Cellular Simulations (1):
Analytic, Finite Difference, & Monte Carlo Approaches to Reaction-Diffusion Systems

NIH-NSF BBSI: Simulation and Computer Visualization of Biological Systems at Multiple Scales

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Biomedical Supercomputing Initiative

Review of Diffusion Theory

Fick's Laws

1st: $$\text{Flux } J = -DA\frac{\partial C}{\partial x}$$

2nd: $$\left(\frac{\partial C}{\partial t}\right)_{x,y,z} = D\left[\left(\frac{\partial^2 C}{\partial x^2}\right)_t + \left(\frac{\partial^2 C}{\partial y^2}\right)_t + \left(\frac{\partial^2 C}{\partial z^2}\right)_t\right]$$ 3-D

$$\left(\frac{\partial C}{\partial t}\right)_{\zeta} = D\left(\frac{\partial^2 C}{\partial \zeta^2}\right)_t, \quad \zeta = x, y, z \text{ or } r$$ 1-D

Solution of Fick's 2nd Law in 1-D

point source: $$C(r,t) = \frac{M}{(4\pi Dt)^{3/2}} e^{-r^2/4Dt}$$

line source: $$C(r,t) = \frac{M}{(4\pi Dt)} e^{-r^2/4Dt}$$

plane source:

$$C(x,t) = \frac{M}{(4\pi Dt)^{1/2}} e^{-x^2/4Dt}$$

$$C(x,t) = \frac{M}{\sigma\sqrt{2\pi}} e^{-x^2/2\sigma^2}, \quad \sigma = \sqrt{2Dt}$$

Mean distances:

$\bar{l}_r$ is equal to $2\sqrt{4Dt/\pi}$

$\bar{l}_r^{\,2}$ is equal to $6Dt$

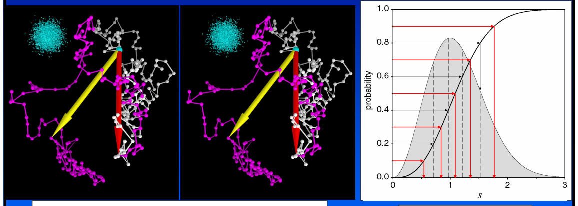
$\bar{l}_x$ is equal to $\sqrt{4Dt/\pi}$

$\bar{l}_x^{\,2}$ is equal to $2Dt$

What impact does this have on the velocity of molecular motion in a random walk algorithm?

Monte Carlo Probabilities for Bimolecular Associations

Velocity of Molecular Motion - Brownian Dynamics Random Walk



$$p_r = \frac{1}{(4\pi D_L \Delta t)^{3/2}} e^{-r^2/4D_L\Delta t} (4\pi r^2\, dr)$$

$$\bar{l}_r = 2\sqrt{\frac{4D_L\Delta t}{\pi}} \qquad \bar{l}_\perp = \sqrt{\frac{4D_L\Delta t}{\pi}}$$

$$s = r\big/\sqrt{4D_L\Delta t}$$

$$p_s = \frac{4}{\sqrt{\pi}} s^2 e^{-s^2}\, ds$$

Solution of Fick's 2nd Law in 1-D

point source:

$$C(r,t)=\frac{M}{(4\pi Dt)^{3/2}}e^{-r^2/4Dt}$$

Plot for constant time

line source:

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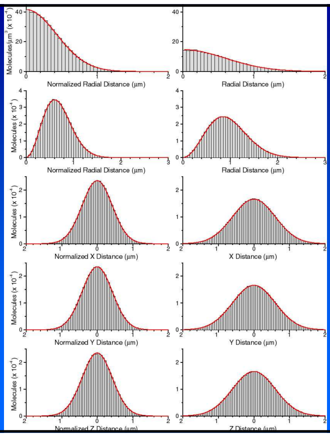

Solution of Fick's 2nd Law in 1-D

point source:

$$C(r,t)=\frac{M}{(4\pi Dt)^{3/2}}e^{-r^2/4Dt}$$

Plot for constant distance

line source:

$$C(r,t)=\frac{M}{(4\pi Dt)}e^{-r^2/4Dt}$$

plane source:

$$C(x,t)=\frac{M}{(4\pi Dt)^{1/2}}e^{-x^2/4Dt}$$

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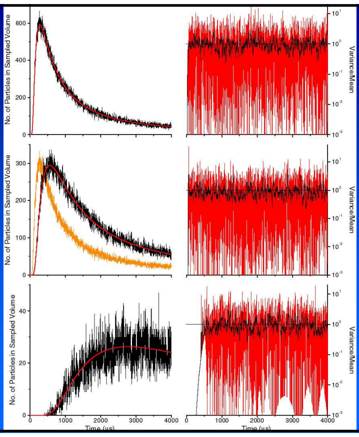

