Incorporating Cellular Substructure into Reaction-Diffusion Models

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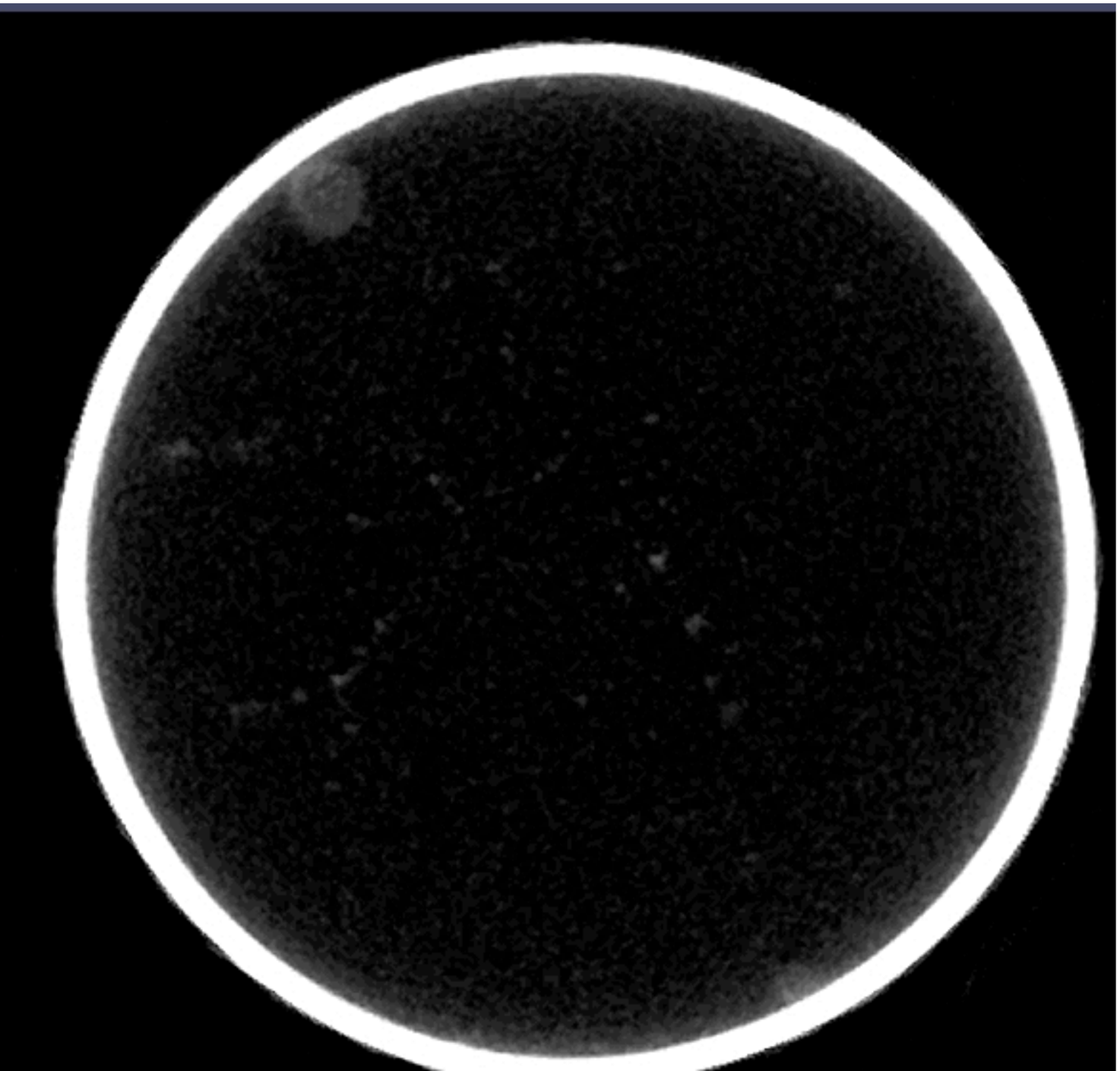
What does the cellular environment look like?

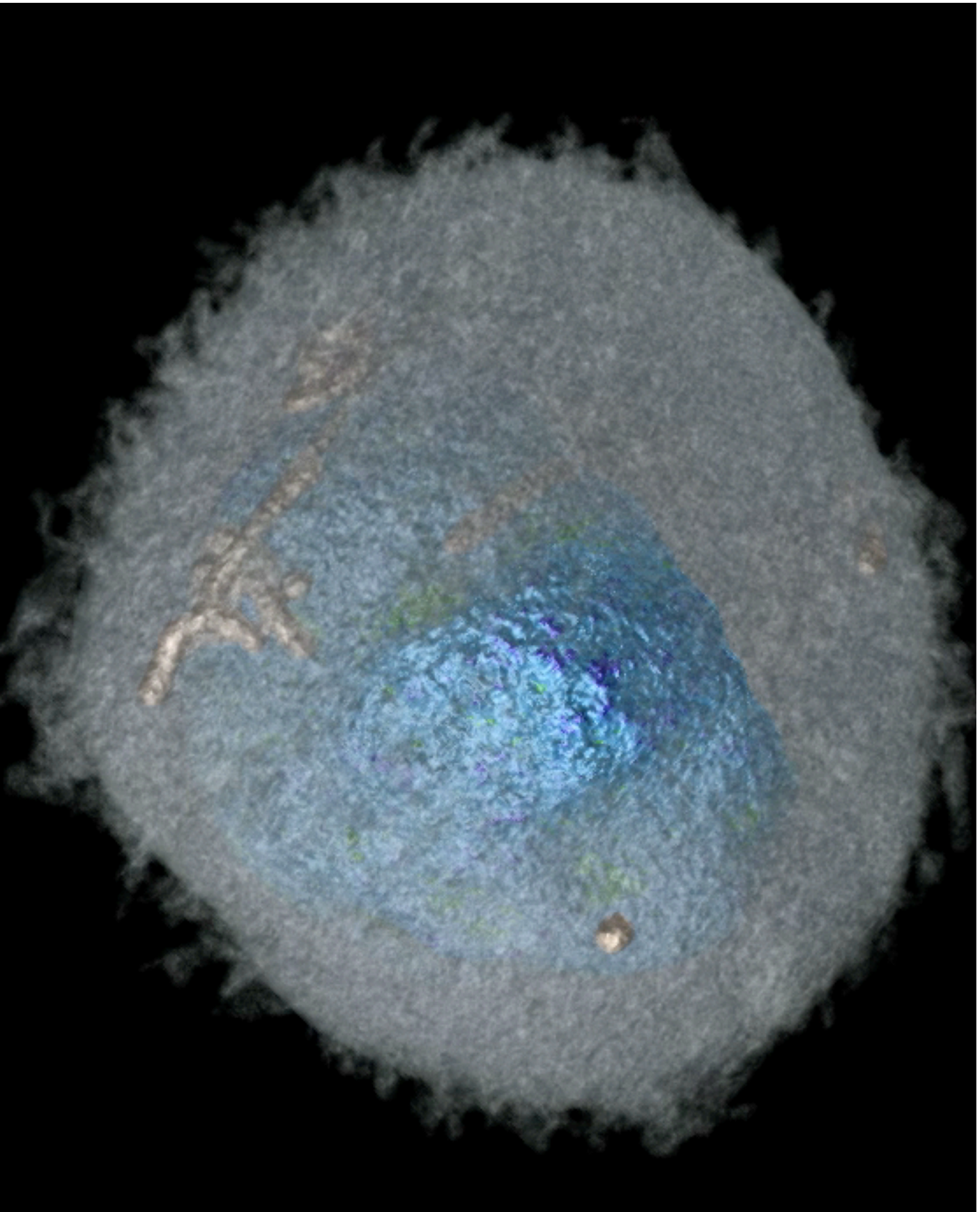
- This is a soft X-ray tomography reconstruction of a human B cell. (Data - C. Larabell)
- The cell has been cyro-preserved.
- Pixel intensity corresponds to the linear absorption coefficient (LAC) within that voxel.
  - LACs are directly proportional to the density of organic material within that voxel.



