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.

• We 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

$$\frac{dP(\boldsymbol{m})}{dt} = \sum_{i=1}^{N}\sum_{j=1}^{N}\sum_{l=1}^{L}\left(k_{ij}^{l}\left(m_{j}^{l}+1\right)P(\boldsymbol{m}+\boldsymbol{e}_{j}^{l}-\boldsymbol{e}_{i}^{l})-k_{ji}^{l}m_{i}^{l}P(\boldsymbol{m})\right)$$
$$+ \sum_{i=1}^{N}\sum_{j=1}^{N}\sum_{l=1}^{L}\left(\kappa_{ij}^{l}\left(m_{j}^{l}+1\right)P(\boldsymbol{m}+\boldsymbol{e}_{j}^{l}-\boldsymbol{e}_{i}^{l})-\kappa_{ji}^{l}m_{i}^{l}P(\boldsymbol{m})\right)$$
$$+ \sum_{i=1}^{N}\sum_{k=1}^{K}\left(a_{i}^{k}(\boldsymbol{m}_{i}-\boldsymbol{\nu}_{k})P(\boldsymbol{m}-\boldsymbol{e}_{i}\boldsymbol{\nu}_{k})-a_{i}^{k}(\boldsymbol{m}_{i})P(\boldsymbol{m})\right).$$

Here m_{i}^{l} gives the number of the l'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 a_{i}^{k} are specified, however, the diffusive and active transport jump rates, k_{ij}^{l} and κ_{ij}^{l} 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 tranport process to pass through the membrane.
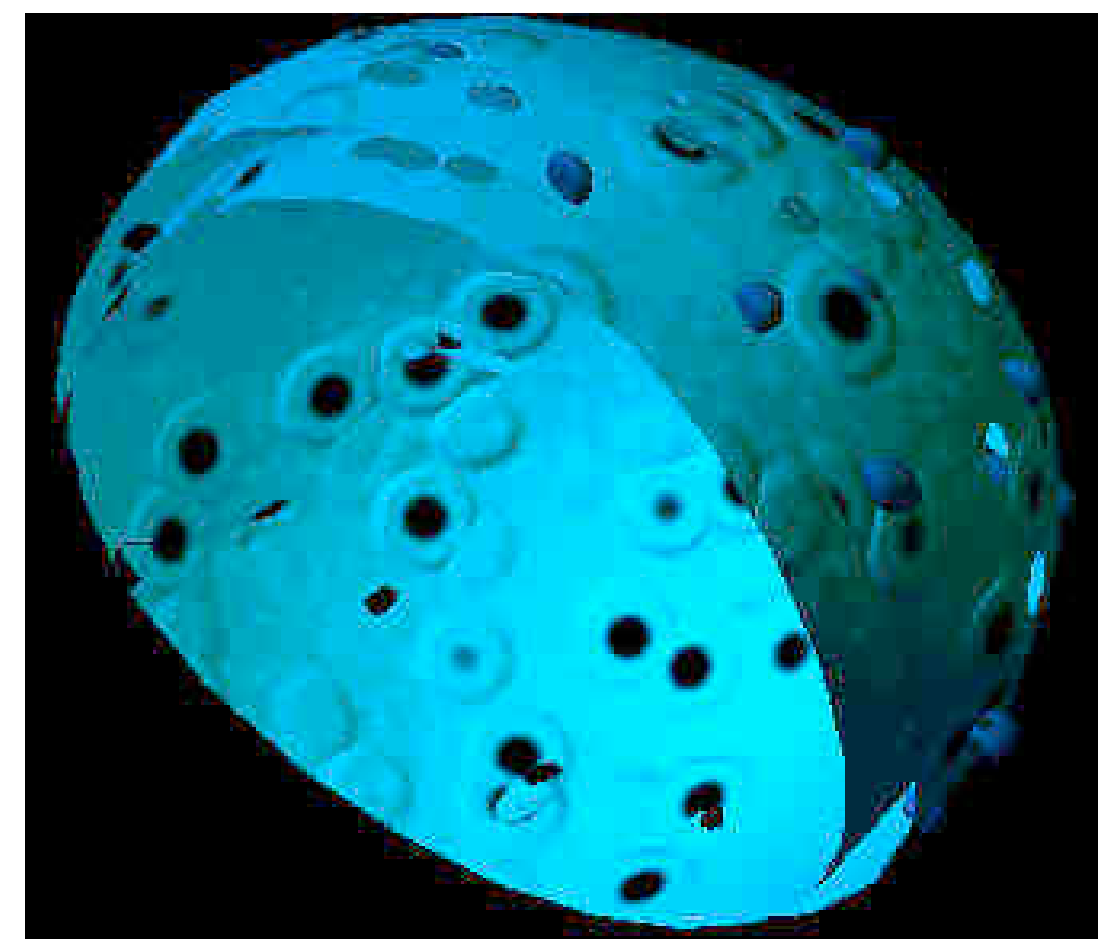
Nuclear membrane reconstruction showing nuclear pore locations.

