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130. We thank S. Christensen, N. Golding, M. Larkum, T. Margrie, P. Monsivais, S. Redman, A. Roth, N. Urban, S. Wang, and S. Williams for their comments and suggestions and the Wellcome Trust (M.H. and G.J.S.), the European Commission (M.H.), NSF, NIH, and the Klingenstein Fund (N.S.) for financial support.

REVIEW

Untangling Dendrites with Quantitative Models

Idan Segev and Michael London

Our understanding of the function of dendrites has been greatly enriched by an inspiring dialogue between theory and experiments. Rather than functionally ignoring dendrites, representing neurons as single summing points, we have realized that dendrites are electrically and chemically distributed nonlinear units and that this has important consequences for interpreting experimental data and for the role of neurons in information processing. Here, we examine the route to unraveling some of the enigmas of dendrites and highlight the main insights that have been gained. Future directions are discussed that will enable theory and models to keep shedding light on dendrites, where the most fundamental input-output adaptive processes take place.

It has been known since the beginning of the 20th century that the gray matter in our cortex is composed mostly of dendrites, that communication in cortical networks is made via connections made on dendrites, and that dendrites have exquisite shapes specific to different brain regions. It was thus for the last 100 years, and still is, very natural to wonder "What do dendrites do?"

But alas, dendrites are thin (~1 μm in diameter) and many of them are decorated with thousands of even tinier "leaves"—the dendritic spines. Until very recently, dendrites were therefore inaccessible to direct measurements and most of what we knew about dendrites came from recordings made from the relatively large soma (cell body). Settling at the soma, however, was an unsatisfactory deal between the experimenter and the concealing dendrites. The advantage is that the soma is a stable recording site con-

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nected to the axon where the output, in the form of action potentials, is typically generated. The disadvantage is that at the soma, the view is very restricted because one sits far from where the happening is, where synaptic inputs play their music with the dendrites.

But then keen modelers demonstrated that with the help of a good theory it is possible to "peek" into the dendritic tree from the soma, without actually visiting them. This "virtual" visit provided critical predictions that encouraged new experimental studies and vice versa. In the last "decade of the dendrites," tremendous technical advances enabled us to start paying intimate visits to dendrites, electrically, optically and with molecular methods (*1*). Models then became essential in providing functional interpretations for the vast data that emerged from these experiments. Here, we review the role of theory in the progress that has been made during the last 40 years in understanding the electrical processes in dendrites and in unraveling their possible function. Dendritic research provides a canonical demonstration that theory and models, when closely linked to experiments, are indispensable for forming a comprehensive understanding of any complex biological system.

Key Biophysical Insights Gained from Reduced Models of Dendrites

Although modelers were well aware of the richness of dendritic structures, dendrites were neglected until the late 1950s. The assumption was that functionally, the dendritic tree could be represented as a single point where synaptic influences are summed and, if this sum reaches threshold, an output spike is evoked in the axon. This "point-neuron" model served both as the basis for the interpretation of experimental results as well as for analyzing the behavior of neuronal networks.

In 1959, Wilfrid Rall (*2*) revived the interest in dendrites by explicitly modeling them as membrane cylinders connected to each other to form a tree. As a first approximation, the membrane of these cylindrical core conductors was assumed to be passive. Current flow in such trees was described by the linear one-dimensional passive cable equation (*3*),

$$\lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} - \tau_m \frac{\partial V(x,t)}{\partial t} - V(x,t) = 0 \quad (1)$$

where V is the voltage difference across the membrane, $\lambda = (r_m/r_i)^{1/2}$ is the space constant; r_i (in ohm/cm) is the axial resistance; r_m (in ohm · cm) is the membrane resistance; $\tau_m = r_m c_m$, is the membrane time constant (in s), and c_m (in F/cm) is the membrane capacitance. The mathematical challenge was to solve this equation for arbitrary dendritic geometries. The analytical solution enabled Rall (*2*) to expose the significant effect of dendrites on the electrical behavior of neurons [reviews in (*4–6*)].

Dendrites Shape the Voltage Response at the Soma

The first surprise was that dendrites impose a huge conductance load on the soma and, consequently, a significant portion of the current that is applied via an electrode to the soma "escapes" into the dendritic tree. The result is an enhancement of the charging (and discharging) rate of the soma membrane, as compared to the case of a soma without dendrites. This removed the apparent discrepancy between the behavior of transient potentials measured experimentally at the soma and the predictions from the "point-neuron" model (see next section).

