

# Diffusion 1.6

## Learning Objectives

- Define flow and flux
- Describe the meaning of the continuity equation
- Write Fick's First Law of Diffusion
- Recognize Fick's Second Law of Diffusion
- Identify the units of the diffusion coefficient
- Identify the three major assumptions of the one-dimensional random walk
- Describe the diffusion coefficient in terms of the parameters of the one-dimensional random walk
- Describe what is meant by the time of diffusion and its dependence on distance
- Describe the diffusion coefficient in the cytoplasm compared to that in water
- Write the Stokes–Einstein equation and identify the parameters in it

## FICK'S FIRST LAW OF DIFFUSION WAS PROPOSED IN ANALOGY TO FOURIER'S LAW OF HEAT TRANSFER

Adolph Fick (1829–1901) was a German physiologist who enunciated what we now call Fick's First Law of Diffusion in 1855. Fick argued from analogy to two well-known laws of physics involving flows and their driving forces. The first was Fourier's Law of Heat Transfer:

$$[1.6.1] \quad J_H = -\lambda \frac{\partial T}{\partial x}$$

where  $J_H$  is the rate of heat energy transfer per unit area per unit time and  $\partial T/\partial x$  is the temperature gradient. The second law was Ohm's law:

$$[1.6.2] \quad J_e = -\sigma \frac{\partial \psi}{\partial x}$$

where  $J_e$  is the electrical flux and  $\partial \psi/\partial x$  is the voltage or potential gradient. By analogy, Fick wrote:

$$[1.6.3] \quad J_s = -D \frac{\partial C}{\partial x}$$

This is Fick's First Law of Diffusion in one dimension. This law says that the positive  $J$  is in the direction of the negative spatial slope of the concentration. In analogy to the other laws, this law says that solutes move from regions of high concentrations to low concentrations, and that the driving force for such a movement is the concentration **gradient**. The term gradient has a specific meaning that is defined by vector calculus, as described in Chapter 1.3. Fluxes are usually expressed in units of moles per square centimeter per second. Since concentration is in units of moles  $\text{cm}^{-3}$ , and  $x$  is in units of cm, the gradient is in units of moles  $\text{cm}^{-4}$ . Dividing the units of  $J$  by the units of the gradient, we have the units of the diffusion coefficient as  $\text{cm}^2 \text{s}^{-1}$ . In free water solutions, most low molecular weight materials have diffusion coefficients on the order of  $1 \times 10^{-5} \text{ cm}^2 \text{s}^{-1}$ . Larger materials diffuse more slowly, as we will see.

## FICK'S SECOND LAW OF DIFFUSION FOLLOWS FROM THE CONTINUITY EQUATION AND FICK'S FIRST LAW

In Chapter 1.2, we derived the **continuity equation** from the conservation of material flowing along one dimension. It was given as

$$[1.6.4] \quad \frac{\partial C(x, t)}{\partial t} = -\frac{\partial J(x)}{\partial x}$$

If we differentiate Fick's First Law (see Eqn [1.6.3]) with respect to  $x$ , we obtain

$$[1.6.5] \quad \frac{\partial J_s}{\partial x} = -D \frac{\partial^2 C}{\partial x^2}$$

By substitution into the continuity equation, we obtain

$$[1.6.6] \quad \frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}$$

This is **Fick's Second Law of Diffusion**. It follows from the First Law of Diffusion by application of the continuity equation. It relates changes in concentration with time with the spatial distribution of solute particles. Given initial conditions of  $C(x, 0)$  and boundary conditions, solutions of this equation, or its three-dimensional analogue, allow one to determine concentration as a function of time and position ( $C(x, t)$ ).

## FICK'S SECOND LAW CAN BE DERIVED FROM THE ONE-DIMENSIONAL RANDOM WALK

Fick's Second Law of Diffusion can be derived from molecular kinetic theory elucidated by Maxwell and Boltzmann in the latter half of the 19th century. This can be accomplished by analyzing the statistics of the random walk. Application of the continuity equation to the Second Law can then result in the derivation of Fick's First Law. It should become clear, then, that both these laws describing diffusion are a consequence of the random motion of particles. The process of diffusion thus appears to be a statistical result only, there being no literal "driving force" for the diffusive flux. Despite this, we will find that there is energy associated with concentration or dilution of solutes, and that opposition of diffusion, e.g., during active transport, requires real forces.

The random walk we will discuss is a one-dimensional model of real events. We choose to simplify the analysis because otherwise it is intractable and because it turns out to be a good model due to the enormously large number of collisions which occur during diffusion of real solute particles. The main assumptions of the model are:

- Each particle moves in a straight line between collisions.
- The motion consists of steps of length  $\lambda$  taken either to the left or to the right.
- The probability of making a step to the right is equal to the probability of taking a step to the left.

This surprisingly simple model will allow us to derive a one-dimensional form of Fick's Second Law.

If the probability of taking a step to the right is  $p$  and the probability of taking a step to the left is  $q$ , the third assumption gives  $p = q = 1/2$ . The question we ask first is this: if a particle starts out at  $x = 0$ , what is the probability that, after some elapsed time,  $t$ , it will be found some distance  $x$  away, where  $x$  is an integral multiple of  $\lambda$ ? We can take  $\lambda$  to be a measure of the **mean free path**. If  $t_c$  is the time between collisions, and we wait for the interval  $t$ , then there will be  $t/t_c$  collisions in this time. These simple assumptions allow us to derive an expression for the probability density that a particle starting at  $x = 0$  will be found in a distance interval centered at  $x$  at time  $t$ .

First we will convert the elapsed time to the number of steps taken in that interval. The size of the steps to the right and to the left is  $\lambda$ , the mean free path between collisions. If the average speed is  $v$ , then the average speed times the time between collisions,  $t_c$ , will be equal to  $\lambda$ . Thus

$$[1.6.7] \quad t_c = \frac{\lambda}{\langle v \rangle}$$

The number of collisions in the time  $t$  is given as the time  $t$  divided by the time between collisions:

$$[1.6.8] \quad N = \frac{t}{t_c}$$

Note that we are using  $N$  now to count the number of steps a particle of average speed  $v$  and mean free path  $\lambda$  will make in the interval  $t$ . In this derivation, it does not signify the number of solute molecules. Now the original problem can be reformulated: what is the probability that, after  $N$  steps, the particle will be found at a distance  $x = m\lambda$ , where  $m$  is an integer, away from its starting place?

Let  $R$  be the number of steps to the right and  $L$  be the number of steps to the left. Then

$$[1.6.9] \quad \begin{aligned} N &= R + L \\ R - L &= m \end{aligned}$$

where the total number of steps is  $N$ . To travel a distance  $m\lambda$  away from the starting point in steps of size  $\lambda$ ,  $R - L = m$ . The desired probability of making  $R$  steps to the right and  $L$  steps to the left out of a total of  $N$  steps is given by the binomial probability distribution:

$$[1.6.10] \quad P_N(R, L) = \left(\frac{1}{2}\right)^N \frac{N!}{R!L!}$$

This is simply the probability that with  $N$  trials,  $R$  trials will be to the right and  $L$  trials will be to the left. From Eqn [1.6.9], we have