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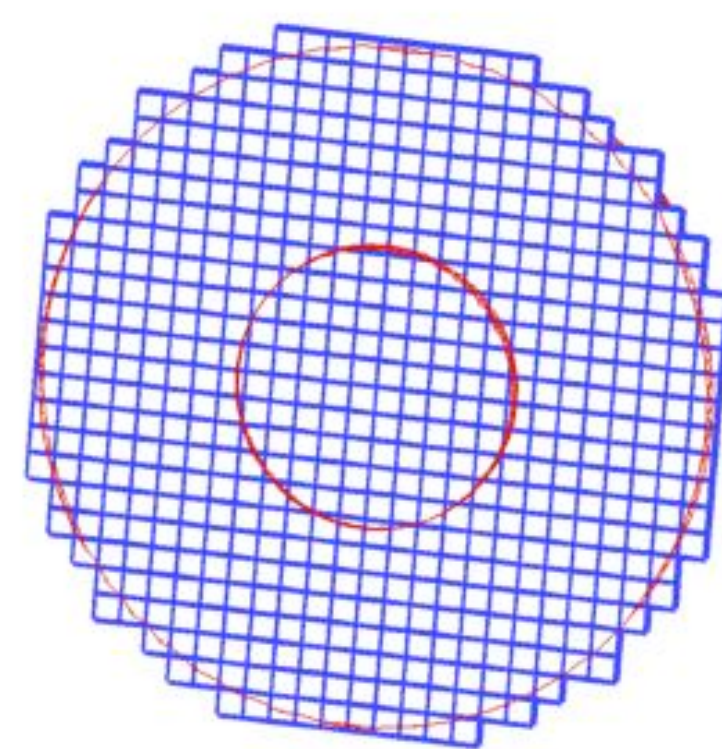
Cross section of spherical cell and nuclear membranes embedded in Cartesian grid.

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

$$k_{ij}^{\alpha} = \frac{D A_{ij}^{\alpha}}{h V_{j}^{\alpha}}.$$
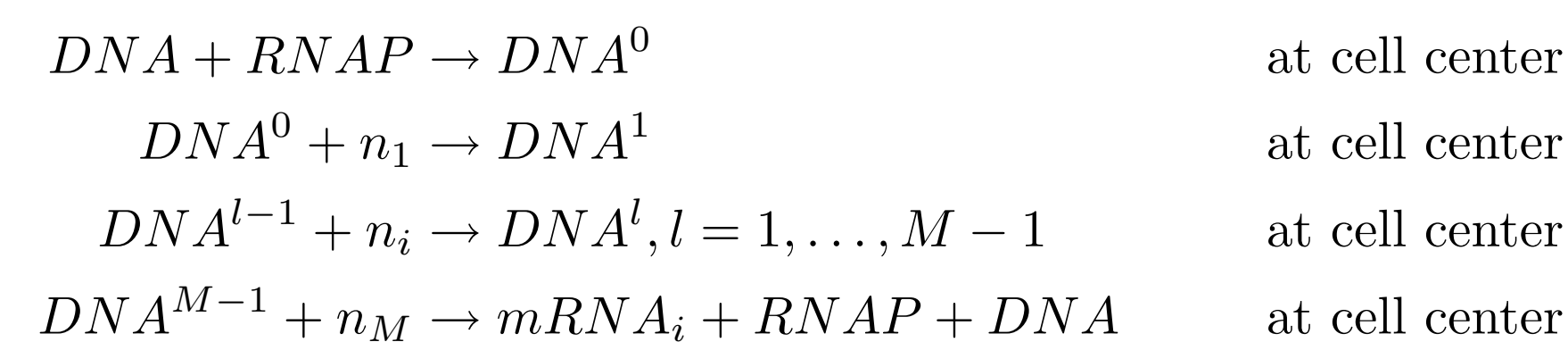
The trans-nuclear membrane jump rate is

