D.10 A diffusing pair of mutually-inhibiting genes.

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Abstract

Gene regulation often occurs in spatially heterogeneous environments. Often, diffusion leads to distinct spatial patterns in gene expression. In this study, we simulate diffusion in a pair of mutually-inhibiting genes using reaction-diffusion model. We explore how different initial conditions impact the spatial variations of our mutually-inhibitory gene pair. Our study finds that the process of diffusion can create multiple localized regions with unique steady state. In addition, the initial location and concentration of our gene pair determines the size, location and amount of localized regions.

Introduction

In a well-mixed system, bistability emerges when one gene predominantly expressed while the other is suppressed. However, in a spatially varying system, localized regions may appear where one gene dominates over the other leading to heterogeneous expression patterns. To capture the spatial dynamics of gene expression, we will use a reaction-diffusion model as defined below:

$$\frac{\partial[X_{\text{rna}}]}{\partial t} = \mu\left(1 - \frac{[Y_{\text{prot}}]^2}{K_{1/2}^2 + [Y_{\text{prot}}]^2}\right) - \chi_{\text{rna}}[X_{\text{rna}}] + D_{\text{rna}}\nabla^2[X_{\text{rna}}]$$

$$\frac{\partial[X_{\text{prot}}]}{\partial t} = \omega[X_{\text{rna}}] - \chi_{\text{prot}}[X_{\text{prot}}] + D_{\text{prot}}\nabla^2[X_{\text{prot}}]$$

$$\frac{\partial[Y_{\mathrm{rna}}]}{\partial t} = \mu\left(1 - \frac{[X_{\mathrm{prot}}]^2}{K_{1/2}^2 + [X_{\mathrm{prot}}]^2}\right) - \chi_{\mathrm{rna}}[X_{\mathrm{rna}}] + D_{\mathrm{rna}}\nabla^2[Y_{\mathrm{rna}}]$$

$$\frac{\partial[Y_{\mathrm{prot}}]}{\partial t} = \omega[Y_{\mathrm{rna}}] - \chi_{\mathrm{prot}}[Y_{\mathrm{prot}}] + D_{\mathrm{prot}}\nabla^2[Y_{\mathrm{prot}}]$$

- $[X_{rna}]$: Concentration of mRNA for species X.
- $[X_{prot}]$: Concentration of protein for species X.
- $[Y_{rna}]$: Concentration of mRNA for species Y.
- $[Y_{prot}]$: Concentration of protein for species Y.
- μ: Maximum transcription rate.
- $K_{1/2}$: Half-maximal inhibition concentration.
- χ_{rna}: Degradation rate of mRNA.
- ω: Translation rate of mRNA into protein.
- χ_{prot}: Degradation rate of protein.
- D_{rna}: Diffusion coefficient of mRNA.
- D_{prot}: Diffusion coefficient of protein.

The Laplacian operator, ∇^2, represents the diffusion process and is computed using finite differences in a discrete grid. In a one-dimensional model, $[X_{rna}]$, $[X_{prot}]$, $[Y_{rna}]$ and $[Y_{prot}]$ are functions of a single position variable r as well as time t and $\nabla^2 c = \frac{\partial^2 c}{\partial r^2}$.

To integrate a reaction-diffusion in 1 dimension, we may loop over both time and the single spatial dimension, updating concentrations for the next time point at each position using the Forward Euler update:

$$\frac{\partial^2 c(i,t)}{\partial r^2} \approx \frac{c(i+1,t) + c(i-1,t) - 2c(i,t)}{(\Delta r)^2}$$

The finite difference calculation of the Laplacian, ∇^2, requires additional information at the boundaries; that is, what to do with i - 1 or i + 1 are

outside the range of grid points. With absorbing boundary conditions, we set these boundary values to zero, so that we have the special cases:

$$\frac{\partial^2 c(1,t)}{\partial r^2} \approx \frac{c(2,t) - 2c(1,t)}{(\Delta r)^2}$$

and

$$\frac{\partial^2 c(i_{\max},t)}{\partial r^2} \approx \frac{c(i_{\max}-1,t) - 2c(i_{\max},t)}{(\Delta r)^2}$$

