Physiological Models and Computations

Exercises

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0. Repetition of Linear Algebra, Differential equations and MATLAB

Solve the following exercises by hand. If you are unsure about how to solve the exercises, please go back to your Linear algebra and Analysis books and review the material needed.

0.1

a. Find the solution to the differential equation below when $x(0) = 1$,

$$\frac{dx}{dt} = c$$

b. Find the solution to the differential equation below when $x(0) = 1$,

$$\frac{dx}{dt} = cx$$

c. Find the solution to the differential equation below when $x(0) = 1$ and $x \neq 0$ for any t,

$$\frac{dx}{dt} = 2tx^2$$

d. Rewrite the differential equation into a system of first order differential equations. Discuss some possible structure in a physiological system the model could describe.

$$\begin{aligned} \ddot{y} + 7\dot{y} - 3y &= 0 \\ y(0) &= 0 \\ \dot{y}(0) &= 1 \end{aligned}$$

Solve the following exercises using `MATLAB`. These exercises are inspired by or fully extracted from *EDA017: Föreläsningsanteckningar, OCTAVE/MATLAB* by Christian Söderberg.

0.2 In `MATLAB`, find the commands necessary to derive the following results for matrices A and B

$$A = \begin{pmatrix} 2 & 0 & 0 \\ 0 & 3 & 4 \\ 0 & 4 & 9 \end{pmatrix}, \quad B = \begin{pmatrix} 1 \\ 2 \\ 3 \end{pmatrix}$$

a. calculate $A \cdot B$ and $B^T \cdot A$. What about $B \cdot A$?

b. Give the eigenvalues and eigenvectors of A.

c. Give the transpose and the determinant of A.

d. Give the inverse of A and review how the inverse is derived by hand for a 2-by-2 matrix.

0.3

a. Plot $y(x) = e^{-x/2}\cos(2\pi x)$ when $-6 \leq x \leq 3$ by using the function handle to create an anonymous function. Give your plot a title as well as labels on the axes. Useful commands: `fplot`, `xlabel`, `ylabel`, `title`.

b. Modify your code such that you only show values $-4.5 \leq x \leq -1$ and $-10 \leq y \leq 10$. Useful command: `axis`.

c. Integrate the function for $-4.5 \leq x \leq -1$.
Useful commands: `integral`, `quad`.

d. Find the solution to $f(x) = 0$ when $f(x) = x^3 + 2x - 1$. Comment on the answer. Useful command: `fsolve`.

0.4 Write a function which for every matrix A gives you the sum of the diagonal elements of that matrix. Useful commands: `diag`, `sum` and `size`.

0.5 Solve the differential equation

$$\begin{aligned} \ddot{y} + 7\dot{y} - 3y &= 0 \\ y(0) &= 0 \\ \dot{y}(0) &= 1 \end{aligned}$$

in the interval $0 \leq t \leq 5$ by using MATLABs solver `ode45`.

Solve the following exercises using SIMULINK in MATLAB. These exercises are taken from *Exercises in MATLAB/Simulink, Signals and Systems* by Thomas Munther.

0.6 Investigate the bacterial growth in a jam pot. Assume that the number of born bacteria is increasing proportional to the existing number of bacteria x and the number dying is proportional to the existing number in square. This gives the following differential equation

$$\frac{dx}{dt} = bx - px^2$$

where $b = 1$ [1/hour] is the birth rate constant and
$p = 0.5$ [1/(bacteria·hour)] is the death rate constant.
Assume $x(0) = 100$ [bacteria]. Use SIMULINK to show what the solution to the differential equation looks like.

0.7 Some physiological systems are better described in discrete time which gives rise to difference equations. Show the behavior of y in the two following difference equations

a.

$$y_t = -0.5 \cdot y_{t-1} + x_t$$

b.

$$y_t = 0.5 \cdot y_{t-1} + x_t$$

where x is the input signal to the system, in shape of a step starting in $t = 0$ with amplitude 1 and $y_{-1} = 1$. y_t is the value of y in time step t.

0.8 Get familiar with some of the blocks that will be used in the course; `From Workspace`, `To Workspace`, `Constant`, `Scope`, `Step` and `Sine Wave`. Look at how `Step` and `Sine Wave` can be altered and how they look by the use of a `Scope`. Try to save the result to the workspace by `To Workspace` and plot it. Save the plots as an .eps-file. Create a document, write something nice about the plot, add the plot with a figure text, save the document as a .pdf-file.

1. Biochemical Reactions

1.1 Use the law of mass balance to derive the differential equations govering the production of X and Y:

a.

$$X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Y$$

b.

$$X + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Y$$

c.

$$3X + Y \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Z$$

1.2 Simulate and plot the concentrations for the substrate S, enzyme E, substrate-enzyme complex C and the end product P for the basic enzymatic reaction

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} P + E$$

using the following set of parameters; $k_1 = 0.1$, $k_{-1} = 0.01$ and $k_2 = 0.02$, and with the following initial conditions $[S]_0 = 0.15$ [mmol/l], $[E]_0 = 0.01$ [mmol/l], $[C]_0 = 0$ [mmol/l] and $[P]_0 = 0$ [mmol/l]. What happens if the initial concentration of the enzyme is doubled? What happens if the initial concentration of the substrate is doubled? How does these results correspond to the Michealis-Menten parameters?

1.3 The data in Table 1.1 describes the concentration and reaction rates of a chemical process. Is it an enzymatic reaction following the Michaelis-Menten relationship? Can you give some rough estimates of V_{max} and K_m from this graph? Plot the inverse of the concentration versus the inverse of the reaction rate. This plot is commonly reffered to as a Lineweaver-Burk plot. Can you give some rough estimates of V_{max} and K_m from this graph as well?

1.4 Competetive Inhibition: Some enzymes may bind other substances than the target substrate to the binding site, thereby inhibiting the formation of the intended substrate-enzyme complex and the subsequent end-product. Such a situation is characterized by the following reaction dynamics:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \xrightarrow{k_2} P + E$$

$$I + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2$$

Table 1.1 Reaction Data for problem 3

Substrate Concentration [mM]	Reaction Velocity [mM/s]
0.1	0.04
0.2	0.08
0.5	0.17
1.0	0.24
2.0	0.32
3.5	0.39
5.0	0.42

Derive the following relationship for the reaction velocity of the product reaction, considering steady-state conditions for the enzyme and enzyme complexes and preservation of the total enzyme content:

$$V = \frac{V_{max}[S]}{[S] + K_m(1 + [I]/K_I)}$$

where $[I]$ is the concentration of the inhibitor, $K_m = (k_{-1} + k_2)/k_1$ and $K_I = k_{-3}/k_3$.

1.5 Alcohol metabolism: Clearance of the blood alcohol level (BAL) $[A]$ [mg/dl] from the liver is metabolized by more than 20 different enzymes. From experimental data the total clearance effect of these enzymes has been lumped into a common Michaelis-Menten relationship with population average $V_{max} = -15$[mg/(dl· h)] and a $K_m = 5$ [mg/dl].

$$\frac{d[A]}{dt} = \frac{V_{max}[A]}{K_m + [A]}$$

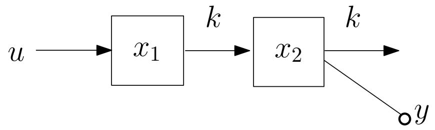
To calculate the BAL, the total distribution volume of the body for alhocol has to be known. The following relationship between the total water volume, representing this distribution volume V_D $[l]$, and the weight m_{BW} [kg], gender and age Y [years] of the person has been suggested.

$$\begin{aligned} V_D &= 20 + 0.36m_{BW} - 0.1Y, \quad Men \\ V_D &= 14 + 0.25m_{BW}, \qquad Women \end{aligned}$$

Assuming that a 25 year old man of 80 kg consumes a drink containing 2 cl of alcohol (density 800 kg/m^3) at a fasting state. Digestion of alcohol is very rapid on an empty stomach, and you may assume that the total alcohol content has reached the blood stream after 20 minutes whereafter metabolization is considered to start. Simulate and plot the BAL level for the four hours following the drink.

2. Model Building and Linearization

2.1 Given the compartment model below



assume that x_1 and x_2 represent quantities of a substance subject to conservation. y is a measurement of x_2.

a. Give the balance equations when $k = 1$. What are the states, the input and the output of the system?

b. From the balance equations derive the state space representation for the system.

c. Determine the transfer function of the system analytically and by using functions from the control toolbox in `MATLAB`.

2.2 Give the state-space representation of the system

$$\dddot{y} + 3\ddot{y} + 2\dot{y} + y = u$$

where $u(t)$ and $y(t)$ are the input and output, respectively. Choose states $x_1 = y$, $x_2 = \dot{y}$ and $x_3 = \ddot{y}$.

2.3 A process with output $y(t)$ and input $u(t)$ is described by the differential equation

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

a. Introduce states $x_1 = y$, $x_2 = \dot{y}$ and give the state space representation of the system.

b. Find all stationary points (x_1^0, x_2^0, u^0) of the system.

c. Linearize the system around the stationary point corresponding to $u^0 = 1$.

2.4 Linearize the system

$$\begin{aligned} \dot{x}_1 &= x_1^2 x_2 + \sqrt{2}\sin u && (= f_1(x_1, x_2, u)) \\ \dot{x}_2 &= x_1 x_2^2 + \sqrt{2}\cos u && (= f_2(x_1, x_2, u)) \\ y &= \arctan\frac{x_2}{x_1} + 2u^2 && (= g(x_1, x_2, u)) \end{aligned}$$

around the stationary point $u^0 = \pi/4$.

2.5 Blood Doping: Everyday about $2.5 \cdot 10^{11}$ (0.25 trillion) new red blood cells (RBCs) are released from the bone marrow into the peripheral circulation, and in steady-state the same number of depleted RCB:s are cleared by the spleen. Assume that the average lifespan of a RCB is 120 days, and the cleared amount between two days k and $k-1$ is a constant fraction f of the total cell population $R(k-1)$ at day $k-1$. The cell population $R(k)$ is R_{ref} [trillion cells] at steady state. Furthermore, the rate of production $r(k)$ [trillion cells/day] is controlled by the level of erythropoietin EPO $u(k)$ [Units/ml] according to the outlined dynamics below (changes in the EPO level do not fully effect the production rate directly, but the production rate $r(k)$ is partly dependent on the production rate the previous day $r(k-1)$):

$$r(k) = 0.9 \cdot r(k-1) + u(k), \quad r(0) = f \cdot R_{ref}, u(0) = 0.025 \tag{2.1}$$

Set up the difference equations for the red blood cell population $R(k)$ and the production rate $r(k)$. Assume that we are at steady state with a total cell population R_{ref} of $120 \cdot 0.25$ trillion cells. Create a Simulink model according to Fig. 2.1 and simulate the system for 100 days. Assume that the level of EPO normally is constant at 0.025 Units/ml, but that it is artificially elevated to the double normal level by injections for 20 consecutive days between day 21 and 40.

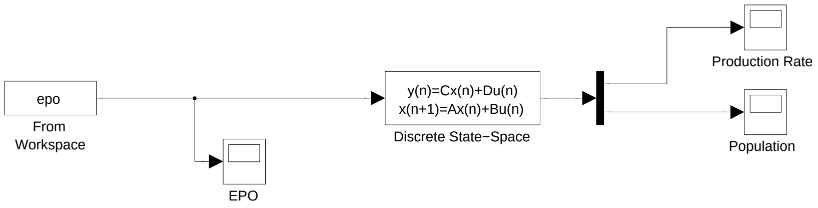


Figure 2.1 Simulink model for the red blood cell system

2.6 Infection; Bacteria-Leukocytes Predator-Prey System: Neuthrophiles are specialised white blood cells (leukocytes), specialising in defending against bacterial infections. Let $B(t)$ denote the number of bacteria in a wound and $N(t)$ the number of neuthrophiles. The bacterial growth factor is α [bacteria/hour] and the killing factor of the neuthrophiles β [bacteria/hour] and assume that the entry rate of new neuthrophiles is $u(t)$ [neutrophiles/hour].

$$\frac{dB}{dt} = \alpha B(t) - \beta \cdot B(t) \cdot N(t) \tag{2.2}$$

$$\frac{dN}{dt} = -\gamma N(t) + u(t) \tag{2.3}$$

Simulate the system in Simulink with $\alpha = 3, \beta = 1.1, \gamma = 1.5$, and with initial conditions $B(0) = 100, N(0) = 0$ and let $u(t)$ be a step with magnitude 10. What happens if α becomes large (> 8)?

3. Control in Physiology 1

3.1 Determine the transfer functions and give differential equations, describing the relation between input and output for the following systems, respectively.

a.

$$\dot{x} = \begin{pmatrix} -2 & 0 \\ 0 & -3 \end{pmatrix} x + \begin{pmatrix} 5 \\ 2 \end{pmatrix} u$$
$$y = \begin{pmatrix} -1 & 1 \end{pmatrix} x + 2u$$

b.

$$\dot{x} = \begin{pmatrix} -7 & 2 \\ -15 & 4 \end{pmatrix} x + \begin{pmatrix} 3 \\ 8 \end{pmatrix} u$$
$$y = \begin{pmatrix} -2 & 1 \end{pmatrix} x$$

3.2 Determine the impulse and step responses of the systems in assignment 3.1 both analytically and through MATLAB. The step response is defined as the output of the system when the input is the step function $u(t) = 1$ for $t > 0$ and $u(t) = 0$ for $t < 0$.

