CHAPTER 7

Spatial Modeling

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All of the models considered in previous chapters have relied on the implicit assumption that chemical concentrations are uniform in space. This assumption is reasonable when the region of space in which the reaction takes place is confined and quite small. However, there are many situations in which chemical concentrations are not uniform in space. A well-known example in which nonuniform distributions are crucial is the propagation of an action potential along the axon of a nerve fiber (Figure 1.1). When a nerve cell "fires," a wave of membrane depolarization is initiated at the base of the axon (where it connects to the cell body; see Figure 2.1) and propagates along the axon out to its terminus. During propagation, large spatial gradients in membrane potential and local currents are created. The interaction between these spatial gradients and voltage-sensitive ion channels in the axonal membrane drives the wave along the axon. In order to understand the propagation of a nerve impulse, we must first master the basic principles of molecular diffusion and the interactions between chemical reaction and diffusion.

Many other questions arise in molecular cell biology that demand at least an elementary understanding of molecular diffusion. For instance, how long does it take for a chemical signal generated at the cell membrane to diffuse to the nucleus? Why are expensive transport systems required to move some materials in cells, for example between a nerve cell body and synapses in axons and dendrites? How fast can molecules or ions pass through protein channels in membranes?

In Chapter 4 and Chapter 5 we faced the problem of nonuniform Ca^{2+} concentration in the vicinity of Ca^{2+} channels. There we made a simplifying assumption that the Ca^{2+} concentration is high in a small region adjacent to the channel (domain Ca^{2+}). To

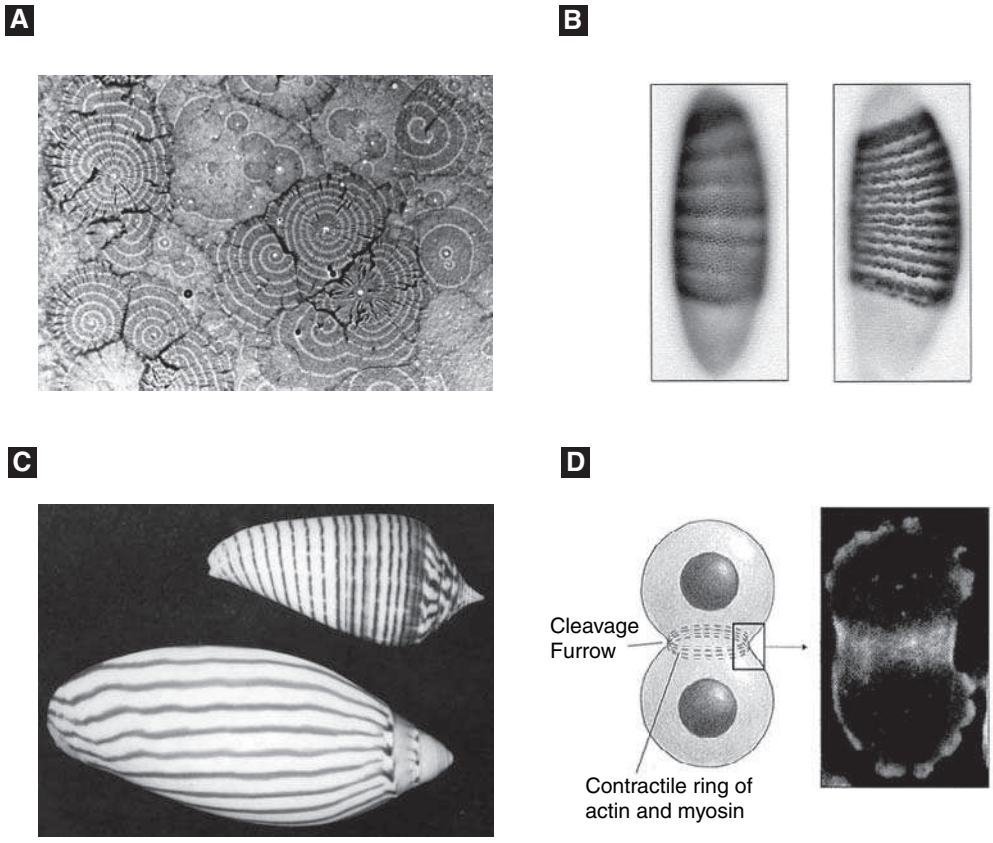

Figure 7.1 Spatial phenomena in cell biology. (A) Waves of aggregation in fields of slime mold amoebae. The light and dark bands correspond to regions where the amoebae are actively moving or not. The amoebae collect at the center of each pattern, where they form a multicellular slug. The collective motion of the cells is organized by waves of cyclic AMP that propagate throught the extracellular medium. Courtesy of Peter Newell. (B) Stripes of gene expression (*ftz* and *eve*) in a fruit fly embryo at (left) 3 hr. after fertilization and (right) 3 1/2 hr. after fertilization. Reprinted from Lawrence (1992). For an introductory discussion of the segmentation genes in Drosophila, see Alberts et al. (1994). (C) Pigmentation patterns on sea shells. From Meinhardt (1998). (D) The cleavage furrow in a dividing cell. Reprinted from Alberts et al. (1994); original by Yoshio Fukui. A dividing slime mold amoeba is stained for actin and myosin. The actomyosin ring in the center of the cell contracts like a purse-string to divide the cell in half.

improve on the domain Ca^{2+} approximation and other simplified approaches to spatial nonuniformity, we will need the spatial modeling principles described here.

A more sophisticated example of spatiotemporal organization in living cells is the phenomenon of Ca^{2+} waves that propagate through eggs after fertilization. These waves will be modeled in great detail in Chapter 8, after we have studied reaction–diffusion

equations in this chapter. Similar to Ca^{2+} waves in eggs are waves of cyclic AMP that propagate through fields of slime mold amoebae shown in Figure 7.1A. By directing the motion of the amoebae, these chemical waves organize the complex behaviors of this primitive multicellular organism: aggregation of simple amoebae into a multicellular slug, motility of the slug, and formation of the fruiting body. Other interesting examples of spatial organization include gap-gene expression in early fruit fly embryos (Figure 7.1B), seashell patterns (Figure 7.1C), and medial ring placement at cell division (Figure 7.1D). Although we will not attempt to model any of these phenomena in this book, a starting point for such investigations is this chapter.

The chapter is organized along the following lines: First, we consider diffusion in one dimension, such as we might find in a long thin tube like a nerve axon. We distinguish between a *conservation law* (how the law of conservation of matter relates molecular flux to local changes in concentration) and a *constitutive relation* (how molecular flux is determined by concentration gradients, fluid transport, and electrophoresis). These principles are expressed in the precise mathematical terms of *partial differential equations* (PDEs). We show the exact solution to these equations for a number of important illustrative cases. Because PDEs cannot be solved exactly in most realistic situations, we next describe a numerical procedure, called the method of lines, that is easily implemented. Also, because very few spatial nonuniformities are effectively one-dimensional, we show how to formulate the conservation law and constitutive relations in two and three dimensions. We then couple molecular diffusion to nonlinear chemical reactions in order to study wave propagation in one spatial dimension. The theory is applied to the FitzHugh–Nagumo equations of nerve impulse propagation introduced in Chapter 2.

7.1 One-Dimensional Formulation

7.1.1 Conservation in One Dimension

Many equations in biology are consequences of *conservation laws*. A conservation law is simply a mathematical statement describing how some quantity is created or destroyed or moves about.

Consider a chemical species C whose concentration $c(x, t)$ varies in time and space, where the spatial variation is restricted to one spatial variable x. This situation is illustrated in Figure 7.2, where the chemical species C is contained in a long, thin tube with

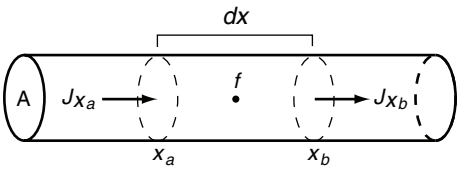

Figure 7.2 Conservation in one dimension.

constant cross-sectional area A. In any fixed region R along the tube, the conservation of C can be expressed in words as

$$\begin{aligned}&\text{time rate of change of the total amount of C within R} =\\ &\quad \text{rate at which C flows in to R}\\ &\quad -\text{rate at which C flows out of R}\\ &\quad +\text{rate at which C is produced within R}\\ &\quad -\text{rate at which C is destroyed within R.}\end{aligned} \tag{7.1}$$

The total amount of chemical C contained in a small slice of tube between x and $x + dx$ is $c(x,t)A\,dx$. At any time t, the total amount of C in some arbitrary interval $x_a < x < x_b$ can be computed by integrating $c(x,t)A$ over that interval:

$$\text{total amount of C in the interval } [x_a, x_b] = \int_{x_a}^{x_b} c(x,t)\,A\,dx. \tag{7.2}$$

It is important to distinguish between concentration (amount/ volume) and the "total amount." If c has units of micromolar (micromol/liter), then the total amount has units of micromoles.

