

## Information Processing in Dendritic Trees

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This review considers the input-output behavior of neurons with dendritic trees, with an emphasis on questions of information processing. The parts of this review are (1) a brief history of ideas about dendritic trees, (2) a review of the complex electrophysiology of dendritic neurons, (3) an overview of conceptual tools used in dendritic modeling studies, including the cable equation and compartmental modeling techniques, and (4) a review of modeling studies that have addressed various issues relevant to dendritic information processing.

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### 1 Introduction

Dendritic trees come in many shapes and sizes, and are among the most beautiful structures in nature (Fig. 1). They account for more than 99% of the surface area of some neurons (Fox and Barnard 1957), are studded with up to 200,000 synaptic inputs (Linás and Walton 1990), are the largest volumetric component of neural tissue (Sirevaag and Greenough 1987), and consume more than 60% of the brain's energy (Wong-Riley 1989). Most importantly, though, they are the computing workhorses of the brain.

This review concerns the question as to how information is processed in dendritic trees. In order to achieve focus, the scope of this review is limited in several ways. First, we bias our discussion toward studies that bear directly on questions of information processing. Less attention is devoted to work that is primarily biophysical in nature, such as studies aimed at matching dendritic neuron models to experimental data—for a thorough recent review see (Rall *et al.* 1992). Second, we focus on questions that pertain specifically to *dendritic* computation, i.e., for which the spatially extended structure of the dendritic tree is essential. Questions of relevance to general neuronal computation are not emphasized here, such as the nature of information coding in spike trains (Attick and Redlich 1990; Bialek *et al.* 1991; McClurkin *et al.* 1991; Theunissen and Miller 1991; Softky and Koch 1993), or the mechanisms underlying complex neuronal spiking behavior (Traub and Linás 1979; Traub 1982; Traub *et al.* 1985; Borg-Graham 1987; Lytton and Sejnowski 1991; Traub *et al.* 1991). Third, we consider computation on fast time scales only. Thus, the central topic

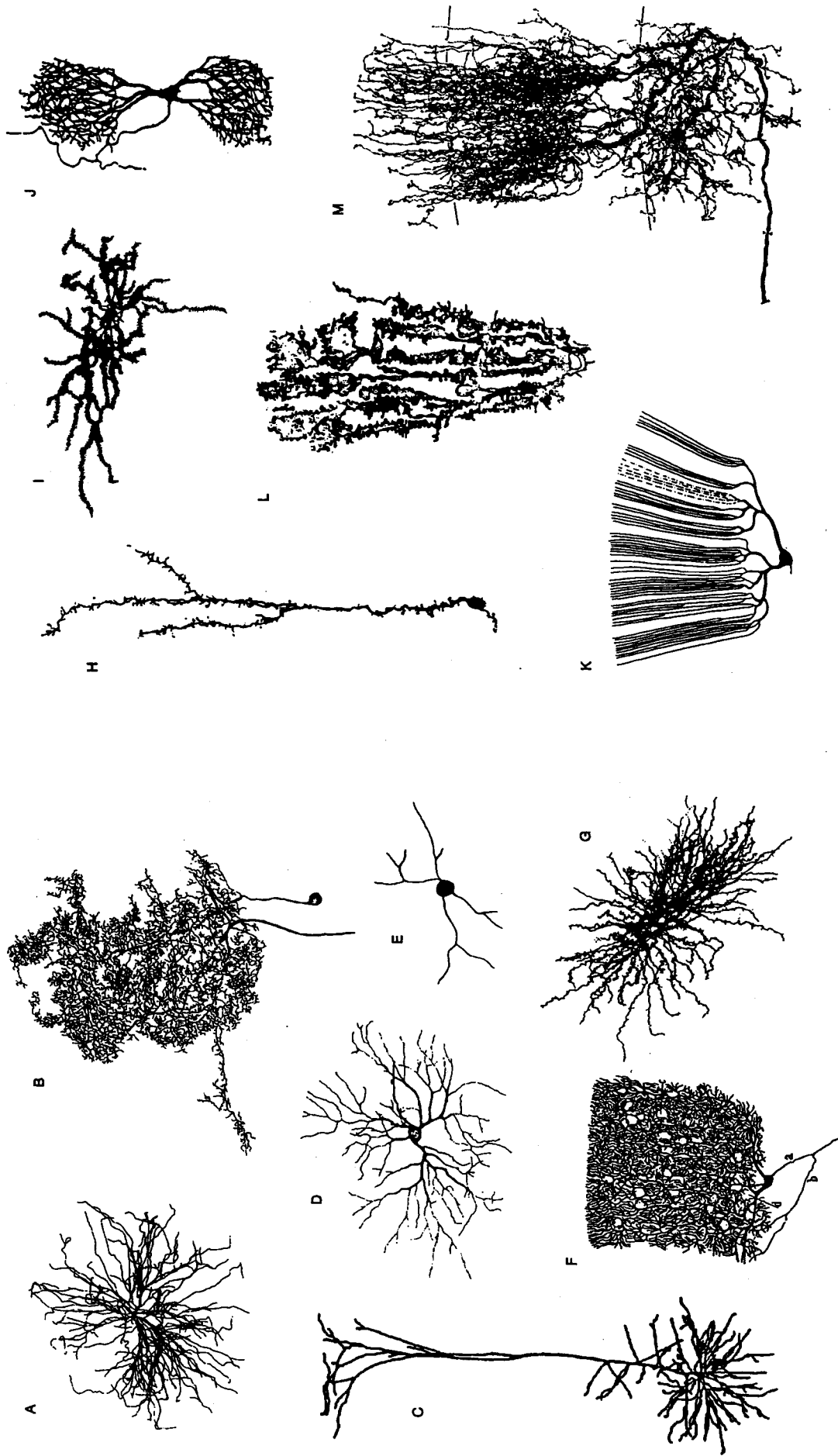


Figure 1: Continued.

Figure 1: Caption on overleaf.

1.1 History of Ideas about Dendrites. Historical notes that trace the progression of ideas about dendritic physiology and information processing are available elsewhere and may be consulted by the interested reader (Brazier 1959; Lorente de N6 and Condouris 1959; Purpura 1967; Jack *et al.* 1975; Spencer 1977; Rall 1977; Kandel and Schwartz 1985; Shepherd and Koch 1990; Segev 1992). A few historically significant conceptual landmarks have been collected below.

