A MODEL FOR THE POLARIZATION OF NEURONS BY EXTRINSICALLY APPLIED ELECTRIC FIELDS

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ABSTRACT A model is presented for the subthreshold polarization of a neuron by an applied electric field. It gives insight into how morphological features of a neuron affect its polarizability. The neuronal model consists of one or more extensively branched dendritic trees, a lumped somatic impedance, and a myelinated axon with nodes of Ranvier. The dendritic trees branch according to the 3/2-power rule of Rall, so that each tree has an equivalent cylinder representation. Equations for the membrane potential at the soma and at the nodes of Ranvier, given an arbitrary specified external potential, are derived. The solutions determine the contributions made by the dendritic tree and the axon to the net polarization at the soma. In the case of a spatially constant electric field, both the magnitude and sign of the polarization depend on simple combinations of parameters describing the neuron. One important combination is given by the ratio of internal resistances for longitudinal current spread along the dendritic tree trunk and along the axon. A second is given by the ratio between the DC space constant for the dendritic tree trunk and the distance between nodes of Ranvier in the axon. A third is given by the product of the electric field and the space constant for the trunk of the dendritic tree. When a neuron with a straight axon is subjected to a constant field, the membrane potential decays exponentially with distance from the soma. Thus, the soma seems to be a likely site for action potential initiation when the field is strong enough to elicit suprathreshold polarization. In a simple example, the way in which orientation of the various parts of the neuron affects its polarization is examined. When an axon with a bend is subjected to a spatially constant field, polarization is focused at the bend, and this is another likely site for action potential initiation.

INTRODUCTION

Electrical stimulation of neurons is a powerful investigative tool and has practical applications in the area of applied neural control, which seeks to restore functionality to impaired regions of the nervous system. Despite the ubiquitous use of electrical stimulation there have been few basic studies of the biophysics of the process. Ranck (1975) provided a comprehensive review of the area up to that time, and recently we have published (Chan and Nicholson, 1986) an experimental study of the interaction of electric fields and neurons. This paper addresses theoretical problems.

The fundamental issue is how the electric field generated by the passage of a defined current through brain tissue modulates the activity or neurons. The solution to this problem will depend on the relationship between the orientation of the applied field and the geometry of the neuron.

At first sight it might seem that the local inhomogeneity of the tissue or the increasingly evident nonlinearities of neuronal membranes would complicated the problem to such an extent that any general solution would be of little utility. Fortunately our experiments indicate that, at least for moderate field intensities, the modulation of neuronal activity is a relatively simple function of orientation of the neuronal processes with respect to the applied field; with this result in mind we set out to develop an appropriate theoretical framework.

To solve the problem we needed to be able to compute the membrane potential in various regions of a neuron subjected to an applied field. When the morphology of the dendritic tree is complex, the equations governing the membrane potential must be solved numerically; but this approach does not give immediate insight into how the various physical parameters describing the neuron affect the solution. We have avoided this problem by developing analytic solutions for the membrane potential of an idealized neuron subjected to an applied field.

Our solutions have been derived from an application of basic cable theory (see Rall, 1977, for a review) to the dendritic tree. A novel feature is the inclusion of a myelinated axon in the model. We discovered that the axon can play a significant role in the polarization of the soma when the whole neuron is exposed to an electric field. In certain configurations the dendritic tree and the axon even make antagonistic contributions to the polarization of the soma.

Our theoretical studies confirm and extend our experimental findings that neuronal geometry is a crucial factor in determining the response to applied electric fields.

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Selected regions of a neuron can be polarized by an appropriately applied field and, in combination with intracellular recording, this can provide a powerful tool for the study of membrane properties (Chan et al., 1985). Finally, the relation between electric fields and neuronal depolarization is relevant to the present discussions of electric field effects in epileptic activity (e.g., Jeffreys, 1981; Snow and Dudek, 1984; Taylor et al., 1984; Traub et al., 1985). A survey of the other literature is provided elsewhere (Chan and Nicholson, 1986).

GLOSSARY

Terms for Dendritic Tree

$v_1(x, t)$	Difference between physical internal voltage (potential) and resting voltage at position x and time t in the dendrite (in volts).
$I_1(x, t)$	Physical membrane current per unit length across the dendritic membrane (in amperes per centimeter).
r	Internal axial resistance per unit length of dendrite (in ohms per centimeter).
r_t	r for the trunk of dendritic tree (in ohms per centimeter).
x	Distance of a point in the dendritic tree from the soma as measured along the dendrites (in centimeters).
t	Time (in seconds).
$u_1(x, t)$	Physical voltage external to dendrite (in volts).
$v(x)$	Complex coefficient for voltage internal to dendrite when the voltage fluctuates with a sinusoidal time course; $v_1(x, t) = \mathrm{Re}\,\{v(x)e^{i2\pi ft}\}$ (in volts).
$u(x)$	Complex coefficient for voltage external to the dendrite; $u_1(x, t) = \mathrm{Re}\{u(x)e^{i2\pi ft}\}$ (in volts).
$I(x)$	Complex coefficient for current per unit length of dendritic membrane; $I(x, t) = \mathrm{Re}\{I(x)e^{i2\pi ft}\}$ (in amperes per centimeter).
$Y(f)$	Admittance per unit area of dendritic membrane at frequency f (in reciprocal ohms per square centimeter).
a	Diameter of dendrite (in centimeters).
ρ	Resistivity of cytoplasm (in ohm centimeters).
$q^2(f)$	Ratio of admittance at frequency f to that at frequency zero; $q^2(f) = Y(f)/Y(0)$ (dimensionless).
λ	DC exponential length constant (cable constant) for dendrite; $\lambda^2 = a/[4\rho Y_0]$ (in centimeters).
λ_k	λ for the k^{th} generation of dendritic branch.
λ_t	λ for the trunk of dendritic tree $\lambda_t \equiv \lambda_0$.
X	Dimensionless distance (measured in units of DC length constants) of a point in the dendritic tree from the soma; $X = g(x)$, where $g(x) = \int_0^x dy/\lambda(y)$.
$V(X)$	Complex coefficient for sinusoidally fluctuating internal voltage for dendrite as a function of dimensionless distance X. $V(X) \equiv v(x)$, where $X = \int_0^x dy/\lambda(y)$ (in volts).
$U(X)$	Complex coefficient for external voltage corresponding to $V(X)$ above (in volts).
k, ℓ	Pair of superscripts denoting the generation and branch of a dendrite $V^{(k,\ell)}(X)$ is the internal voltage in generation k, branch ℓ, at position X. With symmetrical branching, $\ell = 0, 1, 2, \ldots 2^k - 1$.
X_k	Dimensionless distance from soma to branch point between generations k and $k + 1$.
$\overline{V}^{(k)}(X)$	Average (over branches) of the complex coefficient for the internal potential at position X in the kth generation (in volts).
$\overline{U}^{(k)}(X)$	Average external potential corresponding to $\overline{V}^{(k)}(X)$ above (in volts).
d	Physical distance along the dendrites from the soma to the terminus of the dendritic tree (in centimeters).
L	Dimensionless distance corresponding to d; $L = \int_0^d dy/\lambda(y)$.
$Z_{se}^{\text{in,den}}$	Sealed-end input impedance for dendritic tree. When current I is injected at the origin of the dendritic tree with a sealed end, the membrane potential $\overline{V}(0) - \overline{U}(0) = I\,Z_{se}^{\text{in,den}}$ results. $Z_{se}^{\text{in,den}} = r_t\lambda_t/(q \tanh qL)$. (in ohms)
E_d	Component of electric field oriented along the dendrite (in volts per centimeter).

Terms for the Axon

$v_1(k, t)$	Difference between physical internal voltage and resting voltage at node k in the axon at time t (in volts).
$u_1(k, t)$	Physical external voltage corresponding to $v_1(k, t)$ above (in volts).
$v(k)$	Complex coefficient for internal voltage when it fluctuates with a sinusoidal time course; $v_1(k, t) = \mathrm{Re}\{v(k)e^{i2\pi ft}\}$ (in volts).
$u(k)$	Complex coefficient for external voltage corresponding to $v(k)$ above (in volts).
Z	Impedance of node of Ranvier (in ohms).
R	Axial internodal resistance (in ohms).
D	Distance between nodes of Ranvier (in centimeters).
r_a	Axial resistance per unit length, $R = r_a D$ (in ohms per centimeter).
γ	Exponential length constant for axon, defined by $e^{D/\gamma} + e^{-D/\gamma} = 2 + R/Z$ (in centimeters).
$v_{se}(k)$	Complex coefficient for the internal potential at node k in the sealed-end axon problem (in volts).
$v_{ci}(k)$	Complex coefficient for the internal potential at node k in the current-injection axon problem (in volts).
$Z_{se}^{\text{in,ax}}$	Sealed-end input impedance of axon. When current I is injected at the origin of the axon with a sealed end, the membrane potential $v(0) - u(0) = I\,Z_{se}^{\text{in,ax}}$ results. $Z_{se}^{\text{in,ax}} = R/(1 - e^{-D/\gamma})$ (in ohms).
μ	External voltage difference between nodes for the spatially constant electric field problem (in volts).
E_a	Component of electric field oriented along the axon (in volts per centimeter).

Terms for Coupled Axon, Dendritic Tree, and Soma

Z_{soma}	Lumped impedance of the soma (in ohms).
α	Coefficient of the sealed-end solution for the dendritic tree;

$$\alpha = \frac{1}{1 + \left(\dfrac{r_t\lambda_t}{Rq}\right)\left(\dfrac{1 - e^{-D/\gamma}}{\tanh qL}\right)} = \frac{Z_{se}^{\text{in,ax}}}{Z_{se}^{\text{in,ax}} + Z_{se}^{\text{in,den}}}.$$

β	Coefficient of the sealed-end solution for the axon; $\beta = 1 - \alpha$.

MODEL

We consider a neuron consisting of a soma, one or more dendritic trees, and a myelinated axon with nodes of Ranvier (Fig. 1 *A*). Each dendritic tree branches symmetrically. The diameters of the dendritic branches conform to the 3/2-power rule of Rall (1962, 1977), so that the 3/2 power of the diameter of each daughter branch is equal to half the 3/2 power of the diameter of the parent branch. This rule makes the dendritic tree mathematically equiva-

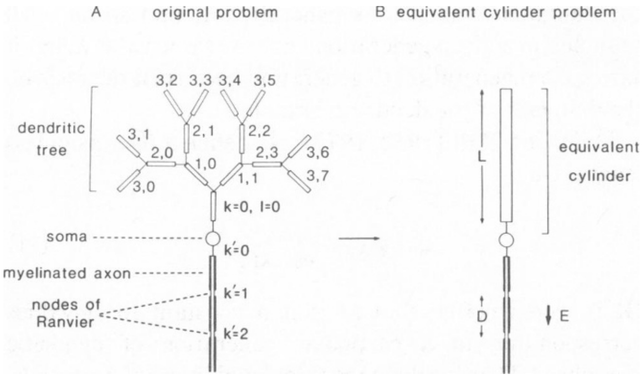

FIGURE 1 (*A*) Schematic diagram of a neuron consisting of a dendritic tree, soma and myelinated axon with nodes of Ranvier. The dendritic tree branches symmetrically. The generation of branching is indexed by k and the branch within a generation is indexed by ℓ, where $\ell = 0, 1, 2, \ldots, 2^k - 1$. the descendents of branch k, ℓ are $k+1, 2\ell$ and $k+1, 2\ell+1$. The trunk is indexed by 0, 0. The diameters of the dendritic branches conform to the 3/2-power rule of Rall, where the 3/2 power of the diameter of each daughter branch is equal to half the 3/2 power of the diameter of the parent branch. (This geometrical feature is not represented in the diagram.) The myelinated axon is semi-infinite with a fixed distance D between nodes. The nodes are indexed by $k' = 1, 2, 3, \ldots$. the soma designated by $k' = 0$ is modeled as a lumped impedance (distinct from the nodal impedance). (*B*) The dendritic tree in Fig. 1 *A* is replaced by its equivalent cylinder. For the purposes of computing the membrane potential at the soma and nodes of Ranvier, the simple neuron in Fig. 1 *B* is equvalent to that in Fig. 1 *A*.

lent to a cylinder (Fig. 1 *B*) under appropriate conditions. Although actual neurons can deviate from this geometry, this simplification is widely used because it is a good approximation and it makes analytic solutions feasible. We assume that the dendritic membrane is uniform throughout the tree. The dendritic membrane may have nonlinear time- and voltage-dependent conductance mechanisms, but we examine only the linear regime of the neuron. To do this the electrical properties of both the dendritic and axonal membranes are modeled with phenomenological impedances that result from linearizing the equations governing the time dependence of the membrane voltage. These equations describe the behavior of the neuron when perturbations of its resting membrane potential are small, as is the case before generation of action potentials. Moreover, recent experimental studies (Chan and Nicholson, 1986) suggest that, at low applied fields, spikes are generated in the vicinity of the soma and dendritic properties remain passive. The soma is idealized as a point with a lumped impedance. For the axon we assume that the nodes of Ranvier are evenly spaced, and that the myelin sheath is a perfect insulator. In Appendix B an axon with a leaky myelin sheath is treated. We assume that the axon is long compared to the distance over which signals spread by passive electrotonic conduction (i.e., a semi-infinite axon). The neural tissue in which the neuron is embedded is approximated as a bulk conductor of uniform conductivity in which the neuron does not distort the applied electric field. This allows us to calculate the external potential at each point of the neuron.

