Improved two-regime method for spatial stochastic simulations of cellular signaling

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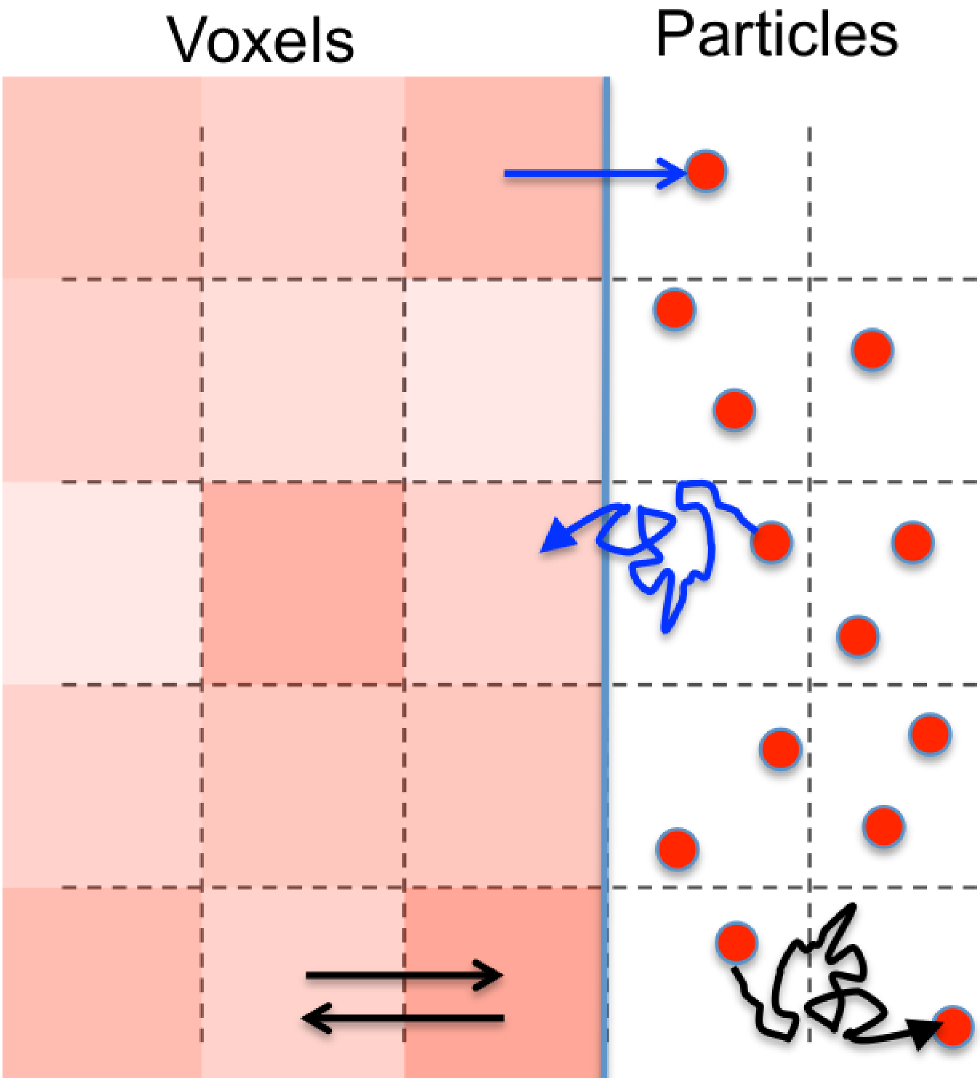
Voxels
Particles

0. Outline

1. Compartment-based simulations
2. Particle-based simulations
3. Hybrid model
4. Offset particle-based simulations
5. Improved hybrid model
6. Conclusion and outlook

0. Outline

1. **Compartment-based simulations**
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1. Compartment-based simulations

- Divide the space Ω_C into U compartments $V_1, \ldots, V_U$ called voxels.
- For a given voxel ν the number of particles is denoted as N_ν.
- According to Gillespie , the next diffusion event in voxel ν is given by the putative time

$$t_\nu = t + \varepsilon_\nu. \tag{1}$$

ε : exponential distributed r. n. of mean $\mu_{\varepsilon_\nu} = \frac{1}{\alpha(N_\nu)} = \frac{1}{k_{\text{jump}}^{\nu \to \kappa} N_\nu} = \frac{1}{\frac{D_i}{h^2} \cdot N_\nu}$

Algorithm 1 Gillespie

Require: Ω_C, t, t_{End}, $\triangle t$, $[N_1, \ldots, N_U]$
while $t < t_{\text{End}}$
  $[t', \nu] =$ `getFirstDiffusionTime`$() = \text{minloc}\left([t_1, \ldots, t_U]\right)$
  $t = t'$
  $N_\nu = N_\nu - 1$
  $t_\nu = t + \varepsilon_\nu$
  $\kappa =$ `selectNewVoxel`$()$ *(New voxel has to be adjacent)*
  $N_\kappa = N_\kappa + 1$
  $t_\kappa = t + \varepsilon_\kappa$
endwhile

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2. Particle-based simulations

- Particle-based simulations that track every molecule on its diffusive path through the cell. $\longrightarrow$ **Brownian motion**

- The diffusion of the j-th particle is computed as follows with the Brownian dynamics:

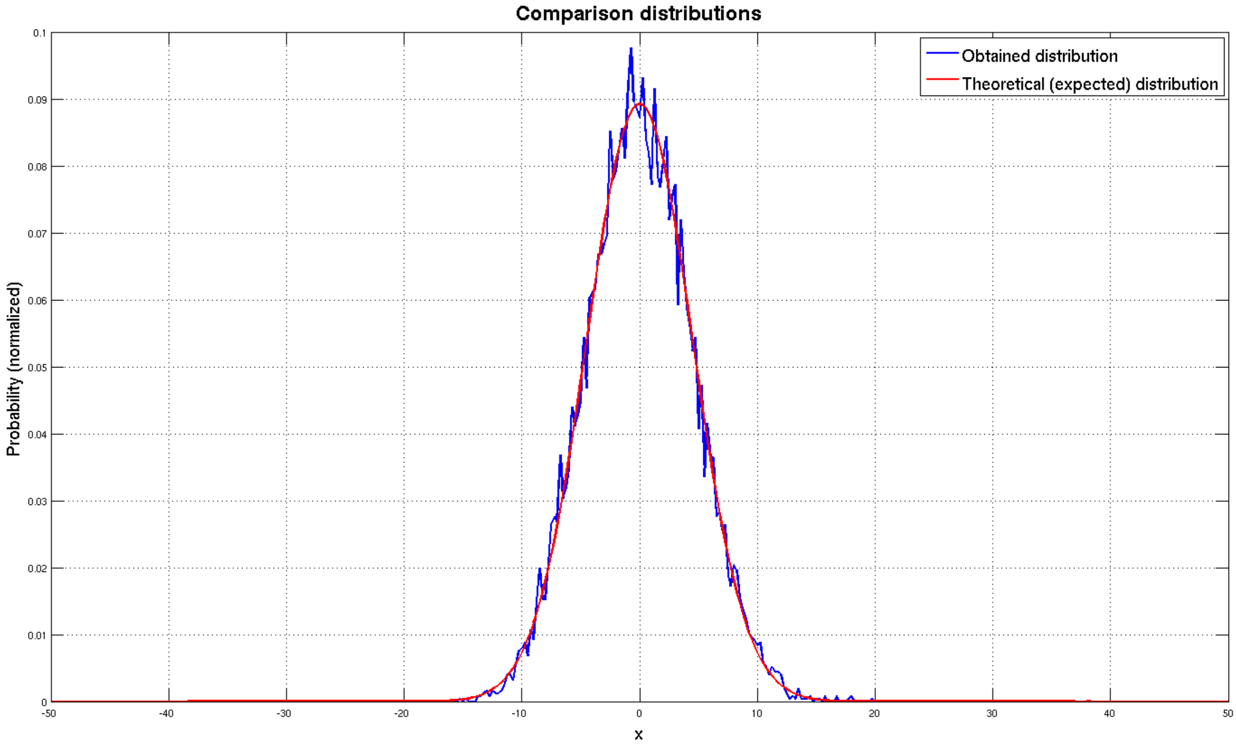
$$\mathbf{x}_j\left(t+\triangle t\right)=\mathbf{x}_j\left(t\right)+\triangle\mathbf{x}\cdot\xi \tag{2}$$

ξ : three-dimensional zero-mean Gaussian random vector of unit variance
$\triangle\mathbf{x}=\sqrt{2D_j\triangle t}$: moved distance.

- The expected theoretical distribution is

$$p(\mathbf{x}, t) = \frac{1}{\sqrt{4\pi D t}} \exp\left(-\frac{1}{2}\left(\frac{\mathbf{x} - \mathbf{x}_0}{\sqrt{2Dt}}\right)^2\right) \tag{3}$$

for a delta distribution, where at the beginning all the particles are located at position $\mathbf{x}_0$.


Comparison distributions
Obtained distribution
Theoretical (expected) distribution
Probability (normalized)
x
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
-50
-40
-30
-20
-10
0
10
20
30
40
50

