Problem 1: Noise-induced oscillations (Ingalls 7.8.27, 45 points)

Stochastic systems can exhibit a range of oscillatory behaviors, ranging from near-perfect periodicity to erratic cycles. To explore this behavior, consider a stochastic relaxation oscillator studied by José Vilar and colleagues (Vilar et al., 2002). The system involves an activator and a repressor. The activator enhances expression of both proteins. The repressor acts by binding the activator, forming an inert complex. A simple model of the system is:

Name and description	Reaction	Reaction propensity
R_1 (activator synthesis)	$\varnothing \longrightarrow \mathrm{b_A A}$	$\frac{\gamma_A}{b_A} \cdot \frac{\alpha_0 + N_A/K_A}{1 + N_A/K_A}$
R_2 (repressor synthesis)	$\varnothing \longrightarrow \mathrm{b_R R}$	$\frac{\gamma_R}{b_R} \cdot \frac{N_A/K_R}{1 + N_A/K_R}$
R_3 (activator decay)	$\mathrm{A} \longrightarrow \varnothing$	$\delta_A N_A$
R_4 (repressor decay)	$\mathrm{R} \longrightarrow \varnothing$	$\delta_R N_R$
R_5 (association)	$\mathrm{A} + \mathrm{R} \longrightarrow \mathrm{C}$	$k_C N_A N_R$
R_6 (dissociation w/ activator decay)	$\mathrm{C} \longrightarrow \mathrm{R}$	$\delta_A N_C$

Here, N_A, N_R, and N_C are the molecular counts for the activator, repressor, and activator-repressor complex. The parameters b_A and b_R characterize the expression burst size. The Hill-type propensities of the synthesis reactions are not well-justified at the molecular level, but these expressions nevertheless provide a simple formulation of a stochastic relaxation oscillator.

a) Take parameter values $\gamma_A = 250$, $b_A = 5$, $K_A = 0.5$, $\alpha_0 = 0.1$, $\delta_A = 1$, $\gamma_R = 50$, $b_R = 10$, $K_R = 1$, $k_C = 200$, and $\delta_R = 0.1$. Run a Gillespie SSA simulation of this model and verify its quasi-periodic behavior.

b) The deterministic version of this model is:

$$\frac{da}{dt} = \gamma_A \frac{\alpha_0 + a/K_A}{1 + a/K_A} - k_C a r - \delta_A a$$
$$\frac{dr}{dt} = \gamma_R \frac{a/K_R}{1 + a/K_R} - k_C a r + \delta_A c - \delta_R r$$
$$\frac{dc}{dt} = k_C a r - \delta_A c$$

where a, r, and c are the concentrations of activator, repressor, and complex. Run a simulation with the same parameter values as in part (a). Does the system exhibit oscillations? How is the behavior different if you set $\delta_R = 0.2$?

c) The contrast between the behavior of the models in parts (a) and (b), for $\delta_R = 0.1$, can be explained by the excitability of this relaxation oscillato. Run two simulations of the deterministic model ($\delta_R = 0.1$), one from initial conditions $(a, r, c) = (0, 10, 35)$ and another from initial conditions $(a, r, c) = (5, 10, 35)$. Verify that in the first case, the activator is quenched by the repressor, and the system remains at a low-activator steady state, whereas in the second case, this small quantity of activator is able to break free from the repressor and invoke a (single) spike in expression. Explain how noise in the activator abundance could cause repeated excitations by allowing the activator abundance to regularly cross the threshold. This is referred to as *noise-induced oscillation*.

Problem 2: Effect of autorepression (55 points)

Consider the open system

$$\varnothing \xrightarrow{k_1} \mathrm{A} \xrightarrow{k_2} \varnothing$$

a) Find the master equation for this system.

b) Show that, at steady state,

$$P(N_A = n) = \frac{k_1}{k_2 n} P(N_A = n-1, t)$$

c) Use the Taylor series for e^x to derive the steady-state probability distribution:

$$P(N_A = n) = \frac{\left(\frac{k_1}{k_2}\right)^n e^{-k_1/k_2}}{n!}$$

d) Perform a Gillespie SSA simulation of the open system above with $k_1 = 10, k_2 = 1$. Estimate the probability distribution $P(n)$ from the timecourse $A(t)$. (Exercise your judgment in ignoring data early in the simulation and choosing an appropriate timescale for the simulation.) Plot the Poisson probability density function with $\lambda = k_1/k_2$ on the same axes for comparison.

Now consider a related molecule that exhibits hyperbolic autorepression, i.e.

$$\varnothing \xrightarrow{k_1/(1+k_3 B)} \mathrm{B} \xrightarrow{k_2} \varnothing$$

e) Perform a Gillespie SSA simulation of this system with $k_1 = 100, k_2 = k_3 = 1$ and estimate the probability distribution $P(n)$ from the timecourse $B(t)$. Fit a Poisson distribution to $P(n)$ and plot both on the same axes (e.g. using `poissfit()` and `poisspdf()` in MATLAB). Does the negative autoregulation system have more or less variance than expected for the simple regulation system?