Kinetics: Theory & Methods

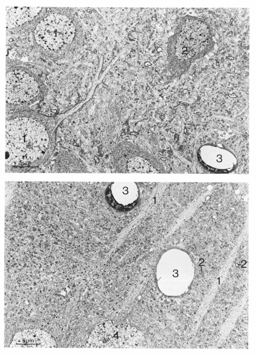
Joel R. Stiles, MD, PhD

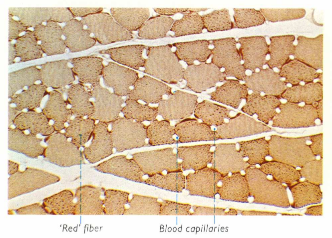
PITTSBURGH SUPERCOMPUTING CENTER

Biomedical Supercomputing Initiative

Introduction to Diffusion

Physiological Importance





Introduction to Diffusion

Physiological Importance

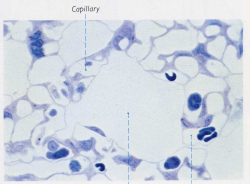


Fig. 321.

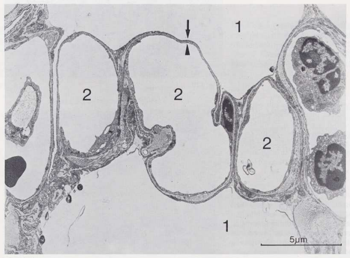


Fig. 323a.

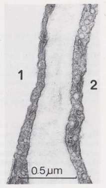


Fig. 323b.

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

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

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

Introduction to Diffusion

Solution of Fick's 2nd Law

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

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

Consider unbounded radial diffusion from a point source:

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

Substituting from (1) into (2):

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

Reformulate (3) using:

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

To obtain:

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

From a table of standard integrals:

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

Therefore (5) becomes:

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

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

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

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

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

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

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

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

$$p_{s,r} = \frac{4}{\sqrt{\pi}}\, s^2 e^{-s^2}\, ds \tag{11}$$

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

$$\bar{l}_r = \text{expectation of } r = \int_0^\infty r \cdot p_r \tag{12}$$

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

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

From a table of standard integrals:

$$\int_0^\infty u^{2n+1} e^{-au^2}\, du = \frac{n!}{2a^{n+1}} \tag{14}$$

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 :

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

From:

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

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:

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

and:

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

or:

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

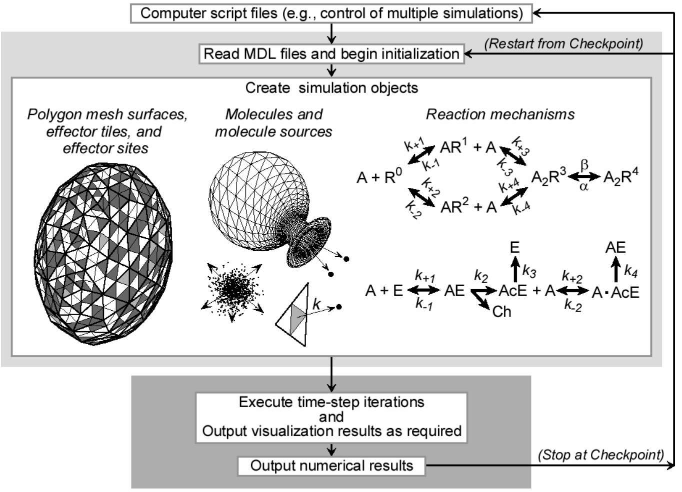
The mean linear displacement is obtained from the expectation of *x* :

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

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

Polygon mesh surfaces, effector tiles, and effector sites

Molecules and molecule sources

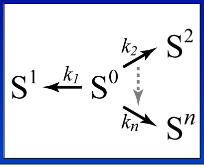
Reaction mechanisms

Execute time-step iterations
and
Output visualization results as required

Output numerical results

(Stop at Checkpoint)

