Stochastic Simulation of Spatially-Distributed Models Arising in the Life Sciences

(with a focus on applications to modeling cellular processes)

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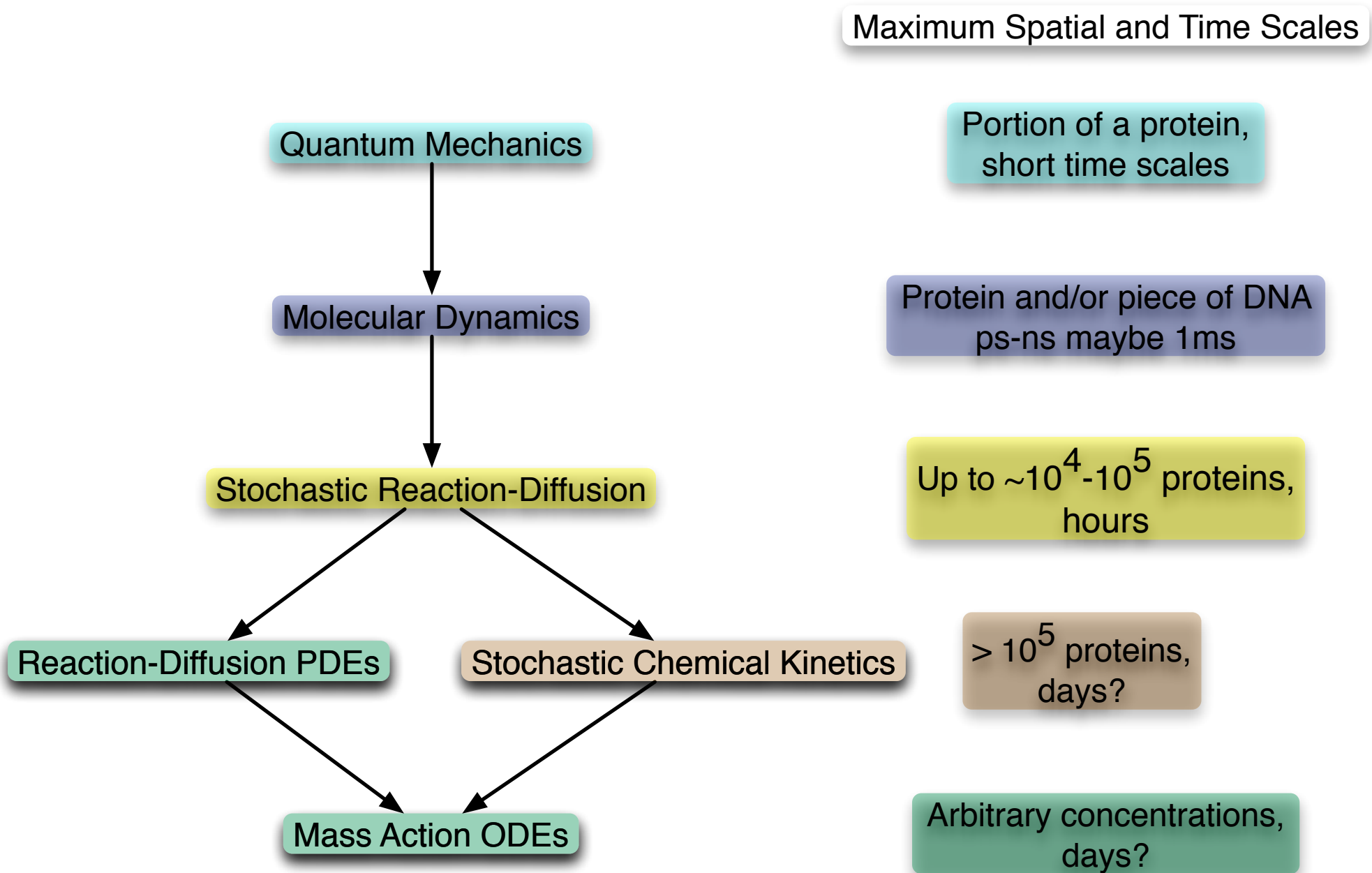
How might we model biochemical processes within cells?

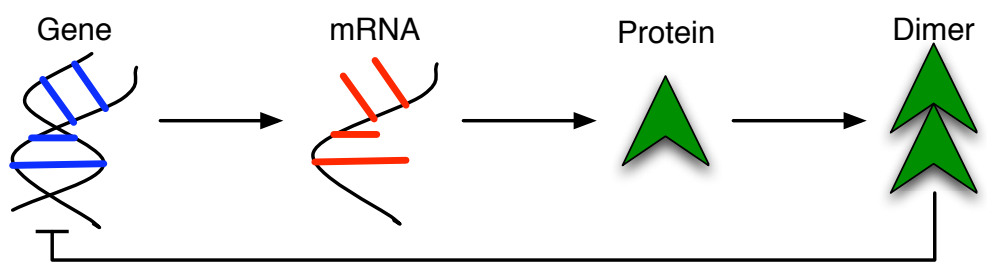


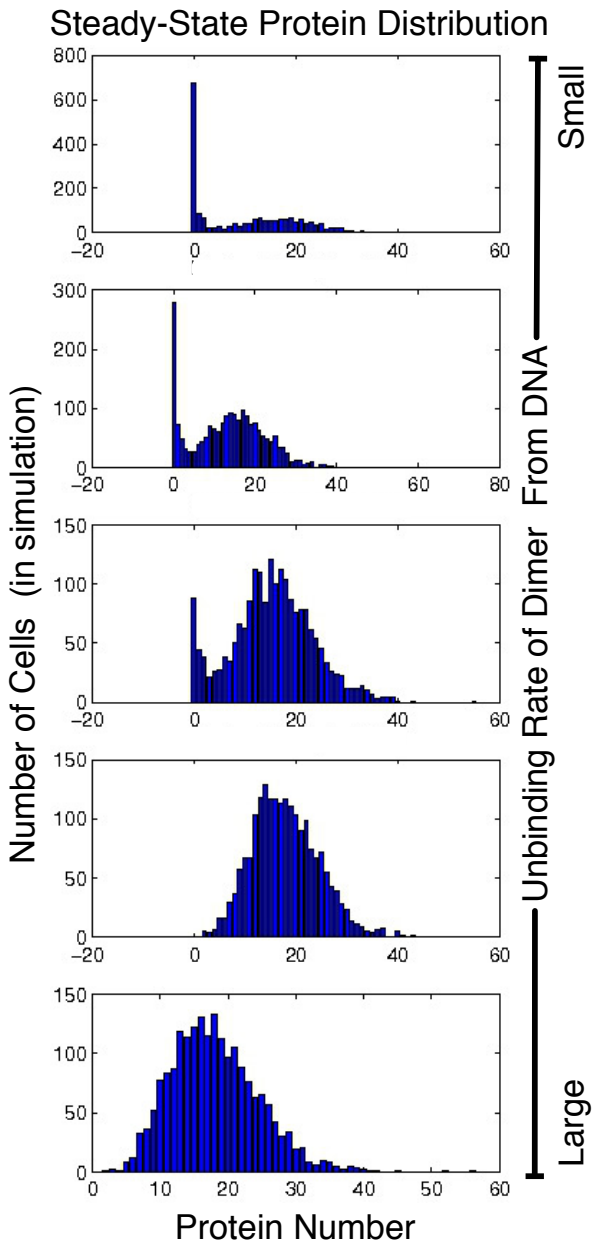
Outline of tutorial:

- **Why model stochasticity in the chemical reaction process and the explicit spatial movement of proteins and mRNAs?**
- What are the types of particle-based stochastic reaction-diffusion models that have been used to study biological systems at the scale of individual cells?
- How can we numerically simulate these models?
  - What are some of the tradeoffs in using particular simulation methods?
- What are some biological systems to which these models have been applied?

Why is stochasticity in biochemical reactions important?

- Present in many cellular processes. Evolution.
- Arises from discreteness of chemical species populations.
- For example, gene expression.
  - Seen experimentally and theoretically.
  - See Arkin, Collins, Elowitz...
- Can serve useful biological purpose. See, for example, competence in *Bacillus subtilis*.





How do proteins and mRNAs move within cells?

1. Diffusion

- Occurs in cytosol and nucleus
- Used by transcription factors to find DNA binding sites.
- Often coupled with reaction, *i.e.* diffusion to membrane and scaffolding bound objects.
- Rates from ~ .01 to 100μm^2 per sec

Vargas *et al.* PNAS 2005

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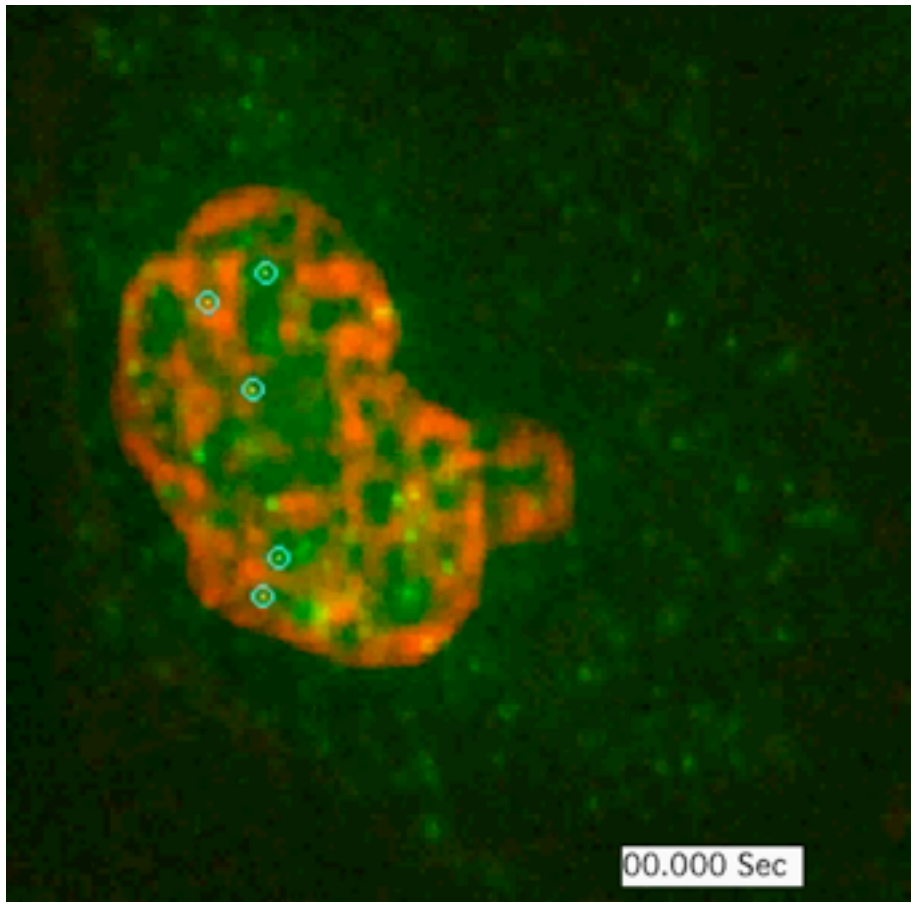

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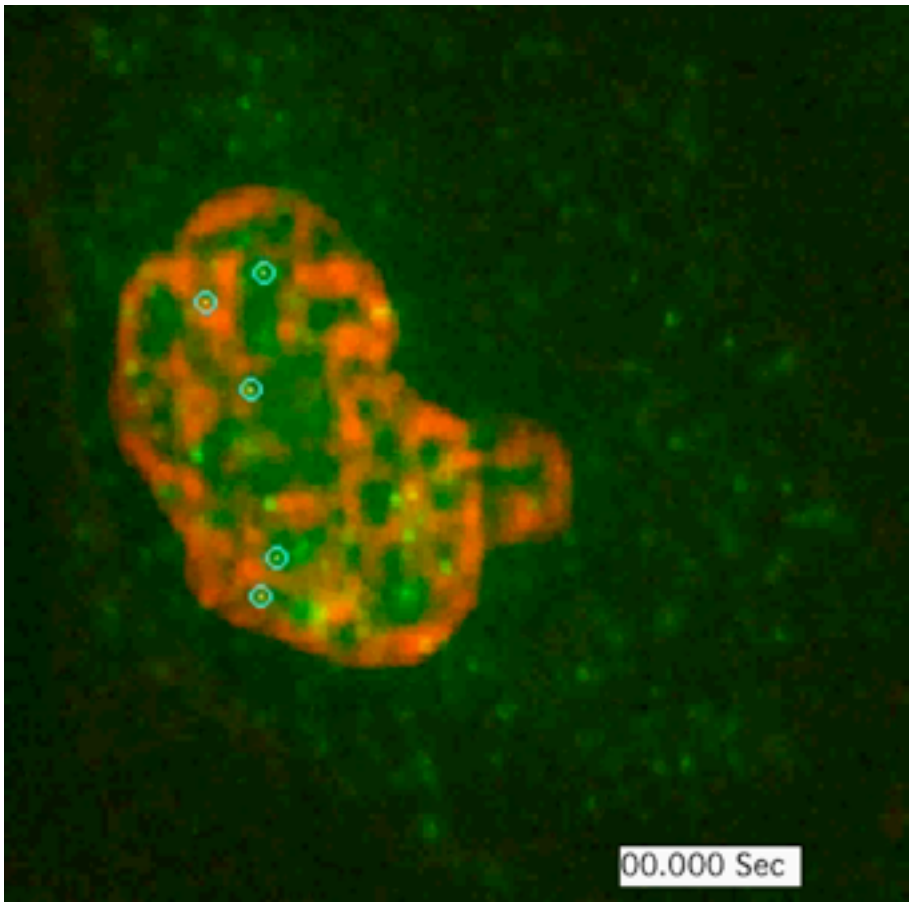

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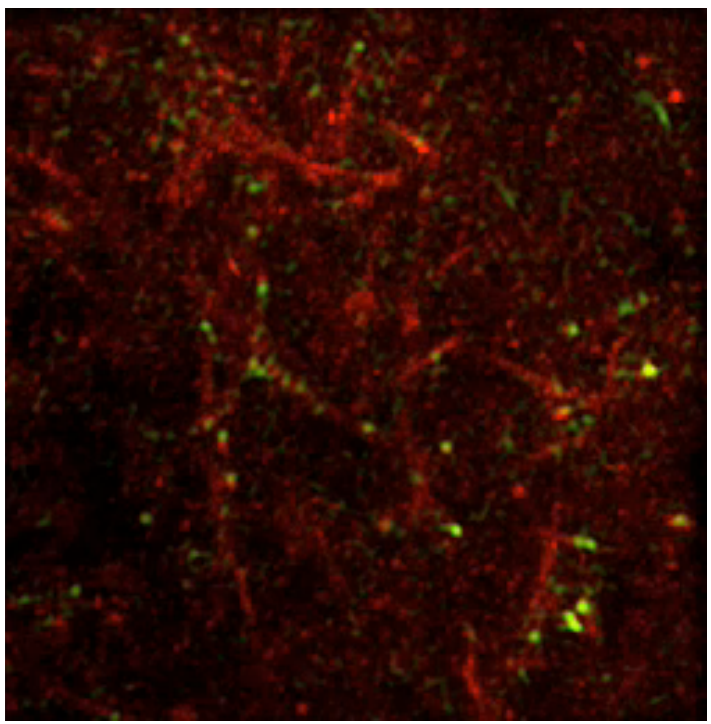

M. Gustafsson, HHMI Website.

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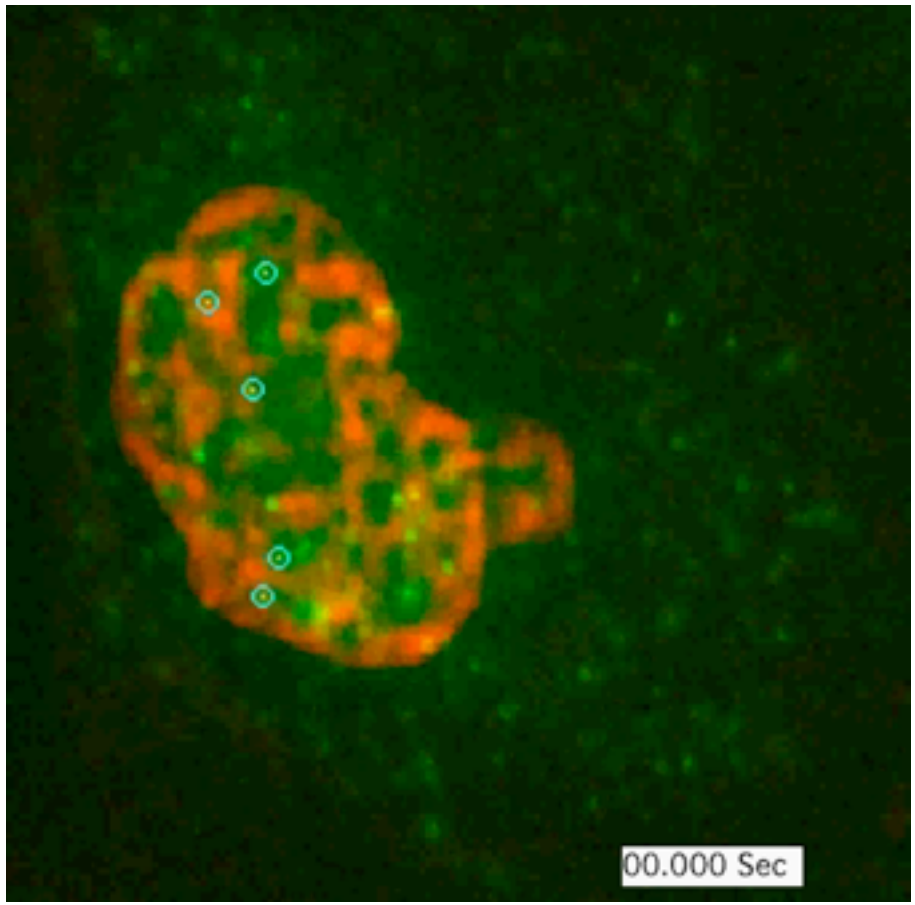

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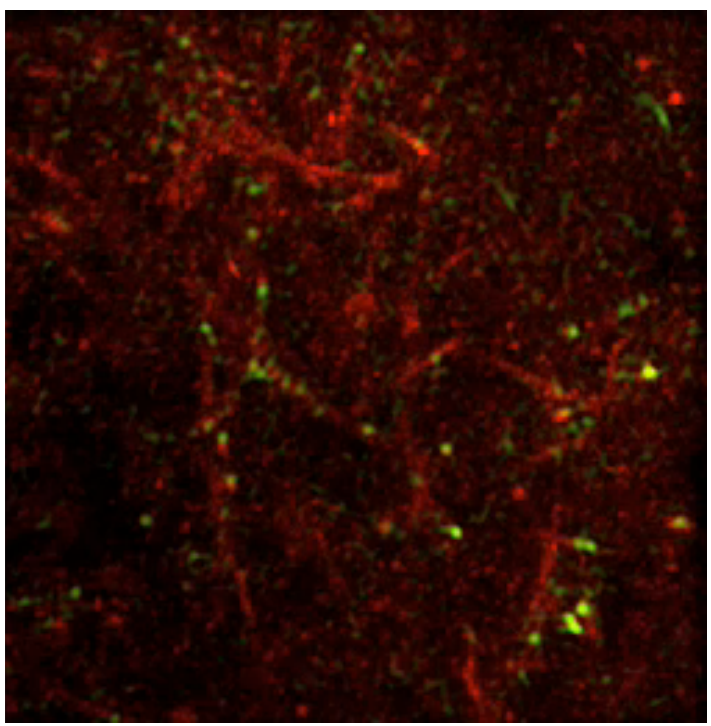

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We focus on diffusion today.

