# 6

# Random Movements in Space and Time

## Introduction

Many biological phenomena, at all levels of organization, can be modeled by treating them as random processes, behaving much like the diffusion of ink in a container of water. In this chapter, we discuss some biological aspects of random processes, namely, the movement of oxygen across a human placenta. While these processes might seem to be quite different at first glance, they actually act according to very similar models.

We begin with a description of biological membranes, structures that regulate the movement of material into, out of, and within the functional compartments of a cell. At the core of a membrane is a layer of water-repelling molecules. This layer has the effect of restricting the free transmembrane movement of any substance that is water soluble, although water itself can get past the layer. The transmembrane movement of the normal water-soluble compounds of cellular metabolism is regulated by large biochemical molecules that span the membrane. They are called *permeases*, or *transport proteins*. Permeases have the ability to select the materials that cross a membrane. Other membranes anchor critical cellular components that promote chemical reactions through catalysis.

A human fetus requires oxygen for its metabolic needs. This oxygen is obtained from its mother, who breathes it and transfers it via her blood to the placenta, an organ that serves as the maternal–fetal interface. Because the blood of mother and child do not mix, material exchange between them must take place across a group of membranes. The chemical that transports the oxygen is hemoglobin, of which there are at least two kinds, each exhibiting a different strength of attachment to oxygen molecules. Further, chemical conditions around the hemoglobin also affect its attachment to oxygen. The conditions at the placenta are such that there is a net transmembrane movement of oxygen from maternal hemoglobin to fetal hemoglobin.

This chapter also serves as an introduction to the discussions of the blood vascular system of Chapter 9, of biomolecular structure of Chapter 8, and of HIV in Chapter 10.

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## 6.1 Biological Membranes

*Biological membranes do much more than physically separate the interior of cells from the outside world. They provide organisms with control over the substances that enter, leave, and move around their cells. This is accomplished by selective molecules that can recognize certain smaller molecules whose transmembrane movement is required by the cell. A waterproof layer in the membrane otherwise restricts the movement of these smaller compounds. In addition, membranes maintain compartments inside a cell, allowing the formation of specific chemical environments in which specialized reactions can take place.*

*The molecular structure of a substance determines its solubility in water.*

Distinctions between oil and water are everywhere. We have all seen how salad oil forms spherical globules when it is mixed with watery vinegar. Likewise, we say that two hostile people "get along like oil and water.'' On the other hand, a drop of ink or food coloring dissolves immediately in a glass of water. These experiences seem to suggest that all materials are either water soluble or not. This is an oversimplification: ethyl alcohol is infinitely soluble in water (gin is about half alcohol, half water), but isopropanol (rubbing alcohol), table salt, and table sugar all have moderate water-solubility. Salt and sugar have very low solubility in gasoline and benzene (erstwhile dry-cleaning fluid). On the other hand, benzene will easily dissolve in gasoline and in fatty substances.

The electronic basis for water-solubility will be described in Chapter 8, but for now it is sufficient that we recognize that the ability of a substance to dissolve in water is determined by its electronic structure. Further, an appropriate structure is found in ions (like sodium and chlorine from salt) and in molecules with oxygen and nitrogen atoms (like sugars and ammonia). Such substances are said to be *hydrophilic*, or *polar*. Hydrophilic structures are not found in electrically neutral atoms, nor in most molecules lacking oxygen and nitrogen. This is especially true when the latter molecules have a very high proportion of carbon and hydrogen (e.g., benzene, gasoline and fatty substances). These latter materials are said to be *hydrophobic*, or *nonpolar*.

*Both faces of a membrane are attracted to water, but the interior of the membrane repels water.*

The biological world is water based.[1] Therefore, cells face a bit of a problem in that water is a major component of the external world, which could lead to too much interaction between a cell's contents and its environment. To deal with this problem, cells are surrounded by a water-proofing, or hydrophobic, membrane layer. We should be glad for this structural feature of our bodies—it keeps us from dissolving in the shower!

[1] Our bodies must resort to special tricks to solubilize fats that we eat. Our livers produce a detergent-like substance, called bile, that allows water to get close to the fats. The hydrocarbon-metabolizing microorganisms that are useful in dealing with oil spills often use similar methods.

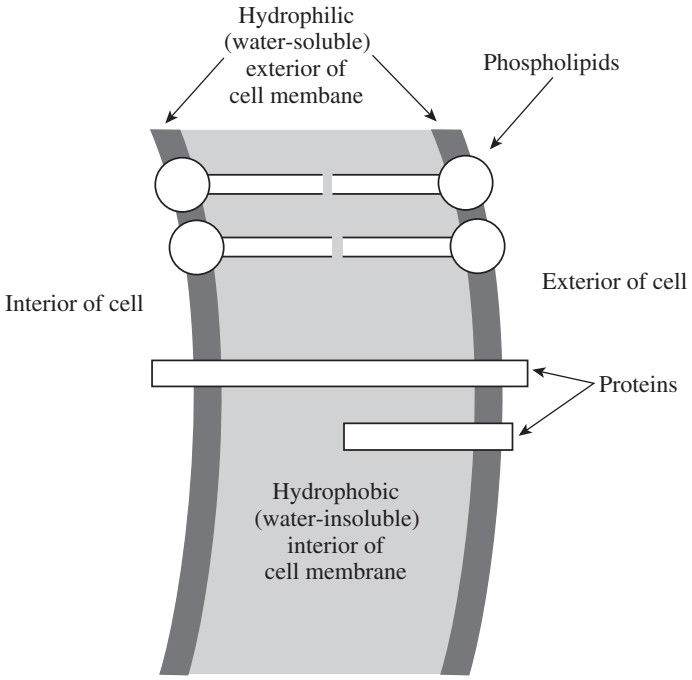


**Fig. 6.1.1.** A model of a cell membrane, showing the hydrocarbon (hydrophobic, water-insoluble) interior and hydrophilic (water-soluble) exterior of the membrane. This dual nature of the membrane is the result of the orientation of many phospholipid molecules, only four of which are actually shown in the figure. Figure 8.2.5 will show how the chemical nature of a phospholipid leads to hydrophobic and hydrophilic parts of the membrane. Two proteins in the figure are also shown to demonstrate that some span the membrane completely and others only pierce the outside halfway through (on either side of the membrane).

Figure 6.1.1 shows a model of a cell membrane. The side facing the cellular interior is hydrophilic because it must interact with the cell's internal environment; the outside is also hydrophilic because it interacts with the external world.[2] The interior of the membrane, however, is strongly hydrophobic, being a kind of *hydrocarbon* (constructed from hydrogen and carbon only). This arrangement is thermodynamically favorable because there are no direct interactions between hydrophilic and hydrophobic groups.[3] Attached to, and sometimes piercing, the membrane are complicated biological molecules called proteins, which will be described in more detail in Chapter 8.

No material can enter or leave the cell unless it negotiates its way past this membrane, because the membrane completely envelope the cell. Clearly, the efficiency

[2] It might be easiest here to picture a single-celled organism in a pond.

[3] The arrangement of molecules in the membrane of Figure 6.1.1 is called a *bilayer* because it consists of two leaflets of molecules, arranged back to back.

of transmembrane movement of a substance will be determined by the ability of the substance to interact with the membrane's components, especially the interior, hydrophobic, layer of the membrane.

*Only a few kinds of substances can diffuse freely across the hydrophobic layer of a membrane.*

The substances that can move across the hydrophobic layer in response to a concentration gradient fall into two groups. The first group, surprisingly, contains water and carbon dioxide, a fact that seems contrary to our earlier discussion. What seems to happen is that water and $CO_2$ molecules are small enough that they can slip past the large hydrocarbon fragments in the membrane. A nice demonstration of this is seen by placing human red blood cells into distilled water. The interior of the cell contains materials that cannot go through the membrane, so the water there is at a *lower* concentration than in the surroundings. Thus water moves into the cell and eventually bursts it like a balloon. This movement of water (or any other solvent) is called *osmosis*.

The second kind of material that easily passes through the membrane hydrocarbon layer is a hydrocarbon. Of course, our cells are almost never exposed to hydrocarbons, so this material is of little interest. We will, however, point out in Chapter 9 that one route of lead into our bodies is through our skin: if we spill leaded gasoline on ourselves, the hydrocarbons of the gasoline can carry the lead right across our hydrophobic membrane barriers and into our bloodstream.

*Selective channels control the passive and active movements of ions and large molecules across membranes.*

Many relatively large hydrophilic particles, such as ions and sugars, can pass through membranes—after all, these particles are essential components of cellular systems. They do not move directly through the bulk of the membrane. Rather, their movement is regulated by large proteins that completely penetrate the membrane and act like specialized channels, choosing which substances get past the membrane (see Figure 6.1.1). These proteins are called *permeases*, or *transport proteins*, and they are very selective: The substitution of a single atom in a transportable molecule with molecular weight of several hundred can cause the molecule to be excluded by its normal permease. Permeases thus act like selective gates to control material transport into and out of a cell.

Materials can move across membranes via permeases by two different mechanisms, both often called *facilitated transport*. First, the *passive* movement of a material in response to a concentration gradient (diffusion) is usually facilitated by permeases. The point is that only those substances recognized by a permease will behave in this way. Any other substances will diffuse up to the membrane and then be stopped by the hydrophobic layer of the membrane.

Second, many materials are pumped *against* a concentration gradient past a membrane. This process, called *active transport*, requires energy because it is in the oppo-

site direction to the usual spontaneous movement of particles. Active transport also requires a facilitating permease.

Facilitated transport is discussed further in Chapter 8, in the text by Beck et al. [1], and in the reference by Yeargers [2].

*Some cellular membranes face the outside world and regulate intercellular material movement.*

The day-to-day processes that a cell must perform require that nutrients and oxygen move into the cell and that wastes and carbon dioxide move out. In other words, the cell must maintain constant, intimate communication with its external environment. The cell membrane provides the interface between the cell and the outside world, and membrane permeases, because of their selectivity, control the transmembrane movement of most of the substances whose intercellular transport is required.

What about water? It moves across membranes irrespective of permeases and would therefore seem to be uncontrollable. In fact, cells can regulate water movement, albeit by indirect means. They accomplish this by regulating other substances and that, in turn, affects water. For example, a cell might pump sodium ions across a membrane to a high concentration. Water molecules will then follow the sodium ions across the membrane by simple osmosis, to dilute the sodium.

*Some cellular membranes are inside the cell and regulate intracellular material movements.*

Students are sometimes surprised to learn that the interior of a cell, exclusive of the nucleus, is a labyrinth of membranes. A mechanical analogue can be obtained by combining some confetti and a sheet of paper, crumpling up the whole mess into a wad, and then stuffing it into a paper bag. The analogy cannot be pushed too far; membranes inside the cell often have very regular structures, lying in parallel sheets or forming globular structures (like the nucleus). In short, the interior of a cell is a very complicated place.

