Matching Dendritic Neuron Models to Experimental Data

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I. PROLOGUE

We are very pleased to contribute to this special issue commemorating the pioneering research contributions of Hodgkin, Huxley, and Katz. All of us have been greatly influenced and encouraged by their example of using theory to design experiments that yield values for

key model parameters. W. Rall was privileged to get an early glimpse of this research on the special occasion when Alan Hodgkin visited K. S. Cole at the University of Chicago, in the spring of 1948, and presented a biophysics seminar about research done at Plymouth, in September 1947, with Bernard Katz (51, 52; see Ref. 16, p. 267, and Ref. 49, p. 17). Later, W. Rall and J. J. B. Jack

were in Dunedin, New Zealand, on the special occasion when J. C. Eccles reported the exciting new results and interpretations of Hodgkin, Huxley, and Katz that he had learned from attending a Cold Spring Harbor Symposium on Quantitative Biology (June, 1952). Thus the classic series of papers, published in the *Journal of Physiology (London)* in 1952, did not come as a surprise to us in Dunedin; it came rather as an impressive fulfillment of expectations already raised.

The concept of separating the ionic fluxes and treating them as electric currents governed by a time-varying conductance and a time-varying difference of potential (membrane potential minus ionic reversal potential) was of critical importance. It facilitated both qualitative thinking about membrane phenomena and quantitative treatment of experimental data. This concept also was central to thinking about neuromuscular junctions (33) and synapses (19) and to the modeling of synaptic conductance transients in dendrites (97, 99). The subsequent realization of ionic conductance in terms of specific ion channels is a remarkable development that is covered in other reviews in this commemorative issue.

The explicit mathematical model presented by Hodgkin and Huxley (50) provided a giant step forward in capturing the nonlinear properties of nerve membrane. The effort to increase functional insight into this class of nonlinear dynamical systems was significantly advanced by FitzHugh (35) with his introduction of a nonlinear two-variable system (cubic BVP), which captured the essential qualitative nonlinear dynamics of nerve membrane. By studying this system in a two-dimensional phase space, FitzHugh was able to distinguish different physiological states: the resting point, the active region, the refractory regions (both absolute and relative), and regions of depressed and enhanced excitability, as well as "no man's land" (35). Many valuable insights related to the physiological states of classic physiology were communicated in this paper and in an outstanding review chapter (36). Fruitful study of this reduced system (now known as the FitzHugh-Nagumo equations) has continued. For example, by using a piecewise-linear approximation to the cubic nonlinearity, Rinzel and Keller (116) succeeded in solving this system of equations explicitly, providing pulse and periodic solutions together with a rigorous analysis of the stability of these solutions. Insights gained by using the phase-plane approach of the qualitative theory of differential equations can be found in two reviews (115, 116). In addition, the impact of the Hodgkin-Huxley equations on mathematical biology and applied mathematics has been reviewed recently (114).

II. INTRODUCTION

A. Some History

From the beginning, the conceptual models of nerve membrane of necessity emphasized nonlinear mem-

brane properties in idealized membrane cylinders, deliberately avoiding the complications posed by the branched geometry of neurons or nonuniform membrane properties. By concentrating on relatively simple reference cases, they provided strong intuitive insights that are the essential groundwork to understanding more complex situations. In the same spirit of not treating all complications at once, early models of dendritic neurons focused on analytical treatment of idealized dendritic branching and deliberately avoided the complications of nonlinear and nonuniform membranes. More recently, the challenge has been to extend cable theory to branched systems, still assuming a uniform passive membrane, to see if the results could be used to interpret experimental data obtained with intracellular microelectrodes placed in a neuron soma (13, 31, 67-69, 95-101, 105, 112).

Physiologically interesting properties, such as the amplitude decrement and temporal widening exhibited by a brief voltage transient propagating along a passive dendrite, as well as the effects of the possible boundary conditions at branch terminals and at branch points, have dominated the literature of neuronal models. These passive cable properties are sometimes referred to as passive membrane "electrotonus," following from the classic papers by Hodgkin and Rushton (54) and by Davis and Lorente de No (24). These authors followed the axonal core conductor tradition due to Hermann, who had recognized and avoided an erroneous theory of electrotonus that had been proposed by du Bois Reymond (see Refs. 8, 101, 145 for additional historical details and references). It seems fair to say that, over the past three decades, the idealized equivalent cylinder model (with uniform passive membrane and sealed ends) has provided widely accepted insights about the electrotonic properties of dendrites and their influence on synaptic events generated at different distances from the neuron soma (4, 60, 61, 64, 68, 97-99, 113, 116, 117).

B. Voltage-Dependent Membrane Conductances

It is abundantly clear that neurons contain many different types of ionic channels that open and close in response to changes in membrane potential (for reviews see Refs. 2, 47, 71, 78, 80, 118, 123, 124, 137; see other reviews in this commemorative issue). Different channel types are opened and closed at different membrane potentials, and it appears that in many neurons there is no potential (within the range from resting potential to threshold potential for spike initiation) at which the membrane behaves linearly, even for small voltage perturbations.

In the context of our present attempts to define passive cable models of a neuron, we consider two types of voltage-dependent conductances: 1) those that turn on or off without significant time delay (instantaneous voltage dependence) and that do not inactivate and 2)

those that exhibit time as well as voltage dependence, including conductances that inactivate and those where channels openings and closings lag the voltage change. From the standpoint of neuron modeling, the conductances with instantaneous voltage dependence pose less of a problem than those that exhibit time dependence.

The presence of nonlinear conductances in the cell under study can be recognized by their effect on membrane voltage perturbations introduced by current injection or by well-defined synaptic actions. Some of these membrane channels cause "sag" and rectification in the voltage response to a maintained current step (65, 138) and generate currents that do not return to baseline values when a voltage-clamp step is applied. They also generate a small undershoot that follows excitatory postsynaptic potentials (EPSPs) evoked in motoneurons, regardless of peak amplitude (67). A similar undershoot also appears after ~ 10 ms in the response of motoneurons to a brief (200 μ s) and small (1–2 nA) depolarizing or hyperpolarizing current (37, 64, 65, 152).

There are several approaches that can be taken to help avoid distortion of the passive neuron response by voltage-dependent currents. One is to specify (i.e., assume) the voltage-dependent response empirically and to subtract it from the observed response, leaving the passive response to be analyzed (11, 65, 152). The problem with this approach is that, at present, most active processes have been insufficiently characterized to allow an accurate empirical description, and the distribution of the responsible channels over the neuronal surface is largely unknown (see Ref. 37). Another approach is to remove the voltage-dependent currents by pharmacological procedures before making voltage- and current-clamp measurements (see Ref. 138). Although the procedures used by these authors did not remove all the active currents, such pharmacological removal may provide the best experimental approach in the future, as more is discovered about these currents.

A third method is to try to find a combination of membrane potential and quality of penetration conditions where obvious signs of active responses are missing or are very small. In some neurons the response to a brief current pulse, and the initial dendritic charging current in response to a voltage-clamp step, may appear to be sufficiently rapid as to be almost complete before an active response becomes significant. The problem is to demonstrate that this interpretation is true. Furthermore, if a measurement of neuron input resistance is an essential part of the analysis (as it usually is), it will be compromised by the presence of active conductances. In some situations the nonlinearities obviously dominate, as in several examples of computed antidromic impulse propagation along an axon to a soma with dendrites (26, 27, 110, 146; see also Ref. 44). In other cases, the effects of nonlinear membrane may be negligible, whereas in still others, the nonlinearity cannot be ignored but may still be manageable (see APPENDIX in Ref. 37). This third approach is the least satisfactory, but it may remain the only practical approach until the data required to use the other methods become available.

C. Linear Versus Nonlinear Models

It is important to emphasize that modeling of neurons today, given current access to computing power and sophisticated software, is not limited to passive membrane electrotonus. The compartmental model approach can incorporate both complex geometry and nonuniform membrane properties (including time- and voltage-dependent nonlinearities), provided that these attributes can be specified with reasonable detail (10, 32, 37, 83, 84, 98, 104, 110, 125, 129). Given this flexibility and the fact that most neuronal membranes exhibit nonlinear behavior over a wide range of conditions (see other reviews in this commemorative issue), one might ask whether passive neuronal models have outlived their utility. Our response to this question is twofold. First, neuronal models that have realistic morphological complexity introduce serious problems of interpretation that have not been fully explored with passive membrane assumptions. This review grew out of an extended discussion of such problems among the authors (see ACKNOWLEDGEMENT). Second, the relatively intuitive passive models provide reference cases that we believe are essential to the interpretation of more elaborate (and presumably more realistic) models with nonlinear properties. There are few, if any, neurons for which the densities, spatial distributions, and kinetics of time- and voltage-dependent conductances are known with any certainty (e.g., see Ref. 147). In such cases, empirical model results can lend support to initial assumptions; however, for neurons with complex geometry, the passive case will remain the essential reference against which to evaluate the changes introduced by membrane nonlinearities.

Neuron models can combine passive and active properties to obtain useful insights. For example, with the assumption of excitable properties in spine head membrane attached to passive dendritic shafts, computations have shown that synaptic input to a spine head could produce a local action potential in the spine head membrane for certain combinations of model parameters, leading to an increased amount of current delivered to the dendrite, thus amplifying the efficacy of the synapse (83, 90, 129; see also Ref. 20). Furthermore, with sufficient depolarization of local dendritic branches, nearby spine heads can fire action potentials without direct synaptic input, resulting in a chain reaction involving clusters of excitable spines. This can have, in principle, many interesting consequences for the processing and discrimination of different synaptic input combinations (108, 109, 133, 134). This type of result may direct future experimental tests of spine head membrane properties. Recently, there has also been considerable interest in the effect of localized concentrations of voltage-dependent conductances in particular parts of dendritic trees (77). Eventually, we anticipate development of dynamic neuronal models that can incorporate an arbitrarily complex assortment of morphological and electrophysiological specifications, including a variety of membrane nonlinearities.

D. Purpose of This Review

The reason for developing neuronal models is to provide a quantitative framework for studying the spread and summation of synaptic potentials in neurons. Our objective is to provide a conceptual basis for going beyond the idealized equivalent cylinder model toward less reduced systems. The discussion concentrates on neuronal representations that include dendrites of different electrical lengths and cases where the somatic and dendritic membrane resistivities differ. We do not consider cases with nonlinear membrane properties for the reasons outlined. This review is organized to provide some basic concepts needed to understand the electrotonic architecture of neurons and how this relates to cell morphology. Then we consider the problem of reconciling electrophysiological measurements with realistic representations of cell morphology and note some of the remaining uncertainties in this process. Finally, we mention some aspects of the effect of electrotonic architecture on integrative function. The treatment cannot be comprehensive but is intended to supplement existing reference sources (e.g., see Refs. 10, 36, 89, 95, 97, 98, 101, 145) by introducing some new ideas and formulations.

E. Glossary

A_D	Total membrane surface area of the dendrites, cm^2
A_S	Soma membrane surface area, cm^2
C_m	Capacitance per unit area of membrane, F/cm^2
d	Diameter of membrane cylinder, cm
$F_{\text{dga}} = \rho\beta/(A_D/A_S)$ $= G_D/G_{\text{md}}A_D$	Robust factor that $\rightarrow 1$ as $L \rightarrow 0$; dendritic electrotonic decrement makes this factor < 1 ; note, if dendrites were isopotential, then $G_D = G_{\text{md}}A_D$
$G_\infty = G_{\text{md}}\pi\lambda d$	Input conductance at near end of uniform cylinder with diameter d and semi-infinite length, S
$G_D = \sum_{j=1}^n G_{\text{dj}}$	Combined parallel input conductance of n dendritic trees belonging to neuron in question, S
$G_{\text{in}} = G_\infty \tanh(L)$	Input conductance of finite length cylinder, having a sealed-end boundary condition at far end (see Eq. 3 for more general case), S
$G_m = 1/R_m$	Conductance per unit area of membrane; usually for passive membrane, $\text{S}/\text{cm}^2 = (\Omega \cdot \text{cm}^2)^{-1}$
$G_{\text{md}} = 1/R_{\text{md}}$	Conductance per unit area of dendritic membrane, usually assumed uniform over all dendrites, S/cm^2
$G_{\text{ms}} = 1/R_{\text{ms}}$	Conductance per unit area of soma membrane, S/cm^2

$G_N = G_S + G_D$	Input conductance of whole neuron (axon neglected), S
G_S	Total conductance across soma membrane, which may include a soma shunt; see Eq. 5, S
l	Actual finite length of a uniform cylinder, cm
$L = l/\lambda$	Electrotonic length of finite cylinder
L_{de}	Effective value of L for combined dendrites in parallel; obtained from value of F_{dga} in Eq. 13
L_{avg}	Average of separate L values when all terminal branches of dendritic trees are given equal weight
R_i	Specific resistance of intracellular medium, $\Omega \cdot \text{cm}$
$R_m = 1/G_m$	Membrane resistivity, i.e., resistance for a unit area of membrane, $\Omega \cdot \text{cm}^2$
$R_N = 1/G_N$	Input resistance of whole neuron, Ω
$V = V_m - E_r$	Departure of membrane potential difference V_m (inside – outside) from its resting value E_r , V
$\beta = G_S/G_{\text{md}}A_S$	Shunt factor; ratio of actual G_S to value it would have if $G_{\text{ms}} = G_{\text{md}}$, with zero shunt conductance
$\lambda = (R_m d/4R_i)^{1/2}$	Length constant of uniform cylinder, when exterior is assumed to be isopotential, cm
$\rho = G_D/G_S$	Ratio of combined dendritic input conductance to soma conductance (which may include a shunt)
$\rho\beta = G_D/G_{\text{md}}A_S$	Ratio that is independent of soma shunting; this equals reference value of ρ when $\beta = 1$
$\tau_m = R_m C_m$	Passive membrane time constant, $\text{s} = \Omega \cdot \text{F} = \text{s}$

