

BIOPHYSICS OF COMPUTATION

*Information Processing in
Single Neurons*

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DIFFUSION, BUFFERING, AND BINDING

In Chap. 9 we introduced calcium ions and alluded to their crucial role in regulating the day-to-day life of neurons. The dynamics of the free intracellular calcium is controlled by a number of physical and chemical processes, foremost among them *diffusion* and *binding* to a host of different proteins, which serve as calcium *buffers* and as calcium *sensors* or *triggers*. Whereas buffers simply bind Ca^{2+} above some critical concentration, releasing it back into the cytoplasm when $[\text{Ca}^{2+}]_i$ has been reduced below this level, certain proteins—such as calmodulin—change their conformation when they bind with Ca^{2+} ions, thereby activating or modulating enzymes, ionic channels, or other proteins.

The calcium concentration inside the cell not only determines the degree of activation of calcium-dependent potassium currents but—much more importantly—is relevant for determining the changes in structure expressed in synaptic plasticity. As discussed in Chap. 13, it is these changes that are thought to underlie learning. Given the relevance of second messenger molecules, such as Ca^{2+} , IP_3 , cyclic AMP and others, for the processes underlying growth, sensory adaptation, and the establishment and maintenance of synaptic plasticity, it is crucial that we have some understanding of the role that diffusion and chemical kinetics play in governing the behavior of these substances.

Today, we have unprecedented access to the spatio-temporal dynamics of intracellular calcium in individual neurons using *fluorescent calcium dyes*, such as fura-2 or fluo-3, in combination with *confocal* or *two-photon microscopy* in the visible or in the infrared spectrum (Tsien, 1988; Tank et al., 1988; Hernández-Cruz, Sala, and Adams, 1990; Ghosh and Greenberg, 1995). The data gleaned from these methods of directly visualizing calcium in the dendritic tree, cell body, and presynaptic terminals are quantitative enough to allow detailed comparison with numerical models, commencing with the work of Hodgkin and his colleagues in the squid axon (Blaustein and Hodgkin, 1969; Baker, Hodgkin, and Ridgway, 1971) and continuing with the study of calcium transients in the presynaptic terminal (Llinás, Steinberg and Walton, 1981a,b; Zucker and Stockbridge, 1983; Stockbridge and Moore, 1984; Simon and Llinás, 1985; Zucker and Fogelson, 1986; Parnas, Hovav, and Parnas, 1989; Yamada and Zucker, 1992) as well as in dendrites, cell bodies and spines (Connor and Nikolakopoulou, 1982; Gamble and Koch, 1987; Sala and Hernández-Cruz, 1990; Holmes

and Levy, 1990; Carnevale and Rosenthal, 1992; Zador and Koch, 1994; DeSchutter and Bower, 1994a,b; DeSchutter and Smolen, 1998; Borg-Graham, 1998; Yamada, Koch, and Adams, 1998).

In this chapter, we study the physics of diffusion and buffering, dwelling at some length on the fundamental limitations imposed by physics on how fast substances can diffuse. We will develop certain analogies between the reaction-diffusion equation and the cable equation and discuss the potential relevance of these processes for information processing and computation. While these results apply to any substance diffusing inside cells and binding to other molecules, we will focus on Ca^{2+} ions, given their crucial role in the day-to-day life of neurons and, in fact, in all cells. The control and regulation of calcium in neuronal structures is a vast subject, which we can only briefly hint at. For more details on calcium signaling in neurons the reader is urged to consult Hille's monograph (1992), the articles by Ghosh and Greenberg (1995) and by Clapham (1995), or the insightful Meyer and Stryer (1991) review. Finally, for the computational methods, consult DeSchutter and Smolen (1998). We end by discussing some general aspects of information processing using calcium.

Let us commence by deriving the diffusion equation that underlies the distribution of ions inside and outside cells.

11.1 Diffusion Equation

Historically, the diffusion equation was first derived from a macroscopic, deterministic point of view by Fick (1855), who postulated a force arising between molecules proportional to their concentration difference. Although such a phenomenological approach does lead to the correct equation, we now know that no such force exists. Instead, diffusion is due to the constant agitation of molecules arising from their thermal energy. The physically correct probabilistic interpretation of this *Brownian motion* was advanced by Einstein (1905), who used the theory of random walk. Because of the simplicity and elegance of his arguments, we will develop here a heuristic derivation of the diffusion equation using this stochastic perspective.

11.1.1 Random Walk Model of Diffusion

The starting point of the molecular theory of heat is that molecules and small particles at the absolute temperature T have, on average, a kinetic energy $kT/2$ associated with movement along each dimension. The resulting velocities of these particles in solution do not allow them to travel very far since they collide within picoseconds with other molecules, changing their direction of travel as a result. This incessant and random agitation of molecules due to thermal energy is the basis of diffusion.

