

Chapters 1+2

Random Walks in Biology
Expanded Edition

Howard C. Berg

Princeton University Press

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Introduction

Biology is wet and dynamic. Molecules, subcellular organelles, and cells, immersed in an aqueous environment, are in continuous riotous motion. Alive or not, everything is subject to thermal fluctuations. What is this microscopic world like? How does one describe the motile behavior of such particles? How much do they move on the average? Questions of this kind can be answered only with an intuition about statistics that very few biologists have. This book is intended to sharpen that intuition. It is meant to illuminate both the dynamics of living systems and the methods used for their study. It is not a rigorous treatment intended for the expert but rather an introduction for students who have little experience with statistical concepts.

The emphasis is on physics, not mathematics, using the kinds of calculations that one can do on the back of an envelope. Whenever practical, results are derived from first principles. No reference is made to the equations of thermodynamics. The focus is on individual particles, not moles of particles. The units are centimeters (cm), grams (g), and seconds (sec).

Topics range from the one-dimensional random walk to the motile behavior of bacteria. There are discussions of Boltzmann's law, the importance of kT , diffusion to multiple receptors, sedimentation, electrophoresis, and chromatography. One appendix provides an introduction to the theory of probability. Another is a primer on differential equations. A third lists some constants and formulas worth committing to memory. Appendix A

should be consulted while reading Chapter 1 and Appendix B while reading Chapter 2. A detailed understanding of differential equations or the methods used for their solution is not required for an appreciation of the main theme of this book.

Chapter 1

Diffusion: Microscopic Theory

Diffusion is the random migration of molecules or small particles arising from motion due to thermal energy. A particle at absolute temperature T has, on the average, a kinetic energy associated with movement along each axis of $kT/2$, where k is Boltzmann's constant. Einstein showed in 1905 that this is true regardless of the size of the particle, even for particles large enough to be seen under a microscope, i.e., particles that exhibit Brownian movement. A particle of mass m and velocity v_x on the x axis has a kinetic energy $mv_x^2/2$. This quantity fluctuates, but on the average $\langle mv_x^2/2 \rangle = kT/2$, where $\langle \rangle$ denotes an average over time or over an ensemble of similar particles. From this relationship we compute the mean-square velocity,

$$\langle v_x^2 \rangle = kT/m, \quad (1.1)$$

and the root-mean-square velocity,

$$\langle v_x^2 \rangle^{1/2} = (kT/m)^{1/2}. \quad (1.2)$$

We can use Eq. 1.2 to estimate the instantaneous velocity of a small particle, for example, a molecule of the protein lysozyme. Lysozyme has a molecular weight 1.4×10^4 g. This is the mass of one mole, or 6.0×10^{23} molecules; the mass of one molecule is $m = 2.3 \times 10^{-20}$ g. The value of kT at 300°K (27°C) is 4.14×10^{-14} g cm²/sec². Therefore, $\langle v_x^2 \rangle^{1/2} = 1.3 \times 10^3$ cm/sec. This is a sizeable speed. If there were no obstructions, the molecule would cross a typical classroom in about 1 second. Since the protein is not in a vacuum but is immersed in an aqueous medium, it does not go very far before it bumps into molecules of

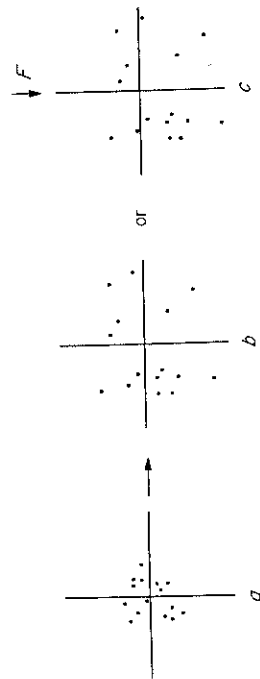


Fig. 1.1. Particles confined initially in a small region of space (a) diffuse symmetrically outward (b) or outward and downward (c) if subjected to an externally applied force, F .

water. As a result, it is forced to wander around: to execute a random walk. If a number of such particles were confined initially in a small region of space, as shown in Fig. 1.1a, they would wander about in all directions and spread out, as shown in Fig. 1.1b. This is simple diffusion. If a force were applied externally, such as that due to gravity, the particles would spread out and move downward, as shown in Fig. 1.1c. This is diffusion with drift. In this chapter, we analyze simple diffusion from a microscopic point of view. We look at the subject more broadly in Chapters 2 and 3. Diffusion with drift is considered in Chapter 4.

One-dimensional random walk

In order to characterize diffusive spreading, it is convenient to reduce the problem to its barest essentials, and to consider the motion of particles along one axis only, say the x axis, as shown in Fig. 1.2. The particles start at time $t = 0$ at position $x = 0$ and execute a random walk according to the following rules:

- 1) Each particle steps to the right or to the left once every τ seconds, moving at velocity $\pm v_x$ a distance

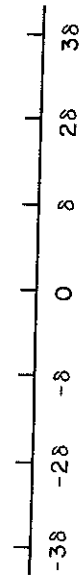


Fig. 1.2. Particles executing a one-dimensional random walk start at the origin, 0, and move in steps of length δ , occupying positions 0 , $\pm\delta$, $\pm 2\delta$, $\pm 3\delta$,

$\delta = \pm v_x \tau$. For simplicity, we treat τ and δ as constants. In practice, they will depend on the size of the particle, the structure of the liquid, and the absolute temperature T .

- 2) The probability of going to the right at each step is $1/2$, and the probability of going to the left at each step is $1/2$. The particles, by interacting with the molecules of water, forget what they did on the previous leg of their journey. Successive steps are statistically independent. The walk is not biased.

- 3) Each particle moves independently of all the other particles. The particles do not interact with one another. In practice, this will be true provided that the suspension of particles is reasonably dilute.

These rules have two striking consequences. The first is that the particles go nowhere on the average. The second is that their root-mean-square displacement is proportional not to the time, but to the square-root of the time. It is possible to establish these propositions by using an iterative procedure. Consider an ensemble of N particles. Let $x_i(n)$ be the position of the i th particle after the n th step. According to rule 1, the position of a particle after the n th step differs from its position after the $(n - 1)$ th step by $\pm\delta$:

$$x_i(n) = x_i(n - 1) \pm \delta. \quad (1.3)$$

According to rules 2 and 3, the $+$ sign will apply to roughly half of the particles, the $-$ sign to the other half. The mean displacement of the particles after the n th step can be found by summing over the particle index i and

dividing by N :

$$\langle x(n) \rangle = \frac{1}{N} \sum_{i=1}^N x_i(n). \quad (1.4)$$

On expressing $x_i(n)$ in terms of $x_i(n-1)$, Eq. 1.3, we find

$$\begin{aligned} \langle x(n) \rangle &= \frac{1}{N} \sum_{i=1}^N [x_i(n-1) \pm \delta] \\ &= \frac{1}{N} \sum_{i=1}^N x_i(n-1) = \langle x(n-1) \rangle. \end{aligned} \quad (1.5)$$

The second term in the brackets averages to zero, because its sign is positive for roughly half of the particles, negative for the other half. Eq. 1.5 tells us that the mean position of the particles does not change from step to step. Since the particles all start at the origin, where the mean position is zero, the mean position remains zero. This is the first proposition. The spreading of the particles is symmetrical about the origin, as shown in Fig. 1.3.