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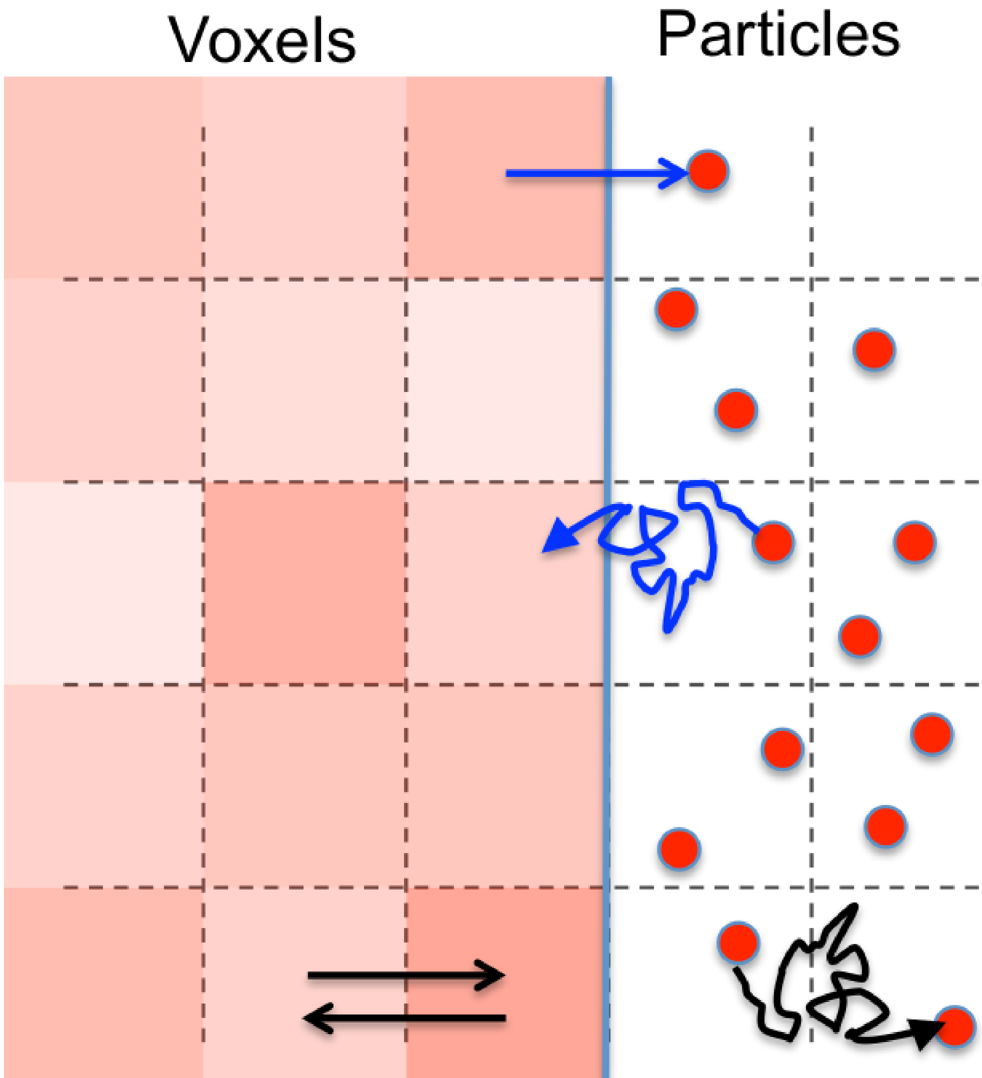
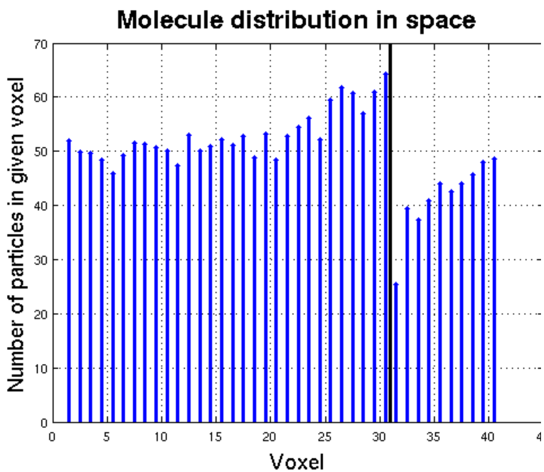


Voxels
Particles

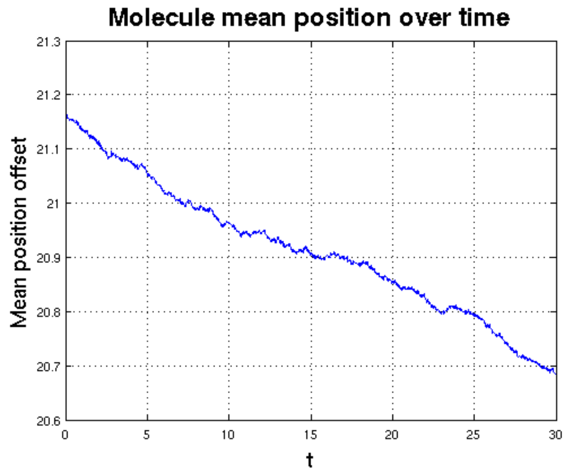
3. Hybrid method

- Domain is split into two regions:
  - Ω_C is the Gillespie region, where voxels of size h containing number of particles $[N_1, \ldots, N_U]$ are defined.
  - Ω_M is the space where the particles move according to the Brownian dynamics.
- A key feature of this hybrid algorithm are the putative times. Some useful notation of Flegg et al. was taken.
  - t_C denotes the time for the next Gillespie C-event
  - t_M is the time until the next Particle M-event.

- **Simulation:** for $\mathbf{N}_{\text{particles}} = 10000$ particles distributed with a standard uniform distribution, where $\Omega_C = [1.0, 31.0]$ and $\Omega_M = [31.0, 41.0]$, thus the interface is at $I = 31.0$.
- Simulated from $t = 0$ s to $t_{\text{End}} = 10$ s, with time intervals $\triangle t = 0.01$ s.
- Do 10 runs and average the results for better statistics.