For passive decay transients (assuming a linear system)

C_0	Coefficient of slowest decay: $\exp(-t/\tau_0)$, V
C_1	Coefficient of $\exp(-t/\tau_1)$, V
C_2	Coefficient of $\exp(-t/\tau_2)$, V
$L = \pi(\tau_m/\tau_1 - 1)^{-1/2}$	Electrotonic length for uniform cylinder, with two sealed ends
$L_{\text{peel}} = \pi(\tau_0/\tau_{1\text{peel}} - 1)^{-1/2}$	Estimate based on peel of transient; not reliable, in general, but it can be useful for trees whose branch L values lie within 20% and is useful with unbranched “equivalent” cable model, both of which include the soma

$$\tau_m/\tau_1 = 1 + (\pi/L)^2$$

$$\tau_n = \tau_m/(1 + \alpha_n^2)$$

$$\tau_0 = \tau_m/(1 + \alpha_0^2)$$

$$\tau_{1\text{peel}}$$

$$\tau_{\text{vel}}$$

For uniform passive membrane cylinder, with two sealed ends

Time constants of the system, where α_n values are eigenvalues of system matrix (note: n is either zero or a positive integer), s

Largest time constant of system (note: $\tau_0 = \tau_m$, for uniform passive membrane with no shunts or voltage clamps), s

Estimate of τ_1 obtained from transient by subtracting $C_0 \exp(-t/\tau_0)$ from decay of $V(t)$, s

Largest time constant of current transient, when voltage clamp is applied at one end (the soma), s

III. NEURON MODELS WITH REALISTIC MORPHOLOGY: STEADY-STATE ANALYSIS

The advent of intracellular labeling methods, primarily using horseradish peroxidase (HRP), has enabled detailed study of the dendritic morphology of several neuron types (e.g., see Refs. 7, 12, 21, 22), which in turn has led to interest in defining the electrotonic

structure of specific neuron types. Various recent studies have been devoted to reconciling the detailed dendritic morphology of an individual neuron with the electrophysiological properties of that same neuron (4, 14, 15, 29, 30, 37, 42, 74, 79, 84, 86, 119, 120, 122, 132, 148–150). This involves not only estimating the membrane resistivity (R_m), the membrane capacitance (C_m), and the cytoplasmic specific resistivity (R_i) but also evaluating key assumptions about membrane uniformity and membrane linearity and about the possible presence of electrical shunting at the site of cell penetration (usually the soma). These parameters and assumptions, together with the morphology, determine the electrotonic properties of the neuron. In special situations where an idealized membrane cylinder and spherical soma are a reasonable approximation of reality, we can use established theoretical formulas for reliable estimations of the parameter values from experimental data. However, such situations are rare, and erroneous assumptions are likely to result in erroneous estimates. This review addresses errors due to such mismatches and other sources of error.

The morphology revealed by intracellular HRP labeling (e.g., see Fig. 1) suggests, for several important neuron types, that dendritic branching does not satisfy the requirements for transformation of an entire tree to an equivalent cylinder. It is therefore important to evaluate the changes in theoretical predictions (and computed responses) that result from more complex geometry. Although the simplifying assumption of a uniform,

FIG. 1. Comparison of 2-dimensional representations of a camera lucida drawing of a cat α -motoneuron that had been filled with horseradish peroxidase and completely reconstructed (A) and computer-generated drawing from a file in which soma and dendritic trees were represented by finite compartments (B). Soma in computer file was represented by a sphere with a diameter that matched observed average soma diameter. Dendritic trees were represented as connected sequences of cylinders ($n = 777$) with 3-dimensional spatial coordinates, as well as measured lengths and diameters. [From Cullheim et al. (22).]

FIG. 2. Two representations of a single dendritic tree with moderate complexity from a cat α -motoneuron. *A*: Sholl dendrogram, with branches represented as cylindrical segments, each with constant diameter (note diameter scale at *bottom right*). Distance scale is in units of electrotonic distance from soma, calculated using a uniform membrane resistivity (R_m) value of $11,000 \Omega \cdot \text{cm}^2$ and cytoplasmic resistivity (R_i) value of $70 \Omega \cdot \text{cm}$. These values were selected to match whole neuron electrical properties (see Ref. 37; their cell M43/5). *B*: unbranched "equivalent" cable calculated for same tree, drawn to same diameter and electrotonic length scales (see text for details).

passive membrane underlies most analytical solutions for steady-state and transient neuronal responses, it should be noted that compartmental models (98, 125) can accommodate any arbitrary complexity of branching and of nonuniform membrane properties that one is prepared to specify. It may also be mentioned that newer analytical formations can also deal with branching structures with arbitrary complexity (1). Although these anatomic and physiological complications represent a disagreeable but challenging intrusion of reality into the well-behaved world of passive cylinder models, the available mathematical and computational tools appear equal to the task of dealing with them in a responsible way.

A. Cable Encoding of Neuron Morphology

The process of modeling anatomically defined neurons begins by abstracting the cell morphology into a format that is suitable for computational analysis. This process, termed "cable encoding," requires the measurement of the lengths and diameters of all branches in each dendritic tree, as well as measurement of the somatic dimensions (e.g., see Ref. 21). The data can be displayed as two- and three-dimensional representations of the full cell morphology (Fig. 1) or as schematic dendrograms (Fig. 2*A*). The number of cylindrical elements used to represent the dendritic trees depends partly on practical considerations of the file size in relation to computer memory and partly on the requirements of compartmental theory. Long cylindrical branches work well in the steady-state computations

and also in transient computations using the method of Holmes (55). In compartmental simulations of transients, however, the electrotonic length of compartments must be kept small ($0.05\text{--}0.1\lambda$, where λ is the electrotonic length constant) near the points of perturbation and of recording, whereas larger values can be used for compartments located progressively further from the action. Here, of course, the physical lengths implied depend on the choice of R_m and R_i . The concept that small compartments and branches can be dynamically lumped together during computation when they are far from an action potential (or sites of perturbation), and that they need to be "unlumped" when the activity comes near, has recently been implemented in an efficient computer program, named AXONTREE (81, 82).

The soma membrane is regarded as effectively isopotential as long as the soma shape (whether sphere, ellipsoid, or polyhedron) lacks a restricted cross section that can act as a barrier to current flow (95). One therefore needs only an estimate of the soma surface area (A_s). Soma shape enters only indirectly in the process of choosing the anatomic boundary where the soma ends and the dendrites begin and then estimating A_s . It is reasonable to choose a boundary near where the initial taper of each dendritic trunk reduces to its average diameter; although more explicit rules can reduce ambiguity, an exact boundary is usually not critical, especially for large trunk diameters where λ is large.

When the focus of neuron modeling is on passive dendritic properties, the axon is usually not treated explicitly for several reasons. There is limited information about detailed axonal morphology, and what is known for spinal motoneurons suggested a significant con-

striction of axon diameter near its origin from the axon hillock (18). This constriction suggests that the passive input resistance of the axon would be large compared with the dendritic trunks and that the axon would make a relatively small (assumed negligible) contribution to the cell electrical properties evaluated at the soma. With the availability of improved morphological data, these assumptions may need to be reconsidered for different neuron types. The axon must obviously be included in any model that seeks to treat the generation of impulse activity resulting from soma-dendritic integration of synaptic inputs. Also, the axon was necessarily explicit in the early computations of antidromic propagation along the axon to the soma and dendrites of motoneurons and of mitral cells (26, 27, 110). The axons of invertebrate neurons usually do not take origin from the soma but instead usually arise from some major branch point of the dendritic system (9, 70, 143).

B. Branch Encoding for Steady-State Analysis

The first and simplest objective in attempts to match electrophysiological properties with neuron morphology is to calculate the steady-state input resistance (R_N) implied by the dendritic structure, using various choices of R_m and R_i . If this is all that is desired, a simple reduction of the dendritic branching can be used. Where the cross-sectional area of a dendritic branch remains constant, the branch can be replaced by a uniform cylinder having the same length and cross-sectional area. When taper is present, it is most conveniently represented as a cascade of uniform cylinders, each having a diameter equal to the mean diameter of the tapered section it replaces. Tapering sections could alternatively be represented by truncated cones or by segments with exponential taper (44, 60, 93, 97).

To construct an electrotonic dendrogram (135) like that shown in Figure 2A, we need to rescale the branch lengths to values that are proportional to l/λ , where l represents the actual branch length (in cm or μm). The value of λ has a square-root dependence on the branch diameter (d) and on the resistivity ratio (R_m/R_i) as follows

$$\lambda = \left(\frac{d}{4}\right)^{1/2} \left(\frac{R_m}{R_i}\right)^{1/2} \quad (1)$$

A useful reference combination of resistivities, such as $R_m = 10,000 \Omega \cdot \text{cm}^2$ with $R_i = 100 \Omega \cdot \text{cm}$, implies $\lambda = 500 \mu\text{m}$ when $d = 1 \mu\text{m}$; a fourfold increase of either d or R_m/R_i would double the value of λ .

For a general scaling of lengths, it is useful to consider the equality

$$\left(\frac{l}{\lambda}\right) \left(\frac{R_m}{R_i}\right)^{1/2} = l \left(\frac{d}{4}\right)^{-1/2} \quad (2)$$

which is based on Equation 1. Because the right-hand side of this equality depends only on branch dimensions,

this can be regarded as a resistivity-free, caliber-scaled length for any given branch. When this quantity is divided by a particular value of $(R_m/R_i)^{1/2}$, one obtains the dimensionless l/λ value of that branch for this particular resistivity combination. Depending on personal preference, one can construct the dendrogram and the computer files in terms of either the resistivity-free caliber-scaled lengths of Equation 2 or the dimensionless l/λ values calculated for some convenient reference combination of resistivities. If R_m is uniform for all dendritic branches (and R_i is assumed constant), then the entire dendrogram and the computer file of l/λ values can be rescaled by the proportionality factor appropriate for each of the values of R_m chosen to be included in a set of computations. Nevertheless, it is important to recognize that the input conductance values defined by Equation 3 (see next section) must be recalculated for each value of R_m [because the values of the reference input conductance (G_∞) and $\tanh(l/\lambda)$ in that equation are both changed].

C. Computing Input Conductance of a Neuron

To calculate the input conductance of a branched cascade of cylinders representing some particular dendritic tree, one uses the formulas below in an iterative manner, beginning with the terminal segments and continuing back to the dendritic trunk (95, 103, 125). This can be readily implemented on a small computer and is also available in several software packages.

The input conductance (G_{in}) of a cylinder of length l and diameter d is given by

$$G_{in} = G_\infty \frac{(G_{out}/G_\infty) + \tanh(l/\lambda)}{1 + (G_{out}/G_\infty) \tanh(l/\lambda)} \quad (3)$$

where G_{out} represents the outward or onward conductance confronted by the axial current at the distal end of this segment and G_∞ represents the reference input conductance for this cylinder (i.e., its limiting value, were its length to be infinitely extended). The value of G_{out} is set equal to zero for the "sealed end" assumed present at the distal end of a terminal segment; otherwise, G_{out} is set equal to the input conductance of the next segment (or pair of segments, if this is a branch point). The sealed-end boundary condition was originally based on a consideration of the very high resistance expected for a small area of terminal membrane (95; experimental support was later provided in Ref. 29, Fig. 7 in Ref. 69, Fig. 4 in Ref. 64). For each terminal segment, setting G_{out} to zero in Equation 3 reduces the right-hand side to $G_\infty \tanh(l/\lambda)$.

The reference input conductance can be expressed as

$$G_\infty = \left(\frac{\pi}{2}\right) d^{3/2} (R_m R_i)^{-1/2} = G_m \pi \lambda d \quad (4)$$

The second equality shows that G_∞ equals the membrane conductance across one λ length of the membrane cylinder. Several useful alternative expressions for G_∞ , and for its reciprocal, can be found in Reference 103 (p. 21).

When computing the input conductance of a particular dendritic geometry, it is usual to assume R_i to be constant for all segments, whereas R_m might be constant or spatially nonuniform. Iterative computation using *Equation 3*, from terminals to the stem segment of the tree, provides the input conductance for the complete tree. Such steady-state computations can incorporate complete dendritic morphology and are easily implemented. Reduction of the complete morphology to an approximately equivalent unbranched cable (where the value of $d^{3/2}$ usually varies with distance; see Fig. 2B) is a straightforward procedure (see sect. VB) and can also be used for steady-state computations of dendritic input conductance.