Imagine a particle moving along an one-dimensional line. Both space and time are discretized, such that the particle can only be at locations $\pm m \Delta x$, where m is an integer. Each time step Δt , the particle can move either with 50% probability to the right or with 50% probability to the left, in both cases by the amount Δx . The particle cannot remain in place or move by more than Δx . Finally, we assume that the particle has no memory of any locations it has previously visited.

These rules allow us to define a probability distribution $p(x, t)$ that the particle will be at position x at time t . The only way the particle could have arrived at position x is if it was at either one of the two adjacent positions in the previous time step. That is,

$$p(x, t) = \frac{1}{2} (p(x - \Delta x, t - \Delta t) + p(x + \Delta x, t - \Delta t)) . \quad (11.1)$$

Subtracting $p(x, t - \Delta t)$ from both sides as well as dividing by Δt yields

$$\frac{p(x, t) - p(x, t - \Delta t)}{\Delta t} = \frac{(\Delta x)^2 p(x - \Delta x, t - \Delta t) - 2p(x, t - \Delta t) + p(x + \Delta x, t - \Delta t)}{(\Delta x)^2} \quad (11.2)$$

The left-hand side of this equation is nothing but the first-order approximation of the first temporal derivative of p , while the term on the right-hand side corresponds to the second-order approximation of the second spatial derivative of $p(x, t - \Delta t)$. In the limit as Δx and Δt approach zero in such a way that

$$\frac{(\Delta x)^2}{2\Delta t} = D \quad (11.3)$$

converges toward a finite constant (with units of cm^2/sec), we end up with the partial differential *diffusion equation*

$$\frac{\partial p(x, t)}{\partial t} = D \frac{\partial^2 p(x, t)}{\partial x^2} . \quad (11.4)$$

It describes how the probability function $p(x, t)$ evolves over time and is also known under the generic name of *Fokker-Planck equation*. We will reencounter this class of equations in Chap. 15.

The simplest interpretation of diffusion can be given if the single particle is replaced by a cloud of N independently moving particles that all start off at the origin, $x = 0$. What is the expected mean position of this cloud of particles and the variance around this mean position? According to our simple model, $x_i(t)$ for particle i at time $t = n\Delta t$ can only differ from the previous position by $\pm\Delta x$,

$$x_i(n\Delta t) = x_i((n-1)\Delta t) \pm \Delta x . \quad (11.5)$$

The average position of the cloud, $\langle x(n\Delta t) \rangle$, at time $n\Delta t$ is given by summing over all the individual particles,

$$\langle x(n\Delta t) \rangle = \frac{1}{N} \sum_{i=1}^N x_i(n\Delta t) = \frac{1}{N} \sum_{i=1}^N [x_i((n-1)\Delta t) \pm \Delta x] . \quad (11.6)$$

Since we assumed earlier that each particle has an equal chance of moving to the left or to the right (and that no boundaries impede the motion of the particles), the last term in brackets averages zero for large numbers of particles. This equation then tells us that the mean position of the cloud at time $n\Delta t$ does not change from its previous position, $\langle x(n\Delta t) \rangle = \langle x((n-1)\Delta t) \rangle$. If the cloud starts off at the origin, we conclude that the average location of the cloud will never move,

$$\langle x(n\Delta t) \rangle = 0 . \quad (11.7)$$

If we incorporate a systematic drift into the motion of the particles, for instance, by applying an electric field that imposes a preferred direction of motion (assuming that the moving

(11.1) particle is charged), this result will have to be modified. However, in the absence of such a bias, the cloud will remain centered at the origin.

How much does the cloud spread out over time? As anybody can observe when placing a drop of ink into a water glass, at first a small part of the water is stained an intense blue. Later on, the spot of blue becomes less intense and larger, dispersing eventually throughout the entire glass. One measure of this spreading is the variance of the mean position of the cloud. This is defined as

$$(11.2) \quad \langle x(n\Delta t)^2 \rangle = \frac{1}{N} \sum_{i=1}^N x_i(n\Delta t)^2$$

$$= \frac{1}{N} \sum_{i=1}^N [x_i((n-1)\Delta t)^2 \pm 2\Delta x \cdot x_i((n-1)\Delta t) + (\Delta x)^2]$$
(11.8)

(11.3) (we here used Eq. 11.5). Because the random walk is unbiased, the second term in this equation will be zero on average, resulting in

$$\langle x(n\Delta t)^2 \rangle = \langle x((n-1)\Delta t)^2 \rangle + (\Delta x)^2. \quad (11.9)$$

(11.4) We can, of course, recursively apply the same decomposition for $\langle x((n-1)\Delta t)^2 \rangle$, ending up in n steps with $\langle x(0)^2 \rangle$. Since the entire population started out at the origin, this last term is zero. Setting $t = n\Delta t$ and remembering that $(\Delta x)^2/(2\Delta t) = D$, we conclude

$$\langle x(t)^2 \rangle = 2Dt. \quad (11.10)$$

Thus, while the mean position of the cloud does not move, the variance or width of the cloud increases linearly with time and its standard deviation as the square root of time. Interpreted in terms of single particles, Eq. 11.7 implies that the mean position of a single particle does not change while the probability of finding it at larger and larger distances from the origin increases as the square root of time (Eq. 11.10).

