Homework Exercises for Mathematics 6780 - Spring 2020

Remark: Solutions may include maple files or matlab files.

Assignment 1: (due March 17, 2020)

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,

$$\mathrm{A} + \mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{B},$$

$$\mathrm{A} + \mathrm{B} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathrm{C}.$$

   (a) Use the law of mass action to find the rate of production of the trimer C.

   (b) Suppose $k_{-1} \gg k_{-2}, k_2\mathrm{A}$. 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 $[\mathrm{A}]^3$. 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

$$\mathrm{A}_1 + \mathrm{A}_1 \xrightarrow{k_+} \mathrm{A}_2. \tag{1}$$

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

$$\mathrm{A}_1 + \mathrm{A}_n \xrightarrow{k_+} \mathrm{A}_{n+1}. \tag{2}$$

   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. 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

$$S_1 + E \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} S_1E.$$

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

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2), \quad (3)$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2. \quad (4)$$

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.

6. (a) 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.

(b) 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 μl total capacity. In addition, with external concentrations C_0 of 2.5, 4.6, 5.0, and 12.0 $\times 10^7$ bacteria per milliliter, counts of 1,350, 2,300, 3,400, and 6,200 were found at $t = 10$ minutes. Estimate D.

7. 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?

8. 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?

9. (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 $T = 300$K. What will be the height of the water in the tube at equilibrium? (The weight of a sugar molecule is 3×10^{-22} gm, and the density of water is 1 gm/cm^3).
   (b) Two columns with cross-sectional area 1 cm^2 are initially filled to a height of one meter with water at $T = 300^\circ$ 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?

10. 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 $27^\circ C$.)

11. Intestinal epithelial cells have a glucose–Na^+ symport that transports one Na^+ ion and one glucose molecule from the intestine into the cell. Model this transport process. Is the transport of glucose aided or hindered by the cell's negative membrane potential?

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

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

Assignment 2 (due April 7, 2020)

1. Explore the behavior of the reduced Hodgkin-Huxley model (you may use the code hhred.ode).
   (a) 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.
   (b) For what values of the potassium Nernst potential are there oscillatory solutions? Produce a bifurcation diagram with potassium Nernst potential as bifurcation parameter.
2. Morris and Lecar (1981) proposed the following two-variable model of membrane potential for a barnacle muscle fiber:

$$C_m \frac{dV}{dT} + I_{\text{ion}}(V, W) = I_{\text{app}}, \tag{5}$$

$$\frac{dW}{dT} = \phi\Lambda(V)[W_\infty(V) - W], \tag{6}$$

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

$$I_{\text{ion}}(V, W) = g_{\text{Ca}} M_\infty(V)(V - V^0_{\text{Ca}}) + g_{\text{K}} W(V - V^0_{\text{K}}) + g_{\text{L}}(V - V^0_{\text{L}}), \tag{7}$$

$$M_\infty(V) = \frac{1}{2}\left(1 + \tanh\left(\frac{V - V_1}{V_2}\right)\right), \tag{8}$$

$$W_\infty(V) = \frac{1}{2}\left(1 + \tanh\left(\frac{V - V_3}{V_4}\right)\right), \tag{9}$$

$$\Lambda(V) = \cosh\left(\frac{V - V_3}{2V_4}\right). \tag{10}$$

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

(a) Make a phase portrait for the Morris–Lecar equations. Plot the nullclines and show some typical trajectories, demonstrating that the model is excitable.

(b) 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.)

3. The Hodgkin-Huxley equations are

$$C_m \frac{dv}{dt} = -\bar{g}_K n^4 (v - v_K) - \bar{g}_{Na} m^3 h (v - v_{Na}) - \bar{g}_L (v - v_L) + I_{app}, \quad (11)$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m, \quad (12)$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n, \quad (13)$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h, \quad (14)$$

with the functions α_j and β_j, in units of $(\text{ms})^{-1}$,

$$\alpha_m = 0.1 \frac{25 - v}{\exp\left(\frac{25-v}{10}\right) - 1}, \quad (15)$$

$$\beta_m = 4 \exp\left(\frac{-v}{18}\right), \quad (16)$$

$$\alpha_h = 0.07 \exp\left(\frac{-v}{20}\right), \quad (17)$$

$$\beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right) + 1}, \quad (18)$$

$$\alpha_n = 0.01 \frac{10 - v}{\exp\left(\frac{10-v}{10}\right) - 1}, \quad (19)$$

$$\beta_n = 0.125 \exp\left(\frac{-v}{80}\right). \quad (20)$$

For these expressions, the potential v is the deviation from rest, measured in units of mV, current density is in units of $\mu\text{A/cm}^2$, conductances are in units of mS/cm^2, and capacitance is in units of $\mu\text{F/cm}^2$. The remaining parameters are

$$\bar{g}_{Na} = 120, \quad \bar{g}_K = 36, \quad \bar{g}_L = 0.3, \quad C_m = 1, \quad (21)$$

and with shifted equilibrium potentials

$$v_{Na} = 115, \quad v_K = -12, \quad v_L = 10.6. \quad (22)$$

(a) Simulate these equations with current input $I_{app} = 0$. What are the steady state values for all variables?