The respective MATLAB code to simulate mutually-inhibiting gene pair using the reaction-diffusion model is given in Figure 1.

```
% Setting model paramenters
K_half = 0.33; % mM
mu = 1; % s^-1
chi_r = 1; % s^-1
chi_p = 1; % s^-1
omega = 1; % s^-1
Dr = 1e-4; % um^2/s
Dp = 1e-4; % um^2/s

% Setting simulation parameters
total_time = 120; % s
time_step = 0.01; % s
num_time_steps = total_time / time_step;
total_dist = 3.0; % um
dist_step = 0.02; % um
num_dist_steps = total_dist / dist_step + 1;
t_values = 0:time_step:total_time;
r_values = 0:dist_step:total_dist;

% Initialize concentration matrices
X_rna = zeros(num_dist_steps, num_time_steps+1);
X_pro = zeros(num_dist_steps, num_time_steps+1);
Y_rna = zeros(num_dist_steps, num_time_steps+1);
Y_pro = zeros(num_dist_steps, num_time_steps+1);
% Initial conditions
X_rna(1, 1) = 1;
X_pro(1, 1) = 1;
Y_rna(end, 1) = 1;
Y_pro(end, 1) = 1;

% Calculating rate of change and applying to the Forward Eular method
for i = 1:num_time_steps % Going over time
    for j = 1:num_dist_steps % Going over our 1d space
        if j == 1 %Calculating our laplacian operator
            laplacian_X_rna = (X_rna(2, i) - 2 *X_rna(1,i))/ (dist_step^2);
            laplacian_X_pro = (X_pro(2, i) - 2 *X_pro(1,i))/ (dist_step^2);
            laplacian_Y_rna = (Y_rna(2, i) - 2 *Y_rna(1,i))/ (dist_step^2);
            laplacian_Y_pro = (Y_pro(2, i) - 2 *Y_pro(1,i))/ (dist_step^2);
        elseif j == num_dist_steps
            laplacian_X_rna = (X_rna(j-1, i) - 2 *X_rna(j,i))/ (dist_step^2);
            laplacian_X_pro = (X_pro(j-1, i) - 2 *X_pro(j,i))/ (dist_step^2);
            laplacian_Y_rna = (Y_rna(j-1, i) - 2 *Y_rna(j,i))/ (dist_step^2);
            laplacian_Y_pro = (Y_pro(j-1, i) - 2 *Y_pro(j,i))/ (dist_step^2);
        else
            laplacian_X_rna = (X_rna(j+1, i) + X_rna(j-1, i) -2 * X_rna(j, i))/(dist_step^2);
            laplacian_X_pro = (X_pro(j+1, i) + X_pro(j-1, i) -2 * X_pro(j, i))/(dist_step^2);
            laplacian_Y_rna = (Y_rna(j+1, i) + Y_rna(j-1, i) -2 * Y_rna(j, i))/(dist_step^2);
            laplacian_Y_pro = (Y_pro(j+1, i) + Y_pro(j-1, i) -2 * Y_pro(j, i))/(dist_step^2);
        end

        % Calculating rate of change respective to both time and change
        dXrna_dt = mu * (1 - (Y_pro(j, i)^2 / (K_half^2 + Y_pro(j, i)^2))) - chi_r * X_rna(j, i) + Dr * laplacian_X_rna;
        dXpro_dt = omega * X_rna(j, i) - chi_p * X_pro(j, i) + Dp * laplacian_X_pro;
        dYrna_dt = mu * (1 - (X_pro(j, i)^2 / (K_half^2 + X_pro(j, i)^2))) - chi_r * Y_rna(j, i) + Dr * laplacian_Y_rna;
        dYpro_dt = omega * Y_rna(j, i) - chi_p * Y_pro(j, i) + Dp * laplacian_Y_pro;

        % Forward Eular Method
        X_rna(j, i+1) = X_rna(j, i) + time_step * dXrna_dt;
        X_pro(j, i+1) = X_pro(j, i) + time_step * dXpro_dt;
        Y_rna(j, i+1) = Y_rna(j, i) + time_step * dYrna_dt;
        Y_pro(j, i+1) = Y_pro(j, i) + time_step * dYpro_dt;
    end
end
```