Monte Carlo Probabilities for Unimolecular Transitions

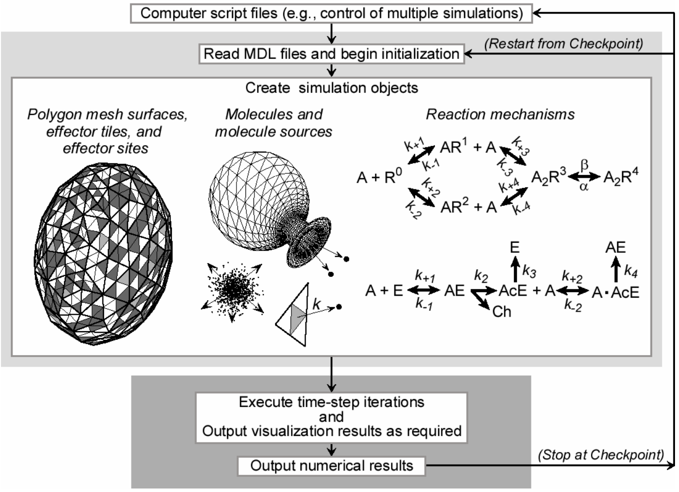


$$-d(\mathrm{S}^0) = d(\mathrm{S}^1) + d(\mathrm{S}^2) + \ldots d(\mathrm{S}^n) = (k_1 + k_2 + \ldots k_n)(\mathrm{S}^0)\,dt = \left(\sum_1^n k_i\right)(\mathrm{S}^0)\,dt$$

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

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

MCell Simulations



Rate Equations for AChR

Assuming identical binding sites:

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

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

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

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

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

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

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)

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

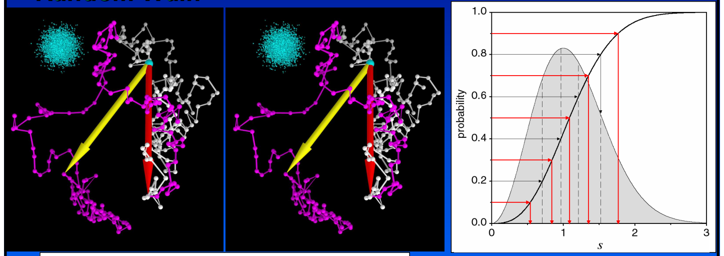
where D_L and D_E are diffusion coefficients (distance squared per unit time) and N_a is Avogadro's number. Setting the previous rate equation equal to the above yields the ***Smoluchowski equation*** for $k_{+,max}$:

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

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



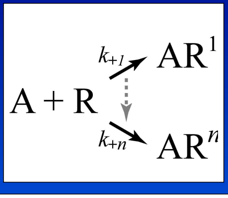
$$p_r = \frac{1}{(4\pi D_L \Delta t)^{3/2}} e^{-r^2/4D_L\Delta t} \; (4\pi r^2 \, dr)$$

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

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

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

Monte Carlo Probabilities for Bimolecular Associations



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

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

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

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

Monte Carlo Probabilities for Bimolecular Associations

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

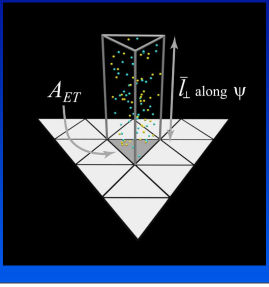
For small Δt, $(1 - p_b)^{N_H}$ approaches $\left(1 - N_H \cdot p_b\right)$

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

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

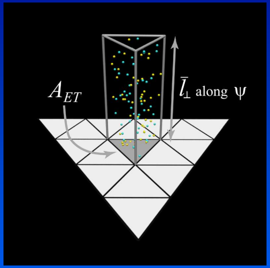


$$N_H = (N_a)(\bar{l}_\perp/\Delta t)(A_{ET})(\mathrm{A})_\mathrm{o}\int_\mathrm{o}^{\Delta t} dt = (N_a)(\bar{l}_\perp/\Delta t)(A_{ET})(\mathrm{A})_\mathrm{o}\,\Delta t$$

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

Monte Carlo Probabilities for Bimolecular Associations

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



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