

Mathematical Modeling in Systems Biology problem sets - Ch3: 3.7.3, 3.7.5

3.7.3 Reversible Michaelis-Menten kinetics.

a) Derive the reversible Michaelis-Menten rate law (equation (3.9)) as follows. Apply a quasi-steady-state assumption to the complex C in reaction scheme (3.8) to arrive at a description of its concentration:

$$c^{qss} = \frac{k_1 e_T s + k_{-2} e_T p}{k_1 s + k_{-2} p + k_{-1} + k_2}.$$

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Next, confirm that the reaction rate is

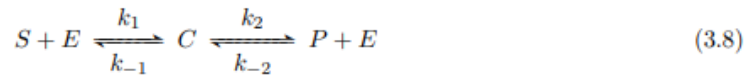
$$v = \frac{d}{dt}p(t) = \frac{k_1 k_2 e_T s - k_{-1} k_{-2} e_T p}{k_1 s + k_{-2} p + k_{-1} + k_2}.$$

b) Express the parameters in equation (3.9) (i.e. V_f , V_r , K_S , K_P) in terms of the rate constants k_1 , k_2 , k_{-1} and k_{-2} .

c) Confirm that when k_{-2} is zero, the irreversible Michaelis-Menten rate law is recovered.

Reversible reactions

When both substrate and product are present, the enzyme-catalysed reaction scheme is



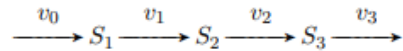
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Assuming the complex C is in quasi-steady-state with respect to S and P , the reaction rate (which can now take negative values) is given by the reversible Michaelis-Menten rate law:

$$\text{net rate of } S \rightarrow P = \frac{V_f \frac{s}{K_S} - V_r \frac{p}{K_P}}{1 + \frac{s}{K_S} + \frac{p}{K_P}}, \quad (3.9)$$

where V_f and V_r are the maximal rates of the forward and reverse reactions, and K_S and K_P are the Michaelis constants for S and P respectively (details in Problem 3.7.3). In some cases, the product re-binds to the free enzyme, but the rate of the reverse reaction is negligible. This is referred to as product inhibition (Problem 3.7.4).

3.7.5 Michaelis-Menten kinetics: first-order approximation. Consider the reaction chain



in which the v_i are labels for the reaction rates (not mass-action constants). Take the rate v_0 as fixed and presume the other reactions follow Michaelis-Menten kinetics, with

$$v_i = \frac{V_{\max}^i s_i}{K_{Mi} + s_i},$$

where $s_i = [S_i]$. Take parameter values (in mM/min) $v_0 = 2$, $V_{\max}^1 = 9$, $V_{\max}^2 = 12$, $V_{\max}^3 = 15$; (in mM) $K_{M1} = 1$, $K_{M2} = 0.4$, $K_{M3} = 3$.

a) Simulate the system from initial conditions (in mM) $(s_1, s_2, s_3) = (0.3, 0.2, 0.1)$. Repeat with initial condition $(s_1, s_2, s_3) = (6, 4, 4)$.

b) Generate an approximate model in which the rates of reactions 1, 2, and 3 follow first-order mass-action kinetics (i.e. $v_i = k_i s_i$, for $i = 1, 2, 3$). Choose values for the rate constants k_i that give a good approximation to the original nonlinear model. Explain your reasoning. (Hint: Exercise 3.1.2(b) provides one viable approach.)

c) Simulate your simpler (mass-action based) model from the sets of initial conditions in part (a). Comment on the fit. If the approximation is better in one case than the other, explain why.