Modelling spatial heterogeneity and macromolecular crowding with membrane systems

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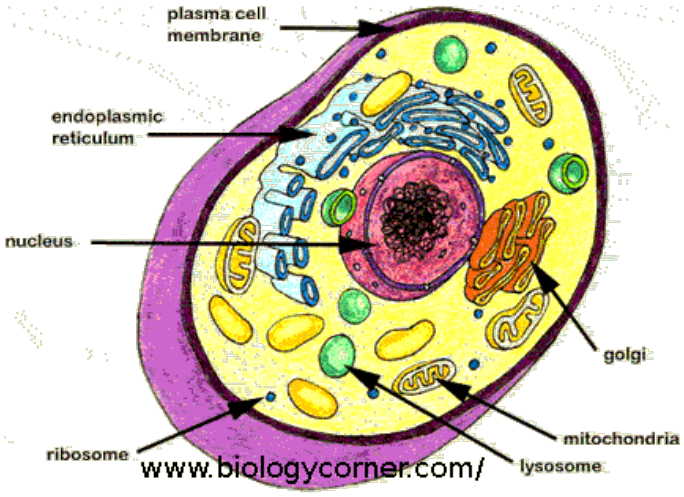
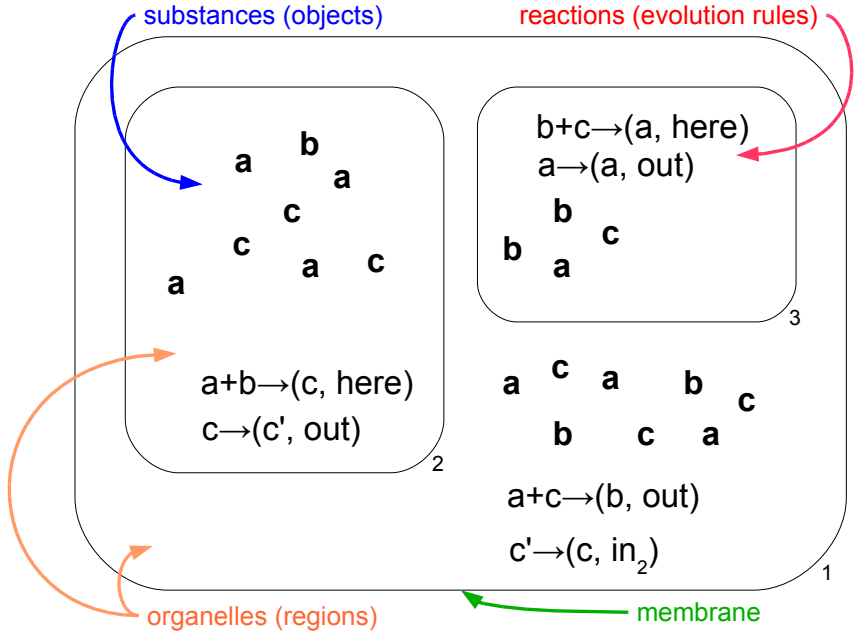
Outline

Motivations





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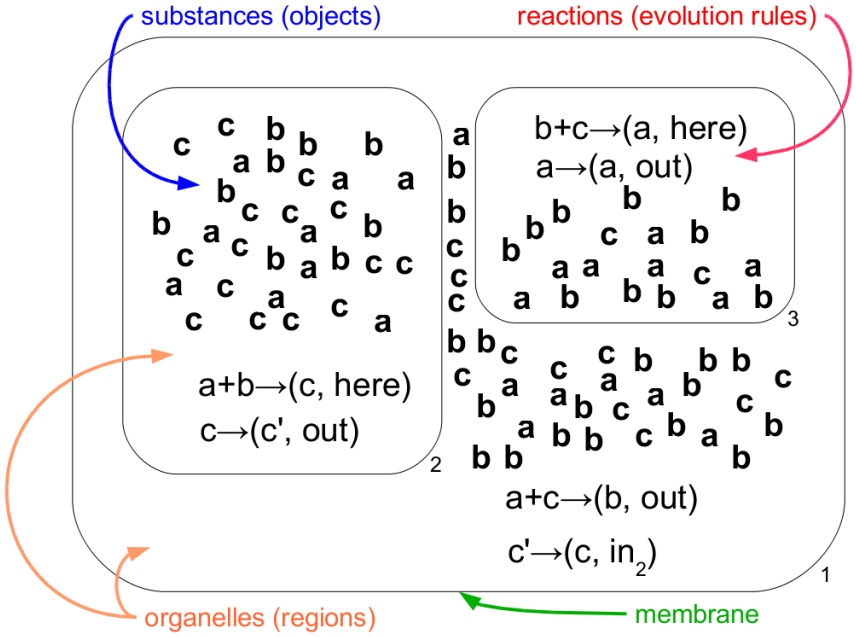
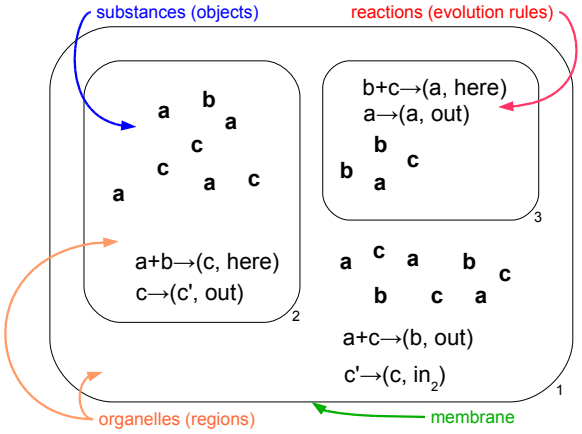