THEORY

Outline of Solution Method

To determine the internal potential at the soma when the neuron is subjected to an applied electric field, given the linearity of the system, it is sufficient to solve for the average (over branches) internal potential at a distance x (measured along the tree) from the soma. The average internal potential at $x = 0$ is the internal potential itself at the soma. The equations take a particularly simple form when the tree branches symmetrically according to the 3/2 power rule of Rall and when distance from the soma is measured in appropriate dimensionless units. Averaging reduces the system of differential equations and boundary conditions for the various branch generations to a single differential equation with only two boundary conditions (Rall, 1962, 1977; Rall and Rinzel, 1973; Peskin, 1976). This equation is the cable equation corresponding to a single unbranched dendrite with a given external potential, i.e., the "equivalent cylinder" problem. Note that the external potential in this problem also transforms and bears a simple relationship to the specified external potential in the original problem. This ensures that the simplified cable model represents the original problem.

A complication is that the dendritic tree is coupled to an axon. The full solution to the problem can be obtained by solving two simpler problems for the dendritic tree and two simpler problems for the axon and then combining these solutions. One simpler problem for the equivalent cylinder is obtained by replacing the boundary condition at the soma in the original problem with a sealed-end boundary condition (sealed-end solution). The other simpler problem for the equivalent cylinder is obtained by specifying an axial current at the origin of the equivalent cylinder and by specifying the external potential to be zero everywhere ("current-injection solution"). A linear combination of the solutions to these two problems satisfies the differential equation and boundary conditions of the original problem (Coddington, 1961; Rall and Rinzell, 1973). Similar methods are used for the axon.

Equations for the Dendritic Tree

As a consequence of Ohm's law and the principle of current conservation, the internal potential at each point in the dendritic tree satisfies the cable equation

$$\frac{\partial^2 v_1}{\partial x^2} = r I_1, \tag{1}$$

where v_1 is the internal potential, x is the distance from the soma, I_1 is the membrane current per unit length, and r is the (internal) axial resistance per unit length, which depends on the diameter of the dendritic branch.

We assume that the applied electric field is modulated with a sinusoidal time course. There are two motivations for this. First, because of linearity, one can use the solutions for sinusoidally modulated fields to construct the solution for an electric field modulated with an arbitrary waveform. Second, low-frequency electric fields modulated with a sinusoidal time course at low frequencies have been used experimentally (Chan and Nicholson, 1986; Bawin et al., 1986).

For the sinusoidal case, the external potential u_1 is of the form

$$u_1(x, t) = \mathrm{Re}\{u(x)e^{i2\pi ft}\}, \tag{2}$$

where f is the frequency in Hz. The linearity of the problem ensures that the internal potential v_1 and membrane current I_1 will also vary with a sinusoidal time course:

$$v_1(x, t) = \mathrm{Re}\{v(x)e^{i2\pi ft}\} \tag{3}$$

$$I_1(x, t) = \mathrm{Re}\{I(x)e^{i2\pi ft}\}. \tag{4}$$

Eqs. 2–4 allow us to rewrite the cable equation (Eq. 1) in the form

$$\frac{d^2v}{dx^2} = rI. \tag{5}$$

Eq. 5 holds for each branch of each dendritic tree. The current per unit length of dendrite I, is related to the voltage difference across the membrane by Ohm's law

$$I = \pi aY(v - u), \tag{6}$$

where a is the diameter of the dendrite and Y is the admittance per unit area of dendritic membrane (a function of frequence f). Combining Eqs. 5 and 6 gives

$$\frac{d^2v}{dx^2} = r\pi aY(v - u). \tag{7}$$

The resistance per unit length of cable, r is given by $r = 4\rho/(\pi a^2)$, where ρ is the resistivity of cytoplasm, so Eq. 17 becomes

$$\frac{d^2v}{dx^2} = \frac{4\rho}{a}Y(v - u). \tag{8}$$

Now we define the dimensionless quantity $q(f)$ such that $Y(f) = q^2(f)Y_0$, where $Y_0 \equiv Y(0)$. Then Eq. 8 becomes

$$\frac{d^2v}{dx^2} = \left(\frac{4\rho}{a}Y_0\right)q^2(v - u). \tag{9}$$

If we define the DC length constant λ by $\lambda^2 = a/[4\rho Y_0]$, then Eq. 9 can be rewritten

$$\frac{\lambda^2}{q^2}\frac{d^2v}{dx^2} - v = -u. \tag{10}$$

Eq. 10 holds in each branch of each generation of the dendritic tree. (The trunk is defined as generation zero and the daughter branches as generation 1, and so on.) All branches of a given generation have the same value λ, but it varies from generation to generation because it depends on the diameter of the dendritic branch.

Following Rall (1962, 1977), we define a dimensionless length X by

$$X = g(x) = \int_0^x \frac{dy}{\lambda(y)}. \tag{11}$$

(It is worth noting that $\lambda(y)$ is a constant for y-values corresponding to a particular generation of dendritic branches.) Then we define external and internal potentials, as functions of this new variable X, by

$$U(X) \equiv u(x) \tag{12}$$

and

$$V(X) \equiv v(x), \tag{13}$$

where $X = g(x)$ is given by Eq. 11.

Then Eqs. 11, 12, and 13, together with Eq. 10, give

$$\frac{1}{q^2}\frac{d^2V}{dX^2} - V = -U. \tag{14}$$

There is one equation of the form of Eq. 14 for each branch of each generation of each tree.

We will consider a neuron with only one dendritic tree with symmetrical branching structure. In Appendix C the more general case where the neuron has several trees, possibly different in branching structure, is considered. Let us index the generation of branching by the integer k. For the trunk $k = 0$; the daughter branches have index $k = 1$, etc. Let us index the branches within a generation by the integer ℓ, where $\ell = 0, 1, 2, \ldots, 2^k - 1$. In this method of indexing (Peskin, 1976), the descendents of branch k, ℓ will be $k + 1, 2\ell$ and $k + 1, 2\ell + 1$ as indicated in Fig. 1.

If we denote the internal potential V in the branch with indices k and ℓ by $V^{(k,\ell)}$ and the corresponding external potential by $U^{(k,\ell)}$, Eq. 14 gives

$$\frac{1}{q^2}\frac{d^2V^{(k,\ell)}}{dX^2} - V^{(k,\ell)} = -U^{(k,\ell)}. \tag{15}$$

At each branch point there is a boundary condition that stems from the principle of current conservation: The axial current flowing from a parent branch into a branch point must equal the sum of the axial currents flowing away from the branch point in the daughter branches. Therefore

$$\frac{1}{r_k}\frac{\partial v_1^{(k,\ell)}}{\partial x} = \frac{1}{r_{k+1}}\left\{\frac{\partial v_1^{(k+1,2\ell)}}{\partial x} + \frac{\partial v1_1^{(k+1,2\ell+1)}}{\partial x}\right\}. \tag{16a}$$

This boundary condition in terms of our transformed voltage and distance reads

$$(a_k)^{3/2}\frac{dV^{(k,\ell)}}{dX} = (a_{k+1})^{3/2}\left\{\frac{dV^{(k+1,2\ell)}}{dX} + \frac{dV^{(k+1,2\ell+1)}}{dX}\right\},$$

at

$$X = X_k, \tag{16b}$$

where a_k is the diameter of the dendrite in the k^{th} generation, and X_k is the (dimensionless) distance from the soma to a branch point between generation k and generation $k + 1$.

Following the strategy outlined earlier, we will now obtain an equation for the average (over branches indexed by ℓ) of the internal potential $V^{(k,\ell)}$ at a distance X from the soma in the k^{th} generation. If we denote this average internal potential by $\bar{V}^{(k)}$ and the average external potential by $\bar{U}^{(k)}$, then by the definition of average

$$\bar{V}^{(k)}(X) = \frac{1}{2^k} \sum_{\ell=0}^{2^k-1} V^{(k,\ell)}(X) \tag{17}$$

and

$$\bar{U}^{(k)}(X) = \frac{1}{2^k} \sum_{\ell=0}^{2^k-1} U^{(k,\ell)}(X). \tag{18}$$

Eqs. 17 and 18 together with Eq. 15 give

$$\frac{1}{q^2}\frac{\mathrm{d}^2\bar{V}^{(k)}}{\mathrm{d}X^2} - \bar{V}^{(k)} = -\bar{U}^{(k)}, \tag{19}$$

If Eq. 16 is similarly averaged over ℓ, we obtain

$$(a_k)^{3/2}\frac{\mathrm{d}\bar{V}^{(k)}}{\mathrm{d}X} = 2(a_{k+1})^{3/2}\frac{\mathrm{d}\bar{V}^{(k+1)}}{\mathrm{d}X}, \quad \text{at } X = X_k. \tag{20}$$

According to the 3/2-power rule of Rall, $(a_{k+1})^{3/2} = (1/2)(a_k)^{3/2}$. In this case, Eq. 20 becomes

$$\frac{\mathrm{d}\bar{V}^{(k)}}{\mathrm{d}X} = \frac{\mathrm{d}\bar{V}^{(k+1)}}{\mathrm{d}X}, \quad \text{at } X = X_k. \tag{21}$$

Eq. 21 merely states that the first derivative of the potential $\bar{V}$ is continuous across branch points. Since we already know that $\bar{V}$ itself is continuous across branch points, the branch points can be regarded as points internal to a larger domain: the domain of $X = 0$ to $X = \int_0^d \mathrm{d}y/\lambda(y) \equiv L$, where d is the physical distance of the terminus of the dendritic tree from the soma. Thus, the superscript in Eq. 19 can be dropped to give

$$\frac{1}{q^2}\frac{\mathrm{d}^2\bar{V}}{\mathrm{d}X^2} - \bar{V} = -\bar{U}. \tag{22}$$

Eq. 22 applies to the domain $X = 0$ to $X = L$. Now there are only two boundary conditions; one stems from the sealed end condition at each terminal branch of each tree:

$$\frac{\mathrm{d}\bar{V}}{\mathrm{d}X} = 0, \quad \text{at } X = L; \tag{23}$$

the other comes from current conservation at the soma and will be discussed later.

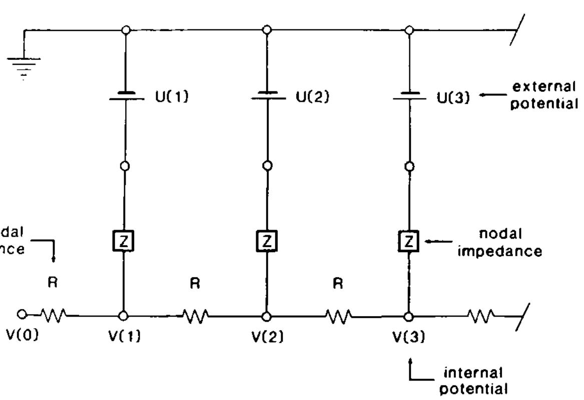

FIGURE 2 Equivalent circuit for the myelinated axon depicted in Fig. 1. The internal potential at node k' is denoted by $v(k')$. The special case of $k' = 0$ corresponds to the soma. The external potential for node k' is denoted by $u(k')$. The internodal (internal) axial resistance is labeled R. The transmembrane nodal impedance is labeled Z. The myelin sheath is assumed to be a perfect insulator, so that the only path for membrane current is at the nodes.

Equations for the Axon

Fig. 2 depicts the equivalent circuit of our myelinated axon model, isolated from the rest of the neuron; the interaction of axon with dendritic tree will be considered later.

As in the dendritic tree problem, we assume that the external potential is modulated with a sinusoidal time course. Thus, the internal potential at the kth node $v_1(k, t)$ is of the form

$$v_1(k, t) = \mathrm{Re}\,\{v(k)\,e^{i2\pi ft}\}, \tag{24}$$

and the external potential at the kth node, $u_1(k, t)$, is

$$u_1(k, t) = \mathrm{Re}\,\{u(k)\,e^{i2\pi ft}\}. \tag{25}$$

In analogy with Eq. 10 for the dendrite, the difference equation for the internal potential in the axon is

$$\frac{Z}{R}\{v(k-1) - 2v(k) + v(k+1)\} - v(k) = -u(k),$$

$$\text{for } k = 1, 2, 3, \ldots, \tag{26}$$

where Z is the impedance of the node, and R is the internodal resistance (see BeMent and Rank, 1969).