After stepwise computation has been completed for each of n dendritic trees, the resulting input conductance values (G_{dj}) are summed because they are electrically in parallel with each other, as well as with the soma conductance (G_S) and the axonal input conductance (G_{ax} ; which is usually not included explicitly). Thus the input conductance of the entire neuron (G_N), measured at the soma, can be expressed as

$$G_N = G_S + G_D + G_{ax} \quad (5)$$

where the combined parallel input conductance of dendrites (G_D) can be expressed as

$$G_D = \sum_{j=1}^n G_{dj} \quad (6)$$

and

$$G_S = G_{shunt} + G_{ms}A_S \quad (7)$$

Here a soma shunt conductance (G_{shunt} ; assumed to be caused by microelectrode penetration) is explicitly included, leaving its magnitude to be determined. Also, A_S represents the area of the isopotential soma membrane, and G_{ms} represents the specific membrane conductivity (conductance per unit area, i.e., $\Omega^{-1} \cdot \text{cm}^{-2}$) of the undamaged soma. This formulation leaves open the possibility that G_{ms} could differ from the specific membrane conductivity of the dendrites (G_{md}), because the ion channel densities at the soma may be different.

D. Soma Shunting (or Nonuniformity) Factor

If we assume G_{md} to be uniform everywhere, we can define the useful soma shunting factor (β) as

$$\beta = \frac{G_S}{G_{md}A_S} = \frac{G_{shunt} + G_{ms}A_S}{G_{md}A_S} \quad (8)$$

These expressions allow for both an explicit shunt conductance and a possible difference in the actual specific conductivities of dendritic and somatic membrane. The reference case of $\beta = 1$ requires that $G_{shunt} = 0$ and also $G_{ms} = G_{md}$, meaning uniform membrane conductance over dendrites and soma. Experimental estimates of β for six motoneurons studied by Fleshman et al. (37) ranged between 25 and 300. In the absence of information about the existence of an explicit shunt conductance, one can set $G_{shunt} = 0$ and compute an effective value of G_{ms} ; then *Equation 8* reduces to

$$\beta = \frac{G_{ms}}{G_{md}} = \frac{R_{md}}{R_{ms}} \quad (9)$$

(where R_{md} and R_{ms} are the dendritic and soma membrane resistivities, respectively), which corresponds to the definition of β introduced by Iannsek and Redman (64). This definition has been used also by Kawato (72), whereas its reciprocal has been used by others (28, 92).

There exists an inverse proportionality between the parameters, β and ρ , where ρ is the ratio of dendritic input conductance to soma conductance

$$\rho = \frac{G_D}{G_S} \quad (10)$$

For any given neuron, the value of ρ decreases as the value of β (and of G_S) increases, but it is important to note that the product, $\rho\beta$, remains constant. This follows from *Equations 8* and *10*, which together imply that

$$\rho\beta = \frac{G_D}{A_S G_{md}} \quad (11)$$

In other words, whatever the amount of shunting, $\rho\beta$ remains constant at the same value of ρ that corresponds to $\beta = 1$ (i.e., no shunting and $G_{ms} = G_{md}$). Fleshman et al. (37) estimated values of ρ ranging between 0.17 and 1.15 for six cat α -motoneurons, and the estimated values of $\rho\beta$ for these cells ranged between 30 and 80, as given in Table 1, which provides specific examples of the use of this and other factors discussed in this review.

E. Robust Factor Relating Dendritic Input Conductance to Dendritic Surface Area

For the special case where all of the dendritic trees are equivalent to cylinders with the same value for the dendritic electrotonic length (L), a useful expression for $\rho\beta$ is the following

$$\rho\beta = \frac{A_D \tanh(L)}{A_S L} \quad (12)$$

where A_D is the total surface area of the dendritic trees. Note that A_D/A_S depends only on anatomy but that $L =$

TABLE 1. *Parameter estimates and experimental data for six α -motoneurons*

ID	Type	R_N	A_D/A_S	ρ	β	$\rho\beta$	F_{dga}	L_{de}	L_{avg}	L_{peel}
35/4	S	4.2	50.0	1.14	28.6	32.6	0.653	1.33	1.34	1.7
36/4	S	2.0	49.3	1.09	34.1	37.1	0.754	1.03	1.13	1.4
42/4	FR	1.1	74.6	0.32	141.7	45.8	0.613	1.47	1.24	1.6
43/5	FR	1.4	81.5	1.15	48.9	56.3	0.690	1.21	1.45	2.0
41/2	FF	0.7	65.7	0.18	285.7	50.9	0.775	0.96	1.05	1.8
38/2	FF	0.7	100.6	0.30	257.6	78.3	0.778	0.95	0.98	1.9
Mean		1.68	70.3	0.698	132.8	50.2	0.710	1.16	1.20	1.7

Cell identifications (ID and motor unit type), R_N , and A_D/A_S data are for 6 motoneurons studied intensively by Fleshman et al. (37). Also given are newly computed values for parameters discussed in text, using a model in which $R_{ms} < R_{md}$ and R_{md} is spatially uniform. L_{peel} estimates were obtained by graphical peeling of τ_0 and τ_{1peel} from transient responses calculated for unbranched "equivalent" cable representations of each cell and from eigenvalues of compartmental representations of same model. These estimates agreed to within 5%. FF, fast twitch, fatigable; FR, fast twitch, fatigue resistant; S, slow twitch. For definitions of other abbreviations, see text.

l/λ depends on R_m/R_i as well as anatomy. Equation 12 follows from knowing that $G_D = G_\infty \tanh(L)$, for an equivalent cylinder with a sealed end at $X = L$, and knowing that the surface area of the equivalent cylinder can be expressed as $A_D = \pi l d = L \pi \lambda d = L G_\infty / G_{md}$ (which makes use of Eq. 4).

An important insight about Equation 12 is based on noting that the factor $(\tanh L)/L$ is close to unity when L is very small (then the dendritic membrane is essentially isopotential, for steady current applied to the soma), which implies that the conductance ratio G_D/G_S equals the area ratio A_D/A_S . This factor becomes smaller as L increases, because the dendritic membrane is less and less isopotential due to increasingly significant electrotonic decrement from the soma to the distal dendritic membrane. For example, as L increases from 0.4 to 1.5, G_D/G_S becomes smaller than A_D/A_S by a factor of 0.95–0.60.

Equation 12 holds exactly when all of the dendritic trees can be treated as one equivalent cylinder, but a somewhat similar dependence on the degree of dendritic isopotentiality must hold also for dendritic trees that depart from the equivalent cylinder constraints. This leads to the concept of a generalized correction factor (F_{dga}) that appears to be relatively invariant for a given type of neuron (see Table 1) but needs to be determined for different types of dendritic trees. This generalized factor can be defined by several equivalent expressions

$$F_{dga} = \frac{\rho\beta}{A_D/A_S} = \frac{G_D}{A_D G_{md}} = \frac{\tanh(L_{de})}{L_{de}} \quad (13)$$

where the subscript dga was chosen to indicate dendritic conductance versus area. The last expression provides a new definition of an estimator, L_{de} , for the effective electrotonic length of any type of dendritic tree. The expressions in Equation 13 assume no constraint on dendritic branching and are valid for any dendritic architecture. Both F_{dga} and L_{de} are robust under a variety of conditions, as discussed in section IIIH.

Table 1 gives examples of how these factors relate to other characteristics in six motoneurons studied by

Fleshman et al. (37). Shown are the measured values for R_N and for A_D/A_S and the values for ρ and β that were estimated for the $R_{ms} < R_{md}$ that were chosen to best fit the experimental data, with R_{md} spatially uniform (see Ref. 37). Table 1 also shows recently calculated values for $\rho\beta$ and for F_{dga} that follow from the values given for R_N , A_D/A_S , ρ , and β . In addition, estimates of electrotonic length computed in three different ways are given: L_{de} , which is implied by Equation 13, which in these cases is comparable to the arithmetic average, L_{avg} , for all terminating paths in each neuron (see Ref. 37 and sect. VE), and L_{peel} , the estimate obtained by peeling a simulated voltage transient.

It is encouraging to find that the values for F_{dga} show considerably less variability than those for ρ , β , and even for $\rho\beta$. The large variability of β (its range involves a factor of 10) and of ρ (its range involves a factor of 6.5) is presumably due to significant differences in the shunt conductance values for the six neurons. However, the product $\rho\beta$ is independent of shunt conductance and exhibits much less variability (its range involves a factor of only 2.4). Moreover, the variability in $\rho\beta$ is correlated with that in A_D/A_S , as should be expected from Equation 12. Consequently, F_{dga} shows the least variability (its range involves a factor of only 1.27). These results provide support for the concept that F_{dga} is robust; it has a value that depends neither on β , on neuron size, nor even on A_D/A_S . Rather, the dependence of F_{dga} on dendritic architecture involves two factors: 1) the relative areas of proximal versus distal membrane and 2) the magnitude of voltage attenuation (i.e., the departure from isopotentiality) from proximal to distal membrane regions. The combination of a large distal membrane fraction with significant voltage attenuation reduces the value of F_{dga} and increases the value of L_{de} .

The results summarized in Table 1 suggest that, for cat spinal motoneurons under particular experimental conditions (37), the factor F_{dga} has a mean value of 0.71 and shows relatively little variation from cell to cell. Therefore, if one has a reasonable average value for F_{dga} for a given type of neuron, its value can help to make preliminary estimates of other electrotonic parameters

despite incomplete information, as shown in the next section. It will be interesting to determine the value of F_{dga} for a variety of neuron types, because it appears to depend on the particular morphological characteristics of the dendrites. In the case of neurons with several specialized dendrite types, such as pyramidal cells, one should calculate the value of F_{dga} separately for the basal and apical dendrites, as well as for the side branches of the latter (see Fig. 6).

F. Relation of Dendritic Membrane Resistivity to Input Resistance of Neuron

Now that β , ρ , $\rho\beta$, and F_{dga} have all been explicitly defined, we can use *Equations 5–13* to write the following expressions for G_N at the soma

$$G_N = (\rho + 1)G_S = (\rho\beta + \beta)(A_S G_{\text{md}}) = 1/R_N \quad (14)$$

and also the following useful expressions for important conductance and resistance ratios

$$G_N/G_{\text{md}} = R_{\text{md}}/R_N = (\rho\beta + \beta)A_S \quad (15a)$$

$$= F_{\text{dga}}A_D + \beta A_S \quad (15b)$$

As an explicit example, suppose that $\rho\beta = 50$ and $A_S = 10^{-4} \text{ cm}^2$, then if $\beta = 100$ and $R_N = 2 \text{ M}\Omega$, it follows from *Equation 15a* that $R_{\text{md}} = 30 \text{ k}\Omega \cdot \text{cm}^2$. Given also that $A_D = 70 \times 10^{-4} \text{ cm}^2$, it follows from *Equation 10* that $F_{\text{dga}} = 0.714$, whereupon *Equation 15b* is found also to yield $R_{\text{md}} = 30 \text{ k}\Omega \cdot \text{cm}^2$.

It is clear from *Equation 15b* that when we have experimentally measured values for R_N , A_D , and A_S and we wish to estimate the value of R_{md} (assumed to be uniform over the dendrites), we need to have good values for F_{dga} and for β . If we have the complete dendritic anatomy, F_{dga} can be calculated for any given trial value of R_m/R_i . If we do not have the complete dendritic anatomy, the value of this factor can be estimated from earlier results for the same neuron type (e.g., the mean value, 0.71, for motoneurons like those in Table 1). Thus it is uncertainty about the value of β that creates the most serious problem.

G. Normalized Input Resistance as a Function of Soma Shunting Factor

From *Equation 14* it follows that R_N , normalized relative to its value R_{N1} for $\beta = 1$, can be expressed as

$$R_N/R_{N1} = G_{N1}/G_N = (\rho\beta + 1)/(\rho\beta + \beta) \quad (16)$$

which is equivalent to an equation of Durand (28), except that he used ρ where we use $\rho\beta$. The five curves in Figure 3 show how this normalized input resistance decreases from 1.0 as the value of β is increased from 1 to 1,000. For example, $\rho\beta = 20$ and $\beta = 100$ imply that R_N is

FIG. 3. Graph of *Eq. 16* showing dependence on shunt factor (β) of neuron input resistance (R_N), normalized to its value, R_{N1} , for $\beta = 1.0$. Influence of cell morphology on this relation is illustrated by curves for different values of $\rho\beta$ (see text).

one-fifth of what it would be for $\beta = 1$. It is noteworthy that Figure 3 and *Equation 16* are valid for dendritic trees with arbitrary branching patterns. Each $\rho\beta$ value can represent a variety of dendritic geometries, with respect to their effective L and F_{dga} values.

One may think of the increase of β either in terms of increasing somatic shunting or as reducing the effective R_{ms} while R_{md} is held constant. The 100-fold range of $\rho\beta$ shown here can also be thought of in two different ways. From one point of view, the soma size is held constant, with a fixed A_S , and we compare dendritic trees of six different sizes (assuming fixed dendritic membrane properties). Then $\rho\beta = 1$ represents the smallest trees, and this case shows the most reduction of input resistance for the shunting that corresponds to any particular value of β . In contrast, $\rho\beta = 100$ represents the largest trees, and this case shows the least reduction of input resistance for any value of β .