3.3 Derive the formula $G(s) = C(sI - A)^{-1}B + D$ for a general system

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

3.4 Consider the system

$$G(s) = \frac{1}{s^2 + 4s + 3}$$

a. Calculate the poles and zeros of the system. Is the system stable?

b. Calculate the impulse response by hand and plot it in MATLAB.

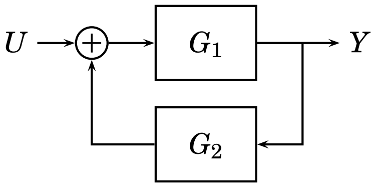
3.5 Consider the linear time invariant system

$$\frac{dx}{dt} = \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} x + \begin{pmatrix} 1 \\ 0 \end{pmatrix} u$$
$$y = \begin{pmatrix} 1 & -1 \end{pmatrix} x$$

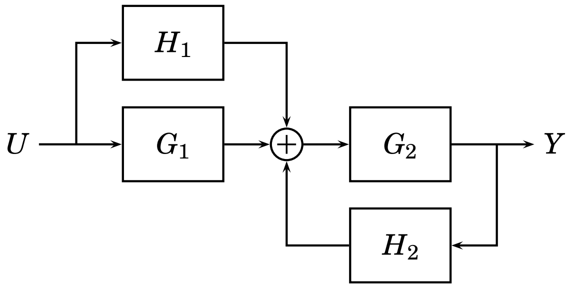
Is the system stable? Plot the step response of the system.

3.6 Determine the transfer function from U to Y for the systems below.

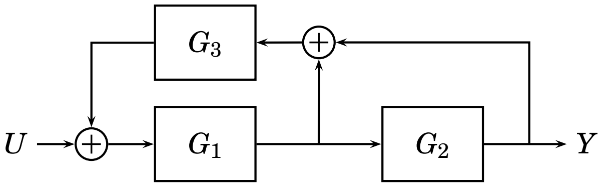
a.



b.



c.



3.7 Assume that the system

$$G(s) = \frac{0.01(1+10s)}{(1+s)(1+0.1s)}$$

is subject to the input $u(t) = \sin 3t, \quad -\infty < t < \infty$

a. Determine the output $y(t)$.

b. The Bode plot of the system is shown in figure 3.1. Determine the output $y(t)$ by using the Bode plot instead.

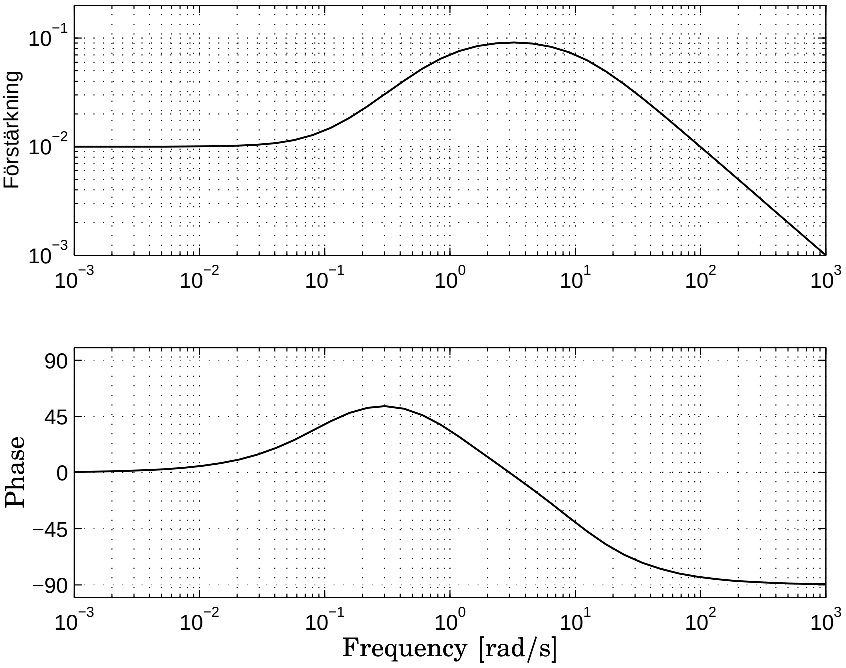


Figure 3.1 The Bode plot in assignment 3.7.

4. Control in Physiology 2

4.1 Assume that the amount of some substrate y inside a cell is described by the differential equation

$$\dot{y}(t) + 0.01y(t) = 0.01u(t)$$

where u is the inflow of the substrate to the cell.

a. Let u be the input and y the output and determine the transfer function $G_P(s)$ of the process.

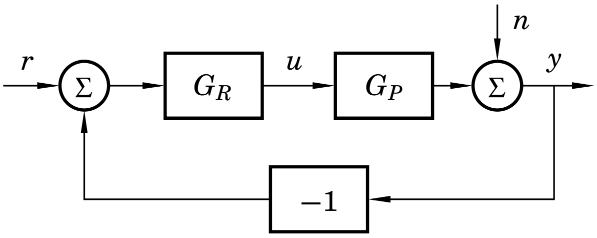
b. This is to be controlled by negative feedback with a controller $G_R(s)$. Draw the block diagram and write down the transfer function of the closed loop system. Be sure to define the input u, output y, error e and reference signal r in the block diagram of the closed loop system.

c. If $G_R(s)$ is a P controller what will the transfer function look like then?

d. Choose K, given that $G_R(s) = K$, such that the closed loop system obtains the characteristic polynomial

$$s + 0.1$$

4.2 A process is controlled by a P controller according to the figure below.



a. Measurements of the process output indicate a disturbance n. Calculate the transfer functions from n to y (the sensitivity function).

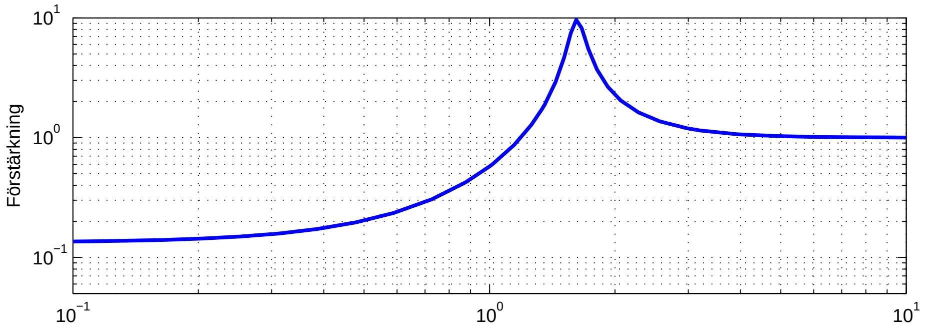
b. Let $G_P(s) = 1/(s+1)$ and $G_R(s) = K$ and assume that the disturbance consists of a sinusoid $n(t) = A \sin \omega t$. What will y become when this disturbance is present?

c. Assume that $K = 1$ and $A = 1$ in the previous sub-assignment. Calculate the amplitude of oscillation y for the cases $\omega = 0.1$ and 10 rad/s, respectively.

4.3 The process given by $G_P(s) = 1/(s+1)^3$ is controlled through negetive feedback by the controller given by $G_R(s) = 6.5$.

a. Determine the sensitivity function $S(s)$.

b. The gain plot of the sensitivity function is given below. How much are constant load disturbances damped by the control circuit (in closed loop, as compared to open loop)? At which angular frequency does the control circuit exhibit the largest sensitivity towards disturbances and by how much are disturbances amplified at most?



4.4 The open-loop transfer function of a system is given by:

$$G_o(s) = G_R(s)G_P(s) = \frac{K(s+10)(s+11)}{s(s+1)(s+2)}$$

For which values of K is the closed-loop system stable?

4.5 Flow control is important in many applications. In e.g. a hemodialysis machine it is very important to keep a steady and constant flow through the filters to achieve optimal filtration. Pump-to-flow dynamics is given by the pump characterstics together with the piping and filter system topology. The following transfer function relationship is assumed to hold between the flow and the control input:

$$G_P(s) = \frac{e^{-9s}}{(1+20s)^2}$$

If a proportional controller is used, how large may the gain constant K become before the system becomes unstable?

5. Pharmacokinetics and Tracers

5.1 The half-life of a penicillin solution that contains 300 units/ml is 8 days, in plasma. What will the concentration in plasma be in 7 days? Assume the drug is eliminated from plasma through a linear process. Plot the concentration over time.

5.2 The half-life of another penicillin solution is 6 days. Assume it is eliminated from plasma as a linear process. How long will it take for the concentration to drop to 40 % of the initial concentration?

5.3 Assume a drug is metabolised from plasma through a linear process. It has an initial potency of 90 mg/ml. After 25 days in a cold room, the concentration is found to be 80 mg/ml. What is the half-life of the drug during the storage conditions?

5.4 A new drug targeting hepatatis has been developed. The drug is administred orally and is believed to exhibit linear pharmacokinetics including gut absorption.

a. Draw a simplified compartment model of the route of a drug including the absoption in the gut, the distribution in the liver and the remaining body and the elimination of the drug from these compartments. In the model, the body compartment represents a lumped compartment for the extra- and intracellular fluid of the body excluding the liver and the gut.

b. Set up a state-space representation of the model with the drug concentration in the liver as output using the parameters found in Table e.

c. Simulate a 500 mg dose, assuming it takes 5 minutes to dissolve at a constant rate (100 mg/min), using `lsim` for a total duration of 168 hours.

d. Try adding more doses with a 24 hour interval, i.e., a new tablet every 24:th hour. The liver concentration will oscillate quite a lot with almost a 2-fold ratio between the highest and the lowest concentrations. Could you suggest some alternative dosing scheme to keep the concentration at a more even level at the same mean concentration value?

e. How large should a constant intravenuous dose (here we assume that iv injections enters the body compartment) be to achieve a steady-state liver concentration of 112 mg/dl?

Parameter	Value	Description
V_G	0.1	Distribution volume Gut [l]
V_B	42	Distribution volume Body [l]
V_L	0.27	Distribution volume Liver [l]
k_{GB}	0.1	Kinetic coefficient Gut-to-blood $[min^{-1}]$
k_{BL}	$4{\cdot}10^{-3}$	Kinetic coefficient blood-to-liver $[min^{-1}]$
k_{LB}	$1{\cdot}10^{-3}$	Kinetic coefficient liver-to-blood $[min^{-1}]$
$k_{e,G}$	0.02	Elimination constant, gut $[min^{-1}]$
$k_{e,B}$	$3{\cdot}10^{-6}$	Elimination constant, blood $[min^{-1}]$
$k_{e,L}$	$8{\cdot}10^{-6}$	Elimination constant, liver $[min^{-1}]$

6. Biomechanics

6.1 Determine a control law $u = l_r r - Lx$ for the system

a.

$$\frac{dx}{dt} = \begin{pmatrix} -0.5 & 0 \\ 1 & 0 \end{pmatrix} x + \begin{pmatrix} 3 \\ 0 \end{pmatrix} u$$
$$y = \begin{pmatrix} 0 & 1 \end{pmatrix} x$$

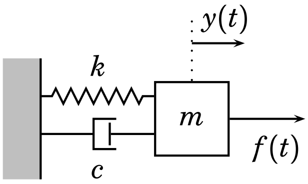
such that the poles of the closed loop system are placed in $-4 \pm 4i$ and the stationary gain, from reference to output, is 1.

b.

$$\frac{dx}{dt} = \begin{pmatrix} -1 & 0 \\ 0 & -2 \end{pmatrix} x + \begin{pmatrix} 1 \\ 2 \end{pmatrix} u$$
$$y = \begin{pmatrix} 1 & 1 \end{pmatrix} x$$

such that the poles of the closed loop system are placed in -4 and the stationary gain is 1. How would you sketch the block diagram of the closed loop system?

6.2 In the right figure, a mass m is attached to a wall with a spring and a damper. The spring has a spring constant k and the damper has a damping constant c. It is assumed that $k > c^2/4m$. An external force f is acting on the mass. We denote the translation of the mass from its equilibrium position by y. Further, we let $f(t)$ be the input signal and $y(t)$ be the output signal. The force equation gives



$$m\ddot{y} = -ky - c\dot{y} + f$$

Introduce the states $x_1 = y$ and $x_2 = \dot{y}$ and write down the state space representation of the system.

6.3 Determine the transfer function and poles of the oscillating mass in the previous exercise. Explain how the poles move if one changes k and c, respectively. Can the poles end up in the right half plane?

6.4 When walking, the body is kept in upright position by some regulatory system. This balancing of the body can be simplified to the problem of controlling an inverted pendulum positioned on a cart, by moving the cart. In Fig. 6.1, a schematic of this inverted pendulum is given.

The control signal is the velocity of the cart v [m/s]. The position of the cart z [m] and the angle of the pendulum φ are measured. The problem is to decide upon a feedback controller wich stabilizes the pendulum in its upright position as well as moves the cart towards some wanted position. If the model for this inverted pendulum is linearized it can be written as

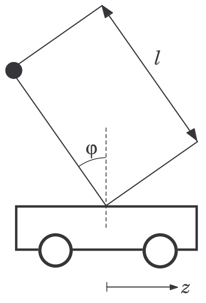


Figure 6.1 Inverted pendulum in exercise 6.4.

$$
\begin{aligned}
\frac{dx_1}{dt} &= \omega_0 x_2 + au \\
\frac{dx_2}{dt} &= \omega_0 x_1 \\
\frac{dx_3}{dt} &= bu
\end{aligned}
$$

where the state variables

$$
\begin{aligned}
x_1 &= k_\varphi \frac{d\varphi}{dt} \\
x_2 &= \omega_0 k_\varphi \varphi \\
x_3 &= k_z z
\end{aligned}
$$

are used. They are all in unit [V]. The scalars k_φ, k_v and k_z are calibration constants. The scalars a, b and ω_0 are given by

$$
a = \frac{\omega_0^2 k_\varphi}{g k_v} \qquad b = \frac{k_z}{k_v} \qquad \omega_0^2 = \frac{g}{\ell}
$$

where g is the gravitational acceleration and ℓ the length of the pendulum.