(11.5) 11.1.2 Diffusion in Two or Three Dimensions

The same concept can be applied to the motion of a particle in more than one dimension. As long as the motion along the x direction is independent of the motion in the y direction, the variance of motion in the plane is the sum of the variances of motion in the two independent directions,

$$(11.6) \quad \langle r(t)^2 \rangle = \langle x(t)^2 \rangle + \langle y(t)^2 \rangle = 4Dt. \quad (11.11)$$

(11.7) A computer simulation of such a random walk is illustrated in Fig. 11.1. Given the square-root relationship between time and distance traversed, it is possible for the particle to explore short distances much more thoroughly than large distances. Thus, the typical pattern evident in Fig. 11.1: the particle tends to return to the same region many times before eventually wandering away. When it does move away, it blindly chooses another region to explore, with no regard for whether or not it had previously visited that area. This reflects the fact that the particle does not move down any gradient in response to a "diffusive" force as postulated by Fick (1855), but acts in a probabilistic manner to spread over the available space; its tracks do not uniformly fill up the available space. For a particle diffusing in three dimensions, exactly the same principle applies, except that now

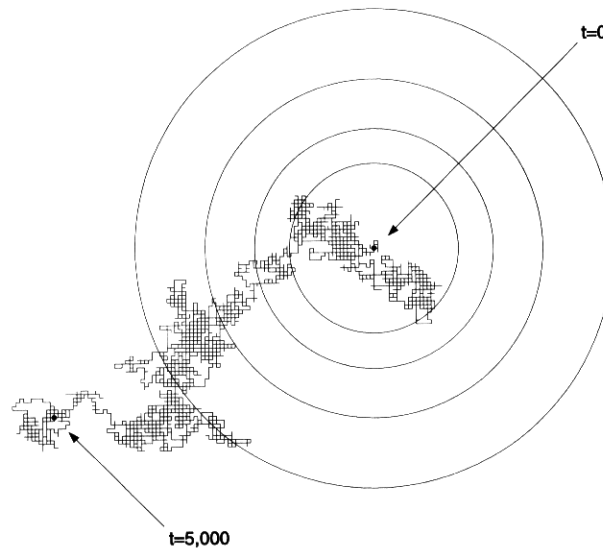


Fig. 11.1 DIFFUSION OF A PARTICLE IN THE PLANE Computer simulation of a single particle executing a random walk on a rectangular grid. At each point in time, it has a probability of 0.25 of moving in any one of four directions. In the limit of an infinitesimally fine grid, this approximates diffusion in a plane. The particle started at the center and after 5000 iterations ended up at the lower left corner. The radii of the four circles correspond to the variance in the locations of the particle after 500, 1000, 2000, and 4000 iterations. The expected time-averaged location of the particle is always at the center of the bull's eye.

$$\langle r(t)^2 \rangle = \langle x(t)^2 \rangle + \langle y(t)^2 \rangle + \langle z(t)^2 \rangle = 6Dt. \quad (11.12)$$

The *random walk* approach to diffusion has been very fruitful in mathematical physics. It is straightforward to derive equations corresponding to particles moving down a gradient caused, for instance, by an applied electric field, or if the space the particle moves in has absorbing or reflecting boundaries such as a membrane. For more details on the mathematics of random walk see the idiosyncratic, but immensely informative, monograph by Mandelbrot (1977); for a delightful text on the use of random walk techniques to describe the motion of bacteria and other small organisms see Berg (1983).

11.1.3 Diffusion Coefficient

In the above, we assumed—see Eq. 11.3—that D is purely dictated by the temporal and spatial discretization steps. However, for real particles in solution—where gravity can be neglected— D must clearly depend on certain physical attributes of the particles themselves as well as on properties of the solution. What precisely determines D and how large is it for real ions, such as Ca^{2+} , and big molecules, such as calmodulin which binds free Ca^{2+} in neurons?