Figure 1: MATLAB code of reaction-diffusion model

All results obtained were using model parameters as specified below:

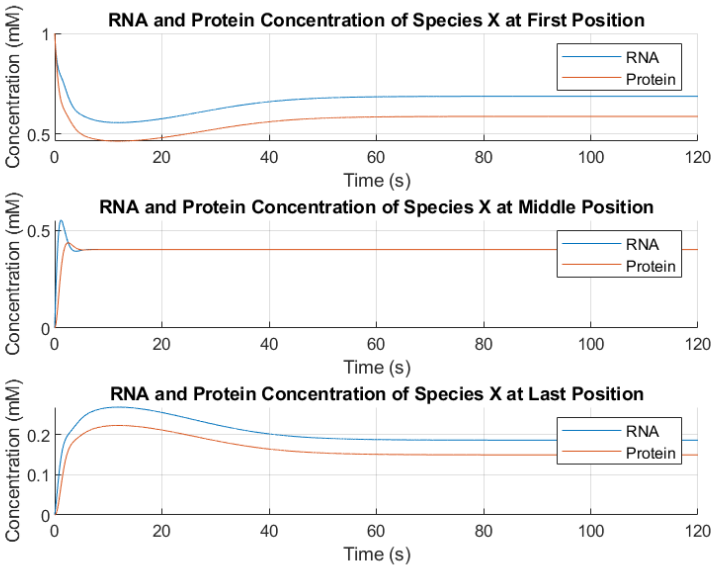
$$\mu = \omega = \chi_{prot} = \chi_{rna} = 1\,\mathrm{s}^{-1}, \quad K_{1/2} = 0.33\,\mathrm{mM}, \quad D_{prot} = D_{rna} = 1{\times}10^{-4}\,\mu\mathrm{m}{\cdot}\mathrm{s}^{-1}$$

Unless otherwise specified, all simulation were conducted with the simulation parameters below:

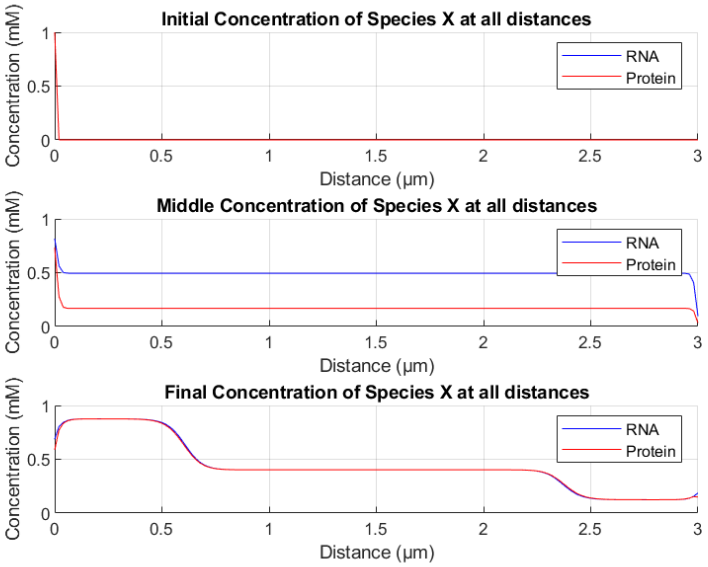
- Time step: $0.01\,\mathrm{s}$
- Total time: $120\,\mathrm{s}$
- Distance step: $0.02\,\mu\mathrm{m}$
- Total distance: $3.0\,\mu\mathrm{m}$

Results and Discussion

We run an initial simulation with specific initial conditions where the concentrations of RNA and protein for species X equal 1.0 mM only at the first spatial position, while the concentrations of RNA and protein for species Y equal 1.0 mM only at the last spatial position, zero everywhere else. The results of the simulation are shown in Figure 2 and 3.