Assume that we can measure the given states. Determine a state feedback regulator which gives a closed loop system with poles in $-\alpha$, and $-\omega\left(\zeta \pm i\sqrt{1-\zeta^2}\right)$.

7. Glucose and Insulin Dynamics

7.1 Insulin Sensitivity: The minimal model is used to estimate the insulin sensitivity $S_I = \partial^2\dot{G}/\partial G \partial I$ from an Intraveneus Glucose Tolerance Test (IVGTT). The minimal model is:

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3(I(t) - I_b), \quad X(0) = 0, I(0) = I_b$$

$$\frac{dG(t)}{dt} = -(p_1 + X(t))G(t) + p_1 G_b + U_G(t)/V_G, \quad G(0) = G_b$$

- $U_G(t)$: Intravenous Glucose Injection.
- V_G: Distribution volume for plasma glucose.
- $X(t)$ represents 'remote insulin'.

According to the model developers, S_I can be calculated as:

$$S_I = -\frac{p_3}{p_2}$$

assuming steady state conditions of insulin. Derive this expression given this assumption. Do you see any problems with this assumption considering the IVGTT experiment?

7.2 Minimal Model Simulation: Create a Simulink model of the minimal model (diff. eqs. in previous exercise) and simulate it with 1-minute interpolated (see e.g. `interp1`) plasma insulin data from Table 1, acting as input, together with the glucose injection at time 0 min of 30 grams of glucose into a distribution volume V_g of 5.45 l, to produce the glucose response data. You may assume that we start in steady state conditions with $I = I_b = 7.3$ and $G = G_b = 85$. The parameters are: $p_1 = 0.0308$, $p_2 = 0.0209$ and $p_3 = 1.06 \cdot 10^{-5}$.

7.3 Digestion Modeling: Consider the digestion model in the Padova simulation model:

$$\begin{aligned}
q_{sto}(t) &= q_{sto1}(t) + q_{sto2}(t) \\
\dot{q}_{sto1}(t) &= -k_{gri} \cdot q_{sto1}(t) + C(t) \\
\dot{q}_{sto2}(t) &= k_{gri} \cdot q_{sto1}(t) - k_{empt} \cdot q_{sto2}(t) \\
\dot{q}_{gut}(t) &= -k_{abs} \cdot q_{gut}(t) + k_{empt} \cdot q_{sto2}(t) \\
R_a(t) &= \frac{f \cdot k_{abs} \cdot q_{gut}(t)}{M_{BW}}
\end{aligned}$$

- $C(t)$ is the amount of ingested carbohydrates.
- q_{sto1} is the solid stomach compartment, and q_{sto2} represents the liquid phase.
- q_{gut} is the glucose mass in the intestine.
- k_{gri} the rate of grinding.

Time [min]	Plamsa Insulin
0	11
2	26
4	130
6	85
8	51
10	49
12	45
14	41
16	35
19	30
22	30
27	27
32	30
42	22
52	15
62	15
72	11
82	10
92	8
102	11
122	7
142	8
162	8
182	7

- k_{empt} is the rate constant of gastric emptying.
- k_{abs} is the rate constant of intestinal absorption.
- $R_a(t)$ is the appearance rate of glucose in the blood.

The model parameters are different for different types of meals. Which parameters would you expect to change between for example cooked potatos and potato mash, and how would those values change?

7.4 Subcutaneous Delay: Show that the interstitial glucose value is a first-order low-pass filtered version of the plasma glucose value considering the kinetics according to Fig. 6.1, i.e., that the transfer function is of the form $G = K\frac{1}{1+s\tau}$.

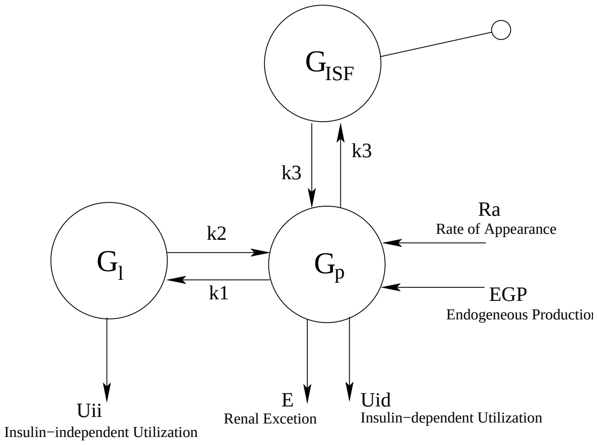


Figure 7.1 Interstitial and Plasma Glucose compartment kinetics.

8. The Hodgkin-Huxley model

8.1 Given the ion concentration in the table below, calculate the equilibrium potentials of Na^+, K^+ and Cl^- at room temperature, 25°C, by the Nernst equation.

Ion	**Inner conc. [μM]**	**External conc. [μM]**
Na^+	12	145
K^+	155	4
Cl^-	4.2	123

How does the potentials change if the temperature is lowered 20 degrees?

8.2 Below is the Goldman Equation, giving the membrane potential V at certain ion concentrations and permeabilities.

$$V = \frac{\mathrm{RT}}{\mathrm{F}}\ln\left(\frac{P_K[K]_2 + P_{Na}[Na]_2 + P_{Cl}[Cl]_2}{P_K[K]_1 + P_{Na}[Na]_1 + P_{Cl}[Cl]_1}\right)$$

P_i - permeability for ion [i], 1 - inner concentration and 2 - external (outer) concentration.

a. How would you describe permeability?

b. Assume some initial permeability for each ion. If the permeability of sodium (Na) would rise, how would this change the membrane potential? You can assume that the ion concentrations are the same as in the previous exercise.

8.3 Write down the differential equation for the membrane potential of the Hodgkin and Huxley model stated in lecture 8. Declare the different constants and functions. Can you give a physiological description to why this differential equation is non-linear? Hint: threshold potential.

8.4 The dynamics of the gating variables m, n and h are:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(V)(1-m) - \beta_m(V)m$$
$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(V)(1-h) - \beta_h(V)h$$
$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V)(1-n) - \beta_n(V)n$$

where the rate functions are, unit [1/ms]:

$$\begin{aligned}
\alpha_m(V) &= 0.1(V+45)/(1-\exp(-(V+45)/10))\\
\beta_m(V) &= 4\exp(-(V+70)/18)\\
\alpha_h(V) &= 0.07\exp(-(V+70)/20)\\
\beta_h(V) &= 1/(1+\exp(-(V+40)/10))\\
\alpha_n(V) &= 0.01(V+60)/(1-\exp(-(V+60)/10))\\
\beta_n(V) &= 0.125\exp(-(V+70)/80)
\end{aligned}$$

a. What do the gating variables correspond to physiologically?

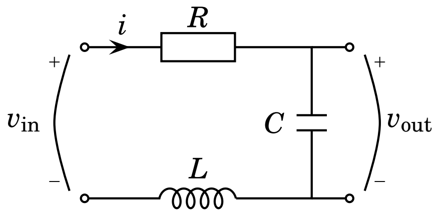
b. Plot $\alpha_m(V)$, $\beta_m(V)$, $\alpha_h(V)$, $\beta_h(V)$, $\alpha_n(V)$ and $\beta_n(V)$ for values of V between -90 and 70 [mV].

8.5 Look at the differential equation of the membrane potential, discussed in exercises 8.3, if only the leakage and external currents are present. That is

$$C_m\frac{\mathrm{d}V}{\mathrm{d}t} = -g_L(V-E_L) + I_{ext}$$

In this case you don't have to mind about the m, n and h functions due to I_L being independent of them. Solve the differential equation in MATLAB when the external current starts at 0 and increases by 5 [μA/cm^2], as a step, every 100 ms for 500 ms. Assume that the initial membrane potential is the equilibrium potential of leakage $E_L = -59.387$ [mV], that $g_L = 0.3$ [mS/cm^2] and the membrane capacitance is $C_m = 1[\mu\text{F/cm}^2]$. What happens?

8.6 The Hodgkin and Huxley model is derived upon the idea of seeing the membrane of the neuron as an electrical circuit. As an example of an electrical circuit see the RLC circuit to the right, the input and output voltages are given by $v_{\text{in}}(t)$ and $v_{\text{out}}(t)$, respectively. By means of Kirchhoff's voltage law we see that



$$v_{\text{in}} - Ri - v_{\text{out}} - L\frac{di}{dt} = 0$$

For the capacitor, we additionally have

$$C\dot{v}_{\text{out}} = i$$

Introduce the states $x_1 = v_{\text{out}}$ and $x_2 = \dot{v}_{\text{out}}$ and give the state space representation of the system.

In the Hodgkin and Huxley model the inductor L is not used. How does the electrical circuit of the Hodgkin and Huxley model look like?

8.7 Determine the transfer function of the RLC circuit in the previous assignment.

Solutions to Chapter 0. Repetition of Linear Algebra, Differential equations and MATLAB

Solve the following exercises by hand. If you are unsure about how to solve the exercises, please go back to your Linear algebra and Analysis books and review the material needed.

0.1 a. $x(t) = ct + 1$.

b. $x(t) = e^{ct}$.

c. The differential equation is separable. Rewrite it as

$$\frac{1}{x^2}dx = 2tdt$$

$$\frac{1}{x^2}dx = 2tdt$$

Integrating on both sides gives

$$-1/x = t^2 + c$$

where c is a constant. Hence, $x(t) = -1/(c + t^2)$. $x(0) = -\frac{1}{c} = 1 \rightarrow c = -1$. The solution to the differential equation is therefore, $x(t) = \frac{1}{1-t^2}$.

d. Introduce $y_1(t) = y(t)$ and $y_2(t) = \dot{y}(t)$ in order to rewrite the initial second-order differential equation into two first-order differential equations as follows

$$\dot{y}_1 = y_2 \tag{0.1}$$

$$\dot{y}_2 = 3y_1 - 7y_2 \tag{0.2}$$

The initial conditions for $y_1(t)$ and $y_2(t)$ are

$$y_1(0) = y(0) = 0$$
$$y_2(0) = \dot{y}(0) = 1$$

(0.1) and (0.2) can be written together on matrix form as follows

$$\begin{pmatrix} \dot{y}_1 \\ \dot{y}_2 \end{pmatrix} = \begin{pmatrix} y_2 \\ 3y_1 - 7y_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ 3 & -7 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$$

Define $\mathbf{v} = \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$. Then, define f as the following function

$$f(t, \mathbf{v}) = f(t, \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}) = \begin{pmatrix} \dot{y}_1 \\ \dot{y}_2 \end{pmatrix}$$

Hence,

$$f(t, \mathbf{v}) = \begin{pmatrix} y_2 \\ 3y_1 - 7y_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ 3 & -7 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}.$$

Solve the following exercises using MATLAB. These exercises are inspired by or fully extracted from *EDA017: Föreläsningsanteckningar, OCTAVE/MATLAB* by Christian Söderberg.

0.2 Use the help function and MathWorks webpage.

0.3 a. Create an anonymous function using the function handle. This function is only saved in your workspace until you close MATLAB (or clear you workspace by the `clear all` command). In case you would like to save your function as a file in your current folder (from where you can reach it at another time), use a function m-file (go to new → function).

```
y = @(x) exp(-x/2)*cos(2*pi*x);

figure
fplot(y,[-6 3])
title('My fancy plot')
xlabel('x')
ylabel('y')
```

`figure` is a command which is useful when you want to create several plots in the same script. Use the `help`-command whenever you need information about one of MATLABs buildt-in functions. In this case you would write `help figure` in the command window and the description of the function should appear.

b.

```
axis([-4.5 -1 -10 10])
```

c.

```
% Rewrite y to be accepted by quad/integral (read in the
% description of quad/integral to understand why).
y = @(x) exp(-x/2).*cos(2*pi*x);

integral(y,-4.5,-1)
% or
quad(y,-4.5,-1)
```

d. `f = @(x) x^3+2*x−1; solution = fsolve(f,0)`

The answer is 0.4534. Write `format long` in the command window (then use the `fsolve` command) to get more decimals in the answer. Due to it being numerically calculated $f(0.4534)$ is approximately zero.

0.4 Go to new → function. A file with a function-shell will appear. The function shell looks like:

```
function [ output_args ] = untitled( input_args )
%UNTITLED Summary of this function goes here
%   Detailed explanation goes here


end
```

Replace `untitled` with the name of your function, `input_args` with the input your function needs and `output_args` with the output your function will give. Between the `function`-row and the `end` you should write the code for the function.

For the particular function of this exercise, it will look as follows

```
function sumOfDiag = sumOfDiagonal(A)
[n,m] = size(A);

if n ≠ m
    error('A is not a square matrix')
end

sumOfDiag = sum(diag(A));
end
```

Where $\neq$ is written as ~= in MATLAB. Save your function as an m-file in your current folder, by the name of your function. In this case it would be "sumOfDiagonal.m". Now you can use your function directly from the command window or from a script which is saved in the same folder as your function.

