Kinetics: Theory & Methods

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

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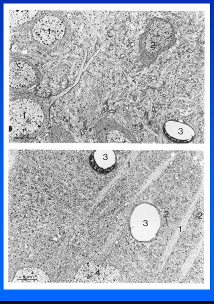
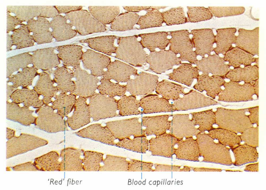
PITTSBURGH
SUPERCOMPUTING
CENTER

Biomedical Supercomputing
Initiative

Introduction to Diffusion

Physiological Importance





Introduction to Diffusion

Physiological Importance

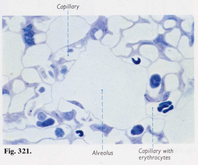


Fig. 321.

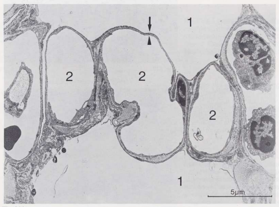


Fig. 323a.

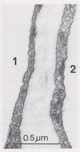


Fig. 323b.

Introduction to Diffusion

Timescale of Brownian Motion (25°C)

$$\text{average speed of water molecule} \approx \sqrt{\frac{3kT}{m}} = 640\ \text{m s}^{-1}$$

(i.e., 1400 mi h^{-1}!)

$$\text{average distance between collisions} \approx 0.2\ \text{nm}$$

$$\text{average time between collisions} = \frac{0.2 \times 10^{-9}\,\text{m}}{640\ \text{m s}^{-1}} = 3 \times 10^{-13}\ \text{s}$$

Introduction to Diffusion

Derivation of Fick's Laws

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

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

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

Introduction to Diffusion

Solution of Fick's 2nd Law

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

General Solution: $C = \dfrac{B}{\sqrt{t}}e^{-\zeta^2/4Dt}$ **(1)**

Consider unbounded radial diffusion from a point source:

$\text{total amount } M = \displaystyle\int_0^{\infty} C\ 4\pi r^2\ dr$ **(2)**

Substituting from (1) into (2):

$$B \;=\; M\sqrt{t} \Big/ 4\pi \int_0^\infty r^2 e^{-r^2/4Dt}\, dr \qquad \textbf{(3)}$$

Reformulate (3) using:

$$\frac{r^2}{4Dt} = s^2 \;\;,\;\; r^2 = 4Dt\;\, s^2 \;\;,\;\; dr = \sqrt{4Dt}\;\; ds \qquad \textbf{(4)}$$

To obtain:

$$B \;=\; M\sqrt{t} \Big/ 4\pi\,(4Dt)^{3/2} \int_0^\infty s^2 e^{-s^2}\; ds \qquad \textbf{(5)}$$

From a table of standard integrals:

$$\int_0^\infty u^2 e^{-u^2} du = \frac{\sqrt{\pi}}{4} \qquad \textbf{(6)}$$

Therefore (5) becomes:

$$B = \frac{M}{(4\pi D)^{3/2}\;\, t} \qquad \textbf{(7)}$$

And substituting from (7) back into (1):

$$C(r,t) = \frac{M}{(4\pi Dt)^{3/2}}\, e^{-r^2/4Dt} \qquad \textbf{(8)}$$

Multiplying (8) by the volume of a spherical shell:

$$N = \frac{M}{(4\pi Dt)^{3/2}}\, e^{-r^2/4Dt}\;(4\pi r^2\; dr) \qquad \textbf{(9)}$$

Dividing both sides of (9) by *M*:

$$p_r \;=\; \frac{1}{(4\pi Dt)^{3/2}}\, e^{-r^2/4Dt}\;(4\pi r^2\; dr) \qquad \textbf{(10)}$$

Use (4) again to reformulate (10) in terms of the dimensionless parameter *s*:

$$p_{s,r} \;=\; \frac{4}{\sqrt{\pi}}\; s^2 e^{-s^2}\; ds \qquad \textbf{(11)}$$

From (6), the total cumulative probability of (11) is equal to one. The mean radial displacement is obtained from the expectation of *r* :

$$\bar{l}_r \;=\; \text{expectation of}\;\; r \;=\; \int_0^\infty r \cdot p_r \qquad \textbf{(12)}$$

After substitution for *r* and p_r , from (4) and (11):

$$\bar{l}_r \;=\; \int_0^\infty \sqrt{4Dt}\cdot s \cdot p_{s,r} \;=\; 4\,\sqrt{\frac{4Dt}{\pi}}\; \int_0^\infty s^3 e^{-s^2}\; ds \qquad \textbf{(13)}$$