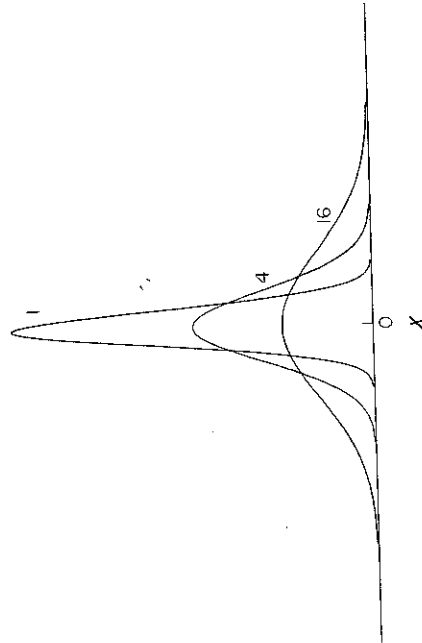


Fig. 1.3. The probability of finding particles at different points x at times $t = 1, 4,$ and 16 . The particles start out at position $x = 0$ at time $t = 0$. The standard deviations (root-mean-square widths) of the distributions increase with the square-root of the time. Their peak heights decrease with the square-root of the time. See Eq. 1.22.

How much do the particles spread? A convenient measure of spreading is the root-mean-square displacement $\langle x^2(n) \rangle^{1/2}$. Here we average the square of the displacement rather than the displacement itself. Since the square of a negative number is positive, the result must be finite; it cannot be zero. To find $\langle x^2(n) \rangle$, we write $x_i(n)$ in terms of $x_i(n-1)$, as in Eq. 1.3, and take the square:

$$x_i^2(n) = x_i^2(n-1) \pm 2\delta x_i(n-1) + \delta^2. \quad (1.6)$$

Then we compute the mean,

$$\langle x^2(n) \rangle = \frac{1}{N} \sum_{i=1}^N x_i^2(n), \quad (1.7)$$

which is

$$\begin{aligned} \langle x^2(n) \rangle &= \frac{1}{N} \sum_{i=1}^N [x_i^2(n-1) \pm 2\delta x_i(n-1) + \delta^2] \\ &= \langle x^2(n-1) \rangle + \delta^2. \end{aligned} \quad (1.8)$$

As before, the second term in the brackets averages to zero; its sign is positive for roughly half of the particles, negative for the other half. Since $x_i(0) = 0$ for all particles i , $\langle x^2(0) \rangle = 0$. Thus, $\langle x^2(1) \rangle = \delta^2$, $\langle x^2(2) \rangle = 2\delta^2$, ..., and $\langle x^2(n) \rangle = n\delta^2$. We conclude that the mean-square displacement increases with the step number n , the root-mean-square displacement with the square-root of n . According to rule 1, the particles execute n steps in a time $t = n\tau$; n is proportional to t . It follows that the mean-square displacement is proportional to t , the root-mean-square displacement to the square-root of t . This is the second proposition. The spreading increases as the square-root of the time, as shown in Fig. 1.3.

To see this more explicitly, note that $n = t/\tau$, so that

$$\langle x^2(t) \rangle = (t/\tau)\delta^2 = (\delta^2/\tau)t, \quad (1.9)$$

where we write $x(t)$ rather than $x(t)$ to denote the fact that x now is being considered as a function of t . For convenience, we define a diffusion coefficient, $D = \delta^2/2\tau$, in units cm^2/sec . The reason for the factor $1/2$ will become clear in Chapter 2. This gives us

$$\langle x^2 \rangle = 2Dt \quad (1.10)$$

and

$$\langle x^2 \rangle^{1/2} = (2Dt)^{1/2}, \quad (1.11)$$

where, for simplicity, we drop the explicit functional reference (t). The diffusion coefficient, D , characterizes the migration of particles of a given kind in a given medium at a given temperature. In general, it depends on the size of the particle, the structure of the medium, and the absolute temperature. For a small molecule in water at room temperature, $D \approx 10^{-5} \text{ cm}^2/\text{sec}$.

A particle with a diffusion coefficient of this order of magnitude diffuses a distance $x = 10^{-4} \text{ cm}$ (the width of a bacterium) in a time $t \approx x^2/2D = 5 \times 10^{-4} \text{ sec}$, or about half a millisecond. It diffuses a distance $x = 1 \text{ cm}$ (the width of a test tube) in a time $t = x^2/2D = 5 \times 10^4 \text{ sec}$, or about 14 hours. The difference is dramatic. In order for a particle to wander twice as far, it takes 4 times as long. In order for it to wander 10 times as far, it takes 100 times as long. Therefore, there is no such thing as a diffusion velocity; displacement is not proportional to time but rather to the square-root of the time. What happens if we try to define a diffusion velocity by dividing the root-mean-square displacement by the time? The result is an explicit function of the time. Dividing both sides of Eq. 1.11 by t , we find

$$\frac{\langle x^2 \rangle^{1/2}}{t} = \left(\frac{2D}{t} \right)^{1/2}. \quad (1.12)$$

Thus, the shorter the period of observation, t , the larger the apparent velocity. For values of t smaller than τ , the apparent velocity is larger than $\delta/\tau = v_x$, the instantaneous velocity of the particle. This is an absurd result.

In Chapter 2 we will speak of adsorption rates or diffusion currents. These expressions refer to the number of particles that are adsorbed at, or cross, a given boundary in unit time. They are bulk properties of an ensemble of particles, proportional to their number. They are not rates that tell us how long it takes a particle, by diffusion, to go from here to there. This time depends on the square of the distance, as defined by Eq. 1.10. When next you come across the expression "diffusion rate," think twice! This phrase is ambiguous, at best, and often used incorrectly.

Two- and three-dimensional random walks

Rules 1 to 3 apply in each dimension. In addition, we assert that motions in the x , y , and z directions are statistically independent. If $\langle x^2 \rangle = 2Dt$, then $\langle y^2 \rangle = 2Dt$ and $\langle z^2 \rangle = 2Dt$. In two dimensions, the square of the distance from the origin to the point (x,y) is $r^2 = x^2 + y^2$; therefore,

$$\langle r^2 \rangle = 4Dt. \quad (1.13)$$

In three dimensions, $r^2 = x^2 + y^2 + z^2$, and

$$\langle r^2 \rangle = 6Dt. \quad (1.14)$$

A computer simulation of a two-dimensional random walk is shown in Fig. 1.4. Steps in the x and y directions were made at the same times, so the particle always moved diagonally. The simulation makes graphic a remarkable feature of the random walk, discussed further in Chapter 3. Since explorations over short distances can be made in much shorter times than explorations over long



Fig. 1.4. An x, y plot of a two-dimensional random walk of $n = 18,050$ steps. The computer pen started at the upper left corner of the track and worked its way to the upper right edge of the track. It repeatedly traversed regions that are completely black. It moved, as the crow flies, 196 step lengths. The expected root-mean-square displacement is $(2n)^{1/2} = 190$ step lengths.

distances, the particle tends to explore a given region of space rather thoroughly. It tends to return to the same point many times before finally wandering away. When it does wander away, it chooses new regions to explore blindly. A particle moving at random has no tendency to move toward regions of space that it has not occupied before; it has absolutely no inkling of the past. Its track does not fill up the space uniformly.

