LUND UNIVERSITY

Department of
AUTOMATIC CONTROL

Exam FRTF01 - Physiological Models and Computation

January 14 2019, 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:

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

Accepted aid

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

Results

The result of the exam will be posted in LADOK no later than February 11. Information on when the corrected exam papers will be shown, will be given on the course homepage.

1. In Fig. 1 the reaction speed as a function of the substrate concentration is plotted for two different enzymatic reactions.

a. Which of the two plots follows a Michaelis-Menten relation? (1 p)

b. Estimate $V_{\max}$ and K_m from the reaction following a Michaelis-Menten relation. (1 p)

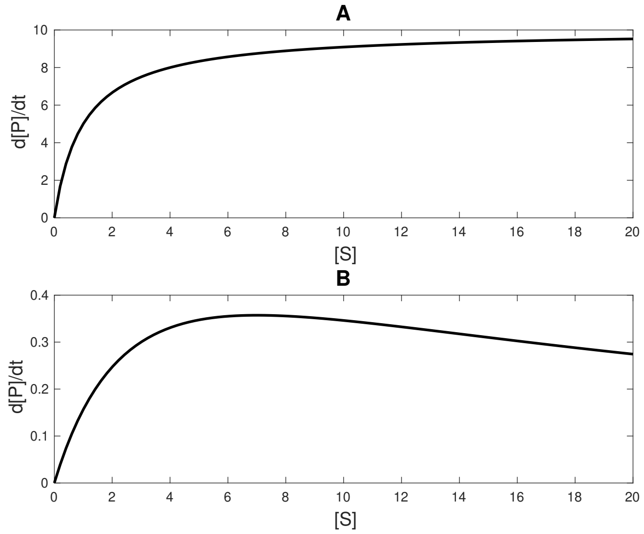


Figure 1: Reaction rate for an enzymatic reaction in Problem 1.

Solution

a. Plot A is following a Michaelis-Menten relationship. It follows a typical Michaelis-Menten relation while Plot B has a decrease in the reaction rate at the substrate increases.

b. Recall that for a Michaelis-Menten reaction the speed is given by

$$\frac{dP}{dt} = \frac{v_{max}S}{K+S}$$

From the graph we can see that $v_{max} \approx 10$. Further, for $S = K$ we should have that $dP/dt = v_{max}/2$. This gives that $K = 1$

2.

a. Which of the two equations below can **not** be a valid linearization of a system $\dot{x} = f(x,u)$, where x and u are scalars? (1 p)

$$\Delta\dot{x} = 1 + \Delta x + \Delta u \tag{1}$$

$$\Delta\dot{x} = 4\Delta x \tag{2}$$

b. Find all the stationary points (x_0, u_0) for $\dot{x} = x^2 - x + u^3 + u$ and $u_0 = 0$. Linearize the system around the stationary point that gives a stable linear system. (2 p)

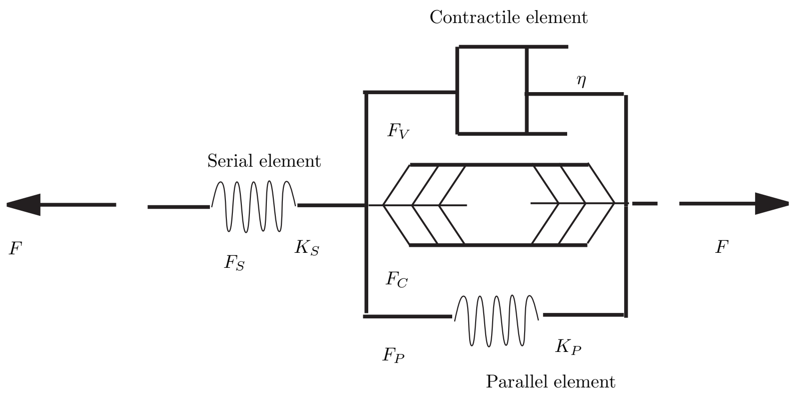


Figure 2: Serial Hill Model for problem 3.

Solution

a. The expression in (1) is not linear due to the constant term. And can thus not be a correct linearization.

b. We have $\dot{x} = f(x) = x(x-1) + u^3 + u$. Which for $u = 0$ is zero for $x_0 = 0$ and $x_0 = 1$. This gives stationary points $(0, 0)$ and $(1, 0)$.