What do passive dendrites do to the transient current inputs that they receive via their synapses? The cable properties of dendrites (the rapid charging of their membrane capacitance) filter high temporal frequencies that compose the postsynaptic potentials (PSPs). In addition, a certain percentage of synaptic current leaks out via the dendritic membrane. As a result, the PSPs attenuate, are delayed and their time course (shape) changes as they spread from the dendrites to the soma. The farther the input from the soma, the slower the rise-time and the broader the resultant somatic PSP (*7–9*). For fast PSPs, the peak attenuation is expected to be severe (on the order of 100-fold) and the peak should be significantly delayed following propagating from distal dendrites to the soma (*10–12*). Indeed, it might take up to $1\tau_m$ (5 to 50 ms) for the peak of distal PSPs to reach the soma. This temporal delay in the propagation of dendritic EPSPs endows neurons with the capability to compute the direction of motion (*13–15*). In contrast to the large attenuation of the PSPs peak, a substantial fraction of the synaptic charge (on the order of 50% for distal synapses) does reach the soma when integrating over a duration of a few τ_m in duration. The reason is that the intracellular (axial) resistance of dendrites is substantially smaller than the membrane resistance, so only a relatively small percentage of the synaptic charge is lost via the dendritic membrane resistance. Thus, even in passive dendrites, distal synapses are expected to affect the output discharge at the axon.

Of particular importance were mathematical results showing that a whole class of dendritic trees could be mapped into a single equivalent cylinder (EC) coupled to a spherical soma (*16*). This reduced ("ball-and stick") model captures the fundamental electrical phenomena found in the original trees. Specifically, the voltage response at the soma is identical in the original tree and in the corresponding EC, provided that the dendritic input is a current source. With the EC, the apparent complexity of the tree is captured by only four key biophysical parameters, derived from the original tree: (i) the cable length L of the dendritic tree, in units of λ; (ii) the membrane time constant τ_m; (iii) the input resistance at the soma end, R_{in}; and (iv) the ratio between the input conductance of the dendrites and that of the soma, ρ. This equivalence emphasizes that what shapes the synaptic response at the soma are these key cable parameters rather than the fine details of the dendritic morphology. Although real dendritic trees are not strictly equivalent to a single cylinder, the main insights provided by the EC approximation are relevant also to arbitrary branched passive trees.

The theoretical analysis also highlights the electrical consequences of the detailed geometry of the tree (*17, 18*). First, large input impedance (and consequently large local voltage change) is expected at distal thin dendritic arbors (and distal spines), on the order of gigaohms. Second, the attenuation of the PSP strongly depends on the direction of current flow leading to asymmetry in voltage attenuation in the dendrites. Because of a huge current sink (axial current "loss") imposed by the rest of the tree on thin dendrites, a very steep voltage attenuation is expected from the distal synaptic input site to the soma and it is generally shallower in the soma-to-dendrites direction (Fig. 1, A and B). This has important implications for the degree of interaction between synapses locally in the tree (the degree of electrical compartmentalization) as well as for the spread of action potentials backward from soma to dendrites and forward from dendrites to soma [see below and review in (*1*)].

Dendrites with Synapses: Regional Nonlinearities and Electrical Scaling

Synapses are not current sources. Rather, synapses impose a conductance change (open ion channels) in the postsynaptic membrane, thus altering the electrical properties of the dendritic membrane. This hinders analytical solutions for passive dendrites with synapses [but see (*19*)]. Consequently, Rall (*13*) developed the compartmental modeling approach to numerically explore nonlinear phenomena in dendrites. User-friendly public domain compartmental models for neurons were recently developed (*20–23*) and are used by experimentalists for interpreting their experimental data.

One consequence of the conductance change associated with the synaptic input is that synapses interact nonlinearly with each other. Compartmental models of passive dendrites with synapses show that adjacent dendritic synapse tend to sum less linearly with each other, unlike distant synapses which tend to sum linearly (Fig. 1C). This sensitiv-

