D.9 A Diffusing Autoregulatory gene

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Abstract

Gene regulation often occurs in spatially heterogeneous environments where diffusion plays a significant role in determining cellular behavior. Traditional mass action kinetic model assumes a well-mixed system, as such a reaction-diffusion model is more appropriate for dealing systems where spatial information matter. In this study we simulate an auto-regulatory system using a reaction-diffusion model and explore trajectories of both RNA and protein concentrations at different initial conditions and how diffusion impacts them. We find that the model has many similar features with mass action kinetics model including steady states and activation thresholds. The existence of steady states and activation thresholds in the reaction-diffusion model implies that while spatial variations add complexity to our simulations, the overall conclusions remain consistent with those of the mass-action kinetic model. Therefore, the reaction-diffusion model should only be used when information about spatial variations are essential to the system being studied. In all other cases mass-action kinetic model maybe sufficient and easier to implement and run.

Introduction

When using mass-action-kinetic to model an autoregulatory gene, it assumes the process is happening in a well-mixed system. However, most biological systems are spatially heterogeneous. This is true at levels ranging from bacterial cells through ecosystems. Many cell-fate decisions are made in spatially-resolved manner. To simulate these spatial variations, in addition

to the temporal variations modeled by the mass-action-kinetic system, we can instead use a reaction-diffusion model for our auto-regulatory gene. The system of equations for such a model is:

$$\frac{\partial[X_{rna}]}{\partial t} = \frac{\mu[X_{prot}]^2}{K_{1/2}^2 + [X_{prot}]^2} - \chi_{rna}[X_{rna}] + D_{rna}\nabla^2[X_{rna}]$$
$$\frac{\partial[X_{prot}]}{\partial t} = \omega[X_{rna}] - \chi_{prot}[X_{prot}] + D_{prot}\nabla^2[X_{prot}]$$

- $[X_{rna}]$: mRNA concentration.
- $[X_{prot}]$: Protein concentration.
- μ: Maximal transcription rate.
- $K_{1/2}$: Half-maximal activation concentration.
- χ_{rna}: mRNA degradation rate.
- ω: Protein translation rate.
- χ_{prot}: Protein degradation rate.
- 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, $[X_{rna}]$ and $[X_{prot}]$ 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 perform our simulation of an autoregulatory gene using the reaction-diffusion model is given in Figure 1.

```
K_half = .33; %mM
mu = 1; %s-1
Xr = 1; %s-1
Xp = 1; %s-1
omega = 1; %s-1
Dr = 1e-4; %um * s^-1
Dp = 1e-4; %um * s^-1

%Setting time and space constraints
total_time = 30; %s
time_step = .01; %s
num_time_steps = total_time/time_step;
total_dist = 3.0; %um
dist_step = .02; %um
num_dist_steps = ceil(total_dist/dist_step)+1;

% Setting our arrays to store discritized time and space values
t_values = 0:time_step:total_time;
r_values = 0:dist_step:total_dist;

% 2d arrays storing the concentration of rna and protein respective to time
% and space
pro = zeros(num_dist_steps, num_time_steps+1);
rna = zeros(num_dist_steps, num_time_steps+1);

%Initial conditions
pro(1, 1) = 1;
rna(1, 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_rna = (rna(2, i) - 2 *rna(1,i))/ (dist_step^2);
            laplacian_pro = (pro(2, i) - 2 *pro(1,i))/ (dist_step^2);
        elseif j == num_dist_steps
            laplacian_rna = (rna(j-1, i) - 2 *rna(j,i))/ (dist_step^2);
            laplacian_pro = (pro(j-1, i) - 2 *pro(j,i))/ (dist_step^2);
        else
            laplacian_rna = (rna(j+1, i) + rna(j-1, i) -2 * rna(j, i))/(dist_step^2);
            laplacian_pro = (pro(j+1, i) + pro(j-1, i) -2 * pro(j, i))/(dist_step^2);
        end
        % Rate of change respective to both time and change
        dr_dt = (mu * pro(j,i)^2)/(K_half^2 + pro(j,i)^2) - Xr * rna(j,i) + Dr * laplacian_rna;
        dp_dt = omega * rna(j,i) - Xp * pro(j,i) + Dp * laplacian_pro;
        % Forward Eular Method
        rna(j, i+1) = rna(j,i) + time_step * dr_dt;
        pro(j, i+1) = pro(j,i) + time_step * dp_dt;
    end
end
```