The binomial distribution

We have learned so far that particles undergoing free diffusion have a zero mean displacement and a root-mean-square displacement that is proportional to the square-root of the time. What else can we say about the shape of the distribution of particles? To find out, we have to work out the probabilities that the particles step different distances to the right or to the left. While doing

so, it is convenient to generalize the one-dimensional random walk and suppose that a particle steps to the right with a probability p and to the left with a probability q . Since the probability of stepping one way or the other is 1, $q = 1 - p$. The probability that such a particle steps exactly k times to the right in n trials is given by the binomial distribution

$$P(k; n, p) = \frac{n!}{k!(n-k)!} p^k q^{n-k}. \quad (1.15)$$

This equation is derived in Appendix A; see Eqs. A.17, A.18. The displacement of the particle in n trials, $x(n)$, is equal to the number of steps to the right less the number of steps to the left times the step length, δ :

$$x(n) = [k - (n - k)]\delta = (2k - n)\delta. \quad (1.16)$$

Since we know the distribution of k , we know the distribution of x . The two distributions have the same shapes. The probability machine shown in Fig. A.3 converts one into the other.

The mean displacement of the particle is

$$\langle x(n) \rangle = (2\langle k \rangle - n)\delta, \quad (1.17)$$

where

$$\langle k \rangle = np; \quad (1.18)$$

see Eq. A.22. The mean-square displacement is

$$\begin{aligned} \langle x^2(n) \rangle &= \langle [(2k - n)\delta]^2 \rangle \\ &= (4\langle k^2 \rangle - 4\langle k \rangle n + n^2)\delta^2, \end{aligned} \quad (1.19)$$

where

$$\langle k^2 \rangle = (np)^2 + npq; \quad (1.20)$$

see Eq. A.23. For the case $p = q = 1/2$, Eqs. 1.17 and 1.19 yield $\langle x(n) \rangle = 0$ and $\langle x^2(n) \rangle = n\delta^2$, as expected.

The Gaussian distribution

A small particle, such as lysozyme, steps an enormous number of times every second. Given the instantaneous velocity estimated from Eq. 1.2, $v_x = \delta/\tau \approx 10^3$ cm/sec, and a diffusion coefficient, $D = \delta^2/2\tau \approx 10^{-6}$ cm²/sec, we can compute the step length, δ , and the step rate, $1/\tau$. The step length is $2D/v_x \approx (10^{-6} \text{ cm}^2/\text{sec})/(10^3 \text{ cm/sec}) = 10^{-9}$ cm, and the step rate is $v_x/\delta \approx (10^3 \text{ cm/sec})/(10^{-9} \text{ cm}) = 10^{12} \text{ sec}^{-1}$. Of these $n = 10^{12}$ steps taken each second, $np = 0.5 \times 10^{12}$ are taken to the right. The standard deviation in this number is $(npq)^{1/2} = 0.5 \times 10^6$; see Eq. A.25. So, to a precision of about a part in a million, half of the steps taken each second are made to the right and half to the left. What happens to the distribution of x in this limit? As stated in Appendix A, when n and np are both very large, the binomial distribution, $P(k; n, p)$, is equivalent to

$$P(k)dk = \frac{1}{(2\pi\sigma^2)^{1/2}} e^{-(k-\mu)^2/2\sigma^2} dk, \quad (1.21)$$

where $P(k)dk$ is the probability of finding a value of k between $k + dk$, $\mu = \langle k \rangle = np$, and $\sigma^2 = npq$; see Eq. A.27. This is the Gaussian or normal distribution. By substituting $x = (2k - n)\delta$, $dx = 2\delta dk$, $p = q = 1/2$, $t = n/\tau$, and $D = \delta^2/2\tau$, we obtain

$$P(x)dx = \frac{1}{(4\pi Dt)^{1/2}} e^{-x^2/4Dt} dx, \quad (1.22)$$

where $P(x)dx$ is the probability of finding a particle between x and $x + dx$. This is the function plotted in Fig. 1.3. The variance of this distribution is $\sigma_x^2 = 2Dt$; its standard deviation is $\sigma_x = (2Dt)^{1/2}$.

The Gaussian or normal distribution is the distribution encountered most frequently in discussions of propagation of errors. It is tabulated, for example, in the *Hand-*

book of Chemistry and Physics, as the "normal curve of error"; see Fig. A.5. About 68% of the area of the curve is within one standard deviation of the origin. Thus, if the root-mean-square displacement of the particles is $(2Dt)^{1/2}$, the chances are 0.32 that a particle has wandered that far or farther. The chances are 0.045 that it has wandered twice as far or farther and 0.0026 that it has wandered three times as far or farther. These numbers are the areas under the curve for $|x| \geq \sigma_x$, $2\sigma_x$, and $3\sigma_x$, respectively.

Visualizing the Gaussian distribution: It is instructive to generate the distributions shown in Fig. 1.3 experimentally. This can be done by layering aqueous solutions of a dye, such as fluorescein or methylene blue, into water. For a first try, layer the dye at the center of a vertical column of water in a graduated cylinder. The dye promptly sinks to the bottom! It does so because it has a higher specific gravity than the surrounding medium. For a second try, match the specific gravity of the medium to the dye by adding sucrose to the water. Now the dye drifts about and becomes uniformly dispersed in a matter of minutes or hours. It does so because there is nothing to stabilize the system against convective flow. Any variation in temperature that increases the specific gravity of regions of the fluid that are higher in the column relative to those that are lower drives this flow. For a final try, layer the dye into a column of water containing more sucrose at the bottom than at the top, i.e., into a sucrose density gradient; a 0-to-2% w/v solution will do. Match the specific gravity of the solution of the dye to that at the midpoint of the gradient and layer it there. Now, patterns of the sort shown in Fig. 1.3 will evolve over a period of many days. The diffusion coefficients of fluorescein, methylene blue, and sucrose are all about

5×10^{-6} cm²/sec. A sucrose gradient $x = 10$ cm high will survive for a period of time of order $t = x^2/2D = 10^7$ sec, or about 4 months. The dye will generate a Gaussian distribution with a standard deviation $\sigma_x = 2.5$ cm in a time $t = \sigma_x^2/2D \approx 6 \times 10^5$ sec, or in about 1 week. Try it!

It is evident from this experiment that diffusive transport takes a long time when distances are large. Here is another example: The diffusion coefficient of a small molecule in air is about 10^{-1} cm²/sec. If one relied on diffusion to carry molecules of perfume across a crowded room, delays of the order of 1 month would be required. Evidently, the makers of scent owe their livelihood to close encounters, wind, and/or convective flow.