To create a matrix in MATLAB use the following principle

```
my_matrix = [1 2; 3 4];
```

`[` and `]` begins and ends the matrix. Elements are separated by space (or comma) and rows are separated by `;`. The resulting matrix is

$$\begin{pmatrix} 1 & 2 \\ 3 & 4 \end{pmatrix}$$

0.5 Introduce $y_1(t) = y(t)$ and $y_2(t) = \dot{y}(t)$ in order to rewrite the initial second-order differential equation into two first-order differential equations as follows

$$\dot{y}_1 = y_2 \tag{0.3}$$
$$\dot{y}_2 = 3y_1 - 7y_2 \tag{0.4}$$

The initial conditions for $y_1(t)$ and $y_2(t)$ are

$$y_1(0) = y(0) = 0$$
$$y_2(0) = \dot{y}(0) = 1$$

(0.1) and (0.2) can be written together on matrix form as follows

$$\begin{pmatrix} \dot{y}_1 \\ \dot{y}_2 \end{pmatrix} = \begin{pmatrix} y_2 \\ 3y_1 - 7y_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ 3 & -7 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$$

Define $\mathbf{v} = \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$. Then, define f as the following function

$$f(t, \mathbf{v}) = f(t, \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}) = \begin{pmatrix} \dot{y}_1 \\ \dot{y}_2 \end{pmatrix}$$

Hence,

$$f(t, \mathbf{v}) = \begin{pmatrix} y_2 \\ 3y_1 - 7y_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ 3 & -7 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}.$$

In MATLAB this can be written as

```
f = @(t,v) [v(2); 3*v(1)-7*v(2)];
```

Or by matrix multiplication

```
f = @(t,v) [0 1; 3 -7]*v;
```

To solve the differential equation write the following code

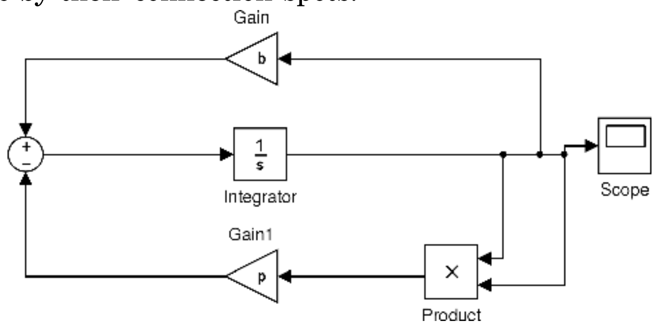
```
[t_ode V] = ode45(f,[0 5],[0 1]);
```

The first input to `ode45` is the right part of the differential equation, the second input is the time span of the solution while the third is the initial condition of the differential equation. `V` is a matrix with two columns, the first column corresponds to $y_1(t) = y(t)$ and the second column corresponds to $y_2(t) = \dot{y}(t)$. `t_ode` is the times between 0 and 5 at which `ode45` has calculated y_1 and y_2. Use the following code to plot $y(t)$ over $0 \leq t \leq 5$

```
plot(t_ode,V(:,1))
```

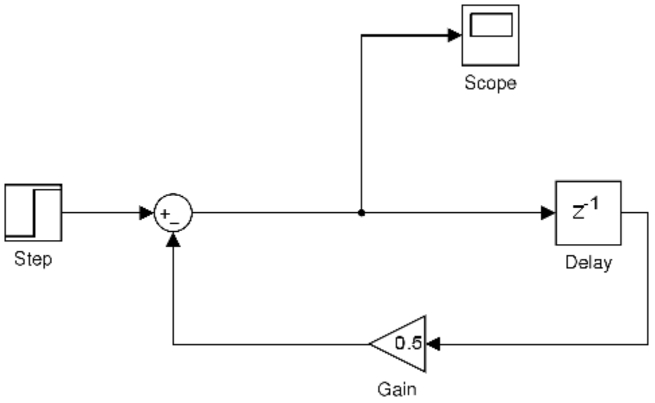
Solve the following exercises using SIMULINK in MATLAB. These exercises are taken from *Exercises in MATLAB/Simulink, Signals and Systems* by Thomas Munther.

0.6 Start SIMULINK by writing `simulink` in the MATLAB command window. This makes the SIMULINK Library Browser window pop up. Go to File → New → Model. In this window you can start to create your SIMULINK model. Use the Library Browser to find appropriate blocks and drag them into the model sheet. You can connect two blocks by their connection spots.

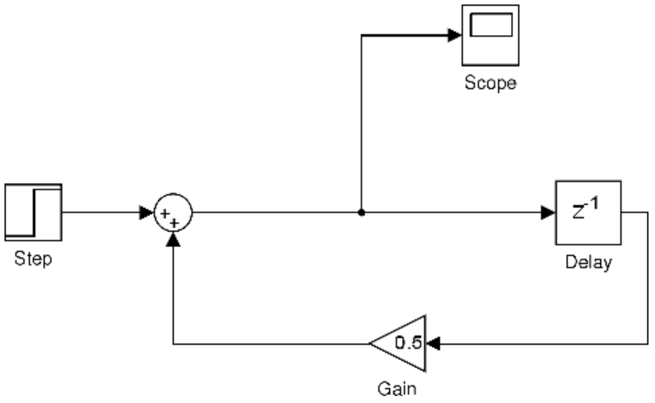


`p` and `b` can be defined in the current workspace. Go to display → blocks and check "Sorted Execution Order". This will numerate the blocks in the order in which they are first activated.

0.7 a. Before running the simulation go to Simulation → Configuration Parameters. In Solver Options choose Fixed-step and Solver → Discrete. Set the sample time in each block to 1 [sec].



b. The only difference from the previous model is that the minus sign in the sum-block is changed to a plus sign.



0.8 Just play around.

Solutions to Chapter 1. Biochemical Reactions

1.1 a. Denote the concentrations $x = [X]$ and $y = [Y]$

$$\frac{dx}{dt} = -k_1 x + k_{-1} y$$
$$\frac{dy}{dt} = k_1 x - k_{-1} y$$

b. Denote the concentrations $x = [X]$ and $y = [Y]$

$$\frac{dx}{dt} = -2k_1 x^2 + 2k_{-1} y$$
$$\frac{dy}{dt} = k_1 x^2 - k_{-1} y$$

c.

Denote the concentrations $x = [X]$, $y = [Y]$ and $z = [Z]$

$$\frac{dx}{dt} = -3k_1 x^3 y + 3k_{-1} z \tag{1.1}$$
$$\frac{dy}{dt} = -k_1 x^3 y + k_{-1} z \tag{1.2}$$
$$\frac{dz}{dt} = k_1 x^3 y - k_{-1} z \tag{1.3}$$
$$\tag{1.4}$$

1.2 A matlab script may look as follows:

```
% Simulation of the substrate, enzyme and product concentrations in a MM
% example
% ds/dt = -k_1 *(se) + k_{-1}*c
% de/dt = -k_1 *(se) + (k_{-1} + k_2)*c
% dc/dt = k_1 *(se) - (k_{-1} + k_2)*c
% dp/dt = k_2 c
%--------------------
% Initial conditions
s(1) = 0.15; % mmol/L
e(1) = 1e-2; % mmol/L
c(1) = 0; % mmol/L
p(1) = 0; % mmol/L
%--------------------
% Parameters
k1 = 0.1;
k3 = 0.01; % k_{-1}
k2= 0.02;
%--------------------
% Run ode-solver simulation
% y = [S E C P]
```

```
dAll = @(t,y) [-k1*y(1)*y(2)+k3*y(3); ...
    -k1*y(1)*y(2)+(k3+k2)*y(3); ...
    k1*y(1)*y(2)-(k3+k2)*y(3); ...
    k2*y(3)];

[t Y] = ode45(dAll,[0 10000],[0.15 1e-2 0 0])

figure(1)
[ax,h1,h2] = plotyy(t,[Y(:,1) Y(:,4)],t,[Y(:,2) Y(:,3)])
legend('Substrate','Product','Enzyme','Complex')
xlabel('time [s]')
ylabel(ax(1),'Substrate/Product Concentration [mmol/L]')
ylabel(ax(2),'Enzyme/Complex Concentration [mmol/L]')
title('Simulation of enzymatic reaction')
%
% Also possible to run approximative discretized simulation
for k = 2:10000
    s(k) = s(k-1) + k3*c(k-1) - k1*s(k-1)*e(k-1);
    e(k) = e(k-1) + (k3+k2)*c(k-1) - k1*s(k-1)*e(k-1);
    c(k) = c(k-1) - (k3+k2)*c(k-1)  + k1*s(k-1)*e(k-1);
    p(k) = p(k-1) + k2*c(k-1);
end

figure(2)
[ax,h1,h2] = plotyy(1:10000,[s' p'],1:10000,[e' c'])
legend('Substrate','Product','Enzyme','Complex')
xlabel('time [s]')
ylabel(ax(1),'Substrate/Product Concentration [mmol/L]')
ylabel(ax(2),'Enzyme/Complex Concentration [mmol/L]')
title('Simulation of enzymatic reaction')
```

Doubling the enzymatic concentration doubles the production rate since $V_{max} = k_2 \cdot e_0$. Likewise since $K_m = (k_2 + k_{-1})/k_1 = 0.3$ and $V = V_{max}s/(K_m + s)$, a doubling of s_0 from $K_m/2$ to K_m means that the initial reaction rate will become 1.5 times greater.

1.3 The plot indicates that the relationship between the reaction rate and the substrate concentration goes to saturation in a M-M-like behavoir, see Fig. 1.1. V_{max} and K_m are estimated as shown in the plot.

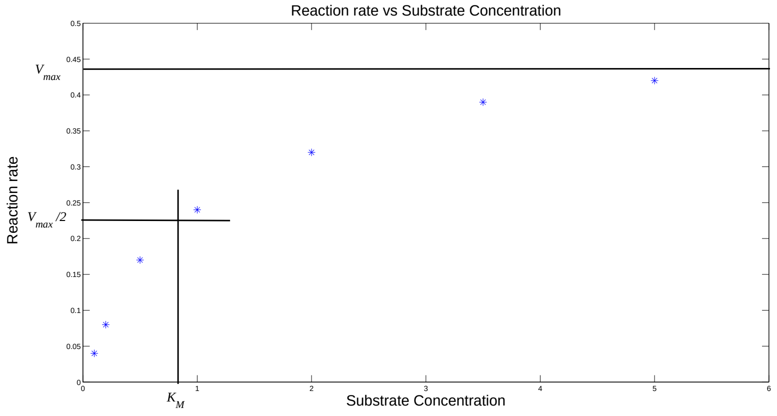


Figure 1.1 Graphical estimation of V_{max} and K_M

Lineweaver-Burke plot: The Michaelis-Menten relationship between substrate concentrations $[S]$ states that:

$$v = \frac{V_{max}[S]}{K_m + [S]}$$

Taking the inverse yields:

$$\frac{1}{v} = \frac{K_m}{V_{max}} \frac{1}{[S]} + \frac{1}{V_{max}}$$

Now, the parameters K_m/V_{max} and $1/V_{max}$ for this linear relationship may be estimated from the plot as seen in Fig. 1.2.

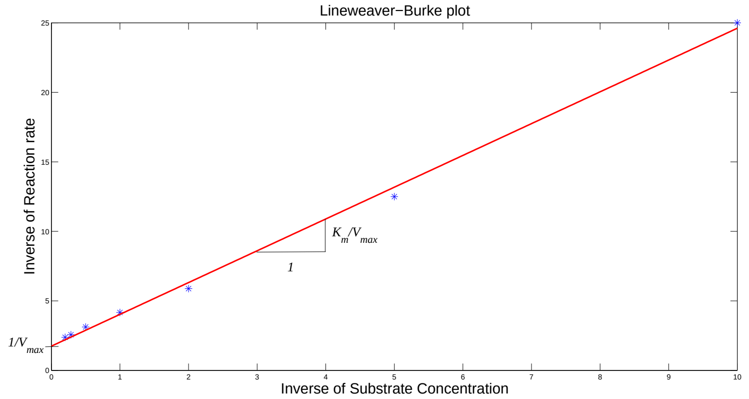


Figure 1.2 Graphical estimation of V_{max} and K_M using the Lineweaver-Burke plot.

