Metabolic Modeling, Spring 2007, Solutions for Exercise 5

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1. *Consider a reaction with Michaelis-Menten type kinetics* $v_k = \frac{V_{max}S_i}{K_m+S_i}$. *Give a detailed derivation for the equations*

   (a) ϵ_i^k

   (b) $\pi_{K_m}^k$

   (c) $\pi_{V_{max}}^k$

   (a) Denote $f(S_i) = V_{max}S_i$ and $g(S_i) = K_m + S_i$. Now $f'(S_i) = V_{max}$ and $g'(S_i) = 1$. We get

   $$\begin{aligned}\epsilon_i^k = \frac{S_i}{v_k}\frac{\partial v_k}{\partial S_i} = \frac{S_i g(S_i)}{f(S_i)} \cdot \frac{f'(S_i)g(S_i) - g'(S_i)f(S_i)}{g(S_i)^2} &= \\ = \frac{S_i g(S_i)}{V_{max}S_i}\frac{V_{max}g(S_i) - V_{max}S_i}{g(S_i)^2}& \\ = \frac{g(S_i) - S_i}{g(S_i)} &= \frac{K_m}{K_m + S_i}\end{aligned}$$

   (b) Denote $g(K_m) = K_m + S_i$

   $$\begin{aligned}\pi_{K_m}^k = \frac{K_m}{v_k}\frac{\partial v_k}{\partial K_m} &= \frac{K_m g(K_m)}{V_{max}S_i}\frac{\partial}{\partial K_m}\frac{V_{max}S_i}{g(K_m)} \\ &= \frac{K_m V_{max} S_i g(K_m)}{V_{max}S_i}\frac{-1}{g(K_m)^2} = \frac{-K_m}{K_m + S_i}\end{aligned}$$

   (c)

   $$\begin{aligned}\pi_{V_{max}}^k = \frac{V_{max}}{v_k}\frac{\partial v_k}{\partial V_{max}} &= \frac{V_{max}(K_m + S_i)}{V_{max}S_i}\frac{\partial}{\partial V_{max}}\frac{V_{max}S_i}{K_m + S_i} = \\ &= \frac{V_{max}(K_m + S_i)}{V_{max}S_i}\frac{S_i}{K_m + S_i} = 1\end{aligned}$$

2. *A simple rate law for irreversible reaction subject to competitive inhibition is given by*

   $$v = \frac{V_{max}S}{(K_m(1 + I/K_I) + S},$$

   where I denotes the concentration of the inhibitor and K_I the equilibrium constant for binding/releasing the inhibitor.

Derive π-elasticity coefficient π_I for inhibitor concentration and interpret the derived coefficient: how do the inhibitor concentration I and the equilibrium constant K_I affect the reaction rate.

Denote $g(I) = K_m(1 + I/K_I) + S$, and $g'(I) = \frac{\partial}{\partial I} g(I) = K_m/K_I$

π-elasticity is given by

$$\pi_I = \frac{I}{v}\frac{\partial v}{\partial I} = \frac{Ig(I)}{V_{max}S} \cdot \frac{\partial}{\partial I}\frac{V_{max}S}{g(I)}$$
$$= \frac{Ig(I)}{V_{max}S} \cdot \frac{-V_{max}Sg'(I)}{g(I)^2} = \frac{-Ig'(I)}{g(I)}$$
$$= \frac{-IK_m/K_I}{K_m(1 + I/K_I) + S} = \frac{-I}{K_I + I + SK_I/K_m} = \frac{-I}{K_I(1 + S/K_m) + I} \quad (1)$$

The following propserties can be noticed:

- $\pi_I < 0$, thus an increase in inhibitor concentration will result in a decrease of the reaction rate
- π_I is a convex function of I, so in very high inhibitor concentrations, the response is toned down
- A high value of K_I also tones down the response.