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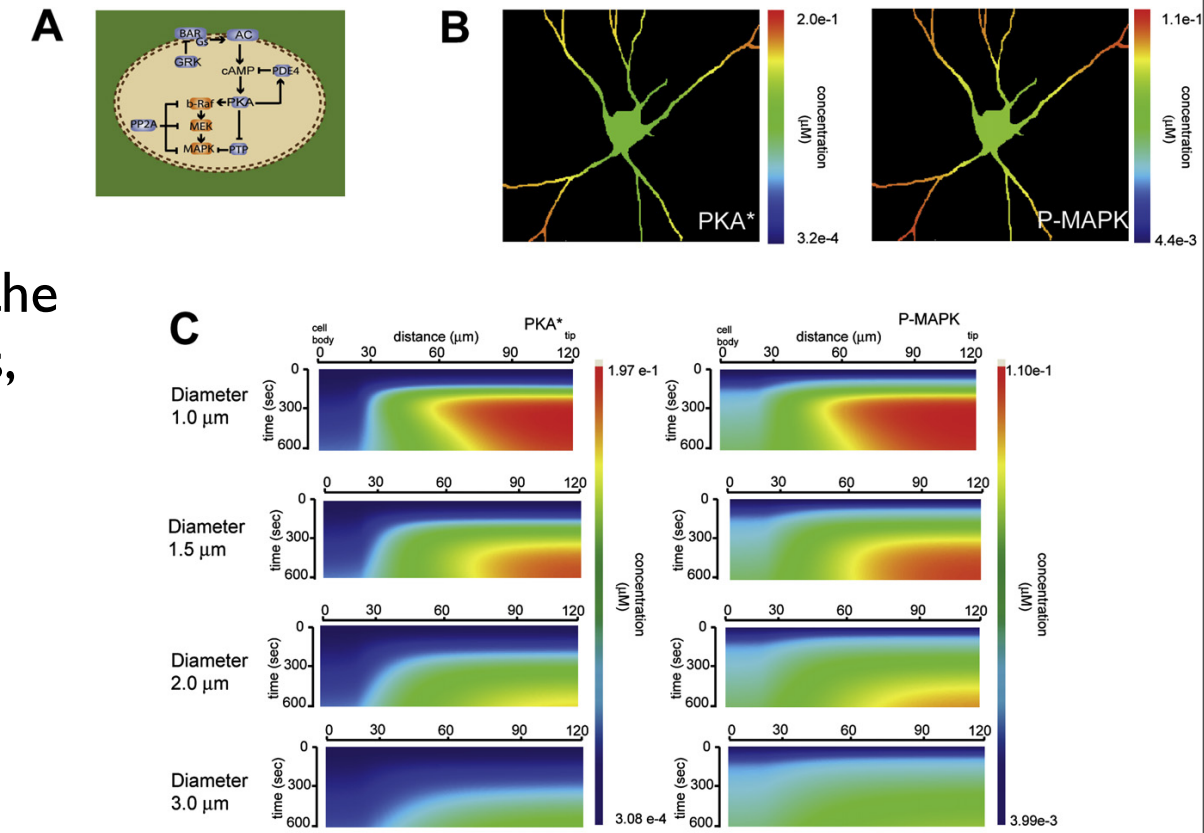

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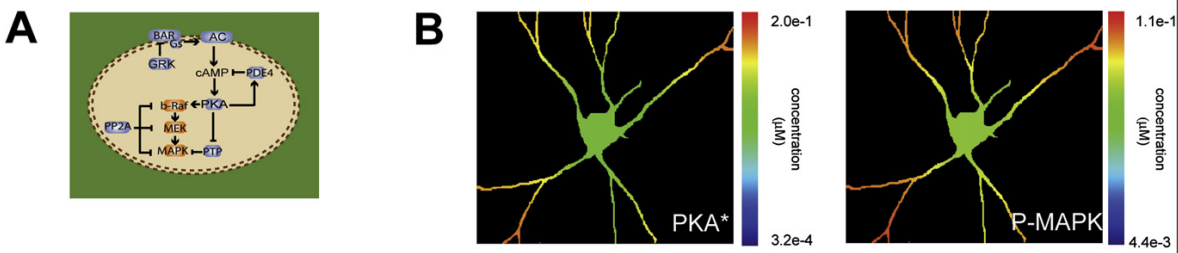

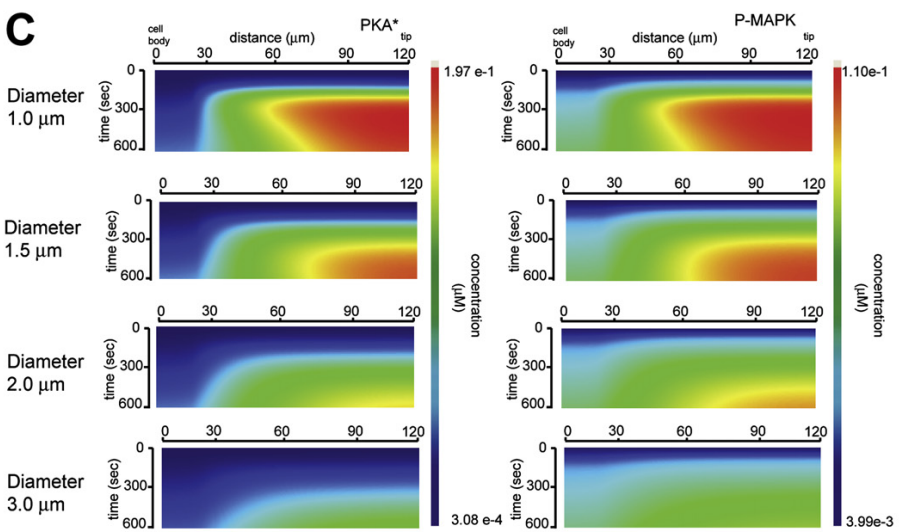

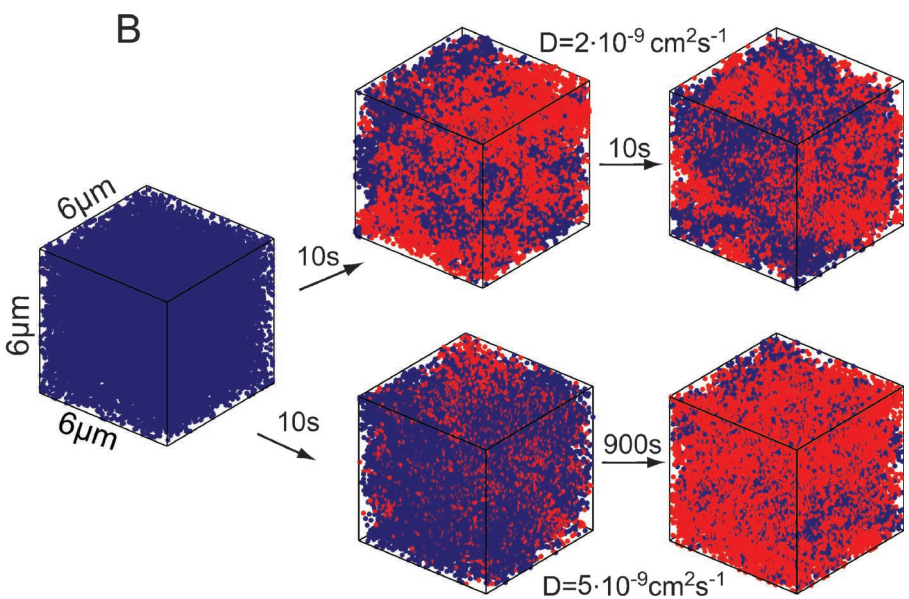

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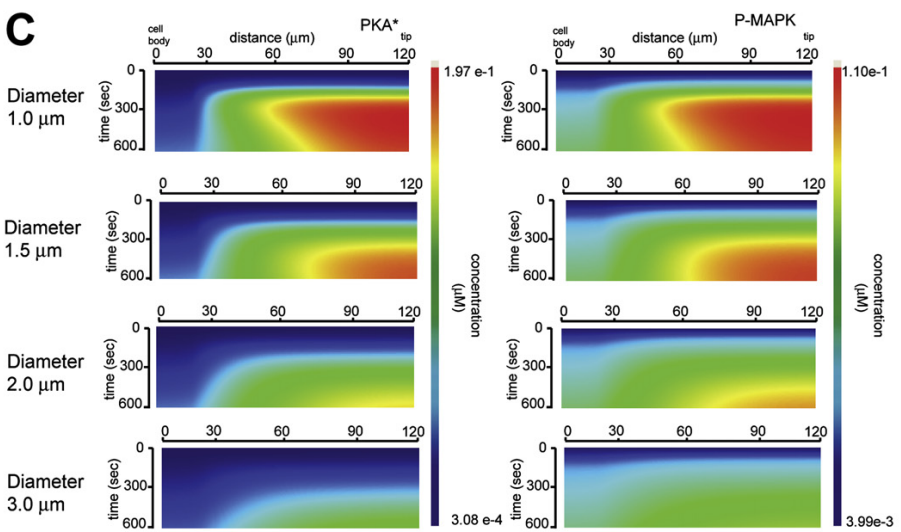

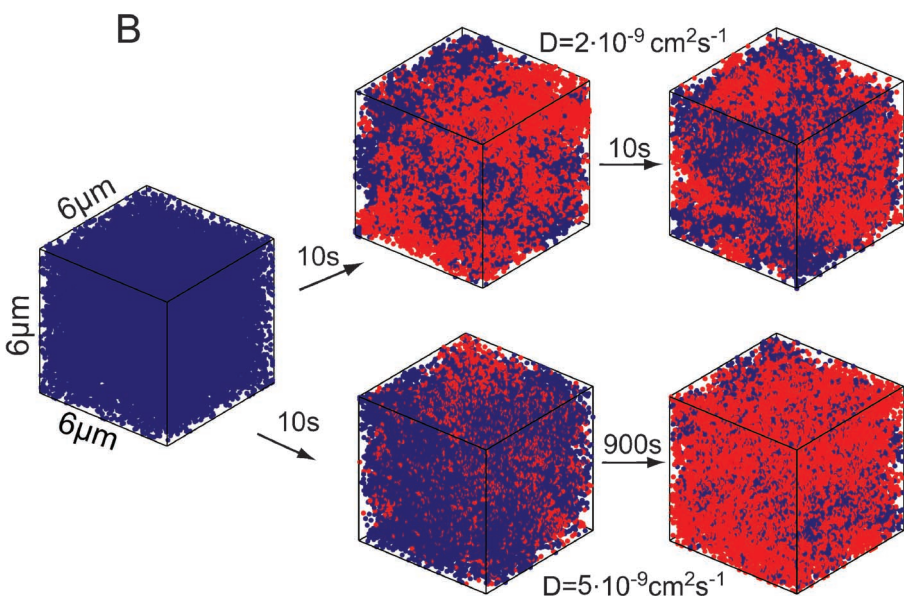

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Cells are not spatially homogeneous test tubes!

What does the inside of a eukaryotic cell look like?

- This is an X-ray CT image of mouse olfactory epithelial cell.
- In this example a mouse cell is imaged inside a glass capillary.
- Pixel intensity is proportional to density of material in pixel.

Mouse Olfactory Epithelial Cell

X-ray CT data courtesy, C. Larabell.

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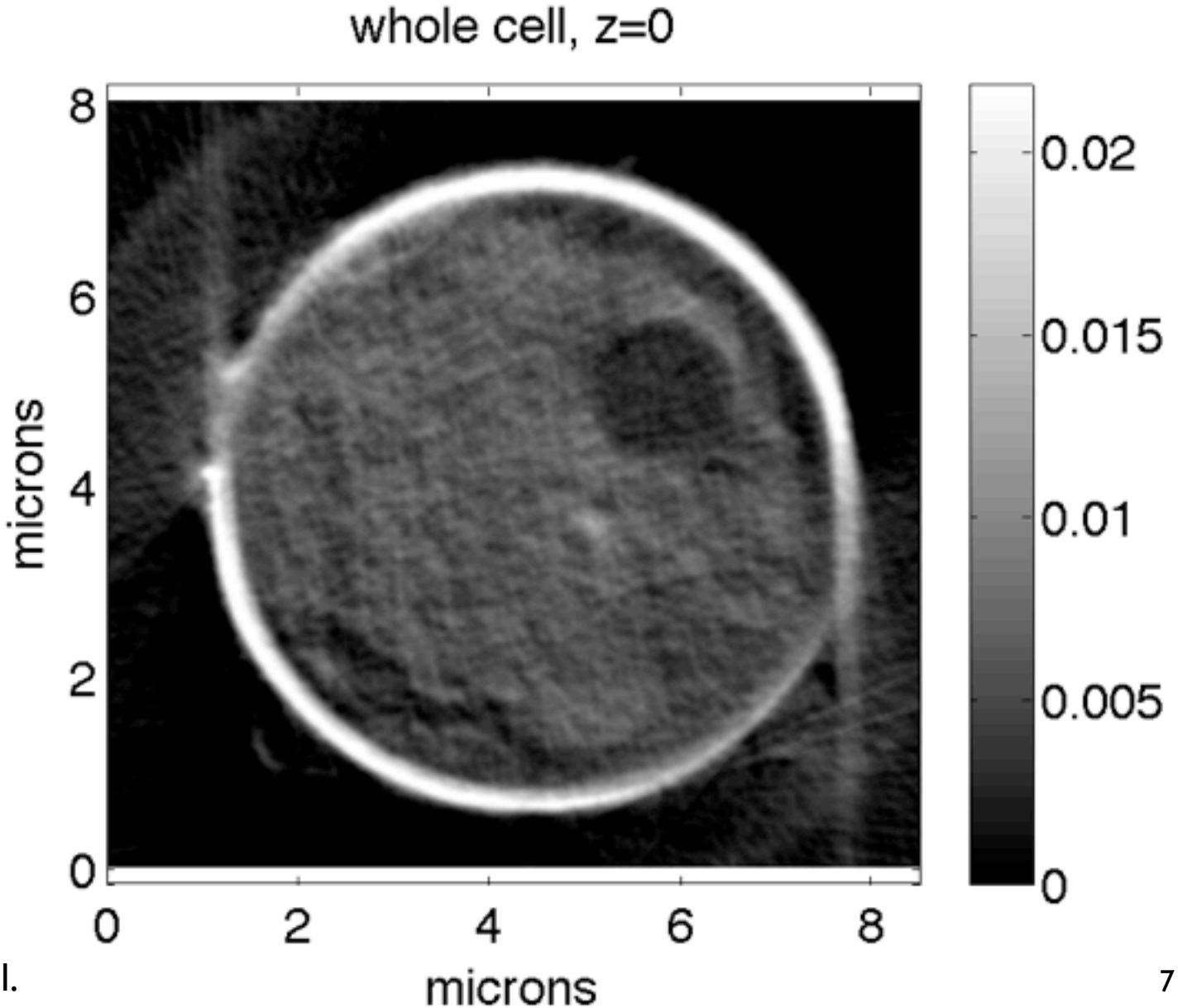

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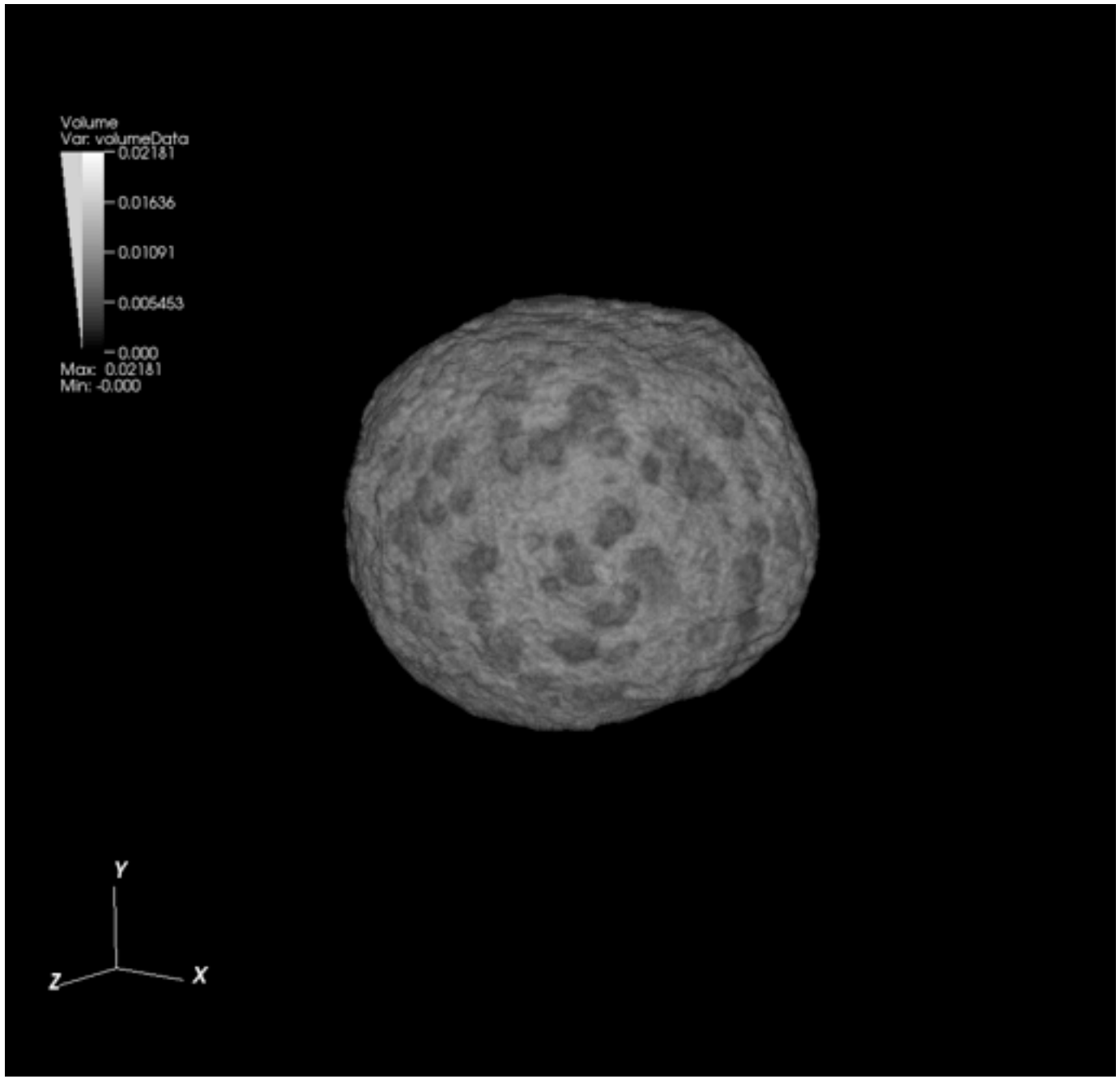

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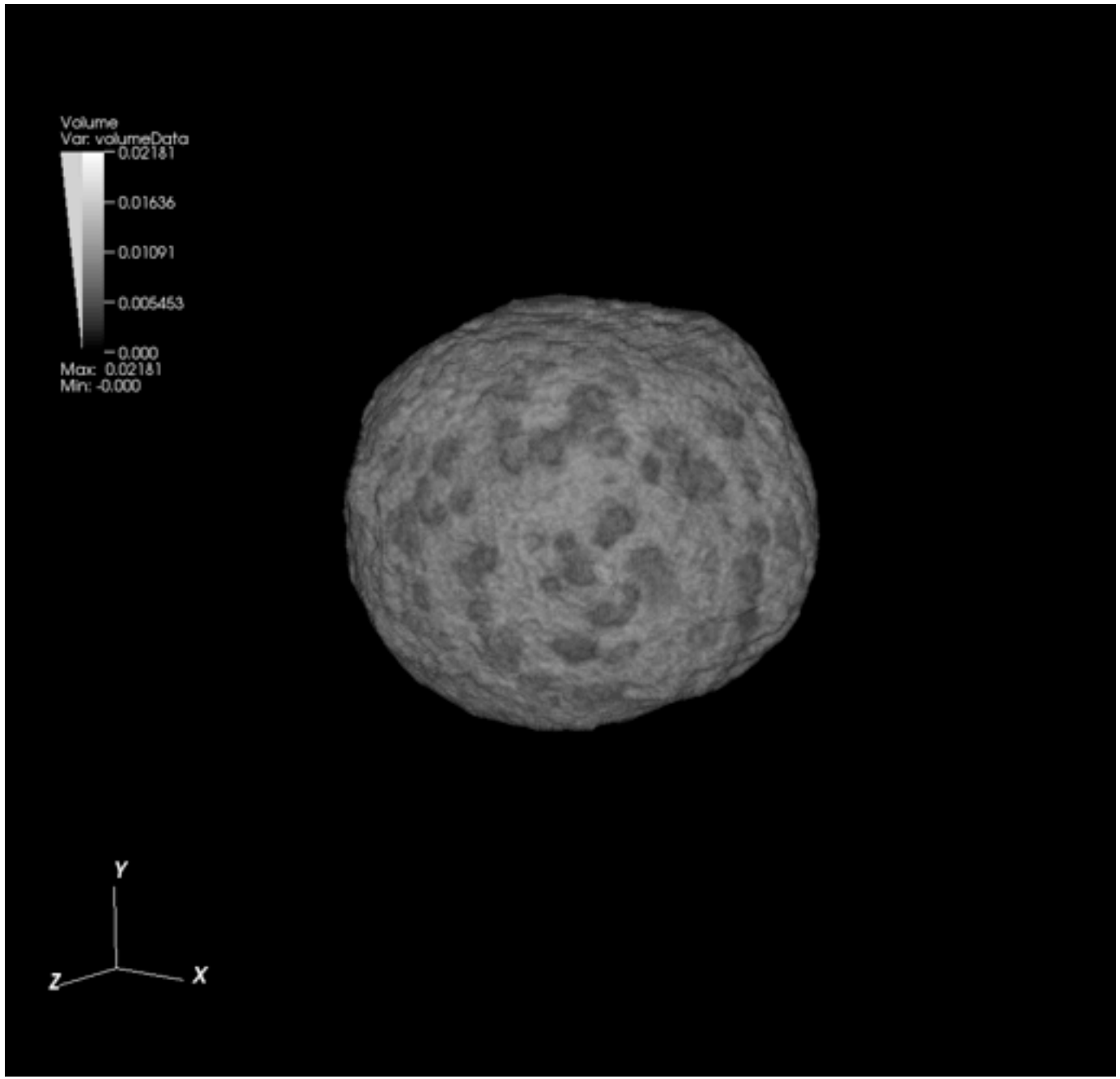

So cells have very complex internal structures!

What might a stochastic reaction-diffusion simulation look like?