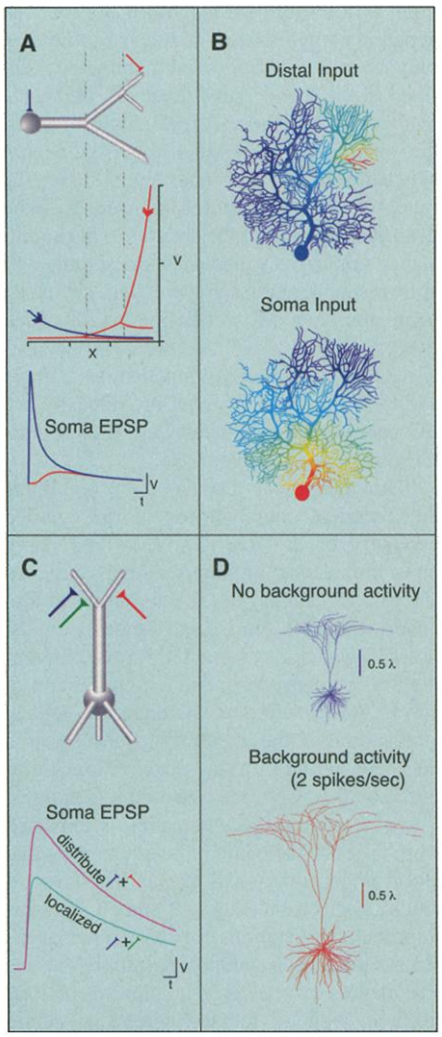

Fig. 1. Fundamental insights from passive cable theory. (**A**) Voltage response to a brief current pulse in a simple branched dendritic model. (Middle) Attenuation of voltage peak is plotted for two cases; somatic input (blue) and dendritic input (red). The attenuation is asymmetric and is much steeper in the dendritic-to-soma direction (red). The voltage response at the input site is much larger for the dendritic input (large input impedance). (Bottom) Voltage transient at the soma for somatic input (blue) and dendritic input (red). The filtering effect of the dendrite gives rise to temporal delay and to an increase in half-width of the distal dendritic input (*17, 18*). (**B**) Electrical compartmentalization in passive dendrites. Current was applied either at a distal dendritic site (top) or at the soma (bottom) in a passive model of cerebellar Purkinje cell. Voltage spread (the "territory of influence") is spatially more restricted for dendritic versus somatic input (red codes for peak voltage at the input site). (**C**) Sublinear summation of synaptic inputs is less pronounced (saturation is reduced) when the inputs are distributed in different dendritic arbors (purple trace at bottom) (*13*). (**D**) Background synaptic activity dynamically rescales the cable structure of the dendritic tree. (Bottom) 10,000 excitatory synapses, randomly distributed and asynchronously activated at two spikes per second each (*96, 97*).

ity to the spatial arrangement of synapses implies that local nonlinear synaptic operations could be performed semi-independently in many dendritic subunits (Fig. 1B) (*14, 24*). Another consequence of dendritic synapses, first highlighted by models, is that they can effectively "re-scale" the cable properties of the dendritic tree. When thousands of synapses bombard the dendritic tree, the dendritic membrane becomes significantly "leakier" and, consequently, the cable parameters of dendrites change dynamically; R_{in} and τ_m decrease with activity whereas L increases (Fig. 1D).

In summary, synapses endow dendrites with a dynamic flavor. Dendrites with synapses constantly change electrically, modifying their input impedance and altering their electrical length like an accordion, in response to the playing of the network they are embedded in. The temporal resolution (sensitivity to input synchronization, which depends on the effective τ_m), and delay dendrites that impose on their synaptic potentials also change dynamically as a function of the background synaptic activity. One can therefore view the "background" activity experienced by dendrites as a "context" under which the neuron operates. Different contexts imply different interpretations of the same input.

Dendrites with Voltage-Gated Ion Channels: Exciting but Puzzling

Dendrites are populated with an amazing plethora of voltage-gated ion channels, typically at a modest density. Some of these ion channels are nonuniformly distributed over the dendritic membrane surface (*1*). Experiments show that these ion channels furnish the dendrites with a rich repertoire of electrical behaviors, from essentially passive responses, to subthreshold active responses, to active backpropagation of the action potential (AP) from the soma into the dendrites, to the initiation of APs in the dendritic tree. Yet, we have only begun to explore the properties of the dendritic ion channels that are responsible for these behaviors, properties such as their density, spatial distribution, and kinetics. The analytical extension of passive cable theory for dendrites with nonlinear membrane is impossible in most cases and difficult for the rest. As in the case of passive dendrites, nonlinear cable theory [which is yet to be developed; see (*4, 25*)] should highlight the key parameters that govern the electrical behavior of active dendrites. Indeed, at these early stages of systematic recordings from dendrites, many uncertainties are obscuring both the experimental and the theoretical picture of dendrites.

The most dramatic (nonlinear) effect of excitable dendritic ion channels is the presence of dendritic action potentials, APs (*1*). The theoretical challenge is to understand how the interplay between dendritic morphology, membrane excitability, and input conditions govern the initiation and propagation of APs in dendrites. Importantly, even in such nonlinear trees, passive cable theory provides key insights. In modestly excitable dendritic trees, spike initiation is sensitively dependent on the local input impedance (a passive measure) and on the degree of axial current loss from the input site to other, not-yet-activated (still passive), dendritic regions. This current loss of the (already limited) excitable current may be so large that the remaining depolarizing current is insufficient to regeneratively excite the local dendritic membrane (*26*).

