7

ELECTRICAL STIMULATION OF EXCITABLE TISSUE

In designing systems for stimulation, a qualitative understanding together with mathematical descriptions of responses to stimulation are essential. The response of excitable cells to naturally occurring or artificial stimuli is a subject of great importance in understanding natural function of nerve and muscle, because most stimuli are produced by the natural system itself. Both electric and magnetic field stimulation are used in research investigations and in clinical diagnosis, therapy, and rehabilitation. This chapter focuses primarily on responses to electrical stimuli, which are more frequent, and examines several biological preparations.

The core idea of stimulation is the following: A current, arising from an external stimulator or natural source, is introduced into a cell or its neighborhood. The current creates transmembrane voltage in nearby membrane. The membrane responds passively (i.e., with constant membrane resistance), so long as the voltage produced is below a threshold level. When the threshold level is reached, the membrane responds with an action potential, or some other active response.

From the perspective of the analysis of the effects of stimulation, critical issues revolve around what strength and time duration of a stimulus is required for the stimulus to cause the tissue to move through its initial, passive state to reach the threshold level for active response.[1] The answers depend, as one would expect, on a number of variables, importantly including the geometry of the tissue being stimulated, its electrical characteristics, and the location of the stimulus electrodes.

Analysis of stimuli focuses especially on mathematical relationships between the current applied as the stimulus and the resulting transmembrane potentials. Such knowledge, when quantitative, then allows one to draw quantitative conclusions about the strength and duration of stimuli that will result in transmembrane potentials above the threshold level in new or future situations, as well as those already explored experimentally.[2]

The initial sections of this chapter provide the simple mathematics giving the transmembrane voltages produced by a constant current stimulus, in a *spherical cell*. These current–voltage equations then are manipulated to produce strength–duration curves. A few real cells can be

idealized as spherical, and the idealization is useful and interesting because, in a spherical cell, the response to stimulus depends only on time.

In other words, the spherical cell has a geometrical uniformity that avoids the additional complexity of spatial variation. Thereby the results for a spherical cell serve as a relatively simple beginning point and reference for more complicated cellular structures. As might be expected, more complicated cell structures lead to a correspondingly more complicated space–time behavior. That is, though idealized and relatively simple, the spherical cell analysis shows most clearly many of the fundamental concepts of stimulation, and also introduces most of the terminology used in stimulation.

The main part of the chapter considers *fibers*. Here fibers are idealized as having cylindrical geometry. Initially, the mathematical expressions relating currents to voltages along the fiber are established. Using these relationships in one spatial dimension, we then evaluate a stimulus just outside the membrane, initially just the steady-state response. Thereafter, the time evolution response (also called the transient response) for an intracellular electrode is found.

With one-dimensional analysis completed, the chapter moves on to field stimulation, a three-dimensional situation as the stimulus electrodes may be moved away from the fiber surface. With field stimulation, we examine both subthreshold and transthreshold situations. Fiber simulations under transthreshold conditions evaluate circumstances where stimuli may lead to propagating action potentials. Such simulations permit an evaluation of the classical concept of threshold, revealing conditions where it is not dependable.

Most fibers evaluated in this chapter are assumed to be infinitely long. That obviously is an approximation, as often a real fiber is much longer than the region affected by a stimulus. To examine it more carefully, however, in the final section, we examine the differences in behavior of a fiber that has a finite rather than infinite length.

7.1. SPHERICAL CELL STIMULATION

We begin with the study of the spherical cell, as illustrated in Figure 7.1. While the spherical cell's shape is a poor model for most biological cells, the simplicity of its electrical behavior makes it of interest. It is interesting because one can analyze the cell's response to a stimulus in a thorough way, taking into account all the central factors. Since the same central factors are present for a much broader set of cell shapes and circumstances, the response of the spherical cell serves as a guide to those also.

An analysis of the response of a spherical cell to an intracellular *subthreshold* stimulating current shows that the intracellular region is isopotential, to a good approximation. If one pictures the cell placed within an extensive extracellular region, then the extracellular volume also will be virtually isopotential. Consequently, all points on the cell membrane elements will have very nearly the same transmembrane potential. (The transmembrane potential has to be uniform because all intracellular potentials are nearly the same, and all extracellular potentials are nearly the same).

Consequently, the response of any patch on the cell's membrane will be the same as any other patch, and the entire membrane will behave synchronously.

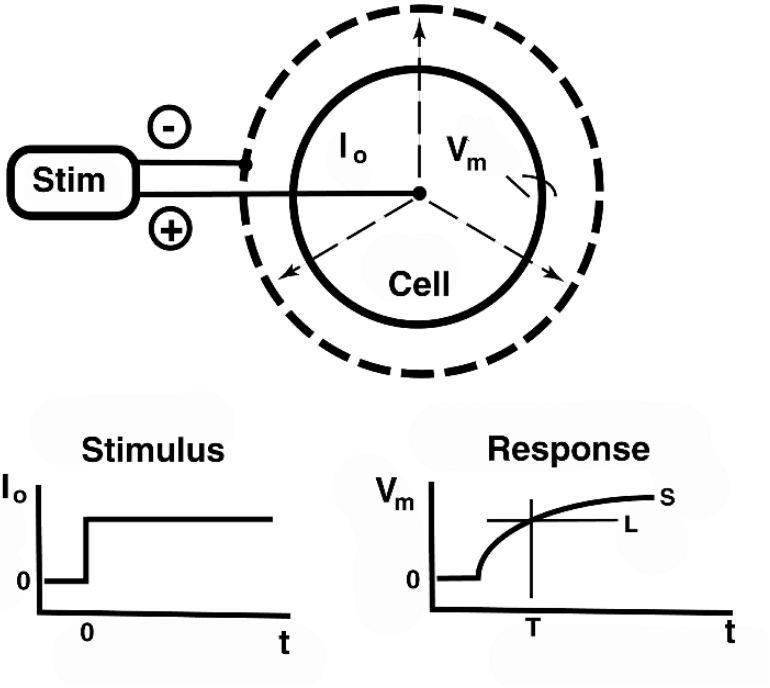

Figure 7.1. Top: A stimulator (left) applies a current I_0 to the center of a spherical cell. Current flows symmetrically outward (arrows) through the membrane (solid circle). Current is collected symmetrically at the periphery of the surrounding extracellular bath (dashed sphere). Bottom: A current step of magnitude I_o is applied (lower left) by the stimulator between the intracellular and extracellular electrodes. The stimulus current continues indefinitely during time t. The current produces a rising transmembrane voltage, v_m (solid curve), that does not have the step waveform of I_0. Even though the stimulus current I_0 continues on, the rise of v_m approaches limiting level $v_m = S$. Level S is called the "strength" of the stimulus. Of particular interest is the time T required to reach a "threshold" voltage level $V_T = L$ (short lines crossing v_m curve at lower right). The v_m curve is sketched as the response if membrane resistance R_m is constant. Furthermore, the concept of this simplified view of stimulation is that R_m will change abruptly once v_m reaches threshold voltage level L, as an active membrane response will occur thereafter.

7.1.1. Spherical Cell's Response to a Current Step

What is the response of an spherical cell to the application of a stimulating subthreshold current step? The arrangement is depicted in Figure 7.1.

Because the intracellular and extracellular regions are essentially isopotential, all membrane elements are electrically in parallel. Thus the entire cell in Figure 7.1 can be represented by a single lumped-*RC* circuit, and both R and C will be constant under subthreshold conditions.

The corresponding electrical circuit is illustrated in Figure 7.2, where, for a membrane surface area A, we have from (2.57)

$$R = \frac{R_m}{A} \tag{7.1}$$

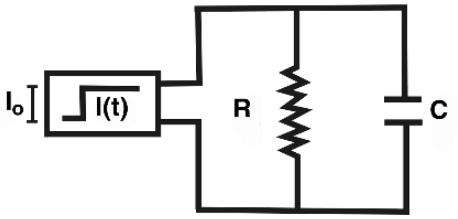

Figure 7.2. Equivalent Electrical Circuit for the Ppreparation of Figure 7.1. The membrane resistance of the cell as a whole is R, and the capacitance of the cell is C. The stimulator (box on left) creates a stimulus current $I(t)$ that is a function of time. In particular, the stimulus current is a current step of magnitude I_0 starting at time zero. Analysis is done for R and C constant. (However, in a real cell R will change when the cell becomes active and ion channels open.) The spherical symmetry of the cell in Figure 7.1 allows this simple electrical equivalent.

and (2.54)

$$C = C_m A \tag{7.2}$$

Here, R_m is the specific leakage resistance (Ωcm^2), C_m is the specific membrane capacitance ($\mu\text{F}/\text{cm}^2$), while R and C are the total membrane resistance (Ω) and capacitance (μF).[3]

The transmembrane potential developed in the cell of Figure 7.1 is readily found from the equivalent circuit in Figure 7.2 and is

$$v_m = I_0 R(1 - e^{-t/\tau}) \tag{7.3}$$

Rewriting (7.3) for a stimulus just strong enough and long enough to reach a threshold voltage level V_T with stimulus duration T, we have

$$V_T = S(1 - e^{-T/\tau}) \tag{7.4}$$

In Eq. (7.4) time constant $\tau = R_m C_m = RC$ and stimulus strength $S = I_0 R$. Note that parameter S is the steady-state voltage approached by v_m as $t \to \infty$. The quantity S can be thought of as a measure of the depolarizing strength of the applied stimulus current I_0; in fact, it is the maximum depolarization that can be produced passively by I_0. We also note that the time constant τ is independent of A (the cell area). Finally, in (7.3) we use v_m (rather than V_m) since the quantity of interest is the change in the transmembrane potential caused by the stimulus, relative to its baseline.

7.1.2. Strength–Duration

It is well known experimentally and theoretically that as stimulus strength S is increased, a shorter stimulus duration T is needed to reach a particular transmembrane voltage. To examine the correspondence mathematically, suppose that the transmembrane voltage threshold needed for initiate activation is fixed at $v_m = V_T$,[4] and a stimulus strength S greater than V_T is used. The consequence by (7.4) will be that membrane voltage V_T will be reached with a shorter stimulus duration, T, than $T \to \infty$.

What stimulus duration T is necessary? Rearranging (7.4) to isolate the term containing T, one gets

$$e^{T/\tau} = \frac{1}{(1 - V_T/S)} \tag{7.5}$$

By taking the natural log of (7.5), one can find either T or τ if the other parameters are known. Thus, where $\log$ is the natural logarithm,

$$T = \tau \log(\frac{1}{(1 - V_T/S)}) = \tau \log(\frac{S}{(S - V_T/S)}) \tag{7.6}$$

A more subtle use of (7.5) occurs when one wishes to find τ from two pairs of values of S and T. In this case one can solve for τ by writing (7.5) twice, and taking the ratio before taking the log.

Weiss–Lapicque equation

Rearranging (7.4) in a different way, one sees that the relationship between stimulus strength S and threshold voltage V_T can be written as

$$S = V_T/(1 - e^{-T/\tau}) \tag{7.7}$$

Division on both sides of (7.7) by the membrane resistance R leads to

$$I_{\rm th} = \frac{I_R}{(1 - e^{-T/\tau})} \tag{7.8}$$

Eq. (7.8) often is called the Weiss–Lapicque equation.[5] There is a specialized terminology used in connection with this equation, as discussed in the next section.

Rheobase

In (7.8) I_R is named the *rheobase*, while $I_{\rm th}$ is the minimum current required to reach threshold with stimulus duration T.

