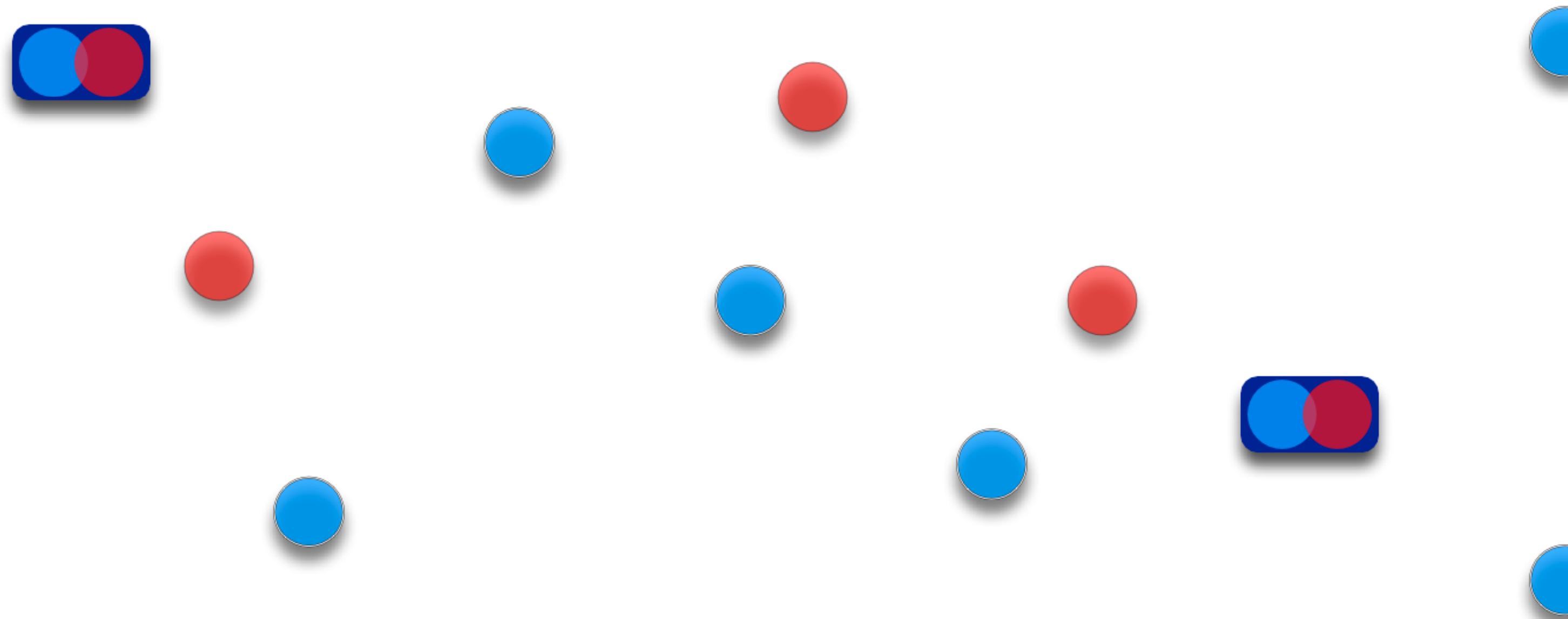


Part II: Simulation of particle-based reaction diffusion models

What are the three stochastic reaction-diffusion models?

1. Contact reactivity model (e.g. Smoluchowski model):

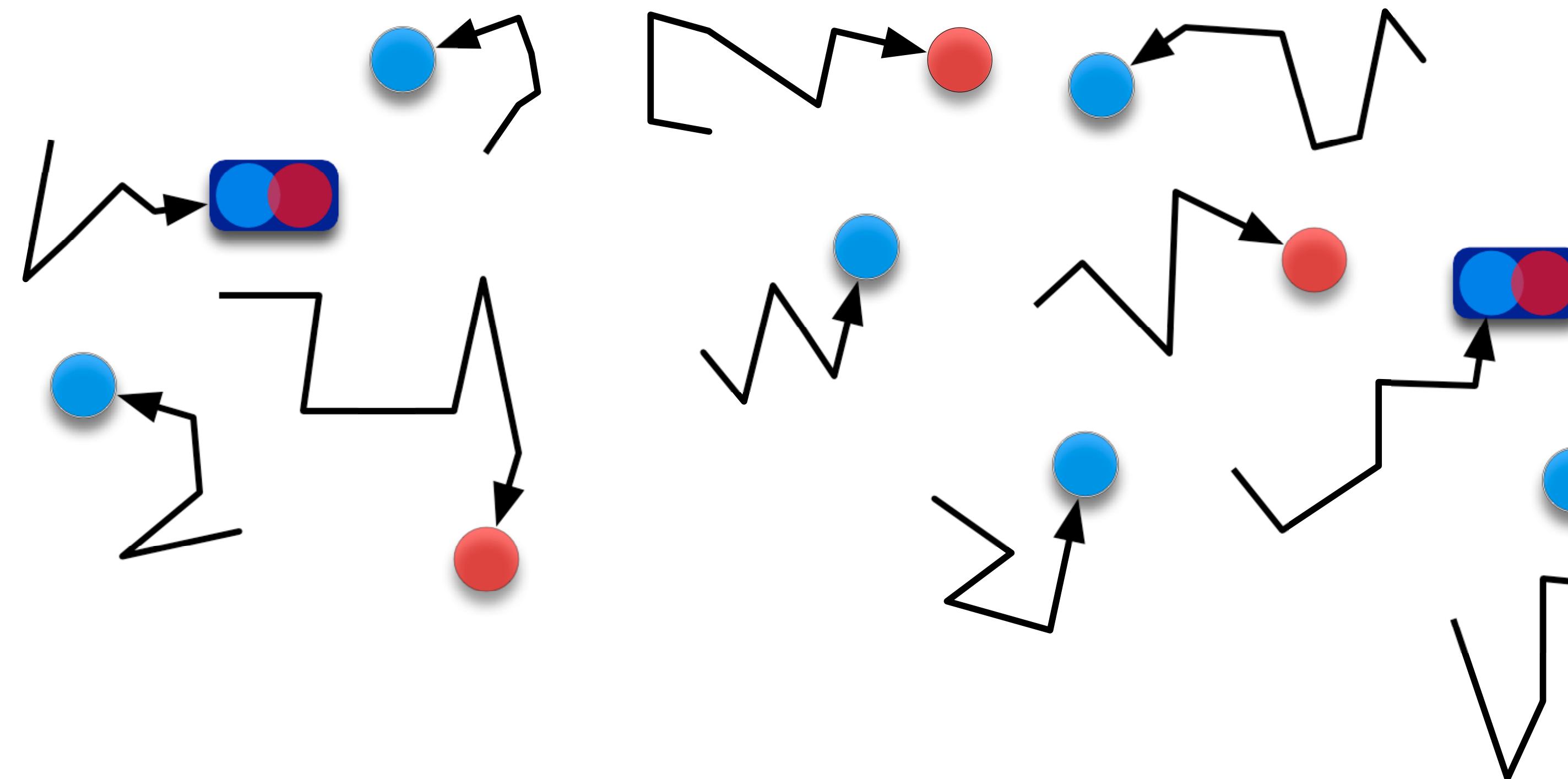
- M. V. Smoluchowski, Z. Phys. Chem. (1917).
- Particles diffuse in continuous space, react / react with some probability upon reaching a fixed separation (called the reaction-radius).
- Reactant pairs can not move closer than the reaction-radius.
- Mathematically, bimolecular reactions are modeled through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