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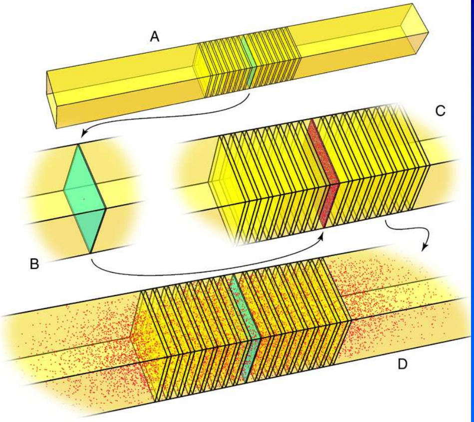

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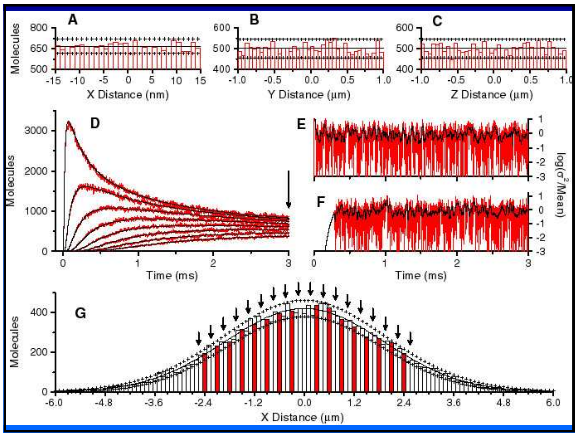
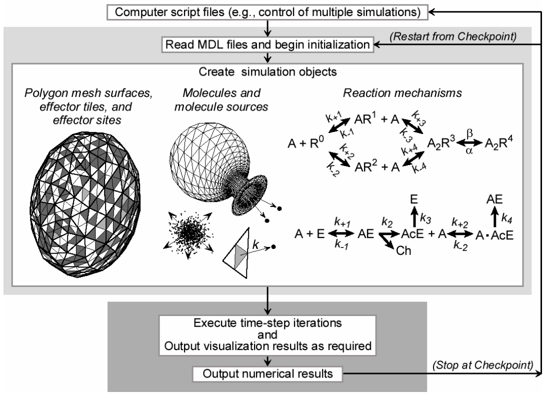
Plot for constant linear distance or time



MCell Simulations



Computer script files (e.g., control of multiple simulations)

Read MDL files and begin initialization

(Restart from Checkpoint)

Create simulation objects

Polygon mesh surfaces, effector tiles, and effector sites

Molecules and molecule sources

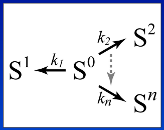
Reaction mechanisms

Execute time-step iterations
and
Output visualization results as required

Output numerical results

(Stop at Checkpoint)

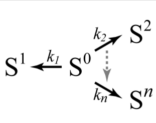
Monte Carlo Probabilities for Unimolecular Transitions



If this reaction proceeds for any time *t* from an initial concentration $(S^0)_o$, the total probability (p_{kt}) that a *single molecule in the* S^0 *state undergoes a transition* is given by the *fraction of* $(S^0)_o$ *that undergoes any transition during time t*:

$$p_{kt}=\frac{(S^1)_t+(S^2)_t+\ldots(S^n)_t}{(S^0)_o}=1-\frac{(S^0)_t}{(S^0)_o}$$

Monte Carlo Probabilities for Unimolecular Transitions



The general rate equation depends only on time and (S^0):

$$-d\,(S^0)=d\,(S^1)+d\,(S^2)+\ldots d\,(S^n)=(k_1+k_2+\ldots k_n)(S^0)\,dt=\left(\sum_1^n k_i\right)(S^0)\,dt$$