Now suppose that C is free to move about inside the tube, so that C moves in and out of the interval by crossing the boundaries of the interval at $x = x_a$ and $x = x_b$. If we denote by $J(x,t)$ the rate at which C moves across the boundary at position x from left to right at time t, then the net movement, or flux, of C into the interval is

$$\text{net rate of entry of C} = AJ(x_a,t) - AJ(x_b,t). \tag{7.3}$$

Since the net rate of entry has units of amount/time and A has units of area, the flux rate $J(x,t)$ has units of amount/area/time. It is also important to remember that $J(x,t)$ is positive when C moves to the right, and negative when C moves to the left.

The total amount of C in the interval can also change because of the production or destruction of C within the interval. If we let $f(x,t,c)$ denote the net rate of increase of C (production − destruction) per unit volume at location x and time t, then the total amount of C produced in the interval at time t is

$$\text{net rate of production of C} = \int_{x_a}^{x_b} f(x,t,c(x,t))\,A\,dx. \tag{7.4}$$

Note that the presence of c in the definition of f allows for the possibility that the rate of production of C depends on c itself. Since the units of the net rate of production of C are amount/time, the units of f must be amount/time/volume. When f is positive, the region is a source (leading to an increase in the total amount of C), and when f is negative, it is a sink. The function f is often called a source function.

The conservation law (7.1) can now be written in mathematical symbols as

$$\frac{d}{dt}\int_a^b c(x,t)\,dx = J(x_a,t) - J(x_b,t) + \int_{x_a}^{x_b} f(x,t,c(x,t))\,dx, \tag{7.5}$$

where the constant A has been factored out. The flux terms can be replaced by

$$J(x_b,t) - J(x_a,t) = \int_{x_a}^{x_b} \frac{\partial}{\partial x} J(x,t)\,dx, \tag{7.6}$$

allowing all the terms in (7.5) to be written as integrals:

$$\frac{d}{dt}\int_{x_a}^{x_b} c(x,t)\,dx = \int_{x_a}^{x_b} \frac{\partial}{\partial x} J(x,t)\,dx + \int_{x_a}^{x_b} f(x,t,c(x,t))\,dx. \tag{7.7}$$

If the function $c(x,t)$ is smooth enough, then the differentiation and integration can be interchanged, and (7.7) can be rewritten as

$$\int_{x_a}^{x_b} \left[\frac{\partial}{\partial t} c(x,t)\,dx - \frac{\partial}{\partial x} J(x,t) - f(x,t,c(x,t))\right] dx = 0. \tag{7.8}$$

Since the interval is arbitrary, the only way this equality can hold is if the integrand is zero. Therefore, we replace (7.8) by the equivalent conservation law in differential form:

$$\frac{\partial c}{\partial t} - \frac{\partial J}{\partial x} = f(x,t,c). \tag{7.9}$$

Notice that in this equation there are two independent variables (x and t), and that the equation contains partial derivatives with respect to both of these. Such equations are called partial differential equations. Since time is one of the independent variables, and this equation describes the evolution of $c(x,t)$ in time, (7.9) is called an evolution equation because it describes how the concentration of C evolves (changes) as time proceeds.

7.1.2 Fick's Law of Diffusion

Equation (7.9) is underdetermined because it is a single equation relating two unknowns: the concentration c and the flux J. To resolve this problem, an additional equation relating c and J is needed.

In contrast to the conservation law (7.9), which follows indubitably from the general principle of material conservation, the relation between c and J must be determined empirically and is not universally valid. To make this distinction, the secondary relation between c and J is usually called a constitutive equation.

One such constitutive relation is called Fick's law, and states that C moves from regions of high concentration to regions of low concentration, at a rate proportional to the concentration gradient. In mathematical symbols, this diffusive flux is

$$J(x,t) = -D\frac{\partial}{\partial x} c(x,t), \tag{7.10}$$

where the proportionality constant D is called the diffusion constant. The negative sign signifies that C moves spontaneously from regions of high concentrations to regions of low concentrations. The value of D depends on the size of C, as well as properties of the

Table 7.1 Molecular weight and diffusion coefficients of some biochemical substances in dilute aqueous solution.

Substance	Molecular Weight	$D/10^7 \text{cm}^2/\text{s}$
glucose	192	660
insulin	5734	210
cytochrome c	13,370	11.4
myoglobin	16,900	11.3
β-lacroglobulin	37,100	7.5
serum albumin	68,500	6.1
hemoglobin	64,500	6.9
catalase	247,500	4.1
urease	482,700	3.46
fibrinogen	339,700	1.98
myosin	524,800	1.10
tobacco mosaic virus	40,590,000	0.46

medium in which it is diffusing. The constant D has units of length^2/time. Diffusion coefficients of some typical biochemicals are given in Table 7.1.

Using Fick's law, (7.9) becomes the reaction–diffusion equation

$$\frac{\partial c}{\partial t} - \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right) = f(x,t,c). \tag{7.11}$$

In this equation, the term $\frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right)$ is the diffusion term, and f is the reaction term. When f is zero, that is, when there are no sources or sinks, (7.11) becomes the diffusion equation

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right). \tag{7.12}$$

7.1.3 Advection

Suppose that there is a uniform macroscopic flow of the solvent, with speed v along the x-axis, which carries solutes along with it. Then, during a small time Δt, all of the C between $x = x_a$ and $x = x_a - v\Delta t$ will cross the point $x = x_a$. The total amount of C crossing x_a during this time is found by multiplying the concentration $c(x,t)$ by the fluid volume $Av\Delta t$. The corresponding flux is therefore (after dividing by Δt to get amount per unit time)

$$J(x,t) = vc(x,t). \tag{7.13}$$

This flux is called the advective flux. Note that whereas the diffusive flux was proportional to the concentration gradient, the advective flux is proportional to the concentration itself.

If there is both diffusive flux and advective flux, then the total flux is the sum of the two:

$$J(x,t) = vc(x,t) - D\frac{\partial}{\partial x}c(x,t). \tag{7.14}$$

Using this constitutive relation, (7.9) becomes a reaction–advection–diffusion equation,

$$\frac{\partial c}{\partial t} + \frac{\partial}{\partial x}\left(vc - D\frac{\partial c}{\partial x}\right) = f(x,t,c). \tag{7.15}$$

7.1.4 Flux of Ions in a Field

If the substance C is an ion and there is an electrical potential gradient, then there will also be a flux of C because of the influence of the potential on the ion. In this case the flux of ions is given by the Nernst–Planck equation

$$J = -D\left(\frac{\partial c}{\partial x} + \frac{zF}{RT}c\frac{\partial \phi}{\partial x}\right), \tag{7.16}$$

where ϕ is the electric potential, z is the number of positive charges on the ion (a negative integer if the ion is negatively charged), F is Faraday's constant, R is the universal gas constant, and T is absolute temperature. Notice that according to this equation, there is movement because of both the concentration gradient and the potential gradient.

7.1.5 The Cable Equation

Suppose that our long one-dimensional tube is bounded by a membrane, as in a nerve axon. In this case, we wish to keep track of the electrical potential across the membrane, rather than some chemical species within the tube. Nonetheless, the rules of conservation are the same, so the derivation of the governing equation is similar.

