9 An Introduction to Partial Differential Equations and Diffusion in Biological Settings

I do not know what I may appear to the world; but to myself I seem to have been only like a boy playing on the seashore, and diverting myself in now and then finding a smoother pebble or prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me.

Isacc Newton (1642–1727) p 90 E. T. Bell (1937) Men of Mathematics Simon & Schuster, N.Y.

Part of our admiration for nature stems from the fact that it continually surprises us with its infinite variation, regardless of the scale of observation. This holds true of microscopic worlds; the surface of a cell for example, consists of myriad buoyant macromolecules distributed haphazardly in a viscous lipid sea. On the broad scale, that of continents or ecosystems, the fabric of habitats is like a patchwork quilt with a wide variety of local conditions, some favoring one species, some favoring another.

For this reason, real natural systems behave in a way that reflects an underlying spatial variation. Despite our idealizations, no species actually consists of identical individuals, since not all individuals are equally exposed to a constant environment. Similarly, on the molecular level, rarely do reactions take place in a homogeneous soup of chemicals. Somehow the effect of spatial organization does influence the way individual particles or molecules interact.

In the three chapters to follow, our purpose is to expose how spatial variation influences the motion, distribution, and persistence of species. We shall see that in the fine balance that exists between interdependent species, the spatial diversity of the system can have subtle but important effects. Conversely, the interactions of unlike species can result in spatial heterogeneity and lead to the appearance of patterns

out of a uniform state. Our initial goal is to introduce the concepts underlying spatially dependent processes and the partial differential equations (PDEs) that describe these. The discussion is somewhat general, with examples drawn from molecular, cellular, and population levels. Later we will apply the ideas to more specific cases with the aim of gaining an understanding of phenomena.

In this chapter we discover primarily how partial differential equations arise and by what procedures they can be assembled into statements that are reasonable mathematically as well as physically. We see that under appropriate assumptions the motion of groups of particles (whether molecules, cells, or organisms) can be represented by statements of mass or particle conservation that involve partial derivatives. Such statements, often called *conservation* or *balance equations*, are universal in mathematical descriptions of the natural sciences. Indeed practically every PDE that depicts a physical process is ultimately based on principles of conservation—of matter, momentum, or energy.

Before undertaking the derivation of balance equations, we devote Section 9.1 to a review of the material that forms much of the structural underpinning of the mathematical framework. Students well versed in advanced calculus may skim through this section. One of the key observations we make is that the spatial variation in a distribution can lead to directional information. This proves conceptually useful in later discussions.

With this preparation we then proceed with the derivation of statements of conservation. This is accomplished in two stages. First, a simple argument for one-dimensional settings is given in Section 9.2. This is followed by more rigorous derivations and a generalization to other geometries and higher dimensions. We then consider several specific phenomena—including convection, diffusion, and attraction—that result in the motion of particles. Each phenomenon leads to special cases of the conservation equation. Such equations are derived in Section 9.4 and explored more fully later.

One example of applying such ideas to a universal process—that of diffusion—is illustrated in Sections 9.5 to 9.9. Derivation of the equation governing diffusion is rather straightforward if one accepts an assumption known as Fick's law. A more fundamental approach based on random-walk models is rather more sophisticated. Okubo (1980) and references therein should be consulted for finer details. Less straightforward is the process of actually solving the diffusion equation (or any other) PDE. Exploring the host of powerful techniques commonly applied by mathematicians in analyzing PDEs is beyond our scope. However, even before attempting to find a full solution, the form of the equation leads to an appreciation for the role of diffusion as a biological transport mechanism. A ubiquitous and metabolically free process on the subcellular level, diffusion proves inefficient or totally useless on somewhat larger distance scales. Some of these observations and their implications are presented in Sections 9.5 to 9.7.

Section 9.8 and the Appendix give some guidance on ways of solving the diffusion equation. We limit ourselves to separation of variables, a technique that is readily applied given a familiarity with ordinary differential equations (ODEs). Several basic solutions are derived, and others are given without formal justification in order to circumvent a lengthy mathematical excursion into the relevant techniques.

Section 9.9 describes an application of the diffusion equation to bioassay for mutation-inducing substances.

For a rapid coverage of the key ideas in this chapter, the following sequence is recommended: Section 9.1 should be included or covered briefly in the interests of review. Sections 9.2 and 9.4 are essential for later material. Sections 9.3 and 9.5 can be assigned as independent reading or further research. Some highlights of the material in Section 9.8 or in the Appendix should be given, with particular emphasis on the role of boundary conditions in solutions of the diffusion equation. Familiarity with the examples may prove helpful but is not essential for mastering the material in Chapter 11.

9.1 FUNCTIONS OF SEVERAL VARIABLES: A REVIEW

We begin this chapter by briefly reviewing the theory of functions of several variables with emphasis on the geometric concepts behind the mathematical ideas. Those of you who have had advanced calculus can skim quickly through this section or go directly to the next one.

First consider a real-valued function of two variables x and y. In this chapter x and y will symbolize spatial coordinates of a point (x, y), and

$$z = f(x, y), \tag{1}$$

the *value* assigned to (x, y) by the function f, will generally represent some spatially distributed quantity. Examples include

1. The density of a population at (x, y).
2. The concentration of a substance at (x, y).
3. The temperature at (x, y).

A *graph* of the function f is the set of points $(x, y, f(x, y))$ in R^3. The value $z = f(x, y)$ can be visualized as the height [assigned by the function f to each point in the plane, (x, y)]. Equation (1) thus describes a surface, as shown in Figure 9.1(*a*).

Similarly, a function of three variables

$$z = g(x, y, w) \tag{2}$$

has a graph consisting of all points $(x, y, w, g(x, y, w))$. This is not as easy to draw, but the idea is analogous. (Every point in space is assigned a value by the function.) Sometimes it is more convenient to depict functions in other ways, some of which are shown in Figure 9.1 for functions of two and three variables. It is common to represent the behavior of a function of two variables by a set of contours for which

$$f(x, y) = \text{constant}. \tag{3}$$

In R^2 these are called *level curves* and are simply loci for which a constant concentration or a constant density (or height) is maintained. As we shall see, they play an important role in the geometry of gradients and gradient fields.

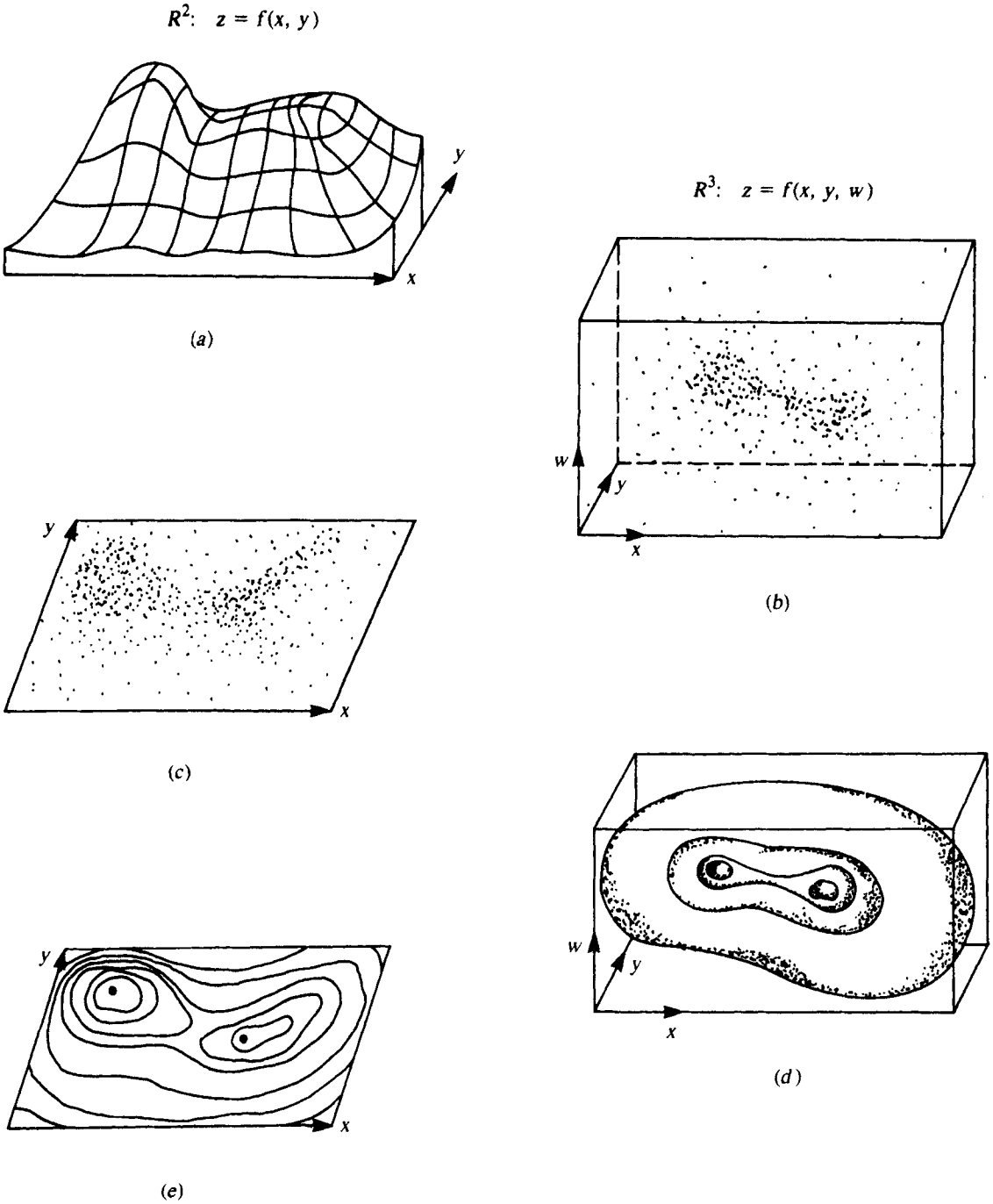


Figure 9.1 *Functions of two or three variables can be represented graphically in several ways: (a) as a surface (two variables only); (b, c) by density distributions in* R^3 *or* R^2*; or (d, e) by loci representing constant* f. *The latter are called (d) level surfaces or (e) level curves.*

In R^3 the function of three variables given by (2) can similarly be represented by sets of points for which

$$f(x, y, w) = \text{constant}. \tag{4}$$

Such loci are a generalized version of level curves, but for obvious reasons these are called *level surfaces* [see Figure 9.1(*d*)]. To clarify with an example, consider a temperature field in three dimensions. The *equitherms* are then surfaces at which some given constant temperature is maintained. If heat sources are located at two points, the resulting equithermal surfaces might look something like those shown in Figure 9.1(*d*).

In the context of this chapter, level curves or surfaces might represent the loci on which (1) population density is constant or (2) chemical concentration is constant.

We shall be concerned primarily with statements about how spatial distributions change with time; frequently it will be clear that the movement of one substance or population is closely linked to the distribution of another.

Consider the following simple example. An organism crawling on a flat surface may adapt its motion to the search for food particles. Imagine then that the dots in Figure 9.1(*c*) represent nutrient particle concentration. The observed path should ideally lead to the site of greatest concentration. To sense an increase in the ambient concentration level, an organism must continually *cross* level curves of the particle distribution. Per unit distance traveled, this crossing can be done most efficiently by maintaining a path *orthogonal* to the level curves; in other words, a tangent vector to the path should be perpendicular to a tangent to a level curve through a given point. This assertion can be verified using rather elementary calculus of several variables. It can also be shown that the destination will be a *critical point* of the function (in this case a local maximum) but not necessarily the *global* maximum.

In calculus a commonplace analogy is often drawn in explaining these ideas. Hikers often use topographical maps which are two-dimensional representations of the height of the terrain. The curves on such maps are level curves for the function $f(x, y)$ = height above sea level at latitude x and longitude y. Mountain peaks, valleys, and mountain passes are critical points of $f(x, y)$ that correspond to local maxima, minima, and saddle points respectively. Using local information only (for example, walking uphill with no information other than the local slope), one can attain a local maximum, but this may or may not be the highest possible peak.

These two-dimensional examples can be extended to higher dimensions. A motile organism that swims in a droplet of water might also use local cues in orienting itself and moving towards sites that have higher nutrient levels. This type of motion, called *chemotaxis*, will be discussed at greater length in Section 10.2. In R^3 the path of a highly efficient chemotactic organism would be orthogonal to the level surfaces of the nutrient distribution $c(x, y, z)$.

The descriptive statements in this section can be made more rigorous by introducing partial derivatives and gradients which are reviewed in the boxed material. Several examples follow the general discussion and definitions.

Partial Derivatives (A Review)

For a function of two variables $f(x, y)$ we define

$$\frac{\partial f}{\partial x} = \lim_{\Delta x \to 0} \frac{f(x + \Delta x, y) - f(x, y)}{\Delta x}. \tag{5}$$

A similar definition holds for $\partial f/\partial y$. Shorthand notation for partial derivatives is f_x and f_y.

To understand the geometrical meaning of these derivatives, imagine standing at a point (x_0, y_0) on a plane. Suppose $f(x_0, y_0)$ is the height of a surface above this location. The expression following "lim" in equation (5) (and similarly for $\partial f/\partial y$) represents the changes in the height of the surface per unit distance as we take a step in the x (or the y) direction. A *partial derivative* is the limit of this quantity as the length of the step shrinks to an infinitesimal size. It is therefore analogous to an ordinary derivative and also represents a *slope*.

To clarify, suppose we slice away part of the surface $z = f(x, y)$ along a direction parallel to the x (or y) axis. (See Figure 9.2.) In such cutaway drawings the partial derivative is the slope of a tangent to the curve forming the surface edge. The idea of a partial derivative is a special case of the somewhat more general concept of *directional derivative*. We shall not deal in more depth with this but rather refer the reader to any standard calculus text for a definition and explanation.

The following properties of partial derivatives follow from their basic definition:

$$\frac{\partial(cf)}{\partial x} = c\frac{\partial f}{\partial x}, \tag{6a}$$

$$\frac{\partial(f + g)}{\partial x} = \frac{\partial f}{\partial x} + \frac{\partial g}{\partial x}. \tag{6b}$$

for functions f and g and constant c. Similar equations ensue for partial differentiation with respect to y.

For functions that are continuously differentiable sufficiently many times, it is also true that mixed partial differentiation in any order produces the same result. For example

$$f_{yx} = \frac{\partial}{\partial x}\left(\frac{\partial f}{\partial y}\right) = \frac{\partial^2 f}{\partial x\, \partial y} = \frac{\partial^2 f}{\partial y\, \partial x} = \frac{\partial}{\partial y}\left(\frac{\partial f}{\partial x}\right) = f_{xy}. \tag{6c}$$

Note: Equation (6c) also defines the equivalent notation used for multiple partial differentiation.

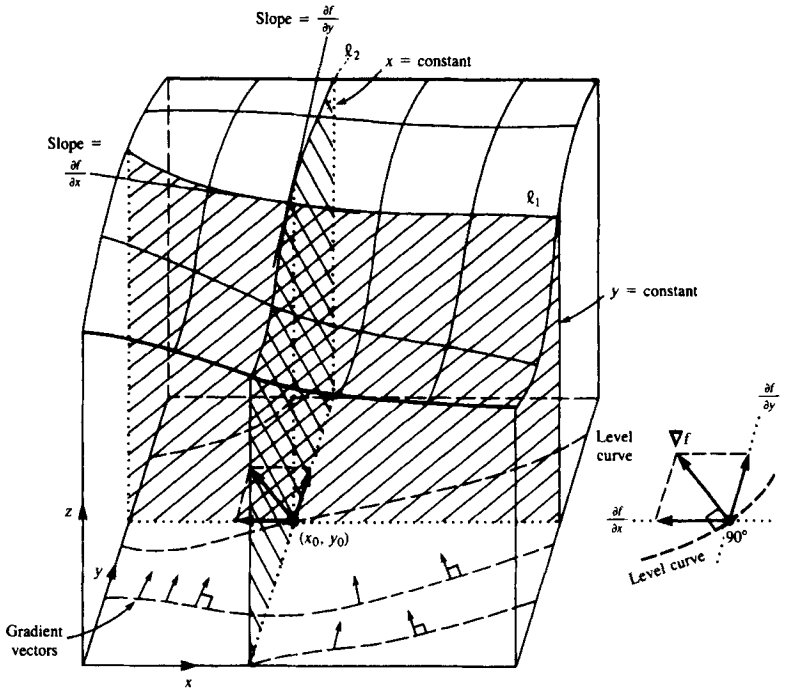


Figure 9.2 *An interpretation of partial derivatives and gradient vectors. The surface* z = f(x, y) *intersects planes for which* y = *constant or* x = *constant along curves* ℓ_1 *and* ℓ_2. *The slope of a tangent to* ℓ_1 *is* ∂f/∂x, *and the slope of a tangent to* ℓ_2 *is* ∂f/∂y. *Gradient vectors,* ∇f [*for* f = f(x, y)] *live in the* xy *plane and have* (∂f/∂x, ∂f/∂y) *as components. These vectors are always orthogonal to level curves of* z = f(x, y), *shown here by dashed lines (see inset).*

Gradients

For a function f of several variables the *gradient*, symbolized ∇f, is a vector consisting of the partial derivatives of f. For example, if $f = f(x, y)$, then

$$\nabla f = \left(\frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}\right). \tag{7}$$

If $f = f(x, y, z)$, then

$$\nabla f = \left(\frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}, \frac{\partial f}{\partial z}\right), \tag{8}$$

and so on for functions of n variables. The symbol ∇ is called the *del operator*, and is discussed in greater detail in Section 9.3.