Monte Carlo Probabilities for Unimolecular Transitions

$$-d\,(S^0)=d\,(S^1)+d\,(S^2)+\ldots d\,(S^n)=(k_1+k_2+\ldots k_n)(S^0)\,dt=\left(\sum_1^n k_i\right)(S^0)\,dt$$

and hence can be integrated directly to obtain p_{kt} :

$$\int_{(S^0)_o}^{(S^0)_t}\frac{d(S^0)}{(S^0)}=-\left(\sum_1^n k_i\right)\int_0^t dt$$

Monte Carlo Probabilities for Unimolecular Transitions

$$\int_{(\mathrm{S}^0)_o}^{(\mathrm{S}^0)_t} \frac{d(\mathrm{S}^0)}{(\mathrm{S}^0)} = -\left(\sum_1^n k_i\right)\int_0^t dt$$

and the solution is:

$$\frac{(\mathrm{S}^0)_t}{(\mathrm{S}^0)_o} = \exp\left[-\left(\sum_1^n k_i\right)t\right]$$

Monte Carlo Probabilities for Unimolecular Transitions

$$\frac{(\mathrm{S}^0)_t}{(\mathrm{S}^0)_o} = \exp\left[-\left(\sum_1^n k_i\right)t\right]$$

From this, the lifetime of S^0 is exponentially distributed. The mean value is given by τ:

$$\tau = 1\Big/\sum_1^n k_i$$

Monte Carlo Probabilities for Unimolecular Transitions

From: $$\frac{(\mathrm{S}^0)_t}{(\mathrm{S}^0)_o} = \exp\left[-\left(\sum_1^n k_i\right)t\right]$$

and: $$p_{kt} = \frac{(\mathrm{S}^1)_t + (\mathrm{S}^2)_t + \ldots(\mathrm{S}^n)_t}{(\mathrm{S}^0)_o} = 1 - \frac{(\mathrm{S}^0)_t}{(\mathrm{S}^0)_o}$$

we obtain: $$p_{kt} = 1 - \exp\left[-\left(\sum_1^n k_i\right)t\right]$$

Monte Carlo Probabilities for Unimolecular Transitions

And finally:

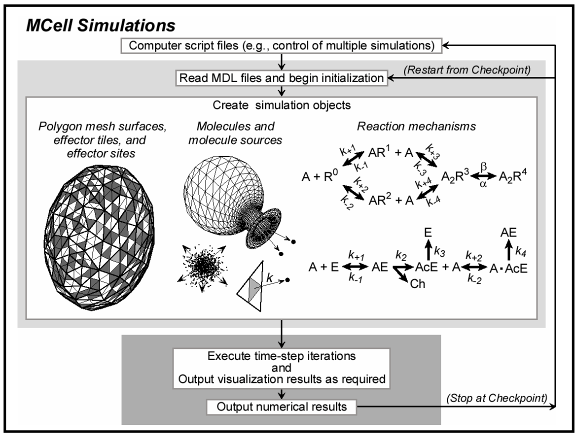
$$p_{kt} = 1 - \exp\left[-\left(\sum_1^n k_i\right)\Delta t\right]$$

$$p_{k1} = p_{kt}\cdot\frac{k_1}{\sum_1^n k_i}, \ldots p_{kn} = p_{kt}\cdot\frac{k_n}{\sum_1^n k_i};\quad \sum_1^n p_{ki} = p_{kt}$$

What is the range of possible p_{kt} values?

How do you use random numbers to test for transitions?

What influences numerical accuracy?



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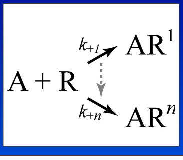
Monte Carlo Probabilities for Bimolecular Associations

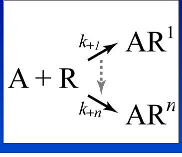


$$p_{bt} = 1 - (1 - p_b)^{N_H}$$

$$p_t \cong \zeta = \left(\sum_1^n k_{+i}\right)(\mathrm{A})_o\Delta t$$

$$1 - (1 - p_b)^{N_H} = p_t \cong \zeta = \left(\sum_1^n k_{+i}\right)(\mathrm{A})_o\Delta t$$

Monte Carlo Probabilities for Bimolecular Associations



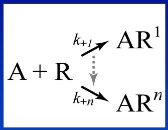
$$A + R \rightarrow AR^1 \ldots AR^n$$

$$p_{bt} = 1 - (1 - p_b)^{N_H}$$

$$\boxed{p_t \cong \zeta = \left(\sum_1^n k_{+i}\right)(\text{A})_\text{o}\Delta t} \quad \textbf{?}$$

$$1-(1-p_b)^{N_H} = p_t \cong \zeta = \left(\sum_1^n k_{+i}\right)(\text{A})_\text{o}\Delta t$$