Chapter 2

Diffusion: Macroscopic Theory

Fick's equations

Most discussions of diffusion start with Fick's equations, differential equations that describe the spatial and temporal variation of nonuniform distributions of particles. I find it more illuminating to derive these equations from the model of the random walk. Suppose we know the number of particles at each point along the x axis at time t , as shown in Fig. 2.1. How many particles will move across unit area in unit time from the point x to the point $x + \delta$? What is the net flux in the x direction, J_x ? At time $t + \tau$, i.e., after the next step, half the particles at x will have stepped across the dashed line from left to right, and half the particles at $x + \delta$ will have stepped across the dashed line from right to left. The net number crossing to the right will be

$$-\frac{1}{2} [N(x + \delta) - N(x)].$$

To obtain the net flux, we divide by the area normal to the

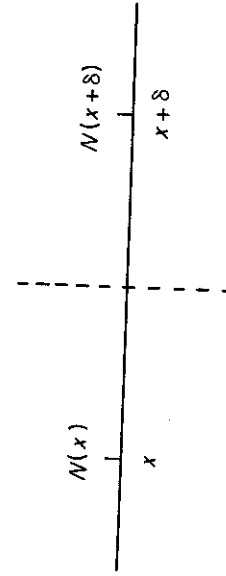


Fig. 2.1. At time t , there are $N(x)$ particles at position x , $N(x + \delta)$ particles at position $x + \delta$. At time $t + \tau$, half of each set will have stepped to the right and half to the left.

x axis, A , and by the time interval, τ ,

$$J_x = -\frac{1}{2} [N(x+\delta) - N(x)]/A\tau.$$

Multiplying by δ^2/δ^2 and rearranging, we obtain

$$J_x = -\frac{\delta^2}{2\tau} \frac{1}{\delta} \left[\frac{N(x+\delta)}{A\delta} - \frac{N(x)}{A\delta} \right].$$

The quantity $\delta^2/2\tau$ is the diffusion coefficient, D . $N(x+\delta)/A\delta$ is the number of particles per unit volume at the point $x+\delta$, i.e., the concentration $C(x+\delta)$. $N(x)/A\delta$ is the concentration $C(x)$. Therefore,

$$J_x = -D \frac{1}{\delta} [C(x+\delta) - C(x)].$$

But δ is very small. In the limit $\delta \rightarrow 0$, by the definition of a partial derivative, as explained in Appendix B, we obtain

$$J_x = -D \frac{\partial C}{\partial x}. \quad (2.1)$$

This is Fick's first equation. It states that the net flux (at x and t) is proportional to the slope of the concentration function (at x and t); the constant of proportionality is $-D$. If the particles are uniformly distributed, the slope is 0, i.e., $\partial C/\partial x = 0$, and $J_x = 0$. If J_x is 0, the distribution will not change with time; the system is at equilibrium. If the slope is constant, i.e., if $\partial C/\partial x$ is constant, J_x is constant. This occurs when C is a linear function of x , as shown in Fig. 2.2. In practice, a gradient of this kind can be maintained only if there is a source for particles at one point and an adsorber for particles at another, e.g., in a pipe connecting reservoirs held at fixed concentrations C_1 and C_2 .

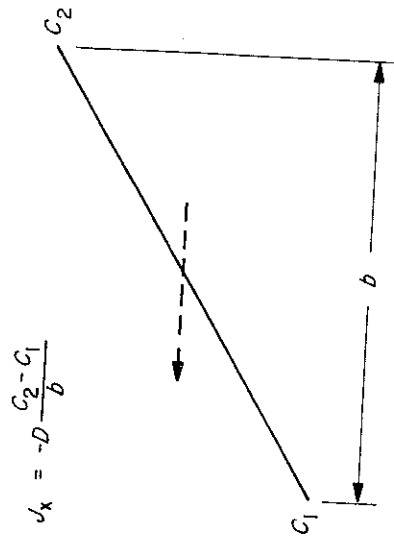


Fig. 2.2. The flux due to a linear concentration gradient ($C_2 - C_1$)/ b . There is a net movement of particles from right to left, solely because there are more particles at the right than at the left.

When we derived Eq. 1.10, we defined $D = \delta^2/2\tau$. The reason for the $1/2$ is now clear; it makes Fick's first equation more tidy. Note that if C is expressed in particles/cm³, J_x is in particles/cm²sec. If C is expressed in moles/cm³, J_x is in moles/cm²sec.

Fick's second equation follows from the first, provided that the total number of particles is conserved, i.e., that the particles are neither created nor destroyed. Consider the box shown in Fig. 2.3. In a period of time τ , $J_x(x)A\tau$ particles will enter from the left and $J_x(x+\delta)A\tau$ particles will leave from the right. The volume of the box is $A\delta$. If particles are neither created nor destroyed, the number of particles per unit volume in the box must increase at the rate

$$\begin{aligned} \frac{1}{\tau} [C(t+\tau) - C(t)] &= -\frac{1}{\tau} [J_x(x+\delta) - J_x(x)]A\tau/A\delta \\ &= -\frac{1}{\delta} [J_x(x+\delta) - J_x(x)]. \end{aligned}$$

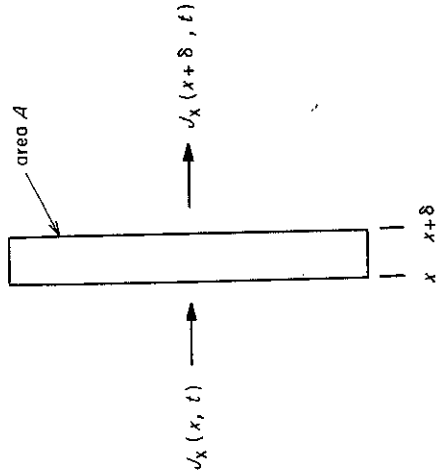


Fig. 2.3. Fluxes through the faces of a thin box extending from position x to position $x + \delta$. The area of each face is A . The faces are normal to the x axis.

In the limit $\tau \rightarrow 0$ and $\delta \rightarrow 0$, this means that

$$\frac{\partial C}{\partial t} = -\frac{\partial J_x}{\partial x}, \tag{2.2}$$

or, given Eq. 2.1, that

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}. \tag{2.3}$$

This is Fick's second equation. It states that the time rate of change in concentration (at x and t) is proportional to the curvature of the concentration function (at x and t); the constant of proportionality is D . If the slope is constant, $\partial^2 C / \partial x^2 = 0$, and the concentration is stationary; just as many particles diffuse in from the region of higher concentration as diffuse out to the region of lower concentration. Eq. 2.3 tells us how a nonuniform distribution of particles will redistribute itself in time. If we know the initial distribution and other boundary conditions, we can figure out all later distributions.

In three dimensions we have $J_x = -D \partial C / \partial x$, $J_y = -D \partial C / \partial y$, and $J_z = -D \partial C / \partial z$. These are components of a flux vector,

$$\mathbf{J} = -D \text{ grad } C. \tag{2.4}$$

The concentration changes with time as

$$\frac{\partial C}{\partial t} = D \nabla^2 C, \tag{2.5}$$

where ∇^2 is the three-dimensional Laplacian, $\partial^2 / \partial x^2 + \partial^2 / \partial y^2 + \partial^2 / \partial z^2$.

If the problem is spherically symmetric, the flux is radial,

$$J_r = -D \partial C / \partial r, \tag{2.6}$$

and

$$\frac{\partial C}{\partial t} = D \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial C}{\partial r} \right). \tag{2.7}$$

Time-dependent solutions to Fick's equations

One way to find solutions to Fick's equations is to look them up! An excellent source is Carslaw and Jaeger (1959), a book dealing with the conduction of heat in solids. The heat equation has the same form as the diffusion equation. In the notation of Carslaw and Jaeger,

$$\frac{\partial \nu}{\partial t} = \kappa \nabla^2 \nu,$$

where ν is the temperature and κ is the thermal diffusivity. So, take their results and read C for ν and D for κ . Sources that do not require such translation include Crank (1975) and Jost (1960). But this strategy requires luck. If you happen to find a discussion of just the problem that you

are trying to solve, well and good. If not, you will soon be lost in a morass of complex equations. Here are some "trivial" examples.