The gradient vector has the following properties:

1. The magnitude of ∇f, $|\nabla f|$, represents the steepness of the local variations in the function f. For example,

$$|\nabla f| = (f_x^2 + f_y^2)^{1/2}. \tag{9}$$

2. (a) The direction of ∇f,

$$\mathbf{u} = \frac{\nabla f}{|\nabla f|},$$

is a unit vector in the direction of steepest (increasing) slope, in the sense that a step in this direction leads to the greatest increase in f per unit distance.

(b) The gradient vector at a point (x_0, y_0) is perpendicular to a level curve $f(x, y) = c$ that goes through (x_0, y_0) as long as (x_0, y_0) is not a local maximum, minimum, or saddle point.

For every point in R^2 (analogously, R^3 or R^n) at which the function f is defined, is continuous, and has partial derivatives, there will be a gradient vector. The vector will have all zero components at the critical points of f.

It is common to visualize a whole collection of these vectors, one at each point in space, as a *vector field*. A vector field that arises thus is called a *gradient field* and has certain special properties. (Note that a gradient field is a vector field, but the converse is not necessarily true.)

Gradient fields can always be paired (up to an arbitrary constant) with differentiable multivariate functions and vice versa (see examples in the following boxes). We see that the variations in a spatial distribution lead to orientation cues that are represented by the geometry of the gradient field.

The proof of the statements in this box are based on the chain rule of functions of several variables and on the properties of curves and vector dot products. These can be found in any text dealing with the calculus of several variables.

Example 1

Consider the function

$$f(x, y) = x^2 - 2x + y^2 + 4y + 5.$$

Level curves of this function have the equation

$$\begin{aligned} c &= x^2 - 2x + y^2 + 4y + 5 \\ &= (x - 1)^2 + (y + 2)^2. \end{aligned}$$

These are circles of radius $c^{1/2}$ centered at the point $(1, -2)$. Partial derivatives of $f(x, y)$ are the following:

$$\frac{\partial f}{\partial x} = 2x - 2, \qquad \frac{\partial f}{\partial y} = 2y + 4,$$

$$\frac{\partial^2 f}{\partial x\, \partial y} = 0, \qquad \frac{\partial^2 f}{\partial y\, \partial x} = 0,$$

$$\frac{\partial^2 f}{\partial x^2} = 2, \qquad \frac{\partial^2 f}{\partial y^2} = 2.$$

The gradient vector at a point (x, y) is

$$\nabla f = \left(\frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}\right) = (2x - 2, 2y + 4).$$

This vector is perpendicular to a level curve going through the point (x, y). A critical point of f occurs at $(1, -2)$, where $\nabla f = (0, 0)$. At this point, $f(1, -2) = 0$. At any other point f is *greater*. For example, $f(1, 1) = 1 - 2 + 1 + 4 + 5 = 9$. Therefore $(1, -2)$ is a local minimum. (A more rigorous *second-derivative test* to distinguish between local minima, maxima, and saddle points is given in most calculus books).

Example 2

Consider the vector field

$$\begin{aligned} \mathbf{F} &= (M(x, y), N(x, y)) \\ &= (2x + 2y + y \cos xy, 2x + x \cos xy). \end{aligned} \tag{10}$$

We would like to determine whether $\mathbf{F}$ is a gradient field, that is, whether there is a function $f(x, y)$ such that

$$\mathbf{F} = \nabla f. \tag{11a}$$

If so, then

$$\mathbf{F} = (M, N) = \left(\frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}\right), \tag{11b}$$

where $M(x, y) = \partial f/\partial x$ and $N = \partial f/\partial y$.

By a previous observation we must have

$$\frac{\partial M}{\partial y} = f_{xy} = f_{yx} = \frac{\partial N}{\partial x}. \tag{12}$$

Checking this, we note that

$$\frac{\partial M}{\partial y} = 2 + \cos xy - xy \sin xy = \frac{\partial N}{\partial x},$$

so that no contradiction results by assuming that (11a) holds. The condition given by (12) in fact guarantees that $\mathbf{F}$ is a gradient field (a fact whose proof will be omitted here).

To find f we need a function whose partial derivatives satisfy the following:

$$\frac{\partial f}{\partial x} = 2x + 2y + y \cos xy, \tag{13a}$$

$$\frac{\partial f}{\partial y} = 2x + x \cos xy. \tag{13b}$$

Integrating each expression with respect to a single variable while holding the other variable constant leads to these results:

$$f(x, y) = \int_{(y=\text{const})} (2x + 2y + y \cos xy)\, dx \qquad (14)$$
$$= x^2 + 2xy + \sin xy + H,$$

and

$$f(x, y) = \int_{(x=\text{const})} (2x + x \cos xy)\, dy \qquad (15)$$
$$= 2xy + \sin xy + G.$$

In ordinary one-variable calculus, a single integration introduces a single arbitrary constant. However, in the *partial integration* of (14) and (15) one must account for the distinct possibility that the integration "constants" H and G may depend on the values given to the fixed variables (to y = const and to x = const). For this reason it is necessary to presuppose that

$$H = h(y) \quad \text{and} \quad G = g(x) \qquad (16)$$

are functions. Indeed, the only possibility for matching the two different expressions, (14) and (15), both of which equal the same function $f(x, y)$, would be to take

$$G(x) = x^2 + c, \qquad H(y) = c,$$

for constant c.

The conclusion then is that

$$f(x, y) = x^2 + 2xy + \sin xy + c. \qquad (17)$$

To check this result, observe that

$$\nabla f = (2x + 2y - y \cos xy, 2x - x \cos xy) = \mathbf{F},$$

which confirms the calculation. Note that adding any constant to $f(x, y)$ results in the same gradient. Thus $f(x, y)$ is defined only up to some arbitrary additive constant.

Example 3

The concentration of nutrient particles suspended in a pond is given by the expression

$$c(x, y, z) = C_0 \exp -\alpha(x^2 + y^2 + z^2). \qquad (18)$$

An organism located at $(x, y, z) = (1, -1, 1)$ moves in the direction of increasing concentration. In which direction should it move? Where is the maximum concentration?

Answer

To find the direction of greatest increase per unit distance, compute the gradient vector. Since c is a function of three variables, ∇c is a vector in R^3:

$$\nabla c = \left(\frac{\partial c}{\partial x}, \frac{\partial c}{\partial y}, \frac{\partial c}{\partial z}\right) \qquad (19a)$$

$$= (-2\alpha x C_0 e^{-\alpha r^2}, -2\alpha y C_0 e^{-\alpha r^2}, -2\alpha z C_0 e^{-\alpha r^2}), \qquad (19b)$$

where

$$r^2 = x^2 + y^2 + z^2 \tag{19c}$$

at $(1, -1, 1)$

$$r^2 = 3 \qquad \text{and} \qquad \nabla c = (-\gamma, \gamma, -\gamma),$$

where

$$\gamma = 2\alpha C_0 e^{-3\alpha}.$$

Furthermore, $\nabla c = 0$ only when $(x, y, z) = (0, 0, 0)$, so that the origin is a critical point. It is readily observed that this is a local *maximum*, since $c(x, y, z)$ is a function that decreases exponentially with distance from the origin. Thus, the maximal concentration of nutrient particles is $c(0, 0, 0) = C_0$. We further observe that equiconcentration loci are surfaces that satisfy

$$C_0 \exp -\alpha(x^2 + y^2 + z^2) = \text{constant}. \tag{20a}$$

After algebraic simplification this becomes

$$x^2 + y^2 + z^2 = K \qquad (K = \text{constant}), \tag{20b}$$

which represents spheres with centers at $(0, 0, 0)$ and radii $\sqrt{K}$.

Thus the organism will move in the direction of the gradient, and its path will eventually end at $(0, 0, 0)$.

In the next section our purpose is to understand the basic process through which a partial differential description of motion through space is obtained. We shall be concerned mainly with the dynamic processes that lead to changes in a spatial distribution over time. Some of the many examples cited pertain to the motion and continuous redistribution of animals, cells, and molecules through space. For this reason we shall deal with functions that depend on both space and time.

9.2 A QUICK DERIVATION OF THE CONSERVATION EQUATION

The *conservation equation* in its various forms is the most fundamental statement through which changes in spatial distributions are described. Most of the PDEs we will encounter are ultimately based on such *statements of balance*. To gain an easy familiarity with the basic concepts we will consider a rather special case and give an informal derivation first, later to be made more rigorous and more general.

Our initial assumptions are that

1. Motion takes place in a single space dimension (as, for example, in the thin tube of Figure 9.3a).
2. The cross-sectional area of the vessel or container is constant along its entire length.

We shall let x represent the distance along the tube from some arbitrary location. Fixing attention on the interval between x and $x + \Delta x$, let us describe changes

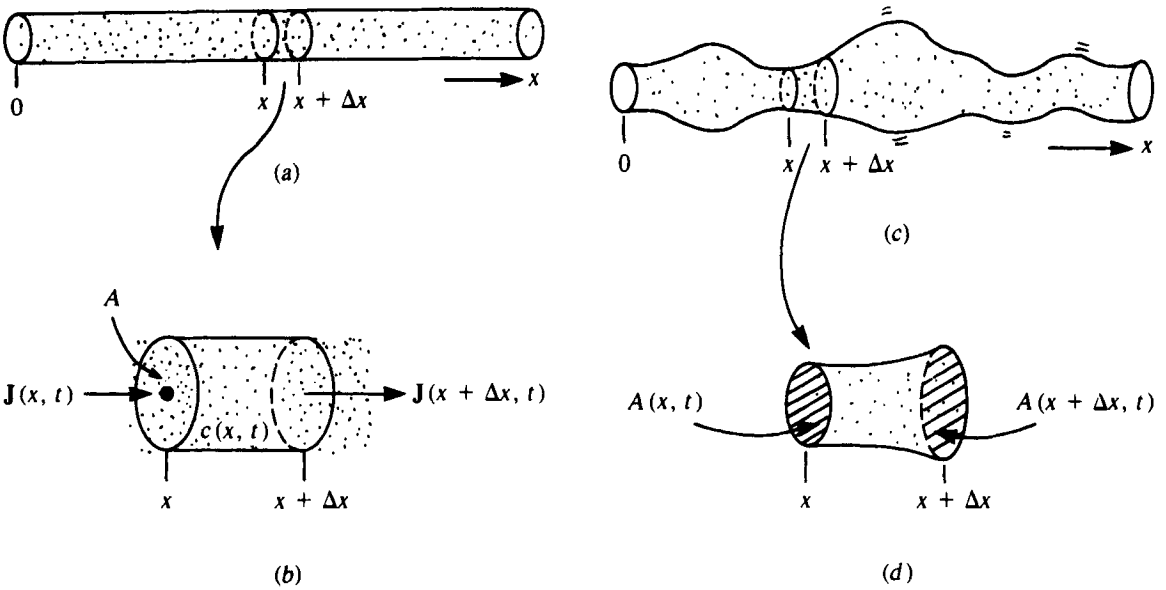


Figure 9.3 *Equations of balance are derived for flow of particles [concentration* c(x, t)*] along a tube. (a) If the tube has uniform cross-sectional area* A*, equation (24) results from a balance of flows into and out of a small section (b) of length* Δx*. (c) If the tube has spatially or temporally varying area* A(x, t)*, one obtains equation (29) by formulating the balance statement for the small region shown in (d).*

in the concentration by accounting for two possible effects: (1) flow of particles into and out of the interval $(x, x + \Delta x)$, and (2) processes that introduce new particles or degrade particles locally (such as through a chemical reaction). The balance equation can be written either in terms of *mass* or *number* of particles. We arbitrarily choose the latter description, and so our statement will be

$$\begin{pmatrix}\text{rate of change}\\ \text{of particle}\\ \text{population in}\\ (x, x + \Delta x)\\ \text{per unit time}\end{pmatrix} = \begin{pmatrix}\text{rate of entry}\\ \text{into } (x, x + \Delta x)\\ \text{per unit time}\end{pmatrix} - \begin{pmatrix}\text{rate of}\\ \text{departure}\\ \text{from}\\ (x, x + \Delta x)\\ \text{per unit time}\end{pmatrix} \pm \begin{pmatrix}\text{rate of}\\ \text{local degra-}\\ \text{dation or}\\ \text{creation per}\\ \text{unit time}\end{pmatrix} \tag{21}$$

To go further, define the following quantities:

$c(x, t)$ = concentration of particles (number per unit volume) at (x, t),

$\mathbf{J}(x, t)$ = flux of particles at (x, t) = number of particles crossing a unit area at x in the positive direction per unit time,

$\sigma(x, t)$ = sink/source density = number of particles created or eliminated per unit volume at (x, t).

We note that the only *flux* that changes the total population is that entering or leaving through the cross sections at x and $x + \Delta x$, namely, $\mathbf{J}(x, t)$ and $\mathbf{J}(x + \Delta x, t)$.

To now translate (21) into a dimensionally correct equation, it is necessary to take into account the following quantities:

A = cross-sectional area of tube,

ΔV = volume of length element $\Delta x = A\,\Delta x$.

Every term in the equation must have the same units as the terms on the LHS of (21): number per unit volume per unit time.

This leads to the following equation:

$$\frac{\partial}{\partial t}[c(x, t)A\,\Delta x] = \mathbf{J}(x, t)A - \mathbf{J}(x + \Delta x, t)A \pm \sigma(x, t)A\,\Delta x. \tag{22}$$

Note that since c depends on two variables, its derivative with respect to time is a partial derivative. Choosing to write equation (22) in terms of x, the coordinate of the *left* boundary of the interval, is entirely arbitrary since we are about to take the limit $\Delta x \to 0$.

We observe that a flux in the positive x direction tends to contribute to the net population positively at x but negatively at $x + \Delta x$; hence the signs of the terms in (22). See Figure 9.3(*b*).

Now dividing through by $A\,\Delta x$, which by assumption is constant, we obtain

$$\frac{\partial c(x, t)}{\partial t} = \frac{\mathbf{J}(x, t) - \mathbf{J}(x + \Delta x, t)}{\Delta x} \pm \sigma(x, t). \tag{23}$$

Taking a limit of this equation as $\Delta x \to 0$, that is, as the slice width gets vanishingly small, we arrive at a local statement, the *one-dimensional balance equation,*

$$\frac{\partial c(x, t)}{\partial t} = \underbrace{-\frac{\partial \mathbf{J}(x, t)}{\partial x}}_{\text{net motion}} \pm \underbrace{\sigma(x, t)}_{\text{source/sink.}} \tag{24}$$

The minus sign on $\partial \mathbf{J}/\partial x$ stems from the fact that the finite difference in (23) has a sign opposite to that in the definition of a derivative.

This is the basic form of the balance law that we shall soon apply to numerous specific problems. Before doing so, we will make a number of extensions and general statements. It is possible to skip this material and go on to Section 9.4 without loss of continuity.

9.3 OTHER VERSIONS OF THE CONSERVATION EQUATION

Tubular Flow

We shall drop assumption (2) and consider the possibility that the cross-sectional area of the tube may vary over space and time. To be somewhat more formal, we take the following definitions: By the *concentration* $c(x, t)$ we mean a quantity such that

$$\int_{x_1}^{x_2} c(x, t)A(x, t)\,dx = \text{total number of particles located within the tube in the interval } (x_1, x_2) \text{ at time } t. \tag{25a}$$

Similarly, the source density $\sigma(x, t)$ is defined by

$$\int_{x_1}^{x_2} \sigma(x, t)A(x, t)\,dx = \text{net rate of particle creation or degradation within the interval } (x_1, x_2) \text{ at time } t. \tag{25b}$$

The equation of balance can then be written in integral form (sometimes called the *weak form*), as follows:

$$\frac{\partial}{\partial t}\int_{x_0}^{x_0+\Delta x} c(x, t)A(x, t)\,dx = \mathbf{J}(x_0, t)A(x_0, t) - \mathbf{J}(x_0 + \Delta x, t)A(x_0 + \Delta x, t) \pm \int_{x_0}^{x_0+\Delta x} \sigma(x, t)A(x, t)\,dx. \tag{26}$$

(This is similar to a derivation in Segel (1980, 1984) for constant area.)

