3

Diffusion and Drug Dispersion

You air that serves me with breath to speak!
You objects that call from diffusion my meanings, and give them shape!
Walt Whitman, *Song of the Open Road* (1856)

Most biological processes occur in an environment that is predominantly water: a typical cell contains 70–85% water and the extracellular space of most tissues is 99%. Even the brain, with its complex arrangement of cells and myelinated processes, is $\approx$ 80% water. Drug molecules can be introduced into the body in a variety of ways (recall Table 2.1); the effectiveness of drug therapy depends on the rate and extent to which drug molecules can move through tissue structures to reach their site of action. Since water serves as the primary milieu for life processes, it is essential to understand the factors that determine rates of molecular movement in aqueous environments. As we will see, rates of diffusive transport of molecules vary among biological tissues within an organism, even though the bulk composition of the tissues (i.e., their water content) may be similar.

The section begins with the random walk, a useful model from statistical physics that provides insight into the kinetics of molecular diffusion. From this starting point, the fundamental relationship between diffusive flux and solute concentration, Fick's law, is described and used to develop general mass-conservation equations. These conservation equations are essential for analysis of rates of solute transport in tissues.

3.1 RANDOM WALKS

Molecules that are initially localized within an unstirred vessel will spread throughout the vessel, eventually becoming uniformly dispersed. This process, called diffusion, occurs by the random movement of individual molecules; molecular motion is generated by thermal energy. Einstein demonstrated

that the average kinetic energy of particles in a system depends on the absolute temperature T [1]:

$$\left\langle \frac{mv_x^2}{2} \right\rangle = \frac{k_B T}{2} \tag{3-1}$$

where v_x is the velocity of the particle on one axis, m is the mass of a particle, and k_B is Boltzmann's constant ($k_B T = 4.4 \times 10^{-14}\,\mathrm{g \cdot cm^2/s^2}$ at 300 K). The root-mean-square (r.m.s.) velocity can be found from this relationship:

$$v_{rms} = \sqrt{\langle v_x^2 \rangle} = \sqrt{\frac{k_B T}{m}} \tag{3-2}$$

Albumin, a protein of 68,000 M_w, has a predicted r.m.s. velocity of 600 cm/s at 300 K. A molecule moving at this speed should travel 2 m (the height of a very tall person) in about 0.33 s, if it moved in a straight line. Experience teaches us that molecules do not move this rapidly. In fact, rates of diffusive transport are much slower than v_{rms} would suggest. Diffusion is slow because molecules do not travel in a straight path; individual molecules collide with other molecules and change directions frequently, producing a pattern of migration known as a random walk (Figure 3.1). Since air and water have different molecular densities, the number of collisions per second—and hence the rate of overall dispersion—differs for these fluids.

These patterns of migration can be simulated by examining particles that follow simple rules for movement: random walkers. Many of the important characteristics of diffusive processes can be understood by considering the dynamics of particles executing simple random walks. The excellent book by Berg [2] provides a useful introduction to the random walk and its relevence in biological systems, which is followed here. Whitney provides a complete, tutorial introduction to a variety of random processes, including the random walk [3].

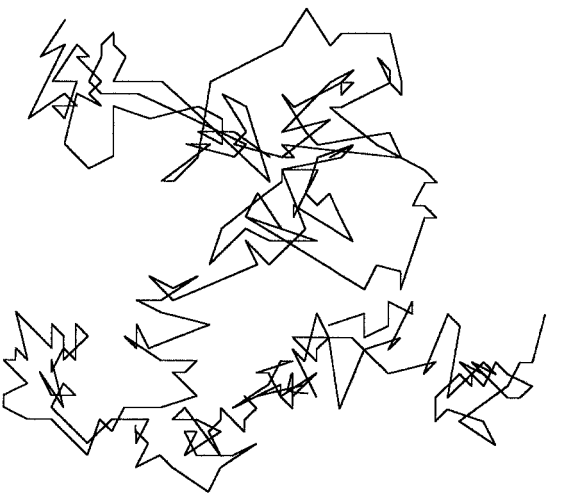

Figure 3.1
Typical pattern of migration for a particle executing a random walk.

Consider, for example, a particle constrained to move on a one-dimensional axis (Figure 3.2). During a small time interval, τ, the particle can move a distance δ, which depends on the particle's velocity v_x: $\delta = v_x\tau$. Further assume that at the end of each period τ the particle changes its direction of movement, randomly moving to the right or the left with equal probability. At each step in the walk, the decision to move left or right is completely random and does not depend on the particle's previous history of movement. If N identical particles, each moving according to these simple rules, begin at the origin of the coordinate system at $t = 0$, one-half of the particles will be at position $-\delta$ and one-half of the particles will be at $+\delta$ at the end of the first interval τ (Figure 3.2). If the location of one particular particle, indicated by the index i, after $n-1$ such intervals is designated $x_i(n-1)$, then the position of that same particle after n intervals is easily determined:

$$x_i(n) = x_i(n-1) \pm \delta \tag{3-3}$$

The mean particle position can be predicted by averaging Equation 4-3 over the ensemble of particles, which becomes:

$$\langle x(n)\rangle = \frac{1}{N}\sum_{i=1}^{N} x_i(n) = \frac{1}{N}\sum_{i=1}^{N}(x_i(n-1) \pm \delta) = \frac{1}{N}\sum_{i=1}^{N} x_i(n-1) + \frac{1}{N}\sum_{i=1}^{N}(\pm\delta) \tag{3-4}$$

upon substitution of Equation 3-3. The averaging operation, designated $\langle\bullet\rangle$, is a conventional arithmetical average:

$$\frac{1}{N}\left(\sum_{i=1}^{N}\bullet_i\right).$$

The second term on the right-hand side of Equation 3-4 is zero, since an equal number of particles will move to the right $(+\delta)$ and to the left $(-\delta)$, which produces:

$$\langle x(n)\rangle = \langle x(n-1)\rangle \tag{3-5}$$

Therefore, the average position of the randomly migrating particles in this ensemble does not change with time. For a group of particles that begin at the origin, $x = 0$ as in Figure 3.2, the average position will always be at the origin.

Although this random migration does not change the average position of the particle ensemble, it does tend to spread the particles over the axis. The extent of spread can be determined by examining the mean square displacement of the particle ensemble, $\langle x^2(n)\rangle$:

$$\langle x^2(n)\rangle = \frac{1}{N}\sum_{i=1}^{N}(x_i(n-1) \pm \delta)^2 = \frac{1}{N}\sum_{i=1}^{N}\left(x_i^2(n-1) \pm 2\delta x_i(n-1) + \delta^2\right) \tag{3-6}$$

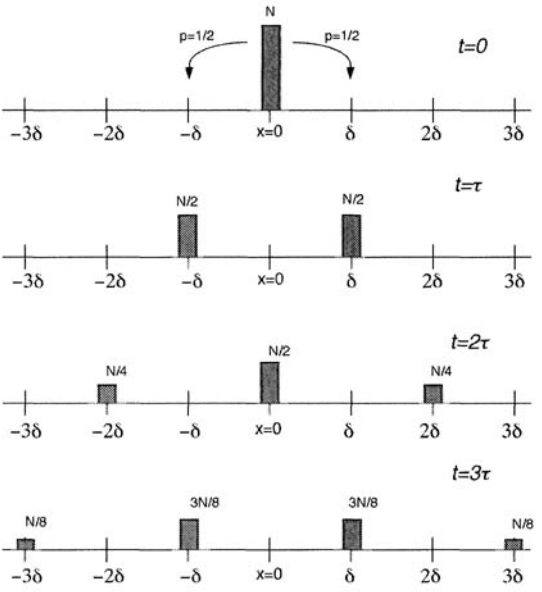

Figure 3.2
Coordinate system for a one-dimensional random walk. Consider a group of N particles that are all located at the original ($x = 0$) at some initial time ($t = 0$). In each increment of time, τ, each particle randomly moves a fixed distance either to the left ($-\delta$) or the right ($+\delta$).