Many thousands of different biochemical reactions occur in a mammalian cell. If these reactions were not coordinated in space and time the result would be chaos. Membranes provide coordinating mechanisms in several ways: First, large biochemical molecules are always assembled stepwise, beginning with small structures and ending up with large ones. Each of the fragments to be added must be close to the nascent biomolecule so that it can be added at the right time. Intracellular membranes provide compartmentalization to keep the reactants and products of related reactions in close proximity to one another. Second, the efficiencies of different cellular biochemical reactions are dependent on environmental conditions, e.g., pH and salt concentration. The specialized environmental needs of each reaction, or set of reactions, are maintained by membrane compartmentalization. Thus a cell is partitioned into many small chambers, each with a special set of chemical conditions. A third point, related to the first two, is that virtually all chemical reactions in a cell are catalyzed by special proteins, and these catalysts often work only when they are attached to a membrane. Refer back to Figure 6.1.1 and note that many of the proteins

do not pierce the membrane, but rather are attached to one side or the other. These proteins represent several of the membrane-bound protein catalysts of a cell. You will read more about these catalysts in Chapter 8.

*Large objects move into and out of a cell by special means.*

Neither simple diffusion nor facilitated transport can move particulate objects such as cellular debris, food, bacteria, and viruses into or out of a cell; those require completely different routes. If a cell is capable of amoeboid movement, it can surround the particle with *pseudopods* and draw it in by *phagocytosis*. If the cell is not amoeboid, it can form small pockets in its surface to enclose the particle; this process is *pinocytosis*, as shown in Figure 6.1.2. Both phagocytosis and pinocytosis can be reversed to rid the cell of particulate waste matter.

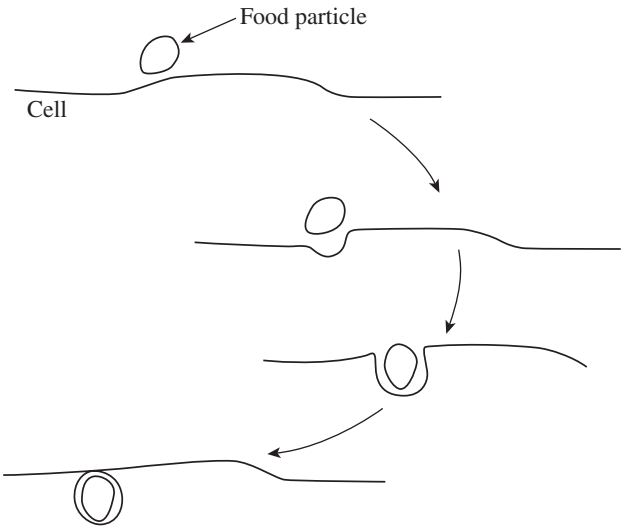


**Fig. 6.1.2.** A schematic diagram showing the process of pinocytosis. A small indentation forms at the particle's point of contact, and the particle is then drawn into the cell's interior.

## 6.2 The Mathematics of Diffusion

*In this section, we derive Fick's laws of diffusion by studying a random walk model. Using the normal approximation to the binomial distribution, we obtain the Gaussian solution of the diffusion equation for a point-source concentration. It is seen that particles disperse on average in proportion to the square root of time.*

*Fick's laws are applied to investigate one aspect of diffusion through biological membranes. It is shown that the rate of mass transport is proportional to the concentration difference across the membrane and inversely proportional to the thickness of the membrane.*

*Random processes in the biosphere play a major role in life.*

In Section 6.1, we described the membrane system that surrounds and pervades a cell. In this section, we show how the random motion of substances can carry materials across these membranes and through the bulk of a cell.

Chance plays a major role in the processes of life. On the microscopic scale, molecules are in constant random motion corresponding to their temperature. Consequently, chance guides the fundamental chemistry of life. On a larger scale, genes mutate and recombine by random processes. Thus chance is a fundamental component of evolution. Macroscopically, unpredictable events such as intraspecies encounter lead to matings or maybe the transmission of disease, which interspecies encounter claims many a prey victim, but not with certainty. The weather can affect living things throughout an entire region and even an entire continent. And on a truly grand scale, random astronomical impacts can cause mass extinction.

*Diffusion can be modeled as a random walk.*

Molecules are in a constant state of motion as a consequence of their temperature. According to the kinetic theory of matter, there is a fundamental relationship between molecular motion and temperature, which is simplified by measuring the latter on an absolute scale, degrees Kelvin. Zero degrees Kelvin, or absolute zero, is $-273.15°$C. Moreover, Albert Einstein showed in 1905 that the principle extends to particles of any size, for instance, to pollen grains suspended in water. Einstein's revelation explained an observation made in 1828 by the Scottish botanist Robert Brown, who reported on seeing a jittery, undirected motion of pollen grains in the water of his microscope plate. We now refer to this phenomenon as *Brownian motion*. It is a visible form of diffusion.

The relationship between temperature and particle motion can be precisely stated: *The average kinetic energy of a particle along a given axis is* $\frac{kT}{2}$, where $T$ is in degrees Kelvin and $k$ is the *universal Boltzmann's constant*, $k = 1.38 \times 10^{-16}$ ergs per degree [4]. The principle is stated in terms of the *time average* of a single particle, but we will assume that it applies equally well to the average of an ensemble or collection of identical particles taken at the same time, the *ensemble average*.

The kinetic energy of an object of mass $m$ and velocity $v$ is $\frac{1}{2}mv^2$. And so the average kinetic energy of $N$ particles of the same mass $m$ but possibly different velocities is

$$\frac{\overline{mv^2}}{2} = \frac{\frac{\sum_{i=1}^{N} mv_i^2}{2}}{N} = \frac{m}{2N}\sum_{i=1}^{N} v_i^2 = \frac{m\overline{v^2}}{2}.$$

In this we have used an overline to denote average ensemble value.

Therefore, for a collection of particles of mass $m$, the kinetic theory gives

$$\frac{\overline{mv^2}}{2} = \frac{kT}{2},$$

or

**Table 6.2.1.** Root mean square (RMS) velocities at body temperature.

| Molecule | Molecular weight | Mass (g) | RMS speed at 36°C (m/sec) |
|---|---|---|---|
| $H_2O$ | 18 | $3 \times 10^{-26}$ | 652 |
| $O_2$ | 32 | $5.4 \times 10^{-26}$ | 487 |
| glucose | 180 | $3 \times 10^{-25}$ | 200 |
| lysozyme | 1,400 | $2.4 \times 10^{-23}$ | 23 |
| hemoglobin | 65,000 | $1 \times 10^{-22}$ | 11 |
| bacteriophage | $6.2 \times 10^6$ | $1 \times 10^{-20}$ | 1.1 |
| *E. coli* | $\approx 2.9 \times 10^{11}$ | $2 \times 10^{-15}$ | 0.0025 |

$$\overline{v^2} = \frac{kT}{m}. \tag{6.2.1}$$

Table 6.2.1 gives the average thermal velocity of some biological molecules at body temperature predicted by this equation.

A particle does not go very far at these speeds before undergoing a collision with another particle or the walls of its container and careers off in some new direction. With a new direction and velocity, the process begins anew, destined to undergo the same fate. With all the collisions and rebounds, the particle executes what can be described as a random walk through space. To analyze this process, we model it by stripping away as much unnecessary complication as possible while still retaining the essence of the phenomenon.

For simplicity, assume that time is divided into discrete periods $\Delta t$ and in each such period a particle moves one step $\Delta x$ to the left or right along a line, the choice being random. After $n$ time periods the particle lies somewhere in the interval from $-n(\Delta x)$ to $n(\Delta x)$ relative to its starting point, taken as the origin 0.

For example, suppose that $n = 4$. If all four choices are to the left, the particle will be at $-4$; if three are left and one right, it will be at $-2$. The other possible outcomes are 0, 2, and 4. Notice the outcomes are separated by two steps. Also notice that there are several ways most of the outcomes can arise, the outcome 2, for instance. We can see this as follows. Let $R$ denote a step right and $L$ a step left. Then a path of four steps can be coded as a string of four choices of the symbols $R$ or $L$. For example, $LRRR$ means that the first step is to the left and the next three are to the right. For an outcome of four steps to be a net two to the right, three steps must be taken to the right and one to the left, but the order does not matter. There are four possibilities that do it; they are $LRRR$, $RLRR$, $RRLR$, and $RRRL$.

In general, let $p(m, n)$ denote the probability that the particle is at position $x = m(\Delta x)$, $m$ steps right of the origin, after $n$ time periods, $t = n(\Delta t)$. We wish to calculate $p(m, n)$. It will help to recognize that our random walk with $n$ steps is something like tossing $n$ coins. For every coin that shows heads, we step right, and for tails we step left. Let $r$ be the number of steps taken to the right and $l$ the number of steps taken to the left; then to be at position $m(\Delta x)$, it must be that their difference is $m$:

$$m = r - l, \quad \text{where } n = r + l.$$

Thus $r$ can be given in terms of $m$ and $n$ by adding these two equations, and $l$ is given by subtracting:

$$r = \frac{1}{2}(n + m) \quad \text{and} \quad l = \frac{1}{2}(n - m). \tag{6.2.2}$$

As in a coin toss experiment, the number of ways of selecting $r$ moves to the right out of $n$ possibilities is the problem of counting combinations and is given by (see Section 2.8)

$$C(n, r) = \frac{n!}{r!(n - r)!}.$$

For example, three moves right out of four possible moves can happen in $\frac{4!}{3!1!} = 4$ ways, in agreement with the explicitly written-out $L\ R$ possibilities noted above. Therefore, if the probabilities of going left and going right are equal, then

$$p(m, n) = \text{probability of } r \text{ steps right} = \frac{C(n, r)}{2^n}, \quad r = \frac{1}{2}(n + m). \tag{6.2.3}$$

This is the *binomial* distribution with $p = q = \frac{1}{2}$. The solid curve in Figure 6.2.1 is a graph of $p(m, 40)$. If the random walk experiment with $n = 40$ steps is conducted a large number of times, then a histogram of the resulting particle positions will closely approximate this figure. This histogram is also shown in Figure 6.2.1. Equivalently, the same picture pertains to the fate of a large number of particles randomly walking at the *same* time, each taking 40 steps, provided they may slide right past each other without collisions.

*Particles disperse in proportion to the square root of time.*

The average, or *mean*, position, $\overline{m}$, of a large number of particles after a random walk

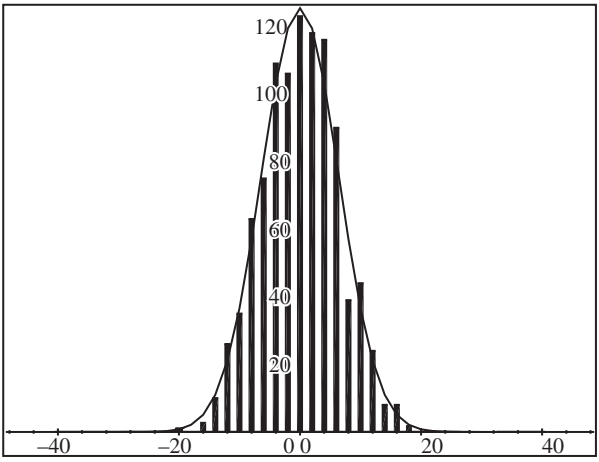


**Fig. 6.2.1.** Graph of $p(m, 40)$.

of $n$ steps with equal probabilities of stepping left or right is 0. To show this, start with (6.2.2) to get $m = 2r - n$. Then since $r$ has a binomial distribution, we can write down its mean and variance from Section 2.8. Equations (2.8.12) and (2.8.13) with $p = \frac{1}{2}$ and $q = 1 - p = \frac{1}{2}$ give

$$\begin{aligned} \overline{r} &= np = \frac{n}{2}, \\ \operatorname{var}(r) &= \overline{(r - \overline{r})^2} = npq = \frac{n}{4}. \end{aligned} \tag{6.2.4}$$

Hence

$$\overline{m} = \overline{2r - n} = 2\overline{r} - \overline{n} = 2\frac{n}{2} - n = 0,$$

since the average value of the constant $n$ is $n$. Unfortunately, knowing that the average displacement of particles is 0 does not help in expressing how quickly particles are moving away from the origin. The negative values of those that have moved to the left cancel the positive values of those that have gone right.

