

Single neurone models: oversimple, complex and reduced

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The single neurone stands in the midst of a controversy among modelers. Some believe that its details are functionally superfluous when the neurone operates in a large network, and very simple models can be used to represent the input/output characteristics of neurones. Others claim that the unique morphology and electrical properties of neurones do play an important role. Complicated models of neurones are developed to reveal how the various kinds of 'neurone-ware' (dendrites, spines, axons, membrane channels and synapses) create a computationally powerful unit. Various models are discussed, including new carefully reduced models that retain essential features of more complex models. Such intermediate models will play a central role in our efforts to understand information processing in large neuronal networks.

In the beginning there was the creative mind and artistic capabilities of Ramón y Cajal. Attracted by the beauty of neurones, Ramón y Cajal abandoned a promising career in bacteriology, and with his beloved microscopes and improved Golgi staining technique, he established the 'neuron doctrine', demonstrating that the neurone with its dendritic and axonal trees is a distinct entity that serves as the basic functional unit of the nervous system^{1,2}. His law of dynamic polarization affirms that dendrites and soma are the receptive areas for inputs arising from axonal terminals of other neurones, and that the output impulses are transmitted unidirectionally by the axon to its collaterals that excite, through axodendritic connections, the dendritic trees and cell bodies of the next neurones in the chain. Because Ramón y Cajal paid close attention to the fine structure of neurones, he was aware that in many instances dendrites are studded with innumerable spines and that the axon collaterals often form varicosities, or boutons, near these sites (Fig. 1). Beautiful three-dimensional pictures from a confocal microscope, using original preparations of Ramón y Cajal were recently published³.

Ramón y Cajal's ideas about the operation of the nervous system stem from information on its structure, measured at the light microscope level. We had to wait 50 years for the development of the electron microscope to confirm and refine his morphological observations. Functionally, Ramón y Cajal did consider the input/output properties of neurones, but did not know of synaptic excitatory or inhibitory mechanisms, nor of NMDA receptors or membrane channels subserving spikes and other membrane nonlinearities. Information on this basic 'neurone-ware' has dramatically increased our understanding of the integrative processes implemented by neurones. Nonetheless, from the point of view of information flow in the nervous system, Ramón y Cajal's work established several important concepts. First, the single neurone is the elementary input/output unit of the nervous system. Second, collaterals of a single axon can

influence many neurones, and, similarly, because of the large surface area of the dendritic tree, a single neurone can receive inputs from a great many sources. Third, in most neurones, the input region is anatomically separated from the output region. This may imply that the output events are temporally separated, or delayed, from the input events. Finally, as confirmed by electron microscope studies, most of the synaptic contacts are made at very localized dendritic sites that, in many cases, bear the morphology of spines. As discussed below, this, coupled with the extensive arborization of dendrites, seems to be significant for the computational capabilities of neurones.

Ramón y Cajal was well aware of the possible functional significance of dendrites when he asked what happened when several inputs coming from the dendrites compete for the right of way. Or, in other

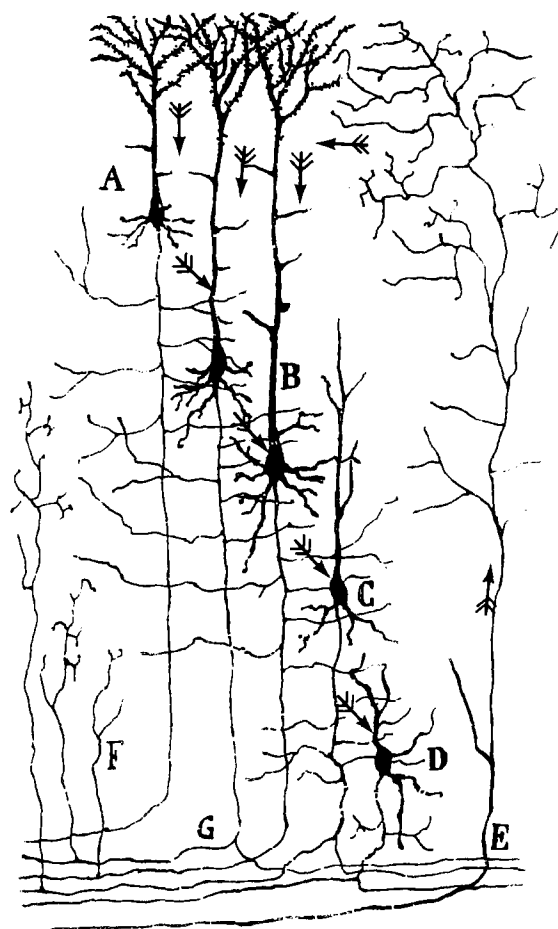


Fig. 1. Ramón y Cajal's view of the probable direction of current flow (colored arrows) and pattern of axo-dendritic connections between cells in the cerebral cortex. The detailed morphology of the neurone is depicted, including the dendritic branches and spines, the soma and the axonal tree. Dendrites and soma receive inputs from many cells via terminal arborization of axon collaterals¹.

words, Ramón y Cajal essentially asked how information, conveyed by the input, is processed at the dendrites. He erroneously thought that it was the soma that determined which input should have priority. However, only 50 years later did questions regarding dendritic processing become the focus of serious theoretical work.