Molecule distribution in space
Number of particles in given voxel
Voxel
0
10
20
30
40
50
60
70
0
5
10
15
20
25
30
35
40



Molecule mean position over time
Mean position offset
t
20.6
20.7
20.8
20.9
21
21.1
21.2
21.3
0
5
10
15
20
25
30

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4. Offset particle-based simulations

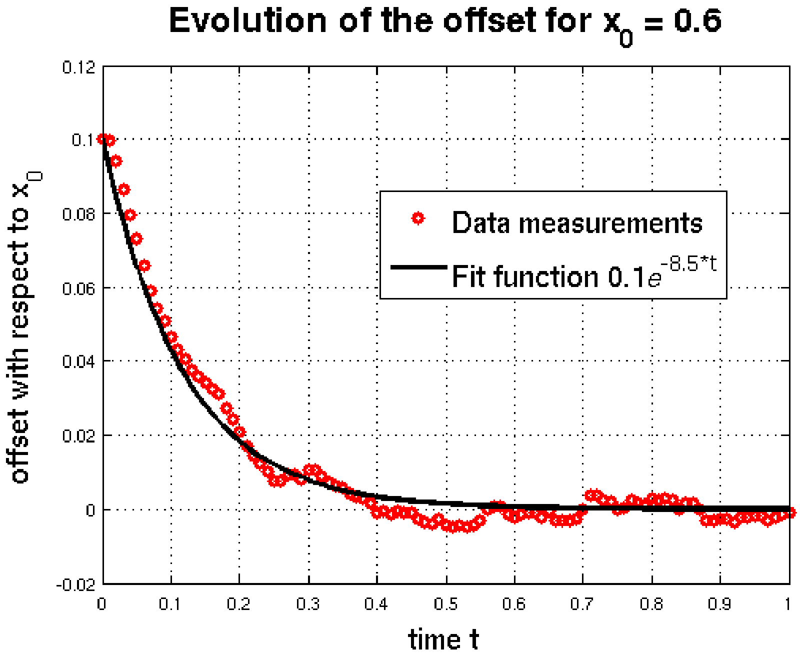
- **Diffusion experiment:** assume $\Omega_M = [0.0, 1.0]$ and $\mathbf{N}_{\text{particles}} = 10000$ particles distributed with a delta distribution at different starting positions $x_0 = \{0.6, 0.7, 0.8, 0.9\}$.

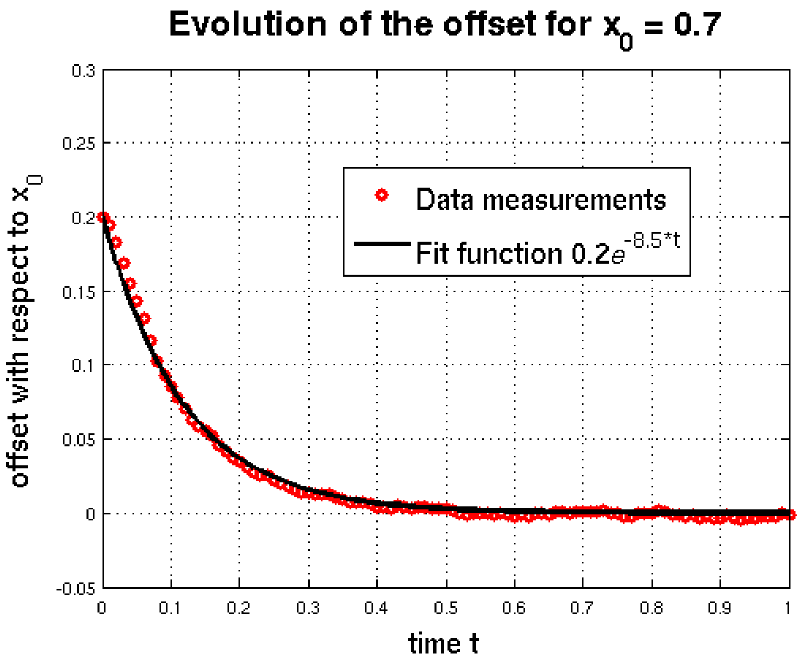
  Simulated from $t = 0$ s to $t_{\text{End}} = 1$ s, with fixed time intervals $\triangle t = 0.01$ s.

- The exponential function

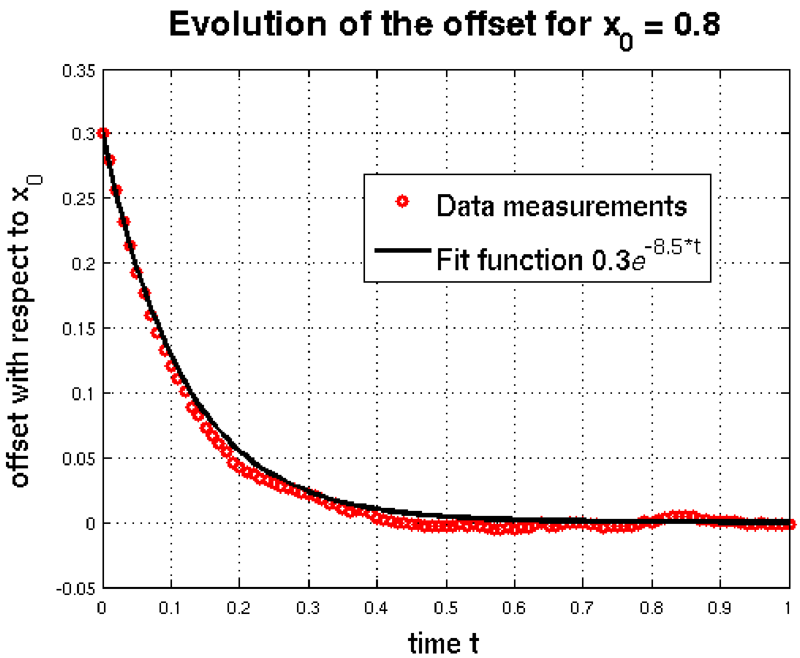
$$f\left(t\right) = \left(x_0 - x_0^*\right) \cdot e^{-c_2 \cdot t} \tag{4}$$

  is fitted to the offset, where c_2 is the decaying constant and $x_0^* = 0.5$ the domain center .