Solution for Coupled Axon and Dendritic Tree

The solution for the full neuron problem must satisfy the principle of current conservation at the soma. That is, the total current flowing from the soma into the dendritic trees, the current flowing from the soma into the axon, and the current flowing across the soma membrane must sum to zero. In our model the soma is a point with a lumped impedance. This gives the boundary condition

$$\frac{\bar{V}(0) - \bar{U}(0)}{Z_{\text{soma}}} + \frac{v(0) - v(1)}{R} = \frac{1}{r_t\lambda_t}\frac{\mathrm{d}\bar{V}}{\mathrm{d}X}\bigg|_{X=0} \tag{27}$$

The problem of determining the membrane potential at the soma of the neuron and at the nodes of Ranvier amounts to solving Eq. 19 and Eq. 26 simultaneously with one boundary condition given by Eq. 23 and another boundary condition given by Eq. 27.

The solution for the average internal potential $\overline{V}(X)$ in the dendritic tree can be expressed as a linear combination of two solutions: one is the solution $\overline{V}_{se}(X)$ to the equivalent cylinder problem with external potential $\overline{U}(X)$ and with a sealed end boundary condition at the soma end; the other is the solution $\overline{V}_{ci}(X)$ to the equivalent cylinder problem with external potential equal to zero everywhere and with a specified current injected at the soma end. That is to say, $\overline{V}_{se}(X)$ is the solution to

$$\frac{1}{q^2}\frac{d^2\overline{V}}{dX^2} - \overline{V} = -\overline{U}, \quad 0 < X < L \tag{28}$$

$$\frac{d\overline{V}}{dX} = 0, \quad \text{at } X = L \text{ and at } X = 0. \tag{29}$$

$\overline{V}_{ci}(X)$ is the solution to

$$\frac{1}{q^2}\frac{d^2\overline{V}}{dX^2} - \overline{V} = 0, \quad 0 < X < L \tag{30}$$

$$\frac{d\overline{V}}{dX} = 0, \quad \text{at } X = L \tag{31}$$

$$\frac{d\overline{V}}{dX} = -1, \quad \text{at } X = 0, \tag{32}$$

where the right-hand side of Eq. 32 has been chosen as -1 for simplicity.

Analogously, the solution to the original axon problem can be written as a linear combination of solutions to two other problems. Let us define $v_{se}(k)$ as the solution to

$$\frac{Z}{R}\{v(k-1) - 2v(k) + v(k+1)\} - v(k) = -u(k), \quad \text{for } k = 1, 2, 3, \ldots \tag{33}$$

$$v(1) - v(0) = 0. \tag{34}$$

Let us define $v_{ci}(k)$ as the solution to

$$\frac{Z}{R}\{v(k-1) - 2v(k) + v(k+1)\} - v(k) = 0 \tag{35}$$

$$v(1) - v(0) = -1. \tag{36}$$

As shown in the Appendix A,

$$\overline{V}_{se}(X) = \frac{q}{\sinh qL}\left\{\cosh[q(X-L)]\int_0^X \cosh qX'\,\overline{U}(X')\,dX' + \cosh qX \int_X^L \cosh[q(X'-L)]\,\overline{U}(X')\,dX'\right\} \tag{37}$$

and

$$\overline{V}_{ci}(X) = \frac{\cosh[q(X-L)]}{q \sinh qL}. \tag{38}$$

The analogous two solutions for the axon problem (see Appendix A) are

$$v_{se}(k) = \left(\frac{R}{Z}\right)\frac{1}{2\sinh(D/\gamma)}\left\{u(1)\,e^{-kD/\gamma} + \sum_{j=1}^{\infty}\left[u(j)\,e^{-|k-j|D/\gamma} + u(j+1)\,e^{-(k+j)D/\gamma}\right]\right\} \tag{39}$$

and

$$v_{ci}(k) = \frac{e^{-kD/\gamma}}{1 - e^{-D/\gamma}}, \tag{40}$$

where γ is defined by $e^{D/\gamma} + e^{-D/\gamma} = 2 + R/Z$.

The solution $\overline{V}(X)$ for the average (over branches) internal potential in the dendritic tree coupled to the axon, and the solution $v(k)$ for the internal potential at the kth node in the axon coupled to the dendritic tree can be written

$$\overline{V}(X) = \overline{V}_{se}(X) + A\,\overline{V}_{ci}(X) \tag{41}$$

and

$$v(k) = v_{se}(k) + B\,v_{ci}(k). \tag{42}$$

The constants A and B can now be found by solving the following two equations:

$$v(0) = \overline{V}(0), \tag{43}$$

together with Eq. 27. These represent continuity of potential and current conservation at the soma, respectively.

Let us consider the case where there is no leakage of current across the soma (i.e., the impedance of the soma is large compared to the input impedance of the dendritic tree and axon). The case of a leaky soma is considered in Appendix D. In the case considered here Eqs. 41–44 give

$$A = \frac{q[\tanh qL][v_{se}(0) - \overline{V}_{se}(0)]}{1 + \left(\frac{Rq}{r_t\lambda_t}\right)\left(\frac{\tanh qL}{1 - e^{-D/\gamma}}\right)} \tag{44}$$

and

$$B = \frac{(1 - e^{-D/\gamma})[\overline{V}_{se}(0) - v_{se}(0)]}{1 + \left(\frac{r_t\lambda_t}{Rq}\right)\left(\frac{1 - e^{-D/\gamma}}{\tanh qL}\right)}. \tag{45}$$

Thus, Eqs. 37–42, 44, and 45 provide the general solution to the average (over branches) internal potential in the dendritic tree and the internal potential at the nodes of Ranvier in the axon when the neuron is subjected to a specified external potential.

APPLICATIONS

Polarization at the Soma

Because the soma is a site at which initiation of action potentials usually occurs, we will examine the potential there. When Eq. 41 is evaluated at $X = 0$, with A given by Eq. 44, one finds that $\bar{V}(0)$ is a linear combination (weighted average) of the sealed-end solutions for the dendritic tree and the axon

$$\bar{V}(0) = \alpha\, \bar{V}_{se}(0) + \beta v_{se}(0), \tag{46}$$

where

$$\alpha = \frac{1}{1 + \left(\dfrac{r_t\lambda_t}{R_q}\right)\left(\dfrac{1 - e^{-D/\gamma}}{\tanh qL}\right)} = \frac{Z_{se}^{in,ax}}{Z_{se}^{in,ax} + Z_{se}^{in,den}}, \tag{47}$$

and

$$\beta = 1 - \alpha = \frac{1}{1 + \left(\dfrac{Rq}{r_t\lambda_t}\right)\left(\dfrac{\tanh qL}{1 - e^{-D/\gamma}}\right)} = \frac{Z_{se}^{in,den}}{Z_{se}^{in,ax} + Z_{se}^{in,den}}, \tag{48}$$

and where $Z_{se}^{in,den}$ and $Z_{se}^{in,den}$ are the sealed-end input impedances of the dendritic tree and axon, respectively.

Note that, because the coefficients of $\bar{V}_{se}(0)$ and $v_{se}(0)$ in Eq. 46 sum to 1, the net internal potential $\bar{V}(0)$ lies between $\bar{V}_{se}(0)$ and $v_{se}(0)$.

It is the transmembrane potential at the soma, $\bar{V}(0) - \bar{U}(0)$, which is of physiological significance. If we use Eq. 46 for $\bar{V}(0)$, then the membrane potential at the soma can be expressed as

$$\bar{V}(0) - \bar{U}(0) = \alpha[\bar{V}_{se}(0) - \bar{U}(0)] + \beta[v_{se}(0) - u(0)], \tag{49}$$

where we have made use of the facts that $\bar{U}(0) = u(0)$, $\alpha + \beta = 1$, and $\bar{U}(0) = \alpha\bar{U}(0) + \beta u(0)$. Eq. 49 says that the membrane potential at the soma in the intact neuron is a weighted average of two hypothetical membrane potentials, one corresponding to the neuron without an axon and the other to the neuron without the dendritic tree. In other words, the actual membrane polarization at the soma lies somewhere between that polarization obtained at the soma when the axon is cut off and the end is sealed and that polarization obtained at the soma when the dendritic tree is cut off and the end is sealed.

In certain limiting cases, the polarization at the soma is contributed entirely by either the axon or the dendritic tree. For example, in one limit, ($Z_{se}^{in,ax} \gg Z_{se}^{in,den}$) where the input impedance of the axon is much greater than that of the dendritic tree, β (Eq. 48) approaches zero and α approaches 1. That is, the polarization at the soma is contributed entirely by the dendritic tree. If, on the other hand, $Z_{se}^{in,den} \gg Z_{se}^{in,ax}$, then α (Eq. 47) approaches zero, and β approaches 1. Then the polarization at the soma is contributed entirely by the axon.

Polarization at the Nodes of Ranvier

Eqs. 42, 40, and 45 lead to the conclusion that the internal potential at the nodes of Ranvier in the intact neuron is given by the sum of two terms. One term is the sealed-end solution for the axon and another term that decays exponentially from the soma

$$v(k) = v_{se}(k) + \alpha[\bar{V}_{se}(0) - v_{se}(0)]\, e^{-kD/\gamma}, \tag{50}$$

where α is defined as in Eq. 48.

Spatially Uniform Applied Electric Fields and Straight Axons

In the remainder of this paper dealing with implications of the theoretical results above, we will focus attention on applied electric fields that are constant over space at each instant in time. This is the type of stimulus used in the experimental study of Chan and Nicholson (1986). The case where the axon is straight is particularly easy to analyze, because, in this case, the external potential at the kth node is given by $u(k) = u(0) + k\mu$. The constant μ is the external potential difference between nodes and is given by $\mu = -E_a D$, where E_a is the component of the electric field parallel to the axon (in the direction from soma to node 1), and D is the distance between nodes. The membrane potential at the kth node, $v(k) - u(k)$, takes the simple form (see Appendix A)

$$v(k) - u(k) = \left\{\alpha[\bar{V}_{se}(0) - \bar{U}(0)] + \beta\left(\frac{\mu}{1 - e^{-D/\gamma}}\right)\right\} e^{-kD/\gamma}. \tag{51}$$

Because the term $\mu/(1 - e^{-D/\gamma})$ is the membrane potential at the soma in the sealed end axon problem, Eq. 51 has a simple interpretation: The membrane potential at the kth node in the intact neuron is the membrane potential at the soma (the term in curly brackets) attenuated by a factor of $e^{-kD/\gamma}$.

An important implication of Eq. 51 is that the magnitude of the membrane potential in the semi-infinite axon is greatest at the soma and decreases exponentially with distance from the soma.

Site of Action Potential Initiation

If membrane polarization is sufficient to initiate an action potential in the axon-soma system, it seems plausible that the site of initiation is that which experiences the greatest polarization, i.e., the soma. Therefore, from Eq. 51 it appears that the threshold level for action potential initiation will first be reached at the soma when straight axons are subjected to (spatially) constant electric fields.

Interplay of Axon and Dendritic Tree: Soma Polarization

To consider selective modulation of the activity of specific morphological types of neurons, we need to know the relative contributions to the net polarization at the soma made by the dendritic tree and by the axon. Whether the axon and dendritic tree make antagonistic or synergistic contributions will be determined in part by the geometry of the neuron, and the sign of the net polarization will be determined by the weights with which the sealed-end solutions for the axon and dendritic tree are combined. Eq. 51 has several interesting implications with respect to these questions. According to Eq. 51 the membrane potential at the soma $v(0) - u(0)$ is given by

$$v(0) - u(0) = \alpha[\bar{V}_{se}(0) - \bar{U}(0)] + \beta\left[\frac{\mu}{1 - e^{-D/\gamma}}\right]. \qquad (52)$$

Eq. 52 can be worked into another form by algebraic manipulations that use the definition of α, and the facts that $\beta = 1 - \alpha$ and $\mu = -E_a D$:

$$v(0) - u(0) = \alpha\left\{[\bar{V}_{se}(0) - \bar{U}(0)] - \left[\left(\frac{r_t}{r_a}\right)\left(\frac{\lambda_t}{q \tanh qL}\right)E_a\right]\right\}, \qquad (53)$$

or equivalently

$$v(0) - u(0) = \alpha\left\{[\bar{V}_{se}(0) - \bar{U}(0)] - \left[\left(\frac{Z_{se}^{\text{in,den}}}{r_a}\right)E_a\right]\right\}, \qquad (54)$$

where r_a is the internal resistance per unit length of axon cylinder (i.e., $R = r_a D$). The first term in square brackets in Eq. 54 is the sealed-end membrane potential for the dendritic tree. The second term in square brackets is contributed by the axon; its magnitude increases with E_a, and increases with the ratio of the (sealed-end) input impedance of the dendritic tree to the axial resistance of the axons.

