

NATIONAL TAIWAN UNIVERSITY,
GRADUATE INSTITUTE OF BIOMEDICAL ENGINEERING AND BIOINFORMATICS

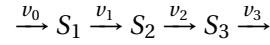
BEBI5009:
Mathematical Modeling of System Biology
Homework 2

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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) $K_{M1} = 1$, $K_{M2} = 0.4$, $K_{M3} = 3$.

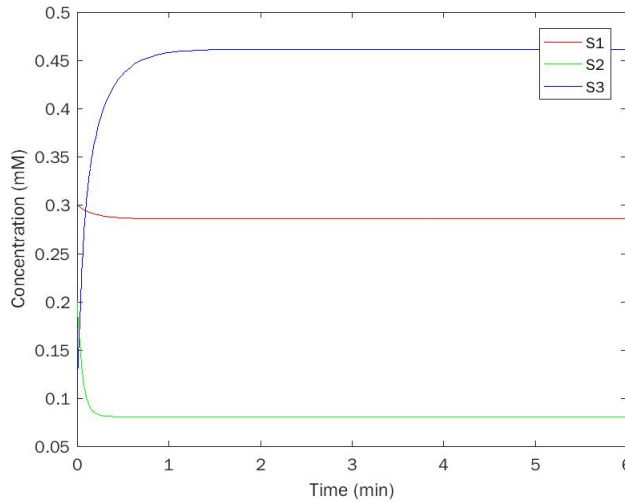
- a) Simulate the system from initial conditions (in mM) $(s_1, s_2, s_3) = (0.3, 0.2, 0.1)$. Repeat with initial condition $(s_1, s_2, s_3) = (6, 4, 4)$.

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

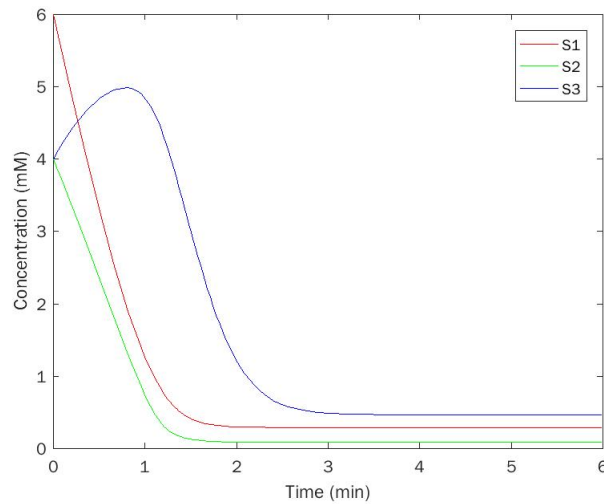
$$\frac{dS_i}{dt} = v_i - v_{i-1} = \begin{cases} \frac{V_{max}^1 s_1}{K_{M1} + s_1} - v_0 & \text{if } i = 1 \\ \frac{V_{max}^i s_i}{K_{Mi} + s_i} - \frac{V_{max}^{i-1} s_{i-1}}{K_{Mi-1} + s_{i-1}} & \text{if } i = 2, 3 \end{cases}$$

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



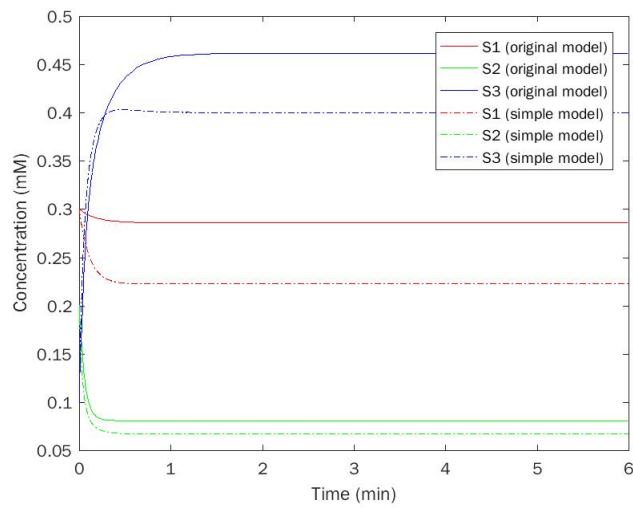
- b) Generate an approximate model in which the rates of reactions 1, 2, and 3 follow first-order mass-action kinetics (i.e. $v_i = k_i s_i$, for $i = 1, 2, 3$). Choose values for the rate constants k_i that give a good approximation to the original nonlinear model. Explain your reasoning. (Hint: Exercise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