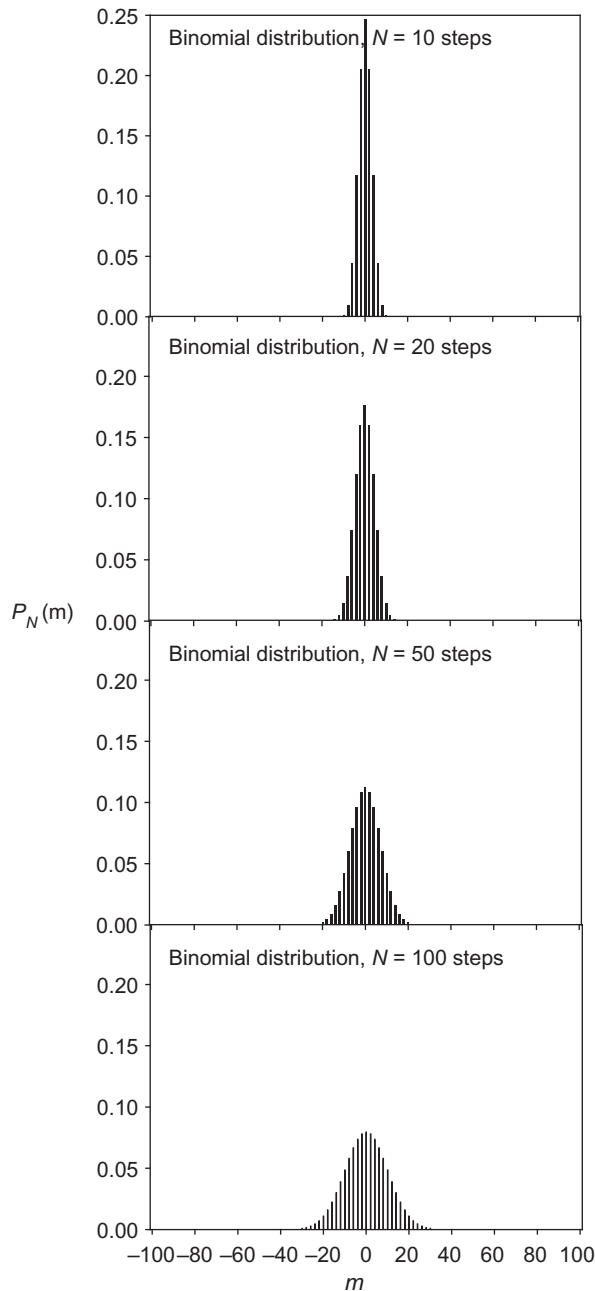
$$[1.6.11] \quad \begin{aligned} R &= \frac{N + m}{2} \\ L &= \frac{N - m}{2} \end{aligned}$$

which can be substituted back into Eqn [1.6.10] to give

$$[1.6.12] \quad P_N(R, L) = P_N(m) = \left(\frac{1}{2}\right)^N \frac{N!}{((N + m)/2)!((N - m)/2)!}$$

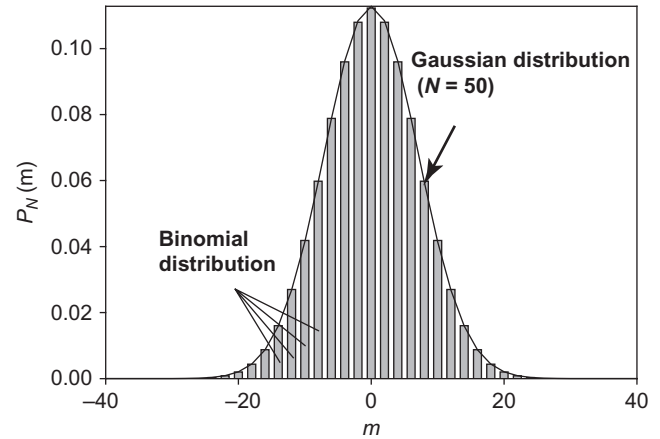
In this form the probability distribution is a discrete variable, with only integral values of  $m$ . This random walk model of diffusion is shown in Figure 1.6.1 where the distribution models diffusion from an initially sharp distribution at  $m = 0$  and  $P = 1.0$ . After 10 steps, the material is distributed between  $-10 \leq m \leq 10$ ; after 20 steps, the material is distributed between  $-20 \leq m \leq 20$ , but the probability at the extreme ends of the distribution is small. The probability profile loses density in the center and gradually spreads out with the number of steps. Remember here that the number of steps is directly proportional to the time according to Eqn [1.6.8]. This behavior corresponds subjectively to the idea of diffusion: the material gradually diminishes at its source and spreads out with time.

If you look carefully at the binomial probability distribution in Figure 1.6.1, you will notice that its profile appears to be a fairly well-behaved function. As written, it is a discrete probability function, being defined for only integral values of  $N$  and  $m$ . What we would like is a continuous distribution that describes the envelope of the binomial probability distribution. Now normally the value of  $N$ , the number of collisions in the time interval  $t$  is extraordinarily large. In a gas at room temperature, there are typically  $5 \times 10^9$  collisions per second, while

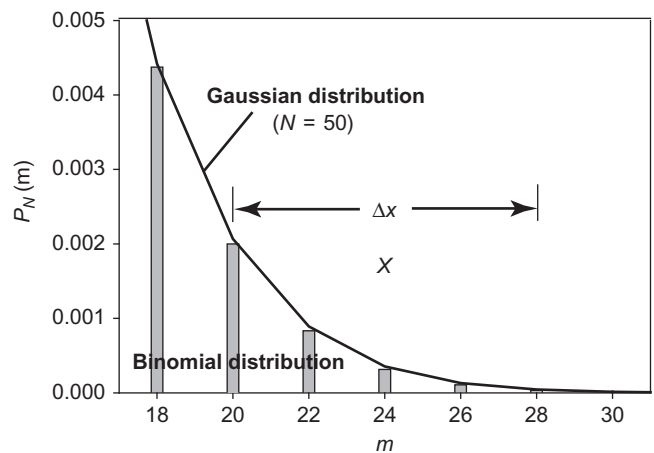


**FIGURE 1.6.1** Binomial probability density for the probability of finding a particle that initially was placed at  $m = 0$ , as a function of the number of steps,  $N = 10, 20, 50$ , and  $100$ . Note that material initially present in a narrow band centered at the origin spreads out with increasing number of steps, corresponding to increasing time.

the mean free path is typically  $10^{-5}$  cm or so. We cannot count the number of steps accurately nor can we measure the distance accurately, so we resort to a simpler question: What is the probability that a particle starting at  $x = 0$  and  $t = 0$  will end up in the displacement interval  $\Delta x$  centered at  $x$  at time  $t$ ? We can get this probability from  $P_N(m)$  first by letting  $N$  get very large to justify the use of Stirling's approximation, and then by counting the number of  $m$ 's which land the particle in the displacement interval  $\Delta x$  centered at  $x$ .



**FIGURE 1.6.2** Binomial probability distribution for  $N = 50$ , with the envelope of the Gaussian distribution with  $N = 50$ . The binomial probability distribution is discrete, with only integral values of  $m$  allowed. The Gaussian distribution is continuous.



**FIGURE 1.6.3** Enlargement from Figure 1.6.2.

Stirling's formula for  $n$  factorial is

$$[1.6.13] \quad n! = \sqrt{2\pi n} e^{n \ln(n-n)}$$

This truly amazing formula is the key to converting the discrete probability distribution into a continuous one. Using Stirling's formula in Eqn [1.6.13], plus the approximation that  $\ln(1 + \alpha) \approx \alpha$  for small values of  $\alpha$ , it is possible to convert Eqn [1.6.12], by a lot of algebraic manipulation, to

$$[1.6.14] \quad P_N(m) = \sqrt{\frac{2}{\pi N}} e^{-(m^2/2N)}$$

This is the **Gaussian** approximation to the probability distribution function  $P_N(m)$ . This function provides a continuous **envelope** to the discrete probability function given in Eqn [1.6.12], as shown schematically in Figure 1.6.2. The Gaussian probability distribution is discussed in Appendix 1.2.A2.

