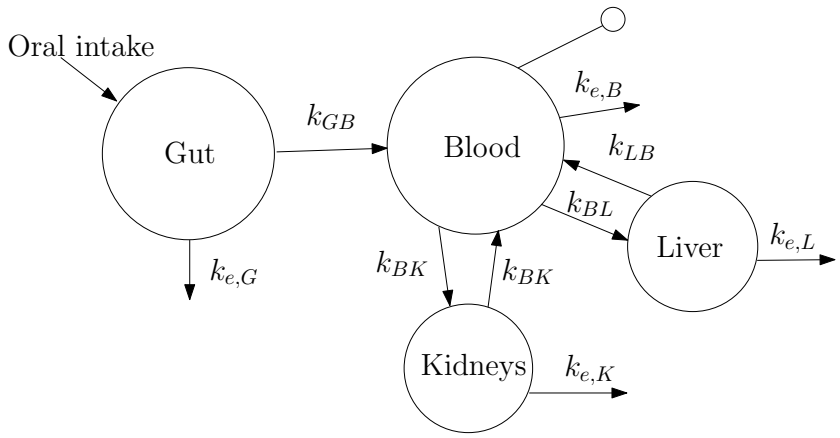


Figure 1: Sketch of compartment model, one proposal.

2.

a. Given the ion concentrations in Tab. 3 below, calculate the equilibrium potentials of each of the three ions, Ion_1, Ion_2 and Ion_3, at room temperature, 25°C, by the Nernst equation.

Table 3: Ion concentrations and valence charge

Ion	**Inner conc. [μM]**	**External conc. [μM]**	**Valence charge**
Ion_1	25	150	+2
Ion_2	130	8.0	+1
Ion_3	6.2	10	-1

Use the following values for the constants, $R = 8.31447$ [J/mol·K] - thermodynamic gas constant, $F = 9.648534 \cdot 10^4$ [C/mol] - Faraday constant.

(1 p)

b. If you want the equilibrium potentials to be increased, given the concentrations in Tab. 3 what should you do with the temperature for each specific ion? If you instead are able to change the inner and/or external concentrations of the ions, how should you change them in order to increase the equilibrium potential of each specific ion?

(1 p)

Solution

a. The Nernst equation for ion [i] is given by

$$E_i = \frac{\mathrm{RT}}{\mathrm{zF}} \ln\left(\frac{C_{out,i}}{C_{in,i}}\right)$$

where z - valence charge, C_{out} the ion concentration outside the cell, C_{in} the ion concentration inside the cell, R - thermodynamic gas constant, F - Faraday constant and T - temperature in Kelvin.

Given $R = 8.31447$ [J/mol·K], $T = 273 + 25$ [K] and $F = 9.648534 \cdot 10^4$ [C/mol] then $RT/F = 0.0257$ [V] or 25.7 [mV].

Using the Nernst equation with the given values of the inner/external concentrations as well as the valence charge results in $E_1 = 23$, $E_2 = -72$ and $E_3 = -12$ [mV].

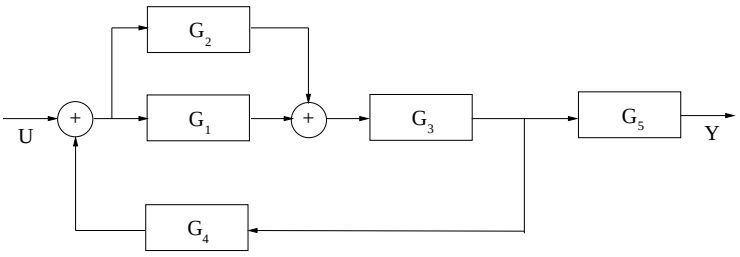
b. Ion_1: The temperature should be increased. The external concentration should be increased and/or the inner concentration decreased.

Ion_2: The temperature should be decreased. The external concentration should be increased and/or the inner concentration decreased.

