Physiological Models and Computations

Exercises

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1. Introduction to computation and simulation in **MATLAB**

The exercises in this chapter are to familiarize yourself with MATLAB. The mathematics should not be new to you. However, if you are unsure about it, please go back to your Linear algebra and Analysis books and review the material needed.

1.1 Matrix algebra

a. Given the following matrix

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

compute the determinant, inverse of A by hand. Also, describe how to calculate the eigenvalues λ.

b. 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 ; .
Consider matrices

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

c. Calculate $A \cdot B$ and $B^T \cdot A$. What about $B \cdot A$? The transpose of a matrix A is written as `A'`.

d. Give the eigenvalues and eigenvectors of A by the function `eig`. To get information about a function in MATLAB write `help FUNCTION`

e. Give the transpose and the determinant of A. The command for the determinant is `det`.

f. Give the inverse of A.

1.2 Anonymous functions and plots

Consider the function $y(x) = 2x$. It can be written in MATLAB as follows

```
y = @(x) 2*x;
```

To plot this function over an interval, `interval = [−1 3]`, use `fplot(y,interval)`.

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

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

c. Integrate the function over $-4.5 \le x \le -1$. 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`.

1.3   Function script

Open a function template and write the script for a function that takes a matrix as its input and the sum of its diagonal elements as its output. Useful commands: `diag`, `sum` and `size`.

1.4   Solve ordinary differential equations

a. Find the solution $x(t)$ to $dx/dt = cx$, when $x(0) = 1$, by hand.

b. In MATLAB, the solver `ode45` can be used to solve ODEs. For instance, if you would like to solve the ODE given in the previous subproblem with $c = -2$, the code could look as follows

```
c = -2;
x_0 = 1;
timespan = [0 6];
f = @(t,x) c*x;
[T,Y] = ode45(f,timespan,x_0);
```

Then, `[T,Y]` includes the solution to $dx/dt = f$ in the time interval `timespan` for the initial condition `x_0`. Use `help ode45` for more details on this solver works. Perform the computations and plot the solution.

c. Consider the following differential equation

$$\ddot{y} + 7\dot{y} - 3y = 0,$$
$$y(0) = 0,$$
$$\dot{y}(0) = 1,$$

where $\dot{y} = dy/dt$ and $\ddot{y} = d^2y/dt^2$. It can be written as a system of first order differential equations by the use of variable transformation. Consider variables $x_1 = y$ and $x_2 = \dot{y}$. Then $\dot{x}_1 = \dot{y} = x_2$ and $\dot{x}_2 = \ddot{y} = -7\dot{y} + 3y = -7x_2 + 3x_1$, and we can write the system as

$$\dot{x}_1 = x_2$$
$$\dot{x}_2 = 3x_1 - 7x_2$$

with $x_1(0) = y(0) = 0$ and $x_2(0) = \dot{y}(0) = 1$. When the system is on first order, we can use MATLABs solver `ode45` to solve it, as in the previous subproblem. Solve the differential equation in the interval $0 \le t \le 5$. Plot the solution.

2. Biochemical Reactions: equilibrium, steady state and control

2.1   The balance equations governing the dynamics of X, Y and Z in the following reaction

$$X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Y \overset{k_2}{\rightarrow} Z,$$
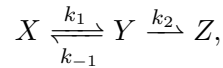
are given as follows,

$$\frac{dx}{dt} = -k_1 x + k_{-1} y,$$
$$\frac{dy}{dt} = k_1 x - (k_{-1} + k_2) y,$$
$$\frac{dz}{dt} = k_2 y,$$

where $x = [X]$, $y = [Y]$ and $z = [Z]$ and parameters k_1, k_{-1}, k_2 are positive and constant. Here, the distribution volume V of each compartment is identical. Thus, we can easily write the balance equations in terms of the concentrations instead of the masses. The mass of each reactant is given by its concentration times V.

**a.** Note that $dx/dt + dy/dt + dz/dt = 0$ and we have that

$$x(t) + y(t) + z(t) = c,$$

where $c > 0$ is some constant. What does this mean?

b. Find the equilibrium of the system in terms of the constant c.

c. Given parameter-values $k_1 = 1$, $k_{-1} = 0.5$, $k_2 = 0.8$, simulate the system with initial values $x_0 = 10$, $y_0 = 0$ and $z_0 = 0$ for 20 time steps. Does the system reach its equilibrium?

d. Assume $k_2 = 0.8(1 + 10/(z - 11)^2)$, i.e., dynamic instead of constant. Simulate the system again, with the given initial condition. How does this change the dynamics? Would you describe this as positive or negative feedback with respect to z?

2.2

a. 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

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} P + E$$
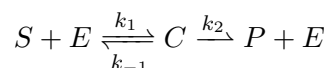
using the following set of parameters; $k_1 = 0.1$, $k_{-1} = 0.01$ and $k_2 = 0.02$, and with the following initial conditions $[S]_0 = 0.15$ [mmol/l], $[E]_0 = 0.01$ [mmol/l], $[C]_0 = 0$ [mmol/l] and $[P]_0 = 0$ [mmol/l].

b. Derive the Michaelis Menten relation for the enzymatic reaction, i.e., determine V_{max} and K_m in

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

when conservation of enzyme and steady state of enzyme and complex is assumed.

c. V_{max} is the maximal rate of the reaction. Can you see why?

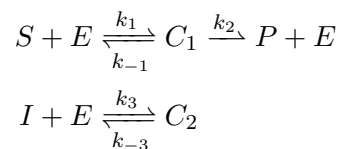**d.** What happens if the initial concentration of the enzyme is doubled?

2.3 The data in Table 2.1 describes the concentration and reaction rates of a chemical process.

a. Plot the velocity versus the Concentration. 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?

b. Plot the inverse of the velocity versus the inverse of the concentration. This plot is commonly referred to as a Lineweaver-Burk plot. Can you give some rough estimates of V_{max} and K_m from this graph?

Table 2.1 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

2.4 Competitive 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:

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

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

where I is the inhibitor.

We can derive the following relationship for the reaction velocity of the product reaction, considering steady-state conditions for the enzyme E

and enzyme complexes C_1 and C_2 and preservation of the total enzyme content, i.e., $[E] + [C_1] + [C_2]$:

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

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

a. Consider $[I]$ to be bounded. Is V_{max} still the maximal reaction rate?

b. Consider $[S]$ to be bounded. What happens if $[I] \to \infty$?

c. What happens if $[I] = 0$?

d. Describe in your own words how the inhibitor I regulates the enzymatic reaction.

3. Compartment models and simulation in **Simulink**

3.1 Consider the balance equations

$$\frac{dx_1}{dt} = -k_1 x_1 + k_{-1} x_2,$$
$$\frac{dx_2}{dt} = k_1 x_1 - (k_{-1} + k_2) x_2,$$
$$\frac{dx_3}{dt} = k_2 x_2 - v,$$
$$y = x_2 / V_2$$

where x_1, x_2 and x_3 are the masses of the quantities of the respective compartments, with distribution volumes V_1, V_2 and V_3. Furthermore, y is a measurement while k_1, k_{-1}, k_2 and v are positive constants. The constant v is the degradation rate of x_3. Draw a schematic of the three-compartment model.

3.2 Consider the schematic of a compartmental model as below
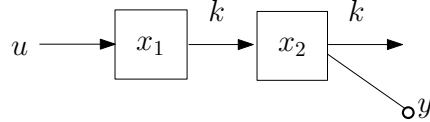
where the distribution volume of the two compartments are both equal to 1 dl, and omitted from the schematic, i.e., the mass and concentration has identical values. Furthermore, y is a measurement of the concentration in compartment 2. The mass x_1 is increased by u and linearly transformed into x_2 with rate k. Furthermore, x_2 is decreased linearly with rate k.

a. The rates are given in per milli second while masses and concentrations are given in mg and mg/dl. Give the units for x_1, x_2, u, y, k, dx_1/dt and dx_2/dt.

b. Give the balance equations of the system.

c. Determine the equilibrium when $u = u^0$.

d. Write the balance equations on the compact form

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

where A, B, C, D are possibly matrices, $x = [x_1 \; x_2]^T$ is the state of the system, u is the input and y is the output (measurement). This is possible as the system is linear.

3.3 Given $k = 1$, determine the transfer function of the system in Problem 3.2 by using functions `ss` and `tf` from the control toolbox in MATLAB. Simulate the system given $u(t) = 1$ for $0 \le t \le 8$ with `lsim`.

Type `help lsim` to get information about the function. What does $y(t)$ tend to as $t \to \infty$?

In the previous exercises of this chapter we treated linear systems. However, nonlinear phenomena is common in physiology (e.g., the enzyme reactions treated in the previous chapter). The analysis of nonlinear systems is more involved than that for linear systems. However, to simulate the systems behavior is often a very useful tool, as we have seen through the use of `ode45`. In this last part of the exercise, we will instead use SIMULINK for simulation, which is a buildt in graphical simulation tool in MATLAB.

3.4 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. Get familiar with some of the blocks that will be used in the course; `From Workspace`, `To Workspace`, `Constant`, `Scope`, `Step` and `Sine Wave`. You can connect two blocks by their connection spots. 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.

3.5 Investigate the bacterial growth in a jam pot. Assume that the fraction of bacteria is increasing proportional to the existing fraction of bacteria x and decaying proportional to x^2. This gives the following differential equation for the dynamics

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

where $b, p > 0$ are the birth and death rates.

a. Determine the equilibria of the system.

b. Assume $x(0) = 0.8$ [fraction of bacteria], $b = 1$ [1/hour] and $p = 2$ [1/(f. o. bac.·hour)]. Use SIMULINK to simulate the behavior of this system. Use the Library Browser to find appropriate blocks and drag them into the model sheet, see the figure below.
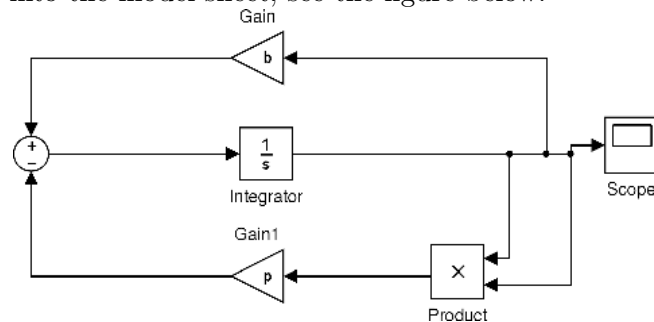
p and b can be defined in the current workspace. You simulate the system by pressing the play button. In the block `Scope`, you can then

view the time trajectory of x. Go to display → blocks and check "Sorted Execution Order". This will numerate the blocks in the order in which they are first activated.

c. Start the system at $x(0) = 0.1$ and $x(0) = 0$, repsectively. What happens with the fraction of bacteria as $t \to \infty$? Compare the behaviour to that simulated in the previous subproblem as well as to the equilibria of the system.

3.6 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].

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

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

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 $u(t) = 10$ for $t \geq 0$ and zero otherwise, i.e., a step with magnitude 10. What happens if α is large (> 8)?

4. Linear systems and linearization

4.1   In this problem we will represent a linear system in two different ways. Consider

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

where u and y are the input and output, respectively. For the first representation, determine the transfer function from u to y via the Laplace transform. For the second representation, choose $x_1 = y$, $x_2 = \dot{y}$ and $x_3 = \ddot{y}$ as the states of the system and rewrite the dynamics as a system of first order differential equations. What is the main difference between these two representations? In the following chapters you will learn when and how to use which representation for analysis of linear systems.

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

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

by means of the Laplace transform.

4.3   Determine the transfer functions and give differential equations, describing the relation between input and output for the following systems. Also, determine the poles of the systems by means of solving $\det(sI - A) = 0$.

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.

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

4.4   Determine the impulse and step responses of the systems in assignment 4.3 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 $t \geq 0$ and $u(t) = 0$ for $t < 0$. Consider impulse and step in MATLAB.

In the previous exercises of this chapter we treated linear systems. The analysis of nonlinear systems is more involved than that of linear systems. However, linearizing the nonlinear dynamics around a stationary point can give us an approximation of the system's behavior locally.

4.5   Approximate the functions $f(x) = (x - 2)^2 - 9$ with a first order Taylor series expansion around $x = 5$. Plot $f(x)$ as well as the Taylor series expansion around $x = 5$. Can you describe how $f(x)$ is approximated?

4.6   Consider the following system

$$\dot{x} = (x - 2)^2 - 9 + u^2$$
$$y = x.$$

a. Find the stationary points (x^0, u^0) for $x^0 = 4$.

b. Linearize the system around the stationary point with positive u^0.

4.7   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 (equilibria) (x_1^0, x_2^0, u^0) of the system parametrized in u^0.

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

4.8   The following differential equations describe the dynamics of the epidemiological model denoted the SIS-model

$$\frac{dS}{dt} = -\beta I S + \gamma I$$
$$\frac{dI}{dt} = \beta I S - \gamma I$$

where $S(t)$ is the fraction of susceptible people and $I(t)$ is the fraction of infected people, at time $t \geq 0$. Furthermore, $\beta > 0$ and $\gamma > 0$ are positive constant parameters and the initial state is given by $S(0) = 0.8$ and $I(0) = 0.2$.

a. Show that $S(t) + I(t) = 1$ for all times $t \geq 0$.

b. Find the stationary points of the SIS-model, denoted (S^0, I^0).

c. Linearize the system around the stationary point(s).

5. Stability of linear systems, and pharmacokinetics

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

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

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

   c. Calculate the step response by hand and plot it in `MATLAB`

5.2   Determine the stability of the systems below. Compare their impulse responses.

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

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

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

5.3   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 5.1. Determine the output $y(t)$ by using the Bode plot instead.

5.4   Consider the linearization of the SIS-model around the two stationary points. Determine for which γ and β each system is marginally stable, i.e., has poles with real-value less than or equal to zero. Can they both be stable at the same time?

