Excitable dendrites and spines: earlier theoretical insights elucidate recent direct observations

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Important advances in experimental methods have made it possible to measure the electrical events in dendrites directly and to record optically from dendritic spines. These new techniques allow us to focus on the input region of the neuron and highlight the excitable properties of the dendritic membrane. Interestingly, some of the recent experimental findings were anticipated by earlier theoretical research, for example, the observation that some spines possess excitable channels that might generate local all-or-none events. Computer models were used previously to explore the conditions for initiating an action potential at the dendritic tree, in particular, at the spine head, and for active propagation between excitable spines and excitable dendritic arbors. The consequences for synaptic amplification, for the extent of active spread in the tree and for non-linear discriminations between different patterns of synaptic inputs were also considered. Here we review the biophysical insights gained from the theory and demonstrate how these elucidate the recent experimental results.

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ALTHOUGH DENDRITES are the predominant elements in neurons, in terms of number and functional importance[1], it is only very recently that the soma has become the preferred focus of the integrative function of nerve cells. This somato-centric viewpoint is due to the favorable dimensions of the soma, which allow the stable recording of electrical activity at this site with conventional electrophysiological methods. The smaller dimensions of dendritic branches and dendritic spines do not lend themselves to systematic recordings with such methods. Although we have a wealth of information about the fine anatomy and biochemistry of dendrites and spines (see reviews in Refs 1–5), very little used to be known about their electrical properties. Until recently, therefore, the electrical events that take place at the input sites of neurons have had to be inferred from somatic recordings. At first it might seem unlikely that much could be gained from sitting at the base of a large dendritic tree (the soma) while trying to learn what happens at its distal, highly ramified, branches. However, with a biophysical theory that describes how electrical current flows from the dendritic input site to the soma, and with carefully designed experiments, much information was gleaned about the electrical properties of dendrites without directly visiting them[6–8]. Fortunately, direct observations are now possible because of several impressive technological advances. With infrared differential interference contrast (IR-DIC) video microscopy[9] it is now possible to view clearly individual processes of dendrites and axons in brain slices (provided that the processes are $\geqslant 1\mu m$ in diameter). This visual control enables patch-pipette recording of the local electrical activity at distal dendritic arbors and the characterization of their membrane properties, including the type and density of excitable channels at these sites (Fig. 1A, Refs 10,11 and reviews in 12–16). The development of Ca^{2+}-dependent dyes, the use of confocal microscopy and, more recently, two-photon microscopy has enabled the optical imaging of Ca^{2+} dynamics in individual dendritic spines (Fig. 1B) in response to synaptic inputs and allowed estimation of their electrical properties (Fig. 1C, see Refs 17–20 and reviews in 21,22). These direct observations confirmed the early results of Llinás *et al.*, who suggested that action potentials (APs) might actively propagate in the dendrites[23,24]. Indeed, it is significant that the new experimental techniques highlight the non-linear nature of signal processing in dendrites and in dendritic spines and it is gratifying that earlier theoretical explorations of the biophysical consequences of such non-linearities are in agreement with the new experimental results. Here we review the route that led to these theoretical results and emphasize the main insights that they provided. We will summarize briefly the recent experimental results and discuss them with reference to these insights.

A brief history of neuron modeling

Neurons are biological cells with highly developed properties of excitation and inhibition that depend upon rapid changes in cell-membrane permeability to certain ions in a way that was systematically elucidated by Hodgkin, Huxley and Katz during the period 1948–1952. They showed that excitation involves a very large increase in membrane permeability to Na^+ ions, and that the resting state depends on a low permeability to Na^+ ions and a relatively high permeability to K^+ ions. Synaptic inhibition could therefore be understood as increased membrane permeability to K^+ and Cl^- ions, which tends to quench excitation and to move the membrane potential towards the inhibitory reversal potential[29–32].