http://sitemaker.umich.edu/schnell.lab

Motivations



Intrinsic noise SSA

Spatial Heterogenity P systems, tau DPP

Molecular Crowding

heavily affect dynamics

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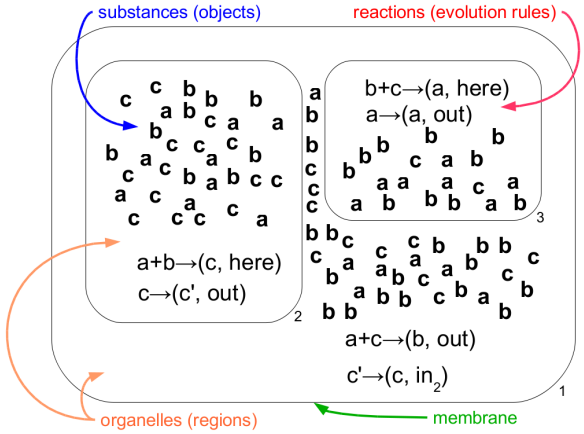

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Outline

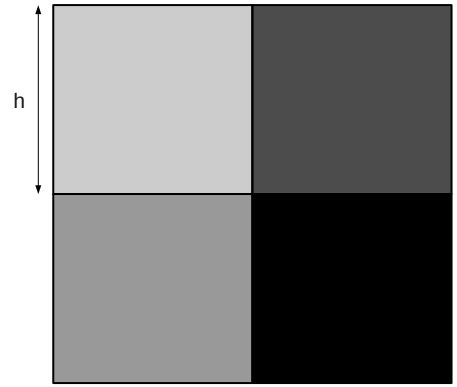
Reaction-Diffusion systems

RD systems are mathematical models used to describe those chemical systems for which the spatial distribution of chemicals influences the overall dynamics.

PDE ⟷ CME

Intrinsic noise

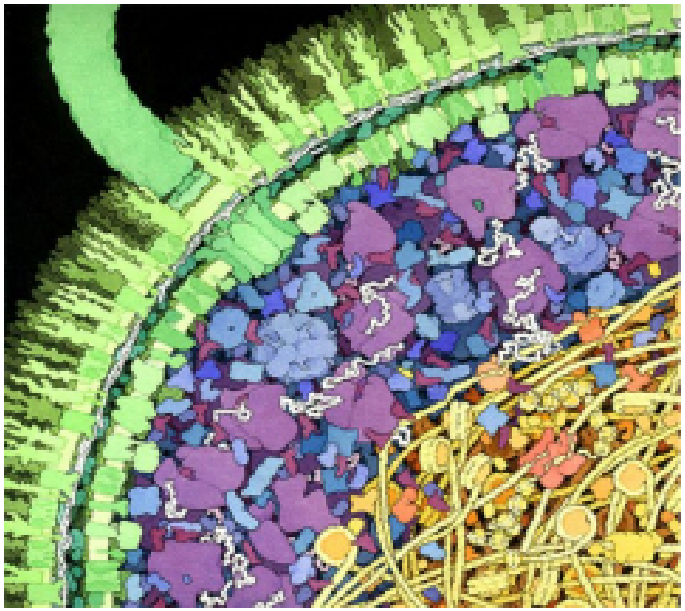
$$\leftarrow \widetilde{D}_{i,v} = \frac{2d}{h_v^2} D_i \rightarrow$$



$$a \xrightarrow{c_D} a, in_v \qquad c_D = \frac{D}{h^2}$$

Outline

Macromolecular crowding



Argonne National Lab

- The intracellular environment is crowded rather than concentrated, because single molecular species may occur at low concentrations, but all species taken together occupy a considerable fraction of the total volume.
- Macromolecular crowding refers to the non-specific influence of steric repulsions on molecular processes that occur in highly volume-occupied media.