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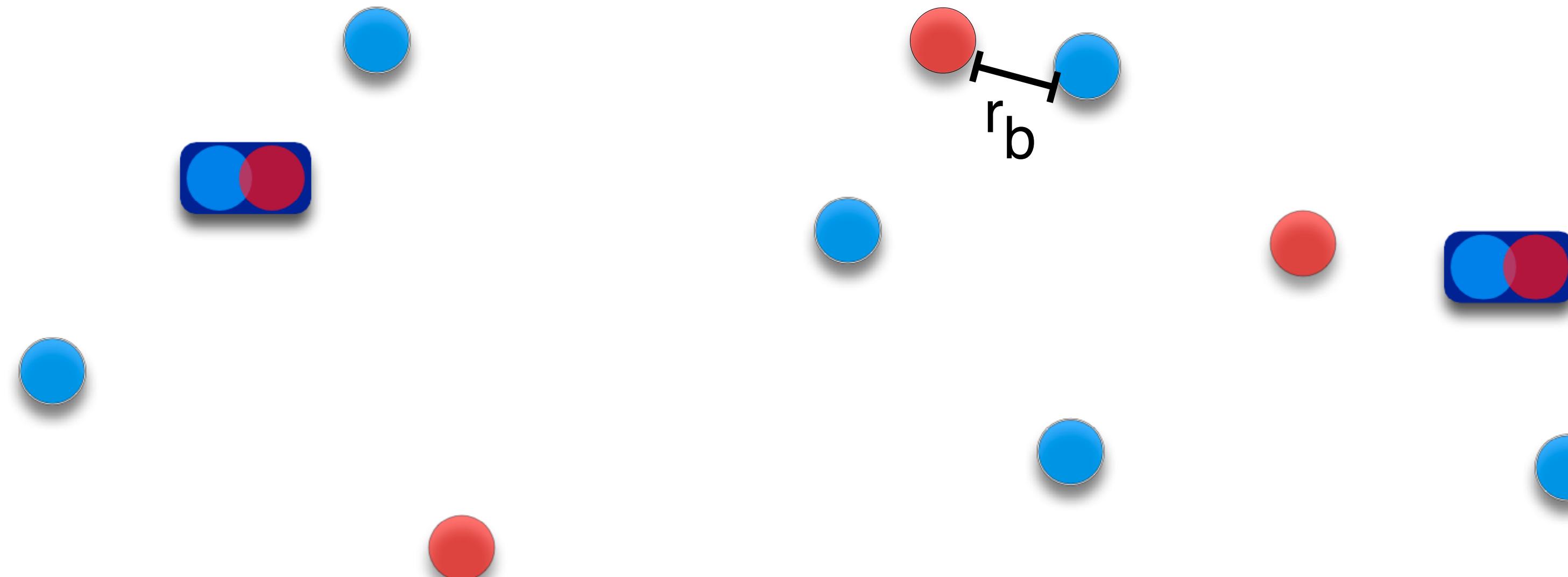
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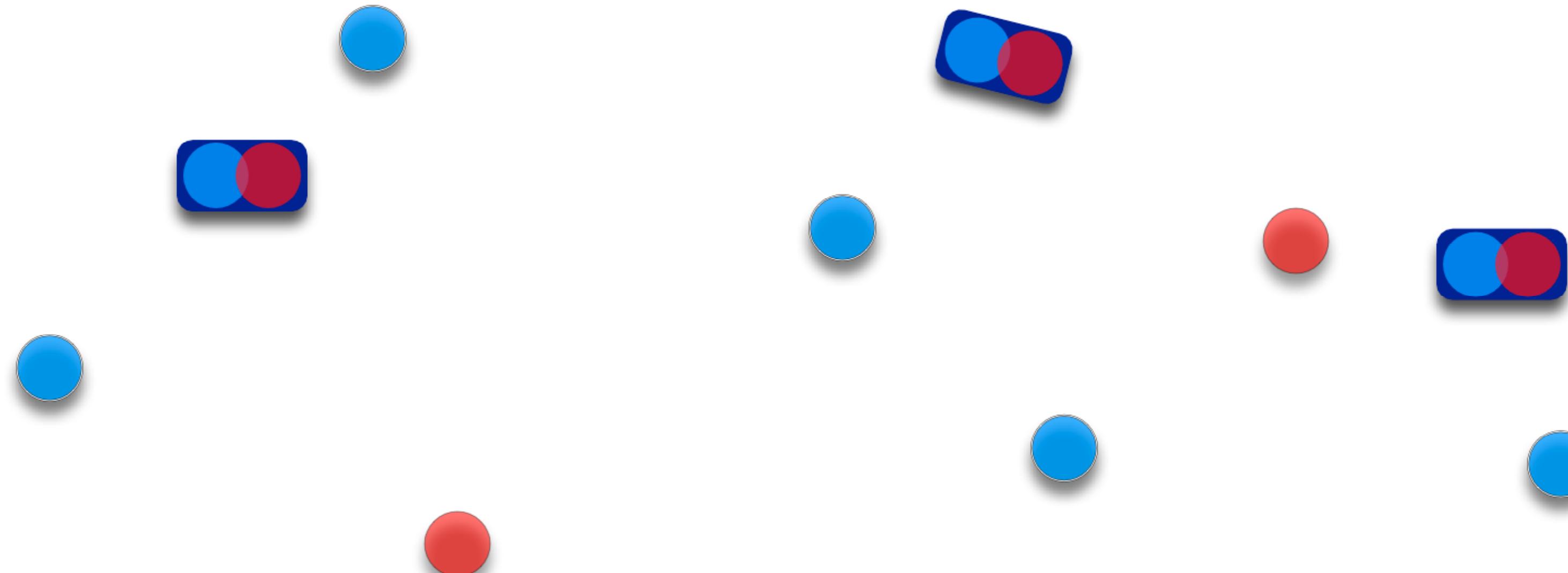
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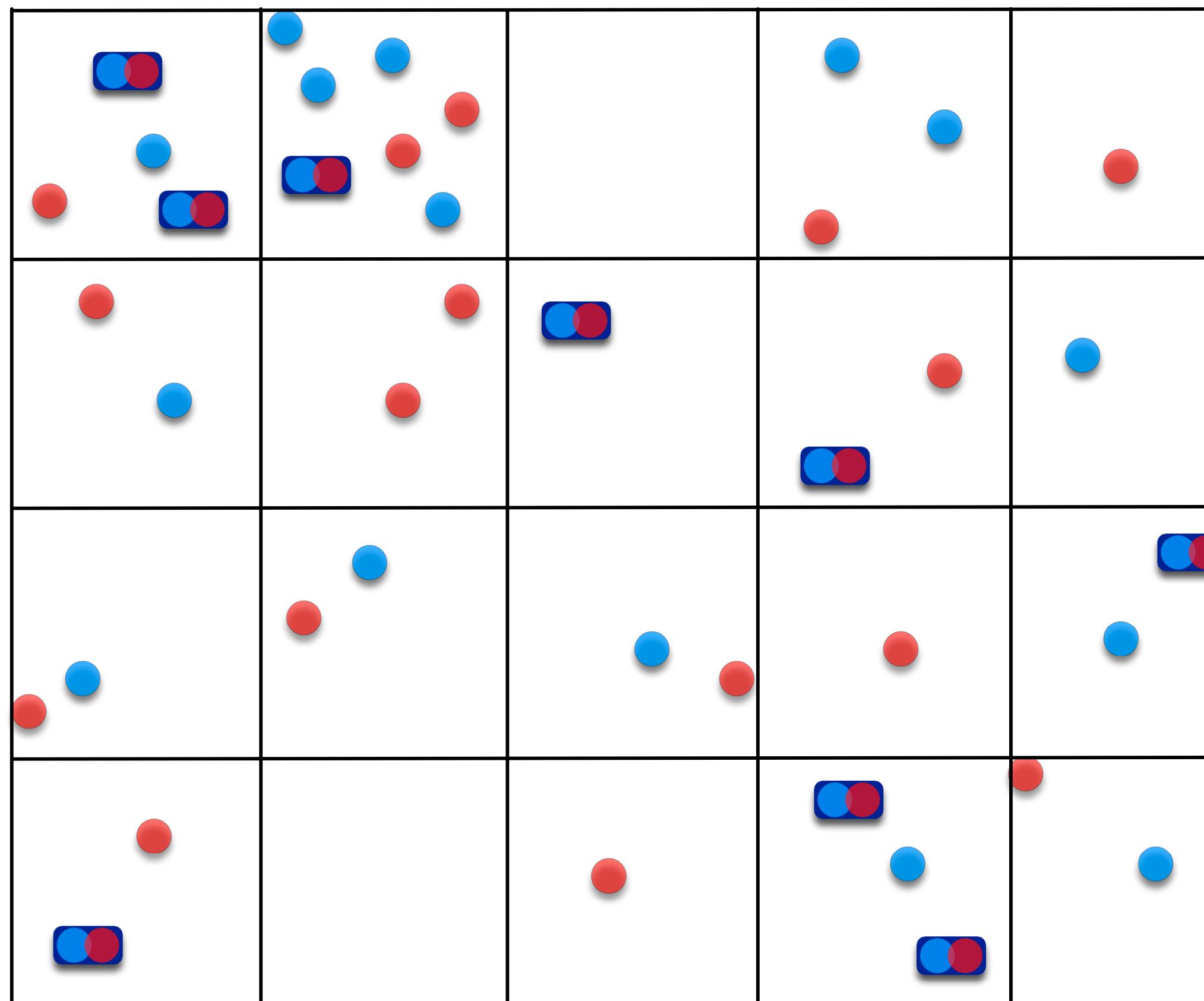
2. Volume reactivity model (e.g. Doi model or λ - ρ model)

- See Doi, *Stochastic Theory of Diffusion-Controlled Reaction*, J. Phys. A (1976).
- Doi attributes the model to Teramoto and Shigesada, Prog. Theor. Phys. (1967).
- Diffusion and linear reactions (zero and first order) are modeled the same as in the contact-reactivity model.
- Two reactants may undergo a bimolecular reaction with a fixed probability per unit time based on their separation.
 - Most common version was popularized by Doi. There, two reactants may react with a fixed probability per time when within a *reaction-radius* of each other.
- Mathematically, reactions are modeled with an interaction function.

What are the three stochastic reaction-diffusion models?