Einstein (1905), arguing that diffusion is thermal agitation of particles opposed by friction, derived a general relationship between diffusion and friction. For particles that can be approximated as spheres much larger than the size of individual water molecules (which are on the order of 1 Å), D is determined by the *Einstein-Stokes relation* as

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$$D = \frac{kT}{6\pi\eta r_s} \quad (11.13)$$

where r_s is the radius of the diffusing particle and η the viscosity of water. The proportionality of D to the absolute temperature T simply reflects the thermal origin of diffusion. For room temperature (20° C), this equation reduces to $D = \alpha/r_s$, with $\alpha = 2.15 \mu\text{m}^2/\text{msec}$ and the radius r_s specified in units of angstrom (\AA). (For a very thorough discussion of this, see Hille, 1992.) The diffusion coefficient is usually specified in cm^2/sec ; however, we will adopt units more convenient to neuronal structures and measure D in units of $\mu\text{m}^2/\text{msec}$.

The Einstein-Stokes relationship—based on classical hydrodynamics—is accurate for large particles, but works less well for small ions. For instance, for the 0.99 \AA radius calcium ion, D should be 2.14 $\mu\text{m}^2/\text{msec}$ but is, in fact, 0.6 $\mu\text{m}^2/\text{msec}$ (Blaustein and Hodgkin, 1969). This mismatch is partially caused by the formation of a hydration shell around the ion, that is, water molecules that lie in direct contact with each ion in solution. For larger and heavier molecules, this is less of a consideration and their radius can be thought of as being approximately proportional to the cubic root of their molecular weight. Table 11.1 lists the diffusion coefficients of a number of ions and molecules for diffusion in an aqueous medium characteristic of the intracellular cytoplasm.

11.2 Solutions to the Diffusion Equation

Before we discuss the impulse response or Green's function of the diffusion equation, let us sketch out its macroscopic phenomenological derivation. The mathematical theory of diffusion in an isotropic milieu is based on the simplest phenomenological expression possible—also called Fick's first law of diffusion (Fick, 1855)—that the rate of transfer $S(x, t)$ of a diffusing substance across a surface of unit area (also called the flux; Eq. 9.2) is proportional to the concentration gradient measured normal to the surface,

$$S(x, t) = -D \frac{\partial C(x, t)}{\partial x} \quad (11.14)$$

TABLE 11.1
Diffusion Coefficients

Ion or molecule	Diffusion coefficient
H ⁺	9.3 ¹
NO	3.8 ²
Na ⁺	1.33 ¹
K ⁺	1.96 ¹
Ca ²⁺	0.6 ³
IP ₃	0.24
Calmodulin	0.13
CaM kinase II	0.034

Diffusion coefficients in an aqueous environment for different ions and second messenger molecules in units of $10^{-5} \text{ cm}^2/\text{sec}$, that is $\mu\text{m}^2/\text{msec}$.

¹ Table 10.1 in Hille (1992).

² In rat cortex; Meulemans (1994); see also Wise and Houghton (1968).

³ Blaustein and Hodgkin (1969).

⁴ Allbritton, Meyer, and Stryer (1992).

where D is the constant of proportionality and the minus sign arises because diffusion occurs against a concentration increase. Since the amount of substance diffusing across the boundary is proportional to the area of the boundary, the diffusion coefficient has dimensions of $\mu\text{m}^2/\text{msec}$.

Because this amount corresponds to a particular number of molecules diffusing, we refer to it using the colloquial, but entirely appropriate, term *stuff* for lack of a more specific term and express it in units of gram molecules or moles (mol) while the concentration C is given in molar (M), that is moles of molecules per liter.¹ The extracellular concentration of Ca^{2+} ions is about 2 mM, while its intracellular concentration at rest is around 10 to 20 nM, a difference of five orders of magnitude.

Consider a cylindrical cable where the concentration C only varies along the x dimension, reducing the problem of solving the diffusion equation from three dimensions to one. The justification of this is identical to the one we made for one-dimensional cable theory in Chap. 2, namely, that the radius of the cylinder is much shorter than its length and that the equilibrium time for radial diffusion is short compared to longitudinal diffusion.

If the concentration inside a compartment centered at x and with boundaries at $x + \Delta x$ and $x - \Delta x$ (Fig. 11.2) varies by $\partial C/\partial t$, the change in the amount of stuff in this compartment is given by

$$\frac{\Delta x \pi d^2}{2} \frac{\partial C(x, t)}{\partial t}. \quad (11.15)$$

This change should be identical to the net rate of transfer across one boundary minus the rate of transfer across the other,

$$\frac{\pi d^2}{4} (S(x - \Delta x, t) - S(x + \Delta x, t)). \quad (11.16)$$

Setting these two expressions equal leads to

$$\frac{\partial C(x, t)}{\partial t} = \frac{S(x - \Delta x, t) - S(x + \Delta x, t)}{2\Delta x}. \quad (11.17)$$