The 'morpho-less', point neurone – two viewpoints

A model is something simple made by the scientist to help them understand something complicated⁴. A good model is one that succeeds to reduce the complexity of the modeled system significantly while still preserving its essential features. The degree of reduction needed clearly depends on the question posed. For some levels of description a very simple model is sufficient, whereas for other questions a more detailed model is required. A feature common to all early modelers is that they chose to neglect the geometrical complexities of nerve cells altogether and represented the neurone as a 'morpho-less', or point, unit. This abstraction is also apparent in drawings of physiologists during the 1930s and 1940s, in which the extensively branched dendritic tree (that, in most CNS neurones occupies more than 90% of the receptive area) is completely absent and all inputs were drawn on the remaining sphere-like soma (e.g. Refs 5, 6). The axon was left as a thin line connecting the presynaptic cell to the various post-synaptic neurones (Fig. 2). In their well-known paper, McCulloch and Pitts⁷ claimed that 'excitation across synapses occurs predominantly from axonal terminations to somata'.

The morpho-less, point neurone served, and is still serving, mathematical models for two very different purposes. One is to explore the dynamical behavior of very large interconnected networks of neurones. For this level of questioning the single neurone is typically (but not always) modeled as a simple digital 'on-off' unit. The rationale for using this simple neurone model is that in many physical systems composed of a large number of simple elements the emergent collective behavior is insensitive to the details of the model. Because the single neurone is not the focus of this class of models, these morpho-less digital neurone models are only briefly discussed below. The other class of morpho-less neurone models pays close attention to the electrical dynamics of the single neurone. The general goal of this approach is to explore how the various underlying membrane currents determine the large repertoire of electrical activity found in real neurones. For this purpose the neurone model is analogue in nature rather than digital, and may become mathematically very complicated when many types of membrane currents (channels) are involved.

Morpho-less digital (discrete) models

This class of models emphasizes the 'all-or-none' characteristic of neurone firing; a unit is represented as a digital, binary device that performs a simple logical operation. These artificial neurones are discrete in nature, both because they have discrete states ('on' or 'off') and because time is quantized. Within each discrete time-unit, each modeled neurone sums the incoming excitatory and inhibitory inputs

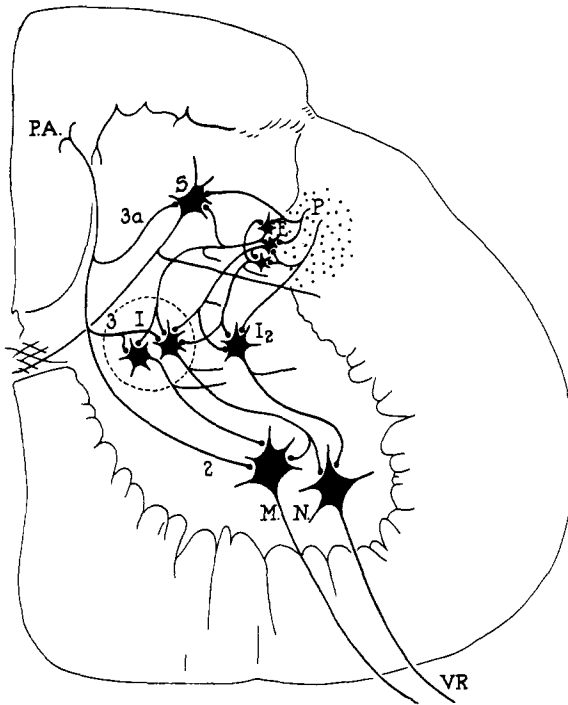


Fig. 2. An example that demonstrates the tendency of physiologists and modelers during the 1940s to neglect dendritic morphology. Dendrites and soma are lumped together into functionally single summing points with axons connecting one point to another. Figure shows a hemi-section through the spinal cord, with soma and dendrites shown as filled bodies⁶.

and, if a certain voltage threshold is reached, an output ('on') is produced. These highly abstract models focus on the emergent properties of massively interconnected large networks of such 'neurones'. Their importance arises from the demonstration that, although the elementary unit is computationally very simple, the collective computational capabilities of the whole (connected) network are immense. Most significant among these 'connectionists' models using binary neurones are those of McCulloch and Pitts⁷, Minsky and Papert⁸ and, recently, of Hopfield⁹.

McCulloch and Pitts were already aware that their description grossly oversimplified the single neurone. Neurones are clearly not simple binary logical devices. Inputs are inherently graded and they last for several milliseconds, sometimes many hundreds of milliseconds. The output of the neurone is delayed with respect to the input due to membrane capacitance. Also, a neurone's output is typically a burst of spikes (rather than a single spike) with a certain temporal pattern. Indeed, it is generally accepted that the processes underlying neuronal activity are continuous rather than discrete in nature. This is why Hopfield¹⁰ extended his earlier work using more realistic models of neurones that had both continuous (sigmoid) input-output relations and integrative time delays. In this influential work, Hopfield showed that the collective properties of networks composed of the unrealistic binary units are preserved in networks composed of the more realistic continuous units. Hence, for some purposes, the binary unit is a good approximation for the continuous case.

