

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

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:

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

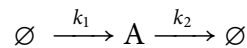
where  $a$ ,  $r$ , and  $c$  are the concentrations of activator, repressor, and complex. Run a simulation with the same parameter values as in part (a). Does the system exhibit oscillations? How is the behavior different if you set  $\delta_R = 0.2$ ?

- 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 oscillator. 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



- Find the master equation for this system.
- Show that, at steady state,

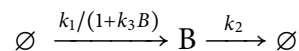
$$P(N_A = n) = \frac{k_1}{k_2 n} P(N_A = n - 1, t)$$

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

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

- 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.



- 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?