Figure 1: Reaction-Diffusion Model in MATLAB

All results obtained were using model parameters as specified below:

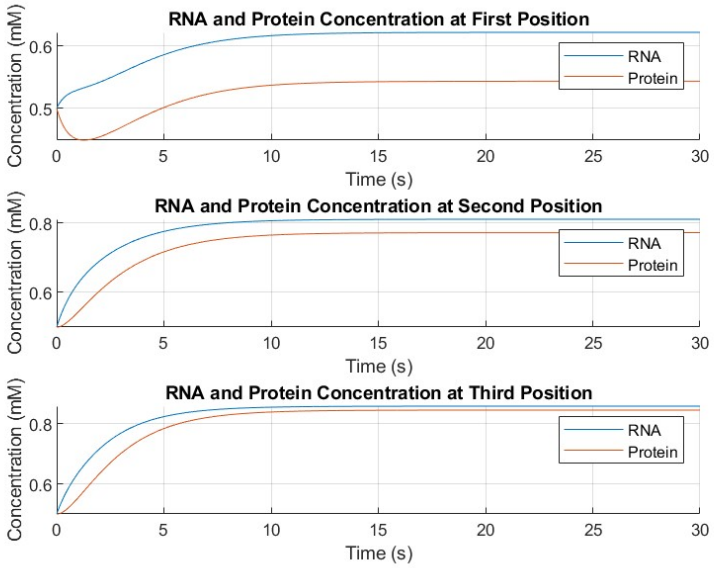
$$\mu = \omega = \chi_{prot} = \chi_{rna} = 1\,\mathrm{s}^{-1}, \quad K_{1/2} = 0.33\,\mathrm{mM}, \quad D_{prot} = D_{rna} = 1{\times}10^{-4}\,\mu\mathrm{m}{\cdot}\mathrm{s}^{-1}$$

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

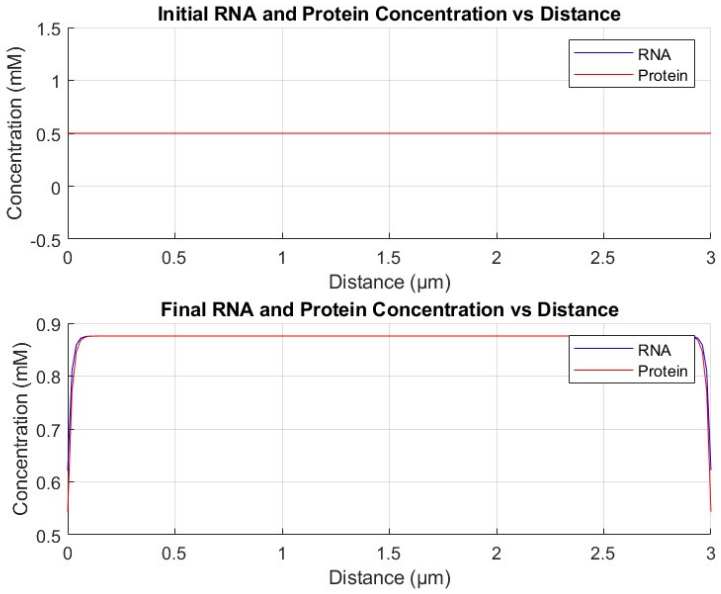
- Time step: $0.01\,\mathrm{s}$
- Total time: $30\,\mathrm{s}$
- Distance step: $0.02\,\mu\mathrm{m}$
- Total distance: $3.0\,\mu\mathrm{m}$

Results and Discussion

We explore how different starting concentrations impact the trajectory of our reaction-diffusion model. In each case, we plot the concentration of both protein and RNA at the first three positions in space as a function of concentration versus time. In addition, we plot the concentration of both protein and RNA versus distance at the first and last points in time. Figure 2, the initial condition of both RNA and protein is equal to .05 mM everywhere in space. Figure 3, the initial concentration of both RNA and protein is equal to .5 mM only in the first spatial position, zero elsewhere. Figure 4, the initial concentration of both RNA and protein is equal to 1.0 mM only in the first spatial position, zero elsewhere.