As mentioned earlier, what we desire is to find the probability that a particle starting at  $x = 0$  and  $t = 0$  will end up in the interval of  $\Delta x$  centered at  $x$  at some time  $t$  later. How we can accomplish this can be made clearer if we enlarge part of Figure 1.6.2, as shown in Figure 1.6.3.

Since each step is of length  $\lambda$ , a net displacement of  $R - L = m$  steps leads to the displacement  $x = m\lambda$ . Thus,  $m = x/\lambda$ , and we may replace  $m$  in Eqn [1.6.14] with  $x/\lambda$  to obtain

$$[1.6.15] \quad P_N(m) = P_N\left(\frac{x}{\lambda}\right) = \sqrt{\frac{2}{\pi N}} e^{-(x^2/2N\lambda^2)}$$

What we desired was the probability that a particle will be in the interval  $\Delta x$  centered at  $x$  at some time  $t$  after beginning the random walk. Specifying the time  $t$  is equivalent to specifying the value of  $N$ , as these are related according to Eqn [1.6.8] as  $N = t/t_c$  where  $t_c$  is the time between collisions. We may substitute this value of  $N$  into Eqn [1.6.15] to obtain

$$[1.6.16] \quad P_N(m) = P_N\left(\frac{x}{\lambda}\right) = P(m, t) = P\left(\frac{x}{\lambda}, t\right) = \sqrt{\frac{2t_c}{\pi t}} e^{-(x^2 t_c / 2\lambda^2 t)}$$

The probability the particle will be in the interval  $\Delta x$  centered at  $x$  is the sum of the probabilities that the value of  $m\lambda$  will fall in this interval. For a given  $N$  (which is the same as for a given time,  $t$ ) values of  $m = R - L$  are either all odd or all even. Thus the possible values of displacement are separated by  $2\lambda$ . The number of values of  $m$  consistent with landing in the interval  $\Delta x$  is thus  $\Delta x / 2\lambda$ . If we take  $P(x/\lambda, t)$  given in Eqn [1.6.16] as the **average** probability in the interval  $\Delta x$ , then the probability of finding the particle in the interval is

$$[1.6.17] \quad \begin{aligned} \sum_{m \in \Delta x} P(m, t) &= \frac{\Delta x}{2\lambda} P\left(\frac{x}{\lambda}, t\right) \\ &= \frac{1}{2\lambda} P\left(\frac{x}{\lambda}, t\right) \Delta x \\ &= \sqrt{\frac{t_c}{2\pi\lambda^2 t}} e^{-t_c x^2 / 2\lambda^2 t} \Delta x \end{aligned}$$

From this result, we define a **probability density function**:

$$[1.6.18] \quad P(x, t) = \sqrt{\frac{t_c}{2\pi\lambda^2 t}} e^{-(t_c x^2 / 2\lambda^2 t)}$$

When multiplied by the length of the interval,  $\Delta x$ , this function gives the probability of finding the particle in the interval  $\Delta x$  at time  $t$ . The **diffusion coefficient** is defined as

$$[1.6.19] \quad D = \frac{\lambda^2}{2t_c}$$

Note that this definition is consistent with the units of the diffusion coefficient of  $\text{cm}^2 \text{s}^{-1}$  that we obtained from Fick's First Law of Diffusion. Using this definition, Eqn [1.6.18] becomes

$$[1.6.20] \quad P(x, t) = \sqrt{\frac{1}{4\pi Dt}} e^{-x^2 / 4Dt}$$

This is still the probability density function for finding a particle in an interval at some time after beginning the

random walk, but all of the parameters of the random walk, the mean free path, and the time between collisions are submerged into a single constant,  $D$ . Thus the diffusion coefficient derives its values from microscopic characteristics of the diffusing substance. Since we have defined the average velocity as  $\langle v \rangle = \lambda/t_c$  (see Eqn [1.6.7]), we see that the diffusion coefficient is related to the square of the average velocity. Thus thermal agitation should increase the average velocity and thereby increase diffusion.

We can use Eqn [1.6.20] to derive an expression for the concentration of solute particles at position  $x$  at time  $t$ , which we denote as  $C(x, t)$ . Ordinarily the concentration is the number of particles per unit volume. In our one-dimensional analogue, it is the number of particles per unit length. At any time,  $t$ , the number of particles per unit length,  $\Delta x$ , at position  $x$  is the sum of all particles which have random walked into the displacement interval from all other areas. This is the probability density function times the initial concentration summed over all intervals. This can be written as

$$[1.6.21] \quad C(x, t) = \int_{-\infty}^{\infty} C_0(x') P(x - x', t) dx'$$

where  $C_0(x')$  is the initial concentration at point  $x'$ . Here

$$[1.6.22] \quad P(x - x', t) = \sqrt{\frac{1}{4\pi Dt}} e^{-(x - x')^2 / 4Dt}$$

Eqn [1.6.21] expresses the concentration at position  $x$  and time  $t$  in terms of the concentration everywhere at an initial time  $t = 0$ . The initial time  $t = 0$  is chosen arbitrarily. We can write

$$[1.6.23] \quad C(x, t + \Delta t) = \int_{-\infty}^{\infty} C(x', t) P(x - x', \Delta t) dx'$$

Let us substitute in  $s = x' - x$ , so that  $C(x', t) = C(x + s, t)$  and  $P(x - x', \Delta t) = P(-s, \Delta t) = P(s, \Delta t)$  (because of symmetry in  $x$  in the probability distribution function) and  $ds = dx'$ . Then Eqn [1.6.23] becomes

$$[1.6.24] \quad C(x, t + \Delta t) = \int_{-\infty}^{\infty} C(x + s, t) P(s, \Delta t) ds$$

We let  $\Delta t$  be small, so that the concentration is altered only by local events. We approximate  $C(x + s, t)$  as

$$[1.6.25] \quad C(x + s, t) = C(x, t) + s \frac{\partial C(x, t)}{\partial x} + \frac{1}{2} s^2 \frac{\partial^2 C(x, t)}{\partial x^2} + \dots$$

which is a Taylor's series expansion of  $C(x + s, t)$ . Inserting Eqn [1.6.25] back into Eqn [1.6.24], we obtain

$$[1.6.26] \quad \begin{aligned} C(x + t, \Delta t) &= C(x, t) \int_{-\infty}^{\infty} P(s, \Delta t) ds \\ &\quad + \frac{\partial C(x, t)}{\partial x} \int_{-\infty}^{\infty} s P(s, \Delta t) ds \\ &\quad + \frac{1}{2} \frac{\partial^2 C(x, t)}{\partial x^2} \int_{-\infty}^{\infty} s^2 P(s, \Delta t) ds \end{aligned}$$

The function  $P(s, \Delta t)$  is given from Eqn [1.6.22] and our definition of  $s = x' - x$  as

$$[1.6.27] \quad P(s, \Delta t) = \sqrt{\frac{1}{4\pi D \Delta t}} e^{-s^2/4D\Delta t}$$

Evaluation of the integrals gives

$$[1.6.28] \quad \begin{aligned} \int_{-\infty}^{\infty} P(s, \Delta t) ds &= 1 \\ \int_{-\infty}^{\infty} s P(s, \Delta t) ds &= 0 \\ \int_{-\infty}^{\infty} s^2 P(s, \Delta t) ds &= 2D\Delta t \end{aligned}$$