When the summation is expanded, the sum resulting from the middle term on the right-hand side is zero, because an equal number of particles move to the left and right. The first and last terms can be reduced, to yield:

$$\langle x^2(n)\rangle = \langle x^2(n-1)\rangle + \delta^2 \tag{3-7}$$

Since the mean square displacement is initially zero, Equation 3-7 indicates that the mean square displacement increases linearly with the number of steps in the random walk:

$$\begin{aligned} \langle x^2(0)\rangle &= 0 \\ \langle x^2(1)\rangle &= \delta^2 \\ \langle x(2)\rangle &= 2\delta^2 \\ &\vdots \\ \langle x^2(n)\rangle &= n\delta^2 \end{aligned} \tag{3-8}$$

Since the total elapsed time t is equal to $n\tau$, the mean square displacement also increases linearly with time:

$$\langle x^2(t)\rangle = \left(\frac{\delta^2}{\tau}\right) t \tag{3-9}$$

and the r.m.s. displacement, x_{rms}, increases with the square root of time:

$$x_{\text{rms}} \equiv \langle x^2(t)\rangle^{1/2} = \sqrt{2Dt} \tag{3-10}$$

where the diffusion coefficient D is defined:

$$D = \delta^2/2\tau \tag{3-11}$$

Experimental measurements, obtained by measuring the rate of spreading of protein molecules in solution (or by a variety of other methods described in Chapter 4), suggest that D for albumin at 300 K is $\sim 8 \times 10^{-7}$ cm^2/s. Since v_x is the particle velocity between changes of direction, which is equal to δ/τ, the distance between direction changes, δ, can be estimated as $2D/v_x$. For albumin, with $v_x = v_{rms} = 600$ cm/s, this yields a value for δ of 3×10^{-9} cm (or 0.3 Å, small compared to the diameter of albumin, which is ≈ 60 Å) and a time between direction changes τ of 4×10^{-12} s. This model suggests a different view of albumin movement than obtained by only considering the r.m.s. velocity of individual particles. The random walk of albumin will require 2.5×10^{10} s or 800 years to travel 2 m (from Equation 3-10), a significantly longer time than the r.m.s. velocity would suggest. This simple calculation illustrates the slow progress of diffusing molecules over meter-scale distances (and explains why humans have a circulatory system).

Note that these calculations suggest several important characteristics for diffusion processes:

- since the r.m.s. displacement increases with the square root of time, a diffusing particle that takes T min to diffuse L mm will take $4T$ to diffuse $2L$;
- the diffusion velocity, which might be defined as x_{rms}/t, is inversely proportional to the square root of time and therefore not a useful measure of molecular speed.

This analysis can be extended to two- and three-dimensional random walks by assuming that particle motion in each dimension is independent. The mean square displacement and r.m.s. displacement for higher dimension random walks become:

$$\begin{aligned} \langle r^2\rangle_{2D} &= \langle x^2\rangle + \langle y^2\rangle = 4Dt \quad \text{or} \quad \langle r^2\rangle_{2D}^{1/2} = \sqrt{4Dt} \\ \langle r^2\rangle_{3D} &= \langle x^2\rangle + \langle y^2\rangle + \langle z^2\rangle = 6Dt \quad \text{or} \quad \langle r^2\rangle_{3D}^{1/2} = \sqrt{6Dt} \end{aligned} \tag{3-12}$$

For particles executing a random walk, like albumin molecules in buffered water, the calculations above suggest that individual steps in the random walk occur very quickly, over a short time interval. As a consequence, during a typical observation time, each particle takes many steps on the axis of Figure 3.2. The probability that a random walking particle took a total of k steps to the right after a sequence of n steps in the random walk is provided by the binomial distribution:

$$P\left\{\begin{array}{l}\text{particle took } k \\ \text{steps to the right} \\ \text{after } n \text{ steps}\end{array}\right\} = P(k; n, q) = \frac{n!}{k!(n-k)!}(q)^k(1-q)^{n-k} \tag{3-13}$$

where q is the probability of moving to the right at each step; $q = 1/2$ for an unbiased random walk. For example, after four steps in an unbiased random walk, the binomial distribution can be used to determine the probabilities of finding particles at any location on the axis, as shown in Table 3.1. The probabilities calculated by Equation 3-13 agree with those indicated in Figure 3.2.

By using the binomial distribution, it is possible to determine $p(x)$, the probability of finding a particle at a position between x and $x + dx$, as a function of time after a large number of individual steps in the random walk have occurred [2]:

$$p(x) = \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt} dx \tag{3-14}$$

Equation 3-14 describes a Gaussian distribution; the random walk model predicts that a group of diffusing particles, initially placed at the origin, will spread over time so that the mean position is unchanged, but the variance in the distribution increases as $2Dt$. In the section below, we will see this same distribution emerge from the solution to the macroscopic equations for molecular diffusion (as we will see in Figure 3.5).

The rate of movement of particles at any particular location can be estimated by considering the net rate of particle movement at any specific position during the random walk. During a single step in the random walk, which occurs over the time interval τ, the net rate of particle movement between two adjacent positions x and $x + \delta$ is $N(x)/2 - N(x + \delta)/2$, where $N(\bullet)$ gives the number of particles at a given location, because half of the particles at position x will move to the right (ending at $x + \delta$) and half the particles at $x + \delta$ will move to the left (ending at x). The particle flux j_x is defined as the net rate of particle movement per unit area, so that:

$$j_x = -\frac{1}{2A\tau}[N(x + \delta) - N(x)] \tag{3-15}$$

Rearranging slightly gives:

$$j_x = -\frac{\delta^2}{2\tau}\left[\frac{C(x + \delta) - C(x)}{\delta}\right] \tag{3-16}$$

Table 3.1 Characterization of random walks with binomial distribution

k	0	1	2	3	4
$n - k$	4	3	2	1	0
x	-4δ	-2δ	0	$+2\delta$	$+4\delta$
$P(k; n, 1/2)$	0.0625	0.25	0.375	0.25	0.0625

The binomial distribution, Equation 3-13, was used to calculate the probability of finding a random walker at position x after 4 steps in an unbiased random walk. The position on a coordinate axis, x, was determined from the number of steps to the right, k, and number of steps to the left, $n - k$: $x = \delta(k - (n - k))$.

where $C(x, N(x)/A\delta)$, is the concentration of particles at a given location, x. Taking the limit of Equation 3-16 as the distance between the adjacent points becomes small yields:

$$j_x = -D\frac{\partial C}{\partial x} \tag{3-17}$$

where the diffusion coefficient D is defined as in Equation 3-11. Thus, this random walk model also provides a relationship between the spatial concentration distribution and the particle flux. Particles move towards locations with lower concentration; the flux of particles is directly proportional to the concentration gradient and the diffusion coefficient is the constant of proportionality. This expression, often called Fick's law [4], will be of considerable practical value in predicting rates of molecular transport through cells and tissues.

3.2 EQUATIONS FOR THE DIFFUSIVE FLUX (FICK'S LAW)

This expression for the diffusive flux can be obtained more rigorously by considering the velocities of individual species in a multi-component system. The mass average flux of component A in a mixture, $\overline{j_A}$, is defined based on the velocity of the species of interest, $\overline{v_A}$, relative to the mass average velocity of the system, $\overline{v}$:

$$\overline{j_A} = \rho_A(\overline{v_A} - \overline{v}) \tag{3-18}$$

where $\overline{j_A}$, $\overline{v_A}$, and $\overline{v}$ are now vector quantities, and the mass average velocity is defined by weighting the velocities of each component by the mass density of that component in the system.[1] The flux defined in this manner is due to the presence of concentration gradients in the system, and depends on the diffusion coefficient D_A:

$$\overline{j_A} = -\rho D_A \nabla \omega_A \tag{3-19}$$

where ρ is the total mass density of the system and ω_A is the mass fraction of component A. There are many equivalent ways to express Fick's law for molar or mass fluxes with respect to molar or mass average velocities (see a text on transport phenomena, such as [5] or [6], for examples). In all cases, however, the diffusion coefficient, D_A, is identical. Strictly speaking, this definition of D_A applies to binary mixtures where D_A is the diffusion coefficient of A in a mixture of A and B. In this book, which is primarily concerned with the diffusion of dilute species in an aqueous system containing many additional dilute components, we will use D_A to denote the diffusion coefficient of the species of interest in a multi-component complex system. When used in this

1. For more complete definitions, the derivation of conservation of mass equations, and application of these equations in conventional chemical engineering analysis, the reader is referred to the classical textbook on transport phenomena [5]. The notation used in the present text follows the notation by Bird *et al.*

manner, D_A is an effective binary diffusion coefficient for A in a multi-component system [5].

Equation 3-19 defines the diffusion coefficient D_A, but is inconvenient for many calculations since the flux $\bar{j}_A$ is defined with respect to a moving coordinate system. For binary systems, $\bar{j}_A$ is simply related to the mass flux of A with respect to a stationary coordinate system, $\bar{n}_A$:

$$\bar{n}_A = \omega_A(\bar{n}_A + \bar{n}_B) + \bar{j}_A = \omega_A(\bar{n}_A + \bar{n}_B) - \rho D_A \nabla \omega_A \qquad (3\text{-}20)$$

The mass flux $\bar{n}_A$ is the sum of the diffusive flux $\bar{j}_A$, which accounts for the movement of A due to concentration gradients, and the quantity $\omega_A(\bar{n}_A + \bar{n}_B)$, which accounts for the movement of A due to bulk motion of the fluid. Equation 3-20 is the appropriate form of the diffusive flux equation to use for most engineering problems, since quantities are usually measured with respect to some fixed frame of reference. For many of the problems considered here, A is a dilute species in water, in which case $\omega_A \approx 0$ and the bulk motion term can be neglected.