3. Reaction diffusion master equation (RDME):

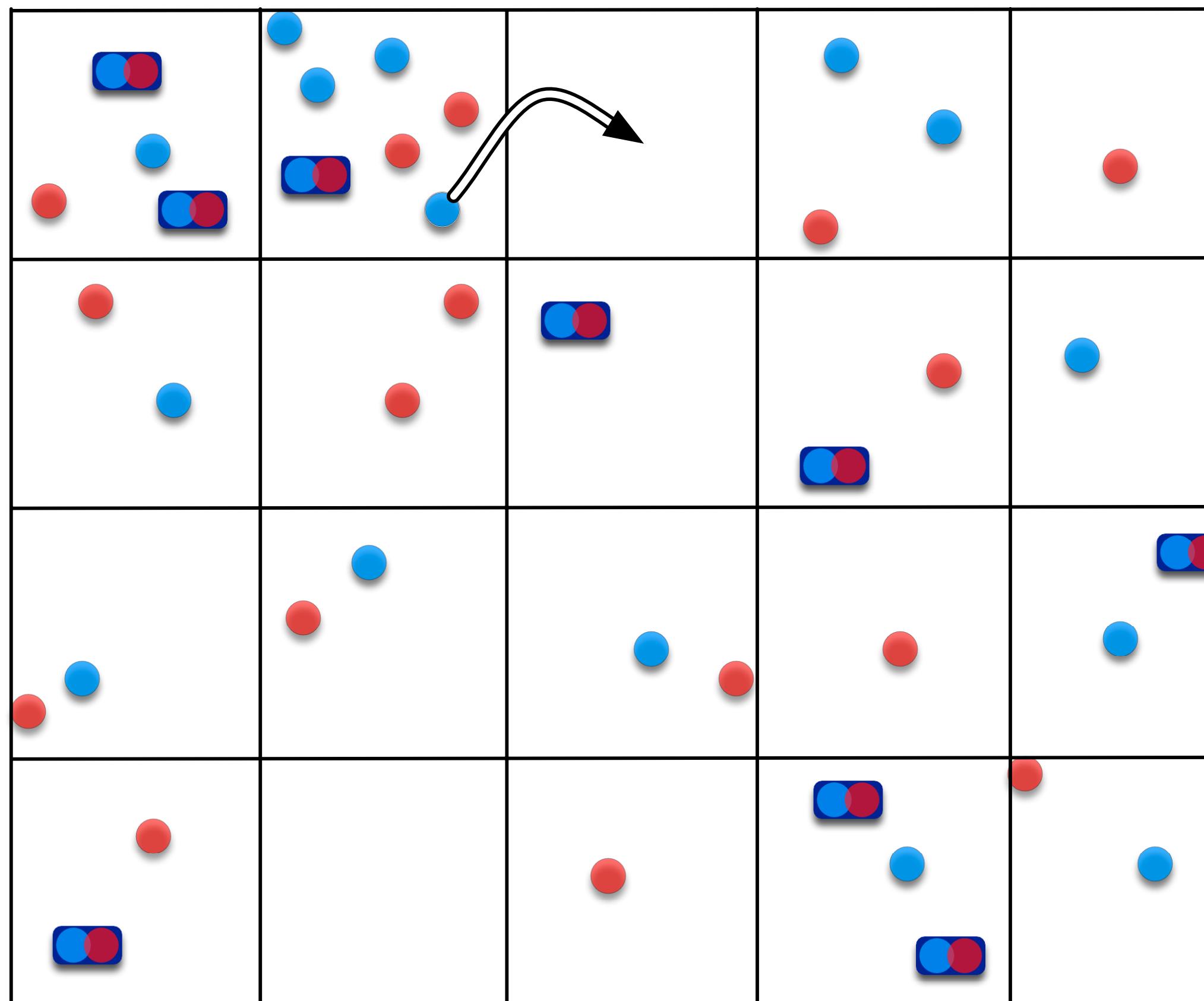
- Goes back to the work of Gardiner, J. Stat. Phys. (1976).
- Space is discretized into a collection of voxels, and particles undergo a continuous-time random walk between voxels.
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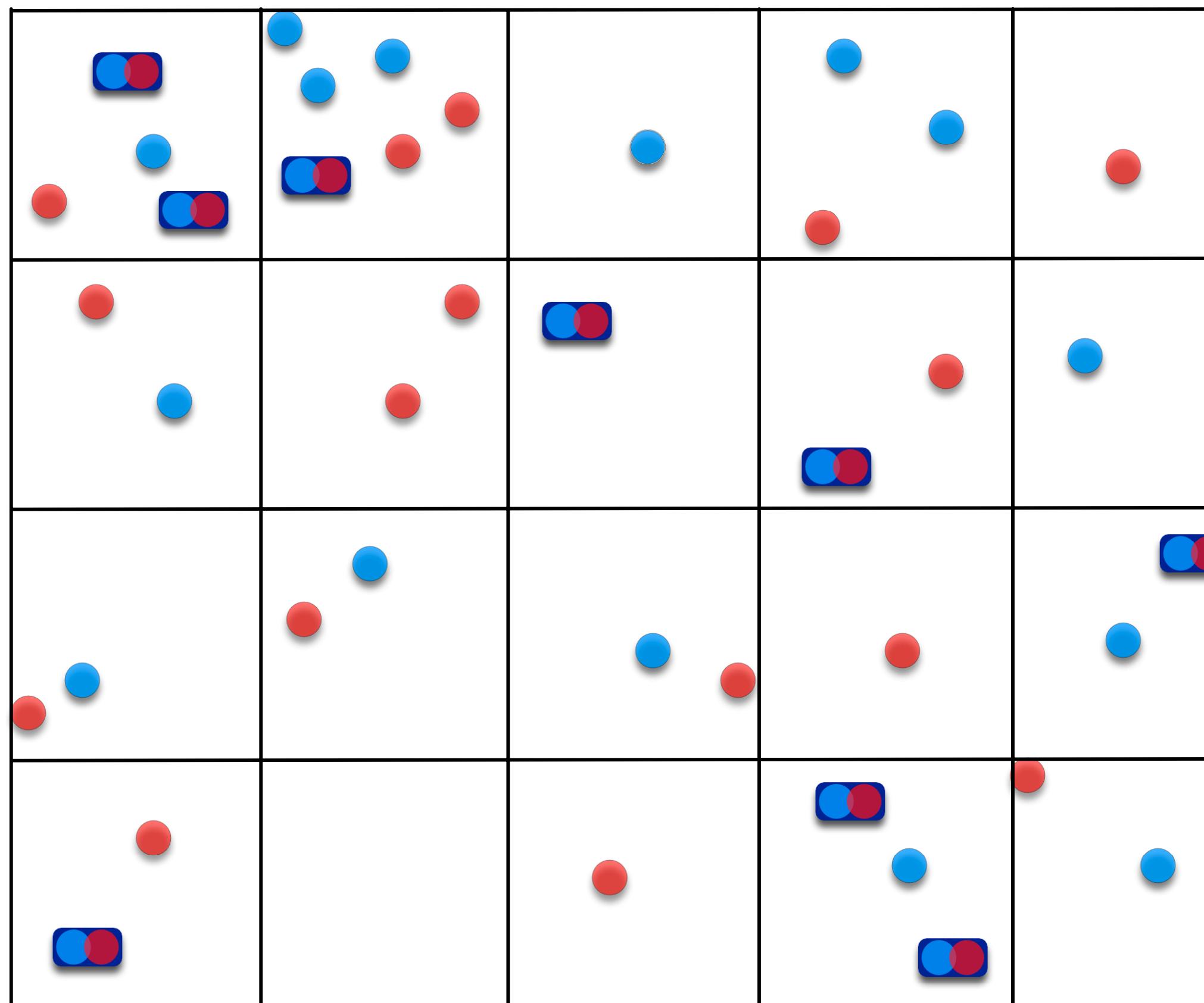
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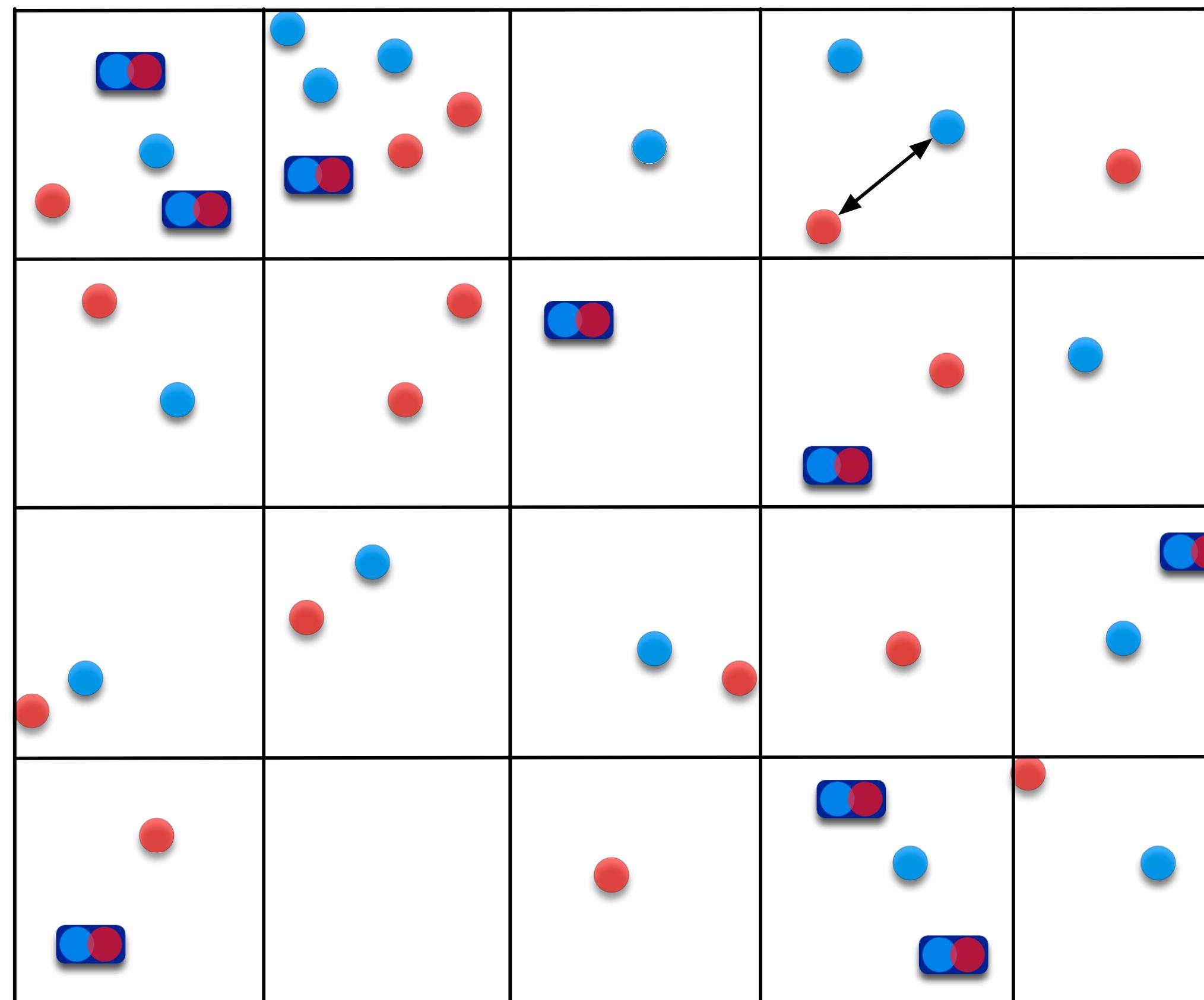
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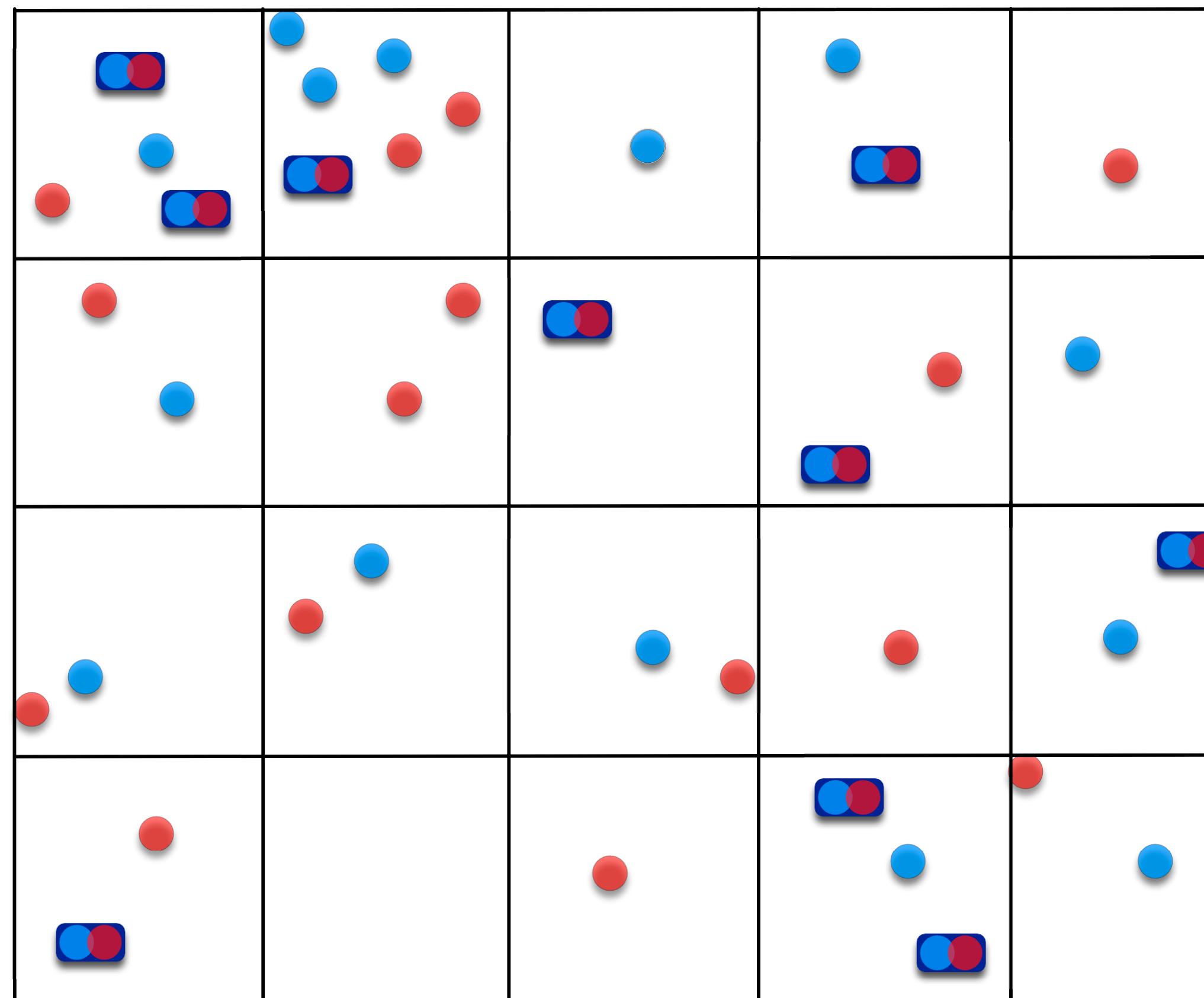
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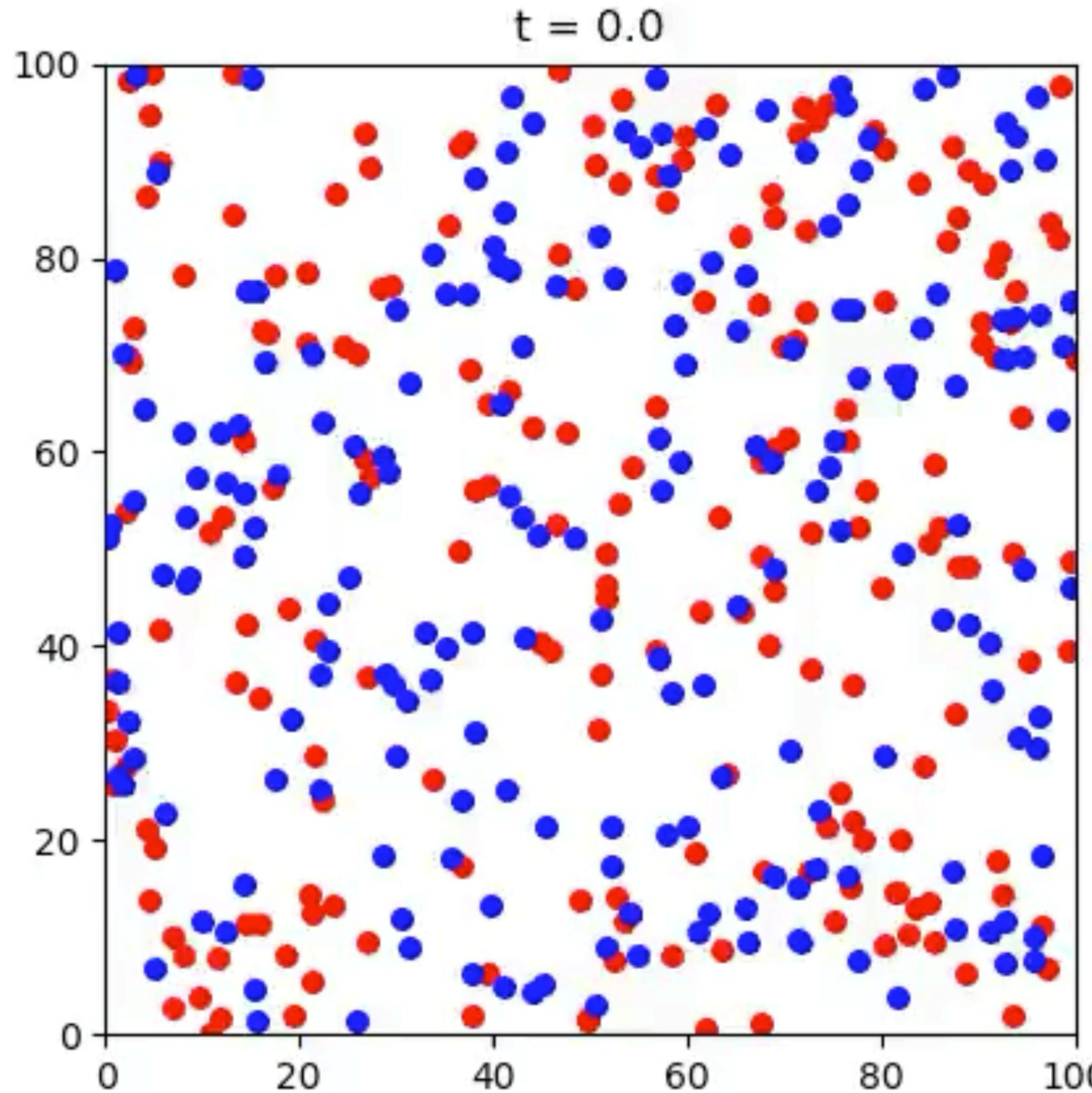
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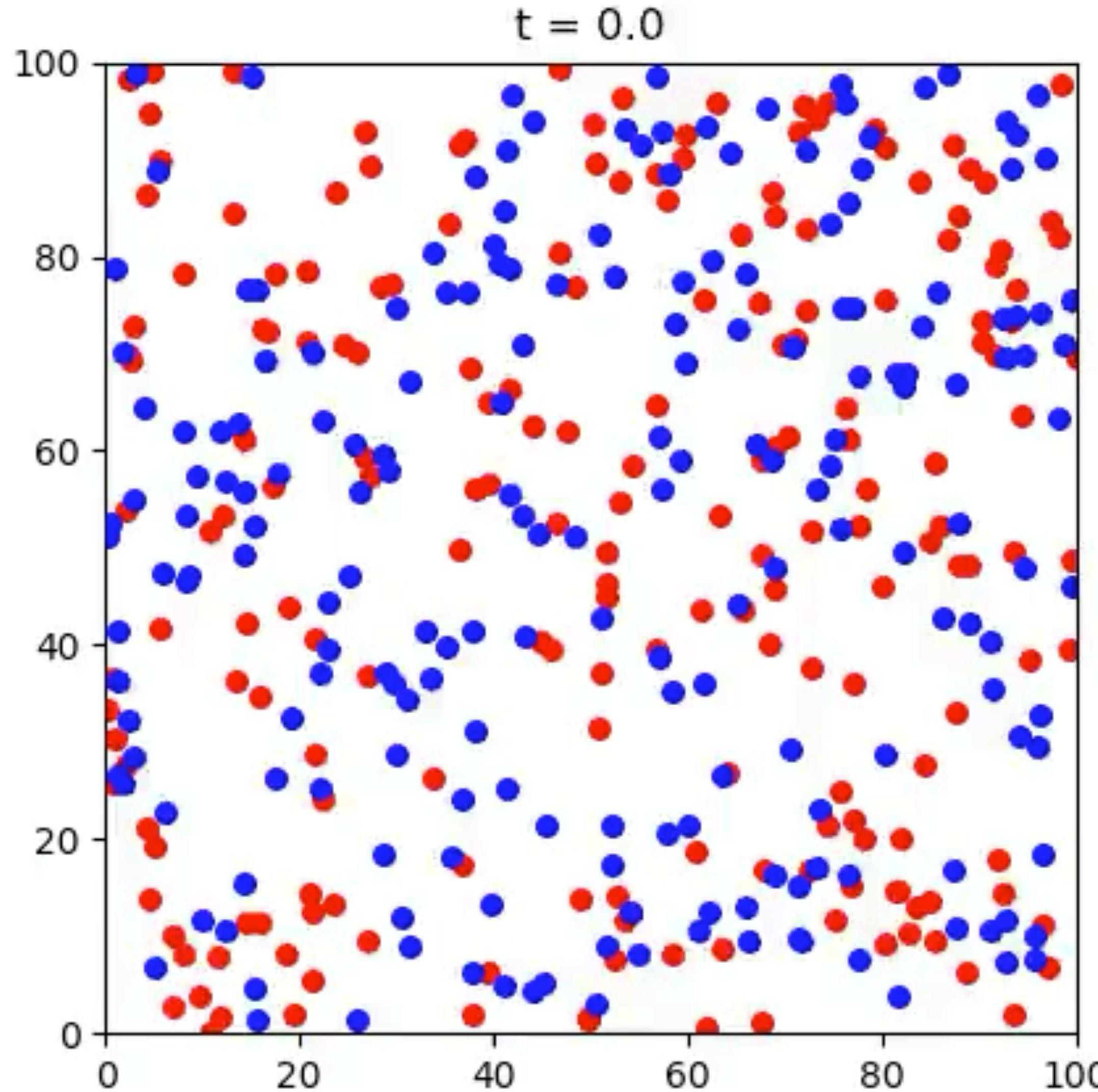