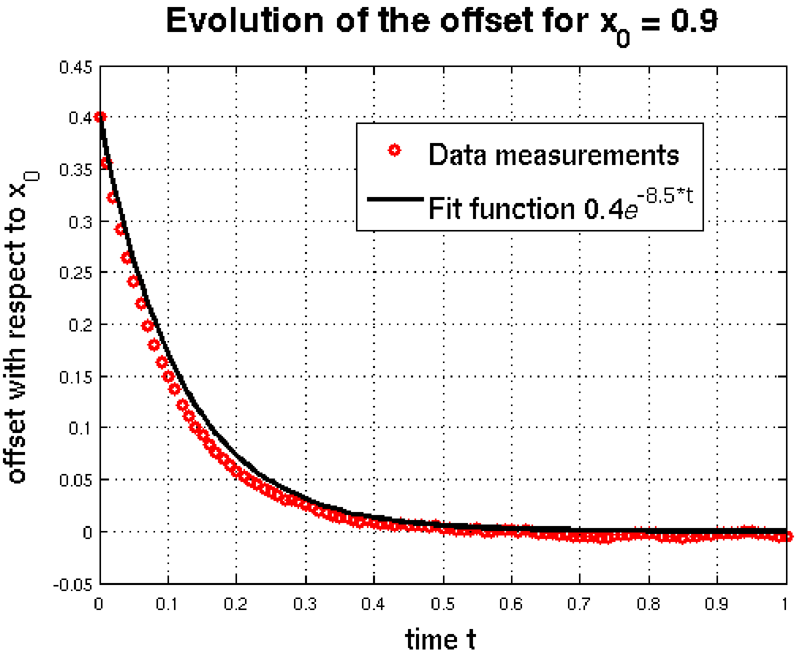

Evolution of the offset for $x_0 = 0.6$
offset with respect to x_0
time t
Data measurements
Fit function $0.1e^{-8.5*t}$
0.12
0.1
0.08
0.06
0.04
0.02
0
-0.02
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1



Evolution of the offset for x_0 = 0.7
Data measurements
Fit function $0.2e^{-8.5*t}$
offset with respect to x_0
time t
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1



Evolution of the offset for $x_0 = 0.8$
Data measurements
Fit function $0.3e^{-8.5*t}$
offset with respect to x_0
time t
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1



Evolution of the offset for $x_0 = 0.9$
Data measurements
Fit function $0.4e^{-8.5*t}$
offset with respect to x_0
time t
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