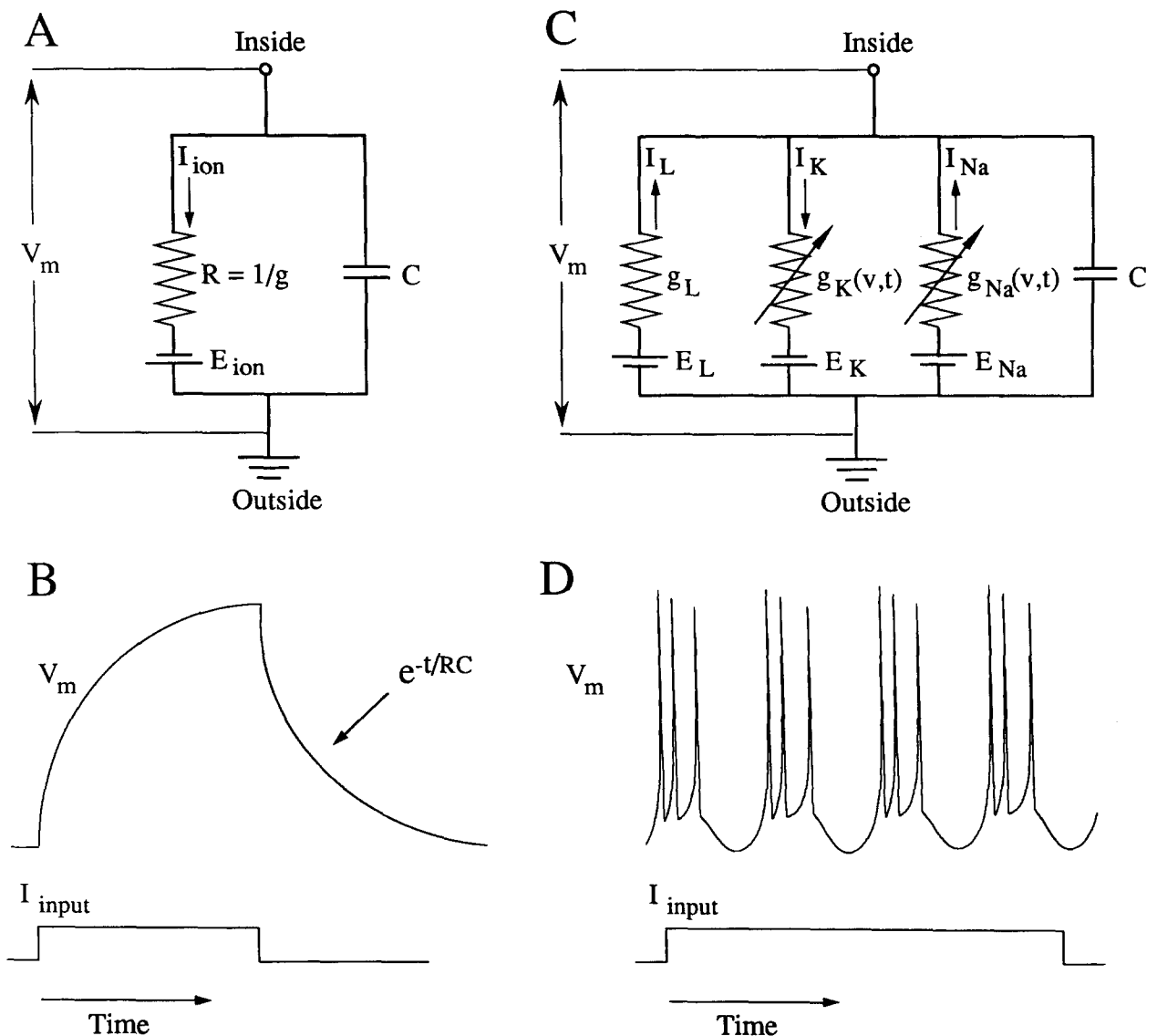


Fig. 3. (A) The analogue model of a small patch of passive membrane consisting of a resistor, R , in parallel with a capacitance, C . Ionic current, I_{ion} , can flow across the membrane only through the resistor. The driving force for this current is the difference between the transmembrane voltage (V_m) and the reversal potential (E_{ion}). **(B)** The voltage response of the circuit shown in (A) to a step current input (I_{input}) follows a single exponent with a time constant RC . **(C)** Hodgkin and Huxley channel-based model of an excitable membrane. It consists of two voltage- and time-dependent channels (Na, K), plus a passive, leakage channel (L). Directions of the corresponding ion currents are shown for the resting potential. This type of model can produce a large repertoire of electrical activity found in neurones including repetitive bursting as shown in **(D)**.