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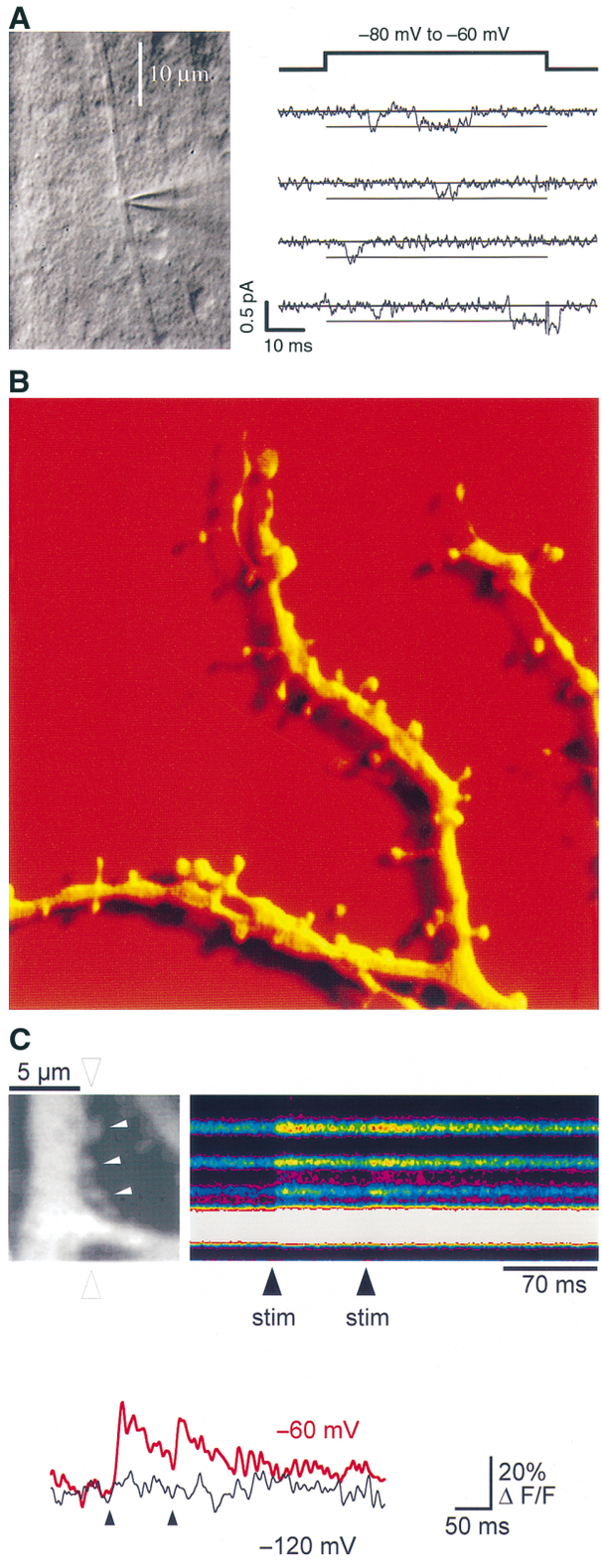

Fig. 1. ***Some important facts about dendrites and their spines.*** **(A)** *Dendrites are endowed with excitable channels. Infrared differential interference contrast (IR-DIC) video microscopy image of a portion of the apical dendrite of a CA1 pyramidal neuron (left panel; the recording patch-pipette is seen to the right of that dendrite) and single-channel recordings of T-type Ca^{2+} channels (right panel). The recordings are from a cell-attached patch in the apical dendrite, about 150 μm from the cell body. A voltage step (from −80 mV to −60 mV) via this patch results in the opening of individual ion channels (transient inward deflections). Courtesy of Jeffrey Magee and Daniel Johnston (see Refs in 9–11,14,16,25–27).* **(B)** *Dendrites of cortical pyramidal neuron are decorated with dendritic spines. A confocal laser-scanned, 3D reconstructed image of spines in a branched dendritic segment of a hippocampal neuron grown in dissociated culture conditions for three weeks. Several spines are seen at a lower density compared to the density under* in vivo *conditions. Average spine length is approximately 1.4 μm. Dendritic spines are the main target for excitatory (asymmetrical) synaptic inputs.* Courtesy of Menachem Segal. **(C)** *Dendritic spines bear voltage-gated channels. Two-photon laser-scanning microscopy of cerebellar Purkinje cell spines. The Purkinje cell was filled with calcium-green via a patch pipette and a cluster of spines was visualized on the thick primary dendrite (left panel). Following stimulation of the climbing fiber (activation line indicated by filled arrowheads in right panel), rapid Ca^{2+} increases were observed in all three spines that were scanned (white arrowheads in left panel), as seen from the line scan (2 ms time resolution) on the right panel (the line scan on the right panel is aligned with the reference image on the left, so one can directly map the calcium signals onto the corresponding spines). Calcium measurements were performed along the vertical line connecting the two open arrowheads in the left panel. The bottom panel shows the relative change in fluorescence intensity in the top spine (averages of 5 trials); hyperpolarization to –120 mV abolished the calcium transients, indicating that they result from calcium influx through voltage-gated calcium channels. Data courtesy of Michael Hausser and Winfried Denk (see Refs 18,20,21,28 for details of two-photon microscopy).*

In the 1930s, well before these membrane (and underlying ion-channel) properties were understood, a 'two-factor' mathematical model of excitation and inhibition was developed by Rashevsky[33] in Chicago, by Monnier[34] in Paris, and by Hill[35] in London. They all used two ordinary first-order differential equations (quite similar to the activation and inactivation variables *m*, *n* and *h* used by Hodgkin and Huxley) that could account for a variety of experimental observations, such as 'break-shock-excitation' and 'strength-duration' curves. Although now obsolete, these were pioneering efforts at that time. A.V. Hill also won a Nobel prize for his research on muscle and established the Biophysics Research Department at University College London, where Bernard Katz did much of his research.

Rashevsky established a mathematical biophysics research and teaching program at the University of Chicago. His textbook[33] and his *Bulletin of Mathematical Biophysics* attracted an active group of students. Together with these students Rashevsky generalized their two-factor theory to 'central excitatory states', a term that was coined by Sherrington and refers to the excitability of several reflex pathways in the spinal cord, and applied this to neural networks. Another example of a mathematical study of neuronal processes from this period appeared in a monograph by Householder and Landahl[36], whose scope can be shown by the following chapter headings: trans-synaptic dynamics; chain of neurons in steady-state activity; parallel interconnected neurons; the dynamics of simple circuits; the general neural net; the dynamics of the single synapse; fluctuation of threshold; psychological discrimination; multidimensional psychophysical analysis; conditioning; a theory of color-vision; some aspects of stereopsis; the Boolean algebra of neural nets and statistical interpretation. Interestingly, the Boolean chapter is based on a widely cited paper by McCulloch and Pitts[37] that arose in the context of Rashevsky's research seminars and was published in his bulletin, together with another paper[38] that examined some statistical consequences of neural nets (see also historical notes in Schwartz[39]).