Ion_3: The temperature should be decreased. The external concentration should be decreased and/or the inner concentration increased.

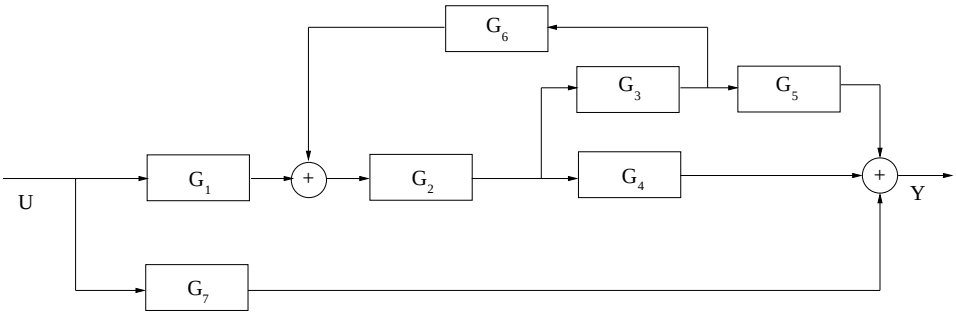
3. Determine the transfer functions from U to Y in the following linear systems

a. System 1:



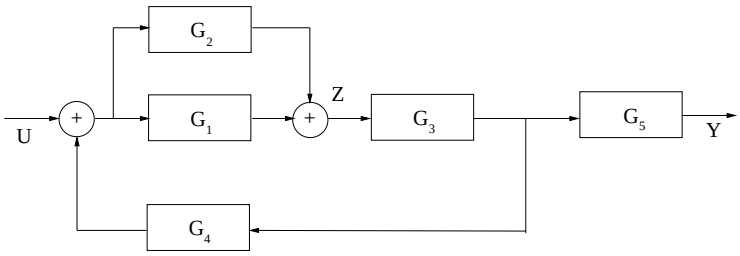
(1 p)

b. System 2:



(1 p)

Solution



a. From the block diagram we can conclude that

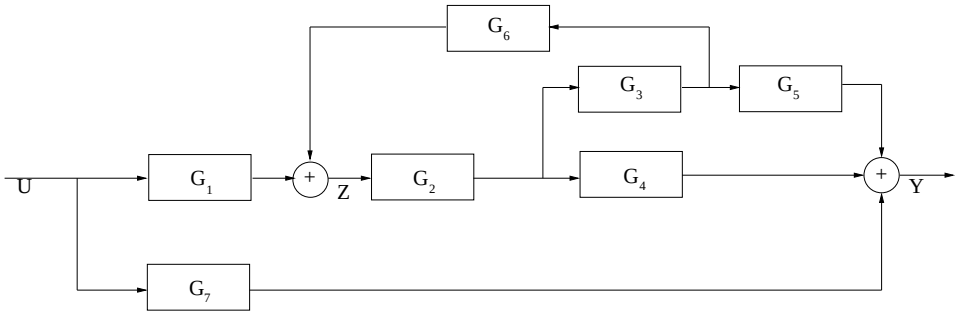
$$Z = (G_1 + G_2)(U + G_4 G_3 Z)$$

and

$$Y = G_5 G_3 Z$$

Thus

$$Y = \frac{(G_1 + G_2)G_5 G_3}{1 - (G_1 + G_2)G_4 G_3} U$$



b. From the block diagram we can conclude that

$$Z = G_1 U + G_6 G_3 G_2 Z$$

and

$$Y = G_7 U + (G_4 + G_5 G_3) G_2 Z$$

Thus

$$Y = (G_7 + \frac{(G_4 + G_5 G_3) G_2 G_1}{1 - G_6 G_3 G_2}) U$$

4. The following nonlinear differential equation describes some system,

$$\ddot{z} + \dot{z}^2 z - z = \sqrt{u}$$

where u is the input signal and the output is given by $y = z^2 + u^2$.