From (7.8) one sees that the rheobase, I_R, is the minimum stimulus intensity that still produces a threshold value of transmembrane voltage, as the stimulation duration grows long (conceptually, as $T \to \infty$). V_T is the strength at rheobase, or *rheobase voltage*. The colorful terminology of *rheobase* and *chronaxie* was introduced by Lapicque [2].[6]

A plot of S versus T for fixed V_T is given in Figure 7.3. The curve depicts the *strength–duration* relationship for a threshold stimulus. The curve shows an exponential decay to the rheobase voltage, and divides all strength–duration combinations into two groups. Those in region A produce transmembrane voltages that exceed threshold. Combinations precisely on the line $V_T = L$ produce transmembrane voltages exactly equal to threshold. Strength–duration combinations in region B produce transmembrane voltages less than threshold. Of these, the

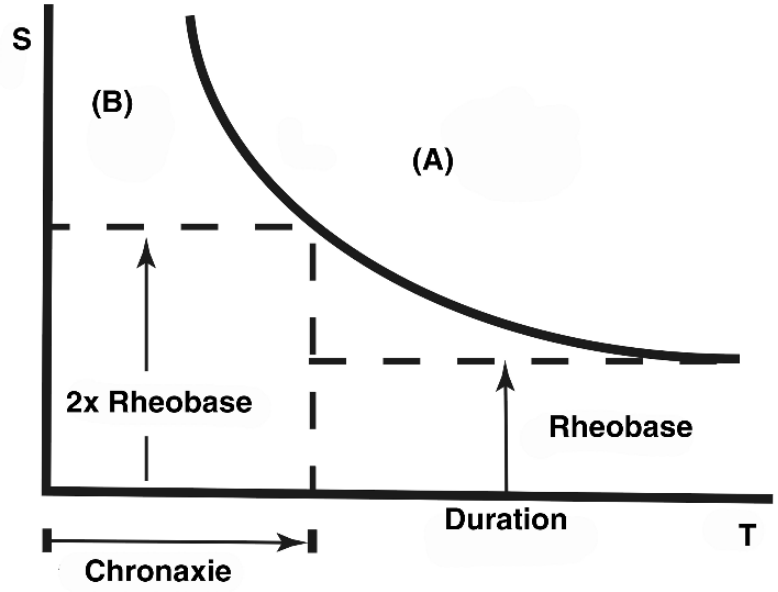

Figure 7.3. Strength–Duration Curve. Line $V_T = L$ shows the combinations of stimulus strength S (on the vertical axis) and stimulus duration T (on the horizontal axis) that are just sufficient to reach the threshold level. Combinations on side A of line L are above threshold and may lead to action potentials, while combinations on side B are below threshold. *Rheobase* is the value of stimulus current that is just sufficient to reach L with a long stimulus duration T. *Chronaxie* is the stimulus duration required to reach L if the stimulus current is set to twice rheobase.

graph makes clear that stimuli with a strength less than the rheobase voltage will never reach threshold, whatever their duration.

Chronaxie

The pulse duration when the stimulus strength S is *twice* rheobase is called *chronaxie*. From (7.7) chronaxie, T_c, can be found analytically, since at chronaxie $S = 2V_T$. Multiplying through by the term in parentheses, we have

$$V_T = 2V_T(1 - e^{-T_c/\tau}) \tag{7.9}$$

Equation (7.9) can be simplified to

$$e^{-T_c/\tau} = 1/2 \tag{7.10}$$

so after inverting, taking the natural log, and solving for T_c one has

$$T_c = \tau \ln 2 = 0.693\tau \tag{7.11}$$

Chronaxie is significant as a practical time period required to reach the threshold voltage when using a practical stimulus strength. In a comparison of different membranes or the same membrane under different conditions, chronaxie provides a nominal measure of excitability.

7.1.3. Stimulus Theory vs Experimental Findings

When the previous analysis is compared to experimental studies the results are modestly in accord, both qualitatively and quantitatively. The agreement is good enough to be useful in providing a qualitative understanding of the way experimental results change, as one or more experimental variables change. For example, the theory provides a guide to understanding why a greater stimulus current can create an action potential despite a shorter stimulus duration, or understanding why a sufficiently low stimulus current never creates an action potential, whatever the stimulus duration.

Even so, significant differences between the simple spherical-cell theory and experimental findings also are evident. Some reasons for such differences are as follows:

1. We assumed that the network in Figure 7.2 was valid up to threshold transmembrane potentials, while from Figure 5.6 we know that linearity holds up to 50% of threshold (if that much). Beyond 50% the assumption is at best a weak approximation.

2. The spherical cell stimulated with an intracellular electrode is a special case. In general, stimulating electrodes are extracellular and produce a response which depends on electrode location as well as the cell geometry. These parameters all affect the distribution and extent to which various membrane elements are depolarized, the conditions that ensue following termination of the stimulus, and hence the outcome regarding the initiation of an action potential. An example will be considered toward the end of this chapter. Some improvements in the model have been suggested based on a time-varying threshold, but even this possibility seems sensitive to the specific geometry and stimulus waveform.

3. A fixed threshold fails to account for its increase with time when the stimulus duration is comparable to the time constant of the inactivation parameter h (i.e., τ_h). The effect is described quantitatively by the Hodgkin–Huxley model based on the change in h with depolarizing or hyperpolarizing stimuli. This phenomena is known as *accommodation* and conflicts with the idea of a fixed threshold. For example, if the stimulus waveform were a ramp that reaches "threshold" after a time delay comparable to τ_h, then a diminished value of h at that point would require a yet higher stimulus. The "threshold," in other words, is now elevated. A slowly rising ramp could be chasing an ever elusive threshold and excitation fail to be elicited even though very high values of voltage are reached.

4. For stimuli with durations that are short (less than the sodium activation time constant τ_m), stimulation will grow more difficult, in that threshold v_m will rise (a fact noted by Lapicque [2]). Because the regenerative activation process will not be initiated at termination of the stimulus, even the transmembrane voltage that would be threshold, if the stimulus was longer, the stimulus may fail to produce a response. In this situation one must investigate whether the effective *RC* membrane can retain an adequate depolarizing voltage following the brief stimulus to continue opening sodium channels to the point that activation occurs. This question will be considered later on in this chapter with an example using an active membrane.

The above reasons are not a rationale for discarding the theory. Rather, they simply say that the theory has to be used with recognition that it is an approximation.

7.2. STIMULATION OF FIBERS

In the preceding section we considered the subthreshold response of a spherical cell, where all parts of the cell membrane were affected or changing in the same way, all the time. Now we examine the response to stimulation of a *fiber*.

At first we examine the behavior of the fiber under subthreshold (electrotonic) conditions, as was the case for the sphere. In fibers we expect subthreshold behavior that is similar to that of spherical cells in some respects, but we also expect that there will be some major differences.

One kind of difference occurs because of the length of fibers. Events at different sites along the fiber will occur at different times, because of the capacitance in the fiber's membrane. A second kind of difference is the corollary of the first: Adjoining segments of the fiber often are responding to a stimulus to different degrees and thus have differing transmembrane voltages, with the result that there are currents flowing within and along the fiber. Finally, fibers are evaluated using stimuli placed in different locations, which may be inside or outside the membrane, or distant from the whole fiber.

All of these aspects of fiber stimulation may occur in real fibers. Because of their number and complexity, addressing these aspects requires a number of the sections that follow.

When the excursion in transmembrane voltage is sufficiently small, the corresponding membrane current can be found from a passive admittance. Such subthreshold conditions are referred to as linear or *electrotonic*. For nerve (and approximately for muscle), the membrane can then be characterized electrically with a parallel *RC* network with constant values of *R* and *C*. This passive description is in contrast with the nonlinear behavior beyond threshold, where the potassium and sodium conductances are no longer independent of v_m.

An examination of membrane properties under linear (subthreshold) conditions is important, since these are frequently present in clinical and experimental studies. Furthermore, in the case of a propagating action potential, regions ahead of the activation site, where critical depolarization is taking place (e.g., region C in Figure 6.5), will be subthreshold during a critical initial interval. In addition, in the design of a stimulator, the membrane may often be considered as linear up to the point of activation.

7.2.1. Fiber Equations

It is immensely valuable in subsequent sections (and in analyzing fibers in general) to have available some basic equations for relationships among voltages and currents at points along the fiber. Thus we develop some of those here. They are of interest in their own right but will prove to be essential starting points in later sections.

Under subthreshold conditions, we have

$$i_m = \frac{v_m}{r_m} + c_m \frac{dv_m}{dt} \tag{7.12}$$

where r_m is the membrane resistance times unit length (Ωcm), c_m is the capacitance per unit length (μF/cm), and i_m is the transmembrane current per unit length (mA/cm). (At transmembrane voltages above threshold (7.12) still applies, but it is less useful because r_m must be treated as a variable.)

An interesting and useful result can be found from (7.12) if one recalls from the cable equations (6.11) that

$$\frac{\partial^2 v_m}{\partial x^2} = (r_i + r_e) i_m + r_e i_p \tag{7.13}$$

Substituting (7.12) into (7.13) gives

$$\lambda^2 \frac{\partial^2 v_m}{\partial x^2} - \tau \frac{\partial v_m}{\partial t} - v_m = r_e \lambda^2 i_p \tag{7.14}$$

where we have defined the following normalizing parameters:

$$\begin{aligned} \lambda &= \sqrt{\frac{r_m}{r_i + r_e}} \\ \tau &= r_m c_m \end{aligned} \tag{7.15}$$

For steady-state conditions ($\partial / \partial t = 0$), Eq. (7.14) simplifies to

$$\lambda^2 \frac{d^2 v_m}{dx^2} - v_m = r_e \lambda^2 i_p \tag{7.16}$$

When the stimulus current is zero ($i_p = 0$), Eq. (7.16) becomes simply

$$\lambda^2 \frac{d^2 v_m}{dx^2} - v_m = 0 \tag{7.17}$$

[which is also the homogeneous form of equation of (7.16)]. The solution of (7.17) is

$$v_m = A e^{-x/\lambda} + B e^{x/\lambda} \tag{7.18}$$

where *A* and *B* are arbitrary constants. Rather than introducing the stimulating current i_p explicitly in (7.16) to obtain the particular solution, we can, instead, impose boundary conditions on the solution for the region where $i_p = 0$, namely, $|x| > 0$. But this solution is that given by (7.18). The boundary conditions at $x = 0$ and $x = \infty$ will serve to evaluate the constants *A* and *B* in (7.18). This approach is illustrated in the following sections.

7.2.2. Space and Time Constants

In the previous section we introduced the constants λ and τ (7.15). These quantities are referred to as the space (or length) constant and time constant of a fiber, respectively. Both are important parameters that characterize the response of a fiber to applied stimuli.

Under steady-state conditions λ is the distance over which the voltage and current change by the factor e, as identified in Eq. (7.18). For spherical-like cells only, τ is the time for the transient response to a current step to differ from its steady-state magnitude by the factor $1/e$, as

seen in (7.4). For a fiber, we will presently show that τ is a measure of the time it takes for the transient response to a current step to reach a particular fraction of its steady-state value, where the fraction depends on the distance from the site to the point of stimulation.

Constants λ and τ are important because, frequently, they can be measured directly. Furthermore, λ and τ have a consistent meaning for many different fiber structures, so they may be used for characterization and comparison.

For circular cylindrical axons with constant membrane properties and with $r_e \approx 0$,

$$\lambda = \sqrt{\frac{r_m}{r_i + r_e}} \approx \sqrt{\frac{r_m}{r_i}}. \tag{7.19}$$

(The condition $r_e \approx 0$ applies when the extracellular space is large.) Converting r_i to R_i and r_m to R_m, by using (2.55) and (2.52), gives

$$\lambda = \sqrt{\frac{R_m/2\pi a}{R_i/\pi a^2}} \tag{7.20}$$

When simplified this equation becomes

$$\lambda = \sqrt{\frac{aR_m}{2R_i}} \tag{7.21}$$

where *a* is the fiber radius. Note that λ varies directly as the square root of fiber radius.