Human B cell

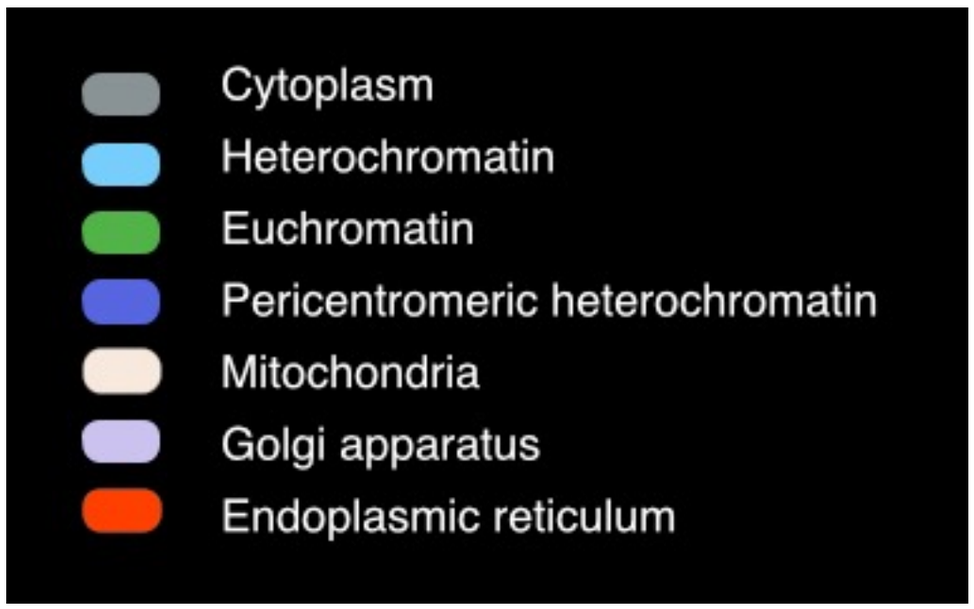
Voxel Dimensions
35nm

How can we use this data in modeling studies?



Same Human B cell
(from culture).

Organelles and substructure
have been labelled in Amira.



By M. Le Gros

So clearly the interior of cells is a very complex, heterogeneous environment.

How does subcellular structure influence the dynamics of biochemical processes within cells?

How might excluded volume from organelles influence the propagation of signals from the cell membrane to the nucleus?

As a lower bound, consider the time needed for a molecule to diffuse from the cell membrane to any point of the nuclear membrane.

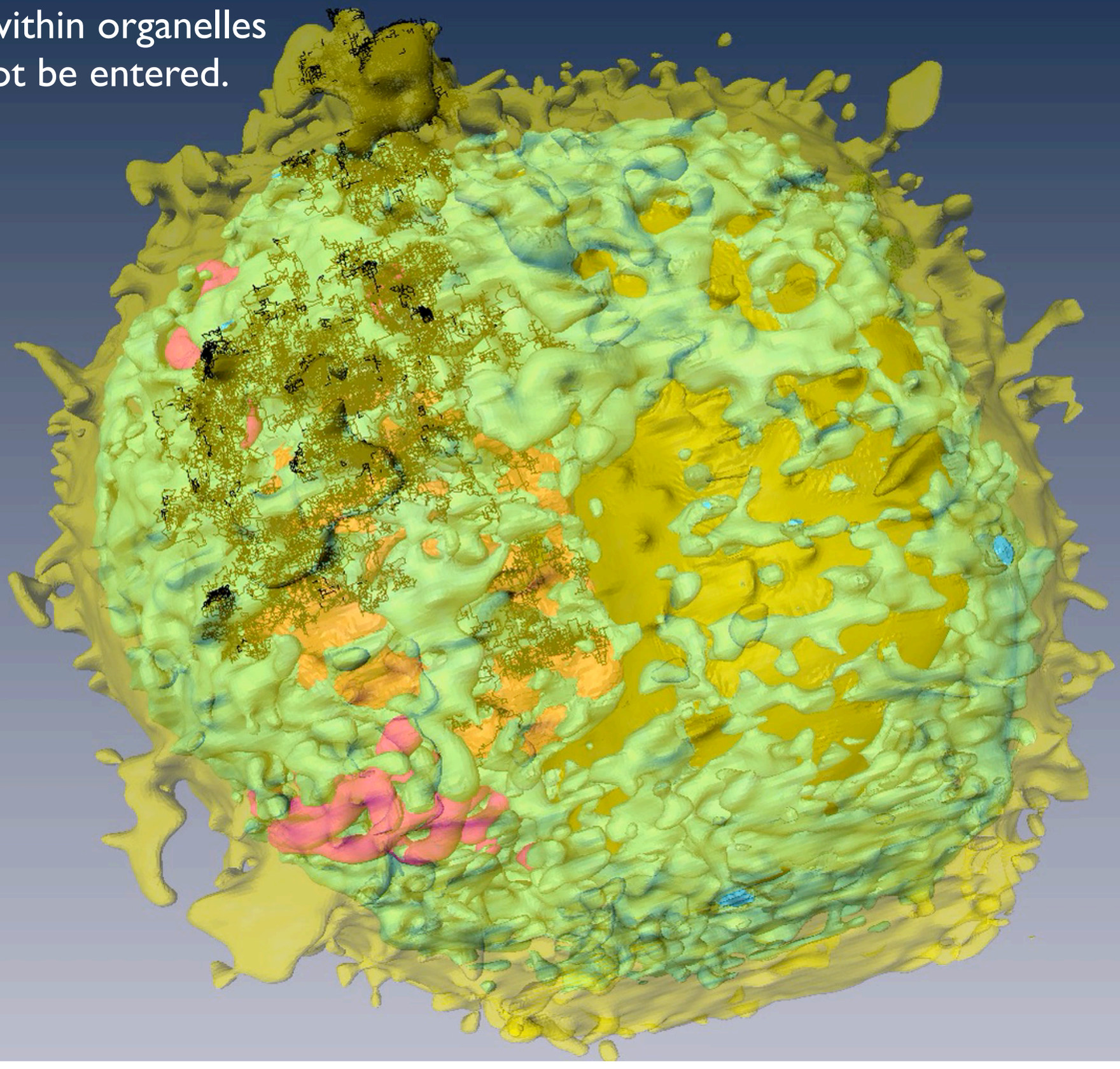
- Approximate the diffusion of the molecule by a continuous time random walk between voxels of the imaging data.
- Excluded volume is modeled by preventing the molecule from hopping into voxels that are labelled as organelles.
- Molecule is started uniformly distributed among voxels that determine the cell membrane.
- The nuclear membrane is modeled as a Dirichlet BC. Simulations terminate when the molecule first hopes across the nuclear membrane.

How does the presence of organelles effect the search process for the nucleus vs searching an empty cytosol?

Protein moves by continuous time random walk among voxels of imaging data.

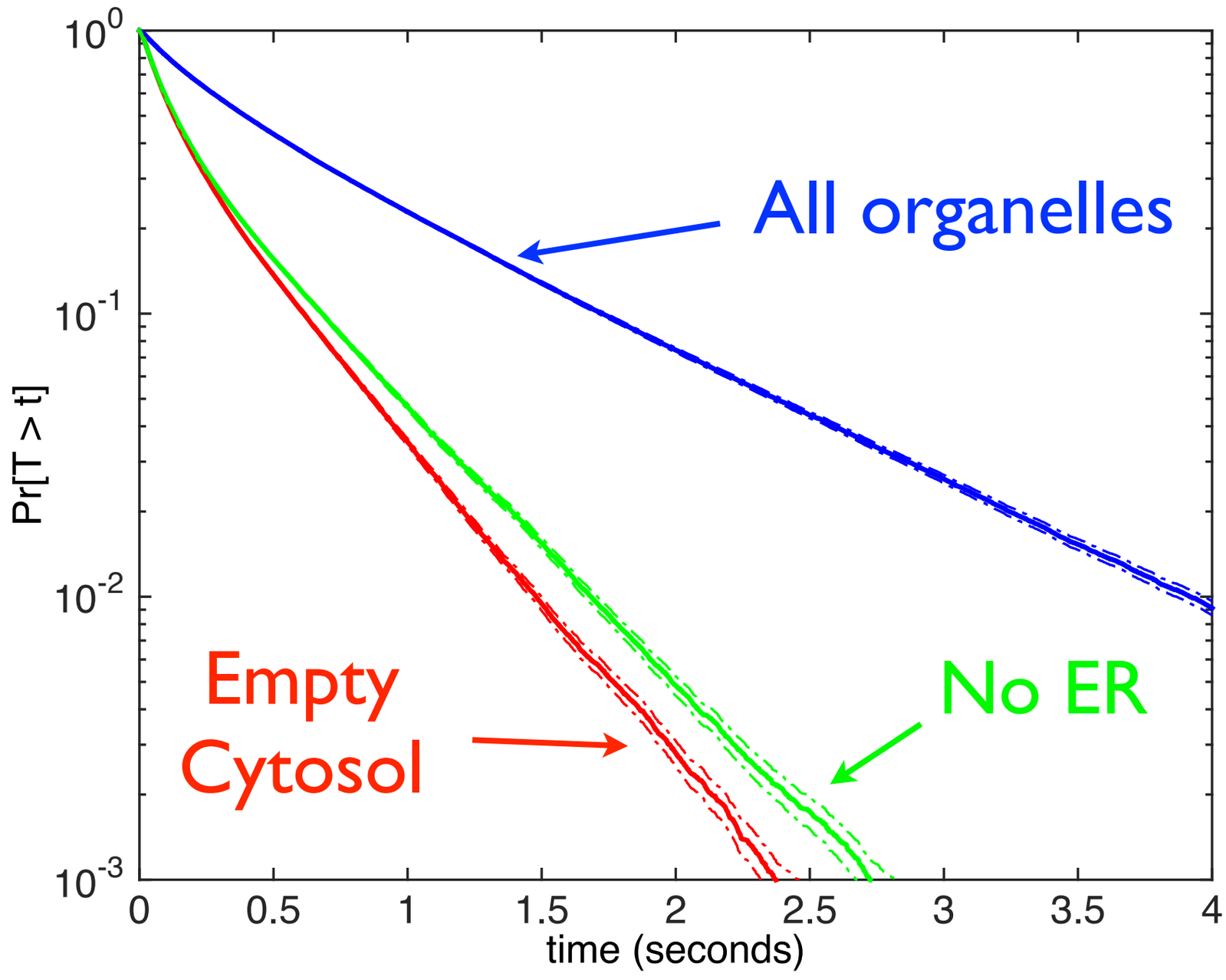
Voxels within organelles can not be entered.