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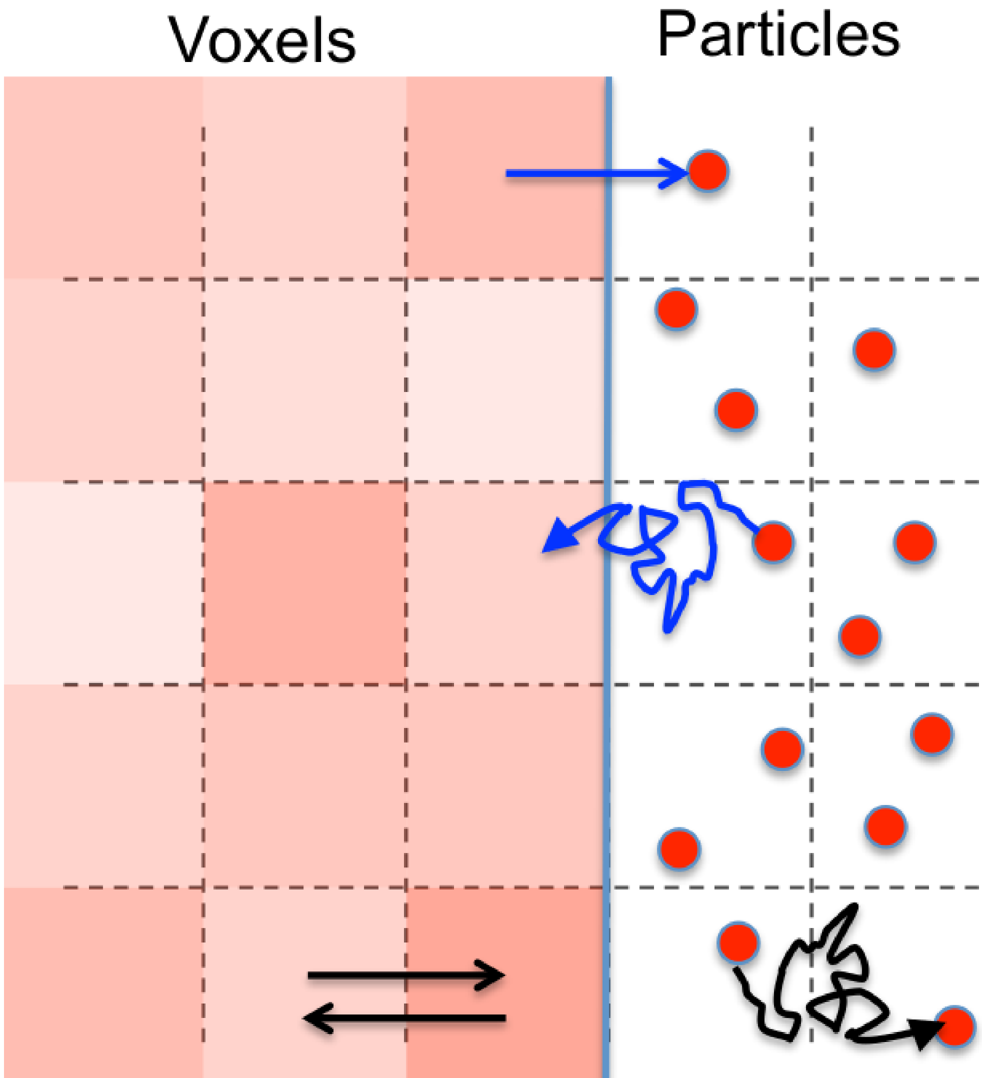
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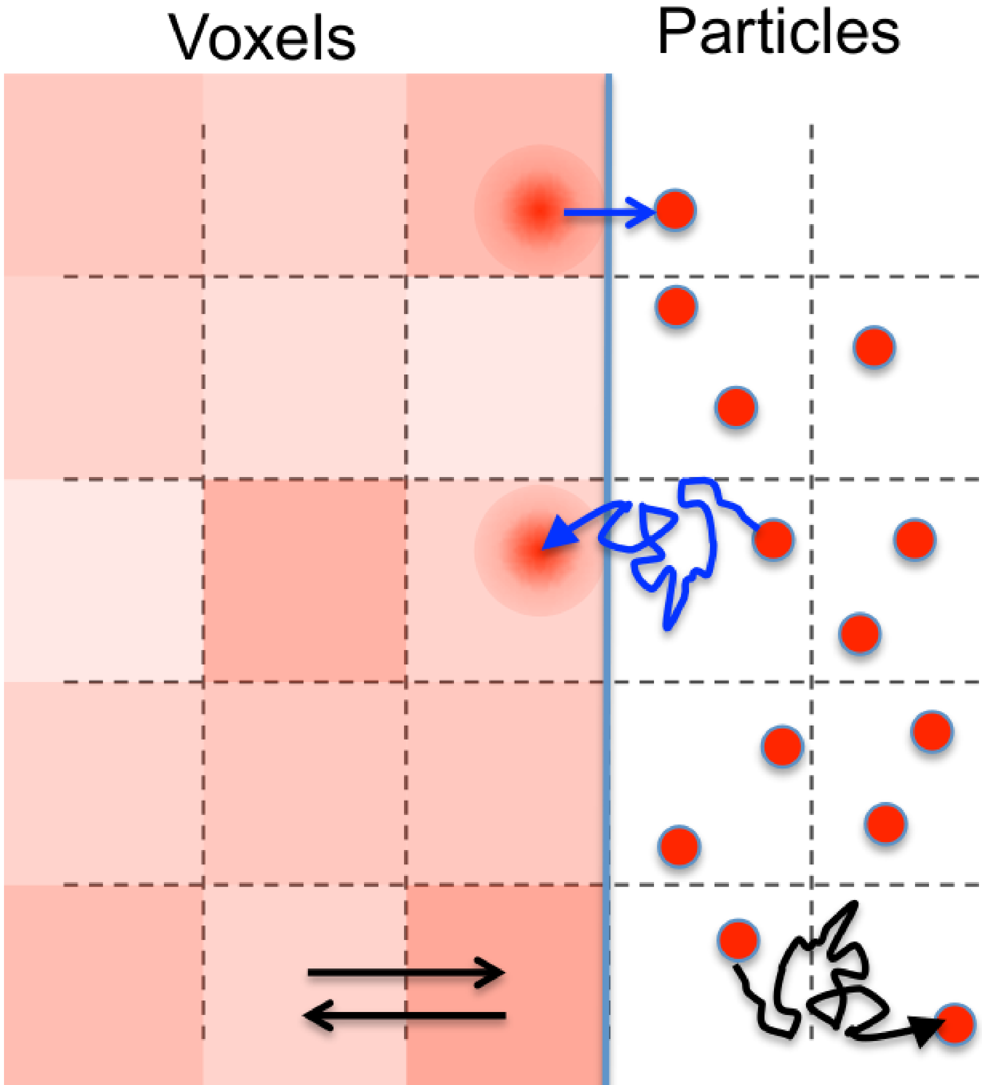

Voxels
Particles

5. Improved hybrid method

- The offset gives a more precise jumping propensity, because the particles are no longer assumed to be in the center of the voxel.
- We assume the offset decays to zero with first order kinetics

$$v_{\text{offset}}(\kappa) = v_{\text{offset}}(\kappa) \cdot e^{-k_{\text{offset}} \cdot (t - t_{\kappa,\text{offset}})}, \tag{5}$$

  where $t_{\kappa,\text{offset}}$ is the time of the last change in voxel κ.

- Actualize $t_{\kappa,\text{offset}}$ to the current time t, and the number of particles in the voxel κ: $N_\kappa = N_\kappa + 1$.

- The jump of a new particle into a voxel κ has as a consequence that the voxel offset $v_{\text{offset}}(\kappa)$ has to be actualized with the addition in a weighted manner,

$$v_{\text{offset}}(\kappa) = \frac{N_\kappa}{N_\kappa + 1} \cdot v_{\text{offset}}(\kappa) + \frac{1}{N_\kappa + 1} \cdot p_{\text{offset}} \tag{6}$$

- Virtual voxel size, which takes into account the voxel offset, is defined as

$$h'(\kappa) = h - 2 \cdot v_{\text{offset}}(\kappa) \tag{7}$$

  for every voxel κ.