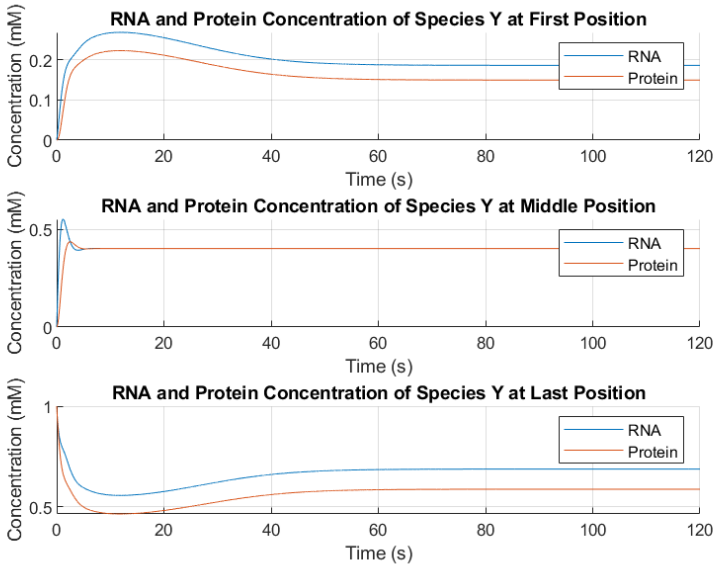


(a) Concentration of species X over time at the first, middle, and last spatial positions

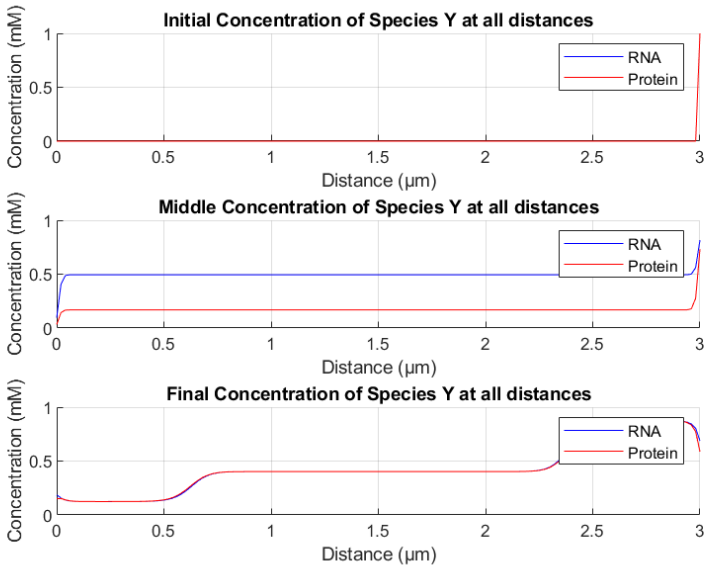


(b) Spatial distribution of species X at initial, intermediate, and final time points

Figure 2: Temporal and spatial distribution of species X, with initial condition such that the concentrations of RNA and protein for species X equal 1.0 mM only at the first spatial position, while the concentrations of RNA and protein for species Y equal 1.0 mM only at the last spatial position



(a) Concentration of species Y over time at the first, middle, and last spatial positions