We can avoid the left vs. right cancellation by using the squares of displacements; we will get thereby the *mean square* displacement, $\overline{m^2}$. Since the mean position is 0, the mean square displacement is equal to the variance here; hence from (6.2.4),

$$\overline{m^2} = \overline{(m - \overline{m})^2} = \overline{(2r - n)^2} = 4\overline{\left(r - \frac{n}{2}\right)^2} = 4\frac{n}{4} = n.$$

Since $m = \frac{x}{\Delta x}$ and $n = \frac{t}{\Delta t}$, we can convert this into statements about $x$ and $t$:

$$\overline{x^2} = \frac{\Delta x^2}{\Delta t} t. \tag{6.2.5}$$

But mean square displacement is not a position, a distance from 0. For one thing, it is measured in square units, $\mathrm{cm}^2$. To rectify this, the square root of mean square displacement, or *root mean square* (*RMS*) displacement, is used to quantify dispersion; taking the square root of the above, we get

$$\sqrt{\overline{m^2}} = \sqrt{n}$$

and

$$\sqrt{\overline{x^2}} = \sqrt{\frac{\Delta x^2}{\Delta t}} \sqrt{t}. \tag{6.2.6}$$

Hence particles disperse in proportion to the square root of time. Thus there is no concept of velocity for diffusion. For the average particle to traverse a distance twice as far requires four times as much time.

The exact equation for $p(m, n)$, (6.2.3), has a simple approximation. There is a real need for such an approximation because it is difficult to compute the combinatorial

factor $C(n, r)$ for large values of $n$. Moreover, the approximation improves with an error that tends to 0 as $n \to \infty$. The binomial distribution (see (6.2.3) and Figure 6.2.1) looks very much like that of a normal distribution, as discussed in Chapter 2. Although *Stirling's formula* for approximating $n!$,

$$n! \approx \sqrt{2\pi n} n^n e^{-n},$$

may be used to prove it, we will not do this. Instead, we will match the means and standard deviations of the two distributions. First, recall that the probability that a normally distributed observation will fall within an interval of width $dm$ centered at $m$ is approximately (see Section 2.8)

$$\frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(m-\mu)^2}{2\sigma^2}} dm,$$

where $\mu$ is the mean and $\sigma$ is the standard deviation of the distribution. On the other hand, $p(m, n)$ is the probability the walk will end between $m-1$ and $m+1$, an interval of width 2, and from above, its mean is 0 and standard deviation is $\sqrt{n}$. Hence

$$p(m, n) \approx \frac{1}{\sqrt{2\pi n}} e^{-\frac{m^2}{2n}}(2) \approx \sqrt{\frac{2}{\pi n}} e^{-\frac{m^2}{2n}}. \tag{6.2.7}$$

Our last refinement is to let $\Delta x$ and $\Delta t$ tend to 0 to obtain a continuous version of $p(m, n)$. Of course, without care, $p(m, n)$ will approach zero too because the probability will spread out over more and more values of $m$. But since each value of $m$ corresponds to a probability over a width of $2\Delta x$, we take the quotient of $p(m, n)$ by this width. That is, let $u(x, t)$ denote the probability that the particle lies in an interval of width $2(\Delta x)$ centered at $x$ at time $t$. Then

$$u(x, t) = \frac{P\left(\frac{x}{\Delta x}, \frac{t}{\Delta t}\right)}{2(\Delta x)} = \frac{1}{2(\Delta x)} \sqrt{\frac{2}{\pi\left(\frac{t}{\Delta t}\right)}} e^{-\frac{\left(\frac{x}{\Delta x}\right)^2}{2\left(\frac{t}{\Delta t}\right)}}.$$

And upon simplification,[4]

$$u(x, t) = \frac{e^{-\left(\frac{x^2}{4\left(\frac{\Delta x^2}{2\Delta t}\right)t}\right)}}{\sqrt{4\pi\left(\frac{\Delta x^2}{2(\Delta t)}\right)t}}.$$

Now keeping the ratio

$$D = \frac{\Delta x^2}{2(\Delta t)} \tag{6.2.8}$$

[4] For more on this and an alternative derivation, see C. W. Gardiner, *Handbook of Stochastic Methods*, Springer-Verlag, Berlin, 1983.

fixed as $\Delta x$ and $\Delta t$ tend to 0, we obtain the Gaussian distribution

$$u(x,t) = \frac{e^{-\frac{x^2}{4Dt}}}{\sqrt{4\pi Dt}}. \tag{6.2.9}$$

The parameter $D$ is called the *diffusion coefficient* or *diffusivity* and has units of area divided by time. Diffusivity depends on the solute, the solvent, and the temperature, among other things. See Table 6.2.2 for some pertinent values.

**Table 6.2.2.** Diffusion coefficients in solution.

| | | | | Seconds to cross | |
|---|---|---|---|---|---|
| **Molecule** | **Solvent** | **T, °C** | $D$ **($10^{-6}$ cm$^2$/sec)** | **0.01 mm** | **1 mm** |
| $O_2$ | blood | 20 | 10.0 | 0.05 | 500 |
| acetic acid | water | 25 | 12.9 | 0.04 | 387 |
| ethanol | water | 25 | 12.4 | 0.04 | 403 |
| glucose | water | 25 | 6.7 | 0.07 | 746 |
| glycine | water | 25 | 10.5 | 0.05 | 476 |
| sucrose | water | 25 | 5.2 | 0.10 | 961 |
| urea | water | 25 | 13.8 | 0.04 | 362 |
| ribonuclease | water | 20 | 1.07 | 0.46 | 4671 |
| fibrinogen | water | 20 | 2.0 | 0.25 | 2500 |
| myosin | water | 20 | 1.1 | 0.45 | 4545 |

Diffusivity quantifies how rapidly particles diffuse through a medium. In fact, from (6.2.6), the rate at which particles wander through the medium in terms of root mean square distance is

$$\text{RMS distance} = \sqrt{\frac{\Delta x^2}{\Delta t}t} = \sqrt{2Dt}. \tag{6.2.10}$$

In Table 6.2.2, we give some times required for particles to diffuse the given distances. As seen, the times involved become prohibitively long for distances over 1 mm. This explains why organisms whose oxygen transport is limited to diffusion cannot grow very large in size.