Suppose the total current along the interior of the axon is I, positive from left to right, and the transmembrane current per unit membrane area is I_{T}, positive outward. Then, conservation of current implies that

$$I(x_a,t) - I(x_b,t) = \int_{x_a}^{x_b} SI_{\mathrm{T}}dx, \tag{7.17}$$

where S is the circumference of the tube. This conservation law can be expressed using integrals as

$$-\int_{x_a}^{x_b}\frac{\partial I}{\partial x}dx = \int_{x_a}^{x_b} SI_{\mathrm{T}}dx, \tag{7.18}$$

and since the interval is arbitrary, the integrands must be equal, so that

$$-\frac{\partial I}{\partial x} = SI_{\mathrm{T}}. \tag{7.19}$$

Recall from Chapter 1 that the total transmembrane current consists of two components, a capacitive current and the ionic currents

$$-\frac{\partial I}{\partial x} = S\left(C_{\mathrm{m}}\frac{\partial V}{\partial t} + I_{\mathrm{ion}}\right), \tag{7.20}$$

where V is the transmembrane potential. Finally, the relationship between current and potential is given by the constitutive relationship known as Ohm's law (also called the core conductor assumption),

$$I = -\frac{A}{R_{\mathrm{c}}}\frac{\partial \phi_i}{\partial x}, \tag{7.21}$$

where R_{c} is the cytoplasmic resistance (with units Ohms length), and ϕ_{i} is the intracellular potential. With this constitutive relationship, our equation becomes

$$\frac{\partial}{\partial x}\left(\frac{A}{R_{\mathrm{c}}}\frac{\partial \phi_{\mathrm{i}}}{\partial x}\right) = S\left(C_{\mathrm{m}}\frac{\partial V}{\partial t} + I_{\mathrm{ion}}\right). \tag{7.22}$$

Finally, we close the model by assuming that the membrane is in a highly conductive bath, so that the extracellular potential ϕ_{e} is a constant. Since $V = \phi_{\mathrm{i}} - \phi_{\mathrm{e}}$, we arrive at the cable equation

$$\frac{\partial}{\partial x}\left(\frac{A}{R_{\mathrm{c}}}\frac{\partial V}{\partial x}\right) = S\left(C_{\mathrm{m}}\frac{\partial V}{\partial t} + I_{\mathrm{ion}}\right). \tag{7.23}$$

For a tube of uniform circular cross section and diameter d, $A/s = d/4$. Typical parameter values for a variety of cells are shown in Table 7.2.

7.1.6 Boundary and Initial Conditions

In the study of ordinary differential equations, it is necessary to specify initial data before one can find a solution trajectory. With partial differential equations, one must specify both initial data and boundary data before a solution can be found. Roughly

Table 7.2 Typical cable parameter values for a variety of excitable cells. From Keener and Sneyd (1998).

parameter	d	R_{c}	R_{m}	C_{m}	λ_{m}
units	10^{-4} cm	Ω cm	$10^3\ \Omega\ \mathrm{cm}^2$	$\mu\mathrm{F/cm}^2$	cm
squid giant axon	500	30	1	1	0.65
lobster giant axon	75	60	2	1	0.25
crab giant axon	30	90	7	1	0.24
earthworm giant axon	105	200	12	0.3	0.4
marine worm giant axon	560	57	1.2	0.75	0.54
mammalian cardiac cell	20	150	7	1.2	0.15
barnacle muscle fiber	400	30	.23	20	0.28

speaking, there must be one condition for each degree of freedom. Thus, since reaction–diffusion equations are of first order in time, there must be one initial condition for each unknown function. Since they are of second order in space, there must be two boundary conditions (conditions at some points in space) for each unknown function.

Initial conditions usually specify the values of the dependent variables at some initial time (usually $t = 0$) at which the solution is known or specified by experimental conditions. Boundary conditions reflect certain physical conditions of the experiment. For example, if the concentration c is specified to be some function $f(t)$ at some boundary point, say $x = x_a$, then the condition $c(x_a, t) = f(t)$ is applied, called a Dirichlet boundary condition. If, on the other hand, the flux at a point is specified, then the condition $-D\frac{\partial c}{\partial x}(x_a, t) = g(t)$, called a Neumann boundary condition, is applied. If the flux is related to the value of c at the boundary, then the Robin condition, $-D\frac{\partial c}{\partial x}(x_a, t) = h(t) - \alpha c(x_a, t)$, is applied.

It is often convenient to assume that a domain is infinite, even though there is no such thing as an infinitely long tube. Even with infinite domains, however, boundary conditions must be specified as constraints on the behavior of the dependent variable in the limit that $x \to \pm\infty$.

7.2 Important Examples with Analytic Solutions

7.2.1 Diffusion Through a Membrane

Consider a membrane separating two large regions of space that contain some chemical C. The concentration on the left is c_1, and the concentration on the right is c_2 (Figure 7.3). There is a small pore in the membrane (a one-dimensional channel of length L) through which the chemical C can freely pass. Suppose that the two regions of space are so large that their concentrations are not changing, even if chemical is flowing from one region to the other.

Let us assume that the transport of C across the membrane has been going on for some time, so that the process is at steady state, i.e., the concentration $c(x, t)$ is independent of time ($\frac{\partial c}{\partial t} = 0$). In this case, $c(x)$ must satisfy the "boundary value problem"

$$\frac{\partial^2 c}{\partial x^2} = 0, \qquad c(0) = c_1,\ c(L) = c_2. \tag{7.24}$$

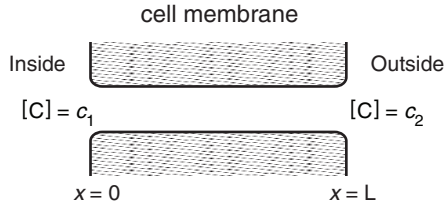

Figure 7.3 Simple diagram of a pore through a membrane.

The solution of this problem is quite easy to find, being

$$c(x) = c_1\left(1 - \frac{x}{L}\right) + c_2\frac{x}{L}. \tag{7.25}$$

Consequently, the steady flux through the channel is proportional to the concentration difference across the membrane,

$$J = -Dc_x = \frac{D}{L}(c_1 - c_2). \tag{7.26}$$

7.2.2 Ion Flux Through a Channel

Suppose that the chemical moving through the channel is an ion, and that there is a potential difference across the channel, with $\phi(0) = \phi_1$ and $\phi(L) = \phi_2$. We make the simplifying approximation that the potential gradient through the channel is constant:

$$\frac{d\phi}{dx} = \frac{\Delta\phi}{L} = \frac{V}{L}, \text{ where } V = \phi_1 - \phi_2. \tag{7.27}$$

If the process is in steady state so that the ion flux everywhere in the channel is the same constant, then, from (7.16),

$$J = -D\left(c_x + \alpha c\frac{V}{L}\right), \tag{7.28}$$

where $\alpha = zF/RT$. We solve this differential equation for $c(x)$ subject to the boundary condition that $c(0) = c_1$ and find that

$$c(x) = c_1 e^{-\alpha V\frac{x}{L}} - \frac{JL}{D\alpha V}\left(1 - e^{-\alpha\Delta\phi x/L}\right). \tag{7.29}$$

Now we can determine the flux J by requiring that $c(L) = c_2$, so that

$$J = -\frac{D}{L}\alpha V\left(\frac{c_2 - c_1 e^{-\alpha V}}{1 - e^{-\alpha V}}\right). \tag{7.30}$$

This expression for flux can be converted to an ionic current I_c by multiplying by zF, in which case we obtain

$$I_c = -\frac{D}{L}zF\alpha V\left(\frac{c_2 - c_1 e^{-\alpha V}}{1 - e^{-\alpha V}}\right). \tag{7.31}$$

This expression is the famous Goldman–Hodgkin–Katz current equation, and it has the important property that $I_c = 0$ when

$$\Delta V = \frac{RT}{zF}\ln\frac{c_1}{c_2}, \tag{7.32}$$

which is called the reversal potential or Nernst potential for the channel. The Nernst potential is the transmembrane potential when the ion is at equilibrium across the membrane for a given transmembrane concentration ratio c_1/c_2.

7.2.3 Voltage Clamping

A typical experiment in electrophysiology is to hold fixed the transmembrane potential at some place on the membrane. For example, with a long axon, one might clamp the voltage at one end and determine the resulting voltage profile along the axon.

