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:

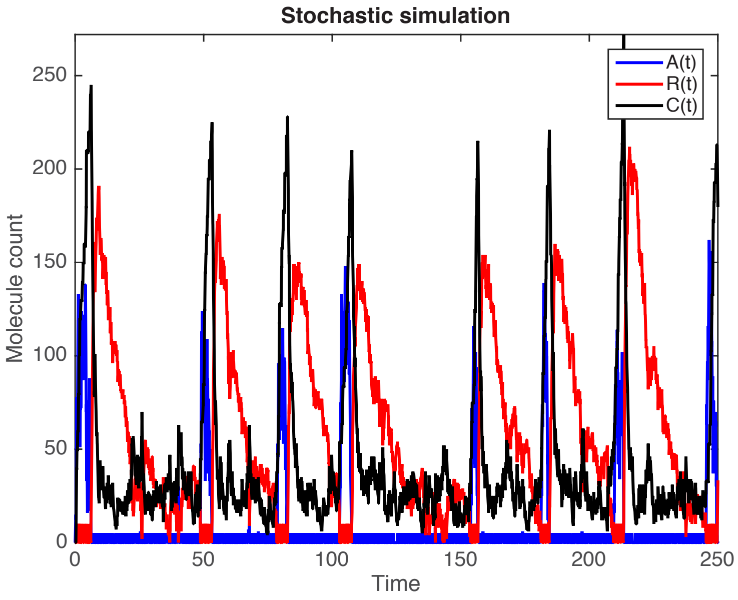
Name and description	Reaction	Reaction propensity
R_1 (activator synthesis)	$\varnothing \longrightarrow \mathrm{b_A A}$	$\frac{\gamma_A}{b_A} \cdot \frac{\alpha_0 + N_A/K_A}{1 + N_A/K_A}$
R_2 (repressor synthesis)	$\varnothing \longrightarrow \mathrm{b_R R}$	$\frac{\gamma_R}{b_R} \cdot \frac{N_A/K_R}{1 + N_A/K_R}$
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.

```
function [] = problem1a()
    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; delta_R = 0.1;
    i = 1; n = 10000;
    a = zeros(1,n); a(1) = 0;
    r = zeros(1,n); r(1) = 0;
    c = zeros(1,n); c(1) = 0;
    t = zeros(1,n); t(1) = 0;

    while i < n
        rates = [ (gamma_A/b_A) * (alpha_0 + a(i)/K_A)/(1 + a(i)/K_A), ...
            (gamma_R/b_R) * (a(i)/K_R)/(1 + a(i)/K_R), ...
            delta_A*a(i), ...
            delta_R*r(i), ...
            k_C * a(i) * r(i), ...
            delta_A * c(i) ];
        t(i+1) = t(i)+exprnd(1/sum(rates));
        event = randsample(6,1,true, rates ./ sum(rates));
        if event == 1
            a(i+1) = a(i) + b_A; r(i+1) = r(i); c(i+1) = c(i);
        elseif event == 2
```

```
            a(i+1) = a(i); r(i+1) = r(i) + b_R; c(i+1) = c(i);
        elseif event == 3
            a(i+1) = a(i) - 1; r(i+1) = r(i); c(i+1) = c(i);
        elseif event == 4
            a(i+1) = a(i); r(i+1) = r(i) - 1; c(i+1) = c(i);
        elseif event == 5
            a(i+1) = a(i) - 1; r(i+1) = r(i) - 1; c(i+1) = c(i) + 1;
        elseif event == 6
            a(i+1) = a(i); r(i+1) = r(i) + 1; c(i+1) = c(i) - 1;
        end
        i = i + 1;
    end

    % Next calculate the probability distribution at the end
    plot(t,a,'b', 'LineWidth', 2); hold on;
    plot(t,r,'r', 'LineWidth', 2);
    plot(t,c,'k', 'LineWidth', 2);
    title('Stochastic simulation')
    xlabel('Time')
    ylabel('Molecule count')
    legend('A(t)', 'R(t)', 'C(t)', 'Location', 'NorthEast')
    set(gca,'FontSize',14)
    axis([100 250 0 max([a, r, c])])

end
```