Protein (blue) searching for binding site (red) in nucleus of the last slide. (RDME simulation)

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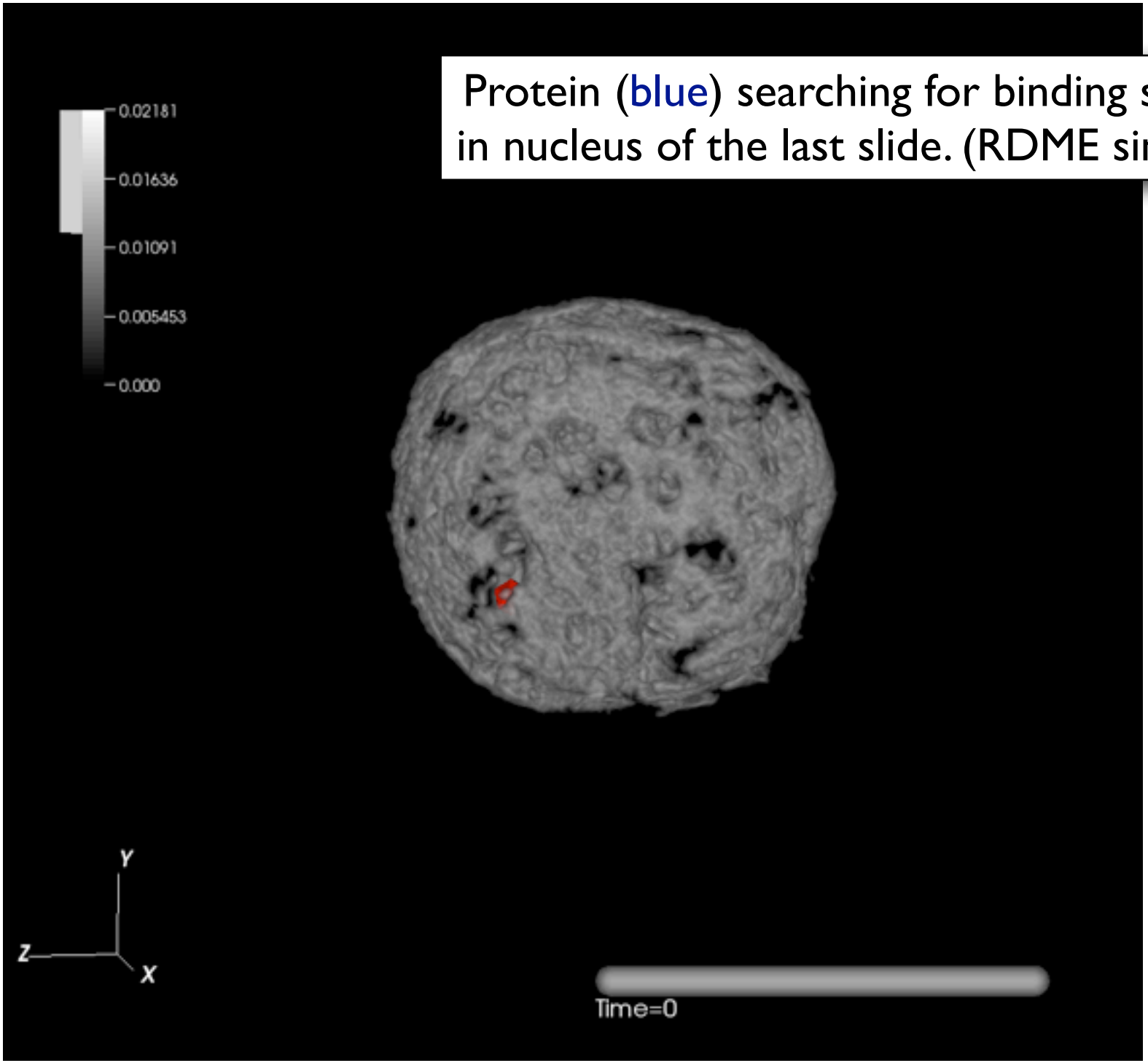
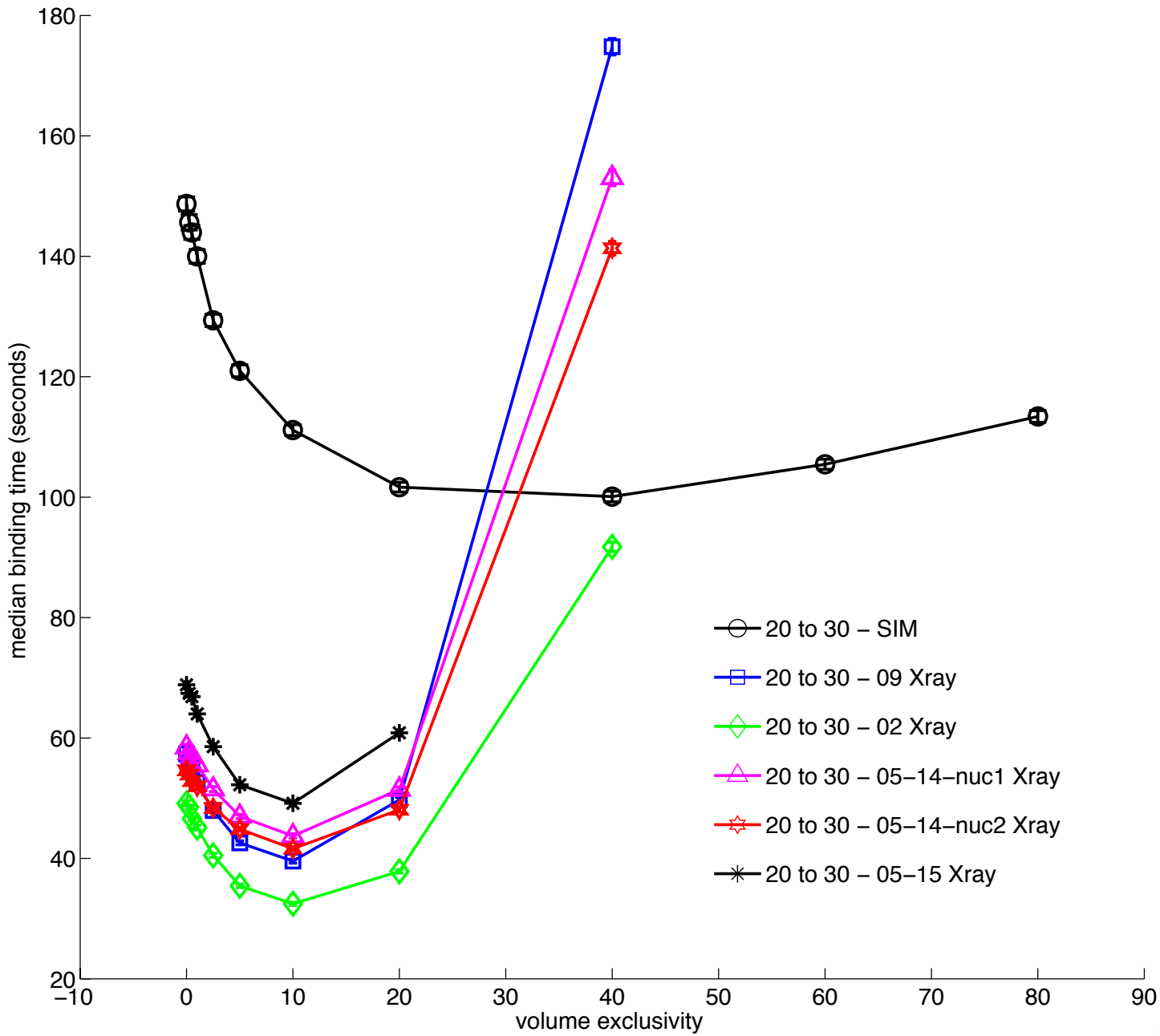


How does volume exclusion due to the varying density of chromatin influence the time needed for the protein to find the binding site?

- Binding site is a randomly placed in regions of euchromatin (low chromatin density)



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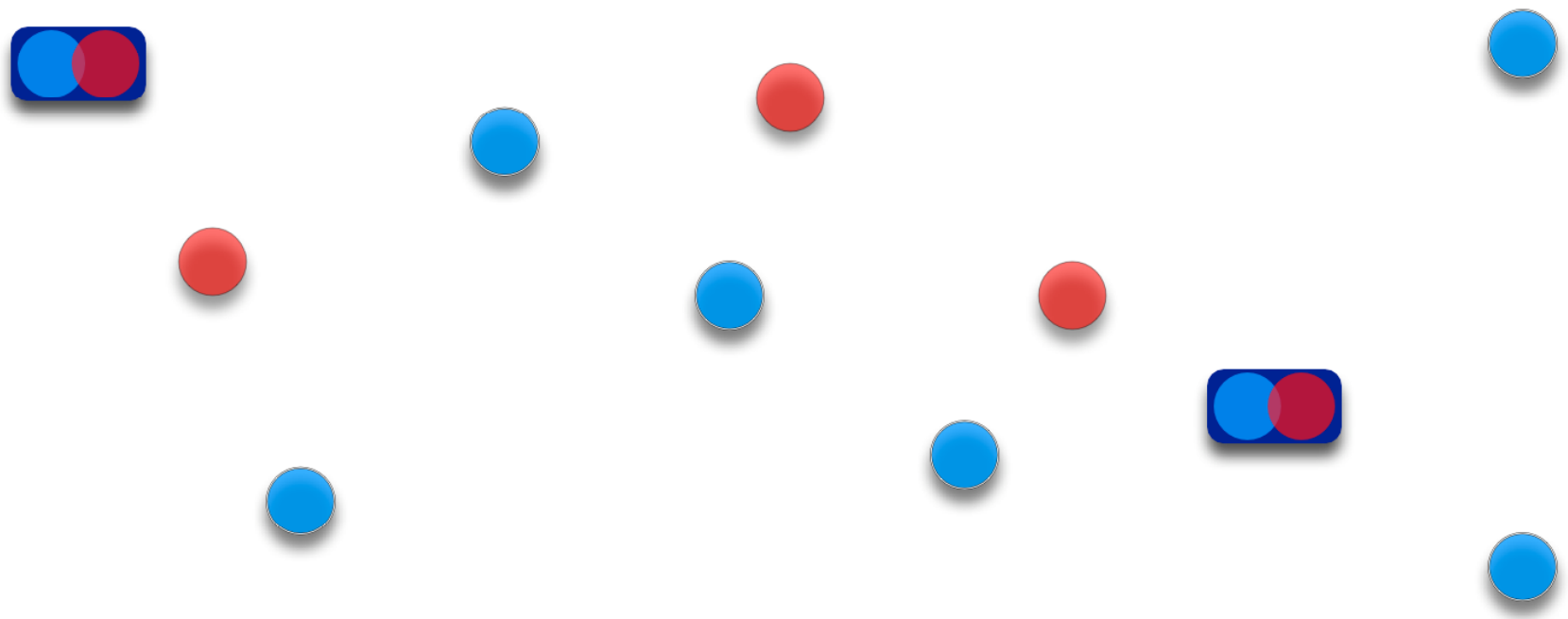
What are the three stochastic reaction-diffusion models?

1. Smoluchowski diffusion limited reaction model:
   - M. V. Smoluchowski, Z. Phys. Chem. (1917).
   - Particles diffuse in continuous space, react / react with some probability upon reaching a fixed separation (called the reaction-radius).
   - Particles can not move closer than the reaction-radius.
   - Mathematically, reactions are modeled through a boundary condition.



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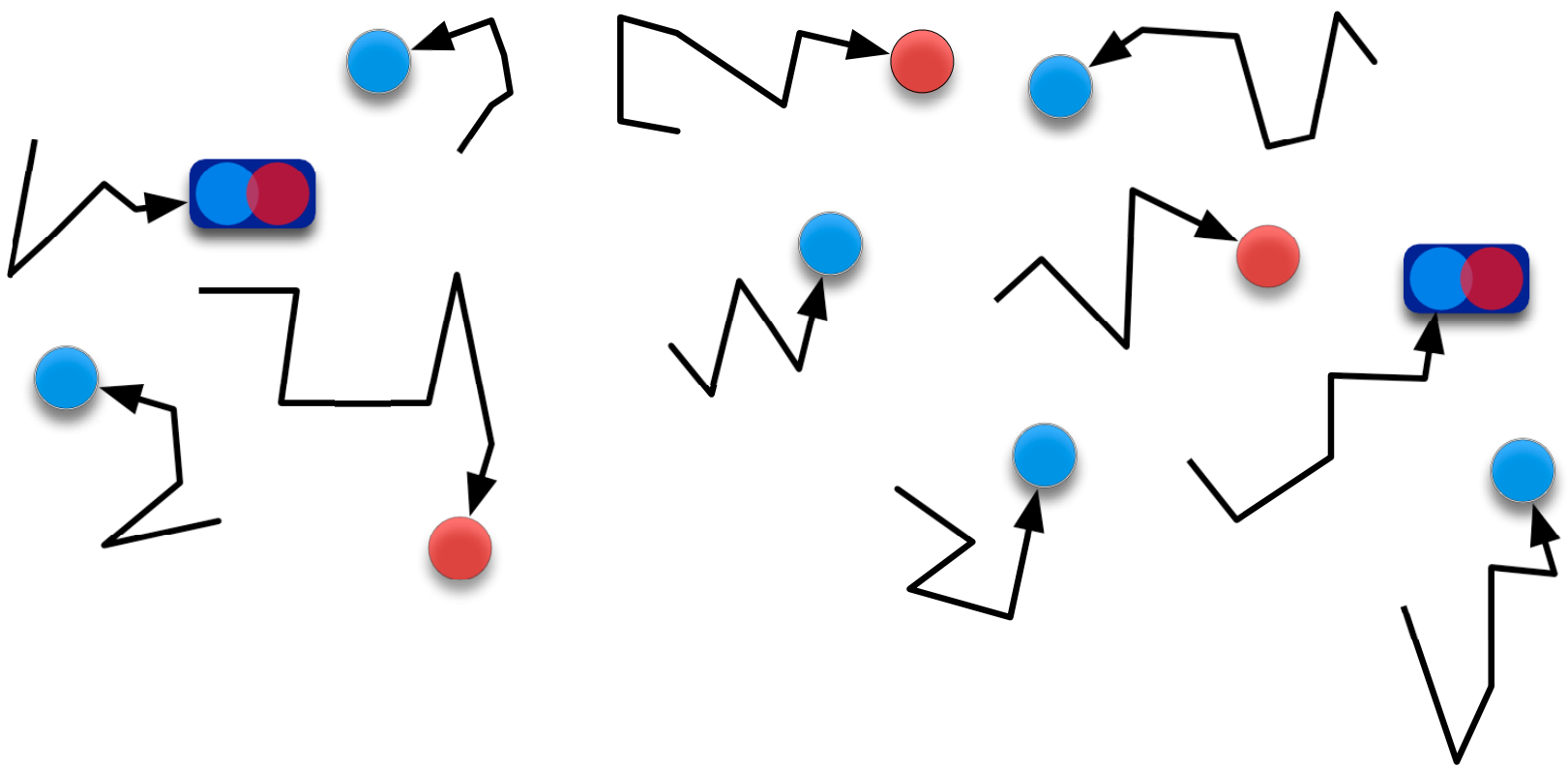

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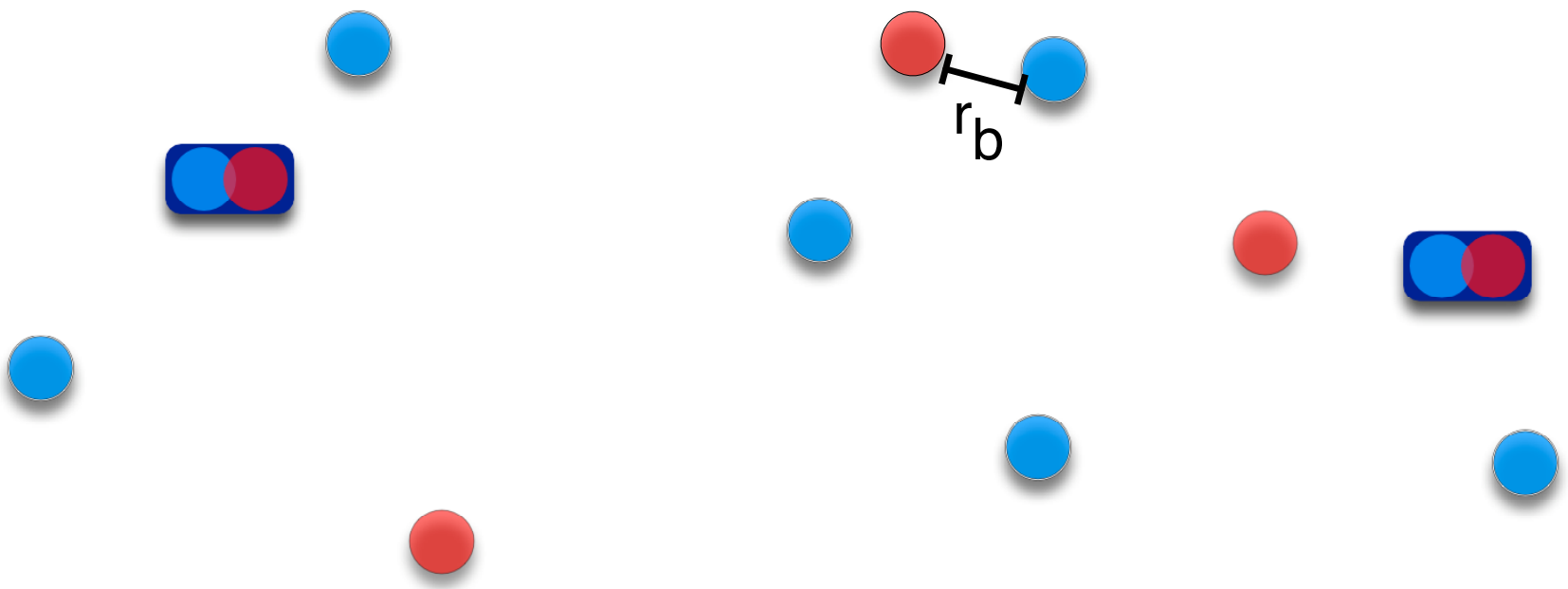

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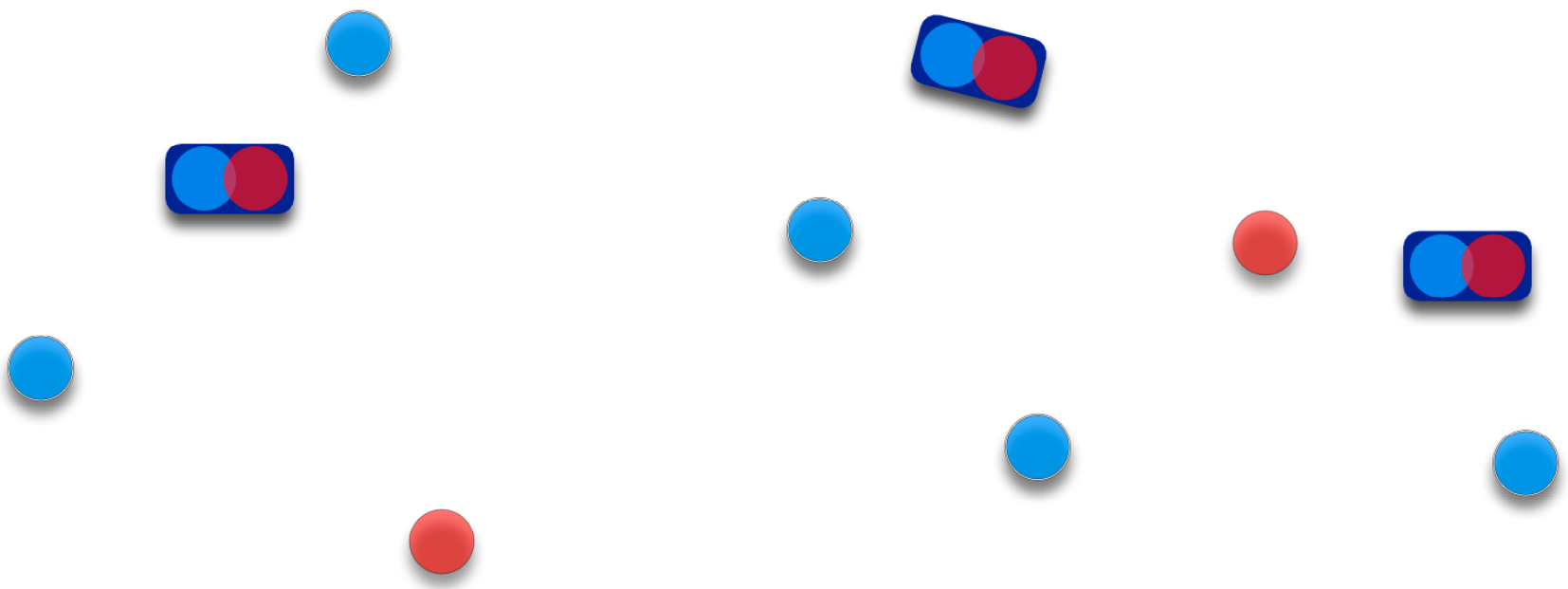

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2. Interaction function reaction model:
    - See Doi, *Stochastic Theory of Diffusion-Controlled Reaction*, J. Phys. A (1976).
    - Doi attributes the model to Teramoto and Shigesada, Prog. Theor. Phys. (1967).
    - Particles diffuse in continuous space, react with fixed probability per unit time when within a fixed reaction-radius.
    - Mathematically, reactions are modeled with an interaction function.
    - Will subsequently call the Doi model.

What are the three stochastic reaction-diffusion models?

3. Reaction diffusion master equation (RDME):
   - Goes back to the work of Gardiner, J. Stat. Phys. (1976).
   - Space is discretized into a collection of voxels, and particles undergo a continuous-time random walk between voxels.
   - Particles assumed "well-mixed" within each voxel.
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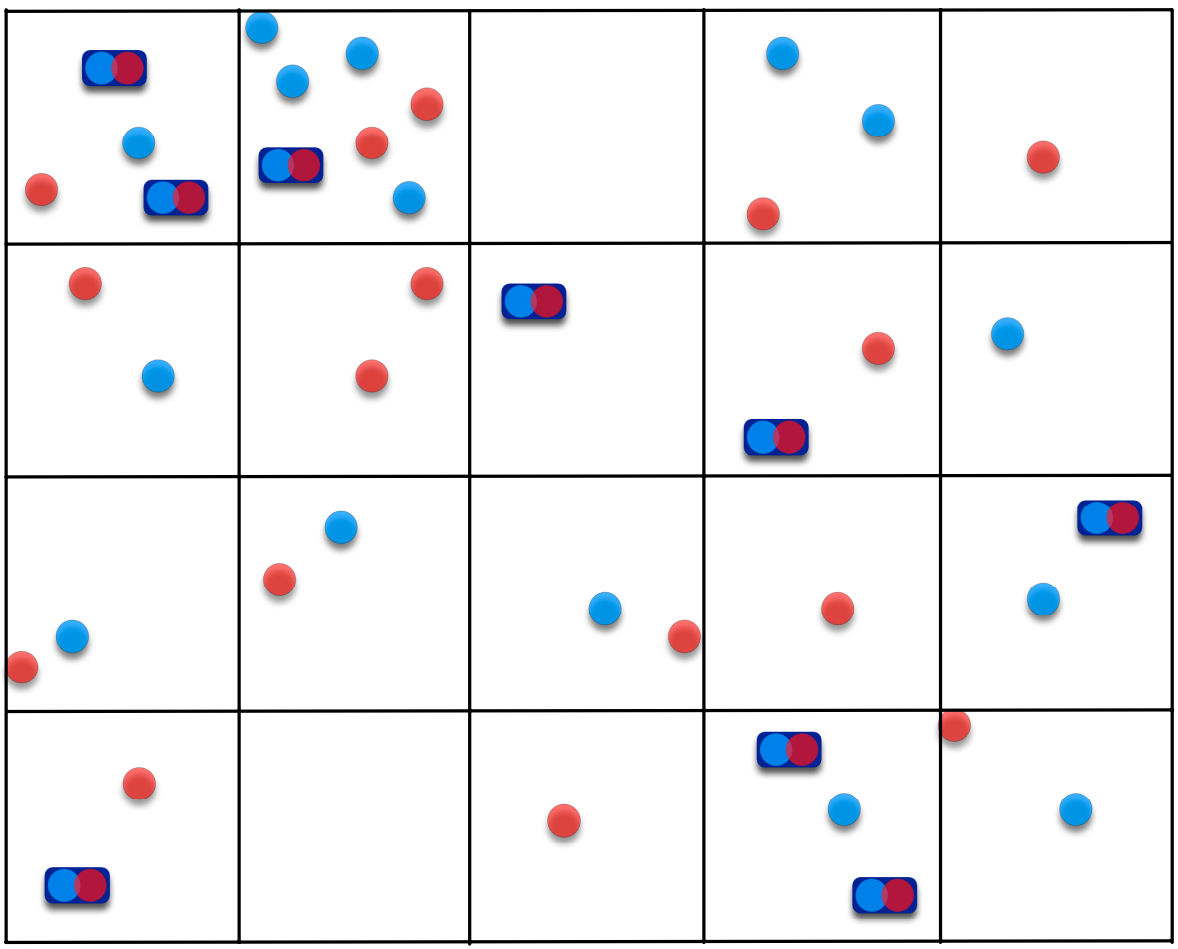