In the limit of an infinitesimally small interval ($\Delta x \rightarrow 0$), the expression $S(x + \Delta x, t) - S(x - \Delta x, t)$ converges to $2\Delta x \partial S(x, t)/\partial x$. Applying Eq. 11.14 we arrive once again at the *diffusion equation*

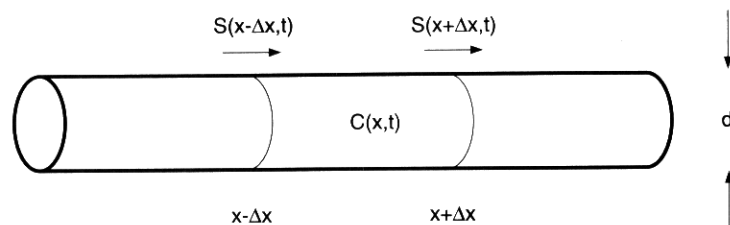


Fig. 11.2 DIFFUSION IN A CYLINDER Diffusion of some substance into and out of a cylindrical compartment with boundaries at $x - \Delta x$ and $x + \Delta x$. $S(x, t)$ corresponds to the rate of transfer across the cross section of area $\pi d^2/4$, and $C(x, t)$ corresponds to the concentration. As in one-dimensional cable theory, under certain conditions the three-dimensional diffusion equation can be reduced to a one-dimensional one.

1. To remind the reader, one mole of water, that is, 18 grams molecules, corresponds to 6.023×10^{23} H_2O molecules. Its concentration is 1000 grams per liter divided by 18 grams per mole, that is 55 M .

$$\frac{\partial C(x, t)}{\partial t} = D \frac{\partial^2 C(x, t)}{\partial x^2} \quad (11.18)$$

This is a linear partial differential equation of the parabolic type, with a unique solution if both an initial and a boundary condition are specified. We wish to point out already here, although we will not exploit this similarity until Sec. 11.7, that Eq. 11.18 is isomorphic to the linear cable equation (Eq. 2.7) if $r_m \rightarrow \infty$ (Fig. 11.3).

11.2.1 Steady-State Solution for an Infinite Cable

What is the steady-state behavior of the diffusion equation? If, in analogy with the cable equation, we “clamp” the concentration at the origin $C(x = 0, t)$ for all times to a fixed value C_0 , Eq. 11.18 reduces to an ordinary differential equation,

$$\frac{d^2 C(x)}{dx^2} = 0. \quad (11.19)$$

Its solution for an infinite cable is $C(x) = C_0$ for all values of x . After enough time has passed, the concentration in the entire cable rises to the concentration at the origin. This behavior is in marked contrast to the exponential decay of the potential in response to a current step (Eq. 2.12) and is a consequence of the fact that none of the diffusing substance “leaks” out across the walls of the cylinder.

11.2.2 Time-Dependent Solution for an Infinite Cable

The simplest time-dependent solution is the one for the concentration change along an infinite one-dimensional cable if an amount S_0 of calcium ions is injected instantaneously

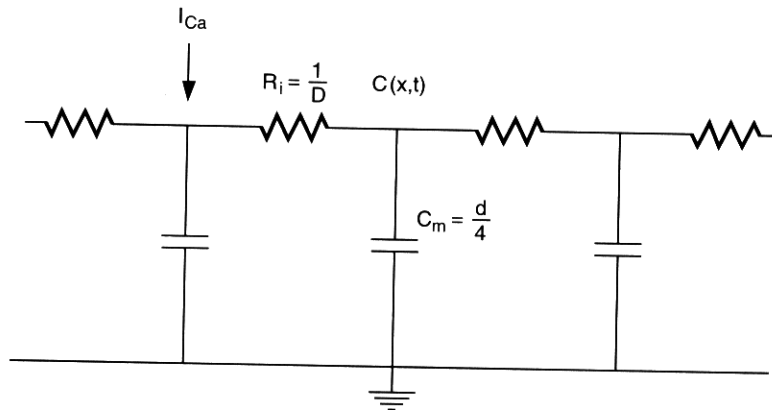


Fig. 11.3 EQUIVALENT ELECTRICAL CIRCUIT ASSOCIATED WITH THE DIFFUSION EQUATION Lumped electrical circuit representation associated with the diffusion of a substance in an elongated fiber. The input here is defined as $2I_{Ca}/Fd$, where d is the diameter of the process, F is Faraday's constant, and I_{Ca} is the calcium current flowing across the membrane. With the membrane capacity c_m set to 1 and $r_a = 1/D$, this circuit can be mapped onto the lumped electrical circuit approximating the cable equation (Fig. 2.3) in the absence of any membrane conductance (that is, $r_m \rightarrow \infty$). As we will show in Sec. 11.7, this analogy to the cable equation can be extended to the presence of a fast buffer and ionic pumps in the membrane. In the limit of infinitely small mesh size, the solution to this circuit approximates the continuous diffusion equation (Eq. 11.18).