Dendritic trees, like terrestrial trees, root systems, and vascular systems, are a class of branched structures well suited for the penetration of a volume, such as for the extraction or delivery of nutrients. Before the advent of electrophysiology, it was reasonable to conclude, as was done by the great neuroanatomist Golgi (1886), that dendrites played a strictly nutritive role in neuronal function. The modern idea, that a dendritic tree exists to extract information from the volume in which it sits, has led some to propose that the need to increase neuronal surface area to make room for more synapses has been the main driving force in the evolution of the vertebrate brain (Purpura 1967). Beyond simply increasing a cell's connective "fan-in," though, it has also been frequently observed that spatially extended dendritic arborizations make possible the physical segregation of functionally distinct input pathways to a cell, a pattern seen in many areas of the vertebrate brain including the olfactory bulb, hippocampus, and cerebellum (Shepherd 1990).

What of the physiological functions of dendritic trees? The "neuron doctrine" of Cajal (1909), and in particular the "principle of dynamic polarization," entailed that signals flowed from the input surfaces of the cell (dendrites and soma) toward the axon, where a wave of nervous energy was then propagated to other neurons through synaptic contacts.<sup>1</sup> How the effects of distinct synaptic inputs were to be combined within the dendrites was at that time a matter beyond the resolution of either experiment or theory. When the all-or-none nature of nervous impulses was first discovered (Goitch 1902; Adrian 1914), the idea that dendrites, too, might conduct nondcremental impulses prevailed for decades. In a dissenting opinion, Lorente de N6 (1934) considered the idea of all-or-none impulse conduction in dendrites to be problematic, pointing out that dendritic integration would in this case degenerate to the propagation of any strong synaptic event directly to the cell's output; the possibility of combining the effects of widely separated synaptic inputs would thus be eliminated (Lorente de N6 and Condouris 1959). In the 1930s and 1940s, a "classical" picture emerged based in large part on the study of spinal motoneurons, which held that the exclusive spike trigger zone in a neuron was the axon initial segment, while the dendrites simply collected and summated synaptic inputs—in essence reducing the single neuron to a McCulloch-Pitts-type "morpho-less" unit (see Segev 1992). In a refinement of this idea, it was commonly believed that inputs onto distal

<sup>1</sup>Cajal came to this conclusion based solely on careful inspection of tissue sections under the microscope.

of this review concerns how dendritic trees transduce complex patterns of synaptic input into a stream of action potentials at the cell body, over periods of tens of milliseconds. Computations on longer time scales are not considered, such as those involving second-messenger systems (Walterhouse *et al.* 1991), ion channel migration or regulation (Popov and Poo 1992; Bell 1992; LeMasson *et al.* 1993), ultrastructural changes (Greenough and Bailey 1988), or any consequence of gene-expression (Esterle and Sandersbush 1991). Fourth, the emphasis of this review is primarily on dendritic function in vertebrate neurons. This is a consequence of the fact that the bulk of dendritic modeling studies to date have dealt with vertebrate neurons. Finally, specific discussion of the computational significance of dendritic spines is left to a number of excellent reports and reviews available elsewhere (Koch and Poggio 1983; Miller *et al.* 1985; Perkel and Perkel 1985; Rall and Segev 1987; Segev and Rall 1988; Koch and Poggio 1987; Shepherd and Greer 1988; Zador *et al.* 1990; Koch *et al.* 1992).

The remainder of this section is devoted to a few historical notes regarding the role of dendrites in neuronal function. In Section 2, experimental evidence is reviewed that proves dendrites to be physiologically highly complex objects. In Section 3, the main conceptual and computational tools that have been applied in the study of dendritic function are introduced, including the cable equation, compartmental modeling, and several useful rules of thumb regarding the flow of current in dendritic trees. Finally, modeling studies relating directly to dendritic information processing are reviewed in Section 4.

Figure 1: Previous two pages. Dendrites and other neural trees structures, reproduced with permission. Lengths given are approximate and correspond to direction of maximal extent. (A) Alpha motoneuron in spinal cord of cat (2.6 mm); from Cullheim *et al.* (1987). (B) Spiking interneuron in mesothoracic ganglion of locust (540  $\mu\text{m}$ ); courtesy G. Laurent. (C) Layer 5 neocortical pyramidal cell in rat (1030  $\mu\text{m}$ ); from Amitai *et al.* (1993). (D) Retinal ganglion cell in postnatal cat (390  $\mu\text{m}$ ); from Maslim *et al.* (1986). (E) Amacrine cell in retina of larval tiger salamander (160  $\mu\text{m}$ ); from Yang and Yazulla (1986). (F) Cerebellar Purkinje cell in human; from Ram6n y Cajal (1909), v. 1, p. 61. (G) Relay neuron in rat ventrobasal thalamus (350  $\mu\text{m}$ ); from Greer (1987). (H) Granule cell from olfactory bulb of mouse (260  $\mu\text{m}$ ); from Penny *et al.* (1988). (I) Nerve cell in the Nucleus of Burdach in human fetus; from Ram6n y Cajal (1909), v. 2, p. 902. (K) Purkinje cell in mormyrid fish (420  $\mu\text{m}$ ); from Meek and Nieuwenhuys (1991). (L) Golgi epithelial (glial) cell in cerebellum of normal-reeler mutant mouse chimera (150  $\mu\text{m}$ ); from Terashima *et al.* (1986). (M) Axonal arborization of isthmotectal neurons in turtle (460  $\mu\text{m}$ ); from Sereno and Ullinski (1987).

dendrites, which were thought to be both weak and slow, acted primarily to modulate the responsiveness of a cell to more powerful, more proximal soma-dendritic inputs (Adrian 1937; Chang 1952; Grundfest 1957; Eccles 1957; Bishop 1958; Purpura 1959).

In the intervening years, a considerable body of data has accumulated showing that the dendrites of many types of neurons in the vertebrate CNS are replete with complex, interacting voltage-dependent membrane conductances, often capable of generating full-blown action potentials and other highly nonlinear behaviors. These data are reviewed in the next section.