Human B cell



How does the time, *T*, to go from a random point on the cell membrane to any point of the nuclear membrane depend on cellular substructure?

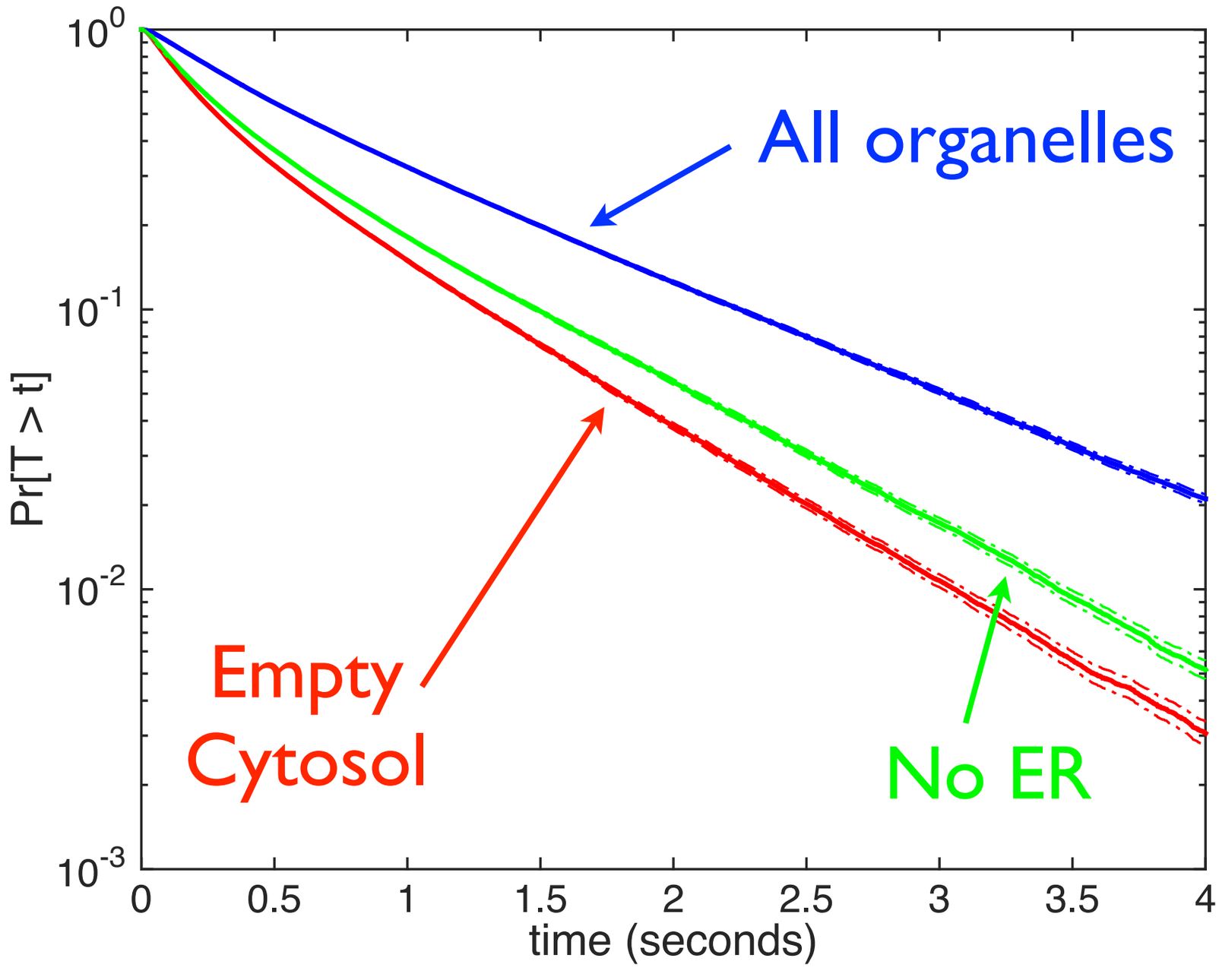
The presence of ER and other organelles slows the median search time by approximately a factor of 3. (.127 to .39 sec)



How dependent is this on the specific cell?

For a second cell, with less ER
(ER occupies 11% of cytosol vs 30% for previous cell)

The presence of ER and other organelles slows the median search time by approximately a factor of 2. (.28 to .58 sec)



How does the MFPT vary across the cell membrane?

Let $u(x, y, z)$ denote the MFPT to diffuse from (x, y, z) to the nuclear membrane.

Then in the cytosol:

$$-\Delta u = \frac{1}{D}$$

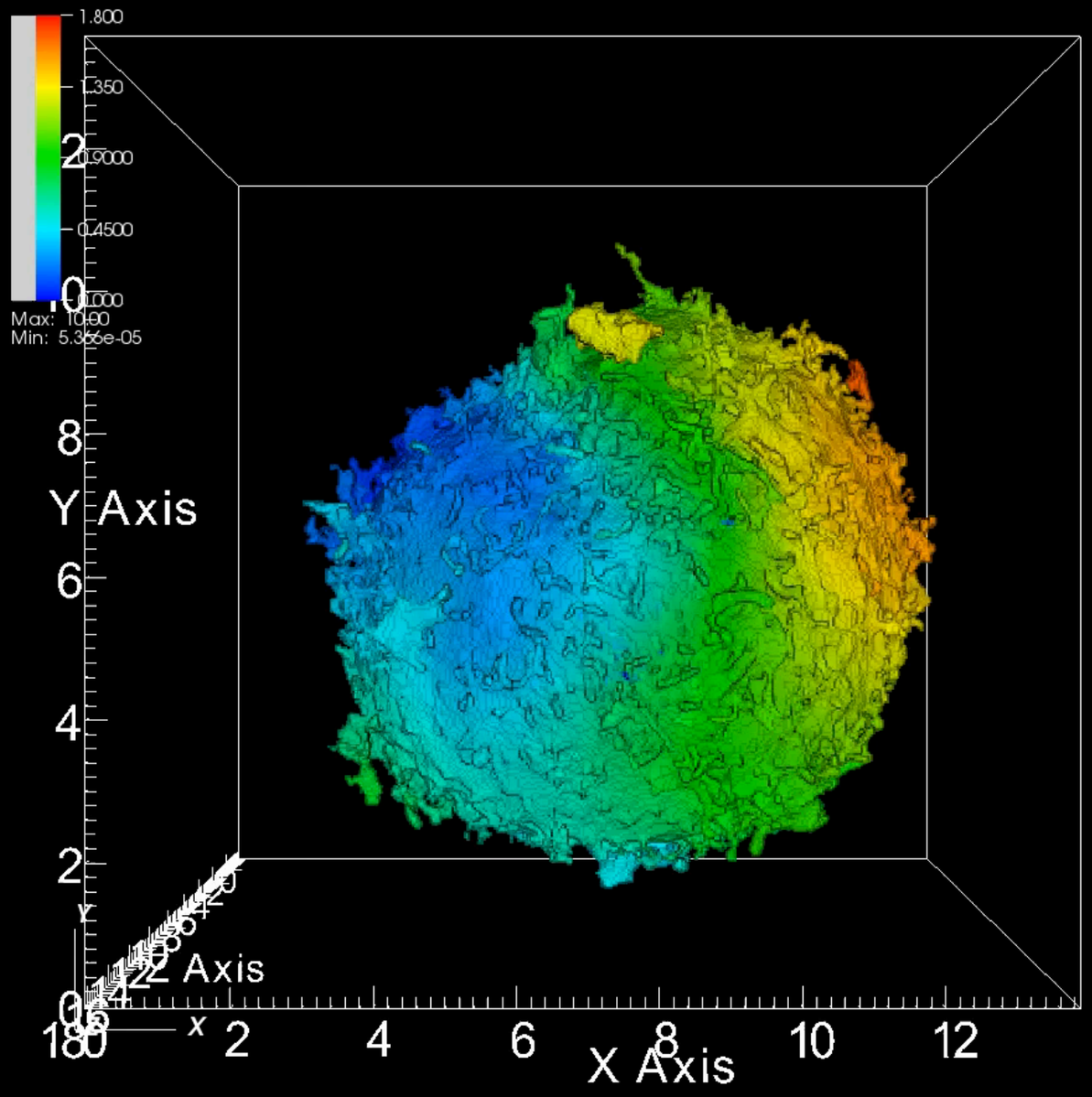
On the cell membrane and organelle boundaries:

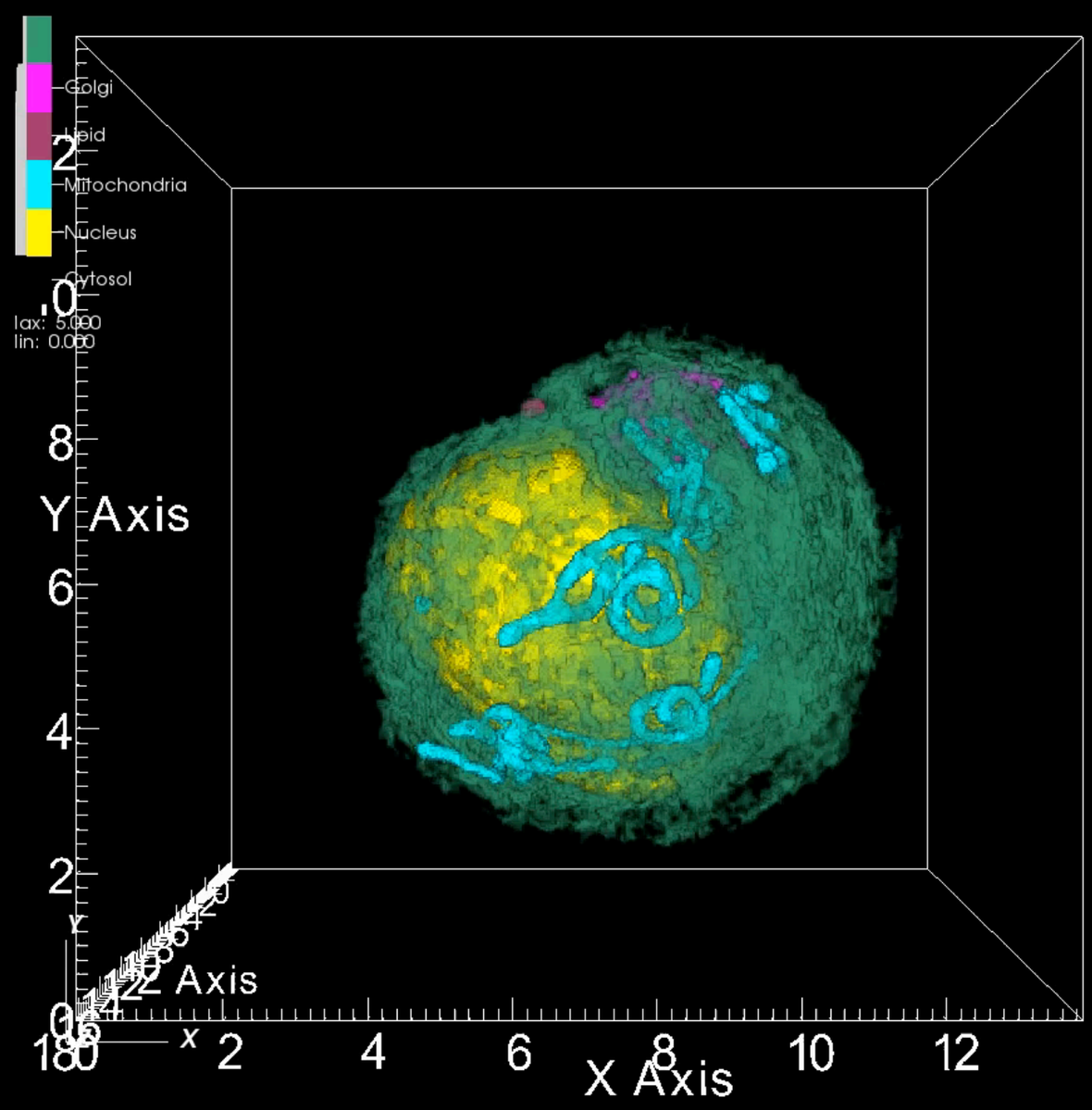
$$\nabla u \cdot \boldsymbol{\eta}(x, y, z) = 0$$

Where $\boldsymbol{\eta}(x, y, z)$ denotes the outward normal.

On the nuclear membrane:

