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.

   Solution

   (a) Using the law of mass action, we find

$$\frac{da}{dt} = 2k_{-1}b - 2k_1a^2 + k_{-2}c - k_2ab, \tag{1}$$

$$\frac{db}{dt} = k_1a^2 - k_{-1}b + k_{-2}c - k_2ab, \tag{2}$$

$$\frac{dc}{dt} = k_2ab - k_{-2}c, \tag{3}$$

   where $a = [\mathrm{A}]$, $b = [\mathrm{B}]$, and $c = [\mathrm{C}]$.

   (b) QSS Approach:
   If k_{-1} is large compared to other rate constants, then b equilibrates rapidly (as an exponential) to its quasi-steady state,

$$b = \frac{k_1a^2 + k_{-2}c}{k_{-1} + k_2a}. \tag{4}$$

   If we substitute this quasi-steady state approximation into the equations governing c and a, we find

$$\frac{dc}{dt} = \frac{k_2k_1a^3 - k_{-2}k_{-1}c}{k_{-1} + k_2a}, \qquad \frac{da}{dt} = -3\frac{dc}{dt}. \tag{5}$$

   If $k_{-1} \gg k_2a$, this further reduces to

$$\frac{dc}{dt} = \frac{k_2k_1}{k_{-1}}a^3 - k_{-2}c. \tag{6}$$

Here, the rate at which the reaction takes place is represented by a cubic term because, since k_{-1} is large, the dimer B comes apart quickly unless it is stabilized by a collision with a third monomer of A.

Fast-Equilibrium Approach:
k_{-1} large implies $\mathrm{A} + \mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{B}$ is almost in equilibrium. Thus, the fast equilibrium approximation is

$$b = \frac{k_1 a^2}{k_{-1}}. \tag{7}$$

The new slow variable equation is

$$\frac{d}{dt}(a + 2b) = -3k_2 ab + 3k_{-2}c, \tag{8}$$

which makes the resulting system

$$\begin{aligned} \frac{da}{dt} &= \frac{-3\frac{k_2 k_1}{k_{-1}}a^3 + 3k_{-2}c}{1 + 4\frac{k_1}{k_{-1}}a} \qquad (9) \\ \frac{dc}{dt} &= \frac{k_1 k_2}{k_{-1}}a^3 - k_{-2}c. \qquad (10) \end{aligned}$$

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

$$\mathrm{A}_1 + \mathrm{A}_1 \xrightarrow{k_+} \mathrm{A}_2. \tag{11}$$

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

$$\mathrm{A}_1 + \mathrm{A}_n \xrightarrow{k_+} \mathrm{A}_{n+1}. \tag{12}$$

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.

Solution

The differential equations describing the dynamics are

$$\frac{da_1}{dt} = -2k_+ a_1^2 + 2k_- a_2 + k_- \sum_{j=3}^{\infty} a_j - k_+ a_1 \sum_{j=2}^{\infty} a_j, \tag{13}$$

and

$$\frac{da_n}{dt} = k_+ a_{n-1}a_1 - k_+ a_n a_1 - k_- a_n + k_- a_{n+1}, \tag{14}$$

for $n \geq 2$. The quantity $A_0 = \sum_{j=1}^{\infty} j a_j$ is conserved by these equations.

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

In steady state, the system for $n \geq 2$ is a linear system of equations with solution

$$a_n = \alpha \lambda^n, \tag{15}$$

with $\lambda = \frac{k_+ a_1}{k_-}$. Of course, it must be that $\lambda < 1$ for this solution to be physically meaningful. To determine α, we substitute this solution into Equation 14 with $n = 2$ and find that $\alpha = \frac{k_-}{k_+}$. since $\sum_{j=2}^{\infty} \alpha \lambda^n = \alpha \left(\frac{1}{1-\lambda} - 1 - \lambda \right)$, it follows that the total amount of monomer is

$$A_0 = \frac{k_-^2 a_1}{(k_+ a_1 - k_-)^2}, \tag{16}$$

which in turn implies that

$$a_1 = \frac{A_0}{2\kappa^2}(1 + 2\kappa - \sqrt{1 + 4\kappa}), \tag{17}$$

where $\kappa = \frac{k_+ A_0}{k_-}$.

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?

   Solution

   (c) Rewrite the equation $V = \frac{V_{\max} s}{K_m + s}$ as

$$V_{\max} - \frac{V}{s} K_m = V. \tag{18}$$

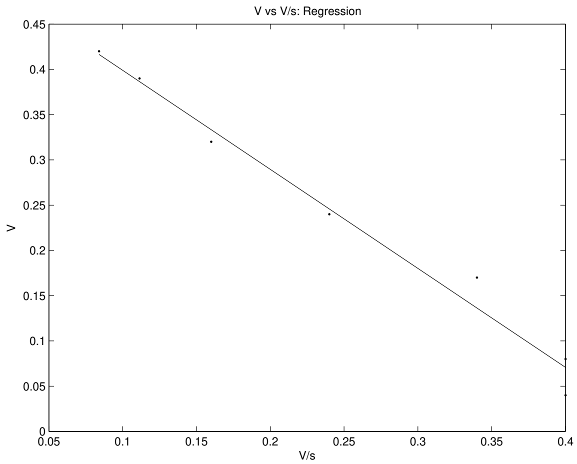

Figure 1:

For each experiment, there is one such equation, so with seven data points we have the linear system of equations

$$A \begin{pmatrix} V_{\max} \\ K_m \end{pmatrix} = \begin{pmatrix} 1.0 & -0.40 \\ 1.0 & -0.40 \\ 1.0 & -0.34 \\ 1.0 & -0.24 \\ 1.0 & -0.16 \\ 1.0 & -0.11 \\ 1.0 & -0.08 \end{pmatrix} \begin{pmatrix} V_{\max} \\ K_m \end{pmatrix} = \begin{pmatrix} 0.04 \\ 0.08 \\ 0.17 \\ 0.24 \\ 0.32 \\ 0.39 \\ 0.42 \end{pmatrix} = b. \tag{19}$$

