CS CM Homework 6

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I completed this written part of the homework, lab report, or exam entirely on my own.

Exercise 1 - Reversible Dimerization of 2 Proteins

Exercise 1

- the equilibrium dissociation constant :

$$K_d = \frac{P_{1\infty} P_{2\infty}}{D_\infty}$$

The ODEs : $-\dot{d}$

$$\dot{P}_1 = \frac{dP_1}{dt} = \frac{-d}{dt} = -k_1 P_1 P_2 + k_{-1} d = -V = -V_1 + V_{-1}$$

$$\dot{P}_2 = \frac{dP_2}{dt} = \frac{-d}{dt} = -k_1 P_1 P_2 + k_{-1} d = -V = -V_1 + V_{-1}$$

$$-\dot{d}$$

The stoichiometric matrix N :

$$N = \begin{bmatrix} -1 & 1 \\ -1 & 1 \\ 1 & -1 \end{bmatrix}$$

An **equilibrium constant**, designated by a upper case K, is the ratio of the **equilibrium concentrations** of reaction products to reactants or vice versa.

For the bimolecular reaction, A+B ⇔ AB, we can define an **equilibrium dissociation constant** (K_d) or an **equilibrium association constant** (K_a), which are reciprocally related, as shown below:

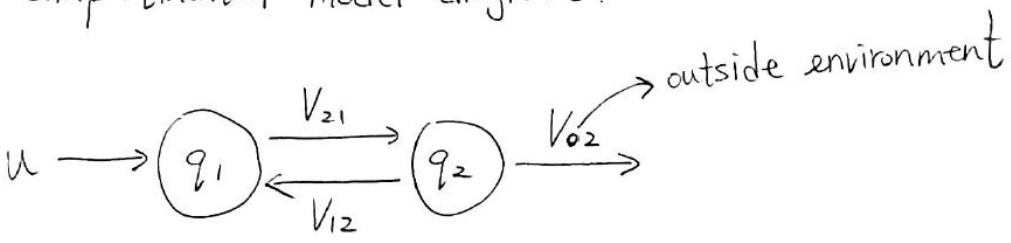
$$K_d = \frac{[A][B]}{[AB]} \qquad K_a = \frac{[AB]}{[A][B]}$$

Exercise 2 : NL PK Modeling from Multiple Experiments

Part (a)

Exercise 2

(a) A compartmental model diagram.



$u \equiv$ constant unit-step input of drug X

$q_1 \equiv$ quantity / amount of drug X in blood compartment

$q_2 \equiv$ quantity / amount of drug X in tissue compartment

$V_{21} \equiv$ the exchange flux / velocity of drug X from blood to tissue

$V_{12} \equiv$ the exchange flux / velocity of drug X from tissue to blood

$V_{02} \equiv$ the efflux of drug X from tissue to outside enviroment, the catabolism process of drug X in tissue

Exercise 2 : NL PK Modeling from Multiple Experiments
Continue Part (a)

Exercise 2

(a) Full ODE model

$$\frac{dq_1}{dt} = -V_{21} + V_{12} + u(t)$$

$$= \boxed{-k_{21} q_1 + \frac{C q_2}{K + q_2} + u(t)}$$

$$\frac{dq_2}{dt} = V_{21} - V_{02} - V_{12}$$

$$= \boxed{k_{21} q_1 - k_{02} q_2 - \frac{C q_2}{K + q_2}}$$

Exercise 2 : NL PK Modeling from Multiple Experiments
Part (b)

Based on the first additional study, I do not need to modify the original model developed in part (a). At the original experiment, we have assumed that all the velocities between the compartments are linear by the law of superposition on input and output responses. For the second repeated experiment, the exogenous step input of 0.5 magnitude of the original study produces a steady state value of half the magnitude of the unit step response. As a result, the law of superposition on input and output responses still holds. So, the original model is still linear.