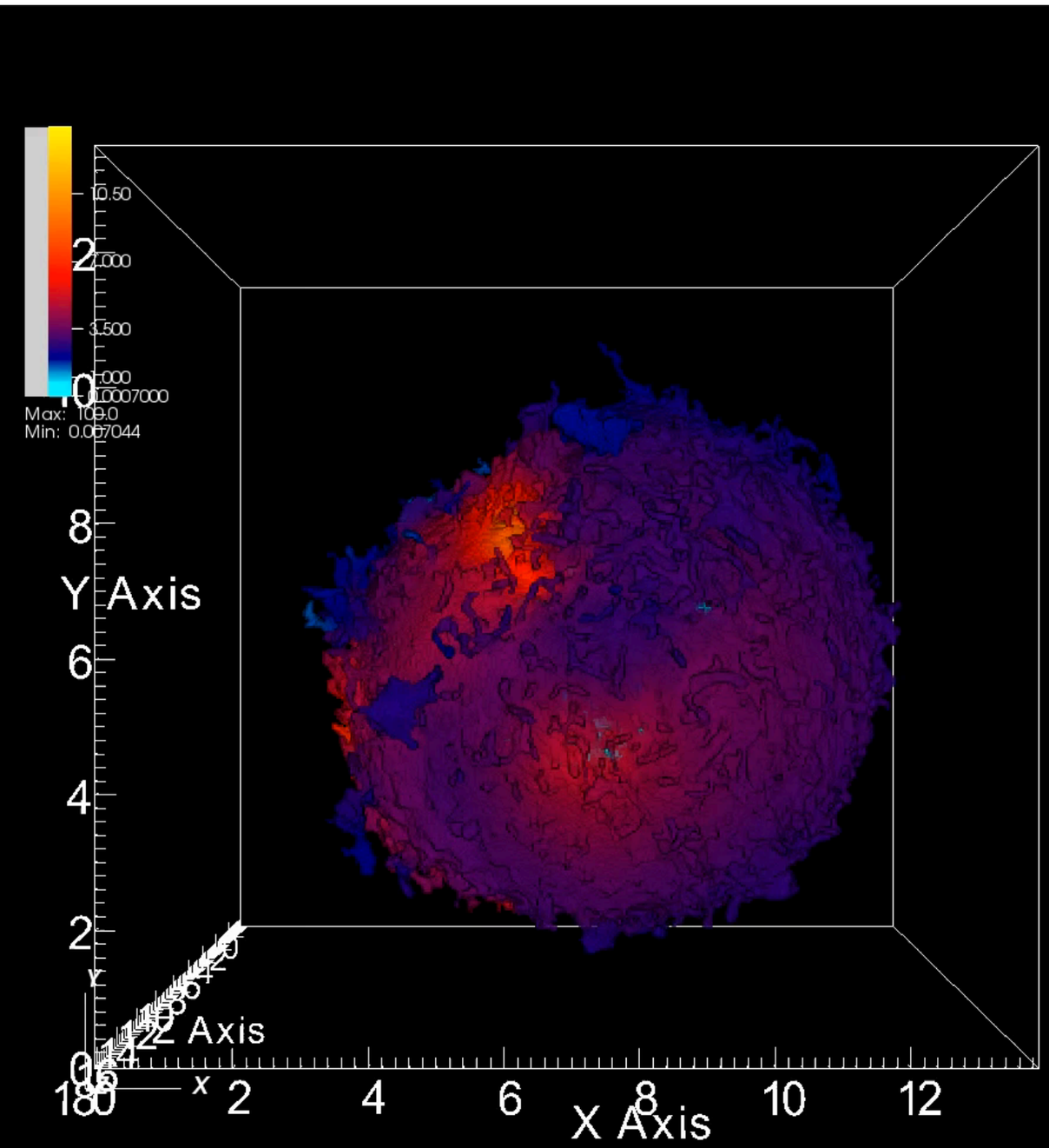
$$u(x, y, z) = 0$$

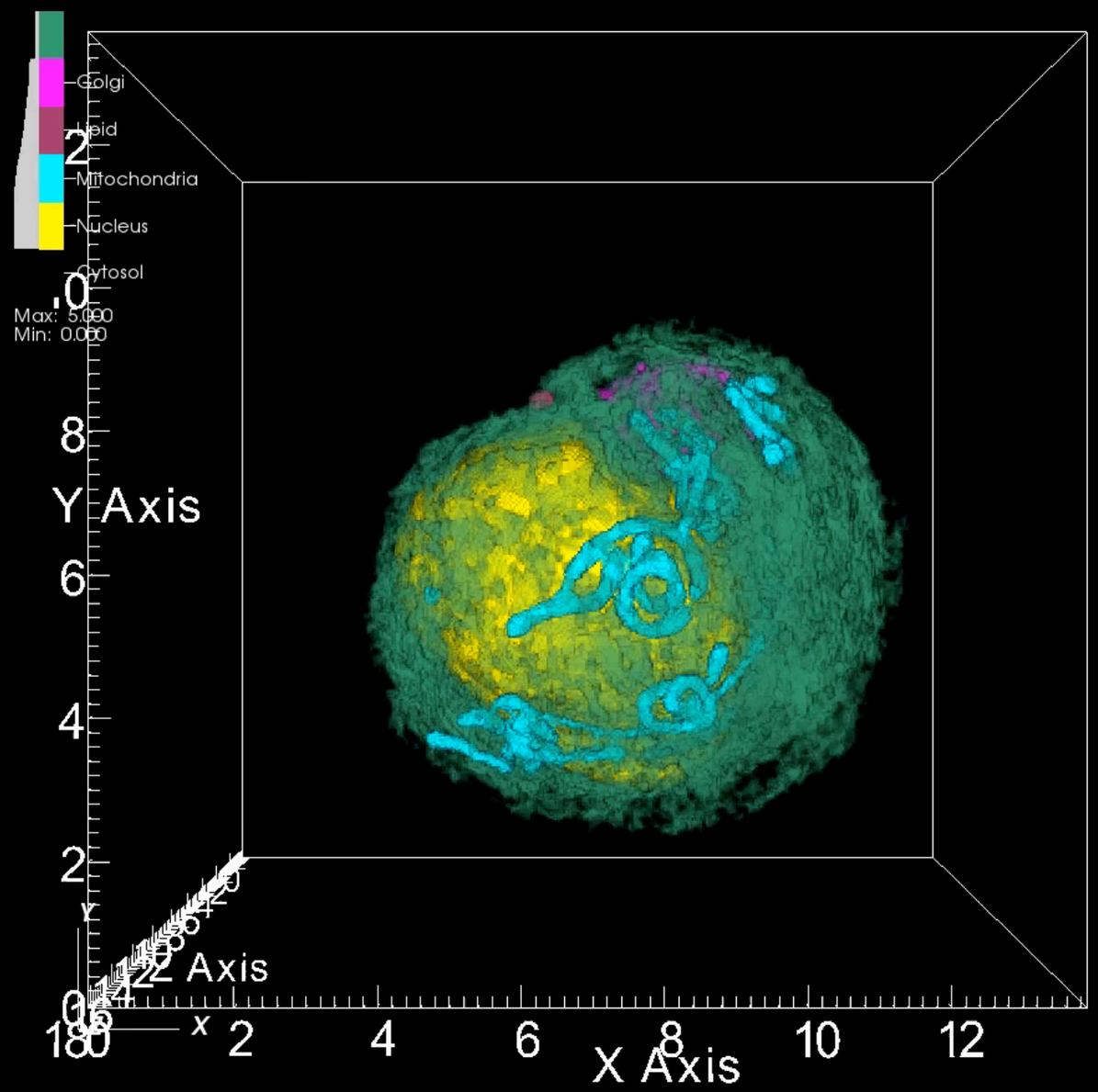




How much does the MFPT change when organelles are present as excluded volumes?

Plot of: $\dfrac{u_{\text{organelles}}(x,y,z)}{u_{\text{no organelles}}(x,y,z)}$ at points on the cell membrane.





However, these studies only involve single molecules!

- We wish to investigate the role of substructure in more general pathways involving thousands of interacting molecules (or more)
  - cell-cycle regulation
  - signal transduction (MAPK)
  - gene regulatory networks
- These require accurate and efficient numerical methods for simulating particle-based stochastic reaction-diffusion models in complex geometries.

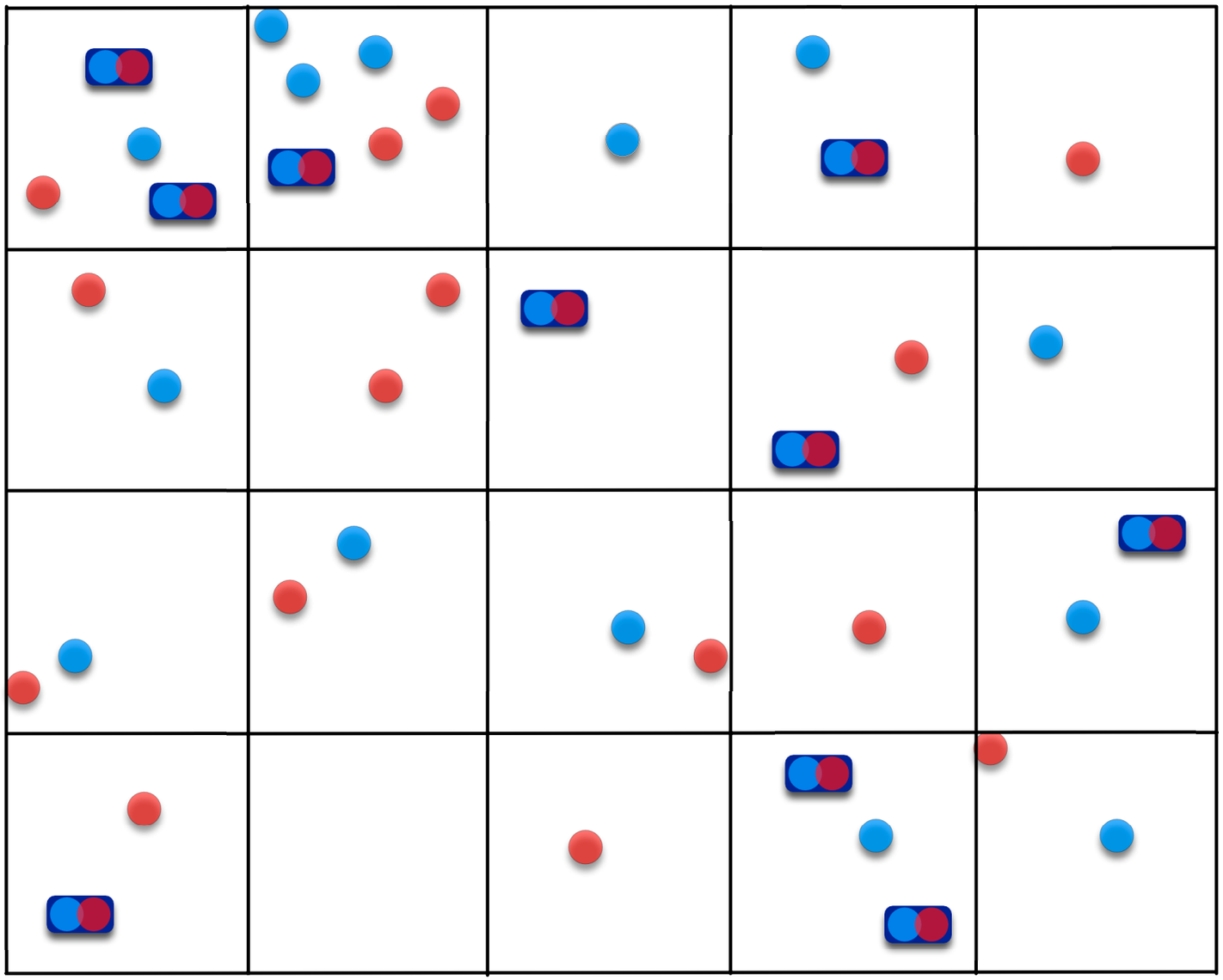
To study such systems we have developed a modified version of the lattice reaction-diffusion master equation (RDME), a widely use particle-based stochastic reaction-diffusion method.

- Our method, the convergent RDME (CRDME), corrects the major drawback to the RDME.

See Isaacson, J. Chem. Phys. 2013 for details on the method.