Ever since that time, many neuron modelers have been content to reduce a neuron to a single node which integrates (with or without leakage) the synaptic excitation (+) and synaptic inhibition (−) delivered to it by other neurons. Several errors caused by these over-simple assumptions were demonstrated by compartmental computations of Rall[32]. In particular, it was demonstrated that excitatory and inhibitory synapses in dendritic trees do not sum linearly with each other and that specific computations can be implemented by exploiting this non-linearity (see also other chapters in Reiss[32] for several interesting early perspectives on neural modeling and also Ref. 40 for a recent demonstration that non-linearity in the summation of synaptic inputs improves sound localization in the auditory brainstem). The mathematical modeling of non-linear, voltage-dependent, membrane properties has been presented and discussed in a pioneering review by FitzHugh[41], and recently in a chapter by Rinzel and Ermentrout[42].

The concept of a nerve axon as an extended core conductor (that is a membrane cylinder with ionic conducting media inside and outside) rather than as a single node goes back to the 1870s, when it was treated mathematically by Hermann and Weber. The concept of passive electrotonus in membrane cylinders and the mathematics of passive-cable theory were explored over the years, culminating in classic papers by Hodgkin and Rushton and by Davis and Lorente de No, both around 1946–1947; see references in Ref. 6. Before 1900, neuroanatomical studies by Ramón y Cajal demonstrated the extensiveness of dendritic branching for most neuron types, which was confirmed by many anatomists. Later (in the 1950s), use of the electron microscope made it possible to verify the existence of very many synapses on dendritic branches and dendritic spines of neurons. These anatomical facts, together with the introduction of intracellular microelectrode recording from the soma of neurons with dendrites (in the 1950s), made it important to extend cable theory to the dendrites of individual neurons. This was begun in the late 1950s and carried forward into the 1960s and 1970s (see reviews in Refs 6,8,22,43–47).

Early dendritic models not restricted to passive membrane

The earliest modeling of dendrites began with the assumption that they had uniform passive membrane properties. However, several early papers included non-uniform membranes that contained regions with (1) different values for the specific membrane resistivity (R_m) (Ref. 31), (2) non-linear efficacy of synaptic inhibitory conductance[32] and also, (3) excitable membrane[48]. The non-linear properties of synaptic interactions in dendritic trees were demonstrated and discussed, and a computational dissection of several related transients of voltage and current were presented[49]. These computations helped to illustrate the importance of synaptic input location and the morphology of the dendritic tree in understanding the relationship between the current generated by the synaptic input, the current loss due to electrotonic spread from the synaptic input site to the rest of the dendritic tree, and the remaining net depolarizing current in any given dendritic region. Several predictions about how the shapes of synaptic potentials (at the soma) are related to the input location were confirmed experimentally[50–52] and most directly in the experiments of Redman and Walmsley[53]. They recorded single Ia fibre excitatory postsynaptic potentials in the somata of α-motoneurons and, in the same neurons, identified the location of the corresponding synaptic connections on the dendrites. Another important prediction of these computational studies is that attenuation of voltage occurs asymmetrically in dendritic trees; a much steeper attenuation is expected in the dendritic-to-somatic direction compared to the attenuation in the reverse direction[54–57]. As discussed below, this asymmetry has important consequences for the spread of excitation in excitable dendritic trees.

Models highlight the functional implications of dendrites: two examples

Mitral and granule cell populations in olfactory bulb

Excitable dendritic membranes were explicitly included in the computations of Rall and Shepherd[48]. Here, the task was to model and compute extracellular field potentials that matched those observed experimentally in olfactory bulb when the mitral cell population was activated in near synchrony by means of an antidromic volley. A nine-compartment model (three axonal, one somatic and five dendritic) was used to simulate antidromic activation of a mitral cell, while a ten-compartment model was used to simulate non-spiking activity in the dendrites of an axonless granule cell. Computations with active dendritic membranes were compared with the passive case (Figs 8 and 10 in Ref. 48); both electrically long active dendrites and electrically short passive dendrites could account for the experimental field potentials observed. An important consequence of this modeling effort was that it led to the prediction of (and the functional interpretation of subsequent electron microscopic evidence for) dendro–dendritic synaptic interactions between the mitral-cell secondary dendrites and granule-cell distal dendrites, which are intermingled in the external plexiform layer of the olfactory bulb[58]. If these cells had been modeled as lumped somata, without dendrites, neither the successful simulation of the experimental field potentials, nor the exciting new insights about a dendro–dendritic pathway for recurrent inhibition would have been possible. Interestingly, active propagation of APs in these dendrites was recently demonstrated, using dual recordings from dendrites and somata of mitral cells[25].