a. Write the system on state-space form (1 p)

b. Determine the stationary points (1 p)

c. Linearize the system around the stationary point that represents $u = 4$. (2 p)

Solution

a. With $x_1 = z$ and $x_2 = \dot{z}$, the state space form of the system is the following,

$$\begin{aligned} \dot{x}_1 &= x_2 && (= f_1(x,u)) \\ \dot{x}_2 &= -x_2^2 x_1 + x_1 + \sqrt{u} && (= f_2(x,u)) \\ y &= x_1^2 + u^2 && (= g(x,u)) \end{aligned} \tag{1}$$

b. In stationarity $x_2^0 = 0$. This gives that $x_1 + \sqrt{u} = 0$ in stationarity. Therefore, the stationary points are given by $(x_1^0, x_2^0, u^0) = (-\sqrt{u_0}, 0, u_0)$, $u_0 \geq 0$. In stationarity the output signal is hence given by $y^0 = u_0 + u_0^2$.

c. $u = u_0 = 4$ gives the stationary point $(x_1^0, x_2^0, u^0, y^0) = (-2, 0, 4, 20)$. The partial derivatives are

$$\frac{\partial f_1}{\partial x_1} = 0, \qquad \frac{\partial f_1}{\partial x_2} = 1, \qquad \frac{\partial f_1}{\partial u} = 0,$$
$$\frac{\partial f_2}{\partial x_1} = -x_2^2 + 1, \qquad \frac{\partial f_2}{\partial x_2} = -2x_2x_1, \qquad \frac{\partial f_2}{\partial u} = \frac{1}{2\sqrt{u}}$$
$$\frac{\partial g}{\partial x_1} = 2x_1, \qquad \frac{\partial g}{\partial x_2} = 0, \qquad \frac{\partial g}{\partial u} = 2u,$$

Use the following variable substitution

$$\begin{aligned} \Delta x &= x - x^0 \\ \Delta u &= u - u^0 \\ \Delta y &= y - y^0. \end{aligned} \tag{2}$$

Then the linearized system is given by,

$$\begin{aligned} \Delta\dot{x} &= \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix} \Delta x + \begin{bmatrix} 0 \\ \frac{1}{4} \end{bmatrix} \Delta u \\ \Delta y &= \begin{bmatrix} -4 & 0 \end{bmatrix} \Delta x + 8\Delta u \end{aligned} \tag{3}$$

5. An unstable process has the transfer function

$$G_p(s) = \frac{4}{s^2 + 3s - 8}$$

and is connected in negative feedback with a P controller $G_r(s) = K$.

a. For what values of K is the closed-loop system (asymptotically) stable?

(2 p)

b. Assume that the reference signal to the closed-loop system is a sinusoidal signal $r(t) = \sin(2t)$, and consider the system after a long time when all transients have disappeared. What is the output signal $y(t)$ of the closed-loop system when $K = 3$?

(1 p)

c. Instead assume the system is controlled by a state feedback controller. One possible state-space representation of the transfer function is

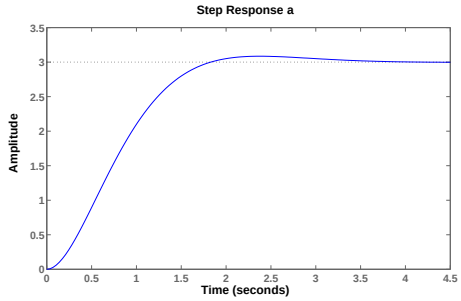
$$\begin{aligned} \dot{x} &= \begin{pmatrix} -3 & 4 \\ 2 & 0 \end{pmatrix} x + \begin{pmatrix} 2 \\ 0 \end{pmatrix} u \\ y &= \begin{pmatrix} 0 & 1 \end{pmatrix} x \end{aligned}$$

Verify that this is a correct state-space representation.