Passive cable theory shows how the input impedance and axial current loss depend on dendritic morphology (see above). In regions with high input impedance (e.g., spine heads) current threshold (the minimal input current required for the initiation of excitation) is expected to be small (because small input current will produce large local depolarization). On the other hand, because thin dendritic arbors and spines suffer huge axial loss of input current, the current threshold at these sites is increased. It is the relative contribution of these two opposing effects that determine how current threshold changes in the dendritic tree (Fig. 2A) (*26–28*).

The propagation of action potentials in the tree is typically more secure toward distal dendritic branches ("backward," from soma to dendrites); it tends to block while spreading proximally. This is the direct result of the asymmetry in voltage attenuation in passive dendrites, as highlighted in Fig. 1, A and B (*1*). A sufficiently strong local excitatory input at distal excitable dendritic arbor is likely to generate a regenerative response (and even a full AP) in only a limited distal portion of the tree. The relatively secure backpropagation may give rise to an interesting backward-forward "ping-pong" game between the axon and the dendrites, thus creating a "handshaking" link—useful for both plastic and computational processes—between dendritic synapses and axonal output. This interaction between soma and dendrites also has an important effect on network dynamics (*28, 29*). Significantly, this complicated spatio-temporal nonlinear behavior can be captured by a reduced model composed of only two ("somatic" and "dendritic") compartments (Fig. 2C) (*30–32*).

Compartmental models of nonlinear dendrites have been used to expose possible biophysical consequences of active channels in dendrites. These models show that many of the (apparent) constraints (e.g., attenuation, relatively large integration time-window) inherent to passive dendrites could be overcome with active dendritic channels. Some of the ideas proposed included: active inward

current in dendrites may serve to (i) boost the synaptic potential (*33, 34*), (ii) reduce the location-dependence of the soma EPSP expected in passive dendrites (*35, 36*), and (iii) introduce a submillisecond coincidence detection mechanism by initiating a fast dendritic spike triggered by precise co-activation of adjacent inputs on thin dendrites (*37, 38*). Active outward current may (iv) linearize the synaptic current by reducing saturation (*39*), (v) scale the electrotonic structure and modulate the temporal resolution (integration window) of dendrites in an activity-dependent manner, thus changing the degree of interaction among synapses (*40*) and (vi) serving as a "shock absorber" by dampening large local depolarizations generated either by synaptic or by excitable currents (*41*). Some of these theoretical ideas have been validated experimentally [e.g., synaptic boosting (*42, 43*) and coincidence detection in dendrites (*44–46*)]. Other ideas remain controversial [e.g., mechanisms rendering distal and proximal synapses equally effective at the soma (*47*)].

An Inspiring Dialogue Between Models and Experiments

Several classical successful cases established the necessity for an intimate interaction between experiments and models. Experimental application of cable theory confirmed that dendrites are electrically distributed rather than isopotential units. The transients recorded at the soma could be fitted by a sum of several exponentials (*48*), rather than by one exponential as expected in "point neurons." The time constants associated with these exponentials were "peeled" from the experimental transients and used to improve estimates for the membrane time constant, τ_m (5 to 50 ms) and for the cable length of dendrites, L (0.5 to 2) (*49*). The EPSP shape indices (rise-time and half-width) at the soma were used for estimating the electrotonic distance, X_{in}, of the synaptic input in the dendritic tree. Redman and Walmsley (*50*) found a remarkable match between the value of X_{in}, estimated from the shape indices and that calculated directly from the anatomical site of connection. Unlike what is expected from passive cable theory, in several neuron types, EPSPs of distal origin (delayed and broad) are similar in amplitude to EPSPs originating at proximal sites. This implies that some "boosting" mechanism (e.g., an increase in the synaptic conductance as a function of distance from the soma) compensates for the voltage attenuation expected in passive dendrites (*47, 50*).

The dialogue with experimentalists forced theoreticians to further explore and refine their models. The most groundbreaking example is the computational study of the field potentials in the olfactory bulb, which was based on the gross anatomy of the bulb layers and the distributions of the field potentials at different depths of the bulb (*51*). Surprisingly, the model predicted mitral to granule cell excitation followed by granule to mitral cell inhibition. Electron microscopy (EM) confirmed the presence of reciprocal dendrodendritic synapses of opposite polarities between mitral and granule cells, dramatically verifying the predictions of the model and representing a triumph for theory.

Theory had particular impact on our understanding of the biophysics of the Lilliputian dendritic spines (Fig. 2A) (*52, 53*). These studies suggested that spines might act as minute electrical and chemical compartments involved in modulating synaptic efficacy. This brought about a wealth of experimental studies aiming at exploring whether spine dimensions change dynamically (*54*) and whether spines are indeed chemical compartments (*46*). Two-photon microscopy now makes it possible to optically image spines and to show that these fascinating little thorns with bulbous heads are indeed calcium compartments that may undergo activity-dependent morphological changes (*55, 56*). Models also show that the huge number of spines (100,000 in a single cerebellar Purkinje cell), which contribute significantly to the total membrane area of dendrites, effectively increase the cable length of dendrites and thus affects their integrative properties (*57*).