5.5   Determine the dissolution rate $\dot{q}$ of a drug with diffusion properties $d = 0.1$, $A = 1$, $D = 0.5$, $C_s = 0.2$ and $C_b = 1$ using the Noyes-Whitney equation.
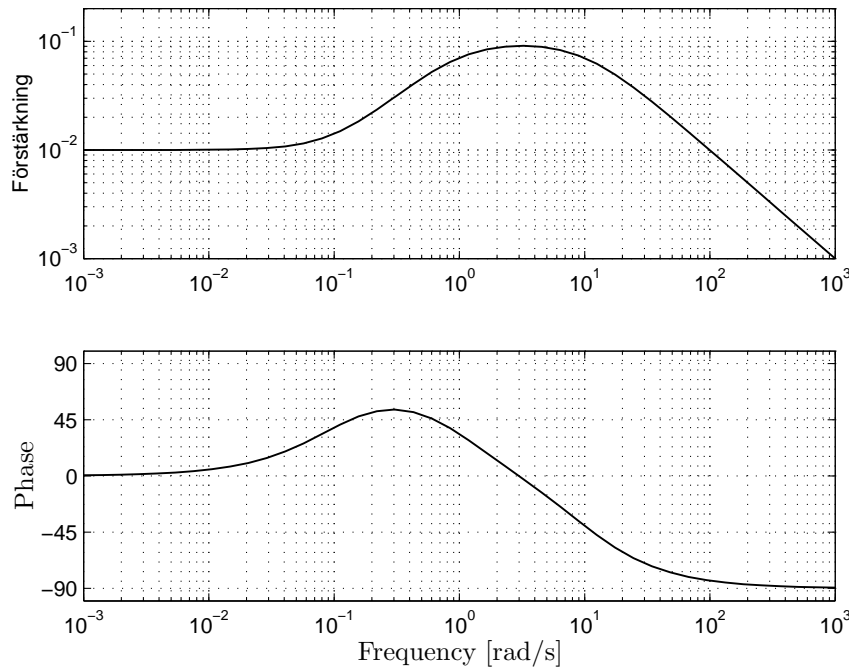
Figure 5.1   The Bode plot in assignment 5.3.

5.6   In plasma, the half-life of a penicillin solution of 300 units/ml is 8 days. Assume the drug exhibits linear pharmacokinetics as it is eliminated from plasma, i.e., the concentration $C(t)$ is governed by the dynamics $\dot{C} = -kC$, where k is some constant.

   a. Are the dynamics stable?

   b. What will the concentration in plasma be in 7 days?

   c. Plot the concentration over time.

   d. How long will it take for the concentration to drop to 40% of the initial concentration?

   e. When stored, the half-life is different from that in plasma. Consider a penicillin solution that 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 these storage conditions?

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

   a. In Table 5.1, the parameters for the pharmakokinetics are given. Draw a 3-compartment model for the route of the drug, including absorption and elimination. The compartments to be used are the gut, liver, and the body. The body represent a lumped compartment for the extra- and intracellular fluid of the body excluding the liver and gut.

   b. Set up a state-space representation of the model with the drug concentration in the liver as output using the parameter notation in Table 5.1.

Table 5.1 Parameters for drug model in Problem 5.7

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}]

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. Add more doses with a 24 hour interval, i.e., a new pill 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, however, at the same mean concentration value?

e. How large should a constant intravenuous dose be, injected in the body compartment, to achieve a steady-state liver concentration of 112 mg/dl?

6. Feedback in linear systems, and tracer kinetics

6.1 Assume that the amount of 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. Determine the transfer function from u to y.

b. There is a regulatory circuit within the cell which regulates the substrate content y via changing the intake, i.e., u. It does this by comparing the current value of y to a reference value r and scaling this difference with a constant K, as follows

$$u = K(r - y).$$

Draw the block-diagram of this feedback circuit.

c. Determine the transfer function of the closed-loop system.

d. Determine the values of K for which the closed-loop system is stable.

e. Given $K = 10$, determine the static gain of the closed-loop system. What does this value tell you?

6.2

a. Repetition of complex numbers: Recall that a complex number z can be written on polar form, $z = Ae^{j\phi}$. A is the amplitude and ϕ is the argument. What happens in the complex plane if ϕ is changed to $\phi + 90°$?

b. What is the amplitude- and phase-margin of the system with Nyquist plot as in Fig. 6.1? The system is stable.

Hint: The phase-margin is the maximum phase-delay the system can withstand and still be stable. A phase-delay of ϕ can be represented as multiplication by $e^{-j\phi}$.

6.3 Given infusion u, the tracer concentration y is given by

$$Y(s) = \frac{e^{-2s}}{(1 + 10s)^2}U(s)$$

where e^{-2s} models a time delay.

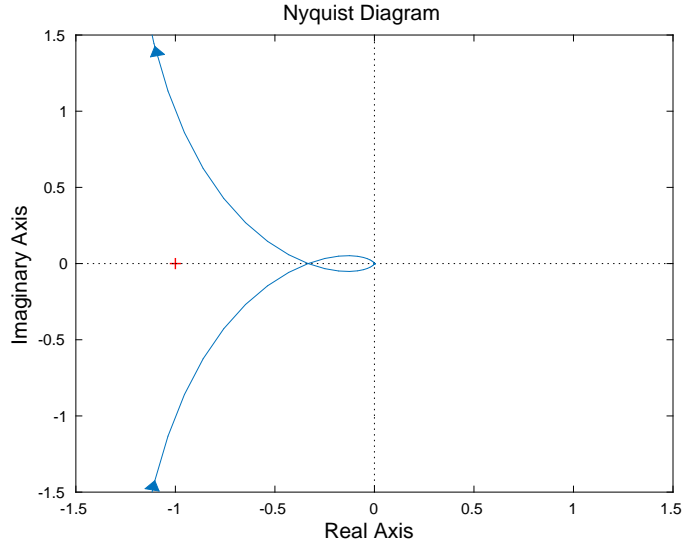**a.** Write down a state space representation of the system from control input u to output y.

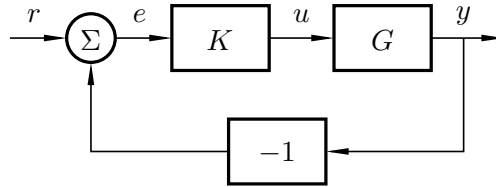**Figure 6.1** Nyquist plot for the system in problem 6.2.

Figure 6.2 Block diagram of process G in negative feedback with controller K

b. If a proportional controller is used, i.e., $u = Ky$, to regulate the tracer concentration, approximately how large may the gain constant K become before the system becomes unstable?

The phase margin is the phase shift that the system can sustain without becoming unstable.

6.4 Consider Problem 6.1. Determine K such that the closed-loop system obtains the characteristic polynomial

$$s + 0.1.$$

What does this imply for the pole(s) of the closed-loop system? Instead, determine K such that the closed-loop system obtains the characteristic polynomial

$$s + 1.$$

Compare the behavior of the two closed-loop systems when the reference is a step normalized by the static gain of the given closed-loop system. Which system is faster at tracking the reference? Relate this to the poles.

6.5   Consider the block diagram in Figure 6.2. Consider the process

$$G(s) = \frac{(s+10)(s+11)}{s(s+1)(s+2)}$$

to be controlled by a controller K as in which values of K is the closed-loop system stable?

6.6   The tracer concentration y given infusion u is governed by

$$Y(s) = \frac{5.3}{2.8+s}U(s).$$

What will the concentration be as time goes to infinity when the infusion is at constant rate u_0?

7. Metabolism, glucose and insulin kinetics

7.1   Assume that your intake of food for one day is 3000 kcal. 2241 kcal are consumed through thermogenesis and energy expenditure at rest. How long can you run if it requires 11.3 kcal/min at a pace of 0.17 km/min without lowering your stored energy?

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

$$\dot{q}_{sto1}(t) = -k_{gri} \cdot q_{sto1}(t) + u(t)$$
$$\dot{q}_{sto2}(t) = k_{gri} \cdot q_{sto1}(t) - k_{empt} \cdot q_{sto2}(t)$$
$$\dot{q}_{gut}(t) = -k_{abs} \cdot q_{gut}(t) + k_{empt} \cdot q_{sto2}(t)$$
$$R_a(t) = \frac{k_{abs}}{V} \cdot q_{gut}(t)$$

where $u(t)$ is the amount of ingested carbohydrates, q_{sto1} is the solid stomach compartment, and q_{sto2} represents the liquid phase. Furthermore, q_{gut} is the glucose mass in the intestine and $R_a(t)$ is the appearance rate of glucose in the blood. The parameters are: k_{gri} the rate of grinding, k_{empt} the rate constant of gastric emptying, k_{abs} the rate constant of intestinal absorption and V the distribution volume of the blood. They are all positive and constant.

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

b. Can the system become unstable with positive parameter values?
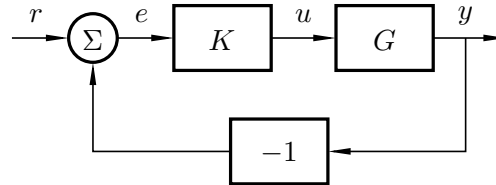
c. Consider the parameter values $k_{gri} = k_{empt} = k_{abs} = 1$ and $V = 1$. You will now analyze the behavior of the closed-loop above where r is a reference signal and $e = r - y$ is the error signal. K is a dynamic controller to be designed and G is the system from u to y stated above. We will design K to be a PID-controller, where P stands for proportional, I stands for integral and D stand for derivative. The controller calculates $u(t)$ based on these three different terms

$$u_P(t) = Ke(t), \quad u_I(t) = K_i \int_0^t e(\tau)d\tau \quad \text{and} \quad u_D(t) = K_d\dot{e}$$
$$\rightarrow u(t) = u_P + u_I + u_D$$

where parameters K, K_i and K_d can be tuned. The proportional part u_P gives a control signal that is directly proportional to $e(t)$. The integral term u_I gives an accumulated response to $e(t)$ that is persistent.
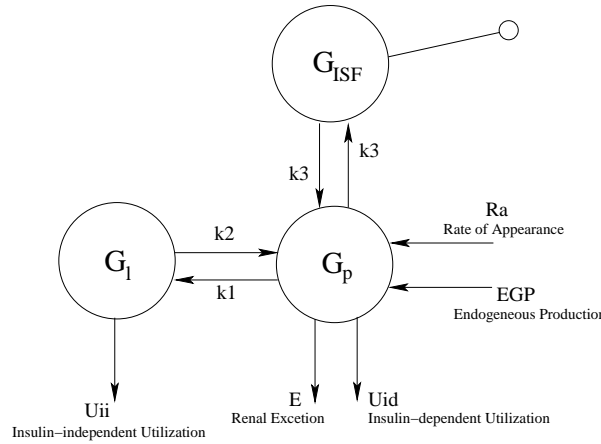
Figure 7.1   Interstitial and Plasma Glucose compartment kinetics.

Finally, the derivative term u_D gives a contribution that is acting on the direction of $e(t)$, thereby trying to foresee the development and act in advance. The Laplace transform of the PID-controller is given by

$$K(s) = K + K_i \frac{1}{s} + K_d s.$$

Given the parameter values of the controller in the table below, write down the closed-loop systems and determine their static gains. What do the static gains imply for the impact of a reference signal r as $t \to \infty$?

| Case Parameter	K	K_i	K_d
P	3.6	0	0
PI	3.2	1.7	0
PID	4.3	3.5	1.3

7.3   Subcutaneous Delay: Consider the compartment model in Fig. 7.1. Write down the balance equation governing the interstitial glucose value, G_{ISF}. Assume that $G_P(t) = sin(\omega t)$. Determine what the amplitude of G_{ISF} becomes for $\omega = 1$ and $\omega = 100$, when $k_3 = 10$. Plot the bode diagram of the system from G_P to G_{ISF}. What can you say about the permeability of signals G_P with different ω?

8. State feedback, biomechanics and posture control

8.1 Given the serial Hill model. What force is given when the muscle contracts 0.1 length units and $K_S = 1$, $K_P = 2$ and $\eta = 0.3$?

8.2 *Viscoelastic model of muscle* 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 $k > c^2/4m$. We denote the translation of the mass from its equilibrium position by y. The force equation gives
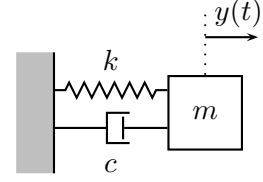
$$m\ddot{y} + c\dot{y} + ky = 0$$

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

b. Determine the poles of the system in terms of m, k and c. Can the poles end up in the right half plane, i.e., can the system become unstable?

8.3 Consider the following simplified model for digestion

$$\dot{q}_{int} = -k_{abs}q_{int} + C(t)$$
$$\dot{q}_{blo} = 0.9 \cdot k_{abs}q_{int} - k_{dec}q_{blo}$$
$$y = \frac{1}{V}q_{blo}$$

where q_{int} [g] is the glucose mass in the stomach and intestines while q_{blo} [g] is the glucose mass in plasma. The input $C(t)$ [g/min] is the rate of ingested carbohydrates. Parameter k_{abs} [min^{-1}] is the intestinal absorption rate while k_{dec} [min^{-1}] is the decay-rate of the glucose mass in the blood (due to energy demand from the cells of the body). The measurement y [g/l] is the glucose concentration in plasma, where V [l] is the distribution volume of plasma. The parameter values are $k_{abs} = 10$, $k_{dec} = 5$ and $V = 5$.

a. Determine the transfer function of the system from C to y as well as its pole(s).

b. What is the static gain of the system? Explain what it means in your own words.

c. We will now use the measurement, i.e., y, in feedback. Consider the control law $C(t) = K(r - y)$ where r is the reference. That is, we determine the carbohydrate intake based on the deviation of the glucose concentration in plasma from the reference value. What are the pole(s) of the closed-loop system from r to y given K?

d. Assume instead that we are able to directly measure both q_{int} and q_{blo}. Consider the control law $C(t) = r - l_1q_{int} - l_2q_{blo}$. What are the pole(s) of the closed-loop system from r to y given l_1 and l_2?

e. Assume that you are free to choose K, l_1 and l_2. Given which of the two control approaches do you have more flexibility in placing the poles?

8.4   Consider the block-diagram in Fig. 8.1. This is an illustration of the state-feedback scheme. Determine a control law $u = l_r r - Lx$ for

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.
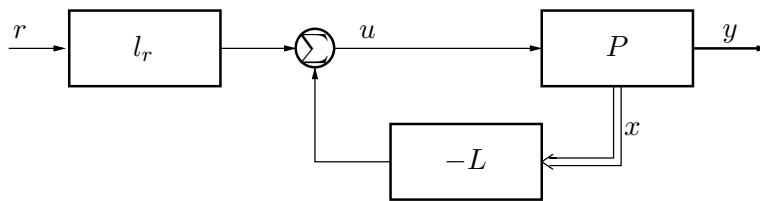

Figure 8.1   The system in Problem 8.4.

8.5   When walking, the body is kept in upright position by a 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. 8.2, a schematic of this inverted pendulum is given.
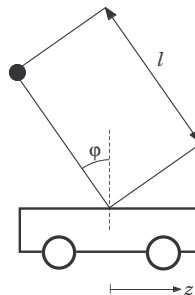

Figure 8.2   Inverted pendulum in exercise 8.5.

