1. **Stochastic simulation of an auto regulatory system.**

For a chemical reaction occurring at rate $r$, the distribution of waiting times $\tau$ between reaction events is given by $\varphi(\tau) d\tau = r e^{-r\tau} d\tau$.

(2) $a$). By integrating over time verify that the distribution is properly normalized.

(3) $b$). Suppose $u$ is a random variable with some distribution $\varphi(u)$, and $\theta(u)$ is a function of $u$. Then the probability that $\theta'$ lies between $\theta(u)$ and $\theta(u + du)$ is the same as the probability that $u'$ lies between $u$ and $u + du$. This gives us a recipe for calculating the distribution $\varphi(\theta)$:

$$\varphi(\theta) d\theta = \varphi(u) du \quad \Rightarrow \quad \varphi(\theta) = \varphi(u) \frac{du}{d\theta}$$

Assuming $u$ is uniformly distributed between 0 and 1, show that the number

$$\theta(u) = \frac{1}{r} \ln \left( \frac{1}{u} \right)$$

is distributed precisely as the waiting times between reaction events.

(4) $c$). Using the idea introduced in $b$ sketch an algorithm for simulating stochastic reactions. In the case in which we are dealing with only one species the output of a simulation run should be a list of the number of molecules at different time points.

Using these ideas we are now ready to try to study these two systems:

**Scheme I**: A system in which protein $X$ is expressed constitutively. In a deterministic setting, the concentration of $X$ would evolve according to

$$\frac{dx}{dt} = A - \gamma x.$$  

**Scheme II**: A system in which protein $X$ represses its own synthesis. We will consider a model that in the deterministic limit reduces to

$$\frac{dx}{dt} = \frac{B}{1 + Kx} - \gamma x.$$  

(1) $d$). Suggest a plausible biochemical origin for the hyperbolic repression term in system II.

(2) $e$). Compute the fixed points of the deterministic systems and their stability.

(6) $f$). If we measure volume in units of cell size, then concentrations are equivalent to molecule numbers. Also note that by rescaling time we can, without loss of generality, set $\gamma = 1$. Write some code to implement a discrete stochastic simulation and for scheme I, both for $A = 10$ and $A = 100$, verify that the variance and mean of the steady state distributions are consistent with
Poisson statistics. Print out histograms of final \( x \) values in each case, as well as a copy of your code. Make sure that you run the system for a long enough time so as to get to steady state.

(6) \( g \). For scheme II set \( K = 1/100 \) and choose \( B \) so that \( \langle x \rangle \equiv 100 \) in steady state. Simulate the system to show that the variance of the autoregulated system is lower than that of the constitutive system with the same mean. Print out the final histograms as well as a copy of your code (or just the differences between the code that you used for this item and the one that you used in \( f \)).

(2) \( h \). Find two examples of biological systems in which the distribution of some protein concentration had been measured. How does the variance compare with the variance of a Poisson variable with the same mean? Has the corresponding network structure been already characterized? If that’s the case, what does it look like?

2. **Comparing deterministic and stochastic descriptions in a system with nonlinear degradation.**

Let’s consider a fixed volume system in which a protein \( X \), which is constitutively expressed at a rate \( k \), acts as its own degradation enzyme, *ie*: once there are enough proteins around, the following irreversible reaction can take place \( X + X \rightarrow X \) with a rate \( \gamma \).

(3) \( a \). If there are \( n \) proteins, in how many different ways can one enzymatic degradation occur?

(4) \( b \). Write the master equation for the process.

(10) \( c \). Write an equation for \( d\langle n\rangle/dt \) in terms of the mean \( \langle n \rangle \) and the variance \( V = \langle n^2 \rangle - \langle n \rangle^2 \). Note that in this case the variance will not go away as it did in the cases shown in class where reaction terms were linear.

(4) \( d \). Write the differential equation for the corresponding deterministic system.

(4) \( e \). Assuming that the variance of the steady state distribution is known, what conditions on it will ensure that the steady state mean is similar to the prediction of the deterministic system?

3. **Concentration gradient due to a pipette tip.**

A pipette is connected to a reservoir of a chemical at concentration \( c_p \), and its tip is placed in a beaker of water. The chemical begins to diffuse from regions of high concentration to those of low concentration, creating a total flux \( F \) out of the reservoir; the resulting drop in the reservoir concentration is negligible. Meanwhile, a concentration gradient is set up in the beaker, with the concentration \( c_p \) at the pipette tip, and zero far from it. The purpose of this problem is to calculate the resulting concentration profile.
(3) \( a. \) Consider a spherical surface of radius \( r \), centered at the pipette tip, through which there flows a flux per unit area \( J(r) \) (see Fig. 1). What is the total flux \( F(r) \) through this surface?

