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

June 15, 2005
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Review of Diffusion Theory

Fick’s Laws

\[ \nabla \cdot \mathbf{J} = -D \frac{\partial C}{\partial x} \]

Solution of Fick’s 2nd Law in 1-D

point source:

\[ C(r, t) = \frac{M}{(4\pi D t)^{1/2}} e^{-r^2/4Dt} \]

line source:

\[ C(r, t) = \frac{M}{(4\pi D t)^{1/2}} e^{-r^2/4Dt} \]

plane source:

\[ C(x, t) = \frac{M}{\sigma \sqrt{4\pi}} e^{-x^2/4Dr} \]

Mean distances:

\[ \bar{r} \]

is equal to \( 2\sqrt{4Dt/\pi} \)

\[ \bar{r}^2 \]

is equal to \( 6Dt \)

\[ \bar{x}_2 \]

is equal to \( \sqrt{4Dt/\pi} \)

\[ \bar{x}^2 \]

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

\[ P_r = \frac{1}{(4\pi D t \Delta t)^{3/2}} e^{-r^2/(4Dt \Delta t)} \]

\[ \bar{r} = 2\sqrt{D \Delta t} \]

\[ \bar{r}^2 = \frac{4D \Delta t}{\pi} \]

\[ \bar{x} = \frac{2D \Delta t}{\pi} \]

\[ \bar{x}^2 = \frac{4D \Delta t}{\pi} \]

\[ \bar{r} = \frac{2D \Delta t}{\pi} \]

\[ \bar{r}^2 = \frac{4D \Delta t}{\pi} \]

\[ \bar{x} = \frac{2D \Delta t}{\pi} \]

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Solution of Fick’s 2nd Law in 1-D

point source: \[ C(r,t) = \frac{M}{(4\pi Dt)^{1/2}} e^{-r^2/(4Dt)} \]

line source: \[ C(r,t) = \frac{M}{(4\pi Dt)^{1/2}} e^{-r^2/(4Dt)} \]

plane source:

\[ C(x,t) = \frac{M}{(4\pi Dt)^{1/2}} e^{-x^2/(4Dt)} \]
\[ C(x,t) = \frac{M}{\sigma \sqrt{2\pi}} e^{-x^2/2\sigma^2} \cdot \sigma = \sqrt{2Dt} \]
Solution of Fick’s 2nd Law in 1-D

point source:
\[ C(r,t) = \frac{M}{(4\pi Dt)^{1/2}} e^{-r^2/4Dt} \]

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plane source:
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Monte Carlo Probabilities for Unimolecular Transitions

If this reaction proceeds for any time \( t \) from an initial concentration \( <S_0> \), the total probability \( \rho_{\text{tot}} \) that a single molecule in the \( S^0 \) state undergoes a transition is given by the fraction of \( <S^0> \) that undergoes any transition during time \( t \):
\[
\rho_{\text{tot}} = \frac{<S_1> + <S_2> + \ldots + <S_n>}{<S_0>} = 1 - \frac{<S^1>}{<S^0>}
\]

The general rate equation depends only on time and \( <S^0> \):
\[
-\frac{d}{dt} <S^0> = \frac{d}{dt} <S^1> + \frac{d}{dt} <S^2> + \ldots = (k_1 + k_2 + \ldots + k_n) <S^0> = \left( \sum_k k_i \right) <S^0> dt
\]

and hence can be integrated directly to obtain \( \rho_{\text{tot}} \):
\[
\int_{<S^1>_{<S^0>}}^{<S^0>_{<S^0>}} \frac{d<S^0>}{<S^0>} = - \left( \sum_{i=1}^{n} k_i \right) \left[ t \right]_{0}^{t}
\]
Monte Carlo Probabilities for Unimolecular Transitions

\[ \int_{(S^0)}^{(S')} d(S') \left( \frac{d(S^0)}{dS^0} \right) = - \left( \sum_{i=1}^{n} k_i \right) t \]

and the solution is:

\[ \left( \frac{S'}{S^0} \right) = \exp \left[ - \left( \sum_{i=1}^{n} k_i \right) t \right] \]

From this, the lifetime of \( S^0 \) is exponentially distributed. The mean value is given by \( \tau \):

\[ \tau = \frac{1}{\sum_{i=1}^{n} k_i} \]