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

$$\frac{dx_1}{dt} = \omega_0 x_2 + au$$

$$\frac{dx_2}{dt} = \omega_0 x_1$$

$$\frac{dx_3}{dt} = bu$$

where the state variables

$$x_1 = k_\varphi \frac{d\varphi}{dt}$$

$$x_2 = \omega_0 k_\varphi \varphi$$

$$x_3 = k_z z$$

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 $-\omega\left(\zeta \pm i\sqrt{1-\zeta^2}\right)$.

9. The Hodgkin-Huxley model

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

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?

9.2   Below is the Goldman Equation, which describes the membrane potential V at certain ion concentrations and permeabilities.

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

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

a. How would you describe permeability?

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

9.3   In the Hodgkin and Huxley model, the dynamics of the gating variables m, n and h are given by:

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$
$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$
$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

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

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

a. 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].

b. What do the gating variables correspond to physiologically?

9.4 Consider the following simplified model for the membrane potential:

$$C_m \frac{dV}{dt} = -g_L(V - E_L) + I_{ext}$$

It only takes into account the leakage and external currents. Solve the differential equation in MATLAB when the external current starts at 0 and increases by 5 $[\mu A/cm^2]$, 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 $C_m = 1[\mu F/cm^2]$. What happens? Compare it to the simulated behavior of the full Hodgkin and Huxley model shown on the Lecture. Can you make it create an action potential?

9.5 The Hodgkin and Huxley model is derived upon the idea of seeing the membrane of the neuron as an electrical circuit, see Fig. 9.1. We will now simulate the behavior of its different electrical components.
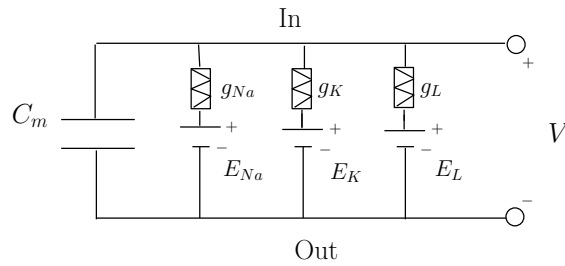

Figure 9.1 Electrical circuit of the HH-model

a. Isolate the capacitance C_m and assume it is fed by a current $i(t)$. The voltage $V(t)$ across the capacitance is then governed by

$$C_m \frac{dV}{dt} = i(t).$$

Given $C_m = 1$, simulate the potential when $i(t) = \sin(2t)$. Describe what happens to the voltage during the course of one period of the current.

b. Isolate the conductance g_L and potential E_L. Assume there is a voltage V across them. The current that runs through the conductance is then given by

$$i_L = -g_L(V - E_L).$$

Assume that $g_L = 0.3$ and $E_L = -59$. Determine the current i_L for $V \in [-90, 70]$. What happens to the direction of the current over this voltage span?

c. The currents through the conductances for Na and K depend in a non-linear fashion on the voltage V. However, if we denote the currents i_{Na}, i_K and i_L we can now determine the current that is fed to the capacitance by Kirchoff's law, i.e., $i(t) = i_{Na} + i_K + i_L$. In the electrical circuit in Fig. 9.1 we have excluded the external current. However it can be included as a current source in parallel with the capacitance. Write down the dynamics for the full circuit.

10. Blood flow control and heart rate dynamics

10.1 What is the cardiac output and index when the stroke volume is 0.05 l, the heart rate is 60 bpm and the body surface area is 1.6 m^2?

10.2 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, i.e., the pump rate:

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

If a proportional controller is used, i.e., $u = Ky$, approximately how large may the gain constant K become before the system becomes unstable?

10.3 Arterial 4-element Windkessel Model: The model is given by the following set of equations:

$$\frac{dp}{dt} = -\frac{1}{RC}p + \frac{1}{C}\dot{q}_i$$
$$\frac{d\dot{q}_L}{dt} = -\frac{R_a}{L}\dot{q}_L + \frac{R_a}{L}\dot{q}_i$$
$$p_a = p - R_a\dot{q}_L + R_a\dot{q}_i$$

  a. Describe what the different elements of the model represents.

  b. Give the transfer function.

  c. Calculate the static gain.

  d. Calculate the poles of the system.

  e. Can the system become unstable given positive parameter values?

10.4 Consider the Van der Pol (VDP) model

$$\ddot{y} - \nu(1 - y^2)\dot{y} + y = 0$$

where ν is a positive constant. It can be used as a simple model for the electrophysical behavior of the heart. Then, y is the electrical activity of the heart.

  a. Compare this model to the viscoelastic model in exercise 7. What is the main difference?

b. Define $c(y) = -\nu(1 - y^2)$ as the function multiplied by $\dot{y}$. Plot this function for $\nu = 1$ over the interval $-2 \leq y \leq 2$. This illustrates the nonlinear damping coefficients dependece on y. Can it take both positive and negative values?

c. Simulate the system

$$\ddot{y} + c\dot{y} + y = 0$$

for $c = 0.1$ and $c = -0.1$, given the initial condition $y(0) = -0.1$, $\dot{y}(0) = 0.1$. What is the difference in behavior with negative and positive c?

d. Choose $x_1 = y$ and $x_2 = \dot{y}$ and write the VDP model on state space form.

e. Simulate y for $\nu = 0.1$ and $\nu = 10$ over 200 time units and initial condition $y(0) = -0.1$, $\dot{y}(0) = 0.1$. What is the difference in behavior?

f. Consider $\nu = 10$. Initialize the system at $y(0) = 3$, $\dot{y}(0) = 0.1$ and simulate. What is the difference in behavior compared to the previous subproblem?

g. Linearize the system around its stationary point.

h. Is the linearized system stable?

11. State estimation and System Identification

11.1 In Lecture 9, a model of the ventilation system based on an electrical analogy may be found. Here, the model is instead derived from a mechanical viewpoint. The respiratory tract (nasal cavity, pharynx, trachea, bronchi) and the lungs (the total collection of alveolars) can be thought of as a tube connected to a (single) flexible membrane of volume V. Considering the gas flow to be both incompressible and isotermic, we know from fluid mechanics that the (laminar) flow rate $\dot{V}$ in a tube is proportional to the pressure difference between the pipe ends:

$$R\dot{V} = (p_{ext} - p_{lung})$$

where R is a constant representing flow resistance, p_{ext} is the external pressure and p_{lung} is the average lung pressure.

The force balance across the lung cavity with compliance C gives:

$$p_{lung} = V/C$$

and, thus:

$$V(s) = \frac{C}{1 + RCs} \cdot p_{ext}(s)$$

We are now to perform some experiments to try and derive values of the constants R and C for a specific set of lungs. Assume that we are able to measure the volume of the lungs $V(t)$ and are able to change the external pressure ρ_{ext}.

a. Our first test is to increase the external pressure by a unit step. The result from the experiment is given below. Determine C from this plot.
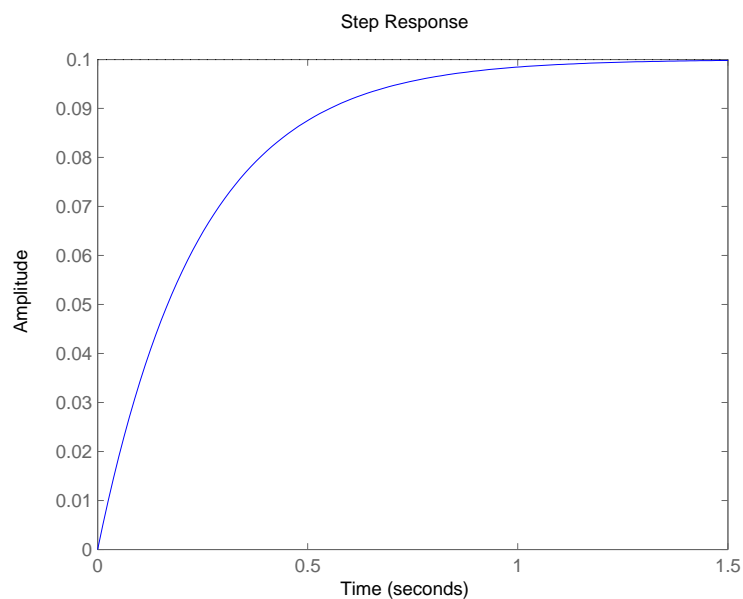
b. For our second test we used $\rho_{ext}(t) = sin(t)$ and got the response below. Can you determine R (given that you know the value of C from the previous subproblem) from this response?
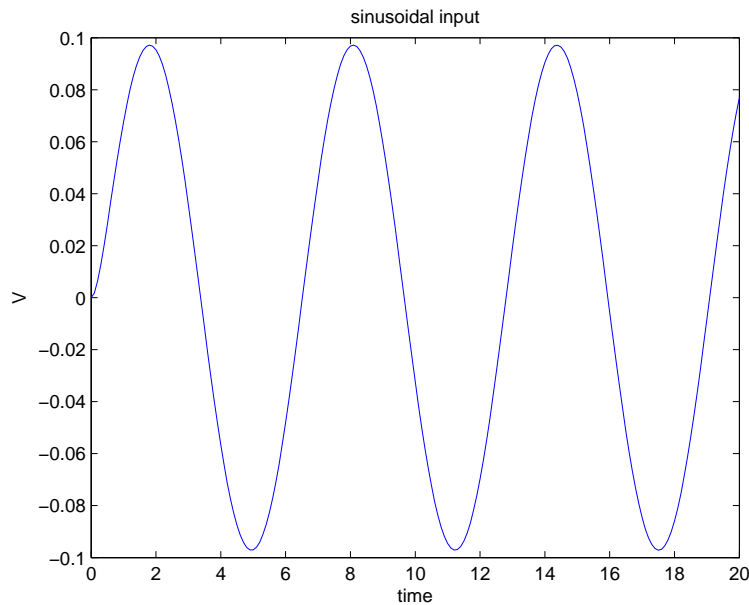
11.2   The following data points (x, y) were derived from an experiment:

x	y
1	3
3	5
5	6
7	7

The underlying relation between x and y is assumed to be given as $y = a + bx$, where a and b are some constants.

a. Estimate values of a and b by the least squares method.

b. Check your estimate in MATLAB by plotting the points and the polynomial obtained.

c. The true parameter values are $(a, b) = (2.7, 0.6)$. Plot the true function $y(x)$ and compare it to your fit.

d. We obtained information that the data point $(x, y) = (5, 6)$ is invalid due to problems in the experimental setup. How does the estimates change when this data point is no longer valid?

11.3

a. Consider the following model,

$$\dot{q}(t) = -kq(t) + u(t)$$
$$y(t) = q(t)/V$$

where $u(t) = D\delta(t)$ is a bolus injection at time $t = 0$ of a drug and $y(t)$ is the measured drug concentration. V is the volume of the compartment and k is the rate constant. Are the parameters k and V identifiable?

b. Consider the following two compartment model where a bolus injection is given at time zero and where the measured variable is the concentration of drug in plasma in compartment 1. The equations describing the model are,

$$\dot{q}_1(t) = -(k_{01} + k_{21})q_1(t) + u(t)$$
$$\dot{q}_2(t) = k_{21}q_1(t)$$
$$y(t) = \frac{q_1(t)}{V_1}$$

where $q_1(0) = q_2(0) = 0$ and V_1 is the volume in compartment 1. Are you able to determine the three unknown parameters k_{01}, k_{21} and V_1? Compare with part **a** of this exercise.

11.4 Consider the data set of paired data in the table below.

u	y
1	6
2	17
3	34
4	57

Adopt the following model

$$y = a + bu + cu^2$$

and

a. estimate the parameters a, b and c by the least squares method.

b. Add noise to some of the measurements y by MATLABs function `randn`. How does this affect the estimates of the parameters?

11.5 Consider the simplified model for digestion studied earlier.

$$\dot{q}_{int} = -q_{int} + u(t)$$
$$\dot{q}_{blo} = 0.9q_{int} - 2q_{blo}$$
$$y = q_{blo}$$

where q_{int} is the glucose in the stomach and intestines and q_{blo} is the glucose mas in plasma. The input $u(t)$ is the rate of ingested carbohydrates.

a. take $x_1 = q_{\text{int}}$ and $x_2 = q_{\text{blo}}$. Write the system on the standard state space form,

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

b. You have access to the input $u(t)$ and the output $y(t)$. However, you want to estimate the states as well. Someone suggests the following estimate $\bar{x}$ of the states

$$\dot{\bar{x}} = A\bar{x} + L(y - C\bar{x}).$$

Let $\tilde{x}$ denote the error of the estimator, ie $\tilde{x} = x - \bar{x}$. Derive the dynamics for $\tilde{x}$. That is, find $\dot{\tilde{x}}$.

c. Let $L = [0, \ l_2]^T$. For which l_2 does the error $\tilde{x}$ go to zero?

11.6 Consider the following scenario: A patient arrives to the hospital with symptoms of methanol poisoning. The person is also heavily intoxicated by ethanol and cannot give any answer to how much, or when, he consumed the ethanol/methanol. As a basis for determining the optimal treatment decision, the doctor would like a prognosis of the level of the toxic metabolite formic acid as well as the methanol concentration. Serum samples are collected once every hour to assess the level of formic acid. A simplified model of the metabolism of methanol and formic acid is provided below.

All methanol is believed to already have been absorbed from the gut, and is modeled by a single compartment with a half-life of 17 hours and a distribution volume V_D of 50 liter. The formic acid is believed to be formed in the liver with a rate proportional to the metanol content with a rate constant $r_L = 0.7mmol \cdot g^{-1} \cdot h^{-1}$. The formic acid is distributed over two compartments, representing blood and liver, with exchange coefficients $k_{LB} = 0.25h^{-1}$ (from liver to blood) and $k_{BL} = 0.2h^{-1}$ (from blood to liver), and is eliminated from the liver with an elimination rate of $k_e = 0.15h^{-1}$. The compartment volumes for the formic acid are $V_L = 1.2$ l (liver) and $V_B = 5.7$ l (blood). Methanol has a density of 0.798 kg/l and a molar weight of 32 g/mol.

a. Derive a state-space model of the system, with the formic acid blood concentration as the output variable y, and methanol content as state x_1 [g], liver content of formic acid as x_2 [mmol] and blood content of formic acid as x_3 [mmol].

b. Now, estimates of the methanol and formic acid levels may be given using the blood formic acid concentration samples and an observer. Let the poles of the observer polynomial be at $-0.6, -0.8, -1.0$. Formulate the analytical expression that needs to be solved in order to calculate the observer gain. Use `place(X, Y, p)`, with $X = A^T$ and $Y = C^T$ and p representing the poles, to derive the numerical result.

c. Use this observer and the formic acid concentration samples (Y) in the file (`Metanoldata.mat`) to estimate the states; $\hat{x}_{k+1|k}$. Initial measurements of the blood methanol and formic acid concentrations at patient arrival are 11.3 mmol/l and 17 mmol/l. You may assume the the liver content of formic acid to be the same as that of blood upon arrival. Use this to set up an initial state $\hat{x}_0$ of your state estimation.

d. Normally formic acid assays are not available, but regular methanol test may be considered. Is it possible to use this biomarker instead to estimate all the state variables?