Diffusion from a micropipette: A micropipette filled with an aqueous solution of a green fluorescent dye is inserted into a large body of water. At time $t = 0$, particles of the dye are injected into the water at the rate i per sec for an infinitesimal period of time dt . The total number of particles injected is $N = i dt$. With these boundary conditions, Eq. 2.7 has the solution

$$C(r, t) = \frac{N}{(4\pi Dt)^{3/2}} e^{-r^2/4Dt}. \quad (2.8)$$

This is a three-dimensional Gaussian distribution; compare Eq. 1.22. Looking through a microscope, one sees the sudden appearance of a green spot that spreads rapidly outward and fades away. The concentration remains highest at the tip of the pipette, but it decreases there as the three-halves power of the time. An observer at radius r sees a wave that peaks at $t = r^2/6D$ at a concentration $C = 0.0736 N/r^3$. He finds that the concentration rises most rapidly at time $t = r^2/16.325D$ at a rate $\partial C/\partial t = 1.054 ND/r^5$.

The wave due to a pulse of length t_0 can be found by integrating Eq. 2.8 with respect to time. For $t \leq t_0$,

$$C(r, t) = \frac{i}{4\pi Dr} \operatorname{erfc} \frac{r}{(4Dt)^{1/2}}, \quad (2.9)$$

where $\operatorname{erfc} x$ is the error function complement, $1 - \operatorname{erf} x$, and $\operatorname{erf} x$ is the error function, defined by the integral

$$\operatorname{erf} x = \frac{2}{\sqrt{\pi}} \int_0^x e^{-u^2} du. \quad (2.10)$$

This function is tabulated, just like $\sin x$ or $\cos x$; see, for

example, Chapter 7 of Abramowitz and Stegun (1972) or Appendix II of Carslaw and Jaeger (1959). Note that $\operatorname{erf} 0 = 0$, $\operatorname{erf} \infty = 1$, and $\operatorname{erf}(-x) = -\operatorname{erf} x$. If the pulse is long enough, the concentration approaches the steady-state value

$$C(r, t) = \frac{i}{4\pi Dr}. \quad (2.11)$$

For $t > t_0$,

$$C(r, t) = \frac{i}{4\pi Dr} \left\{ \operatorname{erfc} \frac{r}{(4Dt)^{1/2}} - \operatorname{erfc} \frac{r}{[4D(t - t_0)]^{1/2}} \right\}. \quad (2.12)$$

Figure 2.4 shows the concentration observed at $r = 10^{-3}$ cm for a pulse of constant injection rate i and length $t_0 = 1$ sec for particles of diffusion coefficient $D = 10^{-5}$, 3×10^{-6} , 10^{-6} , 3×10^{-7} , 10^{-7} , and 3×10^{-8} cm²/sec. If the diffusion coefficient is large, the particles diffuse beyond the observer while the pulse is still on, and the peak concentration is given by Eq. 2.11. If the diffusion coefficient is small, the events occur on a time scale that is long compared with the length of the pulse, and the peak concentration approaches $C = 0.0736 it_0/r^3$, as required by Eq. 2.8. For other examples of diffusion from constrictions, see Jaeger (1965).

Diffusion in a pipe: In principle, one could measure diffusion coefficients with experiments of the kind illustrated in Fig. 2.4, but in practice it is easier to work in one dimension and to follow the spread of a narrow band of particles, as shown in Fig. 1.3. Alternatively, one can expose a column of solution at concentration C_0 to one at concentration 0 and watch the migration of particles from one to the other. In this case, the initial conditions are

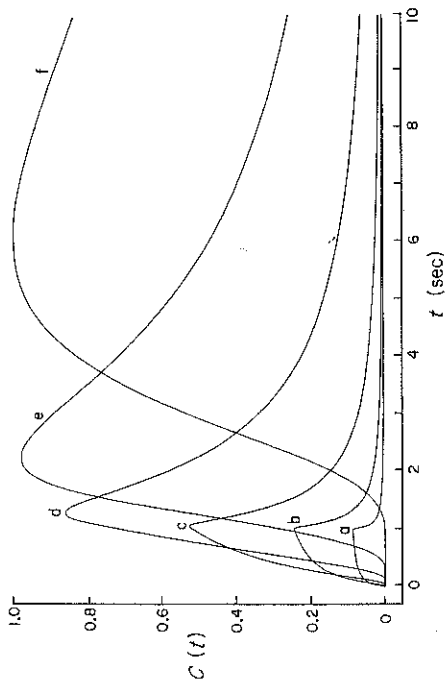


Fig. 2.4. Concentration (in arbitrary units) as a function of time at a distance $r = 10^{-3}$ cm from a point-source in an infinite medium emitting particles at a constant rate from $t = 0$ to $t_0 = 1$ sec, for particles with diffusion coefficient, D (in cm^2/sec): (a) 10^{-5} , (b) 3×10^{-6} , (c) 10^{-6} , (d) 3×10^{-7} , (e) 10^{-7} , and (f) 3×10^{-8} . See Eqs. 2.9 and 2.12.

$C = C_0$ for $x > 0$ and $C = 0$ for $x < 0$, and Eq. 2.3 has the solution

$$C(x,t) = \frac{C_0}{2} \left[1 + \text{erf} \frac{x}{(4Dt)^{1/2}} \right]. \tag{2.13}$$

Since $\text{erf } 0 = 0$, Eq. 2.13 implies that the concentration of particles at $x = 0$ falls abruptly to $C_0/2$ and remains at that value. This behavior is shown in Fig. 2.5. By taking derivatives of $C(x,t)$ with respect to x or t , we obtain

$$\frac{\partial C}{\partial x} = \frac{C_0}{(4\pi Dt)^{1/2}} e^{-x^2/4Dt} \tag{2.14}$$

and

$$\frac{\partial C}{\partial t} = -\frac{x}{2t} \frac{\partial C}{\partial x}. \tag{2.15}$$

Equation 2.14 is similar to Eq. 1.22. Thus, D can be mea-

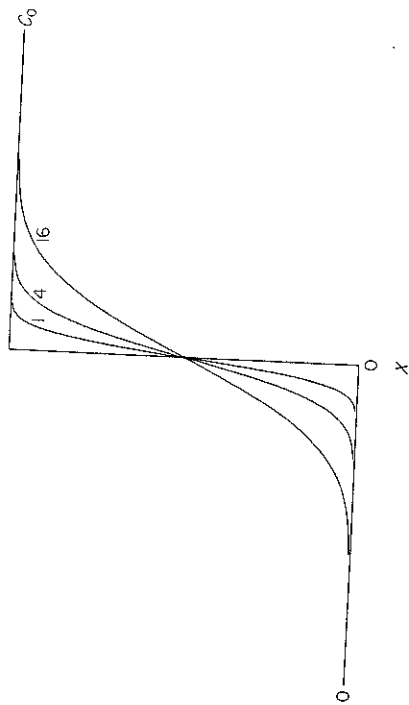


Fig. 2.5. Concentration as a function of position at times $t = 0, 1, 4$, and 16 for diffusion from a column of liquid initially containing particles at a concentration C_0 (right) into a column of liquid initially devoid of particles (left). The horizontal axis in this figure is drawn on the same scale as that of Fig. 1.3, which shows $\partial C/\partial x$. See Eqs. 2.13-2.15.

sured if one measures C as a function of space and/or time. A numerical solution to a similar problem is given in Appendix B, Fig. B.3.