For the linear system to be stable we need $f'_x(x_0, u_0) = 2x - 1 \leq 0$ which means that we should linearize around (0,0). Take $\Delta x = x$ and $\Delta u = u$ Then

$$\Delta\dot{x} = f'_x(0,0)\Delta x + f'_u(0,0)\Delta u = -\Delta x + \Delta u$$

3.

a. Can the main behavior of the Hodgkin-Huxley Model be approximated by a linear model? That is, there being a threshold potential for a spike to occur. (0.5 p)

b. What would it imply physiologically to assume that $K_S = \infty$ in the serial Hill model seen in Fig 2. (0.5 p)

c. Describe how you would choose your regressor matrix Φ if you want to do a least-squares estimation of $y = ax^2 - b$, where you have measurements of x and y. (1 p)

Solution

a. No, a linear system can not replicate that the output can change other than a scaling by scaling the input.

b. That the tendon does not expand when a force is applied to it.

c. You would form the rows of Φ on the form

$$\Phi_i = [x_i^2, -1]$$

(or $\Phi_i = [-1, x_i^2]$).

4. In this problem we consider the system $Y(s) = G(s)U(s)$ with transfer function

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

a. Determine the poles of the system and find a differential equation describing the relationship between $y(t)$ and $u(t)$. (1 p)

b. Find a state-space representation for $G(s)$. (1 p)

c. Find the impulse response of the system. (1 p)

d. Consider output feedback on the form $u = K(r - y)$. Draw a block diagram of the closed-loop system and determine for which K the closed loop system is stable. (2 p)

e. Describe the difference between output feedback and state feedback. (0.5 p)

Solution

a. We can factorize the denominator as $(s + 2)(s + 1)$ which shows that the system has poles in $s = -1$ and $s = -2$.

We have that

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

Taking the inverse Laplace transform gives

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

b. Let $x_1 = y$ and $x_2 = \dot{y}$. Then a state-space representation is given by

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

c. We can rewrite the transfer function as

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

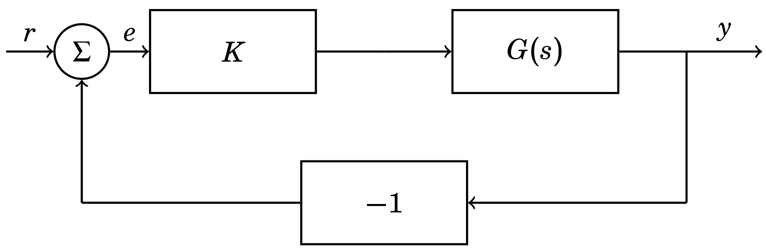
Using that Laplace transform of $\delta(s) = 1$ an the collection of formulae gives that the impulse response to be

$$h(t) = e^{-t} - e^{-2t}.$$

d. A block diagram can be seen bellow. The closed-loop transfer function is

$$\frac{GK}{1 + GK} = \frac{K}{s^2 + 3s + 2 + K}$$

With characteristic polynomial $s^2 + 3s + 2 + K$. This is stable when all coefficients are positive (see Collection of formulae). Thus we have that the closed loop is stable for $K > -2$.



e. For output feedback only the output of the system is used to calculate the input u. For state feedback, all the states of the system are used.

5.

a. Consider a drug with linear pharmacokinetics and a half life of 4 days. Find a differential equation describing the concentration given an initial concentration $C(0) = C_0$. (1 p)

b. Now assume that that we can continuously infuse the patient with the drug. Then the drug concentration is governed by

$$\dot{C} = -k_{p_1c}C + \frac{u(t)}{V}$$

Where V is the volume. The drugs path through the body is depicted in Fig. 3. Describe the system on state space form. Assume that all volumes are 1 and all reactions follows linear reaction speeds.

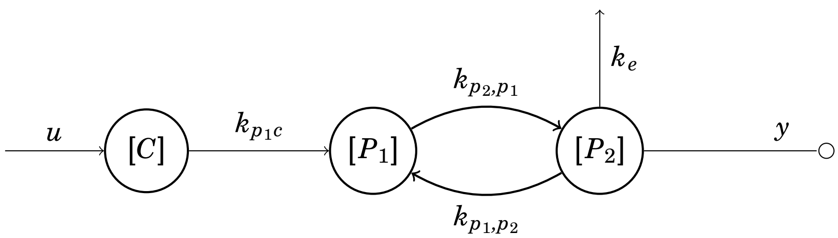


Figure 3: Compartment model for Problem 5.