Solutions to Chapter 1. Introduction to computation and simulation in **MATLAB**

The exercises in this chapter are to familiarize yourself with MATLAB. The mathematics should not be new to you. However, if you are unsure about it, please go back to your Linear algebra and Analysis books and review the material needed.

1.1

  a.

$$\det(A) = a \cdot d - b \cdot c,$$

$$A^{-1} = \frac{1}{ad - bc} \begin{bmatrix} d & -b \\ -c & a \end{bmatrix}$$

Eigenvalues λ are the solutions to $\det(\lambda I - A) = 0$.

  b. Use the help function and MathWorks webpage.

1.2 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 `figure` 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).
% Add a "." before the multiplication sign.

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.

1.3 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 could 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 $\tilde{} =$ 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.

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

b. Use the code given in the problem text and what you've learnt in the previous exercises on how to plot.

c. The ODEs can be written together on matrix form as follows

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} x_2 \\ 3x_1 - 7x_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ 3 & -7 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}.$$

Define the vector $\mathbf{x} = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$. Then, define f as the following function

$$f(t, \mathbf{x}) = f\left(t, \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}\right) = \begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix}.$$

Hence,

$$f(t, \mathbf{x}) = \begin{pmatrix} x_2 \\ 3x_1 - 7x_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ 3 & -7 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}.$$

In MATLAB, this can be written as

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

Or by matrix multiplication

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

To solve the differential equation write the following code

```
[T Y] = 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. Y is a matrix with two columns, the first column corresponds to $x_1(t) = y(t)$ and the second column corresponds to $x_2(t) = \dot{y}(t)$. T is the times between 0 and 5 at which ode45 has calculated x_1 and x_2. Use the following code to plot $y(t)$ over $0 \le t \le 5$

```
plot(T,Y(:,1))
```

Solutions to Chapter 2. Biochemical Reactions: equilibrium, steady state and control

2.1

a. Conservation of mass. Assume that we start out with $x(0) = 8$ while $y(0) = 2$ and $z(0) = 0$. Then, $c = 10$ and at every time instant, the total concentration is always 10, i.e., the total mass (or concentration more specifically in this case) is preserved.

b. The equilibrium is given by the point (x_0, y_0, z_0) for which $dx/dt = dy/dt = dz/dt = 0$. From $dz/dt = k_2 y = 0$ we get that $y_0 = 0$. Then from either of $dx/dt = 0$ or $dy/dt = 0$ we get that $x_0 = 0$. Thus $z_0 = c - x_0 - y_0 = c$ and the equilibrium is given by $(x_0, y_0, z_0) = (0, 0, c)$.

c. Yes. The system can be simulated with the following code:

```
% v = [x,y,z]'; f = [dx/dt,dy/dt,dz/dt]';
% Parameters
k1 = 1;
km1 = 0.5;
k2 = 0.8;

% Initial conditions
x0 = 10;
y0 = 0;
z0 = 0;

% Right hand side of ODE
f = @(t,v) [-k1 km1 0; k1 -km1-k2 0 ; 0 k2 0]*v;

% Solve ODE
[T, sol] = ode45(f,[0 20], [x0,y0,z0])


% Plot solution
plot(T,sol)
legend('x','y','z')
title('System dynamics')
xlabel('time')
ylabel('Concentration')
```

d. The system reaches the equilibrium faster, around 8 time steps instead of 14 as in the previous setting. As z reaches $c = 10$, k_2 grows. That means that the production of z is positively reinforced by the quantity of z. This can be described as positive feedback. Plot $k_2(z)$ over $z \in [0, 10]$ with `fplot` to see that it increases with z. The code below is example code on how to simulate the system with the dynamic k_2.

```
% v = [x,y,z]'; f = [dx/dt,dy/dt,dz/dt]';
% Parameters
k1 = 1;
km1 = 0.5;
```
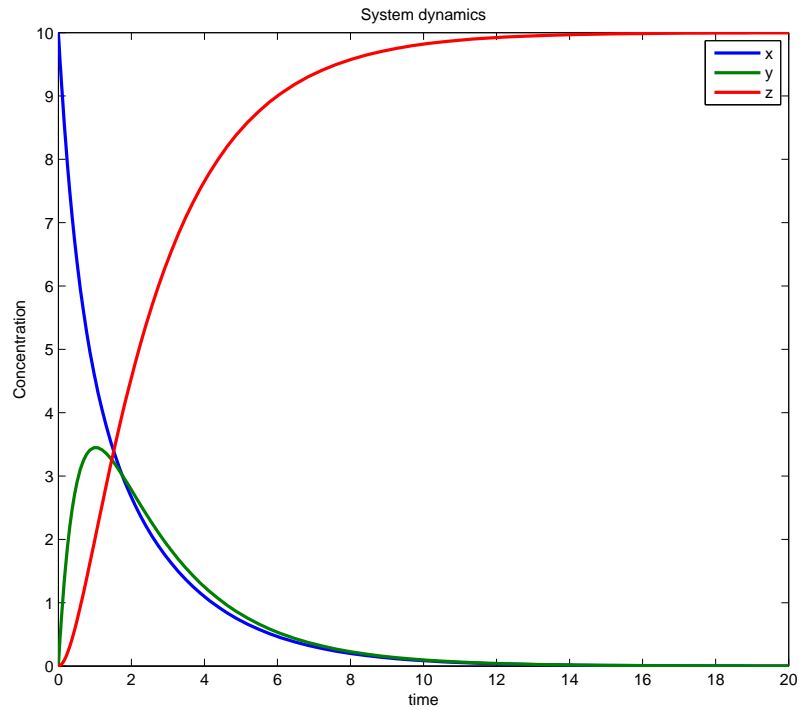
Figure 2.1   Simulated system dynamics in Problem 2.1. The equilibrium is reached within 20 time steps.

```matlab
k2 = @(z) 0.8*(1+10/(z-11)^2);

% Initial conditions
x0 = 10;
y0 = 0;
z0 = 0;

% Right hand side of ODE
f = @(t,v) [-k1 km1 0; k1 -km1-k2(v(3)) 0 ; 0 k2(v(3)) 0]*v;

% Solve ODE
[T, sol] = ode45(f,[0 20], [x0,y0,z0])


% Plot solution
plot(T,sol)
legend('x','y','z')
title('System dynamics')
xlabel('time')
ylabel('Concentration')
```

2.2

a. The balance equations for the enzymatic reaction are given by

$$ds/dt = -k_1 se + k_{-1}c$$
$$de/dt = -k_1 se + (k_{-1} + k_2)c$$
$$dc/dt = k_1 se - (k_{-1} + k_2)c$$
$$dp/dt = k_2 c,$$

where $s = [S]$, $e = [E]$, $c = [C]$ and $p = [P]$. 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
s0 = 0.15; % mmol/L
e0 = 1e-2; % mmol/L
c0 = 0; % mmol/L
p0 = 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],[s0 e0 c0 p0])

figure
[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')
```

b. To derive the Michaelis Menten relation we make the following assumptions:

- Conservation of enzyme and complex: $de/dt + dc/dt = 0$, i.e., $e(t) + c(t) = m$, where $m > 0$ is some constant. From the initial conditions we get that $m = e(0) + c(0) = [E]_0 + [C]_0 = [E]_0$.

- Steady state conditions for enzyme and complex: $de/dt = 0$ and $dc/dt = 0$.

Now, $dc/dt = 0$ with $e(t) = [E]_0 - c(t)$ results in

$$k_1 s(t)([E]_0 - c(t)) - (k_{-1} + k_2)c(t) = 0$$

$$c(t) = \frac{k_1[E]_0 s(t)}{k_{-1} + k_2 + k_1 s(t)} = \frac{[E]_0 s(t)}{(k_{-1} + k_2)/k_1 + s(t)}.$$

Note that $dc/dt = -de/dt$. Finally, dp/dt can now be written as

$$\frac{dp}{dt} = k_2 c = \frac{k_2[E]_0 s(t)}{(k_{-1} + k_2)/k_1 + s(t)}.$$

It is clearly on the form

$$\frac{V_{max}s}{K_m + s},$$

with $V_{max} = k_2 \cdot [E]_0$ is the maximal reaction rate and $K_m = (k_2 + k_{-1})/k_1$.

c. Consider the maximum of dp/dt over $s \in [0, \infty)$. It takes its lowest value for $s = 0$, i.e., $dp/dt = 0$ and since it is an increasing function its maximal value is given by

$$\lim_{s \to \infty} \frac{dp}{dt} = \lim_{s \to \infty} \frac{V_{max}s}{K_m + s} = \lim_{s \to \infty} \frac{V_{max}}{K_m/s + 1} = V_{max}.$$

Hence, when there is an infinite amount of substrate, the reaction rate is bounded by V_{max}.

d. Doubling the enzymatic concentration $[E]_0$ doubles the maximal production rate since $V_{max} = k_2 \cdot [E]_0$.

2.3

a. The plot indicates that the relationship between the reaction rate and the substrate concentration goes to saturation in a M-M-like behavior, see Fig.2.2. V_{max} and K_m are estimated as shown in the plot.
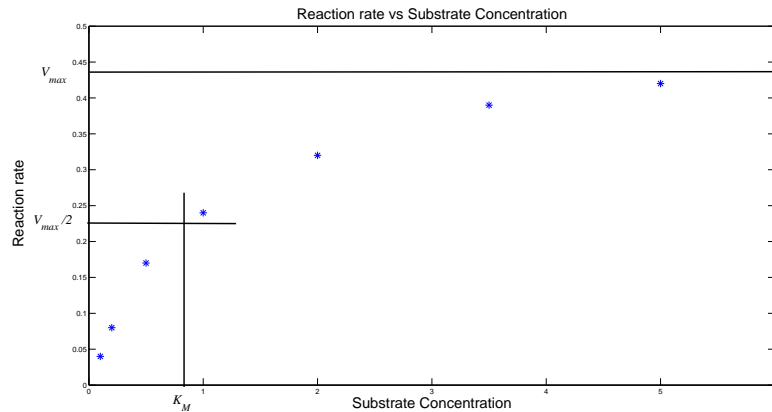

Figure 2.2 Graphical estimation of V_{max} and K_M

b. 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. 2.3.
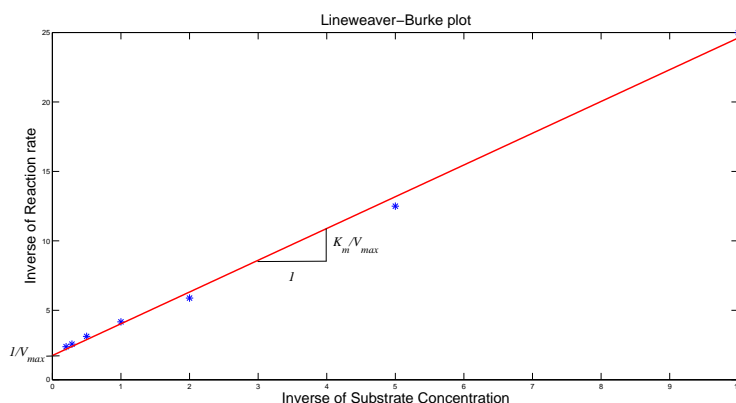

Figure 2.3   Graphical estimation of V_{max} and K_M using the Lineweaver-Burk plot.

2.4

a. Yes. As $[I]$ is bounded we can perform the same analysis in the previous subproblem.

b. $d[P]/dt$ goes to zero.

c. We recover the ordinary enzymatic reaction treated in a previous problem, i.e., without the inhibitor.

d. It binds to the enzyme needed for the enzymatic reaction and stores it in the inactive form C_2. Thus, as there is less enzyme, it will slow down the process. If there is infinite amount of inhibitor, the reaction rate tends to zero.

Solutions to Chapter 3. Compartment models and simulation in **Simulink**

3.1   Compartment model:

3.2
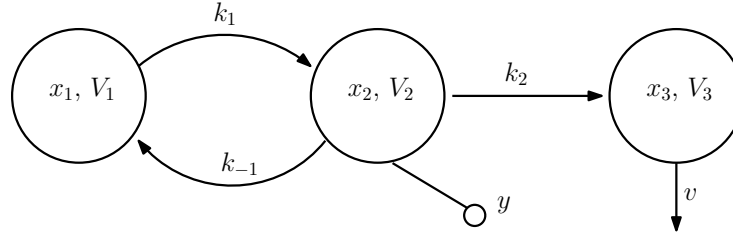
   a. x_1, x_2: mg. u, dx_1/dt, dx_2/dt: mg/(ms). k: 1/ms. y: mg/dl.

   b. The balance equations are given by

$$\frac{dx_1}{dt} = -kx_1 + u$$

$$\frac{dx_2}{dt} = kx_1 - kx_2$$

$$y = x_2/1$$

   c. The equilibrium is characterized by $\frac{dx_1}{dt}, \frac{dx_2}{dt} = 0$. From $\frac{dx_1}{dt} = 0$ and $u = u_0$ we get that $x_1^0 = u^0/k$. Furthermore, from $dx_2/dt = 0$ we get that $x_2^0 = x_1^0 = u_0/k$ and thus $y_0 = x_2^0 = u_0/k$. In summary, the equilibrium point is given by $(x_1, x_2, u, y)^0 = (u^0/k, u^0/k, u^0, u^0/k)$.

   d.

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

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

3.3
```
% System 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)

% Simulate the system
T = 0:0.1:8;
u = ones(length(T),1);
lsim(system,u,T)
```

The measured concentration tends to 1 mg/dl.

In the previous exercises of this chapter we treated linear systems. However, nonlinear phenomena is common in physiology (e.g., the enzyme reactions treated in the previous chapter). The analysis of nonlinear systems is more involved than that for linear systems. However, to simulate the systems behavior is often a very useful tool, as we have seen through the use of `ode45`. In this last part of the exercise, we will instead use `SIMULINK` for simulation, which is a buildt in graphical simulation tool in `MATLAB`.

