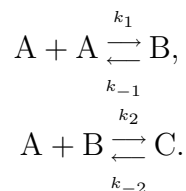


Homework Exercises for Mathematics 6770 - Fall 2009

Remark: Solutions may include maple files or matlab files.

Assignment 1: (due Sept. 29, 2009)

1. In the real world trimolecular reactions are rare, although trimerizations are not. Consider the following trimerization reaction in which three monomers of A combine to form the trimer C,



- (a) Use the law of mass action to find the rate of production of the trimer C.
 - (b) Suppose $k_{-1} \gg k_{-2}, k_2 A$. Use the appropriate quasi-steady state approximation to find the rates of production of A and C, and show that the rate of production of C is proportional to $[A]^3$. Explain in words why this is so.
2. The length of microtubules changes by a process called treadmilling, in which monomer is added to one end of the microtubule and taken off at the other end. To model this process, suppose that monomer A_1 is self-polymerizing in that it can form dimer A_2 via



Furthermore, suppose A_1 can polymerize an n -polymer A_n at one end making an $n + 1$ -polymer A_{n+1}



Finally, degradation can occur one monomer at a time from the opposite end at rate k_- . Find the steady state distribution of polymer lengths after an initial amount of monomer A_0 has fully polymerized.

3. An enzyme-substrate system is believed to proceed at a Michaelis- Menten rate. Data for the (initial) rate of reaction at different concentrations is shown in Table 1.
 - (a) Plot the data V vs. s . Is there evidence that this is a Michaelis-Menten type reaction?
 - (b) Plot V vs. V/s . Is this data well approximated by a straight line?
 - (c) Use linear regression to estimate K_m and V_{max} . Compare the data to the Michaelis-Menten rate function using these parameters. Does this provide a reasonable fit to the data?
4. Suppose the maximum velocity of a chemical reaction is known to be 1 mM/s, and the measured velocity V of the reaction at different concentrations s is shown in Table 2.

Table 1: Data for Problem 3.

| Substrate Concentration (mM) | Reaction Velocity (mM/s) |
|---------------------------------|-----------------------------|
| 0.1 | 0.04 |
| 0.2 | 0.08 |
| 0.5 | 0.17 |
| 1.0 | 0.24 |
| 2.0 | 0.32 |
| 3.5 | 0.39 |
| 5.0 | 0.42 |

Table 2: Data for Problem 4.

| Substrate Concentration (mM) | Reaction Velocity (mM/s) |
|---------------------------------|-----------------------------|
| 0.2 | 0.01 |
| 0.5 | 0.06 |
| 1.0 | 0.27 |
| 1.5 | 0.50 |
| 2.0 | 0.67 |
| 2.5 | 0.78 |
| 3.5 | 0.89 |
| 4.0 | 0.92 |
| 4.5 | 0.94 |
| 5.0 | 0.95 |

- (a) Plot the data V vs. s . Is there evidence that this is a Hill type reaction?
- (b) Plot $\ln(\frac{V}{V_{max}-V})$ vs. $\ln(s)$. Is this approximately a straight line, and if so, what is its slope?
- (c) Use linear regression to estimate K_m and the Hill exponent n . Compare the data to the Hill rate function with these parameters. Does this provide a reasonable fit to the data?
5. Suppose that a substrate can be broken down by two different enzymes with different kinetics. (This happens, for example, in the case of cAMP or cGMP, which can be hydrolyzed by two different forms of phosphodiesterase).
- (a) Write the reaction scheme and differential equations, and nondimensionalize, to get the system of equations

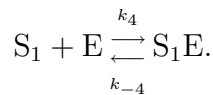
$$\frac{d\sigma}{dt} = -\sigma + \alpha_1(\mu_1 + \sigma)x + \alpha_2(\mu_2 + \sigma)y, \quad (3)$$

$$\epsilon_1 \frac{dx}{dt} = \frac{1}{\lambda_1} \sigma(1-x) - x, \quad (4)$$

$$\epsilon_2 \frac{dy}{dt} = \frac{1}{\lambda_2} \sigma(1-y) - y. \quad (5)$$

where x and y are the nondimensional concentrations of the two complexes. Identify all parameters.