1.4 Draw a graph of the compartment representation, see Fig 1.3. Next,

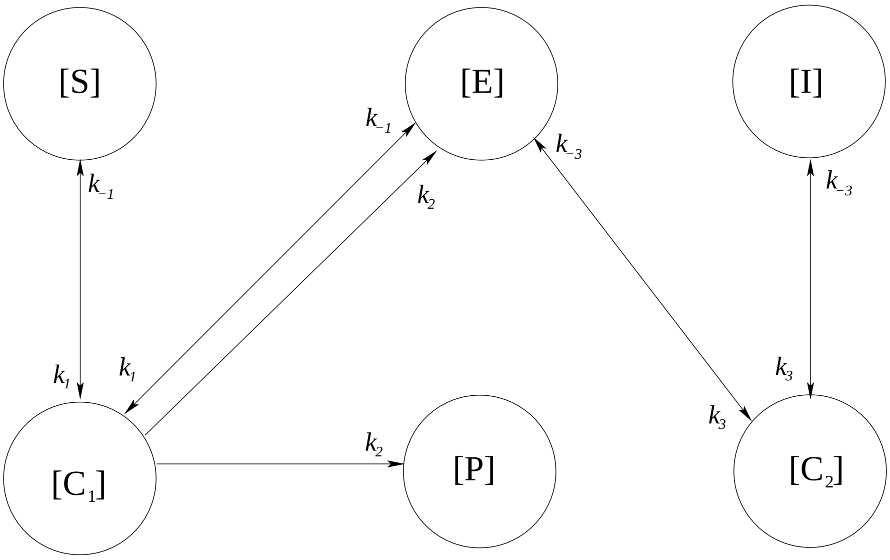


Figure 1.3 Compartment model representation of the enzyme inhibition dynamics.

determine the differential equations governing the reaction dynamics:

$$\frac{d[S]}{dt} = -k_1[S][E] + k_{-1}[C_1] \tag{1.5}$$

$$\frac{d[I]}{dt} = k_{-3}[C_2] - k_3[E][I] \tag{1.6}$$

$$\frac{d[C_1]}{dt} = k_1[S][E] - (k_{-1} + k_2)[C_1] \tag{1.7}$$

$$\frac{d[C_2]}{dt} = k_3[E][I] - k_{-3}[C_2] \tag{1.8}$$

$$\frac{d[E]}{dt} = (k_2 + k_{-1})[C_1] + k_{-3}[C_2] - k_1[S][E] - k_3[E][I] \tag{1.9}$$

$$\frac{d[P]}{dt} = k_2[C_1] \tag{1.10}$$

Next, use the steady-state assumptions; $d[C_1]/dt = d[C_2]/dt = 0$ to get

$$[C_1] = \frac{k_1}{k_{-1} + k_2}[S][E] \tag{1.11}$$

$$[C_2] = \frac{k_3}{k_{-3}}[E][I] \tag{1.12}$$

The conservation of enzymatic mass gives

$$[E_0] = [E] + [C_1] + [C_2] = [E](1 + \frac{k_1}{k_{-1} + k_2}[S] + \frac{k_3}{k_{-3}}[I]) \tag{1.13}$$

Put Eq. (1.10), Eq. (1.11) and Eq. (1.13) together:

$$V = \frac{d[P]}{dt} = \frac{k_2[E_0][S]}{[S] + \frac{k_1}{k_{-1}+k_2}(1 + \frac{k_3}{k_{-3}}[I])} \tag{1.14}$$

1.5 Blood alcohol level
A matlab script may look as follows:

```
% BAL simulation
V = -15;% mg/(l*h)
K_m = 5;% mg/dl
VD = 10*(20 + 0.36*80-0.1*25); % dl

% The 'initial value' of the concentration [A] is actually
% the concentration in t = 20 min when the metabolization
% of the alcohol starts.

initial_value_A = 0.02*1000*0.8*1000/VD; % mg/dl

% Define the differential equation y(t) = [A](t)
dAdt = @(t,y) V/60*y/(K_m+y);

% Solve the differential equation
[t, Y] = ode45(dAdt, [0 220], initial_value_A);
```

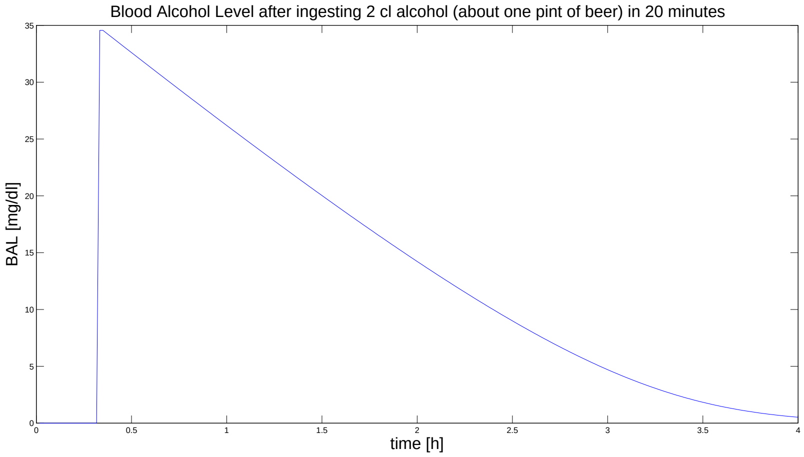


Figure 1.4 Blood alcohol content according to the simulation example.

```
t = (t+20)/60; % Shifting the time vector 20 min, and changing into
% hours instead of minutes.
Y = [zeros(size(0:0.1:(t(1)-0.01))) Y']; % Adding zeros to the
% value-vector for time 0-20 min.
t = [0:0.1:(t(1)-0.01) t']; % Adding the time between 0-20 minutes
% to the time vector.

plot(t,Y)
title('Blood Alcohol Level after ingesting 2 cl alcohol ...
(about one pint of beer) in 20 minutes','Fontsize',10)
ylabel('BAL [mg/dl]','Fontsize',10)
xlabel('time [h]','Fontsize',10)
% or using discreet approx.
BAL_20 = 0.02*1000*800*1000*1000/VD; % mg/dl
BAL(1:20) = zeros(20,1);
BAL(20) = BAL_20;
der = 0;
for k=21:1:240
    BAL(k) = BAL(k-1) + der;
    der = -V/60*BAL(k)/(K_m + BAL(k));
end
plot([1:length(BAL)]/60,BAL)
title('Blood Alcohol Level after ingesting 2 cl alcohol ...
 (about one pint of beer) in 20 minutes','Fontsize',20)
ylabel('BAL [mg/dl]','Fontsize',20)
xlabel('time [h]','Fontsize',20)
```

Running the code generates the plot in Fig. 1.4.

Solutions to Chapter 2. Model Building and Linearization

2.1

a. By concentration of substrate, we have

$$
\begin{aligned}
\frac{dx_1}{dt} &= -x_1 + u \\
\frac{dx_2}{dt} &= x_1 - x_2 \\
y &= x_2
\end{aligned}
$$

The states are x_1 and x_2. The input is u and the output is y.

b.

$$
\begin{aligned}
\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 1 & -1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} 1 \\ 0 \end{pmatrix} u \\
y &= \begin{pmatrix} 0 & 1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}
\end{aligned}
$$

c.

$$
\begin{aligned}
G(s) &= C(sI - A)^{-1}B + D \\
&= \begin{pmatrix} 0 & 1 \end{pmatrix} \begin{pmatrix} s+1 & 0 \\ -1 & s+1 \end{pmatrix}^{-1} \begin{pmatrix} 1 \\ 0 \end{pmatrix} \\
&= \frac{1}{(s+1)^2}.
\end{aligned}
$$

```
% State the state space matrices
A = [-1 0 ; 1 -1];
B = [1 ; 0];
C = [0 1];
D = []; % Empty matrix

% Construct the state space system
system = ss(A,B,C,D);

% Contruct the transfer function
G = tf(system)

% OR after having decided the transfer function
% analytically use
s = tf('s'); % To create the Laplace variable
G = 1/(s+1)^2;
```

2.2

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ -1 & -2 & -3 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} u$$

$$y = \begin{pmatrix} 1 & 0 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

2.3 a.

$$\begin{aligned} \dot{x}_1 &= x_2 \\ \dot{x}_2 &= -\sqrt{x_1} - x_1 x_2 + u^2 \\ y &= x_1 \end{aligned}$$

b. A stationary point implies $\dot{x}_1 = \dot{x}_2 = 0$. From the first equation we directly obtain $x_2 = 0$. Subsequently, the second equation yields $\sqrt{x_1} = u^2$. Hence there are infinitely many stationary points and they can be parametrized through t as $(x_1^0, x_2^0, u^0) = (t^4, 0, t)$.

c. $u^0 = 1$ gives the stationary point $(x_1^0, x_2^0, u^0) = (1, 0, 1)$. We let

$$\begin{aligned} f_1(x_1, x_2, u) &= x_2 \\ f_2(x_1, x_2, u) &= -\sqrt{x_1} - x_1 x_2 + u^2 \\ g(x_1, x_2, u) &= x_1 \end{aligned}$$

Do taylorexpansion of these functions in the stationary point and use only the linear terms to linearize the system. Start by computing the partial derivatives

$$\begin{aligned} &\frac{\partial f_1}{\partial x_1} = 0 && \frac{\partial f_1}{\partial x_2} = 1 && \frac{\partial f_1}{\partial u} = 0 \\ &\frac{\partial f_2}{\partial x_1} = -\frac{1}{2\sqrt{x_1}} - x_2 && \frac{\partial f_2}{\partial x_2} = -x_1 && \frac{\partial f_2}{\partial u} = 2u \\ &\frac{\partial g}{\partial x_1} = 1 && \frac{\partial g}{\partial x_2} = 0 && \frac{\partial g}{\partial u} = 0 \end{aligned}$$

At the stationary point we have

$$\begin{aligned} &\frac{\partial f_1}{\partial x_1}(x_1^0, x_2^0, u^0) = 0 && \frac{\partial f_1}{\partial x_2}(x_1^0, x_2^0, u^0) = 1 && \frac{\partial f_1}{\partial u}(x_1^0, x_2^0, u^0) = 0 \\ &\frac{\partial f_2}{\partial x_1}(x_1^0, x_2^0, u^0) = -\frac{1}{2} && \frac{\partial f_2}{\partial x_2}(x_1^0, x_2^0, u^0) = -1 && \frac{\partial f_2}{\partial u}(x_1^0, x_2^0, u^0) = 2 \\ &\frac{\partial g}{\partial x_1}(x_1^0, x_2^0, u^0) = 1 && \frac{\partial g}{\partial x_2}(x_1^0, x_2^0, u^0) = 0 && \frac{\partial g}{\partial u}(x_1^0, x_2^0, u^0) = 0 \end{aligned}$$

Use the following variable substitution

$$
\begin{aligned}
\Delta x_1 &= x_1 - x_1^0 \\
\Delta x_2 &= x_2 - x_2^0 \\
\Delta u &= u - u^0
\end{aligned}
$$

The linearized system is then

$$
\begin{aligned}
\begin{pmatrix} \Delta\dot{x}_1 \\ \Delta\dot{x}_2 \end{pmatrix} &= \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(x_1^0, x_2^0, u^0) & \frac{\partial f_1}{\partial x_2}(x_1^0, x_2^0, u^0) \\ \frac{\partial f_2}{\partial x_1}(x_1^0, x_2^0, u^0) & \frac{\partial f_2}{\partial x_2}(x_1^0, x_2^0, u^0) \end{pmatrix} \begin{pmatrix} \Delta x_1 \\ \Delta x_2 \end{pmatrix} + \begin{pmatrix} \frac{\partial f_1}{\partial u}(x_1^0, x_2^0, u^0) \\ \frac{\partial f_2}{\partial u}(x_1^0, x_2^0, u^0) \end{pmatrix} \Delta u \\
\Delta y &= \begin{pmatrix} \frac{\partial g}{\partial x_1}(x_1^0, x_2^0, u^0) & \frac{\partial g}{\partial x_2}(x_1^0, x_2^0, u^0) \end{pmatrix} \begin{pmatrix} \Delta x_1 \\ \Delta x_2 \end{pmatrix} + \frac{\partial g}{\partial u}(x_1^0, x_2^0, u^0)\Delta u
\end{aligned}
$$

Where the derivates are given as their value in the stationary point. Using the specific values gives

$$
\begin{aligned}
\begin{pmatrix} \Delta\dot{x}_1 \\ \Delta\dot{x}_2 \end{pmatrix} &= \begin{pmatrix} 0 & 1 \\ -\frac{1}{2} & -1 \end{pmatrix} \begin{pmatrix} \Delta x_1 \\ \Delta x_2 \end{pmatrix} + \begin{pmatrix} 0 \\ 2 \end{pmatrix} \Delta u \\
\Delta y &= \begin{pmatrix} 1 & 0 \end{pmatrix} \begin{pmatrix} \Delta x_1 \\ \Delta x_2 \end{pmatrix}
\end{aligned}
$$

2.4 At the sought operating point it holds that

$$
\begin{aligned}
0 &= x_1^2 x_2 + 1 \\
0 &= x_1 x_2^2 + 1 \\
y &= \arctan\frac{x_2}{x_1} + \frac{\pi^2}{8}
\end{aligned}
$$

which yields $x_1^0 = -1$, $x_2^0 = -1$ and $y^0 = \frac{\pi}{4} + \frac{\pi^2}{8}$. Computation of the partial derivatives now yields

$$
\begin{aligned}
\frac{\partial f_1}{\partial x_1} &= 2x_1x_2 & \frac{\partial f_1}{\partial x_2} &= x_1^2 & \frac{\partial f_1}{\partial u} &= \sqrt{2}\cos u \\
\frac{\partial f_2}{\partial x_1} &= x_2^2 & \frac{\partial f_2}{\partial x_2} &= 2x_1x_2 & \frac{\partial f_2}{\partial u} &= -\sqrt{2}\sin u \\
\frac{\partial g}{\partial x_1} &= \frac{-x_2}{x_1^2 + x_2^2} & \frac{\partial g}{\partial x_2} &= \frac{x_1}{x_1^2 + x_2^2} & \frac{\partial g}{\partial u} &= 4u
\end{aligned}
$$

With the variable substitution

$$
\begin{aligned}
\Delta u &= u - \frac{\pi}{4} \\
\Delta x_1 &= x_1 + 1 \\
\Delta x_2 &= x_2 + 1 \\
\Delta y &= y - \frac{\pi}{4} - \frac{\pi^2}{8}.
\end{aligned}
$$

the linearized system becomes

$$\begin{pmatrix} \dot{\Delta x_1} \\ \dot{\Delta x_2} \end{pmatrix} = \begin{pmatrix} 2 & 1 \\ 1 & 2 \end{pmatrix} \begin{pmatrix} \Delta x_1 \\ \Delta x_2 \end{pmatrix} + \begin{pmatrix} 1 \\ -1 \end{pmatrix} \Delta u$$

$$\Delta y = \begin{pmatrix} \frac{1}{2} & -\frac{1}{2} \end{pmatrix} \begin{pmatrix} \Delta x_1 \\ \Delta x_2 \end{pmatrix} + \pi \Delta u.$$

2.5 Blood Doping

The system dynamics are:

$$R(k) = (1-f) \cdot R(k-1) + r(k-1), \quad R(0) = R_{ref} \tag{2.1}$$

$$r(k) = 0.9 \cdot r(k-1) + u(k), \quad r(0) = f \cdot R_{ref} \tag{2.2}$$

$$u(k) = \begin{cases} 0.025 & \text{if } k = [1-19, 41-100] \\ 0.05 & \text{if } k = [21-40] \end{cases} \tag{2.3}$$

The matrices in the Simulink discrete state space block thus are:

$$A = \begin{bmatrix} (1-1/120) & 1 \\ 0 & 0.9 \end{bmatrix} \tag{2.4}$$

$$B = \begin{bmatrix} 0 \\ 1 \end{bmatrix} \tag{2.5}$$

$$C = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix} \tag{2.6}$$

$$D = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \tag{2.7}$$

$$\tag{2.8}$$

The initial conditions are:

$$x_0 = \begin{bmatrix} 0.25 \cdot 120 \\ 0.25 \end{bmatrix} \tag{2.9}$$

Define epo in the Matlab workspace as:

```
>> epo(:,1)= 1:100;
>> epo(:,2) = 0.025*ones(100,1);
>> epo(20:40,2)= 0.05;
```

Further, use the discrete time setting in the solver in simulink.