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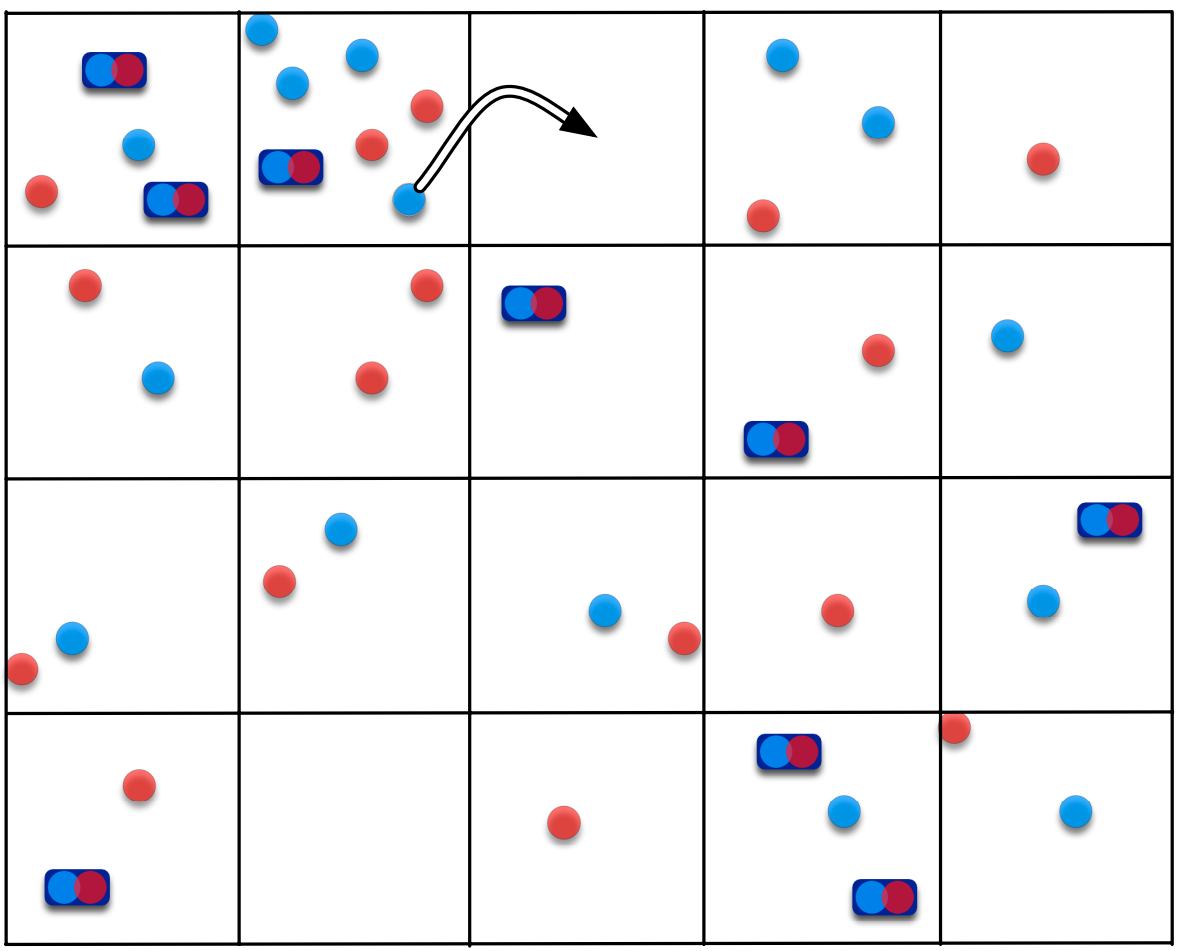

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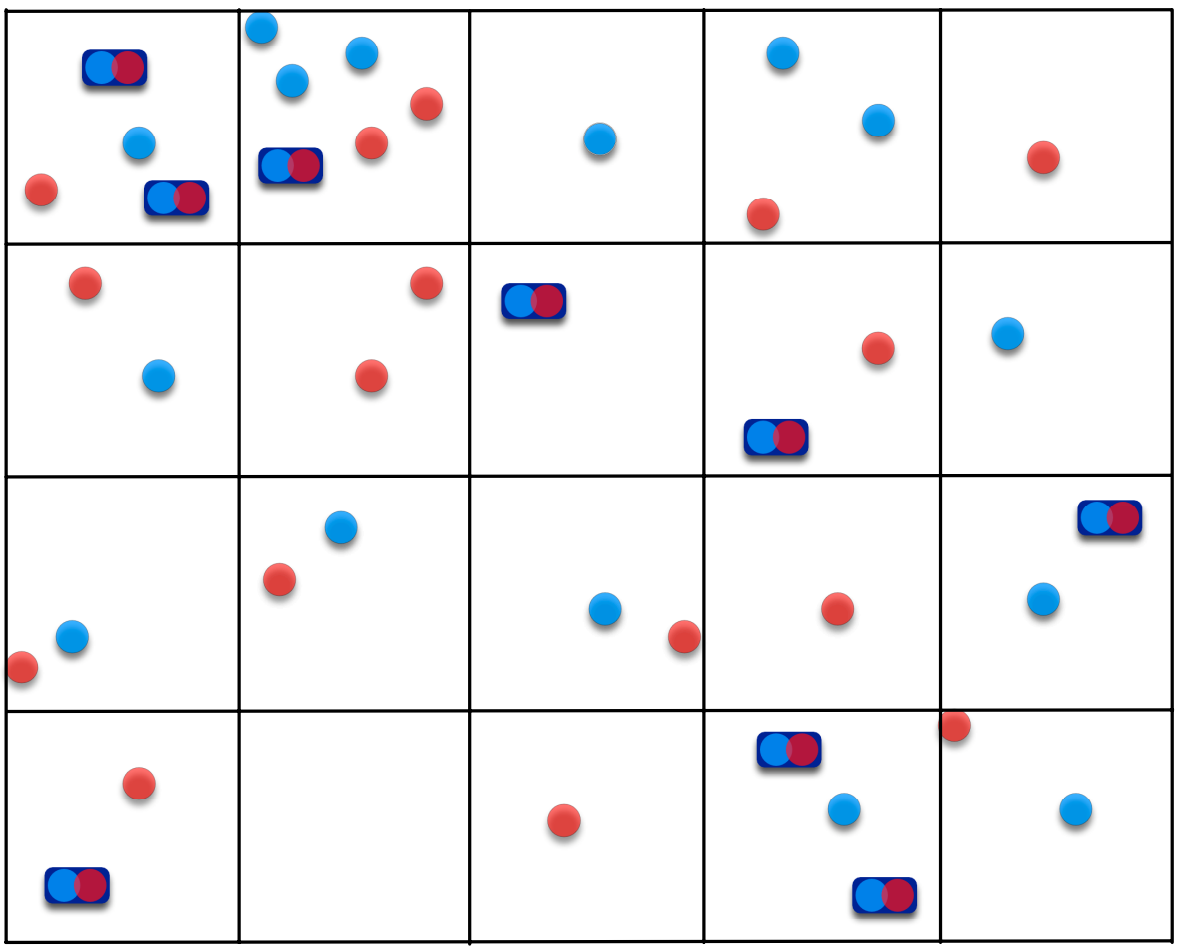

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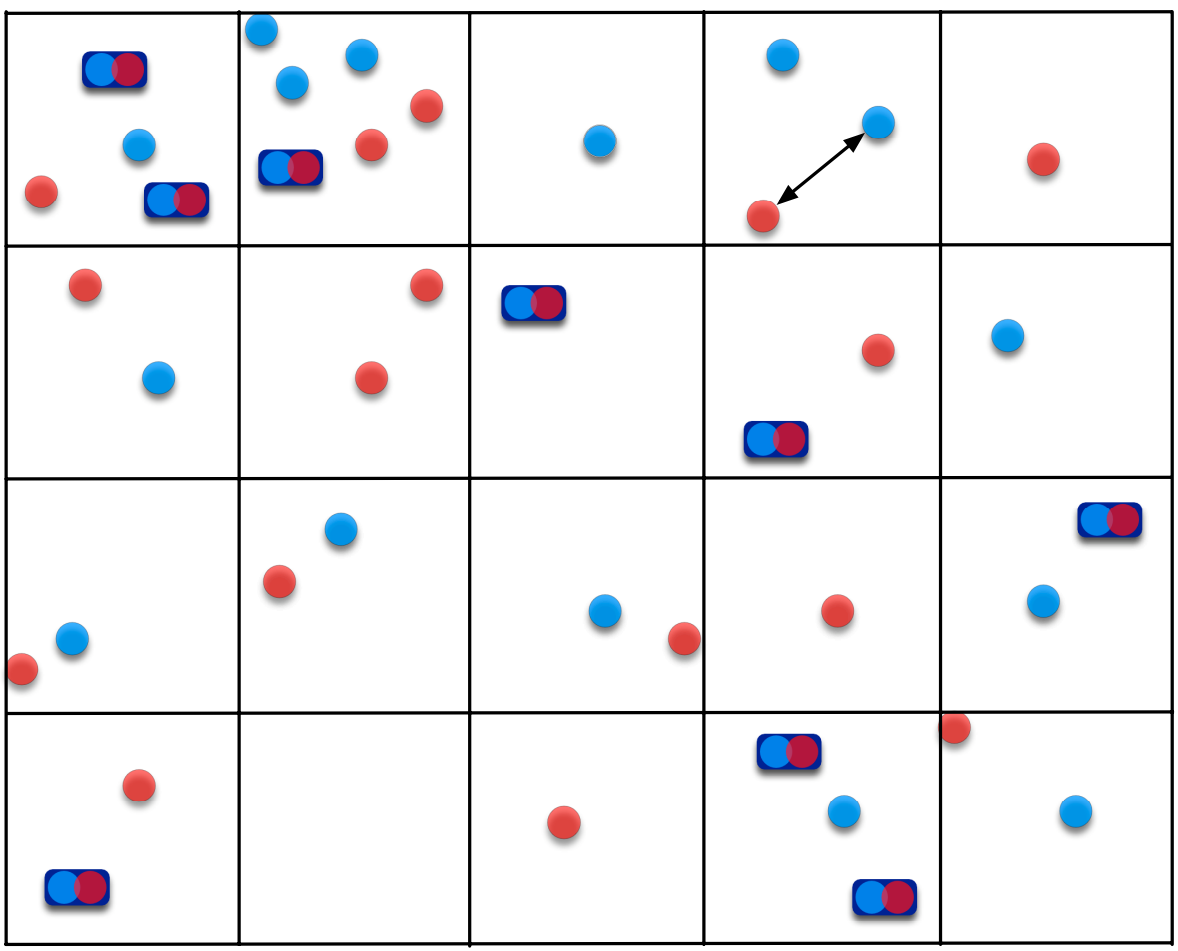

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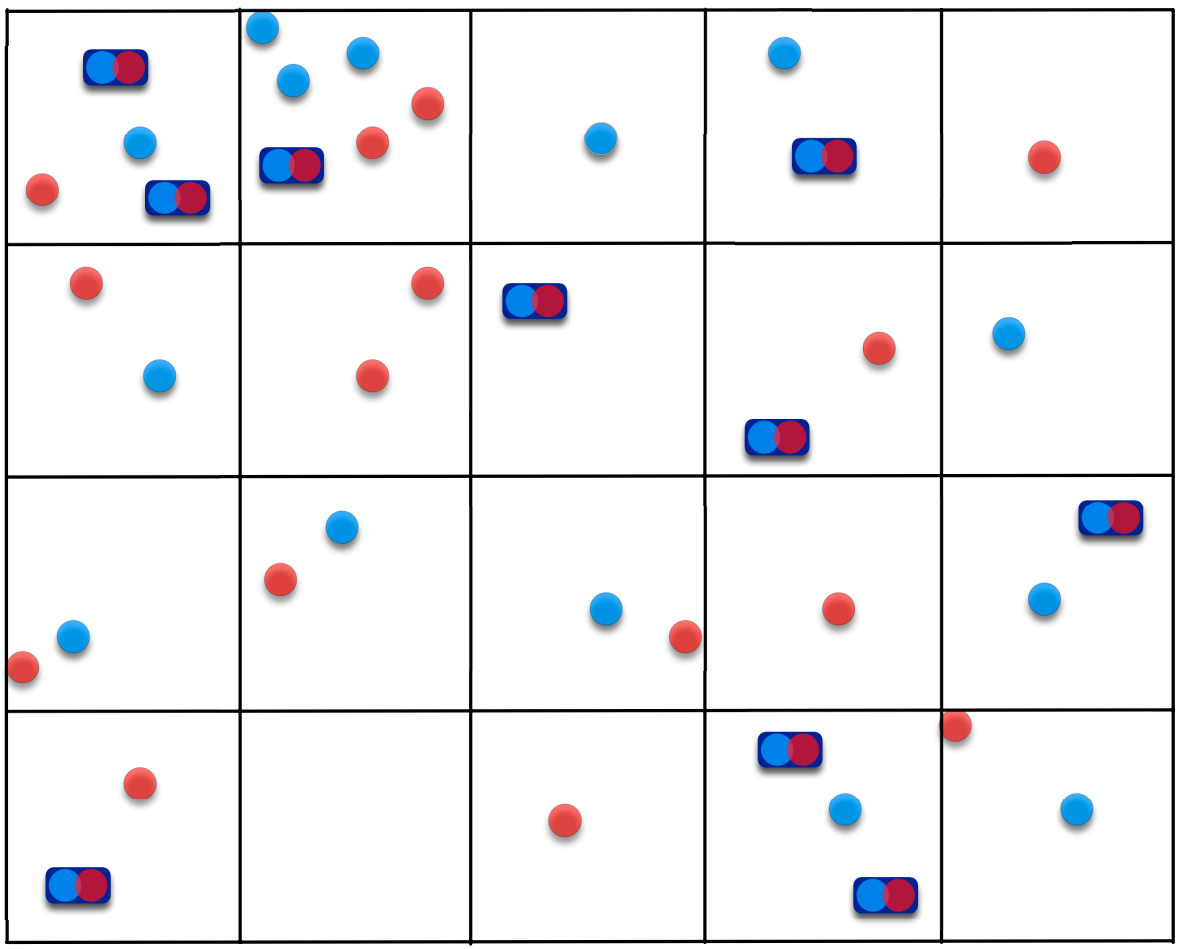

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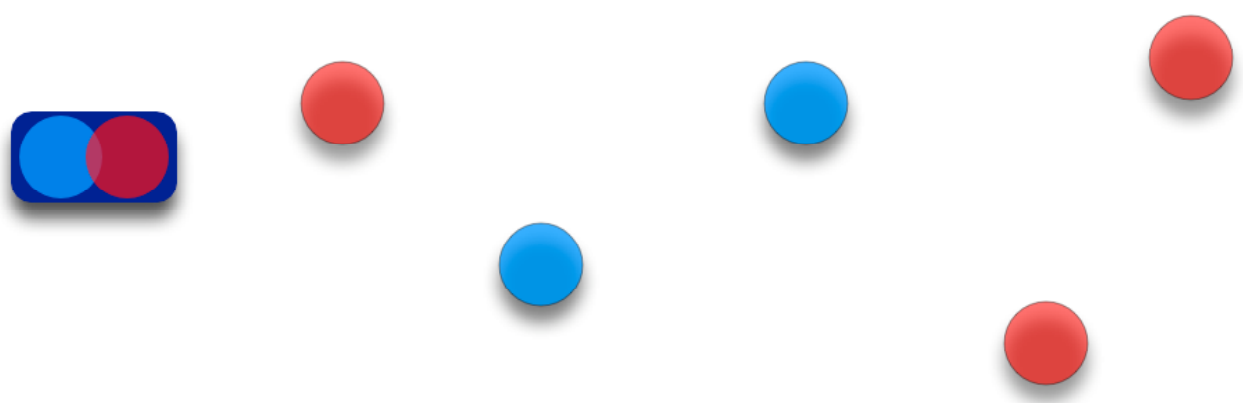
3. RDME
   - System state usually given by the number of each chemical species in each voxel.
   - Can equivalently be written in terms of total number of each species and lattice position of each particle (see Isaacson J. Math. Phys. A (2008)).
   - The probabilities of being in a given state satisfy a coupled, possibly infinite, system of ordinary differential equations.

What are the state variables in the Smoluchowski / Doi models?

- Consider $\mathrm{A} + \mathrm{B} \rightarrow \mathrm{C}$.
- $A(t)$ - the stochastic process for the total number of species A in the system.
- a - value of $A(t)$, i.e. $A(t) = a$.
- $\boldsymbol{q}_l^a \in \mathbb{R}^3$ - location of the l'th molecule of species A when $A(t) = a$.
- $\boldsymbol{q}^a = (\boldsymbol{q}_1^a, \ldots, \boldsymbol{q}_a^a) \in \mathbb{R}^{3a}$ - position vector for all A molecules.



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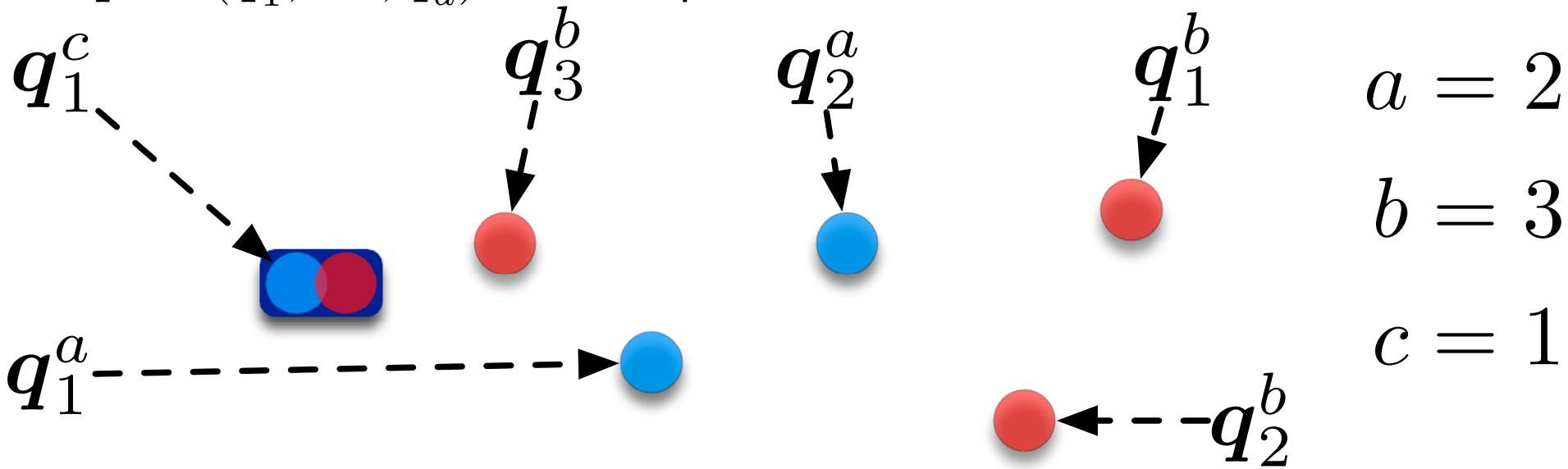

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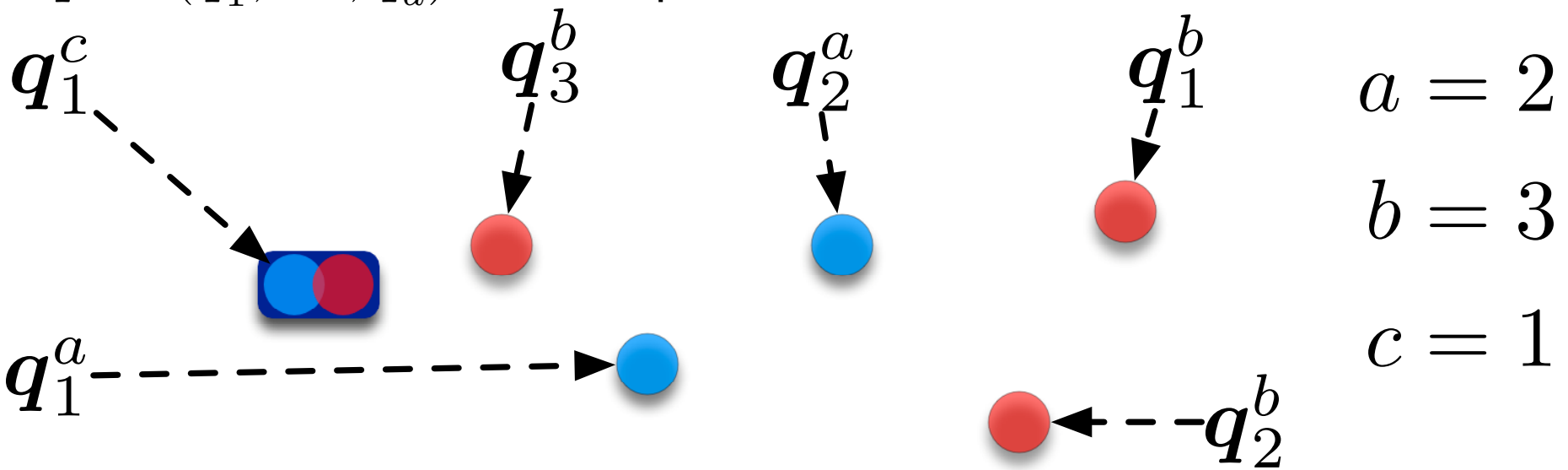

$$\boldsymbol{q}^a = (\boldsymbol{q}_1^a, \boldsymbol{q}_2^a) \quad \boldsymbol{q}^b = (\boldsymbol{q}_1^b, \boldsymbol{q}_2^b, \boldsymbol{q}_3^b) \quad \boldsymbol{q}^c = (\boldsymbol{q}_1^c)$$

What is the associated probability density?

Let $f^{(a,b,c)}(\boldsymbol{q}^a, \boldsymbol{q}^b, \boldsymbol{q}^c, t)$ denote the probability density for there to be a molecules of species A located at the positions in $\boldsymbol{q}^a$, b molecules of species B located at $\boldsymbol{q}^b$, and c molecules of species C located at $\boldsymbol{q}^c$ at time t.

Indistinguishability implies that $f^{(a,b,c)}(\boldsymbol{q}^a, \boldsymbol{q}^b, \boldsymbol{q}^c, t)$ is symmetric function in the components of each of $\boldsymbol{q}^a$, $\boldsymbol{q}^b$, and $\boldsymbol{q}^c$.

See Doi, J. Phys. A: Math. Gen. 1976, and Isaacson, J. Phys. A: Math. Theor. 2008.

What are the evolution equations for the Smoluchowski model?

$$\frac{\partial f^{(a,b,c)}}{\partial t}\left(\boldsymbol{q}^a,\boldsymbol{q}^b,\boldsymbol{q}^c,t\right)=\left(L+R\right)f^{(a,b,c)}\left(\boldsymbol{q}^a,\boldsymbol{q}^b,\boldsymbol{q}^c,t\right),$$

Here

$$\left(Lf^{(a,b,c)}\right)\left(\boldsymbol{q}^a,\boldsymbol{q}^b,\boldsymbol{q}^c,t\right)=\left(D^{\mathrm{A}}\Delta^a+D^{\mathrm{B}}\Delta^b+D^{\mathrm{C}}\Delta^c\right)f^{(a,b,c)}\left(\boldsymbol{q}^a,\boldsymbol{q}^b,\boldsymbol{q}^c,t\right),$$

where $\Delta^a=\sum_{l=1}^{a}\sum_{d=1}^{3}\partial^2_{(\boldsymbol{q}_l^a)_d}$ denotes the Laplacian in $\boldsymbol{q}^a$, and

What are the evolution equations for the Smoluchowski model?