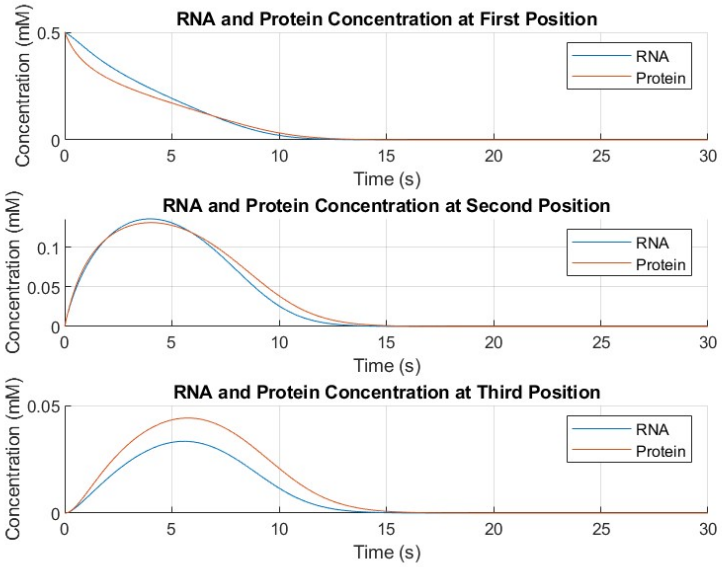


(a) Concentration vs Time of first 3 position in space

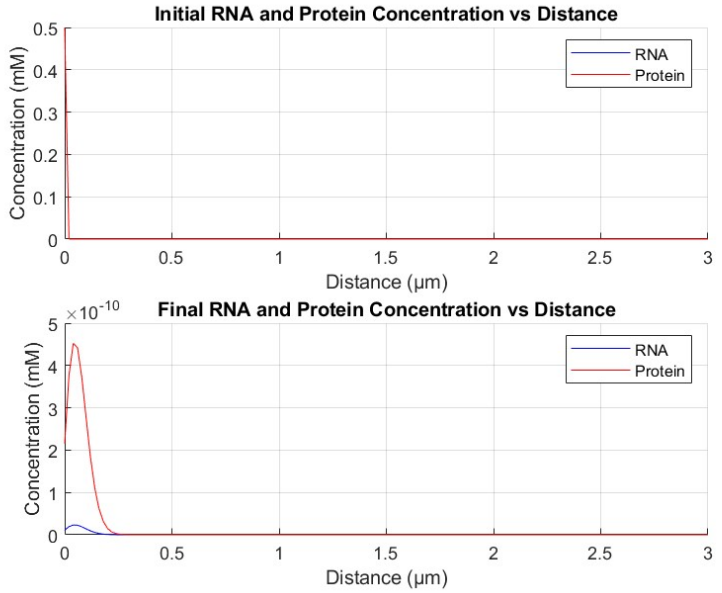


(b) Initial and final concentrations in each space

Figure 2: Simulation results for initial concentration of 0.05 mM in all space

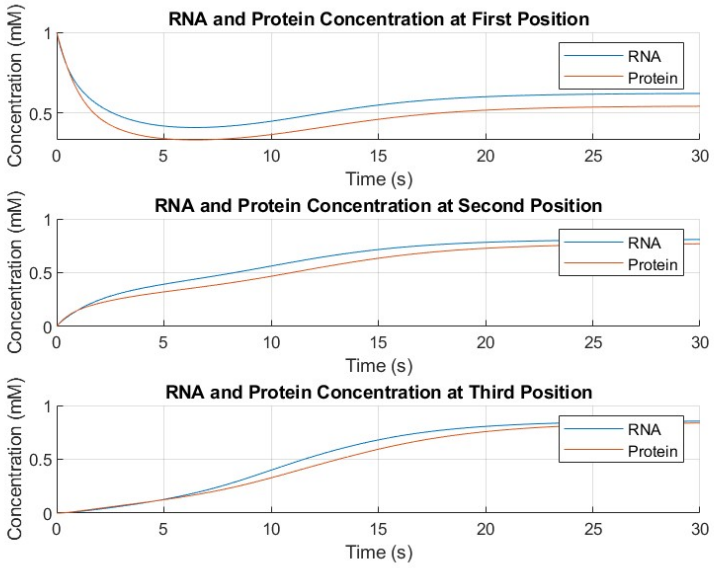


(a) Concentration vs Time of first 3 position in space