The function $u$ has been derived as the probability for the ending point, after time $t$, of the random walk for a single particle. But as noted above, it applies equally well to an ensemble of particles if we assume that they "walk" independently of each other. In terms of a large number of particles, $u$ describes their concentration as a function of time and position. Starting them all at the origin corresponds to an infinite concentration at that point, for which (6.2.9) does not apply. However, for any positive time, $u(x,t)$ describes the concentration profile (in number of particles per unit length); see Figure 6.2.2 for the times 1, 2, 4. Evidently, diffusion transports particles from regions of high concentration to places of low concentration. Fick's first law, derived below, makes this precise.

```
MAPLE
> plot({exp(-x^2/4)/sqrt(4*Pi), exp(-x^2/(4*2))/sqrt(4*Pi*2), exp(-x^2/(4*4))/sqrt(4*Pi*4)},
      x=-10..10,color=BLACK);

MATLAB
  % make an m-file, gaussian.m containing
  % function y=gaussian(x,m,s); % m=mean, s=stddev
  % note 1/sqrt(2*pi) = .3989422803
  % y=(.3989422803/s)*exp(-0.5*((x-m)./s).^2);
> x=[-10:.1:10]; y=gaussian(x,0,1);
> plot(x,y); hold on;
> y=gaussian(x,0,2); plot(x,y);
> y=gaussian(x,0,4); plot(x,y);
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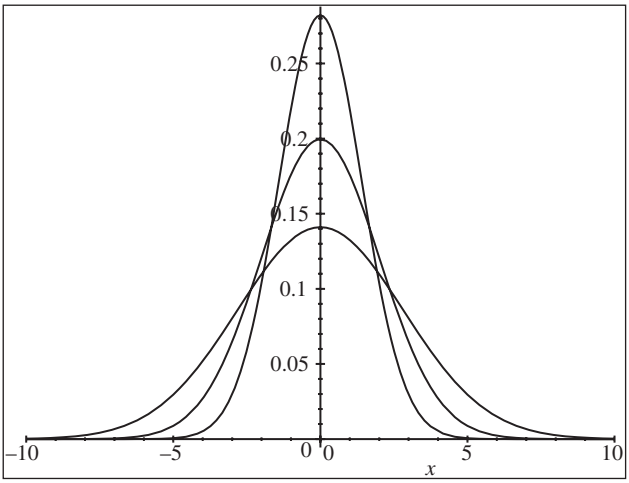


**Fig. 6.2.2.** Dispersion of a unit mass after time 1, 2, and 4.

To treat diffusion in three dimensions, it is postulated that the random walk proceeds independently in each dimension. Hence the mean transport in the $x$, $y$, and $z$ directions is each given by (6.2.10), $\overline{x^2} = 2Dt$, $\overline{y^2} = 2Dt$, and $\overline{z^2} = 2Dt$. In two dimensions, if $r^2 = x^2 + y^2$, then

$$\overline{r^2} = 4Dt,$$

and in three dimensions, if $r^2 = x^2 + y^2 + z^2$, we get

$$\overline{r^2} = 6Dt.$$

*Fick's laws describe diffusion quantitatively.*

Again consider a one-dimensional random walk, but now in three-dimensional space, for example, along a channel of cross-sectional area $A$; see Figure 6.2.3.

Let $N(x)$ denote the number of particles at position $x$. We calculate the net movement of particles across an imaginary plane perpendicular to the channel between

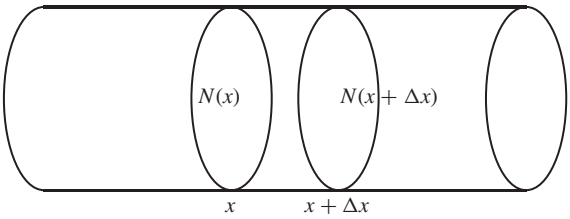


**Fig. 6.2.3.** One-dimensional diffusion along a channel.

$x$ and $x + \Delta x$. In fact, half the particles at $x$ will step to the right and cross the plane, and half the particles at $x + \Delta x$ will step to the left and cross the plane in the reverse direction. The net movement of particles from left to right is

$$-\frac{1}{2}(N(x + \Delta x) - N(x)). \tag{6.2.11}$$

At this point, we introduce the notion of the *flux* of particles, denoted by $J$. This is the net number of particles crossing a unit area in a unit time and is measured in units of moles per square centimeter per second for instance. Hence dividing (6.2.11) by $A\Delta t$ gives the flux in the $x$ direction,

$$J_x = -\frac{1}{2A\Delta t}(N(x + \Delta x) - N(x)).$$

Let $c(x)$ denote the concentration of particles at $x$ in units of number of particles per unit volume such as moles per liter. Since $c(x) = \frac{N(x)}{A\Delta x}$, the previous equation becomes

$$J_x = -\frac{\Delta x}{2\Delta t}(c(x + \Delta x) - c(x)) = -\frac{\Delta x^2}{2\Delta t}\frac{c(x + \Delta x) - c(x)}{\Delta x}.$$

Now let $\Delta x \to 0$ and recall the definition of diffusivity, (6.2.8); we get *Fick's first law*:

$$J = -D\frac{\partial c}{\partial x}. \tag{6.2.12}$$

A partial derivative is used here because $c$ can vary with time as well as location. The sign is negative because the flow of particles is from high concentration to low, i.e., if the concentration increases from left to right, then the flow is from right to left. Multiply (6.2.12) by $A$. and we have

$$\text{net number of particles crossing area } A \text{ per unit time} = -DA\frac{\partial c}{\partial x}. \tag{6.2.13}$$

To obtain Fick's second law, consider the channel again. The number of particles $N(x)$ in the section running from $x$ to $x + \Delta x$ is $c(x, t)A\Delta x$. If concentration is not constant, then particles will diffuse into (or out of) this section according to Fick's first law:

$$\text{the decrease in the number of particles in the section}$$
$$= (\text{the flux out at } x + \Delta x - \text{the flux in at } x)A.$$

More precisely,

$$-\frac{\partial}{\partial t}(c(x,t)A\Delta x) = (J(x+\Delta x,t) - J(x,t))A.$$

Dividing by $\Delta x$ and letting $\Delta x \to 0$ gives

$$-A\frac{\partial c}{\partial t} = A\frac{\partial J}{\partial x}.$$

Canceling the $A$ on each side, we obtain the *continuity equation*,

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x}. \tag{6.2.14}$$

Differentiating $J$ in Fick's first law and substituting into this gives *Fick's second law* of diffusion, also known as the *diffusion equation*,

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}. \tag{6.2.15}$$

Direct substitution shows that the Gaussian distribution $u$, (6.2.9), satisfies the diffusion equation.

*Oxygen transfer by diffusion alone limits organisms in size to about one-half millimeter.*

As an application of Fick's laws, we may calculate how large an organism can be if it has no circulatory system. Measurements taken for many organisms show that the rate of oxygen consumption by biological tissues is on the order of $R_{O_2} = 0.3$ microliters of $O_2$ per gram of tissue per second. Also note that the concentration of oxygen in water at physiological temperatures is 7 microliters of $O_2$ per $cm^3$ of water. Assuming an organism of spherical shape, balancing the rate of oxygen diffusion through the surface with that consumed by interior tissue, we get, using Fick's first law, (6.2.12),

$$AJ = DA\frac{dc}{dr} = VR_{O_2},$$
$$D(4\pi r^2)\frac{dc}{dr} = \frac{4}{3}\pi r^3 R_{O_2}.$$

Isolate $\frac{dc}{dr}$ and integrate; use the boundary condition that at the center of the sphere the oxygen concentration is zero, and at the surface of the sphere, where $r = r_m$, the concentration is $C_{O_2}$. We get

$$\frac{dc}{dr} = \frac{R_{O_2}}{3D}r,$$

$$\int_0^{C_{O_2}} dc = \int_0^{r_m} \frac{R_{O_2}}{3D} r\,dr,$$
$$C_{O_2} = \frac{R_{O_2}}{6D} r_m^2.$$

Using the values for $C_{O_2}$ and $R_{O_2}$ above and the value $2 \times 10^{-5}$ cm/sec for a typical value of $D$, we get

$$\begin{aligned} r_m^2 &= \frac{6DC_{O_2}}{R_{O_2}} \\ &= \frac{6 \times 2 \times 10^{-5}(\text{cm}^2/\text{sec}) \times 7(\mu\text{l}/\text{cm}^3)}{0.3(\mu\text{l}/(\text{gm} \times \text{sec})} \\ &= 0.0028(\text{cm}^2), \end{aligned}$$

where we have assumed that one gram of tissue is about 1 $\text{cm}^3$ water. Taking the square root gives the result

$$r_m = 0.53 \text{ mm}.$$

We will use this value in Chapter 9 as a limitation on the size of certain organisms.

*Resistance to fluid flow is inversely proportional to the fourth power of the radius of the vessel.*

From the discussion above, it is clear that large organisms must actively move oxygen to the site of its use, possibly dissolved in a fluid. In this section, we derive the equation governing resistance to flow imposed by the walls of the vessel through which the fluid passes. In Chapter 9, we will discuss the anatomical and physiological consequences of this resistance to flow.

As a fluid flows through a circular vessel, say of radius $a$, resistance to the flow originates at the walls of the vessel. In fact, at the wall itself, the fluid velocity $u(a)$ is barely perceptible; thus $u(a) = 0$. A little further in from the wall the velocity picks up, and at the center of the vessel the velocity is largest. By radial symmetry, we need only one parameter to describe the velocity profile, namely, the radius $r$ from the center of the vessel. The fluid travels downstream in the form of concentric cylinders, the cylinders nearer the center moving fastest. This results in a shearing effect between the fluid at radius $r$ and the fluid just a little farther out, at radius $r + \delta r$. Shear stress, $\tau$, is defined as the force required to make two sheets of fluid slide past each other, divided by their contact area. It is easy to imagine that the shear stress depends on the difference in velocity of the two sheets, and, in fact, the two quantities are proportional.

Consider a portion of the vessel of length $\ell$ and let $\Delta p$ denote the difference in fluid pressure over this length. This pressure, acting on the cylinder of fluid of radius $r$, is opposed by the shear stress mentioned above. The force on the cylinder is being applied by the difference in pressure acting on its end; thus

$$\text{force} = \Delta p \pi r^2,$$

while the equal opposing force is due to the shear stress acting on the circular side of the cylinder,

$$\text{force} = \tau(2\pi r\ell) = \mu\frac{du}{dr}(2\pi r\ell).$$

Since these forces are equal and opposite,

$$\Delta p\pi r^2 = -\mu\frac{du}{dr}(2\pi r\ell).$$

This simple differential equation can be solved by integrating to obtain

$$u = -\frac{r^2\Delta p}{4\ell\mu} + C,$$

where $C$ is the constant of integration. Using the zero velocity condition at the vessel walls gives the value of $C$ to be

$$C = \frac{a^2\Delta p}{4\ell\mu}.$$

Hence for any radius, the velocity is given by

$$u(r) = \frac{\Delta p}{4\ell\mu}(a^2 - r^2).$$

We see that the velocity profile is parabolic (see Figure 6.2.4).

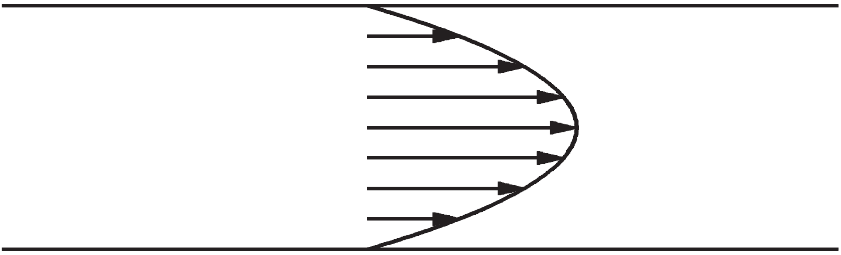

**Fig. 6.2.4.** Parabolic velocity profile of flow in a tube.

Now we can calculate the total flow rate, $Q$, of a volume of fluid through a cross-section of the vessel per unit time. Since a thin ring of fluid all of whose molecules are at the same distance $r$ from the axis of the vessel moves as a unit (see Figure 6.2.5), we consider all these molecules together. The volume of fluid per unit time that passes through a given cross-section of the vessel arising from such a ring, $dQ$, is given as the product of its velocity $u(r)$ and its area $dS$,

$$dQ = u(r)dS = u(r)(2\pi r)dr.$$

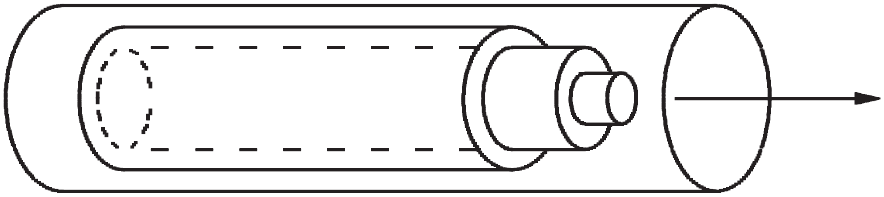

**Fig. 6.2.5.** Circular sheet of fluid all of whose molecules are moving together.

Substituting the velocity profile from above and integrating gives

$$\begin{aligned} Q &= \int_0^a \frac{\Delta p}{4\ell\mu}(a^2 - r^2)2\pi r\,dr \\ &= \frac{\pi\Delta p}{2\ell\mu}\left[\frac{a^2r^2}{2} - \frac{r^4}{4}\right]_0^a \\ &= \frac{\pi\Delta p a^4}{8\mu\ell}. \end{aligned} \tag{6.2.16}$$

This expression is known as *Poiseuille's equation*. It shows that the flow rate increases as the fourth power of the vessel radius. It means that a vessel of twice the radius can carry 16 times the fluid volume for the same pressure drop per unit length.