2.6 The Simulink model can be seen in Fig. 2.1.

If α becomes large the bacteria outgrow the neuthrophiles and uncontrolled bacterial growth occurs.

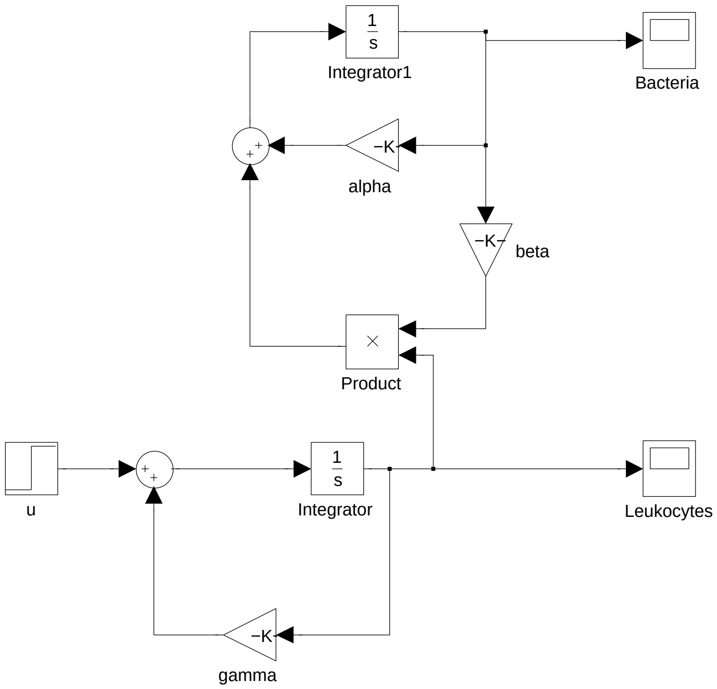


Figure 2.1 Simulink model for the Predator-Prey system

Solutions to Chapter 3. Control in Physiology 1

3.1 a. The transfer function is

$$\begin{aligned}
G(s) &= C(sI - A)^{-1}B + D \\
&= \begin{pmatrix} -1 & 1 \end{pmatrix} \begin{pmatrix} s+2 & 0 \\ 0 & s+3 \end{pmatrix}^{-1} \begin{pmatrix} 5 \\ 2 \end{pmatrix} + 2 \\
&= \frac{2s^2 + 7s + 1}{s^2 + 5s + 6}.
\end{aligned}$$

From the transfer function it is easy to determine the differential equation

$$\begin{aligned}
Y(s) &= G(s)U(s) \\
(s^2 + 5s + 6)Y(s) &= (2s^2 + 7s + 1)U(s) \\
\ddot{y} + 5\dot{y} + 6y &= 2\ddot{u} + 7\dot{u} + u
\end{aligned}$$

b. The transfer function is

$$\begin{aligned}
G(s) &= C(sI - A)^{-1}B + D \\
&= \begin{pmatrix} -2 & 1 \end{pmatrix} \begin{pmatrix} s+7 & -2 \\ 15 & s-4 \end{pmatrix}^{-1} \begin{pmatrix} 3 \\ 8 \end{pmatrix} = \\
&= \frac{2s + 3}{s^2 + 3s + 2}.
\end{aligned}$$

The differential equation becomes

$$\begin{aligned}
Y(s) &= G(s)U(s) \\
(s^2 + 3s + 2)Y(s) &= (2s + 3)U(s) \\
\ddot{y} + 3\dot{y} + 2y &= 2\dot{u} + 3u
\end{aligned}$$

3.2 a. Partial fraction expansion of the transfer function yields

$$G(s) = 2 + \frac{2}{s+3} - \frac{5}{s+2}$$

and by applying the inverse Laplace transform, one obtains the impulse response

$$h(t) = \mathcal{L}^{-1}G(s) = 2\delta(t) + 2e^{-3t} - 5e^{-2t}, \quad t \geq 0.$$

Comment. Because the system matrix was given in diagonal form, another possibility would have been to compute the impulse response as

$$h(t) = Ce^{At}B + D\delta(t) = \begin{pmatrix} -1 & 1 \end{pmatrix} \begin{pmatrix} e^{-2t} & 0 \\ 0 & e^{-3t} \end{pmatrix} \begin{pmatrix} 5 \\ 2 \end{pmatrix} + 2\delta(t), \quad t \geq 0.$$

The step response is computed by e.g. integrating the impulse response

$$
\begin{aligned}
y(t) &= \int_0^t h(\tau)d\tau = \int_0^t \left(2\delta(\tau) + 2e^{-3\tau} - 5e^{-2\tau}\right) d\tau \\
&= 2 + \left[\frac{5}{2}e^{-2\tau} - \frac{2}{3}e^{-3\tau}\right]_0^t \\
&= \frac{1}{6} + \frac{5}{2}e^{-2t} - \frac{2}{3}e^{-3t}, \quad t \geq 0.
\end{aligned}
$$

The step response can also be obtained by the inverse Laplace transform as follows

$$y(t) = \mathcal{L}^{-1}(G(s)\cdot\frac{1}{s}) = \mathcal{L}^{-1}\left(\frac{2}{s} + \frac{2}{s(s+3)} - \frac{5}{s(s+3)}\right) = \frac{1}{6}+\frac{5}{2}e^{-2t}-\frac{2}{3}e^{-3t}, \quad t \geq 0.$$

In MATLAB, the following code can be used

```
% Define the matrices
A = [-2 0 ; 0 -3];
B = [5;2];
C = [-1 1];
D = 2;

% Create the state space representation of the system
system = ss(A,B,C,D);

% Impulse response
impulse(system)

% Step response
step(system)
```

Comment. The $\delta(t)$-part of the impulse response is not depicted when using `impulse` in MATLAB. It would be an infinite spike at $t = 0$.

b. The transfer function has the partial fraction expansion

$$G(s) = \frac{1}{s+1} + \frac{1}{s+2}$$

and the impulse response becomes

$$h(t) = \mathcal{L}^{-1}G(s) = e^{-t} + e^{-2t}, \quad t \geq 0.$$

The step response is thus given by

$$y(t) = \int_0^t h(\tau)d\tau = \frac{3}{2} - e^{-t} - \frac{1}{2}e^{-2t}, \quad t \geq 0.$$

In MATLAB, the following code can be used

```
% Define the transfer function from the result in the previous exercise
s = tf('s'); % Determine frequency variable
G = (2*s+3)/(s^2+3*s+2);

% Impulse response
impulse(G)

% Step response
step(G)
```

3.3 After the Laplace transform, one obtains

$$\begin{aligned} sX &= AX + BU \\ Y &= CX + DU \end{aligned}$$

Solve for X

$$\begin{aligned} (sI - A)X &= BU \\ X &= (sI - A)^{-1}BU \end{aligned}$$

This gives

$$Y = C(sI - A)^{-1}BU + DU = \Big(C(sI - A)^{-1}B + D\Big)U$$

3.4 a. The poles are the solutions of the characteristic equation $s^2+4s+3 = 0$, i.e. $s = -1$ and $s = -3$. The system lacks zeros. The poles are in the left half-plane and the system is therefore stable.

b. The input (an impulse) has the Laplace transform $U(s) = 1$. The output becomes

$$Y(s) = G(s)U(s) = \frac{1}{s^2 + 4s + 3} = \frac{1}{(s + 1)(s + 3)}$$

Inverse Laplace transformation gives

$$h(t) = \frac{e^{-t} - e^{-3t}}{2}$$

The following code results in a plot of the impulse response:

```
s = tf('s');
G = 1/(s^2+4*s+3);
impulse(G)
```

3.5 To be (asymptotically) stable, all eigenvalues of the system matrix A must lie strictly within the left half plane (LHP). I.e. $\text{Re}(\lambda_i) < 0$ $\forall\ i$.

The eigenvalues of A are given by the characteristic equation

$$\det(\lambda I - A) = 0$$

which in this case has two solutions, $\lambda_1 = -i$ and $\lambda_2 = i$. Since the eigenvalues do not lie strictly within the LHP, the system is not (asymptotically) stable.

3.6 a.

$$\begin{aligned} Y &= G_1(U + G_2Y) \\ Y(1 - G_1G_2) &= G_1U \\ Y &= \frac{G_1}{1 - G_1G_2}U \end{aligned}$$

b.

$$\begin{aligned} Y &= G_2(H_1U + G_1U + H_2Y) \\ Y(1 - G_2H_2) &= (G_2H_1 + G_2G_1)U \\ Y &= \frac{G_2H_1 + G_2G_1}{1 - G_2H_2}U \end{aligned}$$

c. Introduce the auxiliary variable Z, being the output of G_1

$$\begin{aligned} Z &= G_1(U + G_3(Z + G_2Z)) \\ Z(1 - G_1G_3 - G_1G_3G_2) &= G_1U \\ Z &= \frac{G_1}{1 - G_1G_3 - G_1G_3G_2}U \\ Y &= \frac{G_2G_1}{1 - G_1G_3 - G_1G_3G_2}U \end{aligned}$$

3.7 a. The output is given by

$$y(t) = |G(3i)| \sin\Big(3t + \arg G(3i)\Big)$$

where

$$|G(i\omega)| = \frac{0.01\sqrt{1 + 100\omega^2}}{\sqrt{1 + \omega^2}\sqrt{1 + 0.01\omega^2}}$$

and

$$\arg G(i\omega) = \arctan 10\omega - \arctan \omega - \arctan 0.1\omega$$

For $\omega = 3$ one obtains $|G(i\omega)| = 0.0909$ and $\arg G(i\omega) = -0.003$ which gives

$$y(t) = 0.0909 \sin(3t - 0.003)$$

b. Reading from the plot yields $|G(3i)| \approx 0.09$ and $\arg G(3i) \approx 0$. We obtain

$$y(t) = 0.09 \sin 3t$$

Solutions to Chapter 4. Control in Physiology 2

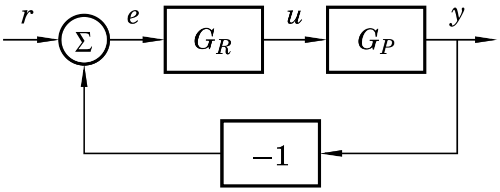
4.1 a. Laplace transformation of the differential equation yields

$$sY(s) + 0.01Y(s) = 0.01U(s)$$

The transfer function $G_P(s)$ is thus given by

$$Y(s) = G_P(s)U(s) = \frac{0.01}{s + 0.01}U(s)$$

b. The block diagram of the closed loop system becomes



The transfer function of the closed loop system becomes

$$G(s) = \frac{G_P(s)G_R(s)}{1 + G_P(s)G_R(s)}$$

c. $G_R(s) = K$, K is a constant, and the transfer function of the closed loop system becomes

$$G(s) = \frac{G_P(s)G_R(s)}{1 + G_P(s)G_R(s)} = \frac{\frac{0.01}{s+0.01}K}{1 + \frac{0.01}{s+0.01}K} = \frac{0.01K}{s + 0.01 + 0.01K}$$

d. The desired and actual characteristic polynomials are the same if all their coefficients match. Identification of coefficients yields

$$0.1 = 0.01 + 0.01K \quad \Leftrightarrow \quad K = 9$$

4.2 a. For the closed loop system it holds that

$$Y(s) = N(s) + G_P(s)G_R(s)R(s) - G_P(s)G_R(s)Y(s)$$

from which one obtains

$$Y(s) = \frac{1}{1 + G_P(s)G_R(s)}N(s) + \frac{G_P(s)G_R(s)}{1 + G_P(s)G_R(s)}R(s)$$

Here we see the transfer function from both inputs, n and r, to y. The one we are interested in is the transfer function from n to y

$$Y(s) = \frac{1}{1 + G_P(s)G_R(s)}N(s) \tag{4.1}$$

b. Inserting $G_P(s) = \frac{1}{s+1}$ and $G_R(s) = K$ into (4.1) yields the relations

$$Y(s) = \frac{s+1}{s+1+K} N(s) =: G_{yn}(s)N(s)$$

In stationarity it holds that

$$\begin{aligned} y(t) &= A|G_{yn}(i\omega)| \sin(\omega t + \arg G_{yn}(i\omega)) \\ &= A\frac{\sqrt{1+\omega^2}}{\sqrt{(K+1)^2+\omega^2}} \sin\left(\omega t + \arctan\omega - \arctan\frac{\omega}{K+1}\right) \end{aligned}$$

c. With $A = 1$ and $K = 1$ the amplitudes of the oscillations

$$A = \sqrt{\frac{1+\omega^2}{4+\omega^2}}$$

For $\omega = 0.1$ rad/s the amplitude become

$$A \approx 0.5$$

while $\omega = 10$ rad/s yields

$$A \approx 1$$

4.3 a. The sensitivity function is given by

$$S(s) = \frac{1}{1+G_P(s)G_R(s)} = \frac{1}{1+\frac{6.5}{(s+1)^3}} = \frac{s^3+3s^2+3s+1}{s^3+3s^2+3s+7.5}$$

b. For $\omega = 0$ rad/s we have $|S(i\omega)| = 1/7.5$. Constant load disturbances are thus damped by a factor 7.5. The sensitivity functions has its maximum value $|S(i\omega)| \approx 10$ at $\omega \approx 1.6$ rad/s.

