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BEBI5009: Mathematical Modeling of System Biology Homework 5

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1 5.6.3 Metabolic Control Analysis: supply and demand

Consider the two-step reaction chain $\xrightarrow{v_0} S \xrightarrow{v_1}$, where the reactions are catalysed by enzymes E_0 and E_1 with concentrations e_0 and e_1. The Summation Theorem (Section 5.2.1) states that

$$C^J_{e_0} + C^J_{e_1} = 1$$

A complementary result, the Connectivity Theorem (Heinrich and Schuster, 1996) states that

$$C^J_{e_0}\epsilon^0_S + C^J_{e_1}\epsilon^1_S = 0$$

a) Use these two statements to determine the flux control coefficients of the two reactions as

$$C^J_{e_0} = \frac{\epsilon^1_S}{\epsilon^1_S - \epsilon^0_S}$$
$$C^J_{e_1} = \frac{-\epsilon^0_S}{\epsilon^1_S - \epsilon^0_S}$$

According to Cramer's Rule, it is easy to solve these two variables equations:

$$C^J_{e_0} = \frac{\begin{vmatrix} 1 & 1 \\ 0 & \epsilon^1_S \end{vmatrix}}{\begin{vmatrix} 1 & 1 \\ \epsilon^0_S & \epsilon^1_S \end{vmatrix}} = \frac{\epsilon^1_S}{\epsilon^1_S - \epsilon^0_S}$$
$$C^J_{e_1} = \frac{\begin{vmatrix} 1 & 1 \\ \epsilon^0_S & 0 \end{vmatrix}}{\begin{vmatrix} 1 & 1 \\ \epsilon^0_S & \epsilon^1_S \end{vmatrix}} = \frac{-\epsilon^0_S}{\epsilon^1_S - \epsilon^0_S}$$

b) In addressing the control of flux through the pathway, we can think of v_0 as the 'supply rate' and v_1 as the 'demand rate'. Given the result in part (a), under what conditions on the elasticities ϵ^0_S and ϵ^1_S will a perturbation in the rate of supply affect pathway flux more than an equivalent perturbation in the rate of demand?

c) Suppose the rate laws are given as $v_0 = e_0(k_0X - k_{-1}[S])$ and $v_1 = e_1k_1[S]$, where X is the constant concentration of the pathway substrate. Verify that the elasticities are

$$\epsilon^0_S = \frac{k_{-1}[S]}{k_0X - k_{-1}[S]}$$
$$and \quad \epsilon^1_S = 1$$

Determine conditions on the parameters under which perturbation in the supply reaction v_0 will have a more significant effect than perturbation in the demand reaction v_1. Hint: at steady state $k_0X - k_{-1}s = e_1k_1s/e_0$.

According to the definition of the elasticity,

$$\epsilon_S^0 = \frac{[S]}{v_0}\frac{\partial v_0}{\partial [S]} = \frac{[S]}{e_0(k_0 X - k_{-1}[S])} e_0 k_{-1} = \frac{k_{-1}[S]}{k_0 X - k_{-1}[S]}$$
$$\epsilon_S^1 = \frac{[S]}{v_1}\frac{\partial v_1}{\partial [S]} = \frac{[S]}{e_1 k_1 [S]} e_1 k_1 = 1$$

2 6.8.18 Frequency response analysis of a two-component signaling pathway

a) Following the procedure in Section 6.6.3, determine the linearization of the two-component signaling pathway model of Section 6.1.1 at an arbitrary nominal input value. Use species conservations to reduce the model before linearizing.

The model equations are

$$\frac{d[R](t)}{dt} = -k_1[R](t)[L](t) + k_{-1}[RL](t)$$
$$\frac{d[RL](t)}{dt} = k_1[R](t)[L](t) - k_{-1}[RL](t)$$
$$\frac{d[P](t)}{dt} = -k_2[P](t)[RL](t) + k_3[P^*](t)$$
$$\frac{d[P^*](t)}{dt} = k_2[P](t)[RL](t) - k_3[P^*](t)$$

Species conservationsa are

$$\frac{d[R](t)}{dt} + \frac{d[RL](t)}{dt} = 0$$
$$\frac{d[P](t)}{dt} + \frac{d[P^*](t)}{dt} = 0$$

Let $[R](t) + [RL](t) = R_T$, $[P](t) + [P^*](t) = P_T$. Then, the model equations can be reduced to two differential equations shwon below

$$\frac{d[RL](t)}{dt} = k_1(R_T - [RL](t))[L](t) - k_{-1}[RL](t)$$
$$\frac{d[P^*](t)}{dt} = k_2(P_T - [P^*](t))[RL](t) - k_3[P^*](t)$$

Here, the input signal is the ligand level [L], while the output is the concentration of active $[P^*]$. Comparing with equation (6.3), with $\mathbf{x} = ([RL], [P^*])$ and u = [L], this system defines $\mathbf{f}$ as a vector of function with two coefficients:

$$f_1([RL],[P^*]) = k_1(R_T - [RL](t))[L](t) - k_{-1}[RL](t)$$
$$f_2([RL],[P^*]) = k_2(P_T - [P^*](t))[RL](t) - k_3[P^*](t)$$