## 2 Electrophysiology of Dendrites

As this review is centrally concerned with the question of dendritic information processing, especially the possibility that dendritic trees are intrinsically sophisticated computing devices, the experimental studies cited in the following sections have been chosen to emphasize interesting nonlinear voltage behavior in dendritic trees. For a review of experimental work relevant to the passive cable properties of dendritic trees, see Rall *et al.* (1992).

### 2.1 Motoneurons.

The earliest experiments suggesting active behavior in dendrites were carried out in "chromatolyzed" motoneurons, i.e., spinal motoneurons whose axons to the peripheral musculature had been cut 2-3 weeks prior to recording (Eccles *et al.* 1958). These authors recorded small, spike-like, excitatory potentials several millivolts in height, which they termed *partial responses* (Fig. 2). Partial responses were distinguished from conventional synaptic EPSPs in three ways: (1) they were brief and spike-like in character, (2) they occurred with a greater range of latencies in response to synaptic stimulation, and (3) they were blocked in all-or-none fashion by hyperpolarizing current injection at the soma; EPSPs would normally *increase* in size under these conditions. A distal dendritic origin was inferred since the partial responses could only be blocked with large hyperpolarizing currents at the cell body. Kuno and Llinás (1970) provided further evidence for a distal dendritic origin of partial responses in chromatolyzed motoneurons by showing that they were more easily blocked by synaptic inhibition delivered to the distal dendrites than by hyperpolarizing currents at the soma. They emphasized that somatic action potentials could arise from partial responses of different sizes, suggesting multiple sites of spike origin in the dendritic tree. In spite of the profoundly abnormal anatomical and physiological condition of these axotomized cells (see Eccles *et al.* 1958), the idea that dendrites could contain discrete excitable "hot spots" first gained popularity in these early results. The methodological problems associated with the study of chromatolyzed motoneurons were later highlighted

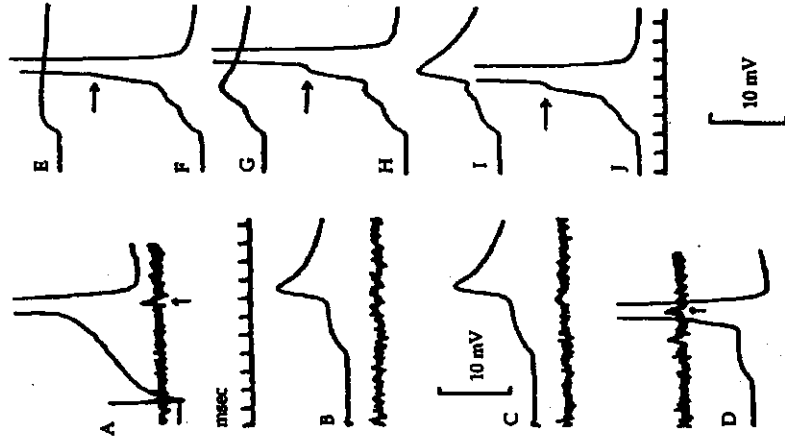


Figure 2: Partial responses in chromatolyzed motor neurons (Eccles *et al.* 1958). (A) Response to depolarizing current pulse that generated an action potential. (B-J) Responses to afferent synaptic volleys. Traces in E-J were selected to show the wide range of variability of partial responses that are superimposed on the EPSP shown in E. Arrows indicate initiation of full spikes.

(Sernagor *et al.* 1986), where it was suggested that dendritic spikes in these cells may result from a pathological redistribution of excitable  $\text{Na}^+$  channels into the dendrites that might otherwise have been destined for the severed axon.

### 2.2 Cerebellar Purkinje Cells.

Cerebellar Purkinje cells have yielded one of the most clearcut examples of dendritic spiking among vertebrate neurons (Fig. 3). In early work in cerebellar slices, Hild and Tasaki (1962) recorded spike-like blips from an extracellular electrode pressed

dependent calcium "plateau potentials" of between 10 and 30 mV, i.e., noninactivating excitatory potentials that could outlast a small depolarizing current stimulus by hundreds of milliseconds (Llinás and Sugimori 1980). In these experiments, calcium spiking and plateau potentials were ubiquitous in Purkinje cell dendrites; more recent optical recording experiments have established that calcium influx occurs across essentially the entire dendritic tree (Tank *et al.* 1988; Sugimori and Llinás 1990; Ross *et al.* 1990). In contrast, Na<sup>+</sup>-mediated spiking and plateau channels were found to be localized near the soma (Llinás and Sugimori 1980; Hounsgaard and Midtgaard 1988).

**2.3 Hippocampal Pyramidal Cells.** Spencer and Kandel (1961) first observed "fast prepotentials" (FPPs) in hippocampal pyramidal cells, citing similarities to the partial responses described by Eccles *et al.* (1958). Somatic or axonal origins of the spikes were again ruled out since they were not blocked by hyperpolarizing current injection. Following Eccles (1957) the authors conjectured that the spike-like prepotentials may have originated at the main bifurcation of the apical dendritic tree, where a patch of excitable membrane could act as a booster to otherwise ineffective distal synaptic inputs (Fig. 4). Subsequent studies using a variety of techniques have provided extensive further evidence for dendritic spiking mechanisms in hippocampal pyramidal cells (Andersen and Lomo 1966; Purpura *et al.* 1966; Schwartzkroin and Slawsky 1977; Wong *et al.* 1979; Schwartzkroin and Prince 1980; Bernardo *et al.* 1982; Masukawa and Prince 1984; Herrerias 1990; Poolos and Kocsis 1990; Turner and Richardson 1991; Wong and Stewart 1992). In the first direct intradendritic recording in CA1 and CA3 hippocampal cells *in vitro*, Wong *et al.* (1979) showed that bursts consisting first of fast Na<sup>+</sup>-dependent spikes followed by slow (presumably Ca<sup>2+</sup>-dependent) spikes, could occur either spontaneously or in response to depolarizing current pulses. A subsequent study on CA1 dendrites that had been surgically isolated from their cell bodies (Bernardo *et al.* 1982) showed similar mixtures of fast Na<sup>+</sup> and slow Ca<sup>2+</sup> spikes (as well as spikes of intermediate duration) in response to intradendritic current injections (Fig. 5A). The dependence of fast and slow dendritic spikes on sodium and calcium channels, respectively, was demonstrated in CA1 pyramidal cells by Poolos and Kocsis (1990), as illustrated in Figure 5B. The occurrence of multiple points of inflection and mixtures of spikes of differing amplitudes in these studies was interpreted as evidence of multiple dendritic sites of spike generation; other workers have reached similar conclusions (Masukawa and Prince 1984; Jones *et al.* 1989; Turner and Richardson 1991; Wong and Stewart 1992). The relative independence of dendritic and somatic action potentials was explicitly demonstrated by impaling the same neuron with two electrodes (Wong and Stewart 1992), as illustrated in Figure 5C. Finally, in a recent optical recording study, Jaffe *et al.* (1992) reported that when potassium currents were blocked with TEA, voltage-dependent cal-

