## Homework Exercises and Solutions for Mathematics 6770 - Fall 2016

Remark: Solutions may include maple files or matlab files.

Assignment 1: (due Sept. 27, 2016)

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,

$$A + A \underset{k_{-1}}{\overset{k_1}{\underset{k_{-1}}{\longrightarrow}}} B,$$
$$A + B \underset{k_{-2}}{\overset{k_2}{\underset{k_{-2}}{\longrightarrow}}} C.$$

- (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.

#### Solution

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

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

$$\frac{db}{dt} = k_1 a^2 - k_{-1} b + k_{-2} c - k_2 a b, \qquad (2)$$

$$\frac{dc}{dt} = k_2 a b - k_{-2} c, \tag{3}$$

where a = [A], b = [B], and c = [C].

(b)  $\underline{\text{QSS Approach}}$ :

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

$$b = \frac{k_1 a^2 + k_{-2} c}{k_{-1} + k_2 a}.$$
(4)

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

$$\frac{dc}{dt} = \frac{k_2 k_1 a^3 - k_{-2} k_{-1} c}{k_{-1} + k_2 a}, \qquad \frac{da}{dt} = -3 \frac{dc}{dt}.$$
(5)

If  $k_{-1} \gg k_2 a$ , this further reduces to

$$\frac{dc}{dt} = \frac{k_2 k_1}{k_{-1}} a^3 - k_{-2} c. \tag{6}$$

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 A + A  $\stackrel{k_1}{\underset{k_{-1}}{\rightleftharpoons}}$  B is almost in equilibrium. Thus, the fast equilibrium approximation is

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

The new slow variable equation is

$$\frac{d}{dt}(a+2b) = -3k_2ab + 3k_{-2}c,\tag{8}$$

which makes the resulting system

$$\frac{da}{dt} = \frac{-3\frac{k_2k_1}{k_{-1}}a^3 + 3k_{-2}c}{1 + 4\frac{k_1}{k_{-1}}a}$$
(9)

$$\frac{dc}{dt} = \frac{k_1 k_2}{k_{-1}} a^3 - k_{-2} c. \tag{10}$$

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

$$A_1 + A_1 \xrightarrow{k_+} A_2. \tag{11}$$

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

$$A_1 + A_n \xrightarrow{k_+} A_{n+1}. \tag{12}$$

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

$$\frac{da_1}{dt} = -2k_+a_1^2 + 2k_-a_2 + k_-\sum_{j=3}^{\infty} a_j - k_+a_1\sum_{j=2}^{\infty} a_j,$$
(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  $n \ge 2$ . The quantity  $A_0 = \sum_{j=1}^{\infty} j a_j$  is conserved by these equations.

Substrate	Reaction
Concentration (mM)	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 1: Data for Problem 3

In steady state, the system for  $n \ge 2$  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  $\alpha$ , 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

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

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

$$A^{T}A\left(\begin{array}{c}V_{\max}\\K_{m}\end{array}\right) = A^{T}b,$$
(20)

which in this case is the  $2 \times 2$  system

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

having the solution  $V_{\text{max}} = 0.5084$ ,  $K_m = 1.0942$ . A plot of the line  $y = V_{\text{max}} - K_m x$  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	Reaction
Concentration (mM)	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

$$A\left(\begin{array}{c}-n\ln K_{m}\\n\end{array}\right) = \begin{pmatrix} 1.0 & -1.6094\\ 1.0 & -0.6931\\ 1.0 & 0.04055\\ 1.0 & 0.6931\\ 1.0 & 0.9163\\ 1.0 & 1.2528\\ 1.0 & 1.3863\\ 1.0 & 1.5041\\ 1.0 & 1.6094 \end{pmatrix} \begin{pmatrix} -n\ln K_{m}\\n \end{pmatrix} = \begin{pmatrix} -4.5951\\ -2.7515\\ 0\\ 0\\ 0\\ 0.7082\\ 1.2657\\ 2.0907\\ 2.4423\\ 2.7515\\ 2.9444 \end{pmatrix} = b.$$

$$(23)$$

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

$$A^{T}A\left(\begin{array}{c}-n\ln K_{m}\\n\end{array}\right) = A^{T}b,$$
(24)

which in this case is the  $2 \times 2$  system

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

$$\frac{d\sigma}{dt} = -\sigma + \alpha_1(\mu_1 + \sigma)x + \alpha_2(\mu_2 + \sigma)y, \qquad (26)$$