We shall not prove these integration results. You should note their meaning, however. The first integration result is the **normalization** of the probability distribution, which means that the particle must be somewhere with the probability equal to 1. The second result is the **average displacement** about the initial zero displacement  $s$ . The zero value of the average displacement means that the distribution is symmetrical: displacement to the right and to the left are equally likely in the random walk. Recall by the definition of  $s = x' - x$  that  $s$  may be both negative and positive, so that the average is zero. The last integration gives the average square displacement. Both positive and negative values of  $s$  contribute to  $s^2$ . This integration gives the **variance**, or the average squared displacement, for the distribution. For the case of this one-dimensional model of diffusion, the variance is  $2D\Delta t$ . Inserting these integration results into Eqn [1.6.26] gives

$$[1.6.29] \quad C(x, t + \Delta t) = C(x, t) + \frac{1}{2} \frac{\partial^2 C(x, t)}{\partial x^2} 2D\Delta t$$

This may be rewritten as

$$[1.6.30] \quad \frac{C(x, t + \Delta t) - C(x, t)}{\Delta t} = D \frac{\partial^2 C(x, t)}{\partial x^2}$$

If we take the limit as  $\Delta t \rightarrow 0$ , we recognize the left-hand side of Eqn [1.6.30] as the partial derivative of the concentration with respect to time. We then have

$$[1.6.31] \quad \frac{\partial C(x, t)}{\partial t} = D \frac{\partial^2 C(x, t)}{\partial x^2}$$

This is Fick's Second Law of Diffusion. From the continuity equation, Fick's First Law can be derived. Although Fick's First Law was originally derived on phenomenological grounds and the Second Law followed it from the continuity equation, this derivation shows that it can be done the other way using a quite simple model which nevertheless embodies the main ideas giving rise to diffusion: there are an enormous number of collisions which give rise to a random motion of particles from one region of space to another.

## THE TIME FOR ONE-DIMENSIONAL DIFFUSION INCREASES WITH THE SQUARE OF DISTANCE

How long does it take for a given material to diffuse some distance,  $x$ ? This question is deceptively simple.

It is not asking how long it takes the first molecule to get to  $x$ , or how long it takes for the concentration at  $x$  to reach a particular value. It is asking about the *population* of molecules that are moving from high concentration to low concentration. From Figure 1.6.1, you can see that an initially sharp distribution gradually broadens with time because of diffusion. What we want is a quantitative measure of the *shape* of the concentration profile. The time of diffusion is usually calculated from the **variance** of the Gaussian distribution:

$$[1.6.32] \quad \bar{x}^2 = \int_{-\infty}^{+\infty} x^2 \sqrt{\frac{1}{4\pi D \Delta t}} e^{-x^2/4D\Delta t} dx = 2D\Delta t$$

where the elapsed time of diffusion is  $\Delta t$ . For two-dimensional diffusion, the variance is  $4D\Delta t$ ; for three-dimensional diffusion it is  $6D\Delta t$ . The elapsed time for diffusion,  $\Delta t$ , is the time taken for the inflection point of the distribution to move from  $x = 0$  to  $x = x$ , given an initially sharp distribution at  $x = 0$ . The time taken to diffuse a given distance,  $x$ , is the mean square displacement divided by  $2D$ . Alternatively, we can calculate the distance of diffusion in time  $\Delta t$  as

$$[1.6.33] \quad x = \sqrt{\bar{x}^2} = \sqrt{2D\Delta t}$$

For distances smaller than the cell (0–10  $\mu\text{m}$ ), diffusion takes less than a ms up to a few ms. For distances on the order of the diameter of muscle cells (40–100  $\mu\text{m}$ ), diffusion takes several seconds.

## DIFFUSION COEFFICIENTS IN CELLS ARE LESS THAN THE FREE DIFFUSION COEFFICIENT IN WATER

If the initial concentration of a substance is very narrow, then the subsequent distribution some time later due to diffusion will be given by Eqn [1.6.20] as

$$[1.6.34] \quad C(x, t) = C_0 \sqrt{\frac{1}{4\pi D t}} e^{-x^2/4Dt}$$

This equation can be shown to obey Fick's Second Law of Diffusion, Eqn [1.6.31], which is left as an exercise for the student (see Problem 15 in Problem Set 1.2). Dividing Eqn [1.6.34] by  $C_0$  and taking the logarithm of both sides, we obtain:

$$[1.6.35] \quad \begin{aligned} \ln \frac{C(x, t)}{C_0} &= \ln \sqrt{\frac{1}{4\pi D t}} + \ln e^{-x^2/4Dt} \\ &= -\frac{x^2}{4Dt} - \ln(2\sqrt{\pi D t}) \end{aligned}$$

Kushmerick and Podolsky (Ionic mobility in cells, *Science* 166:1297–1298, 1969) microinjected a 3–6 mm segment of muscle fiber from the semitendinosus muscle of the frog with small amounts of tracer materials, and then allowed the materials to diffuse along the fibers for various periods of time. They immersed the fibers in oil to avoid diffusion through the water phase outside the muscle. After the prescribed period, the muscles were dehydrated in acetone, stained, embedded in paraffin,



**Example 1.6.1 Time of One-Dimensional Diffusion**

The diffusion coefficient for  $\text{Ca}^{2+}$  in water is  $D_{\text{Ca}} = 0.8 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ ; for calbindin, a 9500-Da protein that binds  $\text{Ca}^{2+}$  with high affinity,  $D_{\text{p}} = 0.12 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ . How long does it take for  $\text{Ca}^{2+}$  or calbindin to diffuse  $x = \{0.1, 1, 10, 20, 50, 100 \mu\text{m}\}$ ?

Here we use Eqn [1.6.32] to calculate  $\Delta t = x^2/2D$ . As a representative calculation, we find  $\Delta t$  for  $\text{Ca}^{2+}$  for  $0.1 \mu\text{m}$ :

$$\Delta t = \frac{(0.1 \times 10^{-6} \text{ m} \times 10^2 \text{ cm m}^{-1})^2}{2 \times 0.8 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}} = 6.25 \times 10^{-6} \text{ s}$$

which is amazingly quick. The other times can be calculated by the same method, and we can fill out Table 1.6.1.

Variation of this calculation was performed by A.V. Hill in 1949 to show that a diffusible substance could not be the activator of muscle cells because the delay between nervous excitation and contraction of the muscle was too fast, only a few ms.

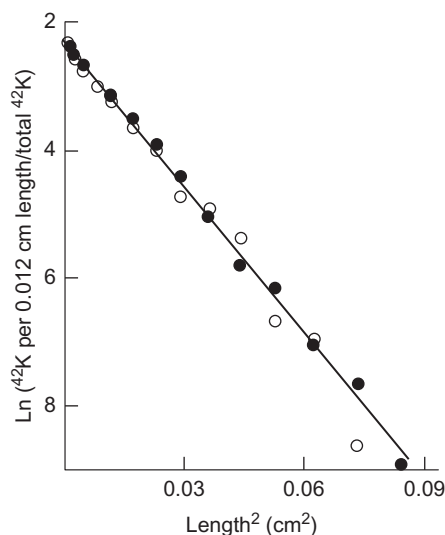
**TABLE 1.6.1** The Calculated Time for One-Dimensional Diffusion of Free  $\text{Ca}^{2+}$  and Calbindin in Water for Various Distances