3.3 EQUATIONS OF MASS CONSERVATION (FICK'S SECOND LAW)

Consider the migration of species A through a homogeneous region of space, like a small volume of tissue (Figure 3.3). General differential equations can be developed to describe the variation of concentration of compound A, C_A, with time and position in the tissue by first considering the conservation of mass within this small volume.

Molecules of A can enter through any face of the volume element; they can be generated or consumed within the volume by chemical reaction; they can accumulate within the volume. A general balance equation (in − out + generation = accumulation) yields:

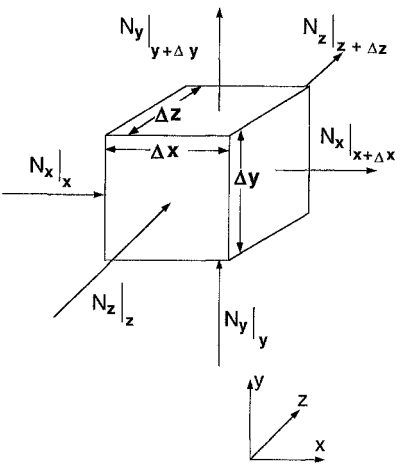

Figure 3.3
Differential mass balance on a characteristic element. This diagram shows a simple mass balance in a rectangular coordinate system. Not shown are the possible sources of consumption or generation of mass within the volume element, which may be important if the element is a small section of tissue.

$$\left[n_x|_x \Delta y \Delta z - n_x|_{x+\Delta x} \Delta y \Delta z\right] + \left[n_y|_y \Delta x \Delta z - n_y|_{y+\Delta y} \Delta x \Delta z\right] + \left[n_z|_z \Delta x \Delta y - n_z|_{z+\Delta z} \Delta x \Delta y\right] + \psi_A \Delta x \Delta y \Delta z = \frac{\partial \rho_A}{\partial t} \Delta x \Delta y \Delta z \tag{3-21}$$

where the first three bracketed terms account for the movement of A through the faces of the volume element, ψ_A is the rate of generation (or negative the rate of consumption) of A per unit volume, and ρ_A is the mass density of A in the volume ($\rho_A = \omega_A \rho$). Dividing each term by the volume ($\Delta x \Delta y \Delta z$) and taking the limit of the resulting expression as the differential volume becomes very small yields:

$$-\frac{\partial n_x}{\partial x} - \frac{\partial n_y}{\partial y} - \frac{\partial n_z}{\partial z} + \psi_A = \frac{\partial \rho_A}{\partial t} \tag{3-22}$$

which can be written more simply as:

$$-\nabla \cdot \overline{n_A} + \psi_A = \frac{\partial \rho_A}{\partial t} \tag{3-23}$$

which was derived by considering a volume element in rectangular coordinates; identical expressions could be obtained in cylindrical or spherical coordinates.

The mass balance procedure produced a partial differential equation with two dependent variables, solute flux and concentration. To complete this analysis, an appropriate form of Fick's law must be substituted into Equation 3-23. Substituting Equation 3-20 yields:

$$-\nabla \cdot (\omega_A(\overline{n_A} + \overline{n_B}) - \rho D_A \omega_A) + \psi_A = \frac{\partial \rho_A}{\partial t} \tag{3-24}$$

By recognizing that the sum of the fluxes $\overline{n_A} + \overline{n_B}$ is equal to the density times the mass average velocity, $\rho \bar{v}$, this equation reduces to:

$$-\nabla \cdot (\rho_A \bar{v}) + \nabla \cdot (\rho D_A \nabla \omega_A) + \psi_A = \frac{\partial \rho_A}{\partial t} \tag{3-25}$$

which is a general expression of the conservation of mass of solute A. Expressions equivalent to Equation 3-23 through Equation 3-25 could also be written for component B of a binary system; the sum of these individual mass balance equations produces the total mass conservation, or continuity, equation:

$$-\nabla \cdot \rho \bar{v} = \frac{\partial \rho}{\partial t} \tag{3-26}$$

The aqueous systems considered in this text are incompressible (i.e., the total density ρ is constant). For incompressible fluids, Equations 3-25 and 3-26 can be written as:

$$\cdot D_A \nabla \rho_A + \psi_A = \frac{D\rho_A}{Dt} \tag{3-27}$$

$$\nabla \cdot \bar{v} = 0 \tag{3-28}$$

where Equation 3-28 has been used to eliminate the term involving velocity gradient in Equation 3-27 and the substantial derivative is defined:

$$\frac{D}{Dt}(\bullet) = \frac{\partial}{\partial t}(\bullet) + \bar{v} \cdot \nabla(\bullet) \tag{3-29}$$

Equations 3-27 and 3-28 provide the most compact and general form of the equation of conservation of mass. These expressions are limited only by the assumption that the fluid is incompressible; this assumption is reasonable for all of the problems discussed in this text.

Equations 3-20 to 3-28 can be written in terms of molar concentrations and molar fluxes, as well. A summary of the most important equations, expressed in both molar and mass units, is provided in Table 3.2.

The equations provided in Table 3.2 assume that diffusion is isotropic: i.e., that the flux of diffusing molecules through some particular plane within a system is proportional to the concentration gradient measured orthogonal to the plane. This assumption is not true for anisotropic media, in which the diffusion characteristics depend on the direction of diffusion. Anisotropic

Table 3.2 The basic equations for mass transfer, derived on a mass and molar basis for isotropic diffusion

	Mass	Molar
Average velocity	$\bar{v} = \frac{1}{\rho}\sum_{i=1}^{u} \rho_i \bar{v}_i$	$\bar{V} = \frac{1}{c}\sum_{i=1}^{u} c_i \bar{v}_i$
Flux with respect to coordinate system moving at average velocity	$\bar{j}_A = \rho_A(\bar{v}_A - \bar{v}) = -\rho D_A \nabla \omega_A$	$\bar{J}_A = c_A(\bar{v}_A - \bar{V}) = -cD_A \nabla x_A$
Flux with respect to stationary coordinate system (binary system)	$\bar{n}_A = -\rho D_A \nabla \omega_A + \omega_A(\bar{n}_A + \bar{n}_B)$	$\bar{N}_A = -cD_A \nabla x_A + x_A(\bar{N}_A + \bar{N}_B)$
General form of conservation of mass for component A (binary system)	$-\nabla \cdot (\rho_A \bar{v} - \rho D_A \nabla \omega_A) + \psi_A = \frac{\partial \rho_A}{\partial t}$	$-\nabla \cdot (c_A \bar{V} - cD_A \nabla x_A) + \psi_A^m = \frac{\partial c_A}{\partial t}$
Conservation of mass for component A (binary system, incompressible fluid, constant D_A)	$D_A \nabla^2 \rho_A + \psi_A = \frac{D\rho_A}{Dt}$	$D_A \nabla^2 c_A + \overset{m}{A} = \frac{Dc_A}{Dt}$

The symbols are defined in the text: ψ_A^m indicates molar rate of generation of A (mol/cm^3 · s)

media usually have oriented physical structures, such as crystals or polymers, that provide varying resistances of diffusion in different directions. Anisotropic diffusion may be important in diffusion in biological systems, since the cytoplasm of cells or the extracellular space of tissues can contain highly organized and oriented structures. Consider, for example, the diffusion of compounds in the extracellular space of the brain, which may be anisotropic in regions where myelinated fibers run in a particular direction.

In the case of anisotropic diffusion, Fick's law (Equation 3-19), must be written:

$$j_{A_x} = -\rho\left[D_{11}\frac{\partial \omega_A}{\partial x} + D_{12}\frac{\partial \omega_A}{\partial y} + D_{13}\frac{\partial \omega_A}{\partial z}\right]$$

$$j_{A_y} = -\rho\left[D_{21}\frac{\partial \omega_A}{\partial x} + D_{22}\frac{\partial \omega_A}{\partial y} + D_{23}\frac{\partial \omega_A}{\partial z}\right] \tag{3-30}$$

$$j_{A_z} = -\rho\left[D_{31}\frac{\partial \omega_A}{\partial x} + D_{32}\frac{\partial \omega_A}{\partial y} + D_{33}\frac{\partial \omega_A}{\partial z}\right]$$

where fluxes depend not only on the concentration gradient in the orthogonal direction, but may also depend on gradients in the other directions as well. The diffusion coefficients in Equation 3-30, D_{nm}, indicate the significance of diffusion in the n-direction due to gradients in the m-direction. Equation 3-30 reduces to Fick's law for isotropic diffusion when the off-diagonal terms are 0—i.e., $D_{nm} = 0$ for $n \neq m$—and the diagonal terms are all equal—i.e., $D_{nm} = D_A$ for $n = m$. In some cases, appropriate coordinate transformations can be used to reduce the equations describing diffusion in anisotropic media to analogous equations in isotropic media; these techniques are discussed by Crank [7].