$$k_{i}^{\alpha\alpha'} = \frac{A_{i}^{B_{n}}\rho}{V_{i}^{\alpha'}}.$$

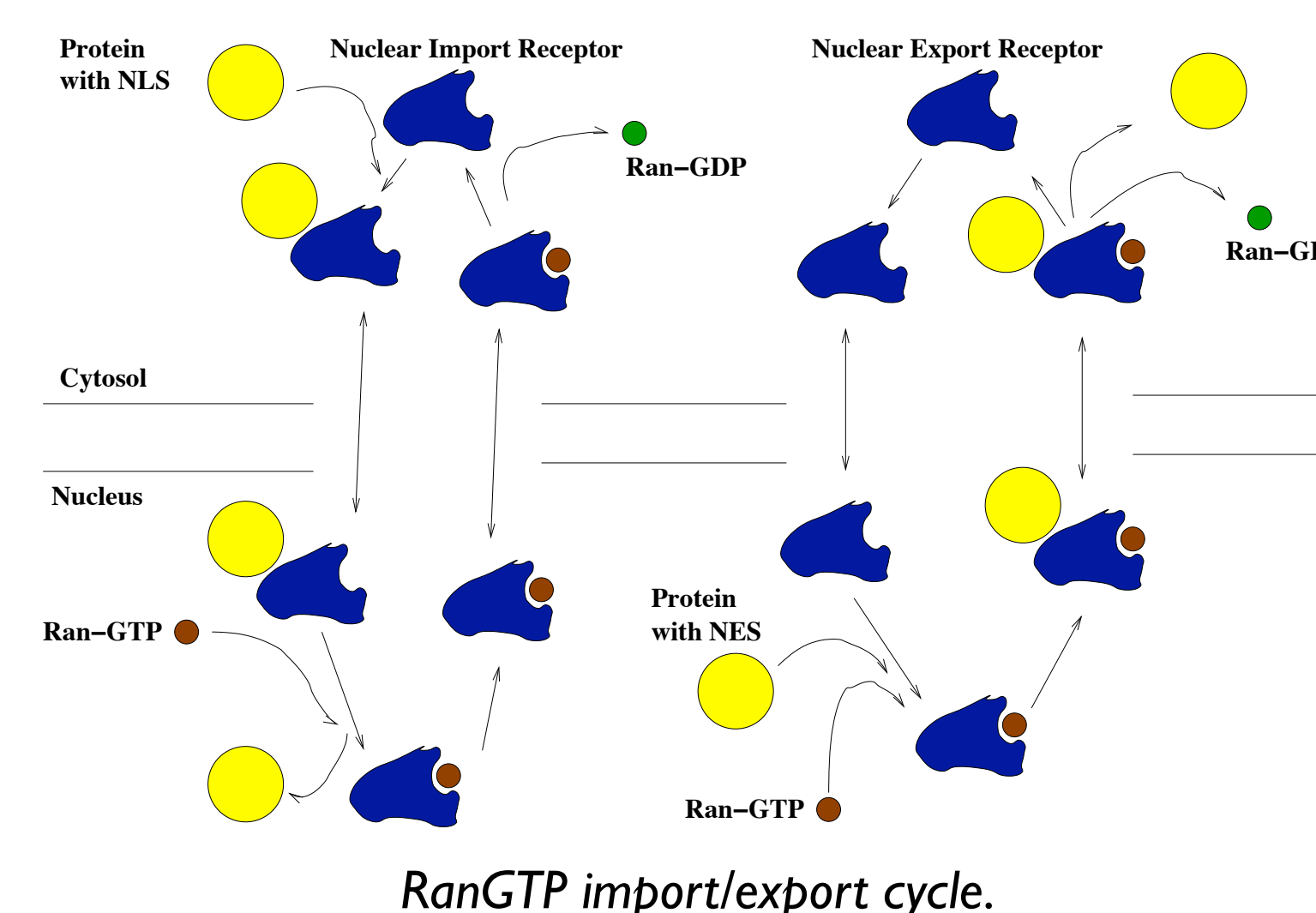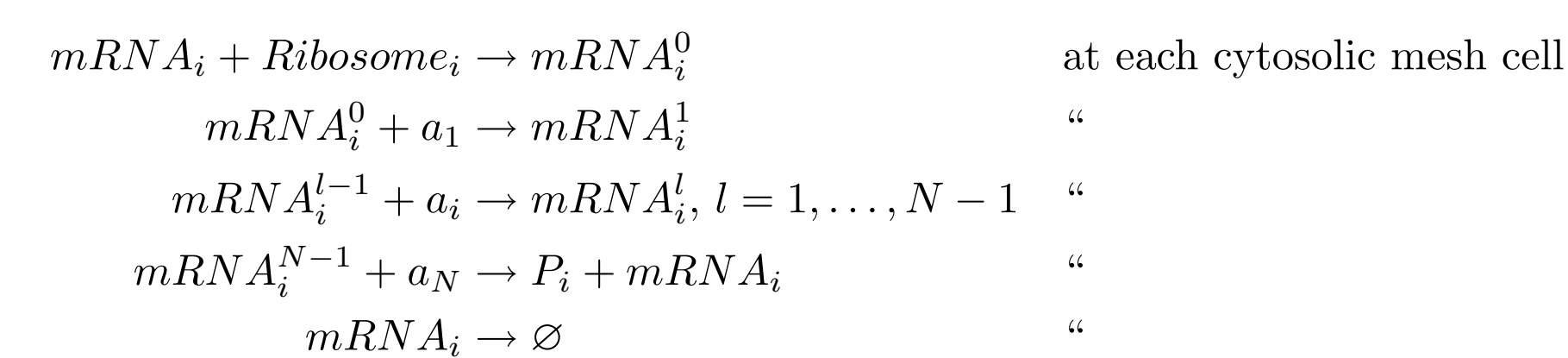The active transport jump rate is derived to be