3.4   -

3.5

  a. The equilibria are characterized by $dx/dt = x(b-px) = 0$. Thus, $x_0 = 0$ and $x_0 = b/p$ are the equilibria.

  b. -

  c. When starting at $x(0) = 0.8$ and $x(0) = 0.1$, the fraction of bacteria reaches the equilibrium $b/p = 0.5$, i.e., this equilibrium is attracting the dynamics from both above and below. When the dynamics are initiated in $x(0) = 0$, it stays there, as is expected due to it being an equilibrium.

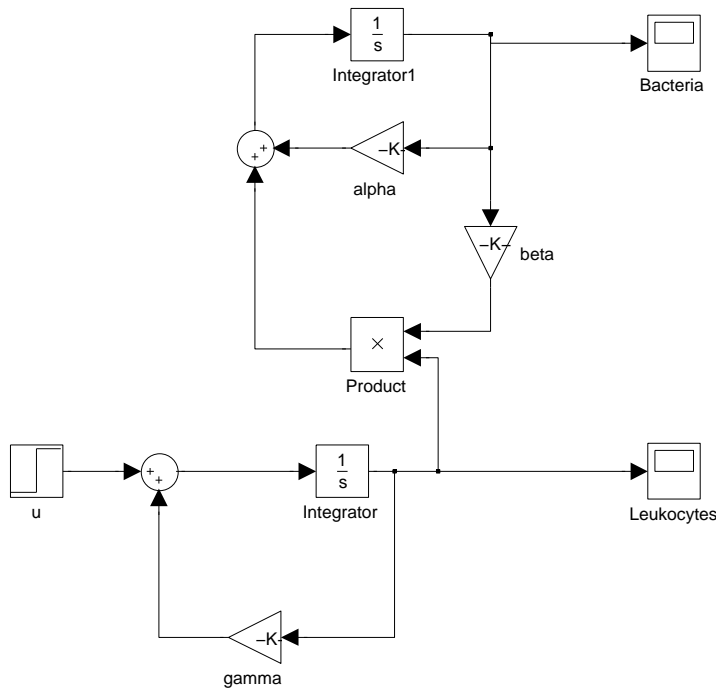**3.6**   The Simulink model can be seen in Fig. 3.1.

Figure 3.1   Simulink model for the Predator-Prey system

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

Solutions to Chapter 4. Linear systems and linearization

4.1 Transfer function representation: Laplace transform the equation

$$\mathcal{L}(\dddot{y} + 3\ddot{y} + 2\dot{y} + y) = \mathcal{L}(u)$$

and denote $Y(s) = \mathcal{L}(y(t))$ and $U(s) = \mathcal{L}(u(t))$. This results in

$$(s^3 + 3s^2 + 2s + 1)Y(s) = U(s)$$

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

and the transfer function, which we denote by $G(s)$, is given by

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

The transfer function representation lives in the frequency domain with variable s (unit e.g. rad/s or Hz).

State-space representation:

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

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

The state-space representation lives in the time domain with variable t (unit e.g. s, min, hours).

The main difference between the two representations are the domains they are described in, i.e., frequency and time.

4.2 After the Laplace transform, one obtains

$$sX = AX + BU$$
$$Y = CX + DU$$

Solve for X

$$(sI - A)X = BU$$
$$X = (sI - A)^{-1}BU$$

This gives

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

4.3 a. The transfer function is

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

$$= (\,-1 \quad 1\,) \begin{pmatrix} s+2 & 0 \\ 0 & s+3 \end{pmatrix}^{-1} \begin{pmatrix} 5 \\ 2 \end{pmatrix} + 2$$

$$= \frac{2s^2 + 7s + 1}{s^2 + 5s + 6}.$$

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

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

The poles of the system are given by -2 and -3.

b. The transfer function is

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

$$= (\,-2 \quad 1\,) \begin{pmatrix} s+7 & -2 \\ 15 & s-4 \end{pmatrix}^{-1} \begin{pmatrix} 3 \\ 8 \end{pmatrix}$$

$$= \frac{2s+3}{s^2 + 3s + 2}.$$

The differential equation becomes

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

The poles of the system are given by $(-2, -1)$.

4.4 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

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

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

$$y(t) = \int_0^t h(\tau)d\tau = \int_0^t \left(2\delta(\tau) + 2e^{-3\tau} - 5e^{-2\tau}\right)d\tau$$

$$= 2 + \left[\frac{5}{2}e^{-2\tau} - \frac{2}{3}e^{-3\tau}\right]_0^t$$

$$= \frac{1}{6} + \frac{5}{2}e^{-2t} - \frac{2}{3}e^{-3t}, \quad t \geq 0.$$

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

$$y(t) = \int_0^t h(\tau)d\tau = \frac{3}{2} - e^{-t} - \frac{1}{2}e^{-2t}, \quad t \geq 0.$$
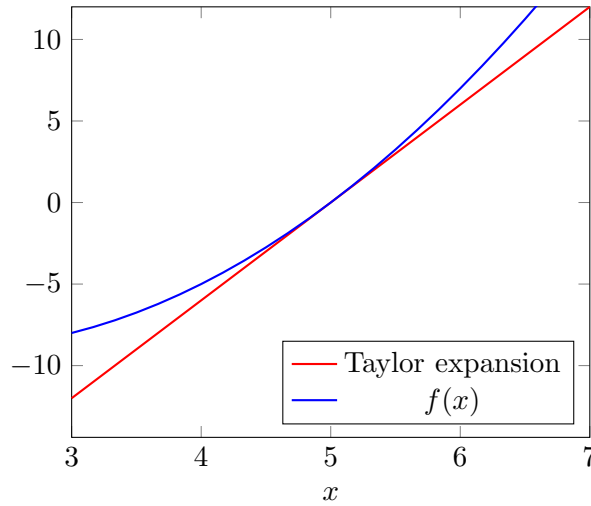
In MATLAB, the following code can be used

Figure 4.1 Plot of $f(x) = (x-2)^2 - 9$ and its first order Taylor serires expansion around $x = 5$.

```
% 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)
```

In the previous exercises of this chapter we treated linear systems. The analysis of nonlinear systems is more involved than that of linear systems. However, linearizing the nonlinear dynamics around a stationary point can give us an approximation of the system's behavior locally.

4.5 Recall that a first order taylor expansion is given by

$$f(x) \approx f(x_0) + \frac{df}{dx}(x_0)(x - x_0).$$

This is a linear approximation of $f(x)$ around $x = x_0$. $\frac{df}{dx} = 2(x-2)$. Then,

$$f(x) \approx \frac{df}{dx}(5)(x - 5) = 6x - 30.$$

See Figure 4.1 for a plot.

4.6 a. For $x^0 = 4$ we have $\dot{x} = -5 + u^2$. A stationary point is achieved for $u^0 = \pm\sqrt{5}$.

b. Calculations gives

$$\frac{\partial f}{\partial x}(x^0, u^0) = 4, \quad \frac{\partial f}{\partial u}(x^0, u^0) = 2\sqrt{5}, \quad \frac{\partial y}{\partial x}(x^0) = 1.$$

Let

$$\Delta x = x - x^0$$
$$\Delta u = u - u^0$$
$$\Delta y = y - y^0,$$

with $y^0 = x^0$. The linearized system is then given by

$$\Delta \dot{x} = 4\Delta x + 2\sqrt{5}\Delta u$$
$$\Delta y = \Delta x.$$

4.7 a.

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

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

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

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

$$\frac{\partial f_1}{\partial x_1} = 0 \qquad\qquad \frac{\partial f_1}{\partial x_2} = 1 \qquad\qquad \frac{\partial f_1}{\partial u} = 0$$

$$\frac{\partial f_2}{\partial x_1} = -\frac{1}{2\sqrt{x_1}} - x_2 \qquad \frac{\partial f_2}{\partial x_2} = -x_1 \qquad \frac{\partial f_2}{\partial u} = 2u$$

$$\frac{\partial g}{\partial x_1} = 1 \qquad\qquad \frac{\partial g}{\partial x_2} = 0 \qquad\qquad \frac{\partial g}{\partial u} = 0$$

At the stationary point we have

$$\frac{\partial f_1}{\partial x_1}(x_1^0, x_2^0, u^0) = 0 \qquad \frac{\partial f_1}{\partial x_2}(x_1^0, x_2^0, u^0) = 1 \qquad \frac{\partial f_1}{\partial u}(x_1^0, x_2^0, u^0) = 0$$

$$\frac{\partial f_2}{\partial x_1}(x_1^0, x_2^0, u^0) = -\frac{1}{2} \qquad \frac{\partial f_2}{\partial x_2}(x_1^0, x_2^0, u^0) = -1 \qquad \frac{\partial f_2}{\partial u}(x_1^0, x_2^0, u^0) = 2$$

$$\frac{\partial g}{\partial x_1}(x_1^0, x_2^0, u^0) = 1 \qquad \frac{\partial g}{\partial x_2}(x_1^0, x_2^0, u^0) = 0 \qquad \frac{\partial g}{\partial u}(x_1^0, x_2^0, u^0) = 0$$

Use the following variable substitution

$$\Delta x_1 = x_1 - x_1^0$$
$$\Delta x_2 = x_2 - x_2^0$$
$$\Delta u = u - u^0$$
$$\Delta y = y - y^0$$

The linearized system is then

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

$$\Delta y = \begin{pmatrix} \frac{\partial g}{\partial x_1}(x_1^0, x_2^0, u^0) & \frac{\partial g}{\partial x_2}(x_1^0, x_2^0, u^0) \end{pmatrix} \begin{pmatrix} \Delta x_1 \\ \Delta x_2 \end{pmatrix} + \frac{\partial g}{\partial u}(x_1^0, x_2^0, u^0)\Delta u$$

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

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

4.8

a. Using the fact that

$$\frac{dS}{dt} + \frac{dI}{dt} = -\beta IS + \gamma I + \beta IS - \gamma I = 0,$$

it follows that

$$S(t) + I(t) = C,$$

where C is a constant. We know that for time $t = 0$

$$C = S(0) + I(0) = 0.8 + 0.2 = 1$$

and thus, $S(t) + I(t) = 1$.

b.

$$\frac{dS}{dt} = - \beta IS + \gamma I = 0$$
$$\frac{dI}{dt} = \beta IS - \gamma I = 0$$

gives that $I(\beta S - \gamma) = 0$. Using the fact that $I(t) + S(t) = 1$ for all t,
two stationary points can be derived

$$\left(S^0, I^0\right)_1 = (1, 0) \text{ and } \left(S^0, I^0\right)_2 = (\gamma/\beta, 1 - \gamma/\beta).$$

c. Denote $dS/dt = f_1(S, I)$ and $dI/dt = f_2(S, I)$. The partial derivatives are given by

$$\frac{\partial f_1}{\partial S} = -\beta I \qquad\qquad \frac{\partial f_1}{\partial I} = -\beta S + \gamma$$

$$\frac{\partial f_2}{\partial S} = \beta I \qquad\qquad \frac{\partial f_2}{\partial I} = \beta S - \gamma.$$

Further, the linearized system around (S^0, I^0) can be written as

$$\begin{bmatrix} \dot{\Delta S} \\ \dot{\Delta I} \end{bmatrix} = \begin{bmatrix} -\beta I^0 & -\beta S^0 + \gamma \\ \beta I^0 & \beta S^0 - \gamma \end{bmatrix} \begin{bmatrix} \Delta S \\ \Delta I \end{bmatrix}$$

where $\Delta S = S - S^0$ and $\Delta I = I - I^0$.