What stochastic process does the RDME describe?

- Space is discretized into a collection of voxels.
- Molecules move by undergoing continuous time random walks between voxels.
- Molecules are assumed "well-mixed" within a voxel.
- First order reactions occur through internal Poisson clocks.
- Bimolecular reactions occur with a specified probability per unit time for any two molecules within the **same** voxel.



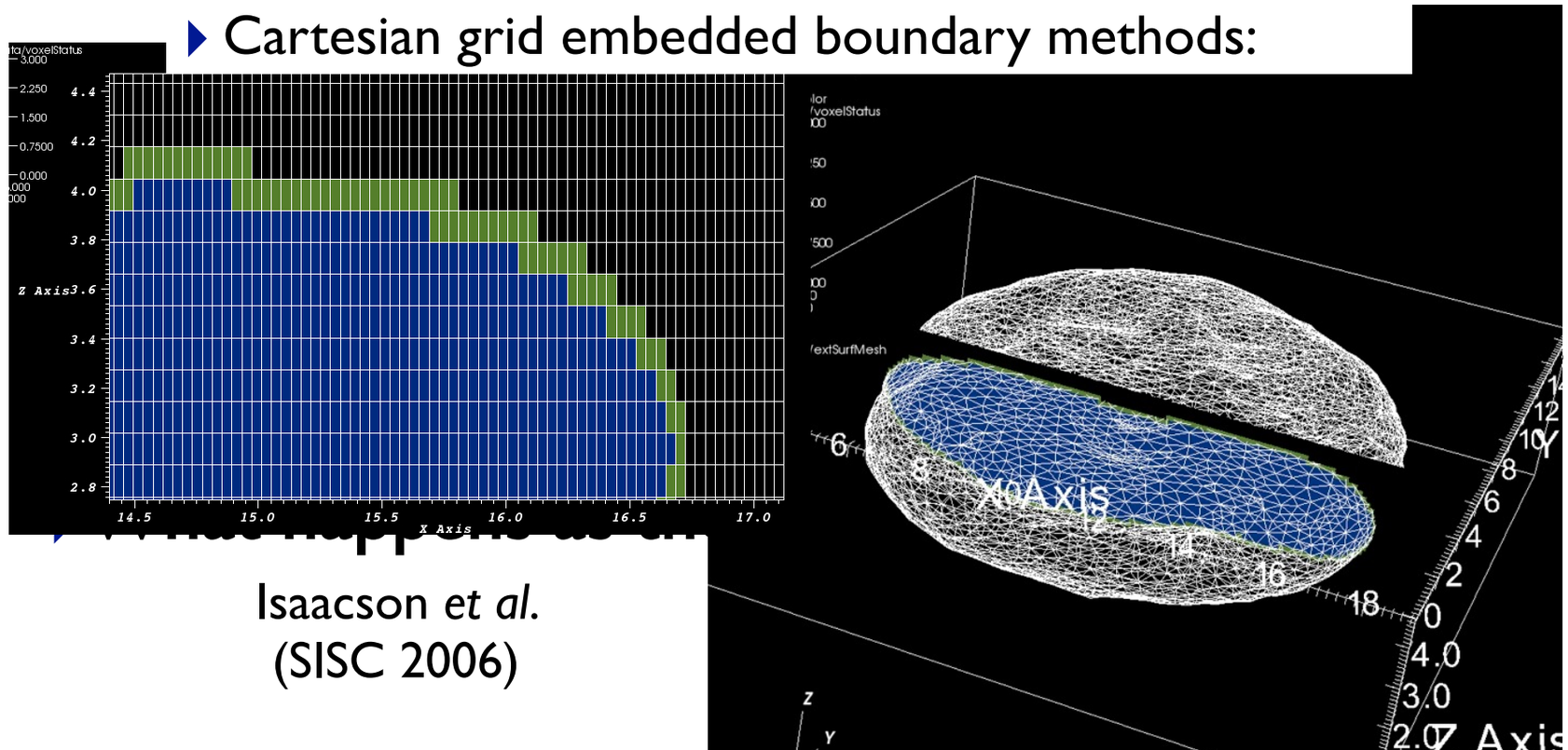
Can generate exact realizations of this process using the:

Stochastic Simulation Method (SSA) / Gillespie Method / Kinetic Monte Carlo

The RDME is a possibly infinite system of ODEs for the probability this stochastic process has a given value. Due to its high dimensionality, in practice we must use the SSA to simulate the underlying process.

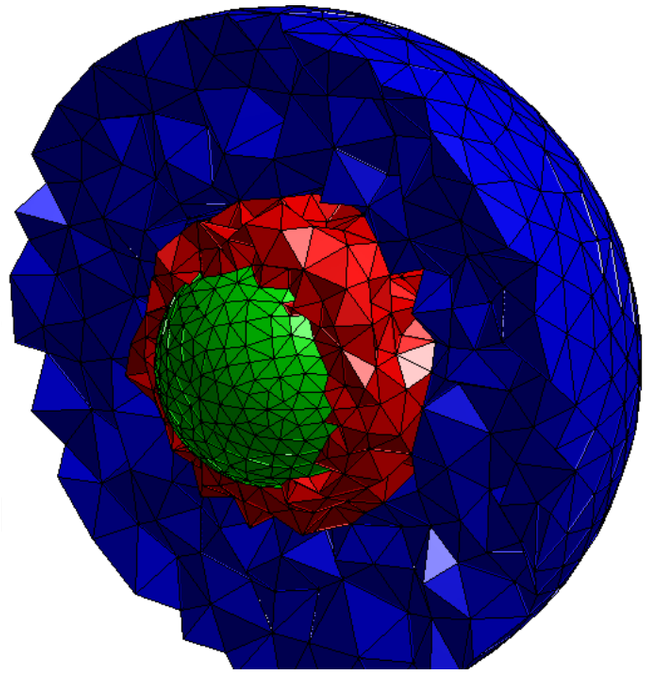
Why use the RDME approach for studying biological systems?

- SSA generates *exact* samples of the underlying stochastic process.
- Method is relatively simple to implement.
- Several publicly available simulators that can handle general chemical systems in complex geometries (Lattice Microbes, STEPS, URDME,...).
- Requires less parameters than the other methods. (Only needs well-mixed reaction rates.)
- Many extensions using existing PDE discretization techniques / tools:
  - AMR methods, advection, drift due to potentials, and GPU optimized versions.
  - Multiscale couplings to deterministic RD-PDE or tau-leaping methods.
  - Can handle complex geometries using PDE-based meshing approaches:
    - Cartesian grid embedded boundary methods:



Isaacson *et al.* (SISC 2006)

    - Finite element methods:



Hellander *et al.* (SISC 2009)

What does the RDME converge to as $h \to 0$ in R^d? ($d > 1$)

- We consider the simplified case of just two molecules undergoing an annihilation reaction $\mathrm{A} + \mathrm{B} \to 0$.
- Let i and j label the lattice sites containing the A and B molecules.

RDME:
$$\frac{dp_{ij}}{dt} = (D^A \Delta_h^A + D^B + \Delta_h^B) p_{ij}(t) - \frac{K}{h^d} \delta_{ij} p_{ij}(t)$$

$$\Big\downarrow \quad h \to 0$$

Diffusion Equation:
$$\frac{\partial p}{\partial t}(\boldsymbol{x}, \boldsymbol{y}, t) = (D^A \Delta_{\boldsymbol{x}} + D^B \Delta_{\boldsymbol{y}}) p(\boldsymbol{x}, \boldsymbol{y}, t)$$

So bimolecular reactions are lost!

The RDME is not a convergent approximation of any reasonable spatially-continuous stochastic reaction-diffusion model incorporating bimolecular reactions (*in two or more dimensions*).

(see Isaacson and Isaacson PRE 2009, Isaacson SIAP 2009)

How can we construct a convergent RDME-like model?

We start with a continuous particle-dynamics model popularized by Doi:

$$\frac{\partial p}{\partial t}(\boldsymbol{x}, \boldsymbol{y}, t) = (D^{\mathrm{A}}\Delta_{\boldsymbol{x}} + D^{\mathrm{B}}\Delta_{\boldsymbol{y}})p(\boldsymbol{x}, \boldsymbol{y}, t) - \lambda \mathbb{1}_{[0,r_{\mathrm{b}}]}(|\boldsymbol{x} - \boldsymbol{y}|)p(\boldsymbol{x}, \boldsymbol{y}, t),$$

where $\mathbb{1}_{[0,r_{\mathrm{b}}]}$ is the indicator of $[0, r_{\mathrm{b}}]$.