$$\kappa_{\boldsymbol{i}\pm\boldsymbol{e}_{k},\boldsymbol{i}}^{\alpha} = \begin{cases} \dfrac{A_{\boldsymbol{i}\pm\frac{1}{2}\boldsymbol{e}_{k}}^{\alpha}}{V_{\boldsymbol{i}}}\left|(\boldsymbol{v}_{k})_{\boldsymbol{i}\pm\frac{1}{2}\boldsymbol{e}_{k}}^{\alpha}\right|, & \text{if } \pm(v_{k})_{\boldsymbol{i}\pm\frac{1}{2}\boldsymbol{e}_{k}}^{\alpha} \geq 0, \\ 0, & \text{else.} \end{cases}$$

Gene Expression Model

Transcription

$DNA + RNAP \rightarrow DNA^{0}$	at cell center
$DNA^{0} + n_{1} \rightarrow DNA^{1}$	at cell center
$DNA^{l-1} + n_{i} \rightarrow DNA^{l}, l = 1, \ldots, M-1$	at cell center
$DNA^{M-1} + n_{M} \rightarrow mRNA_{i} + RNAP + DNA$	at cell center

mRNA Translation and Decay

$mRNA_{i} + Ribosome_{i} \rightarrow mRNA_{i}^{0}$	at each cytosolic mesh cell
$mRNA_{i}^{0} + a_{1} \rightarrow mRNA_{i}^{1}$	"
$mRNA_{i}^{l} + a_{i} \rightarrow mRNA_{i}^{l}, l = 1, \ldots, N-1$	"
$mRNA_{i}^{N-1} + a_{N} \rightarrow P_{i} + mRNA_{i}$	"
$mRNA_{i} \rightarrow \varnothing$	"