The conservation of mass equations listed in the final row of Table 3.2 are frequently used to describe the movement of solutes through tissues and cells. These equations were developed by assuming that the tissue is homogeneous throughout the region of interest. Diffusing solute molecules must have equal access to every possible position within the volume of interest and D_A must be constant with respect to both space and time. This assumption is not valid for the diffusion of certain molecules in tissues; for example, consider a molecule that diffuses through the extracellular space of the tissue and does not readily enter cells. The limitations of this assumption are discussed in Chapter 4.

3.4 SOLUTIONS TO THE DIFFUSION EQUATION WITH NO SOLUTE ELIMINATION OR GENERATION

When appropriately applied, the equations derived in the section above can be used to predict variations in drug concentration within a tissue following administration. For the description of molecular transport in cells or tissues, the mass conservation equations must be simplified by making appropriate

assumptions that are specialized for the geometry of interest. For example, the mass conservation equation in terms of molar fluxes assuming no bulk flow ($\bar{v} = 0$) and no chemical reaction ($\psi_A = 0$) is:

$$D_A \nabla^2 c_A = \frac{\partial c_A}{\partial t} \tag{3-31}$$

a commonly used form that is frequently referred to as Fick's second law. When solved subject to the appropriate boundary and initial conditions, this differential equation yields the concentration c_A as a function of time and position within the volume of interest. Since equations equivalent to Equation 3-31 arise in a variety of physical settings, detailed solutions for many situations already exist (see the excellent books by Crank [7] and Carslaw and Jaeger [8]).

3.4.1 Rectangular Coordinates

Consider a solute A that is neither consumed nor generated, but diffuses with a constant diffusion coefficient, D_A. Assume that a bolus of N molecules is injected into a long cylinder (Figure 3.4a), so that all of the molecules are present within an infinitesimal volume at the origin of the coordinate system at $t = 0$. After injection, the molecules will diffuse along the axis of the cylinder, where bulk flow is negligible. This situation will not occur frequently in physiological systems, although it may be a reasonable model for the microinjection of inert tracers into the axon or dendrite of a neuron [9]. On the other hand, *in vitro* experimental systems are often intentionally arranged into this geometry, which greatly simplifies the subsequent analysis [10, 11].

The concentration of A as a function of time and distance from the site of initial injection can be predicted by solving Equation 3-31, expressed in a one-dimensional rectangular coordinate system:

$$D_A \frac{\partial^2 c_A}{\partial x^2} = \frac{\partial c_A}{\partial t} \tag{3-32}$$

subject to the following initial and boundary conditions:

$$\begin{aligned} c(x, t) &= N\delta(x) \quad -\infty < x < \infty \quad t = 0 \\ c(x, t) &= 0 \quad x \to \infty \quad t > 0 \\ c(x, t) &= 0 \quad x \to -\infty \quad t > 0 \end{aligned} \tag{3-33}$$

where $\delta(x)$ is the unit impulse or Dirac delta function centered at $x = 0$. This equation can be solved by Laplace transform techniques to produce the solution:

$$c_A(x, t) = \frac{A}{\sqrt{t}} e^{-x^2/4D_A t} \tag{3-34}$$

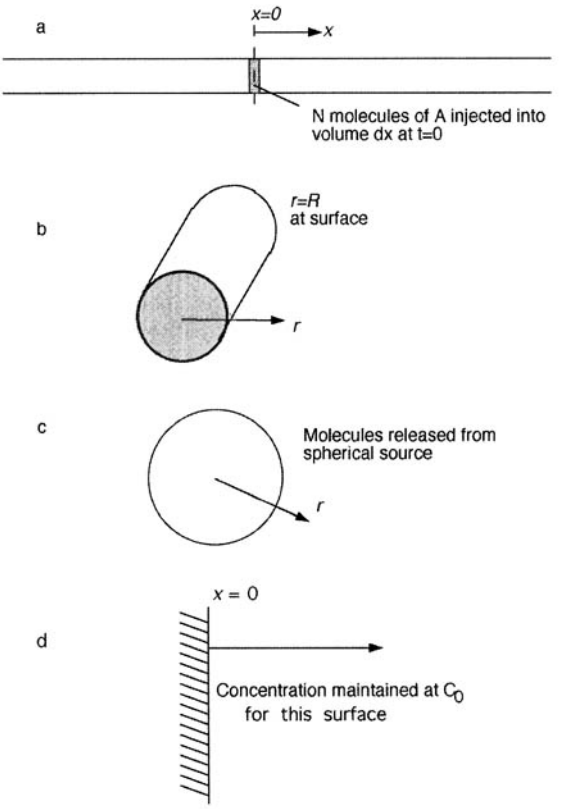

Figure 3.4
Typical problems of diffusive transport. Many real examples of diffusion in organs and tissues can be analyzed in terms of simple solutions to the diffusion equation in rectangular, cylindrical, or spherical coordinates: (a) a bolus of molecules is injected into a cylindrical volume of infinite extent; (b) a cylindrical source of molecules in an infinite volume; (c) a spherical source of molecules in an infinite volume; or (d) drug concentration is maintained at a constant value at the surface of a semi-infinite medium.

where A is a constant of integration. The constant A can be determined by integrating Equation 3-34 with respect to x, to obtain the total number of diffusing molecules:

$$\int_{-\infty}^{\infty} c_A(x,t)\cdot \pi R^2 dx = \pi R^2 \frac{A}{\sqrt{t}} \int_{-\infty}^{\infty} e^{-x^2/4D_A t} dx = 2\pi R^2 A\sqrt{\pi D_A} = \frac{N}{N_{Av}} \quad (3\text{-}35)$$

where R is the radius of the cylinder cross-section and N_{Av} is Avogadro's number. This definite integral reduces to $\sqrt{4D_A t\pi}$. Since the value of the constant A can be determined from Equation 3-35, the complete solution is:

$$c_A(x,t) = \frac{N}{N_{Av}} \frac{1}{2\sqrt{\pi D_A t}} \frac{1}{2\pi R^2} e^{-x^2/4D_A t} \quad (3\text{-}36)$$

This expression is plotted in Figure 3.5. The similarity of Equation 3-36, which is a solution to the conservation of mass equations, to the Gaussian distribution obtained from random walk calculations (see Equation 3-14) is obvious.

A similar analysis can be used to predict concentration profiles in the region on one side of a planar boundary after suddenly raising the concentration on the opposite side (Figure 3.4d). In this case, the differential equation is still Equation 3-32, but the boundary conditions must be modified slightly:

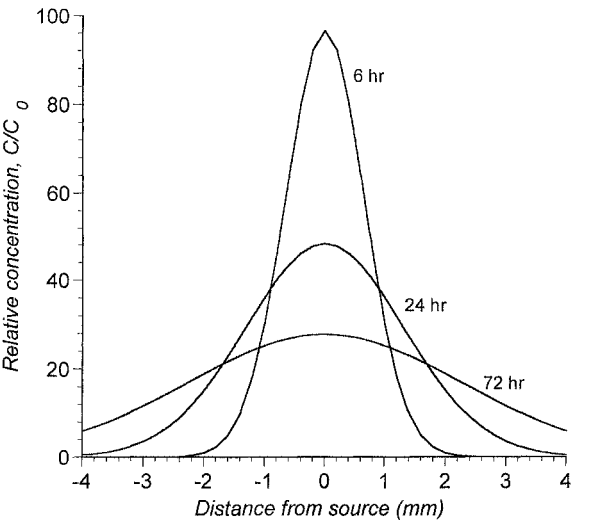

Figure 3.5
Concentration profiles for diffusion from a point source. When a concentrated bolus of solute is deposited within a small region of an infinitely long cylinder, as shown in Figure 3.4a, the molecules slowly disperse along the axis of the cylinder. The curves shown here are realization of Equation 3-34 for a solute with $D_A = 10^{-7}\,cm^2/s$, $R = 0.1\,cm$, $N = N_{Av}$, and $t = 6$, 24, and 72 h.

$$\begin{aligned} c(x,t) &= 0; \quad \text{for } 0 < x < \infty; \quad t = 0 \\ c(x,t) &= c_0; \quad \text{for } x = 0; \quad t > 0 \\ c(x,t) &= 0; \quad \text{for } x \to \infty; \quad t > 0 \end{aligned} \tag{3-33'}$$

The solution of Equation 3-32 in this situation yields:

$$\frac{c_A}{c_0} = \text{erfc}\left(\frac{x}{2\sqrt{D_A t}}\right) \tag{3-37}$$

where erfc(•) is the error function complement, which is simply related to the error function, erf(•):

$$\text{erf}(z) = 1 - \text{erfc}(z) = \frac{2}{\sqrt{\pi}} \int_0^z \exp(-\eta^2) d\eta \tag{3-38}$$

The error function occurs frequently in solutions to the diffusion equation: extensive tables of error functions are available as well as series expansions for approximation [12]. Some values are tabulated in Appendix B. Equation 3-37 can be used to examine the penetration of drug molecules into a tissue when suddenly presented at a surface (Figure 3.6).