Direct validation of the predictions of passive cable theory became possible with the use of paired recordings from the soma and apical dendrite of pyramidal neurons. The filtering effect of dendrites and direction-dependent voltage attenuation was assessed in layer V cortical pyramidal cells (*12*) but is less pronounced in CA1 pyramids (*58*). Note that measurements of voltage attenuation have not yet been made from large fractions of most dendritic trees (the thin arbors) so that the steep voltage profile predicted for inputs to thin arbors (Fig. 1A) was not assessed experimentally. The effect of the background synaptic activity on the cable parameters was recently confirmed in both in vivo and in vitro experiments (*59, 60*). Finally, theoretical ideas regarding the role of dendritic inhibition for computing the direction of visual motion (*14*) have stimulated intense experimental research aimed at exploring if, indeed, directional selectivity in cortical neurons is associated with a significant synaptic shunt (*61, 62*).

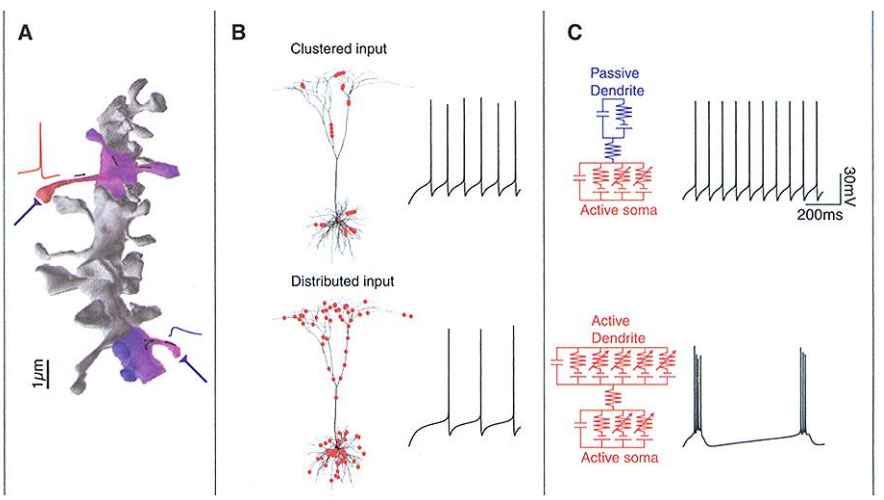

Fig. 2. Fundamental insights for excitable trees. **(A)** Dendritic spines consisting of voltage-gated (and/or NMDA-mediated) ion channels, in particular spines with thin and long necks, are favorable sites for boosting the local excitatory synaptic input and for accumulation of calcium ions (red top left spine) (*37, 53*). Spine morphology implies a significant attenuation of both voltage and for calcium concentration from the spine head to the spine base (picture from Synapse Web, Boston University, http://synapses.bu.edu/). **(B)** In excitable dendrites, a certain degree of spatial clustering of excitatory synapses (top) may result in a significant boosting of the synaptic charge that reaches the soma, because it produces larger local depolarization which may be sufficient for activating the local excitable channels. As a consequent, the axon fires more vigorously (right). In both cases, 100 excitatory synapses were used; top, 10 clusters of 10 synapses each; bottom, clusters of 1 synapse. Each synapse was activated 40 times/s for 1 s. The dependence of the axon output on the degree of synaptic clustering in the dendrites could be used for implementing input classification task (*34*). **(C)** Backward-forward "ping-pong" interaction between the axon and the excitable channels in dendrites shapes the output pattern of spikes firing in the axon. Two models of a cortical pyramidal neuron were used; one with passive dendrites (top) and the other with excitable dendrites (bottom) [excitable model as in (*31*)]. For passive dendrites, the axon fires regularly in response to steady soma depolarization whereas in the model with excitable dendrites it fires repeated spike bursts. The geometry of the dendritic tree plays a crucial role in this "ping-pong" interaction, as demonstrated using reduced two-compartment model [left column, see (*30*)].