An *integral mean value theorem* allows one to conclude that at some locations (x_1, x_2) (where $x_0 \le x_i \le x_0 + \Delta x$ for $i = 1, 2$) the following is true:

$$\frac{\partial}{\partial t}[c(x_1, t)A(x_1, t)]\,\Delta x = \mathbf{J}(x_0, t)A(x_0, t) - \mathbf{J}(x_0 + \Delta x, t)A(x_0 + \Delta x, t) \pm [\sigma(x_2, t)A(x_2, t)]\,\Delta x. \tag{27}$$

Now dividing through by Δx and letting $\Delta x \to 0$, we get $x_1 \to x_0$ and $x_2 \to x_0$, so that in the limit equation (27) becomes

$$\frac{\partial}{\partial t}[c(x_0, t)A(x_0, t)] = -\frac{\partial}{\partial x}[\mathbf{J}(x_0, t)A(x_0, t)] \pm [\sigma(x_0, t)A(x_0, t)] \tag{28}$$

Special cases

1. If $A(x_0, t) = \tilde{A}$ is constant, dividing by $\tilde{A}$ reduces equation (28) to equation (24).
2. If $A(x, t) = \tilde{A}(x) \neq 0$ (that is, if the area does not change with time), then the equation can be written in the form

$$\frac{\partial c(x, t)}{\partial t} = -\frac{1}{\tilde{A}(x)}\frac{\partial}{\partial x}[\mathbf{J}(x, t)\tilde{A}(x)] \pm \sigma(x, t) \tag{29}$$

When the partial derivative is expanded, one obtains

$$\frac{\partial c(x, t)}{\partial t} = -\frac{\partial \mathbf{J}(x, t)}{\partial x} - \frac{\mathbf{J}(x, t)}{\tilde{A}(x)}\frac{\partial \tilde{A}(x)}{\partial x} \pm \sigma(x, t). \tag{30}$$

The equation is thus similar to (24) but contains an extra term which accounts for an effect similar to dilution; that is, a change in concentration that stems from local changes in the fluid volume "felt" by particles as they move along the length of the tube.

3. If $A(x, t) = \tilde{A}(t) \neq 0$ (if the area of the tube is uniform along its length but possibly time varying), then equation (28) leads to the following:

$$\tilde{A}(t)\frac{\partial c(x, t)}{\partial t} + c(x, t)\frac{\partial \tilde{A}(t)}{\partial t} = -\tilde{A}(t)\frac{\partial \mathbf{J}(x, t)}{\partial x} \pm \sigma(x, t)\tilde{A}(t). \tag{31}$$

After some rearranging, this becomes

$$\frac{\partial c(x,\,t)}{\partial t} = -\frac{c(x,\,t)}{\tilde{A}(t)}\frac{\partial \tilde{A}(t)}{\partial t} - \frac{\partial \mathbf{J}(x,\,t)}{\partial x} \pm \sigma(x,\,t). \tag{32}$$

Again the equation resembles (24), with an additional term that roughly speaking also describes a dilution effect as the tube expands or contracts.

4. In a situation where the cross-sectional area varies both spatially and temporally $[A = A(x,\,t)]$ it follows that equation (28) can be written

$$\frac{\partial c(x,\,t)}{\partial t} = -\frac{\partial \mathbf{J}(x,\,t)}{\partial x} \pm \sigma(x,\,t) - \frac{1}{A(x,\,t)}\left[\mathbf{J}(x,\,t)\frac{\partial A(x,\,t)}{\partial x} + c(x,\,t)\frac{\partial A(x,\,t)}{\partial t}\right] \tag{33}$$

Flows in Two and Three Dimensions

To write a balance equation analogous to (24) in higher dimensions we consider a small rectangular element of volume $\Delta V = \Delta x \Delta y \Delta z$ situated in R^3 and account for motion of particles into and out of the region. First it proves necessary to extend somewhat our definition of flux, for now both direction *and* magnitude of flow have to be considered.

Let us focus attention on a point $(x_0,\, y_0,\, z_0)$ in R^3. We shall define *flux* by counting the number of particles per unit time that traverse an imaginary unit area A suspended at $(x_0,\, y_0,\, z_0)$ with some particular *orientation*. As the orientation of the "test area" is varied, the rate of crossings changes. Indeed, the highest rate of crossing is achieved when the predominant flow direction is orthogonal to the area that it must cross. This leads us to define *flux* as a vector in the direction $\mathbf{n}$ whose magnitude is given by:

$$|\mathbf{J}(x,\,y,\,z,\,t)| = \begin{array}{l}\text{net number of particles crossing}\\ \text{a unit area at } (x,\,y,\,z) \text{ per}\\ \text{unit time at time } t\end{array} \tag{34}$$

where $\mathbf{n}$ is the unit normal vector to that element of area that admits the greatest net crossings. [See Figure 9.4(*a*).]

We shall symbolize the components of $\mathbf{J}$ (in R^3) as follows:

$$\mathbf{J}(x,\,y,\,z) = (J_x,\,J_y,\,J_z). \tag{35}$$

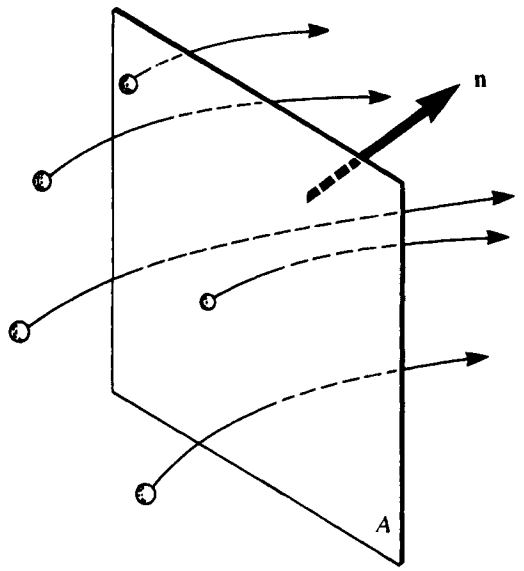
Each of the components J_x, J_y, and J_z may in general depend on both space and time.

In three dimensions the magnitude of flux is given by the quantity

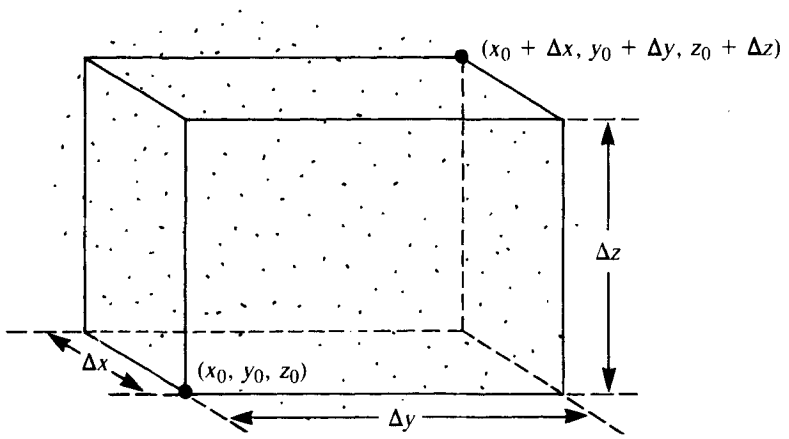
$$|\mathbf{J}| = (J_x^2 + J_y^2 + J_z^2)^{1/2} = (\mathbf{J}\cdot\mathbf{J})^{1/2} \tag{36}$$

(where $\cdot$ represents a vector dot product). Given some test area A, this definition of flux allows one to calculate the number of particle crossings N that take place in a given time t. If $\mathbf{m}$ is a unit vector perpendicular to the test area, one obtains

$$N = (\mathbf{J}\cdot\mathbf{m})A\,\Delta t. \tag{37}$$



(a)



(b)

Figure 9.4 *(a) In* R^3 *flux* **J** *is a vector. Its magnitude represents the net number of particles crossing an imaginary unit area per unit time. Its direction is given by the normal vector* **n** *to the given area* A. *(b) The equation of conservation (39) is derived by considering net flow into a small rectangular volume of dimensions* $\Delta x \times \Delta y \times \Delta z$.

To illustrate this idea, consider a wall of unit area at the point $(-1, 0, 3)$ orthogonal to the direction $m = (1, 0, 0)$, and a flux $\mathbf{J} = (z - y, x - z, y - x)$. At the point in question,

$$\mathbf{J} = (3, -4, 1),$$

so that the number of crossings is

$$N = (\mathbf{J} \cdot \mathbf{m})\, 1\Delta t = [(3, -4, 1) \cdot (1, 0, 0)]\, \Delta t = 3\Delta t.$$

Thus three particles traverse the wall per unit time.

Given a small rectangular volume as shown in Figure 9.4(*b*), the statement of balance must accommodate, as before, local creation and entry or departure through *each of the six* planar surfaces. Since these planes are parallel to the coordinate planes, we can readily determine their normal vectors and calculate the net number of particles crossing (inwards) through each wall. (See Table 9.1.)

The net rate of change of concentration inside the volume that accrues from combining all these factors is the following:

$$\begin{aligned}\frac{\partial c}{\partial t} = &\frac{J_x(x_0, y_0, z_0) - J_x(x_0 + \Delta x, y_0, z_0)}{\Delta x} \\ &+ \frac{J_y(x_0, y_0, z_0) - J_y(x_0, y_0 + \Delta y, z_0)}{\Delta y} \\ &+ \frac{J_z(x_0, y_0, z_0) - J_z(x_0, y_0, z_0 + \Delta z)}{\Delta z} \pm \sigma(x, y, z). \qquad (38)\end{aligned}$$

Taking the limit as $\Delta x \to 0$, $\Delta y \to 0$, and $\Delta z \to 0$, one obtains

$$\frac{\partial c}{\partial t} = -\left(\frac{\partial J_x}{\partial x} + \frac{\partial J_y}{\partial y} + \frac{\partial J_z}{\partial z}\right) \pm \sigma(x, y, z). \qquad (39)$$

$$\frac{\partial c}{\partial t} = -\nabla \cdot \mathbf{J} \pm \sigma \qquad (40)$$

where $\nabla \cdot \mathbf{J}$, called the *divergence of* $\mathbf{J}$, is the parenthetical term in equation (39). This scalar quantity can be described roughly as the net tendency of particles to leave an infinitesimal volume at the point (x, y, z). More details about the del operator ∇ are given in the box.

We have completed the derivation of the three-dimensional conservation equation. Note the similarity of equations (40) and (24). The two-dimensional case is left as an easy exercise for the reader. We must next turn to the question of what induces the motion of particles, molecules, or organisms so we can relate the idea of flux to the functions that describe spatial distributions.

Table 9.1 ***Particles Entering the Box (See Figure 9.4b.)***

Wall number	*Location on the plane*	*Inwards normal vector* $\mathbf{n}$	*Net inwards crossing* $\mathbf{J} \cdot \mathbf{n}$
1	$x = x_0$	$(1, 0, 0)$	$J_x(x_0, y_0, z_0)$
2	$x = x_0 + \Delta x$	$(-1, 0, 0)$	$-J_x(x_0 + \Delta x, y_0, z_0)$
3	$y = y_0$	$(0, 1, 0)$	$J_y(x_0, y_0, z_0)$
4	$y = y_0 + \Delta y$	$(0, -1, 0)$	$-J_y(x_0, y_0 + \Delta y, z_0)$
5	$z = z_0$	$(0, 0, 1)$	$J_z(x_0, y_0, z_0)$
6	$z = z_0 + \Delta z$	$(0, 0, -1)$	$-J_z(x_0, y_0, z_0 + \Delta z)$

The Del Operator ∇

Loosely speaking, the quantity ∇ behaves like a vector whose components in R^3 are

$$\nabla = \left(\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}\right). \tag{41}$$

We can think of the components as partial derivatives "hungry for a function to differentiate." The del operator can be combined with vector or scalar functions in several ways that parallel standard vector operations, as shown in Table 9.2.

Table 9.2 Analogies between Vector and Del Operations

	Ordinary vector operations	*Analogous del operations*
Scalar multiplication	For $\mathbf{v} = (v_1, v_2, v_3)$ and a scalar α, $\alpha\mathbf{v} = (\alpha v_1, \alpha v_2, \alpha v_3)$. The result is a *vector*.	For ∇ as defined in (41) and a function $f(x, y, z)$, $\nabla f = \left(\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}\right) f = \left(\frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}, \frac{\partial f}{\partial z}\right)$. This is the *gradient* of f and is a *vector*.
Dot products	For $\mathbf{v} = (v_1, v_2, v_3)$ and $\mathbf{u} = (u_1, u_2, u_3)$, $\mathbf{v} \cdot \mathbf{u} = v_1u_1 + v_2u_2 + v_3u_3$. The result is a *scalar*.	For ∇ as defined in (41) and $\mathbf{v} = (v_1, v_2, v_3)$, $\nabla \cdot \mathbf{v} = \left(\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}\right) \cdot (v_1, v_2, v_3) = \frac{\partial v_1}{\partial x} + \frac{\partial v_2}{\partial y} + \frac{\partial v_3}{\partial z}$. This is the *divergence* of the vector field $\mathbf{v}$ and is a *scalar* quantity.
Cross products	For two vectors $\mathbf{v}$ and $\mathbf{u}$ as defined above, $\mathbf{v} \times \mathbf{u} = \begin{pmatrix} \mathbf{i} & \mathbf{j} & \mathbf{k} \\ v_1 & v_2 & v_3 \\ u_1 & u_2 & u_3 \end{pmatrix} = (v_2u_3 - u_2v_3, v_3u_1 - v_1u_3, v_1u_2 - v_2u_1)$. The result is a *vector*.	For ∇ and $\mathbf{v}$ as defined above, $\nabla \times \mathbf{v} = \begin{pmatrix} \mathbf{i} & \mathbf{j} & \mathbf{k} \\ \frac{\partial}{\partial x} & \frac{\partial}{\partial y} & \frac{\partial}{\partial z} \\ v_1 & v_2 & v_3 \end{pmatrix} = \left(\frac{\partial v_3}{\partial y} - \frac{\partial v_2}{\partial z}, \frac{\partial v_1}{\partial z} - \frac{\partial v_3}{\partial x}, \frac{\partial v_2}{\partial x} - \frac{\partial v_1}{\partial y}\right)$. This is the *curl* of the vector field $\mathbf{v}$ and is a *vector*.

In descriptive terms, the vector ∇f measures local variations in a function and points to the direction of greatest steepness. The scalar quantity $\nabla \cdot \mathbf{v}$ measures the tendency of a vector field to represent the divergence (departure) of a fluid; the vector $\nabla \times \mathbf{v}$ (called the *curl* of $\mathbf{v}$) depicts a magnitude and axis of rotation (for example, of fluid in a vortex). Figure 9.5 demonstrates several vector fields that have net curl or divergence. We shall not concern ourselves too greatly with curl since in biological situations rotation is rarely encountered. (It does play a role in other physical sciences such as meteorology, where rotating atmospheric flows can be viewed as generating turbulent storms.) As equation (40) indicates, however, divergence is more relevant since we attempt to keep track of changes in densities of biological substances or populations. More details and basics about the properties of vector fields and the operations on them can be obtained in most standard calculus texts.