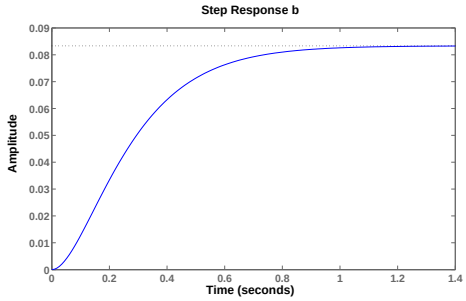
(1 p)

d. Given the state-space representation above, determine the state-feedback controller $u = -Lx + r$ that assigns the poles of the closed-loop system, from reference r to output y, to $(-6, -8)$.

(2 p)



(a)



(b)

e. The plots above, a and b, show the step response of the two closed-loop systems, with P regulator where $K = 3$ and with state-feedback controller with poles in $(-6, -8)$. Which plot shows which system? Motivate your answer.

(1 p)

Solution

a. The closed-loop transfer function is given by

$$G_{cl}(s) = \frac{K\frac{4}{s^2+3s-8}}{1+K\frac{4}{s^2+3s-8}} = \frac{4K}{s^2+3s-8+4K}$$

The poles of the system are thus given by:

$$p = -\frac{3}{2} \pm \sqrt{\frac{41}{4} - 4K}$$

The closed-loop system will be asymptotically stable when all the poles have negative real part.

Therefore, the following must hold

$$\sqrt{\frac{41}{4} - 4K} < \frac{3}{2}$$
$$4K > \frac{41}{4} - \frac{9}{4} = 8$$
$$K > 2$$

The closed-loop system will be asymptotically stable for $K > 2$.

b. After the transient has decayed, the output signal is

$$y(t) = |G_{cl}(2i)| \sin(2t + \arg G_{cl}(2i))$$

where

$$G_{cl}(2i) = \frac{4K}{(2i)^2 + 3 \cdot 2i - 8 + 4K} = \frac{12}{-4 + 6i - 8 + 12} = \frac{12}{6i}$$

This gives

$$y(t) = 2 \sin(2t - \pi/2)$$

c. If the state-space representation is given by,

$$\dot{x} = Ax + Bu$$
$$y = Cx$$

the transfer function of the system can be determined by,

$$\begin{aligned} G(s) = C(sI - A)^{-1}B &= \begin{pmatrix} 0 & 1 \end{pmatrix} \left(sI - \begin{pmatrix} -3 & 4 \\ 2 & 0 \end{pmatrix} \right)^{-1} \begin{pmatrix} 2 \\ 0 \end{pmatrix} \\ &= \begin{pmatrix} 0 & 1 \end{pmatrix} \begin{pmatrix} s+3 & -4 \\ -2 & s \end{pmatrix}^{-1} \begin{pmatrix} 2 \\ 0 \end{pmatrix} \\ &= \begin{pmatrix} 0 & 1 \end{pmatrix} \frac{1}{(s+3)s - 8} \begin{pmatrix} s & 4 \\ 2 & s+3 \end{pmatrix} \begin{pmatrix} 2 \\ 0 \end{pmatrix} \\ &= \frac{1}{s^2 + 3s - 8} \begin{pmatrix} 2 & s+3 \end{pmatrix} \begin{pmatrix} 2 \\ 0 \end{pmatrix} = \frac{4}{s^2 + 3s - 8} \end{aligned}$$

This is the correct transfer function and therefore the state-space representation is valid.

d. We want to find a state feedback control law

$$u = -Lx + lr$$

such that the poles are located in -6 and -8. $L = \begin{pmatrix} l_1 & l_2 \end{pmatrix}$

The desired characteristic polynomial is $(s+6)(s+8) = s^2 + 14s + 48$. With feedback the characteristic polynomial is $\det(sI - A + BL) = s^2 + (3 + 2l_1)s - 8 + 4l_2$.