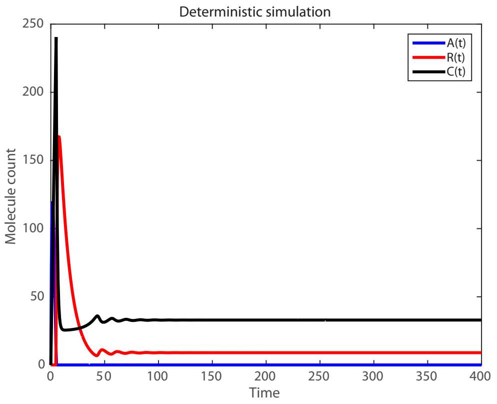
b) The deterministic version of this model is:

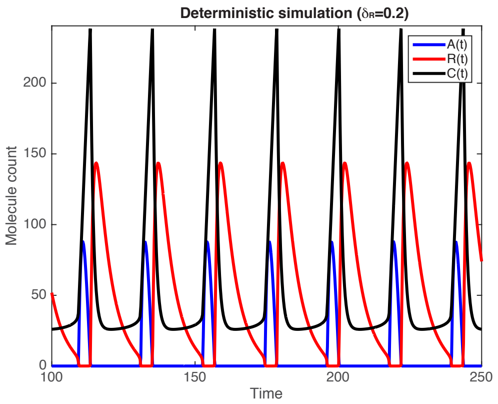
$$\frac{da}{dt} = \gamma_A \frac{\alpha_0 + a/K_A}{1 + a/K_A} - k_C ar - \delta_A a$$
$$\frac{dr}{dt} = \gamma_R \frac{a/K_R}{1 + a/K_R} - k_C ar + \delta_A c - \delta_R r$$
$$\frac{dc}{dt} = k_C ar - \delta_A c$$

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 $\delta_R = 0.2$?

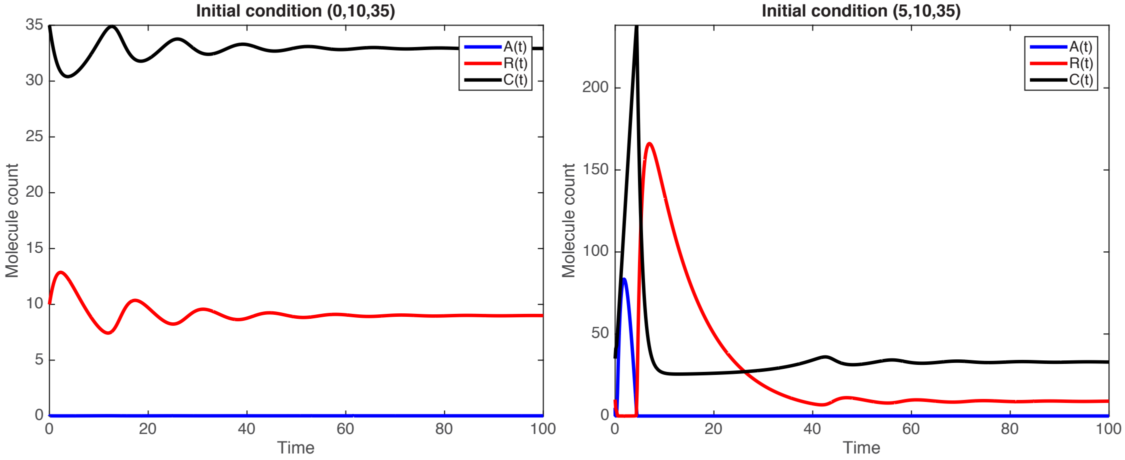
```
function [] = problem1b2()
    global gamma_A b_A K_A alpha_0 delta_A gamma_R b_R K_R k_C delta_R
    gamma_A = 250; b_A = 5; K_A = 0.5; alpha_0 = 0.1; delta_A = 1;
    gamma_R = 50; b_R = 10; K_R = 1; k_C = 200; delta_R = 0.2; % or delta_R = 0.1

    initial_concentrations = [5, 10, 35];
    time_interval = [0, 250];
    [timepoints, concentrations] = ode45(@chain1ddt, ...
        time_interval, initial_concentrations);

    % Next calculate the probability distribution at the end
    plot(timepoints, concentrations(:,1), '-b', 'LineWidth', 3); hold on;
    plot(timepoints, concentrations(:,2), '-r', 'LineWidth', 3);
    plot(timepoints, concentrations(:,3), '-k', 'LineWidth', 3);
    title('Deterministic simulation (\delta_R = 0.2)')
    xlabel('Time')
    ylabel('Molecule count')
    legend('A(t)', 'R(t)', 'C(t)', 'Location', 'NorthEast')
    set(gca,'FontSize',14)
    axis([0 250 0 max(max(concentrations))])

end

function changes_in_concentrations = chain1ddt(time, current_concentrations)
    global gamma_A b_A K_A alpha_0 delta_A gamma_R b_R K_R k_C delta_R

    A = current_concentrations(1);
    R = current_concentrations(2);
    C = current_concentrations(3);

    change_in_A = gamma_A*(alpha_0 + A/K_A)/(1+A/K_A) - k_C*A*R - delta_A*A;
    change_in_R = gamma_R*(A/K_R)/(1+A/K_R) - k_C*A*R + delta_A*C - delta_R*R;
    change_in_C = k_C*A*R - delta_A*C;

    changes_in_concentrations = [change_in_A; change_in_R; change_in_C];
end
```