From a different point of view, the dendritic trees are held constant with a fixed G_D , and we compare six somas of different size, such that A_S covers a 100-fold range. Then the largest $\rho\beta$ corresponds to the smallest soma area, and this implies the smallest amount of shunt conductance for any particular value of β ; consequently, the curve for $\rho\beta = 100$ shows the least reduction of input resistance with increasing β . Also, from this second point of view, we can more easily recognize the near equivalence of those combinations of β and $\rho\beta$ that imply the same amount of somatic shunt conductance relative to G_D . To make this concept completely explicit, we consider the expression

$$G_{\text{shunt}}/G_D = (\beta - 1)/(\rho\beta) \quad (17)$$

which follows from *Equations 8–11*, when $G_{\text{ms}} = G_{\text{md}}$. For example, G_{shunt} equals G_D for each of the following combinations: $\rho\beta = 100$ with $\beta = 101$, $\rho\beta = 20$ with $\beta = 21$, $\rho\beta = 10$ with $\beta = 11$, $\rho\beta = 5$ with $\beta = 6$, and $\rho\beta = 1$ with $\beta = 2$.

Because these combinations all correspond to the same shunt conductance for the same dendritic tree, it is not surprising that inspection of Figure 3 shows that these combinations yield essentially the same normalized input resistance. These cases are not exactly the same, however, because each case implies a different area of passive soma membrane; exact matching would be based on Equation 16.

We have spent some time on these considerations because they have an important practical implication: a measured input resistance value can be very different from its unshunted reference value. This can result in erroneously low estimates of dendritic membrane resistivity if the effects of soma shunting are not taken into account. Equation 16 provides the reciprocal correction factor for input resistance when good values for β and $\rho\beta$ are available or when reasonable trial values can be assumed.

H. Effective Value of Electrotonic Length for Nonideal Trees

When a dendritic tree satisfies the constraints for an equivalent cylinder, there is no problem in calculating L because all terminal branches necessarily end with the same value of L . However, in trees where the sum of $d^{3/2}$ changes with distance and/or where terminal branches end at different values of L , there is uncertainty about how best to define an effective L (i.e., a measure of electrotonic compactness) for the tree. The simplest approach is to average the L values of all terminal pathways, L_{avg} , as given in Table 1 (37). The disadvantage of L_{avg} is that all dendritic paths are given equal weight, irrespective of different diameters and branching patterns.

Although the L_{avg} values for the motoneurons in Table 1 are comparable to the values of L_{de} derived from Equation 13 for the same cells, we note that L_{de} has the advantage that it is inherently weighted by the contributions that various portions of the tree make to the input conductance of the whole tree. The data in Table 1 support the notion that L_{de} and F_{dga} reflect important details of dendritic architecture. Neuron 42/4 in Table 1 is different from the others in that it has the smallest value for F_{dga} and the largest value for L_{de} , and it is the only neuron for which L_{de} is greater than L_{avg} . These differences correlate with a noticeable difference in the branching pattern: the equivalent unbranched cable (summed $d^{3/2}$ value) for this cell shows a bulge between $L = 0.5$ and 1.0 , which is different from all of the other five cells (see Fig. 9 in Ref. 37). This difference in branching pattern places relatively more dendritic membrane at locations with significant voltage decrement, thus providing an intuitive physical explanation for the smaller F_{dga} value (see sect. III E and Eq. 13).

Two other methods for estimating effective L can be mentioned very briefly. One method avoids the equal weighting of terminals used for L_{avg} ; instead, branches are weighted by their relative input conductance values

(referred to as L_G in Ref. 37, p. 66 and Tables 2 and 4, "Step Model"). Values for L_G were usually larger than L_{avg} , but they may not be better in view of the results shown in Table 1. A different approach is to use the inverse hyperbolic tangent of the ratio G_D/G_∞ (104), which works well for trees where the sum of $d^{3/2}$ does not increase with distance from the soma. However, this method is not robust, because it fails for trees where the value of G_D exceeds G_∞ . The general idea of making use of the dendritic input conductance calculations is implemented more successfully by using L_{de} , as defined in Equation 13; these values share the robustness of F_{dga} .

IV. ESTIMATING PARAMETER VALUES FROM MORPHOLOGY AND INPUT RESISTANCE

A. Estimating Membrane Resistivity

In principle, there are three parameters that are essential to computational neuronal models, namely R_m , C_m , and R_i . Of these, R_m is both the most variable in published studies and the least well constrained by experimental data. Estimates of R_i are discussed in section VII B. A value for R_m cannot be measured directly in conventional microelectrode studies; rather, its value(s) can only be inferred from a combination of measurements and underlying assumptions. In principle, however, R_m estimates might be derived from patch electrode measurements for membrane patches torn free of the neuron (45). Estimating the membrane conductivity as $G_m = G_p/A_p$, where G_p is patch conductance and A_p is patch area, is subject to significant error because A_p has been difficult to measure. It may be better to estimate the time constant (τ) of the membrane patch (which is independent of membrane area) and then infer the value of $R_m = \tau/C_m$, assuming $C_m = 1.0 \mu\text{F}/\text{cm}^2$. This approach may provide the best means of studying membrane non-uniformity if it becomes possible to compare values obtained for patches torn from different soma-dendritic locations.

To deduce R_m from an input resistance measurement of a branched neuron, one cannot avoid having to make assumptions about the underlying model complexity. The literature does include early estimates based simply on dividing the input conductance by the total membrane surface area, but such estimates are probably erroneous because they neglect the cable properties of the dendrites and the likelihood of soma shunting. Knowledge of cable theory has permitted us to use Equations 3–15 to define the relation of R_m to R_N for the encoded morphology, but our estimates still depend on what assumptions are made about membrane uniformity, soma shunting, and the value of R_i .

It is interesting that the first studies to use anatomic and physiological measurements from individual cat spinal motoneurons (3, 79; see also Table 3 and p. 49 of Ref. 101) did contain evidence that their R_m estimates were too low. This evidence concerned the membrane

capacitance estimate, $C_m = \tau_m/R_m$, based on assuming a uniform passive membrane (where τ_m is the membrane time constant), which came out two to five times larger than the widely accepted value of $1 \mu\text{F}/\text{cm}^2$ established by Cole (16) and others. With the much more complete HRP morphology now available, such R_m estimates seem too low also because they imply low values for λ , which make the l/λ values come out too large, implying dendritic trees with electrotonic lengths up to five times greater than the values of 1–1.5 that are in agreement with EPSP shape characteristics (67, 105, 126). Also, when such low estimates for R_m were used in computational simulations of transient responses (making use of cable-encoded morphology and assuming reasonable values for C_m and R_i) the resulting computed transients did not agree with those recorded experimentally (15, 29, 37, 119, 120, 132).

Such erroneously low estimates of R_m can be avoided by using *Equations 3–15* and by assuming that β has a value significantly greater than unity. Such values could be due to a somatic shunt conductance and/or to a soma membrane conductance that is larger than the dendritic membrane conductance. It is simplest to assume 1) that R_m nonuniformity is present only as a difference between the soma and a uniform dendritic membrane; then one can make use of *Equation 15* to obtain easy preliminary estimates. However, we have also found it possible to match the experimental data with an alternative assumption 2) that R_m increases continuously with dendritic distance away from the soma, according to any one of several convenient functions (37, 102).

B. Comment on Nonuniqueness

It is apparent that various combinations of *assumptions 1 and 2* can be used to match a given data set and that all such cases would represent nonunique solutions to the problem. Resolution of such nonuniqueness would depend on new data, perhaps obtained by patch electrode studies (45). Without such direct resolution, we can reduce or even eliminate the nonuniqueness by imposing constraints, such as *assumption 1*, and by requiring the model to fit some aspects of the experimental voltage transients, as discussed in section v. The effects of various constraints can be explored in two rather different ways. The first is to begin with a highly reduced and idealized model and then add model complexity, step by step. An alternative is to begin with a large compartmental model (composed of thousands of compartments and several thousand degrees of freedom) and then reduce the degrees of freedom by encoding the morphology and making explicit assumptions about uniform or nonuniform membrane properties and about certain parameter values (15, 37, 58, 59, 104, 142).

C. Comment on Whole Cell Patch Recording

Because the soma shunting that is believed to be caused by microelectrode penetration (in conventional

intracellular recording) produces significant complications, it is important to mention whole cell patch recording. This technique employs an electrode of the patch-clamp type, with a very high-resistance ($G\Omega$) seal to the cell and with the membrane patch broken to provide low-resistance access to the cell interior (45). Such a recording succeeded first in tissue culture (45), but it has since been used for cells in a retina cup preparation (17), in tissue slice preparations (6, 31, 85, 136, 139, 141), in isolated cells (91), and in the spinal cord of the chick embryo maintained in vitro (131). Problems with connective tissue interference and with visualization of electrode-membrane contact have delayed the application of this technique to mammalian neurons recorded in situ.

Such whole cell patch recordings yield R_N values that are much larger (by 4–10 times) than those found with sharp microelectrodes. It is thought that whole cell patch recording may not produce a significant artifactual soma shunt conductance (139). Also, the recording of transients is improved, because the lower input impedance of the patch electrode decreases the recorded noise and stimulus artifact and also improves high-frequency resolution that is important in the early, rapid portion of a recorded transient. It has been found, however, that the whole cell patch method introduces another uncertainty resulting from dialysis (or “washout”) of intracellular material. This can produce significant “rundown” in minutes, as shown by experiments that also demonstrate the superiority of a “perforated” (nystatin) patch (63, 73). More recently, it has been suggested that substituting amphotericin B for nystatin can produce a perforated patch with lower access resistance (94). These methods offer great promise, but it seems too early to be sure how much (or little) systematic error may be present in these new input resistance measurements either because of “washout” with the whole cell method or because of specific effects of the antibiotic used in the perforated patch. Nevertheless, where they can be used successfully, these whole cell patch and perforated patch techniques provide a special opportunity to obtain improved data that should be amenable to simpler theoretical analysis; the value of β may be close to unity, unless the soma, in fact, has higher ionic channel densities than the dendrites in the unmoled neuron. These methods can provide valuable new data, as well as an opportunity to assess further the effects of sharp, conventional intracellular microelectrodes that have been used for so many years.

D. Comment on Dendritic Spines

Thousands of dendritic spines are present on certain types of neurons. For a neuron possessing spines, any model that ignores the anatomic and physiological effects of spines is bound to produce erroneous results (55, 56, 58, 130, 142). However, one does not have to include every spine explicitly in a model. In the case of centrifugal current from the dendritic shaft into a pas-

sive spine, the resistance of the spine head membrane is so much larger than the spine stem resistance that little current flows through the spine stem, leaving the spine head and stem essentially isopotential (this has been confirmed even in computations with R_i as large as $500 \Omega \cdot \text{cm}$; W. R. Holmes, unpublished studies). Thus G_m and C_m of the spine head and spine stem are effectively in parallel with those of the dendritic shaft despite the large spine stem resistance (129). In contrast, for centripetal current from the spine head through the stem and into the dendritic shaft, the relative input resistance of the parent branch is usually small enough so that significant current can flow through the spine stem, producing a significant potential drop along it. It may be noted that this asymmetry of voltage decrement (for oppositely oriented core current) resembles that shown for short terminal dendritic branches (106). Thus passive spines can be modeled using methods that take the spine membrane area into account; only those spines that actually receive synaptic input (or activated excitable spines) need to be explicitly modeled.

There are at least two different ways in which spines can be included in models implicitly. First, if it is assumed that dendritic and spine membrane have the same R_m and C_m values, then spines can be implicitly included in a model by increasing C_m and reducing R_m according to the proportion of total dendritic membrane due to spines. For example, if spines are responsible for one-half of the total membrane area of a dendritic segment, then spines can be implicitly included by halving R_m and doubling C_m of the segment. Because spines are nonuniformly distributed over a cell's surface, one could choose different adjustment factors for R_m and C_m for each dendritic segment, as has been done for models of cortical pyramidal cells (55, 62), hippocampal dentate granule cells (56), and cerebellar Purkinje cells (130). It has been found that whether spines are implicitly or explicitly included in the model, the input resistance at the soma is the same, as are experimental transients (the first 200 time constants and coefficients in Eq. 18) and EPSP shapes (55, 58). Although this approximation has been useful for many modeling questions, it does mean that R_m and C_m in the model have different values on each dendritic segment, depending on spine density and dimensions. Therefore, if one wishes to estimate R_{md} , one must save R_m and C_m adjustment factors for each dendritic compartment or segment.

A second approach for implicitly modeling spines has been used by Stratford et al. (142). In this method, R_m and C_m are kept constant, but the length and diameter of each segment are increased to include the spine membrane area while maintaining a consistent effective intracellular resistance. To do this, the length and diameter are increased in such a way that the ratio l/d^2 remains constant. For example, if a dendritic segment with $l = 40 \mu\text{m}$ and $d = 2 \mu\text{m}$ (membrane area $80\pi \mu\text{m}^2$) is covered with dendritic spines having total membrane area of $190\pi \mu\text{m}^2$, then an equivalent segment implicitly including spines would have $l = 90 \mu\text{m}$ and $d = 3 \mu\text{m}$. The membrane area of this equivalent segment would be 270

μm^2 ($80 + 190$), but the l/d^2 ratio would still be 10. As in the first approach, input resistance at the soma, voltage transient time constants, and EPSP shape at the soma are the same, whether the spines are implicitly or explicitly included in the model.