Macromolecular crowding: effects

The net decrease of the available volume amplifies the rate of bio-chemical process e.g.:

- binding of macromolecules
- folding of proteins and nucleic-acid chains into more compact shapes
- formation of aggregates

Anomalous diffusion:

$$\langle r^2(t) \rangle = 6\ D\ t^{\alpha} \begin{cases} \alpha < 1 & \text{anomalous subdiffusion} \\ \alpha = 1 & \text{normal diffusion} \\ \alpha > 1 & \text{anomalous superdiffusion} \end{cases}$$

Outline

Classic computational approaches

- molecular dynamics: detailed trajectories, high computationally expensive
- brownian motions: particle-based stochastic approach (single molecule tracks), high computationallyexpensive
- PDE: continuous and deterministic approach
- cellular automata: lattice of cells with a finite set of states which evolve according to the neighbours state

ordered by decreasing computational costs and level of details

τ-DPP

Quantitative (stochastic) simulation of complex systems

Features

- The P system framework is used to describe the system
- Chemical reactions as multiset rewriting rules
- A modified tau-leaping procedure, placed inside every volume, is used to describe the behaviour of the system

Problems

- Complexity of the algorithm: $O(MN)$
- The molecules are uniformly distributed inside the volumes

τ-DPP: How it works

The iterative macrosteps of the algorithm are:

1. Compute the probabilities of the rules
2. Compute a candidate time increment
3. Select the smallest time increment among volumes
4. Select the set of reactions to execute
5. Update the system

P. Cazzaniga, D. Pescini, D. Besozzi, G. Mauri, **Tau leaping stochastic simulation method in P Systems**, Membrane Computing, 7th International Workshop, WMC 2006,(H.J.Hoogeboom, G. Paun, G. Rozenberg, A. Salomaa, eds.) LNCS 4361, 298–313, 2006.

Sτ-DPP

- it is based on basic tissue P systems;
- it exploits dynamics description of τ-DPP;
- the structure is independent from the communication channels between membranes, hence, two different graphs are used in the description. One denotes the membranes topology (i.e., membrane structure), the other the connections between membranes which allow the communication of objects;
- encompasses sizes of objects and membranes;
- the rules are enabled only if there is sufficient space.

P. Cazzaniga, G. Mauri, L. Milanesi, E. Mosca, D. Pescini. **A novel variant of tissue P systems for the modelling of biochemical systems**. Proceedings of the 10th International Workshop on Membrane Computing, WMC 2009 (G. Paun, M.J. Perez-Jimenez, A. Riscos-Nunez, G. Rozenberg, A. Salomaa, eds.), LNCS ,5957, 210-226,2009.

Sτ-DPP

Given the internal state M_i of a membrane V_i together with the species sizes in $\mathcal{D}_X$, it is possible to define the occupied volume in V_i as:

$$O(V_i) = \sum_{j=1}^{M} (m_j \cdot D_{X_j}) + \sum_{V_l \in a_\tau(V_i)} D_{V_l}$$

Hence, it is possible to define the amount of the free space in V_i as:

$$F(V_i) = D_{V_i} - O(V_i)$$

Free space updating equation:

$$F(V_i) = F(V_i) - \sum_{j=1}^{M} (\beta_j - \alpha_j) \cdot D_{X_j}$$

where α_j and β_j are the stoichiometric coefficients of the chemical species occurring in the executed rule.

The propensity functions for second and third order: $a(\mathbf{x}, \mathbf{V}) = \dfrac{c \cdot h}{F(V)}$

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Heat equation

It is a PDE which describes the heat distribution in a region during time (special case of diffusion equation) where the diffusion coefficient D is constant in time and space:

$$\frac{\partial u(\vec{x}, t)}{\partial t} = D \, \Delta u(\vec{x}, t)$$

where $u(\vec{x}, t)$ is the density.