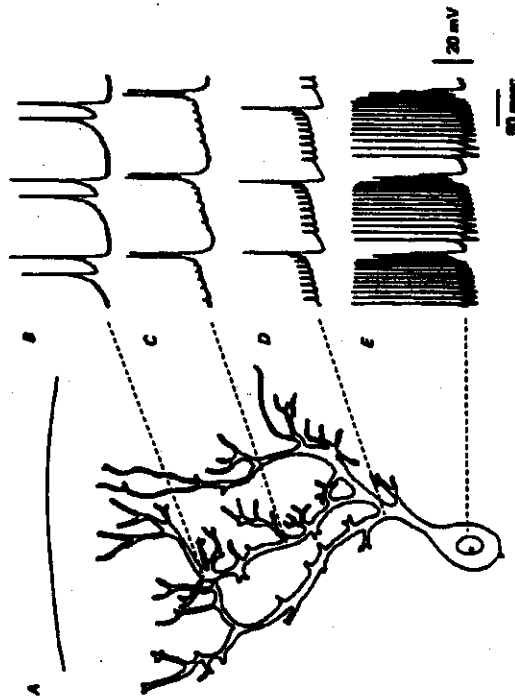


Figure 3: Composite picture showing the relationship between somatic and dendritic action potentials following DC current injection through the recording electrode. A clear shift in amplitude of the somatic spike against the dendritic Ca<sup>2+</sup>-dependent potentials is seen when comparing the more superficial recording in B with the somatic recording in E. Note that at increasing distances from the soma the fast spikes are reduced in amplitude and are barely noticeable in the more peripheral recordings. Reprinted with permission from Llinás and Sugimori (1980).

up against a dendritic branch of a Purkinje cell. Intradendritic recordings from Purkinje cells both *in vitro* and *in vivo* have since confirmed the existence of active dendritic spike generation in mammalian (Fujita 1968; Llinás and Sugimori 1980; Ross *et al.* 1990; Sugimori and Llinás 1990), avian (Llinás and Hess 1976), reptilian (Llinás *et al.* 1968; Llinás and Nicholson 1971), and amphibian (Hounsgaard and Midtgaard 1988) cerebella. The probability that dendritic spikes in Purkinje cells were due to Ca<sup>2+</sup> and not Na<sup>+</sup> currents was first demonstrated by Llinás and Hess (1976). Unlike fast somatic sodium spikes that peak in 1–2 msec, dendritic calcium spikes were slow rising, typically reaching a peak of 30–60 mV at 5–10 msec, and could be evoked by a 10 mV depolarizing intradendritic current injection (Llinás & Nicholson 1971; Llinás & Sugimori 1980b; Fig. 3). A subsequent detailed study of the electrophysiological properties of dendritic membrane in these cells also revealed voltage-

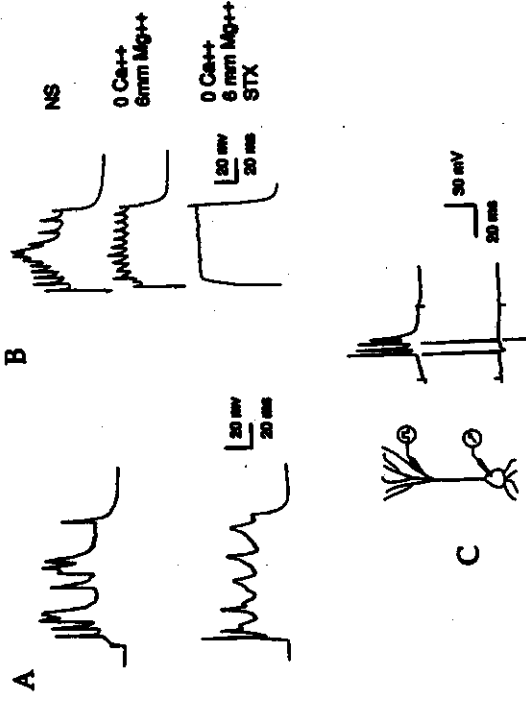


Figure 5: (A) Recordings from intact (upper trace) and surgically isolated (lower trace) dendrites of CA1 pyramidal cells reveal complex spiking traces in response to current injections (Benardo *et al.* 1982); recordings were made between 100 and 350  $\mu\text{m}$  from the cell body (reprinted with permission). (B) Intracellular recordings at more than 200  $\mu\text{m}$  from the cell body in CA1 pyramidal cells in response to 0.9 nA current injections are shown for the same cell under three conditions: normal saline (upper), 0-calcium (middle), and STX (lower). Note disappearance of underlying slow spike when calcium was removed from the bath, and disappearance of fast spikes in the presence of a sodium channel blocker (reprinted with permission from Poolos and Kocsis 1990). (C) Simultaneous recording in apical dendrites and soma in CA1 pyramidal cell in response to direct dendritic depolarization. Somatic response (lower trace) to dendritic burst (like that in upper trace) reveals independence of dendritic and somatic spiking activity. Reprinted with permission from Wong and Stewart (1992).

ment of the EPSP accounts for half the peak current and three quarters of the total injected synaptic charge. This experiment argues that the voltage dependence of the NMDA channels is likely to be an important nonlinearity influencing subthreshold synaptic integration (see also Salt 1986). An NMDA-dependent potentiation in the dendritic spiking response in CA1 cells following a tetanus has also been shown (Poolos and Kocsis 1990), revealing an intricate interplay between at least two kinds of excitatory, voltage-dependent nonlinearities in these cells. In-