3. *Give a detailed derivation for the equations given on Lecture 10, slides 28 and 30, for the flux control coefficients FCC_1^J, FCC_2^J and the concentration control coefficients CCC_1^S, CCC_2^S.*

   (a) Flux control coefficients. From flux control connectivity theorem ($\sum_{k=1}^{r} FCC_{v_k}^{J_j}\epsilon_{S_i}^{v_k} = 0$) we get $FCC_2^J = FCC_1^J \frac{-\epsilon_S^1}{\epsilon_S^2}$. Insert this to the flux control summation theorem ($\sum_{k=1}^{r} FCC_k^j = 1$)to obtain $FCC_1^J = 1 - FCC_1^J \frac{-\epsilon_S^1}{\epsilon_S^2}$ which simplifies by rearranging the terms into

   $$FCC_1^J(1 - \frac{-\epsilon_S^1}{\epsilon_S^2}) = 1$$

   and further into

   $$FCC_1^J \frac{\epsilon_S^2 + \epsilon_S^1}{\epsilon_S^2} = 1$$

   which gives the result

   $$FCC_1^J = \frac{\epsilon_S^2}{\epsilon_S^2 + \epsilon_S^1}$$

   An analogous derivation gives the coefficeint $FCC_2^J = \frac{-\epsilon_S^1}{\epsilon_S^2 + \epsilon_S^1}$.

   (b) Concentration control coefficients. From concentration control connetivity theorem $CCC_1^S\epsilon_S^1 + CCC_2^S\epsilon_S^2 = -1$ we obtain $CCC_2^S = -\frac{CCC_1^S\epsilon_S^1 + 1}{\epsilon_S^2}$

Substituting this to the concentration control summation theorem $CCC_2^S + CCC_1^S = 0$ we get

$$CCC_1^S - \frac{CCC_1^S \epsilon_S^1 + 1}{\epsilon_S^2} = 0,$$

$$CCC_1^S - CCC_1^S \frac{\epsilon_S^1}{\epsilon_S^2} = \frac{1}{\epsilon_S^2},$$

and

$$CCC_1^S(\frac{\epsilon_S^2 - \epsilon_S^1}{\epsilon_S^2}) = \frac{1}{\epsilon_S^2}$$

which gives the results $CCC_1^S = \frac{1}{\epsilon_S^2 - \epsilon_S^1}$

An analogous derivation gives the coefficient $CCC_2^S = \frac{-1}{\epsilon_S^2 - \epsilon_S^1}$

4. *Consider a metabolic network with three reactions $r_1 : A \rightarrow B, r_2 : B \rightarrow C, r_3 : B \rightarrow D$. Assume that the elasticity coefficients have been determined as $\epsilon_B^1 \approx -0.5, \epsilon_B^2 \approx 0.25, \epsilon_B^3 \approx 0.5$, and the flux control coefficient $FCC_{v_1}^{J_2} \approx 0.25$ for the flux J_2 from B to C.*

   Determine the coefficients $FCC_{v_2}^{J_2}$ and $FCC_{v_3}^{J_2}$.

   Hint: use the flux summation ($\sum_{k=1}^{r} FCC_k^j = 1$) and connectivity ($\sum_{k=1}^{r} FCC_{v_k}^{J_j} \epsilon_{S_i}^{v_k} = 0$) theorems.

   (a) Solution by pen and paper:
   Substitute $FCC_1^2 = 0.25$ to the flux control summation theorem $FCC_1^2 + FCC_2^2 + FCC_3^2 = 1$ to obtain $FCC_3^2 = 0.75 - FCC_2^2$.
   Substitute the above value for FCC_3^2, the elasticity coefficients, and $FCC_1^2 = 0.25$ to the flux control connectivity theorem $FCC_1^2 \epsilon_B^1 + FCC_2^2 \epsilon_B^2 + FCC_3^2 \epsilon_B^3 = 0$ to obtain

   $$0.25 \cdot (-0.5) + FCC_2^2 \cdot 0.25 + (0.75 - FCC_2^2) \cdot 0.5 = 0$$

   $$FCC_2^2 = 1$$

   and $FCC_3^2 = 0.75 - FCC_2^2 = -0.25$

   (b) Solution by Matlab:
   Notice that when the elasticities are given, both flux control summation and flux control connectivity are linear equations with FCC's as the unknowns.
   Construct coefficient matrix $A = \begin{bmatrix} 1.0000 & 1.0000 & 1.0000 \\ -0.5000 & 0.2500 & 0.5000 \\ 1.0000 & 0 & 0 \end{bmatrix}$ and vector $b = \begin{bmatrix} 1 \\ 0 \\ 0.25 \end{bmatrix}$ where the first row represents the flux control summation, the next line the flux control connectivity with the elasticities as the coefficients, and the third line represents the given coefficient $FCC_1^2 = 0.25$.
   Solve $FCC = pinv(A)b$ to obtain $FCC = (0.25, 1, -0.25)^T$