Modelling Spatio-Temporal Dynamics of Proteins

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Introduction

This document provides a detailed analysis of a stochastic reaction-diffusion simulation code designed to model the dynamics of chemical species (DNA, mRNA, Protein) in a cellular environment. The code integrates processes such as transcription, translation, degradation, and diffusion, and employs a modified version of the Gillespie algorithm [1] [2] to capture the stochastic temporal evolution of molecular events. Visualization techniques such as heatmaps and concentration plots are also included for analyzing spatial and temporal changes in the system.

Detailed Code Analysis

Lattice Structure and Initialization

- **Grid Representation:** The simulation domain is a 2D grid ($n \times n$), representing the entire cell. A smaller central sub-grid ($m \times m$) represents the nucleus.
- **Species Concentrations:**
  - DNA is initialized uniformly in the nucleus (`DNA_concentration`).
  - Protein and mRNA concentrations are initialized throughout the cell (`Protein_concentration`, `mRNA_concentration`).
- **Diffusion Coefficients and Rate Constants:**
  - Separate diffusion rates for mRNA and protein in the cytoplasm and nucleus (`Diffusion_mRNA_cytoplasm`, `Diffusion_protein_nucleus`).
  - Reaction rates for transcription, translation, and degradation are explicitly defined (`k_transcription`, `k_translation`, etc.).

Boundary and Region Definitions

- **Boundary Indices:** Outer boundaries of the cytoplasm (`left_boundary`, `right_boundary`, etc.) and nucleus (`inner_boundary_left_indices`, `outer_boundary_left_indices`) are clearly identified to regulate diffusion and compartmental interactions.
- **Nuclear and Cytoplasmic Regions:** Indices for the nucleus and cytoplasm are dynamically calculated, ensuring scalability if n or m changes.

Reaction Propensity Calculation

- Each reaction is associated with a propensity, computed using species concentrations and reaction-specific rate constants:
  - **Transcription:** DNA concentration in the nucleus produces mRNA.
  - **Translation:** mRNA in the cytoplasm produces proteins.
  - **Degradation:** mRNA and proteins degrade based on their respective rates.
  - **Diffusion:** Molecules diffuse between neighboring grid points, with separate rules for cytoplasm and nucleus regions.
  - **Autopositive Feedback:** Protein concentration influences transcription through feedback (`k_autopositive_feedback_protein`).
- The cumulative propensity sum defines partitions of reaction probabilities, enabling stochastic reaction selection.

Modified Gillespie Algorithm

The Gillespie algorithm has been modified to simulate spatially distributed reaction-diffusion systems on a 2D lattice. The modifications include:

- **Reaction-Diffusion Integration:** The algorithm considers both chemical reactions and spatial diffusion events. Each reaction or diffusion event is assigned a propensity based on its rate constant and the local species concentrations.
- **Stochastic Time Steps:** The time step for the next reaction is calculated as:

$$\tau = -\frac{\ln(r_1)}{\text{Rate\_Sum}}$$

  where r_1 is a uniformly distributed random number and `Rate_Sum` is the sum of all propensities.
- **Reaction Selection:** A second random number r_2 determines which reaction or diffusion event occurs by mapping it to the cumulative sum of propensities.
- **Spatial Dynamics:** Diffusion events are treated as stochastic reactions, where molecules move between neighboring lattice sites. Boundary conditions prevent unphysical diffusion outside the lattice.

These modifications extend the Gillespie algorithm to handle spatially distributed systems, making it suitable for reaction-diffusion modeling.

Diffusion Modeling

- **Directional Diffusion:** Diffusion of mRNA and protein is explicitly modeled in all four directions (left-right, up-down).
- **Boundary Conditions:** Boundary conditions are implemented to handle diffusion near edges, ensuring no species escape the lattice.
- **Inter-compartmental Transport:** Diffusion between nucleus and cytoplasm is controlled by transport rates (`k_transport_mRNA_nc`, `k_transport_protein_cn`).

Visualization

- **Heatmaps:** Two heatmaps display the spatial distribution of mRNA and protein concentrations. These heatmaps update every 50 iterations.
- **Global Concentration Plots:** Total mRNA and protein concentrations are tracked and plotted over time, providing a temporal perspective on system dynamics.

Key Strengths

1. **Comprehensive Modeling:** The code effectively integrates transcription, translation, degradation, and diffusion processes in a spatially explicit framework.
2. **Stochastic Framework:** The use of stochastic simulation ensures realistic temporal dynamics, capturing molecular randomness.
3. **Scalability:** Modular boundary and reaction definitions facilitate scalability to larger grids or more complex systems.
4. **Visualization:** Heatmaps and concentration plots provide intuitive insights into spatial and temporal dynamics.

Potential Limitations and Suggestions

1. **Performance Optimization:** Diffusion calculations are computationally expensive. Using parallel processing or sparse matrices could improve performance.
2. **Boundary Conditions:** Incorporating reflective or periodic boundary conditions may enhance biological realism.
3. **Biological Extensions:** Adding additional molecular species or regulatory networks would increase the system's complexity and realism.
4. **Sensitivity Analysis:** Analyzing the influence of rate constants could identify critical factors driving system dynamics.

Conclusion

This code provides a robust framework for simulating reaction-diffusion dynamics in cellular systems. The integration of stochastic modeling with spatial compartmentalization captures the nuanced behavior of molecular species. With minor optimizations and extensions, this code can serve as a powerful tool for systems biology research.
An Example Code can be found in this Github Repository.

References

[1] Daniel T Gillespie. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *Journal of Computational Physics*, 22(4):403–434, 1976. ISSN 0021-9991. doi: https://doi.org/10.1016/0021-9991(76)90041-3. URL https://www.sciencedirect.com/science/article/pii/0021999176900413.

[2] Daniel T. Gillespie. Exact stochastic simulation of coupled chemical reactions. *The Journal of Physical Chemistry*, 81(25):2340–2361, Dec 1977. ISSN 0022-3654. doi: 10.1021/j100540a008. URL https://doi.org/10.1021/j100540a008.