We discretize this model to derive an RDME-like model:

- We partition $\mathbb{R}^d$ into a uniform Cartesian mesh of width h.
- Let $\boldsymbol{i} \in \mathbb{Z}^d$ and $\boldsymbol{j} \in \mathbb{Z}^d$ label the mesh voxels, $V_{\boldsymbol{i}}$ and $V_{\boldsymbol{j}}$ with centers $\boldsymbol{x}_{\boldsymbol{i}} = \boldsymbol{i}h$ and $\boldsymbol{y}_{\boldsymbol{j}} = \boldsymbol{j}h$.
- Let $|V_{\boldsymbol{i}}| = h^d$ denote the volume of $V_{\boldsymbol{i}}$.
- $V_{\boldsymbol{ij}} \equiv V_{\boldsymbol{i}} \times V_{\boldsymbol{j}} \in \mathbb{R}^{2d}$

What is our discretization procedure?

We make the *approximation* that

$$P_{\boldsymbol{i},\boldsymbol{j}}(t) \equiv \Pr\left[(\boldsymbol{x},\boldsymbol{y}) \in V_{\boldsymbol{ij}} \text{ at time } t\right] = p(\boldsymbol{x}_{\boldsymbol{i}},\boldsymbol{y}_{\boldsymbol{j}},t)\left|V_{\boldsymbol{ij}}\right|.$$

To derive an equation for $P_{\boldsymbol{i},\boldsymbol{j}}(t)$:

- We integrate the PDE for $p(\boldsymbol{x},\boldsymbol{y},t)$ over $V_{\boldsymbol{ij}}$.
- Use a standard finite volume approximation for the Laplacians.

$$\int_{V_{\boldsymbol{ij}}} \Delta_{\boldsymbol{x}} p(\boldsymbol{x},\boldsymbol{y},t)\,d\boldsymbol{x}\,d\boldsymbol{y} \approx \Delta_h^{\mathrm{A}} P_{\boldsymbol{ij}}$$

$$= \frac{1}{h^2}\sum_{k=1}^{d}\left[P_{\boldsymbol{i}+\boldsymbol{e}_k,\boldsymbol{j}} + P_{\boldsymbol{i}-\boldsymbol{e}_k,\boldsymbol{j}} - 2P_{\boldsymbol{i},\boldsymbol{j}}\right]$$

- We approximate the reaction term by

$$\lambda\int_{V_{\boldsymbol{ij}}} \mathbb{1}_{\mathcal{R}}(|\boldsymbol{x}-\boldsymbol{y}|)p(\boldsymbol{x},\boldsymbol{y},t)\,d\boldsymbol{x}\,d\boldsymbol{y} \approx \frac{\lambda}{|V_{\boldsymbol{ij}}|}P_{\boldsymbol{i},\boldsymbol{j}}(t)\int_{V_{\boldsymbol{ij}}} \mathbb{1}_{\mathcal{R}}(|\boldsymbol{x}-\boldsymbol{y}|)\,d\boldsymbol{x}\,d\boldsymbol{y}$$

$$= \frac{\lambda\left|\mathcal{R}\cap V_{\boldsymbol{ij}}\right|}{|V_{\boldsymbol{ij}}|}P_{\boldsymbol{i},\boldsymbol{j}}(t).$$

What is the CRDME?

Let the volume fraction

$$\phi_{ij} = \frac{|\mathcal{R} \cap V_{ij}|}{|V_{ij}|}.$$

Then our new RDME, subsequently called the CRDME, is

$$\frac{dP_{i,j}}{dt}(t) = \left(D^{\mathrm{A}}\Delta_h^{\mathrm{A}} + D^{\mathrm{B}}\Delta_h^{\mathrm{B}}\right) P_{i,j}(t) - \lambda\phi_{ij}P_{i,j}(t).$$

- Diffusion is the same as the RDME, molecules hop from a voxel to a neighbor with rate D/h^2.
- Molecules in voxels i and j may react with rate $\lambda\phi_{ij}$.

Still has the form of a master equation, so for many-molecule systems we can generate exact realizations of the corresponding stochastic process with the SSA!

What else is needed to simulate general biochemical systems?

Bimolecular reactions:

- When two molecules bind, where to place the product?
  - We use center of mass, consistent with continuous model.
- When two molecules unbind, where to place the products?
  - We developed a detailed balance preserving discretization for general bounded domains.

Unstructured meshes for complex geometry:

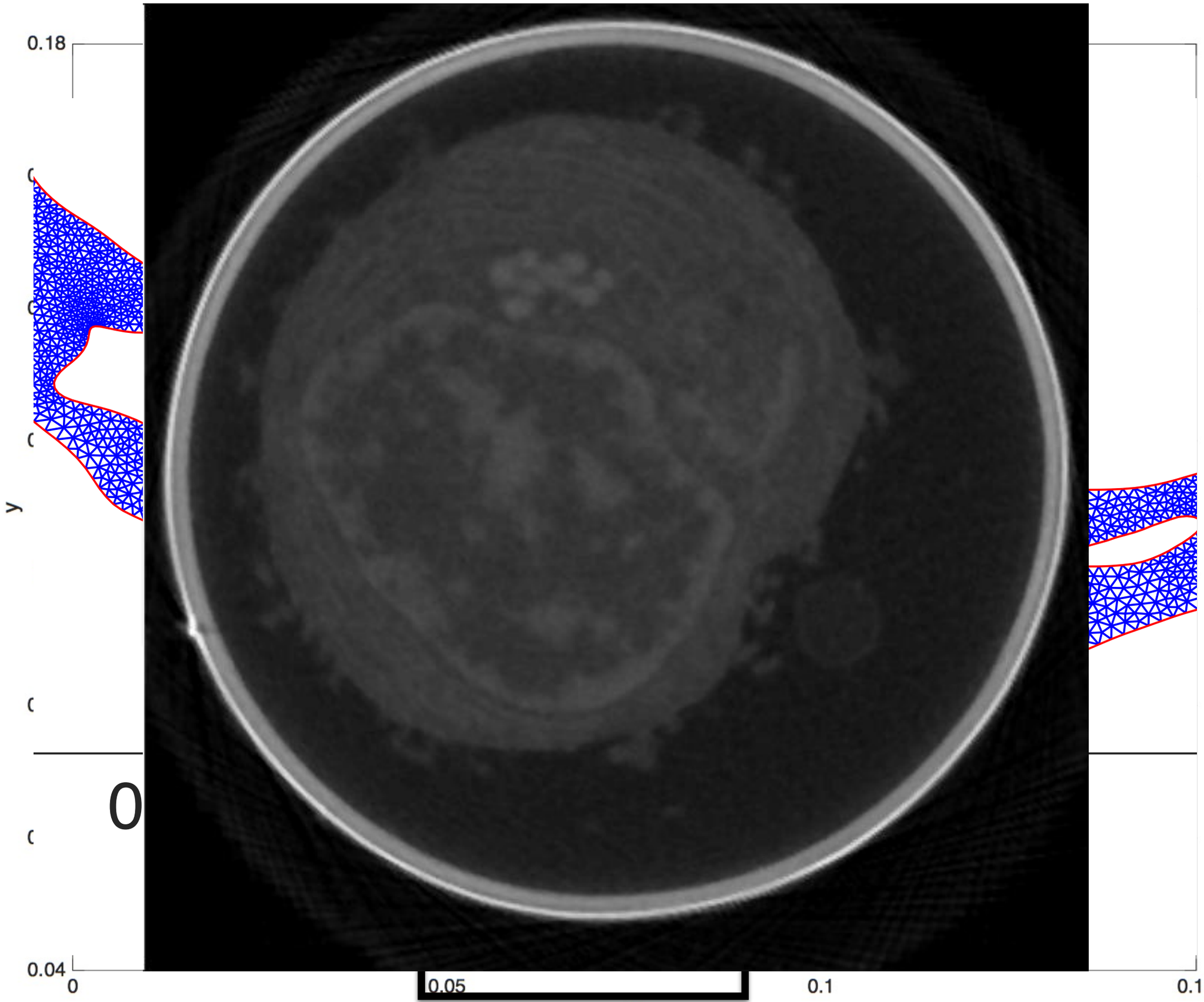
- We extend the CRDME to handle bimolecular reactions on general polygonal meshes using Finite Volume discretization methods.
- Spatial hops determined by Finite Element Method of Engblom et al (2009).