Similarly, if a drug is initially confined to a linear band of width $2w$ and concentration c_o, the drug molecules will spread in both directions with time:

$$\frac{c_A}{c_o} = \frac{1}{2}\left[\text{erf}\left(\frac{w+x}{2\sqrt{D_A t}}\right) + \text{erf}\left(\frac{w-x}{2\sqrt{D_A t}}\right)\right] \tag{3-39}$$

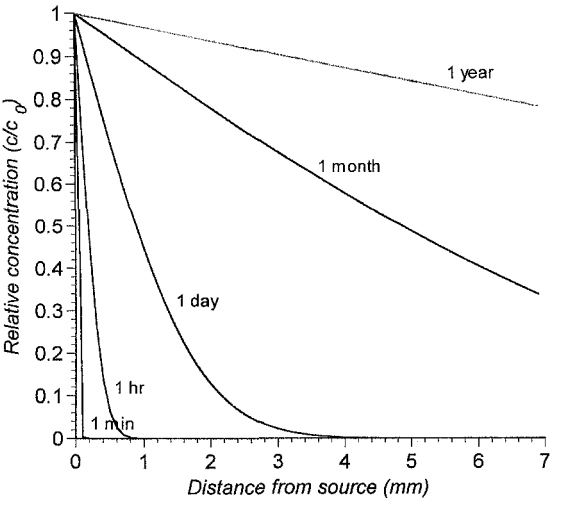

Figure 3.6
Concentration profiles for diffusion in a semi-infinite medium. When the concentration of solute is increased within one region of an unbounded space, as shown in Figure 3.4d, the molecules slowly penetrate into the adjacent region. The curves shown here are realizations of Equation 3-37 for a solute with $D_A = 10^{-7}\,cm^2/s$, $R = 0.1\,cm$, $N = N_{Av}$.

3.4.2 Cylindrical Coordinates

Consider the diffusion of solute A from the surface of a cylinder of radius R into a homogeneous tissue (Figure 3.4b). For example, the cylinder might represent the external surface of a capillary that contains a high concentration of a drug. The concentration within the tissue, in the region $r > R$, can be determined by solving Equation 3-31 in cylindrical coordinates:

$$D_A \frac{1}{r}\frac{\partial}{\partial r}\left[r\frac{\partial c_A}{\partial r}\right] = \frac{\partial c_A}{\partial t} \tag{3-40}$$

If the concentration of A in the tissue outside the cylinder is initially zero, and the concentration at the outer surface of the cylinder is maintained at c_0, the initial and boundary conditions can be written as:

$$\begin{aligned} c(r, t) &= 0; \quad \text{for } R \le r; \quad t = 0 \\ c(r, t) &= c_0; \quad \text{for } r = R; \quad t > 0 \\ c(r, t) &= 0; \quad \text{for } r \to \infty; \quad t > 0 \end{aligned} \tag{3-41}$$

Solving Equation 3-40 subject to Equation 3-41 yields:

$$\frac{c_A}{c_0} = 1 + \frac{2}{\pi}\int_0^\infty e^{-D_A u^2 t}\frac{J_0(ur)Y_0(ua) - J_0(ua)Y_0(ur)}{J_0^2(ua) - Y_0^2(ua)}\frac{au}{u}\,du \tag{3-42}$$

where J_0 and Y_0 are Bessel functions of the first and second kind of order 0. Equation 3-42 is shown graphically in Figure 3.7. When the concentration of the solute is maintained at c_0, solute will continue to penetrate into the adjacent medium. For a solute with $D_A = 10^{-7}\,cm^2/s$ and a cylinder with $R = 0.1\,cm$, the solute will penetrate $\approx 0.2\,mm$ in the first 6 hr, $\approx 0.4\,mm$ in the first 24 h, and $\approx 0.6\,mm$ in the first 100 h.

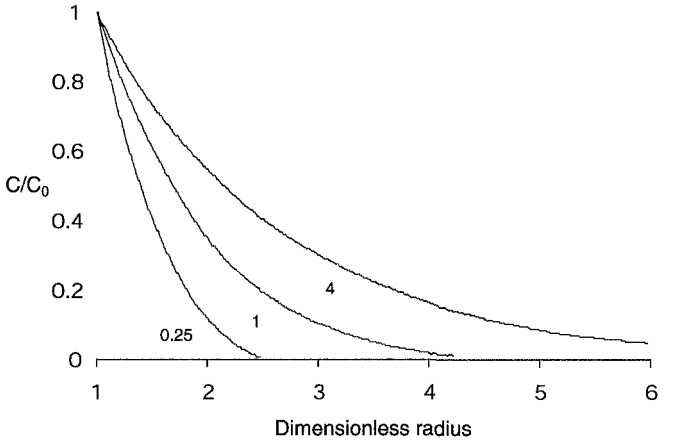

Figure 3.7 Concentration of solute diffusing from the surface of a cylinder. Redrawn from [7], p. 87. Each curve represents the concentration profile at a different dimensionless time ($D_A/t/a^2$). Dimensionless concentration is shown as a function of dimensionless distance from the center of the cylinder (r/R). For $D_A = 1 \times 10^{-7}$ cm^2/s and $R = 0.1$ cm, the dimensionless times correspond to 7, 28, and 110 h.

3.4.3 Spherical Coordinates

Biological systems often exhibit spherical symmetry, or something near it. For example, certain cells are assumed to be spherical as are vesicles within cells and synthetic vesicles. Therefore, it is frequently convenient to examine the transport of solutes in a spherical coordinate system. Equation 3-31 can be expressed in spherical coordinates:

$$D_A \frac{1}{r^2}\frac{\partial}{\partial r}\left[r^2 \frac{\partial c_A}{\partial r}\right] = \frac{\partial c_A}{\partial t} \tag{3-43}$$

where gradients in the θ and ϕ directions are neglected due to symmetry, so that diffusion occurs only in the radial direction. This differential equation can be simplified by making the substitution $u = rc_A$, which produces:

$$D_A \frac{\partial^2 u}{\partial r^2} = \frac{\partial u}{\partial t} \tag{3-44}$$

an equation identical to the one obtained for one-dimensional diffusion in a rectangular coordinate system, Equation 3-32.

Consider the flux of solute A towards a spherical cell in suspension (Figure 3.4c). If solute is consumed at the surface of the cell, and the rate of consumption is rapid, solute concentrations in the vicinity of the cell can be predicted by solving Equation 3-43 subject to the following conditions:

$$\begin{aligned} c_A(r, t) &= c_0; \quad \text{for } r \geq R; \quad t = 0 \\ c_A(r, t) &= 0; \quad \text{for } r = R; \quad t > 0 \\ c_A(r, t) &= c_0; \quad \text{for } r \to \infty; \quad t > 0 \end{aligned} \tag{3-45}$$

where the initial concentration of solute in the medium surrounding the cell is c_0. The solution to these equations is closely related to the solution of the equations for one-dimensional diffusion in a semi-infinite medium (see Chapter 3 of reference [7]):

$$\frac{c_A}{c_0} = 1 - \left(\frac{R}{r}\right)\text{erfc}\left[\frac{r - R}{2\sqrt{D_A t}}\right] \tag{3-46}$$

For long observation times, Equation 3-46 reduces to the steady-state solution:

$$\frac{c_A}{c_0} = 1 - \frac{R}{r} \tag{3-47}$$

Solute concentration in the vicinity of a sphere is shown in Figure 3.8. Again, D_A is assumed to be 10^{-7} cm^2/s and R to be 1 mm. The change in concentration penetrates ~ 0.5 mm in the first 1 h of absorption by the sphere; as time increases, the decrease in concentration moves progressively deeper into the medium. For the conditions specified in Figure 3.8, the approach to steady