Steady-state solutions to Fick's equations

If sources and adsorbers are present, the final distribution of particles will not be uniform; instead, the concentration will approach a steady-state value that is higher near sources, lower near adsorbers. In this limit, $\partial C/\partial t = 0$, and Eq. 2.5 reduces to

$$\nabla^2 C = 0. \tag{2.16}$$

For problems with spherical symmetry, Eq. 2.7,

$$\frac{1}{r^2} \frac{d}{dr} \left(r^2 \frac{dC}{dr} \right) = 0. \tag{2.17}$$

We already have seen the steady-state solutions for diffusion in one dimension from a plane at concentration C_2 to a plane at concentration C_1 , Fig. 2.2, and for diffusion in three dimensions from a continuous point-source in an infinite medium, Eq. 2.11. Here are some other examples.

Diffusion to a spherical adsorber: Consider a spherical adsorber of radius a in an infinite medium, as shown in Fig. 2.6. Every particle reaching the surface of the sphere is gobbled up, so the concentration at $r = a$ is 0. The concentration at $r = \infty$ is C_0 . With these boundary conditions, Eq. 2.17 has the solution

$$C(r) = C_0 \left(1 - \frac{a}{r} \right). \quad (2.18)$$

The flux, Eq. 2.6, is

$$J_r(r) = -DC_0 \frac{a}{r^2}. \quad (2.19)$$

The net migration of molecules is radially inward, as shown by the dashed arrows in Fig. 2.6. The particles are

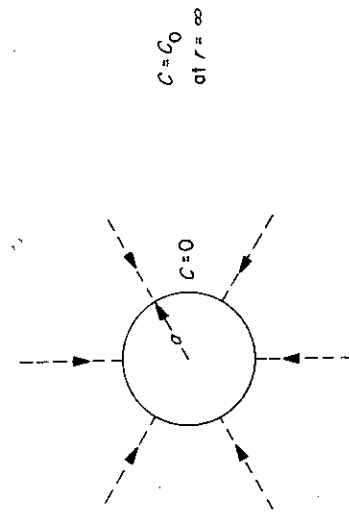


Fig. 2.6. A spherical adsorber of radius a in an infinite medium containing particles at an initial concentration C_0 . The dashed arrows are lines of flux.

adsorbed by the sphere at a rate equal to the area, $4\pi a^2$, times the inward flux, $-J_r(a)$:

$$I = 4\pi DaC_0. \quad (2.20)$$

If C_0 is expressed in particles/cm³, I is in particles/sec. We will refer to this adsorption rate, I , as a diffusion current. Note that this current is proportional not to the area of the sphere but to its radius. As the radius, a , increases, the area increases as a^2 , but the concentration gradient, to which the flux is proportional, decreases as $1/a$.

Diffusion to a disk-like adsorber: Next, consider a disk-shaped adsorber of radius s in a semi-infinite medium, as shown in Fig. 2.7. Every particle reaching the surface of the disk is gobbled up, so the concentration at the disk is 0. The concentration at $x = \infty$ is C_0 . This problem is cylindrically symmetric rather than spherically sym-

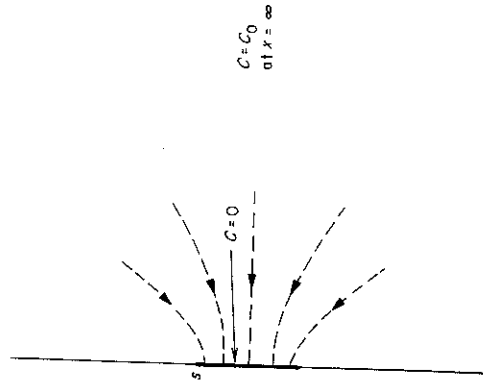


Fig. 2.7. A disk-like adsorber of radius s on one edge of a semi-infinite medium, $x \geq 0$, containing particles at an initial concentration C_0 . The dashed arrows are lines of flux.

metric, so the mathematics is not so easy; see, for example, p. 42 of Crank (1975). But the answer turns out to be simple. The diffusion current is

$$I = 4DsC_0. \quad (2.21)$$

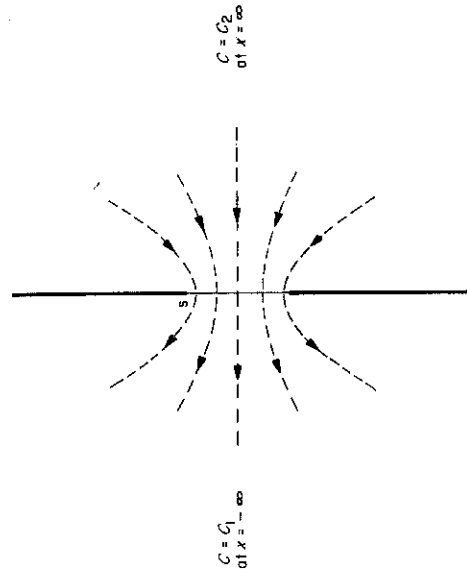


Fig. 2.8. A circular aperture of radius s in a nonadsorbing barrier separating two semi-infinite media, $x < 0$ and $x \geq 0$, containing particles at initial concentrations $C_2 > C_1$. The dashed arrows are lines of flux.

An analogous problem, illustrated in Fig. 2.8, involves diffusion through a circular aperture of radius s in a nonadsorbing barrier separating two semi-infinite media. The concentration at $x = -\infty$ is C_1 and the concentration at $x = \infty$ is C_2 . The current through the aperture is

$$I_{2,1} = 2Ds(C_2 - C_1). \quad (2.22)$$

These currents are proportional not to the area of the disk (or aperture) but to its radius. As the radius, s , increases, the area increases as s^2 , but the concentration gradient, to which the flux is proportional, decreases as $1/s$.

Diffusion to an ellipsoidal adsorber: Next, consider a cigar-shaped adsorber, an ellipsoid of revolution with semi-axes $a > b = c$. The concentration at the surface of the ellipsoid is 0, and the concentration at $r = \infty$ is C_0 . If the ellipsoid is relatively thin, in particular, if $a^2 \gg b^2$, the diffusion current is

$$I = 4\pi DaC_0/\ln(2a/b), \quad (2.23)$$

where \ln denotes the natural logarithm. This current is smaller than that found for a sphere of radius a given in Eq. 2.20 by the factor $\ln(2a/b)$. This factor is not as large as one might expect. For example, if $b = 10^{-2}a$, $\ln(2a/b) = 5.3$; if $b = 10^{-4}a$, $\ln(2a/b) = 9.9$. Once again, the current is proportional not to the area of the adsorber but roughly to its length.