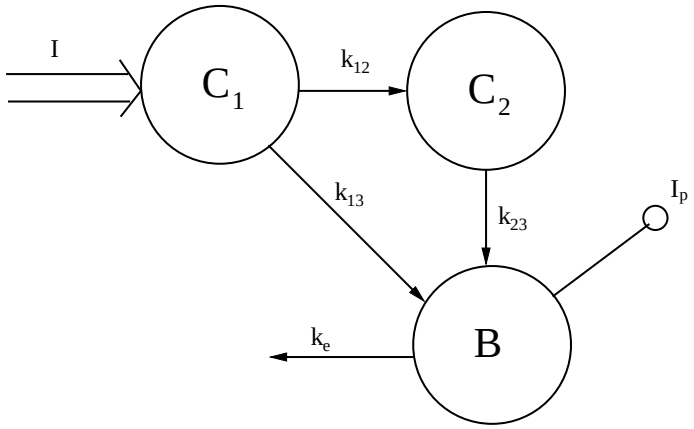
Matching coefficients gives $l_1 = 11/2$ and $l_2 = 14$.

e. a: P regulator
b: State-feedback regulator

Motivate with static gain, rise time of the system or oscillative behavior.

6. A new ultra-slow insulin has been developed and the pharmacokinetics has been suggested to follow a second-order compartment model according to Fig. 3. Here, C_1 and C_2 represent two subcutaneous depots, B is the blood plasma compartment, I is the amount of injected insulin and I_p is the plasma insulin concentration. k_{12}, k_{13}, k_{23} are the rate coefficients between the subcutaneous compartments and the blood plasma compartment and k_e is the elimination rate from plasma. All kinetics are assumed to be linear. The blood plasma volume is V_D.

Figure 3: Insulin pharmacokinetics.



a. Determine a state-space representation of the system with the insulin injection I as input and I_p as the measured output. (2 p)

b. Determine the transfer function from input to output. (2 p)

c. Which of the two parameter sets in Tab. 4 would you consider to be most appropriate for the ultra-slow insulin (taken once a day and intended to provide an as even as possible basal level until the next injection)? V_D has been chosen to let the two parameter sets produce the same static gain. Motivate your answer. (1 p)

Table 4: Suggested parameter sets for the insulin kinetics.

Parameter	Set A	Set B
k_{12} $[min^{-1}]$	$1.6 \cdot 10^{-3}$	$1.6 \cdot 10^{-3}$
k_{13} $[min^{-1}]$	$4 \cdot 10^{-2}$	$4 \cdot 10^{-4}$
k_{23} $[min^{-1}]$	$2.3 \cdot 10^{-2}$	$2.3 \cdot 10^{-2}$
k_e $[min^{-1}]$	$2 \cdot 10^{-2}$	$2 \cdot 10^{-4}$
V_D $[ml]$	50	5000

d. Sketch an impulse response for the first 1400 minutes of the system using the parameter values you chose from Tab. 4. (1 p)

Solution

a. With $x_1 = Q_{C_1}$, $x_2 = Q_{C_2}$ and $x_3 = Q_B$, where Q stands for the amount of insulin, the system becomes

$$\dot{x} = \begin{bmatrix} -(k_{12}+k_{13}) & 0 & 0 \\ k_{12} & -k_{23} & 0 \\ k_{13} & k_{23} & -k_e \end{bmatrix} x + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} I$$

$$I_p = \begin{bmatrix} 0 & 0 & 1/V_D \end{bmatrix} x$$

b. With

$$Z = (sI - A)^{-1}$$

The transfer function

$$G(s) = C(sI - A)^{-1}B$$

becomes

$$G(s) = CZB = \frac{Z_{31}}{V_D}$$

According to the 'collection of common results booklet'

$$Z_{31} = \frac{1}{\det(sI - A)}(-1)^{3+1} \det M_{13}$$

where M_{13} is the matrix which is left after removing row 1 and column 3 from the $sI - A$ matrix. Thus