V. ANALYSIS OF TRANSIENTS FOR MORPHOLOGICALLY DEFINED NEURONS

Given a neuron with defined morphology, knowledge of R_N alone is insufficient to constrain the possible choices of R_{ms} and R_{md} in the presence of a somatic shunt or when membrane resistivity is otherwise nonuniform. However, if the system time constant (τ_0) is measured, the problem is much more tractable. In fact, if one is prepared to assume values for R_i and C_m , as well as to assume that R_{md} is spatially uniform in the dendritic tree, only one combination of R_{ms} and R_{md} values can satisfy a particular combination of observed R_N , τ_0 , and morphology. Additional time constants that can be extracted from voltage transient responses, although more difficult to interpret (as discussed in the next section), may help to constrain the problem. It is thus important to consider the influence of realistic morphologies and the complications introduced by somatic shunts and other sources of nonuniform membrane resistivity on transient responses.

Here we focus on interpretation of voltage transients produced in neurons by injection of short current pulses, although some studies have used AC currents (40, 85a, 85b). We deal first with the slowest time constant, τ_0 , which is the most important value that can be extracted from the transient response. If R_m is uniform everywhere in the cell (i.e., $\beta = 1$), then $\tau_0 = \tau_m$ ($\tau_m = R_m C_m$). In this case, after an initial voltage perturbation the transmembrane voltage rapidly equalizes to become essentially uniform over the entire membrane; then the late decay is governed by τ_m everywhere. However, when R_m is not spatially uniform ($\beta > 1$), as appears likely with sharp intracellular microelectrodes, then τ_0 is less than τ_{md} . Here, the late decay involves a nonuniform voltage distribution because the shunt conductance draws current from the dendrites. Nevertheless the late decay of this nonuniform voltage is governed by τ_0 everywhere, including all dendritic locations.

A. Theoretical Time Constants for Different Models

Whether membrane properties are spatially uniform, the validity of theoretical time constants and coefficients that can be computed for neuronal models with different geometry depends unavoidably on the simplifying assumption of linear membrane properties over the entire surface of the neuron. Also, we assume uniform C_m and R_i everywhere in the neuron, and we consider both uniform and nonuniform R_m values. Regardless of neuron geometry, we have a general result that the voltage transient $[V(t)]$ during a current step, and during the decay following a brief current pulse, can be expressed as a sum of many exponential decays

$$V(t) = V_{ss} + \sum_{n=0}^{\infty} C_n \exp\left(\frac{-t}{\tau_n}\right) \quad (18)$$

where V_{ss} is the steady-state value, the index n represents positive integers, τ_0 represents the slowest time constant, and τ_1, τ_2 , etc., represent smaller “equalizing” time constants (100) that are associated with rapid reduction of voltage differences between different membrane regions. It is always possible to extract a reliable value for τ_0 from $V(t)$ in simulated responses; however, with experimental data the reliability of the extracted τ_0 depends on noise and possible contributions of membrane nonlinearities. Depending on the relative values of the coefficients C_n (not to be confused with membrane capacitance, C_m), it is often possible to recover one or more of the faster time constants from an experimental transient; this is much easier with noise-free transients computed for neuronal models than with noisy experimental data.

The extraction of time constants and their coefficients from transients can be accomplished in several ways, including graphical “peeling” (100), by mathematical techniques such as nonlinear regression, by transform methods (e.g., by the software package DISCRETE), or by optimization methods (discussed in Ref. 60). As a practical matter, it is usually advisable to evaluate transient records (especially those obtained from experiments) using graphical peeling, regardless of whether the “more objective” mathematical techniques are also utilized, to avoid serious errors due to baseline miscalculation and to detect the presence of nonlinear behavior in experimental data.

If we consider the (ideal) reference case of a single uniform cylinder with sealed ends, the equalizing time constants, τ_n , are related to τ_0 by an expression that depends on the dimensionless L of the cylinder (100). For this ideal case, we have

$$\frac{\tau_0}{\tau_n} = 1 + \left(\frac{n\pi}{L}\right)^2 \quad (19)$$

where n represents an integer corresponding to one of the n indexes in Equation 18. This relation provides a basis for estimating L from ratios, such as τ_0/τ_1 , provided that the simplifying assumptions required for the equivalent cylinder representation in fact apply to the problem at hand. In these and other situations discussed in section VD, the first equalizing time constant that can be extracted from the transient is referred to as $\tau_{1\text{peel}}$, which may or may not correspond to the theoretical τ_1 .

Because the theoretical values of C_n in Equation 18, depend on the point of observation and on the initial conditions (or input distribution) (100, 101, 128), there can be noteworthy effects of symmetry with regard to the $\tau_{1\text{peel}}$ that can be extracted from a simulated or experimental transient. For example, if we observe (record) at the midpoint of the uniform cylinder, symmetry causes all odd-numbered coefficients (i.e., C_1, C_3) to equal zero, whereas C_2 and all even-numbered coefficients

are nonzero numbers. It would then be impossible to extract τ_1 , but one might be able to extract τ_2 from the resulting transient, either by peeling or by numerical curve-fitting methods. If the point of observation were shifted only slightly away from the midpoint, then the odd-numbered coefficients would no longer be zero, but they would still be very small compared with even coefficients. The result would, in practice, be indistinguishable from the symmetrical case. With increasing shift of the point of observation off center, the magnitudes of the odd-numbered coefficients become increasingly significant, and the $\tau_{1\text{peel}}$ extracted from the transient might in fact be τ_1 , especially from a noise-free, computed transient. However, it is important to understand that this identity is not likely in most neurons, whether real or simulated.

These symmetry considerations have very important implications for the interpretation of transients from multipolar neurons (57, 61, 128). For example, a neuron with two dendritic trees, represented by two equivalent cylinders with nearly the same value of L , closely resembles the slightly off-center case above; the $\tau_{1\text{peel}}$ extracted from the transient would be τ_2 . As can be explained in terms of odd and even eigenfunctions (61), this τ_2 is associated with charge equalization between proximal and distal regions of each equivalent cylinder (i.e., soma vs. dendritic terminals, over distance L), whereas the actual τ_1 is associated with charge equalization between the two distal regions (i.e., tip to tip, over distance $2L$), with no voltage disturbance at the midpoint near the soma.

Augmenting such a model with more dendritic trees of slightly different values of L (and/or including dendritic branching) adds many pathways for charge equalization between different pairs of terminal branches, and these pathways correspond to added time constants. The added time constants associated with path lengths close to $2L$ might have values close to τ_1 and, because of path symmetry with respect to the soma, correspondingly small coefficients. However, less symmetrical pathways can have larger coefficients, but as long as the asymmetry is relatively minor, the largest coefficient will be associated with the time constant (called τ_{even} in Ref. 61) for equalization between all distal dendrites and the soma plus proximal dendrites (i.e., associated with path lengths close to L). In favorable cases it is this time constant (or a weighted combination of several time constants with large coefficients) that can be expected to correspond to $\tau_{1\text{peel}}$.

When a neuron model includes such geometrical complications, and/or nonuniform membrane or a somatic shunt, it is important to emphasize that Equation 18 remains valid but that Equation 19 is not generally valid. In such nonideal cases, the values of τ_n and C_n correspond to much more complicated expressions. Analytical results for models where the dendritic trees are equivalent cylinders of different length are provided in Reference 61 (see APPENDIX), and some implications of the relative values found for C_n are discussed there. Numerical methods involving matrix inversion can be used

FIG. 4. Dynamic simulations of somatic membrane voltage transients $V(t)$ in dendritic structures shown in Fig. 2, with addition of a soma with diameter = 10 μm [membrane resistivity of soma (R_{ms}) = membrane resistivity of dendrite (R_{md}) = 11,000 $\Omega \cdot \text{cm}^2$, $R_i = 70 \Omega \cdot \text{cm}$, membrane capacitance (C_m) = 1.0 $\mu\text{F}/\text{cm}^2$]. Fully branched tree and unbranched “equivalent” cable produced similar but not identical transients; late (tail) portions were identical [system time constant (τ_0) = 11 ms], but early portions between 0 and 4 ms, representing contribution of “equalizing” time constants, were not. *Inset*: expanded early time scale (see text).

when the model complexity is expressed in terms of a compartmental model with linear membrane properties (46, 57, 59, 89, 98). The results displayed in Figure 7 were obtained in this way.

B. Reduced Unbranched “Equivalent” Cable Models

When detailed morphological information and estimates of R_N and τ_0 are available and it is known or suspected that $\beta \neq 1$, computational simulation of transients is useful to evaluate the values chosen for R_{ms} , R_{md} , R_i , and C_m . Calculations of transient responses for cases of detailed dendritic morphology usually depend on reduction of the dendritic tree to a compartmental representation in which each compartment is approximately isopotential over its length at the highest frequencies of interest. This usually means that compartments should correspond to dendritic segments not longer than 0.1λ , and this can result in a model composed of thousands of compartments. It is not our intention to provide the details of several schemes for constructing compartmental models of dendritic trees and whole neurons (see Refs. 15, 32, 37, 48, 88, 98, 126, 127, 132, 142, 147, 151). With modern supercomputers, the simulation of transients using models with thousands of compartments is relatively fast, but with less powerful computers, excessive computation time can be a problem. In practice, reduced models are valuable when using simulated transients from neuronal models to match electrophysiological data obtained from reconstructed neurons. For cat spinal motoneurons, recent work (15, 37) has shown that the electrical response at the soma to current or voltage perturbations applied at the soma can be calculated using a reduced approxima-

tion to fully branched dendritic trees, with enormous savings in computer time.

The reduction of a fully branched dendritic tree to an unbranched “equivalent” (nonylindrical) cable is most readily done once the tree has been subdivided into sequential segments of equal electrotonic length (see Equation 1 and sect. III). One can combine all segments located at the same electrical distance from the soma by defining the equivalent diameter (d_{eq}) of the unbranched “equivalent” cable, as follows

$$d_{eq}^{3/2} = \sum_{j=1}^n d_j^{3/2} \quad (20)$$

where the right-hand side represents a sum for the diameters d_j of the n dendritic branch segments at the same electrotonic distance from the soma. The axial resistance, membrane resistance, and membrane capacitance of each compartment in the reduced, unbranched cable are calculated by combining the corresponding resistances and capacitances of the component branch segments (compartments) as parallel elements.

When the unbranched “equivalent” cable and the completely branched model have identical values of R_m , R_i , and C_m , then they also have nearly identical values for τ_0 and R_N . However, their transient responses are not identical, because the respective values of τ_n and C_n are different for $n > 0$. Figure 4 shows transients computed for a complete dendritic tree (Fig. 4, solid line) and for the unbranched “equivalent” cable representation (Fig. 4, dashed line). These transients have the same final decay, but Figure 4, *inset*, shows that they differ at earlier times (e.g., 0.5–3 ms). Because this difference has a significant impact on the estimated values

FIG. 5. Equalizing time constants “peeled” from full transient records; semilog plot of difference, $V(t) - C_0 \exp(-t/\tau_0)$, where $V(t)$ is from Fig. 4 and C_0 is the coefficient. Note that the small difference between 2 curves in Fig. 4, *inset*, results in significantly different fitted values for $\tau_{1\text{ peel}}$ (dashed lines; 2.78 ms for branched tree vs. 1.63 ms for equivalent cable).

of $\tau_{1\text{ peel}}$ (Fig. 5; see next section), this difference cannot be dismissed as negligible. This is why we prefer to use the qualifying quotation marks when referring to the unbranched “equivalent” cable.

The transient response of the unbranched “equivalent” cable differs from that of the full dendritic tree because the two systems are imperfectly matched in electrotonic structure. In a fully branched tree, compartments at equal electrotonic distance in different dendritic branches will usually not be at identical potentials. This is because dendritic terminations usually occur at different electrical distances from the soma in different subtrees (see Fig. 2A) and the admittance into various subtrees departs from idealized constraints. These local variations are averaged out in constructing the “equivalent” cable. Thus, although “equivalent” cable analogues of fully branched dendritic structures can be useful in obtaining preliminary estimates of membrane resistivities through matching observed and simulated values of τ_0 , they cannot serve as entirely accurate replicas of the electrotonic characteristics of actual branched trees.

A compromise between fully branched structures and unbranched equivalent cable analogues can be obtained by combining equivalent cables to represent subtrees within a branched structure. For example, in discussing reduced models for pyramidal cells, the Oxford group (142) found it important to distinguish between a “double profile” representation (an unbranched cable but with the soma located not at one end but at about one-third along its length) (Fig. 6A) and a somewhat more detailed cable representation that includes several lumped side branches (Fig. 6B). These authors found that simulations of voltage transients with this reduced branched cable model were clearly superior to those with the “double profile.” They have illustrated the dif-

ferences between simulations for all three of these models (142). This provides an example that for certain types of neurons, particularly pyramidal cells, and other cells with several different types of dendritic trees, partial reductions using equivalent cable structures in a branched arrangement deserve consideration as first approximations.

C. Time Constants of Fully Branched and Unbranched Models

An illuminating illustration of the effect of model morphology on time constants is provided in Figure 7. The graphs show τ_n , shown in Figure 7A, and C_n values, shown in Figure 7B, for two models, the fully branched dendritic tree and its unbranched “equivalent” cable representation. In both cases, $\tau_0 = 11$ ms and $C_0 = 0.73$. Figure 7A shows that the branched tree model has many more time constants with values between 11 and 1.0 ms than does the unbranched “equivalent” cable model (~ 25 compared with 1, respectively). It is noteworthy that for $n > 1$, many of the τ_n for the tree model are almost as large as τ_1 . In contrast, the values for τ_n for

FIG. 6. Two simplified representations of dendritic geometry for a typical pyramidal neuron. A: “double profile” representation in which basal and apical dendrites have been collapsed separately into equivalent diameter profiles, each linked to a spherical soma. Vertical scale shows diameters of soma and respective dendritic profiles in μm . B: “cartoon” representation of same pyramidal neuron. Basal dendrites have been collapsed into equivalent cable. Apical trunk and apical oblique side branches have been collapsed into separate equivalent cables. Oblique branches located at similar electrotonic distances are connected to apical trunk at appropriate distances. [From Stratford et al. (142).]