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- Reaction operator, R, incorporates the incoming flux from the state with $(a+1,b+1,c-1)$ molecules when an $\mathrm{A}+\mathrm{B}\to\mathrm{C}$ reaction occurs.
- Dirichlet boundary condition is added to model outgoing reaction flux:

  $$f^{(a,b,c)}\left(\boldsymbol{q}^a,\boldsymbol{q}^b,\boldsymbol{q}^c\right)=0,\quad \left|\boldsymbol{q}_l^a-\boldsymbol{q}_m^b\right|=r_{\mathrm{b}},$$

  for any l and m.

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  for any l and m.
- For general chemical systems get, possibly infinite, coupled system of partial integro-differential equations.

What are the evolution equations for the Doi model?

- Let λ denote the probability per unit time the two molecules react when their separation is less than r_{b}.
- By $\boldsymbol{q}^a \cup \boldsymbol{q}$ we mean the state vector $\boldsymbol{q}^a$ with one particle added at position $\boldsymbol{q}$.
- Similarly, $\boldsymbol{q}^c \setminus \boldsymbol{q}_l^c$ will denote the state where the lth particle has been removed from $\boldsymbol{q}^c$.

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- Similarly, $\boldsymbol{q}^c \setminus \boldsymbol{q}_l^c$ will denote the state where the lth particle has been removed from $\boldsymbol{q}^c$.
- We remove the reactive boundary condition, and modify the reaction operator to get:

$$(Rf^{(a,b,c)})\left(\boldsymbol{q}^a,\boldsymbol{q}^b,\boldsymbol{q}^c,t\right) = -\lambda\sum_{l=1}^{a}\sum_{l'=1}^{b}\mathbf{1}_{[0,r_{\mathrm{b}}]}\left(\left|\boldsymbol{q}_l^a-\boldsymbol{q}_{l'}^b\right|\right)f^{(a,b,c)}(\boldsymbol{q}^a,\boldsymbol{q}^b,\boldsymbol{q}^c,t)$$
$$+\lambda\sum_{l=1}^{c}\int_{\boldsymbol{q}\in B_l^C} f^{(a+1,b+1,c-1)}\left(\boldsymbol{q}^a\cup\boldsymbol{q},\boldsymbol{q}^b\cup\left(2\boldsymbol{q}_l^c-\boldsymbol{q}\right),\boldsymbol{q}^c\setminus\boldsymbol{q}_l^c,t\right)\,dB_l^c.$$

What are the evolution equations for the RDME model?

Discretize $\mathbb{R}^3$ and let

- $\boldsymbol{q}_l^a = h\boldsymbol{j}$, where $\boldsymbol{j} \in \mathbb{Z}^3$, denote the center of the $\boldsymbol{j}$'th voxel.
- $f_h^{(a,b,c)}(\boldsymbol{q}^a, \boldsymbol{q}^b, \boldsymbol{q}^c, t)$ denote discrete-space probability density.

Then

$$\frac{df_h^{(a,b,c)}}{dt}\left(\boldsymbol{q}^a, \boldsymbol{q}^b, \boldsymbol{q}^c, t\right) = (L_h + R_h)\, f_h^{(a,b,c)}\left(\boldsymbol{q}^a, \boldsymbol{q}^b, \boldsymbol{q}^c, t\right),$$

where $L_h \approx L$ is given by

$$L_h f_h^{(a,b,c)}\left(\boldsymbol{q}^a, \boldsymbol{q}^b, \boldsymbol{q}^c, t\right) = \left(D^{\mathrm{A}}\Delta_h^a + D^{\mathrm{B}}\Delta_h^b + D^{\mathrm{C}}\Delta_h^c\right) f_h^{(a,b,c)}\left(\boldsymbol{q}^a, \boldsymbol{q}^b, \boldsymbol{q}^c, t\right).$$

Here Δ_h^a denotes the discrete Laplacian acting on the $\boldsymbol{q}^a$ coordinate.

What are the evolution equations for the RDME model?

$R_h \approx R$ is given by

$$\left(R_h f_h^{(a,b,c)}\right)\left(\boldsymbol{q}^a, \boldsymbol{q}^b, \boldsymbol{q}^c, t\right) = k\Bigg[\sum_{l=1}^{c} f_h^{(a+1,b+1,c-1)}\left(\boldsymbol{q}^a \cup \boldsymbol{q}_l^c, \boldsymbol{q}^b \cup \boldsymbol{q}_l^c, \boldsymbol{q}^c \setminus \boldsymbol{q}_l^c, t\right) - \sum_{l=1}^{a}\sum_{m=1}^{b} \delta_h\left(\boldsymbol{q}_l^a - \boldsymbol{q}_m^b\right) f_h^{(a,b,c)}\left(\boldsymbol{q}^a, \boldsymbol{q}^b, \boldsymbol{q}^c, t\right)\Bigg],$$

with

$$\delta_h\left(\boldsymbol{q}_l^a - \boldsymbol{q}_m^b\right) = \begin{cases} \frac{1}{h^3}, & \boldsymbol{q}_l^a = \boldsymbol{q}_m^b, \\ 0, & \text{else.} \end{cases}$$

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This is a non-standard form of the RDME, tracking molecule positions instead of the number of molecules of each species in each voxel.

Theorem (Isaacson J. Phys. A: Math. Theor. 2008)

The solution to the standard RDME, $P_h\left(\boldsymbol{a},\boldsymbol{b},\boldsymbol{c},t\right)$, satisfies

$$P_h\left(\boldsymbol{a},\boldsymbol{b},\boldsymbol{c},t\right) = \left(\prod_{\boldsymbol{i}\in\mathbb{Z}^3}\frac{1}{a_{\boldsymbol{i}}!\,b_{\boldsymbol{i}}!\,c_{\boldsymbol{i}}!}\right) f_h^{(a,b,c)}\left(\boldsymbol{q}^a,\boldsymbol{q}^b,\boldsymbol{q}^c,t\right) h^{3(a+b+c)}.$$

How is the linear RDME system related to nonlinear reaction-diffusion PDE systems?

Let $\mathcal{A}_{\boldsymbol{i}}(t)$ denote the stochastic process for the **concentration** of species A within voxel $\boldsymbol{i}$. Define $\mathcal{B}_{\boldsymbol{i}}(t)$ and $\mathcal{C}_{\boldsymbol{i}}(t)$ similarly.

Using the RDME we can show

$$\frac{d\,\mathbb{E}\left[\mathcal{A}_{\boldsymbol{i}}\right]}{dt} = \frac{D^{\mathrm{A}}}{h^2} \sum_{\pm} \sum_{d=1}^{3} \left(\mathbb{E}[\mathcal{A}_{\boldsymbol{i}\pm\boldsymbol{e}_d}] - \mathbb{E}\left[\mathcal{A}_{\boldsymbol{i}}\right]\right) - k\,\mathbb{E}\left[\mathcal{A}_{\boldsymbol{i}}\mathcal{B}_{\boldsymbol{i}}\right].$$

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Note, the boxed term is the standard discrete Laplacian.

Since generally

$$\mathrm{Cov}(\mathcal{A}_{\boldsymbol{i}}, \mathcal{B}_{\boldsymbol{i}}) \neq 0,$$

we have that

$$\mathbb{E}\left[\mathcal{A}_{\boldsymbol{i}}\mathcal{B}_{\boldsymbol{i}}\right] \neq \mathbb{E}\left[\mathcal{A}_{\boldsymbol{i}}\right]\mathbb{E}\left[\mathcal{B}_{\boldsymbol{i}}\right].$$

How to obtain a reaction-diffusion PDE system?

- *If* $\mathbb{E}\left[\mathcal{A}_i \mathcal{B}_i\right] = \mathbb{E}\left[\mathcal{A}_i\right] \mathbb{E}\left[\mathcal{B}_i\right]$ the mean concentrations satisfy a closed system of ODEs.
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- Fix $\boldsymbol{x} = h\boldsymbol{i}$ as $h \to 0$.
- Let $\bar{A}(\boldsymbol{x}, t) = \lim_{h\to 0} \mathbb{E}\left[\mathcal{A}_{\boldsymbol{i}}(t)\right]$.
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$$\frac{\partial \bar{A}}{\partial t}(\boldsymbol{x}, t) = D^{\mathrm{A}}\Delta\bar{A}(\boldsymbol{x}, t) - k\bar{A}(\boldsymbol{x}, t)\bar{B}(\boldsymbol{x}, t),$$
$$\frac{\partial \bar{B}}{\partial t}(\boldsymbol{x}, t) = D^{\mathrm{B}}\Delta\bar{B}(\boldsymbol{x}, t) - k\bar{A}(\boldsymbol{x}, t)\bar{B}(\boldsymbol{x}, t),$$
$$\frac{\partial \bar{C}}{\partial t}(\boldsymbol{x}, t) = D^{\mathrm{C}}\Delta\bar{C}(\boldsymbol{x}, t) + k\bar{A}(\boldsymbol{x}, t)\bar{B}(\boldsymbol{x}, t).$$

So the reaction-diffusion PDEs can be interpreted as a coarse-grained approximation to the RDME.

Outline of tutorial:

- Why model stochasticity in the chemical reaction process and the explicit spatial movement of proteins and mRNAs?
- What are the types of particle-based stochastic reaction-diffusion models that have been used to study biological systems at the scale of individual cells?
- **How can we numerically simulate these models?**
  - What are some of the tradeoffs in using particular simulation methods?
- What are some biological systems to which these models have been applied?

What are the most common numerical solution methods for these models?

Smoluchowski model (Doi too, but not as well-developed at this time):

- Brownian Dynamics
  - Many different approaches, common ones include those implemented in the software programs Smoldyn, MCell, and ChemCell.
  - All are timestep-based, and split reaction and diffusion into separate events.
  - We will focus on the Smoldyn approach by Andrews *et al.* (Phys. Biol. 2004)
  - Recently extended to the Doi model by Erban *et al.* (Phys. Biol 2009)
- First Passage Kinetic Monte Carlo Method (FPKMC)
  - Generates exact realizations of the stochastic process described by the Smoluchowski Model.
  - Introduced by Opplestrup *et al.* (PRL 2006), extended in Oppelstrup *et al.* (PRE 2009), Donev *et al.* (JCP 2010), and Takahashi *et al.* (PNAS 2010).
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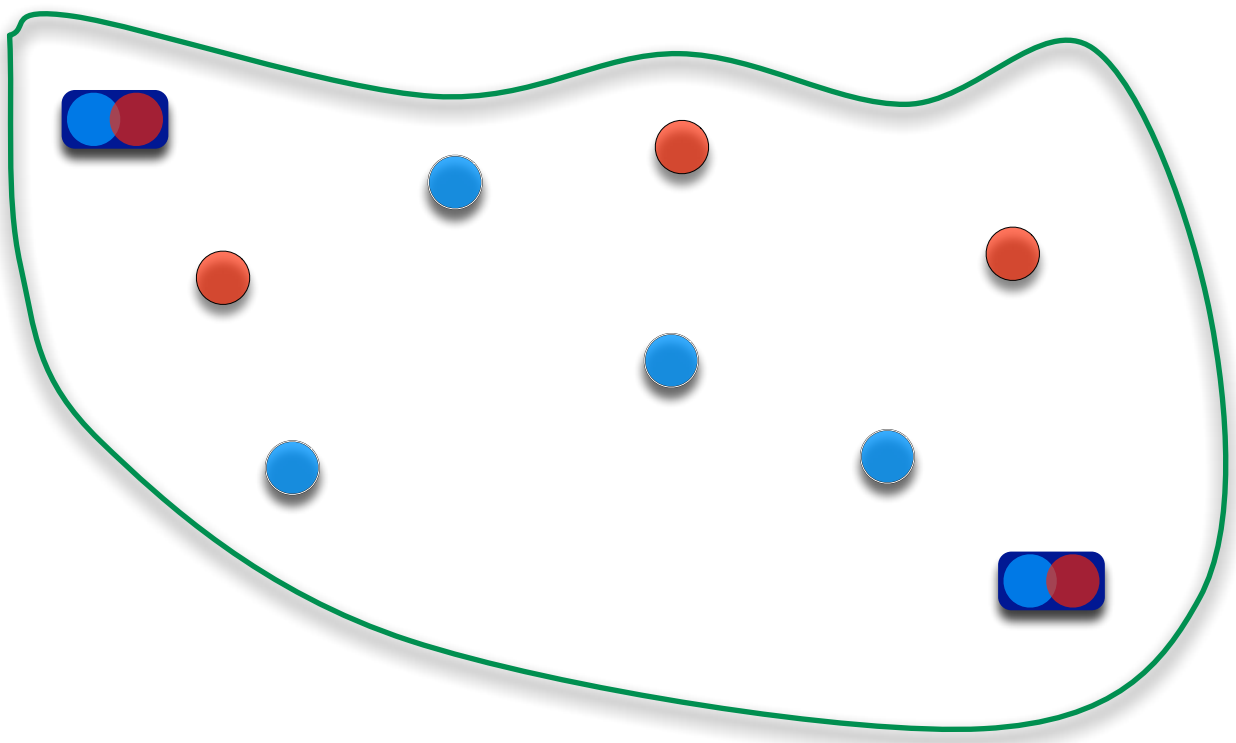
RDME:

- Gillespie Method
  - Generates exact realizations of the stochastic process described by the RDME.
  - Has been implemented in URDME, STEPS, MesoRD, and SmartCell.

What is the Brownian Dynamics Method?

- Brownian Dynamics is a timestep, Δt, based method for simulating the Smoluchowski and Doi models.
- We focus on its implementation in Smoldyn for the pure absorption Smoluchowski model, but note there are a number of other formulations (as used in MCell, or for simulating the Doi model).



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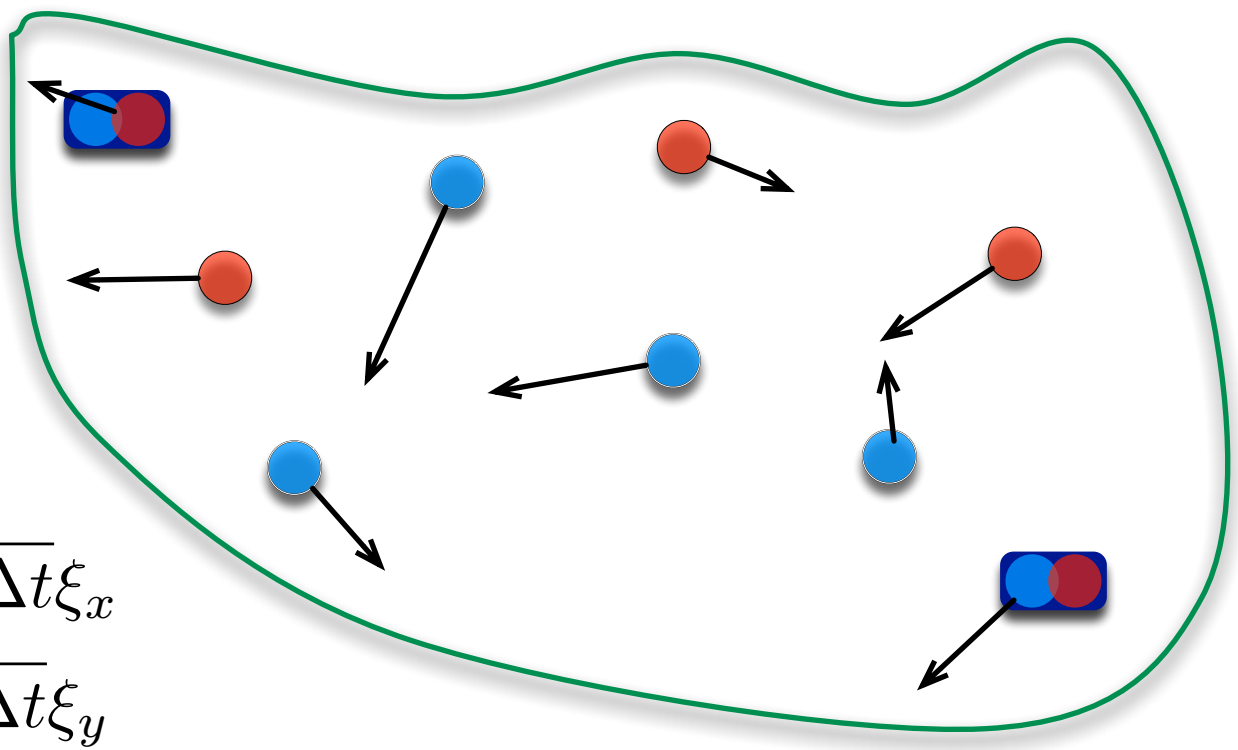
During one time step:

- Molecules diffuse by sampling from a Gaussian.
- In the absence of boundaries this exactly samples the Brownian Motion of each molecule over one timestep.



$$X(t+\Delta t) = X(t) + \sqrt{2D\Delta t}\xi_x$$

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The ξ's are sampled from a normal distribution with mean zero and unit variance.

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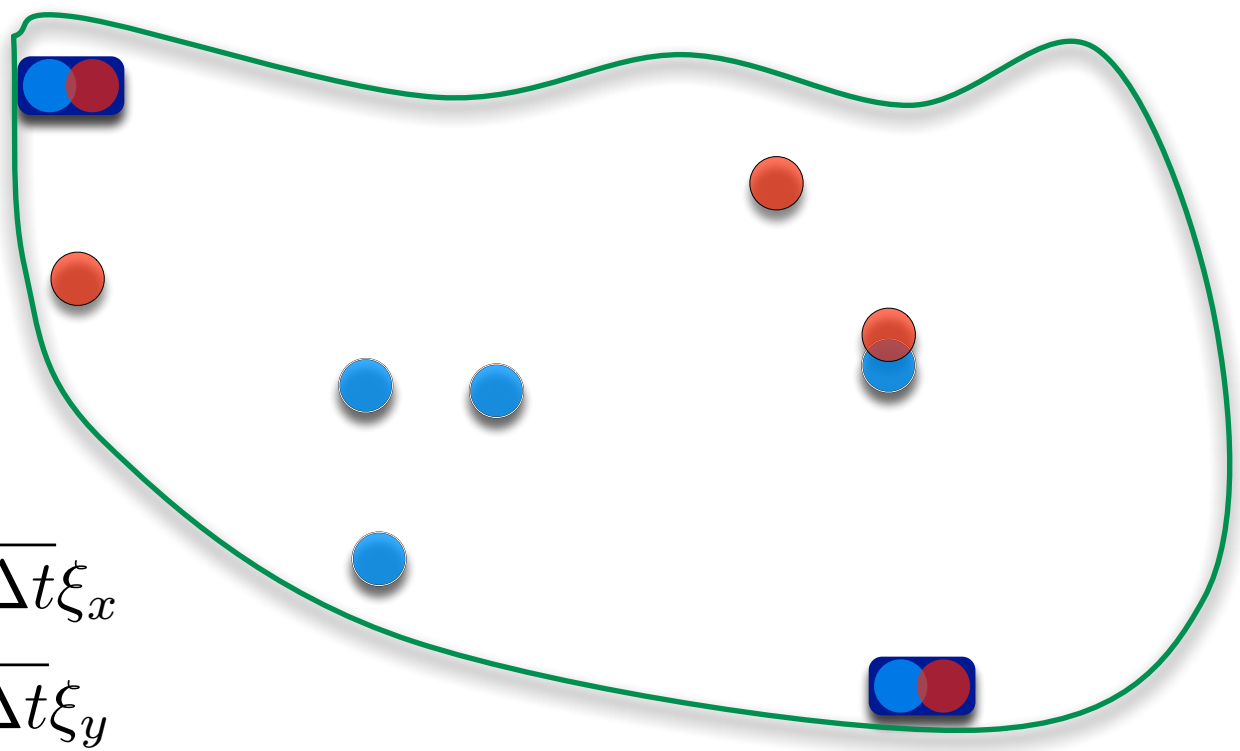

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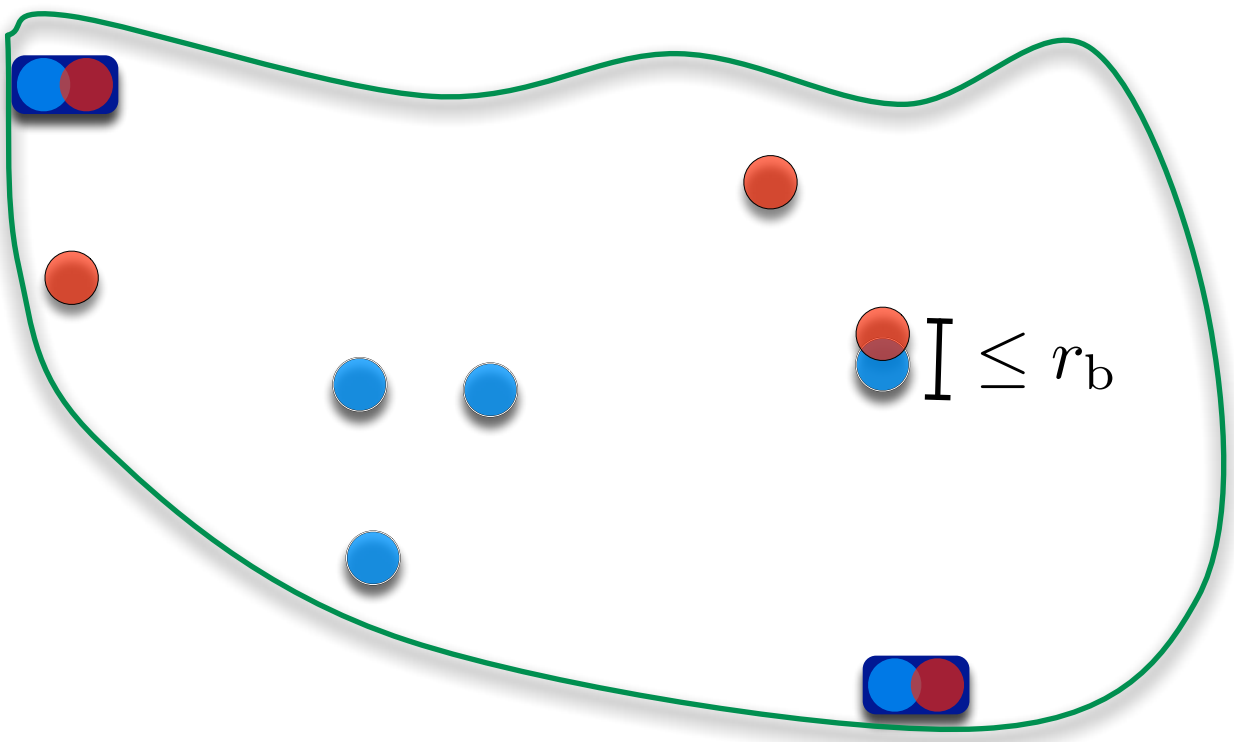
- Any two reactants within a reaction radius are allowed to react.