7.3. FIBER STIMULATION

The stimulus currents to be discussed are introduced into a biological preparation with the goal of changing the transmembrane voltage. In most situations, the electrode or electrodes through which the current is injected are outside the target fiber(s).

If injecting current extracellularly changes the transmembrane potential, by how much does it do so? And where? The following material examines these questions in an idealized geometry, but one that nonetheless includes the essential elements needed for insight into a experimental and clinical situations.

7.3.1. Extracellular Stimulus, Steady-State Response

Suppose a single small electrode is placed in the bounded extracellular space just outside a cylindrical fiber, while a pair of electrodes to remove the current lie extracellularly at $\pm\infty$. Suppose the fiber is at rest, infinitely long, the location of the proximal electrode identifies the coordinate origin ($x = 0$), and the fiber structure satisfies the assumptions of the core-conductor model. Note that this arrangement imposes symmetry between positive and negative regions. Also, we expect that a portion of the injected current will enter and flow within the intracellular space of the fiber; it will be constrained to flow longitudinally along the *x* axis.

With the above arrangement, where will current go? As a first guess it might seem that the injected current would remain in the extracellular space until removed by the distal electrodes.

This would be the case if the membrane was a perfect insulator. But for biological membranes it is reasonable to expect current to cross the membrane, particularly if the fiber is long (since the effective leakage resistance can become very low given an adequate axial distance).

With increasing x, this inflowing transmembrane current builds up the total intracellular current, I_i, while the extracellular current decreases by an equal amount. An equilibrium is reached for large enough x, where $r_i I_i = r_e I_e$. At this point the spatial rate of decreasing voltage is the same in both intracellular and extracellular space so, from a Kirchhoff loop, the transmembrane voltage and hence transmembrane current is zero. (Thus for $x \to \infty$ there is no further change in either I_e or I_i.)

In summary, one can expect the transmembrane current to be greater in the region near the stimulus site and to diminish to essentially zero at sites more distant from the stimulus. In the limited region where the stimulus produces a transmembrane current it must also produce an associated transmembrane potential. Thus we conclude somewhat intuitively that stimuli from extracellular electrodes can be used to create hyperpolarizing or depolarizing potentials over an extent of fiber near the stimulus electrode.

We now move to examine these expectations quantitatively. The current entering the preparation from the electrode can be idealized *as a spatial* delta-function source, that is,

$$i_p = I_0 \delta(x) \tag{7.22}$$

where $\delta(x)$ is a unit delta function.

The definition of $\delta(x)$ has three parts:

$$\begin{aligned} \delta(x) &= 0 \quad \text{for } x \neq 0 \\ \delta(0) &= \infty \\ \int_{-\infty}^{\infty} \delta(x) dx &= 1 \end{aligned} \tag{7.23}$$

Note that the delta function is zero except at the origin, where it is infinite, but its integral is finite (equal to unity) provided the interval of integration includes the origin.

From (7.22) and (7.23) we can identify I_0 as the total applied current while $i_p(x)$ is the current density (current per unit length); the latter is zero except at the origin, where it is infinite. If the delta-function source is used in the equations governing v_m under subthreshold and steady-state conditions, we have from Eq. (7.16)

$$\lambda^2 \frac{d^2 v_m}{dx^2} - v_m = r_e \lambda^2 I_0 \delta(x) \tag{7.24}$$

Now we seek the solution to the differential equation in (7.24). A good strategy is to first find the solution to the corresponding homogeneous equation, as that solution will apply to all points other than $x = 0$. Then, with that solution viewed as a boundary-value problem, we evaluate undetermined coefficients through the boundary conditions at the origin (which result from the introduction of the applied current at this point). We will follow that strategy in the following section.

Boundary conditions around the stimulus site

To establish the boundary condition at the stimulus site, the origin, suppose Eq. (7.24) is integrated from $x = 0^-$ to $x = 0^+$, i.e., from just to the left of the origin to just to the right of it. The result is

$$\lambda^2 \frac{dv_m}{dx}\Big|_{x=0^+} - \lambda^2 \frac{dv_m}{dx}\Big|_{x=0^-} - [v_m(0^+) - v_m(0^-)]\Delta x = r_e \lambda^2 I_0 \tag{7.25}$$

where $\Delta x = 0^+ - |0^-|$. As distance Δx approaches zero, the middle term goes to zero, since (on physical grounds, at least) v_m is continuous. Note that the term on the right-hand side no longer contains the δ function (whose integral was replaced by unity).

Rewriting (7.25) we obtain

$$\lambda^2 \left(\frac{dv_m}{dx}\Big|_{x=0^+} - \frac{dv_m}{dx}\Big|_{x=0^-} \right) = r_e \lambda^2 I_0 \tag{7.26}$$

and we note that $\partial v_m / \partial x$ is discontinuous at $x = 0$. The discontinuity, furthermore, is proportional to the strength of the current source I_0.

We will use this result below and evaluate derivatives near the stimulus site, to get the boundary condition needed there.

The homogeneous solution at steady state

For sites along the fiber away from the origin there are no applied currents, so the homogeneous equation (7.17) applies, namely,

$$\lambda^2 \frac{d^2 v_m}{dx^2} - v_m = 0 \tag{7.27}$$

Equation (7.27) has the solution

$$v_m(x) = Ae^{-x/\lambda} + Be^{x/\lambda} \tag{7.28}$$

Thus one sees that v_m at all points along the fiber can be found from (7.28) once values for constants A and B are determined from the boundary conditions.

We now consider the appropriate choices of constants *A* and *B*. The choices must satisfy the conditions imposed by the source at $x = 0$ and also the requirements when $|x| \to \infty$.

The necessary outcomes are summarized in Table 7.1. The choice of $A = 0$ for $x < 0$ and $B = 0$ for $x > 0$ is necessary because the solution for v_m caused by applying a finite current I_0 must go to zero as the distance from the stimulus becomes large. Because v_m must be symmetric about the origin, there being no physical difference between the positive x side versus the negative side, it is also concluded in Table 7.1 that both *A* and *B* are equal to the same constant, *C*.

Table 7.1. Boundary Conditions

x range	A	B
$x < 0$	0	C
$x > 0$	C	0

These choices of A and B are required for the transmembrane potential to decline to zero far from the stimulus site.

Imposing these conditions results in equal but opposite axial currents at symmetric points about the origin, an outcome that is consistent with the symmetry. Thus Eq. (7.28) can be written as

$$\begin{aligned} v_m(x) &= Ce^{x/\lambda} \quad x \le 0 \\ v_m(x) &= Ce^{-x/\lambda} \quad x \ge 0 \end{aligned} \tag{7.29}$$

A more compact form of (7.29) is

$$v_m(x) = Ce^{-|x|/\lambda} \tag{7.30}$$

Imposing the boundary condition at the origin

The coefficient C in (7.30) can now be found, since the solution must also satisfy (7.26). To impose this boundary condition at the origin dv_m/dx is first evaluated from Eq. (7.29). The result is

$$\begin{aligned} \frac{dv_m}{dx} &= \frac{C}{\lambda}e^{x/\lambda} \quad x < 0 \\ \frac{dv_m}{dx} &= -\frac{C}{\lambda}e^{x/\lambda} \quad x > 0 \end{aligned} \tag{7.31}$$

Substituting (7.31) into (7.26) gives

$$\left(-\frac{C}{\lambda}e^{-x/\lambda}\Big|_{x=0^+} - \frac{C}{\lambda}e^{x/\lambda}\Big|_{x=0^-}\right) = r_e I_0 \tag{7.32}$$

The solution for C from (7.32) is

$$C = -\frac{r_e \lambda I_0}{2} \tag{7.33}$$

The steady-state solution

Using the value of C obtained in (7.33) and substituting into (7.30) gives the desired solution, namely,

$$v_m = -\frac{r_e \lambda I_0}{2} e^{-|x|/\lambda} \tag{7.34}$$

Inspection of Eq. (7.34) provides a quantitative response to the questions and speculations posed at the beginning of this section. These are summarized below.

1. The stimulus clearly affects the transmembrane potential, since v_m is nonzero for all values of *x*.

2. The effect of the stimulus varies markedly with *x*. The largest change in transmembrane potential occurs at the site of the stimulus, where $x = 0$. As one moves away from the stimulus site, v_m decreases exponentially, falling by a factor of *e* every length λ.

3. For a given stimulus current I_0, the magnitude of the change in transmembrane potential increases as extracellular resistance r_e increases.

4. Note from the sign of (7.34) that a *positive* current injected at the origin leads to a more *negative* transmembrane potential. That is, membrane under an *anode* becomes *hyperpolarized* as a result of current influx into the intracellular region.

5. Note that the space constant λ may also be regarded as a measure of the distance from a source (at the origin) to which the disturbance in v_m essentially extends.

7.3.2. Intracellular Stimulus, Time-Varying Response

We now turn our attention to an investigation of the *temporal transient* behavior under the same stimulus condition, rather than the *steady-state* response evaluated above.

Determining transient behavior requires a solution to the general expression of (7.14). As before, we first seek a solution to the homogeneous equation and introduce the applied current through a boundary condition at the origin. We consider an unbounded extracellular medium and assume that the stimulus current is introduced *intracellularly*.

This geometry permits introducing the simplification that $r_e \approx 0$. The resulting equation is

$$\lambda^2 \frac{\partial^2 v_m}{\partial x^2} - \tau \frac{\partial v_m}{\partial t} - v_m = 0 \tag{7.35}$$

The space constant λ and time constant τ are as defined in (7.15). (If the applied current is introduced extracellularly, the solution obtained here can be converted to this condition, as described in a later section.)

A simplified notation results from introducing the normalized spatial and temporal variables (*X,T*), defined by

$$X = \frac{x}{\lambda} \quad \text{and} \quad T = \frac{t}{\tau} \tag{7.36}$$

Hence (7.35) becomes

$$\frac{\partial^2 v_m}{\partial X^2} - \frac{\partial v_m}{\partial T} - v_m = 0. \tag{7.37}$$

We seek the transmembrane potential, v_m, arising from the introduction of a current step at the origin.

Reduction to one variable by the Laplace transform method

We proceed by taking Laplace transforms with respect to T of each term in (7.37). The Laplace transform of $\partial v_m/\partial T$ is $s\overline{v}_m - v_m(0, X)$, where the overbar indicates a Laplace transform.

The initial condition of v_m at $t = 0$, namely $v_m(0, X)$, is assumed to be zero. It is initially zero because we consider the response of a resting cable to an applied current that starts at $t \geq 0$. Consequently, we get

$$\frac{\partial^2 \overline{v}_m}{\partial X^2} - (s+1)\overline{v}_m = 0 \tag{7.38}$$

The advantage of introducing the Laplace transform is that the partial differential equation (7.37) in X and T has been converted into an ordinary differential equation in X (7.38).

The solution to (7.38) is

$$\overline{v}_m = Ae^{-X\sqrt{s+1}} + Be^{X\sqrt{s+1}} \tag{7.39}$$

Because $\overline{v}_m$ cannot increase without bound for $x \to \infty$, $B = 0$ (for the infinite cable). Thus

$$\overline{v}_m = Ae^{-X\sqrt{s+1}}, \quad X \geq 0 \tag{7.40}$$

The boundary condition at the origin

At $x = 0$, the site of introduction of the current I_0 into the intracellular space, because of symmetry, $I_0/2$ flows into the positive x region and $I_0/2$ into the region $x < 0$.