Subsequently, Dodge and Cooley[59] utilized compartmental modeling to compute antidromic impulse invasion for a motoneuron with dendrites (see also Refs 60,61). Computations of AP propagation in regions of changing core conductor geometry were performed by Goldstein and Rall[62]. This paper provided computed illustrations of the changing shape and velocity of the AP near points of step change in diameter and branch points with impedance mismatch between parent and daughter branches. It analysed cases of delay and failure in forward propagation from parent branch to daughter branches and also an example of reflected back-propagation at the branch point (see also Refs 63–65).

CA3 network rhythmogenesis

A 19-compartment branched-cable model for hippocampal CA3 pyramidal-cell dendrites was developed

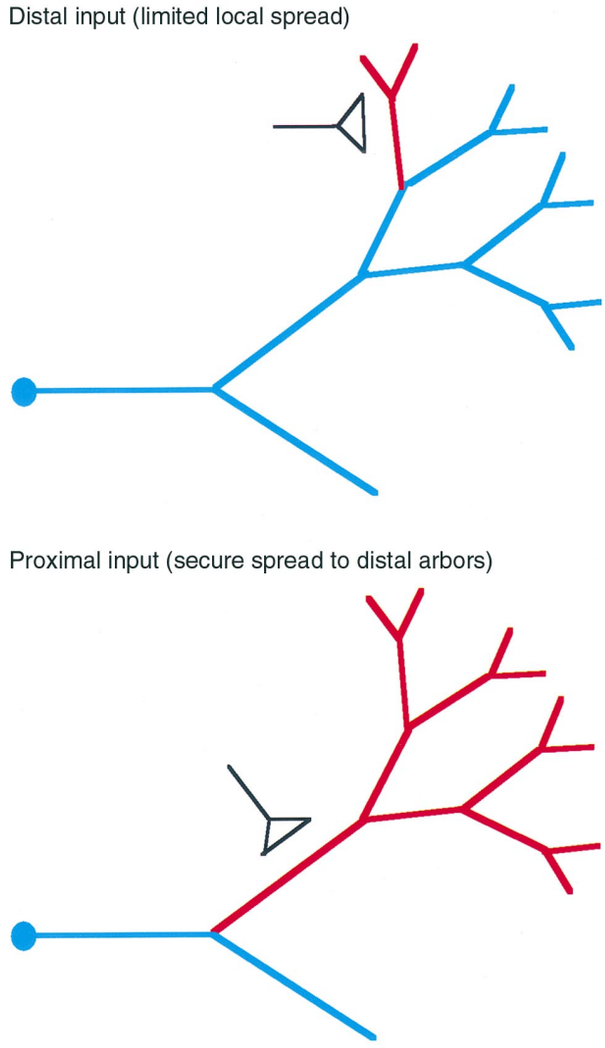

Fig. 2. ***Active propagation in dendritic tree is more secure towards distal branches and usually blocks proximally.*** *In a model of uniformly excitable dendritic tree, a local excitatory input restricted to a distal dendritic arbor initiates a regenerative response in only a limited portion of the dendritic tree (red in top schematics). In contrast, when the action potential is initiated at more proximal sites (for example, near the soma) it is likely to propagate securely towards distal regions and, thus, actively invades a large portion of dendritic tree, including the dendritic spines*[15,78,81,82].

by Traub *et al.*[66] Experimentally based parameters were chosen for each dendritic compartment, using up to six active ionic conductances, each controlled by ten channel-gating variables. A network of such model neurons could simulate several important aspects of the repertoire of experimental rhythmogenesis. Traub *et al.* did recognize that their successful simulations depended on specifying significantly different ion channel types and different densities for the soma and for the dendrites; however, the crucial importance of this difference was made starkly clear by the modeling of Pinsky and Rinzel[67]. They obtained essentially the same behavioral repertoire by using a network composed of only two compartments per pyramidal cell. One compartment represented the soma and proximal dendrites which was equipped with ion channels for fast spiking currents (inward sodium and delayed rectifier). The other compartment represented the distal dendrites and contained the ion channels for the slower calcium currents (inward calcium and calcium-modulated currents). These results show that at least two compartments per neuron are needed for simulations of this behavior; a single lumped compartment, with all of the ion channels in parallel, could not produce the same behavior, especially the rhythm, which basically involves an alternating flow of current between the two coupled compartments[68]. Clearly, the reduced (two-compartments) neuron model is much simpler than the 19-compartments model; it enables the exploration of the extent to which the interesting behavior depends on the values of key parameters. Consequently, the behavior of very large networks can be explored more efficiently using such a reduced-neuron model. Further study might show that the two-compartment model cannot match the fuller model in certain important tests. Other examples of specific computations that require more than one lumped compartment per neuron can be found in Refs 32,40,44,69–73.

Models of excitable dendritic spines

Increasing evidence that the dendrites of many neuron types are equipped with excitable channels raised the interesting possibility that spine membrane (which, depending on neuron type, occupies 20–70% of the total dendritic membrane) also bears excitable channels. The implication of excitable channels in the spine head membrane for amplification of excitatory synaptic inputs was first discussed rigorously by Jack[43]. Transient computations for excitable spines and exploration of conditions for initiating an AP at the spine head were reported simultaneously in Refs 74,75 and, with greater computational detail, in Ref. 76. The implications for the spread of a chain reaction of AP firing between neighboring excitable spines in distal dendritic arbors are discussed in Refs 77–79 and see also Refs 44,80,81.