The system does not exhibit oscillations when $\delta_R = 0.1$ (left figure). However, when $\delta_R = 0.2$, oscillations are restored (right figure).





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*.



Code is a straightforward modification of the above. The "burstiness" of expression could easily cause the activator to exceed its threshold abundance of ≤5, particularly since the bust size $b_A = 5$. (Even without bursting, A will sometimes cross the activity threshold due to chance.)

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.

The trick to this problem is to recognize that the rate of the degradation reaction $\sim nk_2$ while the rate of the synthesis reaction is constant:

$$\frac{dP(n,t)}{dt} = \begin{cases} k_2 P(1,t) - k_1 P(0,t) & : n = 0 \\ [n+1]\, k_2 P(n+1,t) + k_1 P(n-1,t) - [k_1 + nk_2]\, P(n,t) & : n > 0 \end{cases}$$

b) Show that, at steady state,

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

We will show this by induction. For the base case:

$$\frac{dP(0,t)}{dt} = 0 \implies P(1,t) = \frac{k_1}{k_2} P(0,t)$$

Now suppose that the stated formula is true for some value x, i.e. $P(x,t) = \frac{k_1}{k_2 x}P(x-1,t)$. We will show that the formula holds for $x+1$:

$$\begin{aligned}\frac{dP(x,t)}{dt} = 0 \implies P(x+1,t) &= \frac{1}{k_2(x+1)}\left[-k_1 P(x-1,t) + (k_1 + xk_2)\,P(x,t)\right]\\ &= \frac{1}{k_2(x+1)}\left[-k_2 x P(x,t) + (k_1 + xk_2)\,P(x,t)\right]\\ &= \frac{k_1}{k_2(x+1)}P(x,t)\end{aligned}$$

Thus the stated formula applies for all $n \geq 0$. As the probability distribution does not depend on time at steady state, the argument t can be omitted.

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

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

Express our result from part (b) in terms of $P(0)$:

$$P(n) = \frac{k_1}{k_2 n}P(n-1) = \frac{\left(\frac{k_1}{k_2}\right)^2}{n(n-1)}P(n-2) = \frac{\left(\frac{k_1}{k_2}\right)^n}{n!}P(0)$$

We can find $P(0)$ using the fact that the probabilities must sum to one:

$$\begin{aligned}1 &= P(0)\left[1 + \frac{k_1}{k_2} + \frac{k_1^2}{2k_2^2} + \dots\right]\\ &= P(0)\sum_{i=0}^{\infty}\frac{\left(\frac{k_1}{k_2}\right)^i}{i!} = e^{k_1/k_2}P(0) \implies P(0) = e^{-k_1/k_2}\end{aligned}$$