- Function `createParticle`(), which creates a particle if the jump is from Ω_C to Ω_M, has to be adapted. Subtle difference depending on whether the jump is to the **right**, in which case the formula is

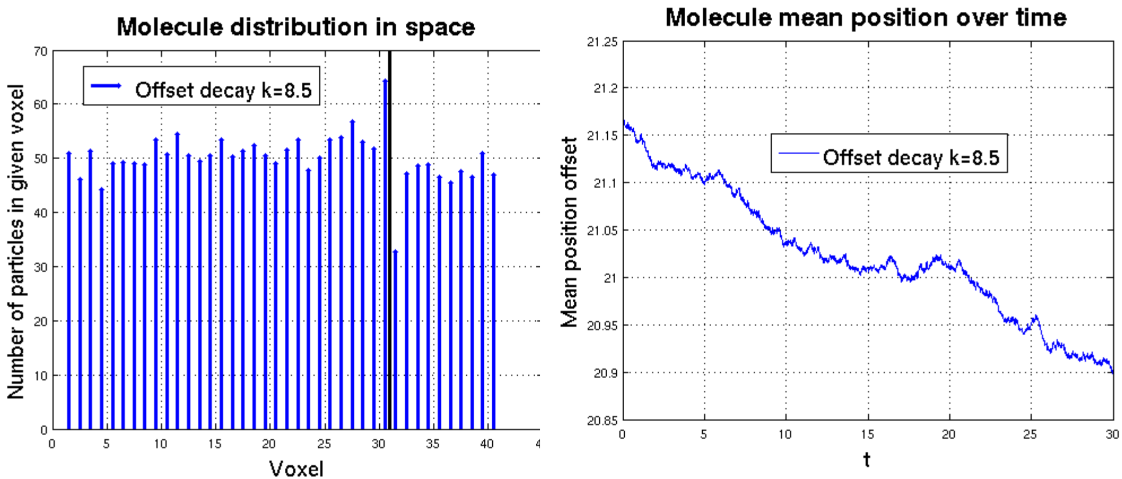
  $$x_j(t) = \kappa + h + \min(h', 1) \cdot \xi, \tag{8}$$

  or if the jump is to the **left**

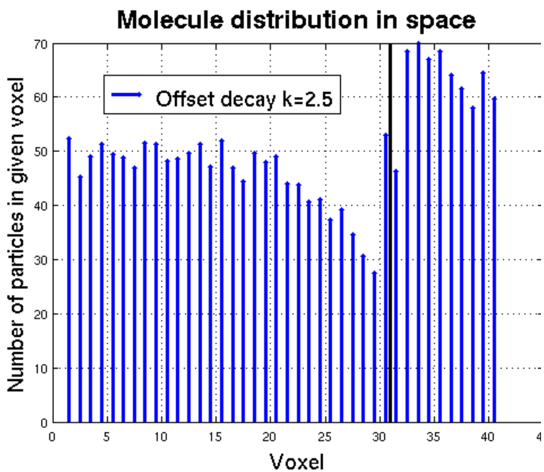
  $$x_j(t) = \kappa - \min(h', 1) \cdot \xi, \tag{9}$$

  where ξ is a normal distributed random number .

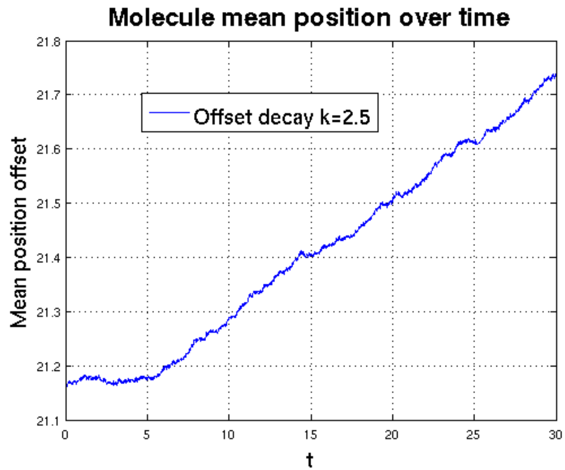
- **Offset simulation:** for $\mathbf{N}_{\text{particles}} = 10000$ particles distributed with a standard uniform distribution, where $\Omega_C = [1.0, 31.0]$ and $\Omega_M = [31.0, 41.0]$, thus the interface is at $I = 31.0$.
- Use 2 different k_{offset}: $k_{\text{offset}} = \{8.5, 2.5\}$.
- Do 10 runs and average the results for better statistics.