Distance ( $\mu\text{m}$ )	Calcium $D_{\text{Ca}} = 0.8 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$	Calbindin $D_{\text{p}} = 0.12 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$
0.1	$6.3 \times 10^{-6}$	$42 \times 10^{-6}$
1.0	$0.6 \times 10^{-3}$	$4.2 \times 10^{-3}$
10.0	$62.5 \times 10^{-3}$	$420 \times 10^{-3}$
20.0	0.25	1.67
50.0	1.56	10.4
100.0	6.25	41.7

and cut into  $25 \mu\text{m}$  sections, which were then counted. The plots of  $\ln$  (counts at distance  $x$ /total counts) were linear with the square of the distance, as predicted by Eqn [1.6.35], and the diffusion coefficient in the muscle was estimated from the slope. An example of their results for  $^{42}\text{K}$  is shown in Figure 1.6.4. Kushmerick and Podolsky found that the diffusion coefficient for most substances they injected was about one-half of the free water diffusion coefficient. These materials included  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{SO}_4^{2-}$ , sorbitol, sucrose, and ATP. For  $\text{Ca}^{2+}$ , however, the apparent diffusion coefficient was about 50 times less than the free water diffusion. From this they concluded that  $\text{Ca}^{2+}$  was retarded by interaction with fixed components within the muscle cell. It is important to recognize that this effect is a reduction in the *apparent* diffusion coefficient because the total  $\text{Ca}^{2+}$  is being partitioned between a freely diffusible form and a bound or fixed form. Thus the apparent diffusion coefficient is reduced because they calculated the diffusion from the total concentration and not just the free concentration.

## EXTERNAL FORCES CAN MOVE PARTICLES AND ALTER THE DIFFUSIVE FLUX

The mathematical relations describing the diffusion of nonelectrolytes have been presented to you in the form of Fick's First and Second Laws of Diffusion. These expressions were derived from the one-



**FIGURE 1.6.4** Typical results for the Kushmerick and Podolsky experiment. The longitudinal distribution of  $^{42}\text{K}^+$  at  $0.02 \text{ cm}$  intervals after diffusion for  $320 \text{ s}$  at  $20^\circ\text{C}$  was plotted as a logarithmic transform of the diffusion equation for an infinite slab from an infinitely thin distribution:  $\ln$  (counts at distance  $x$ /total cts)  $= -x^2/4Dt - \ln 2(\pi Dt)^{1/2}$ .

dimensional random walk, which considered that the probability of making a step to the right and to the left was the same. Under some circumstances, this is not true. For example, diffusive flux is altered when a

bulk flux of fluid occurs simultaneously with the diffusive flux. In this case, we write

$$[1.6.36] \quad J_s(x, t) = -D \frac{\partial C(x, t)}{\partial x} + J_v(t)C(x, t)$$

The first term on the right describes the diffusive flux and the second term describes the flux of solute due to **solvent drag**. Here  $J_v$  is the **volume flux**, equal to the volume of fluid moving across an area per unit area per unit time. This volume times the concentration of solute will give the amount of solute moving across that area per unit area per unit time.  $J_v$  is equal to the velocity of fluid flow: the volume flux is  $V/(A\Delta t) = (A\Delta x)/(A\Delta t) = \Delta x/\Delta t$ , the velocity of fluid flow. [Eqn \[1.6.36\]](#) is the **convection–diffusion equation**, because the bulk flow is described as **convection**.

There are other circumstances which alter the flux from that described by Fick's First Law. These circumstances occur when there are external forces applied to the solute particles. Examples of these forces include electrical forces and gravitational forces. Recall in Chapter 1.3 that we considered that electrical forces accelerate ions in solution until they reach a terminal velocity in which the electrical force is balanced by the drag force. The drag force,  $F_d$ , is proportional to the terminal velocity. We wrote:

$$[1.6.37] \quad \begin{aligned} F_e &= zeE \\ F_d &= -\beta v \\ F_e + F_d &= 0 \\ F_e &= \beta v \end{aligned}$$

where  $\beta$  is the frictional coefficient or drag coefficient. It is given as

$$[1.6.38] \quad \beta = \frac{kT}{D}$$

as originally proposed by Einstein in 1905 (see [Appendix 1.6.A1](#)). Here  $k$  is Boltzmann's constant, the ideal gas constant divided by Avogadro's number:  $k = R/N_0$ , and  $D$  is the diffusion coefficient. This result makes sense: a large diffusion coefficient is usually associated with small particles, and these would have a small frictional coefficient, encountering less resistance to movement. Incorporating this definition of  $\beta$  into the last equation in [Eqn \[1.6.37\]](#), we have

$$[1.6.39] \quad F_e = \frac{kT}{D} v$$

In Chapter 1.3, we also established that the ratio of  $J$  to  $C$  defines an average velocity of movement of particles:

$$[1.6.40] \quad J = v C$$

Substituting for  $v$  from [Eqn \[1.6.40\]](#) into [Eqn \[1.6.39\]](#) and rearranging, we obtain

$$[1.6.41] \quad J = \frac{D}{kT} F_e C$$

What this equation means is that, in the absence of a concentration gradient, an external force will produce a flux that is linearly related to the magnitude of the

force per particle and the concentration, with a coefficient related to the diffusion coefficient. We have derived this for an electric force, but the result is completely general for any external force.

In the presence of a concentration gradient, we expect the diffusive flux to add to the flux caused by the application of an external force. From Fick's First Law of Diffusion and [Eqn \[1.6.41\]](#), we obtain, for one dimension, Fick's First Law of Diffusion for solutes subjected to an external force:

$$[1.6.42] \quad J = -D \frac{\partial C}{\partial x} + \frac{D}{kT} fC$$

This can be written in vector notation as

$$[1.6.43] \quad J = -D \nabla C + \frac{D}{kT} CF$$

## THE STOKES–EINSTEIN EQUATION RELATES THE DIFFUSION COEFFICIENT TO MOLECULAR SIZE

Stokes showed that for a spherical particle, the drag force was related to its size and to the viscosity of the medium:

$$[1.6.44] \quad F_d = -\beta v = -6\pi\eta a_s v$$

where  $\eta$  is the **viscosity** of the fluid and  $a_s$  is the radius of the sphere. Clearly, Stokes derived an expression for the frictional coefficient. From [Eqns \[1.6.38\]](#) and [\[1.6.44\]](#), we can write

$$[1.6.45] \quad \begin{aligned} 6\pi\eta a_s &= \frac{kT}{D} \\ D &= \frac{kT}{6\pi\eta a_s} \end{aligned}$$

The last expression is the **Stokes–Einstein equation**. It indicates that the diffusion coefficient for a spherical particle should be a function of its radius, the absolute temperature, and the viscosity of the fluid in which it is diffusing.

Recall earlier that Kushmerick and Podolsky found that the apparent diffusion coefficient of readily diffusible substances like  $K^+$ ,  $Na^+$ , and sucrose inside cells was about one-half of their diffusion coefficients in water. From the Stokes–Einstein equation, it would seem that the variable most likely responsible for these decreases in diffusion coefficients is the viscosity of the medium. Thus the cytoplasm appears to be a watery environment, where most small molecular weight materials are free to diffuse but with reduced diffusion coefficients owing to the greater viscosity of the cytoplasm. The **tortuosity** of the path is not included in this analysis. This refers to the blockade of direct diffusion by large structures in the cytoplasm, including organelles and cytoskeleton. Because materials cannot diffuse in a straight line, the diffusion apparently takes longer because the actual path length in the microscopic domain is larger than the apparent path length. In fact, tortuosity and

increased viscosity are both partial explanations for the reduced diffusion coefficient inside cells.