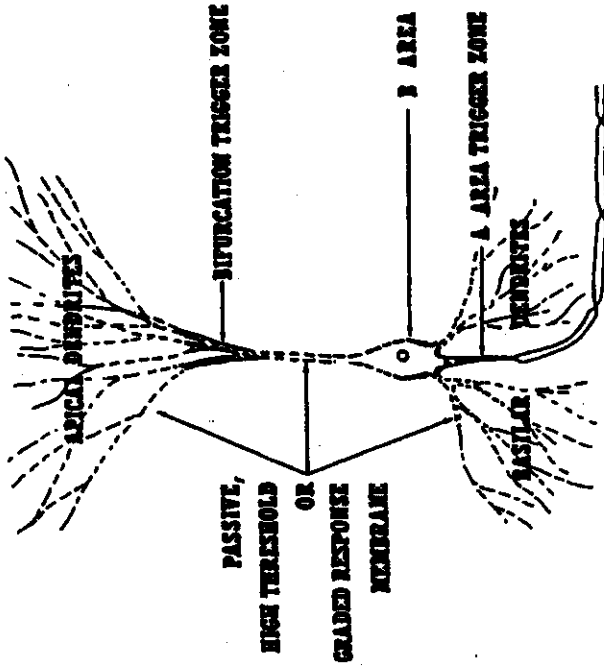


Figure 4: The idea that fast prepotentials recorded at the cell body arise from a patch of excitable membrane at the main apical bifurcation of a hippocampal pyramidal cell was illustrated by Spencer and Kandel (1961); reprinted with permission.

cium entry could be recorded across the entire apical and basilar dendritic tree of a CA1 cell, whereas rapid sodium entry indicative of active penetration of sodium spikes was present only in proximal dendrites up to a distance of 200  $\mu\text{m}$  from the cell body.

In addition to dendritic spikes, subthreshold voltage-dependent conductances have been observed in intact and isolated CA1 dendrites that give rise to larger responses to depolarizing (excitatory) than hyperpolarizing (inhibitory) current pulses (Benardo *et al.* 1982). This anomalous rectification was considered to be due either to voltage-dependent  $\text{Ca}^{2+}$  channels or to background activation of NMDA channels, whose negative slope conductance near resting potential (Mayer and Westbrook 1987) can result in an apparent increase in input resistance with depolarization (Sutor and Hablitz 1989). In hippocampal dentate granule cells depolarized to  $-50$  mV, Keller *et al.* (1991) have shown that when synaptic inhibition has been blocked, the NMDA (vs. non-NMDA) compo-

terestingly, neither fast nor slow spikes were generated in the dendrites of dentate granule cells in response to large depolarizing current pulses (Bernardo *et al.* 1982), highlighting the fact that significant differences are found in the distribution of membrane nonlinearities in different types of neurons within the same brain area, even among closely related neuron types.

**2.4 Neocortex.** Unlike their hippocampal and cerebellar counterparts, the dendritic trees of neocortical pyramidal cells are not confined to specific neural laminae that are essentially free of cell bodies (such as *stratum radiatum* in hippocampus or *stratum moleculare* in cerebellum). It is therefore technically difficult to systematically record from neocortical dendrites in order to study their electrophysiological properties directly. Early evidence for active dendritic responses in neocortical pyramidal cells was mostly indirect (Chang 1952; Cragg and Hamlyn 1955; Purpura and Shofer 1964; Spear 1972; Arikuni and Ochs 1973; Spencer 1977). Deschenes found fast prepotentials in 40% of the fast-conducting pyramidal tract neurons of the primary motor cortex in anesthetized cats, of a form very similar to those previously described in the hippocampus (Spencer and Kandel 1961) and elsewhere (see Spencer 1977). However, the possibility that the FFPs were electrotonically attenuated spikes from other neurons transmitted through gap junctions was not entirely ruled out (Deschenes 1981). In cultured neonatal pyramidal cells from rat sensorimotor cortex, Huguenard *et al.* (1989) demonstrated the existence of voltage-dependent  $\text{Na}^+$  channels on the proximal apical dendrites up to at least 80  $\mu\text{m}$  from the cell body, using cell-attached patch and whole cell recordings. Evidence for distal dendritic calcium spikes has also been provided in mature neocortical neurons *in vitro* (Staflstrom *et al.* 1985). In these experiments, depolarizing clamp voltages at the cell body were frequently seen to initiate large uncontrolled  $\text{Ca}^{2+}$  spike currents, suggesting that the  $\text{Ca}^{2+}$  spikes were occurring in an electrotonically remote dendritic location. Also in somatic recordings, Reuveni *et al.* (1993) blocked  $\text{Na}^+$  spikes using TTX and  $\text{K}^+$  currents using TEA to reveal prolonged  $\text{Ca}^{2+}$  spike-plateaus. Since repolarization of the calcium spike was often seen to occur in several discrete steps (Fig. 6A), and based on the results of modeling studies, the calcium spikes were concluded to originate from several discrete dendritic  $\text{Ca}^{2+}$  hot spots separated by passive membrane. In the most direct evidence for dendritic excitability in these cells, intradendritic recordings from layer 5 pyramidal cells have been reported by Pockberger (1991) and Amitai *et al.* (1993; Fig. 6B), in both cases showing complex superpositions of spikes of varying widths and amplitudes in response to constant current injections. In another vein, Caulier and Connors (1992) have shown *in vitro* that stimulation of layer 1 afferents alone is sufficient to drive strong responses at the cell bodies of layer 5 pyramidal cells. In an attempt to understand this result using compartmental modeling techniques, they subsequently demon-