To find the linear regression solution (also called the least-squares solution) of this system, solve the normal equations

$$A^T A \begin{pmatrix} V_{\max} \\ K_m \end{pmatrix} = A^T b, \tag{20}$$

which in this case is the 2×2 system

$$\begin{pmatrix} 7.0000 & -1.7354 \\ -1.7354 & 0.5383 \end{pmatrix} \begin{pmatrix} V_{\max} \\ K_m \end{pmatrix} = \begin{pmatrix} 1.6600 \\ -0.2933 \end{pmatrix}, \tag{21}$$

having the solution $V_{\max} = 0.5084$, $K_m = 1.0942$. A plot of the line $y = V_{\max} - K_m x$ is shown with data points in Fig. 1, and a plot of the reaction velocity with data points is shown in Fig. 2. This solution can be found by running the Matlab code ex_Burk.m.

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.

   (a) Plot the data V vs. s. Is there evidence that this is a Hill type reaction?

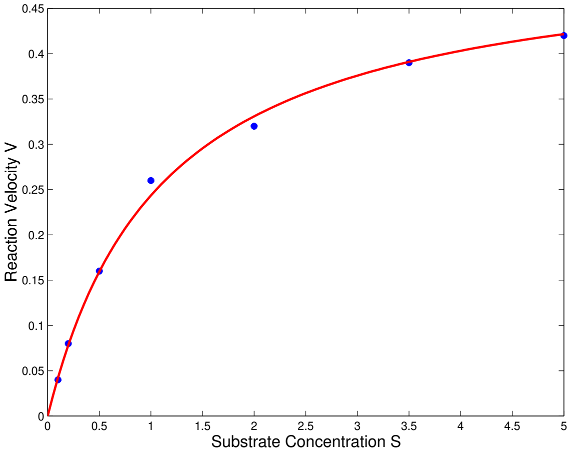

Figure 2: Michaelis-Menten growth curve for data of Problem 3.

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

(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?

Solution

(c) Rewrite the equation $V = \frac{V_{\max}s^n}{K_m^n+s^n}$ as

$$-n \ln K_m + n \ln s = \ln\left(\frac{V}{V_{\max} - V}\right), \tag{22}$$

and view n and $-n \ln K_n$ as unknown variables. For each experiment, there is one such equation, so with ten data points we have the linear system of equations

$$A\begin{pmatrix} -n\ln K_m \\ n \end{pmatrix} = \begin{pmatrix} 1.0 & -1.6094 \\ 1.0 & -0.6931 \\ 1.0 & 0 \\ 1.0 & 0.4055 \\ 1.0 & 0.6931 \\ 1.0 & 0.9163 \\ 1.0 & 1.2528 \\ 1.0 & 1.3863 \\ 1.0 & 1.5041 \\ 1.0 & 1.6094 \end{pmatrix}\begin{pmatrix} -n\ln K_m \\ n \end{pmatrix} = \begin{pmatrix} -4.5951 \\ -2.7515 \\ -0.9946 \\ 0 \\ 0.7082 \\ 1.2657 \\ 2.0907 \\ 2.4423 \\ 2.7515 \\ 2.9444 \end{pmatrix} = b. \tag{23}$$

To find the linear regression solution of this system, solve the normal equations

$$A^T A \begin{pmatrix} -n\ln K_m \\ n \end{pmatrix} = A^T b, \tag{24}$$

which in this case is the 2×2 system

$$\begin{pmatrix} 10.0000 & 5.4649 \\ 5.4649 & 12.8990 \end{pmatrix}\begin{pmatrix} -n\ln K_m \\ n \end{pmatrix} = \begin{pmatrix} 3.8616 \\ 25.8358 \end{pmatrix}, \tag{25}$$

having the solution $n = 2.4$, $K_m = 1.47$. A plot of the line $y = n \ln s - n \ln K_m$ is shown with data points in Fig. 3, and a plot of the reaction velocity with data points is shown in Fig. 4. This solution can be found by running the Matlab code ex_Hill.m.

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

$$\mathrm{S}_1 + \mathrm{E} \underset{k_{-4}}{\overset{k_4}{\rightleftarrows}} \mathrm{S}_1\mathrm{E}.$$

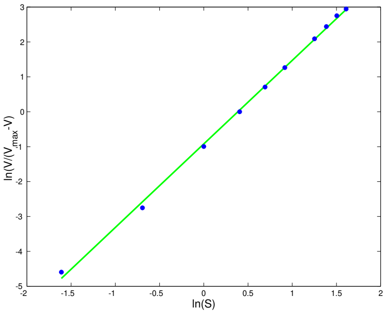

Figure 3:

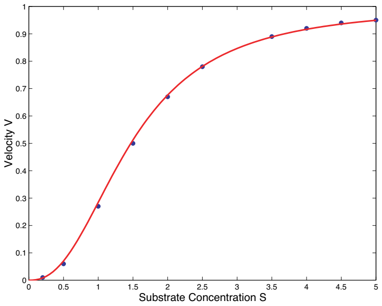

Figure 4: Hill curve for data of Problem 4.

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

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2), \tag{26}$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2. \tag{27}$$

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.