into the cylinder at $x = 0$. We can show by simple differentiation that the resulting spatio-temporal evolution of C is given by

$$C_\delta(x, t) = \frac{S_0}{\sqrt{2\pi}} \frac{1}{(2Dt)^{1/2}} e^{-\frac{x^2}{4Dt}}. \quad (11.20)$$

The associated concentration profile is plotted in Fig. 11.4 for different values of t and x . In comparing this function with the impulse response function of the infinite, passive cable (Eq. 2.31 and Fig. 2.6), we notice the absence of an e^{-t} term (caused by the lack of a finite, membrane leak conductance for the diffusion equation). As a consequence, the total amount of substance is conserved, $\int C_\delta(x, t) dx = S_0$, at all times t . The absence of this exponential causes the Green's function for the diffusion equation to decay less rapidly than the corresponding Green's function for the cable equation. In particular, and not surprisingly, given our earlier result concerning the variance in the mean position of a cloud of randomly moving particles, the variance of the impulse response function increases linearly with time. We expand upon this point in the following section.

11.2.3 Square-Root Relationship of Diffusion

For any fixed time t , Eq. 11.20 can be expressed as a Gaussian, as can be seen upon inspection of Fig. 11.4A,

$$C_\delta(x, \sigma) = \frac{S_0}{\sigma\sqrt{2\pi}} e^{-\frac{x^2}{2\sigma^2}} \quad (11.21)$$

with

$$\sigma = \sqrt{2Dt}. \quad (11.22)$$

The variance of the Gaussian increases linearly with t , or the standard deviation increases with the square root of time. This has important consequences.

Let us consider the concentration in a semi-infinite cylinder, where the concentration at one end is held fixed: $C(x = 0, t) = C_0$ for all times. In the case of the cable equation, this would be equivalent to clamping the voltage at one end of the cable. We can solve for $C(x, t)$ directly by using either Fourier or Laplace transforms (Crank, 1975),

$$C(x, \sigma) = C_0 \operatorname{erfc}\left(\frac{x}{\sigma\sqrt{2}}\right) \quad (11.23)$$

where $\operatorname{erfc}(x)$ is the complementary error function defined as

$$\operatorname{erfc}(z) = \frac{2}{\sqrt{\pi}} \int_z^{+\infty} e^{-y^2} dy \quad (11.24)$$

with $\operatorname{erfc}(0) = 1$. The propagation of this concentration increase along the cylinder—illustrated in Fig. 11.5—involves only the dimensionless parameter $x/(\sigma\sqrt{2})$. Due to the square-root relationship between σ and t , it follows that the time required for any location to reach a given concentration is proportional to the square of the distance. If we ask at what time $t_{1/2}(x)$ the concentration at x reaches half of the source concentration, that is, $C_0/2$, we solve for t in Eq. 11.23, with its left-hand side set to $C_0/2$. By consulting tables for the error function (such as in Crank, 1975), we see that $\operatorname{erfc}(0.5) \approx 1/2$ within a few percent. In other words, $x/(2\sqrt{Dt_{1/2}}) \approx 1/2$, or