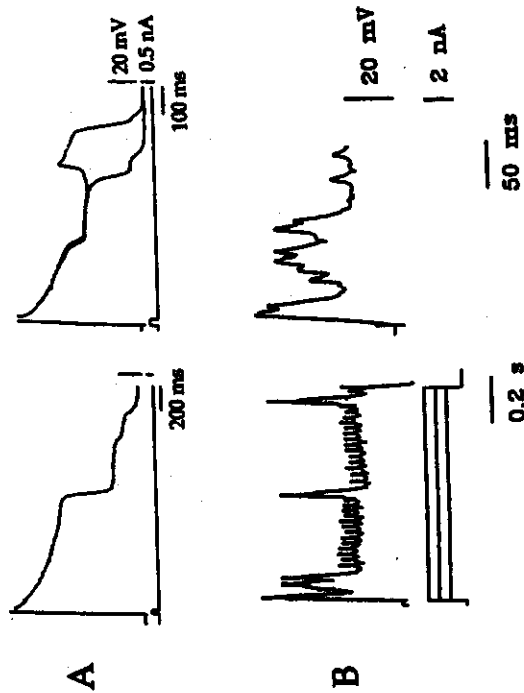


Figure 6: (A) Stepwise repolarization in neocortical pyramidal cells of calcium plateaus induced by small intracellular current pulses in TTX-TEA medium. Duration of plateaus was variable from trial to trial, but breakpoint voltages remained relatively constant. Two plots are from two different neurons. Reprinted with permission from Figure 1C,D, Reuveni *et al.* (1993). (B) Intradendritic recording near main apical branchpoint (200–300  $\mu\text{m}$  from the cell body) also in a neocortical pyramidal cell (reprinted with permission from Amitai *et al.* 1993). Complex superposition of fast and slow spikes were seen in response to a 2 nA current injection. Two plots are same trace at different time scales.

strated that in a cell with a purely passive dendritic tree, stimulation of distal apical synapses was never sufficient to generate cell responses of a magnitude observed in their experiments. Their conclusion: active dendritic conductances are involved in the amplification of distal dendritic input in these neurons.

As in hippocampus, another type of voltage-dependent nonlinear membrane mechanism known to play an important role in dendritic integration in neocortex is the NMDA channel (Mayer and Westbrook 1987). In pharmacological blocking studies, NMDA channels have been shown to account for a major proportion of the excitatory synaptic drive onto neocortical pyramids (Miller *et al.* 1989; Fox *et al.* 1990), consistent with histochemical labeling studies that reveal relatively high concentrations of NMDA receptor binding sites in the superficial, synapse-rich layers

voltage-dependent NMDA-type channels; in some cases the NMDA component may predominate, such as in response to high-frequency stimulation and/or "natural" sensory input (Jones and Baughman 1988; Salt 1986; Miller *et al.* 1989; Fox *et al.* 1990; Keller *et al.* 1991).

In the next section, we review the mathematical and conceptual tools that have been used to model the electrical behavior of dendritic trees.

### 3 Conceptual and Computational Tools

**2.5 Other Cells.** Evidence for voltage-dependent dendritic membrane mechanisms has been acquired in other types of vertebrate neurons, including cells in the thalamus (Maekawa and Purpura 1967; Jahnsen and Llinás 1984), inferior olive (Llinás and Yarom 1981), and substantia nigra (Llinás *et al.* 1984). Maekawa and Purpura reported fast depolarizing potentials in response to synaptic stimulation, distinct from slow EPSPs, which they interpreted as possible partial spikes of dendritic origin that could account for the "extraordinary responsiveness" of these cells to synaptic input. In another study of thalamic neurons, Jahnsen and Llinás (1984) reported high-threshold  $Ca^{2+}$  spikes lasting 18–22 msec in presumed intradendritic recordings that were similar to those observed in Purkinje cell dendrites. In the inferior olive, Llinás and Yarom (1981) have described a number of voltage-dependent conductances, including multiple all-or-none high-threshold  $Ca^{2+}$  spikes of presumed dendritic origin. Finally, in the substantia nigra, Llinás *et al.* (1984) provided evidence for two types of dendritic  $Ca^{2+}$  spikes, one low- and the other high-threshold with respect to somatic current injection. In these cells, the  $Ca^{2+}$  spikes are thought to be involved in the dendritic release of dopamine.

**2.6 Summary.** While it is difficult to achieve a meaningful summary of the experimental work discussed above, certain general tendencies in the experimental data may be identified. For several important classes of vertebrate neurons, the conception of the dendritic tree as an essentially passive collector of synaptic inputs has not been borne out in the results of 30 years of electrophysiological work. First, in several major types of output neurons in the cerebellum and mammalian forebrain, mechanisms capable of generating dendritic spikes of one or more ionic varieties have been either positively demonstrated to exist through intradendritic recordings, or are strongly suggested in intrasomatic recordings or through a variety of other techniques. Dendritic calcium spikes are a particularly widespread phenomenon, having been observed in cerebellar Purkinje cells, hippocampal and neocortical pyramidal cells, and cells in the thalamus and inferior olive.

Second, in many of these same neuron types, especially hippocampal and neocortical pyramidal cells, but also neurons in the pyriform cortex, thalamus, basal ganglia, midbrain, spinal cord, and other areas (Nicoll *et al.* 1990; Mayer and Westbrook 1987; Cotman *et al.* 1987), a component of the excitatory synaptic input to the dendrites is carried by

In order to understand computation in dendritic trees, it is necessary to first understand the principles that govern the flow of electric current in dendrites. For example, when an excitatory synapse is activated on a dendritic spine, where does the injected current flow, how long does it take, and what is its effect on the membrane potential both locally and elsewhere in the dendritic tree? In this section we review conceptual and computational tools and basic results relevant to current flow in dendrites. There are excellent introductory reviews of the biological mechanisms underlying membrane resistance and capacitance, membrane potential, time constants, and basic steady state and transient responses of passive and active membranes (Kandel and Schwartz 1985; Hille 1984; McCormick 1990; Shepherd and Koch 1990; Jack *et al.* 1975; Rall 1977). A working knowledge of these concepts is assumed in the following.

One of the most important early developments in the study of neural information processing was the application of the one-dimensional "cable" equation to problems of current flow in branched, passive neuronal structures (Rall 1959, 1964). To begin, we present the cable equation, consider the physical interpretation of its terms, and discuss an important analytical solution. We then enumerate several useful rules regarding the electrical behavior of passive dendritic trees. Finally, we introduce the enterprise of compartmental modeling, a discretized numerical approach to the solution of the cable equation that allows treatment of arbitrary neuronal geometries and voltage-dependent membrane mechanisms.