Appeal to an electrical analogue: The time-independent diffusion equation, Eq. 2.16, is analogous to Laplace's equation for the electrostatic potential in charge-free space. As explained elsewhere (Berg and Purcell, 1977), this implies that the diffusion current to an isolated adsorber of any size and shape can be written as

$$I = 4\pi DcC_0, \quad (2.24)$$

where c is the electrical capacitance (in cgs units of centimeters) of an isolated conductor of that size and shape. Since the electrical capacitances of a variety of conductors have been worked out, Eq. 2.24 can save some labor. For example, Eq. 2.23 was obtained from an expression for the electrical capacitance of a conducting ellipsoid [by using formula 195.02 of Dwight, 1961, to evaluate the integral 5.02 (4) of Smythe, 1950, and converting from mks to cgs units by multiplying by $1/4\pi\epsilon_0$]. Smythe used the same integral in another limit to compute the capacitance of a conducting disk, which led us to Eq. 2.21. We

could have derived Eq. 2.20 in a similar fashion, but it was more instructive, given the spherical symmetry, to solve the diffusion equation directly.

Diffusion to N disk-like adsorbers on the surface of a sphere: Given that diffusion currents to spheres, disks, and prolate ellipsoids of similar size are roughly equal, it seems likely that diffusion currents to other adsorbers of similar size should be roughly equal. This turns out to be true, even for nonadsorbing objects sprinkled with small adsorptive patches. Suppose N disk-like adsorbers, each of radius s , are distributed over the surface of an otherwise impenetrable nonadsorbing sphere of radius $a \gg s$, as shown in Fig. 2.9. The concentration at $r = \infty$ is C_0 .

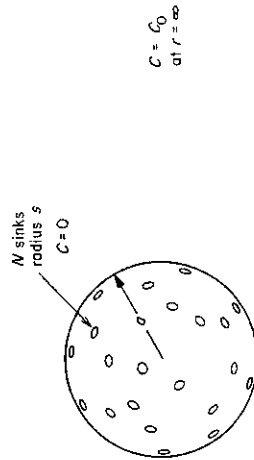


Fig. 2.9. An impenetrable nonadsorbing sphere of radius a covered with N disk-like adsorbers, each of radius s , in an infinite medium containing particles at an initial concentration C_0 .

This is a reasonable model for N chemoreceptors or N transport proteins on the surface of a cell. How does the total adsorption rate vary with N ? If N is very small, two adsorbers should do twice as well as one, so the rate should increase as $4DN_sC_0$, Eq. 2.21. But when N is very large, almost the entire surface of the sphere is adsorbing, and the rate should approach $4\pi DaC_0$, Eq. 2.20. What happens in between? In this regime, the distance between

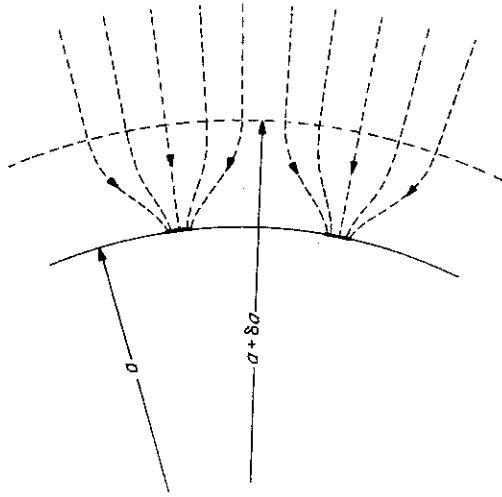


Fig. 2.10. Two disk-like adsorbers of the sphere shown in Fig. 2.9. The dashed arrows are lines of flux. These lines become radial at a distance δa from the surface of the sphere, a distance roughly equal to the distance between adjacent adsorbers.

receptors is large compared with their radius but small compared with the radius of the cell, as shown in Fig. 2.10. The lines of flux are radial for $r > a + \delta a$ (as in Fig. 2.6) but converge on the adsorbers for $a < r < a + \delta a$ (as in Fig. 2.7). Evidently, the concentration at $r = a + \delta a$ is constant at some intermediate value between 0 and C_0 .

This problem is formally equivalent to one in electricity in which current flows through a medium of finite resistivity to N conductive patches on an insulating sphere, with the medium a large distance away at potential V_0 and the patches at potential 0. The concentration, C , is an analogue of the potential, V . In the electrical case, we have Ohm's law, which states that the current through a resistor is equal to the potential drop across its terminals divided by its resistance. For steady-state diffusion, we have $I = C/R$, where I is the diffusion current, C is the concentration difference, and R is the diffusion resistance.

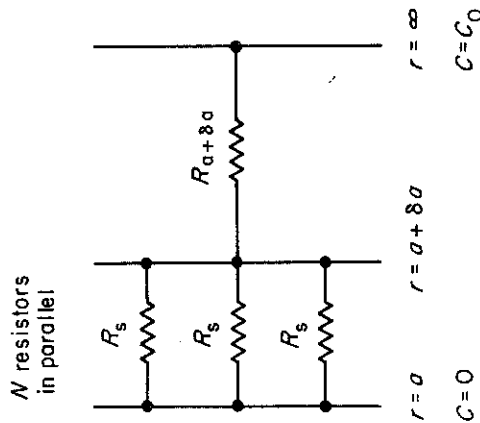


Fig. 2.11. An electrical model for the problem of N adsorbers of radius s on the surface of a sphere of radius a , the problem illustrated in Figs. 2.9 and 2.10.

By appealing to this relation, we note that the diffusion resistance for the adsorbing sphere, Eq. 2.20, is $R_a = 1/4\pi Da$, and that the diffusion resistance for the disk-like adsorber, Eq. 2.20, is $R_s = 1/4Ds$. These resistances are shown as discrete elements in Fig. 2.11. The total resistance of this circuit is $R = R_{a+\delta a} + R_s/N = 1/[4\pi D(a + \delta a)] + 1/4DNs$. Since $\delta a \ll a$, $R \approx 1/4\pi Da + 1/4DNs = (1/4\pi Da)(1 + \pi a/Ns) = R_a(1 + \pi a/Ns)$. We conclude that the diffusion resistance for a sphere covered with N disk-like adsorbers is larger than the diffusion resistance for the completely adsorbing sphere by a factor $1 + \pi a/Ns$. The diffusion current is smaller by the same factor:

$$\frac{I}{I_0} = \frac{1}{1 + \pi a/Ns}, \tag{2.25}$$

where $I_0 = 4\pi DaC_0$, Eq. 2.20. I is plotted as a function of N in Fig. 2.12. If N is small, the rate increases as $4DNsC_0$. If N is large, the rate approaches $4\pi DaC_0$. This is the asymptotic behavior that we predicted.

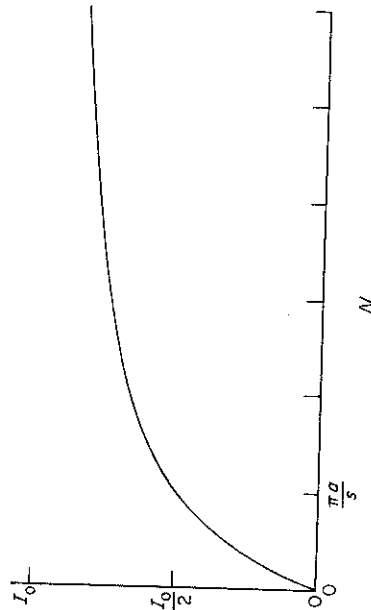


Fig. 2.12. The diffusion current, or rate of adsorption, I , as a function of the number of adsorbers, N , for disk-like adsorbers of radius s on the surface of a sphere of radius a . See Eq. 2.25. I_0 is the diffusion current for the completely adsorbing sphere, Eq. 2.20.