- (b) Apply the quasi-steady-state approximation to find the equation governing the dynamics of substrate σ . Under what conditions is the quasi-steady state approximation valid?
- (c) Solve the differential equation governing σ .
- (d) For this system of equations, show that the solution can never leave the positive octant $\sigma, x, y \geq 0$. By showing that $\sigma + \epsilon_1 \lambda_1 \alpha_1 x + \epsilon_2 \lambda_2 \alpha_2 y$ is decreasing everywhere in the positive octant, show that the solution approaches the origin for large time.
6. ATP is known to inhibit its own dephosphorylation. One possible way for this to occur is if ATP binds with the enzyme, holding it in an inactive state, via



- (a) Add this reaction to the Sel'kov model for glycolysis and derive the corresponding equations governing glycolysis of the form

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2), \quad (6)$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta \sigma_2. \quad (7)$$

Explain from the model why this additional reaction is inhibitory.

- (b) Give an analysis of these equations using xpp. In particular, modify the file `selkov.ode` and find phase portraits of periodic solutions as well as the bifurcation diagram, similar to Fig. 1.9 in the text.

Assignment 2: (due Nov. 4, 2009)

1. A fluorescent dye with a diffusion coefficient of $D = 10^{-7} \text{ cm}^2/\text{s}$ and binding equilibrium of $K_{\text{eq}} = 30 \text{ mM}$ is used to track the spread of hydrogen ($D_h = 4.4 \times 10^{-5} \text{ cm}^2/\text{s}$). Under these conditions the measured diffusion coefficient is $8 \times 10^{-6} \text{ cm}^2/\text{s}$. How much dye is present? (Assume the dye is a fast buffer of hydrogen.)
2. Suppose a semi-infinite tube with cross-sectional area A initially has only water, and that the concentration of a chemical species (with diffusion coefficient D), in a large bath at the end of the tube has fixed concentration C_0 . Find the total number of molecules in the tube at time t .
3. The following data were used by Segel, Chet and Henis (1977) to estimate the diffusion coefficient for bacteria. With the external concentration C_0 at $7 \times 10^7 \text{ ml}^{-1}$, at times $t = 2, 5, 10, 12.5, 15,$ and 20 minutes, they counted N of 1,800, 3,700, 4,800, 5,500, 6,700, and 8,000 bacteria, respectively, in a capillary of length 32 mm with $1 \mu\text{l}$ total capacity. In addition, with external concentrations C_0 of 2.5, 4.6, 5.0, and 12.0×10^7 bacteria per milliliter, counts of 1,350, 2,300, 3,400, and 6,200 were found at $t = 10$ minutes. Estimate D .
4. Find the maximal enhancement for diffusive transport of carbon dioxide via binding with myoglobin using $D_s = 1.92 \times 10^{-5} \text{ cm}^2/\text{s}$, $k_+ = 2 \times 10^8 \text{ cm}^3/\text{M} \cdot \text{s}$, $k_- = 1.7 \times 10^{-2}/\text{s}$. Compare the amount of facilitation of carbon dioxide transport with that of oxygen at similar concentration levels.
5. Almost immediately upon entering a cell, glucose is phosphorylated in the first reaction step of glycolysis. How does this rapid and nearly unidirectional reaction affect the transmembrane flux of glucose (Find an expression for glucose flux that incorporates this reaction.) How is this reaction affected by the concentration of ATP?
6. A 1.5 oz bag of potato chips (a typical single serving) contains about 200 mg of Na^+ . When eaten and absorbed into the body, how many osmoles does this bag of potato chips represent?
7. (a) Consider a vertical tube with a cross-sectional area of 1 cm^2 . The bottom of the tube is closed with a semi-permeable membrane and 1 gram of sugar is placed in the tube. The membrane-closed end of the tube is then put into an inexhaustible supply of pure water at $T = 300\text{K}$. What will be the height of the water in the tube at equilibrium? (The weight of a sugar molecule is $3 \times 10^{-22} \text{ gm}$, and the density of water is $1 \text{ gm}/\text{cm}^3$).
- (b) Two columns with cross-sectional area 1 cm^2 are initially filled to a height of one meter with water at $T = 300^\circ \text{ K}$. Suppose 0.001 gm of sugar is dissolved in one of the two columns. How high will the sugary column be when equilibrium is reached?.

- (c) Suppose in the previous question 1 gm of sugar is dissolved in one of the two columns. What is the equilibrium height of the two columns?
8. Ouabain is known to compete with K^+ for external potassium binding sites of the Na,K-ATPase. Many animal cells swell and burst when treated with the drug ouabain. Why? (How would you include this effect in a model of cell volume control?)