Solution

The addended Sel'kov model with $s_1 = [S_1]$, $s_2 = [S_2]$, $e = [E]$, $c_1 = [ES_2^\gamma]$, $c_2 = [S_1ES_2^\gamma]$,and $c_3 = [S_1E]$ is

$$\frac{ds_1}{dt} = -k_1s_1c_1 + k_{-1}c_2 - k_4s_1e + k_{-4}c_3 + v_1 \tag{28}$$

$$\frac{ds_2}{dt} = -\gamma k_3 s_2^\gamma e + k_{-3}\gamma c_1 + k_2c_2 - v_2s_2 \tag{29}$$

$$\frac{dc_1}{dt} = -k_1s_1c_1 + k_{-1}c_2 + k_2c_2 + k_3es_2^\gamma - k_{-3}c_1 \tag{30}$$

$$\frac{dc_2}{dt} = k_1 s_1 c_1 - k_{-1} c_2 - k_2 c_2 \tag{31}$$

$$\frac{dc_3}{dt} = k_4 s_1 e - k_{-4} c_3 \tag{32}$$

with conservation equation

$$e = e_0 - c_1 - c_2 - c_3. \tag{33}$$

Nondimensionalizing this using $\sigma_1 = \frac{k_1 s_1}{k_2 + k_{-1}}$, $\sigma_2 = \left(\frac{k_3}{k_{-3}}\right)^{1/\gamma} s_2$, $x = c_1/e_0$, $y = c_2/e_0$, $z = c_3/e_0$, and $t = \frac{k_{-1}+k_2}{e_0 k_1 k_2}\tau$ gives

$$\frac{d\sigma_1}{d\tau} = -\frac{k_{-1}+k_2}{k_2}\sigma_1 x + \frac{k_{-1}}{k_2} y - \frac{k_4(k_{-1}+k_2)}{k_1 k_2}\sigma_1(1-x-y-z) + \frac{k_{-4}}{k_2} z + \nu \tag{34}$$

$$\frac{d\sigma_2}{d\tau} = \alpha\left[y - \frac{\gamma k_{-3}}{k_2}\sigma_2^\gamma(1-x-y-z) + \frac{\gamma k_{-3}}{k_2} x\right] - \eta\sigma_2 \tag{35}$$

$$\epsilon\frac{dx}{d\tau} = -\sigma_1 x + y + \frac{k_{-3}}{k_{-1}+k_2}(\sigma_2^\gamma(1-x-y-z) - x) \tag{36}$$

$$\epsilon\frac{dy}{d\tau} = \sigma_1 x - y \tag{37}$$

$$\epsilon\frac{dz}{d\tau} = \frac{k_4}{k_1}\sigma_1(1-x-y-z) - \frac{k_{-4}}{k_{-1}+k_2} z, \tag{38}$$

where $\epsilon = \frac{e_0 k_1 k_2}{(k_{-1}+k_2)^2}$, $\nu = \frac{v_1}{k_2 e_0}$, $\alpha = \frac{k_{-1}+k_2}{k_1}\left(\frac{k_3}{k_{-3}}\right)^{1/\gamma}$, and $\eta = \frac{v_2(k_{-1}+k_2)}{e_0 k_1 k_2}$. In quasi-steady state

$$x = \frac{\sigma_2^\gamma}{1+\sigma_2^\gamma+\beta\sigma_1+\sigma_1\sigma_2^\gamma} \tag{39}$$

$$y = \frac{\sigma_1\sigma_2^\gamma}{1+\sigma_2^\gamma+\beta\sigma_1+\sigma_1\sigma_2^\gamma} \tag{40}$$

$$z = \frac{\beta\sigma_1}{1+\sigma_2^\gamma+\beta\sigma_1+\sigma_1\sigma_2^\gamma}, \tag{41}$$

where $\beta = \frac{(k_{-1}+k_2)k_4}{k_1 k_{-4}}$. Thus,

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2) \tag{42}$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2, \tag{43}$$

where

$$f(\sigma_1, \sigma_2) = \frac{\sigma_1\sigma_2^\gamma}{1+\sigma_2^\gamma+\beta\sigma_1+\sigma_1\sigma_2^\gamma}. \tag{44}$$

A typical phase portrait is shown in Fig. 5.

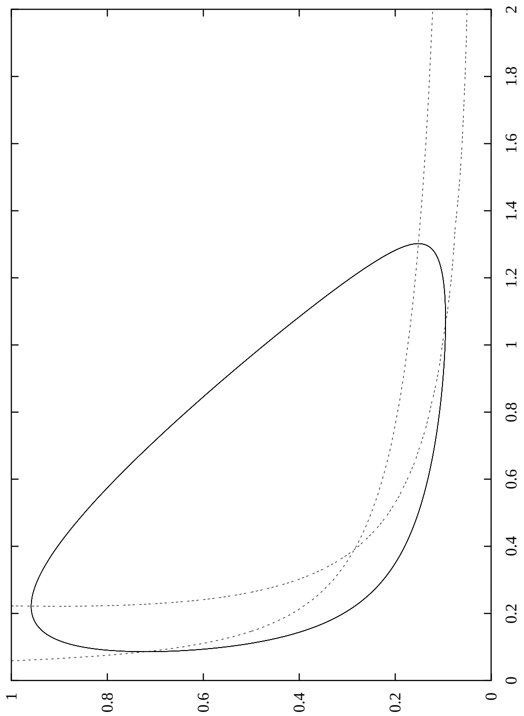

Figure 5: Phase portrait of periodic solutions with $\nu = 0.0285$, $\eta = 0.1$, $\alpha = 1$, $\gamma = 2$, and $\beta = 0.0001$.

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.
   Solution
   $$N = 2C_0A\sqrt{\frac{TD}{\pi}}. \tag{45}$$
   (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.

   Solution

   According to the formula (**??**)
   $$D = \frac{\pi N^2}{4C_0^2A^2T}. \tag{46}$$
   the ratio $\frac{N^2}{T}$ should be a constant. In fact, this number varies between 1.6×10^6 and 3.2×10^6, giving an estimate of D =0.4-0.9 $\times 10^{-4}\text{cm}^2/\text{s}$. For the second data set, with T fixed, the estimate is D =0.3-0.6$\times 10^{-4}\text{cm}^2/\text{s}$.

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?