Morpho-less analogue (continuous) models

The other class of morpho-less neurone models are analogue in nature; they are more realistic by emphasizing the nonlinear dynamical properties of the neurone, specifically excitability and related phenomena such as threshold, refractoriness, membrane voltage oscillations, etc. Because the focus is on the dynamics of the various relevant parameters, in particular that of the membrane voltage, time is continuous in these models, rather than discrete as in the morpho-less digital models. These continuous models are all based on the electrical circuit model of a small isopotential patch of membrane (Fig. 3A), consisting of a capacitor (C) in parallel with a linear (or nonlinear) resistor (R). This resistor represents the conductivity of transmembrane channels through which specific ion currents flow across the membrane. The capacitor, corresponding to the part of the membrane that lacks ion channels, separates the

charges on each side of the membrane (see Ref. 11 for a review). This R-C model for the nerve membrane predicts that the voltage response of the neurone lags in time behind the current input, as is indeed found experimentally. Of further importance, this circuit sums inputs temporally, and a voltage change persists for some time following a transient input ('memory') (Fig. 3B).

Mathematically, analogue neurone models are represented using differential equations. They range from phenomenological models to the realistic, channel-based biophysical models. Phenomenological models include the 'integrate-and-fire' type of model, in which inputs are integrated in time (due to the membrane capacitance), but the threshold is arbitrarily assumed¹². Namely, the threshold is a point of discontinuity in the description of the model. Also, to this family belongs the important model of FitzHugh and Nagumo (FHN), in which the electrical properties

of the membrane are represented by two variables (two coupled differential equations) – the membrane voltage and a slow recovery variable; each satisfies a differential equation with polynomial nonlinearity (see Refs 4, 13 and a review in Ref. 14). Unlike in integrate-and-fire models, threshold is not arbitrarily predefined in the FHN model; it is an emergent property of the model. An advantage of two-variable models is that voltage dynamics, such as excitability, threshold behavior and repetitive firing, can be understood qualitatively by employing phase-plane analysis^{4,15}. Indeed, FHN-type models have proven very useful for gaining mathematical insights on the membrane nonlinearities underlying the electrical behavior of nerve cells. However, the parameters used to define these models have no direct physical interpretation.

Of the channel-based models, the Hodgkin and Huxley (HH)¹⁶ three-channel model is prominent (Fig. 3C). In this class of models the various membrane currents, characterized using voltage-clamp techniques, are described mathematically. The model is then used to study the contribution of the various ion currents to the overall complex electrical behavior of the modeled neurone (Fig. 3D). One can also predict, by systematically varying the many model parameters, the possible repertoire of electrical activity of a neurone having such an array of channels. For the biologist, these models are particularly attractive because they are based on experimentally measurable biophysical entities such as ionic concentration, membrane conductance, etc.

As in the FHN models, the threshold for generation of a spike (or several spikes) is an inherent characteristic of the HH-type models. The original HH formulation consists of four coupled differential equations, one for the membrane voltage, and three voltage- and time-dependent state variables, two for the Na^+ current and one for the K^+ current. With this model, phenomena such as threshold, refractoriness, subthreshold voltage oscillations, etc. can be understood on physical grounds. Yet, the model is too complicated for mathematical analysis and computationally quite demanding. For this reason several attempts were made in recent years to reduce the HH model systematically, from four to two differential equations, while keeping the parameters physically meaningful^{17,18}. Again, phase-plane methods are applicable for these reduced HH models.

The other direction that is gaining momentum in recent years is to build elaborate, instead of reduced, HH-type morpho-less neurone models consisting of many channel types^{19–21}. In these cases numerical techniques are typically employed, although it was demonstrated that when some state variables operate on a significantly different timescale from others, it is still possible to understand the behavior of this more complicated system using phase-plane methods²². Last year Mahowald and Douglas²³ introduced a state-of-the-art approach to model single neurones. They used analogue complementary metal-oxide semiconductor (CMOS) very large scale integration (VLSI) technology to emulate the physics of membrane channels and synapses directly. This powerful method enables one to construct models that are also able to encompass the complex morphology of neurones.

Dendritic morphology revisited

They were there all the time, the dendrites. However, they appeared in models only after the experimental data could not be correctly interpreted by ignoring them. Indeed, the decay of synaptic potentials measured in motoneurones using the newly developed intracellular electrodes²⁴ were loosely fitted by a single exponential decay that was expected from the morpho-less passive R–C neurone model of Figs 3A,B. There was also the need to re-examine a widely accepted assertion made by Lorente de Nó (Ref. 5) that spatial summation between several synapses impinging on the soma is very focal, and that synapses sum successfully only if they are close to each other. What then happens to distributed synapses impinging on the dendritic tree? Is it true that they are virtually ineffective? And what may be the functional role of dendrites? A solid theoretical framework for analysing how electrical currents spread in dendritic trees was, therefore, critically needed.