RanGTP import/export cycle.

mRNA Export

$mRNA_{i} + NR\text{-}Rt_{i} \rightarrow mRNA\text{-}NR\text{-}Rt_{i}$	at each nuclear mesh cell
$mRNA\text{-}NR\text{-}Rt_{i} \rightleftharpoons mRNA\text{-}NR\text{-}Rt\text{-}Rb_{i}$	at each cytosolic mesh cell
$mRNA\text{-}NR\text{-}Rt\text{-}Rb_{i} \rightarrow mRNA_{i} + NR_{i} + RanGDP_{i}$	"
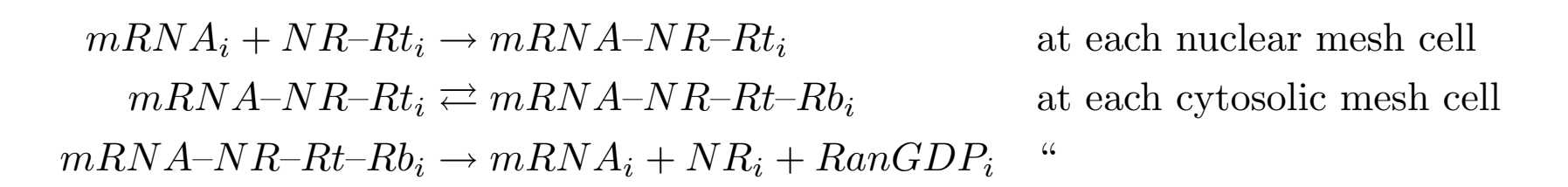
Protein Import and Gene Regulation

