LUNDS
UNIVERSITET

Institutionen för
REGLERTEKNIK

Exam FRTF01 - Physiological Models and Computation

December 19 2013, 14-19

Points and grades

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

Betyg 3: 0–16.5 points
4: 17 –21.5 points
5: 22 –25 points

Accepted aid

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

Results

The result of the exam will be posted in LADOK no later than January 15. Information on when the corrected exam papers will be shown, will be given on the course homepage.

1. The half-life of a drug solution is 4 days. Assume it is eliminated from plasma as a linear process. If injected with the drug solution, how long will it take for the concentration in plasma to drop to 10 % of the initial concentration?

(2 p)

Solution

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

$$C(0) = C_0 \text{ [units/volume]}$$
$$\frac{dC}{dt} = -kC$$

The solution of the differential equation is

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

After 4 days, the concentration is halved. Therefore, if the half-life is stated as $t_{1/2} = 4$, 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,

$$k = \frac{\ln(2)}{t_{1/2}} = \frac{0.6931}{4} = 0.017 \text{ days}^{-1}$$

Then use the following equation

$$t = \frac{1}{k} \cdot \ln\left(\frac{C_0}{0.1 \cdot C_0}\right)$$

It takes approximately 13,5 days.

2. The data in Table 1 describes the concentration and reaction rates of a chemical process. It is an enzymatic reaction following the Michaelis-Menten relationship. Use the least-squares method to estimate the parameters V_{max} and K_m.

(3 p)

Tabell 1 Reaction Data for problem 2

Substrate Concentration [mM]	Reaction Velocity [mM/s]
0.1	0.04
1.0	0.24
2.0	0.32
5.0	0.42

Solution

The Michaelis-Menten relationship between substrate concentrations $[S]$ and reaction velocity v is:

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

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 as follows:
Let the regressor matrix be

$$\Phi = \begin{pmatrix} 1 & 1/s_1 \\ 1 & 1/s_2 \\ 1 & 1/s_3 \\ 1 & 1/s_4 \end{pmatrix} = \begin{pmatrix} 1 & 10 \\ 1 & 1 \\ 1 & 0.5 \\ 1 & 0.2 \end{pmatrix}$$

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

$$\begin{pmatrix} \hat{a} \\ \hat{b} \end{pmatrix} = \left(\Phi^T\Phi\right)^{-1}\Phi^T y = \begin{pmatrix} 1.9 \\ 2.3 \end{pmatrix}$$

where $y = \begin{pmatrix} 1/v_1 & 1/v_2 & 1/v_3 & 1/v_4 \end{pmatrix}^T$, $\hat{a} = 1/\hat{V}_{max}$ and $\hat{b} = \hat{K}_m/\hat{V}_{max}$.
Therefore

$$\hat{V}_{max} = 1/\hat{a} = 0.52 \quad [\text{mM/s}]$$
$$\hat{K}_m = \hat{b} \cdot \hat{V}_{max} = 1.2 \quad [\text{mM}]$$

3. The Hodgkin and Huxley model: Assume we have a neuron wich can be modeled by the Hodgkin and Huxley model stated in lecture 8. A neurotoxin lowers the permeability of the ion Na^+ across the neuron's membrane to approximately zero. What happens to the signaling properties of the cell?

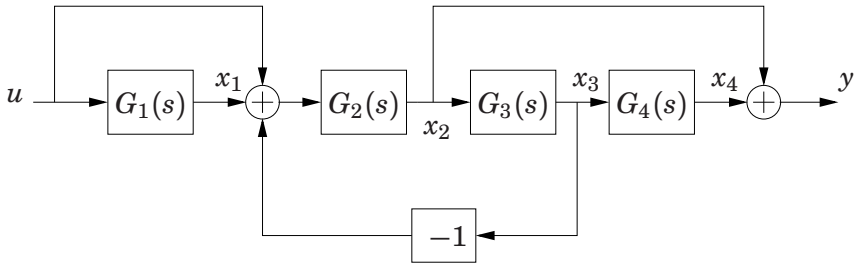
(1 p)

Solution

Due to the permeability of Na^+ being approximately zero, no such ions will flow across the neuron's membrane. Thus, I_{Na} will be zero. Then, the opening of the Na^+-channel will not have any effect on the membrane potential and the neuron will have difficulties depolarizing as usual (might not be able to spike).