It is natural to think of the shear stress in the moving fluid due to its contact with the walls as a *resistance* to flow. Fluid resistance $R$ is defined as $R = \frac{\Delta p}{Q}$ and hence is given by

$$R = \frac{8\mu\ell}{\pi a^4}. \tag{6.2.17}$$

It is seen that the fluid resistance is inversely proportional to the fourth power of the radius. We will note in Chapter 9 that this dependence affects the size of vertebrates' hearts.

A biological membrane is a complicated structure, as explained in Section 6.1, and we will take account of some of the details of the structure in the next section. In this section, we want to illustrate the decay of transient phenomena, in the form of startup effects, in diffusion. Further, while crude, this slab approximation shares with real membrane diffusion its dependence on the concentration difference to the first power as the driving force behind the transport of solute particles.

By a slab we mean a solid homogeneous material throughout which the diffusivity of solute particles is $D$. The slab has thickness $h$ but is infinite in its other two dimensions, and so diffusion through it takes place one-dimensionally.

To complete the statement of the problem, additional information, referred to as *boundary conditions* or *initial conditions*, must be specified. We will assume that the concentrations of solute on the sides of the slab are maintained at the constant values of $C_0$ at $x = 0$ and $C_h$ at $x = h$; assume that $C_0 > C_h$:

$$c(0, t) = C_0, \qquad c(h, t) = C_h \quad \text{for all } t \geq 0.$$

This could happen if the solvent reservoirs on either side of the slab were so large that the transport of solute is negligible. Or it could happen if solute particles are whisked away as soon as they appear at $x = h$ or are immediately replenished at $x = 0$ as they plunge into the slab. Or, of course, any combination of these. Further, we assume the startup condition that the concentration in the slab is 0:

$$c(x, 0) = 0, \quad 0 \le x \le h.$$

We begin by assuming that the solution, $c(x, t)$, can be written in the form of a product of a function of $x$ only with a function of $t$ only:

$$c(x, t) = X(x)T(t).$$

Then $\frac{\partial c}{\partial t} = X(x)T'(t)$ and $\frac{\partial^2 c}{\partial x^2} = X''(x)T(t)$. Substituting into the diffusion equation, (6.2.15), and dividing, we get

$$\frac{1}{T}dT\,dt = \frac{D}{X}\frac{d^2X}{dx^2}. \tag{6.2.18}$$

Now the left-hand side of this equation is a function of $t$ only and the right-hand side is a function of $x$ only, and the equality is maintained over all values of $x$ and $t$. This is possible only if both are equal to a constant, which we may write as $-\lambda^2 D$. Then (6.2.18) yields the two equations

$$\frac{1}{T}\frac{dT}{dt} = -\lambda^2 D \tag{6.2.19}$$

and

$$\frac{1}{X}\frac{d^2X}{dx^2} = -\lambda^2. \tag{6.2.20}$$

It is easy to verify that the solution of (6.2.19) is

$$T = Ae^{-\lambda^2 Dt},$$

and the solution of (6.2.20) is

$$X = \begin{cases} ax + b & \text{if } \lambda = 0, \\ c \sin \lambda x + d \cos \lambda x & \text{if } \lambda \neq 0, \end{cases}$$

where $A$, $a$, $b$, $c$, and $d$ are constants.

The solution so far is

$$c(x, t) = \begin{cases} ax + b & \text{if } \lambda = 0, \\ (c \sin \lambda x + d \cos \lambda x)e^{-\lambda^2 Dt} & \text{if } \lambda \neq 0. \end{cases}$$

The constant $A$ has been absorbed into the other constants, all of which have yet to be determined using the boundary conditions. For $\lambda = 0$, the conditions on either side of the slab give

$$a0 + b = C_0 \quad \text{and} \quad ah + b = C_h.$$

Hence it must be that $b = C_0$ and $a = -\frac{C_0 - C_h}{h}$. But this solution cannot satisfy the initial condition, we will use the $\lambda \neq 0$ case for that.

First, note that if two functions $c_1(x, t)$ and $c_2(x, t)$ both satisfy the diffusion equation, then so does their sum, as follows:

$$\frac{\partial(c_1 + c_2)}{\partial t} = \frac{\partial c_1}{\partial t} + \frac{\partial c_2}{\partial t}$$

and

$$-D\frac{\partial^2(c_1 + c_2)}{\partial x^2} = -D\frac{\partial^2 c_1}{\partial x^2} - D\frac{\partial^2 c_2}{\partial x^2}.$$

And so

$$\frac{\partial(c_1 + c_2)}{\partial t} = -D\frac{\partial^2(c_1 + c_2)}{\partial x^2}.$$

In particular, the sum of the $\lambda = 0$ and $\lambda \neq 0$ solutions,

$$c(x, t) = -\frac{C_0 - C_h}{h}x + C_0 + (c \sin \lambda x + d \cos \lambda x)e^{-\lambda^2 Dt}, \tag{6.2.21}$$

will satisfy the diffusion equation. It remains to satisfy the boundary conditions.

At $x = 0$ in (6.2.21),

$$C_0 = -\frac{C_0 - C_h}{h}0 + C_0 + (c \sin \lambda 0 + d \cos \lambda 0)e^{-\lambda^2 Dt}.$$

Upon simplifying, this becomes

$$0 = de^{-\lambda^2 Dt},$$

which must be valid for all $t$; thus $d = 0$. Continuing with the $x = h$ boundary condition in (6.2.21), we have

$$C_h = -\frac{C_0 - C_h}{h}h + C_0 + (c \sin \lambda h)e^{-\lambda^2 Dt},$$

or

$$0 = (c \sin \lambda h)e^{-\lambda^2 Dt}.$$

As before, this must hold for all $t \geq 0$. We cannot take $c = 0$, for then the initial condition cannot be satisfied. Instead, we solve $\sin \lambda h = 0$ for $\lambda$, which is as yet unspecified. The permissible values of $\lambda$ are

$$\lambda = \frac{\pm n\pi}{h}, \quad n = 1, 2, \ldots, \tag{6.2.22}$$

known as the *eigenvalues* of the problem. The negative values of $n$ may be absorbed into the positive ones, since $\sin \lambda_{-n} x = -\sin \lambda_n x$. Remembering that solutions of the diffusion equation may be added, we can form an infinite series solution with a term for each eigenvalue, and, possibly, each with a different coefficient, $c_n$,

$$c(x, t) = -\frac{C_0 - C_h}{h} x + C_0 + \sum_{n=1}^{\infty} (c_n \sin \lambda_n x) e^{-\lambda_n^2 Dt}. \tag{6.2.23}$$

Finally, in order to fulfill the initial condition, the coefficients $c_n$ must be chosen to satisfy the initial condition

$$c(x, 0) = 0 = -\frac{C_0 - C_h}{h} x + C_0 + \sum_{n=1}^{\infty} (c_n \sin \lambda_n x) e^{-\lambda_n D0},$$

or upon simplifying,

$$\sum_{n=1}^{\infty} c_n \sin \lambda_n x = \frac{C_0 - C_h}{h} x - C_0.$$

We will not show how to calculate the $c_n$s; we note only that it can be done [7]. The infinite series is referred to as the *Fourier series* representation of the function on the right.

Thus the solution occurs in two parts; in one part, every term contains the decaying exponential $e^{-\lambda_n Dt}$ for constants $\lambda_n$ given above. These terms tend to zero and, in time, become negligible. That leaves the *steady-state* part of the solution,

$$c(x, t) = -\frac{C_0 - C_h}{h} x + C_0,$$

a linear concentration gradient. The amount of solute delivered in the steady state is the flux given by Fick's first law,

$$J = -D \frac{\partial c}{\partial x} = \frac{D}{h} (C_0 - C_h). \tag{6.2.24}$$

In summary, the rate of material crossing a membrane is directly proportional to the concentration difference and inversely proportional to the thickness of the membrane.

*Membrane diffusion decays exponentially as particles accumulate.*

The structure of cell membranes was described in Section 6.1. It consists of a double layer of lipid molecules studded with proteins. Some of the latter penetrate entirely through the lipid bilayer and serve to mediate the movement of various substances into and out of the cell's interior. This section is not about the transport of such substances. Rather, we describe the transport of those molecules that pass through the lipid bilayer itself by diffusion. These are mainly lipid-soluble molecules.[5]

However, the membrane molecules themselves have two ends: a hydrophilic head and lipid tail. Functionally, the head end of one layer faces outward in contact with the aqueous environment of the cell, while the head end of the other layer faces inward in contact with the aqueous interior of the cell. The lipid tails of both layers face together and constitute the interior of the membrane. Thus the concentration of solute just under the head of the membrane molecule is not necessarily the same as in the aqueous phase. Denote by $C'$ the solute concentration just inside the membrane on the environmental side, and by $c'$ the concentration just inside the membrane on the cell interior side. As we saw in the derivation of Fick's first law, (6.2.12), the flux of solute through the lipid part of the membrane is proportional to the concentration difference and inversely proportional to the separation distance, so we have

$$J = \frac{D}{h}(C' - c').$$

We next assume a linear relation between the concentrations across the molecular head of the membrane molecule; thus

$$C' = \Gamma C \quad \text{and} \quad c' = \Gamma c,$$

where $C$ is the environmental concentration of the solute and $c$ is the concentration inside the cell. The constant $\Gamma$ is called the *partition coefficient*. With this model, the partition coefficient acts as a diffusivity divided by thickness ratio for the diffusion of solute across the head of the membrane molecule. The partition coefficient is less than 1 for most substances, but can be greater than 1 if the solute is more soluble in lipid than in water.

Combining the development above, we calculate flux in terms of exterior and interior concentrations as

$$J = \frac{\Gamma D}{h}(C - c); \tag{6.2.25}$$

this is in moles/cm$^2$/sec, for instance.

As solute molecules accumulate inside the cell, the concentration difference in (6.2.25) diminishes, eventually shutting off the transport. Denote the volume of the cell by $V$ and the surface area by $S$. The quantity $SJ$ is the rate of mass transport across the membrane in moles/sec, that is,

[5] In Section 6.1, we noted that water and carbon dioxide, although polar molecules, can move through the lipid part of a membrane.

$$SJ = \frac{dm}{dt} = V\frac{dc}{dt},$$

since concentration is mass per unit volume. Therefore, multiplying (6.2.25) by $S$ and using this relation, we get

$$V\frac{dc}{dt} = \frac{S\Gamma D}{h}(C - c),$$

or

$$\frac{dc}{dt} = k(C - c),$$

where $k = \frac{S\Gamma D}{Vh}$ is a constant. The solution, given by integration, is

$$c = C - c_0 e^{-kt},$$

where $c_0$ is the initial concentration inside the membrane. In summary, the interior concentration becomes exponentially asymptotic to that of the environment.

### Exercises/Experiments

**1.** Instead of presenting a theoretical distribution of the position of particles after 40 steps, we simulate the random movement using the built-in random number generator of the computer system. Simulate a random walk of 40 steps for each of 500 particles and histogram the place they end up.

MAPLE

