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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,

$$\epsilon_S^0 = \frac{[S]}{v_0}\frac{\partial v_0}{\partial [S]} = \frac{[S]}{e_0(k_0X - k_{-1}[S])}e_0 k_{-1} = \frac{k_{-1}[S]}{k_0X - k_{-1}[S]}$$
$$\epsilon_S^1 = \frac{[S]}{v_1}\frac{\partial v_1}{\partial [S]} = \frac{[S]}{e_1 k_1[S]}e_1 k_1 = 1$$

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.

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

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

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 [numden]=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).