What does a volume reactivity (Doi) model simulation of $A + B \rightleftharpoons C$ look like?



- ▶ Particles move by diffusion (or drift-diffusion)
- ▶ Substrates that are close enough have a probability per time to react.

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How can we mathematically describe the continuous-space model dynamics in a unified manner?

- ▶ We'll restrict to the reversible $A + B \rightleftharpoons C$ reaction in bounded domain $\Omega \subset \mathbb{R}^d$.
- ▶ Assume there is one A at x and one B at y , or one C at z .

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Rate Function Notation:

- ▶ Similar notation used by M. Doi, M. Lachowicz, and others.

$\kappa^+(z|x, y)$ probability density per unit time an $A + B \rightarrow C$ reaction successfully occurs producing a C at z , given an A at x and a B at y tried to react.

$\kappa^-(x, y|z)$ probability density per unit time a $C \rightarrow A + B$ reaction successfully occurs producing an A at x and a B at y , given that a C at z tried to dissociate.

$$\kappa^+(x, y) := \int_{\Omega} \kappa^+(z|x, y) dz$$

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Respective probabilities per time each reaction can occur.

How can we mathematically describe the continuous-space model dynamics in a unified manner?

For the (vector) stochastic process for the particle states and positions at a given time, we can either

- ▶ Study equations for how the process itself evolves.
 - To my knowledge, one can generally only write a weak measure-valued stochastic processes (MVSP) for the associated random (singular) concentration fields.
- ▶ Study equations for the probability density the process has a given value at a given time.
 - i.e. the Kolmogorov Forward / Backward Equations, and for multi particle systems Doi's Fock Space representation.

The most common numerical methods for simulating the process of particles moving and reacting are actually derived from the latter representation, so let's focus on it!

What is the Forward Equation for the two-particle $A + B \rightleftharpoons C$ reaction?

Let

- ▶ $p(x, y, t)$ = the probability density the particles are unbound, with the A particle at x and the B particle at y at time t .
- ▶ $p_b(z, t)$ = the probability density the particles are bound, with the C particle at z at t .

The associated forward equations are:

$$\frac{\partial p}{\partial t}(x, y, t) = (D^A \Delta_x + D^B \Delta_y)p(x, y, t) - \kappa^+(x, y)p(x, y, t) + \int_{\Omega} \kappa^-(x, y|z)p_b(z, t) dz$$

$$\frac{\partial p_b}{\partial t}(z, t) = D^C \Delta_z p_b(z, t) - \kappa^-(z)p_b(z, t) + \int_{\Omega^2} \kappa^+(z|x, y)p(x, y, t) dx dy$$

(with, for example, reflecting BC, but we will ignore them today)

What choices of rate functions give the (Doi) Volume Reactivity model?

A+B→C reaction:

- ▶ $\mathcal{R} = \{(x, y) \in \Omega^2 \mid |x - y| < \varepsilon\} \subset \mathbb{R}^{2d}$ denotes the association reaction region.
- ▶ ε is the reaction-radius
- ▶ λ denotes the probability per time of reacting when an A and B are within ε .
- ▶ $\gamma \in [0, 1]$

$$\kappa^+(z|x, y) = \lambda \mathbb{1}_{\mathcal{R}}(x, y) \delta(z - (\gamma x + (1 - \gamma)y))$$

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C→A+B reaction:

- ▶ μ denotes the probability per time of a C molecule dissociating.

$$\kappa^-(x, y|z) = \mu \left[\frac{1}{|B_{(1-\gamma)\varepsilon}(\mathbf{0})|} \mathbb{1}_{B_{(1-\gamma)\varepsilon}(z)}(x) \right] \delta\left(y - \frac{z - \gamma x}{1 - \gamma}\right)$$

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- ▶ This is equivalent to placing the (weighted) center of mass of the A and B particles at z and sampling their separation vector from the ball of radius ε .
- ▶ This choice is not universal; several alternative functions have been used in the literature. However, this choice is consistent with **detailed balance** holding at equilibrium.

How can we simulate the stochastic process associated with this model?

Two common approaches:

- ▶ *Discretize these equations in space* to give a forward (master) equation for a spatial jump process (i.e. a spatial version of our stochastic chemical kinetics models).
 - Associated process of particles hopping and reacting on a mesh can be simulated with standard SSAs, or spatially-optimized SSAs!
 - The Convergent Reaction Diffusion Master Equation (CRDME) and RDME are lattice approximations/models of this form.
- ▶ *Discretize these equations in time* using a splitting method.
 - Can then simulate the processes associated with diffusion and reaction separately and progressively.
 - Brownian Dynamics methods are of this form.

How do we derive a lattice spatial jump process (i.e. master equation) approximation?

- ▶ Assume $\Omega \subset \mathbb{R}^d$ is a (hyper) cube for simplicity.
- ▶ Discretize Ω into a Cartesian mesh of cubic voxels, V_i , of width h , with centroids x_i , $i = 1, \dots, K$.
- ▶ Let $V_{ij} = V_i \times V_j$ and $V_{ijk} = V_i \times V_j \times V_k$.
- ▶ And define:

Probability particles are in the unbound state with A particle in V_i and B particle in V_j .

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$$P_{ij}(t) = \int_{V_{ij}} p(\mathbf{x}, \mathbf{y}, t) d\mathbf{x} d\mathbf{y} \approx p(x_i, y_j, t) |V_{ij}| .$$

Probability particles are in the unbound state with A particle in V_i and B particle in V_j .

$$P_{bk}(t) = \int_{V_k} p_b(\mathbf{z}, t) d\mathbf{z} \approx p_b(z_k, t) |V_k| .$$

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Probability particles are in the bound state with C particle in V_k .

We now integrate the two forward equations over V_{ij} and V_k respectively and apply the preceding approximation.

How do we discretize the diffusion terms:

We approximate the continuous Laplacians by standard discrete Laplacians and ignore reaction terms (for now).

- Let $\mathcal{N}(i)$ denote the 2^d Cartesian grid nearest-neighbors of voxel i .

After integrating we obtain

$$\frac{dP_{ij}}{dt} = L_h P_{ij} = (L_h^A + L_h^B) P_{ij},$$

$$\frac{dP_{\mathbf{b}_k}}{dt} = L_h^C P_{\mathbf{b}_k},$$

with

$$L_h^A P_{ij} = \frac{D^A}{h^2} \sum_{i' \in \mathcal{N}(i)} P_{i'j} - P_{ij},$$

L_h^B and L_h^C are defined analogously to act on the B and C particle coordinates.

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- This is a master equation for the jump process (i.e. continuous time random walk) of the particles hopping on the mesh from a voxel to an individual nearest (Cartesian) neighbor with rate D/h^2 !

How do we discretize the diffusion terms: (2)

- ▶ Let $X_i(t)$ denote the stochastic process for the number of A particles at location i (i.e. 0 or 1), with $Y_j(t)$ and $Z_k(t)$ defined analogously for the B and C particles.
- ▶ Let $i' \in \mathcal{N}(i)$ label a nearest-neighbor voxel of i , with j' and k' defined analogously.

We can observe that our discretized equation is equivalent to the jump process defined by the “reactions”

$$\{X_i \xrightarrow{D^A/h^2} X_{i'}\}_{i=1,\dots,K, i' \in \mathcal{N}(i)}$$

$$\{Y_j \xrightarrow{D^B/h^2} Y_{j'}\}_{j=1,\dots,K, j' \in \mathcal{N}(j)}$$

$$\{Z_k \xrightarrow{D^C/h^2} Z_{k'}\}_{k=1,\dots,K, k' \in \mathcal{N}(k)}$$

Hence we can just simulate the particle(s) hopping on the mesh with a standard SSA!

