Prof. Dr. Joachim Krug
Alexander Klug
Benjamin Schmiegelt
Suman G. Das

Summer term 2021

Biological Physics II

Problem Set 3

Please hand in your solutions before 12:00 noon on Wedenesday, May 19, 2021.

1. Hopf bifurcation *4+4=8pts*

A Hopf bifurcation occurs when a fixed point loses stability and a limit cycle appears. The bifurcation is *supercritical* if the limit cycle is stable and *subcritical* if unstable. A characteristic of a Hopf bifurcation is that a pair of complex conjugate eigenvalues of the Jacobian cross the imaginary axis. As an application, consider a system consisting of three proteins X_1, X_2 and X_3 (with concentrations x_1, x_2 and x_3) such that X_1 inhibits the expression of X_2, X_2 inhibits that of X_3, and X_3 that of X_1. A simplified quantitative model for this is given below.

$$\begin{aligned}\dot{x}_1 &= \frac{1}{1+x_3^n} - \frac{1}{2}x_1 \\ \dot{x}_2 &= \frac{1}{1+x_1^n} - \frac{1}{2}x_2 \\ \dot{x}_3 &= \frac{1}{1+x_2^n} - \frac{1}{2}x_3, \end{aligned} \tag{1.1}$$

where the parameter $n > 0$.

a) Show that there is only one fixed point in this system with positive x_1, x_2, and x_3. Find the threshold n_c such that the fixed point is stable for $n < n_c$. Show that a Hopf bifurcation occurs at n_c by examining the eigenvalues.

b) For $n = 4.5$, simulate $x_1(t)$, $x_2(t)$ and $x_3(t)$ from any suitable initial condition and for long enough such that the asymptotic behavior is observed. Plot[1] the three variables as a function of time. Also make a 3D plot of the orbit of (x_1, x_2, x_3) for the same time interval. From the plot, determine if the Hopf bifurcation at $n = 4$ is supercritical or subcritical (assume that no additional bifurcations happen between $n = 4$ and $n = 4.5$).

2. Genetic oscillations: the "repressilator" *3+7+4+4+4=22 pts*

Here we examine a more detailed model of an oscillatory genetic circuit, called the repressilator. As before, consider the three repressor proteins with their respective concentrations denoted by the same variables. The mRNA concentrations of the proteins are y_1, y_2 and y_3 respectively. Now we take into account the fact that the mRNA transcription processes are affected by the

[1] In this and other exercises, the word *plot* always refers to numerical plots. For drawing by hand, the word *sketch* is used.

repressor proteins, and this is what leads to the inhibition of protein synthesis. The equations for this model are:

$$\begin{aligned} \dot{x}_i &= -\beta(x_i - y_i) \\ \dot{y}_i &= -y_i + \alpha_0 + \frac{\alpha}{1 + x_{i-1}^n} \end{aligned} \tag{2.1}$$

for $i = 1,\ 2,\ 3$, and we define $x_0 \equiv x_3$. All parameters are positive.[2]

a) Show that the unique fixed point of the system with positive concentrations satisfies $x_i = y_i = p$, where p is the positive solution of

$$p = \frac{\alpha}{1 + p^n} + \alpha_0. \tag{2.2}$$

b) The stability condition of the fixed point is (we prove this later)

$$\frac{(\beta + 1)^2}{\beta} > \frac{3z^2}{4 + 2z}, \tag{2.3}$$

where

$$z = -\frac{\alpha n p^{n-1}}{(1 + p^n)^2}.$$

For $\alpha_0 = 0$ and $n = 1.9$, find p as a function of α by solving (2.2) numerically, for α between 1 and 10^4. Plot this function on a log-log scale. Using this data (and the expression for z) in (2.3), plot the boundary separating the stable from unstable regions in the $\alpha - \beta$ plane on a log-log scale, where α covers the above-mentioned range, and β is between 1 and 10^4. (While doing the numerics, space your chosen α and β values exponentially, so that they are linearly spaced in the log-log plot.) Indicate the stable and unstable regions. Now repeat this exercise for $\alpha_0/\alpha = 10^{-3}$ and $n = 1.9$.

c) For $\alpha_0 = 0$ and $n = 2.1$, numerically find the approximate value of α above which the fixed point is never stable. (You do not need to be too precise.)

d) For $\alpha_0 = 0$, $n = 1.9$, $\alpha = 200$ and $\beta = 5$, numerically simulate and plot the protein concentrations as functions of time (the asymptotic behavior should be visible).

e) In the present exercise we have seen three proteins such that X_1 inhibits X_2, X_2 inhibits X_3, and X_3 inhibits X_1, and the system can exhibit oscillations. If instead X_3 activated (i.e increased the expression of) X_1, would we still see oscillations? If we had N proteins X_i where $i = 1, 2 \ldots N$ such that each one inhibits the next (and X_N inhibits X_1), then what is the condition on N such that the system can exhibit oscillations? (Explain in words. No equations necessary.)

f) **Bonus:** Prove the stability condition (2.3). **Hint:** You can look up the theory of *circulant matrices*. Alternatively, the following identity may help. Let M be a square matrix such that

$$M = \begin{bmatrix} A & B \\ C & D \end{bmatrix},$$

where A, B, C and D are square matrices of identical dimensions, and C and D commute. Then $det\ M = det\ (AD - BC)$. This is useful in simplifying the characteristic equation. Further hint: When the fixed point loses stability, a Hopf bifurcation occurs. It is therefore useful to watch out for the complex conjugate eigenvalues.

[2] This model was introduced in: *Elowitz, M. B., and Leibler, S. (2000). A synthetic oscillatory network of transcriptional regulators. Nature, 403(6767), 335-338.*