FIG. 7. Graphs showing values for first 25 time constants (τ_n) and coefficients (C_n) for transient responses from models of fully branched tree shown in Fig. 2 (143 compartments) and for its equivalent cable (38 compartments). Both τ_n and C_n values are obtained from eigenvalues of simulation matrix, where maximum n equals number of compartments in each model. A: graph of τ_n vs. n . Note that $\tau_0 = 11$ ms and $C_0 = 0.73$ in both cases, but τ_n for any $n > 0$ are quite different, although both models show monotonic decline as n increases. Values of $\tau_{1,peel}$ obtained from noise-free simulated transients (as shown in Fig. 5) are indicated; $\tau_{1,peel}$ for equivalent cable (1.63 ms, implying $L_{peel} = 1.31$) was only slightly smaller than the theoretical τ_1 (1.67 ms), whereas $\tau_{1,peel}$ for fully branched structure (2.78 ms, implying $L_{peel} = 1.83$) was near the theoretical τ_{10} (2.53 ms), for which C_{10} had a relatively large value ($C_{10} = 0.022$; see B). B: graph showing relation between τ_n and C_n extracted from both transients for $1 \leq n \leq 25$. Note that values for C_n are small (< 0.01) for most n in branched tree case, except for $n = 10$ and 21, and that the theoretical $C_1 = 0$. See text for discussion.

the unbranched cable model drop much more rapidly with increasing n , as is also the case for idealized equivalent cylinder models.

Figure 7B shows that most of the C_n for the fully branched model have small values (< 0.01) and, indeed, $C_1 = 0$ ($\tau_1 \approx 4.45$ ms). Except for $C_0 = 0.73$, the largest coefficient for the tree model is C_{21} ($\tau_{21} = 1.52$ ms), but the next largest is C_{10} ($\tau_{10} = 2.53$ ms). In contrast, C_n and τ_n values for the unbranched cable model decrease monotonically as n increases. When the computed transients were analyzed by graphical peeling, it was encouraging to find that $\tau_{1,peel}$ for the unbranched cable was 1.63 ms, which is in rather good agreement with 1.67 ms for the τ_1 value obtained from the simulation matrix. This illustrates a potential merit of the unbranched "equivalent"

cable representation, as discussed further in the next section.

On the basis of studies of peeling with both noisy and noise-free transients (61), we would expect that the extracted time constants would be different if noise were added to this computed transient. In particular, it seemed likely that τ_{10} would not be resolved, and $\tau_{1,peel}$ would correspond to some weighted average dominated by the τ_n values for $n = 10$ and 21 (1.52 and 2.53 ms, respectively). When random noise was added to the transient from the fully branched model, $\tau_{1,peel} = 2.07$ ms, midway between τ_{10} and τ_{21} . This example, which involves a relatively simple case of one dendritic tree connected to a soma, reveals a gray area in the interpretation of peeled time constants for branched neurons whose dendritic terminals have a large scatter in their L values (see Fig. 2A; see also Ref. 37). Also, when several time constants with significant coefficients are closely spaced, peeling cannot resolve the individual time constants, especially in a noisy transient. Rather, a complex weighted average is obtained, which is difficult to interpret.

D. Estimating Electrotonic Length Using Estimates of Time Constants From Peel of Transient

The idea of estimating the value of L from time constant ratios was based on Equation 19, which is valid only for the ideal case of an equivalent cylinder with sealed ends

$$L = \pi \left(\frac{\tau_0}{\tau_1} - 1 \right)^{-1/2} \quad (21)$$

The literature contains many estimates of dendritic L using this equation with experimentally derived values of $\tau_{1,peel}$ substituted for τ_1 in cases where the idealized equivalent cylinder was probably not applicable. To reduce confusion, such estimates should be designated as L_{peel} . In such cases, also, the meaning of L_{peel} is ambiguous because there is no single value of L that applies to all dendritic paths.

It is nevertheless useful for functional interpretations to have some index of the overall electrotonic compactness of the neuron under study. For this reason, several measures of overall electrotonic compactness appear in the literature and deserve comment. In the comparison shown in Figure 7, the $\tau_{1,peel}$ value of 1.63 ms for the unbranched cable yields an $L_{peel} = 1.31$, which compares favorably with other values of L computed for the fully branched tree, such as $L_{avg} = 1.24$ and $L_{de} = 1.16$ computed using F_{dga} (see Eq. 13).

Considering now the fully branched tree model, Equation 21 with the true τ_1 (whose coefficient is 0) yields an L estimate of 2.59, which is essentially $2L$, namely, about twice $L = 1.31$ found when using the true τ_1 of the unbranched equivalent cable model. This $2L$ corresponds to the average charge equalization path from tip to tip in the longest paths, whose symmetry

does not perturb the soma, as noted in section vA. When $\tau_{21} = 1.52$ ms is put into Equation 21 as " τ_1 ," one gets an L estimate of 1.26, which is close to the 1.31 and other L estimates for the tree. This time constant thus corresponds to the charge equalization path from the soma to distal dendrites. Finally, when $\tau_{10} = 2.53$ ms is used as " τ_1 ," one gets an intermediate L value of 1.72, which can be viewed as an asymmetric charge equalization path between the terminals of a relatively short subtree versus a those of a longer subtree (see Figs. 5–7 in Ref. 61).

When the electrotonic lengths of all of the dendritic terminal paths differ by less than $\pm 10\%$ from their mean value, then the coefficients of the many time constants will be small and one can use $\tau_{1\text{peel}}$ in Equation 21 to get a reasonable estimate of effective L (61, 128). However, if the lengths of the dendritic trees differ by more than this amount, then the coefficients of some long time constants (between τ_1 and τ_{even} ; see Ref. 61) will not be negligible, and this will significantly influence the extracted value of $\tau_{1\text{peel}}$, producing estimates of L somewhere between the average L and the sum of the two longest L values. Even longer L estimates are possible, depending on the relative diameters of the dendritic trees (128). The additional effects of dendritic taper and of a soma shunt on estimates of L are discussed in Reference 60.

Finally, Table 1 provides a comparison of values for L_{avg} , L_{de} , and L_{peel} calculated for six cat motoneurons. The values of L_{avg} and L_{de} were computed for the fully branched dendritic trees, whereas the values of L_{peel} were derived from simulated transients in unbranched "equivalent" cable models for the same six neurons. As before, the values of L_{peel} are consistently larger than the other estimators and, in addition, exhibit considerable variation from cell to cell. We can understand that L_{peel} is larger than the other measures because it depends on properties of the transient that depend on the presence of a soma. The effective L of a whole neuron estimated from transients is larger than the steady-state estimates based on the dendritic trees alone (100, 101).

E. How Does the System Time Constant Depend on the Soma Shunting Factor?

As noted, the largest system time constant, τ_0 , becomes necessarily smaller than the time constant of the dendritic membrane, $\tau_{\text{md}} = R_{\text{md}}C_{\text{m}}$, when either a voltage clamp or a leaky shunt conductance is added to a model with otherwise uniform R_{md} and C_{m} (see Ref. 100, p. 1498–1503, for the equivalent cylinder case). It is useful to remember that the voltage-clamp boundary condition corresponds to the limiting case of a leaky shunt, as the shunt conductance increases to infinity. For a uniform cylinder with one end sealed and the other end shunted, we can express this as

$$\lim_{\beta \rightarrow \infty} \frac{\tau_0}{\tau_{\text{md}}} = \frac{\tau_{\text{vc1}}}{\tau_{\text{md}}} = \left[1 + \left(\frac{\pi}{2L} \right)^2 \right]^{-1} \quad (22)$$

where τ_{vc1} represents the largest "voltage clamp" time constant (i.e., the time constant of the current transient recorded with a voltage clamp at one end), L is the electrotonic length of the cylinder, and β represents the shunt factor at one end. This limiting ratio has a value of ~ 0.29 for $L = 1$ and ~ 0.63 for $L = 2$. For smaller leak conductance at one end, this ratio depends on the root of a transcendental equation (see Eq. 43 in Ref. 100) that can be implemented easily on a small computer. Note that the limiting expression at right holds also for a passive neuron model with any size soma, provided that the dendritic trees are equivalent to a single uniform equivalent cylinder with electrotonic length L .

An intuitive physical understanding of this limiting ratio can be based on the following considerations. A short circuit of the soma membrane cannot instantly discharge the entire dendritic membrane because of dendritic cable properties. Nevertheless, the shunt current does speed the decay of membrane potential toward its nonuniform steady state (i.e., $\tau_0/\tau_{\text{md}} < 1$). For example, in an ideal cylinder the fact that $\tau_{\text{vc1}}/\tau_{\text{md}} = 0.29$ for $L = 1$, but 0.63 for $L = 2$, can be understood by considering that the distal membrane capacitance is more remote (electrotonically sheltered) from the somatic shunt when $L = 2$ than when $L = 1$; the current flowing from the distal capacitance to the shunt has to traverse more dendritic core resistance. The effect of a soma shunt (or of $R_{\text{ms}} < R_{\text{md}}$) has been presented and discussed in several papers (15, 28, 37, 64, 72, 92).

In Figure 8, we summarize the results of computations that show how the value of τ_0 becomes reduced as a function of a graded increase in shunt conductance at the soma while R_{md} is kept uniform and constant. The ratio, τ_0/τ_{md} , is used to provide normalized ordinates. This τ_{md} represents a useful reference value, because we have assumed R_{md} to be constant and uniform in these computations. The parameter β (used for the abscissa scale in Fig. 8) has already been defined and discussed in section IIID (see Eq. 8). As β increases from 1 to 1,000, one can think in terms of increasing somatic shunting or in terms of reducing R_{ms} , recalling that R_{md} is constant.

Figure 8A summarizes computations for three cylinders showing how τ_0/τ_{md} decreases as β increases. The middle curve (for $L = 1.0$) falls to a limiting value of ~ 0.29 , defined by Equation 22 for $L = 1$, as β increases. The practical meaning of this result is that using an experimentally estimated τ_0 uncritically as an estimate of τ_{md} can easily underestimate the correct τ_{md} value by a factor of 2 or 3 if $L = 1$ or even more if L is smaller. The other two curves in Figure 8A correspond to different dendritic electrotonic lengths, represented by cylinders whose diameters were adjusted to preserve dendritic input conductance relative to a constant soma surface area. This ensured that the conductance ratio, $\rho = G_{\text{D}}/G_{\text{S}}$, was the same in each case of Figure 8A (in all three cases, $\rho = 12.7$ for $\beta = 1$, implying that $\rho\beta = 12.7$ for all points in Fig. 8; see Eqs. 8–11). The three curves in Figure 8A differ little for small values of β , but it is clear that, as β increases, the value of τ_0 decreases least for the largest value of L because of the electrotonic shel-

FIG. 8. Graphs to illustrate several features of dependence of ratio τ_0/τ_{md} on β under different model conditions for soma plus equivalent cylinder models in which electrotonic length (L) of each dendritic compartment was 0.05λ and $\rho = 12.7$ when $\beta = 1$; here $R_{md} = 20,000 \Omega \cdot \text{cm}^2$ and $C_m = 1.0 \mu\text{F}/\text{cm}^2$. *A*: increasing influence of somatic shunt (increasing β) on value of τ_0/τ_{md} as dendritic L was shortened from 2.0 to 0.30. *B*: similar influence is evident in nonlinear decline in relation between τ_0/τ_{md} and β for 5 values of $\rho\beta$. *C*: influence of model structure on relation between τ_0/τ_{md} and β . Idealized equivalent cylinder ("one cyl"), as well as tapered and flared structures; all had $L = 1.0$. In 2-cylinder case, 1 cylinder had $L = 0.5$, and other had $L = 1.0$. In tapered and flared structures, value of $d^{3/2}$ changed in a stepwise manner (with constant increments of l/λ such that final value was 0.05 of initial value for tapered case and 1.95 times initial value for flared case).

tering of the distal dendritic membrane capacitance from the somatic shunt when L is large. In contrast, when L is very small, the dendritic membrane becomes almost an isopotential patch of membrane exposed directly to the somatic shunt, resulting in a large decrease in τ_0 as β increases.

Figure 8B shows complementary results for five val-

ues of $\rho\beta$, all with $L = 1$. If we remember that $\rho = G_D/G_S$, the 100-fold range of $\rho\beta$ shown here can be thought of in terms of increasing neuron size. For a fixed soma area and fixed dendritic membrane properties, the curves compare dendritic trees of five different sizes (all with $L = 1$) such that the $d^{3/2}$ values of the five equivalent cylinders cover a 100-fold range in G_D . Then $\rho\beta = 1$ represents the smallest tree, which shows the most reduction of τ_0 for the shunting that corresponds to any given value of β , whereas $\rho\beta = 100$ represents the largest tree, which shows the least reduction of τ_0 for any given β .