Insights from theoretical models of excitable dendrites and spines

The key insights that were gained from these theoretical studies, which are directly relevant to the recent experimental findings, are summarized as follows: (1) In an excitable dendritic tree with uniform ion channel densities, the propagation of the AP is more secure towards distal branches; it is usually blocked proximally. In the distal direction (from soma to dendrites), the AP typically propagates from thicker to thinner branches, and towards the favorable (sealed-end) boundary conditions in the distal terminal tips. In the proximal direction, however, the increasing diameter, the sister branches and cousin arbors, as well as other trees, all impose a significant load (sink) for the excitable channels in a thin distal branch. Consequently, most of the active current which is generated by these channels is dissipated by the rest of the dendritic tree; the resulting depolarizing membrane current density is typically insufficient to fire the thicker, more proximal, branches. Hence, a local input to a distal excitable dendritic arbor is likely to generate a regenerative response in only a limited distal portion of the tree (such as a sister branch). In contrast, when the AP is initiated near the soma it is likely to propagate backward and invade the whole dendritic tree, including the dendritic spines (Fig. 2, Refs 78,82); (2) the threshold for initiating an AP in distal arbors and spines depends crucially on the spatial

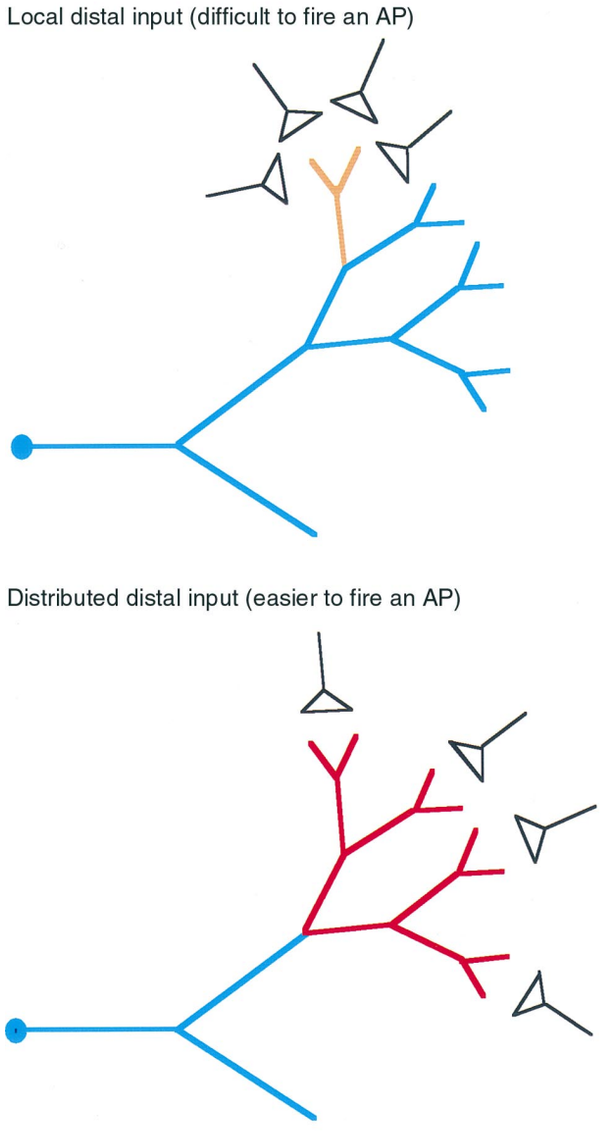

Fig. 3. ***Spatially distributed input in distal dendritic arbors improves both the condition for the initiation of the action potential (AP) in these arbors and for more securely propagating proximally.*** *The large conductance load imposed on individual distal arbors by the rest of the dendritic tree implies that, for local inputs, the threshold for AP initiation is high and possibly even infinite* (top schematics). *This conductance load is effectively decreased (reduced sink), and the tree becomes more uniformly polarized when the input is more widely distributed over several distal arbors. Consequently, threshold conditions for AP initiation in the distal arbors are improved and the safety factor for AP propagation towards proximal regions is increased. In this case, the AP starts simultaneously at several distal sites and spreads more securely to invade a larger proximal portion of the dendritic tree* (lower schematic). See Ref. 81 and M. Rapp and I. Segev, unpublished observations.