Heuristic Example with Semi-infinite Unbranched Dendrite

It is instructive to look at a simple case where the dendritic tree is simply a single unbranched dendrite of infinite length. In this case the solution for $\bar{V}_{se}(0)$ can be easily obtained by carrying out the integration in Eq. 37. One finds the well known result that $\bar{V}_{se}(0) - \bar{U}(0) = -(\lambda_t/q)E_d$, where E_d is the component of the field oriented along the dendrite (Rank, 1975). Therefore, because $\tanh qL \longrightarrow 1$ as $L \longrightarrow \infty$, Eq. 53 gives

$$v(0) - u(0) = -\alpha\left(\frac{\lambda_t}{q}\right)\left\{E_d + \left(\frac{r_t}{r_a}\right)E_a\right\}. \qquad (55)$$

The soma membrane potential is proportional to the sum of two terms: one is the component of the electric field oriented along the dendrite, and the other is the component of the field oriented along the axon but weighted by a factor of r_t/r_a. When the axon and dendrite form a single straight line, $E_{ax} = -E_d$, and

$$v(0) - u(0) = -\alpha\, E_d\left(\frac{\lambda_t}{q}\right)\left\{1 - \frac{r_t}{r_a}\right\}. \qquad (56)$$

Consequently, the sign of the soma membrane potential is simply determined by whether $r_t/r_a > 1$ or $r_t/r_a < 1$.

Finite Unbranched Dendrite

When the unbranched dendrite is finite in length, the net soma polarization is determined in part by the length of the dendrite. The solution for $\bar{V}_{se}(0)$ can be found again by integrating Eq. 37 to give

$$\bar{V}_{se}(0) - \bar{U}(0) = -\left(\frac{\lambda_t}{q}E_d\right)\left[\frac{\cosh qL - 1}{\sinh qL}\right], \qquad (57)$$

another well-known result (Sten-Knudsen, 1960; Rank, 1963, 1975). Eq. 53 in combination with Eq. 57 gives

$$v(0) - u(0) = -\alpha\left(\frac{\lambda_t}{q}\right) \cdot \left\{\left[\frac{\cosh qL - 1}{\sinh qL}\right]E_d + \left[\frac{1}{\tanh qL}\right]\left(\frac{r_t}{r_a}\right)E_a\right\}. \qquad (58)$$

Eq. 58 is similar to Eq. 55; both terms in square brackets approach 1 as L approaches ∞, and in the limit $L \longrightarrow \infty$ Eq. 58 becomes identical to Eq. 55. As the length of the dendrite increases from zero to ∞, the first term in square brackets in Eq. 58 increases from zero to 1, and the second term in square brackets decreases from ∞ to 1. (The right-hand side of Eq. 58 remains bounded because the coefficient α that multiplies the terms in curly brackets approaches zero as L approaches zero.)

When the length of the dendrite is small compared to the length constant λ_t ($L \ll 1$), the soma membrane potential is approximated by

$$v(0) - u(0) = -\left[\frac{D}{1 - e^{-D/\gamma}}\right]\left\{(qL)^2\left(\frac{r_a}{r_t}\right)E_d + E_a\right\}, \qquad (59)$$

provided that $r_t\lambda_t$ is of the same order of magnitude as R. Eq. 59 shows that the contribution made by the dendrite to the net soma polarization depends quadratically on the length of the dendrite when the length is small.

To get a better qualitative idea of how the length of the dendrite affects the soma membrane potential, we consider the situation where the dendrite and axon are oriented along a single straight line. Fig. 3 is a plot of the soma membrane potential versus the electrotonic length L of dendrite.

All computations in Fig. 3 were for a DC stimulus (or one of sufficiently low frequency such that $q \approx 1$). The combination of parameters $-E_d \cdot \lambda_t$, the sealed-end membrane potential at the soma end in the semi-infinite dendrite, was set equal to 1 mV. We have assumed, arbitrarily, that $e^{-D/\gamma}$, the internodal signal attenuation

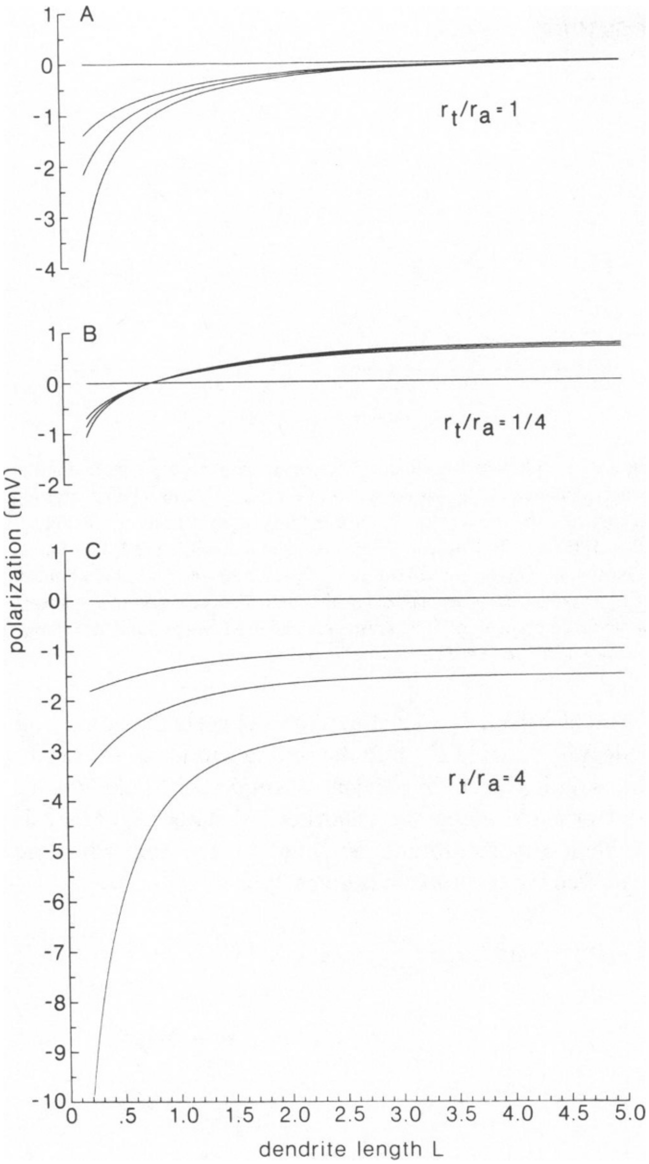

FIGURE 3 The soma membrane potential for a neuron subjected to a constant field for various dendrite/axon geometries. The neuron has a "dendritic tree" consisting of a single unbranched dendrite of finite length L. The dendrite and axon form a single straight line, and the field is oriented parallel to this line as in Fig. 1 *B*. Panels *A*, *B*, and *C* plot the soma membrane potential as a function of electrotonic length of the dendrite L, for different ratios of r_t and r_a, where r_t is the internal resistance per unit length of dendrite, and r_a is the corresponding resistance for the axon. Each panel contains three curves corresponding to three different ratios of the DC cable (length) constant of the dendrite λ_t and the internodal spacing for the axon D: $\lambda_t/D = 1$ (*upper curve*), $\lambda_t/D = 1/2$ (*middle*), $\lambda_t/D = 1/10$ (*lower*). (Note that the sequence of curves reverses order with increasing L in *B*.) (*A*) $r_t/r_a = 1$. (*B*) $r_t/r_a = 1/4$. (*C*) $r_t/r_a = 4$. Negative ordinates indicate hyperpolarization relative to the resting level, positive values, depolarization. For $r_t/r_a = 1$, as in *A*, the soma is always hyperpolarized for a short length of dendrite, but the resting membrane potential is unperturbed by the field when the dendrite is long. For $r_t/r_a < 1$, as in *B*, the soma is hyperpolarized for short dendrites and depolarized for long dendrites. For $r_t/r_a > 1$, as in *C*, the soma is always hyperpolarized regardless of the length of dendrite.

factor, is equal to ½. In Fig. 3 *A* the axial resistances of dendrite and axon are equal ($r_t = r_a$); the three curves correspond to different ratios λ_t/D as indicated by the labels on the curves. When $r_t = r_a$, and $E_d < 0$, the soma is hyperpolarized for any finite length of dendrite. As $L \longrightarrow \infty$, the soma membrane potential approaches zero.

In Fig. 3 *B*, $r_t < r_a$; the soma is hyperpolarized for a short length of dendrite, and, for a sufficiently long dendrite, the soma is depolarized.

In Fig. 3 *C*, $r_t > r_a$, and the soma is hyperpolarized for all lengths of dendrite.

ORIENTATION EFFECTS

When a neuron is subjected to a (spatially) constant electric field, the net soma polarization is determined in part by the orientation with respect to the field of the various dendritic branches and the axon. Here we consider a simple example where the dendritic tree is Y-shaped with a trunk and two daughter branches (Fig. 4). The trunk is oriented at an angle θ_1 with respect to the electric field E, and the daughter branches are oriented at angles θ_2 and $-\theta_2$ with respect to the trunk. The physical length of the trunk is $L_0\lambda_0$, and the physical length of each daughter branch is $L_1\lambda_1$. (Note that $\lambda_1 = 2^{-1/3}\ \lambda_0$ and that λ_t is equivalent to λ_0.) The axon is oriented at an angle ϕ with respect to E.

The first step in the solution of this problem is to find the sealed end membrane potentials for the dendritic tree and the axon. The sealed end membrane potential for the dendritic tree evaluated at the soma is given by (see

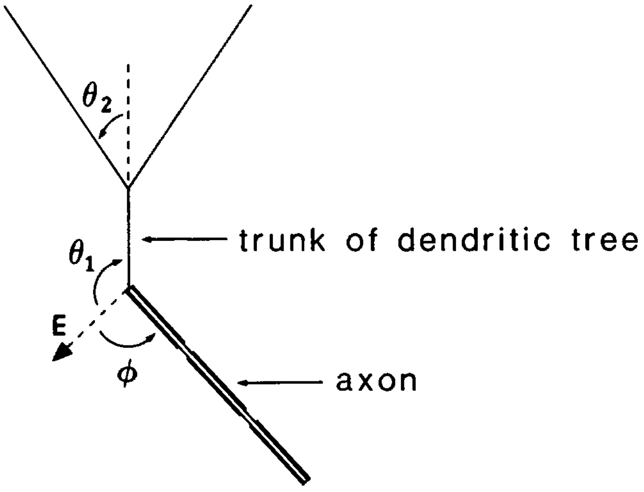

FIGURE 4 Orientation effects. A neuron with a simple dendritic tree is depicted. There is only one generation of branching, and the tree is Y-shaped. The field E is oriented at an angle θ_1 with respect to the trunk of the dendritic tree. The daughter branches branch at an angle θ_2 with respect to the trunk. The field is oriented at an angle ϕ with respect to the axon. The equation for the membrane potential at the soma for the neuron is given by Eq. 61 in the text. Fig. 5 shows how the soma membrane potential depends on the branching angle θ_2.

Appendix A)

$$\bar{V}_{se}(0) - \bar{U}(0) = -E\left(\frac{\lambda_0}{q}\right)\frac{1}{\sinh qL}$$
$$\cdot \{\cos\theta_1 (\cosh \mathrm{qL} - \cosh qL_1)$$
$$+ 2^{-1/3} (\cos\theta_1 \cos\theta_2) [\cosh qL_1 - 1]\}, \quad (60)$$

where $L = L_0 + L_1$.

Eq. 60 with Eq. 53 gives the solution for the soma membrane potential in the intact neuron

$$v(0) - u(0) = -\alpha E\left(\frac{\lambda_t}{q}\right)\left\{\frac{1}{\sinh qL}[\cos\theta_1(\cosh qL - \cosh qL_1)\right.$$
$$+ 2^{-1/3}(\cos\theta_1 \cos\theta_2)(\cosh qL_1 - 1)]$$
$$\left. + \left(\frac{r_t}{r_a}\right)\cos\theta\frac{1}{\tanh qL}\right\}. \quad (61)$$

The relative magnitudes of the various terms in Eq. 61 are more apparent when the term sinh qL is factored out of the curly brackets to give

$$v(0) - u(0) = \frac{-\alpha E}{\sinh qL}\left(\frac{\lambda_t}{q}\right)\left\{\cos\theta_1(\cosh qL - \cosh qL_1)\right.$$
$$+ 2^{-1/3}(\cos\theta_1 \cos\theta_2)(\cosh qL_1 - 1)$$
$$\left. + \left(\frac{r_t}{r_a}\right)\cos\theta \cosh qL\right\}. \quad (62)$$

The first, second and third terms in curly brackets in Eq. 62 are contributed by the dendritic tree trunk, the branches, and the axon, respectively.