Heat equation

In the unidimensional case it reduces to:

$$\frac{\partial [S](x,t)}{\partial t} = D \frac{\partial^2 [S](x,t)}{\partial x}, \ \forall x \in \Omega$$

when $\Omega = [0,1]$ and with the Neumann boundary conditions

$$\frac{\partial [S](0,t)}{\partial x} = \frac{\partial [S](1,t)}{\partial x} = 0$$

has solution:

$$[S](x,t) = S^{\Omega} \left[1 + \tfrac{1}{2} \exp^{-\pi^2 \gamma^2 t} \cos(\gamma \pi x)\right]$$

$\gamma = 3$ and $S^{\Omega} = 500$

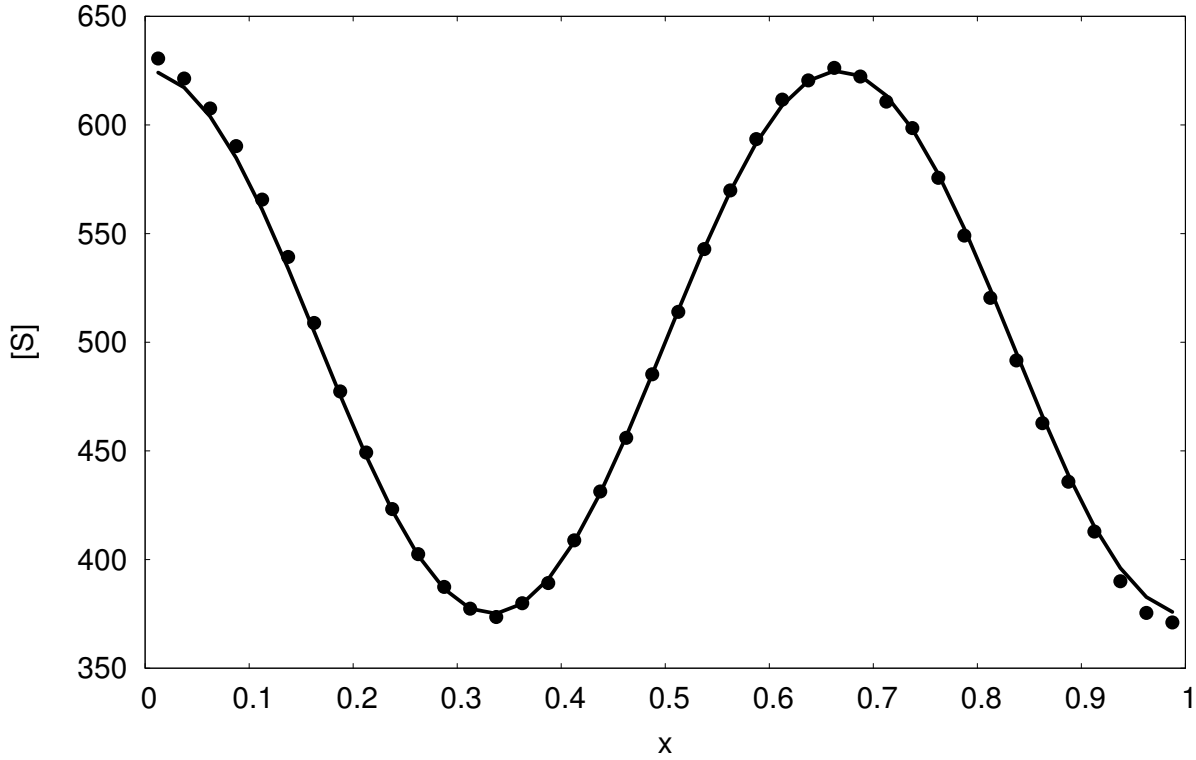
τ-DPPdefinition

The region Ω is divided into N smaller adjacent regions V_v such that $\Omega = \bigoplus_v V_v$

The initial conditions are computed using:

- $[S_v] = \dfrac{S_v}{V_v}, \ \forall v$
- $V_v = \dfrac{1}{N}$
- $x_v = \dfrac{V_v}{2} + (v-1)V_v, \quad v = 1, \ldots, N$
- $[S](x_v, t = 0) = S^{\Omega}\ [1 + \frac{1}{2} \exp^{-\pi^2\gamma^2 0} \cos(\gamma\pi x_v)]$

Simulation



The exact solution (line) and τ-DPP average results (dots)

- $t = 0.0078034$ simulation halting time
- $S^{\Omega} = 500$ total number of molecules
- $G = 10^4$ number of runs
- $\gamma = 3$ parameter
- $V_v = 0.025$ volume $1/N$ of each membrane