Based on the second additional study, I need to modify the original model developed in part (a). At the original experiment, we have assumed that all the velocities between the compartments are linear by the law of superposition on input and output responses. However, when the repeated experiment has infused a dose 5 times greater in the first input study, it yields a steady state response about 3 times the magnitude of the first input study. As a result, the law of superpositions of input and output responses does not hold anymore. Therefore, we cannot assume all the velocities between the compartments are linear. So, the original model needs to be modified as a non-linear model.

Exercise 2 : NL PK Modeling from Multiple Experiments
Part (c)

In order to simulate the "mechanistic" modification, we need to treat the exchange velocity as nonlinear functions as linear when q1 values are low, but the exchange velocity becomes saturated / increases when input u increases.

Both the original model and the first variation of the experiment is linear since the steady state value of the magnitude of the unit-step response is proportional to the magnitude of the exogenous step-input. However, the second variation of the experiment infused a dose 5 times greater than the first input study and yielded a steady state response about 3 times the magnitude of the first input study.

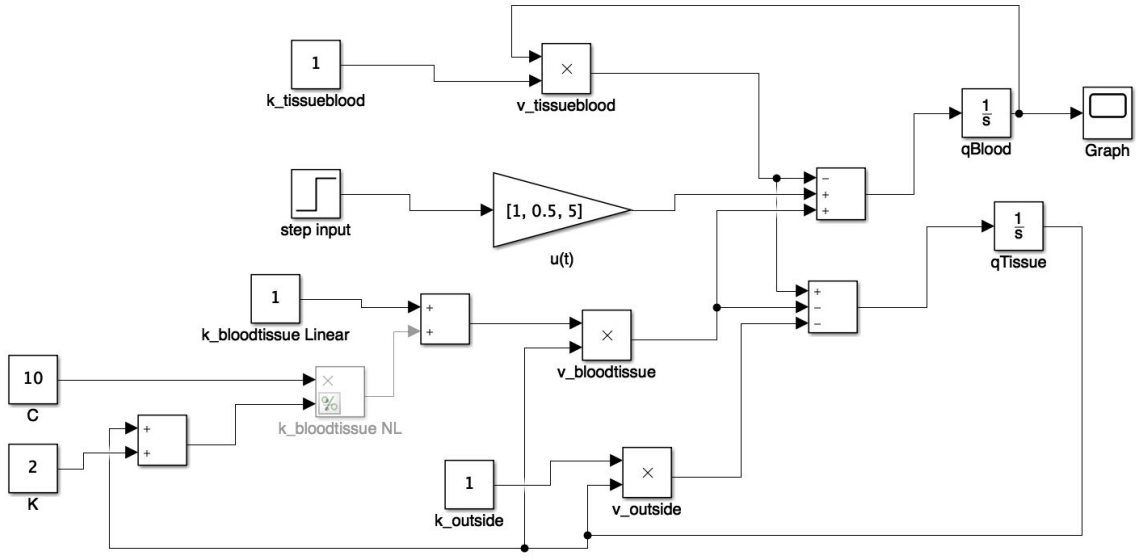
Therefore, the second experiment clearly shows the model has nonlinear influx of material into compartment 1 from compartment 2, of Michaelis Menten form, and linear front transfer.