$$t_{1/2} \approx \frac{x^2}{D}. \quad (11.25)$$

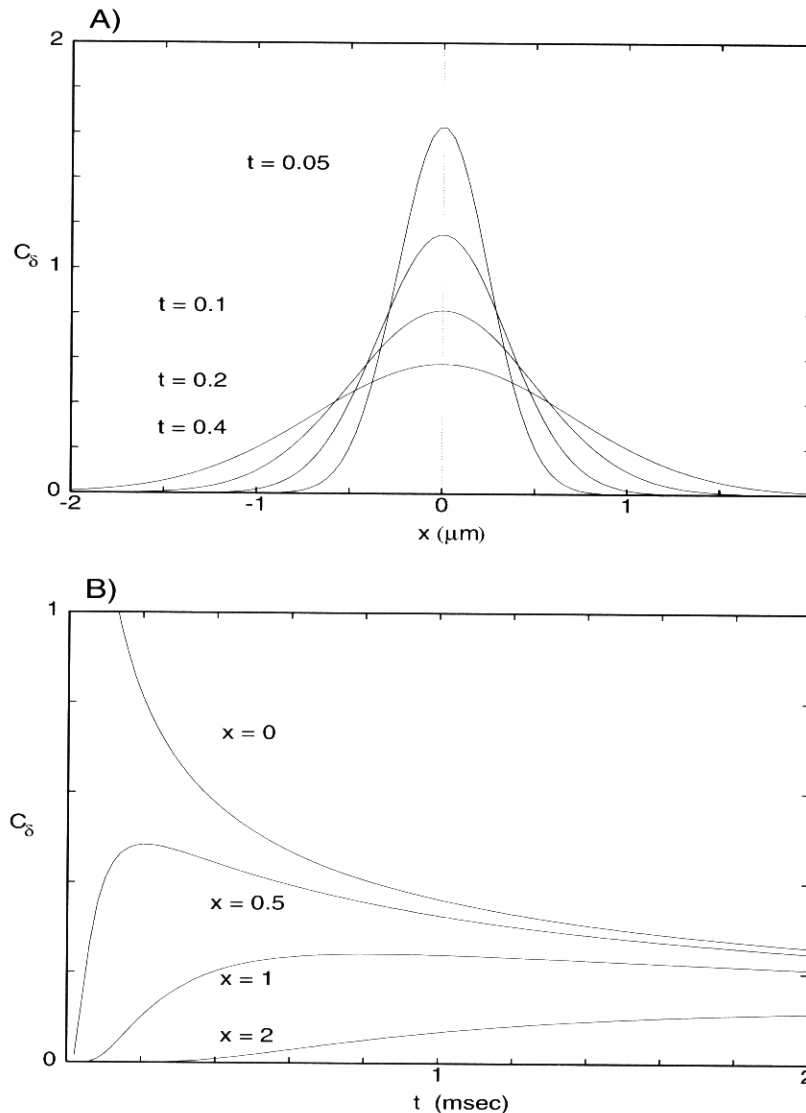


Fig. 11.4 IMPULSE RESPONSE OF THE DIFFUSION EQUATION IN AN INFINITE CABLE Concentration $C_\delta(x, t)$ in an infinite cylinder in response to an instantaneous injection of substance at $t = 0$ at the origin $x = 0$ as a function of space (A) or time (B; see Eq. 11.20). This Green's function decays more slowly than the Green's function of the linear cable equation (Eq. 2.31). As is clear from panel A, for any fixed time t the impulse response function can be described as a Gaussian, whose variance increases linearly with time.

Note that the approximation only involves the numerical factor in front of the square. We can reformulate this equation by stating that for a given duration t from the onset of the concentration step, the distance $x_{1/2}$ at which the concentration has reached half of its peak value is given by