4.4 Open-loop transfer function:

$$G_o(s) = \frac{K(s+10)(s+11)}{s(s+1)(s+2)} = K\frac{Q(s)}{P(s)}$$

Closed-loop system becomes:

$$G(s) = \frac{G_o(s)}{1+G_o(s)} = \frac{KQ(s)}{P(s)+KQ(s)}$$

Characterstic equation:

$$P(s) + KQ(s) = 0 \quad \Leftrightarrow$$

$$s(s+1)(s+2) + K(s+10)(s+11) = 0 \quad \Leftrightarrow$$
$$s^3 + (3+K)s^2 + (2+21K)s + 110K = 0$$

Requirement for stability is that all coefficients of:

$$s^3 + (3+K)s^2 + (2+21K)s + 110K$$

are positive, and that

$$(3+K)(2+21K) > 110K$$

THe inequality gives

$$K^2 - \frac{15}{7}K + \frac{2}{7} > 0$$

Which is fulfilled for $K > 2$ and $K < 1/7$. Thus, the closed-loop system is stable for:

$$0 < K < \frac{1}{7}$$

and

$$K > 2$$

4.5 The problem is solved using the Nyquist criterium. The open-loop system is given by:

$$G_P(s) = \frac{e^{-9s}}{(1+20s)^2}$$

The phase of the process is:

$$\arg G_P(i\omega) = -9\omega - 2\arctan(20\omega)$$

We want to find the frequency for which the phase is $-180°$. This can be calculated by:

$$-9\omega - 2\arctan(20\omega) = -\pi$$

This equation lacks analytical solutions. After an initial guess and some numerical iterations we get:

$$\omega_0 \approx 0.1$$

Next we determine the gain at this frequency:

$$|G(i\omega_0)| = \frac{1}{1+400\omega_0^2} = 0.2$$

This yields the amplitude margin:

$$A_m = \frac{1}{G(i\omega_0)} = 5$$

Therefore, the gain $K = 5$ is the largest gain we can allow and still maintain stability.

Solutions to Chapter 5. Pharmacokinetics and Tracers

5.1 $C(t)$ is the concentration at time t. The initial condition and balance equation of the system are the following

$$C_0 = 300 \text{ [units/ml]}$$
$$\frac{dC}{dt} = -kC$$

The solution of the differential equation is

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

After 8 days, the concentration is halved. Therefore, if the half-life is stated as $t_{1/2} = 8$, 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,

$$k = \frac{\ln(2)}{t_{1/2}} = \frac{0.6931}{8} = 0.0866 \text{ days}^-1$$

Hence the formula for the concentration is given by

$$C(t) = C_0 e^{-0.0866 \cdot t} \text{ [units/ml]} \tag{5.1}$$

When $t = 7$ [days]

$$C(7) = C_0 e^{-0.0866 \cdot 7} = 163 \text{ [units/ml]}$$

Plot equation (5.1) using `MATLAB`

5.2 Use the same procedure as in exercise 5.1 to get k. Then use the following equation

$$\log(\frac{C_0}{0.4 \cdot C_0}) = \frac{k \cdot t}{2.3}$$

or of course if you use the natural logarithm,

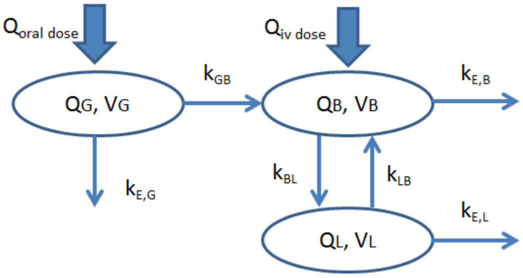
$$\ln(\frac{C_0}{0.4 \cdot C_0}) = k \cdot t$$

It takes approximately 8 days.

5.3 Use the same equation as in exercise 5.2. Set $t = 25$ [days] and $C_0/C = 90/80$ to determine k. Then determine $t_{1/2}$ by using the derived k and $\frac{C_0}{C} = 2$.
The half-life is 147 days.

5.4

a. Start by drawing a diagram of the compartments.



b. The state-space representation only considering the oral input becomes:

$$\begin{bmatrix} \dot{Q}_G \\ \dot{Q}_B \\ \dot{Q}_L \end{bmatrix} = \begin{bmatrix} -(k_{e,G}+k_{GB}) & 0 & 0 \\ k_{GB} & -(k_{e,B}+k_{BL}) & k_{LB} \\ 0 & k_{BL} & -(k_{e,L}+k_{LB}) \end{bmatrix} \begin{bmatrix} Q_G \\ Q_B \\ Q_L \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} Q_{od}$$

$$y = \frac{1}{V_L} \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} Q_G \\ Q_B \\ Q_L \end{bmatrix}$$

where Q_G, Q_B, Q_L [mg/dl], are the drug masses in the gut, body and liver compartment, and Q_{od} [mg/min] is the rate of the orally administered drug.

c. Simulating the system with this oral prescription produces the curve in Fig. 5.1 below. Se code in the end of the solution to this exercise.

d. Simulating the system with this oral prescription every 24 hours produces the blue curve in Fig. 5.2 below. The output oscillates heavily with a 24 hour period. An alternative medication strategy to reduce the oscillations and to keep the concentration more even could be to administer the drug in half the dose every 12 hours instead (green curve).

e. To determine the constant iv-dose we need to augment the original model to incorporate this extra input. The new system, with Q_{iv} [mg/min] as the intravenuous injection rate, becomes:

$$\begin{bmatrix} \dot{Q}_G \\ \dot{Q}_B \\ \dot{Q}_L \end{bmatrix} = \begin{bmatrix} -(k_{e,G}+k_{GB}) & 0 & 0 \\ k_{GB} & -(k_{e,B}+k_{BL}) & k_{LB} \\ 0 & k_{BL} & -(k_{e,L}+k_{LB}) \end{bmatrix} \begin{bmatrix} Q_G \\ Q_B \\ Q_L \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} Q_{od} \\ Q_{iv} \end{bmatrix}$$

$$y = \frac{1}{V_L} \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} Q_G \\ Q_B \\ Q_L \end{bmatrix}$$

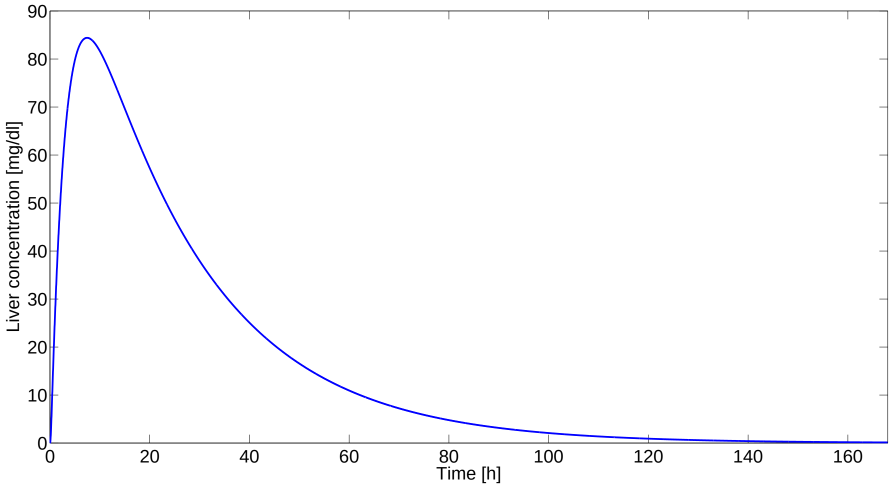


Figure 5.1 Liver concentration at 500 mg dose

To determine the constant dose Q_{iv}^c needed to maintain a steady-state concentration $y^c = 104$ mg/dl, the static gain $G_{YQ_{iv}}(0)$ of the transfer function from input Q_{iv} to the output y is calculated. The transfer function is:

$$G_{YQ_{iv}}(s) = C(sI - A)^{-1}B_2$$

where B_2 is the second column of the B-matrix. A natural starting point is to calculate the inverse of $sI - A$, here called Z. Calculating the inverse to a 3x3 matrix by hand is generally a strenious and boring task. However in this case we can exploit the fact that our B and C matrices only single out one of the elements of Z:

$$G_{YQ_{iv}}(s) = \begin{bmatrix} 0 & 0 & \frac{1}{V_L} \end{bmatrix} Z \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} = \frac{1}{V_L} Z_{32}$$

Now, from the 'book of common results', p. 2, where M_{23} is the matrix retrieved when eliminating row 2 and column 3 from A:

$$\begin{aligned} Z_{32} &= -\frac{|M_{23}|}{|sI - A|} \\ &= \frac{(k_1 + k_e1)k_23}{(s + k_12 + k_e1)((s + k_23 + k_e2)(s + k_32 + k_e3) - k_23k_32)} \end{aligned}$$

$$\begin{aligned} Z_{32}(0) &= \frac{(k_{12} + k_{e1})k_{23}}{((k_{12} + k_{e1}))((k_{23} + k_{e2})(k_{32} + k_{e3}) - k_{23}k_{32})} \\ &= \frac{k_{23}}{k_{23}k_{e3} + k_{32}k_{e2} + k_{e2}k_{e3}} \end{aligned}$$

$$G_{YQ_{iv}}(0) = \frac{1}{V_L} Z_{32}(0) = 396.12$$

and, thus:

$$Q_{iv}^c = \frac{y^c}{G_{YQ_{iv}}(0)} = 0.2625$$

Simulations in Matlab (red curve) in Fig 5.2 below confirms that the constant intravenous injection eliminates the oscillations in liver concentration.

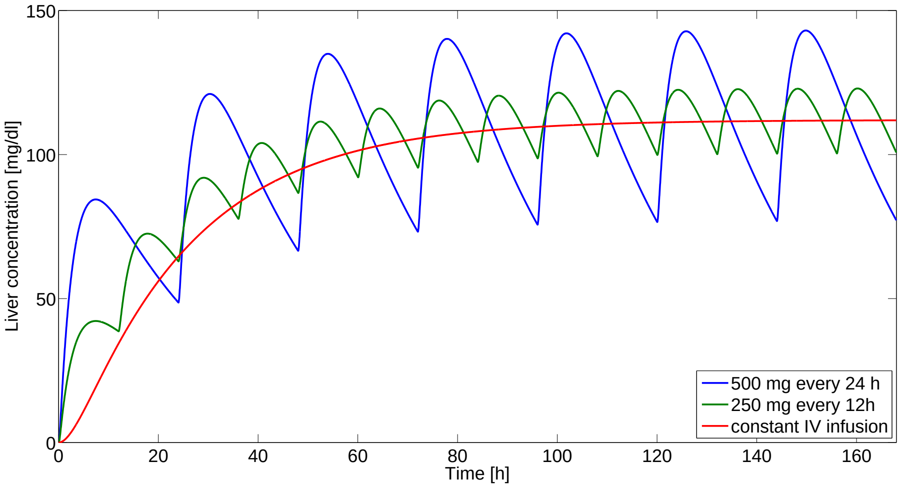


Figure 5.2 Liver concentration at different medication strategies

Code for simulating the system with all three types of input.

```
%————————————
% Parameters
%————————————
ke1 = 0.02;% min^—1
ke2 = 3e—4;% min^—1
ke3 = 8e—4;% min^—1
k12 = 0.1;% min^—1
k23 = 4e—3;% min^—1
k32 = 1e—3;% min^—1
VL = 2.7; %dl
%—————————————
% Define system
%—————————————
A = [—(ke1+k12) 0        0;...
    k12      —(ke2+k23)  k32;...
    0        k23     —(ke3+k32)];
B = [1 0;0 1;0 0]; % First input corresponds to oral and the second to iv
C = 1/VL*[0 0 1]; % Liver concentration [mg/dl]
D = [];
sys = ss(A,B,C,D);
%——————————————
% Setting up the input signals for the different cases
% 1. Oral dose 500 mg/24 hours
u_tab = [100*ones(5,1); zeros(24*60—5,1)]; % 500 mg tablet dissolved
% over 5 min
u = repmat(u_tab,7,1); %repeat the dose
% 2. With half dose and 12 hour interval
```

```
u_tab = [50*ones(5,1); zeros(12*60-5,1)]; % 250 mg tablet dissolved
% over 5 min
u2 = repmat(u_tab,14,1); %repeat the dose
% 3. Constant iv infusion
% Determine iv dose size
static_gain = dcgain(sys);
u_iv_mag = 112/static_gain(2); % U2(0) = Y(0)/G(0);
u_const = u_iv_mag * ones(length(u),1);
%----------------------
% Simulation time
T = [0:1:length(u)-1];
% Initial values
x0 = [0;0;0]; % We assume that we start without any drug in the body
% Simulate
[y_1,T,x] = lsim(sys,[u zeros(size(u))],T,x0);
[y_2,T,x_alt] = lsim(sys,[u2 zeros(size(u))],T,x0);
[y_3,T,x_alt] = lsim(sys,[zeros(size(u)) u_const],T,x0);

figure
plot(T/60,[y_1 y_2 y_3],'Linewidth',2)
legend('500 mg every 24 h','250 mg every 12h','constant IV infusion',...
'Location','SouthEast')
ylabel('Liver concentration [mg/dl]')
xlabel('Time [h]')
set(findall(gcf,'-property','FontSize'),'FontSize',20)
xlim([0 168])
```