The output function(equation(6.4)) takes the simple form

$$h([RL],[P^*]) = [P^*]$$

The linearization takes the form of a linear input-output system:

$$\frac{d\mathbf{x}(t)}{dt} = \mathbf{A}\mathbf{x}(t) + \mathbf{B}u(t)$$
$$y(t) = \mathbf{C}\mathbf{x}(t) + Du(t)$$

where the Jacobian

$$\mathbf{A} = \begin{bmatrix} \frac{\partial f_1}{\partial [RL]} & \frac{\partial f_1}{\partial [P^*]} \\ \frac{\partial f_2}{\partial [RL]} & \frac{\partial f_2}{\partial [P^*]} \end{bmatrix} = \begin{bmatrix} -k_1[L] - k_{-1} & 0 \\ k_2(P_T - [P*]) & -k_2[RL] - k_3 \end{bmatrix},$$

the linearized input map

$$\mathbf{B} = \begin{bmatrix} \frac{\partial f_1}{\partial [L]} \\ \frac{\partial f_2}{\partial [L]} \end{bmatrix} = \begin{bmatrix} k_1(R_T - [RL] \\ 0 \end{bmatrix},$$

the linearized output map is

$$\mathbf{C} = \begin{bmatrix} \frac{\partial h}{\partial [RL]} & \frac{\partial h}{\partial [P^*]} \end{bmatrix} = \begin{bmatrix} 0 & 1 \end{bmatrix},$$

and no feed-through:

$$D = \frac{\partial h}{\partial [L]} = 0$$

b) Simulate the model to determine the steady state corresponding to a nominal input of $L_T = 0.04$. Use MATLAB to generate the magnitude Bode plot of the corresponding frequency response (details in Appendix C).

Since $H(\omega) = \mathbf{C}(i\omega\mathbf{I} - \mathbf{A})^{-1}\mathbf{B} + D$, based on the result of a), we can derive that

$$H(\omega) = \begin{bmatrix} 0 & 1 \end{bmatrix} (\begin{bmatrix} i\omega & 0 \\ 0 & i\omega \end{bmatrix} - \begin{bmatrix} -k_1[L] - k_{-1} & 0 \\ k_2(P_T - [P*]) & -k_2[RL] - k_3 \end{bmatrix})^{-1} \begin{bmatrix} k_1(R_T - [RL] \\ 0 \end{bmatrix} + 0$$

Let $k_1 = 5$, $k_{-1} = 1$, $k_2 = 6$, $k_3 = 2$, $R_T = 2$, and $P_2 = 8$ (initially, [RL]=0 and $[P^*]$=0). When [L] = $L_T = 0.04$,

$$H(\omega) = \begin{bmatrix} 0 & 1 \end{bmatrix} (\begin{bmatrix} i\omega & 0 \\ 0 & i\omega \end{bmatrix} - \begin{bmatrix} -1.2 & 0 \\ 48 & -2 \end{bmatrix})^{-1} \begin{bmatrix} 10 \\ 0 \end{bmatrix} + 0 = \begin{bmatrix} 0 & 1 \end{bmatrix} (\begin{bmatrix} i\omega + 1.2 & 0 \\ -48 & i\omega + 2 \end{bmatrix})^{-1} \begin{bmatrix} 10 \\ 0 \end{bmatrix}$$
$$= \begin{bmatrix} 0 & 1 \end{bmatrix} \frac{1}{-\omega^2 + 3.2i\omega + 2.4} \begin{bmatrix} i\omega + 2 & 0 \\ 48 & i\omega + 1.2 \end{bmatrix} \begin{bmatrix} 10 \\ 0 \end{bmatrix} = \frac{480}{-\omega^2 + 3.2i\omega + 2.4}$$

Then, we can also obtain the gain of the system:

$$Gain(\omega) = \frac{480}{\sqrt{(2.4 - \omega^2)^2 + 10.24\omega^2}}$$

Low frequency gain is then

$$Gain(0) = \frac{480}{\sqrt{(2.4)^2}} = 480/2.4 = 200$$

c) Repeat part (b) for a nominal input of of $L_T = 0.4$. Use Figure 6.3 to explain the difference in the frequency response at these two nominal input values.

Similar to the procedure of b), we can get

$$H(\omega) = \begin{bmatrix} 0 & 1 \end{bmatrix} (\begin{bmatrix} i\omega & 0 \\ 0 & i\omega \end{bmatrix} - \begin{bmatrix} -3 & 0 \\ 48 & -2 \end{bmatrix})^{-1} \begin{bmatrix} 10 \\ 0 \end{bmatrix} + 0 = \begin{bmatrix} 0 & 1 \end{bmatrix} (\begin{bmatrix} i\omega+3 & 0 \\ -48 & i\omega+2 \end{bmatrix})^{-1} \begin{bmatrix} 10 \\ 0 \end{bmatrix}$$
$$= \begin{bmatrix} 0 & 1 \end{bmatrix} \frac{1}{-\omega^2+5i\omega+6} \begin{bmatrix} i\omega+2 & 0 \\ 48 & i\omega+3 \end{bmatrix} \begin{bmatrix} 10 \\ 0 \end{bmatrix} = \frac{480}{-\omega^2+5i\omega+6}$$

Then, we can also obtain the gain of the system:

$$Gain(\omega) = \frac{480}{\sqrt{(6-\omega^2)^2+25\omega^2}}$$

Low frequency gain is then

$$Gain(0) = \frac{480}{\sqrt{(6)^2}} = 480/6 = 80$$

Appendix C- Frequency response analysis

As discussed in Section 6.6, a linear input-output system can be specified as a set of four matrices: A,B, C, and D. Once these are specified in MATLAB, the frequency response can be easily generated and the corresponding Bode plots can be produced. The command [num den]=ss2tf(A,B,C,D) determines the transfer function for the system, specified in terms of the coefficients of the numerator and denominator polynomials. A MATLAB transfer function can then be created with the command sys=tf(num,den), from which Bode plots can be produced with bode(sys).