Monte Carlo Probabilities for Unimolecular Transitions

From:

\[ \frac{\left( S' \right)}{\left( S^0 \right)} = \exp \left[ - \left( \sum_{i=1}^{n} k_i \right) t \right] \]

and:

\[ p_{lt} = \frac{(S')_l + (S')_s + \ldots (S')_n}{(S')_0} = 1 - \left( \frac{S'}{S^0} \right) \]

we obtain:

\[ p_{lt} = 1 - \exp \left[ - \left( \sum_{i=1}^{n} k_i \right) t \right] \]

And finally:

\[ p_{lt} = 1 - \exp \left[ - \left( \sum_{i=1}^{n} k_i \right) \Delta t \right] \]

\[ p_{lt} = p_{lt} \cdot \frac{k_1}{\sum k_i} \ldots \frac{k_n}{\sum k_i} \quad \sum p_{lt} = p_{lt} \]

What is the range of possible \( p_{lt} \) values?
How do you use random numbers to test for transitions?
What influences numerical accuracy?

Monte Carlo Probabilities for Bimolecular Associations

\[ p_{ln} = 1 - (1 - p_{ln})^{n} \]

\[ p_{lt} = \xi \left[ \sum_{i=1}^{n} k_i \right] \Delta t \]

\[ 1 - (1 - p_{lt})^{n} = p_{lt} = \xi \left[ \sum_{i=1}^{n} k_i \right] \Delta t \]
After integration, final analytic expressions for \( p_t \) are:

\[
p_t = \alpha - (1 - \alpha) e^{-\sum k_{ii} (A)_{ii} \Delta t}
\]

or

\[
p_t = \frac{\sum [AR']_o - (AR')_t}{(R)'_o} \quad \text{or given } \sum (AR')_o = 0
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After integration, final analytic expressions for \( p_t \) are:

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or

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p_t = \frac{\sum [AR']_o - (AR')_t}{(R)'_o} \quad \text{or given } \sum (AR')_o = 0
\]
Monte Carlo Probabilities for Bimolecular Associations

If the interval of time is very short, so that $t = \Delta t$ and $\sum (AR)^{\text{int}}$ is much less than both $(A)_b$ and $(R)_b$, then:

$[A_0 - \sum (AR)^{\text{int}}] \equiv (A)_b$ and $[R_0 - \sum (AR)^{\text{int}}] \equiv (R)_b$

So:

$\sum_{\text{int}} d[\sum (AR)] = (\sum k_{\text{int}})(A)(R)dt = (\sum k_{\text{int}})(A_0 - \sum (AR)^{\text{int}})(R_0 - \sum (AR)^{\text{int}})dt$

becomes:

$\sum_{\text{int}} \int_{\text{int}} d[\sum (AR)] = (\sum k_{\text{int}})(A_0 - \sum (AR)^{\text{int}})(R_0 - \sum (AR)^{\text{int}})dt$

Thus, for a short interval of time $\Delta t$:

$P_t = \frac{\sum (AR)}{(R)_b} \equiv \xi = (\sum k_{\text{int}})(A)_b\Delta t$

where $(A)_b$ 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

$1 - (1 - p)^{\Delta t} = p_t \equiv \xi \equiv (\sum k_{\text{int}})(A)_b\Delta t$

$1 - (1 - p)^{\Delta t} = p_t \equiv \xi \equiv (\sum k_{\text{int}})(A)_b\Delta t$

After substitution and rearrangement:

$p_t = \left(\sum k_{\text{int}}\right)\frac{(A)_b\Delta t}{N_H} : \text{for small } \Delta t$

Monte Carlo Probabilities for Bimolecular Associations

$p_b = \left(\sum k_{\text{int}}\right)\frac{(A)_b}{N_H} \frac{\Delta t}{N_H}$

$N_H = (N_e)\int_\Delta (A)_e (A)_b \int_\Delta (A)_e (A)_b dt = (N_e)\int_\Delta (A)_e (A)_b \Delta t$

$p_b = \left(\sum k_{\text{int}}\right) \frac{1}{2(N_e \sigma_x A_x) \frac{\pi \Delta t}{D_x}}$
Monte Carlo Probabilities for Bimolecular Associations

\[ p_n = \sum p_n = \sum (f_i \cdot k_i) X = f_i \cdot k_i \cdot X + \ldots + f_i \cdot k_i \cdot X \cdot \frac{f_i \cdot \sigma_m}{2 \cdot \pi} \left( \frac{\pi \cdot \sigma_n}{D_n} \right)^n \]

What is the range of possible \( p_n \) 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?