Error estimate

The per membrane error is computed as

$$\epsilon_v = \frac{1}{G} \sum_{e=1}^{G} \left(1 - \frac{[S^*_{v,e}]}{[S_v]} \right)$$

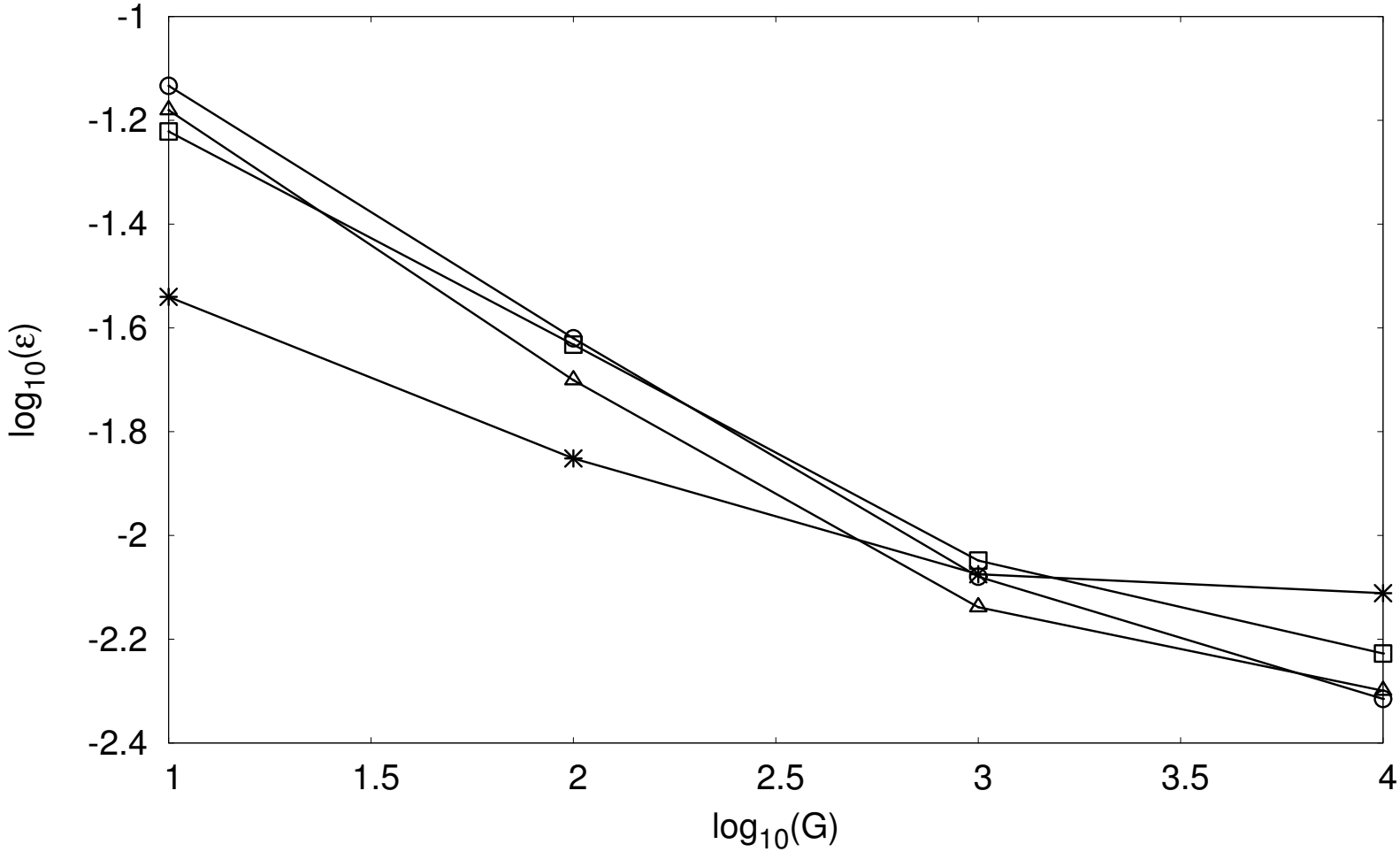
with:

- $[S_v]$ expected value
- $[S^*_{v,e}]$ observed value
- $e = 1, \ldots, G$ simulation runs