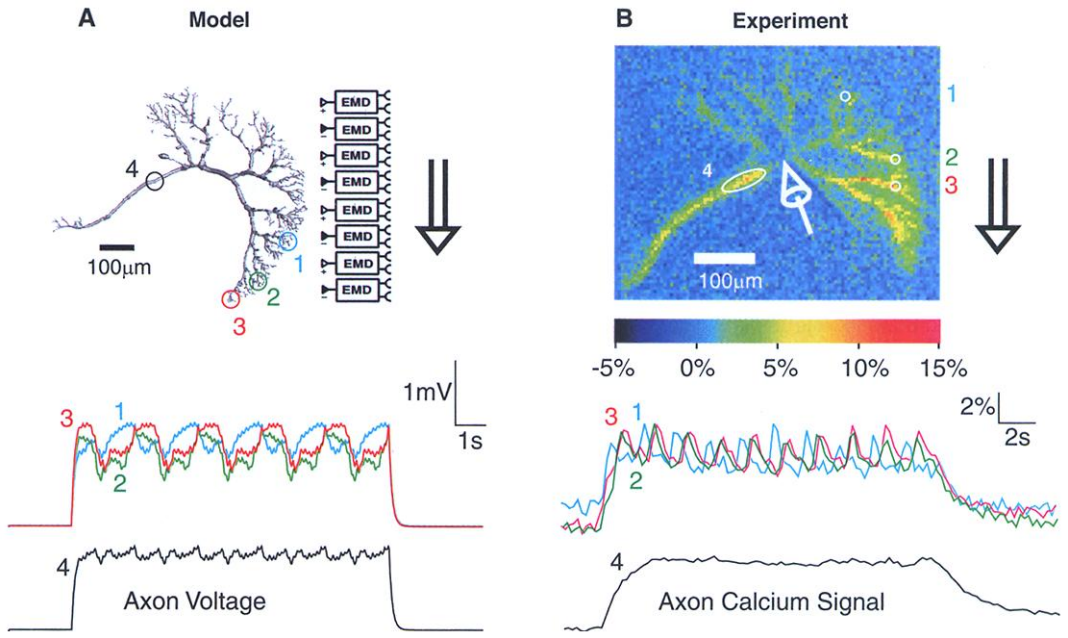

Fig. 3. Computing with dendrites. (**A**) A model of a TC neuron in the fly visual system, activated by the Elementary Motion Detectors (EMD) array, in the preferred direction of motion. (**B**) In vivo calcium imaging from the dendrites of TC-cell during motion of a periodic grating in the cell's preferred direction. Calcium fluctuates within individual dendrites in response to both changes in local contrast pattern as well as due to motion of the whole pattern. Filtering in the dendrites effectively cancels out the responses due to local patterns while retaining the overall direction of motion. Furthermore, to maximize efficacy of input integration, the fanlike dendritic arbor is oriented so that neurons sensitive to vertical motion have their fans aligned with the dorsal-ventral axis, whereas horizontally sensitive neurons have their arbors arrayed orthogonally. Interestingly, the dendritic mechanisms used for implementing this computation (i.e., nonlinear summation of synaptic inputs, amplifications using voltage-dependent ion channels) where previously proposed on theoretical grounds, but this is the first direct demonstration that they are indeed used to implement specific computation in dendrites. [Figure adapted from (*80*).]

Dendritic Computation

The computer has become more than just another metaphor for the brain, like other human made devices in the past. The computer is a unique machine in that it is universal. We believe that it can "simulate" any other computation, discrete or analog, mechanical or biological (*63*). Moreover, as Turing so eloquently put it, mechanical simulation of intelligence cannot be distinguished from intelligence itself.

The Turing machine operates in an algorithmic fashion in which a series of simple operations relates a given input to a desired output. Similarly, a series of operations are implemented by the nervous system before the sensory input is transformed to a desired behavioral output. These operations can be characterized as computations (*64*). Single neurons often reflect these operations; they show orientation selectivity, velocity tuning, coding for spatial location, and so forth. It is still largely an open question what is the role of single neurons, and in particular of their dendrites, in implementing these neuronal computations, and whether the algorithmic framework is natural for describing the computations performed at the single-neuron level.

What is clear is that dendrites and their synapses transform the digital presynaptic spike trains to an analog signal delivered to the axon of the postsynaptic cell. The sophisticated nonlinear machinery that dendrites possess could, in principle, be used for performing nontrivial transformation (computations) of their synaptic input. Evidence for "low-level" processing in dendrites, such as filtering, amplification and coincidence detection of synaptic inputs, have already been demonstrated (see above). But are these dendritic processes actually used for implementing a specific computation? To answer this question, in vivo recordings during the performance of a specific computation are required.

Until very recently, in vitro recordings from dendrite were rare, not to mention in vivo recordings which were extraordinary (*65, 66*). Thus, models were used to suggest ways in which dendrite with their synapses could, in principle, implement specific computation. It was suggested that dendrites could compute the direction of motion (*13–15*) improve sound localization (*24*), provide gain control (*67*) and perform a multidimensional input classification task (*68*). Active dendrites have also been shown to produce spatial invariance, orientation tuning and binocular disparity visual responses [(*69, 70*) and reviews in (*71, 72*)].