Cable theory – complex passive trees

The breakthrough was made by Rall²⁵ in a study that laid out the groundwork for a quantitative biophysical approach for exploring the physiological significance of dendrites. Indeed, our present understanding of the functional role of dendrites emerged from this theory²⁶. Rall decided not to treat all morphological and electrical complications at once, and first chose to avoid membrane nonlinearities, focussing on the analytical treatment of passive trees. The task was then to derive mathematical expressions that describe how current flows (and voltage, V , spreads) in time (t) and space (x) within morphologically complex, but electrically passive, trees. For this purpose the analytical cable theory was developed^{25,27–29}. In this approach, the continuous cable equation, a second order partial differential equation for V in t and x , already established for cylindrical axons by Hodgkin and Rushton³⁰, is solved with the boundary conditions imposed by the tree structure (e.g. a soma may be at one end of the dendritic segment with a branch point or a termination at the other end, Figs 4A, B). The theory enables one to characterize the input/output properties of an arbitrarily complex passive tree; namely, to analytically compute the voltage response at any point in a tree to a current injected at any other point. The amplitude and timecourse of the synaptic potential at its dendritic location can thus be estimated, as well as the voltage attenuation and the resultant synaptic potential at the soma. Also, the distance from the soma (in units of the space constant, λ) of the synaptic input location could be estimated from the shape of the postsynaptic potential as measured at the soma^{31–33}. The analytical result, demonstrating that the voltage decay in distributed (non-isopotential) passive trees is governed by a sum of many exponential decays²⁸ rather than by one exponent as in a R–C point model, prompted many experiments all of which concluded that dendrites are electrically distributed with an average electrical length of $0.5–2\lambda$. One important implication of this result is that, in principle, even distal dendritic inputs contribute a significant charge to the soma. Recently, using Rall's cable theory, an analytical solution was derived for the signal