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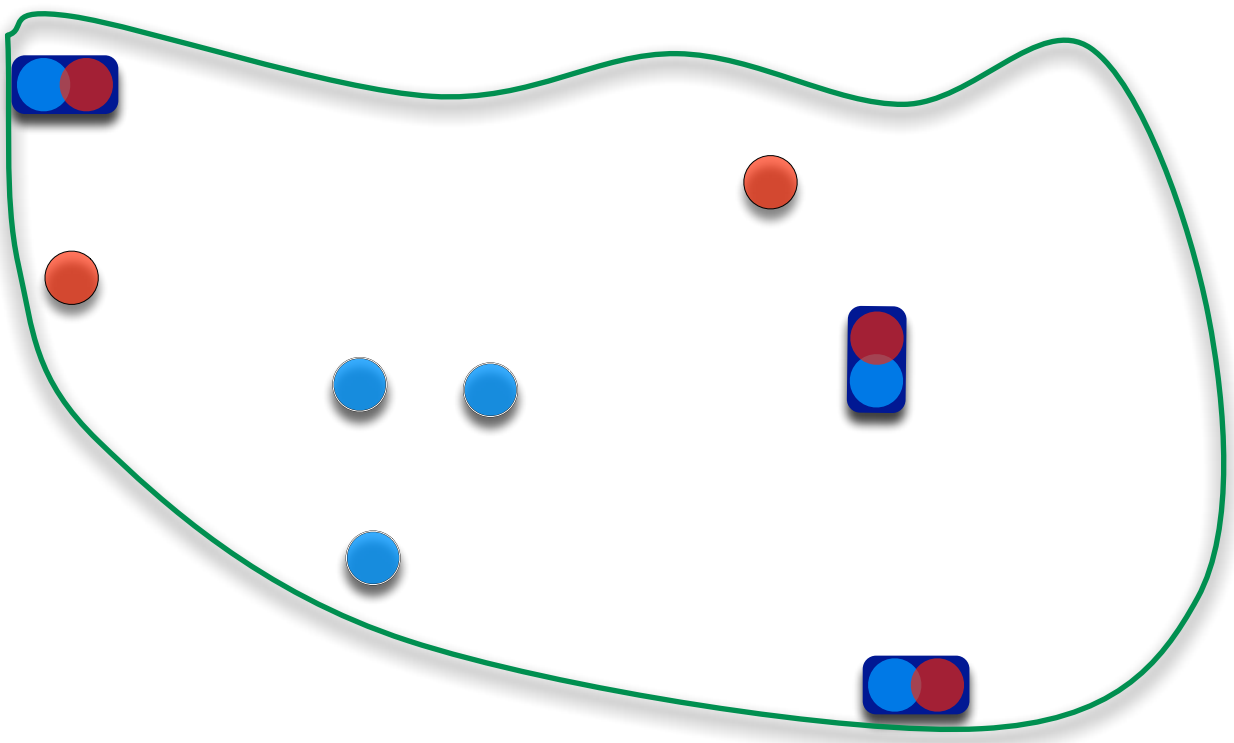

What have we left out?

- First order reactions like $A \rightarrow B$.
  - Represent internal processes; in Smoldyn the probability the first order reaction occurred during a timestep is calculated and sampled after the diffusive timestep but before bimolecular reactions are executed.
  - In MCell each molecule gets a "clock", an exponentially distributed random time, for when the reaction will occur.
- Unbinding reactions like $AB \rightarrow A+B$.
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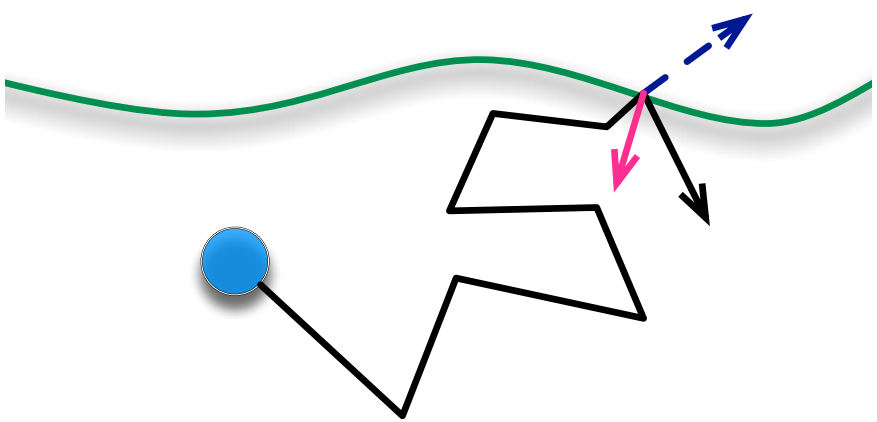
- How to handle complex geometries?
  - For piecewise linear / planar surfaces numerical methods for SDEs can be used.
  - For example, Neumann BC are implemented by reflection if a molecule ends a timestep outside the domain.



Andrews *et al.* (Phys. Biol. 2004)

What are some of the advantages/disadvantages of this approach?

Advantages:

- Method is much simpler to implement than the FPKMC, and probably simpler than RDME approaches.
- Timestep is decoupled from density of molecules. (Coupling indirect only.)
- Several well-designed publicly available simulators that can handle general chemical systems in complex geometries (such as Smoldyn and MCell).
- Can be extended with standard SDE techniques to include spatially varying drift and diffusion.
- Method should be convergent to underlying Smoluchowski model.

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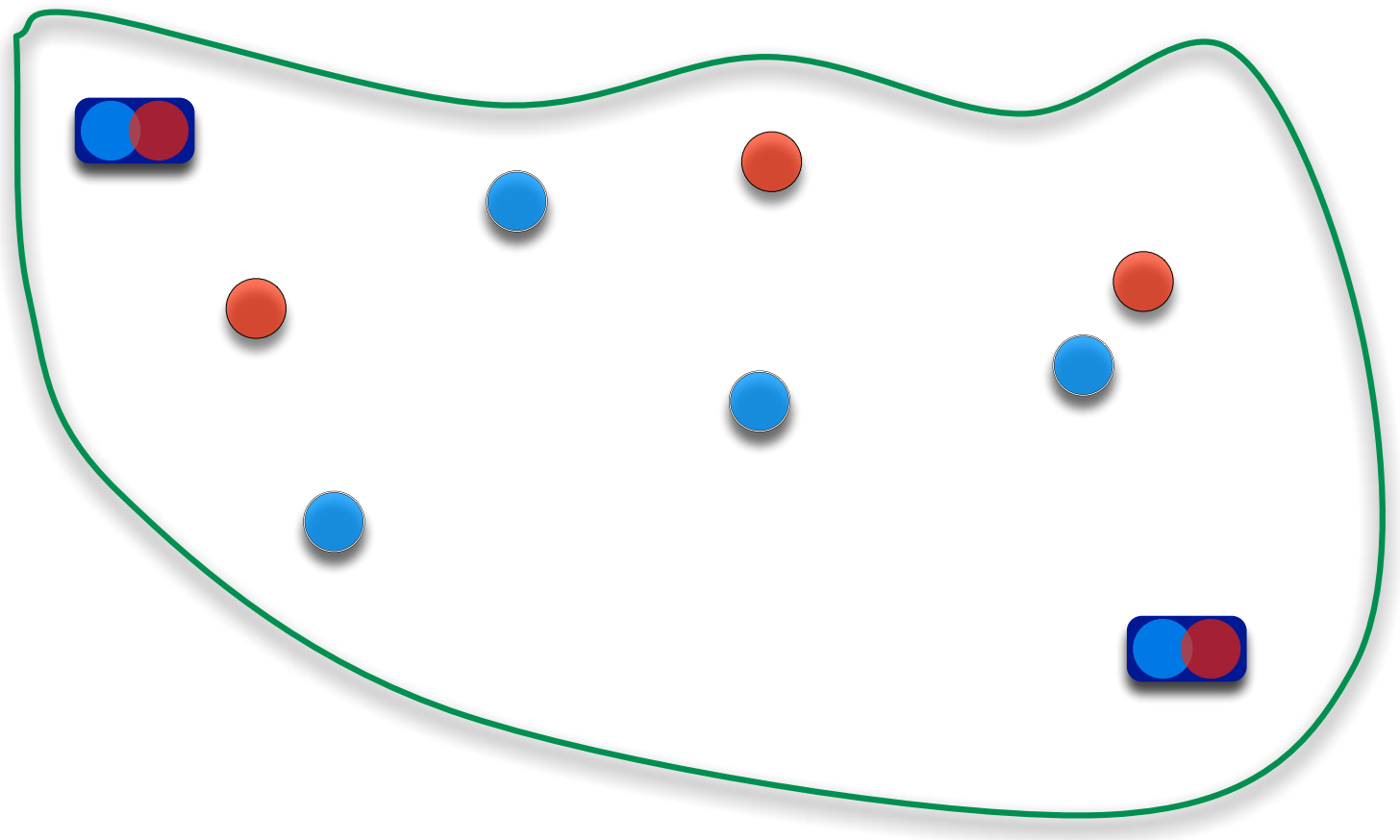
- Method should be convergent to underlying Smoluchowski model.

Disadvantages:

- No rigorous proofs of convergence or order of accuracy.
- Only $O(\sqrt{\Delta t})$ or $O(\Delta t)$ accuracy in handling typical boundary conditions.
- Requires extra parameters vs. RDME approach (reaction radius, unbinding radius, partial absorption rates).
- To accurately resolve bimolecular reactions may need to take very *small* timesteps.

How does the FPKMC method for the Smoluchowski model work?

- Each particle is covered by an individual protective domain.
  - Circles are the most common choice, but rectangles are advantageous in complex geometries.
  - Two particles that may react, and are sufficiently close, are covered by a pair protective domain.



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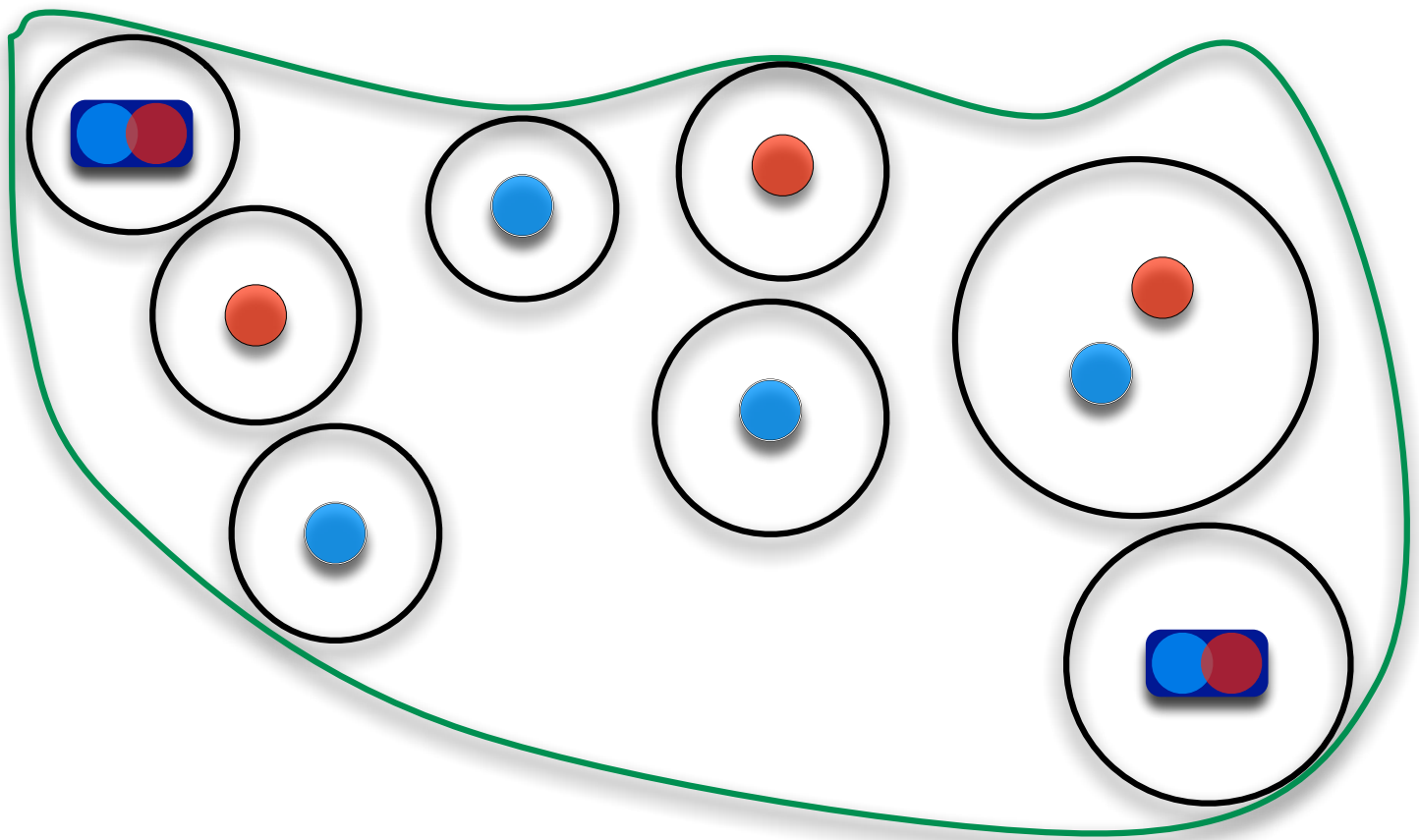

- Each protective domain is chosen as large as possible.
  - It is desirable that the size of each domain be about the same.

How does the FPKMC method for the Smoluchowski model work?

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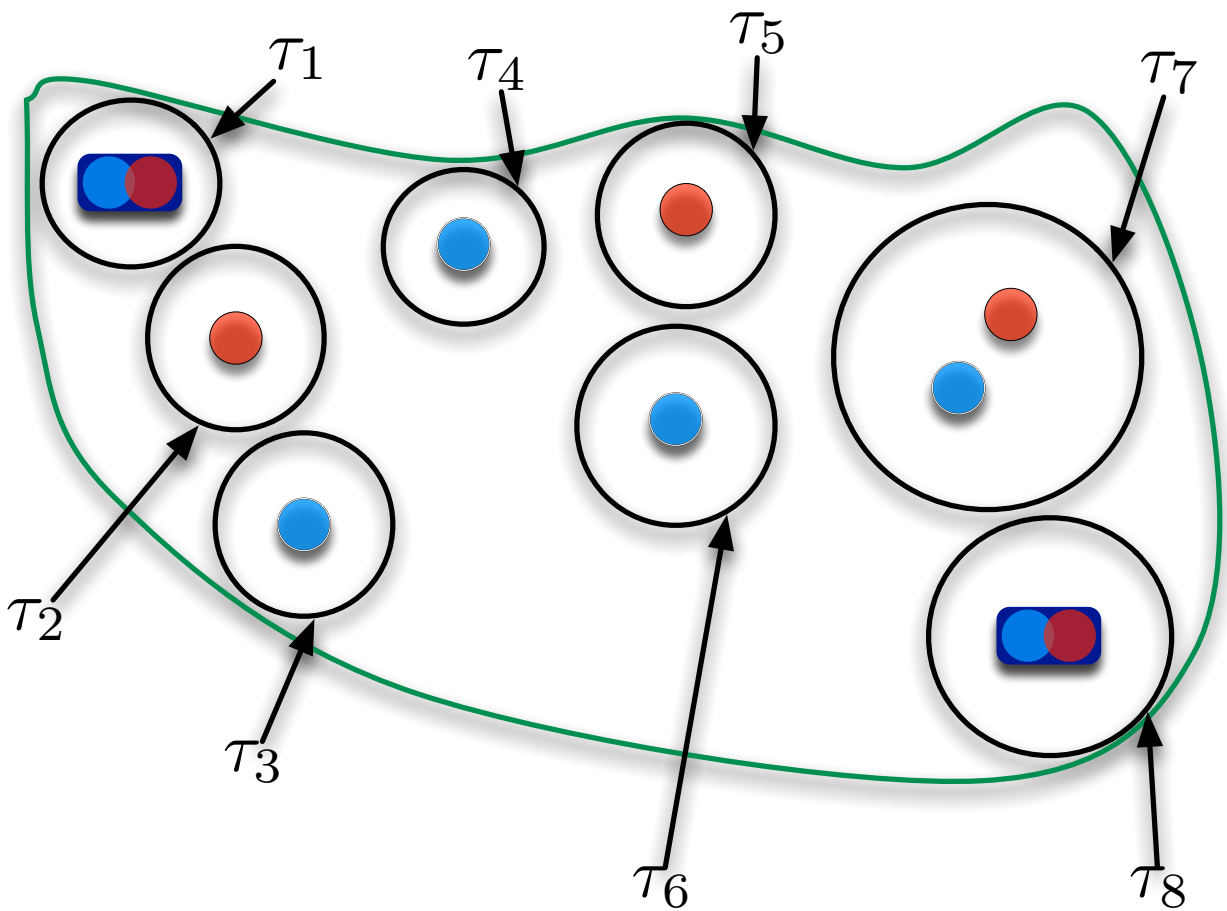

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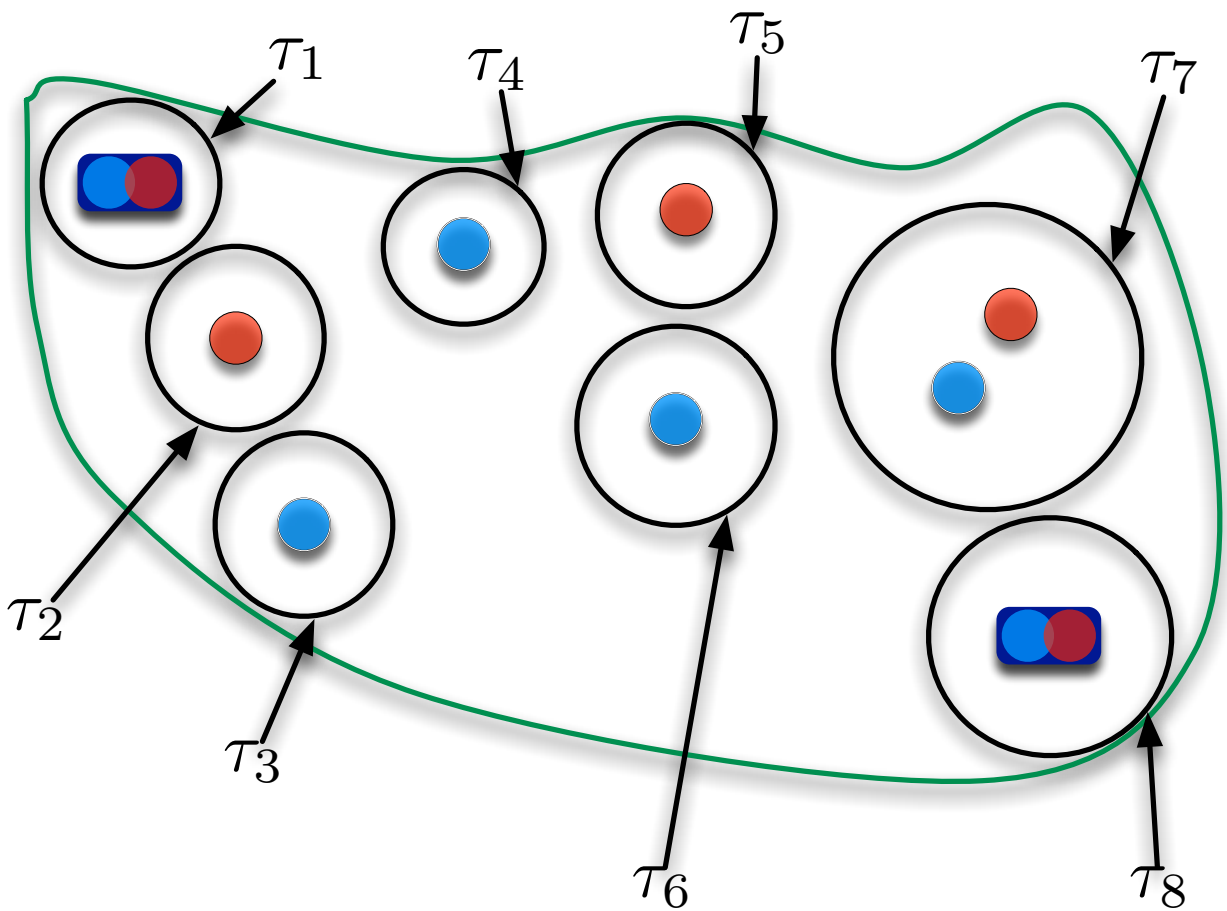

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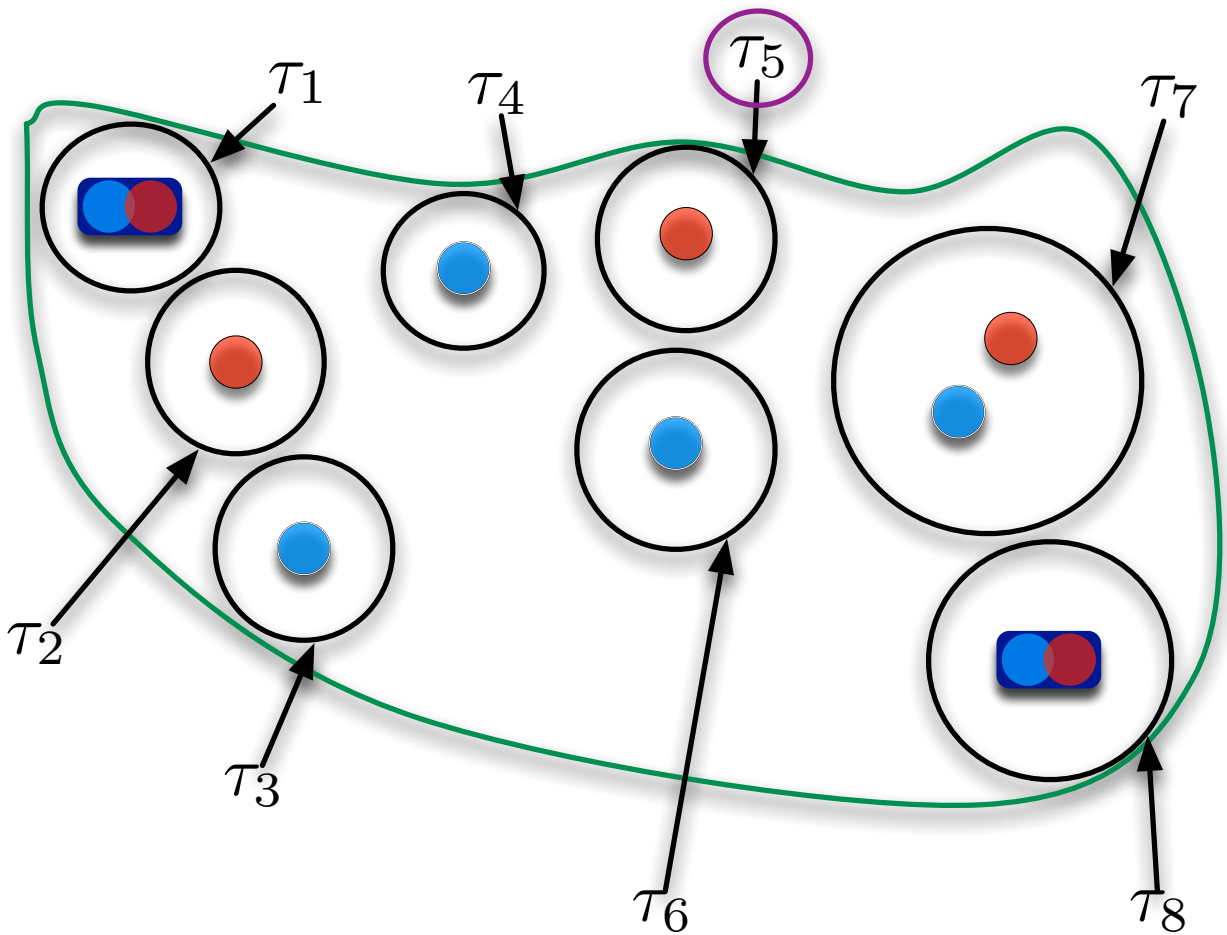

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How does the FPKMC method for the Smoluchowski model work?