How do we discretize the reaction terms?

Ignoring diffusion terms, integrating the equation for $p(\mathbf{x}, \mathbf{y}, t)$ over V_{ij} :

$$\begin{aligned}\frac{dP_{ij}}{dt} &= - \int_{V_{ij}} \kappa^+(\mathbf{x}, \mathbf{y}) p(\mathbf{x}, \mathbf{y}, t) d\mathbf{x} d\mathbf{y} + \int_{\Omega} \left[\int_{V_{ij}} \kappa^-(\mathbf{x}, \mathbf{y} | \mathbf{z}) d\mathbf{x} d\mathbf{y} \right] p_b(\mathbf{z}, t) d\mathbf{z}, \\ &\approx -\frac{1}{|V_{ij}|} P_{ij}(t) \int_{V_{ij}} \kappa^+(\mathbf{x}, \mathbf{y}) d\mathbf{x} d\mathbf{y} + \sum_k \frac{1}{|V_k|} P_{bk}(t) \int_{V_{ijk}} \kappa^-(\mathbf{x}, \mathbf{y} | \mathbf{z}) d\mathbf{x} d\mathbf{y} d\mathbf{z}, \\ &= -\kappa_{ij}^+ P_{ij}(t) + \sum_k \kappa_{ijk}^- P_{bk}(t),\end{aligned}$$

where for $|V_i| = h^d$ and $|V_{ij}| = h^{2d}$ we've defined

$$\kappa_{ij}^+ := \frac{1}{|V_{ij}|} \int_{V_{ij}} \kappa^+(\mathbf{x}, \mathbf{y}) d\mathbf{x} d\mathbf{y},$$

Probability per time an A in V_i and B in V_j react.

$$\kappa_{ijk}^- := \frac{1}{|V_k|} \int_{V_{ijk}} \kappa^-(\mathbf{x}, \mathbf{y} | \mathbf{z}) d\mathbf{x} d\mathbf{y} d\mathbf{z}.$$

Probability per time a C in V_k dissociates into an A in V_i and B in V_j .

How do we discretize the reaction terms? (2)

Similarly, ignoring diffusion terms and integrating the equation for $p_b(z, t)$ over V_k :

$$\begin{aligned}\frac{dP_{bk}}{dt} &= - \int_{V_k} \kappa^-(z) p_b(z, t) dz + \int_{\Omega^2} \left[\int_{V_k} \kappa^+(z|x, y) dz \right] p(x, y, t) dx dy, \\ &\approx -\frac{1}{|V_k|} P_{bk}(t) \int_{V_k} \kappa^-(z) dz + \sum_{i,j} \frac{1}{|V_{ij}|} P_{ij}(t) \int_{V_{ijk}} \kappa^+(z|x, y) dx dy dz, \\ &= -\kappa_k^- P_{bk}(t) + \sum_{i,j} \kappa_{ijk}^+ P_{ij}(t),\end{aligned}$$

where

$$\kappa_k^- := \frac{1}{|V_k|} \int_{V_k} \kappa^-(z) dz,$$

Probability per time a C in V_k dissociates.

$$\kappa_{ijk}^+ := \frac{1}{|V_{ij}|} \int_{V_{ijk}} \kappa^+(z|x, y) dx dy dz.$$

Probability per time an A in V_i and B in V_j react to create a C in V_k .

How are the different transition rates related?

It follows that

$$\kappa_{ij}^+ = \sum_k \kappa_{ijk}^+,$$

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These four transition rates define two equivalent jump process reaction models:

- ▶ Let A_i denote the number of A molecules in V_i .
- ▶ Define B_j and C_k similarly.

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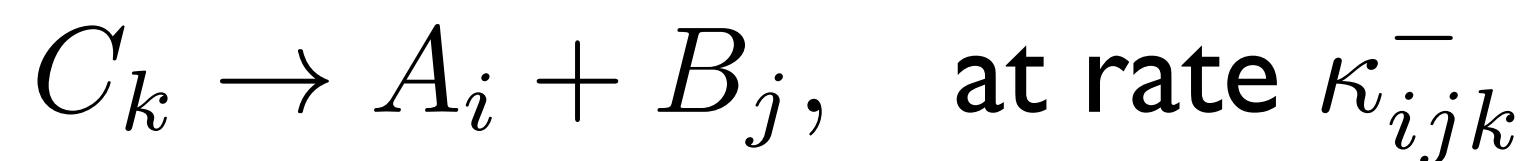
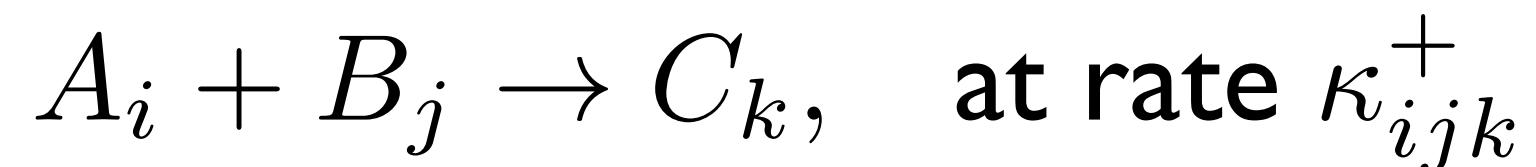
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Reaction Model I



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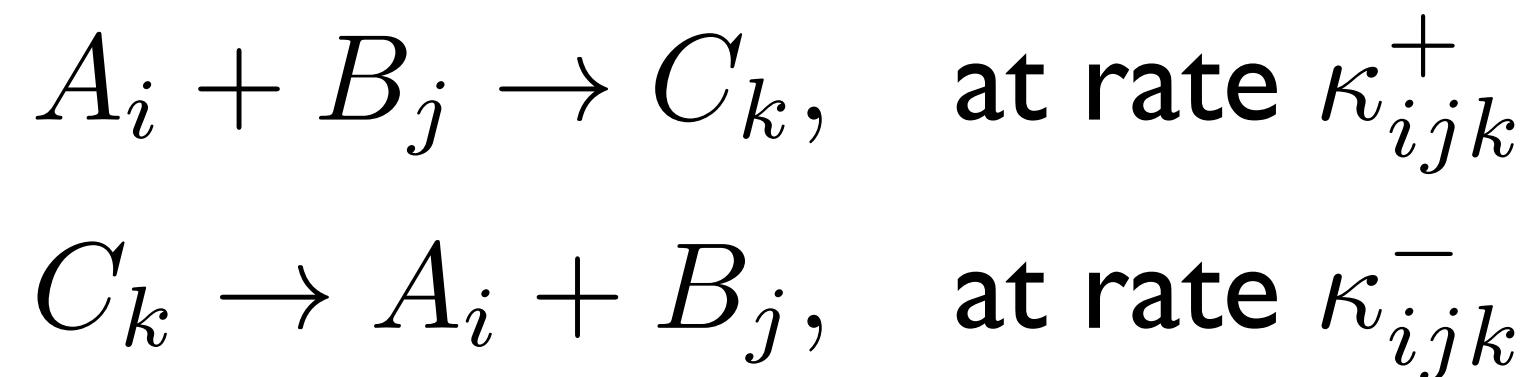
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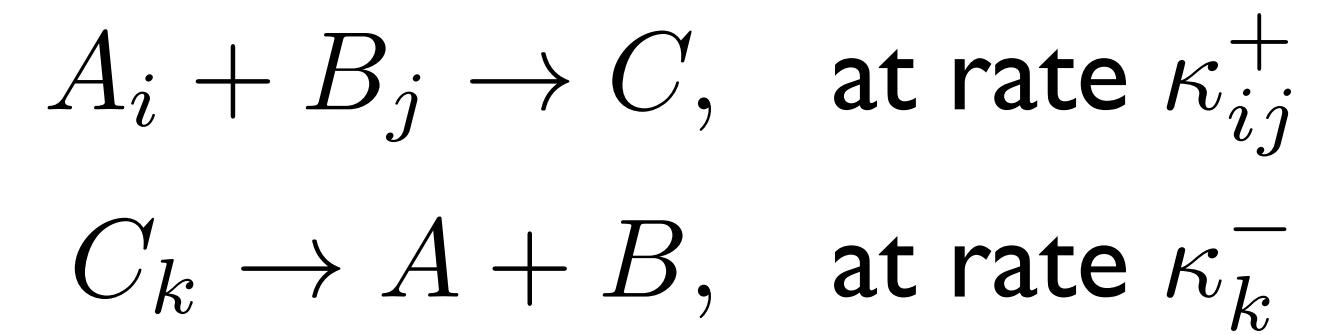
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Reaction Model I



Reaction Model II



and we must then sample the position
of the C (res. A and B) molecules.

For Reaction Model II how do we determine particle placement after a reaction?

We may define:

$$\kappa_{k|ij}^+ := \frac{\kappa_{ijk}^+}{\kappa_{ij}^+}$$

For $A_i + B_j \rightarrow C$, this gives the probability of placing the new C molecule in V_k .

$$\kappa_{ij|k}^- := \frac{\kappa_{ijk}^-}{\kappa_k^-}$$

For $C_k \rightarrow A + B$, this gives the probability of placing the new A molecule in V_i and B in V_j .

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For $C_k \rightarrow A + B$, this gives the probability of placing the new A molecule in V_i and B in V_j .

So we have two different ways to simulate reactions!

The difference between them is analogous to the difference between the first reaction and direct methods.

What is the final master equation discretization of the full model?

Combining the two discretizations we arrive at the master equation model:

$$\frac{dP_{ij}}{dt} = L_h^{\mathbf{A}} P_{ij}(t) + L_h^{\mathbf{B}} P_{ij}(t) - \kappa_{ij}^+ P_{ij}(t) + \sum_{k=1}^K \kappa_{ijk}^- P_{\mathbf{b}k}(t),$$

$$\frac{dP_{\mathbf{b}k}}{dt} = L_h^{\mathbf{C}} P_{\mathbf{b}k}(t) - \kappa_k^- P_{\mathbf{b}k}(t) + \sum_{i,j=1}^K \kappa_{ijk}^+ P_{ij}(t).$$

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We call this model the *convergent reaction-diffusion master equation (CRDME)**.