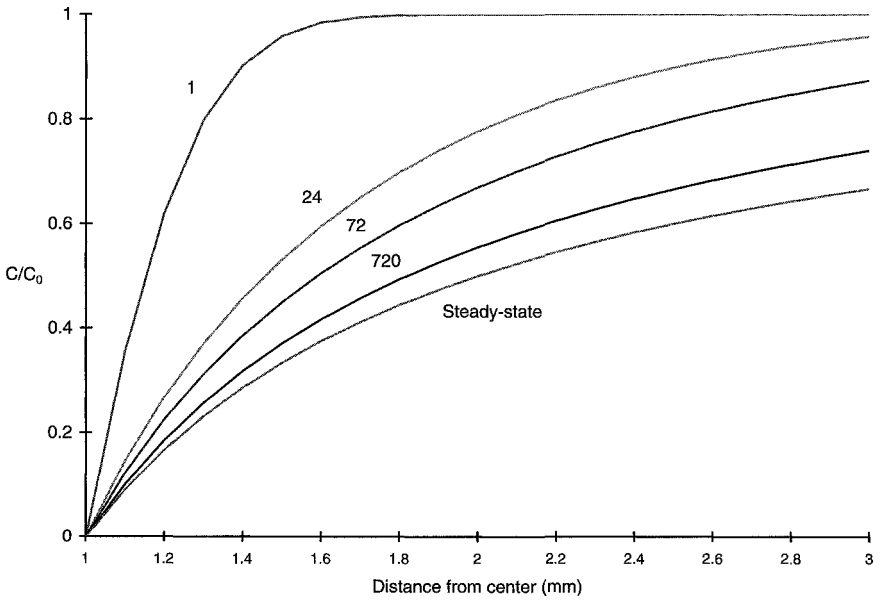

Figure 3.8 Concentration profiles in the vicinity of absorbing sphere. When a perfectly absorbing sphere is placed within an infinite medium, the concentration varies near the surface of the sphere. Concentration profiles are indicated at 1, 24, 72 and 720 h for a diffusing solute with $D_A = 10^{-7}$ cm^2/s for a sphere of radius 1 mm.

state is slow; even after 720 h (30 days) the concentration profile is still significantly different from the steady-state profile.

The rate of solute diffusion to the surface of the cell can be calculated from the flux:

$$\text{Rate of disappearance} = -D_A(4\pi R^2)\left.\frac{dc_A}{dr}\right|_{r=R} = 4\pi D_A R c_0 \tag{3-48}$$

Equation 3-48 permits the definition of a rate constant for diffusion-limited reaction at a cell surface, k_+. The rate constant, defined as (rate of disappearance) $= k_+ c_0$, is

$$k_+ = 4\pi D_A R \tag{3-49}$$

This expression for the rate constant, first described by Smoluchowski [13], will be useful in the analysis of rates of diffusion and reaction during ligand–receptor binding (see Chapter 4).

3.5 SOLUTIONS TO THE DIFFUSION EQUATION WITH SOLUTE BINDING AND ELIMINATION

In many cases, the concentration of solute or drug within a region of tissue will depend not only on diffusion, but also on other physiological processes. For example, a solute may be generated or consumed within a cell or tissue region by a chemical reaction, usually one mediated by enzymes. Alternatively, the solute could be eliminated from the diffusion process by immobilization to some fixed element, binding to the cytoskeleton or an organelle, or by partitioning from the extracellular space into a capillary, where it enters the circulatory system. Similarly, when considering diffusion through the extracellular space of a tissue, the solute could be eliminated by enzymatic conversion to another form, immobilized by some fixed element in the extracellular space, eliminated by internalization into cells or capillaries, or generated by secretion from a cell. When a diffusing solute is generated or consumed homogeneously within some region of interest in a tissue, the differential mass balance in molar concentrations (see Table 3.2) becomes:

$$D_A \nabla^2 c_A + \psi_A^m = \frac{\partial c_A}{\partial t} \tag{3-50}$$

where the diffusion coefficient is assumed constant, bulk flow is neglected ($v = 0$), and ψ_A^m is the molar rate of generation (or consumption) of solute per volume within the differential volume element.

3.5.1 Diffusion with Reversible Binding to Immobilized Elements

Consider a solute that diffuses within the extracellular space of the tissue, but also interacts with the tissue by reversibly binding to some fixed component of the tissue. For example, the diffusing solute might bind to a protein on the cell surface or to a protein in the extracellular matrix. When bound the solute may

be considered to be completely immobilized; when released it is free to diffuse again within the extracellular space. If the conversion of the diffusible solute, A, to the bound form, B, is rapid and characterized by an equilibrium constant $K_b = c_B/c_A$, the local rate of elimination of solute A, $-\phi_A^m$, is then equal to the rate of formation of the bound form B, which is $\partial c_B/\partial t$. Therefore, this situation can be represented by a form of Equation 3-50:

$$D_A \nabla^2 c_A - \frac{\partial c_B}{\partial t} = \frac{\partial c_A}{\partial t} \tag{3-51}$$

Upon substitution of the equilibrium relationship and the assumption that K_b is constant with time, this equation becomes

$$\frac{D_A}{K_b + 1} \nabla^2 c_A = \frac{\partial c_A}{\partial t} \tag{3-52}$$

Therefore, the net effect of a homogeneous, rapid, reversible reaction is to retard the rate of diffusion of solute through the tissue. Solutions to this equation are identical to solutions of the pure diffusion equation (compare Equation 3-31 with Equation 3-52), except that the diffusion coefficient is reduced by a factor equal to the binding constant plus unity. These same equations can be used to evaluate penetration into tissues when more complicated equilibrium expressions are appropriate, by substituting the non-linear equilibrium expression into Equation 3-50 and solving the resulting equation (see [7]).

Numerical values for the term K_b, defined above, can be obtained from information on the equilibrium association (K_a) or dissociation (K_d) constants for receptor–ligand pairs. These constants are usually defined:

$$\begin{gathered} L + R \underset{k_r}{\overset{k_f}{\rightleftarrows}} L - R \\ K_d = \frac{1}{K_a} = \frac{[L][R]}{[L-R]} = \frac{k_r}{k_f} \end{gathered} \tag{3-53}$$

where L is the ligand, R is the receptor and L–R is the ligand–receptor complex. Consider the case of a drug molecule, which can be assigned the role of binding ligand [L] = c_A, interacting with a binding site R, which is present on the surface of cells or stationary molecules in the extracellular space, to form bound complexes [L-R] = c_B. Assuming that the receptor concentration is constant in the tissue, the binding constant K_b, is easily related to the dissociation constant:

$$K_b = \frac{c_B}{c_A} = \frac{[L-R]}{[L]} = \frac{[R]}{K_d} \tag{3-54}$$

Some values for the dissociation constant are presented in Table 3.3.

Table 3.3 Values for receptor dissociation constants

Ligand	Receptor	$K_d(M)$	R_T	Reference
NGF	trkA	10^{-11}		[18]
NGF	$p75^{NTR}$	10^{-9}		[19]
Insulin	Insulin receptor	1.2×10^{-8}	100,000 to 250,000/liver cell	[20]
Biotin	Avidin	10^{-15}		
Transferrin	Transferrin receptor	3.3×10^{-8}	50,000/HepG2 cell	Reported in [21]
FNLLP	Chemotactic peptide receptor	2×10^{-8}	50,000/neutrophil	Reported in [21]
TNF	TNF receptor	1.5×10^{-10}	6,600/A549 cell	Reported in [21]
Hydroxybenzylpindolol	β-Adrenergic	1×10^{-10}	?/turkey RBC	Reported in [21]
Insulin	Insulin receptor	2.1×10^{-8}	10^5/rat fat-cell	Reported in [21]
EGF	EGF receptor	6.7×10^{-7}	25,000/fetal rat lung	Reported in [21]
Fibronectin		8.6×10^{-7}	5×10^5/fibroblast	Reported in [21]
IgE	Fcsub(epsilon)	4.8×10^{-10}	?	Reported in [21]
	β-Adrenergic	10^{-9}	1,300–1,800/frog RBC	[20]
	Cholinergic	10^{-7}	10^{11}/cell	
	Glucagon	1.5×10^{-9}	110,000/liver cell	
	TSH	1.9×10^{-9}	500/thyroid cell	

R_T is the number of receptors on the cell population. Collected from a variety of sources.