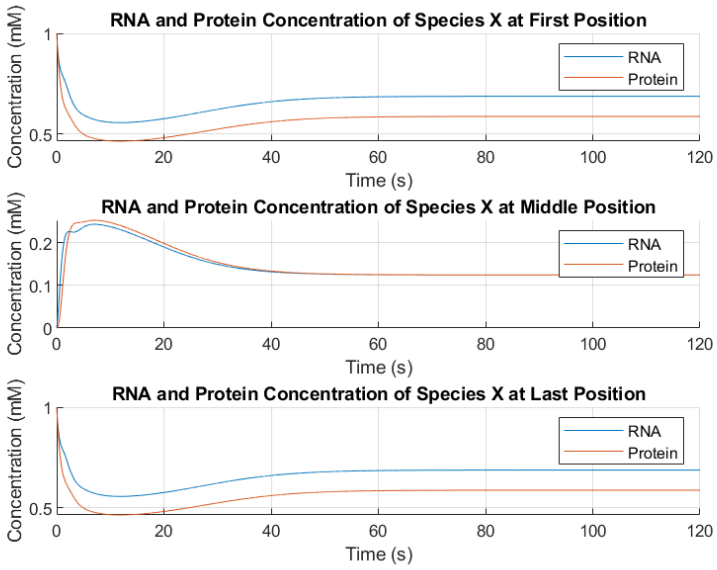


(b) Spatial distribution of species Y at initial, intermediate, and final time points

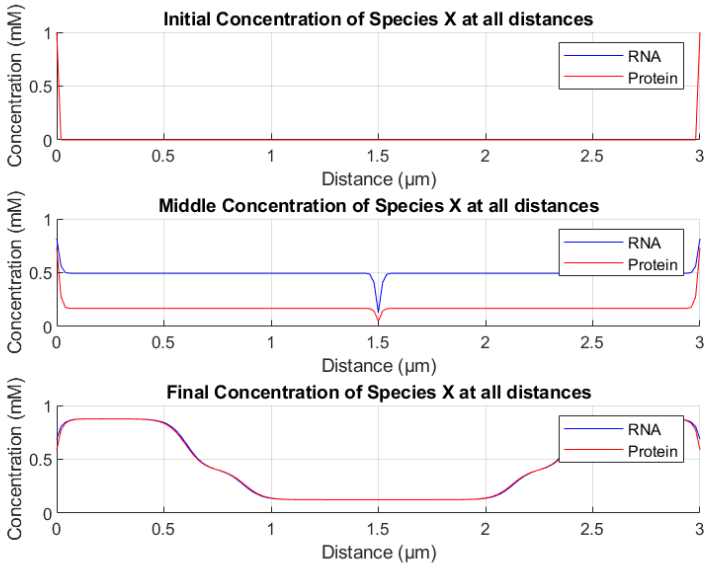
Figure 3: Temporal and spatial distribution of species Y, with initial condition such that the concentrations of RNA and protein for species X equal 1.0 mM only at the first spatial position, while the concentrations of RNA and protein for species Y equal 1.0 mM only at the last spatial position

From the results above, we find that by the end of the simulation, distinct spatial regions emerge each with a different steady state. Figures 2b and 3b show 3 distinct regions with transition regions in between each. In the beginning area, Species X shows higher concentrations of RNA and protein compared to Species Y. In the middle region, both species have similar concentrations of RNA and protein. However, in the last third of our spatial region, Species Y has higher concentrations of RNA and protein compared to Species X. Except for the transition periods, the concentrations of each species is stable in each region, indicating unique steady states in localized areas. The shape and location of these localized regions depend on how long the simulations are run and the initial concentrations of RNA and protein. For example, if the previous simulation was shorter in time, the two spatial regions-near the beginning and the end—would be much smaller, as it takes time for the concentrations to diffuse into the adjacent spaces.

Knowing the location and amount of initial concentrations can help predict where localized steady-state regions will appear and how they might look. For example, lets say the initial concentrations of RNA and protein for species X equal 1.0 mM at the first and last spatial positions, while the initial concentrations of RNA and protein for species Y equal 1.0 mM only at the central spatial position. We can predict that three distinct regions will emerge just like the previous simulation. However, in this case, species X will have a higher steady-state concentration in the beginning and end regions since it is the only species when any concentration of RNA and protein in those regions. Similarly, the middle region will exhibit a steady state dominated by species Y, since Y is the only species in that region at the start of our simulation. To demonstrate this, we run another simulation with the example initial condition. The result of the simulation is given in Figure 4 and 5.