4. Calculate the transfer function from u to y for the linear system in Figure 1.

(2 p)



Figur 1 The system in problem 4.

Solution

With the notation from the figure we get

$$\begin{aligned} X_1(s) &= G_1(s)U(s) \\ X_2(s) &= G_2(s)(U(s)(1+G_1(s)) - X_3(s)) \\ X_3(s) &= G_3(s)X_2(s) \\ X_4(s) &= G_4(s)X_3(s) \end{aligned}$$

Thus,

$$X_2(s) = G_2(s)(U(s)(1+G_1(s)) - G3(s)X_2(s)) = \frac{G_2(s)(1+G_1(s))}{1+G_2(s)G_3(s)}U(s)$$

$$\begin{aligned} Y(s) &= X_4(s) + X_2(s) = G_4(s)G_3(s)X_2(s) + X_2(s) \\ &= \frac{G_2(s)(1+G_4(s)G_3(s))(1+G_1(s))}{1+G_2(s)G_3(s)}U(s) \end{aligned}$$

The transfer function from u to y:

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

5. An unstable process has the transfer function

$$G_p(s) = \frac{3}{s^2 + 3s - 9}$$

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

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

(2 p)

b. Assume that the reference signal to the closed-loop system is a sinusoidal signal $r(t) = \sin(3t)$, and consider the system after a long time when all transients have disappeared. What is the output signal $y(t)$ of the closed-loop system when $K = 5$?

(1 p)

Solution

a. The closed-loop transfer function is given by

$$G_{cl}(s) = \frac{K\frac{3}{s^2+3s-9}}{1 + K\frac{3}{s^2+3s-9}} = \frac{3K}{s^2 + 3s - 9 + 3K}$$

The poles of the system are thus given by:

$$p = -\frac{3}{2} \pm \sqrt{\frac{45}{4} - 3K}$$

The closed-loop system will be asymptotically stable when all the poles are strictly less than zero.
Therefore, the following must hold

$$\sqrt{\frac{45}{4} - 3K} < \frac{3}{2}$$
$$3K > \frac{45}{4} - \frac{9}{4} = 9$$
$$K > 3$$

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

$$y(t) = |G_{cl}(3i)| \sin(3t + \arg G_{cl}(3i))$$

where

$$G_{cl}(3i) = \frac{3K}{-3^2 + 9i - 9 + 3K} = \frac{3K}{3K - 18 + 9i} = \frac{5}{-1 + 3i} = \frac{5(-1 - 3i)}{(-1 + 3i)(-1 - 3i)} = \frac{1}{2}(-1 - 3i)$$

This gives

$$y(t) = \sqrt{\frac{5}{2}} \sin(3t - \pi + \arctan 3)$$

6. A nonlinear system with two states (x_1, x_2) and one input signal (u) is described by the differential equations

$$\begin{aligned}\dot{x}_1 &= (1 - x_1^2)(2 - x_2) + u \\ \dot{x}_2 &= -x_2(x_2^2 - 1).\end{aligned}$$

Locally the equations can be approximated by the *linear* system

$$\Delta\dot{x} = A \cdot \Delta x + B \cdot \Delta u$$

around the stationary points.

a. Find all stationary points for $u = 0$ and determine the matrices A and B for each point. (3 p)

b. For which stationary points are the linear approximations (asymptotically) stable? (1 p)

Solution

a. By denoting $f(x_1, x_2, u) = ((1 - x_1^2)(2 - x_2) + u,\ -x_2(x_2^2 - 1))^T$ we get

$$\begin{aligned}\frac{\partial f}{\partial x} &= \begin{pmatrix} -2x_1(2 - x_2) & -(1 - x_1^2) \\ 0 & -3x_2^2 + 1 \end{pmatrix} \\ \frac{\partial f}{\partial u} &= \begin{pmatrix} 1 \\ 0 \end{pmatrix}.\end{aligned}$$