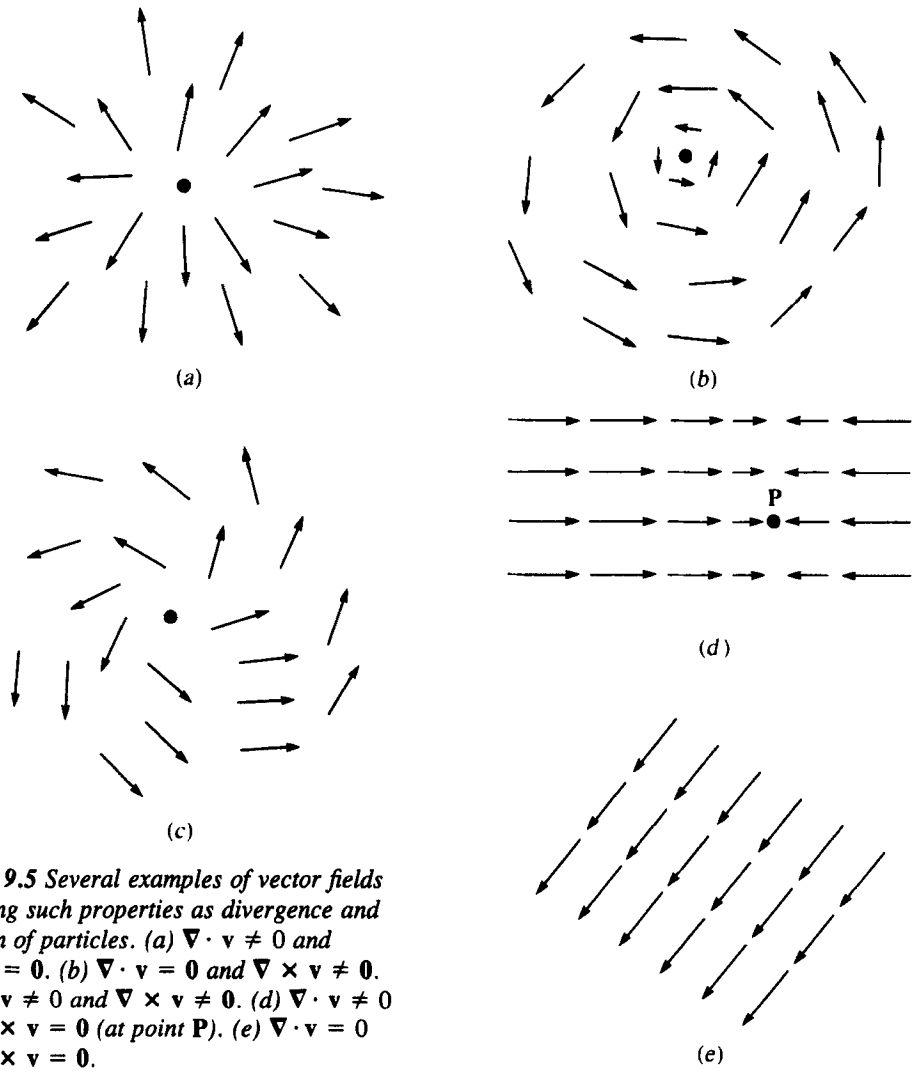


Figure 9.5 *Several examples of vector fields depicting such properties as divergence and rotation of particles. (a)* $\nabla \cdot \mathbf{v} \neq 0$ *and* $\nabla \times \mathbf{v} = \mathbf{0}$. *(b)* $\nabla \cdot \mathbf{v} = \mathbf{0}$ *and* $\nabla \times \mathbf{v} \neq \mathbf{0}$. *(c)* $\nabla \cdot \mathbf{v} \neq 0$ *and* $\nabla \times \mathbf{v} \neq \mathbf{0}$. *(d)* $\nabla \cdot \mathbf{v} \neq 0$ *and* $\nabla \times \mathbf{v} = \mathbf{0}$ *(at point* **P***). (e)* $\nabla \cdot \mathbf{v} = 0$ *and* $\nabla \times \mathbf{v} = \mathbf{0}$.

Example 4. Propagation of the Action Potential Along an Axon

In Section 8.1 equation (9) was derived for the action potential in the membrane of a voltage-clamped nerve axon. (Recall that voltage clamping means keeping the voltage the same all along the axon.) In real axons the action potential is a signal that propagates from the soma (cell body) along the axon to the *terminal synapses*. A space-dependent model must take this into account. Here we derive a balance equation for *charge* that incorporates the effect of transport in the axial direction. Define

x = distance along axon,

$q(x, t)$ = charge density per unit length inside axon at location x and time t,

$\mathbf{J}(x, t)$ = flux of charged particles (= current) at location x and time t.

$\sigma(x, t)$ = rate at which charge enters or leaves axon through its membrane at (x, t).

By referring to Figure 9.3 and to equation (24) one concludes that q is governed by the equation

$$\frac{\partial q}{\partial t} = -\frac{\partial \mathbf{J}}{\partial x} + \sigma. \tag{42}$$

(See problem 18.) In Section 8.1 we established that

$$q(x, t) = 2\pi a C v(x, t), \tag{43}$$

where

C = the capacitance of the axonal membrane,

a = the radius of the axon,

v = the voltage across the membrane.

It has further been shown that the rate at which charge enters the axon is

$$\sigma(x, t) = -2\pi a I_i, \tag{44}$$

where I_i is the net ionic current into the axon. Note that σ is analogous to a local source of charge. (It is the only term that leads to changes in q in the voltage-clamped equation (6) of Section 8.1.)

To find an expression for J we now use *Ohm's law*, which states that the current (in the axial direction) is proportional to a voltage gradient and inversely proportional to the resistance of the intracellular fluid. This implies that the net axial current in the axon would be

$$\mathbf{J} = -\left(\frac{\pi a^2}{R}\right)\frac{\partial v}{\partial x} \tag{45}$$

where $\partial v/\partial x$ is a local voltage gradient and R is the intracellular *resistivity* (ohm-cm).

Making the appropriate substitutions leads to the following equation for voltage:

$$\frac{\partial v}{\partial t} = \frac{a}{2RC}\frac{\partial^2 v}{\partial x^2} - \frac{I_i}{C}. \tag{46}$$

(See problem 18.) This equation with the appropriate assumptions about I_i is used to study propagated action potentials.

9.4 CONVECTION, DIFFUSION, AND ATTRACTION

Equations (24) and (40) are general statements that apply to numerous possible situations. To be more specific, it is necessary to select terms for $\mathbf{J}$ and σ capturing the particular forces and effects that lead to the motion, and to the creation or elimination of particles. The choices may be made on the basis of known underlying mechanisms, suitable approximations, or analogy with classical cases. We deal here with three classical forms of the flux term $\mathbf{J}$.

Convection

Particles in a moving fluid take on the fluid's velocity and participate in a net collective motion. If $\mathbf{v}(x, y, z, t)$ is the velocity of the fluid, one can easily demonstrate that the flux of particles is given by

$$\mathbf{J} = c\mathbf{v}, \tag{47}$$

where all quantities may vary with space and time. (See problem 10 for the key idea in proving this.)

Substituting (47) into equation (24) leads to the following one-dimensional *transport equation:*

$$\frac{\partial c(x, t)}{\partial t} = -\frac{\partial}{\partial x}[c(x, t)\mathbf{v}(x, t)], \tag{48}$$

or, in arbitrary space dimensions,

$$\frac{\partial c}{\partial t} = -\nabla \cdot (c\mathbf{v}). \tag{49}$$

Attraction or Repulsion

Suppose ψ is a function that represents some source of attraction for particles. (For example, the particles could be charged, and ψ could be an electrostatic field.) An attractive force would pull particles towards the site of greatest attraction. The direction and the magnitude of motion would thus be determined by the gradient of ψ (for example, it might be $\alpha\nabla\psi$ for some scalar α); the net flux in that direction would be

$$\mathbf{J} = c\alpha\nabla\psi. \tag{50}$$

(In one dimension this is simply $\mathbf{J} = c\alpha(\partial\psi/\partial x)$.) Substituting into equation (24) results in the following one-dimensional equation for attraction to ψ:

$$\frac{\partial c(x, t)}{\partial t} = -\frac{\partial}{\partial x}\left[c(x, t)\alpha\frac{\partial\psi}{\partial x}\right], \tag{51}$$

or, in arbitrary space dimensions,

$$\frac{\partial c}{\partial t} = -\nabla \cdot (c\,\alpha \nabla \psi). \tag{52}$$

We will later encounter two realistic versions of this general form, one of which depicts the motion of organisms towards sites of high nutrient concentration, and another the avoidance of overcrowding.

Random Motion and the Diffusion Equation

One of the most important sources of collective motion on the molecular level is *diffusion,* which results from the perpetual random motion of individual molecules. Diffusion is an important "metabolically cheap" transport mechanism in biological systems, but as we shall see, its effectiveness decreases rapidly with distance. A familiar assumption made in the context of diffusion through cell membranes is that the rate of flow depends linearly on concentration differences. This is an approximation to a more complicated situation. An extension of this concept to more general situations is known as *Fick's law,* which states that the flux due to random motion is approximately proportional to the local gradient in the particle concentration:

$$\mathbf{J} = -\mathcal{D}\nabla c. \tag{53}$$

The constant of proportionality $\mathcal{D}$ is the *diffusion coefficient.* The net migration due to diffusion is "down the concentration gradient," in a direction away from the most concentrated locations. This makes sense since in most situations where there is a relatively large local concentration, more molecules *leave* on average than return (due to the random character of their motions).

In one dimension, diffusive flux is simply given by $J = -\mathcal{D}(\partial c/\partial x)$, so that upon substitution into equation (24) one gets

$$\frac{\partial c(x,\,t)}{\partial t} = \frac{\partial}{\partial x}\left[\mathcal{D}\,\frac{\partial}{\partial x}\,c(x,\,t)\right] \tag{54}$$

(If $\mathcal{D}$ is a constant and does not depend on c or x, it can be drawn outside the outer derivative, giving the most familiar version of the one-dimensional diffusion equation:

$$\frac{\partial c}{\partial t} = \mathcal{D}\,\frac{\partial^2 c}{\partial x^2}. \tag{55a}$$

In arbitrary dimensions this result would be written

$$\frac{\partial c}{\partial t} = \nabla \cdot (\mathcal{D}\nabla c), \tag{55b}$$

or, if $\mathcal{D}$ is constant, then

$$\frac{\partial c}{\partial t} = \mathcal{D}\,\Delta c = \mathcal{D}\nabla^2 c. \tag{55c}$$

Random Walk and the Diffusion Equation

A collection of particles shown in Figure 9.6 moves randomly with an average step length Δx every time unit τ. Assume that the probability of moving to the left, λ_l, and to the right, λ_r, are both equal; that is, $\lambda_l = \lambda_r = \frac{1}{2}$. The x axis is subdivided into segments of length Δx. We write a discrete equation that describes the change in the number of particles located at x.

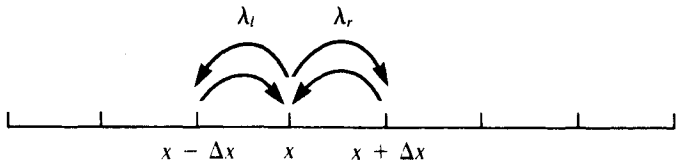


Figure 9.6 *Particles arrive at or depart from* x *randomly, with probabilities* λ_l *and* λ_r *of moving left or right.*

Let $C(x, t)\,\Delta x$ be the number of particles within the segment $[x, x + \Delta x]$ at time t. Then

$$C(x, t + \tau) = C(x, t) + \lambda_r C(x - \Delta x, t) - \lambda_r C(x, t) + \lambda_l C(x + \Delta x, t) - \lambda_l C(x, t). \tag{56}$$

Now we write Taylor-series expansions of these terms, as follows:

$$\begin{aligned} C(x, t + \tau) &= C(x, t) + \frac{\partial C}{\partial t}\tau + \frac{1}{2}\frac{\partial^2 C}{\partial t^2}\tau^2 + \cdots, \\ C(x \pm \Delta x, \tau) &= C(x, t) \pm \frac{\partial C}{\partial x}\Delta x + \frac{1}{2}\frac{\partial^2 C}{\partial x^2}\Delta x^2 \pm \cdots. \end{aligned} \tag{57}$$

Substituting into (56) and using the fact that $\lambda_r = \lambda_l = \frac{1}{2}$, we obtain

$$\frac{\partial c}{\partial t}\tau + \frac{1}{2}\frac{\partial^2 c}{\partial t^2}\tau^2 + \cdots = \frac{1}{2}\frac{\partial^2 c}{\partial x^2}\Delta x^2 + \frac{1}{4}\frac{\partial^4 c}{\partial x^4}\Delta x^4 + \cdots. \tag{58}$$

Dividing through by τ, we look at a limiting form of this equation for $\tau \to 0$, $\Delta x \to 0$ such that

$$\frac{(\Delta x)^2}{2\tau} = \text{constant} = \mathcal{D}. \tag{59}$$

Then the result is

$$\frac{\partial c}{\partial t} = \frac{(\Delta x)^2}{2\tau}\frac{\partial^2 c}{\partial x^2} = \mathcal{D}\frac{\partial^2 c}{\partial x^2}. \tag{60}$$

Note that (60) is equivalent to equation (55a).

Extensions of the random walk model for $\lambda_l \neq \lambda_r$ and for numerous other special cases are described by Okubo (1980).

The symbol Δ is the *Laplacian* of c; it stands for the combination $\nabla \cdot \nabla$ (read "div dot grad"), also written ∇^2. Equations (54) and (55a) are also known as *heat equa-*

tions since they describe equally well the diffusion of heat following *Newton's law of cooling*.

Fick's law is just one version of flux of diffusion and warrants several remarks. Clearly the term $-\mathcal{D}\nabla c$ gives a directionality to $\mathbf{J}$. The diffusion coefficient $\mathcal{D}$ represents the degree of random motion (how "motile" the particles are); $\mathcal{D}$ depends strongly on the size of the particles, the type of solvent, and the temperature.

While the assumption is common that diffusive flux takes the form of equation (53), this is not the only possibility. From a consideration of the Taylor series, diffusive flux can be appreciated as a reasonable first approximation. Since diffusion derives from concentration differences, consider the Taylor-series expansion

$$c(x + \Delta x, t) - c(x, t) = \Delta x \frac{\partial c}{\partial x} + \left(\frac{\Delta^2 x}{2}\right) \frac{\partial^2 c}{\partial x^2} + \ldots .$$

If flux depends linearly on differences in concentrations, for quite small Δx, it is approximately proportional to $\partial c/\partial x$, which is the one-dimensional version of (53).

In more complicated situations (chiefly for high concentrations when interactions between molecules become important), Fick's law is no longer accurate and other versions of diffusion are more applicable. It is a challenging physical problem to deal with such situations. A full treatment of the diffusion equation and of random walks is given in Okubo (1980) along with references and outlines of its extension to more complicated situations.

9.5 THE DIFFUSION EQUATION AND SOME OF ITS CONSEQUENCES

The one-dimensional diffusion equation derived in Section 9.4 is

$$\frac{\partial c}{\partial t} = \mathcal{D} \frac{\partial^2 c}{\partial x^2}. \tag{55a}$$

In radially and spherically symmetric cases in two and three dimensions the equation is slightly different: In two dimensions one obtains

$$\frac{\partial c}{\partial t} = \frac{\mathcal{D}}{r} \frac{\partial}{\partial r}\left(r \frac{\partial c}{\partial r}\right), \tag{61}$$

whereas in three dimensions the result is

$$\frac{\partial c}{\partial t} = \frac{\mathcal{D}}{R^2} \frac{\partial}{\partial R}\left(R^2 \frac{\partial c}{\partial R}\right), \tag{62}$$

where r and R are the distances away from the origin. (See problem 12 for an easy derivation.)

The methods one would apply to solving each of these equations would be somewhat different. However, even without solving them explicitly, certain interesting conclusions can be made. Based on dimensional considerations alone it follows from any one of equations (55a), (61), or (62) that $\mathcal{D}$ has the following units:

$$\mathcal{D} = \frac{(\text{distance})^2}{\text{time}}. \tag{63}$$

Table 9.3 ***Diffusion Coefficients of Biological Molecules***

Temperature (°C)	*Substance*	$\mathcal{D}(cm^2\ sec^{-1})$	*Ref*
0	Oxygen in air	1.78×10^{-1}	1
20	Oxygen in air	2.01×10^{-1}	1
18	Oxygen in water	1.98×10^{-5}	1
25	Oxygen in water	2.41×10^{-5}	1
20	Sucrose in water	4.58×10^{-6}	2

Sources:

1. L. Leyton (1975), *Fluid Behavior in Biological Systems*, Clarendon Press, New York.
2. K. E. Van Holde (1971), *Physical Biochemistry*, Prentice-Hall, Englewood Cliffs, N. J.

From this simple observation follow a number of results whose consequences are important in numerous biological systems. First, as we shortly see, equation (63) implies that

1. The average distance through which diffusion works in a given time is proportional to $(\mathcal{D}t)^{1/2}$.
2. The average time taken to diffuse a distance d is proportional to $d^2/\mathcal{D}$.

The diffusion coefficients of several key biological substances are given in Table 9.3. As a typical magnitude for the diffusion coefficient of small molecules such as oxygen in a medium such as water, we shall take

$$\mathcal{D}_{\text{oxygen}} \simeq 10^{-5}\ \text{cm}^2\ \text{sec}^{-1}.$$

The dimensions of a single cell are roughly 1 to 10 microns ($1\ \mu = 10^{-4}$ cm $= 10^{-6}$ m). As shown in Table 9.4, the amount of time it takes to diffuse through a given distance increases rapidly with the length scale.