For a passive membrane (e.g., a dendritic membrane), the voltage profile should satisfy (7.23) with $I_{\text{ion}} = V/R_{\text{m}}$, where R_{m} is the passive membrane resistance (ohm $\cdot$ cm^2). The steady–state voltage profile $V(x)$ must satisfy

$$\frac{A}{R_{\text{c}}}\frac{\partial^2 V}{\partial^2 x} = \frac{SV}{R_{\text{m}}}, \tag{7.33}$$

subject to the boundary conditions $V(0) = V_{\text{fixed}}$ and $\frac{\partial V}{\partial x}(L) = 0$ if the far end is sealed. The solution of this problem is

$$V(x) = V_{\text{fixed}}\frac{e^{(L-x)/\lambda_{\text{m}}} - e^{(x-L)\lambda_{\text{m}}}}{e^{L/\lambda_{\text{m}}} - e^{-L/\lambda_{\text{m}}}}, \tag{7.34}$$

where $\lambda_{\text{m}} = \sqrt{\frac{AR_{\text{m}}}{SR_{\text{c}}}}$ is the length constant for the axon. For a long axon (L is many length constants), this solution reduces to

$$V(x) = V_{\text{fixed}}e^{-\frac{x}{\lambda_{\text{m}}}}, \tag{7.35}$$

a simple exponential decay away from the voltage–clamped end. Some examples of space constants for a variety of excitable tissues are included in Table 7.2.

7.2.4 Diffusion in a Long Dendrite

All of the above examples examined steady behavior, after initial transients have decayed. However, reaction–diffusion equations also contain information about the temporal evolution of the process to steady state.

Consider calcium diffusing in a long dendrite. Suppose caged calcium is photoreleased from a small region around $x = 0$. If we denote by $c(x,t)$ the concentration of calcium along the length of the dendrite at each time t, then the model becomes

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}, \qquad -\infty < x < \infty, \qquad t > 0, \tag{7.36}$$

$$c(x,0) = C_0\delta(x), \tag{7.37}$$

where C_0 is the total amount of released calcium, and $\delta(x)$ is the Dirac delta function. Because the dendrite is long, we view the domain as infinite. Since we do not expect the concentration of calcium to become appreciable at $x = \pm\infty$ in any finite time, we require $\lim_{x\to\pm\infty} c(x,t) = 0$.

It can be shown (Exercise 2) that the solution of this model is

$$c(x,t) = \frac{C_0}{\sqrt{4\pi Dt}}\exp\left(-\frac{x^2}{4Dt}\right), \tag{7.38}$$

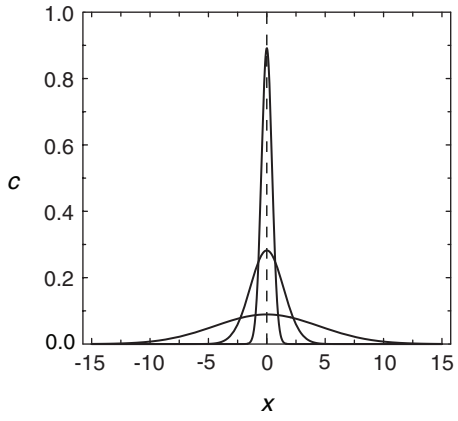

Figure 7.4 Gaussian at 0.1, 1, and 10 s

which is illustrated in Figure 7.4. For each fixed t, this solution is a Gaussian function, and over time, the function becomes wider and the maximal value (at $x = 0$) declines,

$$c(0,t) = \frac{C_0}{\sqrt{4\pi D t}}. \tag{7.39}$$

At any other point $x \neq 0$, the solution is biphasic, initially increasing to a maximum value and then decreasing back to zero. The maximum is attained when $Dt/x^2 = \frac{1}{2}$. This time behavior is illustrated in Figure 7.5.

We can readily calculate that

$$\langle x^2 \rangle = \int_{-\infty}^{\infty} x^2 c(x,t)\, dx = 2Dt, \tag{7.40}$$

so that the "root mean square" (rms) distance moved in time t is

$$\sqrt{\langle x^2 \rangle} = x_{\text{rms}} = \sqrt{2Dt}. \tag{7.41}$$

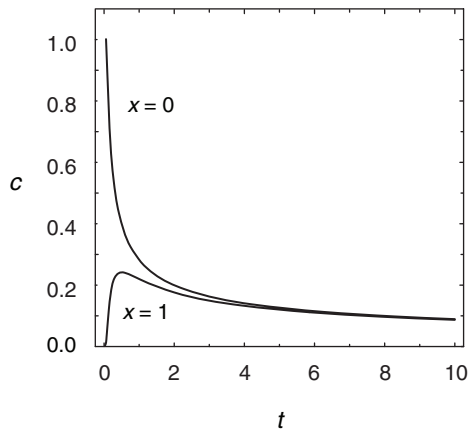

Figure 7.5 Plot of $c(0,t)$ and $c(x \neq 0,t)$ from (7.38).

7.2.5 Diffusion into a Capillary

Suppose that a long capillary (open at one end) filled with water is inserted into a solution of known chemical concentration C_0, and the chemical species diffuses into the capillary through the open end. The concentration of the chemical species should depend only on the distance down the tube and so is governed by the diffusion equation

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}, \qquad 0 < x < \infty, \qquad t > 0, \tag{7.42}$$

where for convenience we assume that the capillary is infinitely long. Because the solute bath in which the capillary sits is large, it is reasonable to assume that the chemical concentration at the tip is fixed at $C(0,t) = C_0$, and because the tube is initially filled with pure water, $C(x,0) = 0$.

The solution of this problem is given by

$$C(x,t) = 2C_0\left(1 - \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{z}\exp\left(-\frac{s^2}{2}ds\right)\right), \qquad z = \frac{x}{\sqrt{2Dt}}. \tag{7.43}$$

If the cross-sectional area of the capillary is A, then the total number of molecules that enter the capillary in a fixed time T is

$$N = A\int_0^\infty C(x,T)dx = 2C_0A\sqrt{\frac{TD}{\pi}}. \tag{7.44}$$

From this equation it is possible to determine the diffusion coefficient by solving (7.44) for D, yielding

$$D = \frac{\pi N^2}{4C_0^2A^2T}. \tag{7.45}$$

Segel, Chet, and Henis used this formula to estimate the diffusion coefficient for bacteria (Segel et al. 1977). With C_0 at 7×10^7/ml, and times T = 2, 5, 10, 12.5, 15, and 20 minutes, they counted N of 1800, 3700, 4800, 5500, 6700, and 8000 bacteria in a capillary of length 32 mm with 1 μl total capacity. In addition, with concentrations C_0 of 2.5, 4.6, 5.0, and 12.0 $\times 10^7$ bacteria per milliliter, counts of 1350, 2300, 3400, and 6200 were found at $T = 10$ minutes. Using (7.45) a value of D in the range of 0.1–0.3 cm^2/hour was found.

A second useful piece of information is found from (7.43) by observing that $C(x,t)/C_0$ is constant on any curve for which z is constant. Thus, the curve $t = x^2/D$ is a level curve for the concentration, and gives a measure of how fast the substance is moving into the capillary. The time $t = x^2/D$ is called the diffusion time for the process. To give some idea of the effectiveness of diffusion in various cellular contexts, in Table 7.3 are shown typical diffusion times for a variety of cellular structures. Clearly, diffusion is quite effective when distances are short, but totally inadequate for longer distances, such as along a nerve axon. Obviously, biological systems must employ other transport mechanisms in these situations in order to survive.

Table 7.3 Estimates of diffusion times for cellular structures of typical dimensions, computed from the relation $t = x^2/D$ using $D = 10^{-5}\text{cm}^2/\text{s}$.

x	t	Example
10 nm	100 ns	thickness of cell membrane
1μm	1 ms	size of mitochondrion
10μm	100 ms	radius of small mammalian cell
100μm	10s	diameter of a large muscle fiber
250μm	60 s	radius of squid giant axon
1 mm	16.7 min	half-thickness of frog sartorius muscle
2 mm	1.1 h	half-thickness of lens in the eye
5 mm	6.9 h	radius of mature ovarian follicle
2 cm	2.6 d	thickness of ventricular myocardium
1 m	31.7 yrs	length of a nerve axon

7.3 Numerical Solution of the Diffusion Equation

In order to attack more complex situations of reaction and diffusion, it is usually necessary to resort to numerical solutions of the partial differential equation. With the advent of cheap powerful computers, this approach has become increasingly useful. Here we describe the simplest numerical method to solve reaction–diffusion equations. While other more sophisticated numerical methods are available, this method is adequate for our purposes, and can be readily implemented using your favorite numerical integrator.