$$G(s) = \frac{1}{V_D} \frac{k_{12}k_{23} + (s + k_{23})k_{13}}{(s + (k_{12} + k_{13}))(s + k_{23})(s + k_e)}$$

c. The most appropriate parameter set is set B. This becomes apparent when looking at the magnitude of the time constants. The system is dominated by the slowest eigenvalue of the system matrix A, and for the first parameter set this is in the magnitude of 60 minutes $(1/k_{12})$. For parameter set B, the slowest eigenvalue is $1/k_e = 2 \cdot 10^{-4}$, which corresponds to a time constant of 5000 minutes. The first parameter set produces a fast response and corresponds to a rapid-acting insulin. With these parameters the insulin level is well back to zero after 24 hours and could not be used to produce a steady basal level from a single daily injection. The system according to the parameter set B on the other hand is very slow, and there is a significant effect left after 24 hours. These aspects also become apparent when plotting the impulse responses (see below).

d. To determine the impulse response we turn to the 'collection of common results booklet' to find the inverse Laplace transform of the transfer function. In this case it is number 27 and 30 that are relevant. With

$$\begin{aligned} a &= k_{12} + k_{13} \\ b &= k_{23} \\ c &= k_e \end{aligned}$$

The response becomes:

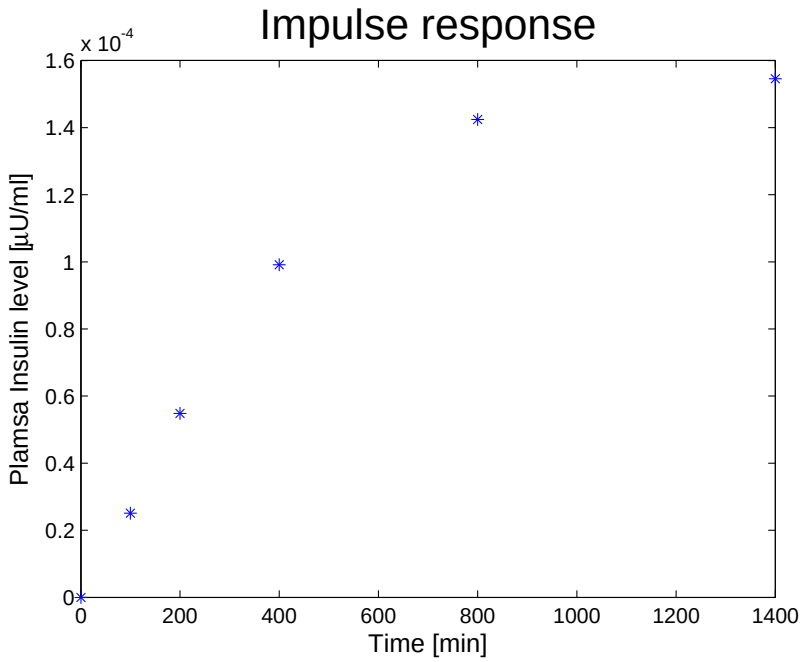
$$\begin{aligned} f(t) = &\frac{k_{23}(k_{12} + k_{13})}{V_D} \cdot \frac{(b - c)e^{-at} + (c - a)e^{-bt} + (a - b)e^{-ct}}{(b - a)(c - a)(b - c)} \\ &- \frac{k_{13}}{V_D} \cdot \frac{a(b - c)e^{-at} + b(c - a)e^{-bt} + c(a - b)e^{-ct}}{(b - a)(c - a)(b - c)} \end{aligned}$$

With the parameter values from parameter set B:

$$f(t) = -2.4 \cdot 10^{-4}e^{-at} + 1.6 \cdot 10^{-5}e^{-bt} + 2.24 \cdot 10^{-4}e^{-ct}$$

Evaluate at a couple of points (e.g. at t=[100, 200, 400, 800, 1400]) and sketch (see Fig. 4).

Figure 4: Impulse response of the insulin pharmcokinetic model



Good Luck!