```
> with(stats): with(plots):
> for i from 1 to 100 do
    count[i]:=0; od: # initialize a counter
> N:=rand(0..1): #random integer 0/1
> particles:=500; steps:=40;
> for m from 1 to particles do
  place:=sum('2*N(p)-1','p'=1..steps)+steps:
  count[place]:=count[place]+1: # record endpt
  od:
  # histogram the endpoints
> ranges:=[seq(-steps/2+2*(i-1)..-steps/2+2*i,i=1..steps/2)];
> movement:=[seq(count[20+2*j],j=1..20)];
> diffusion:=[seq(Weight(ranges[i],movement[i]),i=1..20)];
> statplots[histogram](diffusion);
```

MATLAB

```
> particles=500; steps=40;
> for k=1:particles
    steplog=fix(2*rand(1,steps)); % random vectors of 0s/1s
    steplog = 2*steplog-1; % random vectors of -1/+1
    place(k) = sum(steplog); % endpt for this 40 step walk
  end
> x=-20:2:20;
> hist(place,x)
```

(a) Plot the Gaussian distribution of (6.2.9) with $D = 1$ and for $t = 1, 2$, and 3.

```
MAPLE
> plot({exp(-x^2/4)/sqrt(4*Pi), exp(-x^2/(4*2))/sqrt(4*Pi*2), exp(-x^2/(4*3))/sqrt(4*Pi*3)},x=-10..10);
```

```
MATLAB
% Equation (6.2.9) is the gaussian with mean = 0 and stddev = sqrt(2Dt).
% Therefore make an m-file gaussian.m (already done in Section 2.6, repeated here):
% function y=gaussian(x,m,s); y=(.3989422803/s)*exp(-0.5*((x-m)./s).^2);
% Part (a)
> D=1; t=1; s=sqrt(2*D*t);
> x=[-10:.1:10]; y=gaussian(x,0,s);
> plot(x,y); hold on;
> D=1; t=2; s=sqrt(2*D*t);
> y=gaussian(x,0,s); plot(x,y);
> D=1; t=3; s=sqrt(2*D*t);
> y=gaussian(x,0,s); plot(x,y);
```

(b) Verify that (6.2.9) satisfies the partial differential equation (6.2.15) with $D = 1$.