3.5.2 Diffusion with Elimination

Upon substitution of an appropriate kinetic expression for the rate of generation or consumption of solute within the tissue space, Equation 3-50 can be solved to determine concentration as a function of time and position. Full analytical solutions are generally difficult to obtain, unless both the kinetic expression and the geometry of the system are simple. For example, consider the linear diffusion of solute from an interface where the concentration is maintained constant (as in Figure 3.4d). If the diffusing solute is also eliminated from the tissue, such that the volumetric rate of elimination is first order with a characteristic rate constant k, Equation 3-51 can be reduced to:

$$D_A \frac{\partial^2 c_A}{\partial x^2} - k c_A = \frac{\partial c_A}{\partial t} \tag{3-55}$$

This equation can be solved subject to the initial and boundary conditions:

$$\begin{aligned} &c_A(x, t) = 0: \quad \text{for } x \geq 0; \quad t = 0 \\ &c_a(x, t) = c_0; \quad \text{for } x = 0; \quad t > 0 \\ &c_A(x, t) = 0; \quad \text{for } x \to \infty; \quad t > 0 \end{aligned} \tag{3-56}$$

to yield:

$$\frac{c}{c_0} = \frac{1}{2}\exp\left\{-x\sqrt{k/D_A}\right\}\operatorname{erfc}\left\{\frac{x}{2\sqrt{D_A t}} - \sqrt{kt}\right\} + \frac{1}{2}\exp\left\{x\sqrt{k/D_A}\right\} \operatorname{erfc}\left\{\frac{x}{2\sqrt{D_A t}} + \sqrt{kt}\right\} \tag{3-57}$$

The corresponding steady-state solution to Equation 3-55 can be found:

$$\frac{c_A}{c_0} = \exp\left(-x\sqrt{\frac{k}{D_A}}\right) \tag{3-58}$$

Concentration profiles predicted by Equations 3-57 and 3-58 are shown in Figure 3.9. In panel (a), the approach to steady state is shown for the situation where $D = 1 \times 10^{-7}$ cm^2/s and $k = 1 \times 10^{-6}$/s. After approximately sufficient time, the transient equations are identical to the steady-state solution. In panel (b), steady-state solutions are shown for the same D, with k varying between 1×10^{-8} and 1×10^{-4}/s. Clearly, the rate of elimination of a solute from the tissue space can have a profound influence on the ability of the solute to penetrate from a localized source.

3.6 A FEW APPLICATIONS

Solutions to the diffusion equation are helpful in interpreting a variety of biological phenomena. This idea is illustrated with examples from developmental biology, drug design, and neuroscience.

Application 1: Developmental Biology. Maternal effect genes are segregated to defined regions in the developing embryo; one of these genes, which encodes a protein called bicoid, is concentrated at the anterior end of *Drosophila* embryos [14]. Bicoid produced at the anterior end diffuses toward

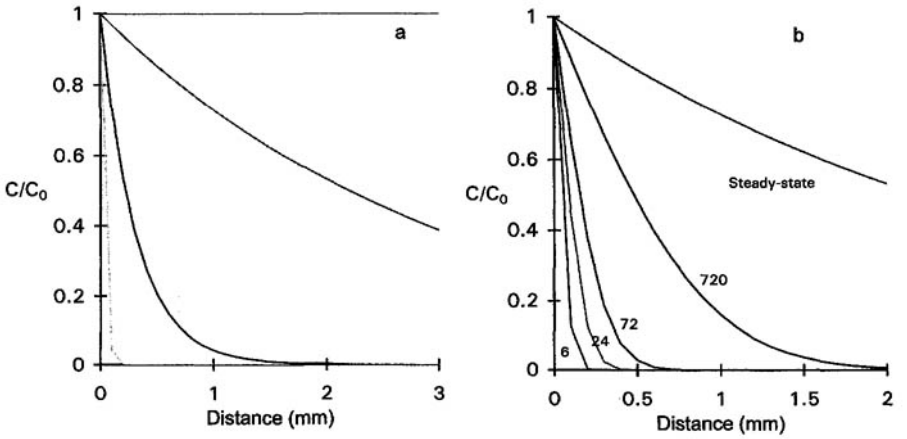

Figure 3.9 Concentration of solute diffusing with first-order elimination. (a) Steady-state profiles for $D_A = 10^{-7}$ cm^2/s and k varying from 0, 10^{-8}, 10^{-6}, 10^{-4} s^{-1}; (b) the approach to steady state for a solute with $D_A = 10^{-7}$ cm^2/s and $k = 10^{-8}$ s^{-1}.

the posterior pole; as the protein diffuses, it can be metabolized. Simultaneous diffusion and elimination produce a stable protein gradient (Figure 3.10); the cells of the embryo respond to the local concentration of bicoid by expressing certain genes. In this way, the bicoid gradient provides positional information to cells throughout the embryo. These events are critical for the formation of structures throughout the organism; they are achieved by a mechanism for gradient formation—diffusion with homogeneous elimination—which can be explained by the simple steady-state model of Equation 3-58.

Application 2: Drug Penetration in Tissue. The diffusion equation can be used to develop a simple, quantitative method for predicting the extent of drug penetration into a tissue following the introduction of a local source. Consider the simple geometry shown in Figure 3.4d, where drug is maintained at a constant value, c_0, at the interface of a semi-infinite medium. From the steady-state solution, Equation 3-58, it is possible to

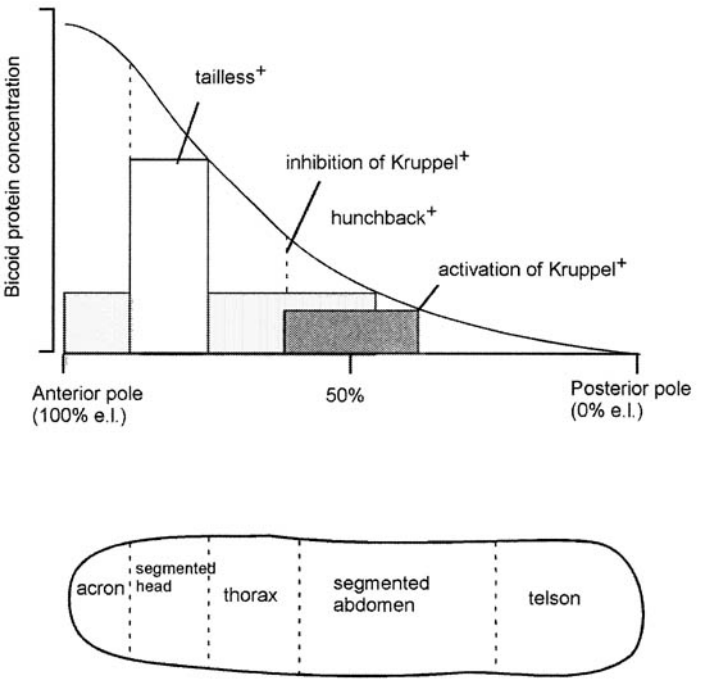

Figure 3.10 Concentration gradient of bicoid in the developing fruitfly. Concentration of bicoid protein has been measured in developing embryos as a function of location on the anterior–posterior axis. When present at high levels, biocoid protein activates the gene tailless$^+$ at intermediate levels, inhibits the gene Kruppel$^+$, and activates hunchback$^+$. Spatial localization of gene expression is thereby achieved with a simple mechanism for protein-gradient formation.

quantify drug penetration in the local tissue. When a gradient of drug concentration is present, the region of tissue nearest the implant will be exposed to high, possibly toxic, drug levels; the region farthest from the implant will be untreated. We define the effectiveness of drug delivery, η, as the ratio of average drug concentration within a given tissue volume to drug concentration at the implant/tissue interface, c_0 (i.e., the maximum concentration of drug in the tissue):

$$\eta = \frac{\bar{c}_A}{c_0} \quad \text{where} \quad \bar{c}_A = \frac{\int_0^L c_A(x)dx}{\int_0^L dx} \tag{3-59}$$

where L is the distance into the tissue that requires treatment with the drug. For values of η near unity, the overall concentration profile is nearly flat, and solute delivery to this region of tissue is effective. Steep concentration profiles yield values of η near zero, or ineffective delivery.

Substitution of Equation 3-58 into Equation 3-59 gives:

$$\eta = \frac{1}{\phi}(1 - e^{-\phi}) \tag{3-60}$$

where the dimensionless parameter ϕ is defined:

$$\phi^2 = \frac{L^2 k}{D} \tag{3-61}$$

Equation 3-61 is shown graphically in Figure 3.11.[2] As ϕ increases, the rate of drug diffusion decreases with respect to the rate of elimination. This results in steep concentration gradients, or ineffective solute delivery to the tissue. Similar calculations can be performed in other geometries; these calculations are useful for evaluating the influence of physiochemical properties of the drug, which determine ϕ, on the extent of drug penetration in tissue [16].