   Solution
   $$J = \frac{(s_e - s_i)kk_+k_-}{(2k_+^2s_es_i + 2(s_e + s_i)(k + k_-)k_+ + 4k_-k + 2k_-^2)} \tag{47}$$
   where
   $$\begin{aligned} 0 &= 2k_as_i(k_+^2s_es_i + kk_+s_e + kk_+s_i + k_-k_+s_e + k_-k_+s_i + 2kk_- + k_-^2) \\ &\quad +kk_-k_+(s_i - s_e) \end{aligned} \tag{48}$$
   We can solve this for k_a as a function of s_i. Set $S_e = k_+s_e$, $S_i = k_+s_i$, to get
   $$\begin{aligned} 0 &= 2k_aS_i(S_iS_e + (k + k_-)(S_e + S_i) + 2kk_- + k_-^2) \\ &\quad +k_+kk_-(S_i - S_e) \end{aligned} \tag{49}$$
   The important observation is that $s_i \to 0$ as $k_a \to \infty$.

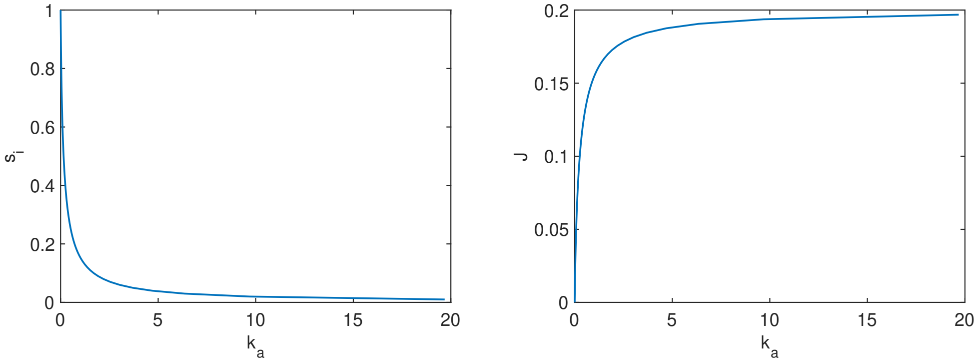

Figure 6: A: Plot of s_i as a function of k_a and B: Plot of J as a function of k_a, with $s_e = k = k_- = k_+ = 1$.

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?

   Solution

   The gram molecular weight of sodium is 23, while the gram molecular weight of chloride is 35.5. Therefore 200 grams of sodium is 8.7 moles of sodium. since salt has equal amounts of sodium and chloride, 200 grams of sodium gives 17.4 osmoles.

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 $T = 300\text{K}$. 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 $T = 300°$ 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?

   Solution

   (a) The units of RcT are $10^3\text{Jm}^{-3} = 10^3\text{Nm}^{-2} = 10^3\text{Pa}$.
   If $\rho g h = 25\text{atm} = 2.533 \times 10^6\text{N m}^{-2}$, then $h = 256.6$ m.
   since a gram of sugar has $\frac{1}{3} \times 10^{22}$ molecules, $\frac{nkT}{\rho g A} = 14.12\text{m}^2$. The column will have height 3.76m.

   (b) $h_1 = \frac{h_0}{2} + \frac{1}{2}\sqrt{h_0^2 + \frac{2nkT}{\rho g A}} = 1.007\text{m}.$

   (c) There is not enough water to balance the osmotic pressure.

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 $27°C$.)

Solution:

From the text, equilibrium is when

$$\frac{c_i}{c_e} = \frac{n_i^3}{n_e^3} e^{\frac{FV}{RT}} \tag{50}$$

The Nernst potential is $V_{Na} = \frac{RT}{F} \ln\left(\frac{n_e}{n_i}\right)$, so that

$$\frac{n_e}{n_i} = e^{\frac{FV_{Na}}{RT}} \tag{51}$$

so that

$$\frac{c_i}{c_e} = e^{\frac{F(V-3V_{Na})}{RT}} = 9.8 \times 10^{-5} \approx 1 \times 10^{-4}. \tag{52}$$

Thus, with $c_e = 1$mM, $c_i = 0.1\mu$M.

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?

Solution

The flux is of the form

$$J = K(g_e n_e e^{-\frac{FV_{Na}}{RT}} - g_i n_i) \tag{53}$$

Clearly, the flux is enhanced by the negative membrane potential.

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.

   Solution

   The bifurcation diagram is shown on the left panel of Fig.7 and a phase portrait for $I_0 = 91.8$, showing periodic limit cycle solution is shown on the right panel. There are two Hopf bifurcation points, at $I_0 = 8.817$ and $I_0 = 372.6$.

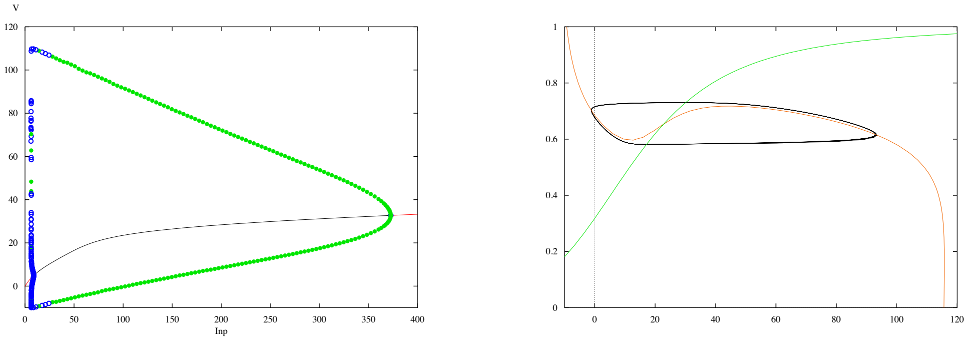

Figure 7: Left: The bifurcation diagram for the Reduced HH equations and Right: a phase portrait for $I_0 = 91.8$, showing a periodic limit cycle solution.