From a table of standard integrals:

$$\int_0^\infty u^{2n+1} e^{-au^2} du = \frac{n!}{2a^{n+1}} \qquad \textbf{(14)}$$

So the integral in (13) evaluates to ½, and :

$\bar{l}_r$ is equal to $2\sqrt{4Dt/\pi}$ **(15)**

The mean square radial displacement is given by the expectation of r^2 :

$$\bar{l}_r^{\,2} \;=\; \int_0^\infty r^2 \cdot p_r \;=\; 4Dt \int_0^\infty s^2 \cdot p_{s,r} \;=\; \frac{16Dt}{\sqrt{\pi}} \int_0^\infty s^4 e^{-s^2}\; ds \qquad \textbf{(16)}$$

From:

$$\int_0^\infty u^{2n} e^{-au^2} du = \frac{1\cdot 3\cdot 5 \ldots (2n-1)}{2^{n+1} a^n} \sqrt{\frac{\pi}{a}} \qquad \textbf{(17)}$$

the integral in (16) evaluates to $3\sqrt{\pi}/8$ and,

$\bar{l}_r^{\,2}$ is equal to $6Dt$ **(18)**

Consider linear diffusion from a plane source:

$$\text{total amount } M = \int_{-\infty}^{+\infty} C\,dx \qquad (19)$$

and:

$$C(x,t) = \frac{M}{(4\pi Dt)^{1/2}} e^{-x^2/4Dt} \qquad (20)$$

or:

$$C(x,t) = \frac{M}{\sigma\sqrt{2\pi}} e^{-x^2/2\sigma^2}, \ \sigma = \sqrt{2Dt} \qquad (21)$$

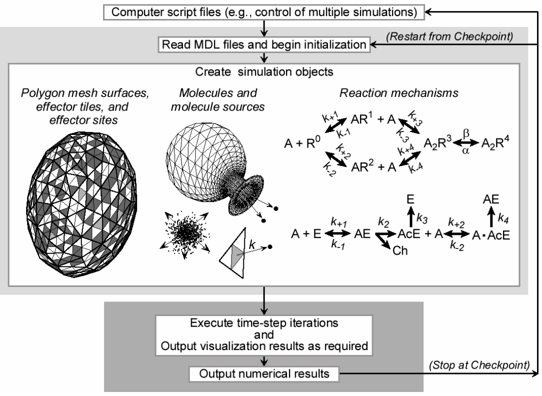
The mean linear displacement is obtained from the expectation of *x* :

$$\bar{l}_x = \int_0^{\infty} x \cdot p_x = 2\sqrt{\frac{4Dt}{\pi}} \int_0^{\infty} s e^{-s^2}\, ds \qquad (22)$$

and: $\bar{l}_x$ is equal to $\sqrt{4Dt/\pi}$ (23)

and: $\bar{l}_x^{\ 2}$ is equal to $2Dt$ (24)

MCell Simulations



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

Read MDL files and begin initialization

(Restart from Checkpoint)

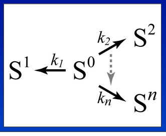
Create simulation objects

Execute time-step iterations
and
Output visualization results as required

Output numerical results

(Stop at Checkpoint)

Monte Carlo Probabilities for Unimolecular Transitions

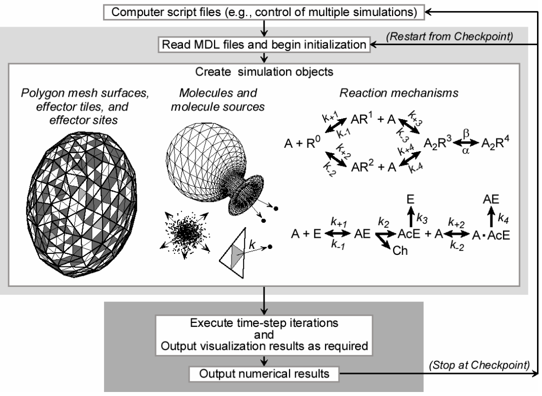


$$-d(\mathrm{S}^0) = d(\mathrm{S}^1) + d(\mathrm{S}^2) + \ldots d(\mathrm{S}^n) = (k_1 + k_2 + \ldots k_n)(\mathrm{S}^0)\,dt = \left(\sum_1^n k_i\right)(\mathrm{S}^0)\,dt$$