Recently, in a most impressive series of experiments, in vivo recording from dendrites was accomplished (*73–76*). Using combined imaging and electrophysiological methods, it is possible to infer the electrical activity of large portions of the dendritic tree. Of direct relevance to dendritic computation is the study of Borst and colleagues (*77–81*) on the processing information in the fly visual system, where a population of large interneurons spatially integrates the output signals of many thousands of columnar neurons, each being sensitive to a very small part of the visual scene. These so-called tangential cells (TCs) are all motion-sensitive: they become excited by motion in one direction and are inhibited by motion in the opposite direction. Using both intracellular recordings as well as calcium imaging from dendrites in vivo (Fig. 3B), Borst *et al.* discovered two major processing steps implemented by the TC dendrites. Through the processing of opponent input elements having opposite preferred direction, the direction selectivity of presynaptic neurons is significantly enhanced in the TCs. Models predict (Fig. 3A) and experiments confirm (Fig. 3B) (*78–80*) that dendritic filtering helps in distinguishing a change in contrast due to stimulus motion from changes due to purely local patterns of the stimulus. The result of this integration is a graded depolarization in the axon of the cells; this depolarization represents information about image velocity with high fidelity (Fig. 3) (*80, 81*). With these in vivo experiments, a breakthrough is at our door; and we should expect that soon we will gain a deeper understanding of the extent to which dendrites contribute to the computations that performed by the nervous system.

The Future of Dendrites

Dendrites and their spines are beginning to surrender to the sophisticated optical and electrical techniques that were developed in the last decade. In the coming years we will witness intense research into dendrites (and probably also into axons) and their role in information processing will be exposed.

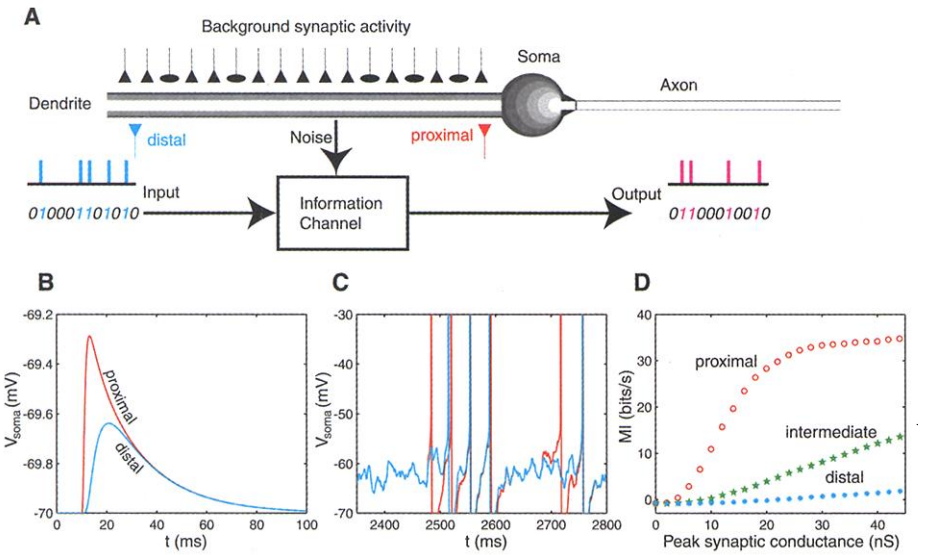

Fig. 4. Exploring dendritic input-output relation using information theory. **(A)** Reduced model of a neuron consisting of a passive dendritic cylinder, a soma and an excitable axon. The dendritic cylinder is bombarded by spontaneous background synaptic activity (400 excitatory synapses, each activated 10 times/s; 100 inhibitory synapses, each activated 65 times/s). When activated, each synapse produces a transient conductance change; the input to each synapse is a train of temporally random presynaptic action potentials, modeled as a string of 0's and 1's, similar to the output of the postsynaptic axon. **(B)** Soma EPSPs for a proximal (red line) and a distal (blue line) synapse. **(C)** Two sample traces of the output spike train measured in the modeled axon. Identical background activity was used in both cases; the location of only one excitatory synapse was displaced from proximal to distal. For some time epochs, this displacement noticeably changes the output spike train. **(D)** The mutual information (MI), which measures how much could be known about the input (the presynaptic spike train) by observing the axonal output, is plotted as a function of the maximal synaptic conductance change for the three input locations. Note that the distal synapse transmits significantly less information compared to the proximal synapse. For strong proximal synapses, the MI is saturated because, for large conductance values, each input spike generates a time-locked output spike and no additional information is gained by further potentiating this synapse. The analysis shows that, to a good approximation, the EPSP peak (rather than its time course) is the main determinant of the MI. This method could be used to experimentally measure information transfer in real dendrites.