This applied current as a function of time is in the form of a step that we designate $u(t)$, the unit step function. This function is described by $u(t) = 0$ for $t \leq 0$ and $u(t) = 1$ for $t \geq 0$. There is a discontinuity at $t = 0$. Applying Ohm's law in the intracellular space at $x = 0$, we have

$$\left.\frac{\partial \Phi_i}{\partial x}\right|_{x=0} = -\frac{I_0 u(t) r_i}{2}. \tag{7.41}$$

For the extracellular space at $x = 0$ there is no longitudinal current (it begins to appear when $x > 0$), so

$$\left.\frac{\partial \Phi_e}{\partial x}\right|_{x=0} = 0 \tag{7.42}$$

If we subtract (7.42) from (7.41) and then note from (7.36) that $\partial/\partial x = (1/\lambda)\partial/\partial X$,[7] we get

$$\left.\frac{\partial v_m}{\partial X}\right|_{x=0} = -\frac{I_0 u(t) r_i \lambda}{2} \tag{7.43}$$

Taking the Laplace transform of both sides of (7.43), where the Laplace transform of $u(t)$ is included as $1/s$, gives

$$\left.\frac{\partial \overline{v}_m}{\partial X}\right|_{x=0} = -\frac{I_0 r_i \lambda}{2s} \tag{7.44}$$

We also can evaluate the left-hand side of (7.44) from (7.40). So doing gives

$$\left.\frac{\partial \overline{v}_m}{\partial X}\right|_{X=0} = -A\left[(s+1)^{1/2}e^{-X(s+1)^{1/2}}\right]_{X=0} = -A\sqrt{s+1} \tag{7.45}$$

One obtains an equation for A by equating (7.45) and (7.44). This yields

$$A = \frac{r_i \lambda I_0}{2s\sqrt{s+1}} \tag{7.46}$$

Substituting (7.46) into (7.40) gives $\overline{v}_m$ as a function of s, namely,

$$\overline{v}_m = \frac{I_0 r_i \lambda}{2s\sqrt{s+1}} e^{-X\sqrt{s+1}}, \quad X > 0 \tag{7.47}$$

Time-varying response to stimulus

The desired solution for the time-varying response is found by taking the inverse transform of (7.47). Finding the inverse transform is most readily accomplished by consulting a table of Laplace transforms,[8] which demonstrates that

$$v_m(X,T) = \frac{r_i \lambda I_0}{4}\left\{e^{-X}\left[1 - \operatorname{erf}\left(\frac{X}{2\sqrt{T}} - \sqrt{T}\right)\right] - e^{X}\left[1 - \operatorname{erf}\left(\frac{X}{2\sqrt{T}} + \sqrt{T}\right)\right]\right\} \tag{7.48}$$

This result is for an infinite cable, based on the introduction of I_0 at $X = 0$, and describes conditions for $x > 0$ (those for $x < 0$ can be found by symmetry). One can also replace x by $|x|$, which gives the expected symmetry and an expression valid for all x. On restoring the original coordinates x and t, (7.48) becomes

$$v_m(x,t) = \frac{r_i \lambda I_0}{4}\left\{e^{-|x|/\lambda}\left[1 - \operatorname{erf}\left(\frac{|x|}{2\lambda}\frac{\sqrt{\tau}}{t} - \frac{\sqrt{t}}{\tau}\right)\right] - e^{|x|/\lambda}\left[1 - \operatorname{erf}\left(\frac{|x|}{2\lambda}\frac{\sqrt{\tau}}{t} + \frac{\sqrt{t}}{\tau}\right)\right]\right\} \tag{7.49}$$

In (7.47) and (7.48), erf is the *error function* defined by

$$\operatorname{erf}(y) = \frac{2}{\sqrt{\pi}}\int_0^y e^{-z^2}dz \tag{7.50}$$

Note that $\operatorname{erf}(\infty) = 1$ and $\operatorname{erf}(-\infty) = -1$. The result in (7.49) tacitly assumes sinks of strength $-I_0/2$ at $x = \pm\infty$.[9]

7.3.3. Examination of Temporal Response

For a given value of time the spatial behavior is exponential-like but not exponential. For $t >> \tau$ (i.e., for the temporal condition approaching the steady state), $v_m(x)$ tends toward a

Table 7.2. Temporal Morphology at Different Values of x

x	Steady-state fraction at $t = \tau$
0	0.843
λ	0.632
2λ	0.372
3λ	0.157
4λ	0.0453
5λ	0.00862

Stimulus: current step at $x = 0$.

true exponential in x, as shown in (7.34), and also as obtained from (7.49). The presence of the membrane leakage resistance is responsible for a continuous decrement of v_m with increasing x while λ describes the rate of this effect.

In the temporal behavior of $v_m(x, t)$ given by Eq. (7.49), τ characterizes this behavior. Thus as noted, when $t > \tau$ the response rapidly approaches steady-state values. Figure 7.4 plots families of curves derived from Eq. (7.49), which expresses the above ideas graphically. These results show that time is required to reach steady state owing to the presence of membrane capacitance and resistance, and this membrane time constant is a measure of that time. Further, the response is spatially confined to a region near the site of the stimulus and λ is a measure of its extent.

For a fixed x, the temporal behavior is not a true exponential; its shape is not readily apparent by inspection of (7.49). If we determine from (7.49) the fraction of steady-state amplitude reached at $t = \tau$ as a function of x, the data in Table 7.2 are obtained. The rapid decrease in value seen in Table 7.2 also reflects a temporal waveform that is not exponential. Only at $x = \lambda$ does the magnitude of the fraction of steady-state amplitude reached at $t = \tau$ equal that obtained with an exponential waveform (i.e., $1 - 1/e$).

7.4. AXIAL CURRENT TRANSIENT

Questions: How much axial current does the stimulus generate? Does the axial current start quickly? Where? Current is injected intracellularly, so does it all flow down the intracellular volume, or does some go outside? Is the current flow pattern quickly established, or does it take a long time to reach equilibrium?

Stimuli often are used to manipulate the actions of excitable tissue, so understanding a fiber's response to stimuli as a function of the magnitude or position of the stimulus site has a natural interest and utility. As an example of the mathematical results developed to this point, let us evaluate the response of a semi-infinite fiber with a bounded extracellular space to such a stimulus. In particular, let us consider the application of an intracellular current step, of magnitude I_0, at the coordinate origin ($x = 0$) at $t = 0$. (To simplify the consideration, we assume that the remote electrode is at $+\infty$.)

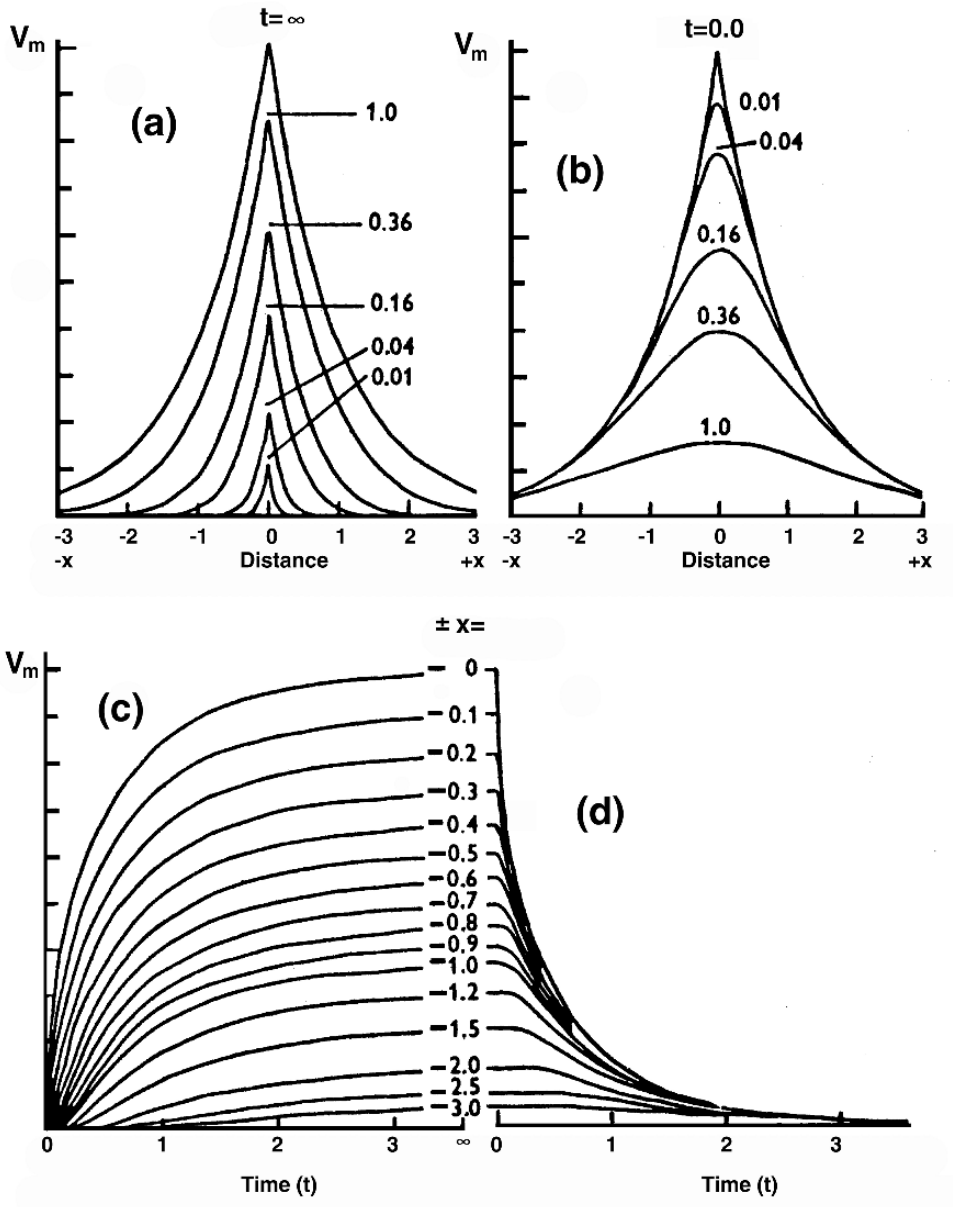

Figure 7.4. Theoretical Distribution of Potential Difference across a passive nerve membrane in response to onset (a and c) and cessation (b and d) of a constant current applied intracellularly at the point $x = 0$. (a) and (b) show the spatial distribution of potential difference at different times, and (c) and (d) show the time course of the potential at different distances along the axon. Time (t) is in time constants, τ, and distance (x) is in space constant, λ. From Aidley DJ. 1978. *The physiology of excitable cells*. Cambridge: Cambridge UP. After Hodgkin AL, Rushton WAH. 1946. The electrical constants of a crustacean nerve fiber. *Proc R Soc London, Ser B* **133**:444–479. Reprinted with permission of Cambridge University Press.

To find quantitative answers to the questions, first we examine the given parameters and observe that

- At $t = 0$, $v_m = 0$ everywhere since the membrane capacitances have yet to receive any charge from the applied current.
- Because $v_m \equiv 0$ signifies a short-circuited membrane, the applied current, at $t = 0$, divides instantaneously between intracellular and extracellular space in inverse proportion to the axial resistances [i.e., $I_i = (r_e/(r_i + r_e))I_0$ and $I_e = (r_i/(r_i + r_e))I_0$].
- Because extracellular space is assumed bounded r_e is not negligibly small.
- Now for $x >> \lambda$ and at steady state, (7.34) describes $v_m \approx 0$, so $r_i I_i = r_e I_e$.
- Also, because $I_i + I_e = I_0$, then $I_i = r_e I_0/(r_i + r_e)$, and $I_e = r_i I_e/(r_i + r_e)$, hence approximating their initial values.