Consider the problem of determining calcium concentration following the photorelease of caged calcium in a sealed dendrite 40 microns long. We define the spatial variable x to extend from 0 to 40 microns, and the starting time $t = 0$ to be the time at which the caged calcium is released. The equations we wish to solve are

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}, \tag{7.46}$$

where

$$c(x,0) = \begin{cases} C_0 & 20\ \mu\text{m} < x < 30\ \mu\text{m} \\ 0 & \text{elsewhere} \end{cases} \tag{7.47}$$

(7.48)

and

$$c_x(0,t) = c_x(40,t) = 0, \tag{7.49}$$

and where C_0 is the concentration of calcium released. Because the dendrite is closed to calcium flux at its ends, no-flux boundary conditions are specified at both ends. The caged calcium is initially confined to the region between 20 and 30 microns.

To solve this problem numerically, we subdivide the spatial domain ($0 < x < 40$) into N equal intervals, with $\Delta x = 40/N$ denoting the length of each interval. If the $N+1$ endpoints of these intervals are denoted by x_n, where $n = 0, 1, 2, \ldots, N$, then we define an approximation to $c(x,t)$ at these points by $c(x_n, t) = c_n(t)$.

Recall from calculus that the definition of the partial derivative of c is

$$\frac{\partial c(x,t)}{\partial x} = \lim_{\Delta x \to 0} \frac{c(x+\Delta x, t) - c(x,t)}{\Delta x}. \tag{7.50}$$

It follows that if Δx is small, but not zero, we have an approximation to the partial derivative:

$$\frac{\partial c(x,t)}{\partial x} \approx \frac{c(x+\Delta x, t) - c(x,t)}{\Delta x}. \tag{7.51}$$

In a similar way an approximation to the second partial derivative is found with Δx small, but not zero:

$$\frac{\partial^2 c(x,t)}{\partial x^2} \approx \frac{c(x+\Delta x, t) - 2c(x,t) + c(x-\Delta x, t)}{\Delta x^2}. \tag{7.52}$$

Using this approximation at each spatial grid point $x = x_n$, we derive a set of ordinary differential equations

$$\frac{\partial c_n(t)}{\partial t} = \frac{D}{\Delta x^2}(c_{n+1}(t) - 2c_n(t) + c_{n-1}(t)). \tag{7.53}$$

Notice that this approximation is valid only at interior grid points with $n = 1, 2, \ldots, N-1$, since for $n = 0$ or $n = N$ equation (7.53) references points c_{-1} and c_{N+1} that are outside the domain, and therefore are not known. However, if we invoke the no-flux boundary conditions, and use the approximation (7.51), we learn that

$$c_{-1}(t) = c_0(t), \qquad c_{N+1}(t) = c_N(t). \tag{7.54}$$

These we apply to (7.53) for $n = 0$ and $n = N$ and obtain

$$\frac{\partial c_0(t)}{\partial t} = \frac{D}{\Delta x^2}\left(c_1(t) - c_0(t)\right), \tag{7.55}$$

and

$$\frac{\partial c_N(t)}{\partial t} = \frac{D}{\Delta x^2}\left(c_{N-1}(t) - c_N(t)\right). \tag{7.56}$$

The system of ordinary differential equations (7.53), (7.55), and (7.56) is a closed system of $N+1$ equations in $N+1$ unknowns that can be simulated with any standard differential equation solver. This conversion of a partial differential equation to a system of ordinary differential equations using difference approximations for the spatial derivatives is called the method of lines.

The initial conditions are found directly from the initial condition for the partial differential equation, with one minor adjustment. Since $c_n(t) = c(x_n, t)$, we set $c_n(0) = c(x_n, 0)$, wherever that is well-defined. However, the initial profile has a jump

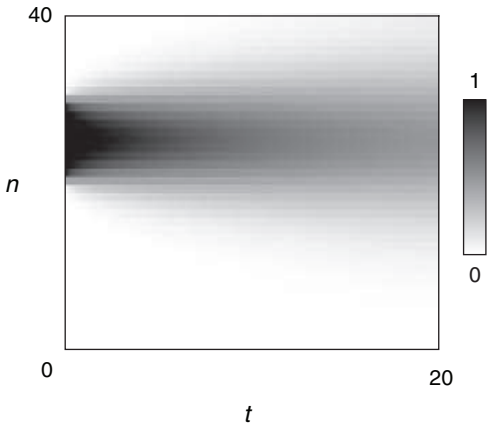

Figure 7.6 Numerical solution of equations (7.46)–(7.49).

discontinuity at $x = 20$ and $x = 30$, so it is preferable to define the value of c at these points to be the average of the limiting values from the left and right.

The solution of this problem is shown in Figure 7.6.

7.4 Multidimensional Problems

The multidimensional formulation of a reaction–diffusion equation is an easy generalization from one dimension. The primary difference is that in multiple dimensions, flux is a vector rather than a scalar. As a vector, flux indicates not only the rate, but also the direction, of transport, and the derivation of the conservation law is an exercise in multidimensional calculus.

7.4.1 Conservation Law in Multiple Dimensions

Consider a chemical species C whose concentration $c(x, y, z, t)$ varies in both time and in some three-dimensional region with volume V. The verbal expression of conservation (7.1) remains valid. At any time t, the total amount of C in the volume can be computed by integrating $c(x, y, z, t)$ over the volume:

$$\text{total amount of C} = \int_V c(x, y, z, t)\, dV. \tag{7.57}$$

Now suppose that C is free to move about randomly, so that C moves in and out of the volume by passing through the volume's surface S. The flux $J(x, y, z, t)$ is a vector, since C can move in any direction. If we denote by $\mathbf{n}(x, y, z)$ the outward unit normal vector on S (see Figure 7.7), then the net flux of C into the region is given by

$$\text{net rate of entry of C} = -\int_S J(x, y, z, t) \cdot \mathbf{n}(x, y, z)\, dA, \tag{7.58}$$

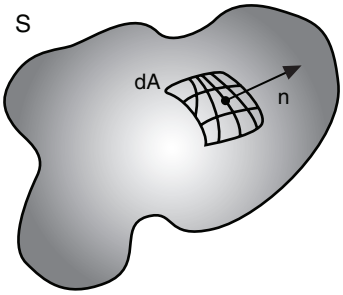

Figure 7.7 Schematic diagram of a multi–dimensional region.

where dA is the surface integration element. Because $\mathbf{n}$ is the outward normal, $J \cdot \mathbf{n}$ is positive when the motion is from inside to outside, which accounts for the negative sign in this equation. The rate of production of C in the volume can be written as $f(x,y,z,t,c)$, where as before, this rate is allowed to depend on c itself. Thus, the total rate of production of C in the region is given by

$$\text{net rate of production of C} = \int_V f(x,y,z,t,c(x,y,z,t))\,dV. \tag{7.59}$$

The conservation equation can now be expressed mathematically as

$$\frac{d}{dt}\int_V c\,dV = -\int_S J \cdot \mathbf{n}\,dA + \int_V f\,dV. \tag{7.60}$$

The surface integral can be replaced by a volume integral using the divergence theorem, which yields the multidimensional integral form

$$\frac{d}{dt}\int_V c\,dV = -\int_V \nabla \cdot J\,dV + \int_V f\,dV, \tag{7.61}$$

where $\nabla\cdot$ is the divergence operator. As before, if the function $c(x,y,z,t)$ is smooth enough, and since the volume V is arbitrary, we can rewrite (7.8) in differential form:

$$\frac{\partial c}{\partial t} + \nabla \cdot J = f. \tag{7.62}$$

Note that there are four independent variables (x, y, z, and t) and that the equation contains partial derivatives with respect to all four variables.

7.4.2 Fick's Law in Multiple Dimensions

Fick's law states that C moves from regions of high concentration to regions of low concentration, at a rate proportional to the concentration gradient. Thus, in multiple dimensions, Fick's law takes the form

$$J(x,y,z,t) = -D\nabla c(x,y,z,t), \tag{7.63}$$

where the diffusion constant D is the proportionality constant, and the negative sign ensures that C moves down the concentration gradient. Even in multiple dimensions, the units of D are length^2/time.

Using Fick's law, (7.62) can be rewritten as a reaction–diffusion equation:

$$\frac{\partial c}{\partial t} - \nabla \cdot (D\nabla c) = f. \tag{7.64}$$

7.4.3 Advection in Multiple Dimensions

Multidimensional advective flux has the same appearance as in the one-dimensional case:

$$J(x,y,z,t) = vc(x,y,z,t). \tag{7.65}$$

Notice, however, that the velocity v is a vector, so the flux vector points in the direction of the velocity vector.