Solutions to Chapter 6. Biomechanics

6.1 a. The closed loop system becomes

$$\begin{cases} \dot{x} = (A - BL)x + Bl_r r \\ y = Cx \end{cases}$$

The characteristic equation is thus

$$\det(sI - A + BL) = s^2 + (0.5 + 3l_1)s + 3l_2 = 0$$

We need $(s + 4 + 4i)(s + 4 - 4i) = s^2 + 8s + 32 = 0$. Identification of coefficients yields $l_1 = 5/2 = 2.5, \quad l_2 = 32/3 = 10.7$. The closed loop transfer function is $G(s) = C(sI - A + BL)^{-1}Bl_r$. The stationary gain is $G(0)$ is unity if

$$G(0) = C(-A + BL)^{-1}Bl_r = \frac{3l_r}{32} = 1$$

yielding $l_r = 32/3$.

b. The closed loop system becomes

$$\begin{cases} \dot{x} = (A - BL)x + Bl_r r \\ y = Cx \end{cases}$$

The characteristic equation is thus

$$\det(sI - A + BL) = s^2 + (3 + l_1 + 2l_2)s + 2(1 + l_1 + l_2) = 0$$

We need $(s + 4)^2 = s^2 + 8s + 16 = 0$. Identification of coefficients yields $l_1 = 9, \quad l_2 = -2$. The closed loop transfer function is $G(s) = C(sI - A + BL)^{-1}Bl_r$. The stationary gain is $G(0)$ is unity if

$$G(0) = C(-A + BL)^{-1}Bl_r = \frac{l_r}{4} = 1$$

yielding $l_r = 4$.

This type of controller can only be designed when the system is *controllable*. Information on *controllability* is given in the basic course in control.

6.2 With $x_1 = y$ and $x_2 = \dot{y}$ the system is given by

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ -\dfrac{k}{m} & -\dfrac{c}{m} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} 0 \\ \dfrac{1}{m} \end{pmatrix} f$$

$$y = \begin{pmatrix} 1 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

6.3 Laplace transformation of the differential equation $m\ddot{y}+c\dot{y}+ky=f$ yields

$$(ms^2+cs+k)Y=F$$

and the transfer function is hence

$$G(s)=\frac{1}{ms^2+cs+k}.$$

The poles are $s=-c/2m\pm i\sqrt{k/m-c^2/4m^2}$. A change in k implies a change of the imaginary part of the poles. A change in c affects both the real and imaginary parts.

The poles cannot end up in the right half plane due to physical reasons, since $c\geq 0$ and $m>0$.

6.4 The system can be written as

$$\dot{x}=\begin{pmatrix}0&\omega_0&0\\\omega_0&0&0\\0&0&0\end{pmatrix}x+\begin{pmatrix}a\\0\\b\end{pmatrix}=Ax+Bu$$

With state feedback, $u=-l_1x_1-l_2x_2-l_3x_3=-Lx$, the characteristic equation of the closed loop system becomes

$$\det\big(sI-(A-BL)\big)=\begin{vmatrix}s+al_1&-\omega_0+al_2&al_3\\-\omega_0&s&0\\bl_1&bl_2&s+bl_3\end{vmatrix}=$$
$$=s^3+(bl_3+al_1)s^2+\omega_0(-\omega_0+al_2)s-\omega_0^2bl_3=0$$

Comparison with the wanted characteristic equation

$$(s+\alpha)(s^2+2\zeta\omega s+\omega^2)=s^3+(\alpha+2\zeta\omega)s^2+(2\alpha\zeta\omega+\omega^2)s+\alpha\omega^2$$

gives

$$\begin{cases}l_1=\dfrac{1}{a}\left(\alpha(1+\dfrac{\omega^2}{\omega_0^2})+2\zeta\omega\right)\\ l_2=\dfrac{1}{a\omega_0}(2\alpha\zeta\omega+\omega^2+\omega_0^2)\\ l_3=-\dfrac{\alpha\omega^2}{b\omega_0^2}\end{cases}$$

Solutions to Chapter 7. Glucose and Insulin Dynamics

7.1 Insulin Sensitivity:

$$\partial\dot{G}/\partial G = -(p_1 + X(t)) \tag{7.1}$$
$$S_I = \partial^2\dot{G}/\partial G\partial I = -\partial X(t)/\partial I \tag{7.2}$$

Steady state conditions of insulin means:

$$\begin{aligned}\frac{dX(t)}{dt} &= 0 = -p_2X(t) + p_3(I(t) - I_b), \quad X(0) = 0, I(0) = I_b\\ X(t) &= \frac{p_3}{p_2}(I(t) - I_b)\\ S_I &= -\partial X/\partial I = -\frac{p_3}{p_2}\end{aligned}$$

The experiment is dynamic and steady-state conditions of the insulin level is not valid for most part of the experiment.

7.2 Minimal Model Simulation: The glucose response can be seen in Fig.

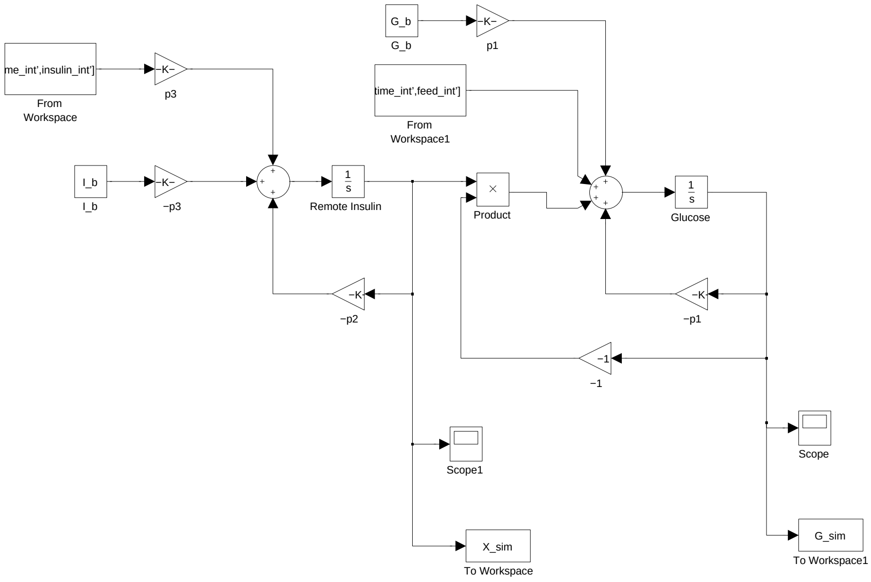


Figure 7.1 Minimal model Simulink model.

2.

7.3 k_{gri} represents the kinetic coefficient between the solid and the liquid compartments of the stomach. In comparison between boiled potatoes and mashed potatoes it seems likely that the mashed potatoes would have a larger value for this parameter, thereby resulting in faster dynamics.

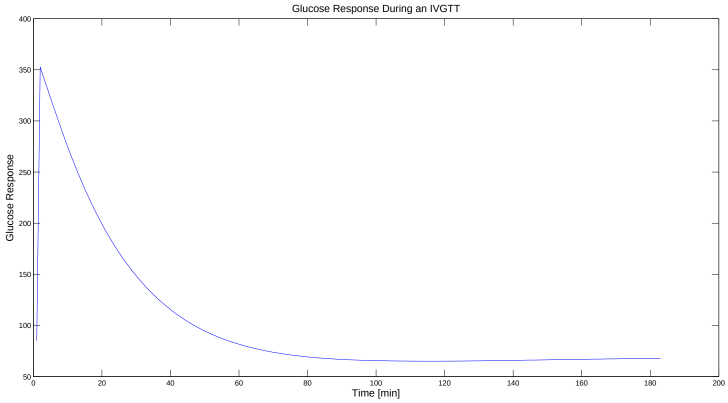


Figure 7.2 Minimal model Simulink model.

7.4 The differential equation becomes:

$$\dot{G}_{ISF}(t) = -k_3 \cdot G_{ISF}(t) + k_3 G_p \tag{7.3}$$

$$L(G_{ISF}) = \frac{k_3}{k_3 + s} L(G_p) \tag{7.4}$$

Thus, $K = 1$ and $\tau = 1/k_3$

Solutions to Chapter 8. The Hodgkin-Huxley model

8.1 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.

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

Ion	**Inner conc. [μM]**	**External conc. [μM]**	**z**
Na^+	12	145	1
K^+	155	4	1
Cl^-	4.2	123	-1

Using the Nernst equation with the given values results in $E_{Na} = 64$, $E_K = -94$ and $E_{Cl} = 86$ [mV].

If T is lowered by 20 degrees all equilibrium potentials will be lowered by $1 - (273 + 25 - 20)/(273 + 25) = 0.0671$, approximately 7 %.

8.2 a. How well a certain ion can pass through the membrane. Larger P_i means that ion i har a large possibility of passing through the membrane, due to many ion-channels being open.

b. If P_{Na} would rise, this would shift the membrane potential closer to the equilibrium potential of sodium (64 [mV]).

8.3

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = -I_{Na} - I_K - I_L + I_{ext}$$

where C_m is the membrane capacitance, I_i is the respective ion currents given by the functions below and I_{ext} is an external applied current.

$$\begin{aligned} I_{Na} &= g_{Na} m^3 h \left(V - E_{Na}\right) \\ I_K &= g_K n^4 \left(V - E_K\right) \\ I_L &= g_L \left(V - E_L\right) \end{aligned}$$

When simulating the behavior of the membrane potential through this differential equation, the notion of the threshold of the neuron describes a non-linear behavior.

8.4 a. $m(t)$ - Na$^+$ activation (of channels)
$h(t)$ - Na$^+$ de-activation (of channels)
$n(t)$ - K$^+$ activation (of channels)

b.

```
% Channel gating kinetics
% Functions of membrane voltage
alpha_m = @(V) 0.1*(V+45)./(1-exp(-(V+45)./10));
beta_m = @(V) 4*exp(-(V+70)./18);
alpha_h = @(V) 0.07*exp(-(V+70)./20);
beta_h = @(V) 1./(1+exp(-(V+40)./10));
alpha_n = @(V) 0.01*(V+60)./(1-exp(-(V+60)./10));
beta_n = @(V) 0.125*exp(-(V+70)./80);

Vsweep = [-90 70];
fplot(alpha_m,Vsweep, 'r-');
hold on
fplot(beta_m,Vsweep, 'r--');

fplot(alpha_h,Vsweep,'g-');
fplot(beta_h,Vsweep, 'g--');
fplot(alpha_n,Vsweep,'b-');
fplot(beta_n,Vsweep, 'b--');
legend('alpha_m', 'beta_m', 'alpha_h', 'beta_h','alpha_n', 'beta_n' , ...
'Location', 'SouthEast');
xlabel('V (mV)');
ylabel('Kinetics Value');
xlim([Vsweep(1) Vsweep(end)]);
title('Channel Gating Kinetics');
```

8.5

```
g_L  = 0.3;
E_L  = -59.387;
C_m = 1;
I_L = @(V) g_L*(V-E_L);

I_ext = @(t) 5.* floor(t ./ 100);

dVdt_leak = @(t, V) (I_ext(t) - I_L(V)) ./ C_m;
[t_leak, V_leak] = ode45(dVdt_leak, [0 500], E_L);

figure
subplot(2,1,1);
plot(t_leak, V_leak, 'k');
title('1B: Leaky Passive Neuron');
ylabel('V (mV)');
xlabel('t (ms)')

subplot(2,1,2);
plot(t_leak, I_ext(t_leak), 'k');
xlabel('t (ms)');
ylabel('I_{ext} (\mu{A}/cm^2)');
ylim([-1 max(I_ext(t_leak))+1]);
```

This simulates a passive membrane, it reacts to the external input by only increasing the membrane potential. It will never create an action potential.

8.6 With states $x_1 = v_{\text{out}}$ and $x_2 = \dot{v}_{\text{out}}$, the system is given by

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ -\frac{1}{LC} & -\frac{R}{L} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} 0 \\ \frac{1}{LC} \end{pmatrix} v_{\text{in}}$$

$$v_{\text{out}} = \begin{pmatrix} 1 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

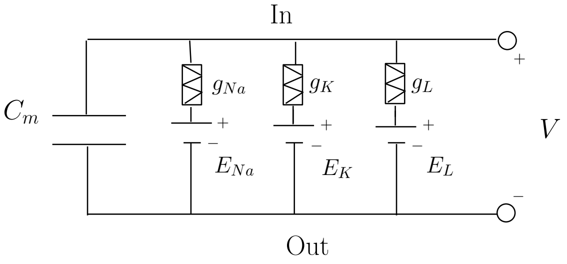


Figure 8.1 Electrical circuit of the HH-model

8.7 $G(s) = \dfrac{1}{LCs^2 + RCs + 1}$