A and B are given by the above Jacobians evaluated at the stationary points. There are six stationary points, that is, solutions to the equation

$$f(x_1^o, x_2^o, 0) = 0,$$

namely $(1, 0)$, $(1, 1)$, $(1, -1)$, $(-1, 0)$, $(-1, 1)$ and $(-1, -1)$.
The approximations are given by $B = (1,\ 0)^T$ for all stationary points, and

$$\begin{aligned} A(1,0) &= \begin{pmatrix} -4 & 0 \\ 0 & 1 \end{pmatrix} & A(1,1) &= \begin{pmatrix} -2 & 0 \\ 0 & -2 \end{pmatrix} \\ A(1,-1) &= \begin{pmatrix} -6 & 0 \\ 0 & -2 \end{pmatrix} & A(-1,0) &= \begin{pmatrix} 4 & 0 \\ 0 & 1 \end{pmatrix} \\ A(-1,1) &= \begin{pmatrix} 2 & 0 \\ 0 & -2 \end{pmatrix} & A(-1,-1) &= \begin{pmatrix} 6 & 0 \\ 0 & -2 \end{pmatrix}. \end{aligned}$$

b. The linearization is asymptotically stable if all eigenvalues to A lie strictly in the left complex halfplane. This is satisfied for the stationary points $(1, 1)$ and $(1, -1)$.

7. We have a second-order system in state space form

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

We want to find a state feedback control law

$$u = l_r r - Lx$$

such that the closed-loop system will get stationary gain 1 from reference r to output y and such that the poles are located in -4 (double pole). Determine l_r and $L = \begin{pmatrix} l_1 & l_2 \end{pmatrix}$ such that the specification is satisfied. (3 p)

Solution

The desired characteristic polynomial is $(s+4)^2 = s^2+8s+16$. With feedback the characteristic polynomial is $\det(sI - A + BL) = s^2 + (4 + l_1)s + 3 + l_2$.

Matching coefficients gives $l_1 = 4$ and $l_2 = 13$.

The static gain is given by $C(-A + BL)^{-1}Bl_r = l_r/16$ and by setting this to equal 1 we get $l_r = 16$.

8. Arsenic Poisoning: Arsenic (I) acts by allosteric inhibition of the metabolic enzyme pyruvate dehydrogenase, PDH (S), which catalyzes the oxidation of pyruvate to acetyl-CoA (P). Allosteric inhibition means that arsenic may bind to the enzyme at another site than the normal active site, thereby forming new complexes that have reduced affinity for the substrate. The reduced rate of oxidation results in severely disturbed cell metabolism, and eventually in cell death. Some simplified enzymatic reactions describing this are:

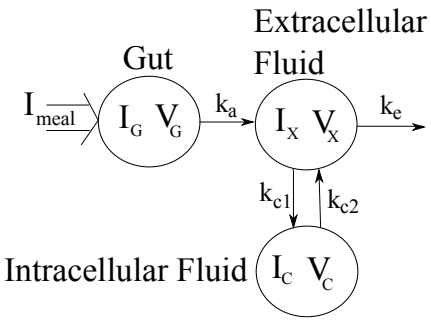
$$\begin{aligned} E + S &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \\ C_1 &\xrightarrow{k_2} E + P \\ E + I &\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \\ C_1 + I &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_3 \\ C_2 + S &\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_3 \end{aligned}$$

where C_1 is a complex formed of E and S, C_2 is a complex formed of E and I, and finally C_3 is a complex formed by binding of I to C_1 or by S to C_2.

a. Derive the differential equations for the substrate, enzyme, inhibitor and complex concentrations.