2. Morris and Lecar (1981) proposed the following two-variable model of membrane potential for a barnacle muscle fiber:

$$C_m \frac{dV}{dT} + I_{\text{ion}}(V, W) = I_{\text{app}}, \tag{54}$$

$$\frac{dW}{dT} = \phi\Lambda(V)[W_\infty(V) - W], \tag{55}$$

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

$$I_{\text{ion}}(V, W) = g_{\text{Ca}} M_\infty(V)(V - V_{\text{Ca}}^0) + g_{\text{K}} W (V - V_{\text{K}}^0) + g_{\text{L}}(V - V_{\text{L}}^0), \tag{56}$$

$$M_\infty(V) = \frac{1}{2}\left(1 + \tanh\left(\frac{V - V_1}{V_2}\right)\right), \tag{57}$$

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

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

$$W_\infty(V) = \frac{1}{2}\left(1 + \tanh\left(\frac{V - V_3}{V_4}\right)\right), \tag{58}$$

$$\Lambda(V) = \cosh\left(\frac{V - V_3}{2V_4}\right). \tag{59}$$

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.)

Solution

(a) A phase portrait for $I_{app} = 137$ showing a periodic limit cycle solution is shown in Fig.8.

(b) There are Hopf bifurcations at $I_{app} = 94$ and $I_{app} = 212$, shown in the bifurcation diagram in Fig.9.

3. The Hodgkin-Huxley equations are

$$C_m \frac{dv}{dt} = -\bar{g}_{\text{K}} n^4 (v - v_{\text{K}}) - \bar{g}_{\text{Na}} m^3 h (v - v_{\text{Na}}) - \bar{g}_{\text{L}} (v - v_{\text{L}}) + I_{\text{app}}, \tag{60}$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m, \tag{61}$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n, \tag{62}$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h, \tag{63}$$

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

$$\alpha_m = 0.1 \frac{25 - v}{\exp\left(\frac{25-v}{10}\right) - 1}, \tag{64}$$

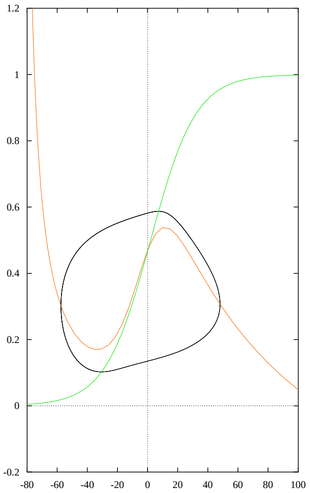

Figure 8: A phase portrait for $I_{app} = 137$, showing periodic limit cycle solution.

$$\begin{aligned}
\beta_m &= 4 \exp\left(\frac{-v}{18}\right), & (65)\\
\alpha_h &= 0.07 \exp\left(\frac{-v}{20}\right), & (66)\\
\beta_h &= \frac{1}{\exp(\frac{30-v}{10}) + 1}, & (67)\\
\alpha_n &= 0.01 \, \frac{10 - v}{\exp(\frac{10-v}{10}) - 1}, & (68)\\
\beta_n &= 0.125 \exp\left(\frac{-v}{80}\right). & (69)
\end{aligned}$$

For these expressions, the potential v is the deviation from rest, measured in units of mV, current density is in units of μA/cm^2, conductances are in units of mS/cm^2, and capacitance is in units of μF/cm^2. The remaining parameters are

$$\bar{g}_{\mathrm{Na}} = 120, \qquad \bar{g}_{\mathrm{K}} = 36, \qquad \bar{g}_{\mathrm{L}} = 0.3, \qquad C_m = 1, \tag{70}$$

and with shifted equilibrium potentials

$$v_{\mathrm{Na}} = 115, \qquad v_{\mathrm{K}} = -12, \qquad v_{\mathrm{L}} = 10.6. \tag{71}$$

(a) Simulate these equations with current input $I_{\mathrm{app}} = 0$. 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.

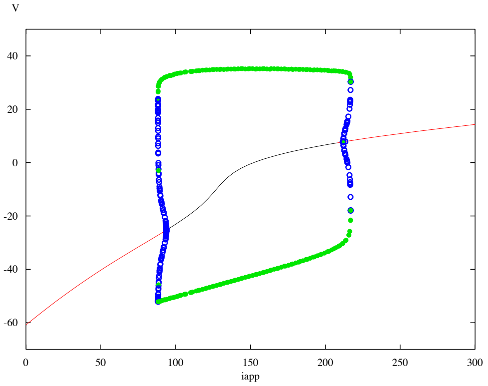

Figure 9: The bifurcation diagram for the Morris Lecar equations.

Solution

(a) The steady solution is $V = 0$, $n = 0.3177$, $m = 0.053$, $h = 0.596$.

(b) With $I_{app} < 13.3$ the response is subthreshold while with $I_{app} > 13.4$ the response is superthreshold, as depicted in Fig.10.

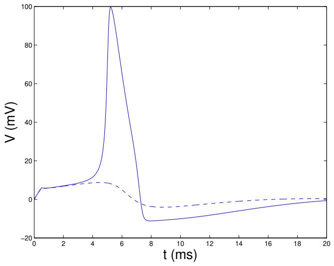

Figure 10: V as a function of t for the HH equations following a stimulus of length 0.5 ms with amplitude $I_{app} = 13.3$ (dashed) and $I_{app} = 13.4$ (solid).

(c) There are Hopf bifurcations at $I_{app} = 9.78$ and $I_{app} = 154.4$. The bifurcation diagram is shown in Fig.11.

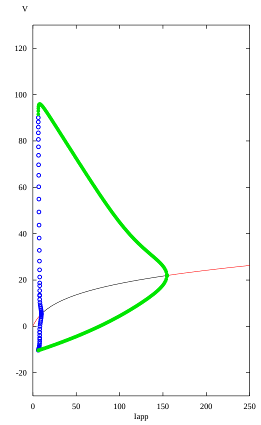

Figure 11: The bifurcation diagram for the HH equations.