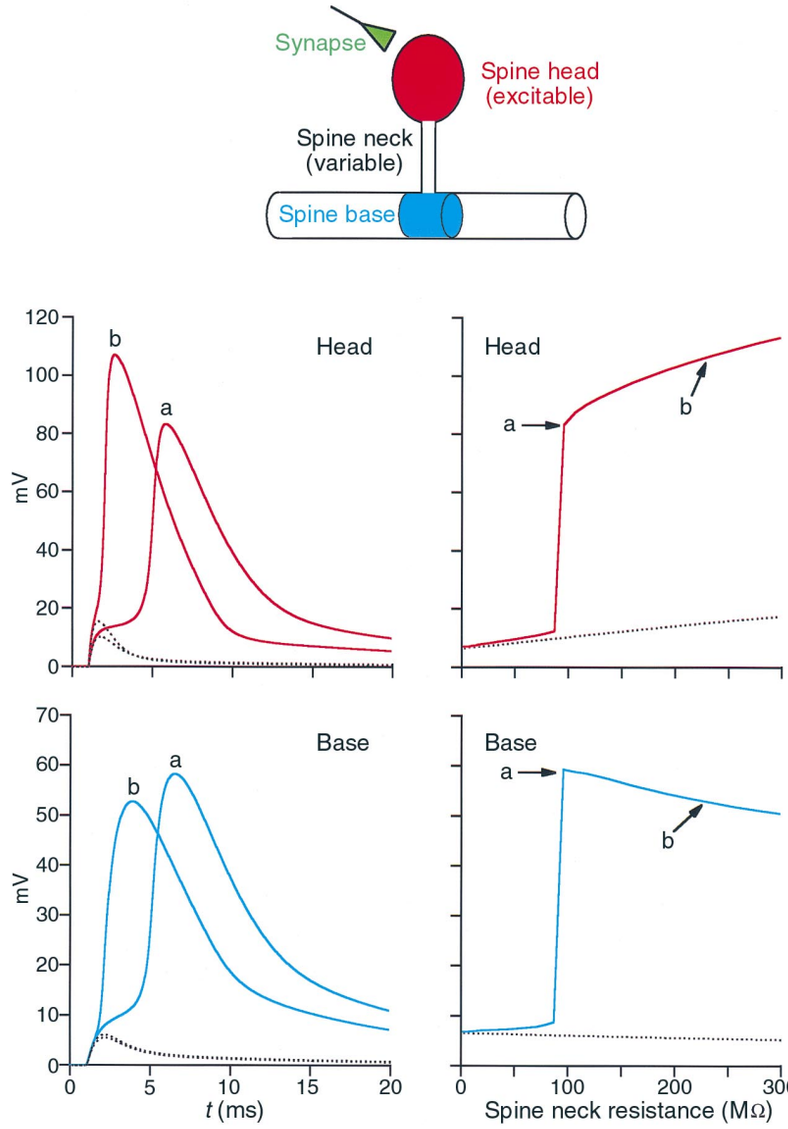

Fig. 4. ***The spine-head membrane bearing excitable channels is a favorable site for action potential (AP) initiation.*** *Dendritic-spine model with excitable spine-head membrane (red) that receives a brief excitatory synaptic input (green), and is connected via the spine neck to a cylindrical dendrite is schematically depicted in the top inset. The only variable parameter in this figure is the value of the spine-neck resistance. The transient voltage response at the spine head and the spine base for two values of spine-stem resistance (a = 95 MΩ; b = 230 MΩ) are shown in the left panels. Curves on the right summarize the peak value of voltages computed for a range of spine-neck resistance values. Continuous curves are for the excitable spine head and the dotted lines are for the reference case with passive spine-head membrane. This figure shows that threshold conditions for AP initiation at the spine-head membrane are improved owing to the partial electrical decoupling (provided by the spine-neck resistance) of the excitable channels at the spine head from the conductance load (current sink) imposed by the dendritic tree. Indeed, these excitable channels are essentially ineffective in boosting the local synaptic input when the spine-stem resistance is below a certain critical value, for example, when the spine head directly contacts the spine base. Only when this resistance is sufficiently large, can an AP be initiated at the spine head membrane. All model parameters are as in Ref. 76, but with a −5 mV shift in the Hodgkin and Huxley activation variables, α_m and β_m, and a decrease in the time constants τ_n and τ_h by a factor of 2.5 to better approximate a low threshold Ca^{2+} AP. The length of the passive cylindrical dendrite was 500 μm and its diameter was 1 μm, with specific membrane resistivity, R_m = 20 000 Ωcm and axial resistivity, R_i = 150 Ωcm.*

distribution of the excitatory input (that is, on the input conditions in the tree). In general, a spatially distributed and synchronously activated input (whereby many synapses depolarize a large area of the dendrites simultaneously and, consequently, the tree becomes effectively more isopotential) improves the conditions for AP initiation as compared to a spatially restricted input (Fig. 3); (3) the spine-head membrane, when equipped with excitable channels, provides a favorable site for the activation of a regenerative response, and even for the initiation of an AP, in response to an excitatory synaptic input. First, the spine-head membrane typically receives such an input. Second, the input impedance at the spine head is large so that a small excitatory conductance can produce a large local depolarization. Third, and most important, the thin spine neck provides an axial resistance that partially decouples the excitable channels at the spine head from the conductance load imposed by the dendritic tree (Fig. 4); (4) for distal dendritic locations, the firing of one or a few excitable spines