(2 p)

b. In many developing countries the drinking water quality is low, and with significant levels of arsenic. A simplified compartment model describing the kinetics of the arsenic following digestion is given in Fig. 2. Here, I_n represents the amount of arsenic in the compartment with subscript n, and V_n the corresponding volume of distribution of that compartment. Set up a state-space representation of the system using the arsenic load I_{meal} as



Figur 2 Simplified arsenic kinetics model.

Tabell 2 Parameter values for the arsenic kinetics model

Parameter	Value
V_{max}	0.05 $[s^{-1}]$
K_i	1 $[\mu M]$
K_s	10 $[mM]$
k_a	0.05 $[min^{-1}]$
k_{c1}	0.03 $[min^{-1}]$
k_{c2}	0.001 $[min^{-1}]$
k_e	$5 \cdot 10^{-4}$ $[min^{-1}]$
V_G	1.2 [L]
V_X	11.1 [L]
V_C	6.4 [L]

input u and the intracellular concentration of arsenic as output y. Also provide the transfer function between these variables.

(3 p)

c. Based on the enzymatic reactions above, the production rate V of acetyl-CoA can be shown (under some assumptions not of relevance here) to follow:

$$V = \frac{V_{max}}{1 + [I_c]/K_i} \cdot \frac{[S]}{K_s + [S]}$$

where the subscript index c refers to the intracellular compartment. Assume that drinking the contaminated water can be approximated by a constant supply of 0.02 mg/day (0.27μmol/day). Calculate the maximum possible steady-state production rate of acetyl-CoA under these conditions given the set of parameters in Table 2.

(2 p)

Solution

Solution Arsenic Poisoning:

a. The differential equations become:

$$\begin{aligned}
\dot{e} &= -k_1 es + (k_{-1} + k_2)c_1 - k_3 ei + k_{-3}c_2 \\
\dot{s} &= -k_1 es + k_{-1}c_1 - k_3 c_2 s + k_{-3}c_3 \\
\dot{c}_1 &= k_1 es - (k_{-1} + k_2)c_1 - k_1 ic_1 + k_{-1}c_3 \\
\dot{c}_2 &= k_3 ei - k_{-3}c_2 - k_3 c_2 s + k_{-3}c_3 \\
\dot{c}_3 &= k_1 c_1 i - k_{-1}c_3 + k_3 c_2 s - k_{-3}c_3 \\
\dot{i} &= -k_3 ei + k_{-3}c_2 - k_1 c_1 i + k_{-1}c_3
\end{aligned}$$

b. With $x = [I_G \quad I_X \quad I_C]^T$, $u = I_{meal}$ and $y = I_C/V_C$, the state-space representation:

$$\begin{aligned}
\dot{x} &= Ax + Bu \\
y &= Cx + Du
\end{aligned}$$

becomes:

$$A = \begin{bmatrix} -k_a & 0 & 0 \\ k_a & -(k_e + k_{c1}) & k_{c2} \\ 0 & k_{c1} & -k_{c2} \end{bmatrix}$$

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

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

$$D = 0$$

The transfer function becomes:

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

Let

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

Multiplication with C and B gives:

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

Here,

$$Z_{31} = \frac{k_a k_{c1}}{\det(sI - A)}$$

and

$$\det(sI - A) = (s + k_a)((s + k_e + k_{c1})(s + k_{c2}) - k_{c1}k_{c2})$$

Thus,

$$G(s) = \frac{k_a k_{c1}}{V_C(s + k_a)((s + k_e + k_{c1})(s + k_{c2}) - k_{c1}k_{c2})}$$

c. First, determine the static gain:

$$G(0) = \frac{k_{c1}}{V_C k_e k_{c2}}$$

With the given parameter values and constant arsenic load of $0.27 \cdot 10^{-6}/1440$ mol/min, the concentration becomes:

$$[I_C]_{SS} = G(0)I_{meal} = 1.76\mu M$$

The maximal production rate of acetyl-CoA when arsenic is present is:

$$\frac{V_{max}}{1 + [I_C]_{SS}/K_i} = 0.018 \quad s^{-1}$$

Good Luck and Merry Christmas!