Extensions to allow for more general reaction functions:

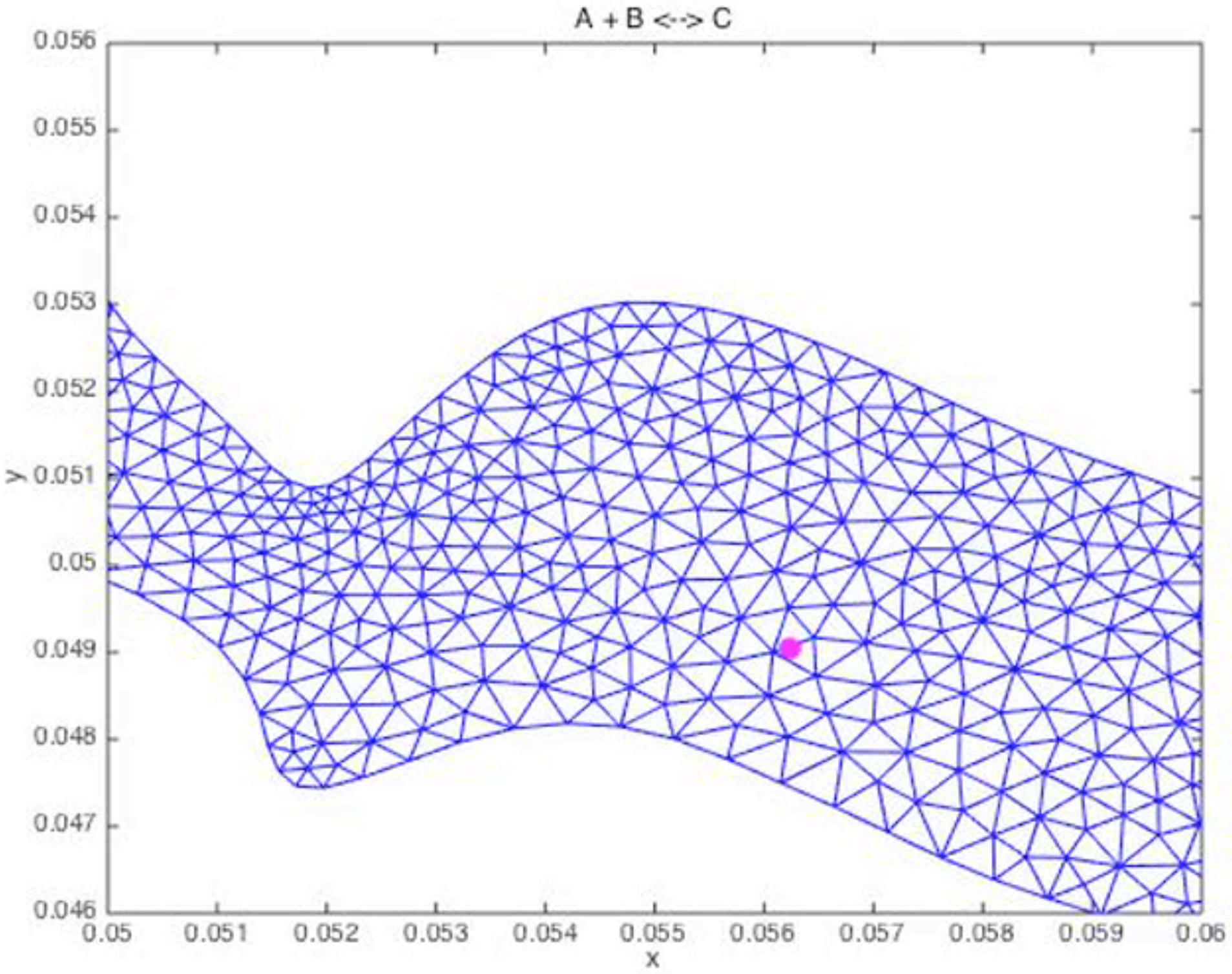
- Can extend to general interaction functions in separation of reactants.
- We are applying this to membrane models of T cell receptor signaling, where reactions occur between unstructured cytosolic tails of proteins.

See "A novel SPR assay for tethered enzymatic reactions with application to the tyrosine phosphatase SHP-1", Goyette et al, in review (2016).

How are we using the CRDME with cellular geometries?

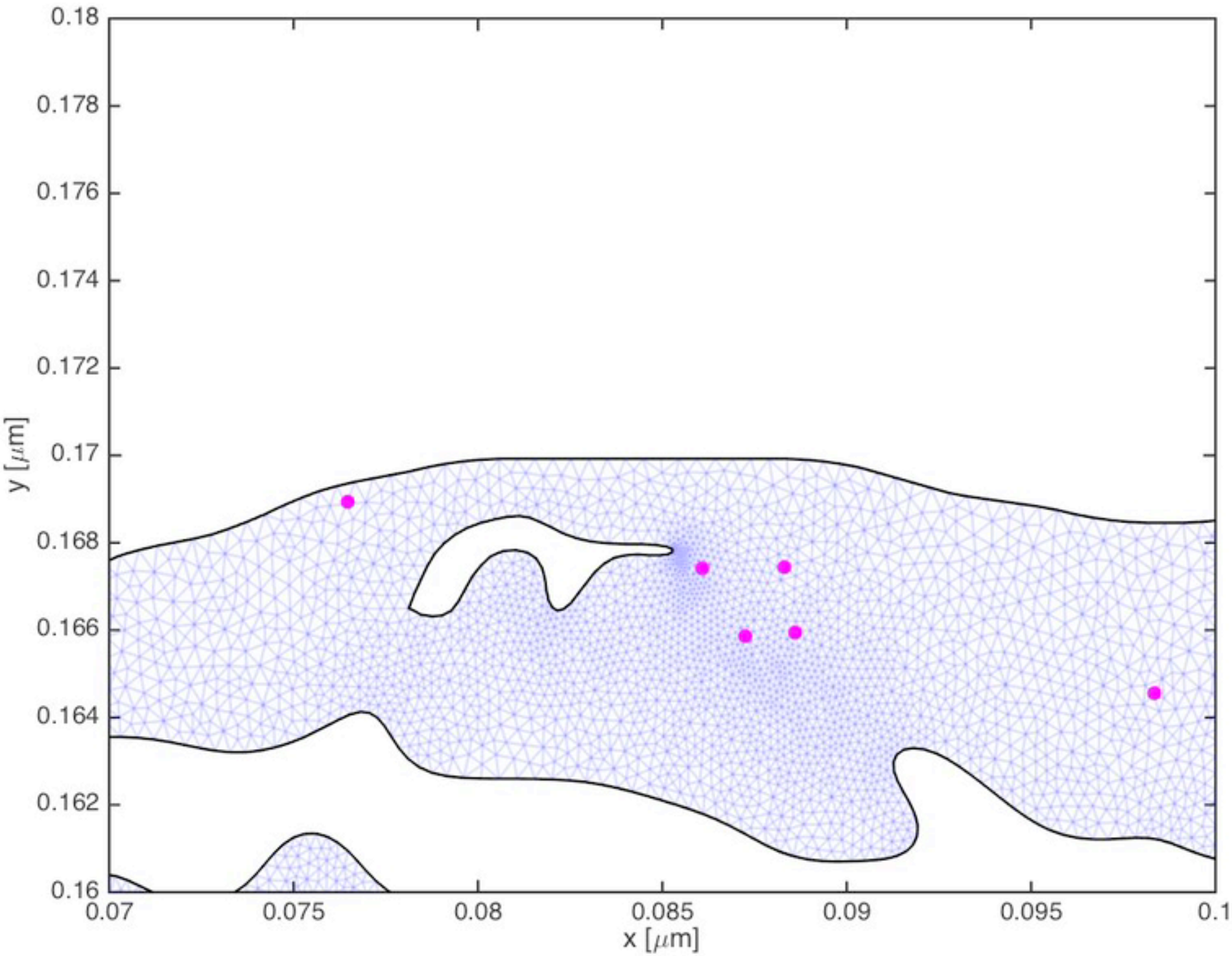


How are we using this with cellular geometries?



How are we using this with cellular geometries?

$$A + B \leftrightarrows C, \quad \varnothing \rightarrow C$$



What are some advantages of the CRDME?

- Provides a convergent, RDME-like approximation to the Doi model.
- Mathematically identical to the RDME, except bimolecular reactions can occur for molecules in neighboring voxels.
  - Can therefore reuse many extensions of the RDME (i.e. methods for complex geometries, improved SSAs, AMR methods, multiscale couplings...)
- RDME converges to CRDME as the lattice spacing is *coarsened*.
- Allows for an alternative "multiscale" approach. Instead of coupling RDME to continuous-space particle methods, use non-uniform meshes / AMR to achieve desired accuracy.

What are some disadvantages of the CRDME vs. RDME?

- More reaction channels to resolve.

For general many-particle formulation in N-dimensional space, and implementation details in 2D see:
"A Convergent Reaction-Diffusion Master Equation", S. A. Isaacson, J. Chem. Phys. 2013.
Available at: http://math.bu.edu/people/isaacson/

Acknowledgements

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  - Hosting me in their lab Fall 2014.
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- NSF and NIH for support.

Thank you for coming and inviting me!

See Isaacson, J. Chem. Phys. 2013 for details on the CRDME.