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,

$$\frac{dc}{dt} = r - kc - f(c, c_e), \tag{72}$$

$$\frac{dc_e}{dt} = f(c, c_e), \tag{73}$$

$$f(c, c_e) = J_{\text{uptake}} - J_{\text{release}} - k_f c_e, \tag{74}$$

where

$$J_{\text{uptake}} = \frac{V_1 c^n}{K_1^n + c^n}, \tag{75}$$

$$J_{\text{release}} = \left(\frac{V_2 c_e^m}{K_2^m + c_e^m}\right)\left(\frac{c^p}{K_3^p + c^p}\right). \tag{76}$$

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

k	$=$	$10\ s^{-1}$	K_1	$=$	$1\ \mu$M
K_2	$=$	$2\ \mu$M	K_3	$=$	$0.9\ \mu$M
V_1	$=$	$65\ \mu\mathrm{M}s^{-1}$	V_2	$=$	$500\ \mu\mathrm{M}s^{-1}$
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).

bifurcation points and locate the branch of stable limit cycle solutions. Plot some typical limit cycle solutions for different values of r.

Solution

(a) Introduce dimensionless variables $x = \frac{c}{K_1}$, $y = \frac{c_e}{K_1}$, and $\tau = k_f t$, in terms of which the nondimensional equations are

$$\frac{dx}{d\tau} = \rho - \kappa x - \widehat{f}(x, y), \tag{77}$$

$$\frac{dy}{d\tau} = \widehat{f}(x, y), \tag{78}$$

$$\widehat{f}(x, y) = \nu_1 \frac{x^n}{1 + x^n} - \nu_2 \left(\frac{y^m}{k_2^m + y^m}\right)\left(\frac{x^p}{k_3^p + x^p}\right) - x, \tag{79}$$

with the six nondimensional parameters $\rho = \frac{r}{k_f K_1}$, $\kappa = \frac{k}{k_f}$, $\nu_1 = \frac{V_1}{K_1 k_f}$, $\nu_2 = \frac{V_2}{K_1 k_f}$, $k_2 = \frac{K_2}{K_1}$, and $k_3 = \frac{K_3}{K_1}$.

(b) Set $\rho = \kappa = 0$, and then x satisfies the first order differential equation

$$\frac{dx}{d\tau} = -\widehat{f}(x, X_T - x), \tag{80}$$

where $X_T = x + y$ is the total calcium in the cell. Solutions of a first order differential equation are monotone increasing or decreasing, never oscillatory.

(c) At steady state $x = \frac{\rho}{\kappa}$, and $f(x, y) = 0$ determines y, but not easily.

(d) The bifurcation diagram in terms of the variable c, using r as a parameter, is shown in Figure 12. As expected, the steady state of cytosolic calcium changes linearly with r. However, there are supercritical Hopf bifurcations at $r = 3.109$ and $r = 6.652$. Thus, as the diagram shows, for $r \in [3.109, 6.652]$, a stable oscillation exists.

Sample traces of the calcium dynamics are shown in Figure 13 for $r = 3.54$ and $r = 5.92$. Notice that as r increases the amplitude of the calcium oscillations decreases, while their frequency increases.

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

$$\frac{dx}{dT} = y - x^3 + 3x^2 + I - z, \tag{81}$$

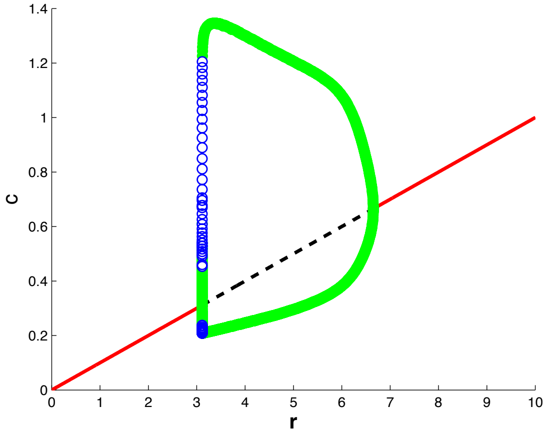

Figure 12: Bifurcation diagram of c with r as the parameter.

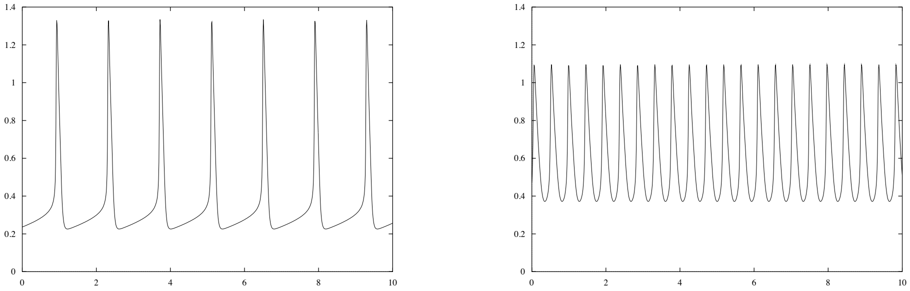

Figure 13: Some traces of the stable limit cycle for $r = 3.54$ (left) and $r = 5.92$ (right).

$$\frac{dy}{dT} = 1 - 5x^2 - y, \tag{82}$$

$$\frac{dz}{dT} = r[s(x - x_1) - z], \tag{83}$$

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?

Solution

(a) XPP was used to create the bifurcation diagram shown in Figure 14 of the fast subsystem (variables x and y), using the slow variable z as a parameter, and

$I = 2$. As the digram illustrates, as z decreases from a large value, oscillations begin via a homoclinic saddle node bifurcation. These oscillations eventually end via a supercritical Hopf bifurcation.

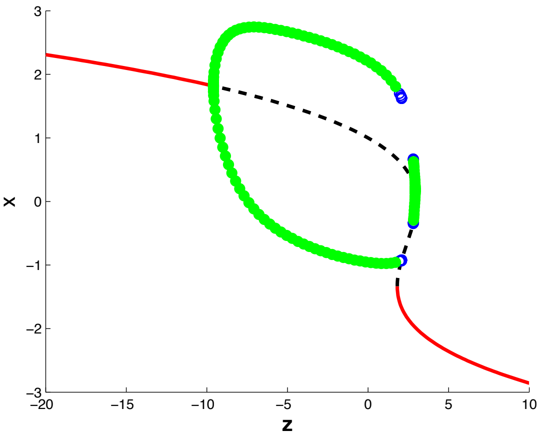

Figure 14: The bifurcation diagram for the slow system (81,82).