On the scale of intracellular structures, diffusion is an extremely rapid process and can thus act as a metabolically free transport mechanism, in the sense that no energy need be expended by the cell to maintain it. On somewhat larger scales, (such as 1 mm), diffusion is already inadequate for such critical functions as oxygen transport. The longest cells of the human body are neurons; some of these have axons that are at least 1 m in length. Transport of small molecules from one end to the other would take roughly 30 years if diffusion were the only available mechanism.

Table 9.4 ***Time Taken to Diffuse Through a Given Distance***

Distance	*Diffusion time*
$1\ \mu\text{m} = 10^{-6}$ m	10^{-3} sec
$10\ \mu$m	0.1 sec
1 mm	10^3 sec $\simeq$ 15 min
1 cm	10^5 sec $\simeq$ 25 h $\simeq$ 1 day
1 m	10^8 sec $\simeq$ 27 years

The following simple arguments due to, for example, Haldane (1928) and LaBarbera and Vogel (1982) lead to a number of deductions about the limitations of diffusion.

Consider a spherical cell of radius r. The volume and surface area of such a cell are

$$V = \tfrac{4}{3}\pi r^3, \qquad S = 4\pi r^2. \tag{64}$$

Suppose that the cell metabolizes a given substance completely, so that its concentration at $r = 0$ is $c(r, t) = 0$, while its concentration at the surface is c_0. The gradient thus established is c_0/r (concentration difference per unit distance). Thus a diffusive flux of magnitude $\mathcal{D}c_0/r$ would admit molecules through the cell surface. The total number of molecules entering the cell per unit time would be

$$JS \simeq \mathcal{D}\frac{c_0}{r}4\pi r^2 = 4\pi\mathcal{D}c_0 r. \tag{65}$$

The rate of degradation of substance, however, is generally proportional to the volume of the cell:

$$\text{rate used} \simeq \frac{4}{3}\frac{\pi r^3}{\tau}, \tag{66}$$

where τ is the time constant for the degradation process. Thus

$$\frac{\text{rate supply}}{\text{rate used}} \simeq 3\mathcal{D}c_0\frac{\tau}{r^2}. \tag{67}$$

Since for a viable cell this ratio should not fall below 1, it is necessary that

$$1 \simeq 3\mathcal{D}c_0\frac{\tau}{r^2}, \tag{68}$$

or

$$c_0 = \frac{r^2}{3\tau\mathcal{D}}. \tag{69}$$

To match supply and demand the minimum external substance concentration must be proportional to the square of the cell radius. It is therefore unrealistic to expect spherical cells whose radii are large to rely solely on diffusion as a means of conveying crucial substances inside the cell.

LaBarbera and Vogel (1982) point out some of the most common ways adopted by organisms to reduce the limitations due to diffusion. These are highlighted below.

Size and shape

Geometry influences diffusion rates. Flat shapes (such as algal leaves) or long branched filaments (such as fungi, filamentous algae, roots, and capillaries) are ideally suited for organisms that rely heavily on direct absorption of substances from their environment; these shapes can increase in volume (for example, by getting longer) without changing the distance through which diffusion must act (that is, the

radius of the cylinder). La Barbera and Vogel suggest a dimensionless *flatness index*

$$\gamma = \frac{S^3}{V^2} \tag{70}$$

as an appropriate description of shape; they point out that with increasing size, an organism relying on diffusion must increase its flatness.

Dimensionality

It can be shown that the diffusion time taken to reach some internal sink depends differently on length scales in one, two, and three dimensions; one obtains somewhat different results from the equations (55a), (61), or (62). With the geometries given in Figure 9.7 one can establish the results that the diffusion time is as follows:

$$\text{in one dimension:} \quad \tau_1 \simeq \frac{L^2}{2\mathcal{D}_1}. \tag{71a}$$

$$\text{in two dimensions:} \quad \tau_2 \simeq \frac{L^2}{2\mathcal{D}_2} \ln \frac{L}{a}. \tag{71b}$$

$$\text{in three dimensions:} \quad \tau_3 \simeq \frac{L^2}{2\mathcal{D}_3} \frac{2}{3} \frac{L}{a}. \tag{71c}$$

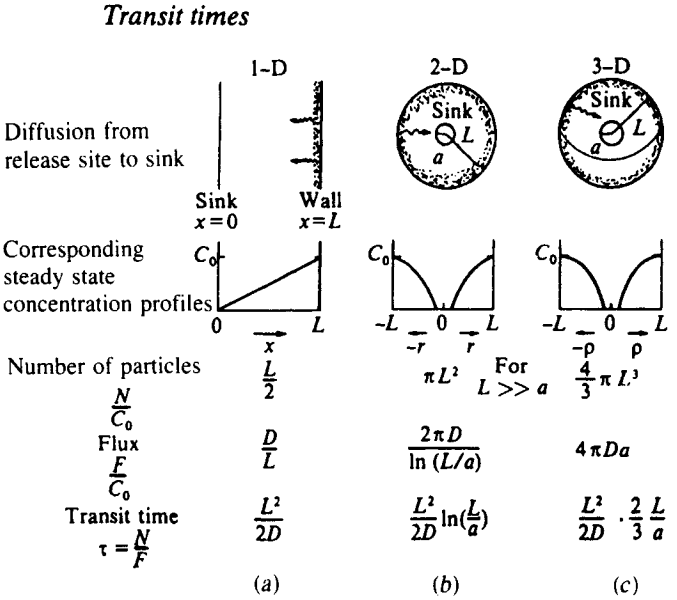


Figure 9.7 *The average time it takes a particle to diffuse from a source to a sink, called the transit time τ, depends on the dimensionality. (a) In one dimension, τ is proportional to L^2 where L is the distance. (b) In two dimensions, τ is greater by a factor of* $\ln(L/a)$ *where* a *is the radius of the sink. (c) In three dimensions the multiplicative factor is* L/a. *[From Hardt, S. (1980). Transit times. Fig. 6.2.1, p. 455. Copyright © 1980 by Cambridge University Press and reprinted with their permission.] In L. A. Segel,* Mathematical Models in Molecular and Cellular Biology. *Cambridge University Press, England.*

Here L is the cell radius and a is the radius of an internal sink (for example, an enzyme molecule that degrades substance). (See details in Figure 9.7 and Section 9.6.)

Murray (1977, chap. 3) gives an in-depth analysis and application of the effects of dimensionality to the antenna receptors of moths. In a set of papers, S. Hardt describes a convenient way of calculating transit times without explicitly solving the time-dependent diffusion equation.

We thus see that diffusion acts much more quickly in one- or two-dimensional settings than in three dimensions. This provides an advantage for intracellular organization of chemical reactions on membranes (which are two-dimensional) rather than on "loose" enzymes in the cytoplasm. Hardt (1978) compares the two- and three-dimensional cases where a represents the dimensions of an enzyme ($\sim$10 Å) and $\mathcal{D}_2 \simeq 100\mathcal{D}_3$. She concluded that for the cells of diameter larger than 1 μ, the organism benefits by arranging enzymes on internal membranes.

Circulatory systems

Where *geometric* solutions to diffusion limitations have failed, organisms have evolved ingenious mechanisms to convey substances to their desired destinations. From the intracellular *cytoplasmic streaming* and assorted mechanochemical methods to the circulatory system of macroscopic organisms, the ultimate purpose is to overcome the deficiency of long-distance diffusion and to transport substances efficiently. A fascinating account of the minimal design principle necessary to make a circulatory system work is given by LaBarbera and Vogel.

9.6 TRANSIT TIMES FOR DIFFUSION

Despite limitations on large distance scales, diffusion is of great importance in many processes on the cellular level. To give one example, communication between neighboring neurons is based on a chemical information system. Substances such as *acetylcholine* (called a *neurotransmitter*) are released by vesicles at the terminal branches of a given neuron, diffuse across the synapses, and relay messages to the neighboring neuron. An important consideration, particularly so in this example, is the average length of time taken to diffuse a given distance and how this time depends on particular features of the geometry.

Until a recent innovation suggested by Hardt, the problem of *diffusion transit times* was addressed by solving the time-dependent diffusion equation in the geometry of interest and using the resulting solution to derive a relationship. This process tends to be rather cumbersome for all but the simplest cases because solving diffusion equations in complicated geometries is a nontrivial task. Thus the approach was less than ideal.

A simpler method, proposed by Hardt (1978), is based on the observation that the *mean transit time* τ of a particle is independent of the presence or absence of other particles (given that no interactions occur) and can thus be computed in a steady-state situation. Hardt remarked that τ is then given by a simple ratio of two quantities that can be calculated in a straightforward way once the steady-state diffusion equation is solved. Solving the latter is always easier than solving the time-de-

pendent problem, since it is an ordinary differential equation. To establish Hardt's result we define the following quantities:

N = total number of particles in the region,

F = total number entering the region per unit time,

λ = average removal rate of particles,

$\tau = 1/\lambda$ = average time of residency in the region.

Regardless of spatial variations, one can make an approximate general statement about the total number of particles in a given region. For instance, if particles enter at some constant rate F and are removed at a sink with rate λ, then

$$\frac{dN}{dt} = \begin{matrix}\text{entering}\\ \text{rate}\end{matrix} - \begin{matrix}\text{removal}\\ \text{rate}\end{matrix} = F - \lambda N. \tag{72}$$

In steady state ($dN/dt = 0$) we obtain the result that

$$F = \lambda N = \frac{N}{\tau} \Rightarrow \tau = \frac{N}{F}. \tag{73}$$

Example 5

Consider the one-dimensional geometry shown in Figure 9.7(a), with particles entering at $x = L$ and diffusing to $x = 0$. Then assuming particles cannot leave the region (the interval $[0, L]$), the mean residency time for a particle is the same as the mean time it takes to diffuse from the source (wall at $x = L$) to the sink (at $x = 0$). (It is assumed that particles are removed only at the sink.)

The time-dependent particle concentration is given by equation (55a). However, according to Hardt's observation, to compute the mean time for diffusion it suffices to find the steady-state quantities. To do so we consider the steady-state equation

$$\frac{\partial}{\partial x}\left(\mathcal{D}\frac{\partial c}{\partial x}\right) = 0, \tag{74}$$

and assume that $c(L) = C_0$, $c(0) = 0$. (These are *boundary conditions*, to be discussed in more detail in Section 9.8 and the Appendix. In the equation to be solved c depends only on x, so we have an ODE whose solution is easily found to be

$$c(x) = \alpha x + \beta. \tag{75}$$

By using the boundary conditions we find $\alpha = C_0/L$ and $\beta = 0$, so that

$$c(x) = C_0\frac{x}{L}. \tag{76}$$

(See problem 21.) The total number of particles is

$$N = \int_0^L C(x)\,dx = \frac{C_0}{L}\int_0^L x\,dx = \frac{C_0}{L}\frac{L^2}{2} = C_0\frac{L}{2}. \tag{77}$$

Particles enter through $x = L$ due to diffusive flux,

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

Assuming a wall of unit area at $x = L$, we obtain the result that

$$F = \text{flux} \times \text{area} = J \times 1 = \mathcal{D}\frac{C_0}{L}. \tag{78}$$

Note that in higher dimensions it will be necessary to take into account the *area* through which particles can enter, which depends in a less trivial way on the geometry of the region (see problems 19 and 20).

Thus the mean transit time from source to sink is

$$\tau = \frac{N}{F} = \frac{C_0 L}{2}\frac{L}{\mathcal{D}C_0} = \frac{L^2}{2\mathcal{D}}. \tag{79}$$

Derivations of similar results for two and three dimensions are outlined in the problems.

9.7 CAN MACROPHAGES FIND BACTERIA BY RANDOM MOTION ALONE?

Macrophages are cells that are implicated in a number of defense responses to infection in the body. One of their important roles is to clear the lung surface of the bacteria we inhale with every breath. Macrophages are motile, crawling about on the walls of *alveoli* (the small air sacs in the lung at which gas exchange with the blood takes place) until they locate and eliminate an invader. Although the whole process is a complicated one involving several types of cells and chemical intermediates, the basic goal can be summarized simply: the macrophage response must be sufficiently rapid and accurate to prevent the proliferation of invading microorganisms. A good summary of the macrophage response to the bacterial challenge is given by Lauffenburger (1986) and Fisher and Lauffenburger (1986).

These authors propose an interesting question regarding the motion of the defending macrophages: Is random motion by the macrophages adequate to find their bacterial targets before rapid population increase has occurred? To answer this question, Lauffenburger observes that a macrophage moves at a characteristic speed s. The direction of motion is typically fairly constant for a time duration τ, and then some reorientation may occur. If the motion is truly random, it is possible to define an "effective diffusion coefficient" for macrophages.

$$\mathcal{D} = \tfrac{1}{2}\tau s^2. \tag{80}$$

(This can be based on rigorous random-walk calculations; see problem 22.)

We now consider a simple two-dimensional geometry such as the one shown in Figure 9.7(*b*). The sink (or "target") will represent a bacterium, assumed to have an approximate radius of detection a, and the disk (with radius R) will depict the surface of an alveolus. We shall assume that a macrophage enters the region through its circular boundary and searches until it arrives at its target. The transit time based on a purely random motion is given by equation (71b). According to Lauffenburger and Fisher (1986), the values of constants that enter into consideration are as follows:

a = radius of bacterial cell = 20 μ,

s = speed of motion of macrophage = 3 μ min^{-1}

ϵ = time spent moving in given direction = 5 min,

A = area of alveolus = 2.5×10^5 μ^2,

N = number of bacteria = 1,

ν = reproductive rate of bacteria = 0.2 hr^{-1}.

Then the radius of the disk is

$$L = \left(\frac{A}{\pi}\right)^{1/2} = \left(\frac{2.5 \times 10^5}{\pi}\right)^{1/2} = 2.8 \times 10^2\ \mu. \tag{81}$$

The effective diffusion coefficient is

$$\mathcal{D} = \frac{s^2\epsilon}{2} = (3\ \mu)^2 \times \frac{5\ \text{min}}{2} = 22.5\ \mu^2\ \text{min}^{-1}. \tag{82}$$

Thus the average time to reach the bacterial cell is

$$\tau = \frac{L^2}{2\mathcal{D}} \ln \frac{L}{A} = \frac{(2.8 \times 10^2)^2}{(2)(22.5)} \ln \frac{2.8 \times 10^2}{20}, \tag{83}$$

$$= 1.74 \times 10^3\ (2.64) \simeq 4.6 \times 10^3\ \text{min} = 76\ \text{h}.$$

However, the bacterial doubling time τ_d is given by

$$\tau_d = \frac{1}{\nu} = \frac{1}{0.2} = 5\ \text{h}. \tag{84}$$

Thus if random motion was the only means of locomotion, the macrophage would on average be unable to find its target before proliferation of bacteria takes place.

By contrast, if macrophages are perfectly sensitive to the relative location of their targets, the time taken to reach the bacteria would be

$$T = \frac{L}{s} = 2.8 \times \frac{10^2}{3} = 93\ \text{min} \simeq 1.5\ \text{h}. \tag{85}$$

In practice, neither one of these two extremes is totally accurate; the orientation of the macrophage is indeed governed by gradients in chemical factors produced as byproducts of infection, although some random motion is also present. We shall discuss chemotaxis more fully in the following chapters.

9.8 OTHER OBSERVATIONS ABOUT THE DIFFUSION EQUATION

In this section we make some general observations about the mathematical properties of the diffusion equation, leaving certain technical details to the Appendix at the end of this chapter.

Consider the one-dimensional diffusion equation

$$\frac{\partial c}{\partial t} = \mathcal{D} \frac{\partial^2}{\partial x^2} c. \tag{86}$$

By a solution to equation (86) we mean a real-valued function of (x, t) whose partial derivatives satisfy (86). We first remark that (86) is linear. Thus if $c = \phi_1(x, t)$ and $c = \phi_2(x, t)$ are two solutions of (86), then so is $c = A\phi_1(x, t) + B\phi_2(x, t)$. This follows from the superposition principle, as in linear difference or differential equations.

We can reinforce the connection between partial and ordinary differential equations by writing (86) in "operator notation":

$$\frac{\partial c}{\partial t} = \mathcal{L}c, \tag{87a}$$

where

$$\mathcal{L} = \mathcal{D}\frac{\partial^2}{\partial x^2}. \tag{87b}$$

$\mathcal{L}$ is a *linear operator,* also called the *diffusion operator;* it is an entity that takes a function c and produces another function ($\mathcal{D} \times$ the second x partial derivative of c). It will soon be clear why such notation is helpful.