(1.5 p)

c. Find the transfer function of the system.

Hint: You may find the following useful

$$\begin{bmatrix} a & 0 & 0 \\ b & c & d \\ 0 & e & f \end{bmatrix}^{-1} = \frac{1}{acf - eda} \begin{bmatrix} cf - ed & 0 & 0 \\ -bf & fa & -da \\ be & -ea & ca \end{bmatrix}.$$

(1.5 p)

d. Let

$$u = \begin{cases} 1 & t \geq 0 \\ 0 & t < 0. \end{cases}$$

Find $[P_2]$ as $t \to \infty$

(1 p)

Solution

a. A drug with linear pharmacokinetics follows $\dot{C}(t) = -kC(t)$, with solution $C(t) = C_0 e^{-kt}$. We know that $C(4) = C_0/2$. This gives that

$$e^{-4k} = \frac{1}{2} \Rightarrow -4k = \log\frac{1}{2} \Rightarrow k = \frac{1}{4}\log 2$$

b. Let $x_1 = [C]$, $x_2 = [P_1]$ and $x_3 = [P_2]$. Then the system is described by

$$\begin{aligned} \dot{x} &= \begin{bmatrix} -k_{p_1c} & 0 & 0 \\ k_{p_1c} & -k_{p_2,p_1} & k_{p_1,p_2} \\ 0 & k_{p_2,p_1} & -k_{p_1,p_2} - k_e \end{bmatrix} x + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} u \\ y &= \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} x \end{aligned}$$

c. The transfer function is given by $C(sI - A)^{-1}B$. Using the hint we find that

$$G(s) = C(sI-A)^{-1}B = C \begin{bmatrix} s + k_{p_1c} & 0 & 0 \\ -k_{p_1c} & s + k_{p_2,p_1} & -k_{p_1,p_2} \\ 0 & -k_{p_2,p_1} & s + k_{p_1,p_2} + k_e \end{bmatrix}^{-1} B$$

$$= \frac{k_{p_1,c} k_{p_2,p_1}}{(s + k_{p1,c})(s + k_{p_2,p_1})(s + k_{p_1,p_2} + k_e) - k_{p_2,p_1} k_{p_1,p_2}(s + k_{p_1c})}$$

d. The answer is given by the static gain of the system,

$$G(0) = \frac{k_{p_1,c} k_{p_2,p_1}}{(k_{p1,c})(k_{p_2,p_1})(k_{p_1,p_2} + k_e) - k_{p_2,p_1} k_{p_1,p_2}(k_{p_1c})} = \frac{1}{k_e}$$

6. Cerebral blood flow can be modeled by the following compartment model

$$\begin{aligned} \dot{C}_b(t) &= k_1 C_a(t) - k_2 C_b(t) \\ C_v(t) &= \lambda C_b(t) + (1-\lambda) C_a(t), \end{aligned}$$

where:

C_a is the blood concentration in arterial plasma.

C_b is the blood concentration in brain plasma.

C_v is the blood concentration in venous plasma.

λ is the relative perfusion index.

a. You want to use a tracer to estimate the parameters of the model. What are desirable characteristics of the tracer? (0.5 p)

b. Find a, b and d such that

$$\frac{C_v(s)}{C_a(s)} = \frac{b}{s+a} + d.$$

Now assume that a, b and d is know. Find expressions for k_1, k_2 and λ. (2 p)