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

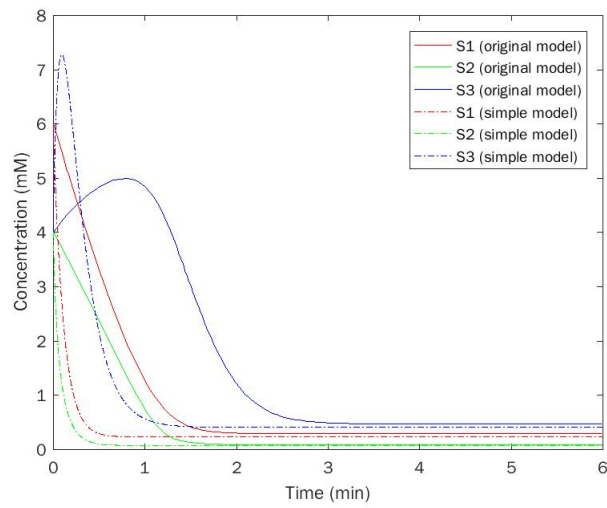
$$v_i = \frac{V_{max}^i s_i}{K_{Mi} + s_i} \approx \frac{V_{max}^i s_i}{K_{Mi}}$$

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

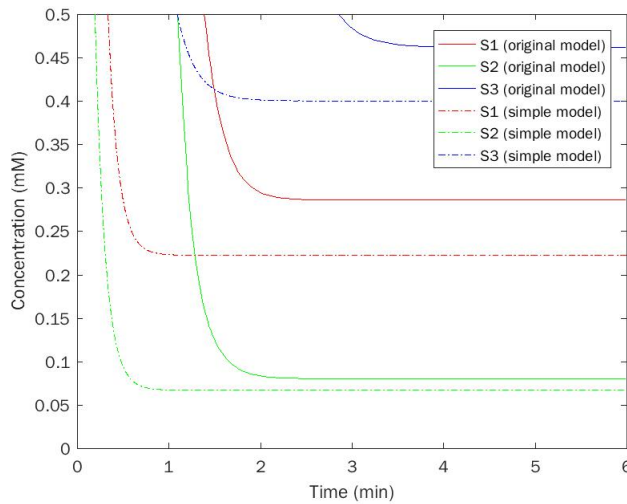
- c) Simulate your simpler (mass-action based) model from the sets of initial conditions in part (a). Comment on the fit. If the approximation is better in one case than the other, explain why.
- i) Simulation result with initial condition (in mM) $(s_1, s_2, s_3) = (0.3, 0.2, 0.1)$.



ii) Simulation result with initial condition (in mM) $(s_1, s_2, s_3) = (6, 4, 4)$.



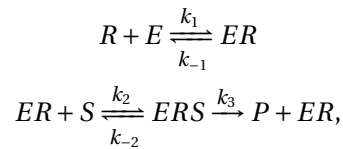
Result at closer scale:



The simpler model fits better with initial condition (in mM) $(s_1, s_2, s_3) = (0.3, 0.2, 0.1)$ than $(s_1, s_2, s_3) = (6, 4, 4)$. It's because of the underlining assumption of simpler model that s should be small. That is, s_i with initial condition (in mM) $(s_1, s_2, s_3) = (0.3, 0.2, 0.1)$ is small enough. However, s_i with initial condition (in mM) $(s_1, s_2, s_3) = (6, 4, 4)$ is not small enough.

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

First, we can write down the differential equations for all species:

$$\begin{aligned}
\frac{d[R]}{dt} &= -k_1[R][E] + k_{-1}[ER] \\
\frac{d[E]}{dt} &= -k_1[R][E] + k_{-1}[ER] \\
\frac{d[ER]}{dt} &= k_1[R][E] - k_{-1}[ER] - k_2[ER][S] + k_{-2}[ERS] + k_3[ERS] \\
\frac{d[S]}{dt} &= -k_2[ER][S] + k_{-2}[ERS] \\
\frac{d[ERS]}{dt} &= k_2[ER][S] - k_{-2}[ERS] - k_3[ERS] \\
\frac{d[P]}{dt} &= k_3[ERS] = v
\end{aligned}$$