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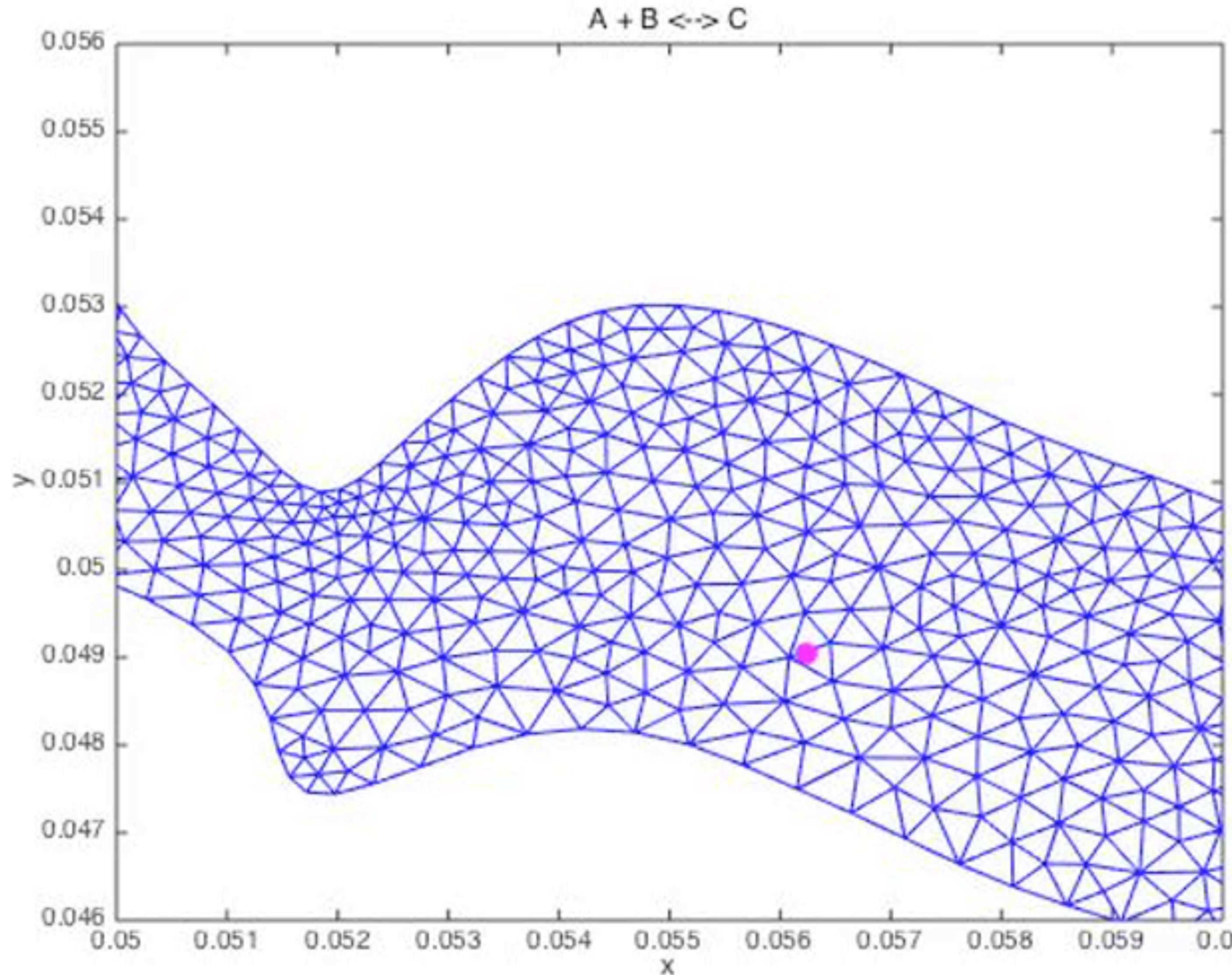
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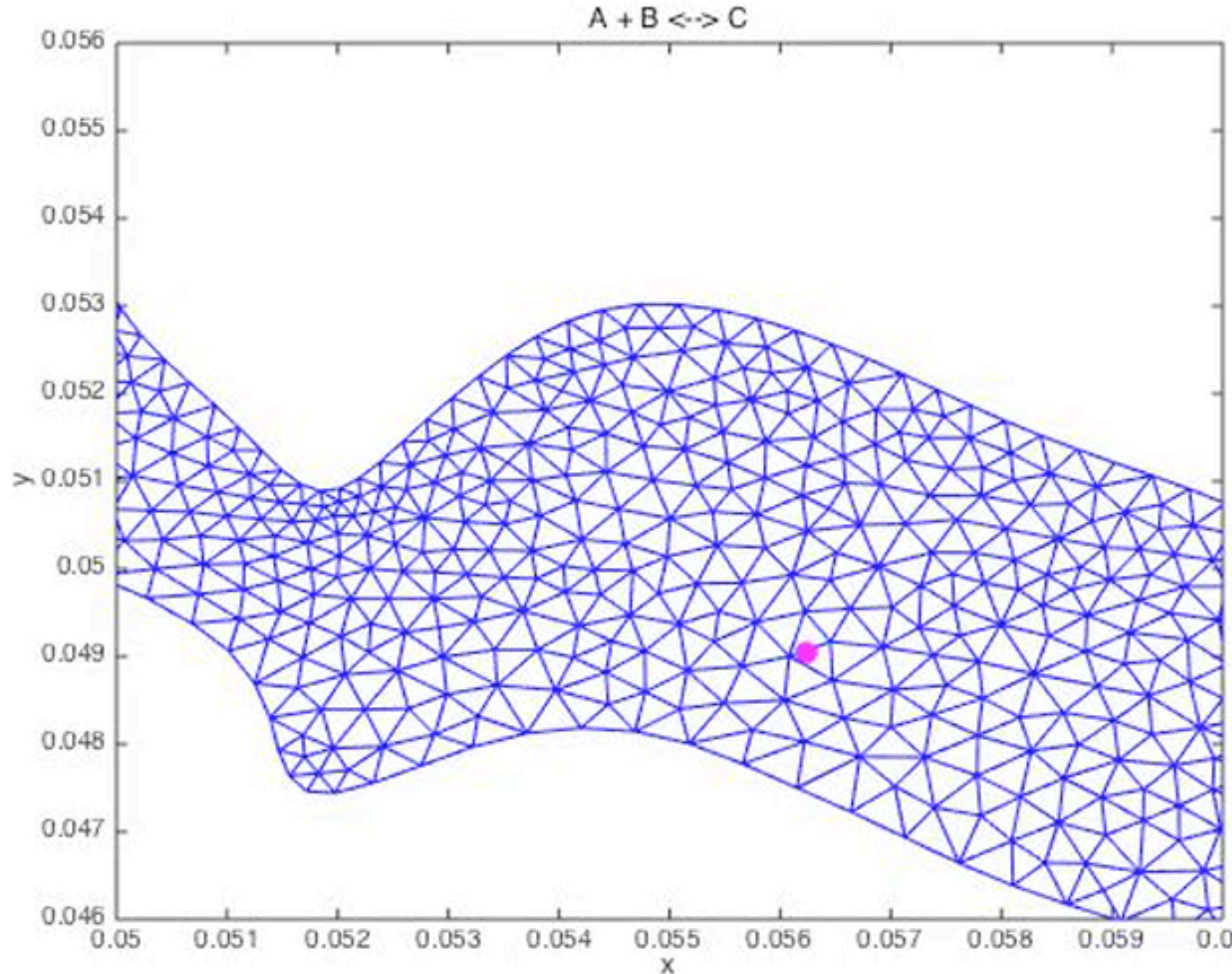
Let's look at a simulation of this system!

What does a simulation of jump process associated with the $A + B \rightleftharpoons C$ CRDME look like?



Note this is from an unstructured grid CRDME, where the diffusion transition rates arise from a finite element discretization.

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So far assuming only at most one molecule of each species!

The whole procedure can be generalized to systems with arbitrary numbers of each chemical species.
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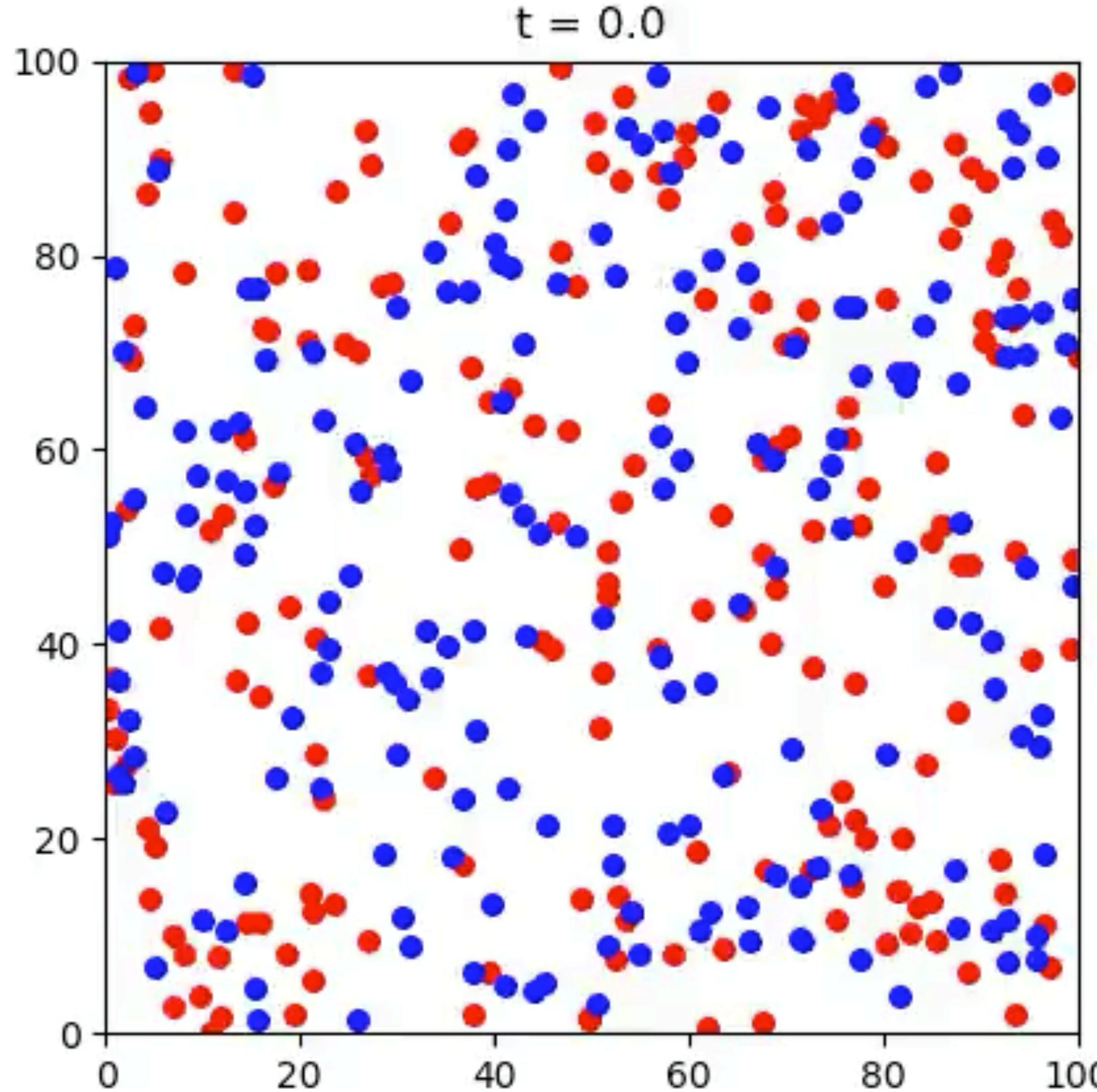
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For a_i the number of species A molecules in V_i at t , i.e. $A_i(t) = a_i$, with b_j and c_k defined similarly:

	Reactions	Transition Rates	Upon Reaction Event
Diffusive hopping:	$A_j \rightarrow A_i$	$(L_h^A)_{ij} a_j$	$A_i := A_i + 1, A_j := A_j - 1,$
	$B_j \rightarrow B_i$	$(L_h^B)_{ij} b_j$	$B_i := B_i + 1, B_j := B_j - 1,$
	$C_j \rightarrow C_i$	$(L_h^C)_{ij} c_j$	$C_i := C_i + 1, C_j := C_j - 1,$
Chemical Reactions:	$A_i + B_j \rightarrow C$	$\kappa_{ij}^+ a_i b_j$	$A_i := A_i - 1, B_j := B_j - 1.$ Sample k from $\{\kappa_{k ij}^+\}_{k=0,\dots,K}.$ Set $C_k := C_k + 1.$
	$C_k \rightarrow A + B$	$\kappa_k^- c_k$	$C_k := C_k - 1.$ Sample (i, j) from $\{\kappa_{ij k}^-\}_{i,j=0,\dots,K}.$ Set $A_i := A_i + 1, B_j := B_j + 1.$