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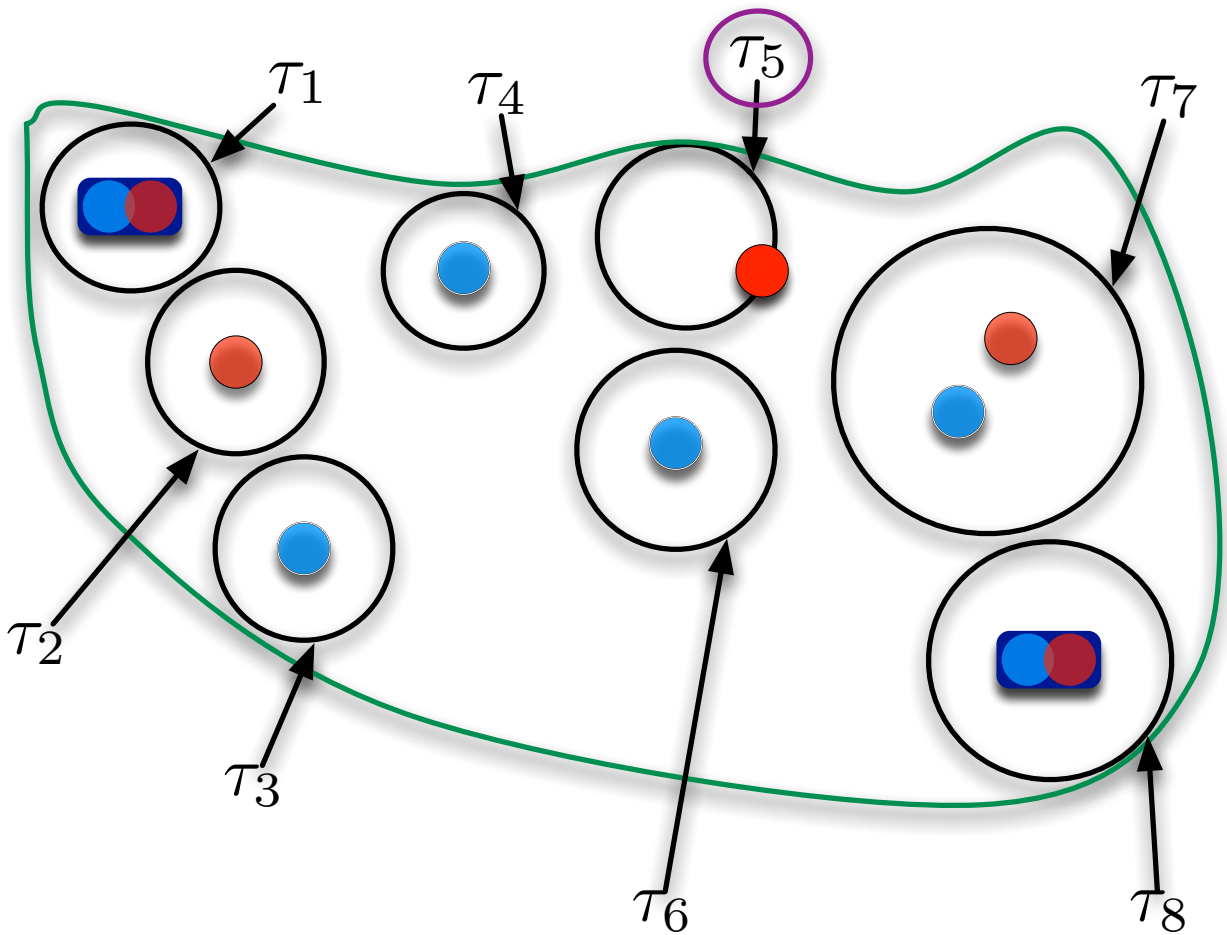

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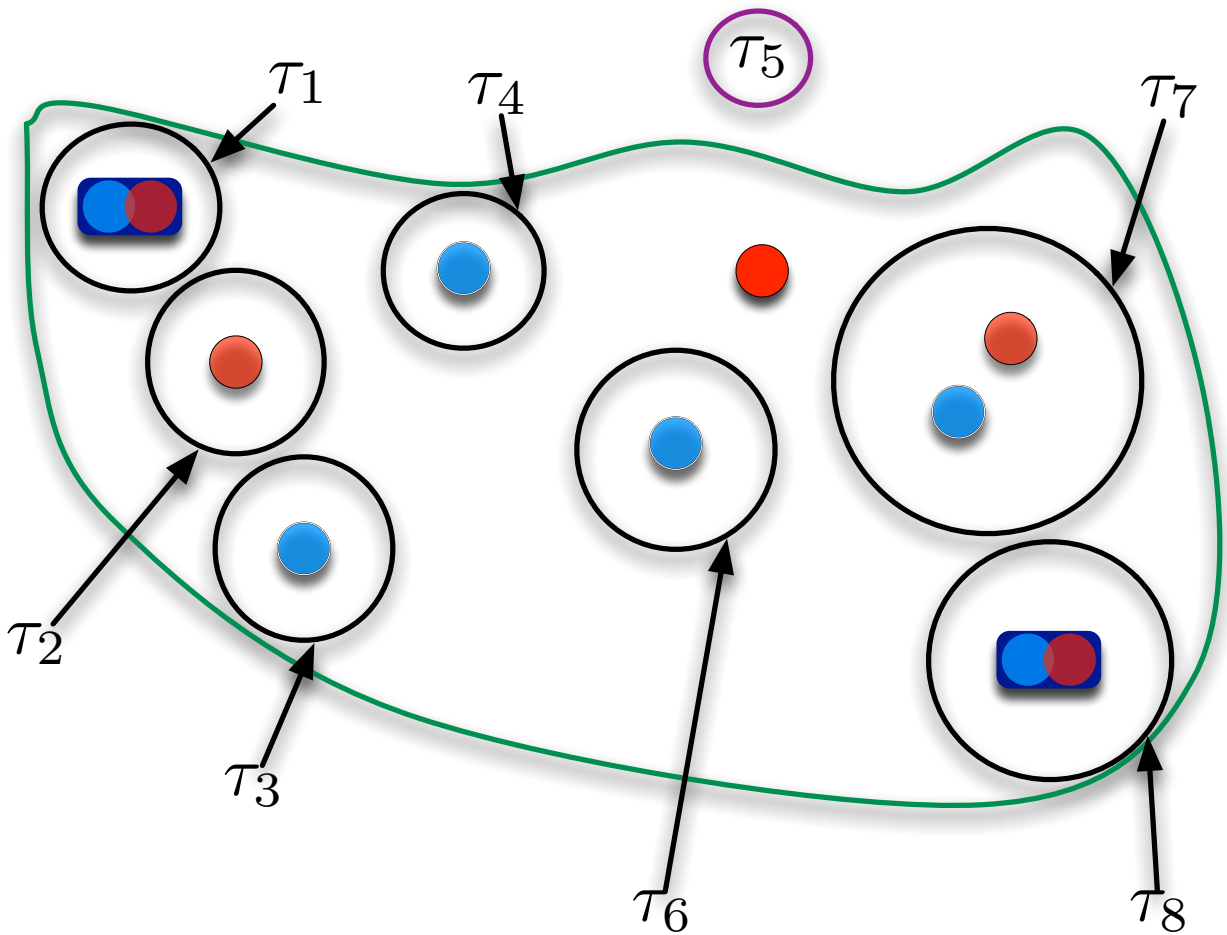

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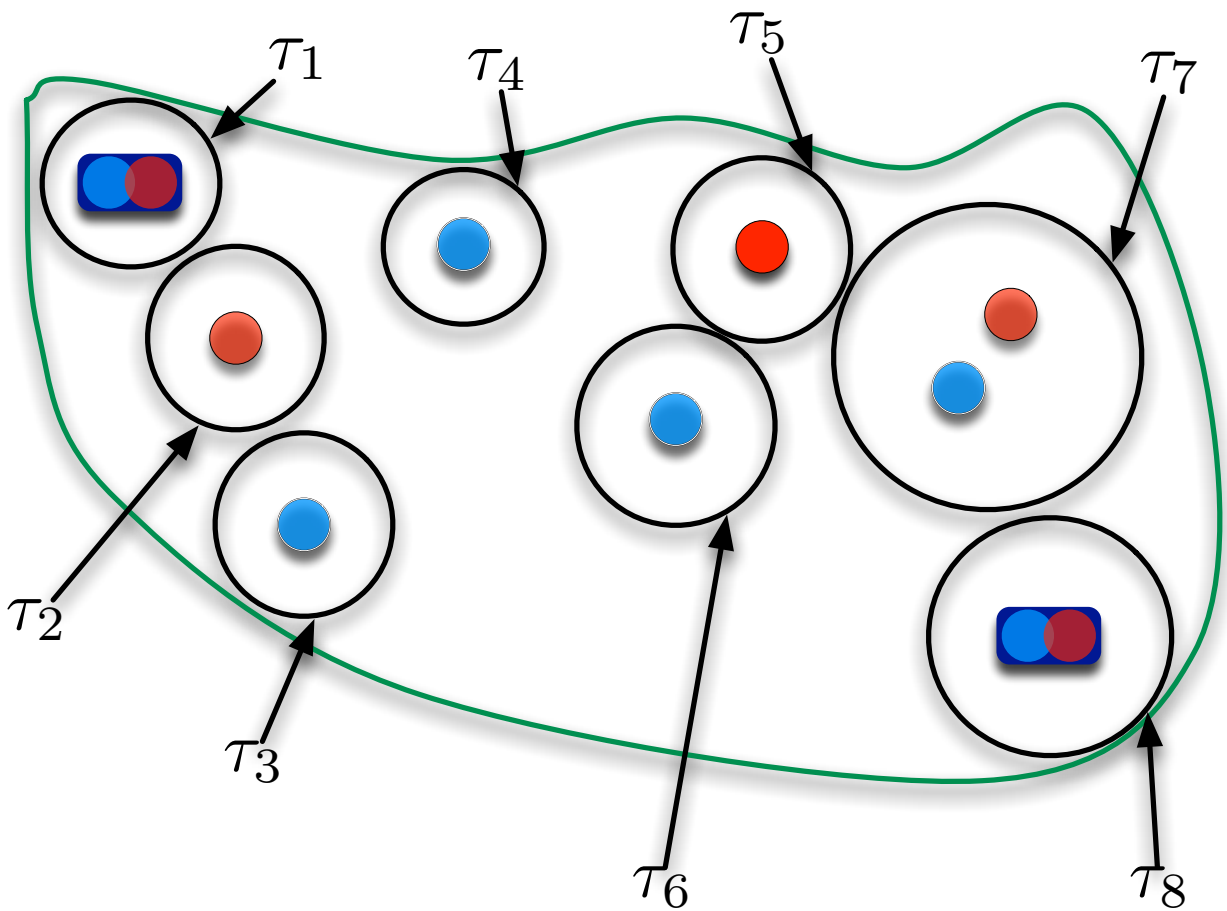
  - To keep the domains roughly the same size it may be necessary to update some of its immediate neighbors too.



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How do we calculate the exit time for a single protected molecule?

Let

- $\boldsymbol{x}_0$ denote the initial position of the molecule.
- D denote the diffusion constant of the molecule.
- U denote the protective domain (circle or rectangle).
- ∂U denote the boundary of U.
- $p(\boldsymbol{x}, t)$ denote the probability density the molecule is at $\boldsymbol{x} \in U$ at time t.

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$$\frac{\partial p}{\partial t}(\boldsymbol{x}, t) = D\Delta p, \quad \boldsymbol{x} \in U$$

with the initial condition that $p(\boldsymbol{x}, 0) = \delta(\boldsymbol{x} - \boldsymbol{x}_0)$ and the Dirichlet boundary condition that $p(\boldsymbol{x}, t) = 0$ for $\boldsymbol{x} \in \partial U$.

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By choosing U to be a simple domain (circle/rectangle) we can analytically solve for $p(\boldsymbol{x}, t)$.

How do we calculate the exit time for a single protected molecule?

The first exit time can be sampled from the probability distribution:

$$\text{Prob}\left[T_{\text{exit}} < t\right] = G(t) = 1 - \int_U p(\boldsymbol{x}, t)\, d\boldsymbol{x}$$

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The exit position, x, is given by sampling the exit position density at the sampled exit time, t:

$$\rho(\boldsymbol{x}, t) = \frac{-D\nabla\rho(\boldsymbol{x}, t) \cdot \boldsymbol{\eta}(\boldsymbol{x})}{\int_{\partial U} -D\nabla\rho(\boldsymbol{y}, t) \cdot \boldsymbol{\eta}(\boldsymbol{y})\, dS(\boldsymbol{y})}$$

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To rebalance protective regions it may be necessary to update the position of several neighboring particles. For these we sample the no-passage density:

$$n(\boldsymbol{x}, t) = \frac{p(\boldsymbol{x}, t)}{1 - G(t)}$$

How do we calculate the event time for a pair of molecules?

Consider a pair that can undergo the reaction $\mathrm{A} + \mathrm{B} \to \varnothing$. Let

- $\boldsymbol{x}$ and $\boldsymbol{y}$ denote the positions of the A and B molecules.
- D^{A} and D^{B} denote their diffusion constants.
- U denote the protective domain (circle or rectangle).
- ∂U denote the boundary of U.
- $p(\boldsymbol{x}, \boldsymbol{y}, t)$ denote the probability density the molecules are at $\boldsymbol{x} \in U$ and $\boldsymbol{y} \in U$ respectively at time t.

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Then

$$\frac{\partial p}{\partial t}(\boldsymbol{x}, \boldsymbol{y}, t) = D^{\mathrm{A}} \Delta_{\boldsymbol{x}} p + D^{\mathrm{B}} \Delta_{\boldsymbol{y}} p, \quad \boldsymbol{x} \in U, \boldsymbol{y} \in U$$

with the initial condition that $p(\boldsymbol{x}, \boldsymbol{y}, 0) = \delta(\boldsymbol{x} - \boldsymbol{x}_0)\delta(\boldsymbol{y} - \boldsymbol{y}_0)$ and the Dirichlet boundary conditions

$$p(\boldsymbol{x}, \boldsymbol{y}, t) = 0, \quad \boldsymbol{x} \in \partial U, \text{ or } \boldsymbol{y} \in \partial U, \text{ or } |\boldsymbol{x} - \boldsymbol{y}| = r_{\mathrm{b}}.$$

How do we calculate the event time for a pair of molecules?

- Generally such two-body problems can not be solved analytically.
- However, by changing coordinates it is possible to solve for $p(\boldsymbol{x},\boldsymbol{y},t)$ analytically.
  - We switch to separation, $\boldsymbol{w}$, and center of mass, $\boldsymbol{v}$, coordinates:

$$\boldsymbol{w} = \boldsymbol{x} - \boldsymbol{y} \qquad \boldsymbol{v} = \frac{D^{\mathrm{A}}\boldsymbol{x} + D^{\mathrm{B}}\boldsymbol{y}}{D^{\mathrm{A}} + D^{\mathrm{B}}}$$

  - We work with the domain $\{(\boldsymbol{x},\boldsymbol{y}) \mid r_{\mathrm{b}} < |\boldsymbol{w}| < R,\ |\boldsymbol{v}| < \rho\}$
  - The PDE for $p(\boldsymbol{x},\boldsymbol{y},t)$ can now be converted to an equation in $\boldsymbol{w}$ and $\boldsymbol{v}$.
  - The new equation for $p(\boldsymbol{x},\boldsymbol{y},t)$ can be factored into two independent equations in the $\boldsymbol{w}$ and $\boldsymbol{v}$ coordinates.
  - These can be separately sampled to calculate a possible reaction time in the $\boldsymbol{w}$ coordinate, and possible protective domain exit times from both the $\boldsymbol{w}$ and $\boldsymbol{v}$ coordinates.
  - Using the minimal exit time a reaction is executed, or an exit position is sampled.
  - See Donev *et al.* (JCP 2010) or Takahashi *et al.* (PNAS 2010) for more details.

What have we left out?

- First order reactions like $A \rightarrow B$.
  - Represent internal processes -- each molecule gets a "clock", an exponentially distributed random time, for when the reaction will occur.
- How to choose the protective regions and when to rebalance them?
  - This is still an open problem, current methods use heuristics to decide what to do.
- How to handle partial absorption reactive boundary conditions?
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- How to extend to include drift or non-uniform diffusivities?
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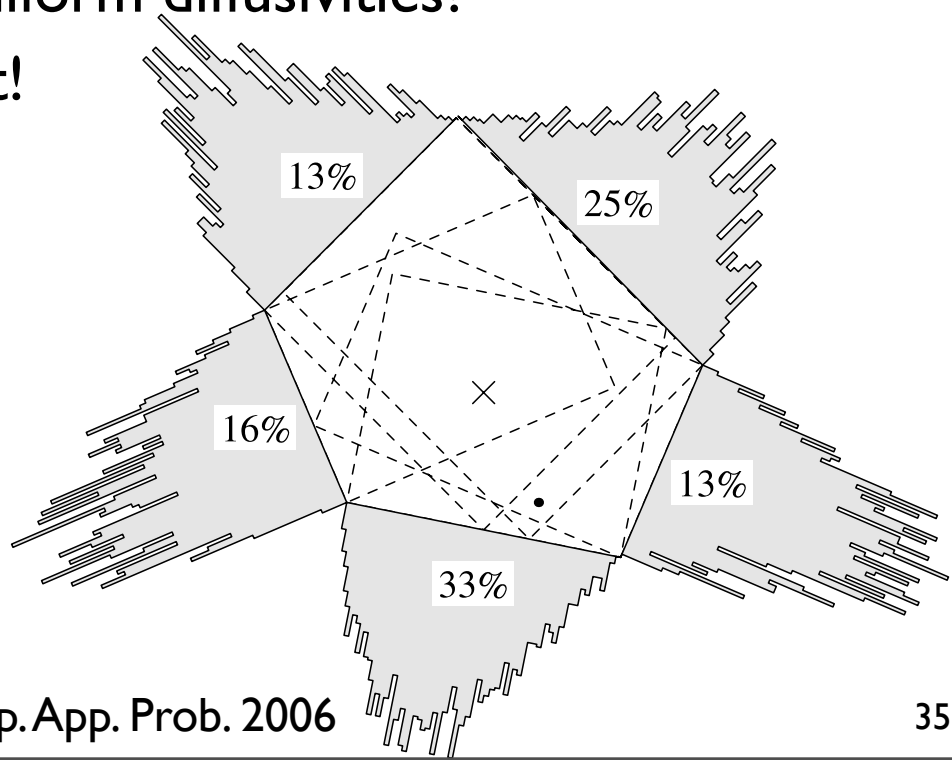
- How to handle complex geometries?
  - For piecewise linear / planar surfaces can use boundary conforming squares / cubes as the protective domains. This allows exact enforcement of Dirichlet, Neumann, or Robin boundary conditions.



Deaconu *et al.* Meth. Comp. App. Prob. 2006

What are some of the advantages/disadvantages of this approach?

Advantages:

- Method can generate exact realizations of stochastic process described by Smoluchowski model, even with more general partial absorption Robin BC.
- Method can be made to generate *exact* samples for standard BC in piecewise linear/planar geometries of arbitrary complexity.
- In dilute systems allows for large time jumps from reactive event to reactive event. Avoids simulating many diffusion events (unlike RDME / BD methods).