Equation (86) has two spatial derivatives and one time derivative. Thus, in order to select out a single (*unique*) solution from an infinite class of possibilities, it is necessary to specify, in addition to (86), two other spatial constraints (boundary conditions) and one time constraint (an initial condition). However, were this done in an arbitrary or haphazard way, the problem might be such that no sensible solutions to it would exist. ("Sensible" solutions are those that conform to real physical processes.) The problem is then said to be ill posed. What constitutes a *well-posed problem* depends on the character of the PDE and the combination of added conditions. (Mathematicians are particularly concerned with proving *well-posedness,* since this is essentially equivalent to guaranteeing that a unique and meaningful solution exists.) We shall avoid this issue entirely since it is beyond our scope.

Several examples of initial and boundary conditions typically applied to equation (86) are given in the Appendix. Physically such conditions specify the initial configuration [the concentration at time zero at every point in the region, $c(x, 0)$] and what happens at the boundary of the domain. It makes intuitive sense that both factors will influence the evolution of the concentration $c(x, t)$ with time. For example, a region for which particles are admitted through the boundaries will support different behavior than one that has impermeable boundaries.

In forming solutions to the diffusion equation, one finds especially useful functions $f(x)$ that satisfy the relation

$$\mathcal{L}f = \lambda f, \tag{88}$$

where $\mathcal{L}$ is given by (87b). Such functions are called *eigenfunctions,* and here again, in terminology previously encountered, λ is an *eigenvalue*. Eigenfunctions of the diffusion operator have the property that their second derivative is a multiple of the original function. Three familiar functions that fall into this category are the following:

$$f_1(x) = \exp(\pm\sqrt{\lambda}x), \tag{89a}$$

$$f_2(x) = \sin(\pm\sqrt{\lambda}x), \tag{89b}$$

$$f_3(x) = \cos(\pm\sqrt{\lambda}x). \tag{89c}$$

By straightforward partial differentiation, the reader may verify that

$$c(x, t) = e^{Kt} f_i(x) \qquad (i = 1, 2, 3) \tag{90}$$

are solutions to (86) if the constant K is chosen appropriately [see problem 15(a,b)]. We arrive at the same result in the Appendix using the technique of separation of variables.

To illustrate an important point, let us momentarily consider a finite one-dimensional domain of length L and assume that at the boundary of the region there is a sink that eliminates all particles. By this we mean that the concentration $c(x, t)$ is zero (and held fixed) at the ends of the interval so that for $x \in [0, L]$ the appropriate boundary conditions are

$$c(0, t) = 0, \tag{91a}$$

$$c(L, t) = 0. \tag{91b}$$

From the form of the solution in (90) it is readily verified that to satisfy (91a) one should select $f_1(x) = \sin(\pm\sqrt{\lambda}x)$, since neither of the other two eigenfunctions are zero at $x = 0$. Further restrictions are necessary to ensure that (91b) too is satisfied. This can be done by choosing

$$\sqrt{\lambda} = n\frac{\pi}{L} \qquad (n = 1, 2, \ldots), \tag{92}$$

since then $\sin(\sqrt{\lambda}L) = 0$.

Now consider a second situation. Suppose that this finite one-dimensional domain has impermeable boundaries, so that particles neither enter nor leave at the ends of the interval. This means that diffusive flux is zero at $x = 0$ and $x = L$. According to our definitions in Section 9.4,

$$\mathbf{J}(0) = \mathbf{J}(L) = \mathscr{D}\frac{\partial c}{\partial x}\bigg|_{\text{boundary}} = 0.$$

Thus *no-flux boundary conditions* are equivalent to the conditions

$$\frac{\partial c}{\partial x} = 0 \qquad \text{at} \qquad x = 0,$$

$$\frac{\partial c}{\partial x} = 0 \qquad \text{at} \qquad x = L.$$

To satisfy the first boundary condition we must choose in the solution (90) the eigenfunction $f_c(x) = \cos(\pm\sqrt{\lambda}\, x)$. (This has a "flat" graph at $x = 0$.) Similarly, to satisfy the second condition we need

$$\sqrt{\lambda} = n\frac{\pi}{L} \qquad (n = 0, 1, 2, \ldots). \tag{92}$$

Since then $\cos(\sqrt{\lambda}\, L) = \cos(n\pi) = \pm 1$. (In other words, the cosine has a "flat" graph also at $x = L$.)

This discussion illustrates the idea that imposing boundary conditions tends to weed out certain classes of solutions (for example, (89a,c) in the first example). Fur-

thermore, in a given class of eigenfunctions only certain members are compatible. (For example, in the first case discussed, only those sine functions that go through zero at both ends of the interval are compatible.) This has important implications that will be touched on in later discussions.

The diffusion equation has many other types of solutions. Some of these will be described in the Appendix. In higher dimensions the geometry of the region may be much more complicated and difficult to treat analytically. At times certain features such as radial symmetry are exploited in solving the two- or three-dimensional diffusion equation. Crank (1979) and Carslaw and Jaeger (1959) describe methods of solution in such cases. An application to chemical bioassay is described in the next section.

9.9 AN APPLICATION OF DIFFUSION TO MUTAGEN BIOASSAYS

Chemical substances that are suspected of being carcinogens are frequently tested for *mutagenic properties* using a bioassay. Typically one seeks to determine whether a critical concentration of the substance causes *genetic mutations* (aberrations in the genetic material), for example in bacteria. The bacteria are grown on the surface of a solid agar nutrient medium to which a small amount of *mutagen* is applied. Generally, the chemical is applied on a presoaked filter paper at the center of a *petri dish* and spreads outwards gradually by diffusion. If the substance has an effect, one eventually observes concentric variations in the density and appearance of the bacterial culture that correlate with different levels of exposure to the substance.

While such qualitative tests have been commonly used for antibiotic, mutagenic, and other chemical tests, more recently quantitative aspects of the test were developed by Awerbuch et al (1979). These investigators noted that the radius of the observed zones of toxicity and mutagenesis (see Figure 9.8) could be used directly in obtaining good estimates of the threshold concentrations that produce these effects.

Working in radially symmetric situations, Awerbuch et al. (1979) used the radial form of the diffusion equation,

$$\frac{\partial c}{\partial t} = \mathcal{D}\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r}\right) - \frac{c}{\tau} \tag{93}$$

where

r = radial distance from the center of the dish,

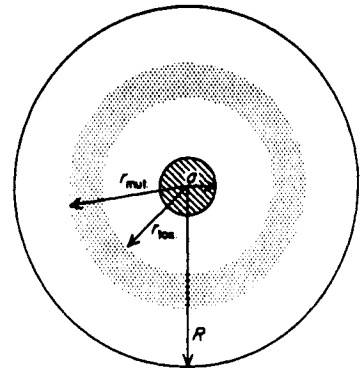
$c(r, t)$ = the concentration at a radial distance r and time t,

$\mathcal{D}$ = diffusion coefficient of the mutagen,

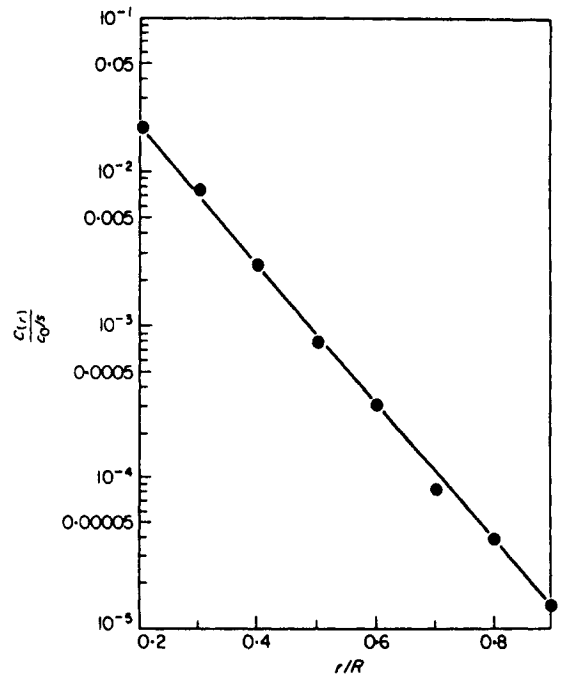
$1/\tau$ = the rate of spontaneous decay of the mutagen. (See problem 17.)

Because the probability of a mutation taking place depends both on the exposure concentration and the exposure duration, a time-integrated concentration was defined as follows:

$$C(r) = \frac{1}{(T_2 - T_1)s}\int_{T_1}^{T_2} c(r, t)\, dt, \tag{94}$$



(a)



(b)

Figure 9.8 *(a) In a test for mutagenicity, Awerbuch et al. (1979) place a mutagen-soaked filter paper (radius = a) at the center of a petri plate (radius = R). The substance diffuses outwards. Beyond some threshold level the substance fails to be toxic but does cause changes in the appearance of the bacteria growing on the plate (due to increased mutation). (b) The time-integrated concentration of mutagen [equation (94)] can be computed as a function of radial distance by solving the diffusion equation; a plot of log* c(r) *versus* r *can then be used to determine the threshold concentrations for toxicity* $c(r_{tox})$ *and for mutagenesis* $C(r_{mut})$*. [From Awerbuch et al. (1979). A quantitative model of diffusion bioassays. J. Theor. Biol., 79, figs. 1 and 2; reproduced by permission of Academic Press Inc. (London)]*

where s is the width of the agar and T_1 and T_2 represent times before and after the diffusion wave arrives at the point r.

The initial situation, shown in Figure 9.8(a), corresponds to a constant mutagen level within the filter paper disk (radius a) at the center of the dish. Thus at $t = 0$ the concentration can be described by the equation

$$c(r, 0) = \begin{cases} c_0 & \text{for } r < a \\ 0 & \text{for } r \geq a \end{cases}$$

This statement is an *initial condition* (see Appendix).

Furthermore, because the walls of the dish (at radius $r = R$) are impermeable to chemical diffusion, there is no radially directed flux of particles at $r = R$. Thus an additional condition is that

$$\frac{\partial c}{\partial r} = 0 \qquad \text{for } r = R.$$

This is the radial equivalent of the one-dimensional no-flux condition discussed in the previous section. It is also trivially true that $\partial c/\partial r = 0$ at $r = 0$ in this example. More discussion of boundary and initial conditions is given in the Appendix.

We will not go into the details of how the radially symmetric diffusion equation (93) is solved (see Awerbuch et al., 1979, and Caslaw and Jaeger, 1959). The methods are well known but not of particular importance to our discussion. Once a solution is obtained, the quantity (94) can be computed and tabulated. Figure 9.8(*b*) demonstrates a typical relationship between the value of $C(r)/c_0 s$ and radial distance that can then be used directly in making a quantitative estimate of the time-averaged mutagen threshold. Observe that if bacteria were exposed to a uniform fixed chemical concentration C_0, the value of $C(r)$ would be the same for all r and would equal C_0. In this way a correspondence can be made between results of the *diffusion bioassay* and similar *homogeneous bioassay* concentrations.

To illustrate the method, Awerbuch et al. (1979) quote the following example for the bacteria *Salmonella typhimurium* and the mutagen *N*-methyl-*N*-nitro-N^1-nitrosoguanidine. Conditions of the bioassay were as follows:

a = radius of chemically treated filter paper = 0.318 cm,
R = radius of petri plate = 2.5 cm,
s = thickness of agar = 0.356 cm,
τ = decay time of mutagen = 2.25 h,
$\mathcal{D}$ = diffusion coefficient of chemical in agar = 7.2×10^{-6} cm^2 sec^{-1},
c_0/S = initial concentration of chemical (applied on filter paper) corrected for agar thickness = 221.04 μg cm^{-3}.

[*Note:* c_0, $c(r, t)$, and $c(r)$ have dimensions of grams per centimeter squared since only two-dimensional diffusion is being considered here. For this reason it is necessary to divide by agar thickness so as to obtain a concentration in grams per centimeter cubed.]

Under these conditions, a ring of mutated bacteria occurs at a radial distance of 2.17 cm. We thus have

$$\frac{r}{R} = \frac{2.17}{2.5} = 0.868.$$

From Figure 9.8(*b*) we observe that corresponding to this radius is a dimensionless time-averaged concentration,

$$\frac{C(r)}{(c_0/s)} = 1.95 \times 10^{-5}.$$

Thus the critical concentration for mutagenicity is

$$C_{\text{mut}} = 1.95 \times 10^{-5} \times 221.04 \ \mu\text{g ml}^{-1},$$
$$= 4.31 \times 10^{-3} \ \mu\text{g ml}^{-1}.$$

The diffusion-based assay is of wide applicability. Considering the older methods of serial dilutions and tests of bacteria cultured at numerous mutagen concentrations, one appreciates the elegance of this simple and time-saving procedure.

PROBLEMS*

Problems 1 through 6 are suitable for reviewing the properties of functions of several variables.

1. For the following functions, sketch the surface corresponding to $z = f(x, y)$ and the level curves in the xy plane:
   (a) $f(x, y) = x^2 + y^2$.
   (b) $f(x, y) = -2x^2 - 2y^2$.
   (c) $f(x, y) = \exp \dfrac{-(x^2 + y^2)}{2}$.
   (d) $f(x, y) = 2x + y$.
   (e) $f(x, y) = xy$.
   (f) $f(x, y) = \sin x \cos y$.

2. For each function in problem 1 find the following:
   (1) $\dfrac{\partial f}{\partial x}$,
   (2) $\dfrac{\partial^2 f}{\partial x \partial y}, \dfrac{\partial^2 f}{\partial y \partial x}$, and
   (3) ∇f.

3. For each function in problem 1, determine whether there are any critical points. Which if any are local maxima?

4. Sketch the level curves described by the following equations. Give an equation for a surface that has these level curves. Sketch the vector field corresponding to ∇f by using its property of orthogonality to level curves:
   (a) $c = \dfrac{x^2}{a^2} + \dfrac{y^2}{b^2}$.
   (b) $c = x^2 + y$.
   (c) $c = x - y$.
   (d) $c = \dfrac{x^2}{a^2} - \dfrac{y^2}{b^2}$.
   (e) $c = (x^2 + y^2)$.

5. For the following vector fields, find $\nabla \times \mathbf{F}$, $\nabla \cdot \mathbf{F}$:
   (a) (x, y, z).
   (b) $(y - z, z - x, x - y)$.
   (c) $(x^2 + 2y + z, y^2 - x, z^2 - y^2)$.
   (d) $(\sin xyz, \cos xyz, e^{xyz})$.
   (e) $\left(\dfrac{1}{x}, \dfrac{1}{y}, \dfrac{1}{z}\right)$.
   (f) $(x + y, y + z, z + x)$.

*Problems preceded by an asterisk (*) are especially challenging.

***6.** Determine whether the following vector fields are gradient fields. If so, find ϕ such that $\mathbf{F} = \nabla\phi$:

(a) (x, y). **(d)** $(x + y, x - y)$.
(b) (y^2, x^2). **(e)** (ye^{xy}, xe^{xy}).
(c) $(\sin xy, \cos xy)$. **(f)** (x^2y, y^2x).

7. **(a)** Verify that terms in equation (22) carry the correct dimensions.
(b) Explain why the integral in equation (25a) represents the number of particles in the interval (x_1, x_2).
(c) Similarly, explain the integral in equation (25b).
(d) Give justification for equation (26).
(e) Verify that equation (27) leads to (28) when the appropriate limit is taken.

8. The cross-sectional area of the small intestine varies periodically in space and time due to peristaltic motion of the gut muscles. Suppose that at position x (where x = length along the small intestine) the area can be described by

$$A(x, t) = \frac{a}{2}[2 + \cos(x - vt)],$$

where v is a constant.

(a) Write an equation of balance for $c(x, t)$, the concentration of digested material at location x.
(b) Suppose there is a constant flux of material throughout the intestine from the stomach [that is, $\mathbf{J}(x, t) = 1$] and that material is absorbed from the gut into the bloodstream at a rate proportional to its concentration for every unit area of intestinal wall. Give the appropriate balance equation.
(c) Show that even if $\mathbf{J}(x, t) = 0$ and $\sigma(x, t) = 0$, the concentration $c(x, t)$ appears to change.

9. For a planar flow, consider a small rectangular region of dimensions $\Delta x \times \Delta y$. Carry out steps analogous to those of Section 9.3 (subsection "Flows in Two and Three Dimensions") to derive the two-dimensional form of the equation of conservation.

10. Consider the fluid shown in the accompanying diagram. Assume that every particle has the same velocity $\mathbf{v}$.

(a) What is the flux of particles through the unit area dA? (*Hint:* Consider all particles contained in an imaginary prism of length $v\Delta t$, where v is the magnitude of $\mathbf{v}$. During a time Δt they will have all crossed the wall dA. Now use the definition of flux to show that (47) holds.
(b) Extend your reasoning in part (a) to the case where $\mathbf{v}$ varies over space and time.