If the random and biased directional motions coexist, the total flux is the vector sum of the diffusive and drift fluxes:

$$J(x,y,z,t) = vc(x,y,z,t) - D\nabla c(x,y,z,t). \tag{7.66}$$

Using this constitutive relation in (7.62), the multidimensional reaction–advection–diffusion equation is

$$\frac{\partial c}{\partial t} + v\nabla c - \nabla \cdot (D\nabla c) = f. \tag{7.67}$$

7.4.4 Boundary and Initial Conditions for Multiple Dimensions

As in one dimension, we must specify both initial and boundary conditions to pose the problem completely. The only difference here is that the functions involved are multidimensional, and so, when the spatial domain is complex, can be quite complicated.

The Dirichlet boundary condition in multiple dimensions specifies the values of the dependent variable c on the boundary, via $c(x,y,z,t) = f(x,y,z,t)$ with x,y,z restricted to the boundary. Similarly, the Neumann boundary condition specifies the flux of c on the boundary via $\mathbf{n} \cdot \nabla c = g$. Finally, the Robin condition specifies some relationship between the flux of c and the value of c on the boundary via $-\mathbf{n} \cdot D\nabla c = h + \alpha c$.

7.4.5 Diffusion in Multiple Dimensions: Symmetry

If the diffusion constant D does not vary in space or time, then the diffusive term can be written

$$\nabla \cdot (D\nabla c) = D\nabla \cdot (\nabla c) = D\nabla^2 c. \tag{7.68}$$

In this expression, ∇^2 is the "Laplacian operator," which in Cartesian coordinates is

$$\nabla^2 c = \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}. \tag{7.69}$$

If the spatial domain is more naturally described by other coordinate systems, then the representation of the Laplacian changes accordingly. For example, if the domain is a long cylindrical tube, and the concentration is not expected to be uniform in tubular cross-sections, then cylindrical coordinates (r, θ, z), where $x = r\cos\theta, y = r\sin\theta$, are most appropriate. In these coordinates

$$\nabla^2 c = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right) + \frac{1}{r^2}\frac{\partial^2 c}{\partial \theta^2} + \frac{\partial c^2}{\partial z^2}. \tag{7.70}$$

If the domain is a sphere, then spherical coordinates (r, θ, ϕ), where $x = r\sin\phi\cos\theta, y = r\sin\phi\sin\theta, z = r\cos\phi$, are most appropriate, in which case the Laplacian operator is

$$\nabla^2 c = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) + \frac{1}{r^2\sin\theta}\frac{\partial}{\partial \theta}\left(\sin\theta\frac{\partial c}{\partial \theta}\right) + \frac{1}{r^2\sin^2\theta}\frac{\partial^2 c}{\partial \phi^2}. \tag{7.71}$$

An important reason for using other coordinate systems is that there may be symmetries that allow the problem to be reduced. For example, suppose that a spherical cell of radius R is suddenly immersed into a large bath containing a high concentration of glucose, and that the glucose can move across the membrane and then diffuse throughout the cell. If the concentration of glucose in the cell is initially uniform ($c = c_0$), then the solution should be independent of ϕ and θ for all time. This implies that

$$\frac{\partial c}{\partial \theta} = \frac{\partial c}{\partial \phi} = \frac{\partial^2 c}{\partial \phi^2} = 0. \tag{7.72}$$

Thus, a reasonable model for this problem is

$$\frac{\partial c}{\partial t} = \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right), \tag{7.73}$$

$$c(r, 0) = c_0, \tag{7.74}$$

$$D\frac{dc}{dr} = j \text{ at } r = R, \tag{7.75}$$

where c_0 is the initial cytosolic glucose concentration, and j is the rate of entry of glucose through the plasma membrane.

7.5 Traveling Waves in Nonlinear Reaction–Diffusion Equations

Consider a reaction–diffusion equation with a nonlinear source term:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} + f(c), \tag{7.76}$$

where $f(c)$ is the cubic polynomial $f(c) = Ac(1-c)(c-\alpha)$, with $0 < \alpha < \frac{1}{2}$. While real chemical reactions are not modeled exactly by a cubic polynomial, the reaction term has features that resemble those of several more realistic reactions, and so is worthy of our attention. This equation can be (and has been) used to understand features of action potential propagation in nerve axons, calcium fertilization waves in frog eggs, and cyclic AMP waves in slime molds.

A key feature of this reaction term is that it has three zeros (0, α, and 1), two of which (0 and 1) are stable. Linear stability is determined by the sign of $f'(c)$ at the rest point, and if $f'(c_0) < 0$, the rest point c_0 is stable. In this problem, however, there is a stronger type of stability in that the solution of the ordinary differential equation $\frac{dc}{dt} = f(c)$ approaches either $c = 0$ or $c = 1$ starting from any initial position except $c = \alpha$.

The function $f(c)$ can be thought of as a switch. If c is somehow pushed slightly away from 0, it returns quickly to 0. However, if c is pushed away from 0 and exceeds α, then it goes to 1. Thus, the level α is a threshold for c. Because it has two stable rest points, equation (7.76) is often called the bistable equation.

7.5.1 Traveling Wave Solutions

An interesting and important problem is to determine the behavior of the bistable equation when a portion of the region is initially above the threshold α and the remainder is initially at zero. To get some idea of what to expect it is useful to perform a numerical simulation. For this numerical simulation we use the method of lines to solve the differential equations

$$\frac{dc_0}{dt} = \frac{D}{\Delta x^2}(c_1(t) - c_0(t)) + f(c_0), \tag{7.77}$$

$$\frac{dc_n}{dt} = \frac{D}{\Delta x^2}(c_{n+1}(t) - 2c_n(t) + c_{n-1}(t)) + f(c_n), \qquad n = 1, 2, \ldots, N-1, \tag{7.78}$$

$$\frac{dc_N}{dt} = \frac{D}{\Delta x^2}(c_{N-1}(t) - c_N(t)) + f(c_N). \tag{7.79}$$

The simulation shows that the variable c quickly changes into a profile that is a transition between $c = 0$ on the bottom and $c = 1$ on the top (Figure 7.8). After this transitional profile is formed, it moves without change of shape from top to bottom at (what appears to be) a constant velocity.

This numerical solution suggests that we should try to find a translationally invariant solution. A translationally invariant solution is one that does not change its value along any straight line $x + st = x_0$, for an appropriately chosen value of s, the wave speed. Thus, we look for special solutions of the bistable equation of the form

$$c(x,t) = U(x + st), \tag{7.80}$$

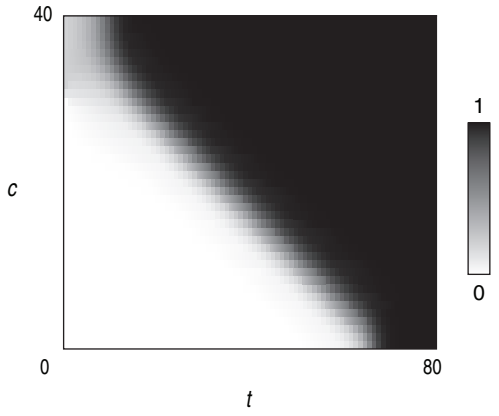

Figure 7.8 Numerically computed solution of the bistable equation, with $A = 1$, α=0.1 and $D = 1$.

with the additional property that $\lim_{\xi\to-\infty} U(\xi) = 0$, $\lim_{\xi\to\infty} U(\xi) = 1$. Notice that since

$$\frac{\partial c(x,t)}{\partial x} = \frac{d}{d\xi}U(\xi)\frac{\partial \xi}{\partial x} = \frac{d}{d\xi}U(\xi) \text{ and } \qquad \frac{\partial c(x,t)}{\partial t} = \frac{d}{d\xi}U(\xi)\frac{\partial \xi}{\partial t} = s\frac{d}{d\xi}U(\xi), \tag{7.81}$$

in this translating coordinate system, the bistable equation becomes the ordinary differential equation

$$s\frac{dU}{d\xi} = D\frac{d^2U}{d\xi^2} + f(U). \tag{7.82}$$

There are two ways to try to solve (7.82). An exact solution can be found in the special case that f is a cubic polynomial. There are several other examples of functions f for which exact solutions can be found, but this method does not work in most cases. A more general method is to examine (7.82) in the phase plane, which we will do below.

