NATIONAL TAIWAN UNIVERSITY,
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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

$$C_{e_0}^J + C_{e_1}^J = 1$$

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

$$C_{e_0}^J \epsilon_S^0 + C_{e_1}^J \epsilon_S^1 = 0$$

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

$$C_{e_0}^J = \frac{\epsilon_S^1}{\epsilon_S^1 - \epsilon_S^0}$$

$$C_{e_1}^J = \frac{-\epsilon_S^0}{\epsilon_S^1 - \epsilon_S^0}$$

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

$$C_{e_0}^J = \frac{\begin{vmatrix} 1 & 1 \\ 0 & \epsilon_S^1 \end{vmatrix}}{\begin{vmatrix} 1 & 1 \\ \epsilon_S^0 & \epsilon_S^1 \end{vmatrix}} = \frac{\epsilon_S^1}{\epsilon_S^1 - \epsilon_S^0}$$

$$C_{e_1}^J = \frac{\begin{vmatrix} 1 & 1 \\ \epsilon_S^0 & 0 \end{vmatrix}}{\begin{vmatrix} 1 & 1 \\ \epsilon_S^0 & \epsilon_S^1 \end{vmatrix}} = \frac{-\epsilon_S^0}{\epsilon_S^1 - \epsilon_S^0}$$

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_S^0 and ϵ_S^1 will a perturbation in the rate of supply affect pathway flux more than an equivalent perturbation in the rate of demand?

When a perturbation in the rate of supply affect pathway flux more than an equivalent perturbation in the rate of demand, $C_{e_0}^J > C_{e_0}^J$, so

$$\frac{\epsilon_S^1}{\epsilon_S^1 - \epsilon_S^0} > \frac{-\epsilon_S^0}{\epsilon_S^1 - \epsilon_S^0}$$

$$\Rightarrow \epsilon_S^1 > -\epsilon_S^0$$

c) Suppose the rate laws are given as $v_0 = e_0(k_0 X - k_{-1}[S])$ and $v_1 = e_1 k_1 [S]$, where X is the constant concentration of the pathway substrate. Verify that the elasticities are

$$\epsilon_S^0 = \frac{-k_{-1}[S]}{k_0 X - k_{-1}[S]}$$

$$and \quad \epsilon_S^1 = 1$$

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 $k_0 X - k_{-1} s = e_1 k_1 s / e_0$.

According to the definition of the elasticity,

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

$$\epsilon_S^1 = \frac{[S]}{v_1} \frac{\partial v_1}{\partial [S]} = \frac{[S]}{e_1 k_1 [S]} e_1 k_1 = 1$$

From the result of b), to get a perturbation in the supplyreaction that has a more significant effect than perturbation in the demand reaction, we need $\epsilon_S^1 > -\epsilon_S^0$, so

$$\epsilon_S^1 = 1 > -\frac{-k_{-1}[S]}{k_0 X - k_{-1}[S]} = -\epsilon_S^0$$

$$\Rightarrow k_0 X - k_{-1}[S] > k_{-1}[S]$$

$$\Rightarrow k_0 X > 2 k_{-1}[S]$$

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] = $L_T = 0.04$,

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

$$= \begin{bmatrix} 0 & 1 \end{bmatrix}\frac{1}{-\omega^2 + 3.2i\omega + 2.4}\begin{bmatrix} i\omega + 2 & 0 \\ 48 & i\omega + 1.2 \end{bmatrix}\begin{bmatrix} 10 \\ 0 \end{bmatrix} = \frac{480}{-\omega^2 + 3.2i\omega + 2.4}$$
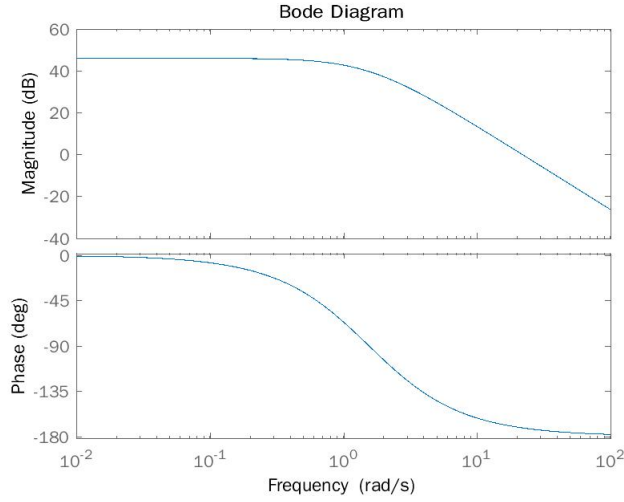
Then, we can also obtain the gain of the system:

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

Low frequency gain is then

$$Gain(0) = \frac{480}{\sqrt{(2.4)^2}} = 480/2.4 = 200 = 46.02dB$$

The MATLAB simulation result is shown below. It also confirms the derivation above.

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

$$H(\omega) = \begin{bmatrix} 0 & 1 \end{bmatrix} \left(\begin{bmatrix} i\omega & 0 \\ 0 & i\omega \end{bmatrix} - \begin{bmatrix} -3 & 0 \\ 48 & -2 \end{bmatrix} \right)^{-1} \begin{bmatrix} 10 \\ 0 \end{bmatrix} + 0 = \begin{bmatrix} 0 & 1 \end{bmatrix} \left(\begin{bmatrix} i\omega + 3 & 0 \\ -48 & i\omega + 2 \end{bmatrix} \right)^{-1} \begin{bmatrix} 10 \\ 0 \end{bmatrix}$$

$$= \begin{bmatrix} 0 & 1 \end{bmatrix} \frac{1}{-\omega^2 + 5i\omega + 6} \begin{bmatrix} i\omega + 2 & 0 \\ 48 & i\omega + 3 \end{bmatrix} \begin{bmatrix} 10 \\ 0 \end{bmatrix} = \frac{480}{-\omega^2 + 5i\omega + 6}$$
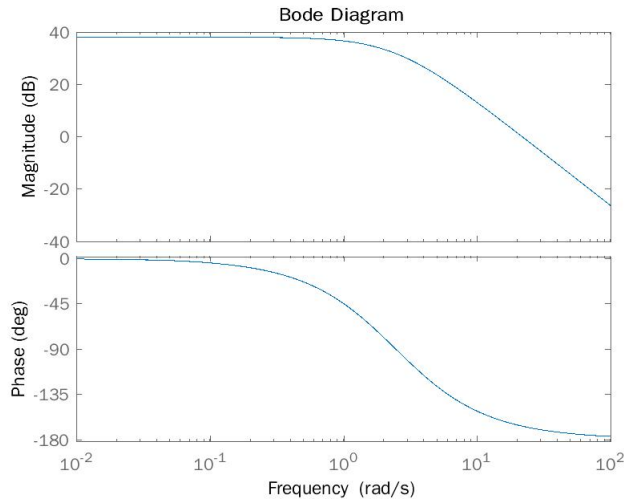
Then, we can also obtain the gain of the system:

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

Low frequency gain is then

$$Gain(0) = \frac{480}{\sqrt{(6)^2}} = 480/6 = 80 = 38.06dB$$

The MATLAB simulation result is shown below. It also confirms the derivation above.

Bode Diagram

The shape of these two bode plot are similar. However, the bode plot of lower L_T shows larger magnitude of gain than higher L_T. This behaviror can be explained by figure 6.3. As you can see in figure 6.3.B, lower total ligand concentration results in higher ratio for response(active response protein) to input signals (slope is larger when the total ligand concentration is lower).

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).