Figure 4: Hill curve for data of Problem 4.

$$\epsilon_1 \frac{dx}{dt} = \frac{1}{\lambda_1} \sigma(1-x) - x, \qquad (27)$$

$$\epsilon_2 \frac{dy}{dt} = \frac{1}{\lambda_2} \sigma(1-y) - y. \tag{28}$$

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  $\sigma$ . Under what conditions is the quasi-steady state approximation valid?
- (c) Solve the differential equation governing  $\sigma$ .
- (d) For this system of equations, show that the solution can never leave the positive octant  $\sigma, x, y \ge 0$ . 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.

## Solution

(a) The chemical equations for the two reactions are

$$\mathbf{S} + \mathbf{E}_1 \underset{k_{-1}}{\overset{k_1}{\longleftrightarrow}} \mathbf{C}_1 \overset{k_2}{\longrightarrow} \mathbf{E}_1 + \mathbf{P},$$

$$S + E_2 \xrightarrow[k_{-3}]{k_3} C_2 \xrightarrow{k_4} E_2 + P.$$

As usual we let lower letters denote concentrations. Applying the law of mass action gives

$$\frac{ds}{dt} = k_{-1}c_1 + k_{-3}c_2 - k_1se_1 - k_3se_2, \qquad (29)$$

$$\frac{dc_1}{dt} = k_1 s e_1 - (k_{-1} + k_2) c_1, \qquad (30)$$

$$\frac{dc_2}{dt} = k_3 s e_2 - (k_{-3} + k_4) c_2.$$
(31)

Since the total amounts of the enzymes are conserved,

$$e_1 + c_1 = e_t,$$
 (32)

$$e_2 + c_2 = e_T,$$
 (33)

and we can eliminate  $e_1$  and  $e_2$  to find

$$\frac{ds}{dt} = k_{-1}c_1 + k_{-3}c_2 - k_1s(e_t - c_1) - k_3s(e_T - c_2), \qquad (34)$$

$$\frac{dc_1}{dt} = k_1 s(e_t - c_1) - (k_{-1} + k_2)c_1, \qquad (35)$$

$$\frac{dc_2}{dt} = k_3 s(e_T - c_2) - (k_{-3} + k_4)c_2.$$
(36)

The most natural nondimensionalization of the concentrations is

$$x = \frac{c_1}{e_t},\tag{37}$$

$$y = \frac{c_2}{e_T},\tag{38}$$

$$\sigma = \frac{s}{s_0},\tag{39}$$

where  $s_0$  is the initial amount of substrate. Since it is not immediately obvious how to scale time, we set  $t = \mu \tau$ , and wait until later to determine  $\mu$ . This change of variables gives

$$\frac{d\sigma}{dt} = k_{-1}\frac{\mu e_t}{s_0}x + k_{-3}\frac{\mu e_T}{s_0}y - \mu k_1\sigma e_t(1-x) - \mu k_3\sigma e_T(1-y), \quad (40)$$

$$\frac{1}{\mu}\frac{dx}{dt} = k_1 s_0 \sigma (1-x) - (k_{-1} + k_2)x, \qquad (41)$$

$$\frac{1}{\mu}\frac{dy}{dt} = k_3 s_0 \sigma (1-y) - (k_{-3} + k_4)y.$$
(42)