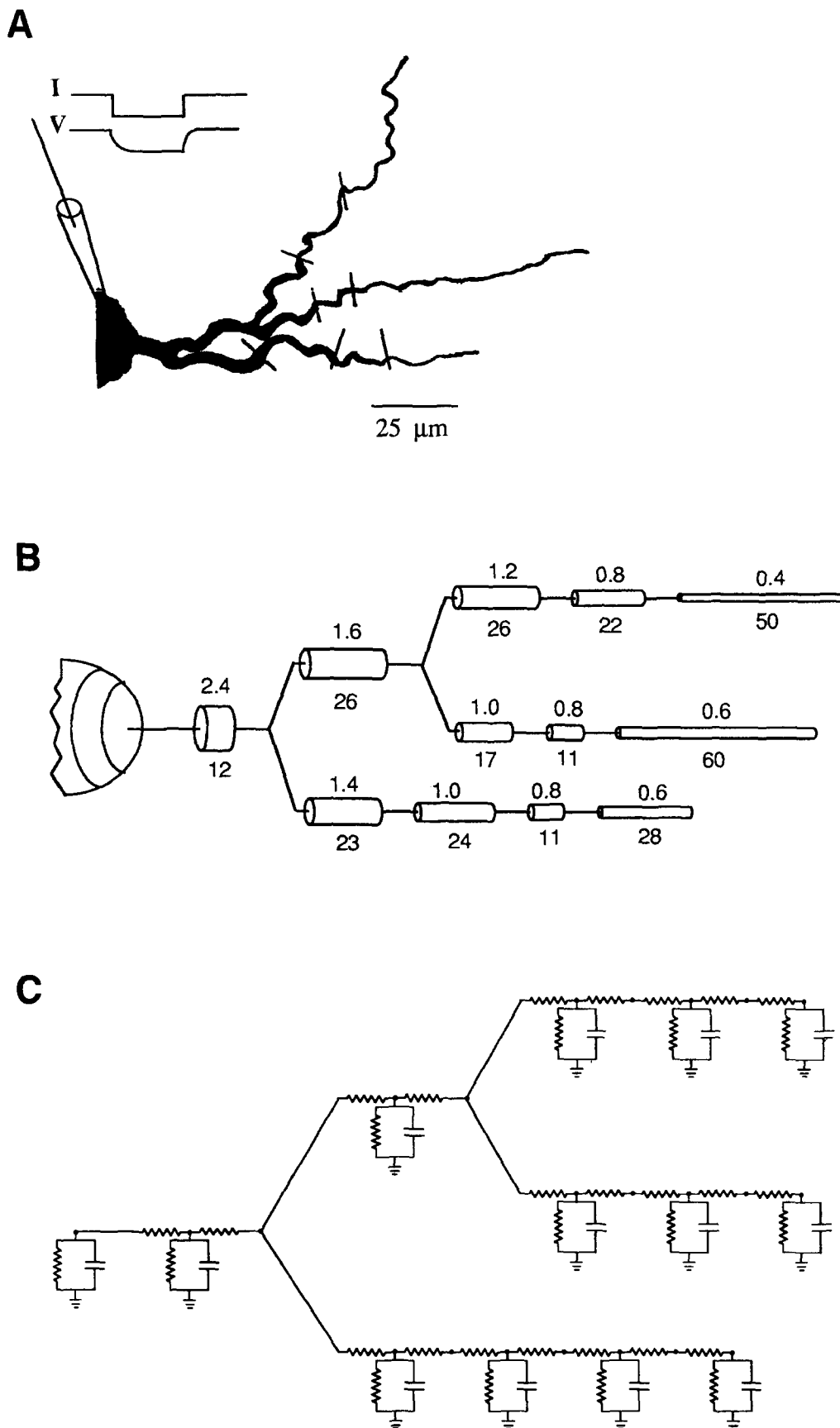


Fig. 4. Cable and compartmental models of a morphologically and physiologically characterized neurone, which is shown in (A). (B) In cable models the dendritic tree is decomposed into branched cylindrical segments. The lengths and diameters in μm of each dendritic segment are indicated below and above the segment, respectively. Electrical properties of membrane and cytoplasm are assigned to the model by directly fitting the experimental results to the theoretical prediction using cable theory. (C) In the compartmental approach the tree is discretized into a set of interconnected R-C compartments; each is a lumped representation of the membrane properties of a sufficiently small dendritic segment. Compartments are connected via axial, cytoplasmic resistances³⁸.

delay and propagation velocity in any passive dendritic tree³⁴.

An important message from cable theory is that the combination of the specific morphology plus the electrical properties of membrane and cytoplasm (namely, the electrotonic structure) determine the processing of electrical signals in the dendritic tree. In other words, two morphologically identical trees with different electrical properties may have very different computational capabilities. This is why Rall and many others (e.g. Refs 25, 33, 35–37) put so much effort in applying cable theory to estimate the three parameters that electrically characterize passive trees: R_m and C_m , the specific membrane resistivity and capacitance, respectively, and R_i , the specific cytoplasm resistivity. Computational methods were developed enabling these biophysical parameters to be estimated by fitting experimental measurements of input resistance, membrane time constant and voltage transients at the soma to the theoretical calculations using the actual morphology of the reconstructed neurone^{25,28,33}. Reviews on reconstructing and encoding the cell's morphology and matching dendritic neurone models to experimental data can be found in Refs 38–40. Applying the theoretical results first to α -motoneurons²⁵, and then to many other types of neurones, it was shown that the dendrites dominate the passive properties of the neurone. Indeed, when dendritic morphology was incorporated into the model, the value estimated for R_m was significantly larger than had been previously assumed.

Compartmental models – complex nonlinear trees

To overcome the constraints on cable theory imposed by the assumption that the membrane is passive, Rall⁴¹ developed a complementary compartmental modeling approach (reviewed in Ref. 38). In recent years this approach has become the most popular modeling approach, both at the single-cell level as well as at the level of very large neural networks. At the single-neurone level the continuous cable representation of the modeled tree (Fig. 4B) becomes discrete (Fig. 4C); dendritic segments that are electrically

short are assumed to be isopotential and are lumped into a single R-C membrane compartment. Compartments are connected to each other via a longitudinal resistivity according to the topology of the tree. Hence, differences in physical properties (e.g. diameter, membrane properties, etc.) and differences in potential occur between compartments rather than within them. Mathematically, the compartmental approach replaces the continuous cable equation by a set, or a matrix, of ordinary differential equations and, typically, numerical methods are employed to solve this system (which can include thousands of compartments) for each timestep. It can be shown that when the dendritic tree is divided into sufficiently small segments (compartments) the solution of the compartmental model converges to that of the continuous cable model.

As first implemented by Rall^{31,41}, the compartmental approach allows one to compute numerically the input/output properties of neurones receiving synaptic (rather than current) perturbations, as well as to model dendritic (and axonal) trees having voltage-dependent membrane conductances. The first computation of voltage-dependent dendritic nonlinearities using compartmental modeling was performed by Rall and Shepherd⁴² for the olfactory bulb. With the advances in the characterization of the various membrane channels and in computational resources, it has become possible to model quite realistically the complexity of neurones in both morphological and electrical domains. A few examples are the simulation of reconstructed α -motoneurones receiving several hundreds of synapses from the Ia input⁴³, the modeling of cortical pyramidal cells⁴⁴ and cerebellar Purkinje cells⁴⁵ receiving massive background synaptic inputs, modeling of clusters of dendritic spines with excitable membranes⁴⁶, modeling of hippocampal and pyramidal neurones with NMDA receptors distributed over their dendritic surfaces^{47,48}, and modeling of action potential propagation in complex axonal trees⁴⁹. Recently Traub and Miles⁵⁰ modeled the collective oscillatory behavior of a hippocampal slice using a network model in which CA3 pyramidal neurones are each represented in detail, compartmentally. Finally, it is worth noting that compartmental techniques are now also being applied to model the diffusion of ions in different parts of the dendritic tree⁵¹⁻⁵³.