Then the overall error is

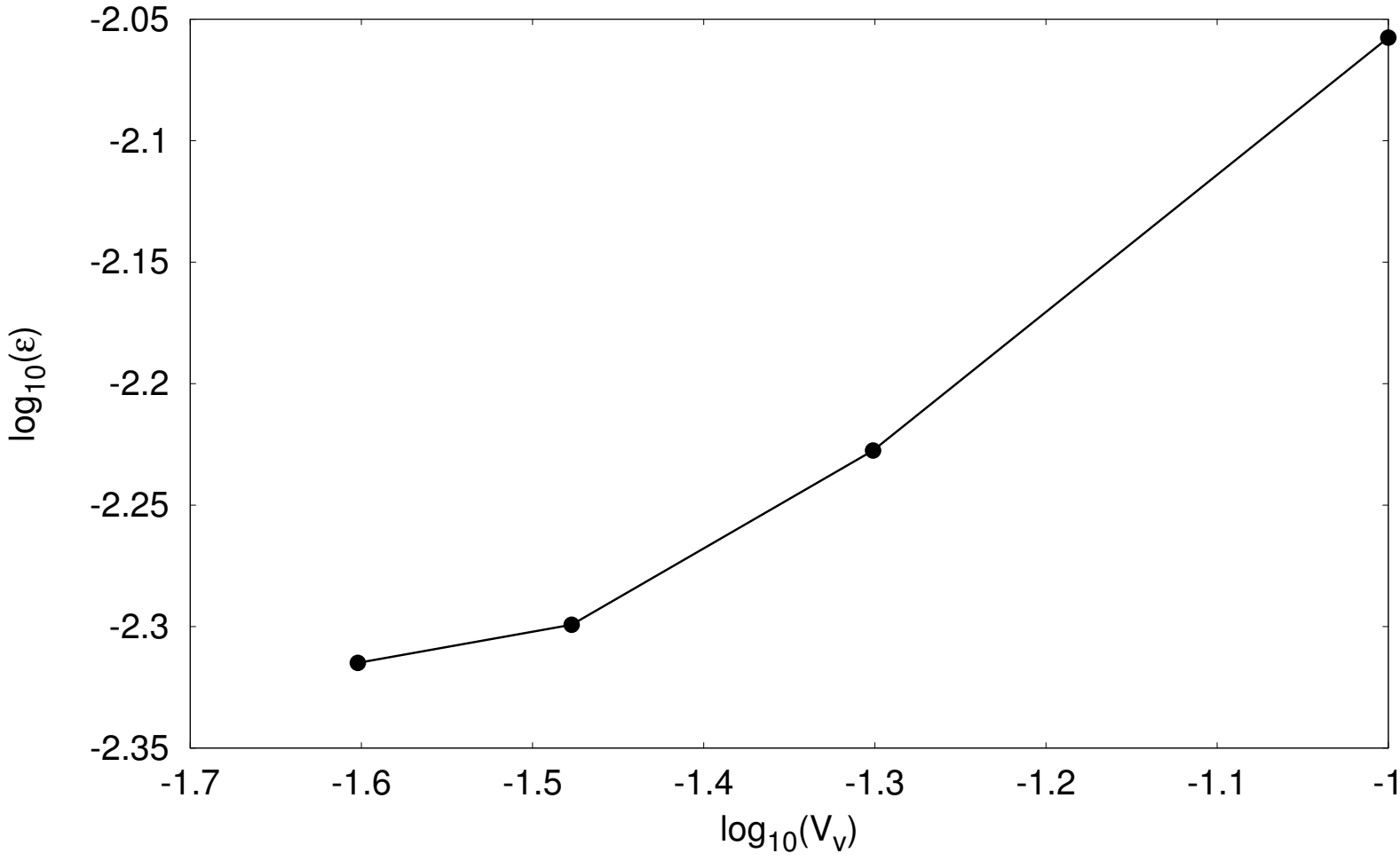
$$\epsilon = \frac{1}{N} \sum_{v=1}^{N} \mid \epsilon_v \mid$$

Error estimate: the error ϵ Vs. the number of simulations G



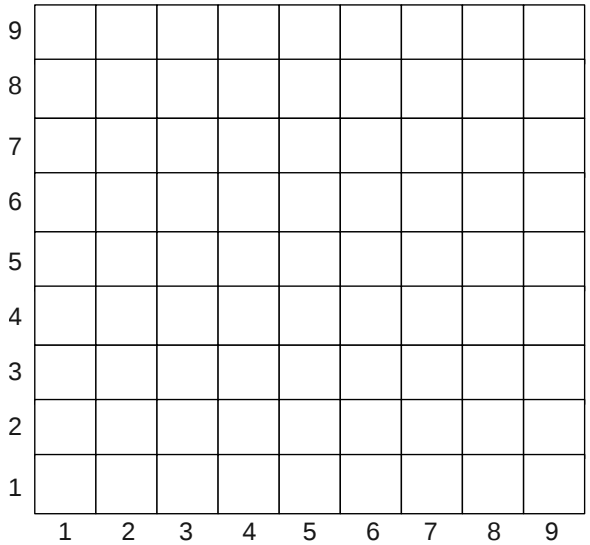
$s_{V_v} = 0.1$ (*), $s_{V_v} = 0.05$ (□), $s_{V_v} = 0.03\bar{3}$ (△), $s_{V_v} = 0.025$ (○), $\gamma = 3$, $t = 0.0078034$