**3.1 The Cable Equation.** Due to their physical construction, neurites (dendrites and axons) have been likened to electrical cables. A cable consists of a long, thin, electrically conducting core surrounded by a thin membrane whose resistance to transmembrane current flow is much greater than that of either the internal core or the surrounding medium. In the case of a dendrite, both the internal cytoplasm and the extracellular space are thought to conduct nearly as well as seawater (see Jack *et al.* 1975, ch. 1). Because the resistance to current flow through the cytoplasm is relatively low, injected current can travel long distances down the dendritic core before a significant fraction leaks out across the highly



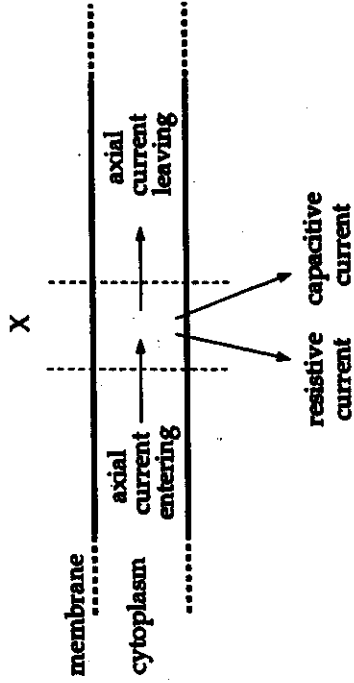


Figure 7: Section  $x$  of a one-dimensional cable. Arrows show axial current flowing into and out of section  $x$ , and the ionic (resistive) and capacitive transmembrane currents. The cable equation (equation 3.1) specifies that, for all  $x$ , these currents must always be in balance.

resistive membrane. The fundamental equation used to describe current flow in passive dendrites is the "cable equation":

$$\frac{1}{r_i} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + \frac{V}{r_m} \tag{3.1}$$

where  $V = V(x, t)$  is the transmembrane voltage at location  $x$  and time  $t$ , and for a unit length of cable,  $r_i$  (in  $k\Omega/cm$ ) is the resistance to internal current flow along the core,  $r_m$  (in  $k\Omega\text{-cm}$ ) is the transmembrane resistance, and  $c_m$  (in  $\mu F/cm$ ) is the membrane capacitance (see Jack *et al.* 1975; Shepherd and Koch 1990; Rall *et al.* 1992 for discussion of units). The cable equation was developed in 1855 as a part of a mathematical theory with practical applications for transatlantic telegraph lines (Kelvin 1855; see Rall 1977 for historical perspective). Derivations and assumptions of the cable equation can be found elsewhere (Jack *et al.* 1975; Rall 1977, 1989; Shepherd and Koch 1990).

The basic cable equation may be easily interpreted as a balance of three kinds of electrical current. Consider a short length of a dendritic branch labeled  $x$  (Fig. 7). A fundamental law of conservation of electrical current (Kirchhoff's current law) tells us that the net accumulation of "axial" current at  $x$  (i.e., axial current entering - axial current leaving) must be equalled by the net current flowing out of the cell across the membrane at location  $x$  (i.e., ionic membrane current + capacitive membrane current). This equality is represented directly in equation 3.1. The single term on

the left represents the net axial current into node  $x$  through the cytoplasm from neighboring "compartments" to the left and right of  $x$ . The second-derivative form of the term indicates that the axial current flowing into  $x$  is, roughly speaking, related to the "curvature" of the voltage profile along the dendritic branch centered at  $x$ . For example, when the voltage at  $x$  is less than the average of its neighbors (positive voltage curvature), then there is a net accumulation of axial current at  $x$ . The two terms on the right represent the capacitive and ionic currents, respectively, that must flow across the membrane at  $x$  in order to balance the net axial current influx. These terms simply state that (1) the capacitive current at  $x$  is proportional to the rate of change of the local transmembrane voltage—rapid changes in voltage are associated with large capacitive currents, and (2) the resistive, or ionic, current at  $x$  is, according to Ohm's law, directly proportional to the membrane voltage at  $x$ .

To summarize, there are three types of current flowing in and around point  $x$  in a dendritic branch: (1) net axial current into  $x$  through the cytoplasm, related to the local membrane voltage "curvature," (2) capacitive current, proportional to the rate of change of membrane voltage, and (3) ionic current, proportional to the membrane voltage itself in the case of a passive dendrite. The cable equation simply says that these three quantities must always be in balance.

**3.2 A Classical Solution to the Cable Equation.** One historically important solution gives the voltage of a uniform infinite cable in response to a current step  $I_0$  injected at the origin  $X = 0$ :

$$V = \frac{r_i I_0 \lambda}{4} \left\{ \exp(-X) \operatorname{erfc} \left( \frac{X}{2\sqrt{T}} - \sqrt{T} \right) - \exp(X) \operatorname{erfc} \left( \frac{X}{2\sqrt{T}} + \sqrt{T} \right) \right\} \tag{3.2}$$

where  $X = x/\lambda$  measures distance from the origin in space constants in a cylinder with infinite extension, and  $T = t/\tau$  measures time in time constants. The space constant  $\lambda = (r_m/r_i)^{1/2}$  is the distance at which the voltage has fallen off to  $V_0/e$ , i.e., to about one-third its value at the site of stimulation; the membrane time constant  $\tau = r_m c_m$  is the time required for an isopotential patch of membrane to charge to within  $1/e$  of its steady-state value. The charging of the infinite cable about the origin during one time constant is plotted in Figure 8. If attention is restricted to the transient voltage change at  $X = 0$ ,

$$V_0(T) = \frac{r_i I_0 \lambda}{2} \operatorname{erf}(\sqrt{T}) \tag{3.3}$$

which represents growth that is significantly faster than a single exponential (bold contour at  $X = 0$ ). If attention is restricted to the steady-state

dendritic tree. Rall (1959) showed that when (1) all branch points in a dendritic tree obey the  $d^{3/2}$  law (see item 4 below), (2) all terminal tips have identical boundary conditions, and (3) all terminal tips lie at same electrotonic distance from the soma, then the entire dendritic tree may be replaced by a single "equivalent" cylinder for certain restricted input conditions, greatly simplifying the calculation of dendritic responses—see (Rall 1977) for details.