The exact solution can be found for the cubic polynomial f as follows. Since we want $\lim_{\xi\to-\infty} U(\xi) = 0$, $\lim_{\xi\to\infty} U(\xi) = 1$, we guess a relationship between $dU/d\xi$ and U of the form

$$\frac{dU}{d\xi} = aU(1-U), \tag{7.83}$$

for some positive number a. It follows that

$$\frac{d^2U}{d\xi^2} = a(1-2U)\frac{dU}{d\xi}. \tag{7.84}$$

Substituting this into (7.82) and factoring out $U(1-U)$, we find that

$$as = a^2D(1-2U) + A(U-\alpha). \tag{7.85}$$

This identity holds for all U only if

$$a^2 = \frac{A}{2D}, \qquad s = \sqrt{AD/2}\cdot(1-2\alpha). \tag{7.86}$$

The solution is found by quadrature from (7.83) to be

$$U(\xi) = \frac{1}{2} + \frac{1}{2}\tanh\left(\frac{1}{2}\sqrt{\frac{A}{2D}}\xi\right). \tag{7.87}$$

The analysis used for finding traveling waves using phase portraits works for any bistable function f. We begin by writing the traveling wave (7.82) as the two-dimensional system

$$\frac{dU}{d\xi} = W, \tag{7.88}$$

$$\frac{dW}{d\xi} = sW - f(U). \tag{7.89}$$

This system has three critical points, at $(U, W) = (0, 0), (\alpha, 0)$, and (1,0). The linearized stability of these critical points is determined by the roots of the characteristic equation

$$\lambda^2 - s\lambda + f'(U_0) = 0, \tag{7.90}$$

where U_0 is any one of the three steady rest values of U.

If $f'(U_0)$ is negative, then the critical point $(U_0, 0)$ is a saddle point. To find a traveling wave solution, we seek a trajectory that leaves the saddle point at $(U, W) = (0, 0)$ and ends up at the saddle point at $(U, W) = (1, 0)$. We can implement this (almost) numerically. If we start with an initial point close to the origin along the straight line $W = \lambda U$ in the positive quadrant, with λ the positive root of the characteristic equation $\lambda^2 - s\lambda + f'(0) = 0$, and integrate for a while, one of two things will occur. If s is relatively small, the trajectory will cross the U–axis before reaching $U = 1$, while if s is relatively large, the trajectory will increase beyond $U = 1$ and become quite large. By adjusting the parameter s one can find trajectories that barely miss hitting the point $(U, W) = (1, 0)$ by crossing the U–axis or by exceeding $U = 1$ and becoming large (Figure 7.9). A trajectory that comes close to the saddle point at $(U, W) = (1, 0)$ is a numerical approximation to the traveling wave solution, and the value of s for which this nearly connecting trajectory is attained is a good approximation for the wave speed.

7.5.2 Traveling Wave in the Fitzhugh–Nagumo Equations

As we have seen in earlier chapters, chemical reaction schemes in cell biology can be quite complicated, involving many species. Furthermore, some species may be free to move, while others are not. Models of nerve axons, for example, include both diffusing species (transmembrane potential) and nondiffusing variables (the ion-gating variables, because ion channels are embedded in the membrane and do not move on the millisecond time scale of an action potential). Similarly, the Ca^{2+} wave induced by fertilization of a frog egg involves both cytosolic calcium, which is a diffusing variable, and ER calcium which, (to a first approximation) is not.

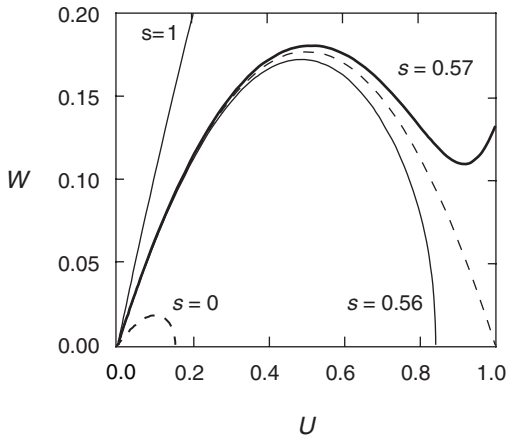

Figure 7.9 Phase plane portrait of possible traveling wave trajectories.

Perhaps the best known example of a reaction–diffusion system is the Hodgkin–Huxley equations discussed in Section 2.5, which describe action potential propagation in a nerve axon. In this model there are four dependent variables: transmembrane potential V and three gating variables, m, n, and h. The equation for transmembrane potential $V(x,t)$ is the cable equation

$$C_{\mathrm{m}}\frac{\partial V}{\partial t} = \frac{R}{2\rho}\frac{\partial^2 V}{\partial x^2} + I_{\mathrm{ion}}(V,m,n,h), \tag{7.91}$$

where C_{m} is the membrane capacitance, R is the axonal radius, ρ is the axoplasmic resistivity, and I_{ion} is the current carried into the axon by ions crossing through voltage-sensitive channels, and $\frac{R}{2\rho}\frac{\partial^2 V}{\partial x^2}$ is the net current along the axon carried by ions in response to spatial gradients of intracellular potential. For the giant axon of the squid, Hodgkin and Huxley report that $R = 240\ \mu$m, $\rho = 0.35\ \Omega\cdot$m, and $C_{\mathrm{m}} = 0.01$ F/m^2.

In the Hodgkin–Huxley equations given in Section 2.5, I_{ion} is a complicated function of transmembrane potential and the gating variables. To simplify the function, FitzHugh lumped the three gating variables into one (called w). The resulting equations in spatial form are

$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} + \frac{B}{V_1 V_2}V(V-V_1)(V_2-V) - C\sqrt{V_1 V_2}w, \tag{7.92}$$

$$\frac{\partial w}{\partial t} = \frac{\epsilon}{\sqrt{V_1 V_2}}(V - V_3 w), \tag{7.93}$$

where $D = R/(2\rho C_{\mathrm{m}}) \approx 0.03$ m^2/s (for squid giant axon), V_1, V_2, and V_3 are positive "voltage" constants, and B, C, and ϵ are rate constants with units 1/s. It is also assumed that $\epsilon \ll B, C$.

By defining $v = V/\sqrt{V_1 V_2}$, we transform (7.92) and (7.93) into

$$\frac{\partial v}{\partial t} = D\frac{\partial^2 v}{\partial x^2} + Bv(v-\beta)(\delta - v) - Cw, \tag{7.94}$$

$$\frac{\partial w}{\partial t} = \epsilon(v - \gamma w), \tag{7.95}$$

where $\beta = V_1/\sqrt{V_1V_2}, \delta = V_2/\sqrt{V_1V_2},$ and $\gamma = V_3/\sqrt{V_1V_2}$. Because $\epsilon \ll B, C$, we can use reduction of scale arguments (see Chapter 4) to justify the assumption that $w(x,t) = w_0 =$ constant. In this case, (7.94) and (7.95) reduce to a single reaction–diffusion equation:

$$\frac{\partial v}{\partial t} = D\frac{\partial^2 v}{\partial x^2} + Bv(v - \beta)(\delta - v) - Cw_0. \tag{7.96}$$

Let us assume that the "reaction" part of (7.96), $G(v) = Bv(v - \beta)(\delta - v) - Cw_0$, has three real steady states

$$G(v_i) \equiv Bv_i(v_i - \beta)(\delta - v_i) - Cw_0 = 0, \text{ for } i = 1, 2, 3;\ v_1 < v_2 < v_3.$$

By defining $c = (v - v_1)/(v_3 - v_1)$, (7.96) becomes identical to (7.76), with A now some nonlinear function of B, β, δ, and Cw_0. Hence, from the results leading to (7.86), we know that for appropriate choices of β, δ, and Cw_0, (7.96) supports traveling wave solutions of velocity

$$s = \sqrt{AD/2} \cdot (1 - 2\alpha).$$

To estimate the velocity of propagation of an action potential wave front, we must have, in addition to $D \approx 0.03$ m^2/s, estimates of the rate constant A and the threshold α in the $f(c)$ term of (7.76). Given that the amplitude of an action potential is ≈ 100 mV, and that the threshold for initiation is ≈ 20 mV (from rest), we set $\alpha \approx 0.2$. During the rise of an action potential, V increases with a doubling time of a fraction of a millisecond (say, 0.2 ms). Trajectories of the reaction equation $dc/dt = f(c)$ depart from the unstable steady state according to

$$c(t) - \alpha = (c_0 - \alpha)\exp(A\alpha(1 - \alpha)t). \tag{7.97}$$

To verify this, set $c = y + \alpha$ and linearize $dc/dt = f(c)$ to get $dy/dt = f'(\alpha)y$ and then solve to obtain (7.97). The doubling time for departure from the unstable steady state is

$$\frac{\ln 2}{A\alpha(1 - \alpha)} \approx 0.2 \text{ ms}.$$

or $A \approx 2 \cdot 10^4$/s. Hence, if the upstroke of the action potential can be approximated by the FitzHugh–Nagumo equations, it should propagate at velocity

$$s \approx \sqrt{\frac{(2 \cdot 10^4/\text{s})(3 \cdot 10^2\text{m}^2/\text{s})}{2}} \cdot (1 - 0.4),$$

or approximately 10 m/s. This compares favorably with the observed velocity of 20 m/s.