This close approximation to the initial values suggests that at large x there is a transient of negligible magnitude. It further suggests that the axial current response to a step is essentially instantaneous. We will examine this hypothesis quantitatively by deriving and evaluating an expression for the axial intracellular steady-state current. That is,

$$I_i = \frac{r_e}{r_i + r_e} I_0 \quad \text{when} \quad x \to \infty$$

so at a more proximal site (smaller *x*) I_i will be greater than this limiting value. It will be greater by an amount equal to the total outflow of transmembrane current between *x* and infinity.

That is, for finite values of *x*

$$I_i(x) = \frac{r_e}{r_i + r_e} I_0 + \int_x^\infty i_m dx \tag{7.51}$$

Equation (7.34) gives the steady-state v_m for a current I_0 applied extracellularly at the origin of an infinite fiber; $I_0/2$ is removed at $\pm\infty$. In view of the intracellular–extracellular symmetry, we obtain a similar expression for a current applied intracellularly by interchanging subscripts i and e; also, there is a change in sign (since transmembrane current is oppositely directed).

Using this reasoning, and since we are now taking I_0 to be the total current in the positive x direction rather than $I_0/2$ in (7.34) (since this is a semi-infinite cable), we get

$$v_m = r_i \lambda I_0 e^{-|x|/\lambda} \tag{7.52}$$

At steady state the transmembrane current is entirely through r_m (i.e., there is no capacitive current), so $i_m = v_m/r_m$. With this relationship and using (7.52), Eq. (7.51) becomes

$$I_i(x) = \frac{r_e}{r_i + r_e} I_0 + \int_x^\infty \frac{r_i \lambda I_0}{r_m} e^{-x/\lambda} dx \tag{7.53}$$

where $0 < x < \infty$. Performing the integration and simplifying the results leads to the expression

$$I_i(x) = \frac{r_e}{r_i + r_e} I_0(1 + \alpha e^{-x/\lambda}) \tag{7.54}$$

where $\alpha = r_i/r_e$. Note that $I_i(0) = I_0$, while $I_i(\infty) = (r_e/(r_i + r_e))I_0$, as expected. For muscle bundles and for cardiac tissue, experimental data support $\alpha = 1$ for estimates of I_i.

It also is informative to use Table 7.2 to examine issues related to the temporal response:

- For values of *x* equal to 2λ or less, the transient amplitude becomes large ($> 13\%$). For this x range, as shown in Table 7.2 the transient time is on the order of τ.

- At $x = 5\lambda$ we have the result that $I_i(5\lambda)$ changes its relative magnitude from $t = 0$ to $t = \tau$ by only 0.862%. From (7.49), we can determine that the time required to achieve 65% of steady state (an effective time constant) is roughly 3τ, hence fairly long. Nevertheless, since the change is so small, so that the time required to achieve it may not matter.

- For $x = 10\lambda$ achieving steady state will take much longer ($\approx 5\tau$), and the change in magnitude during this transient will be even smaller (0.005%). Under many circumstances these changes are insignificant.

7.5. FIELD STIMULUS OF AN INDIVIDUAL FIBER

In this section we examine the subthreshold membrane response of a single fiber of infinite length. The fiber is assumed to be lying in an unbounded conducting medium. The stimulus field arises from an *external* point current source. We picture our goals as follows:

- The site of the stimulus may be away from the fiber, so an expression is to be derived for the induced transmembrane potential given the source–fiber distance, *h*. Also known is the current magnitude, I_0, and fiber and medium properties.

- We wish to find an expression that will permit an examination of the relationship between induced transmembrane potential and the stimulating source field.

- The analysis and thus the result depend on the assumption of linearity (subthreshold conditions) and that $a/h << 1$, where *a* is the fiber radius.[10]

In the subsequent sections the same physical arrangement is considered, but under transthreshold stimulus levels. This additional analysis permits an examination of *threshold* and a determination of its constancy as various parameters are changed.

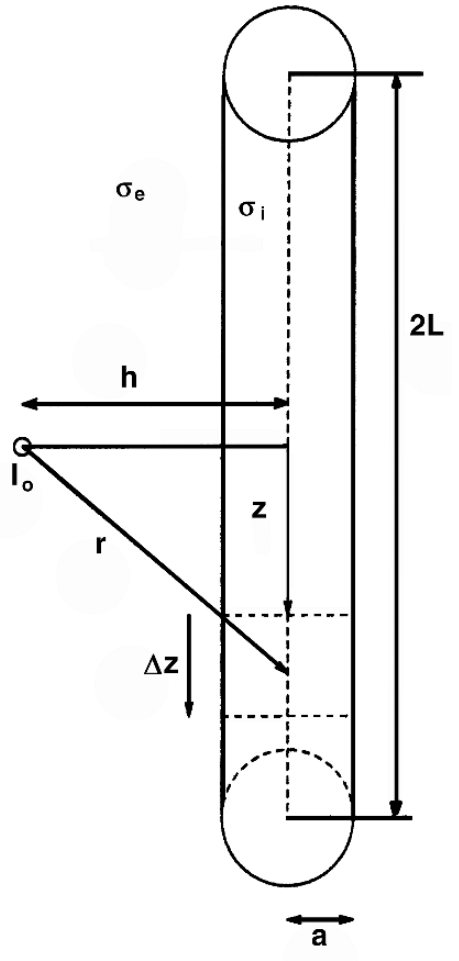

Figure 7.5. Geometry of Source and Fiber. A single current point source of magnitude I_0 is placed at a distance *h* from a circular cylindrical fiber of length *2L*. The extracellular region is unbounded, uniform, and has a conductivity σ_e. The fiber radius is *a* and its intracellular conductivity is σ_i. The fiber's centerline lies along the coordinate z axis. The length is divided into elements Δz for numerical calculations.

7.5.1. The Electric Field from a Point Source

Let us consider the response of an unmyelinated fiber lying in an unbounded conducting medium due to an applied electric field of a point current source. The field, ϕ_a, has the form described in (2.21):

$$\phi_a = I_0/(4\pi\sigma_e r) \tag{7.55}$$

In (7.55) I_0 is the current strength, and σ_e the conductivity of the medium, where the extracellular space being designated with subscript e, and r is the distance from the source to an arbitrary field point. A description of the geometry is given in Figure 7.5.

Under many circumstances the perturbation of the extracellular field resulting from the presence of the fiber itself can be ignored when the fiber diameter is small compared to its distance from the (point) source [5].[11] This condition for small perturbation is generally satisfied under the usual conditions of fiber stimulation.

As a consequence, the extracellular electric field along the fiber is essentially the applied field. Use of the unmodified field is a particularly important simplification for the evaluation of fiber excitation.

The linear core-conductor equation for transmembrane current i_m per unit length of unmyelinated fiber is, from (6.13),

$$r_i i_m = \partial^2 \phi_i / \partial z^2 \tag{7.56}$$

where r_i is the intracellular resistance per unit length, and z now denotes the axial variable. This current must also equal the intrinsic ionic plus capacitive current of the membrane, as discussed in obtaining (6.31). The membrane current is described by $i_{\text{ion}} + c_m \partial v_m / \partial t$, where c_m is the membrane capacitance per unit length.

With these substitutions and some rearrangement, (7.56) may be written as

$$r_i \frac{\partial v_m}{\partial t} = \frac{1}{c_m} \left(-i_{\text{ion}} r_i + \frac{\partial^2 v_m}{\partial z^2} + \frac{\partial^2 \phi_e}{\partial z^2} \right) \tag{7.57}$$

where ϕ_i is replaced by $v_m + \phi_e$.

7.5.2. The Activating Function

Rattay [7] considered the activation of an isolated fiber as quantified by (7.57). He noted that at $t = 0$ the membrane is at rest. At rest several conditions apply:

$$\begin{aligned} v_m &\equiv 0 \\ \partial^2 v_m / \partial z^2 &= 0 \\ i_{\text{ion}} &= v_m / r_m = 0. \end{aligned} \tag{7.58}$$

Using these resting conditions with (7.57), he established that, initially upon application of the stimulus,

$$r_i \partial v_m / \partial t = (1/c_m) \partial^2 \phi_e / \partial z^2 \tag{7.59}$$

Initial change follows activating function

Rattay argues that (7.59) provides a foundation for the following conclusions: Where activation may occur corresponds to the region where $\partial^2 \phi_e / \partial z^2$ is positive, since having $\partial^2 \phi_e / \partial z^2$ positive will make $\partial v_m / \partial t > 0$ initially. Conversely, the region that will hyperpolarize (i.e., where $\partial v_m / \partial t < 0$ for small t) is where $\partial^2 \phi_e / \partial z^2$ is negative, according to (7.57), and this region will not initiate activation. Because of the role played by

$$A(x) = \partial^2 \phi_e / \partial z^2 \tag{7.60}$$

Rattay named the function the *activating function*.

For *subthreshold* linear conditions the ionic current may also be evaluated by v_m/r_m, where r_m is the fiber membrane resistance per unit length. Under steady-state conditions ($\partial v_m/\partial t = 0$) and with $i_{\text{ion}} = v_m/r_m$, (7.57) becomes

$$\frac{\partial^2 v_m}{\partial z^2} - \frac{v_m}{\lambda^2} = -\frac{\partial^2 \phi_e}{\partial z^2} \tag{7.61}$$

where, of course, $\lambda = \sqrt{r_m/r_i}$. Since the axial applied electric field, E_z, is the negative z derivative of ϕ_e, Eq. (7.61) can also be written as

$$\frac{\partial^2 v_m}{\partial z^2} - \frac{v_m}{\lambda^2} = \frac{\partial Ez}{\partial z} \tag{7.62}$$

Equation (7.62) describes the effect of the applied field on the target fiber through the solution for v_m, the induced transmembrane potential. The axial derivative of E_z is seen as the applied or "forcing" function in the differential equation for v_m. For a fiber of infinite length, the response as described by $v_m(z)$ should correspond, more or less, to the applied function.

Thus the peak depolarization, of particular interest in clinical design, could be expected to be located where $\partial E_z/\partial z$ attains its maximum values. To the extent that such a correspondence is true, the activating function is a valuable tool since a possibly complex solution for the actual v_m is avoided.

The activating function is only the beginning

The activating function is not the solution for $V_m(t)$, but only its initial rate of change. $V_m(t)$ changes over time during and after the stimulus interval, and it is clear that the v_m arising from $\partial E_z/\partial z$ depends in some way on the entire function E_z, not just the location and magnitude of its initial values or its peak values.

Furthermore, the v_m response can be expected to depend in some way on the fiber properties, as perhaps described simply by the parameter λ. In addition, for finite fibers, boundary conditions must be introduced into the solution of (7.62) and the boundary conditions may have an important influence on the morphology of v_m.

7.5.3. The V_m Response over Time

From a formal point of view the activating function has the role of an applied function in the differential equation (7.62). While the form of $v_m(x)$ may evolve to become similar to that of the forcing function, another possibility is that $v_m(x)$ will not be the same in important respects.

Consequently, more mathematical results are needed to know what the stimulus does, quantitatively. Thus we now proceed to find a solution for v_m. When that solution is obtained, there will be the opportunity to compare it to the activating function to see what looks the same, and what looks different.

The following mathematical development will show that the transmembrane potential response, over time, can be found by means of a convolution. The convolution shows the interaction between the effects of the external field on the fiber, and the response of the fiber to that field.

In particular, we are considering the case where the stimulus is sufficiently small, so that the membrane behavior is linear and may therefore be described by a parallel resistance and capacitance (r_m in Ωcm and c_m in μF/cm). Equation (7.62) may then be written as

$$r_i c_m \frac{\partial v_m}{\partial t} + r_i \frac{v_m}{r_m} - \frac{\partial^2 v_m}{\partial z^2} = \frac{\partial^2 \phi_e}{\partial z^2} u(t) \tag{7.63}$$

where $i_{\text{ion}} = v_m / r_m$ and $u(t)$ is a unit step (included here to signify that the activating function is switched on at $t = 0$).