For the sake of estimating the contribution of the dendritic tree (whose total electronic length is L) toward the soma membrane potential it is interesting to note that it can be no greater than the contribution made by a single unbranched dendrite (of length L) oriented in the direction of the field.

Fig. 5 shows how the soma membrane potentials for different ratios of λ to D, for the neuron in Fig. 4, depends on the angle the daughter dendritic branches make with respect to the electric field.

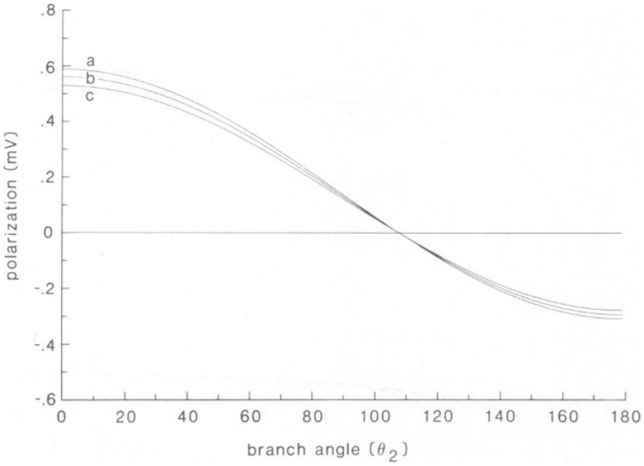

FIGURE 5 Orientation effects. The soma membrane potential for the neuron depicted in Fig. 4 is plotted as a function of the branching angle θ_2. In this case the trunk and axon are both oriented parallel to the field E (θ_1 = 180°; ϕ = 0). Curves a, b, c correspond to λ_t/D = 1/10, 1/2, and 1, respectively. This figure demonstrates how, for a given field, a neuron can be hyperpolarized or depolarized at the soma, depending on the geometry of dendritic branching. The parameters in Eq. 61 were chosen as follows: $-E\lambda_t = 1$ mV; $L = 4$; $L_1 = 3.5$; $e^{-D/\gamma} = 0.5$.

Neurons with Bent Axons

In the foregoing examples of all the axons were straight with no bends. Because many neurons do not have such axons, it is worthwhile to investigate other axon geometries where the analytic solutions are still relatively easy to obtain. The case where the axon is piecewise straight with one bend at a node of Ranvier is only somewhat more difficult than the straight axon case. The complete solution to this problem (still for spatially constant electric field) is provided in Appendix A.

We present the solution for the soma membrane potential in an idealized example (Fig. 6) where the dendritic tree is comprised of a single, unbranched dendrite finite in length. The axon has a bend at node M. The component of the field oriented along the axon between the soma and node M is denoted E_{a_0}, and the component along the rest of the axon is E_{a_1}. As in previous examples, the field component oriented along the dendrite is denoted E_d. For this problem the membrane potential at the soma for the sealed-end axon problem is given by

$$v_{se}(0) - u(0) - \frac{-D}{1 - e^{-D/\gamma}}\{E_{a_0} + e^{-MD/\gamma}(E_{a_1} - E_{a_0})\}. \quad (63)$$

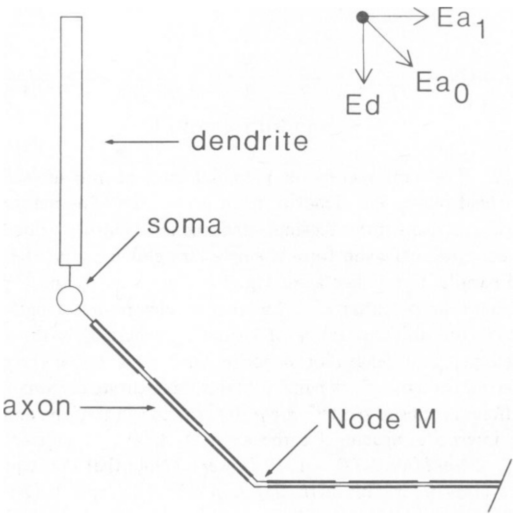

FIGURE 6 Axon with a bend. As shown in the text, polarization can be focused at the bend if the discontinuity in the component of the field oriented along the axon is sufficiently great at the bend. Thus, a bend, such as that labeled node M, is another likely site for action potential initiation when a neuron is subjected to a spatially constant electric field. The equation for the soma membrane potential for the neuron depicted here is given by Eq. 64 in the text.

Interestingly, a great deal of the soma polarization that is contributed by the axon is contributed by the segment between the soma and node 1. To see this, let us look first at the case where the bend is put at $M = \infty$ so that it is as if the axon has no bend at all. In this case the sealed-end soma membrane potential is equal to $-DE_{a_0}/(1 - e^{-D/\gamma})$. Now let us look at the situation where the bend is at node 1, and the electric field E_{a_1} along the bulk of the axon is equal to zero, and the sealed-end soma membrane potential is equal to $-DE_{a_0}$. The membrane potentials for these two situations differ only by a factor of $1/(1 - e^{-D/\gamma})$. This factor is equal to 2 if the internodal signal attenuation factors, $e^{-D/\gamma}$, is equal to ½.

The soma membrane potential for the intact neuron depicted in Fig. 6 is given by

$$v(0) - u(0) = -\alpha\left(\frac{\lambda_t}{q}\right)\left\{\left[\frac{\cosh qL - 1}{\sinh qL}\right]E_d + \left[\frac{1}{\tanh qL}\right]\left(\frac{r_t}{r_a}\right)[E_{a_0} + e^{-MD/\gamma}(E_{a_1} - E_{a_0})]\right\}. \quad (64)$$

Action Potential Initiation at a Bend

A straight axon subjected to a constant electric field suffers the greatest polarization at the soma end. If the axon has a bend, however, the polarization at the bend can be greater than that at nearby nodes on either side of it, and the polarization may be great enough to initiate an action potential at the bend.

The simplest example to consider, to get a qualitative idea of the importance of the bend, is the situation in which the bend is many nodes from the soma end. In this case (according to the solution in Appendix A) the membrane potential falls off exponentially with node number for nodes on one side of the bend and approximately exponentially for nodes on the other (soma) side of the bend. The membrane potential at the bend $w(M)$ is approximately given by

$$w(M) \approx (E_{a_0} - E_{a_1})D\left[\frac{e^{-D/\gamma}}{(1 + e^{-D/\gamma})(1 - e^{-D/\gamma})}\right]. \quad (65)$$

If, for example, the internodal signal attentuation factor $e^{-D/\gamma}$ is equal to ½, then $w(M) \approx (2/3)(E_{a_0} - E_{a_1})D$.

DISCUSSION

Assumptions of the Model

The dendritic tree was idealized in two ways. The tree branched symmetrically and the diameter of each daughter branch was related to that of the parent branch by the 3/2-power rule of Rall. A great simplification in this problem was achieved by noting that, for the purpose of determining the membrane potential at the soma and at the nodes of Ranvier, it is not necessary to solve for the membrane potential at every point in the dendritic tree. Rather, it suffices to solve for the average (over branches) of the membrane potential at each electronic distance X from the soma. The membrane potential at a given position X in the equivalent cylinder can be interpreted as the average of the membrane potential for all points in the dendritic tree that are a distance X from the soma.

Because our model is linear, it makes predictions only about membrane polarization for the subthreshold behavior of the neuron. At least in cerebellar Purkinje cells, nonlinear dendritic conductances (calcium spikes) only seem to be activated at levels of depolarization that significantly exceed those necessary to generate somatic sodium-mediated action potentials (Chan et al., 1985).

We have assumed that the myelin sheath of the axon is a perfect insulator so that no current crosses the internodal membrane. This approximation may be inadequate (Barrett and Barrett, 1982; Funch and Faber, 1984; Blight, 1985), at least for certain neurons. The problem of an axon with a leaky myelin sheath is somewhat more complicated and is treated in Appendix B.

We have approximated the neural tissue, in which the neuron is embedded, as a bulk conductor of uniform conductivity. This approximation describes accurately the voltage one measures with a large-tipped microelectrode, as it is advanced through brain tissue, when an electric field is extrinsically applied (Chan and Nicholson, 1986). The neuron is assumed not to distort the applied field. This amounts to saying that the potential on the surface of the neuron is the same as that measured with the nearby electrode. The utility of the approximation is that it allows one to determine the external potential at a point on the neuron just by knowing its position, the macroscopic electric field, and the bulk impedance of the tissue. It is possible, although unlikely, that the external potential on the surface of the neuron differs significantly from the potential measured with a nearby electrode. It is important to note that, strictly speaking, there is not a single potential on the external surface of a dendrite at a particular distance from the soma because the dendrite is a cylinder. It is actually the radial average of the external potential at a particular distance from the soma which is called simply the external potential. Thus, even if the dendrite causes local distortions of the macroscopic electric field, the local variations of the external potential on the surface of the dendrite will probably average to give an external potential not significantly different from that predicted by the bulk conductor approximation.

Implications of the Model

If the dendritic tree has certain kinds of symmetry resulting in a constant value for the average external potential ($\bar{U}(X)$ = constant), then the dendritic tree contributes nothing to the polarization at the soma. This is because the term $\bar{V}_{se}(0) - \bar{U}(0)$ in Eq. 50 is then equal to zero. The soma polarization is contributed entirely by the axon, and its magnitude is a fraction β of the soma membrane for the sealed-end axon problem.

The membrane potential at the soma was shown to be given by a weighted average of the membrane potential for the isolated dendritic tree (sealed at the soma end) and the membrane potential for the isolated axon. The weights depended on the relative magnitudes of the input impedance for the dendritic tree and the axon.

The axon and dendritic tree may make antagonistic or synergystic contributions to the net soma polarization, depending on the orientation of the field with respect to these neural elements. The analysis indicated that, if a constant field is oriented along the length of the axon, and, if the diameter of the axon is greater than or equal to that of the dendritic trunk, the axon will contribute most to the net polarization at the soma. The polarization contributed by the axon is, of course, less if the axon is not oriented in the direction of the field or if the axon bends away from the field. A surprising result is that the first internodal segment of the axon can contribute a great deal to net polarization at the soma.

When a straight axon is subjected to a constant field, the membrane polarization is greatest at the soma and falls off exponentially with node number from the soma. In this situation, the soma seems a likely site for action potential initiation. In contrast, if the axon is bent, the polarization can be focused at the bend. In this case, when large fields are applied, the threshold for initiation of an action potential may be reached first at the bend. This "focusing" effect may be compared with that noted by Hentall (1985) who showed that axon terminals could experience maximum depolarization with focally applied (point source) electric fields.

APPENDIX A

The Sealed-end Solution for Equivalent Cylinders

The differential equation for the sealed-end potential is (Eq. 28)

$$\frac{1}{q^2}\frac{d^2\bar{V}}{dX^2} - \bar{V} = -\bar{U}, \quad 0 < X < L \tag{A1}$$

with boundary conditions (Eq. 29)

$$\frac{d\bar{V}}{dX} = 0, \quad \text{at } X = L \text{ and } X = 0. \tag{A2}$$

A standard technique for solving this problem is to define $\phi(X, X')$ as the solution to

$$\frac{1}{q^2}\frac{d^2\phi}{dX^2} - \phi = -\delta(X - X') \tag{A3}$$

with boundary conditions

$$\frac{d\phi}{dX} = 0 \quad \text{at } X = L \text{ and } X = 0, \tag{A4}$$

where $\delta(X)$ is the Dirac delta function. Then $\bar{V}(X)$ is given by

$$\bar{V}(X) = \int_0^L \phi(X, X')\,\bar{U}(X')\,dX'. \tag{A5}$$

Eq. A3 is equivalent to the pair of equations

$$\frac{1}{q^2}\frac{d^2\phi}{dX^2} - \phi = 0, \quad 0 < X < X', X' < X < L \tag{A6}$$

$$\frac{1}{q^2}\left\{\left.\frac{d\phi}{dX}\right|_{X=X'^+} - \left.\frac{d\phi}{dX}\right|_{X=X'^-}\right\} = -1. \tag{A7}$$

The solution to Eq. A6 is

$$\phi(X, X') = A\cosh(qX) \quad \text{for} \quad 0 < X < X', \tag{A8a}$$

and

$$\phi(X, X') = B\cosh[q(X - L)] \quad \text{for} \quad X' < X < L. \tag{A8b}$$

The constants A and B are determined from Eq. A7 and voltage continuity at $X = X'$: $\phi(X'^+, X') = \phi(X'^-, X')$. One finds that

$$A = \frac{q}{\sinh qL}\cosh[q(X' - L)], \tag{A9}$$

and

$$B = \frac{q}{\sinh qL}\cosh qX'. \tag{A10}$$

Eqs. A8–A10 together with Eq. A5 give the sealed-end solution Eq. 37.