Computational capabilities of single neurones

Cable and compartmental models provided the essential tools for linking the structure of neurones to

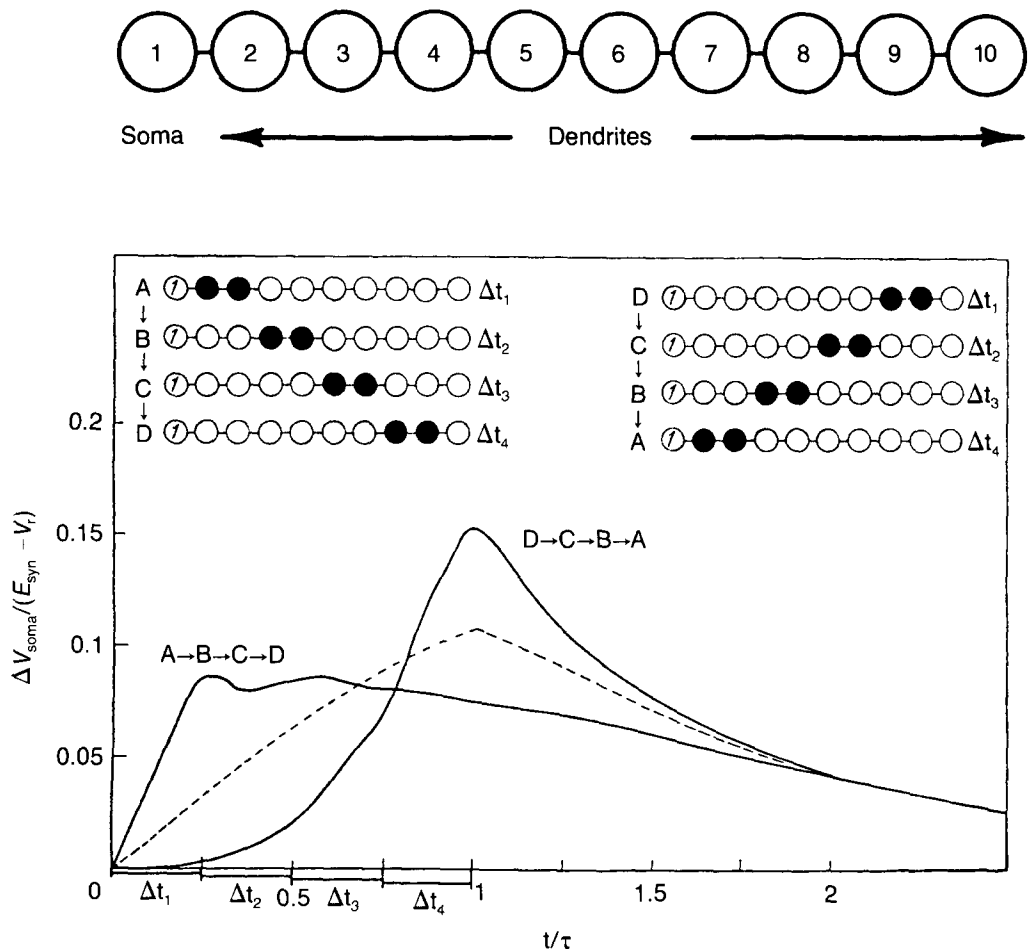
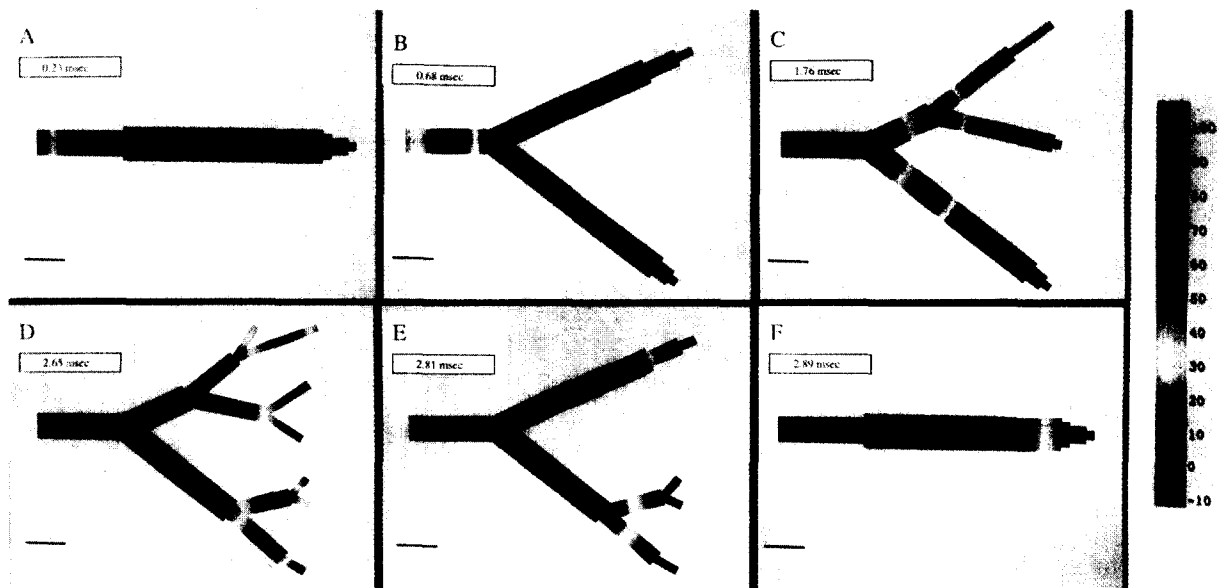