(b) We use XPP to superimpose the bifurcation diagram from part (a) onto the solution of the full system in the $z - x$ plane, shown in Figure 15.

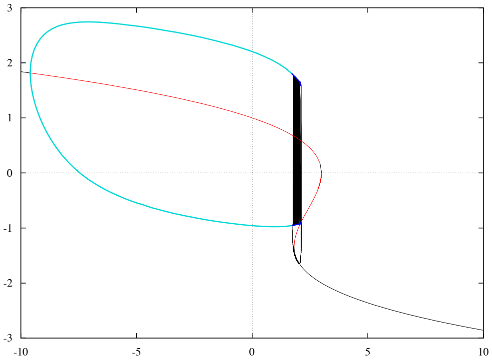

Figure 15: Bifurcation diagram of the fast subsystem.

(c) The bursting mechanism can be described by examining Figure 15 in more detail. Suppose initial conditions place the trajectory along the lower stable branch of the bifurcation diagram. On this branch, the fast variables are approximately at steady state. Further we know that $x < x_1$ and as a result, $\frac{dz}{dt} < 0$.

As z decreases, eventually the saddle node bifurcation is reached, and the system jumps into the oscillatory regime. Here, fast variables are oscillating with $x > x_1$, and consequently, $\frac{dz}{dt} > 0$.

Now, as the slow variable (z) increases, eventually we fall out of the region of oscillation through a homoclinic bifurcation, and the trajectory falls to the lower stable branch. This cycle repeats itself, and bursting occurs.
This bursting behavior is dependent on the parameter I. This is because the quantity $(I + z)$ appears in the governing equation for x, so changing I shifts the bifurcation diagram and hence the transitions between bursting and quiescence.

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

$$\begin{aligned} \frac{dv}{dt} &= f(v) - w - gs(v - v_\theta), && (84) \\ 5\frac{dw}{dt} &= w_\infty(v) - w, && (85) \\ \frac{ds}{dt} &= f_s(s) + \alpha_s(x - 0.3), && (86) \\ \frac{dx}{dt} &= \beta_x\left((1 - x)H(v) - x\right), && (87) \end{aligned}$$

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?

Solution

(a) The numerical simulation of v vs. t is shown in Figure 16. As the figure illustrates, the system bursts very rapidly for approximately 2000 time units. The system then "rests" for 2000 time units before returning to the oscillatory behavior.

(b) The fast-slow analysis of this burster is begun by examining the fast, (v, w) subsystem:

$$\begin{aligned} \frac{dv}{dt} &= f(v) - w - gs(v - v_\theta), && (88) \\ \frac{dw}{dt} &= \frac{w_\infty(v) - w}{5}, && (89) \end{aligned}$$

with s as a parameter. The bifurcation diagram is shown in Figure 17. As the diagram illustrates, there are two homoclinic saddle-node bifurcations, one occurring at $s = 0.1343$ and another at $s = -0.04553$. As a result, for $s \in [-.04553, .1343]$, this fast subsystem is oscillating. For $0.1343 < s < 0.4128$, there are three steady states, with only one of them stable. In this regime, all trajectories go to the low steady state for v. For $-0.3155 < s < -0.04553$, there are also three steady states, but the trajectories are all

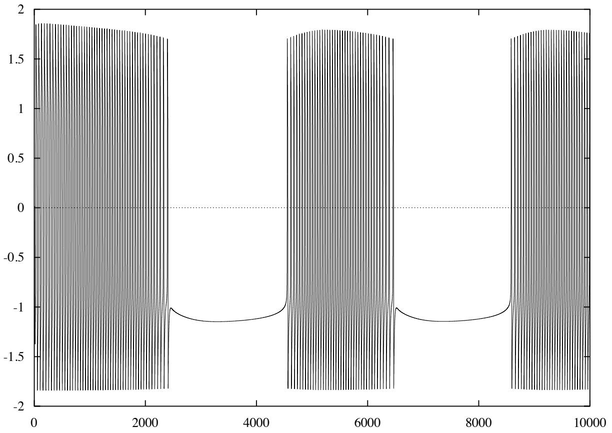

Figure 16: Numerical simulation of the system of differential equations (84-87), with v plotted as a function of t.

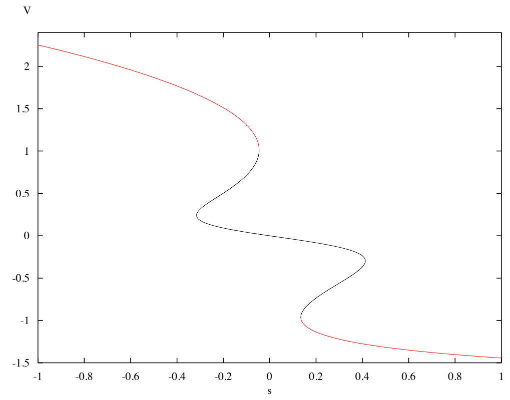

Figure 17: Bifurcation diagram of the fast subsystem (88)-(89) using s as a bifurcation parameter.

attracted to the higher steady state for v. These behaviors are illustrated in the phase portraits shown in Figure 18.