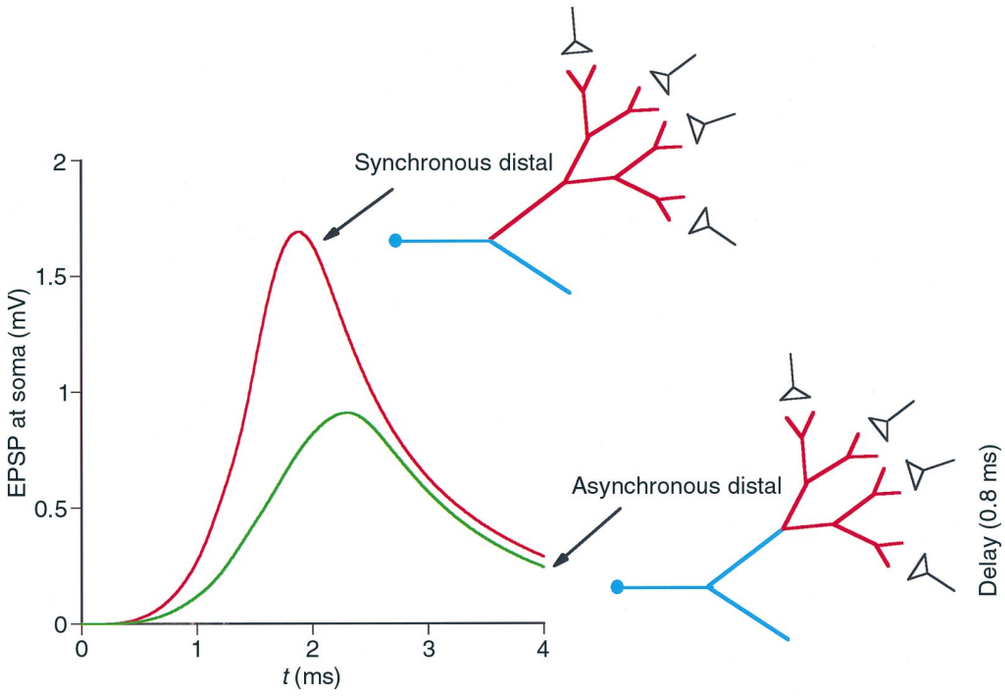

Fig. 5. ***Active propagation in distal dendritic arbors depends crucially on the timing of synaptic activation.*** *Excitatory inputs were distributed over distal dendritic arbors. In one case they were activated simultaneously* (top schematic) *whereas in the other case the synapses on half of the distal arbors were activated with a delay of 0.8 ms compared to the synapses on the sibling branches* (lower schematic). *The resultant voltage transient computed at the soma of the modeled neuron shows that the synchronous (red) transient is almost twice as large as the corresponding asynchronous (green) input. Hence, the active spread towards proximal regions, which usually tends to fail, can be augmented by appropriately timed excitatory inputs.*

could trigger, through the spread of sufficient depolarization along the dendritic shaft (and in distal sister branches), the firing of neighboring excitable spines and spine clusters; (5) the timing of AP initiation, and the spatial extent of active spread in excitable dendrites depends, with non-linear sensitivity, on the timing and location of the excitatory and inhibitory inputs in the dendritic tree (Fig. 5). This is important for input pattern discrimination[32,70]. Additional computations with inputs to excitable spines, where the inputs were located both at distal and proximal dendritic locations, show that in this case it is more effective to activate the proximal inputs with a slight delay compared to the distal inputs rather than activating all inputs simultaneously[78,81]. This result is consistent with earlier computations (done in passive trees) which compared proximal-to-distal versus distal-to-proximal spatiotemporal patterns of inputs to dendrites[32].

Theory illuminates recent experimental results

The new IR-DIC video microscopy clearly demonstrates that dendrites of various cell types are endowed with a variety of excitable channels, including voltage-gated K^+ and Na^+ channels and various Ca^{2+} channel subtypes (Fig. 1A and Refs 11,14,17,26,28). Simultaneous recordings from the soma and dendrites show that the AP usually starts near the soma, probably in the axon beyond the initial segment[83], and then propagates actively backward into the dendrites (review in Ref. 16, see also Refs 25–27,85). In cortical pyramidal neurons, this back-propagating AP is supported by rapidly inactivating voltage-dependent Na^+ channels that are distributed uniformly, in low density, in the soma and the dendrites. Only rather intense stimulation of the distal dendrites can initiate an AP in the dendrites first and this dendritic AP tends to fail in propagating actively towards the soma (but it still spreads passively from the dendrites to soma)[10,11,16,27,84–86]. Interestingly, it was found recently in CA1 hippocampal pyramidal cells that, unlike the dendritic Na^+ channels, the density of dendritic A-type K^+ channels is distributed non-uniformly over the dendritic surface; it is significantly higher at distal dendritic sites and this is expected to increase threshold for AP firing in these sites[26].

Using two-photon microscopy for imaging Ca^{2+} concentration in individual spines, it was shown, in CA1 pyramidal cells[20] and in layer V cortical pyramids[28], that the back-propagating voltage-dependent Na^+ channel AP readily invades the dendritic spines where it leads to a local and rapid rise in Ca^{2+} concentration (see also Ref. 87). This serves as strong evidence for the presence of voltage-gated Ca^{2+} channels in the spine head. Moreover, these channels might be activated in an all-or-none fashion in response to an excitatory synaptic input that (very likely) impinges on the spine head membrane[20,22,28] (Fig. 1C).

These results are well elucidated by the theoretical considerations highlighted above. In agreement with theoretical point (1), it seems that distal-to-proximal propagation of the AP in dendrites is insecure. In agreement with point (2) above, a strong input (probably also more widely distributed) could trigger regenerative response in the dendrites, but this response tends only to spread actively in a localized area[10,16,85]. In contrast, an AP that is initiated near the soma, as is the case in most experimental conditions, does propagate rather securely from the soma towards the dendrites, as predicted in point (1) above. It is worth noting that recent theoretical studies show that the initiation of the AP first in the soma–axon region of neocortical pyramidal cells cannot be explained solely by morphological considerations; the axon must be more excitable than the soma and dendrites[81,88].

