A Stochastic Reaction-Diffusion Active Transport Method for Studying the Control of Gene Expression in Eukaryotic Cells.

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Background
- Want to understand how the complicated spatial geometry of eukaryotic cells influences gene regulatory networks.
- Also interested in stochastic effects that arise in such networks due to small concentrations of regulatory proteins, mRNAs, and DNA binding sites.
- Have developed a stochastic reaction-diffusion active transport model for use in studying spatially distributed chemical systems where molecular noise from the chemical reaction process is important.

Master Equation Model
- Divide comp. domain into mesh cells indexed by \( i = 1 \ldots N \).
- Model diffusion and active transport as jumping of particles between mesh cells, with exponentially distributed rates.

The master equation model is

\[
\frac{dP(m)}{dt} = \sum_{m'} \left( k_{i,m'} P(m) - k_{m',i} P(m') \right) + \sum_{m'} \left( \alpha^i_{m',0} + \alpha^i_{0,m'} P(m) \right).
\]

Here \( m_i \) gives the number of the \( i \)th chemical species in mesh cell \( i \).

- The first term corresponds diffusion.
- The second term to active transport.
- The third to chemical reactions.
- The chemical reaction propensities \( \alpha^i_{m',0} \) are specified; however, the diffusive and active transport jump rates, \( k_{i,m'} \) and \( \alpha^i_{m',0} \) are not.

Boundary Conditions
- We model the nuclear membrane and cell membrane as boundaries.
- Assume no chemicals can leave cell, so have no-flux BC at cell membrane.
- Model nuclear pores as an effective nuclear membrane permeability.
- Permeability is zero for most proteins/mRNAs, as they generally require a chemical transport process to pass through the membrane.

Spatial Jump Rates
- Diffusive, trans-nuclear membrane, and active transport jump rates can be calculated from the discretization weights of a Cartesian grid embedded boundary discretization.

Denote by \( \alpha \in \{ \text{nuc}, \text{cyt} \} \) the domain of a given mesh variable. The diffusive jump rate from the domain \( \alpha \) component of cell \( j \) to the domain \( \alpha' \) component of cell \( i \) is given by our discretization to be

\[
k_{\alpha ij} = \frac{DA_{ij}}{hV_{\alpha}^j}.
\]

The trans-nuclear membrane jump rate is

\[
k_{\alpha ij} = \frac{AB_{ij}}{V_{\alpha}^i}.
\]

The active transport jump rate is derived to be

\[
k_{\alpha ij}^e = \left\{ \begin{array}{ll}
\frac{A^e_{ij}v_{\alpha}}{V_{\alpha}^i} \left| \langle v_{\alpha} \rangle_{k=0} \right|, & \text{if } \pm \langle v_{\alpha} \rangle_{k=0} \geq 0 \\
0, & \text{else}
\end{array} \right.
\]

Gene Expression Model

Transcription

- \( DNA + RNAP \rightarrow DNA\cdot RNAP \)
- \( DNA\cdot RNAP + n_{\alpha} \rightarrow DNA\cdot RNAP + n_{\alpha} \)
- \( RNA\cdot RNAP \rightarrow DNA\cdot RNAP + n_{\alpha} \)
- \( DNA\cdot RNAP + n_{\alpha} \rightarrow DNA\cdot RNAP + n_{\alpha} \)
- \( DNA\cdot RNAP + n_{\alpha} \rightarrow DNA\cdot RNAP + n_{\alpha} \)

mRNA Translation and Decay

- \( mRNA + Ribosome \rightarrow mRNA\cdot Ribosome \)
- \( mRNA\cdot Ribosome \rightarrow mRNA\cdot Ribosome \)
- \( mRNA\cdot Ribosome \rightarrow mRNA\cdot Ribosome \)
- \( mRNA\cdot Ribosome \rightarrow mRNA\cdot Ribosome \)

mRNA Export

- \( mRNA \rightarrow mRNA\cdot Ribosome \)
- \( mRNA\cdot Ribosome \rightarrow mRNA\cdot Ribosome \)
- \( mRNA\cdot Ribosome \rightarrow mRNA\cdot Ribosome \)

Protein Import and Gene Regulation

- \( RNAP \rightarrow RNAP \cdot DNA \)
- \( RNAP \cdot DNA \rightarrow RNAP \cdot DNA \)
- \( RNAP \cdot DNA \rightarrow RNAP \cdot DNA \)
- \( RNAP \cdot DNA \rightarrow RNAP \cdot DNA \)

3D Model Results

References


3D simulation movies available at: http://www.math.nyu.edu/~isaacsas

Cross section of spherical cell and nuclear membranes embedded in Cartesian grid.

Nuclear membrane reconstruction showing nuclear pore locations.

Cartesian grid.

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