The slow variables s and x are governed by the equations

$$\frac{ds}{dt} = f_s(s) + \alpha_s(x - 0.3), \tag{90}$$

$$\frac{dx}{dt} = \beta_x((1 - x)H(v) - x). \tag{91}$$

The fast variable w does not appear in these equations, and the variable v appears only in the differential equation for x. Further, the nullclines for this

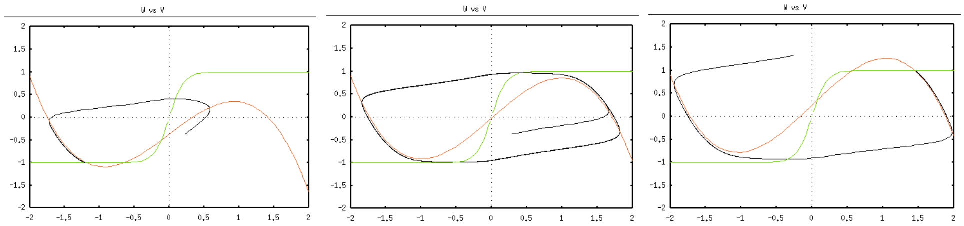

Figure 18: (v, w) phase-plane digram for high s (left), for s between the two homoclinic bifurcations (middle), and for low s (right).

system are

$$s\text{−nullcline}: x = -\frac{-0.2(s-0.05)(s-0.135)(s-0.21)}{\alpha_s} + 0.3, \quad (92)$$

$$x\text{−nullcline}: x = \frac{H(v)}{1+H(v)}. \quad (93)$$

Since v is fast, the slow variable x only "sees" the average value of v over some period of time. Treating v as a parameter, we can look at two possible phase planes of this subsystem. These nullclines can be seen in Figure 19.

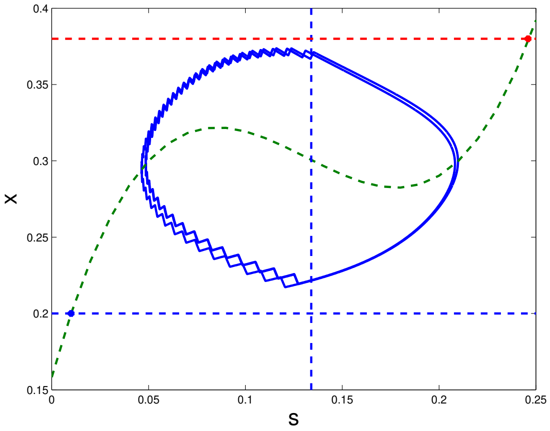

Figure 19: Phase plane of the slow subsystem (90)-(91) with $v \approx -1.2$ (horizontal line at $x = 0.2$) and $v \approx 0.33$ (horizontal line at $x = 0.38$).

(c) Suppose s starts in the non-oscillatory regime of the burster. According to the bifurcation diagram, v is approximately -1.2. With this value of v, the steady state of the slow system is at $s \approx 0.01$ so that s decreases slowly. As it does so, it eventually passes the homoclinic saddle node bifurcation (at $s \approx 0.13$), and the system starts to burst. While bursting, the average value of v, the value that is "seen" by x, is approximately .33. As a result the steady state of the slow subsystem shifts to $x \approx 0.38$, $s \approx 0.25$, so that s increases. Eventually, s crosses the critical point and thereby leaves the oscillatory regime. This process repeats, creating the bursting pattern seen in the simulation.

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.

Solution

Let P_x be the probability that the gene is in the active state. Then,

$$\frac{dP_x}{dt} = k_+ E^m (1 - P_x) - k_- P_x. \tag{94}$$

where E represents the concentration of enzyme. When the gene is in the activated state, the mRNA that codes for the enzyme E is produced at a linear rate. Furthermore, this mRNA produces E at a linear rate, and both mRNA and E decay at a linear rate. It follows that

$$\frac{dM}{dt} = \alpha_m P_x - \alpha_{-m} M, \tag{95}$$
$$\frac{dE}{dt} = \beta_e M - \beta_{-e} E. \tag{96}$$

To give a phase portrait analysis of this system, take Equation (94) to be steady state, so that

$$0 = k_+ E^m (1 - P_x) - k_- P_x \Rightarrow P_x = \frac{k_+ E^m}{k_+ E^m + k_-}. \tag{97}$$

Substituting this into the equation for M yields the equation

$$\frac{dM}{dt} = \alpha_m \frac{k_+ E^m}{k_+ E^m + k_-} - \alpha_{-m} M. \tag{98}$$

Nondimensionalization reduces this system to a system with two parameters

$$\frac{dM}{dt} = \rho \frac{k_+ E^m}{k_+ E^m + k_-} - \kappa M, \tag{99}$$
$$\frac{du}{dt} = m - u. \tag{100}$$

A phase plane portrait for this system with 3 different values of $\rho = 1, 10, 100$ is shown in Figure 20.

Switching behavior is illustrated in the diagram Figure 21.

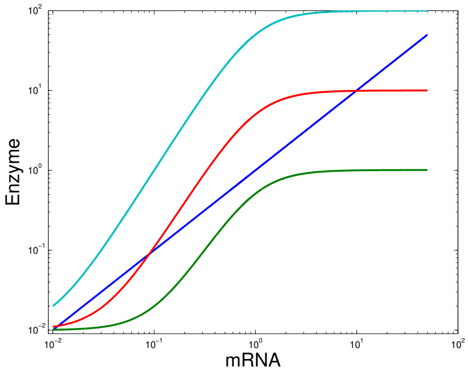

Figure 20: Phase portrait for the system (99)-(100) for 3 different values of $\rho = 1, 10, 100$, plotted on a log-log scale.

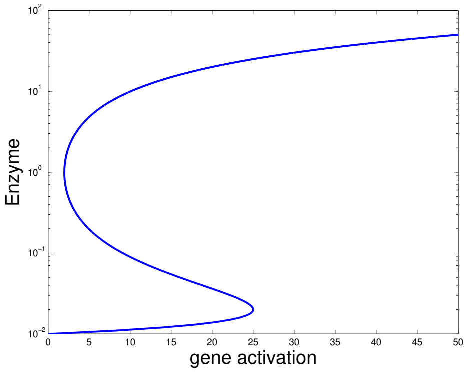

Figure 21: Equilibria for the enzyme level in the system (99)-(100) plotted as a function of ρ.