Problem 5. Master equation for an ensemble of ion channels. Consider the master equation for the two-state ion channel model:
\[
\frac{d}{dt} P(n, t) = \alpha(N - n + 1)P(n - 1, t) + \beta(n + 1)P(n + 1, t) - [\alpha(N - n) + \beta n]P(n, t).
\]

(a) By multiplying both sides by \( n \) and summing over \( n \), derive the following kinetic equation for the mean \( \bar{n} = \sum_{n=0}^{N} nP(n, t) \):
\[
\frac{d\bar{n}}{dt} = \alpha(N - \bar{n}) - \beta \bar{n}.
\]

(b) Derive a corresponding equation for the variance \( \sigma^2 = \langle n^2 \rangle - \langle n \rangle^2 \). That is, multiply both sides of the master equation by \( n^2 \) and sum over \( n \) to determine an equation for the second moment, and then use part (a). Show that the variance decays exponentially at a rate \( 2(\alpha + \beta) \) to the steady-state value
\[
\sigma^2 = \frac{\alpha \beta}{(\alpha + \beta)^2},
\]
and hence deduce that fluctuations become negligible in the large \( N \) limit.

(c) Compare the results obtained from the master equation with the analysis based on the linear noise approximation.

(d) The steady-state distribution is
\[
P_n^* = \frac{\alpha^n \beta^{N-n}}{(\alpha + \beta)^N} \frac{N!}{n!(N-n)!} = p_0^n (1 - p_0)^{N-n} \frac{N!}{n!(N-n)!},
\]
where \( p_0 = \alpha/(\alpha + \beta) \). Taking logarithms of both sides of this equation (3.12) and using Strirling’s formula \( \log(n!) \approx n \log n - n \), show that the steady-state solution of the master equation (3.7) can be written in the form
\[
P(x) \sim e^{-N\Phi(x)},
\]
with quasipotential
\[
\Phi(x) = -x \log(\alpha/\beta) + x \log x + (1 - x) \log(1 - x) = \int_x^\infty \ln \Omega_+(x') dx'.
\]
Compare with the steady-state solution of the Fokker-Planck equation derived using a system-size expansion.

(e) Construct the master equation for an ensemble of \( N \) identical, independent channels each of which has two subunits. That is, determine an equation for the evolution of the probability distribution \( P_{n_0,n_2}(t) \) that there are \( n_j \) ion channels with \( j \) open subunits such that \( N = n_0 + n_1 + n_2 \).
Problem 6. Bistability in an autocatalytic reaction. Consider the following autocatalytic reaction scheme for a protein that can exist in two states $X$ and $Y$:

$$X \xrightarrow{k_1} Y, \quad X + 2Y \xrightarrow{k_3} 3Y.$$ 

Let $[X]$ and $[Y]$ denote the concentrations of the molecule in each of the two states such that $[X] + [Y] = Y_{\text{tot}}$ fixed. The kinetic equation for $[Y]$ is

$$\frac{d[Y]}{dt} = -k_2[Y] + k_1[X] + k_3[Y]^2[X],$$

where $V$ is cell volume.

a) Let $y = [Y]/Y_{\text{tot}}$. Show that after an appropriate rescaling of time, the corresponding kinetic equation for $y$ is

$$\frac{dy}{dt} = y(\mu(1 - y)y - 1) + \lambda(1 - y),$$

where $\mu = k_3Y_{\text{tot}}^2/k_2$, $\lambda = k_1/k_2$. Determine the existence and stability of the fixed points for $y$. Plot the bifurcation diagram with $\mu$ treated as a bifurcation parameter and $\lambda = 0.03$. Hence, show that the system is bistable over a range of values of $\mu$.

b) Suppose that there are $N_0$ molecules, that is, $N_0 = VY_{\text{tot}}$, where $V$ is cell volume. Construct the birth-death master equation for the probability $P_n(t)$ that there are $N(t) = n$ molecules in state $Y$ at time $t$.

c) Show that the steady-state distribution is

$$P^*_n = \frac{C_N N_0!}{n!(N_0 - n)!} \prod_{m=0}^{n-1} \left[ \lambda + \frac{\mu}{N_0^2} m(m - 1) \right].$$

Plot $P^*_n(n)$ as a function of $n$ (treated as a continuous variable over the range $[0, 400]$) for $N_0 = 400$, $\mu = 4.5$ and $\mu = 6$ with $\lambda = 0.03$. Comment on the location of the peaks in terms of fixed points of the deterministic system.

d) Derive the corresponding Fokker-Planck equation using a system-size expansion of the master equation in powers of $1/N_0$, and determine the steady-state solution. Calculate the steady-state solution and compare with the exact solution of part (c) for $N_0 = 40$ and $N_0 = 400$.

Problem 7. Computer simulations: Two-state ion channels. In this problem we investigate the diffusion approximation of the master equation (3.7) for an ensemble of two-state ion channels. Take $\alpha = 1$, $\beta = 2$ and $N = 100$.

(a) Numerically solve the master equation ODE using Euler’s direct method for $t \in [0, 1]$ and $\Delta t = 0.01$. Plot the histogram of $P_n(T)$ for $T = 1$ and compare with the steady-state distribution (3.12).

(b) Use Gillespie’s SSA to generate sample paths for the number $n(t)$ of open ion channels for $t \in [0, 10]$. The two reactions are $n \rightarrow n + 1$ at a rate $\alpha(N - n)$ and $n \rightarrow n - 1$ at a rate $\beta n$. 

By averaging over sample paths, compare the histogram of $n(T)$ with the distribution $P_n(T)$ for $T = 1$.

(c) Use Euler’s direct method to simulate the Langevin equation

$$\Delta X(t) = [\alpha(1 - X) - \beta X] \Delta t + \frac{1}{\sqrt{N}} \sqrt{\alpha(1 - X) + \beta X} \Delta W(t),$$

obtained by carrying out a system-size expansion of the master equation. Here $X(t)$ is the fraction of open ion channels at time $t$. Construct a histogram of $X(T)$ for $T = 1$ and compare with the results of part (b). Repeat for $N = 10$ and $N = 1000$ and comment on the differences.