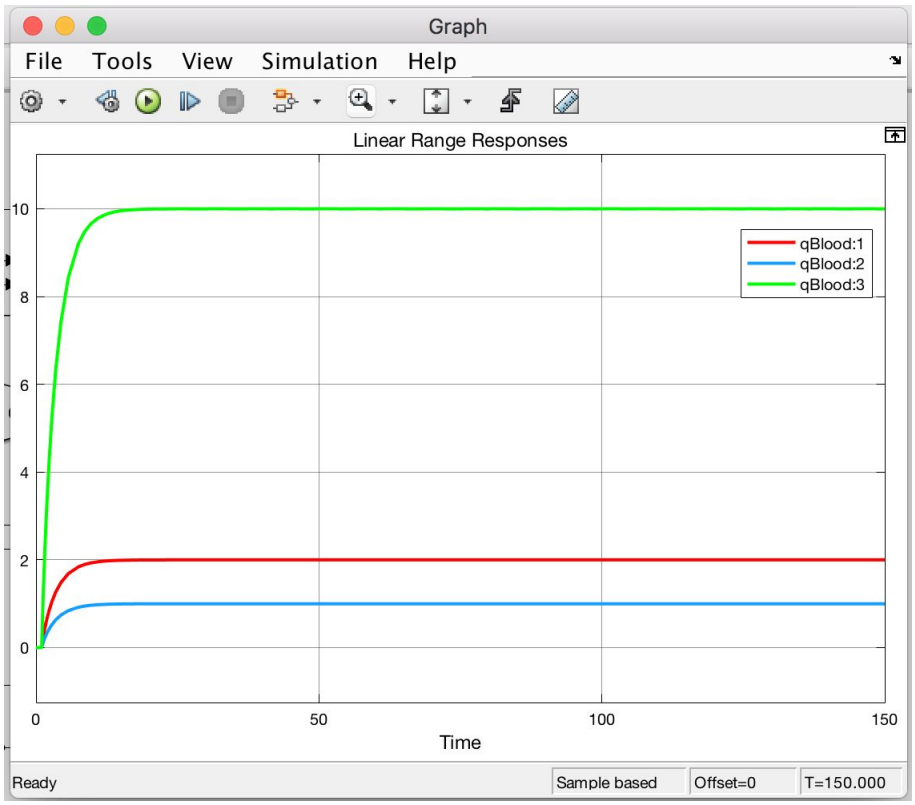
Exercise 2 : NL PK Modeling from Multiple Experiments
Continue Part (c)

Let assume the following for modeling in Simulink :

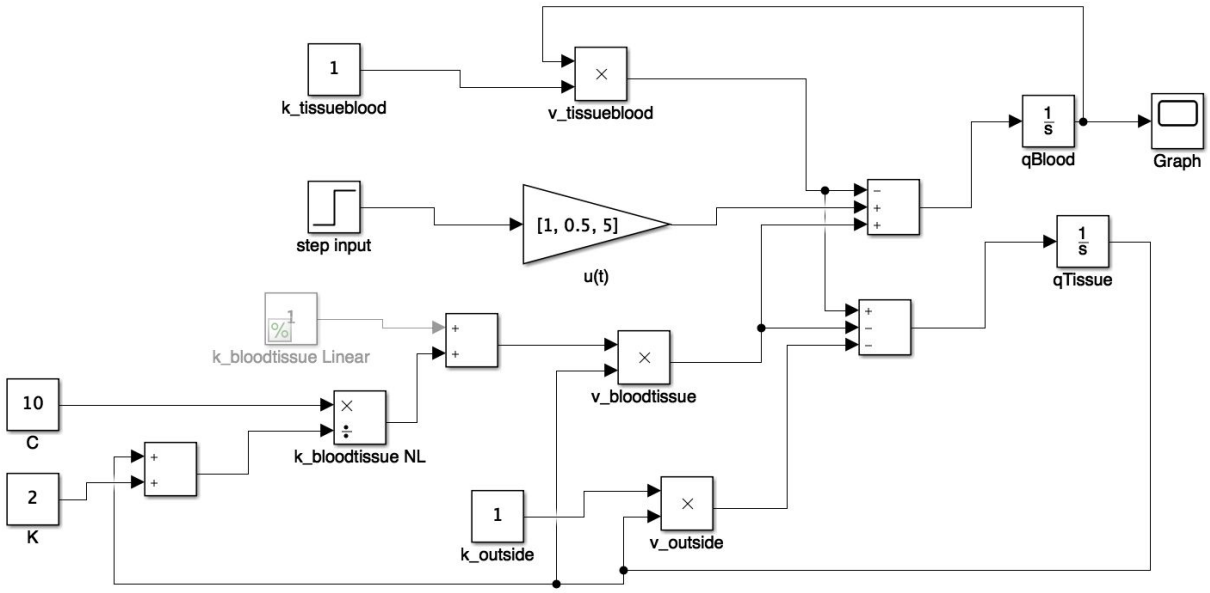
u(t) = D1(t)
C = 10
K = 2
$q_1(0) = q_2(0) = 0$