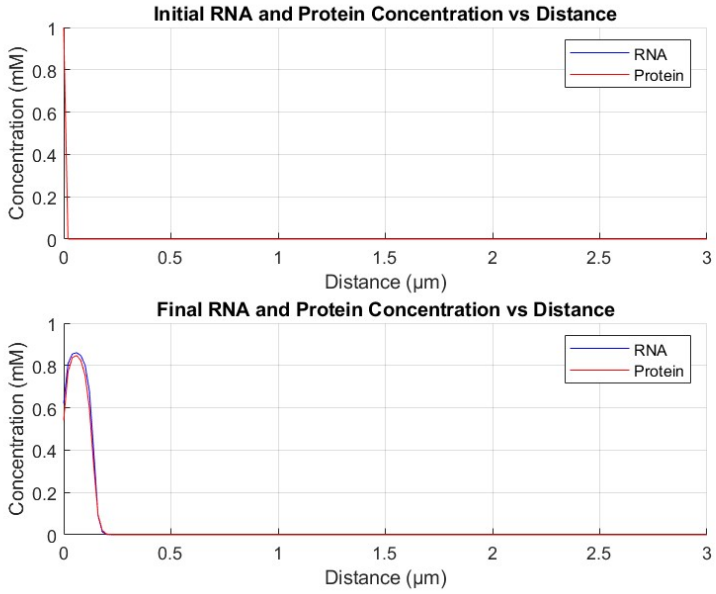


(b) Initial and final concentrations in each space

Figure 3: Simulation results for initial concentration of 0.05 mM at first position



(a) Concentration vs Time of first 3 position in space



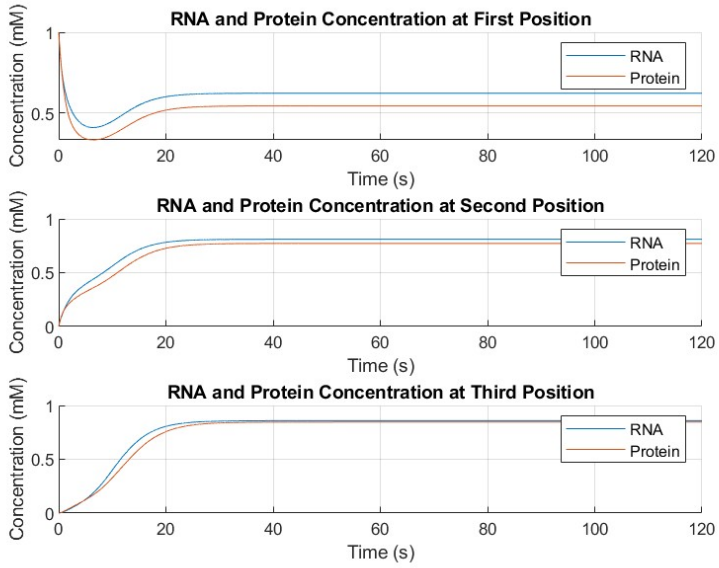
(b) Initial and final concentrations in each space