There is a striking similarity between Figure 8B and Figure 3. In fact, much of the earlier discussion in section IIIG (associated with Fig. 3 and Equation 16), which compares the five curves and notes the near equivalence of different pairs of values for $\rho\beta$ and β , applies also to Figure 8B. The most important conceptual difference is that Figure 8B assumes a dendritic tree that is equivalent to a cylinder with $L = 1$, whereas Figure 3 depends only on $\rho\beta$ and β , without restriction on L or on equivalence to a cylinder. The asymptote, as β approaches infinity, is zero for the curves in Figure 3, whereas it is 0.29 (the limiting expression Eq. 22 with $L = 1$) for the curves in Figure 8B. For example, if $\rho\beta = 20$ with $\beta = 100$, Figure 8B shows that the value of τ_0/τ_m is ~ 0.4 compared with 0.2 for R_N/R_{N1} .

The qualitative features of these computed curves do not depend on the equivalent cylinder idealization of the dendritic tree. Figure 8C was prepared to demonstrate how much quantitative difference can be expected in particular cases of departure from the single equivalent cylinder. Here, all curves correspond to the same soma and the same dendritic input conductance, as specified by $\rho\beta = 12.7$ (also, $L = 1$ in all cases, except in the two-cylinder case, where L values were 0.5 and 1). The computed curves in Figure 8C differ little for small values of β , but they do diverge for larger β . The uppermost curve (flared) corresponds to a normalized $d^{3/2}$ value, which increases (from 1 to 1.95) with distance from the soma; we can understand that τ_0 is reduced least in this case because the flare causes a larger portion of the dendritic membrane to be distal and thus more electrotonically sheltered from the somatic shunt. The bottom curve (tapered) corresponds to a normalized $d^{3/2}$ value that decreases steeply (from 1.0 to 0.05) with distance from the soma; we can understand that τ_0 is reduced most in this case, because a much larger portion of this membrane is proximal and thus more electrotonically vulnerable to the somatic shunt.

The computed results for the two-cylinder case in Figure 8C differ least from the one-cylinder reference case. The fact that its τ_0 is lower than the reference case in the midregion can be understood because the shorter cylinder causes a larger portion of the total dendritic membrane to be more vulnerable to the somatic shunt than in the reference case. The fact that these two curves approach the same asymptote for large values of β can be understood because, when the shunt conductance becomes infinite, the resulting short circuit completely decouples the two cylinders, at which point the

longest time constant corresponds to τ_{vc1} for the longer of the two cylinders, in agreement with the one-cylinder reference case.

When working with experimental records, τ_0 designates the slowest time constant that can be extracted from the transient. Experimental noise and baseline overshoot both contribute to reduced reliability of the tail phase of the transient decay; however, in favorable cases, there is sufficient separation between the two largest τ_n values to permit reliable estimation of the values of τ_0 and C_0 from a semilog plot of the tail decay. However, it should be understood that low estimates of τ_0 are likely when the duration of the reliable portion of tail decay is less than twice the actual τ_0 , as pointed out in Reference 25 (see also Fig. 12 in Ref. 37).

F. Voltage-Clamp Responses Are Independent of the Soma Shunting Factor

If the soma is voltage clamped, the current at the soma and the potential at other sites can again be expressed as a sum of exponential decays as in Equation 18 but with different coefficients and time constants. It is possible to recover the first of these time constants, τ_{vc1} , and in rare cases the second, τ_{vc2} , by peeling exponentials from the experimental current transient. Use of τ_{vc1} and τ_0 , or τ_{vc1} and τ_{vc2} , provides another means to estimate L for an idealized equivalent cylinder model (100). The voltage-clamp time constants are not affected by β because the steady-state shunt current is established very rapidly by a good voltage clamp. In a neuron with many dendritic trees, the value of τ_{vc1} will be governed by the L value of the longest tree and τ_{vc2} by the second longest. However, just as with current-clamp recordings, in a neuron with many long dendritic trees of approximately equal length, τ_{vc1} may be difficult to distinguish from τ_{vc2} , and this may slightly affect the reliability of estimates of τ_{vc1} .

G. Estimating the System Time Constant Without Simulating Transients

It is not always necessary to simulate transients for a given neuron model to estimate the value of τ_0 implied by cell geometry, even when R_m is spatially nonuniform. Indeed, for any compartmental model with passive nonuniform membrane, the value of τ_0 is an algebraic property of the model; it equals $\tau_m/(1 + \alpha^2)$, where α is the smallest eigenvalue of the compartmental system, and this can be computed by means of matrix inversion when the appropriate software is available (46, 61, 89).

There are also other calculations that can yield approximate values of τ_0 for various models with nonuniform membrane. For a smooth nonuniformity of R_m (assuming no discontinuity at the soma but increasing values of R_m with distance along the dendrites), it was found for several different smooth functions in idealized equivalent cylinder models (102) that one can average the membrane conductance values of different regions,

weighted by their corresponding membrane areas. This yields an effective G_m , from which τ_0 can be calculated for an assumed value of C_m .

Such weighting has also been used in computations with neuron models that embody complete dendritic morphology (37) and nonuniform R_m . The reciprocal of the area-weighted mean G_m was designated $R_{m,eff}$. For a neuronal model with uniform R_{md} and step decrease to a smaller value of R_{ms} , this can be expressed as

$$R_{m,eff} = \frac{A_N}{G_{ms}A_S + G_{md}A_D} \quad (23)$$

Fleshman et al. (37; see Fig. 5 therein) found that the product $R_{m,eff}$ and C_m sometimes provided a good approximation of the τ_0 obtained from simulated transients when ρ was relatively large but that there was a significant error (40–60%) for neurons with relatively small values of ρ (i.e., those with the largest soma shunt conductance). This suggested the possibility that τ_0 may be predicted using calculated values of $R_{m,eff}$ and ρ when the morphology is known.

VI. CONSTRAINED INVERSE PROBLEM WITH DIFFERENT MODELS

In the inverse problem, the object is to obtain values for several unknowns given experimental measurements of the transient data, R_N , and the morphology. The inverse problem is never general; rather, it is always constrained by the choice of a class of models and often is constrained also by fixing the values of certain parameters, such as C_m and R_i . It is useful to state explicitly what the unknowns are in any given problem. Assuming we have the complete morphology together with electrical measurements, given that we arbitrarily restrict consideration to that class of membrane nonuniformity that has R_{md} uniform over the dendrites, $R_{ms} < R_{md}$, and given, at least at first, that the value of C_m is assumed uniform and set equal to $1 \mu F/cm^2$, we are left with three unknowns: R_{md} , R_i , and β (or R_{ms}). One could specify a fourth as the shrinkage factor and a fifth as the value of C_m to be estimated from the fit to unusually good data. The parameters L and $\rho\beta$ are not additional primary unknowns, because their values are determined by R_{md} and R_i , together with the shrinkage-corrected morphology. Thus the initial focus is on R_{md} , R_i , and β .

If one first assumes that C_m and R_i are given, together with the morphology, one can find many pairs of values of R_{md} and β that provide agreement with the experimental estimate of R_N . One would then like to find one such pair that also provides agreement with the experimental estimate of τ_0 . However, even such a solution would not be unique, because different solutions would result for different values assumed for R_i . Two approaches to further testing and selection of such solutions involve fitting more of the transient than just τ_0 . One of these involves computing simulated voltage and current transients for a model representing the com-

plete morphology and fitting these simulated transients to those recorded experimentally (15, 142). Another approach is to peel the several slowest exponential terms in the experimental transients and to seek the solution that best fits these τ_n and C_n values (30). In favorable situations, one could also involve estimation of the slowest time constants present in the clamping current when a voltage clamp is applied to the neuron soma.

It is noteworthy that uniqueness problems are severe when reliance is placed on transient analysis without morphology. Even with perfect transient data, such nonuniqueness can be resolved only by taking morphological data into account. Once this point is appreciated, one can devise an approach that distinguishes different morphological types of dendritic branching and then pursue the inverse problem for the appropriate reduced model. If the morphological type is particularly simple, it may be possible to solve the inverse problem analytically (see formulas for various cases in Ref. 60). In general, one may be forced to use compartmental models to pursue the inverse problem. Reduced models that might be appropriate for different neurons include the equivalent cable discussed in section VB (15, 37), two equivalent cylinders of unequal length with soma (61), or multiple equivalent cables connected to the same soma (see Fig. 6). Of course, any kind of branching geometry is possible with compartmental models. Once good estimates of the unknowns are obtained with reduced models, these estimates can be refined using a model with full morphology, assuming such data are available.

It should be noted that nonuniqueness may occur in a reduced model that does not specify the soma membrane area and the dendritic membrane area of each tree; estimates of the unknowns may be very sensitive to errors in these area values. Also, a modeling example (see Table 1 in Ref. 59) provides an illustration of how three different sets of values for R_{md} , R_{ms} , C_m , A_s , A_D , and L can generate identical transients and have the same input resistance; this nonuniqueness is shown to result from the unknown value of R_i and unspecified length and diameter of the equivalent cylinder.

An efficient way to solve the constrained inverse problem is to combine the compartmental modeling approach with a Newton-Raphson algorithm (59). In this approach one decides on a set of known parameters (e.g., 4, consisting of τ_0 , R_N , and any 2 of C_0 , τ_1 , or τ_{vel}) and a set of unknown parameters (e.g., 4, consisting of R_{md} , R_i , C_m , and either β or R_{ms}). Initial guesses of the unknown parameters are used to generate values for the known parameters as in the usual compartmental approach. The difference between these generated values and the actual values of the known parameters is used to determine how good the initial estimates of the unknown parameters are. By computing derivatives, the algorithm picks new estimates for the unknowns. In a few iterations, the algorithm usually settles on estimates of the unknowns that produce the desired values for the known parameters, at least when the initial estimates are reasonably close to correct. It is helpful and sometimes necessary to further constrain the parameter space to phys-

ologically reasonable values; examples of constraints that can prevent convergence to useless (physiologically meaningless) solutions are $A_s < A_D$ and $\tau_0 < \tau_{md}$. When complete morphology was included, the constrained inverse computation (involving the 4 known and 4 unknown parameters) was found to converge to the same solution for a wide range of initial guesses (59). Without complete morphology, however, this method is subject to the nonuniqueness and sensitivity problems noted when there are too many degrees of freedom (59, 104).

VII. DISCUSSION OF UNCERTAINTIES

The matching of a neuron model to biological reality is confronted by difficulties at several levels that merit explicit, if brief, mention. The first level concerns experimental artifacts. The properties of a neuron in the experimental situation can, at least in principle, be altered from the "normal" (i.e., undisturbed) state because of anesthetics, penetration by a micropipette, injection of ions and tracer compounds, and, finally, by tissue fixation. Each of these factors can be responsible for changes that influence the validity of interpretation that can be drawn from the data and some (e.g., the production of somatic shunts by micropipettes) have been discussed (see sect. IV C). The process of experimental observation, which is obviously essential, cannot be overlooked as a source of uncertainty, a point well understood in quantum physics. The second level concerns obvious sources of both random error and systematic measurement error, including noise in experimental records and a long list of problems with anatomic reconstruction. The third level concerns model selection and interpretation. These issues have been dealt with at some length already. Next, a few of the more pertinent problems are touched on.

A. Shrinkage

Dehydration of neural tissue during histological processing may cause the lengths and diameters of neural profiles to be altered, possibly in anisotropic ways. It is usually assumed that shrinkage measured along either axis of a section applies uniformly to all cell profiles aligned with that axis, be they neurons or glial cells. Shrinkage in spinal cord sections was reported by Burke et al. (12) to be from 3 to 10% in sagittal sections and 15 to 20% in transverse sections; Cullheim and Kellerth (23) report 10% shrinkage in longitudinal sections, whereas Barrett and Crill (3) estimated a volume shrinkage of up to 50% for spinal motoneurons (implying up to ~20% linear shrinkage). This poses a serious problem when one attempts to match morphology to electrical measurements, because (unless one corrects for shrinkage) the reconstructed neuron will have a smaller surface area (and smaller dendritic cross sections) than the neuron in which the electrical measurements were made. There are no good ways to measure, or correct for, anisotropic shrinkage, although it seems possible that

visualization of a single neuron with fluorescent tracer in situ, with subsequent labeling of the same cell by HRP, might help in this regard.

B. Uncertainties About Cytoplasmic Resistivity

Cytoplasmic resistivity is difficult to measure directly, and the only reported value of R_i for mammalian neurons is $70 \pm 15 \Omega \cdot \text{cm}$ (3). These authors used a method described by Schanne (121), which is based on the change in electrode resistance when measured in solutions of different resistivity. Other values for R_i in mammalian central nervous system (CNS) neurons have been estimated indirectly and range from 50 to 225 $\Omega \cdot \text{cm}$ (see Ref. 132). Much more information is available about R_i for neurons and axons of marine invertebrates. The value of R_i averages 40 $\Omega \cdot \text{cm}$ for *Aplysia* neurons (39) and 57 $\Omega \cdot \text{cm}$ for the axoplasm of the giant marine worm, *Myxicola* (41) (see Refs. 39, 41 for additional references to earlier work). Because the concentration of the dominant charge carriers in the axoplasm of marine invertebrates is approximately three times that of mammalian CNS neurons (seawater is ~ 3 times as concentrated as mammalian cerebrospinal fluid, but the activity may be only ~ 2.5 times), one is led to consider values of ~ 100 – $150 \Omega \cdot \text{cm}$ for R_i of mammalian neurons. In fact, transients recorded in cerebellar Purkinje cells were best matched to the morphology when R_i is 225–250 $\Omega \cdot \text{cm}$ (130, 132).