$P_{i} \rightarrow \varnothing$	at all mesh cells
$P_{i} + NR_{i} \rightarrow P\text{-}NR_{i}$	at each cytosolic mesh cell
$P\text{-}NR_{i} + Rt_{i} \rightarrow P_{i} + NR\text{-}Rt_{i}$	at each nuclear mesh cell
$P_{i} + DNA \rightleftharpoons DNARep$	at cell center
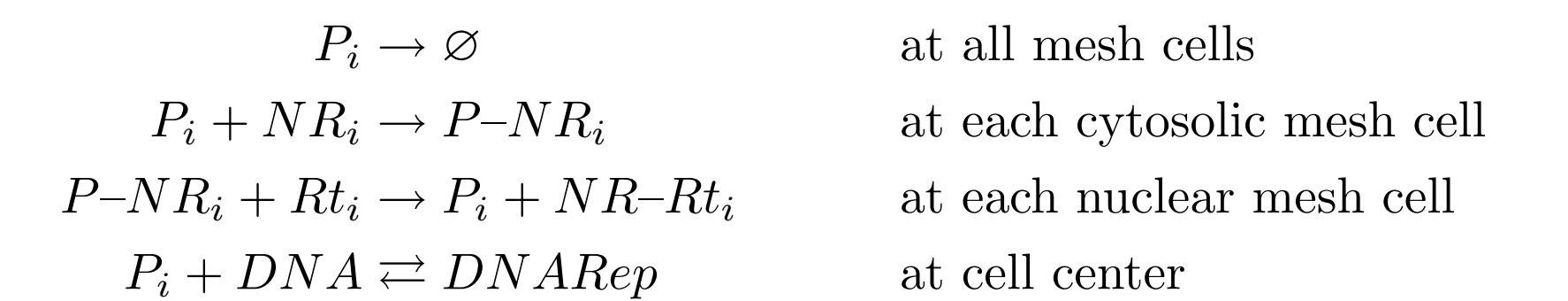
3D Model Results
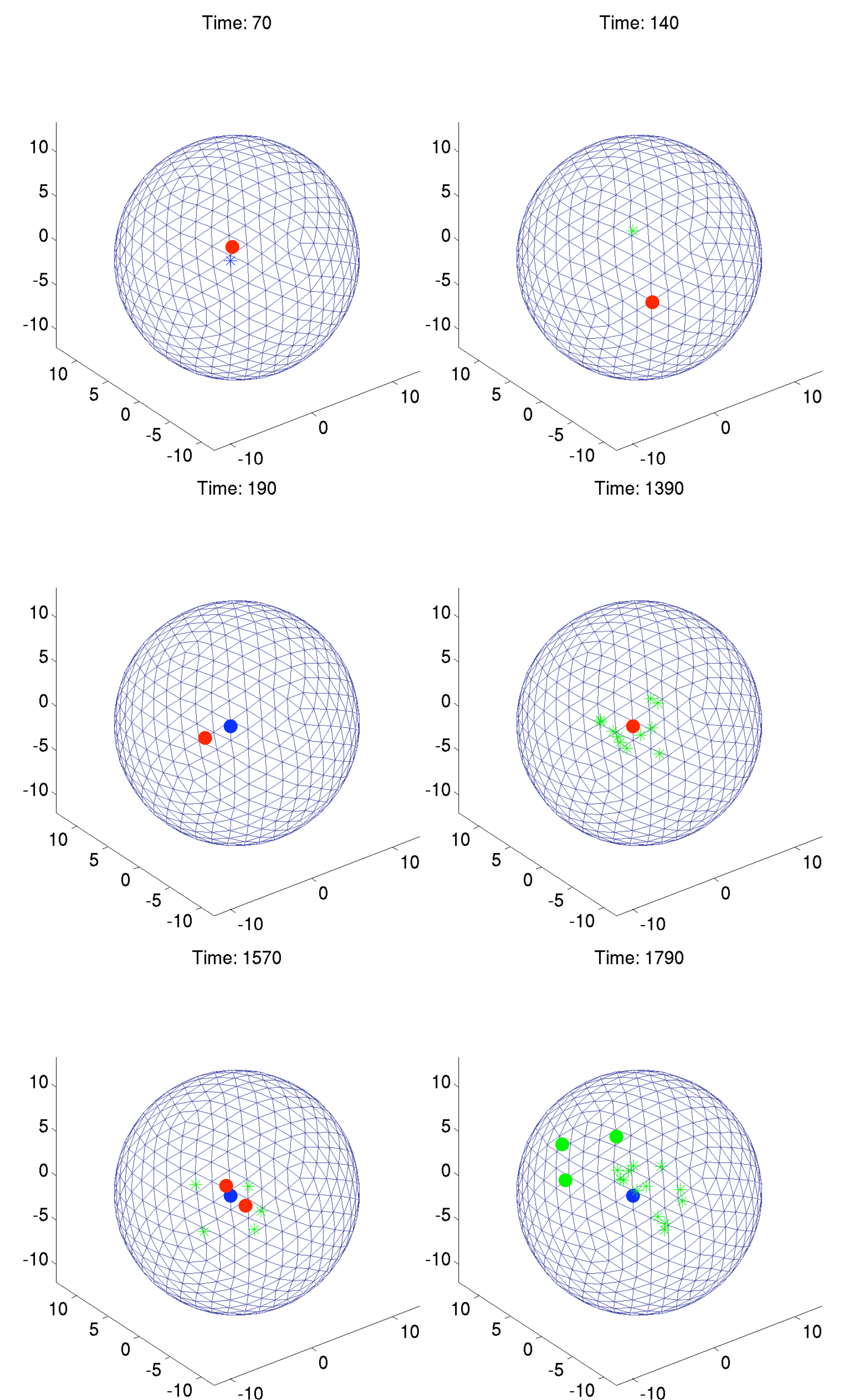
References

• S. A. Isaacson and C. S. Peskin (2005) Incorporating diffusion in complex geometries into stochastic chemical kinetics simulations, SIAM J. Sci. Comp., accepted.

3D simulation movies available at:

http://www.math.nyu.edu/~isaacsas