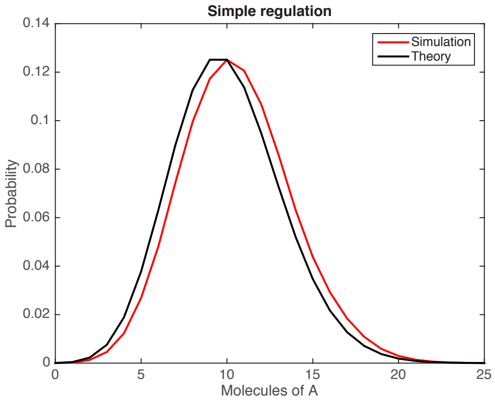
Plugging this into our result above, we obtain the desired expression:

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

Note that this is just a Poisson distribution with parameter $\lambda = k_1/k_2$.

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.

```
function [] = problem1d()
    k1 = 10; k2 = 1;
    i = 1; n = 100000;
    a = zeros(1,n); a(1) = 10;
    t = zeros(1,n); t(1) = 0;

    while i < n
        rates = [k1, a(i)*k2];
        t(i+1) = t(i)+exprnd(1/sum(rates));
        event = randsample(2,1,true, rates ./ sum(rates));
        if event == 1
            a(i+1) = a(i) + 1;
        elseif event == 2
            a(i+1) = a(i) - 1;
        end
        i = i + 1;
    end

    bins = 0:1:max(a);
    a_binned = histc(a(n),bins)./n;
    disp(sprintf('%d %d',length(bins),length(a_binned)));
    plot(bins, a_binned, 'r', 'LineWidth', 2); hold on;
    plot(bins,poisspdf(bins,k1/k2),'k', 'LineWidth', 2)
    title('Simple regulation')
    xlabel('Molecules of A')
    ylabel('Probability')
    legend('Simulation', 'Theory','Location', 'NorthEast')
    set(gca,'FontSize',14)

end
```



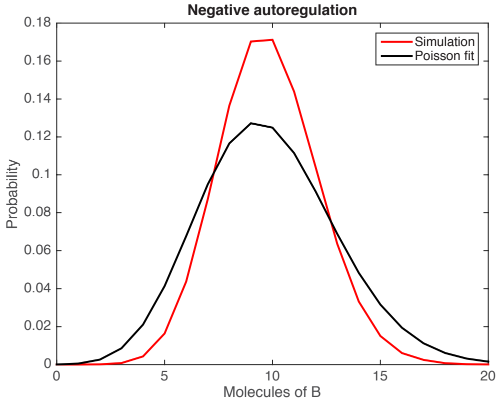
TODO: Figure out if there is a `histc()` issue.

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?

```
function [] = problem1e()
    k1 = 100; k2 = 1; k3 = 1;
    i = 1; n = 100000;
    b = zeros(1,n); b(1) = 10;
    t = zeros(1,n); t(1) = 0;

    while i < n
        rates = [k1/(1 + k3*b(i)), b(i)*k2];
        t(i+1) = t(i)+exprnd(1/sum(rates));
        event = randsample(2,1,true, rates ./ sum(rates));
        if event == 1
            b(i+1) = b(i) + 1;
        elseif event == 2
            b(i+1) = b(i) - 1;
        end
        i = i + 1;
    end

    % Next calculate the probability distribution at the end
    bins = 0:1:max(b);
    b_binned = histc(b,bins)./n;
    plot(bins, b_binned, 'r', 'LineWidth', 2); hold on;
    lambda = poissfit(b);
    plot(bins,poisspdf(bins,lambda),'k', 'LineWidth', 2)
    title('Negative autoregulation')
    xlabel('Molecules of B')
    ylabel('Probability')
    legend('Simulation', 'Poisson fit','Location', 'NorthEast')
    set(gca,'FontSize',14)

end
```



The simulation results for the negative autoregulation system have lower variance than the fitted Poisson distribution; this suggests that one use of negative regulation could be to limit variability.