```
MAPLE (symbolic)
> u:=(t,x)->exp(-x^2/(4*t))/sqrt(4*Pi*t);
> diff(u(t,x),t)-diff(u(t,x),x,x);
> simplify(%);
```

(c) The analogue of (6.2.15) for diffusion in a plane is

```
MAPLE (symbolic)
> diff(U(t,x,y),t) = diff(U(t,x,y),x,x)+diff(U(t,x,y),y,y);
```

Show that the function $U$ given below satisfies this two-dimensional diffusion equation:

```
MAPLE (symbolic)
> U:=(t,x,y)->exp(-(x^2+y^2)/(4*t))/t;
> diff(U(t,x,y),t) - diff(U(t,x,y),x,x)-diff(U(t,x,y),y,y);
> simplify(%);
```

(d) Give visualization to these two diffusions by animation of (6.2.9) and of the two-dimensional diffusion.

```
MAPLE (animation)
> plot({exp(-x^2/4)/sqrt(4*Pi),exp(-x^2 /(4*2))/sqrt(4*Pi*2), exp(-x^2/(4*3))/sqrt(4*Pi*3)},x=-10..10);
> with(plots):
> animate(exp(-x^2/(4*t))/sqrt(4*Pi*t),x=-10..10,t=0.1..5);
> animate3d(exp(-(x^2+y^2)/ (4*t))/t,x=-1..1,y=-1..1,t=0.1..0.5);
```

**2.** A moment's reflection on the form of (6.2.15) suggests a geometric understanding. The left side is the rate of change in time of $c(t, x)$. The equation asserts that this rate of change is proportional to the curvature of the function $c(t, x)$ as a graph in $x$ and as measured by the second derivative. That is, if the second derivative in $x$ is positive and the curve is concave up, expect $c(t, x)$ to increase in time. If the second derivative is negative and the curve is concave down, expect $c(t, x)$ to decrease in time. We illustrate this with a single function. Note that the function $\sin(x)$ is concave down on $[0, \pi]$ and concave up on $[\pi, 2\pi]$. We produce a function such that with $t = 0$, $c(0, x) = \sin(x)$, and for arbitrary $t$, $c(t, x)$ satisfies (6.2.15).

```
> MAPLE (symbolic)
> c:=(t,x)->exp(-t)*sin(x);
```

Here we verify that this is a solution of (6.2.15).

```
> MAPLE (symbolic)
> diff(c(t,x),t)-diff(c(t,x),x,x);
```

Now we animate the graph. Observe where $c(t, x)$ is increasing and where it is decreasing.

```
> MAPLE (animation)
> with(plots): animate(c(t,x),x=0..2*Pi,t=0..2);
```

## 6.3 Transplacental Transfer of Oxygen: Biological and Biochemical Considerations

*A fetus must obtain oxygen from its mother. Oxygen in the mother's blood is attached to a blood pigment called hemoglobin and is carried to the placenta, where it diffuses across a system of membranes to the fetus's hemoglobin. A number of physical factors cause the fetal hemoglobin to bind the* $O_2$ *more securely than does the maternal, or adult, hemoglobin, thus ensuring a net* $O_2$ *movement from mother to fetus.*

*The blood of a mother and her unborn child do not normally mix.*

The circulatory systems of a mother and her unborn child face one another across a platelike organ called the *placenta*. The placenta has a maternal side and a fetal side, each side being fed by an artery and drained by a large vein, the two vessels being connected by a dense network of fine capillaries. The two sides of the placenta are separated by membranes, and the blood of the mother and that of the child do not mix. All material exchange between mother and child is regulated by these placental membranes, which can pass ions and small-to-medium biochemical molecules. Large molecules, however, do not usually transit the placental membranes.

*Hemoglobin carries oxygen in blood.*

The chemical hemoglobin is found in anucleate cells called red blood cells or *erythrocytes*. Hemoglobin picks up $O_2$ at the mother's lungs and takes it to the placenta, where the $O_2$ crosses the placenta to the hemoglobin of fetal red blood cells for distribution to metabolizing fetal tissues.

*Oxygen affinity measures the strength with which hemoglobin binds oxygen.*

A fixed amount of hemoglobin can hold a fixed maximum amount of oxygen, at which point the hemoglobin is said to be saturated. Figure 6.3.1 is an *oxygen dissociation curve*; it shows the extent to which saturation is approached as determined by the *partial pressure* of the oxygen.[6] The partial pressure of $O_2$ at which the hemoglobin is half-saturated is a measure of the *oxygen affinity* of the hemoglobin. Thus hemoglobin that reaches half-saturation at low $O_2$ partial pressure has a high oxygen affinity (see [1] and [3] for further discussion).

[6] The partial pressure of a gas is the pressure exerted by that specific gas in a mixture of gases. The partial pressure is proportional to the concentration of the gas. The total pressure exerted by the gaseous mixture is the sum of the partial pressures of the various constituent gases.

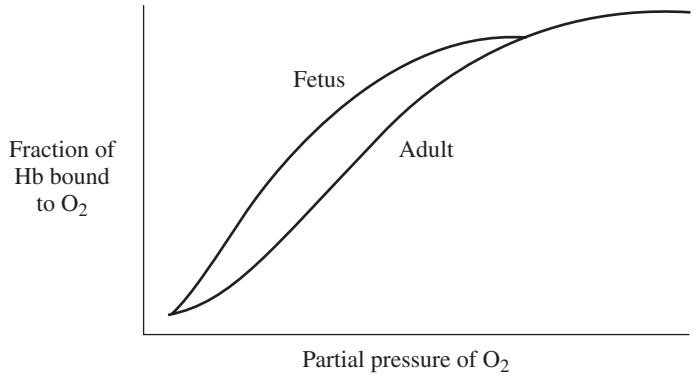


**Fig. 6.3.1.** Oxygen dissociation curves for adult and fetal hemoglobin. Note that for a given partial pressure (concentration) of oxygen, the fetal hemoglobin has a greater fraction of its hemoglobin bound to oxygen than does the adult hemoglobin.

The reversible attachment of $O_2$ to hemoglobin is represented by

$$\underset{\text{hemoglobin}}{\text{Hb}} + \text{O}_2 \rightleftharpoons \underset{\text{oxyhemoglobin}}{\text{O}_2\text{–Hb}} .$$

At equilibrium the relative amounts of hemoglobin and oxyhemoglobin are fixed, the reaction going to the right as often as it goes to the left. The relative amounts of oxyhemoglobin, hemoglobin, and oxygen at equilibrium are determined by the oxygen affinity of the hemoglobin. The greater the oxygen affinity, the more oxyhemoglobin there will be relative to the amounts of hemoglobin and oxygen, i.e., the more the equilibrium will move toward the right in the above reaction scheme.

*Oxygen affinity depends on a variety of factors.*

In practice, the oxygen affinity is determined by multiple factors: First, we would surely expect that the structure of hemoglobin would be important, and that will be discussed below. Second, oxygen affinity is affected by the extent to which oxygen molecules are already attached. Hemoglobin can bind to as many as four $O_2$ molecules. The second, third, and fourth are progressively easier to attach because the oxygen affinity of the hemoglobin increases as more $O_2$ molecules are added. Third, blood pH affects its oxygen affinity. The pH of the blood and the presence of $CO_2$ are related; this will be discussed in Section 9.6. Finally, a chemical constituent of red blood cells, called D-2, 3-*biphosphoglycerate* (*BPG*), plays an important role in the oxygen-binding properties of hemoglobin by binding to it and thereby decreasing its $O_2$ affinity. The role of BPG is a crucial one because the more BPG is bound to hemoglobin, the less tightly the hemoglobin binds oxygen. Therefore, the oxygen will be released more easily and will be provided to metabolizing tissues in higher concentration. In terms of the chemical reaction above, BPG moves the equilibrium toward the left.

*Fetal hemoglobin has a greater affinity for oxygen than does adult hemoglobin.*

Adult and fetal hemoglobins have somewhat different structures. The result is that fetal hemoglobin binds less BPG than does adult hemoglobin, and therefore fetal hemoglobin has the higher oxygen affinity of the two. Figure 6.3.1 shows oxygen dissociation curves for the hemoglobin of an adult and for that of a fetus. Note that at a given partial pressure of $O_2$, the fetal hemoglobin has a greater $O_2$ affinity than does maternal hemoglobin. Thus there is a net movement of oxygen from the mother to the fetus.

We must be very careful here: We must not think that the fetal hemoglobin somehow drags $O_2$ away from that of the mother. This would require some sort of "magnetism" on the part of the fetal hemoglobin, and such "magnetism" does not exist. What does happen is represented by the following diagram:

$$\begin{array}{ccc} O_2\text{–}Hb_{adult} & \rightleftharpoons & O_2 + Hb_{adult} \\ \cdots\cdots\cdots\cdots\cdots & \uparrow\downarrow & \cdots\cdots \text{placenta} \\ & O_2 + Hb_{fetal} & \rightleftharpoons \quad O_2\text{–}Hb_{fetal}. \end{array}$$

Both kinds of hemoglobin are constantly attaching to, and detaching from, oxygen—consistent with their oxygen affinities. The mother's breathing gives her blood a high concentration of oxyhemoglobin, and that leads to a high concentration of *free oxygen* on her side of the placenta. On the fetal side of the placenta, the fetus, which does not breathe, has a low $O_2$ concentration. Therefore, $O_2$, once released from maternal oxyhemoglobin, moves by simple diffusion across the placenta, in response to the concentration gradient. On the fetal side, fetal hemoglobin attaches to the oxygen and holds it tightly because of its high oxygen affinity. Some oxygen will dissociate from the fetal hemoglobin, but little will diffuse back to the maternal side because the concentration gradient of the oxygen across the placenta is in the other direction.[7] In summary, oxygen diffuses across the placenta from mother to fetus, where it tends to stay because of its concentration gradient and the high oxygen affinity of fetal hemoglobin compared with that of adult hemoglobin.

## 6.4 Oxygen Diffusion Across the Placenta: Physical Considerations

*The delivery of fetal oxygen typifies the function of the placenta. In this organ, fetal blood flow approaches maternal blood flow, but the two are separated by membranes. Possible mechanisms for oxygen transfer are simple diffusion, diffusion facilitated by some carrier substance, or active transport requiring metabolic energy. No evidence for facilitated diffusion or active transport has been found. We will see that simple diffusion can account for the required fetal oxygen consumption.*

[7] In Chapter 9, we will see that the concentration of $CO_2$ in the blood also affects the oxygen affinity of hemoglobin.

*The oxygen dissociation curve is sigmoid in shape.*

Oxygen in blood exists in one of two forms, either dissolved in the plasma or bound to hemoglobin as oxyhemoglobin. Only the dissolved oxygen diffuses; oxyhemoglobin is carried by the moving red blood cells. The binding of oxygen to hemoglobin depends mostly on $O_2$ partial pressure but also on blood acidity. The relationship, given by a dissociation curve, possesses a characteristic sigmoid shape as a function of partial pressure (see Figure 6.4.1 and Table 6.4.1).

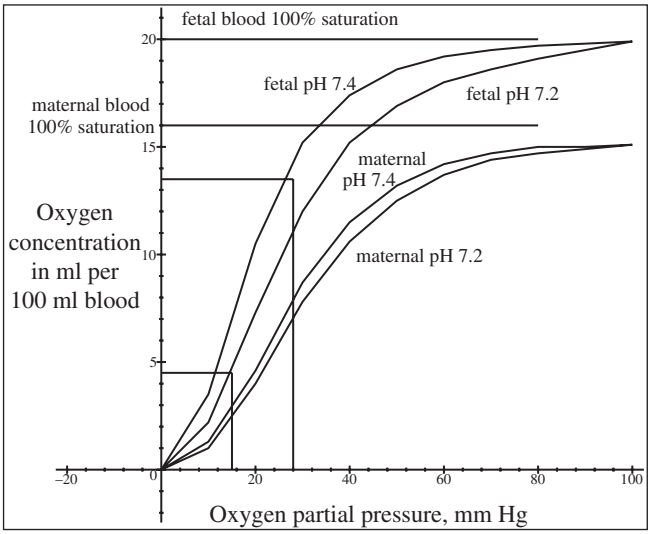


**Fig. 6.4.1.** $O_2$ concentration in ml per 100 ml blood.

**Table 6.4.1.** $O_2$ concentration in ml per 100 ml blood (see [16]).

| **$pO_2$ mm Hg ⟶** | **10** | **20** | **30** | **40** | **50** | **60** | **70** | **80** | **90** | **100** |
|---|---|---|---|---|---|---|---|---|---|---|
| fetal (pH 7.4) | 3.5 | 10.5 | 15.2 | 17.4 | 18.6 | 19.2 | 19.5 | 19.7 | 19.8 | 19.9 |
| fetal (pH 7.2) | 2.2 | 7.3 | 12.0 | 15.2 | 16.9 | 18.0 | 18.6 | 19.1 | 19.5 | 19.8 |
| maternal (pH 7.4) | 1.3 | 4.6 | 8.7 | 11.5 | 13.2 | 14.2 | 14.7 | 14.9 | 15.0 | 15.1 |
| maternal (pH 7.2) | 1.0 | 4.0 | 7.8 | 10.6 | 12.5 | 13.7 | 14.4 | 14.7 | 14.9 | 15.1 |

The effect of increasing acidity is to shift the curve rightward. (The dissociation curves can be constructed using the data in Table 6.4.1.)

MAPLE
```
> with(plots):
> ppo:=[seq(10*(i-1),i=1..11)]:
> fetal74:=array([0,3.5,10.5,15.2,17.4,18.6,19.2,19.5,19.7,19.8,19.9]):
> fetal72:=array([0,2.2,7.3,12.0,15.2,16.9,18.0,18.6,19.1,19.5,19.9]):
> maternal74:=array([0,1.3,4.6,8.7,11.5,13.2,14.2,14.7,15.0,15.0,15.1]):
```