Solutions to Chapter 5. Stability of linear systems, and pharmacokinetics

5.1 a. The poles are the solutions of the characteristic equation $s^2+4s+3 = 0$, i.e. $s = -1$ and $s = -3$. 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)
```

c. The input (a step) has the Laplace transform $U(s) = 1/s$. The output becomes

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

Inverse Laplace transformation gives

$$h(t) = \frac{1}{3} + \frac{1}{6}\left(e^{-3t} - 3e^{-t}\right)$$

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

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

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

The eigenvalues of A are given by the characteristic equation

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

a. The eigenvalues are given by $\lambda_1 = -1$ and $\lambda_2 = -2$. Thus, this system is asymptotically stable.

b. The eigenvalues are given by $\lambda_1 = 1$ and $\lambda_2 = 2$ and the system is unstable.

c. The eigenvalues are given by $\lambda_1 = -i$ and $\lambda_2 = i$. Since the eigenvalues do not lie strictly within the LHP, the system is not asymptotically stable. However, it is defined as *marginally stable* as the eigenvalues do not lie in the right half plane (RHP). It is easy to see the difference in the two stability notions asymptotic stability and marginal stability by comparing the impulse responses of the systems in **a** and **c**.

5.3 a. The output is given by

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

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 $\arg G(3i) \approx 0$. Thus, we obtain

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

5.4 The stationary points are

$$\left(S^0, I^0\right)_1 = (1, 0) \quad \text{and} \quad \left(S^0, I^0\right)_2 = (\gamma/\beta, 1 - \gamma/\beta).$$

Further, the linearized system around (S^0, I^0) can be written as

$$\begin{bmatrix} \dot{\Delta S} \\ \dot{\Delta I} \end{bmatrix} = \begin{bmatrix} -\beta I^0 & -\beta S^0 + \gamma \\ \beta I^0 & \beta S^0 - \gamma \end{bmatrix} \begin{bmatrix} \Delta S \\ \Delta I \end{bmatrix}$$

where $\Delta S = S - S^0$ and $\Delta I = I - I^0$.
Thus the linearized system around $\left(S^0, I^0\right)_1$ is given by

$$\begin{bmatrix} \dot{\Delta S} \\ \dot{\Delta I} \end{bmatrix} = \begin{bmatrix} 0 & -\beta + \gamma \\ 0 & \beta - \gamma \end{bmatrix} \begin{bmatrix} \Delta S \\ \Delta I \end{bmatrix}.$$

It has poles 0 and $\beta - \gamma$. If $\beta - \gamma < 0$ it is marginally stable. Otherwise, unstable.
The linearized system around $\left(S^0, I^0\right)_2 = (\gamma/\beta, 1 - \gamma/\beta)$ is given by

$$\begin{bmatrix} \dot{\Delta S} \\ \dot{\Delta I} \end{bmatrix} = \begin{bmatrix} \gamma - \beta & 0 \\ \beta - \gamma & 0 \end{bmatrix} \begin{bmatrix} \Delta S \\ \Delta I \end{bmatrix}$$

which has poles in 0 and $\gamma - \beta$. It is marginally stable if $\gamma - \beta < 0$ and unstable otherwise.

They can not be stable at the same time. For any given γ and β, one system is stable and the other one unstable.

5.5

$$\frac{dq}{dt} = \frac{DA}{d}(C_s - C_b) = -4$$

The rate is -4.

5.6

a. Let $C(t)$ be 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,

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

and the dynamics are stable.

b. Given the solution to the previous subproblem, the formula for the concentration is given by

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

When $t = 7 \,[\text{days}]$

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

c. Plot equation (5.1) using MATLAB.

d. From the first subproblem we derived the time trajectory of the concentration as

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

We are interested in the time at which $C(t) = 0.4 C_0$. Hence we want to slove for t in

$$0.4 C_0 = C_0 e^{-0.0866 \cdot t} \rightarrow t = -\frac{1}{0.0866} \ln(0.4) = 10.6 \text{ [days]}$$

e. Consider again

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

and set $t = 25$ [days], $C_0 = 90$ and $C(25) = 80$ to determine k. Then determine $t_{1/2}$ by using the derived k and $C(t_{1/2}) = C_0/2$. The half-life is 147 days.

5.7

a. The 3-compartment model is given below. Here we have included both the oral dose entering the gut compartment as well as the intravenous injection entering the body compartment. The intravenous injection will be used in the last subproblem. You can ignore the arrow drawn for the intravenous injection for now.
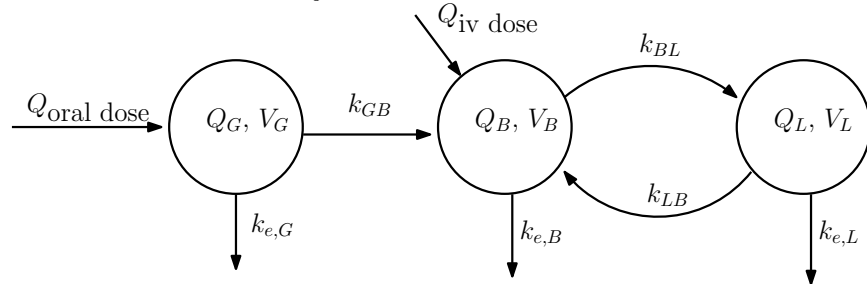
b. The state-space representation becomes:

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

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

where Q_G, Q_B, Q_L [mg], 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. Simulation of 500mg dose is given in Fig. 5.1 below. For code, go to the solution of the last subproblem.
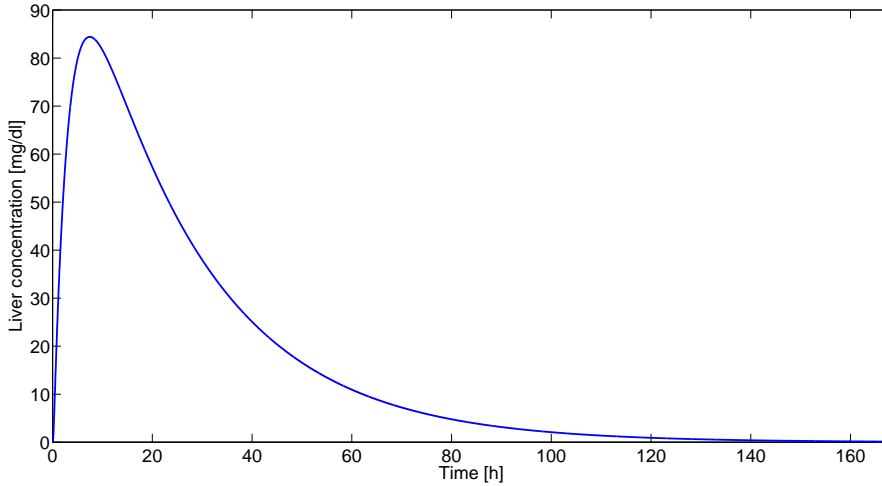
Figure 5.1   Liver concentration at 500 mg dose

d. Simulating the system with an oral prescription of 500mg over five minutes every 24 hours produces the blue curve in Fig.5.2. The output oscillates heavily with a 24 hour period. An alternative medication strategy is to administer the drug in half the dose every 12 hours instead, which is shown by the green curve.

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

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

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

To determine the constant dose Q_{iv}^c needed to maintain a steady-state concentration of $y^c = 104$ mg/dl, we need to determine the static gain of the system. We note in the new system that Q_G is zero, and can thus reduce the system to a smaller one,

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

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

The transfer function from Q_{iv} to y is given by:

$$
G_{yQ_{iv}}(s) = C(sI - A)^{-1} B
$$

The static gain is

$$G_{yQ_{iv}}(0) = V_L \cdot 10 \frac{(k_{e,B} + k_{BL})}{(k_{e,B} + k_{BL})(k_{e,L} + k_{LB}) - k_{LB}k_{BL}} = 396.12.$$

Thus:

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

Simulations in Matlab, illustrated by the red curve in Fig 5.2, confirms that the constant intravenous injection eliminates the oscillations of the drug concentration in the liver.
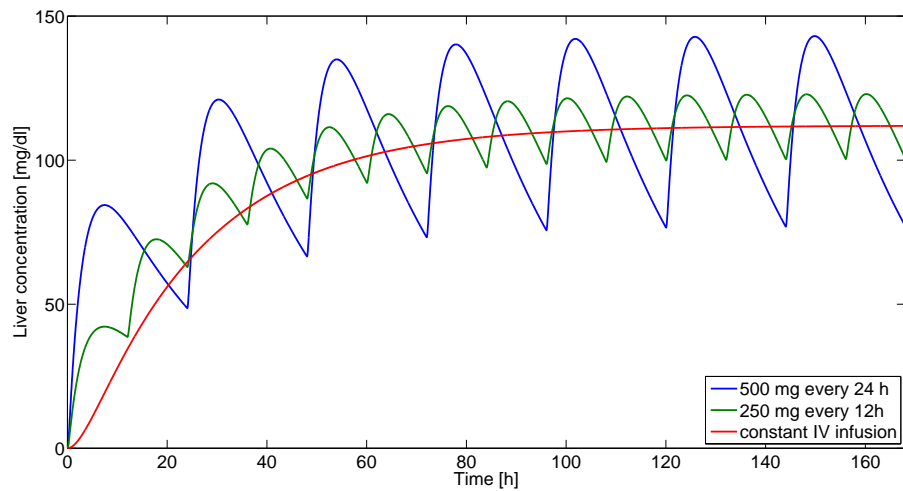
Figure 5.2 Liver concentration at different medication strategies

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

%% Subproblem c

% Define system with oral input
%————————————
A = [−(ke1+k12) 0          0;...
     k12        −(ke2+k23)  k32;...
     0          k23        −(ke3+k32)];
B = [1 0 0]'; % Oral input
C = 1/VL*[0 0 1]; % Liver concentration [mg/dl]
```

```matlab
D = [];
sys = ss(A,B,C,D);

% Oral dose 500 mg, assuming it takes 5 minutes to dissolve.
% Make the trajectory over 168 hours
%——————————
u_oral = [100*ones(5,1); zeros(168*60—5,1)]; % 500 mg tablet dissolved
%over the first 5 minutes

% initial value
x0 = [0 0 0]'; %Assume we start with no drug in the body

% simulation time
T = [0:1:(168*60—1)];

% Simulate
[y_1,T,x] = lsim(sys,u_oral,T,x0);

figure(1)
plot(T/60,y_1)
hold on
ylabel('Liver concentration [mg/dl]')
xlabel('Time [h]')

%% Subproblem d

% add the dosage in subproblem c every 24 hours
u_onedose = [100*ones(5,1); zeros(24*60—5,1)];
u_oral24 = repmat(u_onedose,7,1); % 7 24—hour periods on 168 hours

% Simulate
[y_2,T,x] = lsim(sys,u_oral24,T,x0);

figure(1)
plot(T/60,y_2)

% alternative dosage: half the dosage every 12 hours
u_onedose = [100; 100; 50; zeros(12*60—3,1)];
u_oral12 = repmat(u_onedose,14,1); % 14 12—hour periods on 168 hours

% Simulate
[y_3,T,x] = lsim(sys,u_oral12,T,x0);

figure(1)
plot(T/60,y_3)


%% Subproblem e

% Define system with itravenous input
%——————————
A = [—(ke1+k12) 0          0;...
     k12       —(ke2+k23)  k32;...
     0          k23       —(ke3+k32)];
B = [0 1 0]'; % IV input
C = 1/VL*[0 0 1]; % Liver concentration [mg/dl]
D = [];
sys = ss(A,B,C,D);

figure(2)
step(sys)
```

```matlab
% From the step response it is evident that the static gain of the system
% is approx. 400 mg/dl. Could aso be calculated as follows:
static_gain = dcgain(sys);

% If we want to achieve steady state liver concertration of 112 mg/dl we
% need the following magnitude of the constant iv-input:
u_iv_mag = 112/static_gain; % U(0) = Y(0)/G(0);

% create the time trajectory of the IV-input
u_iv = u_iv_mag*ones(length(T),1);

% simulate
[y_4,T,x] = lsim(sys,u_iv,T,x0);

figure(1)
plot(T/60,y_4)
legend('500 mg once','500 mg every 24 h','250 mg every 12h','constant IV inf
'Location','SouthEast')
```

Of course, another approach is to compute the static gain using MATLAB.
Example code is given below.

```matlab
sys = ss(A,B,C,[]);
static_gain = dcgain(sys);
```

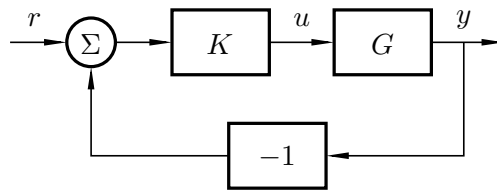# Solutions to Chapter 6. Feedback in linear systems, and tracer kinetics

6.1 a. Laplace transformation of the differential equation yields

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

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

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

b. The block diagram of the closed loop system becomes

c. The transfer function of the closed loop system becomes

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

d. The closed-loop system is stable as long as $s + 0.01 + 0.01K = 0$ has solution with negative real-part. This is equivalent to $-0.01(1+K) < 0$, i.e., $K > -1$.

e. The closed-loop system with $K = 10$ is given by $\frac{0.1}{s+0.11}$. The static gain is thus $\frac{0.1}{0.11} \approx 0.91$. The substrate y will be 91% of the reference value r when $t \to \infty$.

6.2

a. The complex number is rotated 90° degress counter-clockwise. For example, $1 \cdot e^{90j} = e^{(0+90)j} = j$.

b. The exact values are amplitude margin, $A_m = 3$, and phase margin, $\phi_m \approx 34°$. Your results should be similar.

6.3

a. Rewrite the system as

$$(1 + 10s)^2 Y(s) = e^{-2s}U(s),$$
$$(100s^2 + 20s + 1)Y(s) = e^{-2s}U(s)$$

Then, via the inverse Laplace transform, we get

$$100\ddot{y} + 20\dot{y} + y = u(t - 2).$$

Choosing $x_1 = y$ and $x_2 = \dot{y}$, we get the following state-space representation

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -0.01 & -0.2 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} u(t-2)$$

$$y = \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} x_1 & x_2 \end{bmatrix}^T.$$

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

$$G(s) = \frac{e^{-2s}}{(1+10s)^2}$$

The phase of the process is:

$$\arg G(i\omega) = -2\omega - 2\arctan(10\omega)$$

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

$$-2\omega - 2\arctan(10\omega) = -\pi$$

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

$$\omega_0 \approx 0.31.$$

Next we determine the gain at this frequency:

$$|G(i\omega_0)| = \frac{1}{1 + 100\omega_0^2} = 0.095$$

This yields the amplitude margin:

$$A_m = \frac{1}{G(i\omega_0)} = 10.5$$

Therefore, the gain $K \approx 10.5$ is the largest gain we can allow and still maintain stability.

We denote the system as

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

and the controller as $G_R = K$. As in the previous problem, the transfer function of the closed loop system becomes

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

The desired and actual characteristic polynomials are the same if all their coefficients match. Identification of coefficients yields, in the case $s + 0.1$,

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

and in the case $s + 1$,

$$1 = 0.01 + 0.01K \quad \Leftrightarrow \quad K = 99.$$

The static gains of the two closed-loop systems are 10 and 1, respectively. The following code is an example of how to plot the step response of the two systems.

```
s = tf('s');
G_1 = 1/(s+0.1);
G_2 = 1/(s+1);

% normalize
G_1 = G_1/dcgain(G_1);
G_2 = G_2/dcgain(G_2);

% plot

step(G_1,G_2)
legend('G_1','G_2')
```

The second system is faster. It has its pole further to the left in the left half-plane.

6.5   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
$$K > 2$$

6.6   It is determined by the static gain of the system times the rate u_0, i.e., $\frac{5.3}{2.8}u_0$.

Solutions to Chapter 7. Metabolism, glucose and insulin kinetics

7.1   The energy for physical activity is:

$$E_p = E_{in} - E_{DIT} - E_{BMR} - E_S = 3000 - 2241 - 0 = 759 \text{ kcal.}$$

Then you can run for $759/11.3 \approx 66.2$ minutes and with the given pace you will run 11.4 km in that time.

7.2

a. k_{gri} represents the kinetic coefficient between the solid and the liquid compartments of the stomach. In the 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.

b. The system can be written on state space form as

$$\begin{bmatrix} \dot{q}_{sto1} \\ \dot{q}_{sto2} \\ \dot{q}_{gut} \end{bmatrix} = \begin{bmatrix} -k_{gri} & 0 & 0 \\ k_{gri} & -k_{empt} & 0 \\ 0 & k_{empt} & -k_{abs} \end{bmatrix} \begin{bmatrix} q_{sto1} \\ q_{sto2} \\ q_{gut} \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} C(t)$$

$$R_a(t) = \begin{bmatrix} 0 & 0 & \frac{k_{abs}}{V} \end{bmatrix} \begin{bmatrix} q_{sto1} \\ q_{sto2} \\ q_{gut} \end{bmatrix}$$

The poles of the system are given by the solutions to

$$\det(sI - A) = 0 \rightarrow (s + k_{gri})(s + k_{empt})(s + k_{abs}) = 0.$$

That is the poles are given by $-k_{gri}$, $-k_{empt}$ and $-k_{abs}$. As these parameters are always positive, the poles are always negative, and hence the system is stable.

c. Given parameter values $k_{gri} = k_{empt} = k_{abs} = 1$ and $V = 1$, the system G in the frequency domain is given by

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

Given the controller $K(s)$, the closed-loop system is given by

$$G_{yr} = \frac{G(s)K(s)}{1 + G(s)K(s)} = \frac{K(s)}{(s + 1)^3 + K(s)}.$$

In the P-controller case we have $K(s) = 3.6$. Thus,

$$G_{yr} = \frac{3.6}{(s + 1)^3 + 3.6} = \frac{3.6}{s^3 + 3s^2 + 3s + 4.6}$$

and the static gain is $3.6/4.6 \approx 0.78$.