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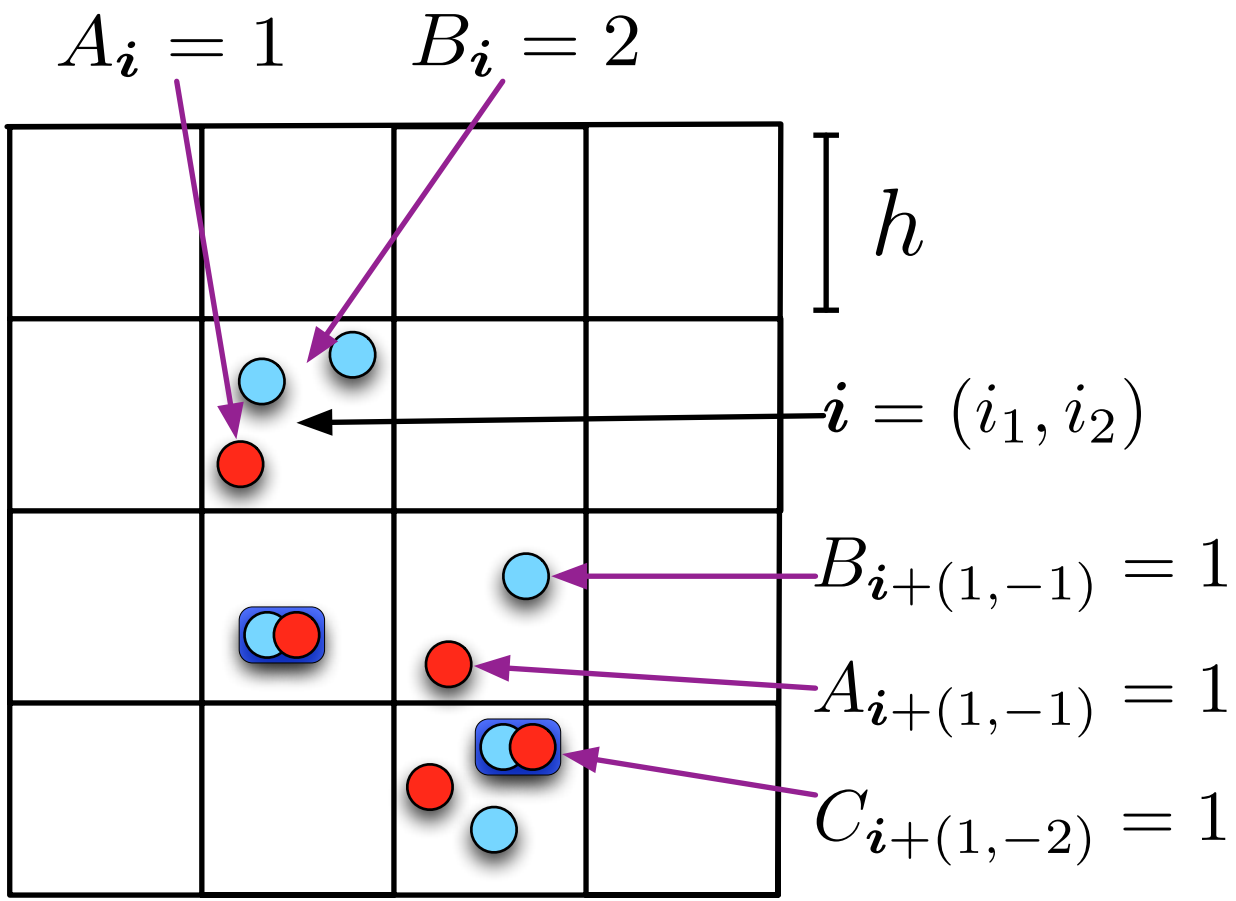
Disadvantages:

- Difficult to program.
- Requires extra parameters vs. RDME approach (reaction radius, partial absorption rates).
- Open problem to determine how to update protective domains and keep their size balanced.
  - Generally the effective "timestep" is given by the smallest domain size.
  - Very skewed domain sizes will lead to inefficient updating and unnecessarily small timesteps.
- (I think) method can not be extended to *exactly* handle spatially varying drift and diffusion constants.

How can we simulate the stochastic process described by the RDME?

- In the RDME we keep track of the number of molecules of each chemical species in each lattice voxel.
- For a simple Cartesian mesh each molecule hops from a given lattice voxel to a neighbor with probability per unit time D/h^2



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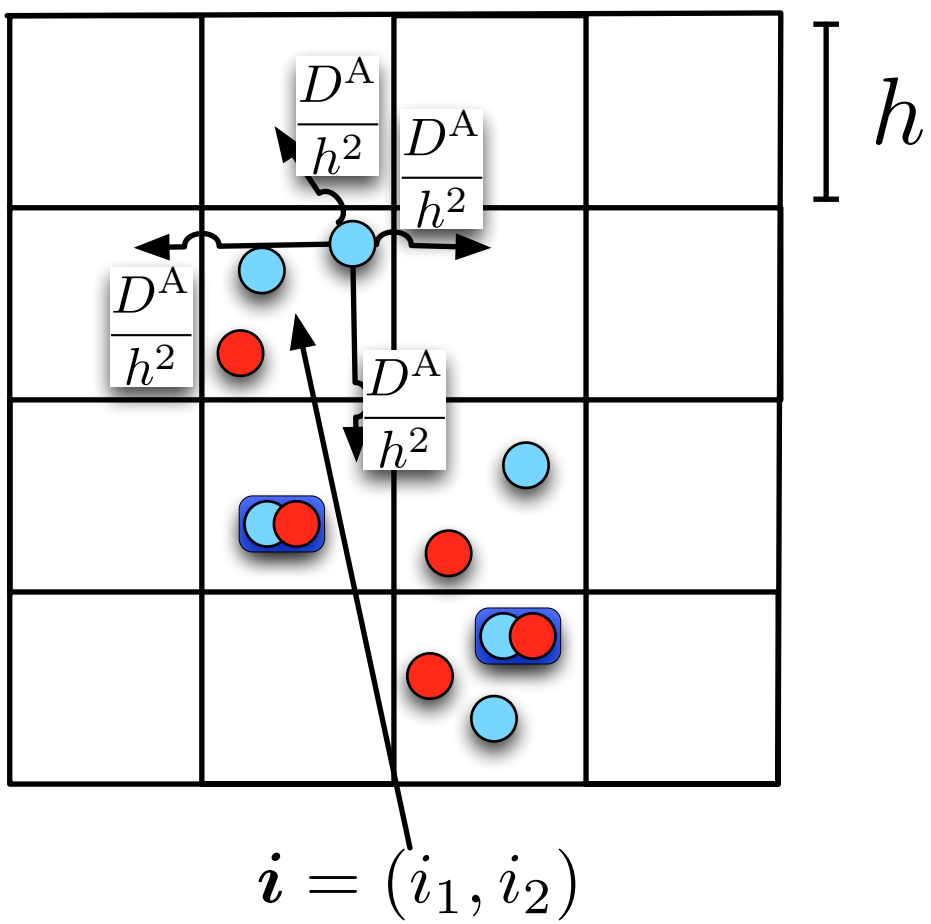

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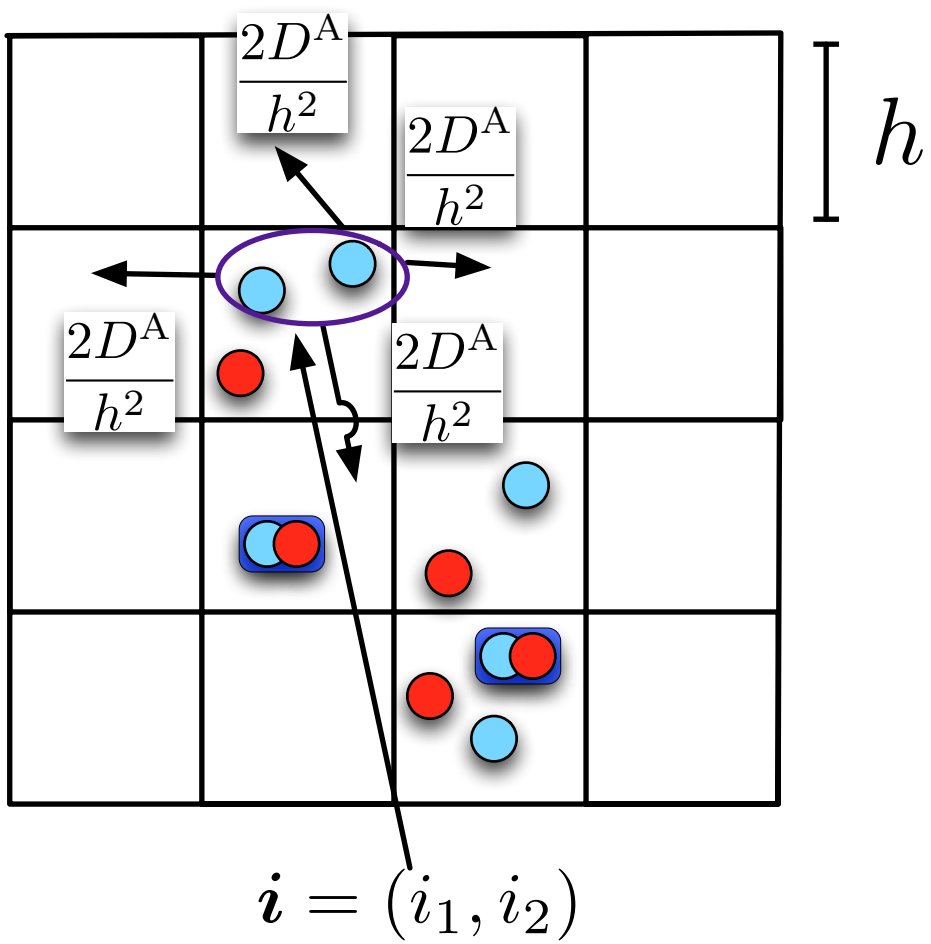
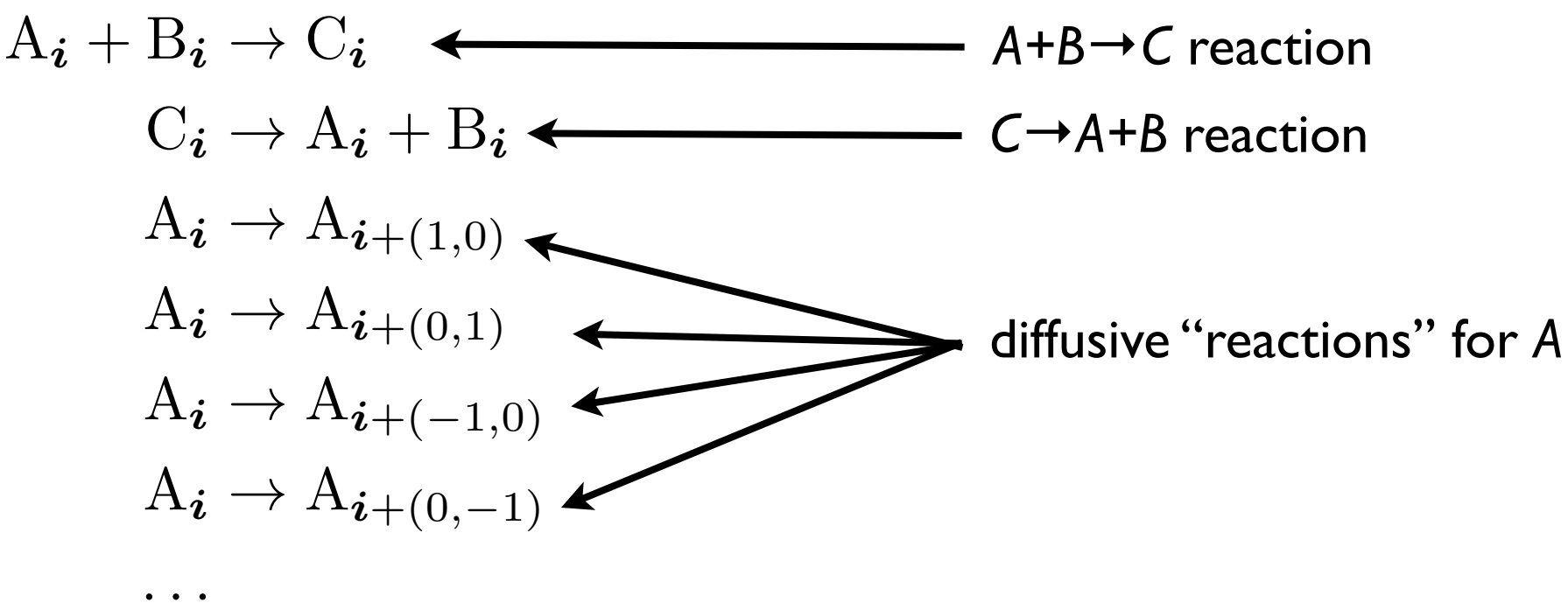


- Each of these hops is a simple first order reaction.
- We can group species in the same lattice voxel together into one effective reaction.
- *i*.e. $A_{\boldsymbol{i}} \rightarrow A_{\boldsymbol{i}+(1,0)}$, with propensity $2D^{\mathrm{A}}/h^2$

How can we simulate the stochastic process described by the RDME?

In this way we can represent all diffusive motions as first order reactions.

For a given system we then have a collection of possible "reactions":



Since this is now just a standard chemical system we can simulate this stochastic process exactly using the Gillespie method (as described in the previous talk)!

What have we left out?

- Extensions include AMR methods, advection, drift due to potentials, and GPU optimized versions.
- Recently several groups have investigated multiscale couplings to deterministic or tau-leaping methods (Erban group and Lötstedt group)
- How to handle complex geometries?

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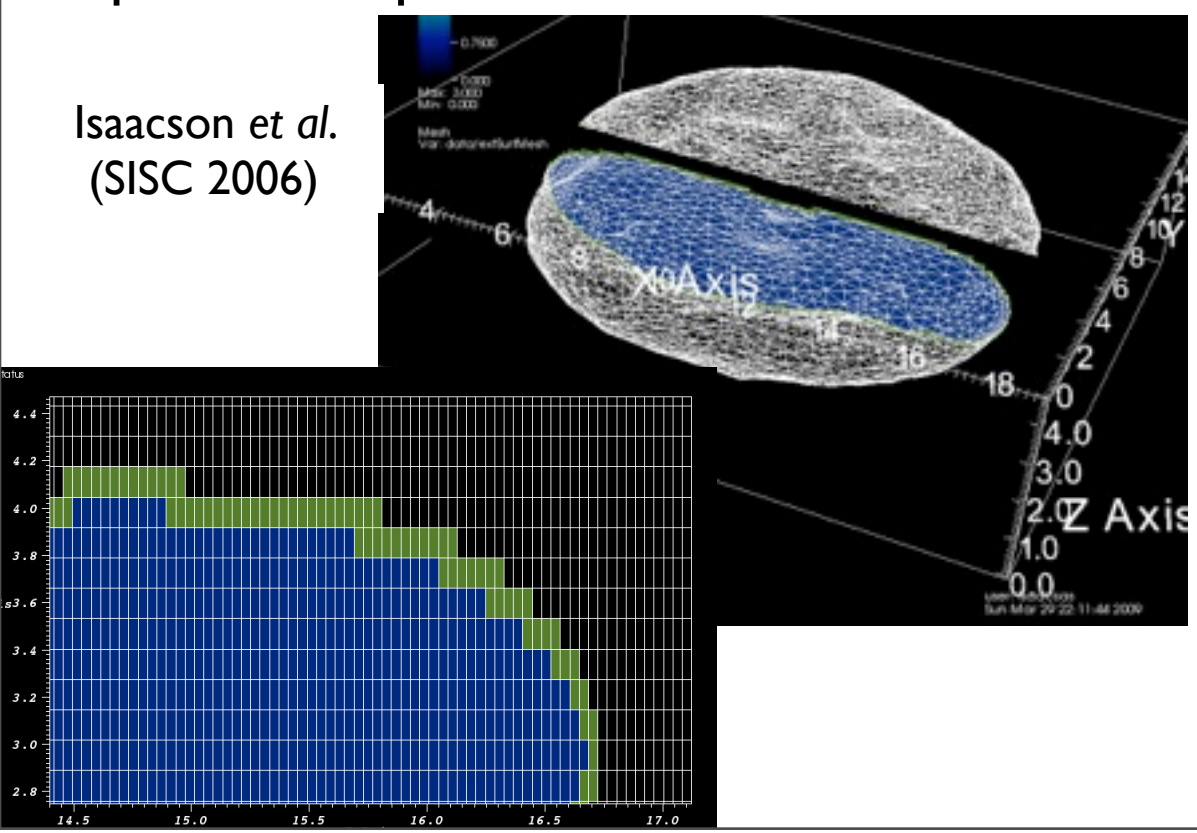
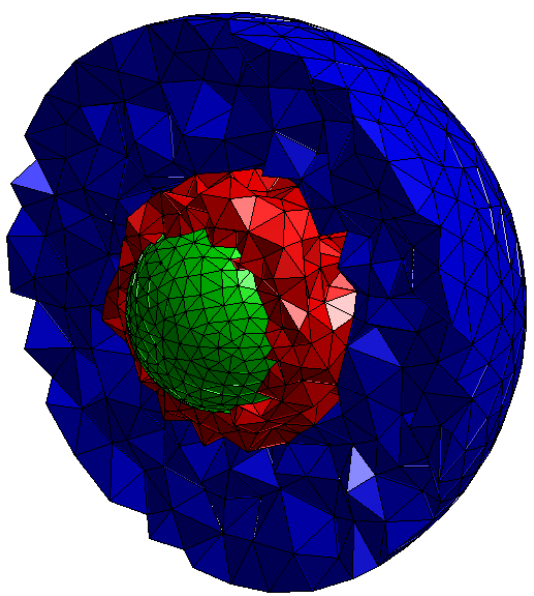
- How to handle complex geometries?
- Can use Cartesian grid embedded boundary methods to derived modified spatial transport rates in cut mesh voxels.
- Can also derive spatial transport rates using finite element methods on more general meshes.

Isaacson *et al.* (SISC 2006)





Hellander *et al.* (SISC 2009)

What are some of the advantages/disadvantages of this approach?

Advantages:

- Simulation method generates *exact* samples of the underlying stochastic process.
- Method is much simpler to implement than FPKMC, *perhaps* a bit more difficult than BD (mainly due to optimizing Gillespie method).
- Many extensions based on leveraging well-developed PDE discretization techniques. See previous slide.
- Several well-designed publicly available simulators that can handle general chemical systems in complex geometries (such as STEPS and URDME).
- Requires less parameters than the other methods. (Only needs well-mixed reaction rates.)

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- Requires less parameters than the other methods. (Only needs well-mixed reaction rates.)

Disadvantages:

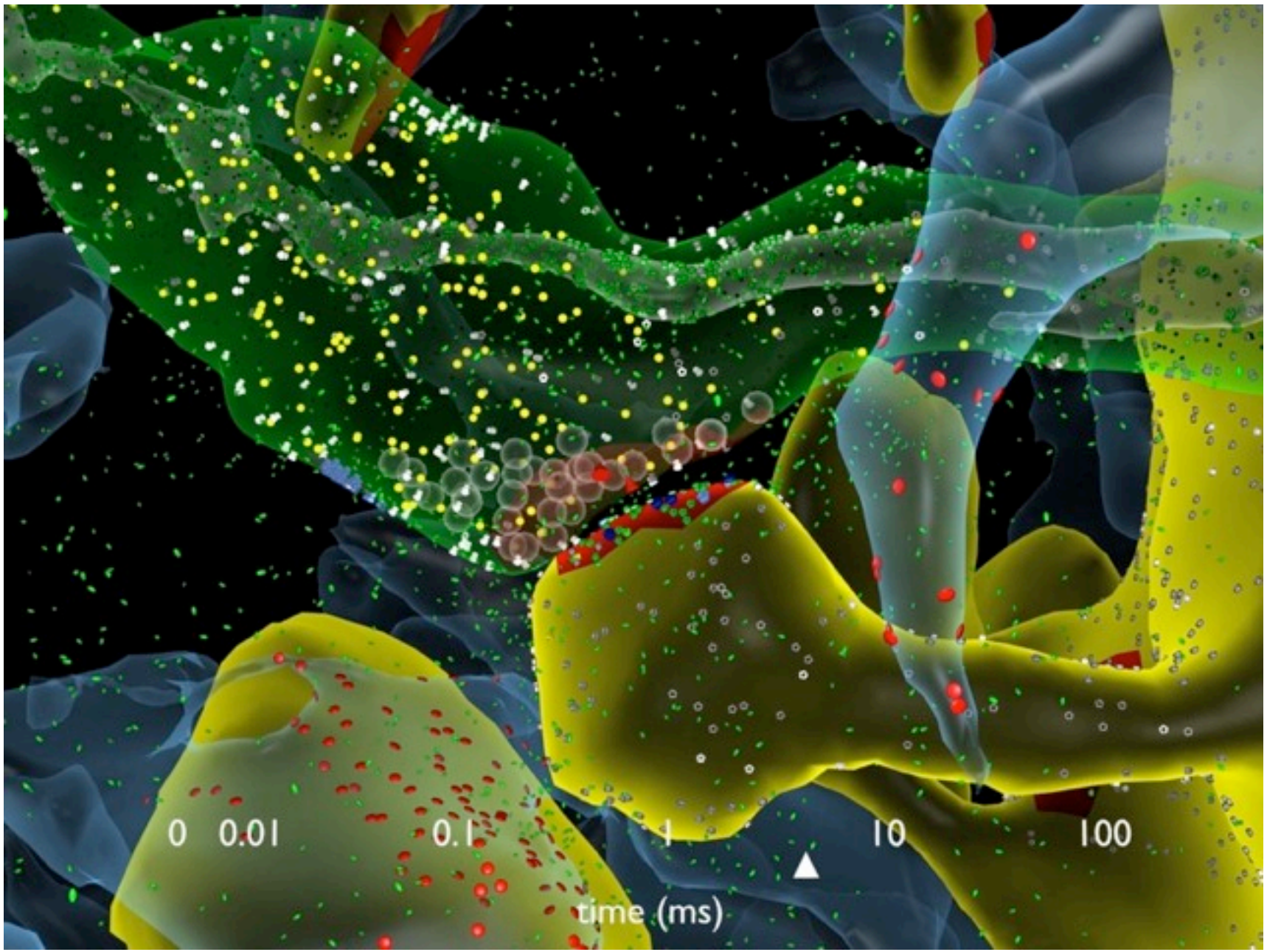
- Can be proven that bimolecular reactions are lost in the continuum limit that the lattice spacing is taken to zero (Isaacson (SIAP 2009))
  - However, method is valid for lattice spacings that are neither too large or small. This can be tricky to satisfy...
- As formulated, spend large portion of computational work simulating hops of molecules between lattice sites.

Outline of tutorial:

- Why model stochasticity in the chemical reaction process and the explicit spatial movement of proteins and mRNAs?
- What are the types of particle-based stochastic reaction-diffusion models that have been used to study biological systems at the scale of individual cells?
- How can we numerically simulate these models?
  - What are some of the tradeoffs in using particular simulation methods?
- **What are some biological systems to which these models have been applied?**

What is the current state of the art?

MCell simulation of action-potential initiation of synaptic release; post-synaptic dynamics; and spine depolarization by back-propagating action potential.



Courtesy
Thomas Bartol

Who is responsible for the preceding simulation?

Movie Credits:

- Kristen Harris - the ssTEM reconstruction.
- Justin Kinney and Chandra Bajaj - the artifact-free, simulation-quality 3D surface mesh generation.
- Suhita Nadkarni, Terry Sejnowski, and Thomas Bartol - the presynaptic terminal model.
- Mary Kennedy, Melani Stefan, Shirley Pepke, Dan Keller, Terry Sejnowski, and Thomas Bartol - the postsynaptic spine model.
- Thomas Bartol - Merged MCell models of pre and post together into one unified model, ran the simulations, and did the visualization of the model in CellBlender.

Acknowledgements

- Collaborators:
  - Carolyn Larabell (UCSF/LBL), X-ray CT data.
  - David McQueen and Charles Peskin, Courant Institute, NYU, modeling and data analysis.
- Ravi Iyengar and SBCNY for support and helpful discussions.
- Thomas Bartol for sharing the MCell simulation movie.
- NSF and NIH for support.

Thank you for coming and inviting me!