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

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

MCell Simulations



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Rate Equations for AChR

Assuming identical binding sites:

$$A + R \underset{k_-}{\overset{2k_+}{\rightleftarrows}} AR,$$

k_+ has units of $M^{-1}\cdot s^{-1}$ (second order)

$$AR + A \underset{2k_-}{\overset{k_+}{\rightleftarrows}} A_2R,$$

k_-, α, β have units of s^{-1} (first order)

$$A_2R \underset{\alpha}{\overset{\beta}{\rightleftarrows}} A_2R^*$$

$$\partial(R) = [k_-(AR) - 2k_+(A)(R)]\partial t$$
$$\partial(AR) = [2k_+(A)(R) + 2k_-(A_2R) - k_-(AR) - k_+(AR)(R)]\partial t$$
$$\partial(A_2R) = [k_+(AR)(R) - (2k_- + \beta)(A_2R)]\partial t$$
$$\partial(A_2R^*) = [\beta(A_2R) - \alpha(A_2R^*)]\partial t$$
$$\partial(A) = [k_-(AR) + 2k_-(A_2R) - 2k_+(A)(R) - k_+(AR)(A)]\partial t$$

Physical Interpretation of k_+

$$L + E \xrightarrow{k_+} LE$$

(isolated bimolecular reaction transition between ligand L and effector E)

$$-d(L) = -d(E) = d(LE) = k_+(L)(E)\,dt$$

The rate of encounters (collisions) between L and E can be estimated from diffusion theory as the flux of L molecules across the surface of E molecules. If L and E are considered to be spherical molecules (radii r_L and r_E) in well mixed solution, the flux can be calculated by integrating Fick's first law for radial diffusion over distances extending from infinity to ($r_L + r_E$), i.e., the distance of closest approach. The result, expressed as the number of encounters per unit volume during an interval of time dt, is:

Physical Interpretation of k_+ (cont'd)

$$\text{number of encounters} = \frac{4\pi(r_L + r_E)(D_L + D_E)(N_a)}{1000}(L)(E)\,dt$$

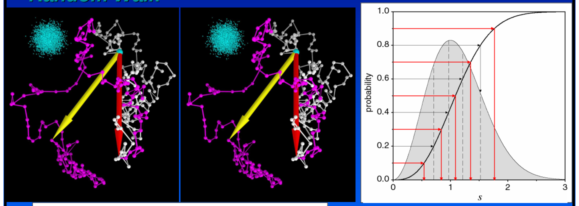
where D_L and D_E are diffusion coefficients (distance squared per unit time) and N_a is Avogadro's number. Setting the previous rate equation equal to the above yields the ***Smoluchowski equation*** for $k_{+,max}$:

$$k_{+,max} = \frac{4\pi(r_L + r_E)(D_L + D_E)(N_a)}{1000}$$

and k_+ would equal $k_{+,max}$ if every encounter led to binding and the reaction had no activation energy (a so-called "diffusion-limited" reaction). Experimental values of k_+ for typical ligands and proteins are generally at least two orders of magnitude less than $k_{+,max}$ (~10^{10} $M^{-1}\cdot s^{-1}$; important exception - ***facilitated diffusion***) and reflect both a non-zero activation energy and the small fraction of a protein's surface that constitutes a binding site. Electrostatic interactions also influence actual values of k_+, but at any scale above that of molecular dynamics, k_+ is a phenomenological scaling factor related to the velocity of molecular motion and an apparent surface area of interaction.

Monte Carlo Probabilities for Bimolecular Associations

Velocity of Molecular Motion - Brownian Dynamics Random Walk



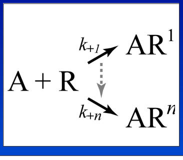
$$p_r = \frac{1}{(4\pi D_L \Delta t)^{3/2}} e^{-r^2/4D_L\Delta t}\,(4\pi r^2\,dr)$$

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

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

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

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

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

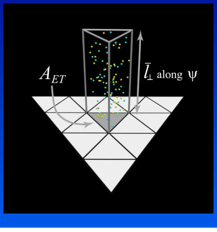
For small Δt, $(1 - p_b)^{N_H}$ approaches $(1 - N_H \cdot p_b)$

After substitution and rearrangement:

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

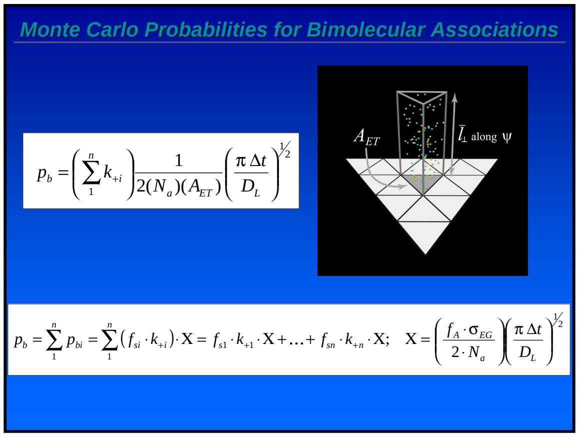
Monte Carlo Probabilities for Bimolecular Associations

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



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

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



Monte Carlo Probabilities for Bimolecular Associations

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

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