11. Suppose the diffusion coefficient of a substance is a function of its concentration; that is,

$$\mathcal{D} = f(c).$$

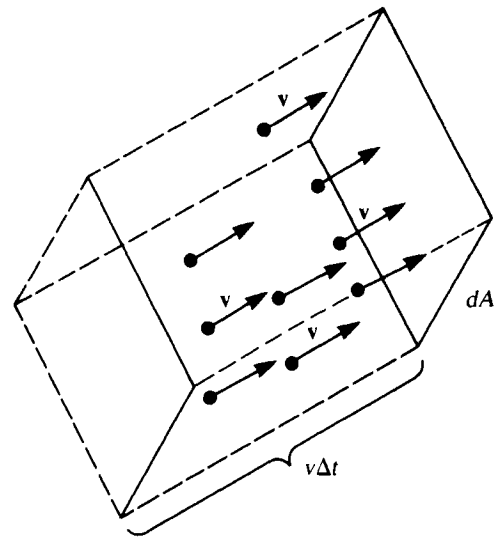


Figure for problem 10.

Show that c satisfies the equation

$$\frac{\partial c}{\partial t} = \mathcal{D}\frac{\partial^2 c}{\partial x^2} + g\left(\frac{\partial c}{\partial x}\right)^2,$$

where $g = f'(c)$.

12. **(a)** Consider a radially symmetric region $\mathcal{D}$ in the plane, and let $c(r, t)$ be the concentration of substance at distance r from the origin and $J(r, t)$ the radical flux. Use the derivation of the conservation laws in Section 9.3 (subsection "Tubular Flow") to show that $c(r, t)$ satisfies the following relation:

$$\frac{\partial c}{\partial t} = -\frac{1}{r}\frac{\partial}{\partial r}(Jr) \pm \sigma(r, t)$$

Hint: consider a pie-shaped "tube," that is, a small sliver removed from a circular disk—see Figure (*a*), and determine how its cross-sectional area changes with radial distance.

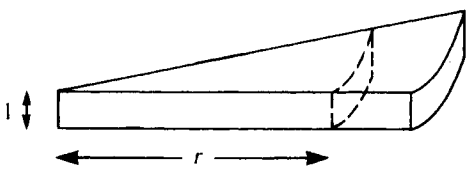


Figure (a) for problem 12.

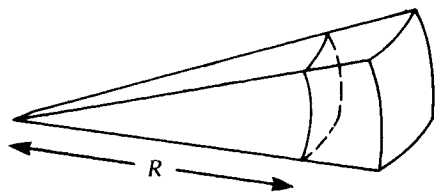


Figure (b) for problem 12.

(b) Extend the idea in part (a) to a spherically symmetric region S in R^3, and show that $c(R, t)$, the concentration at distance R from the origin, satisfies the following:

$$\frac{\partial c}{\partial t} = -\frac{1}{R^2}\frac{\partial(JR^2)}{\partial R} \pm \sigma(R, t).$$

Hint: For the "tube," consider an element of volume of a sphere and determine how its cross-sectional area depends on radial distance. See Figure (*b*).

(c) Use parts (a) and (b) to obtain the radially and spherically symmetric diffusion equations given in Section 9.5.

13. The time to diffuse from source to sink depends on dimensionality as demonstrated in equations (71a–c). Give conditions on the ratio L/a for which $\tau_3 > \tau_2 > \tau_1$.

14. **(a)** Show that the conclusions regarding diffusion transport into a cell hold equally well if the cell is nonspherical (such as a cell that has length l, width w, and girth g), provided that as it grows all three dimensions are expanded.

(b) Find the flatness ratio γ for the following shapes:

(1) An ellipsoid of dimensions $a \times b \times c$.

(2) A sphere of radius R.

(3) A long cylinder of radius r and height h (neglect the top and bottom caps).

(4) A cone whose radius is r when its height is h (neglect the top).

(c) *Extended project.* Make a summary of the various ways in which organisms overcome diffusional limitations, and illustrate these with examples drawn from the biological literature.

15. **(a)** Verify that equation (90) is a solution to equation (86).

(b) Determine what the restrictions are on K.

(c) Show that equations (91a,b) can only be satisfied by choosing

$$f(x) = \sin(\pm\sqrt{\lambda}x), \text{ where } \sqrt{\lambda} = \frac{n\pi}{L}.$$

16. **(a)** Suppose that in a diffusion bioassay for the mutagen *N*-methyl-*N*-nitro-N^1-nitrosoguanidine, one finds that mutations occur at a radial distance $r = 0.4R$, where R is the radius of the petri dish. Using constants quoted in Section 9.9 determine C_{mut}, the threshold concentration for mutation.

(b) Repeat part (a) for $r = 0.6R$.

17. **(a)** Explain equation (93) by expanding equation (61).

(b) Suppose the bioassay devised by Awerbuch et al. (1979) is performed in a thin tube rather than a radially symmetric plate. What would the appropriate equations and conditions of the problem be?

(c) Referring to your answers to part (a), what solutions for $c(x, t)$ would then typically be encountered?

18. *Propagated action potentials.*

(a) Explain equation (42) based on the definitions given for charge density, current, and charge "creation" σ.

(b) Explain equations (43) and (44). What would I_i depend on? (See Section 8.6.)

(c) Ohm's law states that $V = IR$, where V = potential difference across a resistance R, and I = current. How is equation (45) related to this law?

(d) Show that equations (42–45) together imply equation (46).

Problems 19 and 20 suggest generalized versions of mean diffusion transit times. Solution requires familiarity with double and triple integration.

19. In two dimensions consider the radially symmetric region shown in Figure 9.7(*b*) with a sink of radius a and a source of radius L. Assume that

$$c(a) = 0, \qquad c(L) = C_0.$$

(a) Solve the steady-state two-dimensional equation of diffusion

$$0 = \frac{\mathcal{D}}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right).$$

(b) Define

$$N = \iint_{\text{disk}} c\, dA = \int_0^{2\pi}\int_a^L c(r) r\, dr\, d\theta.$$

Compute this integral and interpret its meaning.

(c) Define

$$F = \text{flux} \times \text{circumference of circle}$$
$$= \left(\mathcal{D}\frac{\partial c}{\partial r}\right)(2\pi L)$$

Calculate F.

(d) Find $\tau = N/F$, and compare this with the value given in Figure 9.7.

20. In three dimensions consider the spherically symmetric region of Figure 9.7(*c*), again taking the sink radius to be a and the source radius to be L, where $c(a) = 0$ and $c(L) = C_0$. Let ρ = radial distance from the origin.

(a) Solve the steady-state equation

$$0 = \frac{\mathcal{D}}{\rho^2}\frac{\partial}{\partial \rho}\left(\rho^2\frac{\partial c}{\partial \rho}\right).$$

(b) Define

$$N = \iiint_{\text{sphere}} c dV = \int_0^{2\pi}\int_0^{\pi}\int_a^L c(\rho)\rho^2 \sin\phi\, d\rho\, d\phi\, d\theta.$$

Compute this integral and interpret its meaning.

(c) Define

$$F = \text{flux} \times \text{surface area of sphere}$$
$$= \left(\mathcal{D}\frac{\partial c}{\partial \rho}\right)(4\pi L^2)$$

Find F.

(d) Find $\tau = N/F$.

21. *Transit times for diffusion.* Consider the steady-state equation

$$\frac{\partial}{\partial x}\left(\mathcal{D}\frac{\partial c}{\partial x}\right) = 0$$

with boundary conditions $c(L) = C_0$ and $c(0) = 0$.

(a) Show that the solution is

$$c(x) = C_0\frac{x}{L}.$$

(b) Explain why

$$N = \int_0^L C(x)\,dx$$

is the number of particles in $[0, L]$.

(c) If λ is the average removal rate at the sink, explain why $1/\lambda$ is the average diffusion transit time in example 2 in Section 9.6.

22. *Random versus chemotactic motion of macrophages.*

(a) Define

Δx = average distance traveled by a macrophage in a fixed direction,

ϵ = time taken to move this distance,

$s = \Delta x/\epsilon$ = speed of motion.

Justify the relationship $\mathcal{D} = \frac{1}{2}\epsilon s^2$ based on the results of the random-walk calculation in Section 9.4.

(b) How would the conclusions of Section 9.7 change under each of the following circumstances:

(1) The macrophage moves twice as fast.

(2) The target is twice as big.

(3) The area of the alveolus is half as big.

(4) The reproductive rate of the bacteria is twice as large.

(c) Define

τ = time to reach bacterium based on random motion,

T = time to reach bacterium based on direct motion towards the target,

$R_0 = \tau/T$.

Find an expression for R_0 based on parameters of the problem. Is R_0 ever equal to 1?

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APPENDIX TO CHAPTER 9
SOLUTIONS TO THE ONE-DIMENSIONAL DIFFUSION EQUATION

A.1 REMARKS ABOUT BOUNDARY CONDITIONS

Here we consider a number of boundary conditions that could be suitable for the diffusion equation (86).

1. *Infinite domains*. In some problems one is interested in observing the changes in a finite distribution of particles that are far away from walls or boundaries. See Figure 9.9(*a*). It is then customary to assume that the concentration is "zero at infinity":

$$c(x, t) \longrightarrow 0 \qquad \text{as} \qquad x \longrightarrow \pm\infty. \tag{95}$$

The approximation is valid provided that in the time scale of interest there is little or no reflection at the boundaries.

2. *Periodic boundary conditions*. If diffusion takes place in an annular tube of length L, the concentration at x has to equal that at $x + L$ [see Figure 9.9(*b*)]. Thus periodic boundary conditions lead to

$$c(x, t) = c(x + L, t),$$

or in particular,

$$c(0, t) = c(L, t). \tag{96}$$

3. *Constant concentrations at the boundary*. The hollow tube in Figure 9.9(*c*) is suspended between two large reservoirs whose concentrations are assumed to be fixed. This leads to the following boundary conditions:

$$c(0, t) = C_1, \tag{97a}$$

$$c(L, t) = C_2. \tag{97b}$$

If $C = C_2 = 0$, the boundary conditions are said to be homogeneous.

4. *No flux through the boundaries*. When the ends of the tube are sealed, no particles can cross the barriers at $x = 0$ and $x = L$. This means that the flux, defined by (53) must be zero; that is,

$$\frac{\partial c}{\partial x} = 0 \qquad \text{at} \begin{cases} x = 0, \\ x = L. \end{cases} \tag{98}$$

In general, it is true that the solution of the diffusion equation, or for that matter any PDE, depends greatly on the boundary conditions that are imposed. Carslaw and Jaeger (1959) show the derivations of solutions appropriate for many sets of boundary and initial conditions.

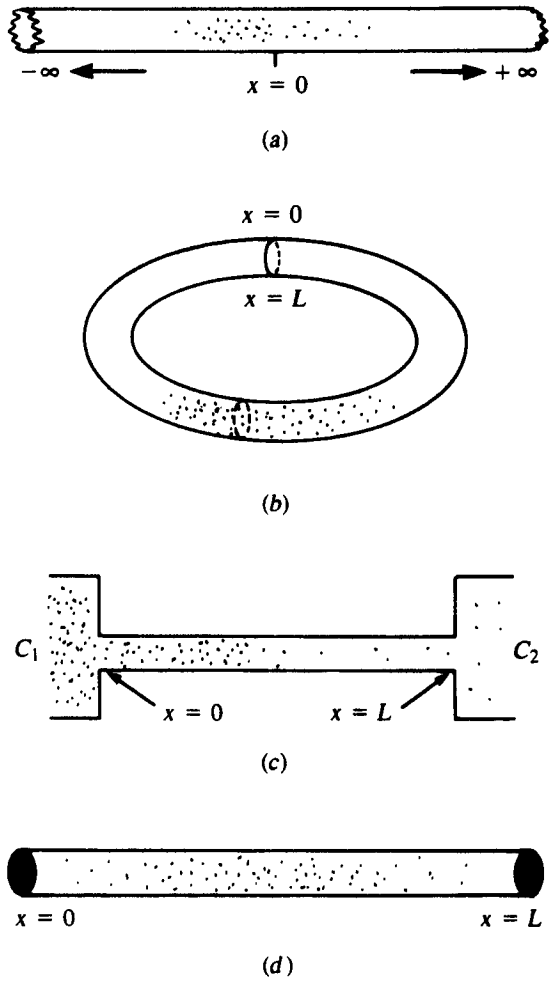


Figure 9.9 *Boundary conditions often used in solving the one-dimensional diffusion equation: (a) no particles at infinity [equation (95)]; (b) periodic boundary conditions [equation (96)]; (c) constant concentrations at one or both boundaries [equations (97a,b); (d) no flux at the boundaries, i.e., boundaries impermeable to particles [equation (98)].*

A.2 INITIAL CONDITIONS

Different initial configurations may be of interest in studying the process of diffusion. These may include the following:

1. *Particles initially absent:*

$$c(x, 0) = 0. \tag{99}$$

This condition is suitable for problems in which particles are admitted through the boundaries.

2. *Single-point release.* If particles are initially "injected" at one location (considered theoretically of infinitesimal width), it is customary to write

$$c(x, 0) = C_0\delta(x). \tag{100}$$

$\delta(x)$ is the *Dirac delta function,* actually a generalized function called a *distribution,*

which has the property that

$$\delta(x) = \begin{cases} \infty & \text{if } x = 0, \\ 0 & \text{if } x \neq 0, \end{cases} \tag{101}$$

and

$$\int_{-\infty}^{\infty} \delta(x)\, dx = 1. \tag{102}$$

See Figure 9.10(*a*).

3. *Extended initial distribution.* The initial configuration shown in Figure 9.10(*b*) would be described by

$$c(x, 0) = \begin{cases} C_0 & x < 0, \\ 0 & x \geq 0. \end{cases} \tag{103}$$

4. *Release in a finite region.* If the concentration is initially constant within a small subregion of the domain [see Figure 9.10(*c*)], the appropriate initial condition is

$$c(x, 0) = \begin{cases} C_0 & -a < x < a, \\ 0 & \text{otherwise.} \end{cases} \tag{104}$$

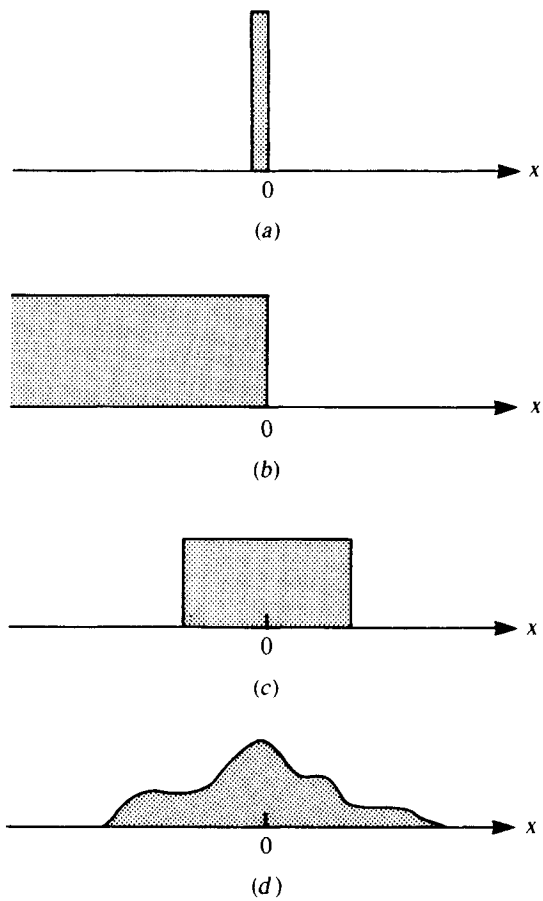


Figure 9.10 *Typical initial conditions for which the diffusion equation might be solved: (a) particles initially at* x = 0 *[equation (100)]; (b) extended initial distribution [equation (103)]; (c) release in a finite region [equation (104)]; (d) arbitrary initial distribution [equation (105)].*

5. *More general initial conditions.* It can more broadly be assumed that

$$c(x, 0) = f(x). \tag{105}$$

See Figure 9.10(*d*). Such initial conditions must generally be handled by Fourier-transform or Fourier-series methods unless $f(x)$ is of an especially elementary form. (Jones and Sleeman, 1983, discuss the details of this case.)

A.3 SOLVING THE EQUATION BY SEPARATION OF VARIABLES

In this section we briefly highlight a way of solving the one-dimensional diffusion equation given a set of boundary and initial conditions. Since this is not meant to be a self-contained guide but rather a quick introduction, the only method we discuss is separation of variables. Serious applied mathematics students should plan on taking a course on partial differential equations in which the more advanced and useful methods of Fourier transforms are taught.