Assignment 3 (due Nov. 24, 2009)

- Suppose the Na^+ Nernst potential of a cell is 56 mV, its resting potential is -70 mV, and the extracellular Ca^{++} concentration is 1 mM. At what intracellular Ca^{++} concentration is the flux of a three-for-one Na^+-Ca^{++} exchanger zero? (Use that $RT/F = 25.8$ mV at $27^\circ C$.)
- Write a computer program to simulate the behavior of the stochastic three-state Na^+ channel shown in Fig. 1, assuming it starts in the closed state. Use $\alpha = 1/ms$, $\beta = 0.4/ms$, $\gamma = 1.6/ms$ and $\delta = 1/ms$. Take the ensemble average of many runs to reproduce its macroscopic behavior. Using the data from simulations, reconstruct the open-time distribution, the latency distribution, and the distribution of N , the number of times the channel opens. From these distributions estimate the rate constants of the simulation and compare with the known values.

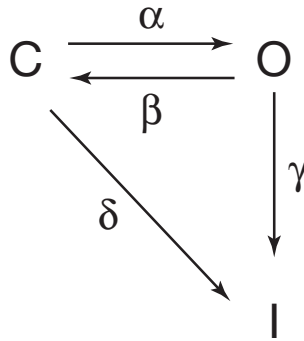


Figure 1: A: Schematic diagram of the states of the Na^+ channel. C, O, and I denote the closed, open, and inactivated states, respectively.

- Explore the behavior of the reduced Hodgkin-Huxley model (you may use the code `hhred.ode`). In particular, for what values of applied current are there oscillatory solutions? Produce phase portraits for several different parameter values showing the different types of possible behaviors, and use `xppaut` to produce a bifurcation diagram.
- Morris and Lecar (1981) proposed the following two-variable model of membrane potential for a barnacle muscle fiber:

$$C_m \frac{dV}{dT} + I_{ion}(V, W) = I_{app}, \quad (8)$$

$$\frac{dW}{dT} = \phi \Lambda(V)[W_\infty(V) - W], \quad (9)$$

| | |
|--|--|
| $C_m = 20 \mu\text{F}/\text{cm}^2$ | $I_{\text{app}} = 0.06 \text{ mA}/\text{cm}^2$ |
| $g_{\text{Ca}} = 4.4 \text{ mS}/\text{cm}^2$ | $g_{\text{K}} = 8 \text{ mS}/\text{cm}^2$ |
| $g_{\text{L}} = 2 \text{ mS}/\text{cm}^2$ | $\phi = 0.04 \text{ ms}^{-1}$ |
| $V_1 = -1.2 \text{ mV}$ | $V_2 = 18 \text{ mV}$ |
| $V_3 = 2$ | $V_4 = 30 \text{ mV}$ |
| $V_{\text{Ca}}^0 = 120 \text{ mV}$ | $V_{\text{K}}^0 = -84 \text{ mV}$ |
| $V_{\text{L}} = -60 \text{ mV}$ | |

Table 3: Typical parameter values for the Morris–Lecar model.

where V = membrane potential, W = fraction of open $\kappa+$ channels, T = time, C_m = membrane capacitance, I_{app} = externally applied current, ϕ = maximum rate for closing $\kappa+$ channels, and

$$I_{\text{ion}}(V, W) = g_{\text{Ca}}M_{\infty}(V)(V - V_{\text{Ca}}^0) + g_{\text{K}}W(V - V_{\text{K}}^0) + g_{\text{L}}(V - V_{\text{L}}^0), \quad (10)$$

$$M_{\infty}(V) = \frac{1}{2} \left(1 + \tanh \left(\frac{V - V_1}{V_2} \right) \right), \quad (11)$$

$$W_{\infty}(V) = \frac{1}{2} \left(1 + \tanh \left(\frac{V - V_3}{V_4} \right) \right), \quad (12)$$

$$\Lambda(V) = \cosh \left(\frac{V - V_3}{2V_4} \right). \quad (13)$$

Typical parameter values for these equations are shown in Table 3.

- Make a phase portrait for the Morris–Lecar equations. Plot the nullclines and show some typical trajectories, demonstrating that the model is excitable.
- For what range of applied current is this system oscillatory? Use XPP to find the bifurcation diagram and determine the types of bifurcations. (You can use the file ML.ode to get started.)