$$x_{1/2} \approx \sqrt{Dt}. \quad (11.26)$$

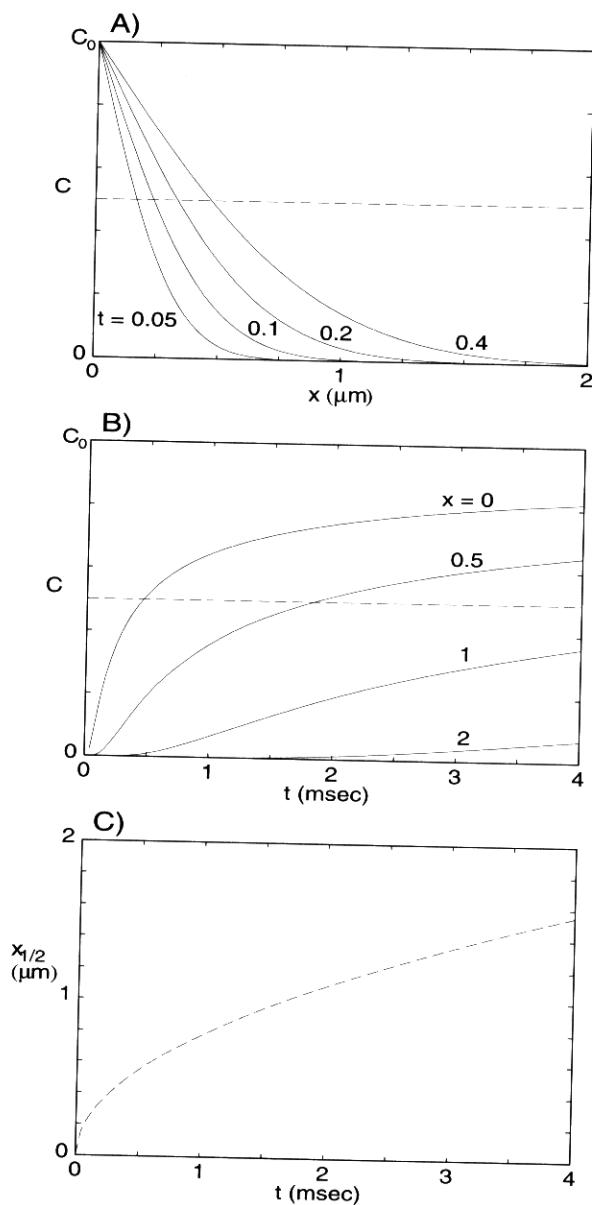


Fig. 11.5 THE SQUARE-ROOT LAW OF DIFFUSION At $t = 0$, the calcium concentration at the origin of a semi-infinite cable is clamped to C_0 . (A) Evolving concentration profile along the cable. (B) As time goes by, the concentration throughout the cable slowly rises to C_0 (different from the solution of the cable equation). At any one instance, we can ask at what location $x_{1/2}$ along the cable the concentration first reaches $C_0/2$ (dashed line). This relationship, shown in (C), is a square-root one. It takes four times as long to diffuse twice the distance (Eq. 11.26). This imposes a fundamental physical constraint on how fast any substance can diffuse in one or more spatial dimensions.

In three-dimensional space, the right-hand side needs to be multiplied by $\sqrt{3}$ (as in Eq. 11.12). If considering diffusion of ions within the porous and highly restricted extracellular space, further adjustments are necessary (see Sec. 20.2).

As an example, let us assume that the concentration of calcium at one end of a one-dimensional cylinder is clamped to $1 \mu\text{M}$. Assuming that no buffer impedes the diffusion of the calcium ions along the cable (and that $D_{\text{Ca}} = 0.6 \mu\text{m}^2/\text{msec}$), a calcium front—defined here as the time at which the concentration at any one location first reaches $0.5 \mu\text{M}$ —moving down the cylinder takes about 1 msec to cover the first $0.77 \mu\text{m}$, 10 msec to propagate

2.5 μm away from the origin and has traveled only 7.7 μm after 100 msec (Fig. 11.5). In neuronal tissues, these times are considerably further reduced due to the binding of calcium to intracellular buffers (Sec. 11.4).

The linear diffusion equation, as a member of the family of parabolic differential equations which also includes the linear cable equation (Sec. 2.3), does not admit to any solution $C(x, t) = C(x - vt)$ that propagates with fixed velocity v along the cable. This behavior is in stark contrast to the linear relationship between distance and time for action potentials propagating down the axon or for the wave of calcium release occurring in eggs following fertilization, making the cells impervious to the entry of additional sperms.

The square-root behavior imposes a fundamental limitation on the time required for concentration changes of calcium or any other intracellular messenger to affect distant sites (in the absence of active transport systems) and is apparent everywhere. For instance, if we keep the concentration of calcium in the shell just below the membrane of a spherical cell constant, the center of the sphere will have reached one half the shell concentration after about $0.04d^2/D$ msec, where d is the diameter of the sphere (in micrometers). For additional solutions to the diffusion equation under various boundary conditions consult Crank (1975) and the monograph by Cussler (1984).

11.3 Electrodiffusion and the Nernst-Planck Equation

In the derivation of the cable equation in the second chapter, we had assumed that the concentration of ions does not vary along the longitudinal direction of the cable. Thus, ions are only propelled along the cable by the voltage gradient, giving rise to the $\partial^2 V / \partial x^2$ term. In the previous section, we discussed the effective motion of ions due to diffusion, down the concentration gradient.

In general, of course, we need to include the movement of ions caused by concentration differences as well as by drift along the electric field. Even if a dendrite is initially at equilibrium with respect to the spatial distribution of sodium, potassium, calcium, and chloride ions, which are most important for fast signaling, the influx and efflux of ions across the membrane disturb this equilibrium. This is particularly true for very small volumes, such as thin dendrites or spines where the influx of even a moderate amount of calcium significantly increases $[\text{Ca}^{2+}]_i$, creating concentration gradients that propel calcium ions down this gradient (in addition to any existing voltage gradient).

In order to account for these effects, we need to combine Fick's law (Eq. 11.14) with Ohm's law, something done by Nernst (1888, 1889) as well as Planck (1890). Assuming that the longitudinal current and ionic concentrations are uniform across the cross section of the cylindrical dendrite or axon and that the random, diffusional motion superimposes linearly onto the electrotonic motions of ions driven by a true "force," we can write the one-dimensional *Nernst-Planck electrodiffusion equation* (Hille, 1992),

$$I_{i,k}(x, t) = -z_k F D_k \frac{\partial C_k(x, t)}{\partial x} - \frac{z_k^2 F^2 D_k C_k(x, t)}{RT} \frac{\partial V_m(x, t)}{\partial x} \quad (11.27)$$

where $I_{i,k}(x, t)$ is the axial current for the ionic species being considered (here labeled k), z_k is its valence, D_k its diffusion coefficient, R the gas constant, and F Faraday's constant.

The $z_k F D_k$ term in front of the concentration gradient converts "stuff" into a current, while the constants in front of the potential gradient express implicitly how the electrical conductance relates to the concentration and the mobility of the ions (see also Eq. 11.13).