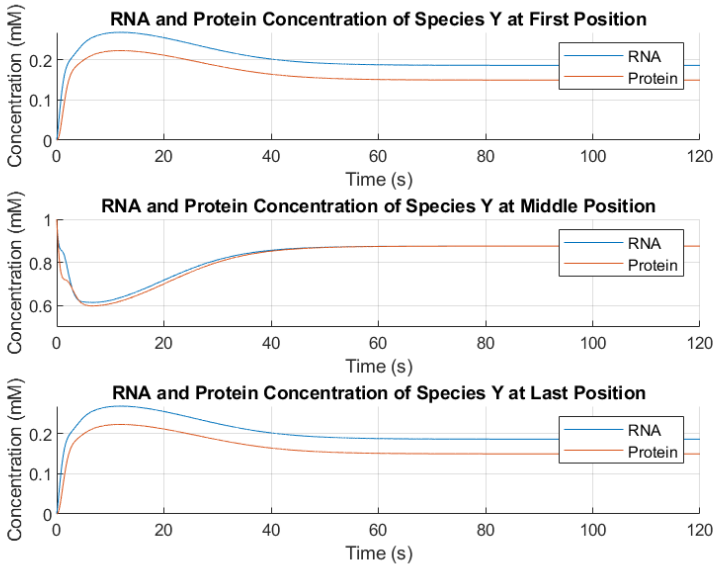


(a) Concentration of species X over time at the first, middle, and last spatial positions

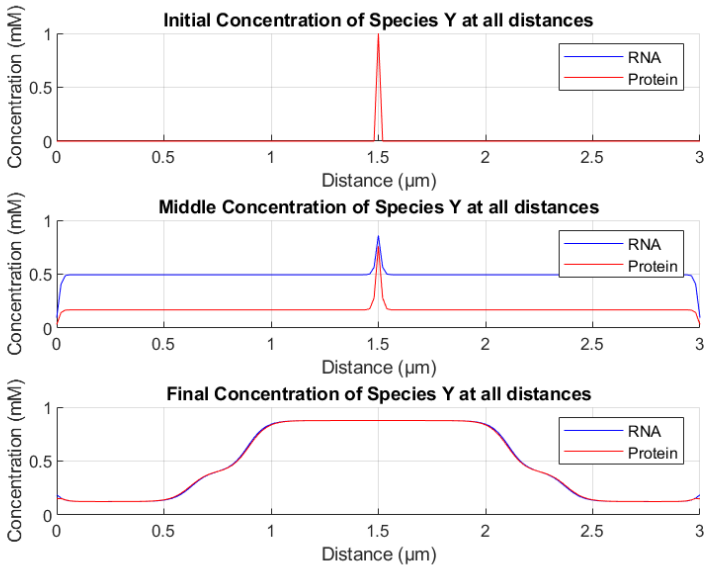


(b) Spatial distribution of species X at initial, intermediate, and final time points

Figure 4: Temporal and spatial distribution of species X, with initial condition such that the concentrations of RNA and protein for species X equal 1.0 mM at the first and last spatial positions, while the concentrations of RNA and protein for species Y equal 1.0 mM only at the central spatial position



(a) Concentration of species Y over time at the first, middle, and last spatial positions



(b) Spatial distribution of species Y at initial, intermediate, and final time points

Figure 5: Temporal and spatial distribution of species Y, with initial condition such that the concentrations of RNA and protein for species X equal 1.0 mM at the first and last spatial positions, while the concentrations of RNA and protein for species Y equal 1.0 mM only at the central spatial position

The results from Figure 4b and 5b support our previous prediction. In the beginning and end regions, we find that Species X maintains a steady concentration of around .85 mM for both RNA and protein where as Species Y maintains a concentration around .5 mM for both RNA and protein. In the middle region Species Y maintains around .85 mM of RNA and protein while Species X now maintain a steady state around .25 mM.

Conclusion

Our simulations reveal the importance of spatial variation in gene expression. We find that diffusion reveals distinct steady-state region emerge based on initial distribution of gene expression. Many cell-fate decisions are made in this spatially-resolved including body segmentation and pigment patterning. Future studies could explore the impact of varying diffusion coefficients or higher dimentional models to better understand the role of spatial gene regulation in biological systems.