## SUMMARY

Solutes move by diffusion from regions of high concentration to regions of low concentration. Fick's First Law of Diffusion states that the flux is proportional to the negative of the gradient of  $C$ :

$$J_s = -\frac{D}{\partial x} \frac{\partial C}{\partial x}$$

where  $J_s$  is the solute flux,  $D$  is the diffusion coefficient, and  $\partial C/\partial x$  is the one-dimensional gradient. The continuity equation states that changes in concentration with time must be due to changes in flux with distance:

$$\frac{\partial C}{\partial t} = -\frac{\partial J_s}{\partial x}$$

Fick's Second Law of Diffusion derives from his First Law and the Continuity Equation:

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

Fick's Second Law can be derived from a random walk model of diffusion in which molecules take large numbers of small steps. Using Stirling's approximation, the discrete binomial probability distribution can be converted to a continuous one, resulting in a Gaussian probability distribution. For a narrow starting distribution at time  $t = 0$ , the distribution of solute at time  $t$  is given as

$$C(x, t) = C_0 \sqrt{1/4\pi Dt} e^{-x^2/4Dt}$$

From the random walk,  $D$  is identified as  $\lambda^2/2t_c$ , where  $\lambda$  is the distance between collisions and  $t_c$  is the time between collisions. The time of diffusion is typically estimated as the variance of the Gaussian distribution, which gives

$$t = \frac{x^2}{2D}$$

Although diffusion is a statistical result, it is equivalent to a force in that it produces a flow of material. Other forces can also make solutes move. These forces include electrical forces on charged solutes, solvent drag (convection), and gravitational forces. An external force applied to solute particles causes a flux given by

$$J = \frac{D}{kT} fC$$

where  $f$  is the force per molecule,  $k$  is Boltzmann's constant ( $k = R/N_0$ ),  $T$  is the absolute temperature, and  $C$  is the concentration. In the presence of a concentration gradient, the total diffusive flux in the presence of an external force is

$$J = -\frac{D}{\partial x} \frac{\partial C}{\partial x} + \frac{Df}{kT} C$$

Stokes derived an equation for the drag force on a spherical object. Einstein combined this with his

expression for the drag force in terms of the diffusion constant and gave us the Stokes–Einstein equation:

$$D = \frac{kT}{6\pi\eta a_s}$$

where  $\eta$  is the viscosity of the medium in which diffusion occurs and  $a_s$  is the radius of a spherical solute.

## REVIEW QUESTIONS

1. Why is diffusive flux proportional to the negative of the gradient and not the gradient?
2. What are the assumptions of the random walk derivation?
3. What are the units of the diffusion coefficient?
4. How does the time of diffusion vary with distance?
5. Why are diffusion coefficients slower in the cytoplasm of cells than in water?
6. What is solvent drag?
7. What is meant by convective flow?
8. How does the diffusion coefficient vary with molecular size? With viscosity of the medium? With temperature? What is Boltzmann's constant?
9. How is Fick's First Law of Diffusion altered in the presence of additional forces acting on the diffusing particles?

## APPENDIX 1.6.A1 DERIVATION OF EINSTEIN'S FRICTIONAL COEFFICIENT FROM MOMENTUM TRANSFER IN SOLUTION

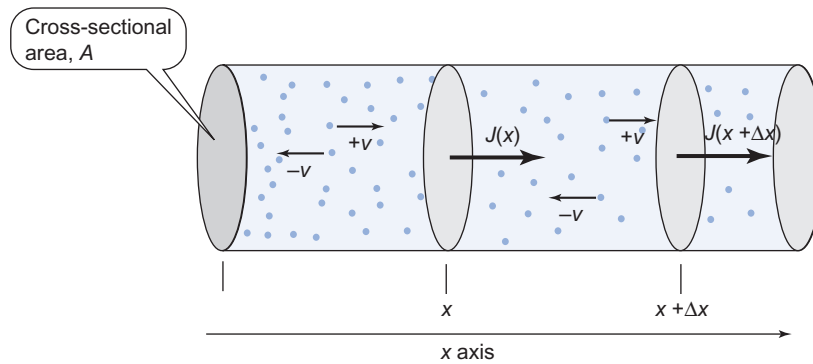
Here we consider a right cylindrical volume  $V$  of cross-sectional area  $A$  and thickness  $\Delta x$ , so that  $V = A\Delta x$ . We imagine that solute particles may move with velocity  $+v$  in the  $x$ -direction (to the right) and velocity  $-v$  (velocity  $v$  to the left), as shown in Figure 1.6.A1.1. Let the number of particles in  $V$  with velocity  $v$  be  $N_+(t)$  and the number with velocity  $-v$  be  $N_-(t)$ . The concentration of particles with velocity  $+v$  or  $-v$  in  $V$  at any time will be given by

$$\begin{aligned} \frac{N_+(t)}{V} &= C_+(t) \\ \frac{N_-(t)}{V} &= C_-(t) \end{aligned} \quad [1.6.A1.1]$$

The number of particles with a given velocity may change with time. This may happen in four different ways: (1) particles with velocity  $+v$  may enter the volume element from the left; (2) particles with velocity  $+v$  may leave the volume element at the right; (3) particles with velocity  $+v$  within the volume  $V$  may convert to particles with velocity  $-v$  by colliding with solvent particles; (4) particles with velocity  $-v$  could convert to velocity  $+v$  by collisions with solvent particles. The entry of particles from the left is given by

$$[1.6.A1.2] \quad Q_i(x) = v A C_+(x)$$





**FIGURE 1.6.A1.1** Solutes within a hypothetical volume. Solutes have a velocity  $+v$  in the positive  $x$ -direction or  $-v$  in the opposite direction. All particles have velocity  $+v$  or  $-v$ , although only a few are shown.

where we recognize that  $vC_+$  is the flux of particles with velocity  $+v$ . The exit of particles at the right is

$$[1.6.A1.3] \quad Q_o(x) = v A C_+(x + \Delta x)$$

The rate of conversion of  $N_+$  to  $N_-$  is proportional to  $N_+$  within the volume  $V$ , with the proportionality constant having dimensions of reciprocal time. This proportionality constant is  $1/t_c$ , where  $t_c$  is the time between collisions. This conversion reduces  $N_+$  within  $V$ , so we may write:

$$[1.6.A1.4] \quad \left( \frac{\partial N_+}{\partial t} \right)_{\text{-collision}} = -\frac{N_+}{t_c} = -\frac{V C_+}{t_c}$$

The rate of conversion of  $N_-$  to  $N_+$  adds to the value of  $N_+$  and is given by a similar expression:

$$[1.6.A1.5] \quad \left( \frac{\partial N_+}{\partial t} \right)_{\text{+collision}} = \frac{N_-}{t_c} = \frac{V C_-}{t_c}$$

The total net change of  $N_+$  is given by the sum of Eqns [1.6.A1.2, 1.6.A1.3, 1.6.A1.4, 1.6.A1.5]:

$$[1.6.A1.6] \quad \left( \frac{\partial N_+}{\partial t} \right) = vA C_+(x) - vA C_+(x + \Delta x) + \frac{V}{t_c} (C_- - C_+)$$

where  $v$  means velocity and  $V$  means volume. We can approximate  $C_+(x + \Delta x)$  by the first two terms of a Taylor's series expansion:

$$[1.6.A1.7] \quad C_+(x + \Delta x) = C_+(x) + \Delta x \left( \frac{\partial C_+}{\partial x} \right) + \dots$$

Insertion of Eqn [1.6.A1.7] into Eqn [1.6.A1.6] gives

$$[1.6.A1.8] \quad \begin{aligned} \left( \frac{\partial N_+}{\partial t} \right) &= vA \left[ C_+(x) - C_+(x) - \Delta x \left( \frac{\partial C_+}{\partial x} \right) \right] + \frac{V}{t_c} (C_- - C_+) \\ \left( \frac{\partial N_+}{\partial t} \right) &= -vA \Delta x \left( \frac{\partial C_+}{\partial x} \right) - \frac{V}{t_c} (C_+ - C_-) \end{aligned}$$