Initial rate of change of V_m

Examining (7.63), one sees that if a stimulus is initiated when the fiber is at rest, then both v_m and $\partial^2 v_m / \partial z^2$ are zero. Thus, rearranging (7.63), one has an equation for the initial rate of change of v_m along the fiber as

$$r_i c_m \frac{\partial v_m}{\partial t} = \frac{\partial^2 \phi_e}{\partial z^2} u(t) \tag{7.64}$$

That is, $\partial v_m / \partial t$ is proportional to the activating function, as noted above. The proportionality coefficient is determined by characteristics of the fiber, specifically its time constant $r_i c_m$.

Transformations to find V_m response

We will find it useful here to have the fiber response to a unit *intracellular* point source. Thus, using (7.63) we seek the solution of

$$\lambda^2 \frac{\partial^2 v_m}{\partial z^2} - \tau \frac{\partial v_m}{\partial t} - v_m = -r_i \lambda^2 \delta(z) u(t) \tag{7.65}$$

where $\delta(x)$ is a unit Dirac delta function (7.23). We see that the desired solution to (7.65) is the solution found for (7.35).

We assume that the extracellular medium being unbounded supports the assumption that $r_e \approx 0$.[12] An examination of (7.65) is facilitated by introducing normalized variables defined by

$$X = \frac{z}{\lambda} \quad \text{and} \quad T = \frac{t}{\tau} \tag{7.66}$$

where $\tau = r_m c_m$ and $\lambda = \sqrt{r_m / r_i}$. Substituting (7.66) into (7.65) results in

$$\frac{\partial^2 v_m}{\partial X^2} - \frac{\partial v_m}{\partial T} - v_m = -r_i \lambda^2 \delta(z) u(t) \tag{7.67}$$

which is essentially (7.37), except that in (7.67) the stimulus current is included explicitly.

The solution to (7.67) is given in (7.48). Since we seek a unit impulse response which divides into the positive and negative z directions, we require $I_0 = 1$ in (7.48). Hence

$$G(X,T) = \frac{r_i \lambda}{4} \left\{ e^{-X} \left[1 - \text{ erf } \left(\frac{X}{2\sqrt{T}} - \sqrt{T} \right) \right] - e^{X} \left[1 - \text{ erf } \left(\frac{X}{2\sqrt{T}} + \sqrt{T} \right) \right] \right\} \tag{7.68}$$

Function G thus gives the transmembrane voltage produced by a unit current at position X and time T.[13]

Transmembrane potential's response to stimulus

We now wish to extend the results found for a delta function source to find results from a distributed source. Applying (7.67) to (7.63) yields

$$\frac{\partial^2 v_m}{\partial X^2} - \frac{\partial v_m}{\partial T} - v_m = -\lambda^2 \frac{\partial^2 \phi_e}{\partial X^2} u(t) \tag{7.69}$$

Comparison of (7.69) and (7.67) shows that they differ only in the forcing function (the terms on the right). Additionally, the one equation (7.67) provides the impulse response while the other equation (7.69) is for a continuous forcing function (namely, $\partial^2 \phi_e / \partial X^2$).

Moreover, the system is linear, since we are restricting consideration to passive membrane. Thus the solution to (7.69) is the convolution of $\partial^2 \phi_e / \partial X^2$ with the fiber impulse response.

If we take into account the additional factor r_i in (7.67) as well as the normalized coordinates, we obtain

$$v_m = \frac{\lambda}{r_i} \int_{-\infty}^{\infty} f(\xi) G(X - \xi, T) d\xi \tag{7.70}$$

where ξ is a dummy variable for X and $f(\xi) = \partial^2 \phi_e / \partial z^2 |_{z=\xi}$. The coefficient λ in (7.70) arises from the change in variable, where $dz = \lambda d\xi$.[14]

The interpretation of Eq. (7.70) is a follows. Function $f(\xi)$ comes from the field stimulus, as it affects the fiber. Function $G(X - \xi)$ is the fiber's response to a stimulus given at one point along the fiber. The convolution integrates (in effect, it adds up) the fiber's responses to the stimuli created along the fiber by the external field.

Equation (7.70) is an application of linear systems theory, where the output to an arbitrary input is expressed in terms of the impulse response (system function). A similar expression appropriate for myelinated fiber stimulation was derived by Warman *et al* [10].

Note that any stimulus may be considered a sequence of impulse functions.

7.5.4. Isolated Single Fiber and a Point Current Source

The problem at hand is described in Figure 7.5, but with $L = \infty$. In other words, the point current source is located at a distance h from the unmyelinated fiber of infinite extent. The foot of the perpendicular determines the origin of the coordinate system. The desired solution is given formally by Eq. (7.70).

Again we consider the subthreshold response. This response can be evaluated using the Fourier transform. Now the Fourier transform of a convolution is the product of the Fourier transform of each convolving function.

Thus if F denotes the Fourier transform and F^{-1} the inverse transform, then (7.70) can be expressed as

$$v_m(X,T) = \frac{\lambda}{r_i} F^{-1}[F[f(X)]F[G(X,T)]] \tag{7.71}$$

The applied field arising from the point current source, (7.55), is simply given by

$$\phi_e(z) = \frac{I_0}{4\pi\sigma_e\sqrt{h^2+z^2}} \tag{7.72}$$

The spatial second derivative of Φ_e, in the direction of the fiber's axis, is

$$f(z) = \frac{\partial^2\Phi_e}{\partial z^2} = \frac{I_0}{4\pi\sigma_e}\frac{2z^2-h^2}{(h^2+z^2)^{5/2}} \tag{7.73}$$

Consequently, where $H = h/\lambda$,

$$f(X) = \frac{I_0}{4\pi\sigma_e\lambda^3}\frac{2X^2-H^2}{(H^2+X^2)^{5/2}} \tag{7.74}$$

Accordingly, substituting (7.68) and (7.74) into (7.71) gives [5]

$$\begin{aligned} v_m(X,T) \quad = \quad & \frac{\lambda}{r_i} F^{-1}\left\{\frac{I_0}{16\pi\sigma_e\lambda} \times F\left[\frac{2X^2-H^2}{(H^2+X^2)^{5/2}}\right] \times \right. \\ & F\left[e^{-X}\left(1-\text{ erf}\left(\frac{X}{2\sqrt{T}}-\sqrt{T}\right)\right)\right. \\ & \left.\left. - e^{X}\left(1-\text{ erf}\left(\frac{X}{2\sqrt{T}}+\sqrt{T}\right)\right)\right]\right\} \end{aligned} \tag{7.75}$$

7.5.5. Activation Function's Prediction versus Response

With the results above, we now can compare the activating function with the actual membrane response. It is helpful to visualize the results. To this end, the transmembrane potential created by (7.75) for one example is plotted in Figure 7.6 at three times following the onset of the stimulus. The example has a point cathodal stimulus at distance h from a fiber, with details given in the Figure caption.

At the first of the three times plotted, 0.01 msec after the start of the stimulus, the wave shape of the activating function is a good approximation to that of the transmembrane potential. Recall that the impulse response, $G(X,T)$, for small T, is approximately a delta function (see Figure 7.4). The consequence is that the early transmembrane potential response has a shape like that of the activating function, consistent with the convolution equation (7.70). Thus for a very short stimulus (short in comparison to the time constant), the activating function is a good predictor of the resulting transmembrane potential and correctly shows the regions of depolarization and hyperpolarization produced by the stimulus.

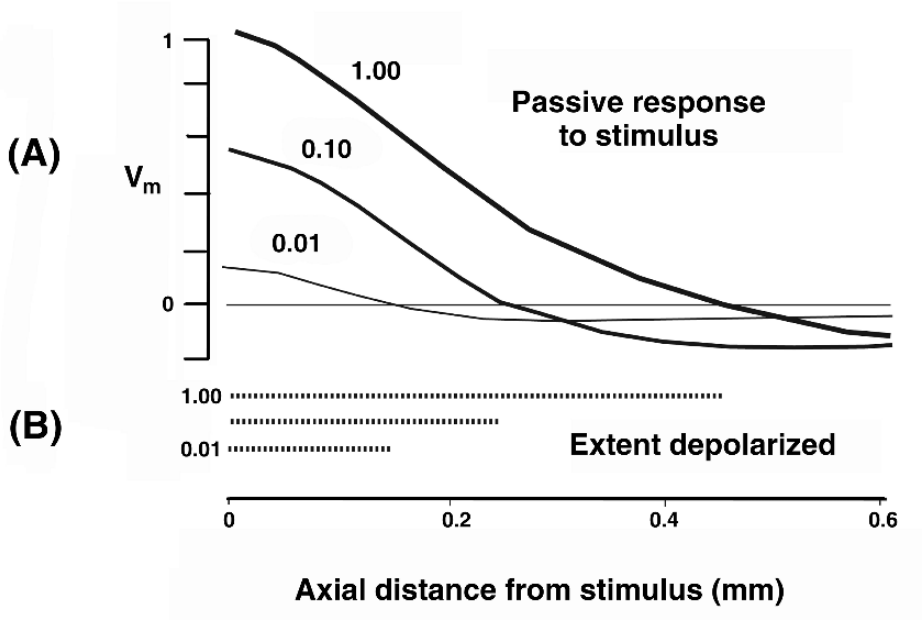

Figure 7.6. Time Evolution of the Induced Transmembrane Voltage along a Fiber. The response is that from a field stimulus, and the three lines shown the response at three times following stimulus onset, i.e., $V_m(x)$ at 0.01, 0.10, and 1.00 msec after the start of a stimulus. The point current stimulus is at distance $h = 0.02$ cm from a fiber described in Figure 7.5. [Other parameters are $\lambda = 0.86$ mm. $\tau = 1.5$ msec, $\sigma_e = 33.3$ mS/cm, and $I_0 = -0.44$ mA.] In the top panel (A), the vertical axis plots V_m on a normalized scale to facilitate comparison of the plots. (A value of 1.0 on the normalized scale is approximately 30 mV.) In the lower panel (B), three horizontal bars show the extent of the depolarized region. The horizontal axis (bottom) applies to both (A) and (B). Distances along the horizontal axis are given in millimeters from the point directly under stimulus and thus also are approximately the distance in space constants. (Only one half of the spatial response is shown, because the two sides are symmetric.) The activating function has a wave shape similar to that of the 0.01 msec curve. Adapted from Plonsey R, Barr RC. 1995. Electric field stimulation of excitable tissue. *IEEE Trans Biomed Eng* **42**:329–336.

It would be convenient if what happened at later times were simple multiples of the result for 0.01 msec. However, such is not the case. Thus the limitations of making estimates using the activating function are seen when examining the true response as the stimulus grows longer, as shown in the plots for 0.10 and 1.00 msec. The result of a longer stimulus is that the transmembrane potential grows larger in magnitude, but not linearly. Thus the peak v_m for the 0.10-msec plot is roughly three times that of the plot for 0.10 msec, and the plot for 1.00 msec is roughly two times that of 0.10 msec, even though the stimulus has $10\times$ the duration. Finally, the peak amplitude never increases much beyond that for 1.00 msec (for this example), even for much longer stimuli.

The transmembrane potential response also grows wider. As the stimulus gets longer, the extent of the fiber that is depolarized by the stimulus grows larger, as seen explicitly in Figure 7.6B, where the extent of the depolarized region is identified by a horizontal line for each time. Further,

the portion of the fiber depolarized changes from a small fraction of a space constant (at 0.01 msec) to substantial fractions (at 0.10 and 1.00 msec). Such a change can be critical to the initiation of a propagated response.