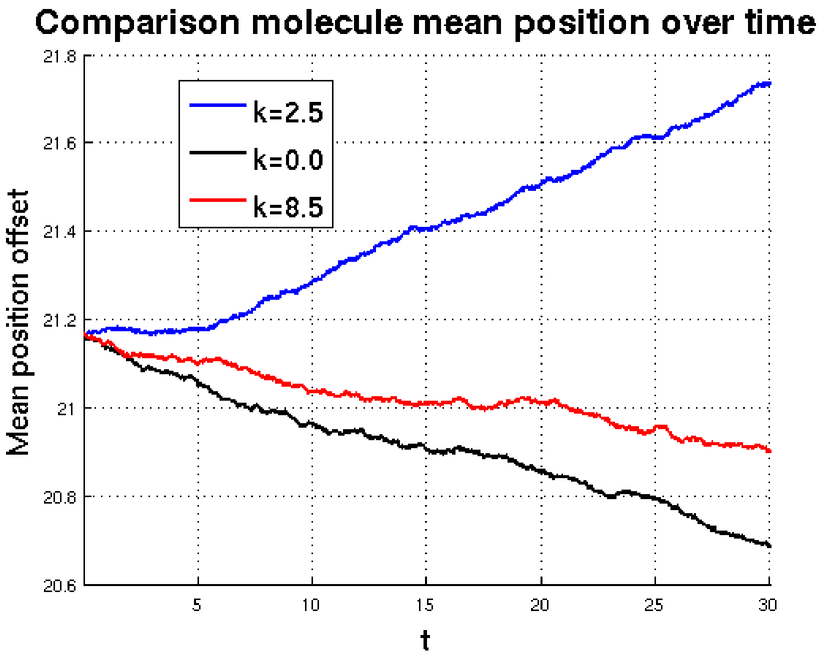
Molecule distribution in space
Offset decay k=8.5
Number of particles in given voxel
Voxel
Molecule mean position over time
Offset decay k=8.5
Mean position offset
t



Molecule distribution in space
Offset decay k=2.5
Number of particles in given voxel
Voxel
0
10
20
30
40
50
60
70
5
15
25
35



Molecule mean position over time
Offset decay k=2.5
Mean position offset
t
21.1
21.2
21.3
21.4
21.5
21.6
21.7
21.8
0
5
10
15
20
25
30



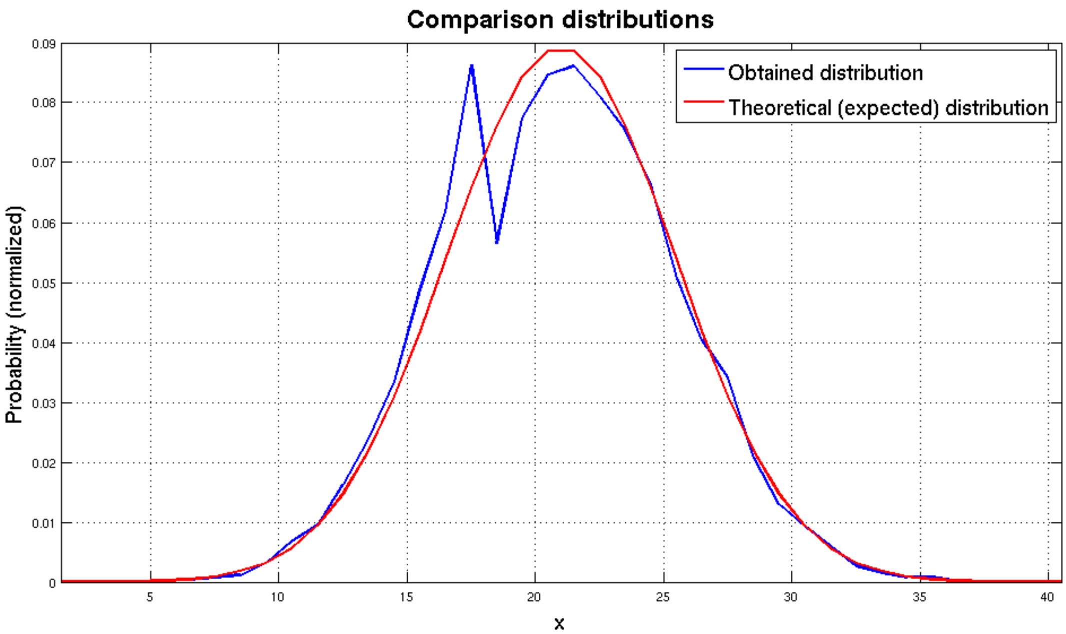
Comparison molecule mean position over time
Mean position offset
t
21.8
21.6
21.4
21.2
21
20.8
20.6
5
10
15
20
25
30
k=2.5
k=0.0
k=8.5

- **Diffusion experiment:** assume $\Omega_M = [18.0, 41.0]$ and $\Omega_C = [1.0, 18.0]$ with $\mathbf{N}_{\text{particles}} = 10000$ particles distributed with a delta distribution at $x_0 = 21.0$.

  Simulated from $t = 0$ s to $t_{\text{End}} = 10$ s, with time intervals $\triangle t = 0.01$ s.

- Do 10 runs and average the results for better statistics..

- Compare to normalized theoretical distribution (3).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Obtained distribution
Theoretical (expected) distribution
Probability (normalized)
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0.03
0.02
0.01
0
5
10
15
20
25
30
35
40

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- Definition of the offset and virtual voxel length h' helps towards a better interface interaction.
- A good selection of c_2, and therefore of the offset decay rate constant $k_{\text{offset}} = \frac{D}{h^2} \cdot c_2$, corrects flux problems.

- Here only 1D problems. Would be interesting to test the principle on 2D and 3D.
- The concentration dent right at the interface should be smoothed in further projects.
- Find an approximative function $c_2\left(t_{\mathrm{End}}, \Delta t\right)$ for the decaying parameter. Find optimal solution.
- The method of Flegg et al. should be implemented for comparison.