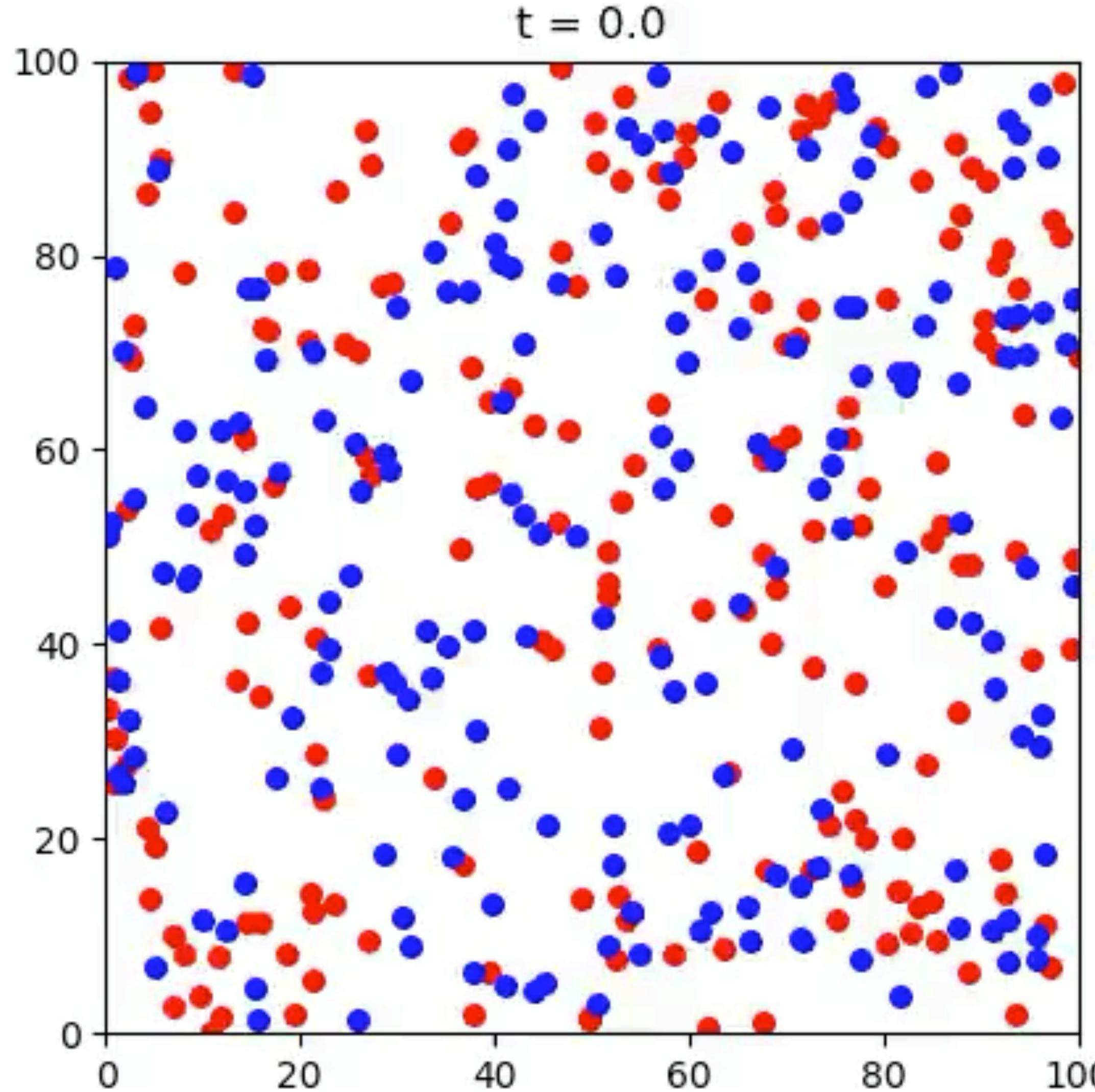
We can then simulate the system of molecules hopping between voxels and reacting using standard SSAs!

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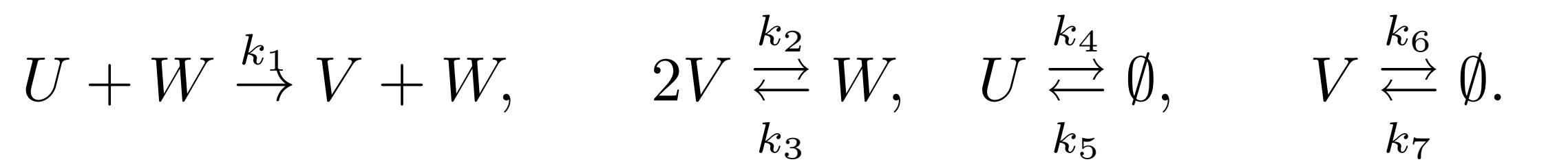


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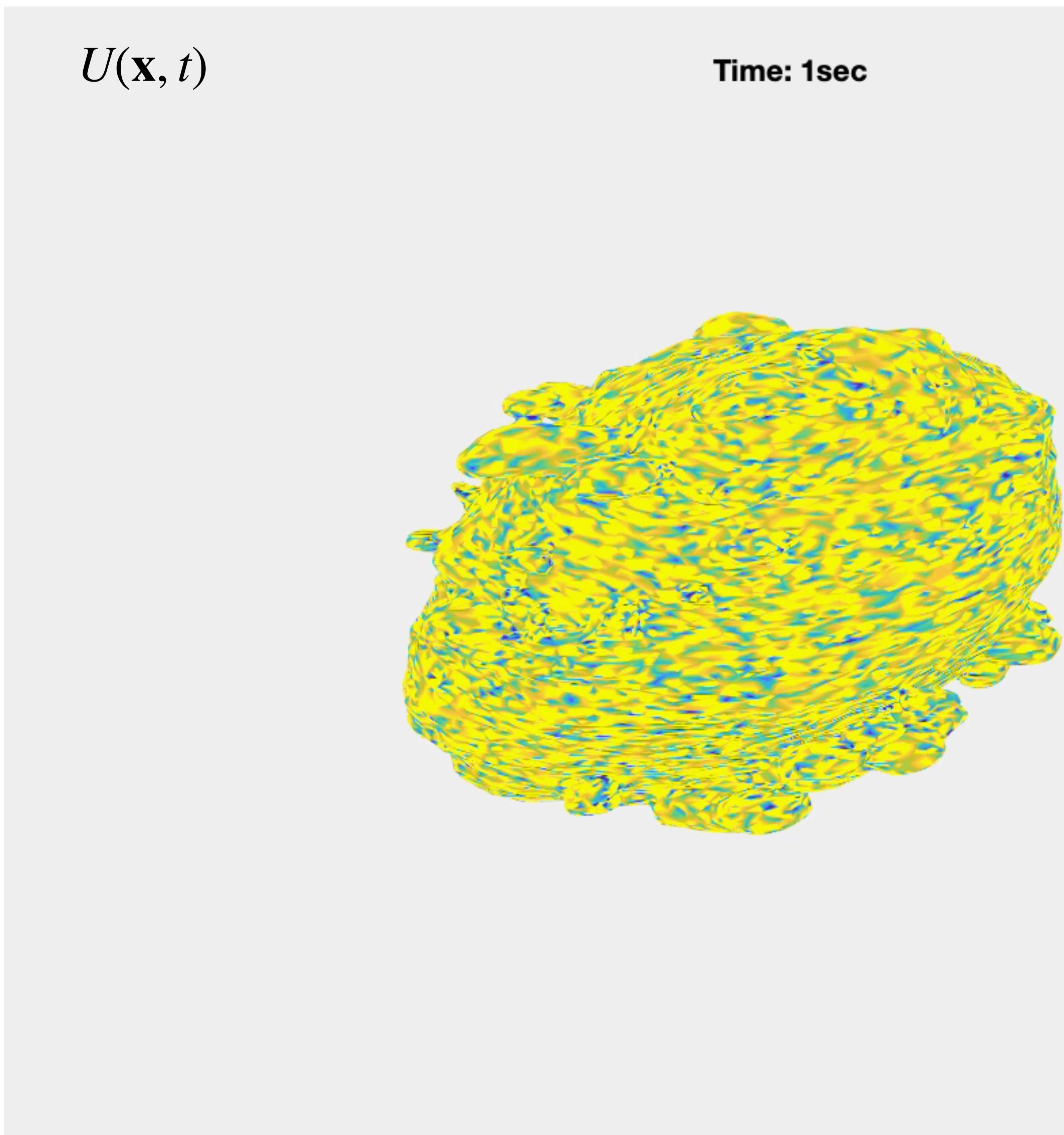
What does a surface CRDME simulation look like?

We can generalize to unstructured grids, drift-diffusion problems, complex geometries, and even surfaces. For example:

Using a reconstructed T cell membrane geometry, we simulate the Baras-Pearson-Mansour pattern formation system on the cell surface:



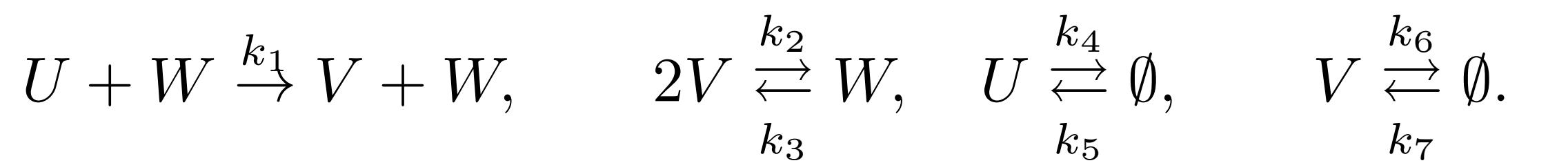
Note, this is a SSA of the CRDME simulation, resolving each individual molecule of each species hopping and reacting on the T cell membrane mesh!



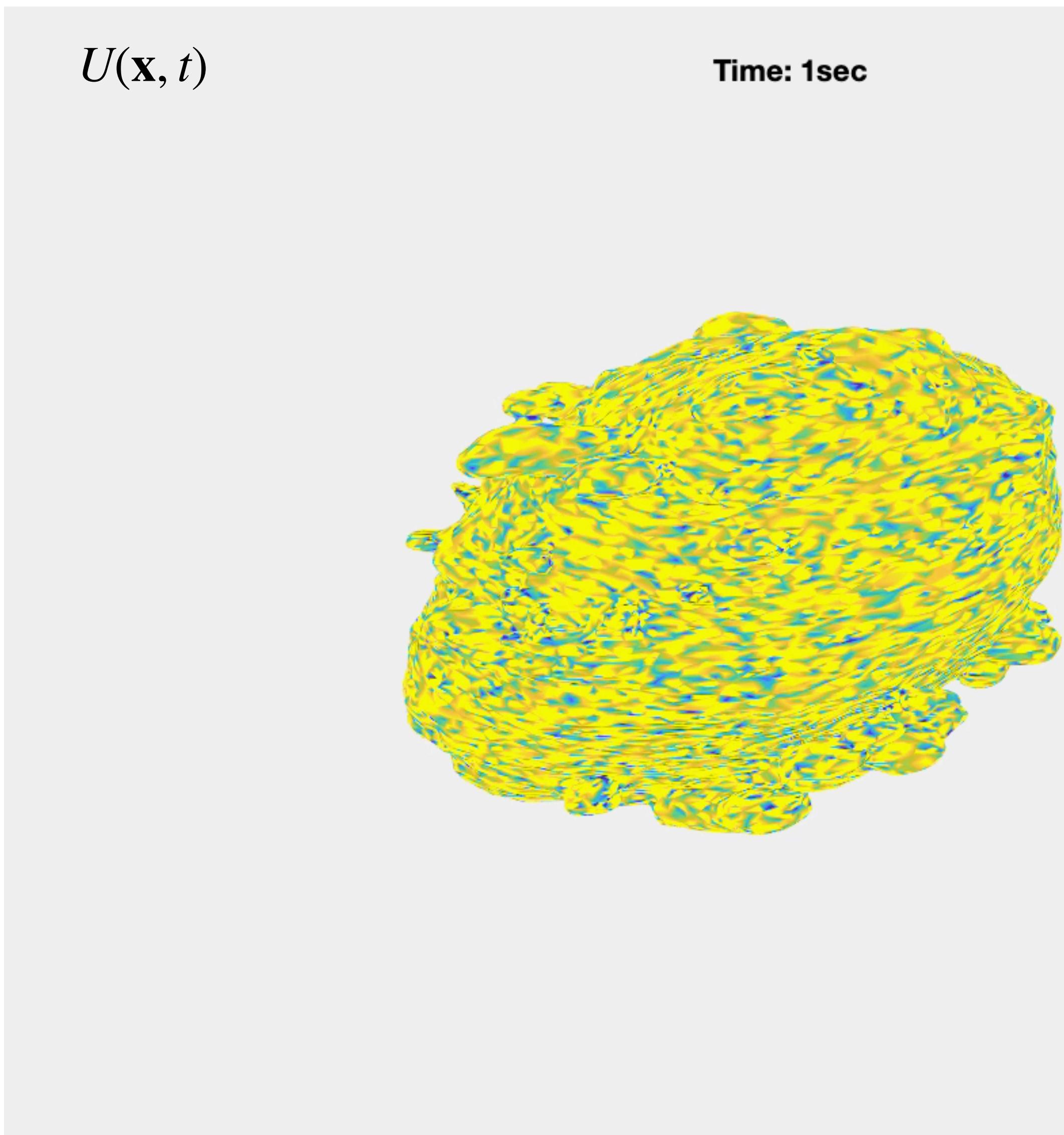
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What about the popular RDME lattice model?