(b) Starting with all variables at steady state, apply a piecewise constant current that is nonzero for 0.5 ms. Plot the voltage response for several different values of I_{app}. Identify the threshold value of I_{app}.

(c) For what range of constant applied current is this system oscillatory? Use XPP to find the bifurcation diagram and determine the types of bifurcations.

k	=	$10\ s^{-1}$	K_1	=	$1\ \mu$M
K_2	=	$2\ \mu$M	K_3	=	$0.9\ \mu$M
V_1	=	$65\ \mu\text{M}s^{-1}$	V_2	=	$500\ \mu\text{M}s^{-1}$
k_f	=	$1\ s^{-1}$	m	=	2
n	=	2	p	=	4

Table 4: Typical parameter values for the two-pool model of Ca^{++} oscillations (Goldbeter *et al.*, 1990).

Assignment 3: (due April 29, 2020)

1. One of the earliest models of Ca^{++} oscillations was the two-pool model of Goldbeter, Dupont and Berridge (1990). They assumed that IP_3 causes an influx, r, of Ca^{++} into the cell and that this influx causes additional release of Ca^{++} from the ER via an IP_3-independent mechanism. Thus,

$$\frac{dc}{dt} = r - kc - f(c, c_e), \tag{23}$$

$$\frac{dc_e}{dt} = f(c, c_e), \tag{24}$$

$$f(c, c_e) = J_{\text{uptake}} - J_{\text{release}} - k_f c_e, \tag{25}$$

where

$$J_{\text{uptake}} = \frac{V_1 c^n}{K_1^n + c^n}, \tag{26}$$

$$J_{\text{release}} = \left(\frac{V_2 c_e^m}{K_2^m + c_e^m}\right)\left(\frac{c^p}{K_3^p + c^p}\right). \tag{27}$$

Here, $k_f c_e$ is a leak from the ER into the cytoplasm. Typical parameter values are given in Table 4. (All the concentrations in this model are with respect to the total cell volume, and thus there is no need for the correction factor γ to take into account the difference in the ER and cytoplasmic volumes.)

   (a) Nondimensionalize these equations. How many non-dimensional parameters are there?

   (b) Show that in a closed cell (i.e., one without any interaction with the extracellular environment) the two-pool model cannot exhibit oscillations.

   (c) How does the steady state solution depend on influx?

   (d) Use a bifurcation tracking program such as XPPAUT to plot the bifurcation diagram of this model, using r as the bifurcation parameter. Find the Hopf bifurcation points and locate the branch of stable limit cycle solutions. Plot some typical limit cycle solutions for different values of r.

2. Use XPPAUT to provide a fast-slow analysis of the polynomial system

$$\frac{dx}{dT} = y - x^3 + 3x^2 + I - z, \tag{28}$$

$$\frac{dy}{dT} = 1 - 5x^2 - y, \tag{29}$$

$$\frac{dz}{dT} = r[s(x - x_1) - z], \tag{30}$$

where $x_1 = -\frac{1}{2}(1 + \sqrt{5})$ is the x-coordinate of the resting state in the reduced two-variable model and where I, is the applied current, with $r = 0.001$ and $s = 4$.

(a) Make a bifurcation diagram of the reduced two variable system, as a function of the "parameter" z, with $I = 2$.

(b) Superimpose this bifurcation diagram over trajectories of the full system in the x-z plane.

(c) Describe the mechanism of this bursting. What happens to the bursting pattern if I is increased or decreased?

3. (a) Numerically simulate the system of differential equations

$$\frac{dv}{dt} = f(v) - w - gs(v - v_\theta), \tag{31}$$

$$5\frac{dw}{dt} = w_\infty(v) - w, \tag{32}$$

$$\frac{ds}{dt} = f_s(s) + \alpha_s(x - 0.3), \tag{33}$$

$$\frac{dx}{dt} = \beta_x\left((1 - x)H(v) - x\right), \tag{34}$$

where $f(v) = 1.35v(1 - \frac{1}{3}v^2)$, $f_s(s) = -0.2(s - 0.05)(s - 0.135)(s - 0.21)$, $w_\infty(v) = \tanh(5v)$, and $H(v) = \frac{3}{2}(1 + \tanh(5v - 2.5))$, and $v_\theta = -2, \alpha_s = 0.002, \beta_x = 0.00025, g = 0.73$.

(b) Give a fast–slow analysis of this burster. Hint: The equations for v, w comprise the fast subsystem, while those for s, x comprise the slow subsystem.

(c) Describe the bursting mechanism in this model. For what kind of burster might this be a reasonable model?

4. Suppose that the production of an enzyme is turned on by m molecules of the enzyme according to

$$\mathrm{G} + m\mathrm{P} \underset{k_-}{\overset{k_+}{\rightleftarrows}} \mathrm{X},$$

where G is the inactive state of the gene and X is the active state of the gene. Suppose that mRNA is produced when the gene is in the active state and the enzyme is produced by mRNA and is degraded at some linear rate. Find a system of differential equations governing the behavior of mRNA and enzyme. Give a phase portrait analysis of this system and show that it has a "switch-like" behavior.