Note that the diffusion current reaches half of its maximum value for $N = \pi a/s$. This number is surprisingly small. Consider a spherical cell of radius $a = 5 \mu\text{m}$ equipped with N transport proteins, each with a binding site of radius $s = 10 \text{ \AA}$. This cell can adsorb substrate molecules at half the rate of a cell completely covered by such sites if $N = \pi a/s = 15,700$. Only a small fraction of the surface of the cell need be specifically adsorbing, namely $N\pi s^2/4\pi a^2 = 1.6 \times 10^{-4}$. The distance between neighboring sites is about $(4\pi a^2/N)^{1/2} = 0.14 \mu\text{m}$, i.e., about 140 times the site radius. Thus, many hundreds of different transport (or receptor) systems can be accommodated on the surface of the cell, each adsorbing particles of a specific kind with an efficiency approaching that of a cell whose entire surface is dedicated to one such task. For other discussions of this problem, see Berg and Purcell (1977), DeLisi and Wiegel (1981), Shoup and Szabo (1982), and Zwanzig (1990). For an application involving detection of insect pheromones, see Futrelle (1984).

It should be stressed that the electrical analogy used in the derivation of Eq. 2.25 does not extend to time-dependent diffusion; it only applies in the steady-state. The flux is proportional to the concentration gradient, but individual particles are not moving like electrons through a wire; they are moving strictly at random. The same restriction applies to the analogy leading to Eq. 2.24.

Diffusion through N circular apertures in a planar barrier: Consider a system in which two plates a distance b apart are held at concentrations C_1 and C_2 , as shown in

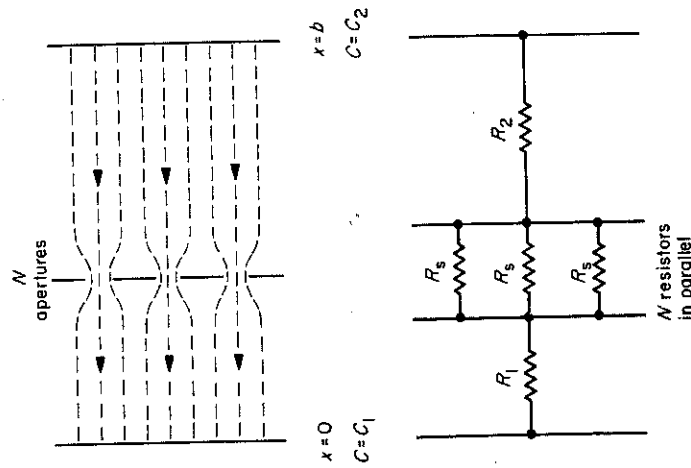


Fig. 2.13. A barrier with $N = nA$ apertures, each of radius s , separating two plates of area A held at concentrations C_1 and C_2 (top), and an electrical model for this system (bottom). See Eq. 2.27.

Fig. 2.2. Let the system have a cross-sectional area A . The diffusion current from one plate to the other is

$$I_{2,1} = DA(C_2 - C_1)/b. \quad (2.26)$$

Now insert somewhere between the two plates a thin barrier containing N apertures, each of radius $s \ll b$, as shown in Fig. 2.13. What is the diffusion current in the new steady state? The diffusion resistance for one aperture is $R_s = 1/2Ds$, Eq. 2.22. The diffusion resistance of the medium between the plates is $R_1 + R_2 \approx R_{2,1} = b/DA$, Eq. 2.26. The diffusion resistance of the entire system is $R_1 + R_2 + R_s/N = R_{2,1} + R_s/N = b/DA + 1/2DNs = (b/DA)(1 + 1/2nbs)$, where n is the number of apertures per unit area. It follows that the barrier decreases the diffusion current by a factor

$$\frac{I}{I_{2,1}} = \frac{1}{1 + 1/2nbs}. \quad (2.27)$$

If this ratio is written as $b/(b + 1/2ns)$, it is evident from the denominator that the effect of the barrier is equivalent to the addition of an extra diffusion path of length $1/2ns$.

The diffusion current reaches half of its maximum value for $n = 1/2sb$. This number is surprisingly small. Consider two cubical cells $10 \mu\text{m}$ on a side joined on one face. Assume that the membranes composing this face are of negligible thickness and penetrated by N pores, each of radius 50 \AA . How many pores are required for the diffusion current between the cells to be half as large as it would be were the barrier not there? Given $N/A = 1/2sb$, with $A = 10^{-6} \text{ cm}^2$, $s = 5 \times 10^{-7} \text{ cm}$, and $b = 2 \times 10^{-3} \text{ cm}$, we find $N = 500$. Only a small fraction of the surface of the barrier need be penetrated, namely $N\pi s^2/A = 3.9 \times 10^{-4}$. The distance between neighboring pores is about $(A/N)^{1/2} = 0.45 \mu\text{m}$, i.e., about 90 times the pore radius.

A similar problem involves the diffusion of gases through the stomata of leaves. In this case, the concentration is clamped at 0 inside the leaf, just to the left of the barrier; so $R_1 = 0$, and the diffusion resistance for each aperture is the same as that for the disk-like adsorber, $R_s = 1/4Ds$. Thus, the stomata add an extra diffusion path of length $1/4ns$, and the diffusion current reaches half of its maximum value for $n = 1/4sb$. This analysis is valid only for the boundary layer near the surface of the leaf, i.e., in still air. For a discussion of this problem, see Chapter 3 of Meidner and Mansfield (1968).

Chapter 3

Diffusion to Capture

In Chapter 2 we compared the steady-state rates of uptake of particles by completely adsorbing objects of various shapes, such as spheres, disks, and ellipsoids. We found that these rates are proportional to the linear dimension of the object rather than to its area, and that the shape is not of crucial importance. For example, the diffusion currents to a sphere of radius a , a two-sided disk of radius a , and an ellipsoid of revolution of length $2a$ and radius $a/10$ fall in the ratios 1 to 0.64 to 0.33. We also found that a reflecting object of a given size and shape sparsely covered with adsorbent patches is nearly as good at sequestering particles as a completely adsorbing object of the same size and shape. From a microscopic point of view, both sets of results reflect the fact that a diffusing particle that finds itself in a given region of space is destined, by that very circumstance, to wander around that region for a time, probing it rather thoroughly before wandering away for good. A particle that finds itself in a spherical space of radius a has a fair chance of blundering into a disk or an ellipsoid inscribed in that space. A particle that bumps into a reflecting object has a fair chance of hitting an adsorbent patch nearby on its surface. This property of the random walk is apparent in the two-dimensional simulation shown in Fig. 1.4. That particle wandered about in some regions at great length but ignored others completely. It is very difficult to get a feel for this mindless ramble from a casual study of the diffusion equation (Eq. 2.5). In this chapter, we try to make these ideas more quantitative by working out some probabilities of capture and mean times to capture.