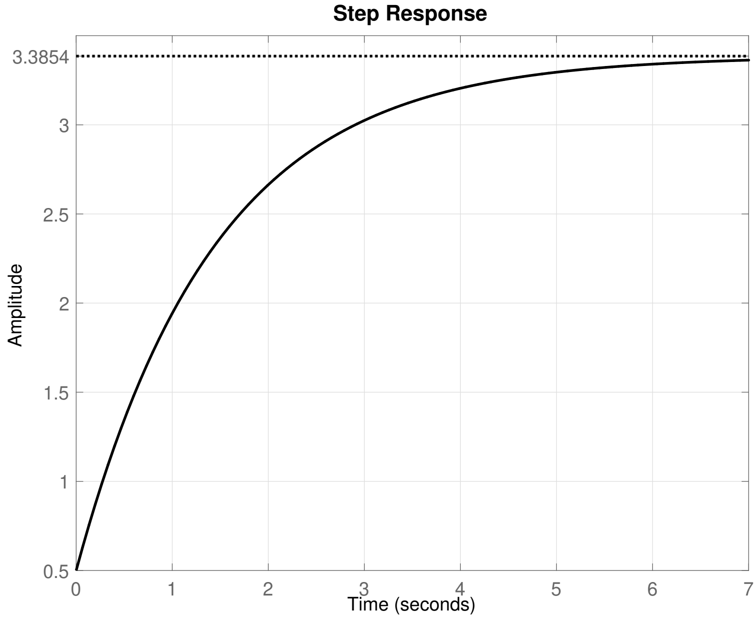


Figure 4: Tracer experiment in Problem 6.

c. A tracer infusion experiment has been conducted. All tracer concentrations are equal to zero before the start of the experiment. The tracer concentration in arterial plasma follows a step change at time zero. The resulting tracer concentration in venous plasma can be seen in Fig. 4 (last page). Estimate a, b and d. (2 p)

Solution

a. The tracer should have the same metabolic behavior as the blood and give no perturbations to the behavior It must also be distinguishable from the blood.

(While not needed for estimation, the tracer should also not have any side effects.) (0.5 p)

b. We have that

$$C_b(s) = \frac{k_1}{s+k_2} c_a$$

Dividing the second equation by C_a gives

$$\frac{C_v(s)}{C_a(s)} = \lambda \frac{C_b(s)}{C_a(s)} + (1-\lambda) = \frac{\lambda k_1}{s+k_2} + (1-\lambda).$$

Where we find that $b = \lambda k_1$, $a = k_2$ and $d = (1-\lambda)$.

This gives that $k_2 = a$, $\lambda = 1-d$ and $k_1 = b/\lambda = b/(1-d)$.

c. We aim to find $C_v(t)$ via the inverse Laplace transform. We have that

$$C_v(s) = \left(\frac{b}{s+a} + d\right)\frac{1}{s}.$$

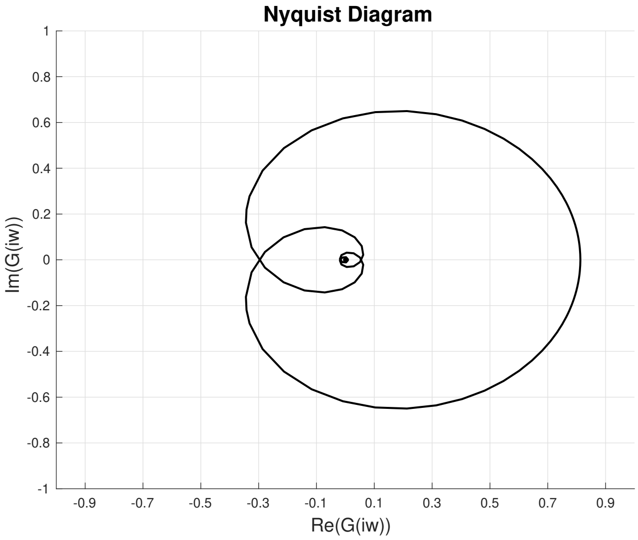


Figure 5: Nyquist plot for $G(s)$ in problem 7.

Which gives

$$C_v(t) = \frac{b}{a}(1 - e^{-at}) + d.$$

We see that $C_v(0) = 0.5$ which gives $d = 0.5$. Furthermore, at time $t = 1$ we have that $e^{-at} \approx 0.5$. which gives $a = \log(2)$. Finally, the final value is equal to $b/a + d$ which gives $b = (3.38 - 0.5) \cdot \log(2) \approx 2$.

7. In this problem we consider a system $G(s)$ with Nyquist diagram in Fig 5. (last page).

a. A friend says that the closed-loop of $G(s)$ has a phase margin of 90°. Is this true or false? Motivation required. (1.5 p)

b. Consider again closing the loop using $u = K(r - y)$, for $K \geq 0$. Another friend says that the closed-loop is only stable for $K < 1/0.8$. Is this true or false? Motivation required. (1.5 p)

Solution

a. False. The phase margin is actually infinite as all points has radius less than 1.

b. False, the points -1 is only encircled when $K > 1/0.3$.

Good Luck!