Now we want to exploit the fact that there is far more substrate than either enzyme, and pick  $\mu$  in a way that emphasizes that under these conditions, x

and y are "fast" variables, compared to  $\sigma$ . Notice that all the linear terms proportional to  $\sigma$  on the right hand side of (40) are multiplied by either  $e_t$  or  $e_T$ , suggesting that this variable is slow. This also suggests that we should pick  $\mu = \frac{1}{k_1 e_t + k_3 e_T}$  in which case we find

$$\frac{d\sigma}{dt} = -\sigma + \frac{e_t(k_{-1} + k_1 s_0 \sigma)}{s_0(k_1 e_t + k_3 s_0 e_T)} x + \frac{e_T(k_{-3} + k_3 \sigma)}{s_0(k_1 e_t + k_3 e_T)} y \quad (43)$$

$$\frac{k_1 e_t + k_3 e_T}{k_{-1} + k_2} \frac{dx}{dt} = \frac{k_1 s_0}{k_{-1} + k_2} \sigma(1 - x) - x, \qquad (44)$$

$$\frac{k_1 e_t + k_3 e_T}{k_{-3} + k_4} \frac{dy}{dt} = \frac{k_3 s_0}{k_{-3} + k_4} \sigma(1 - y) - y.$$
(45)

which is

$$\frac{d\sigma}{dt} = -\sigma + \alpha_1(\mu_1 + \sigma)x + \alpha_2(\mu_2 + \sigma)y, \qquad (46)$$

$$\epsilon_1 \frac{dx}{dt} = \frac{1}{\lambda_1} \sigma(1-x) - x, \qquad (47)$$

$$\epsilon_2 \frac{dy}{dt} = \frac{1}{\lambda_2} \sigma(1-y) - y. \tag{48}$$

where  $\epsilon_1 = \frac{k_1 e_t + k_3 e_T}{k_{-1} + k_2}$ ,  $\epsilon_2 = \frac{k_1 e_t + k_3 e_T}{k_{-3} + k_4}$ ,  $\lambda_1 = \frac{k_{-1} + k_2}{k_{1} s_0}$ ,  $\lambda_2 = \frac{k_{-3} + k_4}{k_3 s_0}$ ,  $\mu_1 = \frac{k_{-1}}{k_{1} s_0}$ ,  $\mu_2 = \frac{k_{-3}}{k_3 s_0}$ ,  $\alpha_1 = \frac{k_1 e_t}{k_1 e_t + k_3 e_T}$ , and  $\alpha_2 = \frac{k_3 e_T}{k_1 e_t + k_3 e_T}$ , with  $\alpha_1 + \alpha_2 = 1$ . (b) Under the assumption that both  $\epsilon_1$  and  $\epsilon_2$  are small, we set  $\epsilon_1 = \epsilon_2 = 0$  and

find the quasi-steady state solution

$$x = \frac{\sigma}{\lambda_1 + \sigma},\tag{49}$$

$$y = \frac{\sigma}{\lambda_2 + \sigma}.$$
 (50)

We substitute these expressions into the differential equation for  $\sigma$  to get the equation for  $\sigma$ ,

$$\frac{d\sigma}{dt} = -\sigma + \alpha_1 \sigma \frac{\mu_1 + \sigma}{\lambda_1 + \sigma} + \alpha_2 \sigma \frac{\mu_2 + \sigma}{\lambda_2 + \sigma}.$$
(51)

(c) The equation (51) can be solved by separating variables. First, we rewrite it as  $\langle \rangle$ ()

$$\frac{(\lambda_1 + \sigma)(\lambda_2 + \sigma)}{\sigma(\theta_1 \sigma + \theta_2)} d\sigma = -dt.$$
(52)

where

$$\theta_1 = \lambda_1 + \lambda_2 - \alpha_1(\mu_1 + \lambda_2) - \alpha_2(\mu_2 + \lambda_1)$$
(53)

$$\theta_2 = \lambda_1 \lambda_2 - \alpha_1 \mu_1 \lambda_2 - \alpha_2 \mu_2 \lambda_1. \tag{54}$$

(It is important to notice that  $\alpha_1 + \alpha_2 = 1$ .) Notice that in original dimensioned parameters these are

$$\theta_1 = k_3 \frac{k_1 e_t k_2 + e_T k_4 k_1}{(k_1 e_t + k_3 e_T) k_1 k_3 s_0}$$
(55)

$$\theta_2 = \frac{1}{(k_1 e_t + k_3 e_T) k_1 s_0 k_3 s_0} k_1 e_t k_2 (k_{-3} + k_4) + k_3 e_T k_4 (k_{-1} + k_2), \quad (56)$$