Suppose we choose our reactive interaction functions in the volume reactivity model to be

$$\kappa^+(z|x,y) = k^+ \delta(x-y)\delta(y-z) \quad \kappa^-(x,y|z) = k^- \delta(x-z)\delta(y-z)$$

*Note that the resulting equations for $p(x,y,t)$ and $p_b(z,t)$ are actually not well-posed in two or more dimensions (or even necessarily well-defined, **so this is very formal!**)*

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Note: if k^+ and k^- are chosen to be the normal **well-mixed** bimolecular and first order rate constants, one obtains consistency in the fast diffusion limit and at equilibrium.

What about the popular RDME lattice model? (2)

So the RDME can be interpreted as a discretization of a (*not well-defined in two or more dimensions*) model where particles must be at the **same** point to react (a probability zero event).

- ▶ The RDME therefore **does not** converge back to any reasonable particle reaction-diffusion model as the mesh spacing is taken to zero!
 - In the continuum limit one loses bimolecular reactions in two or more dimensions since particles can't find each other*.
 - However, for mesh spaces that are neither too large nor too small the RDME can sometimes give good agreement with particle models.
- ▶ Despite these shortcomings, the RDME is still often used due to its simplicity of implementation, and reduced computational complexity from only allowing reactions within the same voxel.

* S. A. Isaacson, *The Reaction-Diffusion Master Equation as an Asymptotic Approximation of Diffusion to a Small Target*, SIAM J. Appl. Math (2009).

How can we build SSAs that are tailored for spatial lattice models like the CRDME and RDME?

- ▶ Assume we have N species, M reactions, and K voxels.
- ▶ In the Next Subvolume Method for the RDME:
 - One stores the total propensity for each lattice site in an indexed priority queue.
 - This allows constant order selection of within which voxel the next reaction / diffusive hop occurs, and $O(\log_2(K))$ updating of these values.
 - The Direct Method is then used to search the propensities for diffusion of each species out of the voxel, and each possible reaction that can occur within the voxel — this is $O(N + M)$ work.
 - The total work is $O(\log_2(K)) + O(N) + O(M)$.

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 - The total work is $O(\log_2(K)) + O(N) + O(M)$.
- ▶ If one instead stores the total propensity at each lattice site within a composition-rejection table with L groups, this can be improved to $O(L) + O(N) + O(M)$.
 - In JumpProcesses we call this the *DirectCRDirect* method.

* Elf and Ehrenberg, *Spontaneous separation of bi-stable biochemical systems into spatial domains of opposite phases*, Systems Biology (2004).

How do these two methods perform in practice as we increase the number of spatial voxels?

https://docs.sciml.ai/SciMLBenchmarksOutput/stable/Jumps/Spatial_Signaling_Sanft/

There is a lot of room for improvement, as there actually aren't more than a handful of spatially adapted SSAs that have been proposed!

(Perhaps because it is so easy to just use the well-mixed SSAs even if they don't offer the best asymptotic work...)

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

Advantages:

- ▶ SSA-based simulation methods generate exact samples of the underlying lattice stochastic process.
- ▶ Many extensions based on leveraging well-developed PDE discretization techniques to handle drift, complex geometries, surface geometries, variable diffusivities, moving domains, etc.
- ▶ Several well-designed publicly available simulators that can handle general chemical systems in complex geometries (such as STEPS, Lattice Microbes, and URDME).
- ▶ `JumpProcess.jl` has `NSM` and `DirectCRDirect` solvers for mass action reaction systems.
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Disadvantages:

- ▶ Can be proven in RDME that bimolecular reactions are lost in the continuum limit that the lattice spacing is taken to zero (Isaacson (SIAP 2009))
 - However, method maybe accurate for lattice spacings that are neither too large or small. This can be tricky to determine...
- ▶ In CRDME reactions can now occur between particles in *sufficiently close voxels* increasing computational expense. Underlying VR model requires more microscopic parameters than RDME.
- ▶ Often spend large portion of computational work simulating hops of molecules between lattice sites.

What are Brownian Dynamics (BD) Approximations to the Volume Reactivity Model?

The core idea is to use a *splitting method* to discretize the forward equation in time!

To solve from time t to time $t + \Delta t$ we

I. Diffuse the particles by solving on $[t, t + \Delta t]$:

$$\frac{\partial p_1}{\partial t}(x, y, t) = (D^A \Delta_x + D^B \Delta_y) p_1(x, y, t),$$

$$\frac{\partial p_{b,1}}{\partial t}(z, t) = D^C \Delta_z p_{b,1}(z, t)$$

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2. React the particles by solving on $[t, t + \Delta t]$:

$$\frac{\partial p_2}{\partial t}(x, y, t) = -\kappa^+(x, y)p_2(x, y, t) + \int_{\Omega} \kappa^-(x, y | z)p_{b,2}(z, t) dz,$$

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with the initial conditions:

$$p_2(x, y, t) = p_1(x, y, t + \Delta t)$$

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3. Set $p(x, y, t + \Delta t) = p_2(x, y, t + \Delta t)$ and $p_b(z, t + \Delta t) = p_{b,2}(z, t + \Delta t)$.

What does this correspond to at the *process level*?

We simulate the stochastic process of the particles reacting and diffusing in the same order, i.e.

Assume (if unbound), at t the A particle has position $X(t)$ and the B particle $Y(t)$, while if bound the C particle has position $Z(t)$. One timestep from t to $t + \Delta t$ proceeds as

I. Diffuse the particles by simulating on $[t, t + \Delta t]$:

If unbound:

$$X_1(t + \Delta t) = X(t) + \sqrt{2D^A \Delta t} N_{d,1}(0,1)$$

$$Y_1(t + \Delta t) = Y(t) + \sqrt{2D^B \Delta t} N_{d,2}(0,1)$$

If bound:

$$Z_1(t + \Delta t) = Z(t) + \sqrt{2D^C \Delta t} N_{d,3}(0,1)$$

Where $N_{d,i}(0,1)$ are each *independent* d -dimensional vectors of samples from Normal Distributions with mean zero and variance one.

What does this correspond to at the *process level*?

II. React the particles by simulating on $[t, t + \Delta t]$ from the post-diffusion positions:

If currently unbound:

React with probability

i.e. if

$$P_R = \kappa^+ (X_1(t + \Delta t), Y_1(t + \Delta t)) \Delta t$$

`rand() < PR`

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If react, sample the product position, $Z(t + \Delta t)$, from:

$$\frac{\kappa^+(Z(t + \Delta t) | X_1(t + \Delta t), Y_1(t + \Delta t))}{\kappa^+(X_1(t + \Delta t), Y_1(t + \Delta t))}$$

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For the Doi model, this corresponds to placing:

$$Z(t + \Delta t) = \gamma X_1(t + \Delta t) + (1 - \gamma) Y_1(t + \Delta t)$$

What does this correspond to at the *process level*?

If currently bound:

Dissociate with probability

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$$\frac{\kappa^-(X(t + \Delta t), Y(t + \Delta t) | Z_1(t + \Delta t))}{\kappa^-(Z_1(t + \Delta t))}$$

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For the Doi model, this corresponds to sampling $X(t + \Delta t)$ and $Y(t + \Delta t)$ by:

- (A) Sampling a separation vector R as a point uniformly within the d -dimensional ball of radius ε .
- (B) Setting the weighted center of mass $W = Z_1(t + \Delta t)$.
- (C) Solving $X(t + \Delta t)$ and $Y(t + \Delta t)$ from:

$$\gamma X(t + \Delta t) + (1 - \gamma)Y(t + \Delta t) = W$$

$$X(t + \Delta t) - Y(t + \Delta t) = R$$

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$$X(t + \Delta t) - Y(t + \Delta t) = R$$

This completes one timestep of a BD simulation!

How does this generalize to multi-particle $A + B \rightleftharpoons C$ systems?

In one timestep from t to $t + \Delta t$ we

1. Diffuse all particles independently on $[t, t + \Delta t]$.
2. For each pair of A and B particles, sample whether they react and if successful, sample where to place the product C particle.
3. For each C particle, sample whether it dissociates, and if successful sample where to place the product A and B particles.

What are some of the advantages/disadvantages of BD Methods?

Advantages:

- ▶ 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 ReaDDy, Smoldyn and MCell).
- ▶ Can be extended with standard numerical SDE techniques to include spatially varying drift and diffusion.
- ▶ Method should be convergent to underlying volume reactivity model as $\Delta t \rightarrow 0$.

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- ▶ Can be extended with standard numerical SDE techniques to include spatially varying drift and diffusion.
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Disadvantages:

- ▶ Only $O(\sqrt{\Delta t})$ or $O(\Delta t)$ accuracy in handling typical boundary conditions or drift.
- ▶ Requires extra microscopic parameters for VR model vs. RDME approach.
- ▶ To accurately resolve bimolecular reactions may need to take very *small* timesteps.
- ▶ Efficient detection of pairs that can react requires cell-list type data structures (otherwise for a and b particles of A and B is $O(ab)$ work).
- ▶ More challenging to adapt BD methods to preserve equilibrium properties like detailed balance of reaction fluxes or drift-diffusion fluxes (compared to lattice methods).

Acknowledgements

- ▶ Catalyst co-developed with Torkel Loman and Chris Rackauckas.
- ▶ JumpProcesses co-developed with Chris Rackauckas with significant contributions from Vasily Iljin and Guilherme Zagatti.
- ▶ Spatial particle models and methods developed in collaboration with former students I. Agbanusi, M. Heldman, J. Ma, A. Mauro, Y. Zhang, current student Q. Liu, and collaborator Prof. K. Spiliopoulos (BU).

Research and software development related to this talk have been funded by



Thank you for inviting me!

Relevant papers on RDME, CRDME, their mean field limits, and numerical methods:

<http://math.bu.edu/people/isaacson/>

Relevant Julia Libraries and Publication Links:

<https://github.com/SciML/Catalyst.jl>

<https://github.com/SciML/JumpProcesses.jl>

What about models with many chemical reactions? (2)

Notation for reactions:

- ▶ M = the number of different reactions that can occur.
- ▶ R_k labels the k th reaction.
- ▶ $a_k(x)$ = the propensity, i.e. probability per time for R_k to occur when $X(t) = x$ (ignoring other reactions).

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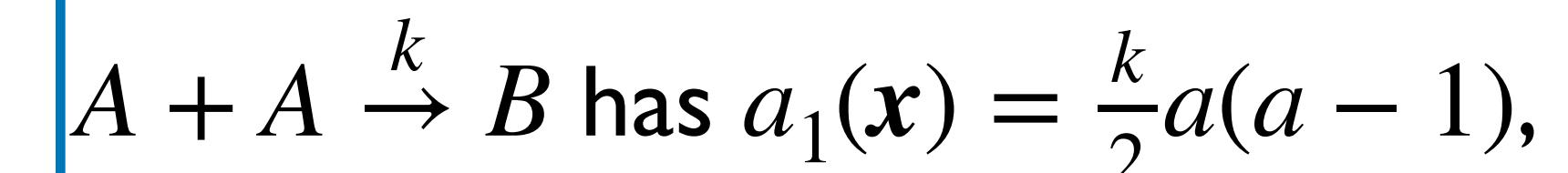
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- ▶ $a_k(x) =$ the propensity, i.e. probability per time for R_k to occur when $X(t) = x$ (ignoring other reactions).
 - For the jump process we are constructing this corresponds to a (state-dependent) transition rate for the k th possible jump type.
 - For a mass action reaction this is just the rate for a *minimal* set of substrates multiplied by the number of combinations of substrates, e.g.
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 - ▶ $a(x) = (a_1(x), \dots, a_M(x)) =$ the propensity vector.
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