Suggestions for Further Reading

- *Random Walks in Biology*, Howard Berg. This is a lovely introductory book on diffusion processes in biology (Berg 1993).
- *Mathematical Problems in the Biological Sciences*, S. Rubinow. Chapter 5 gives a nice introduction to diffusion processes (Rubinow 1973).
- *Diffusional mobility of golgi proteins in membranes of living cells*, N.B. Cole, C.L. Smith, N. Sciaky, M. Terasaki, and M. Edidin. This paper gives an example of how diffusion coefficients are measured in a specific biological context (Cole et al. 1996).
- *Complex patterns in a simple system*, John Pearson. Reaction diffusion equations are used to model many interesting phenomena. A sampler of the kinds of patterns that are seen in reaction diffusion systems is given in this paper (Pearson 1993).
- *The theoretical foundation of dendritic function*, Idan Segev, John Rinzel, and Gordon Shepard. This book contains the collected papers of Wilfrid Rall, a pioneer in the application of cable theory and compartment modeling to neuronal dendrites (Segev et al. 1995).
- *Mathematical Physiology*, James Keener and James Sneyd. Several of the topics presented in this chapter are covered here in more depth (Keener and Sneyd 1998).

7.6 EXERCISES

1. A rule of thumb (derived by Einstein) is that the diffusion coefficient for a globular molecule satisfies $D \approx M^{-1/3}$ where M is the molecular weight. Determine how well this relationship holds for the substances listed in Table 7.1 by plotting D and M on a log-log plot.

2. (a) Verify that the solution of (7.36)–(7.37) is given by (7.38). Verify (7.41).

   (b) Show that the total amount of C, given by $\int_{-\infty}^{\infty} c(x,t)\,dx$, is constant for all time. What is the constant?

3. Verify that (7.43) satisfies the diffusion equation with boundary data $c(0,t) = C_0$ and initial data $c(x,0) = 0$.

4. Using the data given in the text and equation (7.45), estimate the diffusion coefficient for bacteria.

5. Numerically simulate the differential equations (7.53), (7.55), and (7.56) with initial data corresponding to $c(x,0) = 1$ for $20 < x < 30$ and $c(x,0) = 0$ elsewhere, using $N = 40$ discrete intervals and $D = 2.25 \times 10^{-6}$ cm^2/s as a typical diffusion coefficient for calcium. What is the final steady–state distribution of calcium and what is the approximate time constant of decay to this steady solution?

6. Numerically simulate a voltage–clamp experiment on a spatial domain that is 4 space constants long with $V(0,t) = 1$, and $V(x,0) = 0$, using constants appropriate for barnacle fiber and squid giant axon. What are the observable differences between these two simulations?

7. (a) Show that the function

$$c(r,t) = \frac{1}{4\pi D t} e^{\left(-\frac{r^2}{4Dt}\right)}$$

satisfies the diffusion equation in two spatial dimensions,

$$c_t = \frac{D}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right),$$

where $r^2 = x^2 + y^2$.

(b) Show that the total amount of C, given by $2\pi \int_0^\infty c(r,t)rdr$, is constant for all time. What is the constant?

(c) Evaluate r_{rms} where $r_{\text{rms}}^2 = 2\pi \int_0^\infty r^2 c(r,t)rdr$.

(d) When is the maximal value of $c(r,t)$ achieved and what is the maximal value?

8. (a) Show that the function

$$c(r,t) = \frac{1}{(4\pi Dt)^{3/2}} e^{\left(-\frac{r^2}{4Dt}\right)}$$

satisfies the diffusion equation in three spatial dimensions,

$$c_t = \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right),$$

where $r^2 = x^2 + y^2 + z^2$.

(b) Show that the total amount of C, given by $4\pi \int_0^\infty c(r,t)r^2dr$, is constant for all time. What is the constant?

(c) Evaluate r_{rms} where $r_{\text{rms}}^2 = 4\pi \int_0^\infty r^2 c(r,t)r^2dr$.

(d) When is the maximal value of $c(r,t)$ achieved and what is the maximal value?

9. A quantitative estimate of the way proteins diffuse on membranes is provided by *fluorescence recovery after photobleaching* (FRAP) studies, wherein cells are treated with a fluorescent reagent that binds to a specific surface protein, which is uniformly distributed on the surface. A laser light is then focused onto a small area of the surface, irreversibly bleaching the bound reagent and thus reducing the fluorescence in the illuminated area. In time, the fluorescence of the bleached area increases because the unbleached fluorescent surface molecules diffuse into the bleached area while the bleached molecules diffuse out. Model and simulate this experiment in two ways:

(a) Make a one–dimensional model for a domain 10 microns long, with no-flux boundary conditions at both ends. Assume that the first micron is initially bleached and the remaining space is initially unbleached. Assume that the diffusion coefficient of the molecules is 10^{-7} cm^2/s. Determine the spatial profile as a function of time, and the final uniform distribution of unbleached protein.

(b) Make a two–dimensional model for a perfectly circular domain of radius 10 microns with a one–micron circular region at the center that is initially bleached. Assume that $\partial c/\partial r = 0$ at both $r = 0$ and $r = 10$ μm. Use the discretization of the diffusion operator given by

$$\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right) \approx \frac{1}{2r_n}\left((r_{n+1} + r_n)(c_{n+1} - c_n) - (r_{n-1} + r_n)(c_n - c_{n-1})\right).$$

Determine the spatial profile as a function of time and the final uniform distribution. What differences are there between the two-dimensional and the one-dimensional models?

10. Simulate the bistable equation starting from initial data having $V(x,0) > \alpha$ for a small region on the left end of the domain, and $V(x,0) = 0$ elsewhere. What is the speed of the traveling wave that forms?

11. Numerically simulate an experiment on an idealized nerve axon that is stimulated at one end with a time–dependent current input. The equations are

$$\frac{\partial \phi}{\partial t} = \frac{\partial^2 \phi}{\partial x^2} + f(\phi) - w, \qquad f(\phi) = \phi(\phi - 1)(0.1 - \phi),$$
$$\frac{\partial w}{\partial t} = 0.01(\phi - 0.5w),$$

subject to boundary conditions $\partial\phi(0,t)/\partial x = I(t)$, $\partial\phi(10,t)/\partial x = 0$. Pick $I(t)$ to be a square pulse. Vary the height and length of the pulse in order to initiate a traveling wave. Describe the response when the amplitude and/or duration of the stimulating pulse is too small to initiate a traveling wave.

12. Using the method described in Section 7.5.1, compute a traveling wavefront solution to the Morris–Lecar equations described in Section 2.4:

$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} - g_{\mathrm{Ca}} m_\infty(V)(V - V_{\mathrm{Ca}}) - g_{\mathrm{k}} w(V - V_K) - g_{\mathrm{L}}(V - V_L) + I_{\mathrm{app}}$$

where $m_\infty(V) = 0.5[1 + \tanh((V - v_1)/v_2)]$. Use $D = 300$ cm^2/s, $I_{\mathrm{app}} = 60$ pA, and all other parameter values as in Table 2.4. In this approximation, assume that $w(x,t) = w_0 =$ constant; try $w_0 = 0.1$. Plot $V(x,t)$ as in Figure 7.8, and estimate the speed of propagation of the wavefront in cm/s.