By applying a quasi-steady-state assumption to the two complexes ER and ESR, we know that:

$$\begin{aligned}
0 &= k_2[ER]_{ss}[S] - k_{-2}[ERS]_{ss} - k_3[ERS]_{ss} \\
\Rightarrow [ER]_{ss} &= \frac{k_{-2} + k_3}{k_2[S]} [ERS]_{ss} \\
0 &= k_1[R][E] - k_{-1}[ER]_{ss} - k_2[ER]_{ss}[S] + k_{-2}[ERS]_{ss} + k_3[ERS]_{ss} \\
\Rightarrow 0 &= k_1[R](e_T - \frac{k_{-2} + k_3}{k_2[S]} [ERS]_{ss} - [ERS]_{ss}) - k_{-1} \frac{k_{-2} + k_3}{k_2[S]} [ERS]_{ss} - k_2 \frac{k_{-2} + k_3}{k_2[S]} [ERS]_{ss}[S] \\
&\quad + k_{-2}[ERS]_{ss} + k_3[ERS]_{ss} \\
\Rightarrow (k_1[R] \frac{k_{-2} + k_3}{k_2[S]} + k_1[R] + k_{-1} \frac{k_{-2} + k_3}{k_2[S]}) [ERS]_{ss} &= k_1[R] e_T \\
\Rightarrow [ERS]_{ss} &= \frac{e_T [R][S]}{[R] \frac{k_{-2} + k_3}{k_2} + [R][S] + \frac{k_{-1}(k_{-2} + k_3)}{k_1 k_2}} = \frac{e_T [S][R]}{[R] \frac{k_{-2} + k_3}{k_2} + \frac{k_{-1}(k_{-2} + k_3)}{k_1 k_2} + [R][S]} \\
\Rightarrow v = k_3[ERS] &= \frac{k_3 e_T [S][R]}{\frac{k_{-2} + k_3}{k_2} [R] + \frac{k_{-1}(k_{-2} + k_3)}{k_1 k_2} + [R][S]}
\end{aligned}$$

where e_t is from the conservation of enzyme:

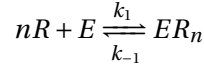
$$e_T = [E] + [ER]_{ss} + [ERS]_{ss}$$

Further substitute the equation with $K_1 = \frac{k_{-2} + k_3}{k_2}$, $K_2 = \frac{k_{-1}(k_{-2} + k_3)}{k_1 k_2}$, $V_{max} = k_3 e_T$. Then, we get the same result which is specified in the question. That is,

$$v = \frac{k_3 e_T [S][R]}{\frac{k_{-2} + k_3}{k_2} [R] + \frac{k_{-1}(k_{-2} + k_3)}{k_1 k_2} + [R][S]} = \frac{V_{max} [S][R]}{K_1 [R] + K_2 + [R][S]}$$

- 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

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

The procedures are really similar to those in part (a). First, we can write down the differential equations for all species:

$$\begin{aligned}\frac{d[R]}{dt} &= -k_1[R]^n[E] + k_{-1}[ER_n] \\ \frac{d[E]}{dt} &= -k_1[R]^n[E] + k_{-1}[ER_n] \\ \frac{d[ER_n]}{dt} &= k_1[R]^n[E] - k_{-1}[ER_n] - k_2[ER_n][S] + k_{-2}[ER_nS] + k_3[ER_nS] \\ \frac{d[S]}{dt} &= -k_2[ER_n][S] + k_{-2}[ER_nS] \\ \frac{d[ER_nS]}{dt} &= k_2[ER_n][S] - k_{-2}[ER_nS] - k_3[ER_nS] \\ \frac{d[P]}{dt} &= k_3[ER_nS] = v\end{aligned}$$

If we use $[R'] = [R]^n$, $[ER'] = [ER_n]$, $[ERS'] = [ER_nS]$ to represent the equations above, we will get the same set equations with $[R']$, $[ER']$, and $[ERS']$ replacing $[R]$, $[ER]$, and $[ERS]$, respectively. So, we can similarly conclude that we get the same result which is specified in the question. That is,

$$v = \frac{k_3 e_T [S] [R']}{\frac{k_{-2}+k_3}{k_2} [R'] + \frac{k_{-1}(k_{-2}+k_3)}{k_1 k_2} + [R'] [S]} = \frac{V_{max} [S] [R']}{K_1 [R'] + K_2 + [R'] [S]} = \frac{V_{max} [S] [R]^n}{K_1 [R]^n + K_2 + [R]^n [S]}$$

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

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

When regulator and substrate are at very low concentration, $K_2 \gg K_1 r^n$ and $K_2 \gg r^n s$, so

$$v = \frac{V_{max} sr^n}{K_1 r^n + K_2 + r^n s} \approx \frac{V_{max}}{K_2} sr^n$$

Then, we have already confirmed the argument.