In summary, in this example, the activating function locates the site of maximum depolarization and is a good indicator of how the fiber responds at the start of the stimulus, showing depolarizing and hyperpolarizing regions. However, it fails to delineate the extent of the region of depolarization for realistic stimulus durations and provides only a weak basis for estimates of their peak magnitude. The extent of the depolarized region grows rapidly as the stimulus duration increases, while the activating function corresponds to the initial conditions. Thus the activating function is not a good predictor of the magnitudes or the regions of the fiber that are depolarized and hyperpolarized, for most stimuli used in practice.

7.6. STIMULUS, THEN SUPRATHRESHOLD RESPONSE

In this section we again consider the response of a fiber from a point current stimulus (as described in Figure 7.5). Here the active membrane properties are included to admit a suprathreshold stimulus. The Hodgkin–Huxley membrane model, described in Chapter 5, is chosen to describe these membrane properties. Since the evaluation was carried out numerically, specific electrophysiological and dimensional values were chosen to reflect realistic conditions.

7.6.1. Numerical Methods for Finding V_m

As in the previous section, the fiber and source geometry is specified in Figure 7.5. The fiber is assumed to be circular cylindrical with radius $a = 0.002$ cm. A stimulus current of magnitude I_0 is located a distance h from the fiber. The duration of the stimulus is denoted by t_d and is varied, as is h.

The stimulus threshold was determined for various combinations of h and t_d by repeated trials. Threshold was judged by the presence or absence of a propagating action potential at sites several space constants, λ, from the site of excitation. The threshold stimulus was such that a 10% increase resulted in propagation. (It was the largest stimulus for which propagation did *not* result.)

7.6.2. Results of Space-Clamped and Field Stimulation

Space-Clamped Threshold. For a reference, threshold was determined for a transmembrane stimulus under space-clamped conditions. A space clamp can be achieved by considering an axially uniform transmembrane potential stimulus. The result is plotted in Figure 7.7 (inset) [1]. One sees that with a space clamp the threshold is nearly independent of stimulus duration and requires 7 mV of depolarization.

Field Stimulation. An examination of Figure 7.7 shows that for field stimulation, the threshold voltage is no longer independent of stimulus duration, in general. The degree of deviation from the space-clamped result is seen to depend on both the stimulus–fiber distance h and the stimulus duration t_d.

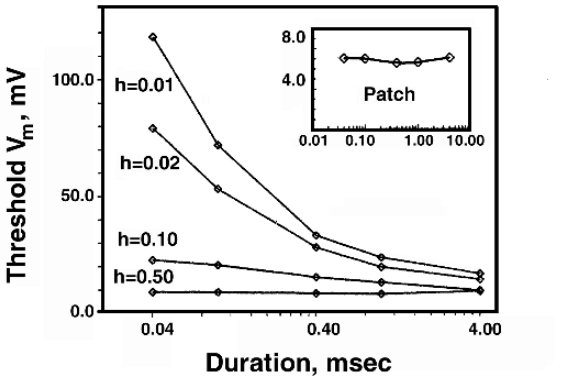

Figure 7.7. Threshold Values of v_m versus Stimulus Duration for a Point Stimulus. (**Inset**: results for patch geometry for comparison.) The transmembrane voltage at the end of the stimulus is shown for a stimulus condition that is just below threshold. Patch data are for the condition of no spatial variation. All potentials shown are relative to a baseline of -57 mV. **Outer**: Each curve is for a different source–fiber distance as shown (h given in cm). Results shown are for $z = 0$, the shortest fiber–stimulus distance. Membrane properties are: $E_K = -72.1$ mV, $E_{\rm Na} = 52.4$ mV, $\overline{g}_{\rm Na} = 120$ mS/cm^2, $\overline{g}_K = 36$ mS/cm^2, $g_l = 0.30$ mS/cm^2. Fiber properties are: $R_m = 0.148\ \Omega$cm^2, $\lambda = 0.086$ cm, $C_m = 1.0\ \mu$F/cm^2. From Barr RC, Plonsey R. 1995. Threshold variability in fibers with field stimulation of excitable membranes. *IEEE Trans Biomed Eng* **42**:1185–1191. Copyright ©1995, IEEE.

The highest thresholds were measured for the smallest duration and smallest value of h. Thus for $t_d = 0.04$ msec and $h = 0.01$ cm, a threshold value of 118 mV was obtained. In contrast, for long stimulus duration and large source–fiber distance, results were obtained that are similar to those for the patch. For example, when $h = 0.5$ cm, the threshold value of 8 mV corresponds to stimulus durations of 0.04–4.0 msec. (One could have anticipated such a result, since the axial variation of the applied field is increasingly uniform, approaching space-clamped conditions, for increasing h.)

Temporal Transmembrane Potential Waveforms. The temporal response following a just subthreshold stimulus is given in Figure 7.8 and is helpful in interpreting all results shown in Figure 7.7. For the shortest durations of 0.01 msec, we see that a transmembrane potential of 118 mV marks the threshold voltage. This elevated voltage is required to maintain a large enough voltage following the termination of the stimulus to open sufficient sodium channels, since the activation gate time constant τ_m is several tenths of a millisecond.

The effect of stimulus decay based on the membrane time constant is a contributing factor in Figure 7.7. But a second contributing factor affecting the membrane decay depends on the source–field distance. To understand this effect, a plot of the spatial transmembrane potential $v_m(z)$ is given in Figure 7.9. Here, we note that the central depolarized region is flanked by hyperpolarized regions.

Thus the depolarized membrane decay is also accelerated by longitudinal current flow into the hyperpolarized regions. This current will be enhanced for smaller values of h, which reduces the distance to the peak hyperpolarized position (in Figure 7.9 it is at around 0.15 cm).

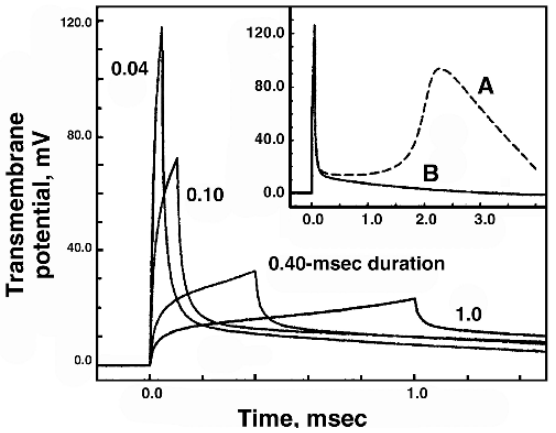

Figure 7.8. Transmembrane Potential as a Function of Time for stimuli that are just below and just above threshold. **Inset**: Curve A is for a just transthreshold stimulus and B for a just subthreshold stimulus. The source–fiber distance is 0.01 cm. Stimulus magnitudes were 1.40 (A) and 1.30 mA (B). **Outer**: Temporal responses for just subthreshold stimuli for stimulus duration as shown (in msec). From Barr RC, Plonsey R. 1995. Threshold variability in fibers with field stimulation of excitable membranes. *IEEE Trans Biomed Eng* **42**:1185–1191. Copyright ©1995 IEEE.

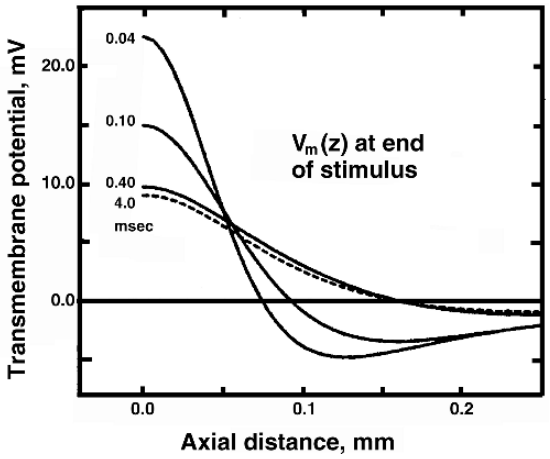

Figure 7.9. Spatial Distribution of Transmembrane Potential, $v_m(z)$, at the End of the Stimulus. Each curve is labeled with the duration of the stimulus. The source–fiber distance is 0.10 cm. In each case the stimulus magnitude is for a just subthreshold response. From Barr RC, Plonsey R. 1995. Threshold variability in fibers with field stimulation of excitable membranes. *IEEE Trans Biomed Eng* **42**:1185–1191. Copyright ©1995 IEEE.

This factor explains the very large threshold requirements for small values of h, seen in Figure 7.7. For $h = 0.5$ cm, the depolarized region is so broad that the behavior is similar to that shown for the patch (membrane decay is entirely due to the *RC* component alone).

7.6.3. Comments on the Concept of Threshold

For the design of a practical stimulator, it is highly desirable to specify a target threshold that can be relied on to achieve fiber activation. Specifying a target threshold allows one to use linear analysis to estimate stimulus parameters. Other factors that arise in a practical stimulator design are introduced in Chapter 12.

What is clear here is that the actual threshold value that exists at the end of just a transthreshold stimulus may range from 7 to 118 mV, depending on the stimulus duration and the distance from the stimulus electrode to the fiber. If a value of $h \approx 0.5$ cm or $h \approx 0.1$ cm and $t_d \approx 0.5$ msec is consistent with other design criteria, then a fixed threshold of around 8 mV can be assumed for an HH membrane. Otherwise, an elevated threshold value must be initially assumed in a linear treatment. In every case, a nonlinear membrane analysis is eventually desired to be followed by appropriate animal and human measurements.

7.7. FIBER INPUT IMPEDANCE

Many questions about the electrical properties of fibers can be framed in terms of the *input impedance*. For example, the effects of cable length are examined in the section below by comparing the input impedance for realistically short lengths with that of infinite lengths.

The input impedance, Z_0, is defined to be

$$Z_0 = v_m / I_i \tag{7.76}$$

and is evaluated at the point where the stimulus is applied. This evaluation requires both polarizing electrodes to be at the origin with one in the intracellular and the other in the extracellular space; the subthreshold applied current, I_i, and the resulting voltage, v_m, enter (7.76) to evaluate the input impedance. Note that the transmembrane voltage appearing in (7.76) is compared to the *longitudinal* intracellular current I_i.

We note first that the assumed stimulus satisfies the condition under which (7.76) is derived, namely, that $i_p = 0$ for $0 < x < \infty$. Consequently, using (7.30), we have

$$v_m = Ce^{-|x|/\lambda} \tag{7.77}$$

Assuming $r_e = 0$ permits (6.9) to be expressed as

$$I_i = -\frac{1}{r_i}\frac{\partial V_m}{\partial x} = -\frac{1}{r_i}\frac{\partial v_m}{\partial x} \tag{7.78}$$

Substituting (7.77) in (7.78) results in[15]

$$I_i = \frac{C}{r_i \lambda} e^{-|x|/\lambda} \tag{7.79}$$

Since $\lambda \approx \sqrt{r_m/r_i}$ when $r_e \approx 0$,

$$I_i = \frac{C}{\sqrt{r_m r_i}} e^{-|x|/\lambda} \tag{7.80}$$

and Z_0 (at $x = 0^+$) is given by

$$Z_0 = \frac{C e^{-|x|/\lambda}}{\frac{C}{\sqrt{r_i r_m}} e^{-|x|/\lambda}} \tag{7.81}$$

or

$$Z_0 = \sqrt{r_i r_m} \tag{7.82}$$

So, for an infinitely long cable with $r_e \approx 0$, the input impedance is the square root of the product of membrane and intracellular resistance.

7.7.1. Cables of Finite Length

Much of the above analysis has been based on the assumption of an infinitely long cable. Of course, no cables are infinitely long. In this section, the consequences of this discrepancy are examined. Specifically, the differences in the steady state are compared for cables of finite and infinite lengths.