Monte Carlo Probabilities for Bimolecular Associations



$$A + R \rightarrow AR^1 \ldots AR^n$$

If this reaction proceeds for some time *t* from initial concentrations $(\text{A})_\text{o}$, $(\text{R})_\text{o}$, and $(\text{AR})_\text{o}$, the mass action probability (p_t) that a *single R molecule becomes bound* is given by the fraction of $(\text{R})_\text{o}$ that becomes bound, i.e.,

$$p_t = \frac{\sum_1^n \left[(\text{AR}^i)_t - (\text{AR}^i)_\text{o}\right]}{(\text{R})_\text{o}} \quad \text{or} \quad \frac{\sum(\text{AR}^i)_t}{(\text{R})_\text{o}} \quad \text{given} \quad \sum = \sum_1^n \quad \sum(\text{AR}^i)_\text{o} = 0$$

Monte Carlo Probabilities for Bimolecular Associations

The general rate equation for production of the *n* bound states is:

$$\partial\left[\sum\left(\text{AR}^i\right)\right] = -\partial(\text{A}) = -\partial(\text{R}) = \left(\sum k_{+i}\right)(\text{A})(\text{R})\,\partial t$$

but this cannot be integrated directly to obtain $(\text{AR})_t$ because (A), (R), and (AR) are functions of space as well as time. In this reaction, the quantity ($D_A + D_R$), i.e., the sum of the diffusion coefficients for A and R, is implicitly included in the values of k_+, together with the sizes and shapes of the molecules, and the activation energy for each binding reaction. If at least one of the diffusion coefficients is large but the k_+ values are small (e.g., because the activation energy is large), then the rate of reaction is not “diffusion-limited”, i.e., the solution is always “well-mixed” because the rate of binding is slow compared to the rate of diffusion.

Monte Carlo Probabilities for Bimolecular Associations

Under such conditions, appreciable spatial concentration gradients do not form as binding proceeds, so the partial differentials can be replaced with ordinary differentials:

$$d\left[\sum\left(\text{AR}^i\right)\right] = -d(\text{A}) = -d(\text{R}) = \left(\sum k_{+i}\right)(\text{A})(\text{R})\,dt$$

Since these concentration terms are independent of space, by definition they are *equally valid* for the bulk solution and at the *local level in the vicinity of single molecules*. This equation can be integrated to determine $(\text{AR})_t$:

$$\int_{\sum(\text{AR}^i)_\text{o}}^{\sum(\text{AR}^i)_t} d\left[\sum\left(\text{AR}^i\right)\right] = \left(\sum k_{+i}\right)\int_\text{o}^t (\text{A})(\text{R})\,dt = \left(\sum k_{+i}\right)\int_\text{o}^t (\text{A}_\text{o} - \sum \text{AR}^i)(\text{R}_\text{o} - \sum \text{AR}^i)\,dt$$

Monte Carlo Probabilities for Bimolecular Associations

After integration, final analytic expressions for p_t are:

$$p_t = \frac{\sum\left(\text{AR}^i\right)_t}{(\text{R})_\text{o}} = \frac{1}{(\text{R})_\text{o}}\left(\frac{\left(b^2+q\right)\left(\exp\left[\left(\sum k_{+i}\right)\cdot t\sqrt{-q}\right]-1\right)}{2\left(b+\sqrt{-q}-\left(b-\sqrt{-q}\right)\exp\left[\left(\sum k_{+i}\right)\cdot t\sqrt{-q}\right]\right)}\right)$$

if $(\text{A})_\text{o} \neq (\text{R})_\text{o}$; where
$b = -(\text{A}_\text{o} + \text{R}_\text{o})$ and
$q = 4(\text{A}_\text{o})(\text{R}_\text{o}) - b^2$

or

$$p_t = \frac{\sum\left(\text{AR}^i\right)_t}{(\text{R})_\text{o}} = \frac{1}{(\text{R})_\text{o}}\left(\frac{\left(\sum k_{+i}\right)(\text{A})_\text{o}^2\,t}{1+\left(\sum k_{+i}\right)(\text{A})_\text{o}\,t}\right) = \frac{\left(\sum k_{+i}\right)(\text{A})_\text{o}\,t}{1+\left(\sum k_{+i}\right)(\text{A})_\text{o}\,t}$$

if $(\text{A})_\text{o} = (\text{R})_\text{o}$

Monte Carlo Probabilities for Bimolecular Associations

Reality check:

From these equations, the probability (p_t) that a single R molecule becomes bound during an arbitrarily long interval of time (t) depends on all the k_+ values, $(\text{A})_\text{o}$, and $(\text{R})_\text{o}$; $p_t = 0$ for $t = 0$, and for $t = \infty$, $p_t = 1$ if $(\text{A})_\text{o} \geq (\text{R})_\text{o}$, or $p_t = (\text{A})_\text{o}/(\text{R})_\text{o}$ if (A)o < (R)o.

Monte Carlo Probabilities for Bimolecular Associations

If the interval of time is very short, so that $t = \Delta t$ and

$\sum\left(\mathrm{AR}^i\right)_{\Delta t}$ is much less than both $(\mathrm{A})_\mathrm{o}$ and $(\mathrm{R})_\mathrm{o}$, then

$\left(\mathrm{A}_\mathrm{o} - \sum(\mathrm{AR}^i)_{\Delta t}\right) \cong (\mathrm{A})_\mathrm{o}$ and $\left(\mathrm{R}_\mathrm{o} - \sum(\mathrm{AR}^i)_{\Delta t}\right) \cong (\mathrm{R})_\mathrm{o}$

So:

$$\int_{\sum(\mathrm{AR}^i)_\mathrm{o}}^{\sum(\mathrm{AR}^i)_t} d\left[\sum\left(\mathrm{AR}^i\right)\right] = \left(\sum k_{+i}\right)\int_\mathrm{o}^{t} (\mathrm{A})(\mathrm{R})\,dt = \left(\sum k_{+i}\right)\int_\mathrm{o}^{t} (\mathrm{A}_\mathrm{o} - \sum \mathrm{AR}^i)(\mathrm{R}_\mathrm{o} - \sum \mathrm{AR}^i)\,dt$$

becomes:

$$\int_{\sum(\mathrm{AR}^i)_\mathrm{o}}^{\sum(\mathrm{AR}^i)_{\Delta t}} d\left[\sum\left(\mathrm{AR}^i\right)\right] \cong \left(\sum k_{+i}\right)(\mathrm{A})_\mathrm{o}(\mathrm{R})_\mathrm{o}\int_\mathrm{o}^{\Delta t} dt$$

Monte Carlo Probabilities for Bimolecular Associations

$$\int_{\sum(\mathrm{AR}^i)_\mathrm{o}}^{\sum(\mathrm{AR}^i)_{\Delta t}} d\left[\sum\left(\mathrm{AR}^i\right)\right] \cong \left(\sum k_{+i}\right)(\mathrm{A})_\mathrm{o}(\mathrm{R})_\mathrm{o}\int_\mathrm{o}^{\Delta t} dt$$

And after integration:

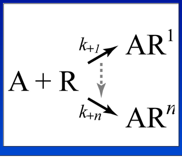
$$\sum\left(\mathrm{AR}^i\right)_{\Delta t} \cong \left(\sum k_{+i}\right)(\mathrm{A})_\mathrm{o}(\mathrm{R})_\mathrm{o}\Delta t$$

Thus, for a short interval of time Δt:

$$p_t = \frac{\sum\left(\mathrm{AR}^i\right)_{\Delta t}}{(R)_\mathrm{o}} \cong \zeta = \left(\sum k_{+i}\right)(\mathrm{A})_\mathrm{o}\Delta t \quad !!$$

where $(\mathrm{A})_\mathrm{o}$ is both the instantaneous local concentration of ligand molecules in the immediate vicinity of a single R molecule, and the average bulk solution ligand concentration.