Error estimate: the error ϵ Vs. the volumes size V_v



Outline

Macromolecular crowding with $S\tau$-DPP



$$V = \{A, B, C, Z\}$$

$$r_1 : A + B \xrightarrow{c_1} C$$

$$r_2 : C \xrightarrow{c_2} A + B$$

$$r_{D_A} : A \xrightarrow{c_A} A, in_*$$

$c_1 = 10^{-4}, c_2 = 10^{-3}$

$c_{D_A} = c_{D_B} = c_{D_C} = 0.16$

$s_A = s_B = 10^{-4}, s_C = 2\ 10^{-4}$

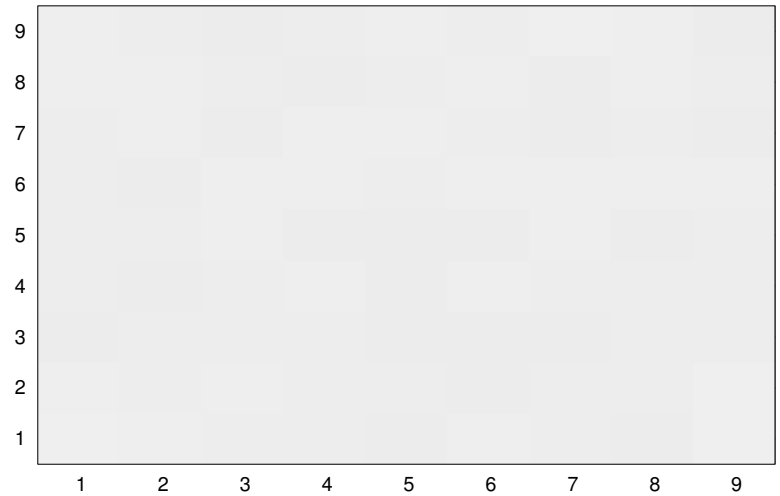
$s_Z = \{0, \frac{V_i}{3}\} = \{0, 0.1\}$

$A_0 = B_0 = 100\ \forall V_v$

$Z_0\ s.t.\ Z_0 \cdot D_z = \Omega/3$, randomly distributed

Macromolecular crowding: propensity functions

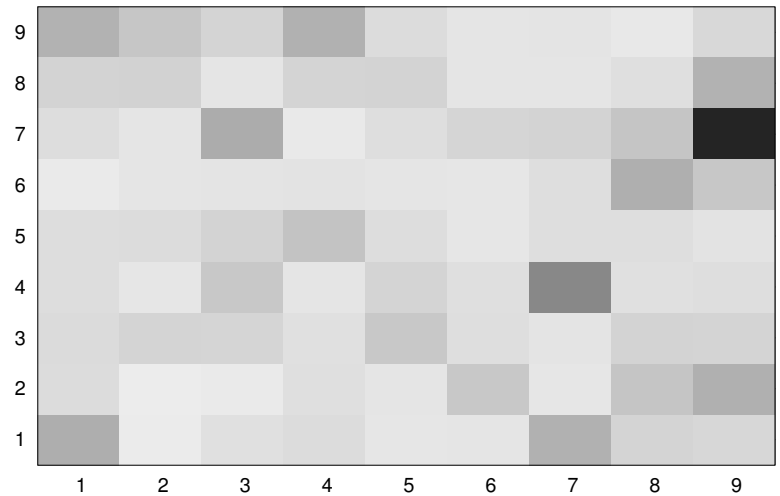
$$a(\mathbf{x}, \mathbf{V}) = \frac{c \cdot h}{F(V)}$$