Since  $A\Delta x = V$ , we write

$$[1.6.A1.9] \quad \begin{aligned} \frac{1}{V} \frac{\partial N_+}{\partial t} &= -v \frac{\partial C_+}{\partial x} - \frac{1}{t_c} (C_+ - C_-) \\ \frac{\partial C_+}{\partial t} &= -v \frac{\partial C_+}{\partial x} - \frac{1}{t_c} (C_+ - C_-) \end{aligned}$$

By completely analogous reasoning, we can determine the rate of change in  $C_-$  in  $V$  as

$$[1.6.A1.10] \quad \frac{\partial C_-}{\partial t} = v \frac{\partial C_-}{\partial x} + \frac{1}{t_c} (C_+ - C_-)$$

Since the total concentration,  $C(x)$  is the sum of  $C_+$  and  $C_-$ , then

$$[1.6.A1.11] \quad \frac{\partial C(x)}{\partial t} = \frac{\partial C_+(x)}{\partial t} + \frac{\partial C_-(x)}{\partial t}$$

and substituting into Eqn [1.6.A1.11] from Eqns [1.6.A1.9] and [1.6.A1.10], we obtain

$$\begin{aligned} \frac{\partial C(x)}{\partial t} &= -v \frac{\partial C_+}{\partial x} - \frac{1}{t_c} (C_+ - C_-) + v \frac{\partial C_+}{\partial x} + \frac{1}{t_c} (C_+ - C_-) \\ &= -v \left( \frac{\partial C_+}{\partial x} - \frac{\partial C_-}{\partial x} \right) \\ &= -\frac{\partial (v(C_+ - C_-))}{\partial x} \end{aligned}$$

$$[1.6.A1.12]$$

Now the net flux across any area element within the volume  $V$  can be described as the difference between two unidirectional fluxes:

$$[1.6.A1.13] \quad \begin{aligned} J &= J_+ - J_- \\ &= v C_+ - v C_- \\ &= v (C_+ - C_-) \end{aligned}$$

Substitution of this relation into Eqn [1.6.A1.12] gives

$$[1.6.A1.14] \quad \frac{\partial C(x)}{\partial t} = -\frac{\partial J(x)}{\partial x}$$

which is the **continuity equation** we derived earlier (see Eqn [1.2.9]). The purpose of deriving the continuity equation in this way was to familiarize you with this method of accounting for all of the particles and to impress upon you that the collisions with the solvent involving changes in the velocity canceled. These collisions did not affect the total number of particles since a particle contributing to  $N_+$  before collision still contributes to  $N_-$  after collision.

Now let us consider what happens to the total momentum,  $P$ , of the particles in volume  $V$ . Let  $m$  be the mass of each solute particle. The total momentum of the particles is

$$[1.6.A1.15] \quad P = (mv)N_+ + (-mv)N_-$$

Because  $N_+$  and  $N_-$  change with time, so does  $P$ . We write

$$[1.6.A1.16] \quad \frac{\partial P}{\partial t} = mv \left( \frac{\partial N_+}{\partial t} \right) - mv \left( \frac{\partial N_-}{\partial t} \right)$$

Since  $N_+ = VC_+$  and  $N_- = VC_-$ , we have

$$[1.6.A1.17] \quad \frac{\partial P}{\partial t} = mvV \frac{\partial C_+}{\partial t} - mvV \frac{\partial C_-}{\partial t}$$

Inserting our earlier results from Eqns [1.6.A1.9] and [1.6.A1.10], we obtain

$$[1.6.A1.18] \quad \frac{1}{V} \frac{\partial P}{\partial t} = -mv^2 \left[ \frac{\partial C_+}{\partial x} + \frac{\partial C_-}{\partial x} \right] - \frac{2mv}{t_c} (C_+ - C_-)$$

Recalling that  $C = C_+ + C_-$ , and using Eqns [1.6.A1.11] and [1.6.A1.13], we obtain

$$[1.6.A1.19] \quad \frac{1}{V} \frac{\partial P}{\partial t} = -mv^2 \frac{\partial C}{\partial x} - \frac{2m}{t_c} J$$

The two terms on the right-hand side of Eqn [1.6.A1.19] have specific interpretations. The first term,  $-mv^2 \partial C / \partial x V$ , represents the net flow of momentum carried by particles with velocity  $+v$  or  $-v$ . The second term,  $-2m/t_c JV$ , is the average force exerted by the solvent particles on the solute particles. To see these interpretations, we write the flow of momentum across area  $A$  at any point  $x$  within the volume  $V$  as

$$[1.6.A1.20] \quad mv(vC_+(x))A + (-mv)(-vC_-(x))A = mv^2 (C_+(x) + C_-(x))A$$

The net flow of momentum into volume  $V$  across the boundaries between  $x$  and  $x + \Delta x$  is

$$[1.6.A1.21] \quad mv^2 (C_+(x) + C_-(x))A - mv^2 (C_+(x + \Delta x) + C_-(x + \Delta x))A$$

Since  $C(x) = C_+(x) + C_-(x)$ , the expression in Eqn [1.6.A1.21] becomes

$$[1.6.A1.22] \quad mv^2 A [C(x) - C(x + \Delta x)]$$

Expanding  $C(x + \Delta x)$  as  $C(x) + \Delta x \partial C / \partial x$ , the expression in Eqn [1.6.A1.22] becomes

$$[1.6.A1.23] \quad -mv^2 \frac{\partial C}{\partial x} \Delta x A = -mv^2 \frac{\partial C}{\partial x} V$$

Thus, in Eqn [1.6.A1.19],  $-mv^2 \partial C / \partial x$  is that part of  $1/V \partial P / \partial t$  which is due to the net momentum change of the particles in  $V$  due to what they carried into or out of the volume.

For the second term in Eqn [1.6.A1.19], note that every time a particle moving with velocity  $+v$  collides with a solvent obstacle, its velocity becomes  $-v$ , and thus it experiences a net momentum change of  $-2mv$ . The total number of such changes per unit time in the volume  $V$  is  $N_+/t_c$ . So the time-averaged change for the momentum change per unit time due to this collision is  $-2mv N_+/t_c$ . In a similar way, particles traveling with velocity  $-v$  experience a momentum change of  $+2mv$  upon collision with the solvent and the time-averaged total change in momentum per unit time for this type of collision in the volume  $V$  is  $+2mv N_-/V$ . The time-averaged rate of net change in momentum for these types of collisions is just their sum:

$$[1.6.A1.24] \quad \begin{aligned} \frac{\partial P_c}{\partial t} &= F_c = -2mv \frac{N_+}{t_c} + 2mv \frac{N_-}{t_c} \\ &= F_c = -\frac{2mv}{t_c} V (C_+ - C_-) \\ \frac{1}{V} \frac{\partial P_c}{\partial t} &= \frac{F_c}{V} = -\frac{2m}{t_c} J \end{aligned}$$

where the subscript  $c$  denotes that the momentum change and force are due to collisions of the solute molecules with the solvent. Thus the second term in Eqn [1.6.A1.19] is identified as the change in momentum produced by collisions with the solvent. It is equivalent to a force per unit volume exerted by the solvent particles on the solute particles. Equation [1.6.A1.24] can be rewritten as a differential equation in  $J(x, t)$ . Recall that the total momentum,  $P$ , of the solute particles in the volume  $V$  is given by Eqn [1.6.A1.15]; substituting in for the definition of the concentration (Eqn [1.6.A1.1] and  $J$ ) Eqn [1.6.A1.13]), we have:

$$[1.6.A1.25] \quad \begin{aligned} P &= (mv)N_+ + (-mv)N_- \\ &= mV v(C_+ - C_-) \\ P &= mV J(x, t) \end{aligned}$$