Figure 5: Plots of  $\sigma$ , x and y for the parameters  $\mu_1 = 0.5$ ,  $\mu_2 = 0.6$ ,  $\lambda_1 = 0.9$ ,  $\lambda_2 = 0.8$ ,  $\alpha_1 = 0.3$ ,  $\alpha_2 = 0.7$ .

both positive. We integrate both sides of (52) to find

$$-\frac{\sigma}{\theta_1} - \frac{\lambda_1 \lambda_2 \ln(\sigma)}{\theta_2} + \left(\frac{\lambda_1 \lambda_2}{\theta_2} - \frac{\lambda_1 + \lambda_2}{\theta_1} + \frac{\theta_2}{\theta_1^2}\right) \ln(\theta_1 \sigma + \theta_2) = t + K, \quad (57)$$

for some constant K. To determine K, we apply the initial condition  $\sigma(0) = 1$ , from which it follows that

$$K = -\frac{1}{\theta_1} + \left(\frac{\lambda_1 \lambda_2}{\theta_2} - \frac{\lambda_1 + \lambda_2}{\theta_1} + \frac{\theta_2}{\theta_1^2}\right) \ln(\theta_1 + \theta_2).$$
(58)

Thus,

$$\frac{1-\sigma}{\theta_1} - \frac{\lambda_1 \lambda_2 \ln(\sigma)}{\theta_2} + \left(\frac{\lambda_1 \lambda_2}{\theta_2} - \frac{\lambda_1 + \lambda_2}{\theta_1} + \frac{\theta_2}{\theta_1^2}\right) \ln\left(\frac{\theta_1 \sigma + \theta_2}{\theta_1 + \theta_2}\right) = t.$$
(59)

We can now plot the solutions. (This is most easily done by considering t to be a function of  $\sigma$ , and then reversing the axes.) The results, for one particular choice of the parameters, are shown in Fig.5.

It is important to realize that the graphs for x and y are incorrect at small times, since at t = 0, x and y are nonzero. This is not physically possible, since all the enzymes start in the unbound form. Hence, using the quasisteady state approximation we have constructed a solution that is incorrect close to t = 0. To correct this requires a knowledge of how to construct asymptotic series solutions to equations of this type (i.e., to singular perturbation problems), a subject which is beyond the scope of this text. This is discussed briefly in the Appendix of this Chapter, as well as in Murray (1989) and Lin and Segel (1988).

However, for larger times this solution is reasonably accurate.

(d) To show that solutions of equations (26)-(28) cannot leave the positive octant, it suffices to show that they cannot cross the boundary. The boundary consists of the three planes, x = 0, y = 0, and  $\sigma = 0$ . When x = 0,  $dx/dt = \frac{\sigma}{\lambda_1}$  which is strictly positive everywhere in the first octant (and hence on the boundary), except at the origin (which is a critical point of the system). Similarly, when y = 0,  $dy/dt = \frac{\sigma}{\lambda_2} > 0$  except at the origin, and when  $\sigma = 0$ ,  $d\sigma/dt = \alpha_1\mu_1x + \alpha_2\mu_2y > 0$  except at the origin. It follows that no solution can leave the first octant.

To show that the solution approaches the origin for large time, we add the three equations together, weighted by 1,  $\lambda_1 \alpha_1$ , and  $\lambda_2 \alpha_2$  respectively to find

$$\frac{d}{dt}(\sigma + \epsilon_1 \lambda_1 \alpha_1 x + \epsilon_2 \lambda_2 \alpha_2 y) = \alpha_1 (\mu_1 - \lambda_1) x + \alpha_2 (\mu_2 - \lambda_2) y$$
(60)

(since  $\alpha_1 + \alpha_2 = 1$ ). Now observe that

$$\mu_1 - \lambda_1 = -\frac{k_2}{k_1 s_0} < 0, \qquad \mu_2 - \lambda_2 = -\frac{k_4}{k_3 s_0} < 0, \tag{61}$$

so that  $\sigma + \epsilon_1 \lambda_1 \alpha_1 x + \epsilon_2 \lambda_2 \alpha_2 y$  decreases whenever x and y are non-negative. However, we already know that x and y cannot be zero unless  $\sigma = 0$  as well. Thus  $\sigma + \epsilon_1 \lambda_1 \alpha_1 x + \epsilon_2 \lambda_2 \alpha_2 y$  is always decreasing, and so approaches zero 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

$$S_1 + E \underset{\underset{k=4}{\leftarrow}}{\overset{k_4}{\leftarrow}} S_1 E$$