The Sealed-end Solution for the Axon

The difference equation for the sealed-end axon problem is Eq. 33

$$\frac{Z}{R}\{v(k-1) - 2v(k) + v(k+1)\} - v(k) = -u(k) \quad \text{for } k = 1, 2, 3, \ldots. \tag{A11}$$

The sealed-end boundary condition at the soma is

$$v(1) - v(0) = 0. \tag{A12}$$

This problem can be solved by a superposition method. First, one formally extends the axon symmetrically to form an infinite axon. Then the external potentials at nodes 1, 2, 3, . . . are reflected about the point half way between node zero and node 1. In this way $u(0) = u(1)$; $u(-1) = u(2)$; $u(-2) = u(3)$; etc. This ensures, by symmetry, that no current will flow internally from node zero to node 1, or, equivalently, it ensures that $v(1) - v(0) = 0$. The superposition method involves solving the difference equation

$$\frac{Z}{R}\{\phi_j(k-1) - 2\phi_j(k) + \phi_j(k+1)\} - \phi_j(k) = -\delta_{kj}, \tag{A13}$$

where δ_{kj} is the Kronecker delta function. The solution to the extended axon problem can be expressed as

$$v_{se}(k) = \sum_{j=-\infty}^{\infty} u(j)\,\phi_j(k). \tag{A14}$$

The solution to Eq. A13 is

$$\phi_j(k) = \frac{R}{Z}\frac{1}{2\sinh(D/\gamma)}\,\mathrm{e}^{-|k-j|D/\gamma}, \tag{A15}$$

where γ is defined by the relation

$$\mathrm{e}^{D/\gamma} + \mathrm{e}^{-D/\gamma} = 2 + \frac{R}{Z}. \tag{A16}$$

Eq. A14 together with Eq. A15 gives the solution Eq. 39 for the sealed-end axon problem.

Polarization of a Straight Axon in a Constant Field

An expeditious way to solve the sealed-end axon problem for the case of a spatially constant electric field is to solve directly for the membrane potential rather than the internal potential. The difference equation for the internal potential is Eq. A11. For a spatially constant field and a straight axon the external potential is of the form $u(k) = u(0) + k\mu$, where μ is the potential difference between two adjacent nodes. The spatially constant field affords a great simplification of the problem because $u(k-1) - 2u(k) + u(k+1) = 0$. Therefore the membrane potential $w(k) = v(k) - u(k)$ satisfies the difference equation

$$\frac{Z}{R}\{w(k-1) - 2w(k) + w(k+1)\} - w(k) = 0. \tag{A17}$$

A solution to Eq. A17 is $w(k) = A\,\mathrm{e}^{-kD/\gamma}$, where γ is defined by Eq. A16. The constant A can be found by satisfying the sealed-end boundary condition $v(1) - v(0) = 0$, which implies that $w(1) - w(0) = -\mu$. This relation gives $A = \mu/(1 - \mathrm{e}^{-D/\gamma})$. Therefore, the solution for the membrane potential is

$$w_{\mathrm{se}}(k) = v_{\mathrm{se}}(k) - u(k) = \frac{\mu}{1 - \mathrm{e}^{-D/\gamma}}\,\mathrm{e}^{-kD/\gamma}, \tag{A18}$$

where we have added the subscript to emphasize that this is the sealed-end solution.

To obtain the solution to the full problem (coupled axon and dendritic tree), we note that Eq. 51 implies that

$$v(k) - u(k) = v_{\mathrm{se}}(k) - u(k) + \alpha[\bar{V}_{\mathrm{se}}(0) - v_{\mathrm{se}}(0)]\mathrm{e}^{-kD/\gamma}. \tag{A19}$$

Using Eq. A18 for $v_{\mathrm{se}}(k) - u(k)$ gives

$$\begin{aligned} v(k) - u(k) &= \frac{\mu}{1 - \mathrm{e}^{-D/\gamma}}\,\mathrm{e}^{-kD/\gamma} + \alpha[\bar{V}_{\mathrm{se}}(0) - v_{\mathrm{se}}(0)]\mathrm{e}^{-kD/\gamma} \\ &= \left\{\frac{\mu}{1 - \mathrm{e}^{-D/\gamma}} + \alpha[\bar{V}_{\mathrm{se}}(0) - v_{\mathrm{se}}(0)]\right\}\mathrm{e}^{-kD/\gamma}. \end{aligned} \tag{A20}$$

Because $v_{\mathrm{se}}(0) - u(0) = \mu/(1 - \mathrm{e}^{-D/\gamma})$, and $1 - \alpha = \beta$, and $u(0) = \bar{U}(0)$, Eq. A20 can be rewritten as

$$v(k) - u(k) = \left\{\alpha[\bar{V}_{\mathrm{se}}(0) - \bar{U}(0)] + \beta\left(\frac{\mu}{1 - \mathrm{e}^{-D/\gamma}}\right)\right\}\mathrm{e}^{-kD/\gamma}. \tag{A21}$$

This is the result given in Eq. 52.

Polarizations of a Neuron with a Y-shaped Dendritic Tree

To compute the membrane potential at the soma we begin by computing the sealed-end, soma membrane potential for the dendritic tree. Using Eq. 37 we find that

$$\bar{V}_{\mathrm{se}}(0) = \frac{q}{\sinh qL}\int_0^L \cosh[q(X' - L)]\,\bar{U}(X')\,\mathrm{d}X'. \tag{A22}$$

This integral can be broken up conveniently into two integrals

$$\bar{V}_{\mathrm{se}}(0) = \frac{q}{\sinh qL}\left\{\int_0^{X_0} \cosh[q(X' - L)]\,\bar{U}(X')\,\mathrm{d}X' + \int_{X_0}^{L} \cosh[q(X' - L)]\,\bar{U}(X')\mathrm{d}X'\right\}, \tag{A23}$$

where X_0 is the branch point between the trunk and the two daughter branches.

To evaluate the integral in Eq. 23 we must find the average external potential $\bar{U}(X)$ for the two intervals $0 \leq X \leq X_0$ and $X_0 \leq X \leq L$. The component of the electric field along the trunk is E $\cos\theta_1$. If we define the external potential at the soma to be zero, for the sake of convenience, then the external potential at position x along the trunk is given by $u(x) = u(0) - (E\cos\theta_1)x$. In terms of the dimensionless position variable, $X = x/\lambda_0$, the external potential is given by

$$U^{(0,0)}(X) = \bar{U}(X) = \bar{U}(0) - (E\lambda_0\cos\theta_1)X, \quad \text{for } 0 \leqq X \leqq X_0. \tag{A24}$$

The component of the electric field (Fig. 4) along the left-hand daughter branch (indices 1, 0) is $E\cos(\theta_1 - \theta_2)$. The external potential for this branch is given, in terms of the physical distance x, by $u^{1,0}(x) = u^{1,0}(x_0) - [E\cos(\theta_1 - \theta_2)](x - x_0)$, where x_0 is the physical distance from the soma to the branch point, and $x_0 \leq x \leq d$. The external potential can be written in terms of the dimensionless distance X by taking note that $X - X_0 = (x - x_0)/\lambda_1$ (for x values in the daughter branch). Therefore,

$$U^{(1,0)}(X) = U^{(1,0)}(X_0) - [E\lambda_1\cos(\theta_1 - \theta_2)](X - X_0), \quad \text{for } X_0 \leqq X \leqq L. \tag{A25}$$

A similar argument can be used for the right-hand branch (Fig. 4) which has indices 1, 1. The component of the electric field along this branch is $E\cos(\theta_1 + \theta_2)$. Therefore,

$$U^{(1,1)}(X) = U^{(1,1)}(X_0) - [E\lambda_1\cos(\theta_1 + \theta_2)](X - X_0) \quad \text{for } X_0 \leqq X \leqq L. \tag{A26}$$

The average external potential for the first generation branches is given by $\bar{U}(X) = [U^{(1,0)}(X) + U^{(1,1)}(X)]/2$, with the result that

$$\bar{U}(x) = \bar{U}(X_0) - (E\lambda_1\cos\theta_1\cos\theta_2)(X - X_0) \quad \text{for } X_0 \leqq X \leqq L. \tag{A27}$$

Now the integrand in Eq. A23 can be evaluated by using Eqs. A24 and A27. The first integral in Eq. A23 can be evaluated to give

$$\begin{aligned} &\int_0^{X_0} \cosh[q(X' - L)]\,\bar{U}(X')\,\mathrm{d}X' \\ &= \int_0^{X_0} \cosh[q(X' - L)]\{\bar{U}(0) - (E\lambda_0\cos\theta_1)X'\}\,\mathrm{d}X' \\ &= \int_0^{X_0} \cosh[q(X' - L)]\,\bar{U}(0)\mathrm{d}X' - \frac{E\lambda_0\cos\theta_1}{q} \\ &\quad \cdot \left\{X_0\sinh[q(X_0 - L)] - \frac{\cosh[q(X_0 - L)]}{q} + \frac{\cosh qL}{q}\right\}. \end{aligned} \tag{A28}$$

The second integral in Eq. A23 can be evaluated to give

$$
\begin{aligned}
&\int_{X_0}^{L} \cosh\,[q(X'-L)]\,\bar{U}(X')\,\mathrm{d}X' \\
&\quad= \int_{X_0}^{L} \cosh\,[q(X'-L)]\{\bar{U}(X_0) \\
&\qquad - (E\lambda_1 \cos\theta_1 \cos\theta_2)(X'-X_0)\}\,\mathrm{d}X' \\
&\quad= \int_{X_0}^{L} \cosh\,[q(X'-L)]\,\bar{U}(X_0)\,\mathrm{d}X' \\
&\qquad - \frac{E\lambda_1 \cos\theta_1 \cos\theta_2}{q}\left\{\frac{\cosh\,[q(X_0-L)]}{q} - \frac{1}{q}\right\} \\
&\quad= \int_{X_0}^{L} \cosh\,[q(X'-L)]\{\bar{U}(0) - E\lambda_0 \cos\theta_1\, X_0\}\,\mathrm{d}X' \\
&\qquad - \frac{E\lambda_1 \cos\theta_1 \cos\theta_2}{q}\left\{\frac{\cosh\,[q(X_0-L)]}{q} - \frac{1}{q}\right\} \\
&\quad= \int_{X_0}^{L} \cosh\,[q(X'-L)]\,\bar{U}(0)\,\mathrm{d}X' \\
&\qquad + \frac{E\lambda_0 \cos\theta_1}{q} X_0 \sinh\,[q(X_0-L)] \\
&\qquad - \frac{E\lambda_1 \cos\theta_1 \cos\theta_2}{q}\left\{\frac{\cosh\,[q(X_0-L)]}{q} - \frac{1}{q}\right\}. \qquad \text{(A29)}
\end{aligned}
$$

Eqs. A28 and A29 together with Eq. A23 give

$$
\begin{aligned}
\bar{V}_{se}(0) - \bar{U}(0) = &- E\left(\frac{\lambda_0}{q}\right)\frac{1}{\sinh qL}\{\cos\theta_1(\cosh qL - \cosh qL_1) \\
&+ 2^{-1/3}(\cos\theta_1 \cos\theta_2)\,[\cosh qL_1 - 1]\}, \qquad \text{(A30)}
\end{aligned}
$$

where we have used the fact that $\lambda_1 = 2^{-1/3}\lambda_0$ and the definition $L_1 = L - X_0$. This is the result given in Eq. 61.