The overall strategy used here is based on the cable input impedance. We have seen that for an infinitely long cable, Z_0 is $\sqrt{r_m r_i}$. Now we consider the input impedance Z_{in} of a cable of arbitrary length, L, terminated by an arbitrary impedance, Z_L.

For the specific case of a fiber of length L terminated in a short circuit ($Z_L = 0$), the input impedance, Z_{in}, will be of interest. This is because the extent to which Z_{in} corresponds to Z_0 provides a quantitative measure of the extent to which the finite cable approaches the input behavior of the infinite length cable.

There are a number of important applications. One arises in an examination of the behavior of a network of neurons, such as found in the central nervous system. This is shown to depend in part on the impedance behavior of short fibers (neurons). Interest in neural networks is not limited to neurophysiologists but to those working on artificial neural networks as computer processors. Further material on both topics is given in [3, 6, 11].

7.7.2. Finding Z_{in} for a Finite Length Cable

Consider an axon in an extensive extracellular medium ($r_e \approx 0$), of finite length ($x = L$), and terminated with an arbitrary load impedance Z_L. Assume an input voltage to the cable of $v_m = v_0$ applied at $x = 0$. For $x > 0$, $i_p = 0$, so the homogeneous form of (7.16) applies, namely, (7.17) or

$$\lambda^2 \frac{\partial^2 v_m}{\partial x^2} - v_m = 0 \tag{7.83}$$

The solution of (7.83) has already been given as (7.18)

$$v_m(x) = Ae^{-x/\lambda} + Be^{x/\lambda} \tag{7.84}$$

Note that since the cable is finite in length we can no longer set $B = 0$ based on the boundary condition at infinity. Now the relationship between v_m and I_i is available from the cable equations. Since $i_p = 0$, except at the origin, (7.78) is valid, and we rewrite it here for convenience as

$$I_i = \frac{1}{r_i} \frac{\partial v_m}{\partial x} \tag{7.85}$$

Substituting (7.84) into (7.85) and evaluating I_i gives

$$I_i(x) = \frac{1}{Z_0}(Ae^{-x/\lambda} - Be^{x/\lambda}) \tag{7.86}$$

where $Z_0 = \sqrt{r_m r_i}$ from (7.82).

At $x = 0$ we have $Z_{\text{in}} = V(0)/I(0)$, so from (7.84) and (7.86) Z_{in} is given by

$$Z_{\text{in}} = Z_0 \left(\frac{A + B}{A - B} \right) \tag{7.87}$$

For a cable of infinite extent, we must set $B = 0$ to avoid a potential that grows indefinitely, and consequently from (7.87), $Z_{\text{in}} = Z_0$, which corresponds to earlier results (i.e., the input impedance of an infinite cable is Z_0).

For cables of finite length and arbitrary termination the input impedance requires the evaluation of *A* and *B* in (7.87). This evaluation is facilitated by an evaluation of a factor involving the terminal impedance known as the *reflection coefficient*. In the next section we define the reflection coefficient and show how it introduces the boundary condition at the load located at $x = L$.

Reflection coefficient: Now at $x = L, Z_L = V_m(L)/I_i(L)$, so dividing (7.84) by (7.86) for $x = L$ gives

$$Z_L = Z_0 \left(\frac{Ae^{-L/\lambda} + Be^{L/\lambda}}{Ae^{-L/\lambda} - Be^{L/\lambda}} \right) \tag{7.88}$$

We define the *reflection coefficient*, Γ, as

$$\Gamma = \frac{Z_L + Z_0}{Z_L - Z_0} \tag{7.89}$$

Substitution of (7.88) in (7.89) and simplification of the resulting expression yields the following relationships:

$$\Gamma = \frac{Ae^{-L/\lambda}}{Be^{L/\lambda}} \tag{7.90}$$

$$Z_L = \left[\frac{\frac{Ae^{-L/\lambda}}{Be^{L/\lambda}} + 1}{\frac{Ae^{-L/\lambda}}{Be^{L/\lambda}} - 1} \right] Z_0 = Z_0 \left(\frac{\Gamma + 1}{\Gamma - 1} \right) \tag{7.91}$$

Table 7.3. Normalized Input Impedance of Finite Length Cable

L/λ	Z_{in}/Z_0
0.1	10.0
0.5	2.16
1	1.31
2	1.04
3	1.01

By substituting (7.90) into (7.87) we obtain an expression for Z_{in} in terms of Γ:

$$Z_{\text{in}} = Z_0 \left(\frac{\Gamma e^{2L/\lambda} + 1}{\Gamma e^{2L/\lambda} - 1} \right) \tag{7.92}$$

The name "reflection coefficient" comes about from similar definitions used in the study of traveling electromagnetic waves, where the wave may by reflected in whole or in part from discontinuities in a cable, such as at its termination.

For example, when $Z_L = Z_0$ the termination is equivalent to an infinite cable and consequently the finite cable itself behaves as the proximal element of an infinite cable. In this case nothing will be "reflected," of course. From (7.89), a termination of $Z_L = Z_0$ results in $\Gamma = \infty$. In contrast, if $Z_L = 0$ (short circuit) or $Z_L = \infty$ (open circuit), then $\Gamma = \pm 1$, and the termination introduces a maximum discontinuity (everything "reflected"). This outcome is recognized in (7.92) with both $\Gamma = \pm 1$ and small L/λ.

While the present nomenclature has been utilized due to a superficial analogy with EM waves, the physical situation is, of course, quite different.[16]

7.7.3. Z_{in} for an Open Circuit Termination

A finite cable with a sealed end can be regarded as a cable that ends in an open circuit. That is, $Z_L = \infty$ and $\Gamma = 1$. For a cable of length L with such a termination, we have from (7.92)

$$Z_{\text{in}} = Z_0 \left(\frac{e^{2L/\lambda} + 1}{e^{2L/\lambda} - 1} \right) = Z_0 \coth \left(\frac{L}{\lambda} \right) \tag{7.93}$$

Equation (7.92) confirms that $Z_{\text{in}} = Z_0$ when $\Gamma = \infty$, while when $\Gamma = \pm 1$, Z_{in} depends on L/λ [e.g., $Z_{\text{in}} = Z_0 \tanh(L/\lambda)$ for $\Gamma = -1$]; further details are found in the next section.

Table 7.3 shows the result of evaluating (7.93) numerically to find Z_{in}/Z_0. It indicates that for short cables, defined by $L < \lambda$, there are substantial deviations in behavior from that of an infinite cable. On the other hand, Table 7.3 also shows that as L increases beyond λ, the input rapidly becomes indistinguishable from that of an infinite cable. In particular, the input impedance is within 1% of Z_0 if L is 3λ or more.

7.8. MAGNETIC FIELD STIMULATION

For an applied time-varying magnetic field, Faraday's law describes an induced (free-space) electric field, namely,

$$\oint \overline{E} \cdot \overline{dl} = -\frac{d}{dt} \int_s \mu_0 \overline{H} \cdot d\overline{S} \tag{7.94}$$

where μ_0 is the permeability (normally taken as free space) and $\overline{H}$ the magnetic field. Induced secondary sources at conductive discontinuities (in particular, the torso–air interface) must be included in a realistic evaluation of $\overline{H}$ and hence the induced electric field at human nerve/muscle from applied external magnetic fields. The electric field at nerve/muscle fibers, once obtained, follows all principles described in this chapter. An overview of magnetic field applications can be found in Stuchly [9], and some theoretical considerations in Plonsey [4].

7.9. NOTES

1. The concept of a voltage threshold as a fixed point of sudden transition to an active response, a classical conceptual starting point, does not hold up consistently when examined in detail.
2. It is worth noting that the behavior of the tissue after it crosses threshold and becomes active (which often means once the sodium channels open) is not usually a focus of the analysis of stimuli. That is because most of the time the active response depends primarily on the tissue's intrinsic membrane response and cellular structure rather than on external stimuli. However, active response also is affected if the external stimulus is large enough and long enough, e.g., in cardiac defibrillation.
3. Often R_m and C_m are used directly, and I_o is converted to Amperes/cm^2.
4. Later in the chapter we examine critically the classical notion that activation is automatically achieved once the transmembrane potential reaches a critical transmembrane voltage.
5. One sees Eq. (7.8), sometimes with alternative variable names, used to relate threshold current and rheobase in many contexts. For example, in Chapter 12 the same equation is used in connection with functional electrical stimulation.
6. Lapicque gave the equation $i = \alpha/(1 - e^{-\beta t})$, where i was intensity, t was duration, and α and β were two constants.[2]
7. If the current had been applied extracellularly, then $\partial\Phi_i/\partial x = 0$ at $x = 0$ and $\partial\Phi_e/\partial x = -I_0 u(t) r_e/2$ at $x = 0$. In this case we would replace (7.43) by $\partial v_m/\partial X = I_0 u(t) r_e \lambda/2$ (i.e., replace $-I_0 r_i$ by $I_0 r_e$). From symmetry, we interchange subscripts i and e and, in addition, change the current sign to reflect it being oppositely directed. These expressions, however, assume a limited extracellular space where currents are essentially axial and a one-dimensional Ohm's law applies.
8. One can use Eq. 30 in Appendix V of Carslaw HS, Jaeger JC. 1959. *Conduction of heat in solids*. Oxford: Oxford UP.
9. If the current were introduced into (a bounded) extracellular rather than intracellular space, then the coefficient on the right-hand side of (7.49) would equal $-r_e \lambda I_0/4$, and one can confirm that this expression reduces to (7.34) when $t \to \infty$. Note that (7.49) applies even if $r_e = 0$ for a fiber in an unbounded extracellular region. For an extracellular applied current, it is required that $r_e \neq 0$ to invoke the aforementioned symmetry.
10. The importance of the subthreshold case is the following: even if the goal of the stimulation is to bring the fiber above threshold, it must pass through a subthreshold state first. Thus the results are broadly applicable.
11. The assumption of a thin fiber and relatively large source–fiber distance assures that the azimuthal potential variation is relatively small compared with the axial variation. For the azimuthal potential behavior, the fiber roughly doubles the values of the applied field at the nerve periphery; these potential variations are relatively small for a thin fiber at a large distance from the source, compared to variations along the axis. The secondary field arising from the axial variations can be shown to be negligible [6].
12. The stimulating current, I_0, is relatively large in order that the field it generates in the *extracellular* volume conductor, given by (7.55), can induce subthreshold or suprathreshold depolarization of the target fiber. When considering the response of the fiber itself to an *intracellular* unit impulse current, its behavior is little affected by the relatively small extracellular field when the extracellular medium is unbounded. The linear core-conductor equation therefore describes the intracellular fields correctly with $r_e = 0$; the large extracellular point source and its field are zero in this situation.
13. Exercise: what are the units for G?

14. Exercise: give the units for each quantity on the right side of (7.70) and show that they combine to give the units needed on the left side.
15. The reason why Eq. (7.79) differs from (7.54) might not be apparent. However, this arises because in deriving (7.54) we assumed an intracellular applied current I_0 located at $x = 0$ with the removal of this current at infinity (whether it is removed intracellularly or extracellularly will have no effect in the region $0 < x < L$ so long as L is finite). In (7.79), the electrode pair carrying I_0 into the intracellular space and out of the extracellular region are both at $x = 0$.
16. Propagation of microwave energy along cables or waveguides results from the injection of energy at the proximal end; this energy diminishes with distance due to losses. For nerve/muscle, only a trigger to initiate a propagating action potential is assumed at the proximal end; the energy is derived and expended all along the fiber and there is no attenuation. An analogy to the biological case (regarding energy) is the behavior of a fuse, except that the fuse can be used only once.

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