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

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2), \tag{62}$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta \sigma_2.$$
(63)

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],  $c_1 = [ES_2^{\gamma}]$ ,  $c_2 = [S_1 E S_2^{\gamma}]$ , and  $c_3 = [S_1 E]$  is

$$\frac{ds_1}{dt} = -k_1 s_1 c_1 + k_{-1} c_2 - k_4 s_1 e + k_{-4} c_3 + v_1 \tag{64}$$

$$\frac{ds_2}{dt} = -\gamma k_3 s_2^{\gamma} e + k_{-3} \gamma c_1 + k_2 c_2 - v_2 s_2 \tag{65}$$

$$\frac{dc_1}{dt} = -k_1 s_1 c_1 + k_{-1} c_2 + k_2 c_2 + k_3 e s_2^{\gamma} - k_{-3} c_1 \tag{66}$$

$$\frac{dc_2}{dt} = k_1 s_1 c_1 - k_{-1} c_2 - k_2 c_2 \tag{67}$$

$$\frac{dc_3}{dt} = k_4 s_1 e - k_{-4} c_3 \tag{68}$$

with conservation equation

$$e = e_0 - c_1 - c_2 - c_3. (69)$$

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

$$\frac{d\sigma_1}{d\tau} = -\frac{k_{-1}+k_2}{k_2}\sigma_1 x + \frac{k_{-1}}{k_2}y - \frac{k_4(k_{-1}+k_2)}{k_1k_2}\sigma_1(1-x-y-z) + \frac{k_{-4}}{k_2}z + \nu$$
(70)

$$\frac{d\sigma_2}{d\tau} = \alpha \left[ y - \frac{\gamma k_{-3}}{k_2} \sigma_2^{\gamma} (1 - x - y - z) + \frac{\gamma k_{-3}}{k_2} x \right] - \eta \sigma_2 \tag{71}$$

$$\epsilon \frac{dx}{d\tau} = -\sigma_1 x + y + \frac{k_{-3}}{k_{-1} + k_2} (\sigma_2^{\gamma} (1 - x - y - z) - x)$$
(72)

$$\epsilon \frac{dy}{d\tau} = \sigma_1 x - y \tag{73}$$

$$\epsilon \frac{dz}{d\tau} = \frac{k_4}{k_1} \sigma_1 (1 - x - y - z) - \frac{k_{-4}}{k_{-1} + k_2} z, \tag{74}$$

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

$$x = \frac{\sigma_2^{\gamma}}{1 + \sigma_2^{\gamma} + \beta \sigma_1 + \sigma_1 \sigma_2^{\gamma}}$$
(75)

$$y = \frac{\sigma_1 \sigma_2'}{1 + \sigma_2^{\gamma} + \beta \sigma_1 + \sigma_1 \sigma_2^{\gamma}}$$
(76)

$$z = \frac{\beta \sigma_1}{1 + \sigma_2^{\gamma} + \beta \sigma_1 + \sigma_1 \sigma_2^{\gamma}},\tag{77}$$

where  $\beta = \frac{(k_{-1}+k_2)k_4}{k_1k_{-4}}$ . Thus,

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2) \tag{78}$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta \sigma_2, \tag{79}$$



Figure 6: Phase portrait of periodic solutions with  $\nu = 0.0285$ ,  $\eta = 0.1$ ,  $\alpha = 1$ ,  $\gamma = 2$ , and  $\beta = 0.0001$ .

where

$$f(\sigma_1, \sigma_2) = \frac{\sigma_1 \sigma_2^{\gamma}}{1 + \sigma_2^{\gamma} + \beta \sigma_1 + \sigma_1 \sigma_2^{\gamma}}.$$
(80)

A typical phase portrait is shown in Fig. 6.