diluted: $S_Z = 0$

$\mu = 0.9237$

$\sigma = 0.001842$

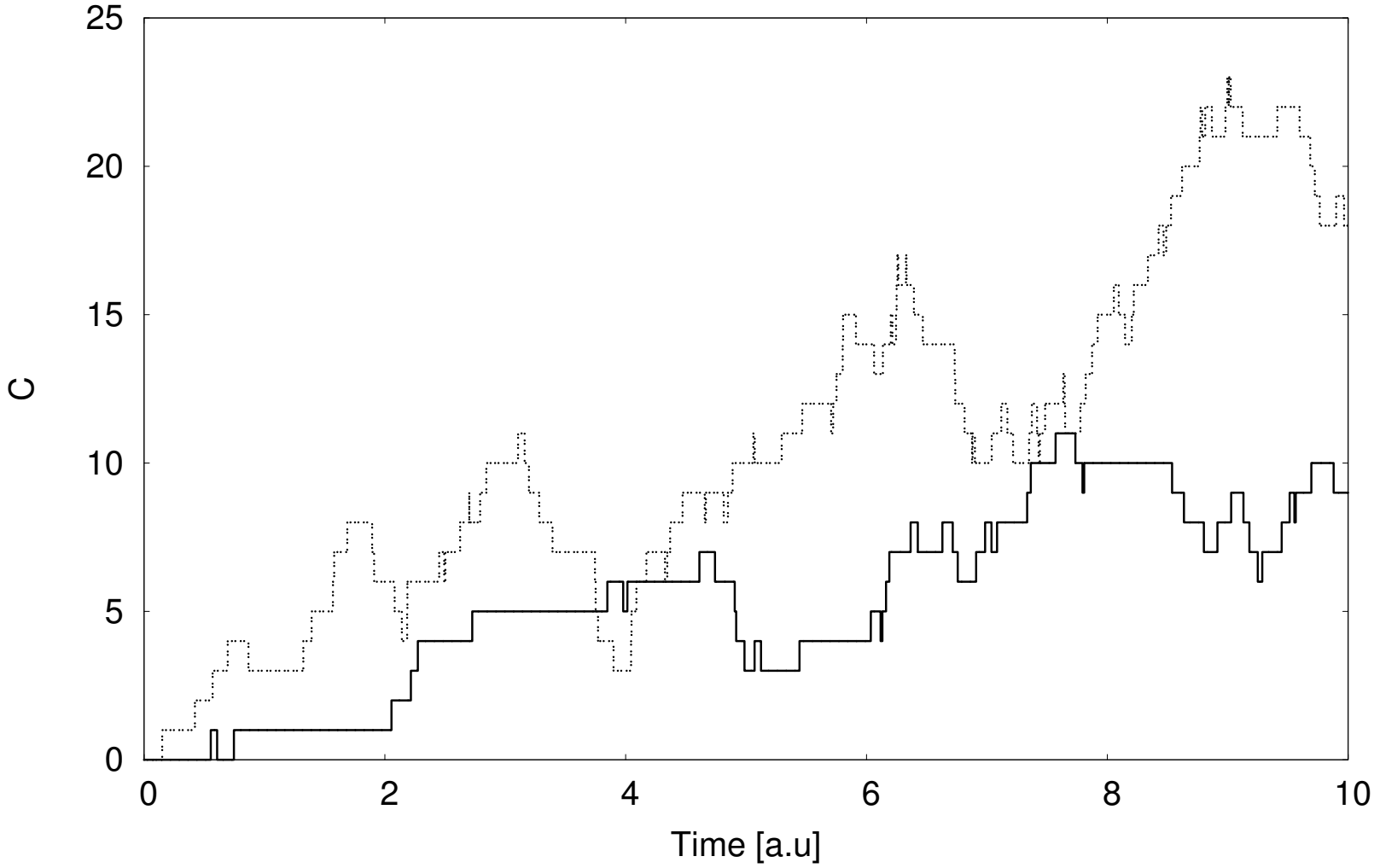


crowded: $S_Z = 0.1$

$\mu = 1.451$

$\sigma = 0.498$

Macromolecular crowding: simulations



Trajectories in volume 78: diluted solid crowded dash lines

Outline

Conclusion

- τ-DPP can reproduce the diffusion of molecules within a spatial region divided in a set of well-mixed sub-volumes according to a defined topology.
- Heat equation: the error that we reported is slightly greater than the one found in [Bernstein2005]. (τ-DPP Vs SSA)
- Heat equation: the loss of accuracy (controllable) is well balanced by the increase in performance that enables simulations of more complex systems.
- the molecular crowding can be explicitly modelled by the Sτ-DPP variant.
- Sτ-DPP can also be used to reproduce the reaction rate amplification observed in crowded media due to the increase of recollision probability determined by the reduction of the available free space in a volume.