Figure 4: Simulation results for initial concentration of 1.0 mM at first position

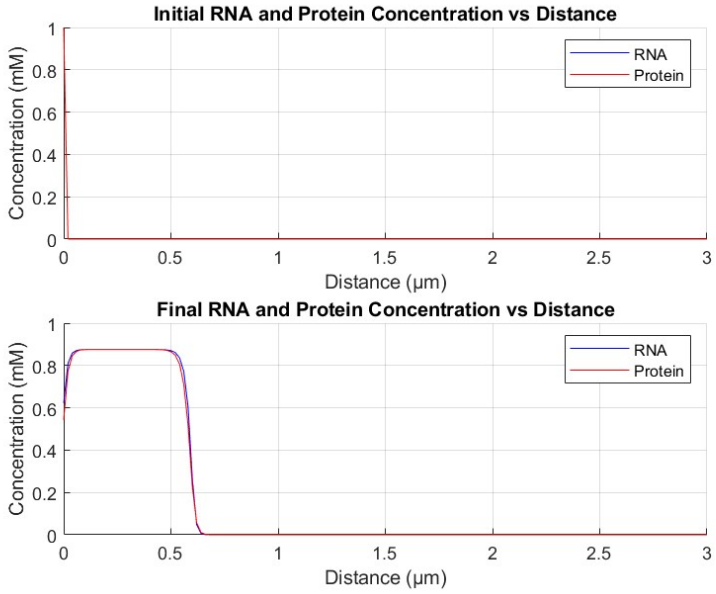
By varying the initial concentrations, we find that distinct trajectories of RNA and protein emerge over time, particularly in terms of how quickly these concentrations approach steady states, if at all. When all positions had an initial concentration of .5 mM it simulates a well mixed ODE system. Both RNA and protein concentrations gradually increased in all positions until they reached a steady state. This is reflected in the concentration vs distance graph in Figure 2b. The final steady-state concentration in all positions, except close to the first and last points, is about .88 mM. The steady-state concentrations correspond to the balance between production and degradation rates of RNA and protein, as described by the mass-action kinetics.

Figures 3 and 4 show results of simulating a system with localized RNA and protein production. In Figure 3, the initial condition is set to 0.5 mM for both RNA and protein at only the first spatial position, with concentrations set to zero elsewhere. Figure 3a demonstrates that an initial concentration of 0.5 mM at the first position is insufficient to reach the activation threshold. While diffusion allows RNA and protein to spread to the second and third positions, the production at the first position eventually diminishes, leading to a decline in RNA and protein concentrations throughout the system. This is also seen in the concentration vs distance graph where the final concentrations are 0 if not close to 0.

In Figure 4, the initial condition is set to 1.0 mM for both RNA and protein at only the first spatial position. Figure 4a shows that a steady state is reached at the first three spatial positions, indicating that we met the activation threshold requirement. Each position after the first has a slower rate of increase of concentration but all spatial positions eventually reach a steady state. This trend is further supported by Figure 4b. However, since the simulation was not run for a sufficiently long time, a steady state has yet to be seen across the majority of spatial positions. Figure 5 gives the results of extending the simulation from Figure 4 to a total of 3 minutes. As the simulation progresses, more spatial positions reach steady state, as illustrated in Figure 5b.



(a) Concentration vs Time of first 3 position in space



(b) Initial and final concentrations in each space

Figure 5: Simulation results for initial concentration of 1.0 mM in all space with a simulation time of 3mins

Conclusion

The results of the reaction-diffusion model demonstrate that spatial initial conditions significantly affect the dynamics of RNA and protein concentrations. Just like the mass action kinetic model, our results show that the reaction-diffusion model also needs to meet an activation threshold or else the entire system will collapse. We can also simulate a well-mixed system if we set the same initial condition for all spatial points. Future simulation could use longer simulation times to better observe convergence of concentrations to steady-states in localized RNA and protein production.