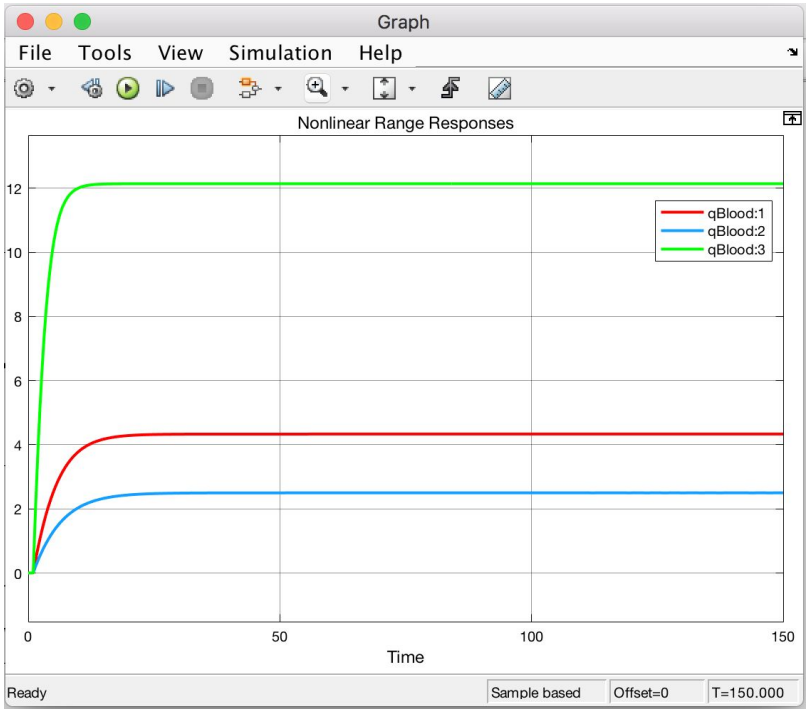
Linear Model





Nonlinear Model





Exercise 3 : NL PK Modeling

Part (a)

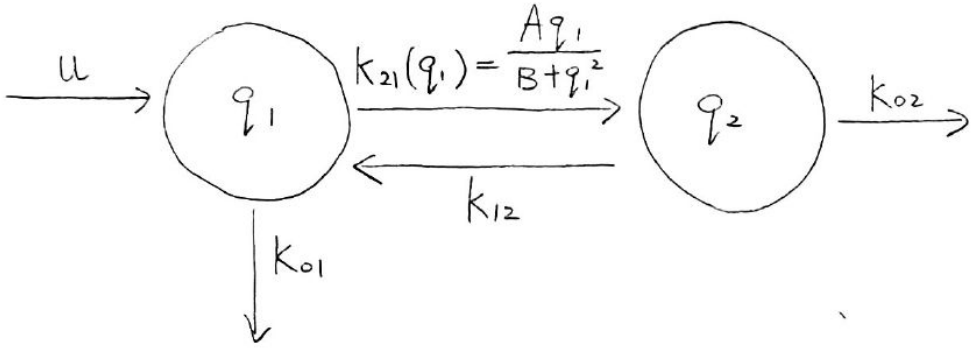
Exercise 3 – NL PK Modeling

(a) The compartmental model diagram

Given equations

$$\dot{q}_1 = -k_{01} q_1 - \frac{A q_1}{B + q_1^2} q_1 + k_{12} q_2 + u$$

$$\dot{q}_2 = \frac{A q_1}{B + q_1^2} q_1 - k_{02} q_2 - k_{12} q_2$$



Exercise 3 : NL PK Modeling
Part (b)