Axon with a Bend

Here we derive the solution for the membrane potential at the nodes of Ranvier for a neuron whose axon is piecewise straight with one bend at the Mth node of Ranvier. In this problem the field is spatially constant. Let us begin by solving for the sealed-end potential for the axons. Because the field is constant between node zero and node M, the sealed-end membrane potential $w_{se}(k) = v_{se}(k) - u(k)$ satisfies the difference Eq. A17 for nodes $1, 2, 3, \ldots M-1$. Eq. A17 has two solutions $e^{-kD/\gamma}$ and $e^{kD/\gamma}$. Both solutions are permissible because $0 \leqq k \leqq M$, and there is no problem with the positive exponential term approaching infinity. Therefore the membrane potential for $0 \leqq k \leqq M$ can be expressed as a linear combination of the two exponentials.

$$
w_{se}(k) = Ae^{-kD/\gamma} + Ce^{kD/\gamma}, \quad \text{for } 0 \leqq k \leqq M. \qquad \text{(A31)}
$$

Because the field is also constant for $k \geqq M$, the membrane potential for this segment also has an exponential solution. This time the term with the positive exponent must be discarded because the membrane potential must remain finite as $k \rightarrow \infty$. Therefore,

$$
w_{se}(k) = Be^{-(k-M)D/\gamma}, \quad \text{for } k \geqq M. \qquad \text{(A32)}
$$

The constants A, B, and C in Eqs. A31 and A32 can be found by satisfying three conditions: First, we are looking for a sealed-end solution, so $v_{se}(1) - v_{se}(0) = 0$. This implies that $w_{se}(1) - w_{se}(0) = u(0) - u(1)$. If the component of the electric field along the first segment of the axon is E_{a_0}, then $u(0) - u(1) = E_{a_0}D$, where D is the distance between nodes. Therefore, we have the boundary condition

$$
w_{se}(1) - w_{se}(0) = E_{a_0}D. \qquad \text{(A33)}
$$

Second, the solution must satisfy the condition of voltage continuity at node M. This implies that $w_{se}^{+}(M) = w_{se}^{-}(M)$, where the plus and minus superscripts are used to denote the solutions for the regions $k \geqq m$ and $0 \leqq k \leqq m$, respectively. Thus

$$
Ae^{-MD/\gamma} + Ce^{MD/\gamma} = B. \qquad \text{(A34)}
$$

Third, the solution must satisfy the condition of current conservation at node M

$$
\left[\frac{v_{se}(m-1) - v_{se}(m)}{R}\right] - \left[\frac{v_{se}(m) - v_{se}(m+1)}{R}\right] = \frac{w_{se}(m)}{Z} \qquad \text{(A35a)}
$$

or

$$
\begin{aligned}
&w_{se}(m-1) - 2w_{se}(m) + w_{se}(m+1) - \frac{R}{Z} w_{se}(M) \\
&\quad = [u(m) - u(m-1)] + [u(m) - u(m+1)] \qquad \text{(A35b)}
\end{aligned}
$$

or

$$
\begin{aligned}
&w_{se}(m-1) - 2w_{se}(m) + w_{se}(m+1) \\
&\quad - \frac{R}{Z} w_{se}(m) = (E_{a_1} - E_{a_0})D, \qquad \text{(A35c)}
\end{aligned}
$$

where E_{a_1} is the component of the electric field oriented along the axon for $k \geqq M$.

One can now solve for the constants A, B, and C by solving Eqs. A33, A34, and A35 simultaneously. The results are

$$
C = -\frac{D}{1 - e^{-D/\gamma}} \frac{e^{-(M+1)D/\gamma}}{1 + e^{-D/\gamma}} (E_{a_1} - E_{a_0})
$$

$$
A = -\frac{D}{1 - e^{-D/\gamma}} \left\{E_{a_0} + e^{-MD/\gamma} \frac{(E_{a_1} - E_{a_0})}{1 + e^{-D/\gamma}}\right\} \qquad \text{(A37)}
$$

$$
\begin{aligned}
B = &-\frac{D}{1 - e^{-D/\gamma}} \\
&\cdot \left\{\frac{(E_{a_1} - E_{a_0})}{1 + e^{-D/\gamma}}\,[e^{-D/\gamma} + e^{-2MD/\gamma}] + E_{a_0}e^{-MD/\gamma}\right\}. \qquad \text{(A38)}
\end{aligned}
$$

Now that A, B, and C have been determined the sealed-end solution can be written explicitly. Eq. A31 with Eqs. A36 and A37 gives

$$
\begin{aligned}
w_{se}(k) = &-\frac{D}{1 - e^{-D/\gamma}} \left\{\left[E_{a_0} + e^{-MD/\gamma} \frac{(E_{a_0} - E_{a_1})}{1 + e^{-D/\gamma}}\right] e^{-kD/\gamma}\right. \\
&\left. + e^{-D/\gamma} \frac{(E_{a_0} - E_{a_1})}{1 + e^{-D/\gamma}} e^{(k-M)D/\gamma}\right\}, \quad \text{for } 0 \leqq k \leqq M. \qquad \text{(A39)}
\end{aligned}
$$

If the sealed-end membrane potential (Eq. A39) is evaluated at the soma ($k = 0$), we obtain

$$
\begin{aligned}
w_{se}(0) = v_{se}(0) - u(0) = &-\frac{D}{1 - e^{-D/\gamma}} \\
&\cdot \{E_{a_0} + e^{-MD/\gamma}(E_{a_1} - E_{a_0})\}. \qquad \text{(A40)}
\end{aligned}
$$

This is the result given in Eq. 63.

The polarization at the nodes of Ranvier for the full neuron model can be computed by using Eq. A39 with Eq. 51. In the following we will derive only the solution for the soma (node zero) membrane potential for the idealized neuron considered in the text. This neuron has a dendritic tree consisting only of a single unbranched dendrite that is finite in length. According to Eq. 50

$$v(0) - u(0) = \alpha[\bar{V}_{se}(0) - \bar{U}(0)] + \beta[v_{se}(0) - u(0)]. \quad \text{(A41)}$$

Using the fact that $\beta = 1 - \alpha$ and the definition of α, Eq. A41 can be rewritten as

$$v(0) - u(0) = \alpha \left\{ [\bar{V}_{se}(0) - \bar{U}(0)] + \left(\frac{r_t \lambda_t}{r_a D q}\right)\left(\frac{1 - e^{-D/\gamma}}{\tanh qL}\right)[v_{se}(0) - u(0)] \right\}. \quad \text{(A42)}$$

Eq. A42 with Eqs. A40 and 57 gives the desired result (Eq. 64)

$$v(0) - u(0) = -\alpha\left(\frac{\lambda_t}{q}\right)\left\{\left[\frac{\cosh qL - 1}{\sinh qL}\right]E_d + \frac{1}{\tanh qL}\left(\frac{r_t}{r_a}\right)[E_{a_0} + e^{-MD/\gamma}(E_{a_1} - E_{a_0})]\right\}. \quad \text{(A43)}$$

APPENDIX B

Axon with a Leaky Myelin Sheath

If the myelin sheath surrounding the axon is leaky to the extent that current crossing the sheath is appreciable compared to the current crossing the nodes of Ranvier, then the axon model presented in the text is inadequate. If current does leak out of the axon in the internodal segments, then each internodal segment is equivalent mathematically to a dendrite.

The following approach is closely related to that of Andrietti and Bernardini (1984). Let us define $v_k(x)$ as the internal potential in the axon for the segment between nodes k and $k + 1$. This potential satisfies the differential equation (Eq. 10), as in the case of the dendrite,

$$\frac{\lambda^2}{q^2}\frac{d^2 v_k}{dx^2} - v_k = -u. \quad \text{(B1)}$$

The term λ in Eq. B1 is the DC space constant for an internodal segment of the axon. Here as in the text, to obtain specific results, we will confine our attention to the case of a spatially constant external electric field and a straight axons. In this case $u(x) = u(0) - E_a x$. Let us define $w_k(x)$ as the membrane potential $v_k(x) - u(x)$ for the kth axonal segment. Because the second derivative of the linear function $u(x)$ is equal to zero, $w_k(x)$ satisfies

$$\frac{\lambda^2}{q^2}\frac{d^2 w_k}{dx^2} - w_k = 0. \quad \text{(B2)}$$

Eq. B12 has two exponential solutions $e^{-qx/\gamma}$ and $e^{qx/\gamma}$, so the solution can be written as a linear combination of these to give

$$w_k(x) = \alpha_k e^{-q(x-kD)/\lambda} + \beta_k e^{q(x-kD)/\lambda}. \quad \text{(B3)}$$

The constants α_k and β_k for each segment can be found by satisfying the conditions of voltage continuity and current conservation at the nodes of Ranvier.

One fairly expeditious way to proceed with this problem is to define m_k as the solution for the membrane potential at node k. If all the m_k's were known this would determine the solution in the internodal region as well, by the following argument. Let us define $x_k = kD$ as the position of node k. Then the conditions that $w_k(x_k) = m_k$ and $w_k(x_k + 1) = m_k + 1$ give two equations that allow us to determine α_k and β_k, namely

$$\alpha_k + \beta_k = m_k \quad \text{(B4)}$$

and

$$\alpha_k e^{-qD/\gamma} + \beta_k e^{qD/\gamma} = m_k + 1. \quad \text{(B5)}$$

Of course, the m_k's are not known a priori; our approach will be to derive a difference equation for the m_k's. Solving Eqs. B4 and B5 for α_k and β_k gives

$$\alpha_k = \frac{m_k e^{qD/\lambda} - m_{k+1}}{e^{qD/\lambda} - e^{-qD/\gamma}} \quad \text{(B6)}$$

and

$$\beta_k = \frac{m_k + 1 - m_k e^{-qD/\lambda}}{e^{qD/\lambda} - e^{-qD/\lambda}}. \quad \text{(B7)}$$

Substituting Eqs. B67 and B7 into Eq. B3 gives

$$w_k(x) = \left(\frac{1}{e^{qD/\gamma} - e^{-qD/\gamma}}\right)\{[m_k e^{qD/\lambda} - m_{k+1}]e^{-q(x-kD)/\lambda} + [m_{k+1} - m_k e^{-qD/\gamma}]e^{q(x-kD)/\lambda}\}. \quad \text{(B8)}$$

Now the condition of current conservation at each node can be used to give a difference equation for the m_k's as follows.

$$\frac{1}{r}\left\{\frac{d}{dx}v_k(x)\bigg|_{x=x_k} - \frac{d}{dx}v_{k-1}(x)\bigg|_{x=x_k}\right\} = \frac{1}{Z}w_k(x_k), \quad \text{(B9a)}$$

which is equivalent to

$$\frac{d}{dx}w_k(x)\bigg|_{x=x_k} - \frac{d}{dx}w_k - 1(x)\bigg|_{x=x_k} = \frac{r}{Z}w_k(x_k), \quad \text{(B9b)}$$

where r is the internal resistance per unit length of axon, and Z is the impedance of a node of Ranvier. When Eq. B8 is substituted into Eq. B9b the following difference equation results

$$m_{k-1} - m_k\left[\left(1 + \frac{r\lambda}{2Zq}\right)e^{qD/\lambda} + \left(1 - \frac{r\lambda}{2Zq}\right)e^{-qD/\lambda}\right] + m_{k+1} = 0. \quad \text{(B10)}$$

Difference equations of the form of Eq. B10 have solutions of the form $m_k = C s^k$. Substituting $m_k = Cs^k$ into Eq. B10 gives a quadratic equation for s whose two roots are

$$s_\pm = \cosh\left(\frac{qD}{\lambda}\right) + \frac{1}{2}\left(\frac{r\lambda}{Zq}\right)\sinh\left(\frac{qD}{\lambda}\right) \pm \left\{\left[\cosh\left(\frac{qD}{\lambda}\right) + \frac{1}{2}\left(\frac{r\lambda}{Zq}\right)\sinh\left(\frac{qD}{\lambda}\right)\right]^2 - 1\right\}^{1/2}. \quad \text{(B11)}$$

In Eq. B11 s_- is the proper choice of the two roots, because $s_- < 1$ and $s_+ > 1$.

If $m_k = Cs^k$ is substituted in Eq. B8, the following solution results:

$$w_k(x) = \frac{Cs^k}{e^{qD/\lambda} - e^{-qD/\lambda}}\{[e^{qD/\lambda} - s]e^{-q(x-kD)/\lambda} + [s - e^{-qD/\lambda}]e^{q(x-kD)/\lambda}\}. \quad \text{(B12)}$$

The constant C in Eq. B12 is determined by the boundary condition at $x = 0$.