In the PI-controller case we have $K(s) = 3.2 + 1.7/s = \frac{3.2s+1.7}{s}$. Thus,

$$G_{yr} = \frac{3.2s + 1.7}{s(s+1)^3 + 3.2s + 1.7} = \frac{3.2s + 1.7}{s^4 + 3s^3 + 3s^2 + 4.2s + 1.7}$$

and the static gain is $1.7/1.7 = 1$.

In the PID-controller case we have $K(s) = 4.3 + 3.5/s + 1.3s = \frac{1.3s^2+4.3s+3.5}{s}$. Thus,

$$G_{yr} = \frac{1.3s^2 + 4.3s + 3.5}{s(s+1)^3 + 1.3s^2 + 4.3s + 3.5} = \frac{1.3s^2 + 4.3s + 3.5}{s^4 + 3s^3 + 4.3s^2 + 5.3s + 3.5}$$

and the static gain is $3.5/3.5 = 1$.

The static gains imply that the reference will be tracked to 78% in the P-controller case, while tracked fully in the PI and PID cases. In other words, the PI and PID controllers can remove stationary errors, i.e., make $e(t) \to 0$ as $t \to 0$.

7.3 The differential equation becomes:

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

In the Laplace-domain:

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

The amplitude for $\omega = 1$ is $10/\sqrt{101} \approx 1$ while the amplitude for $\omega = 100$ is ≈ 0.1. Low frequency signals can pass through unchanged while high frequency signals are attenuated.

Solutions to Chapter 8. State feedback, biomechanics and posture control

8.1 The force is given by

$$F = -(K_S + K_P + \eta)x = -3.3 \cdot (-0.1) = 0.33 \text{ force units.}$$

8.2

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

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

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

b. 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 parameter m is positive as it is the mass. The value under the square-root is always positive as $k > c^2/4m$ by assumption. Thus, the stability is only dependent on the sign of c. $c > 0$ renders a stable system while negative c makes it unstable.

8.3

a. The transfer function is given by

$$G_{yC}(s) = \begin{bmatrix} 0 & 1/V \end{bmatrix} \begin{pmatrix} s + k_{abs} & 0 \\ -0.9k_{abs} & s + k_{dec} \end{pmatrix}^{-1} \begin{bmatrix} 1 \\ 0 \end{bmatrix} = \frac{0.9k_{abs}}{V(s + k_{abs})(s + k_{dec})}.$$

The poles of the system are given by $-k_{abs}$ and $-k_{dec}$. *Alternative solution:* First, consider the transfer function from C to q_{int}. Then construct the transfer function from q_{int} to q_{blo}. Lastly, determine the transfer function from q_{blo} to y, by isolating the three equations. The transfer function from C to q_{int} is given by $k_{abs}/(s + k_{abs})$ (via the Laplace transform of the first system's equation). Similarly, the transfer function from q_{int} to q_{blo} is given by $k_{abs}/(s + k_{dec})$. Lastly, the transfer function from q_{blo} to y is given by $1/V$. We can then construct the transfer function from C to y as follows:

$$G_{yC}(s) = G_{yq_{blo}} \cdot G_{q_{blo}q_{int}} \cdot G_{q_{int}C} = \frac{0.9k_{abs}}{V(s + k_{dec})(s + k_{abs})}.$$

b. The static gain is given by $G_{yC}(0) = 0.9/(Vk_{dec})$. If there is a constant intake of $C(t) = x$ [g/min], then the glucose concentration is plasma will become $0.9x/(Vk_{dec}) \approx 0.04x$ [g/l] as $t \to \infty$.

c. We know that

$$Y(s) = G_{yC}(s)C(s) = \frac{0.9k_{abs}}{V(s + k_{abs})(s + k_{dec})}C(s)$$

and the control law gives that $C(s) = KR(s) - KY(s)$. Hence, $Y = G_{yc}(KR(s) - KY(s))$ which gives us the closed-loop transfer function

$$\frac{Y(s)}{R(s)} = \frac{KG_{yc}}{1 + KG_{yc}} = \frac{K0.9k_{abs}}{V(s + k_{abs})(s + k_{dec}) + K0.9k_{abs}}.$$

The poles are thus given by the solutions of

$$V(s + k_{abs})(s + k_{dec}) + K0.9k_{abs} = 0$$
$$5(s + 10)(s + 5) + K0.9 \cdot 10 = 0$$
$$(s + 10)(s + 5) + 1.8K = 0$$
$$s^2 + 15s + 50 + 1.8K = 0$$

which are $-(15 \pm \sqrt{15^2 - 7.2K})/2$.

d. Consider the open-loop system on state space form

$$\begin{bmatrix} \dot{q}_{int} \\ \dot{q}_{blo} \end{bmatrix} = \begin{bmatrix} -k_{abs} & 0 \\ k_{abs} & -k_{dec} \end{bmatrix} \begin{bmatrix} q_{int} \\ q_{blo} \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} C(t)$$
$$y = \begin{bmatrix} 0 & \frac{1}{V} \end{bmatrix} \begin{bmatrix} q_{int} \\ q_{blo} \end{bmatrix}.$$

Write the control law as

$$C(t) = r - \begin{bmatrix} l_1 & l_2 \end{bmatrix} \begin{bmatrix} q_{int} \\ q_{blo} \end{bmatrix}.$$

The closed-loop system can then be written as

$$\begin{bmatrix} \dot{q}_{int} \\ \dot{q}_{blo} \end{bmatrix} = \left(\begin{bmatrix} -k_{abs} & 0 \\ k_{abs} & -k_{dec} \end{bmatrix} - \begin{bmatrix} 1 \\ 0 \end{bmatrix} \begin{bmatrix} l_1 & l_2 \end{bmatrix} \right) \begin{bmatrix} q_{int} \\ q_{blo} \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} r$$
$$y = \begin{bmatrix} 0 & \frac{1}{V} \end{bmatrix} \begin{bmatrix} q_{int} \\ q_{blo} \end{bmatrix}.$$

and further to

$$\begin{bmatrix} \dot{q}_{int} \\ \dot{q}_{blo} \end{bmatrix} = \underbrace{\begin{bmatrix} -k_{abs} - l_1 & -l_2 \\ k_{abs} & -k_{dec} \end{bmatrix}}_{=A} \begin{bmatrix} q_{int} \\ q_{blo} \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} r$$
$$y = \begin{bmatrix} 0 & \frac{1}{V} \end{bmatrix} \begin{bmatrix} q_{int} \\ q_{blo} \end{bmatrix}.$$

The poles are given by the solution to

$$\det(sI - A) = 0$$
$$(s + k_{abs} + l_1)(s + k_{dec}) + l_2 k_{abs} = 0$$
$$s^2 + (l_1 + k_{abs} + k_{dec})s + (k_{abs} + l_1)k_{dec}l_2 k_{abs} = 0$$
$$s^2 + (l_1 + 15)s + 50(l_1 + 10)l_2 = 0$$

which are $(-(l_1 + 15) \pm \sqrt{(l_1 + 15)^2 + 200(l_1 + 10)l_2})/2$.

e. The poles of the open-loop system are $-k_{abs} = -10$ and $-k_{dec} = -5$. Given the first control law, the poles are

$$p_1 = (-15 + \sqrt{15^2 - 7.2K})/2, \quad p_2 = (-15 - \sqrt{15^2 - 7.2K})/2.$$

If we pick $K = 15^2/7.2$, the expression in the square-root becomes zero. Thus, we have a double pole in $-15/2$, i.e., in between the two poles of the open-loop system. For $K > 15^2/7.2$ the expression under the square-root becomes negative and we get poles $-15/2 \pm ik$ where k is dependent on the magnitude of K. Hence, the speed of the dynamics does not increase, they only become oscillative. For $0 < K < 15^2/7.2$, the poles range between -15 and 0^-. For $K \leq 0$, the system becomes unstable (or neutrally stable).

Given the second control law, the poles are

$$p_1 = (-(l_1 + 15) + \sqrt{(l_1 + 15)^2 + 200(l_1 + 10)l_2})/2$$
$$p_2 = (-(l_1 + 15) - \sqrt{(l_1 + 15)^2 + 200(l_1 + 10)l_2})/2.$$

If we let $l_2 = -\frac{(l_1+15)^2}{200(l_1+10)}$, the expression under the square-root becomes zero. Then, we can choose l_1 to get arbitrarily fast dynamics. Thus, the second control law, i.e., the state feedback law is more flexible.

8.4 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 $l_1 = 5/2 = 2.5$, $l_2 = 32/3 = 10.7$. 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*.)

8.5   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, $u = -l_1 x_1 - l_2 x_2 - l_3 x_3 = -Lx$, the characteristic equation of the closed loop system becomes

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

$$= s^3 + (bl_3 + al_1)s^2 + \omega_0(-\omega_0 + al_2)s - \omega_0^2 bl_3 = 0$$

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

$$\begin{cases} l_1 = \dfrac{1}{a}\left(\alpha\big(1 + \dfrac{\omega^2}{\omega_0^2}\big) + 2\zeta\omega\right) \\[3mm] l_2 = \dfrac{1}{a\omega_0}(2\alpha\zeta\omega + \omega^2 + \omega_0^2) \\[3mm] l_3 = -\dfrac{\alpha\omega^2}{b\omega_0^2} \end{cases}$$

Solutions to Chapter 9. The Hodgkin-Huxley model

9.1 The Nernst equation for ion [i] is given by

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

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 %.

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

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

$$V_{P_{Na}\to\infty} = \lim_{P_{Na}\to\infty} \frac{\text{RT}}{\text{F}}\ln\left(\frac{P_K[K]_2 + P_{Na}[Na]_2 + P_{Cl}[Cl]_1}{P_K[K]_1 + P_{Na}[Na]_1 + P_{Cl}[Cl]_2}\right)$$

$$= \lim_{P_{Na}\to\infty} \frac{\text{RT}}{\text{F}}\ln\left(\frac{\frac{P_K}{P_{Na}}[K]_2 + [Na]_2 + \frac{P_{Cl}}{P_{Na}}[Cl]_1}{\frac{P_K}{P_{Na}}[K]_1 + [Na]_1 + \frac{P_{Cl}}{P_{Na}}[Cl]_2}\right) = \frac{\text{RT}}{\text{F}}\ln\left(\frac{[Na]_2}{[Na]_1}\right)$$

9.3 a.
```
% 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');
```

b. $m(t)$ - Na$^+$ activation (of channels)

$h(t)$ - Na$^+$ de-activation (of channels)

$n(t)$ - K$^+$ activation (of channels)

9.4
```
        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, which only filters the external current through the mebrane. It can not simulate an action potential. Thus, it is the currents of Na and K in response to the external current that are responsible for the action potential.

9.5 a.
```
        V = ss(0,1,1,0);
        T = 0:0.1:2*pi;
        lsim(V,sin(2*T),T)
```

During a period of the current, i.e., $[0, \Pi]$, the voltage is increased from zero to one and then lower again.

b.
```
        g_L = 0.3;
```

```
E_L  =  −59;
i_L  =  @ (V)  −g_L * (V−E_L);
fplot (i_L, [−90 70])
```

The current i_L is positive for $V \in [-90, -E_L]$ and then negative. That is, when the potential V is larger than E_L, the current changes direction.

c. The dynamics are given by

$$C_m \frac{dV}{dt} = i(t) = i_{Na} + i_K + i_L$$

which is exactly the Hodgkin-Huxley model.

Solutions to Chapter 10. Blood flow control and heart rate dynamics

10.1 Cardiac output is the stroke volume times the heart rate, i.e., 3 l/min. The cardiac index is the cardiac output divided by the body surface area, which becomes ≈ 1.9 l/min·m^2.

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

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

The phase of the process is:

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

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.

10.3

a. Parameters: C - arterial compliance, R peripherial resistance, R_a - aortic resistance, L - inertia coefficient of blood flow.

Input: q_i- aortic blood inflow

States: p- aortic blood pressure distally, $\dot{q}_L$ - inertia flow,

Output/measurement: p_a - aortic blood pressure proximally.

b. The system matrices become:

$$A = \begin{bmatrix} -\frac{1}{RC} & 0 \\ 0 & -\frac{R_a}{L} \end{bmatrix}$$

$$B = \begin{bmatrix} \frac{1}{C} \\ \frac{R_a}{L} \end{bmatrix}$$

$$C = \begin{bmatrix} 1 & -R_a \end{bmatrix}$$

$$D = R_a$$

with $x = [p \quad \dot{q}_L]$, $u = \dot{q}_i$ and $y = p_a$.

The transfer function is given by:

$$G(s) = C(sI - A)^{-1}B + D = \frac{R}{RCs + 1} - \frac{R_a}{\frac{L}{R_a}s + 1} + R_a$$

c. Static gain:

$$G(0) = R$$

d. The poles are (which can be seen directly from the A-matrix) $-\frac{1}{RC}$ and $-\frac{R_a}{L}$.

e. The system cannot become unstable since R, C, R_a are positive numbers.

10.4

a. The main difference is that the VDP model is nonlinear while the viscoelastic model is linear. The terms in front of $\dot{y}$ in the VDP and viscoelastic models are $-\nu(1 - y^2)$ and c, respectively, where the first term is nonlinear while the second is just a constant.

b.
```
nu = 1;
c = @(y) -nu*(1-y^2);
fplot(c,[-2 2])
```

Yes, the value of $c(y)$ ranges between positive and negative values for this set of y-values.

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

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ -1 & -c \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

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

The first case with $c = 0.1$ can be simulated as follows:

```
c = 0.1;
f = @(t,x) [0 1; -1 -c]*x;
[T,sol] = ode45(f,[0 100],[-0.1 0.1]);

plot(T,sol(:,1))
```

It illustrates positive damping. The dynamics are damped from their initial state and reach the equilibrium point $y = 0$.

The second case with $c = -0.1$ can be simulated in a similar manner as follows