(b) The stoichiometric matrix

$$\dot{q}_1 = -V_{01} - V_{21} + V_{12} + u$$

$$\dot{q}_2 = V_{21} - V_{02} - V_{12}$$

$$\dot{q} = \begin{bmatrix} \dot{q}_1 \\ \dot{q}_2 \end{bmatrix} = \begin{bmatrix} -1 & 0 & 1 & -1 & 1 \\ 0 & -1 & -1 & 1 & 0 \end{bmatrix} \begin{bmatrix} V_{01} \\ V_{02} \\ V_{12} \\ V_{21} \\ u \end{bmatrix}$$

$$\dot{q}_1 = -V_{01} + V_{12} - V_{21} + u$$

$$\dot{q}_2 = -V_{02} - V_{12} + V_{21}$$

Exercise 4 : NL PK Modeling 2

Part (a) & Part (b)

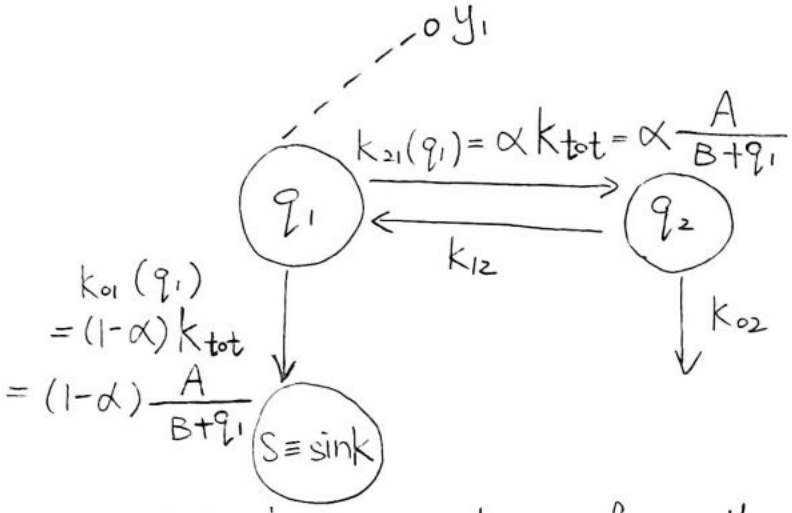
Exercise 4 – NL PK Modeling 2

part (a) The compartmental diagram

Let compartment 1 ≡ liver

Let compartment 2 ≡ gut

Let S ≡ sink connected to compartment 1



part (b) The equation for the model

$$\dot{q}_1 = V_{12} - V_{21} - V_{01} = k_{12} q_2 - \alpha \underbrace{\frac{A q_1}{B+q_1}}_{\to V_{tot}} - (1-\alpha) \frac{A q_1}{B+q_1} = \frac{dq_1}{dt}$$

$$\dot{q}_2 = V_{21} - V_{02} - V_{12} = \alpha \underbrace{\frac{A q_1}{B+q_1}}_{\to V_{tot}} - k_{02} q_2 - k_{12} q_2$$

$y_1 = \frac{q_1}{V_1}$ → mass of substance 1 / volume of substance 1

Exercise 5 : Changing from Concentration to Mass Fluxes in Biomolecule ODE Models

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$$V \equiv \frac{V_{max}\, S}{S + K_m} \quad \text{in} \quad \frac{\text{conc}}{\text{time}} \rightarrow \frac{\text{mass}}{\text{time}}$$

(K_m → constant)

$$S \equiv \frac{\text{mass}}{\text{volume}} \qquad V_{max} \equiv \frac{1}{\text{time}} \times \frac{\text{mass}}{\text{volume}} = \frac{\text{conc}}{\text{time}}$$

Multiply the LHS & RHS by volume, for RHS, multiply the volume top & bottom ($\rightarrow V'$)

$$V \times V' = \frac{V_{max}\, S\,(V')^2}{V'(S + K_m)} = \frac{V_{max}\, q\, V'}{V' S + V' K_m} = \frac{V_{max}\, q\, V'}{q + V' K_m}$$

Let $V_{max} V' \equiv V_{max}'$

Let $V' K_m \equiv K'$ since both V' & K_m are constants

$$\boxed{V \times V' = \frac{V_{max}'\, q}{q + K'}}$$