Important theoretical issues are likely to be encountered, three of which are highlighted below.

In search of new analytical methods. Although we can numerically simulate signal processing in dendrites with nonlinear and nonuniform membrane properties, we still lack analytical tools for modeling such dendrites. While key insights have been gained from numerical exploration of excitable dendrites, experience from passive cable theory tells us that a comprehensive understanding eventually comes from analytical approaches (*6, 82, 83*). We thus hope that a new generation of researchers, equipped with powerful mathematical tools, will join forces to analytically delve into dendrites.

Stability, plasticity and learning in dendrites. Dendrites are highly dynamic and plastic devices; their morphology (*55*) synapses (*84, 85*) and ionic channels undergo constant activity-dependent modulation (*86*). What are the rules that govern these modulations? How do dendrites continue to stably perform their computational tasks in view of these changes? Can we use tools from learning theory to quantify the capabilities and limitations that dendrites have as a computing and learning device? Although initial theoretical work is under way (*87–89*), the road to understanding how dendrites learn is still largely uncharted.

Noise and information capacity of dendrites. Models of dendrites are typically formulated using deterministic equations, thereby ignoring the different noise sources encountered by the input signals that impinge on dendrites. These noise sources include stochastic ion-channel noise, probabilistic synapses, and massive "spontaneous" background synaptic activity (*90–93*). We still lack a systematic characterization of the nature and magnitude of the neuronal noise involved, but we do have theoretical tools from statistical estimation and information theory to quantify the ability of neurons to transmit information about their inputs through their spike outputs in the presence of noise (*94*). Indeed, information theory could provide a unifying framework for assessing the effect of the various neuronal modules (synapses, dendrites, the axonal spike generation mechanism) on the encoding/decoding capabilities of the neuron (Fig. 4) and (*95*). It is hoped that within this framework, we will be able to unravel the design principles by which the dendritic machinery is used for maximizing and stabilizing information transmission in these fascinating building blocks of the nervous system.

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98. We thank N. Spruston, C. Koch, C. Meunier, and M. Häusser for their constructive comments on this manuscript. The U.S.–Israel Binational Science Foundation, the Israeli Science Foundation, and the U.S. Office of Naval Research supported this work.

REVIEW

Signal-Processing Machines at the Postsynaptic Density

Mary B. Kennedy

Dendrites of individual neurons in the vertebrate central nervous system are contacted by thousands of synaptic terminals relaying information about the environment. The postsynaptic membrane at each synaptic terminal is the first place where information is processed as it converges on the dendrite. At the postsynaptic membrane of excitatory synapses, neurotransmitter receptors are attached to large protein "signaling machines" that delicately regulate the strength of synaptic transmission. These machines are visible in the electron microscope and are called the postsynaptic density. By changing synaptic strength in response to neural activity, the postsynaptic density contributes to information processing and the formation of memories.

Dendrites are the principal signal reception and processing sites on vertebrate neurons. The dendrites of each pyramidal neuron are highly branched and contain thousands of synapses made by axons from almost as many neurons. Most of these synapses are located on spines, which are tiny tubular or mushroom-shaped structures about 1 to 3 μm long and less than 1 μm in diameter that protrude from the dendritic shaft (Fig. 1). The typical presynaptic terminal forms a junction with one, or at most two, postsynaptic spines. Spines are the first processing point for synaptic signals impinging on the dendrite. Much of the processing machinery is contained in a highly organized biochemical apparatus attached to the cytosolic surface of the postsynaptic membrane. This protein complex is visible in the electron microscope as a thickening of the postsynaptic membrane, extending approximately 30 nm into the cytosol; it was termed the "postsynaptic density" or PSD by early electron microscopists (Fig. 1) (*1*, *2*).

Nearly all presynaptic terminals that make synapses on dendritic spines release the excitatory neurotransmitter glutamate. The postsynaptic membrane of a typical spine contains at least two distinct types of glutamate receptors concentrated at the site of contact with the presynaptic terminal. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)–type glutamate receptors are ion channels that open when they bind glutamate, allowing sodium and potassium ions to flow across the membrane, producing a small, brief depolarization called the excitatory postsynaptic potential (EPSP). *N*-methyl-D-aspartate (NMDA)–type glutamate receptors are also ligand-gated ion channels. However, opening of their larger channel does not occur when glutamate binds to it, unless the membrane is strongly depolarized to relieve blockade of the channel by extracellular magnesium. The required depolarization is larger than can be achieved by AMPA receptors at a single synapse. Adequate depolarization can, in theory, be produced by coincident firing of several nearby synapses or by a back-propagating action potential (*3*). When the two conditions of glutamate binding and strong depolarization are met, the NMDA receptor channel opens and allows the flow of sodium and calcium ions into the cell. The resulting

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