```
> maternal72:=array([0,1.0,4.0,7.8,10.6,12.5,13.7,14.4,14.7,14.9,15.1]):
> f74plot:=plot([seq([ppo[i],fetal74[i]],i=1..11)]):
> f72plot:=plot([seq([ppo[i],fetal72[i]],i=1..11)]):
> m74plot:=plot([seq([ppo[i],maternal74[i]],i=1..11)]):
> m72plot:=plot([seq([ppo[i],maternal72[i]],i=1..11)]):
> with(plots):
> display({f74plot,f72plot,m74plot,m72plot});
```

MATLAB

```
> ppo=[0:10:100];
> fetal74=[0 3.5 10.5 15.2 17.4 18.6 19.2 19.5 19.7 19.8 19.9];
> plot(ppo,fetal74); hold on
> fetal72=[0 2.2 7.3 12.0 15.2 16.9 18.0 18.6 19.1 19.5 19.9];
> plot(ppo,fetal72)
> maternal74=[0 1.3 4.6 8.7 11.5 13.2 14.2 14.7 15.0 15.0 15.1];
> plot(ppo,maternal74)
> maternal72=[0 1.0 4.0 7.8 10.6 12.5 13.7 14.4 14.7 14.9 15.1];
> plot(ppo,maternal72)
```

When maximally saturated, hemoglobin (Hb) holds about 1.34 ml $O_2$ per gm. Fetal blood contains about 15 gm Hb per 100 ml, while maternal blood has 12 gm per 100 ml. Therefore, maternal blood is 100% saturated at a concentration of $1.34 \times 12 \approx$ 16 ml of $O_2$ per 100 ml of blood, and fetal blood is 100% saturated at 20 ml per 100 ml blood.

Although only the dissolved oxygen diffuses, hemoglobin acts like a moving reservoir on both the maternal and fetal sides of the placenta. On the maternal side, $O_2$ diffuses across the placental membrane from the maternal blood plasma, causing a decrease in the partial pressure of $O_2$, symbolized $pO_2$. But a lower oxygen partial pressure dissociates oxygen out of the hemoglobin to replace what was lost. This chemical reaction is very fast. Consequently, hemoglobin acts to preserve the partial pressure while its oxygen, in effect, is delivered to the fetal side. Of course as more and more oxygen dissociates, $pO_2$ gradually decreases.

On the fetal side, the opposite occurs. The incoming oxygen raises the partial pressure, with the result that oxygen associates with fetal hemoglobin with gradual increase of $pO_2$.

*Fetal oxygen consumption rate at term is* 23 *ml per minute.*

The first step in showing that simple diffusion suffices for oxygen delivery is to determine how much oxygen is consumed by the fetus. By direct measurement, oxygen partial pressure and blood pH at the umbilical cord are as shown in Table 6.4.2.

It follows from Figure 6.4.1 that each 100 ml of venous blood in the fetus contains approximately 13.5 ml $O_2$, while for arterial blood it is about 4.5 ml.

Evidently an $O_2$ balance for fetal circulation measured at the umbilical cord is given by

$$O_2 \text{ in} - O_2 \text{ out} = O_2 \text{ consumed}.$$

For each minute, this gives

$$\begin{aligned} \text{rate } O_2 \text{ consumed} &= 250 \frac{\text{ml blood}}{\text{min}} \times (13.5 - 4.5) \frac{\text{ml } O_2}{100 \text{ ml blood}} \\ &= 22.5 \text{ ml } O_2/\text{min}. \end{aligned}$$

**Table 6.4.2.** Placental oxygen and flow rate data.

| | |
|---|---|
| umbilical artery | $pO_2$: 15 mm Hg, pH: 7.24 [15] |
| umbilical vein | $pO_2$: 28 mm Hg, pH: 7.32 [15] |
| umbilical flowrate | 250 ml per minute [15] |
| maternal artery | $pO_2$: 40 mm Hg [15] |
| maternal vein | $pO_2$: 33 mm Hg [15] |
| maternal flowrate | 400 ml per minute [15] |
| placental membrane surface | 12 square meters [16] |
| placental membrane thickness | $3.5 \times 10^{-4}$ cm [16] |
| $pO_2$ diffusivity (see text) | $3.09 \times 10^{-8}$ $cm^2$/min/mm Hg [15, Figure 5] |

*Maximal oxygen diffusion rate is* 160 *ml per minute.*

Next, we estimate the maximum diffusion possible across the placenta. Recall the membrane transport (6.2.25),

$$J = -\frac{D}{w}\Delta c, \tag{6.4.1}$$

where we have taken the partition coefficient $\Gamma = 1$ and the membrane thickness to be $w$. This holds for those sections of the membrane that happen to have thickness $w$ and concentration difference $\Delta c$. Normally, both these attributes will vary throughout the placenta. However, since we are interested in the maximal diffusion rate, we assume them constant for this calculation. Placental membrane thickness has been measured to be about 3.5 microns ($3.5 \times 10^{-4}$ cm). Since flux is the diffusion rate per unit area, we must multiply it by the surface area, $S$, of the membrane. Careful measurements show this to be about 12 square meters at term [15].

Actually, taking a constant average value for $w$ is a reasonable assumption. But taking $O_2$ concentrations to be constant is somewhat questionable. Mainly, doing so ignores the effect of the blood flow. We will treat this topic below in connection with the countercurrent flow model. For this derivation, we assume that $O_2$ dissociates out of maternal blood in response to diffusion, all the while maintaining the concentration constant on the maternal side. On the fetal side, $O_2$ associates with fetal blood and likewise maintains a constant concentration there. In the countercurrent flow these assumptions tend to be realized.

A lesser difficulty in applying Fick's law has to do with the way an oxygen concentration is normally measured, namely, in terms of partial pressure. By Henry's law [15, p. 1714], there is a simple relationship between them: The concentration of a dissolved gas is proportional to its partial pressure, in this case $pO_2$. Hence

$$c = \delta(pO_2),$$

for some constant $\delta$. Incorporating surface area and Henry's law, (6.4.1) takes the form

$$SJ = -\delta D\frac{S}{w}\Delta(p0_2).$$

The product $\delta D$ has been calculated to be about $3.09 \times 10^{-8}$ cm$^2$/min/mm Hg (derived from data in [15] and investigated in the problems).

For the constant fetal partial pressure, we take the average of the range 15 to 28 mm Hg noted in Table 6.4.2, so about 21.5 mm Hg. Maternal arterial $pO_2$ is 40 mm Hg, while venous $pO_2$ is 33 mm Hg for an average of 36.5 mm Hg. Hence using the values in Table 6.4.2,

$$\begin{aligned} O_2 \text{ diffusion rate} &= 3.09 \cdot 10^{-8} \frac{\text{cm}^2}{\text{min-mm Hg}} \\ &\quad \cdot \frac{12 \text{ m}^2 \cdot 10^4 \frac{\text{cm}^2}{\text{m}^2}}{3.5 \cdot 10^{-4} \text{ cm}} (36.5 - 21.5) \text{ mm Hg} \\ &= 159 \frac{\text{cm}^3}{\text{min}}. \end{aligned}$$

Recalling that only 22.5 ml of oxygen per minute are required, the placenta, in its role of transferring oxygen, need only be about $\frac{22.5}{159} = 14\%$ efficient.

*The fetal flow rate limits placental transport efficiency.*

The placenta as an exchanger is not 100% efficient (it only needs to be 14% efficient) due to (1) maternal and fetal shunts, (2) imperfect mixing, and, (3) most importantly, flow of the working material, which we have not taken into consideration. Let $F$ be the maternal flow rate, $f$ the fetal flow rate, $C$ maternal $O_2$ concentration, and $c$ fetal $O_2$ concentration. Use the subscript $i$ for in and $o$ for out (of the placenta). Let $r$ denote the transfer rate across the placenta ($r = SJ$). From the mass balance equation,

$$O_2\text{/min in} \pm O_2 \text{ gained or lost per min} = O_2\text{/min out},$$

we get

$$f c_i + r = f c_o; \qquad F C_i - r = F C_o, \tag{6.4.2}$$

since the oxygen rates in or out of the placenta are the product of conentration times flow rate. From the membrane equation (6.2.25),

$$r = K(\Delta\text{concentration across membrane}), \quad \text{where } K = \frac{\Gamma D S}{w}.$$

For the fetal and maternal concentrations, we use $C_o$ and $c_o$. From (6.4.2),

$$r = K(C_o - c_o) = K\left(C_i - \frac{r}{F} - \frac{r}{f} - c_i\right).$$

Solve this for $r$ and get

$$r = \frac{C_i - c_i}{\frac{1}{K} + \frac{1}{F} + \frac{1}{f}}. \tag{6.4.3}$$

Now consider the magnitude of the three terms in the denominator. If $F$ and $f$ are infinite, then the denominator reduces to $\frac{1}{K}$ and the transfer rate becomes

$$r = K(C_i - c_i)$$

as before. In this case, diffusion is the limiting factor.

Since the flow terms are not infinite, their effect is to increase the denominator and consequently reduce the transfer coefficient, that is,

$$\frac{1}{\frac{1}{K} + \frac{1}{F} + \frac{1}{f}} < \frac{1}{\frac{1}{K}} = K.$$

Moreover, depending on the relative size of the three terms in the denominator of (6.4.3), diffusion may not be the limiting factor. In particular, the smallest of the quantities $K$, $F$, and $f$, corresponds to the largest of the reciprocals $\frac{1}{K}$, $\frac{1}{F}$, and $\frac{1}{f}$. Using the values of $S$ and $w$ from Table 6.4.2, and taking $\Gamma D = 4 \times 10^{-7}$ cm$^2$/sec (see [15]), gives

$$K = \frac{4 \cdot 10^{-7} \cdot 12 \cdot 10^4}{3.5 \cdot 10^{-4}} = 137 \frac{\text{cm}^3}{\text{sec}}.$$

Compare this with a maternal flow rate $F$ of 400 ml/min, or 6.7 ml/sec, and a fetal flow rate $f$ of 250 ml/min, or 4.2 ml/sec. Thus fetal flow rate is the smallest term and so is the limiting factor. Furthermore, from (6.4.3) we can see that diffusion is a relatively minor factor compared to the maternal and fetal flow rates. That is,

$$\frac{1}{\frac{1}{137} + \frac{1}{6.7} + \frac{1}{4.2}} = 2.53,$$

while

$$\frac{1}{\frac{1}{6.7} + \frac{1}{4.2}} = 2.58.$$

*Countercurent flow is more efficient than concurrent flow.*

In this section, we will compare the diffusion properties of the placenta depending on whether the maternal and fetal blood flow in the same or the opposite directions through the placenta. For this we assume the placenta to be a channel separated by the placental membrane. Assume first that fetal and maternal blood flow in the same direction. As shown in Figure 6.4.2, on the maternal side we take the channel height to be $H$ and the velocity to be $v_m$, while these will be $h$ and $v_f$ respectively on the fetal side. Let the channel width be $b$. Assume that steady state has been reached and take the oxygen concentrations at position $x$ along the maternal and fetal sides to be $C(x)$ and $c(x)$, respectively.

On the fetal side, a block $\Delta V$ of blood at position $x$ gains in concentration in moving distance $\Delta x$ due to the flux $J(x)$ at $x$. Let $\Delta S$ denote the area of contact of the block with the placental membrane. Since the time required to move this distance is $\Delta t = \frac{\Delta x}{v_f}$, we have

$$c(x + \Delta x) = \frac{c(x)\Delta V + J(x)\Delta S\left(\frac{\Delta x}{v_f}\right)}{\Delta V}.$$

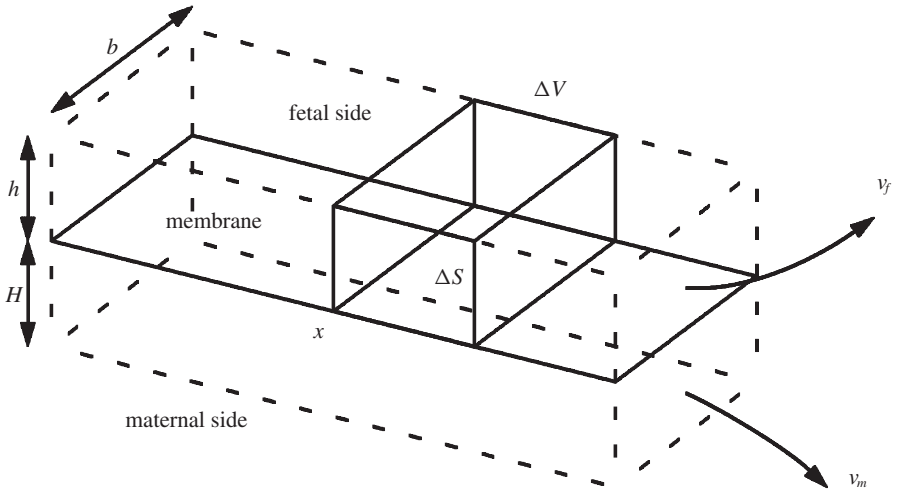


**Fig. 6.4.2.** Diffusion of oxygen into a moving incremental volume.

But from the membrane (6.2.25) (with $\Gamma = 1$),

$$J(x) = \left(\frac{D}{w}\right)(C(x) - c(x)),$$

and so

$$\frac{c(x + \Delta x) - c(x)}{\Delta x} = \frac{D}{w v_f}\frac{\Delta S}{\Delta V}(C(x) - c(x)).$$

Now $\frac{\Delta S}{\Delta V} = h$, and so in the limit we have

$$\frac{dc}{dx} = \frac{\left(\frac{D}{w}\right)}{h v_f}(C - c). \tag{6.4.4}$$

A similar calculation on the maternal side gives

$$\frac{dC}{dx} = -\frac{\left(\frac{D}{w}\right)}{H v_m}(C - c). \tag{6.4.5}$$

Denote by $T$ the *tension* or concentration difference $C(x) - c(x)$. By subtracting the first equation from the second, we get

$$\frac{dT}{dx} = -\frac{D}{w}\left(\frac{1}{H v_m} + \frac{1}{h v_f}\right)T. \tag{6.4.6}$$

For this parallel flow, denote by $k_p$ the constant coefficient,

$$k_p = \frac{D}{w}\left(\frac{1}{H v_m} + \frac{1}{h v_f}\right) = \frac{D}{w}\left(\frac{b}{F} + \frac{b}{f}\right), \tag{6.4.7}$$

where we have replaced the velocities $v_m$ and $v_f$ by the maternal and fetal flow rates $F$ and $f$, respectively, using the fact that a flow rate is the product of velocity with cross-sectional area,

$$F = (bH)v_m \quad \text{and} \quad f = (bh)v_f.$$

Now the solution of the differential (6.4.6) is

$$T = T_0 e^{-k_p x}, \tag{6.4.8}$$

with $T_0$ the initial tension, $40 - 15 = 25$ mm Hg. Assuming that the channel has length $L$ and the final tension is $33 - 28 = 5$ mm Hg (see Table 6.4.2), (6.4.8) with $x = L$ becomes

$$5 = 25e^{-k_p L}; \quad \text{therefore,} \quad k_p L = -\log\left(\frac{1}{5}\right). \tag{6.4.9}$$

Next, we calculate the average tension $\bar{T}$ over the run of the channel. The average of (6.4.8) is given by the integral

$$\begin{aligned}\bar{T} &= \frac{1}{L}\int_0^L T_0 e^{-k_p x}dx = -\frac{T_0}{k_p L}e^{-k_p x}\Big|_0^L \\ &= \frac{T_0 - T_0 e^{-k_p L}}{k_p L} = \frac{25-5}{\log(5)} = 12.4 \text{ mm Hg},\end{aligned}$$

where (6.4.9) was used to substitute for $k_p L$.

Next, consider countercurrent flow. Arguing in the same manner as above, we see that the differential equations for countercurrent flow are similar to (6.4.4) and (6.4.5); the sign of the second is reversed because the flow is reversed here:

$$\frac{dc}{dx} = \frac{\left(\frac{D}{w}\right)}{hv_f}(C - c)$$

on the fetal side and

$$\frac{dC}{dx} = \frac{\left(\frac{D}{w}\right)}{Hv_m}(C - c)$$

on the maternal side. Subtracting, we get

$$\frac{dT}{dx} = -\frac{D}{w}\left(\frac{1}{hv_f} - \frac{1}{Hv_m}\right)T.$$

For this countercurrent flow, denote by $k_c$ the coefficient

$$k_c = -\frac{D}{w}\left(\frac{b}{f} - \frac{b}{F}\right). \tag{6.4.10}$$

As before, the solution is

$$T = T_0 e^{-k_c x}. \tag{6.4.11}$$

Now, however, that $T_0 = 33 - 15 = 18$ mm Hg. And for $x = L$, $T = 40 - 28 = 12$ mm Hg; therefore, $12 = 18e^{-k_c L}$, from which it follows that $k_c L = \log(1.5)$. Hence the average tension in this case is

$$\bar{T} = \frac{T_0 - T_0 e^{-k_c L}}{k_c L} = \frac{6}{\log(1.5)} = 14.8 \text{ mm Hg}.$$

Therefore, countercurrent flow is somewhat more efficient than concurrent flow, by these calculations, $\frac{14.8}{12.4} = 1.2$ times more efficient. Note that the average tension for countercurrent flow is approximately equal to the numerical average, $\frac{18+12}{2} = 15$.

**Exercises/Experiments**

1. Suppose the placenta becomes injured or impaired. How much of it is necessary in order to deliver adequate amounts of oxygen?
2. From Table 6.4.2, maternal $pO_2$ falls from 40 mm Hg to 33 mm Hg in its course through the placenta traveling at 400 ml/min. How much $O_2$ is delivered? (Compare with the text calculation.) If the flow rate falls to 300 ml/min, what must be the corresponding $pO_2$ difference to maintain this rate?
3. For fetal blood at 28 mm Hg $pO_2$, what is the amount of dissolved oxygen for a pH of 7.4? If the pH shifts to 7.2, what must be $pO_2$ so that the blood contains the same amount? Extrapolate to a pH of 7.0.
4. For maternal blood at 40 mm Hg $pO_2$, what is the amount of dissolved oxygen for a pH of 7.4? If the pH shifts to 7.2, what must be $pO_2$ so that the blood contains the same amount? Extrapolate to a pH of 7.0.
5. Modify the calculation to account for the diffusion of $O_2$ through 1 micron of plasma before reaching the placental membrane on the maternal side and 1 micron of plasma upon leaving the placental membrane on the fetal side before entering an erythrocyte.
6. Assume that carbon monoxide, CO, in the maternal blood reaches 5% (as is typical for smokers). Also assume that CO binds 220 times more readily than $O_2$ to hemoglobin. Recalculate diffusion across the placenta under these conditions.

**Questions for Thought and Discussion**

1. Discuss why the evolution of small animals into large animals required the evolution of a closed circulatory system and a concomitant coelom.
2. Starting with the number 2, number the following events in the order in which they occur:

| | |
|---|---|
| blood enters right atrium | 1 |
| fluid from blood enters lymphatic system | |
| blood gives up $CO_2$ at alveoli | |
| blood enters systemic capillaries | |

blood enters pulmonary artery _____
blood enters aorta _____

**3.** What factors determine how large the placenta has to be? By weight (including its blood supply), how large is the placenta relative to its fetus? Does this change over gestation?

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