In analogy with the approach used with the simpler axon problem in the text, the axon solution for the coupled axon-dendritic tree problem can be expressed as a linear combination of the current-injection solution and the sealed-end solution. First, let us derive the sealed-end solution with the external potential that results from the field E. The sealed-end boundary condition,

$$\frac{\mathrm{d}}{\mathrm{d}x} v_0^{se}(x)\bigg|_{x=0} = 0, \tag{B13}$$

is equivalent to

$$\frac{\mathrm{d}}{\mathrm{d}x} w_0^{se}(x)\bigg|_{x=0} = E. \tag{B14}$$

Eq. B12 with boundary condition Eq. B14 gives

$$C = -E\left(\frac{\lambda}{q}\right)\frac{[\mathrm{e}^{qD/\lambda} - \mathrm{e}^{-qD/\lambda}]}{[\mathrm{e}^{qD/\lambda} + \mathrm{e}^{-qD/\lambda} - 2s]}. \tag{B15}$$

Thus, we have the following sealed-end solution (in which the subscript a has been added to some parameters to emphasize that these parameters are for the axon)

$$\begin{aligned} w_k^{se}(x) = {} & -E_a\left(\frac{\lambda_a}{q_a}\right)\left(\frac{1}{\mathrm{e}^{q_aD/\lambda_a} + \mathrm{e}^{-q_aD/\lambda_a} - 2s}\right) \\ & \cdot s^k\{[\mathrm{e}^{q_aD/\lambda_a} - s]\,\mathrm{e}^{-q_a(x-kD)/\lambda_a} \\ & + [s - \mathrm{e}^{-q_aD/\lambda_a}]\,\mathrm{e}^{q_a(x-kD)/\lambda_a}\}. \end{aligned} \tag{B16}$$

The internal potential $v_k^{se}(x)$ is given by

$$v_k^{se}(x) = w_k^{se}(x) + u(x) = w_k^{se}(x) + u(0) - Ex. \tag{B17}$$

For the current-injection solution, where the external potential and hence the field is zero for all x, we have boundary condition

$$\frac{\mathrm{d}}{\mathrm{d}x} v_0^{ci}(x)\bigg|_{x=0} = -1. \tag{B18}$$

This is equivalent to

$$\frac{\mathrm{d}}{\mathrm{d}x} w_0^{ci}(x)\bigg|_{x=0} = -1. \tag{B19}$$

Thus the current-injection solution $w_k^{ci}(x)$ is of the same form as the sealed-end solution $w_k^{se}(x)$ for the special case of constant field. The current-injection solution can be obtained formally by setting $E = -1$ in Eq. B16 (stemming from Eq. B19) and setting $u(0) = E = 0$ in Eq. B17 (from the condition of zero external potential) to give

$$\begin{aligned} v_k^{ci}(x) = {} & \left(\frac{\lambda_a}{q_a}\right)\left(\frac{1}{\mathrm{e}^{q_aD/\lambda_a} + \mathrm{e}^{-q_aD/\lambda_a} - 2s}\right) \\ & \cdot s^k\{[\mathrm{e}^{q_aD/\lambda_a} - s]\,\mathrm{e}^{-q_a(x-kD)/\lambda_a} \\ & + [s - \mathrm{e}^{-q_aD/\lambda_a}]\,\mathrm{e}^{q_a(x-kD)/\lambda_a}\}. \end{aligned} \tag{B20}$$

As in the simpler axon problem considered in the text, the axon solution for the full neuron can be expressed as

$$v_k(x) = v_k^{se}(x) + Bv_k^{ci}(x). \tag{B21}$$

The solution for the dendritic tree is expressed as a linear combination of two solutions identical to those used in the simpler problem:

$$\bar{V}(X) = \bar{V}_{se}(X) + A\,\bar{V}_{ci}(X). \tag{B22}$$

The constants A and B can be evaluated in the same manner used to evaluate the corresponding constants for the simpler problem examined in the text. For the problem considered here (again for nonleaky soma)

$$B = \frac{\dfrac{r_a}{r_t\lambda_t}[\bar{V}_{se}(0) - v_0^{se}(0)]}{\left(\dfrac{r_a\lambda_a}{r_t\lambda_t}\right)\left(\dfrac{1}{q_a}\right)\left[\dfrac{\mathrm{e}^{q_aD/\lambda_a} - \mathrm{e}^{-q_aD/\lambda_a}}{\mathrm{e}^{q_aD/\lambda_a} + \mathrm{e}^{-q_aD/\lambda_a} - 2s}\right] + \dfrac{1}{q_d \tanh q_d L}} \tag{B23}$$

and

$$A = -\frac{r_t\lambda_t}{r_a}B, \tag{B24}$$

where the subscript d has been used to denote dendrite.

Eqs. B23, B21, B20, B16, and B17 determine the solution for the internal potential in the leaky axon problem (provided that the sealed-end solution for the dendritic tree is known).

As in the simpler problem, the soma membrane potential can be expressed as a weighted average of the sealed-end membrane potentials for the dendritic tree and the axon

$$\begin{aligned} \bar{V}(0) - \bar{U}(0) = v_0(0) - u(0) = {} & \alpha'[\bar{V}_{se}(0) - \bar{U}(0)] \\ & + \beta'[v_0^{se}(0) - u(0)]. \end{aligned} \tag{B25}$$

The definition of α' is

$$\alpha' = \frac{1}{1 + \left(\dfrac{r_t\lambda_t q_a}{r_a\lambda_a q_d}\right)\left(\dfrac{1}{\tanh q_d L}\right)\left(\dfrac{\mathrm{e}^{q_aD/\lambda_a} + \mathrm{e}^{-q_aD/\lambda} - 2s}{\mathrm{e}^{q_aD/\lambda} - \mathrm{e}^{-q_aD/\lambda_a}}\right)} \tag{B26}$$

and $\beta' = 1 - \alpha'$.

It is interesting to note that the soma membrane potential for this problem (leaky myelin sheath, constant field, straight axon) is identical in form to that for the corresponding problem with a nonleaky myelin sheath (Eq. 54). The only difference in that α in Eq. 54 is replaced with α'. To see this rewrite Eq. B25 as

$$\begin{aligned} & v_0(0) - u(0) \\ & = \alpha'\left\{[\bar{V}_{se}(0) - \bar{U}(0)] + \left(\frac{1}{\alpha'} - 1\right)[v_0^{se}(0) - u(0)]\right\}. \end{aligned} \tag{B27}$$

Eqs. B16, B26, and B27 give

$$\begin{aligned} & v_0(0) - u(0) \\ & = \alpha'\left\{[\bar{V}_{se}(0) - \bar{U}(0)] - \left[\left(\frac{r_t}{r_a}\right)\left(\frac{\lambda_t}{q_d \tanh q_d L}\right)E_a\right]\right\}, \end{aligned} \tag{B28}$$

which is identical in form to Eq. 54. It can be shown that α' is an increasing function of λ_a with all other parameters held fixed. Thus introducing leakiness of the myelin sheath without changing any other parameters will cause α' to decrease from α to some other value. Therefore, Eq. B28 implies that leakiness of the myelin sheath (with all other things being equal) will attenuate the soma membrane potential but not change its sign.

APPENDIX C

Neurons with Several Dendritic Trees

This problem is not much different than the problem with a single dendritic tree. We introduce the index j for the dendritic tree, where j goes from 1 to N. The internal and external potentials are indexed by j, k, ℓ, where k and ℓ index the generation and branch as before. We treat each tree separately just as we treated the single dendritic tree before. Let us define $\tilde{V}^{(j)}(x)$ as the average internal potential for the jth tree (corresponding to $\bar{V}(x)$ for the single-tree problem). As in the single-tree problem, we write $\tilde{V}^{(j)}(X)$ as the sum of a sealed-end solution and a current-injection solution

$$\tilde{V}^{(j)}(X) = \tilde{V}_{\mathrm{se}}^{(j)}(X) + A_j \tilde{V}_{\mathrm{ci}}^{(j)}(X). \tag{C1}$$

As in the single-tree problem, the internal potential at the kth node of Ranvier in the axon can be written as

$$v(k) = v_{\mathrm{se}}(k) + B v_{\mathrm{ci}}(k). \tag{C2}$$

The constants A_j ($j = 1, 2, \ldots, N$) and B can be determined from the conditions of voltage continuity and current conservation at the soma. Voltage continuity gives

$$\tilde{V}^{(j)}(0) = v(0) \quad \text{for } j = 1, 2, 3, \ldots, N. \tag{C3}$$

Current conservation gives

$$\frac{v(0) - v(1)}{R} = \sum_{j=1}^{N} \frac{1}{r_{\mathrm{t}}^{(j)} \lambda_{\mathrm{t}}^{(j)}} \left. \frac{\mathrm{d}\tilde{V}^{(j)}}{\mathrm{d}X} \right|_{X=0}. \tag{C4}$$

After some algebraic manipulations, Eqs. C3 and C4 lead to solutions for B and A_j

$$\mathrm{B} = \frac{R \sum_{j=1}^{N} \frac{q_j \tanh q_j L_j}{r_{\mathrm{t}}^{(j)} \lambda_{\mathrm{se}}^{(j)}} [\tilde{V}_{\mathrm{se}}^{(j)}(0) - v_{\mathrm{se}}(0)]}{1 + \frac{R}{1 - \mathrm{e}^{-D/\gamma}} \sum_{j=1}^{N} \frac{q_j \tanh q_j L_j}{r_{\mathrm{t}}^{(j)} \lambda_{\mathrm{t}}^{(j)}}} \tag{C5}$$

$$A_j = q_j \tanh q_j L_j \left\{ [v_{\mathrm{se}}(0) - \tilde{V}_{\mathrm{se}}^{(j)}(0)] + \frac{B}{1 - \mathrm{e}^{-D/\gamma}} \right\}. \tag{C6}$$

The internal potential at the soma, in analogy with Eq. 47 for the single-tree problem, is

$$v(0) = \sum_{j=1}^{n} \alpha_j \tilde{V}_{\mathrm{se}}^{(j)}(0) + \beta v_{\mathrm{se}}(0), \tag{C7}$$

where

$$\alpha_j = \frac{\left(\frac{R}{1 - \mathrm{e}^{-D/\gamma}} \right) \left(\frac{q_j}{r_{\mathrm{t}}^{(j)} \lambda_{\mathrm{t}}^{(j)}} \right) \tanh q_j L_j}{1 + \frac{R}{1 - \mathrm{e}^{-D/\gamma}} \sum_{k=1}^{N} \frac{\mathrm{q}_k}{r_{\mathrm{t}}^{(\mathrm{k})} \lambda_{\mathrm{t}}^{(k)}} \tanh q_k L_k}, \tag{C8}$$

and

$$\beta = 1 - \sum_{j=1}^{N} \alpha_j. \tag{C9}$$

APPENDIX D

Leaky Soma

In our neural model the soma has been approximated as a point with a lumped impedance. In the steps following Eq. 44 of the text, we assumed that the impedance of the soma was infinitely large. The approximation is good if the soma impedance is large compared to the input impedance of the dendritic tree and that of the axon. If we relax this constraint and solve for A and B in Eq. 44, we find that

$$B = \frac{R \left\{ \left(\frac{1}{z_{\mathrm{soma}}} + \frac{q \tanh qL}{r_{\mathrm{t}} \lambda_t} \right) [\bar{V}_{\mathrm{se}}(0) - v_{\mathrm{se}}(0)] - \frac{[\bar{V}_{\mathrm{se}}(0) - \bar{U}(0)]}{Z_{\mathrm{soma}}} \right\}}{1 + \frac{R}{Z_{\mathrm{soma}}(1 - \mathrm{e}^{-D/\gamma})} + \frac{Rq \tanh qL}{r_{\mathrm{t}} \lambda_{\mathrm{t}} (1 - \mathrm{e}^{-D/\gamma})}} \tag{D1}$$

$$A = q \tanh qL \left\{ [v_{\mathrm{se}}(0) - \bar{V}(0)] + \frac{B}{1 - \mathrm{e}^{-D/\gamma}} \right\}. \tag{D2}$$

In this problem, as in the case of the nonleaky soma, the membrane potential at the soma can be expressed as a linear combination of the sealed-end membrane potentials for the axon and the dendritic tree.

$$v(0) - u(0) = \alpha'' [\bar{V}_{\mathrm{se}}(0) - \bar{U}(0)] + \beta'' [v_{\mathrm{se}}(0) - u(0)], \tag{D3}$$

where

$$\alpha'' = \frac{Z_{\mathrm{soma}} Z_{\mathrm{se}}^{\mathrm{in,\,ax}}}{Z_{\mathrm{soma}} Z_{\mathrm{se}}^{\mathrm{in,\,den}} + Z_{\mathrm{soma}} Z_{\mathrm{se}}^{\mathrm{in,\,ax}} + Z_{\mathrm{se}}^{\mathrm{in,\,ax}} Z_{\mathrm{se}}^{\mathrm{in,\,den}}} \tag{D4}$$

and

$$\beta'' = \frac{Z_{\mathrm{soma}} Z_{\mathrm{se}}^{\mathrm{in,\,den}}}{Z_{\mathrm{soma}} Z_{\mathrm{se}}^{\mathrm{in,\,den}} + Z_{\mathrm{soma}} Z_{\mathrm{se}}^{\mathrm{in,\,ax}} + Z_{\mathrm{se}}^{\mathrm{in,\,ax}} Z_{\mathrm{se}}^{\mathrm{in,\,den}}} \tag{D5}$$

In the leaky soma case, $\alpha'' + \beta'' \leq 1$, and the equality holds only in the limit $Z_{\mathrm{soma}} \rightarrow \infty$.

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