

NATIONAL TAIWAN UNIVERSITY,
GRADUATE INSTITUTE OF BIOMEDICAL ENGINEERING AND BIOINFORMATICS

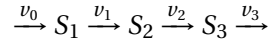
BEBI5009:
Mathematical Modeling of System Biology
Homework 2

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1 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 $(s_1, s_2, s_3) = (6, 4, 4)$.

According to the question, we can easily derive following equations:

$$\frac{dS_i}{dt} = v_i - v_{i-1} = \begin{cases} \frac{V_{max}^1 s_1}{K_{M1} + s_1} - v_0 & \text{if } i = 1 \\ \frac{V_{max}^i s_i}{K_{Mi} + s_i} - \frac{V_{max}^{i-1} s_{i-1}}{K_{Mi-1} + s_{i-1}} & \text{if } i = 2, 3 \end{cases}$$

Thus, we can simulate the system with these equations. The simulation result are shown below.

- i) Simulation result with initial condition (in mM) $(s_1, s_2, s_3) = (0.3, 0.2, 0.1)$.
 - ii) Simulation result with initial condition (in mM) $(s_1, s_2, s_3) = (6, 4, 4)$.
- 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.)

For s is small, the reaction rate of Michaelis-Menten kinetics can be approximated:

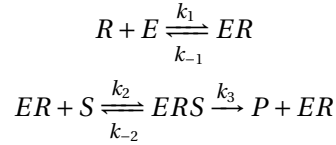
$$v_i = \frac{V_{max}^i s_i}{K_{Mi} + s_i} \approx \frac{V_{max}^i s_i}{K_{Mi}}$$

Then, it is intuitive to choose rate constants $k_i = \frac{V_{max}^i}{K_{Mi}}$

- 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.

2 3.7.8 Allosteric activation

Consider an allosteric activation scheme in which an allosteric activator must be bound before an enzyme can bind substrate. This is called compulsory activation. The reaction scheme resembles a two-substrate reaction, but the enzyme-activator complex stays intact after the product dissociates:



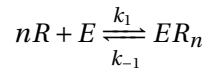
,where R is the allosteric activator (regulator).

- a) Apply a quasi-steady-state assumption to the two complexes ER and ERS (and use enzyme conservation) to verify that the rate law takes the form

$$v = \frac{srk_3e_T}{r\frac{k_{-2}+k_3}{k_2} + \frac{k_{-1}(k_{-2}+k_3)}{k_1k_2} + sr} = \frac{V_{max}sr}{K_1r + K_2 + rs}.$$

where r is the regulator concentration and s is the substrate concentration

- b) Next, consider the case in which catalysis can only occur after n regulator molecules have bound. Assuming the the binding involves strong cooperativity, we can approximate the regulator-binding events by:



Verify that in this case the rate law takes the form

$$v = \frac{V_{max}sr^n}{K_1r^n + K_2 + r^n s}.$$

- c) Confirm that when regulator and substrate are at very low concentration, the rate law in part (b) can be approximated as

$$v = \frac{V_{max}}{K_2} sr^n.$$