Insertion of this result into Eqn [1.6.A1.19] gives

$$[1.6.A1.26] \quad \frac{1}{V} mV \frac{\partial J(x, t)}{\partial t} = -mv^2 \frac{\partial C(x, t)}{\partial x} - \frac{2m}{t_c} J(x, t)$$

This can be rearranged to

$$[1.6.A1.27] \quad \frac{\partial J(x, t)}{\partial t} = \frac{2}{t_c} \left[ -\frac{t_c v^2}{2} \frac{\partial C(x, t)}{\partial x} - J(x, t) \right]$$

Eqn [1.6.A1.27] describes the buildup of  $J(x, t)$  in time. We will pay particular attention to the situation

where the concentration gradient,  $\partial C(x,t)/\partial x$ , is constant and steady-state flux is achieved. Steady-state flux means that  $\partial J(x,t)/\partial t = 0$ . That is, the flux no longer changes with time. Under these circumstances, by Eqn [1.6.A1.27], we obtain the steady-state flux as

$$[1.6.A1.28] \quad J = -\frac{t_c v^2}{2} \frac{\partial C}{\partial x}$$

Comparing this to Fick's First Law of Diffusion,

$$[1.6.A1.29] \quad J = -D \frac{\partial C}{\partial x}$$

we can identify

$$[1.6.A1.30] \quad D = \frac{t_c v^2}{2}$$

In the one-dimensional random walk model of diffusion, we defined the diffusion coefficient to be

$$[1.6.A1.31] \quad \begin{aligned} D &= \frac{\lambda^2}{2t_c} \\ &= \frac{(vt_c)^2}{2t_c} \\ &= \frac{t_c v^2}{2} \end{aligned}$$

Thus the derivation performed here is completely consistent with the random walk model of diffusion. Eqn [1.6.A1.24] describes the momentum change of the solute particles that result from the collisions with solvent. It is given per unit volume as

$$[1.6.A1.32] \quad \frac{1}{V} \frac{\partial P_c}{\partial t} = \frac{F_c}{V} = -\frac{2m}{t_c} J$$

In this equation,  $F_c$  is the force per unit volume on the solute particles. This is the same as the drag force on the solute particles when they move through the solution. If we imagine that the particles are subjected to a uniform external force, then the particles will accelerate until they reach a terminal velocity,  $v$ . The force  $F_c$  will be the sum of all of the drag forces on the particles within the volume, which is the drag force per particle times the number of particles in the volume. The flux,  $J$ , will be given as  $vC$ . Eqn [1.6.A1.32] can then be rewritten as

$$[1.6.A1.33] \quad \frac{f_c N}{V} = -\frac{2m}{t_c} vC$$

where  $f_c$  is the force on a single particle,  $N$  is the number of particles in the volume,  $V$ ,  $v$  is the terminal velocity, and  $C$  is the concentration. Since  $N/V = C$ , the equation is further simplified to

$$[1.6.A1.34] \quad f_c = -\frac{2m}{t_c} v$$

Here the force  $f_c$  is equal to the **drag force** on the particle traveling at velocity  $v$ , and the coefficient is the drag or **frictional coefficient**:

$$[1.6.A1.35] \quad F_D = -\beta v$$

which allows us to identify the drag coefficient as

$$[1.6.A1.36] \quad \beta = \frac{2m}{t_c}$$

The **equipartition theorem** of thermodynamics gives

$$[1.6.A1.37] \quad \begin{aligned} \frac{1}{2} m v^2 &= \frac{1}{2} kT \\ v^2 &= \frac{kT}{m} \end{aligned}$$

where  $k$  is **Boltzmann's constant** ( $= 1.38 \times 10^{-23} \text{ J K}^{-1}$ , which is equal to the gas constant,  $R$ , divided by Avogadro's number). Insertion of this result into the equation for the diffusion coefficient, Eqn [1.6.A1.31] gives

$$[1.6.A1.38] \quad \begin{aligned} D &= \frac{t_c kT}{2m} \\ t_c &= \frac{2mD}{kT} \end{aligned}$$

Insertion of this into Eqn [1.6.A1.36] gives

$$[1.6.A1.39] \quad \beta = \frac{2m}{t_c} = \frac{2m}{\frac{2mD}{kT}} = \frac{kT}{D}$$

This is Einstein's frictional coefficient, given as

$$[1.6.A1.39] \quad \beta = \frac{kT}{D}$$

Recall Eqn [1.6.A1.19] reproduced here:

$$[1.6.A1.19] \quad \frac{1}{V} \frac{\partial P}{\partial t} = -mv^2 \frac{\partial C}{\partial x} - \frac{2m}{t_c} J$$

substituting in  $v^2 = kT/m$  from Eqn [1.6.A1.37] and  $t_c = 2mD/kT$  from Eqn [1.6.A1.38], we obtain

$$[1.6.A1.40] \quad \frac{1}{V} \frac{\partial P}{\partial t} = -kT \frac{\partial C}{\partial x} - \frac{kT}{D} J$$

Recall that this equation describes the rate of momentum change of the **solute** per unit volume  $V$ . It has two components: the first is the net momentum carried into the volume by the diffusing solutes, and the second is the momentum change produced upon collisions with the solvent. Note that if  $C(x)$  is decreasing with increasing  $x$  then the gradient,  $\partial C/\partial x$ , will be negative and the first term on the right-hand side of Eqn [1.6.A1.40] will be positive. In this case of diffusion of solute towards increasing values of  $x$ ,  $J$  will be positive and the second term, denoting the change in momentum by collisions with solvent, will be negative. This second term denotes the drag of solvent on solute movement. Steady-state diffusion occurs when  $\partial P/\partial t$  is zero and  $\partial C/\partial x$  is constant. Under these conditions, Eqn [1.6.A1.40] becomes Fick's First Law of Diffusion.

Suppose now that we add an additional force to the solute particles in the volume  $V$ . Let the force acting on each particle be  $f$ . In the volume element, there are

$N(x) = C(x) V$  particles. The total force acting on these particles is  $f C(x) V$ . This force clearly contributes to the rate of change of the momentum of the solute particles in the volume. Eqn [1.6.A1.40] becomes

$$[1.6.A1.41] \quad \frac{1}{V} \frac{\partial P}{\partial t} = -kT \frac{\partial C}{\partial x} - \frac{kT}{D} J + fC$$

To recapitulate, the first term on the right-hand side of Eqn [1.6.A1.41] represents the rate of momentum change by particles entering or leaving the volume  $V$ ; the second term is due to collisions with the solvent particles; the third term is due to the action of some

external force. At steady state,  $\partial J / \partial t = 0$ , and this implies by Eqn [1.6.A1.25] that  $\partial P / \partial t$  also is zero. Under this constraint, Eqn [1.6.A1.41] gives

$$[1.6.A1.42] \quad J = -D \frac{\partial C}{\partial x} + \frac{D}{kT} fC$$

This is Fick's First Law of Diffusion for solutes subjected to an external force, which is Eqn [1.6.42]. Thus this equation, which forms the basis of the derivation of the electrochemical potential, can be derived using momentum transfer of solutes in a solution and the equipartition theorem of thermodynamics.