Monte Carlo Probabilities for Bimolecular Associations



$$\mathrm{A} + \mathrm{R} \begin{matrix} \xrightarrow{k_{+1}} \mathrm{AR}^1 \\ \vdots \\ \xrightarrow{k_{+n}} \mathrm{AR}^n \end{matrix}$$

$$p_{bt} = 1 - (1 - p_b)^{N_H}$$

$$\boxed{p_t \cong \zeta = \left(\sum_1^n k_{+i}\right)(\mathrm{A})_\mathrm{o}\Delta t} \quad !!$$

$$1 - (1 - p_b)^{N_H} = p_t \cong \zeta = \left(\sum_1^n k_{+i}\right)(\mathrm{A})_\mathrm{o}\Delta t$$

Monte Carlo Probabilities for Bimolecular Associations

$$1 - (1 - p_b)^{N_H} = p_t \cong \zeta = \left(\sum_1^n k_{+i}\right)(\mathrm{A})_\mathrm{o}\Delta t$$

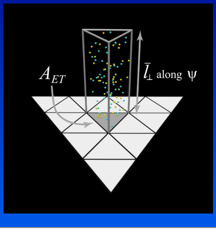
For small Δt, $(1 - p_b)^{N_H}$ approaches $\left(1 - N_H \cdot p_b\right)$

After substitution and rearrangement:

$$p_b = \left(\sum_1^n k_{+i}\right)\frac{(\mathrm{A})_\mathrm{o}\Delta t}{N_H} \quad \text{; for small } \Delta t$$

Monte Carlo Probabilities for Bimolecular Associations

$$p_b = \left(\sum_1^n k_{+i}\right)\frac{(\mathrm{A})_\mathrm{o}\Delta t}{N_H}$$

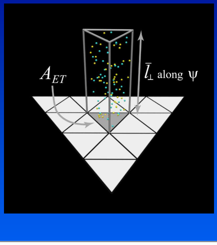


$$N_H = (N_a)\left(\bar{l}_\perp/\Delta t\right)(A_{ET})(\mathrm{A})_\mathrm{o}\int_\mathrm{o}^{\Delta t} dt = (N_a)\left(\bar{l}_\perp/\Delta t\right)(A_{ET})(\mathrm{A})_\mathrm{o}\,\Delta t$$

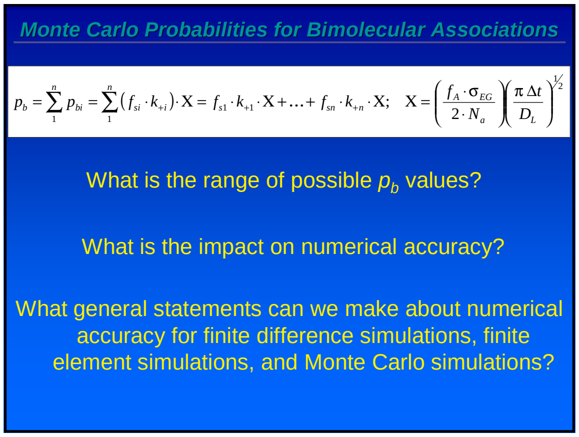
$$p_b = \left(\sum_1^n k_{+i}\right)\frac{1}{2(N_a)(A_{ET})}\left(\frac{\pi\,\Delta t}{D_L}\right)^{1/2}$$

Monte Carlo Probabilities for Bimolecular Associations

$$p_b = \left(\sum_1^n k_{+i}\right)\frac{1}{2(N_a)(A_{ET})}\left(\frac{\pi\,\Delta t}{D_L}\right)^{1/2}$$



$$p_b = \sum_1^n p_{bi} = \sum_1^n \left(f_{si} \cdot k_{+i}\right) \cdot \mathrm{X} = f_{s1} \cdot k_{+1} \cdot \mathrm{X} + \ldots + f_{sn} \cdot k_{+n} \cdot \mathrm{X}; \quad \mathrm{X} = \left(\frac{f_A \cdot \sigma_{EG}}{2 \cdot N_a}\right)\left(\frac{\pi\,\Delta t}{D_L}\right)^{1/2}$$



Monte Carlo Probabilities for Bimolecular Associations

$$p_b = \sum_1^n p_{bi} = \sum_1^n \left(f_{si} \cdot k_{+i}\right) \cdot \mathrm{X} = f_{s1} \cdot k_{+1} \cdot \mathrm{X} + \ldots + f_{sn} \cdot k_{+n} \cdot \mathrm{X}; \quad \mathrm{X} = \left(\frac{f_A \cdot \sigma_{EG}}{2 \cdot N_a}\right)\left(\frac{\pi\,\Delta t}{D_L}\right)^{1/2}$$

What is the range of possible p_b values?

What is the impact on numerical accuracy?

What general statements can we make about numerical accuracy for finite difference simulations, finite element simulations, and Monte Carlo simulations?