Fig. 5. A neurone that computes the direction of motion. The depolarization (ΔV_{soma}) at the soma (compartment 1) is sensitive to the spatio-temporal sequence of synaptic activation. When only excitatory inputs are involved (filled circles), the depolarization at the soma is larger and more delayed when the synaptic activation starts distally and progresses proximally (D→C→B→A). The broken line shows the effect when the same total synaptic conductance is spread uniformly over compartments 2–9 for the full duration ($t = 0 - \tau$). ($E_{syn} - V_r$) is the difference between the excitatory battery and the resting potential⁴¹. The y-axis could be interpreted as firing probability assuming fast kinetics for the action potential generated at the axon.

their electrical function. Combined modeling and experimental efforts of the past 30 years shed bright light on the mechanisms that govern how electrical signals, both synaptic and active, are processed in the dendritic and axonal trees. But what did we learn about the possible computational capabilities that emerge from the specific structure and biophysical properties of single neurones? An answer can only be given in the context of the information-processing task of the network composed of these neurones. Because we still do not know how real neuronal networks process information, only tentative answers can be provided at present. Some of these are listed below, and are also discussed in Ref. 54.

The first example of a possible computation that may be implemented by dendrites was given by Rall⁴¹. He showed that depolarization of the soma, resulting from activation of excitatory inputs on the dendrites, is very sensitive to the temporal sequence of the synaptic activation. The depolarization is always larger, and more delayed, when the synaptic activation starts at distal dendritic sites and progresses proximally, compared to the depolarization when the same synapses are activated in the reverse order in time (Fig. 5). This neurone is, therefore, directionally

Fig. 6. Dynamic reduction of the complexity of a modeled neurone. This example shows the simulation of an HH-action potential propagating along an axonal tree. The degree of complexity of the modeled tree depends on the location of the spike. Inactive regions are grouped into simpler representations⁶⁴. Color scale codes for membrane potential relative to the resting potential. Red represents active regions; blue represents inactive regions.



selective and could be used to detect changes in sound frequency⁵⁵, or to compute the direction of motion⁵⁶. Another theoretical possibility is that the strategic location of inhibitory and excitatory inputs onto the tree can discriminate between different input combinations^{11,41} and implement complicated logical operations⁵⁷. Dendritic spines receiving both excitatory and inhibitory inputs are also good candidates for very specific AND–NOT operations^{58,59}. Another possible biophysical basis for a large repertoire of logical operations in dendritic trees are the clusters of excitable channels ('hot spots') distributed at specific dendritic sites^{46,60}.

An interesting possibility is that the specific morphology of dendritic spines underlies the processes of cellular memory and learning. Theoretical considerations show that activity-dependent changes in spine morphology could serve as a sensitive nonlinear mechanism for very localized and specific modulations in synaptic efficacy⁶¹. Another intriguing suggestion is that spine morphology can provide chemical, rather than electrical, compartmentalization. Simulations show that the very small volume of the spine-head allows for a dramatic, and very localized, increase in Ca^{2+} concentration at the spine-head following the activation of synaptic input at this site. The high local Ca^{2+} concentration may trigger a chain of events that will eventually lead to plastic changes on only those spines that received the input^{47,52,53,62}. Finally, a very elegant recent theoretical study has demonstrated that dendritic trees rich in NMDA receptors respond preferentially to clustered, rather than to random, patterns of synaptic inputs. Such a tree can store (and retrieve) certain spatial patterns of inputs in preference to others⁴⁸.

Carefully reduced models

A good model should not copy reality, it should help to explain it. We have come a long way from the McCulloch and Pitts oversimplified model to the more realistic, but too complex, models of a single neurone that consist of thousands of compartments and many types of channels. What we need now is a way to reduce the complicated models to intermediate models that still retain the essential features of the full

models. Namely, to use the insights gained from the full models and to extract, or formulate, the minimal model that faithfully captures the input/output characteristics of the modeled neurone. Large networks consisting of such reduced neurone models will undoubtedly have an enriched computational capability. They will also be much more biologically realistic than the current network models based on the morpholess, point neurone.

Clearly there are many ways to reduce the full neurone model. The degree of reduction depends heavily on the fidelity required and on the theoretical question asked. Careful exploration of possible ways to reduce the morphological complexity of neurone models has begun. One direction is to apply the principles of cable theory to derive a set of rules for replacing the full (possibly spiny) dendritic tree by a morphologically simpler tree, attempting to map the electrical (and synaptic) properties from the full tree into its 'canonical' representation (e.g. Refs 39, 45, 63). Another suggestion recently raised is to collapse dynamically, rather than statically, the full tree into simpler representations⁶⁴. Depending upon where the signal(s) of interest is located, at a particular moment the tree can perhaps be represented by a single cable, whereas at other times a more complex branching structure is required (Fig. 6). Systematic methods for reducing the electrical complexity of neurone models are also underway^{17,18,65}. Whatever the exact method will be, it is clear that some aspect of the morphology (so characteristic of nerve cells) will gain an essential place in future models of neuronal networks. After all, the function of the brain can not be completely disconnected from the structure of its basic units, the nerve cells.

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