In a recent measurement, R_i for a solution combining 50 mM NaCl and 110 mM KCl in 1% agar at 37°C was found to be 43 $\Omega \cdot \text{cm}$ (15). These concentrations are close to being isosmotic with the cytoplasm of mammalian motoneurons (38), but one might expect that R_i in the cytoplasm should be larger for several reasons: 1) in the cytoplasm most of the Cl^- is replaced by large anions that contribute so little to electric conductivity that one should nearly double the value of R_i to $\sim 80 \Omega \cdot \text{cm}$, and 2) because of charge binding, and the presence of large proteins (in organelles and in the cytoplasmic matrix), there may be another factor of ~ 1.5 , relative to aqueous solutions, that would increase this estimate of R_i to $\sim 120 \Omega \cdot \text{cm}$.

Using too small a value of R_i will result in an overestimate of R_{md} when matching particular values of input resistance and surface areas. Uncertainty about the correct value of R_i is also responsible for uncertainty in the correct value of R_{m} because the ratio R_{m}/R_i appears in Equation 1 for λ and the product $R_{\text{m}}R_i$ appears in Equation 4 for G_{∞} . The nonuniqueness, implied by equally good combinations of R_{md} and R_i values found when matching experimental transients, makes it necessary to seek an independent measure for R_i . Eventually it may be possible to do two-point transfer measurements along a dendrite (in a culture or a slice preparation) with known spacing between the electrodes and known dendritic cross section; this should help to pin down the value of R_i . There also remains the possibility that R_i could increase gradually along the dendrites.

C. Nature of Somatic Shunt Conductance

There seems to be little doubt that microelectrode penetration can introduce a shunt conductance associated with leakage around the microelectrode (66). The leak resistance has been calculated for microelectrode penetration of muscle fibers, where the entry of a second microelectrode has been monitored by the original penetration; there the leak resistance was found to range from 10 M Ω (53) to >20 M Ω (140). Also, whole cell patch-clamp measurements of input resistance of cultured neurons are usually higher than those obtained for similar neuron types when using intracellular microelectrodes (85, 91, 136, 139, 141).

If the somatic shunts calculated for motoneurons were only a direct effect of a purely resistive microelectrode leak, and hence not ion selective, resting membrane potentials approaching 0 mV would be expected (15, 37, 43). Because resting membrane potentials are often more negative than -60 mV, we infer that the electrode damage must be selective, possibly resulting in the opening of ionic channels that tend to hyperpolarize the neuron. An increase of intracellular Ca^{2+} to $>1 \mu\text{M}$ has been observed in neurons immediately after microelectrode penetration (76). Among many other actions, increases in internal Ca^{2+} are known to activate K^+ and Cl^- conductances (75, 87), both of which tend to hyperpolarize neurons. The extent to which such Ca^{2+} -mediated conductances, in parallel with a non-ion-selective conductance around the microelectrode, fully account for the total shunt conductance is difficult to assess. From a knowledge of the shunt magnitude and the resting potential, one could calculate two unknown conductance parameters for specified reversal potentials (15). However, as soon as more channel types and reversal potentials are considered, additional experiments with changed ionic concentrations and channel blockers would be needed to resolve the uncertainties.

It should be emphasized that the likelihood of artifactual shunts produced by micropipette penetration does not, however, exclude the further possibility that ion-selective channels that are open at rest are in fact present in greater densities in somatic membrane than in dendritic membrane, especially in view of the recent direct demonstration of a greater density of voltage-dependent Na^+ channels on the initial segment and soma of Purkinje cells (144). The issue of somatic shunts thus represents an example of the first level of problems discussed at the beginning of this section. At the present time, it seems prudent to regard β as one of the basic unknowns that must be estimated from an analysis of the morphological and electrical data obtained with intracellular microelectrodes.

VIII. IMPLICATIONS FOR NEURAL INTEGRATIVE FUNCTION

As mentioned earlier, the major reason for using explicit neuronal models is to explore the consequences

of neuronal and synaptic morphology on the integration of synaptic information in postsynaptic neurons. Here, we have attempted to provide methods for evaluating passive cable properties in neurons with dendrites that do not collapse to a cylinder of constant diameter and when the somatic membrane resistivity differs from the dendritic membrane resistivity. In this section we discuss some of the implications of these more complicated electrotonic structures for the integrative function of the neuron.

A. *Electrical Compactness and Efficacy of Dendritic Synapses*

As pointed out in sections III and V, R_{md} is underestimated from measurements of R_N or τ_0 unless β (defined by Eq. 8) is taken into account. Recent publications (15, 28, 37, 43, 132) have shown that the value of β may be ≥ 100 for motoneurons of cat spinal cord, and this means that R_{md} for these cells has previously been underestimated by a factor of fourfold or more. Such a factor of four in R_{md} would double all of the implied λ values and thus halve the electrotonic lengths of all dendritic branches. This suggests that the dendritic trees of motoneurons are even more electrically compact than has been hitherto believed, thereby affecting interpretation of voltage-clamp recordings (107) and of the effects of polarizing currents injected at the soma.

It also follows that synapses on relatively remote dendritic branches are nevertheless electrotonically closer to the soma than might be supposed on the basis of the anatomy alone. The same synaptic current injected into the more compact dendritic tree will be transferred more effectively to the soma for several reasons. One reason is obvious, the increased electrotonic proximity of the soma to the synapse. The other reason is less obvious because it results from the increased electrical proximity of dendritic terminations with sealed ends that "reflect" or "dam" the current, which makes the distal membrane more nearly isopotential. The net result is that the fraction of injected charge that reaches the soma from a dendritic synapse will be increased when the entire tree is more compact. However, the voltage that this more effective charge transfer generates at the soma depends on how much shunting actually exists in the neuron before penetration, i.e., how much of β is due to membrane puncture and how much is due to ion channel density differences that could make G_{ms} greater than G_{md} in Equation 8.

B. *Synaptic Potential Shape Indexes*

The shape indexes (half-width and rise time) of synaptic potentials recorded at the soma and generated by synaptic input at various locations along a uniform dendritic cable have provided the basis for estimating synaptic location on the dendritic tree from the time course of an EPSP (67, 68, 105, 113). The computation of

these shape indexes needs to be revised to take account of somatic shunts and changed dendritic electrotonic distances. When a somatic shunt is introduced into a uniform cylinder model and all other parameters remain constant (i.e., only effective R_{ms} is altered), the effect on shape indexes is as follows. The early rate of rise for somatic synapses can be essentially unchanged because the soma capacitance has not been changed; the more rapid the current time course, the greater will be its insensitivity to the shunt, because rapid currents preferentially charge the membrane capacitance (see Refs. 34, 68). As β is increased, the decreased τ_0 has the greatest effect on the decay time course of the EPSP, reducing the half-width (126). The rise time of EPSPs spreading from more distal input locations is also reduced for the same reason. However, the picture becomes more complicated when the shape indexes are normalized relative to τ_0 ; these complications are not elaborated on here. Several interesting examples of computed EPSP shapes and amplitudes are provided and discussed in Reference 126 for different synaptic input locations, using both the "step model" and the "sigmoidal model" of increased dendritic R_m .

When the electrotonic lengths from the soma to the termination of various branches of the dendritic tree are very different, there are important effects on synaptic potentials that depend on local anatomy. It is important to point out that the average dendritic length is an inappropriate reference when one considers the spread of synaptic currents from the input branch toward the soma. The way in which current spreads from a synapse located on a branch that is much longer or shorter than the average electrical length of the tree differs significantly from that expected for a synapse on a branch with the same length as the average for the tree. Under these circumstances, the computation must include the full details of all branches along the main dendritic path, from the synapse to the soma (126). However, the computation can be simplified by substituting reduced versions (collapse to unbranched cable) of the other dendritic trees, which receive no input in the case under study (see example of "other trees" in figures of Refs. 81, 82, 106, 117).

C. *Impact of Network Activity on Neuron Cable Properties*

Many of the neurons in the mammalian CNS have 10^4 – 10^5 synapses per neuron distributed over their dendritic surfaces. Each of these synapses may fire at a rate of a few to many spikes per second. Consequently, the dendritic surface of a neuron may be bombarded by several hundred synaptic activations per millisecond. Such synaptic activity will produce a massive increase of dendritic membrane conductance, thus altering the integrative capabilities of the neuron when compared with the same neuron in a quiescent state.

Three recent studies have explored the impact of

FIG. 9. Graphs showing influence of synaptic input on electrotonic properties of a Purkinje cell model. Purkinje cell was reconstructed (membrane area = $149 \times 10^3 \mu\text{m}^2$) following electrophysiological study ($R_N = 12.9 \text{ M}\Omega$; $\tau_0 = 46 \text{ ms}$) and injection with horseradish peroxidase. Dendritic spines (area assumed to be $1.0 \mu\text{m}^2$ each) receiving 100,000 parallel fiber synapses were incorporated into a compartmental model of this cell. This model was implemented in SPICE (model parameters: $R_{ms} = 400 \Omega \cdot \text{cm}^2$; $R_{md} = 100,000 \Omega \cdot \text{cm}^2$; $C_m = 1.64 \mu\text{F}/\text{cm}^2$; $R_i = 250 \Omega \cdot \text{cm}$). Parallel fiber synapses were assumed to generate an α -function with time to peak = 0.3 ms and peak conductance of 0.4 nS (reversal potential 60 mV positive to resting). A: plot of net somatic depolarization (V_{soma}) produced by steady, asynchronous activation of all parallel fiber synapses at different background frequencies. B: increase in average electrotonic length (L_{av}) of Purkinje cell dendrite produced by same synaptic activation. C: decrease in calculated input resistance (R_N) produced by parallel fiber synaptic activity at different background frequencies. D: decrease in calculated τ_0 produced by parallel fiber synaptic input.

tive capabilities of the neuron can be dynamically altered by the diffused (nonspecific) activity of the network to which the neuron belongs.

IX. CONCLUSIONS

The primary purpose of this review has been to examine some of the interaction between theory and experiment that has taken place in our efforts to understand the implications of complex neuronal architecture. Before it became possible to do both electrophysiological and morphological measurements on the same cell, the application of electrotonic (cable) theory to idealized models of dendritic branching provided valuable insights and helped to stimulate further experiments. Now, as more comprehensive anatomic information becomes available for many different types of neurons, it is important to explore the probable consequences of morphologically realistic branching and synaptic input patterns on the electrotonic and integrative properties of individual neurons. It has become clear that the electrical parameters of the neuron cannot be determined by electrophysiological measurements alone; some morphological information is necessary to resolve problems of nonuniqueness. The explosion of data about time- and voltage-dependent ionic channels provides a further challenge to neuron modeling; when the channel densities can be specified for different membrane areas, their functional implications can be explored by simulations with compartmental models.

In our view, it is essential to have a firm grasp of the consequences of neuronal morphology on electrotonic properties, using passive membrane assumptions, before adding the next layer of problems posed by nonlinear membranes. Given this foundation, modern computational techniques should make it possible to build realistic, nonlinear neuron models as experimental research provides us with constraints about the properties and local densities of these channels for different neuron types. The development of reduced models of intermediate geometric complexity is important for several purposes: to foster functional insights, to facilitate explorations with nonlinear membrane properties, and also to facilitate realistic network simulations.

This review grew out of a workshop shared by the authors, in August of 1987, at the Neurosciences Institute in New York City. A joint writing effort produced a draft manuscript that was distributed among the authors and some friends (May 1988), but final revisions were delayed. Now, with the addition of many recent references, together with some updating of the text, we trust that readers will find this overview to be still timely. We acknowledge research collaborators who were not included in the workshop (it was arbitrarily limited to six persons), particularly John Clements for his part in Reference 15 and Jim Fleshman for his part in References 37 and 126.

We acknowledge helpful support from several sources. The workshop was supported by the Neurosciences Institute, New York City. Preparation of this review was supported by

background synaptic activity on an individual neuron, using detailed models based on neurons of mammalian CNS (5, 62, 111). Some useful results are summarized in Figure 9, for the case of background activity of parallel fiber synapses on the dendritic membrane of cerebellar Purkinje cells (130). Figure 9 shows that the cable properties of the modeled neuron are changed significantly even at low background frequency. The most sensitive parameter is τ_0 (Fig. 9D), which falls by almost a factor of four from 46 ms (for zero background activity) to 12 ms for a background frequency of 5 spikes/s in each of the 100,000 parallel fibers modeled. The input resistance also decreases with increasing frequency (Fig. 9C); however, the effective cable length increases (Fig. 9B). These results imply that the efficacy of individual synaptic inputs becomes decreased very significantly as the background frequency is increased. Note that the reduction in τ_0 means that synaptic potentials will sum better when the inputs are simultaneous than when they are asynchronous (4). These studies show that the integra-

the intramural research program at the National Institutes of Health (Bethesda, Maryland), by the John Curtin School for Medical Research (Canberra, Australia), and by the United States-Israel Binational Science Foundation (Jerusalem, Israel).

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