We consider the equation

$$c_t = \mathcal{D}c_{xx}. \tag{106}$$

We will discuss problems in which the general solution takes the form

$$c(x, t) = c_T(x, t) + \bar{c}(x) \tag{107}$$

where $c_T(x, t)$ is a transient space- and time-dependent function that decays to zero and $\bar{c}(x)$ is the steady-state solution. We use separation of variables to find c_T.

Separation of Variables

Assume that $c_T(x, t)$ can be expressed as a product of two functions:

$$c_T(x, t) = S(x)T(t), \tag{108}$$

where S depends only on the spatial variable and T only on time. Substitute (108) into (106) to obtain

$$S(x)T'(t) = \mathcal{D}S''(x)T(t). \tag{109}$$

Rearranging (109) gives the following:

$$\frac{T'(t)}{T(t)} = \mathcal{D}\frac{S''(x)}{S(x)} = K. \tag{110}$$

This is called *separation of variables*. In equation (110) we have equated both sides to a constant K. This is the only possibility; otherwise by independently varying x and t, it would be possible to change one or the other side of the equation separately and a contradiction would be reached. Three distinct cases arise: $K = 0$, $K < 0$, and $K > 0$. In any of these the solutions to $T(t)$ and $S(x)$ can be obtained by solving

$$T'(t) = KT(t), \tag{111a}$$

$$S''(x) = \frac{K}{\mathcal{D}}S(x). \tag{111b}$$

These are both linear ODEs since each function depends on a single variable. The case $K = 0$ will not concern us since it leads to the somewhat uninteresting situation $T(t) =$ constant. If

$K > 0$, then by problem 24(c),

$$T(t) = \exp Kt, \tag{112a}$$

$$S(x) = \exp\left(\pm \sqrt{\frac{K}{\mathcal{D}}}x\right). \tag{112b}$$

Observe that transient solutions to equation (106) are thus of the form

$$\exp Kt \exp\left(\pm \sqrt{\frac{K}{\mathcal{D}}}x\right). \tag{113}$$

If $K < 0$ then a more convenient way of expressing these is to set

$$K = -\mathcal{D}\lambda, \qquad \frac{\sqrt{K}}{\sqrt{\mathcal{D}}} = -\lambda,$$

where λ is a constant (previously called the eigenvalue in section 9.8). Then complex exponentials lead to sinusoidal terms; one finds that by forming real-valued linear combinations, a (real-valued) transient solution can be written in the form

$$c_T(x, t) = \exp(-\lambda\mathcal{D}t)(A \cos \sqrt{\lambda}x + B \sin \sqrt{\lambda}x). \tag{114}$$

Note that $c_T(x, t) \to 0$ for $t \to \infty$. The values of λ, A, and B depend on the boundary and initial conditions of the problem.

Example 5

Consider equation (106) with the following boundary (BC) and initial (IC) conditions:

$$BC: \quad c(0, t) = c(L, t) = 0, \tag{115a}$$

$$IC: \quad c(x, 0) = f(x) \qquad \text{(to be specified below)}. \tag{115b}$$

It is easily verified that $\bar{c}(x) = 0$ is the steady-state solution (since the steady-state solution must satisfy the boundary condition). The boundary condition further implies that

$$T(t)S(0) = T(t)S(L) = 0. \tag{116}$$

Otherwise, if $T(t) = 0$, one would get $c_T \equiv 0$ for all t. Then observe that equation (111b) together with the first of these conditions leads to the conclusion that

$$S(x) = B \sin \sqrt{\lambda}x, \tag{117}$$

since $\sin(0) = 0$. Thus the separation constant K is necessarily negative in this case. The second condition can only be satisfied by choosing $\sqrt{\lambda}$ to be an integral multiple of π/L:

$$\lambda = \left(\frac{n\pi}{L}\right)^2 \qquad (n = 0, 1, 2, \ldots). \tag{118}$$

There is thus an infinite set of eigenfunctions that satisfy equation (106) and the homogeneous boundary condition. From the previous discussion we must conclude that the solution is of the form

$$c_T(x, t) = B \exp\left[-\left(\frac{n\pi}{L}\right)^2 \mathcal{D}t\right] \sin\left(\frac{n\pi x}{L}\right) \qquad (n = 0, 1, 2, \ldots). \tag{119}$$

In treating this problem, we have thus far neglected the initial condition from consideration. Notice that at $t = 0$ equation (119) reduces to the function

$$c_T(x, 0) = B \sin\left(\frac{n\pi x}{L}\right),$$

which is supposed to match the *a priori* specified initial condition (115b). Thus it would appear that the problem is consistent only with sinusoidal initial distributions. However, what makes its applicability much broader is the fact that all well-behaved functions $f(x)$ can be represented as a superposition of possibly infinitely many trigonometric functions such as sines, cosines or both. Such infinite superpositions are called *Fourier series*. We state this in the following important theorem.

The Fourier Theorem

If f and its derivative are continuous (or piecewise so) on some interval $0 \le x < L$, then on this interval f can be represented by an infinite series of sines:

$$f(x) = \sum_{n=1}^{\infty} (a_n \sin \beta_n x). \tag{120}$$

Equation (120) is called a *Fourier sine series*, and it converges to $f(x)$ at all points where f is continuous. The constants a_n are then related to f by the formula

$$a_n = \frac{2}{L}\int_0^L f(x) \sin \beta_n x \, dx. \tag{121}$$

See Boyce and DiPrima (1969) for more details and for similar theorems about cosine expansions.

Now recall that since equation (106) is linear, any linear superposition of solutions such as equation (119) will be a solution. With this in mind, we return to example 5.

Example 5 (continued)

From the observations in the previous box, we are led to consider solutions of the form

$$c_T(x, t) = \sum_{n=1}^{\infty} a_n \exp\left[-\left(\frac{n\pi}{L}\right)^2 \mathcal{D}t\right] \sin\left(\frac{n\pi x}{L}\right). \tag{122}$$

At $t = 0$ this must satisfy the initial condition. Then

$$\sum_{n=1}^{\infty} a_n e^0 \sin\frac{n\pi x}{L} = \sum_{n=1}^{\infty} a_n \sin\frac{n\pi x}{L} \equiv f(x).$$

According to Fourier's theorem this will hold provided that

$$a_n = \frac{2}{L}\int_0^L f(x) \sin\frac{n\pi x}{L} \, dx. \tag{123}$$

To find the full solution it then remains only to solve for the steady-state solution, $\bar{c}(x)$, which satisfies the equation

$$0 = \frac{\partial^2 c}{\partial x^2}. \tag{124}$$

Two integration steps lead to

$$\bar{c}(x) = \alpha x + \beta, \tag{125}$$

where α and β are integration constants. To satisfy the boundary conditions it is necessary to select $\bar{c}(0)$ and $\bar{c}(L)$ such that

$$\bar{c}(0) = \beta = 0, \tag{126a}$$

$$\bar{c}(L) = \alpha L = 0. \tag{126b}$$

Thus $\alpha = \beta = 0$, and the steady state of this problem is the trivial solution

$$\bar{c}(x) = 0.$$

The full solution is thus

$$c(x, t) = c_T(x, t), \tag{127}$$

where $c_T(x, t)$ is given by (122). For a particular $f(x)$ it is necessary to integrate the expression in equation (123) in order to obtain the values of the constants a_n. For examples and further details see Boyce and DiPrima (1969).

General Summary of Methods

1. Assume the transient solution $c_T(x, t) = S(x)T(t)$, and substitute this into the equation.
2. Separate variables to obtain ODEs for each part S and T separately.
3. Determine whether the separation constant K should be positive or negative by noting which eigenfunctions will satisfy the boundary conditions. ($K < 0$ => sines or cosines; $K > 0$ => exponentials.)
4. Further determine which eigenvalues λ will be consistent with the boundary conditions.
5. Write $c_T(x, t)$ as a (possibly infinite) superposition of solutions of the form $S_\lambda(x)T_\lambda(t)$ as in equation (122).
6. Find the constants a_n by using the initial condition of the problem along with equation (123).
7. Find the steady-state solution $\bar{c}(x)$ of equation (106).
8. The general solution is then

$$c(x, t) = c_T(x, t) + \bar{c}(x).$$

Note: Other boundary conditions may call for other eigenfunctions. (For example, boundary conditions of type 4 are only consistent with cosine eigenfunctions.) The general solution will then consist of Fourier cosine series or possibly of a full Fourier series. Such cases are described in greater detail in any text that treats boundary-value problems and the heat equation.

A.4 OTHER SOLUTIONS

New solutions to equation (106) can always be generated from preexisting ones by forming (1) linear combinations, (2) translations, or by (3) differentiation or integration with respect to a parameter. Also important are the following special classes of solutions that we describe without formal justification.

1. *Point release into an "infinite region."* With initial conditions (101) and boundary conditions (95), it can be shown that the solution to (106) is

$$c(x, t) = \frac{M}{2\sqrt{\pi \mathcal{D} t}} \exp \frac{-x^2}{4\mathcal{D}t}, \tag{128}$$

where M is the total number of particles:

$$M = \int_{-\infty}^{\infty} c \, dx.$$

See Figure 9.11 for the time behavior of this function, which is known as the *fundamental solution* of (106).

2. *Extended initial distributions.* An initial condition (103) with "far away" boundaries as in class 1 can be treated by considering the contributions of a whole array of point sources and summing these (integrating) over the appropriate region. This leads one to define a quantity known as the *error function:*

$$\operatorname{erf} z = \frac{2}{\sqrt{\pi}} \int_0^z \exp(-x^2) \, dx. \tag{129}$$

with the properties that

$$\operatorname{erf}(-z) = -\operatorname{erf} z, \tag{130a}$$

$$\operatorname{erf} 0 = 0, \tag{130b}$$

$$\operatorname{erf} \infty = 1.$$

The solution of (106) can then be written in the form

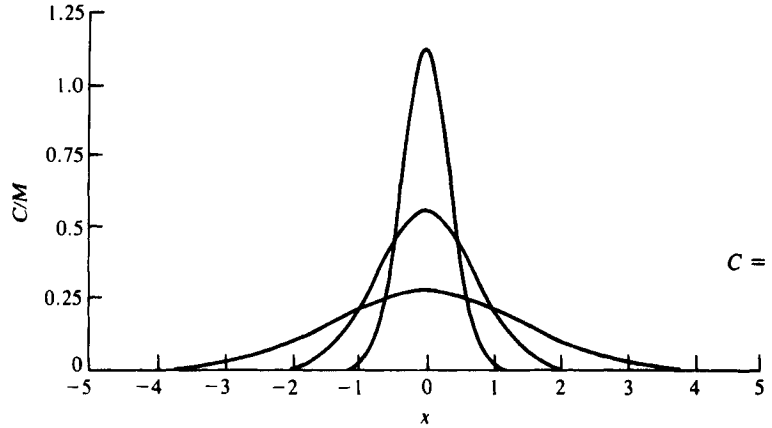
$$c(x, t) = \frac{1}{2} c_0 \left(1 - \operatorname{erf} \frac{x}{2\sqrt{\mathcal{D}t}}\right). \tag{131}$$

While the integral in equation (129) cannot be reduced to more elementary functions, it is a tabulated function of its argument. See most mathematics handbooks for such tables.

3. *Finite initial distributions.* If the initial distribution is concentrated in a finite interval $-h < x < h$, the integration of equation (129) over this domain leads to the solution

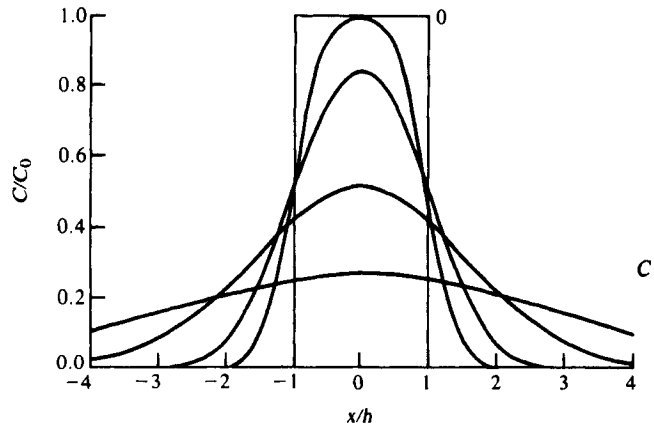
$$c(x, t) = \frac{1}{2} c_0 \left[\operatorname{erf} \frac{h - x}{2\sqrt{\mathcal{D}t}} + \operatorname{erf} \frac{h + x}{2\sqrt{\mathcal{D}t}}\right]. \tag{132}$$

The problem is more complicated if the effects of boundaries are to be considered. See Carslaw and Jaeger (1959) for the detailed treatment of such cases.



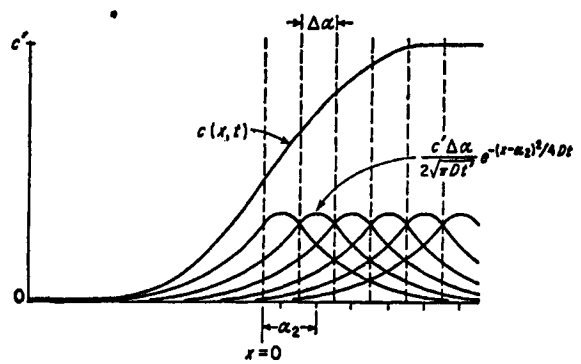
$$C = \frac{M}{2(\pi \mathcal{D}t)^{1/2}} \exp\left(\frac{-x^2}{4\mathcal{D}t}\right),$$

(a)



$$C = \tfrac{1}{2}C_0\left[\operatorname{erf}\frac{h-x}{2\sqrt{(\mathcal{D}t)}} + \operatorname{erf}\frac{h+x}{2\sqrt{(\mathcal{D}t)}}\right].$$

(b)



$$c(x, t) = \frac{c'}{2}\left\{1 + \operatorname{erf}\left[\frac{x}{2\sqrt{\mathcal{D}t}}\right]\right\}$$

$$\operatorname{erf} z = \frac{2}{\sqrt{\pi}}\int_0^z \exp(-\eta^2)\, d\eta$$

(c)

Figure 9.11 *Solutions of the diffusion equation for some discontinuous initial distributions: (a) point release [$c(x, 0) = \delta(x)$]; (b) finite extended distribution [$c(x, 0)$] = 1 for $-1 < x < 1$]; (c) infinite extended distribution [$c(x, 0) = 1$ for $x \geq 0$]. [Parts (a) and (b) from Crank, J. (1979).* The Mathematics of Diffusion. *2 ed. Oxford University Press, London, Figs. 2.1 and 2.4. Part (c) from Shewmon, P. G. (1963).* Diffusion in Solids, *McGraw-Hill, New York, Fig. 1.5.]*

PROBLEMS FOR THE APPENDIX

Problems 23 to 27 are based on the Appendix to Chapter 9.

23. Determine the boundary and initial conditions appropriate for the diffusion of salt in each of the following situations.

(a) A hollow tube initially containing pure water connects two reservoirs whose salt concentrations are C_1 and 0 respectively.

(b) The tube is sealed at one end. Its other end is placed in a salt solution of fixed concentration C_1.

(c) The tube is sealed at both ends and initially has its greatest salt concentrations halfway along its length. Assume the initial distribution is a trigonometric function.

24. In this problem we investigate certain details that arise in solving the diffusion equation by separation of variables.

(a) Show that equation (108) implies (109).

(b) Determine the consequences of assuming $K = 0$ in equation (110).

(c) Show that for $K > 0$ solutions to (110) are given by equations (112a,b).

(d) Justify the assertion that for $K < 0$ solutions are of the form (114).

25. **(a)** What kind of boundary and initial conditions are used in (115)?

(b) Show that the steady-state solution of equation (106) is then trivially $c(x) = 0$.

(c) Show that equations (110) and (115) lead to (117).

(d) Justify the assumption (118).

26. Solve the one-dimensional diffusion equation subject to the following conditions:

(a) $c(0, t) = c(1, t) = 0$,
$c(x, 0) = \sin \pi x$.

(b) $c(0, t) = c(L, t) = 0$,
$$c(x, 0) = \sin\left(\frac{2\pi}{L}x\right) + \sin\left(\frac{3\pi}{L}x\right).$$

27. **(a)** Verify that (128) is a solution to the diffusion equation by performing partial differentiation with respect to t and x.

(b) Similarly, verify that (131) is also a solution.

(c) Use your result in part (b) to argue that (132) is also a solution without calculating partial derivatives. (*Hint:* Use the properties of solutions described in the Appendix, Section A.4.)