It was also gratifying to learn that the theoretical prediction that some dendritic spines are endowed with excitable channels [point (3); Fig. 1B] has been confirmed experimentally. Apparently, the electrical conditions at the spine head (input impedance, magnitude of synaptic input, degree of electrical decoupling) do enable (and even favor) the initiation of an all-or-none event in the spine, as predicted. Correspondingly, the theoretical notion that clusters of spines may operate collectively [point (4) above] found experimental support[89]. Indeed, this work suggests that the basic dendritic functional unit may be comprised of ten or more spines.

The impact of inhibitory dendritic input in controlling the AP initiation site and the time of AP initiation, as well as the extent of propagation within the dendritic

tree [point (5)] was also recently demonstrated experimentally[19,25,90,91]. Indeed, it seems that the interaction between excitable channels and synaptic channels, both excitatory and inhibitory, distributed in the dendritic tree, endows the dendritic tree with a rich repertoire of input–output capabilities. At any given instance, the computation performed within the dendritic tree is sensitively determined by the input conditions (for example, distributed versus localized); input type (inhibitory versus excitatory) and previous activity of this tree (for example, channel inactivation; synaptic depression/facilitation). With such dynamic machinery, the dendritic tree becomes a sophisticated information processing device. It is within this device that input from thousands of other neurons is transformed into a meaningful output for later processing and it is there that memory processes are embedded (perhaps in dendritic spines). The secrets of this device need to be unravelled in order to make a significant step in deciphering how the brain processes information.

Concluding remarks

During the past few years, dendrites have become the focus of very detailed investigations. Within a short period of time many of the characteristics hidden in their membranes and concealed within their dendritic spines, have become experimentally accessible. The fascinating picture that has emerged shows that the dendritic tree is covered non-uniformly with a variety of excitable synaptic channels, each capable of operating on a different time scale and with activity-dependent sensitivity[11,14,17,21,26]. Theoretical studies show that the interaction between the complicated geometry of dendrites and ion channels which they possess, and the large number of combinations of possible input patterns, endow the neuron with sophisticated computational and plastic capabilities[20,70,73,76,78,92,93]. Indeed, it is only natural that individual units are endowed with manifest complexity in a system, such as the brain, that is capable of reacting correctly, learning continuously and dynamically altering its response to an ever changing and unpredictable environment.

In retrospect, it seems reasonable to conclude that dendritic modeling has significantly enriched our understanding of the ways in which neurons process their synaptic inputs. With the rapid advance in experimental methods, a wealth of new information about the fine properties of dendrites (and axons) is likely to emerge in the coming years and theoretical studies will become even more critical for accomplishing four main goals: (1) to integrate the available morphological and physiological data in a model and, in the process of reconciling the theoretical predictions with the experimental results, to estimate the values of model parameters (for example, the passive membrane resistivity, R_m, the axial resistivity, R_i), and to suggest further experiments to refine these estimates[12,43,49,53,58,59,82,88]; (2) to identify the key parameters that determine the input–output behavior of the neuron (for example, the effective time constant for input integration, the voltage attenuation factor)[42,43,47,54,57,59,61,65,67,68,76,77,82]; (3) to provide insights into the principles that govern this behavior (for example, that threshold for AP firing in excitable dendrites is reduced for spatially distributed input or that partial electrical decoupling due to the spine neck resistance favors AP initiation in dendritic spines); and, most importantly, (4) to explore the possible computational role of the dendritic 'hardware' (for example, that excitable channels in dendrites and spines could implement complicated input classification tasks[70,78], or logical AND–NOT-like operations[93], or sub-millisecond coincidence detection[20,32,44,72,76]. We strongly believe that experiments and theory should continue to run like parallel threads that, from time to time, intersect to produce a richer weave of understanding of the 'secrets' of dendrites.

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The Human Brain Project: neuroinformatics tools for integrating, searching and modeling multidisciplinary neuroscience data

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What is neuroinformatics? What is the Human Brain Project? Why should you care? Supported by a consortium of US funding agencies, the Human Brain Project aims to bring to the analysis of brain function the same advantages of Internet-accessible databases and database tools that have been crucial to the development of molecular biology and the Human Genome Project. The much greater complexity of neural data, however, makes this a far more challenging task. As a pilot project in this new initiative, we review some of the progress that has been made and indicate some of the problems, challenges and opportunities that lie ahead.

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THE HUMAN BRAIN PROJECT originated during the 1980s in discussions between neuroscientists and forward-looking program directors at the National Institutes of Health and the National Science Foundation[1]. They realized that the development of new technologies for creating databases and database search tools, and of electronic means for information exchange, was proceeding at a pace that outstripped the abilities of most neuroscientists to use these technologies. From the viewpoint of the funding agencies this was cause for concern, because these were the kinds of 'enabling technologies' that would allow neuroscientists to make much more efficient use of their data (and the agencies to get 'more bang for the buck').

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