(3) \( b. \) Since the chemical is neither created nor degraded in the beaker, the total flux through a sphere at any radius must be a constant; that is, \( F(r) = F \). What does this imply about \( J(r) \)?

(8) \( c. \) Fick’s first law (with diffusion coefficient set to unity) states that \( J(r) = -\frac{\partial c}{\partial r} \). Integrate your answer from part \( b \) to calculate \( c(r) \). If \( r_p \) is the radius of the pipette tip, then \( c(r_p) = c_p \), and \( c(\infty) = 0 \). Calculate the value of \( F \) required for \( c(r) \) to satisfy these boundary conditions. Give expressions for \( c(r) \) and \( J(r) \) in terms of \( c_p \), \( r_p \), and \( r \).

(8) \( d. \) A spherical cell of radius \( \rho_0 \) is placed a distance \( R \) from the pipette tip, with \( \rho_0 << R \). The flux is therefore nearly constant near the cell, and the concentration changes linearly from the leading edge to the trailing edge of the cell. That is, \( J(r) = J(R) \), and \( c(r) = c(R) - J(R)(r - R) \). We now change coordinates, measuring the distance \( \rho \) from the center of the cell and the angle \( \theta \) from its leading edge (see Fig. 2). Calculate the concentration distribution along the cell surface.

(0) \( f. \) CHALLENGE. If the cell is small compared with the distance to the pipette tip it does not disturb the concentration profile significantly and the approximations made in part \( e \) are valid. If, however, the cell is large or close to the pipette tip, these approximations do not hold. Calculate the exact concentration distribution due to a pipette tip in the presence of a nearby cell.

4. \textit{Stability of a reaction diffusion system.}

Consider the following general reaction diffusion system

\[
\frac{\partial u}{\partial t} = A_1 F(u, v) + D_1 \frac{\partial^2 u}{\partial x^2}
\]

\[
\frac{\partial v}{\partial t} = A_2 G(u, v) + D_2 \frac{\partial^2 v}{\partial x^2}
\]

(3) \( a. \) Show that by choosing units properly this system can be rewritten as
\[
\frac{\partial \bar{u}}{\partial t} = \gamma F(u,v) + \frac{\partial^2 \bar{u}}{\partial x^2} = \gamma f(\bar{u}, \bar{v}) + \frac{\partial^2 \bar{u}}{\partial x^2}
\]
\[
\frac{\partial \bar{v}}{\partial t} = \gamma G(u,v) + d \frac{\partial^2 \bar{v}}{\partial x^2} = \gamma g(\bar{u}, \bar{v}) + d \frac{\partial^2 \bar{v}}{\partial x^2}
\]

From now on we will work with this system and we will drop the bars to simplify the notation. Assume \( \gamma > 0 \).

(4) \( b. \) Let’s first consider some homogeneous solution \( u(x,t) = u_0 \) and \( v(x,t) = v_0 \). Write, in terms of the derivatives of the functions \( f \) and \( g \), the conditions that will ensure the stability of this solution. From now on, assume that this solution is stable.

(5) \( c. \) As done in class, now consider inhomogeneous perturbations of the form
\[
\begin{align*}
    u(x,t) &= u_0 + \delta u(t) \cos(x / \ell) \\
    v(x,t) &= v_0 + \delta v(t) \cos(x / \ell)
\end{align*}
\]
and, assuming \( \delta u(t) \) and \( \delta v(t) \) to be small, derive linear differential equations for \( \delta u(t) \) and \( \delta v(t) \).

(5) \( d. \) Show that in order for at least some of these perturbations to be unstable these conditions must hold:
\[
\begin{align*}
    df_u + g_v > 0 \\
    (df_u + g_v)^2 - 4(df_u g_v - f_v g_u) > 0
\end{align*}
\]
where, for instance, \( f_u \) stands for the partial derivative of \( f \) with respect to \( u \) evaluated at \((u_0, v_0)\). Show that these conditions along with the ones derived in part \( b \) imply that the signs of \( f_u \) and \( g_v \) must be different. Additionally show that when we assume that \( f_u > 0 \) then \( d > 1 \).

(5) \( e. \) What are the possible interaction structures compatible with a system that presents this kind of instability? (i.e., How does each variable affect itself and the other near the fixed point? Inhibiting or enhancing production?) Compare these structures with the local-activation-long-range-inhibition picture. What does the condition \( d > 1 \) represent in each case?

(5) \( f. \) Look up in the literature for two examples of pattern forming systems and compare the networks involved with the ones you derived in \( e \).