Application 3: Neurotransmitter Diffusion Across the Synaptic Cleft. These methods can be used to predict the movement of molecules in more complex geometrical arrangements. Consider a portion of the synaptic cleft, which is shown schematically in Figure 3.12a. In this region of space between two neurons—the presynaptic neuron sending a signal and the postsynaptic neuron receiving a signal—several characteristic geometries are present: the rectangular distance across the cleft, the spherical vesicle that releases the neurotransmitter, and the cylindrical patch of receptors that sense the signal on the postsynaptic neuron. The concentration of neurotransmitter within the synaptic cleft, $n(x, y, z, t)$, can be found from the diffusion equation, obtained from Table 3.2 and written on a molar basis in three dimensions:

$$D_n\left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}\right)n(x, y, z, t) + f(x, y, z, t) = \frac{\partial}{\partial t}n(x, y, z, t) \tag{3-62}$$

2. Note the similarity of this analysis to the work of Thiele on diffusion and reaction in heterogeneous catalysis [15].

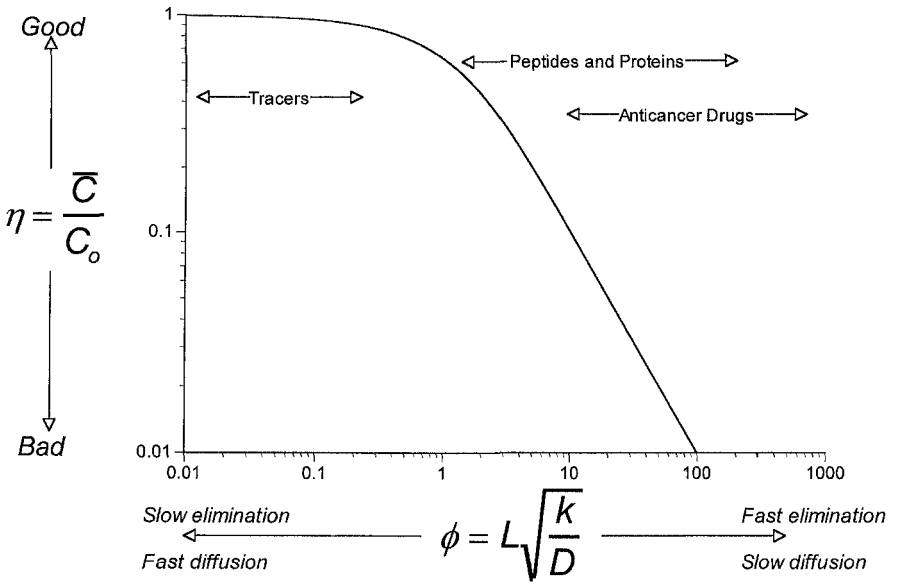

Figure 3.11 The extent of drug penetration in tissue as a function of properties of the drug. Figure redrawn from [16] showing the one-dimensional rectangular coordinate system result.

where D_n, the diffusion coefficient of the neurotransmitter, is assumed constant. The function $f(x, y, z, t)$ is a source term accounting for neurotransmitter release from a single vesicle (Figure 3.12a). A continuous source function that is consistent with existing experimental data is:

$$f(x, y, z, t) = q \cdot \exp\left\{-\frac{x^2 + y^2}{b} - \frac{z^2}{c}\right\} \cdot t^{\alpha} \exp[-\beta t] \tag{3-63}$$

where q is related to the number of neurotransmitter molecules initially in the vesicle, b and c are Gaussian variances in the lateral and z-directions (limited by the size of the vesicle opening and cleft width d_{syn}), and α and β are parameters (Figure 3.12b). Neurotransmitter molecules diffuse in the cleft and do not cross the membrane boundaries:

$$\frac{\partial}{\partial z} n(x, y, z, t) = 0 \quad \text{at } z = 0 \text{ and } z = d_{syn} \tag{3-64}$$

These equations were solved [17] to obtain:

$$n(x, y, z, t) = \frac{qb\sqrt{c}}{4D_n} \sum_{j=-\infty}^{\infty} \int_0^{4D_n t} \frac{(t - s/4D_n)^{\alpha} \exp\{-\beta(t - s/4D_n)\}}{\sqrt{c + s}(b + s)} \exp\left\{-\frac{r^2}{b + s} - \frac{(z - 2jd_{syn})^2}{c + s}\right\} ds \tag{3-65}$$

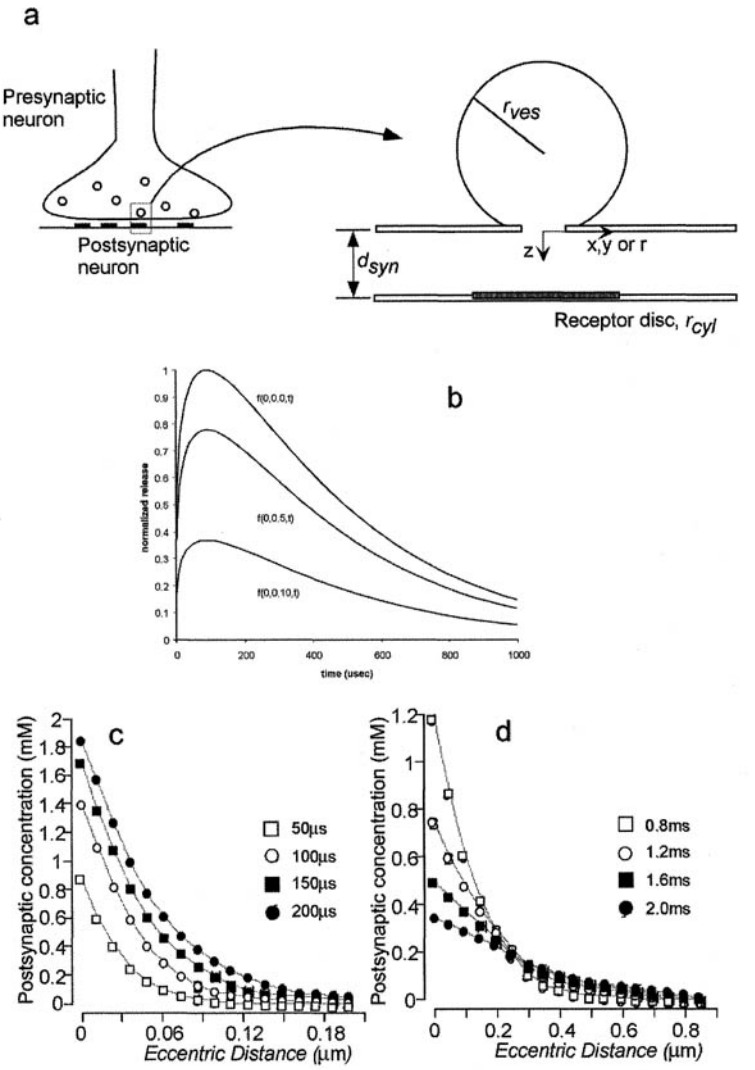

Figure 3.12 Model of diffusion in synaptic cleft. Model from 17. (a) Neurotransmitter molecules are released from vesicles in the presynaptic neuron into the synaptic cleft. The vesicle diameter $r_{ves}$is 20 nm and the cleft width d_{syn} is 20 nm. The origin of the coordinate system is centered at the opening of the vesicle. (b) Release of molecules from the vesicle is simulated by a source $f(x, y, z, t)$. (c) and (d) Concentration of neurotransmitter at the receptor disk, as a function of lateral displacement of the disk center from the vesicle opening. The model was evaluated using parameters that were reasonable for glutamate synapses: $D = 3 \times 10^{-7}$ cm^2/s; $r_{cyl} = 50$ nm; $Q = 2{,}000$ glutamate molecules/vesicle (concentration = 100 mM); $\beta = 1/360\ \mu s^{-1}$; $\alpha = 0.25$.

where $r = \sqrt{x^2 + y^2}$ and the coefficient q is determined by mass balance on the total number of molecules initially contained in the vesicle, Q:

$$Q = q\pi^{3/2} b\sqrt{c} \int t^{\alpha} \exp\{-\beta t\} \mathrm{d}t \tag{3-66}$$

Equation 3-65 can be integrated numerically to calculate neurotransmitter concentrations within the receptor disk as a function of relative position of the disk with respect to the vesicle opening (Figure 3.12d). This model demonstrates that receptor fields on the postsynaptic membrane must be near the vesicle to receive sufficient amounts of the released transmitter chemical to become activated. Receptor disks that are laterally displaced > 200 nm from the vesicle opening will not be affected by neurotransmitter.

SUMMARY

- Molecules disperse in quiescent aqueous media by random walk migration, which is driven by thermal fluctuations in the solvent. As a result, the diffusive flux is proportional to the concentration gradient.
- Equations for describing changes in concentration with time and location can be obtained using Fick's law in combination with a differential mass balance.
- Solutions to the diffusion equation can be used to describe the movement of endogenous chemicals or drugs in physiological situations.

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