```
c = -0.1;
f = @(t,x) [0 1; -1 -c]*x;
[T,sol] = ode45(f,[0 5],[-0.1 0.1]);

plot(T,sol(:,1))
```

However, as you notice, the dynamics are unstable. In fact, this illustrates negative damping, i.e., the opposite of damping, and will move the states away from the equilibrium point.

d. With $x_1 = y$ and $x_2 = \dot{y}$ and the VDP model on state space form is as follows

$$\dot{x}_1 = x_2$$
$$\dot{x}_2 = \nu(1 - x_1^2)x_2 - x_1$$
$$y = x_1.$$

e. $\nu = 0.1$:

```
nu = 0.1;
f = @(t,x) [x(2); nu*(1-x(1)^2)*x(2)-x(1)];

[T,sol] = ode45(f,[0 200],[-0.1 0.1]);

plot(T,sol(:,1))
```

Sinusoidal-looking behavior that reaches a maximum amplitude and then stays there.

$\nu = 10$:

```
nu = 10;
f = @(t,x) [x(2); nu*(1-x(1)^2)*x(2)-x(1)];

[T,sol] = ode45(f,[0 200],[-0.1 0.1]);

plot(T,sol(:,1))
```

Sharper behavior, however, still periodic that also find a maximum amplitude and then stays there.

f. Initialized in $y(0) = 3$, $\dot{y}(0) = 0.1$

```
nu = 10;
f = @(t,x) [x(2); nu*(1-x(1)^2)*x(2)-x(1)];

[T,sol] = ode45(f,[0 200],[3 0.1]);

plot(T,sol(:,1))
```

The trajectory of y finds its way to the same behavior as given the other initial condition.

g. The stationary point is given by $(x_1, x_2)^0 = (0, 0)$. The linearized system around this point is given by

$$\begin{bmatrix} \dot{\Delta x_1} \\ \dot{\Delta x_2} \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -1 & \nu \end{bmatrix} \begin{bmatrix} \Delta x_1 \\ \Delta x_2 \end{bmatrix},$$
$$y = \begin{bmatrix} 1 & 0 \end{bmatrix} \Delta x.$$

h. The eigenvalues of

$$\begin{bmatrix} 0 & 1 \\ -1 & \nu \end{bmatrix}$$

are given by $p(p - \nu) + 1 = 0$, i.e., $p = \frac{\nu}{2} \pm \sqrt{(\nu/2)^2 - 1}$. As $\nu > 0$, the real-part of the eigenvalues will always be positive, i.e., the system is unstable.

Solutions to Chapter 11. State estimation and System Identification

11.1a. The static gain of the system is equal to C and thus, $C = 0.1$ as read from the plot.

  b. Given the sinusoidal input $sin(t)$, the response should have the form $V(t) = Asin(t + \phi)$, where $A = |V(i)| = \frac{C}{\sqrt{1+(RC)^2}}$. Thus, $R = \sqrt{C^2/A^2 - 1}/C = \sqrt{0.1^2/0.097^2 - 1}/0.1 \approx 2.5$.
  The true values are $R = 2.4$ and $C = 0.1$.

11.2a. Let the regressor matrix be

$$\Phi = \begin{pmatrix} 1 & x_1 \\ 1 & x_2 \\ 1 & x_3 \\ 1 & x_4 \end{pmatrix} = \begin{pmatrix} 1 & 1 \\ 1 & 3 \\ 1 & 5 \\ 1 & 7 \end{pmatrix}$$

where x_i is the i-th value of x in the table given in the exercise.
The least squares solution is then

$$\begin{pmatrix} \hat{a} \\ \hat{b} \end{pmatrix} = (\Phi^T \Phi)^{-1} \Phi^T y = \begin{pmatrix} 2.65 \\ 0.65 \end{pmatrix}$$

where $y = \begin{pmatrix} 3 & 5 & 6 & 7 \end{pmatrix}^T$.
Hint: there is a formula on how to compute the inverse of a 2-by-2 matrix.
In MATLAB it could be calculated as

```
P = [1 1; 1 3; 1 5; 1 7];
y = [ 3 5 6 7]';
e = P\y;

% or

e = inv((P'*P))*P'*y;
```

Where a = e(1) and b =e(2). This uses the least squares method to fit $a + bx$ to the points. Plot the points and the line in the same plot to see the fit.

  b.
```
a = e(1);
b = e(2);

f = @(x) a +b*x;
figure
fplot(f,[1 7])
hold on
plot([1 3 5 7],y,'*r')
```

c.
```
f = @(x) 2.7+0.6*x;
hold on
fplot(f,[1 7],'g')
```

d.
```
P = [1 1; 1 3; 1 7];
y = [ 3 5 7]';
e = P\y;

% or

e = inv((P'*P))*P'*y;
```

The estimates are both lowered.

11.3

a. The transfer function is $G(s) = \frac{\beta}{s+\alpha}$ where $\beta = 1/V_1$ and $\alpha = k$. These are both identifiable. The system response can be determined as $y(t) = D\beta e^{-\alpha t}$. By examining the plot of the response β can be detrmined as $\beta = y(0)/D$. Thereafter, α can be determined by any other point on the curve of the system response.

b. The transfer function is $G(s) = \frac{\frac{1}{V_1}}{s+k_{21}+k_{01}} = \frac{\beta}{s+\alpha}$. V_1 is uniquely identifiable but k_{01} and k_{21} are not. Can only determine the sum of k_{01} and k_{21}, not separate them.

11.4

a. Let the regressor matrix be

$$\Phi = \begin{pmatrix} 1 & u_1 & u_1^2 \\ 1 & u_2 & u_2^2 \\ 1 & u_3 & u_3^2 \\ 1 & u_4 & u_4^2 \end{pmatrix} = \begin{pmatrix} 1 & 1 & 1 \\ 1 & 2 & 4 \\ 1 & 3 & 9 \\ 1 & 4 & 16 \end{pmatrix}$$

where u_i is the i-th value of u in the table given in the exercise.
The least squares solution is then

$$\begin{pmatrix} \hat{a} \\ \hat{b} \\ \hat{c} \end{pmatrix} = \left(\Phi^T\Phi\right)^{-1}\Phi^T y = \begin{pmatrix} 1 \\ 2 \\ 3 \end{pmatrix}$$

where $y = \begin{pmatrix} 6 & 17 & 34 & 57 \end{pmatrix}^T$.
Hint: there is a formula on how to compute the inverse of a 3-by-3 matrix.

b. The noise alter the estimates. The larger the noise is, the more it changes the estimates.

11.5

a.

$$A = \begin{bmatrix} -1 & 0 \\ 0.9 & -2 \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} 0 & 1 \end{bmatrix}$$

b. $\dot{\tilde{x}} = \dot{x} - \dot{\hat{x}}$ gives

$$\dot{\tilde{x}} = (A - LC)\tilde{x}$$

c. If we can show that $(A + LC)$ have poles in the left half plane, it follows that $\tilde{x}$ goes to zero. In general we have that

$$|sI - A + BL| = \begin{vmatrix} s+1 & l_1 \\ -0.9 & s+2+l_2 \end{vmatrix}$$

For the specific L it is easy to find that $|sI - A - BL| = (s+1)(s+2+l_2)$. the poles are strictly negative for $l_2 > -2$.

11.6

a. First, let's consider the methanol metabolism. Using the information about the half-life the elimination constant is determined to:

$$k_{e,M} = \frac{\ln 2}{T_{1/2}} = 0.041 h^{-1}$$

Using this together with the information about the formic acid metabolism, a state-space model(A, C, no B or D since there is no input) of the combined compartment models of the methanol and formal acid metabolism becomes:

$$A = \begin{bmatrix} -k_{e,M} & 0 & 0 \\ r_L & -(k_{LB} + k_{e,F}) & k_{BL} \\ 0 & k_{LB} & -k_{BL} \end{bmatrix}$$

$$C = \begin{bmatrix} 0 & 0 & 1/V_B \end{bmatrix}$$

with x_1 representing methanol content, x_2 the liver content of formic acid and x_3 the blood content of formic acid. Using an observer the state estimation becomes

$$\dot{\hat{x}} = A\hat{x} + K(y - \hat{y})$$
$$\hat{y} = C\hat{x}$$

and

$$\tilde{x} = x - \hat{x}$$
$$\dot{\tilde{x}} = (A - KC)\tilde{x}$$

where

$$K = \begin{bmatrix} k_1 \\ k_2 \\ k_3 \end{bmatrix}$$

The characteristic polynomial:

$$\det(sI - A + KC) = \begin{vmatrix} s + k_{e,M} & 0 & k_1/V_B \\ -r_L & s + (k_{LB} + k_{e,F}) & -k_{BL} + k_2/V_B \\ 0 & -k_{LB} & s + k_{BL} + k_3/V_B \end{vmatrix}$$
$$= (s + k_{e,M})(s + (k_{LB} + k_{e,F}))(s + k_{BL} + k_3/V_B) +$$
$$k_{LB}(-k_{BL} + k_2/V_B)) + r_L(k_{LB}k_1/V_B)$$

should match:

$$(s - p_1)(s - p_2)(s - p_3)$$

where $p_i, i = [1, 2, 3]$ are the specified poles. After some algebra we can conclude that:

$$k_1 = \frac{V_B}{r_L k_{LB}}(p_1 p_2 p_3 - (k_{e,M}k_{LB}k_2/V_B + k_{e,M}k_{EF}k_3/V_B$$
$$+ k_{e,M}k_{LB}k_3/V_B + k_{e,M}k_{EF}k_{BL}))$$
$$k_2 = \frac{V_B}{k_{LB}}(p_1 p_2 + p_1 p_3 + p_2 p_3 - k_{e,M}(k_{LB} + k_{e,F} + k_{BL} + k_3/V_B)$$
$$- k_{LB}k_3/V_B - k_{e,F}k_{BL} - k_{e,F}k_3/V_B)$$
$$k_3 = V_B(p_1 + p_2 + p_3 - k_{e,M} - k_{LB} - k_{e,F} - k_{BL})$$

We can use `place` to verify the result:

```matlab
% System
A = [-0.041 0 0 ; 0.7 -0.4 0.2; 0 0.25 -0.2];
C = [0 0 1/V_B]; % We measure the formic acid concentration in blood
D = [];
% Determine observer gain
K = place(A',C',[-0.6 -0.8 -1.0])';
% Verify the eigenvalues of A-KC
eig(A-K*C)
```

b. Now, the measurements can be used as input in the observer system to estimate the states:

$$\dot{\hat{x}} = (A - KC)\hat{x} + Ky$$
$$(\hat{y} = C\hat{x})$$

Below is a matlab script for determining the observer and to try the observer on the data.

```
% Parameters
V_D = 50; % methanol distribution volume [liter]
V_L = 1.2; % Formic acid, liver volume [liter]
V_B = 5.7; % Formic acid, blood volume [liter]
% System
A = [−0.041 0 0 ; 0.7 −0.4 0.2; 0 0.25 −0.2];
C = [0 0 1/V_B]; % We measure the formic acid concentration in blood
D = [];
% Determine observer gain
K = place(A',C',[−0.6 −0.8 −1.0])';
% Simulate with data
load('metanol_data')
% Set up the system for the estimated state using the observer.
% Here, the measurements will act as an input variable, and thus K
% will be our B−matrix.
sys_est = ss(A−K*C,K,C,D);
x1_hat_0 = 11.3e−3*32*50; % Initial value of metanol converted
% to g in V_d
x23_hat_0 = Y(1)*V_B; % Initial value of formic acid in liver
% and in blood
x_hat_0 = [x1_hat_0;x23_hat_0;x23_hat_0];
[Y_hat,T_hat,X_hat] = lsim(sys_est,Y(2:end),[2:length(Y)],x_hat_0);
%─────────────
% Plots
figure
%
subplot 311
plot(Y,'Linewidth',2)
hold all
plot(T_hat,Y_hat,'Linewidth',2)
ylabel(sprintf(['FA blood conc.\n[mmol/l]']))
%
subplot 312
plot(1000*X_met,'Linewidth',2)
hold all
plot(T_hat,1000*X_hat(:,1)/(32*V_D),'Linewidth',2)
ylabel(sprintf('Met. conc.\n [mmol/l]'))
%
subplot 313
plot(X_fliver,'Linewidth',2)
hold all
plot(T_hat,X_hat(:,2)/V_B,'Linewidth',2)
ylabel(sprintf('FA liver conc.\n [mmol/l]'))
xlabel('Time [h]')
legend('Data','Estimate')
set(findall(gcf,'−property','FontSize'),'FontSize',20)
```
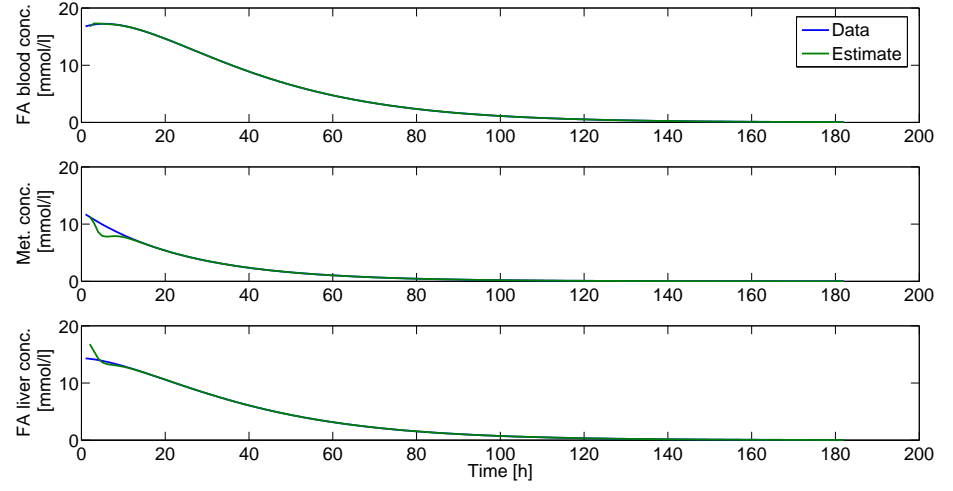
The code produces the plot in Fig. 10.1 below.

c. No, it is not since the system is not fully observable using this measurement. This can be seen from that the observability matrix O does not have full rank.

$$O = \begin{bmatrix} C \\ CA \\ CA^2 \end{bmatrix}$$

when

$$C = \begin{bmatrix} V_D & 0 & 0 \end{bmatrix}$$

Figure 11.1   Measurements

With

$$C = \begin{bmatrix} 0 & 0 & V_B \end{bmatrix}$$

however (using the formic acid blood concentration), the observability matrix becomes

$$O = \begin{bmatrix} 0 & 0 & 0.17 \\ 0 & 0.04 & -0.04 \\ 0.03 & -0.03 & 0.02 \end{bmatrix}$$

and clearly has full rank.