An algorithm for solving the case of arbitrary passive dendritic trees was also first provided by Rall (1959). Butz and Cowan (1974) later developed a graphic method to compute the Laplace transform for arbitrary passive trees, and Horwitz (1981, 1983) extended and actually applied this method for arbitrary trees. Abbott *et al.* (1991) showed how the path integral can be computed for arbitrary dendritic trees, using a method borrowed from statistical physics that is both computationally efficient, and allows the assumption of time and/or spatially varying membrane resistivities. Most recently, Evans *et al.* (1992) and Major *et al.* (1993) have treated arbitrary passive dendritic trees in the most complete way. Another recent paper describes a method for computing explicit signal delays between arbitrary pairs of stimulus and recording sites (Agmon-Snir and Segev 1993), and examine the consequences for a cell's sensitivity to synchronous synaptic inputs. Some interesting analytical extensions of cable theory have also been developed for dendritic trees containing active membrane, including a linearized analysis of active neuronal cables valid for voltage perturbations of a few millivolts (Koch 1984), and a continuum-limit analysis of the propagation of signals in dendrites with active spine heads (Baer and Rinzel 1991).

One of the most important applications of the cable equation and its extensions to branched structures has been to the estimation of biophysical parameters of real neurons based on experimental data, especially membrane and cytoplasmic resistivity ( $R_m$  and  $R_i$ ), and electrotonic length  $L$ . An excellent recent review of this large body of work is available (Rall *et al.* 1992).

**3.3 Dendritic Electrotonus: Rules of Thumb.** One of the most significant legacies of cable theory lies in the rules it has provided relating to the electrical behavior of passive dendritic trees. A paradigmatic assumption common to many electrophysiologists and modelers of single-neuron function has been that a thorough understanding of the electrical behavior of passive neural processes is desirable, even in cases when active voltage-dependent nonlinearities are known to be present *en force*. We thus close our overview of cable theory by consolidating several rules regarding the flow of current and distribution of voltage in passive dendrites and dendritic trees.

1. Voltage signals attenuate with distance. In the reference case of a cylinder with infinite extent, a steady-state input decays exponentially with distance.

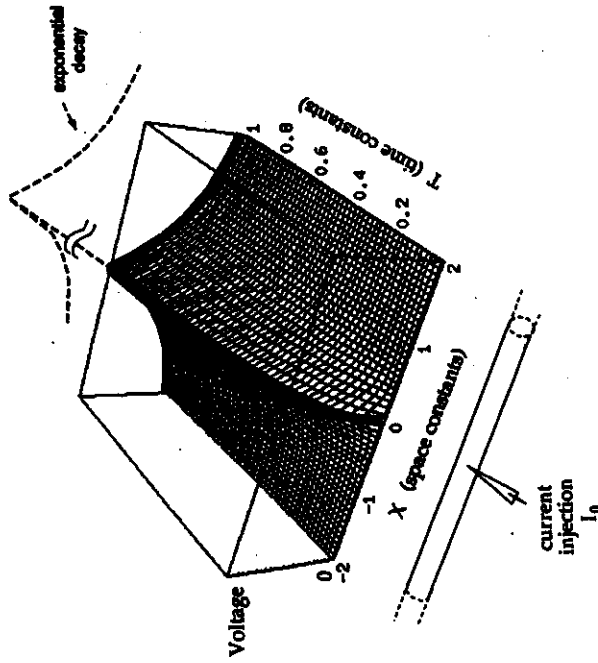


Figure 8: Plot of infinite cable charging in response to current step  $I_0$  at  $X = 0$ . Transient voltage change at  $X = 0$  is faster than exponential, given by equation 3.3. At long times, voltage decays symmetrically and exponentially about  $X = 0$ , as given by equation 3.4.

voltage along the entire cable at long times, we see that the voltage profile at long times is given by

$$V(X) = \frac{r_i I_0 \lambda}{2} \exp(-X), \tag{3.4}$$

a simple exponential decay with distance (dashed contour at  $T \gg \tau$ ). For derivations and solutions of the cable equation under these and a number of other boundary conditions see Jack *et al.* (1975) and Rall (1977), such as the response to step currents for finite or semi-infinite cables, with either sealed or open ends, response to voltage steps for finite or infinite cables, response to noninstantaneous voltage changes, and step changes in membrane conductance; a variety of other quantities, such as input resistance, electrotonic length, and velocity of the propagating decremental voltage wave in response to a stimulus, have also been derived explicitly.

For branched passive cables, an early and historically important contribution was the idea of an "equivalent cylinder" representation of a

inputs, are much more strongly attenuated with distance than are steady-state inputs (Rinzel and Rall 1974; Zador 1993).

3. The input resistance  $R_{in}$  of a neurite is the magnitude of the voltage response at  $T = \infty$  to a unit DC current step. For an infinitely long uniform neural process,  $R_{in} = \sqrt{r_m r_i} / 2$  grows as  $1/d^{3/2}$ . As a consequence, inputs to distal dendritic branches, which are often of very small diameter, can result in large local depolarizations in comparison to identical inputs delivered to large branches, which are often found closer to the cell body. The upper graph in Figure 9A illustrates the variation in  $R_{in}$  that results from changes in branch diameter: the relatively large voltage deflection at  $X = 0$  for the  $1 \mu\text{m}$  diameter case is indicative of its relatively high input resistances; the same is true for the high  $R_m$  case in B.

4. Voltage attenuation depends on boundary conditions, that is, what a branch is connected to (Fig. 9C). For example, when a stimulus is applied near to a branch end (a), the voltage attenuation is significantly reduced in the direction of the closed end, since the charge that would have flowed past the closed end "piles up" locally and causes a relative increase in membrane potential (see Jack *et al.* 1975; Shepherd and Koch 1990). When a dendritic "parent" branch connects to a set of  $k$  smaller daughter branches (b), where  $d_1^{3/2} + \dots + d_k^{3/2} = d_{\text{parent}}^{3/2}$ , then the voltage attenuation is uninterrupted through the branch point, as if the daughter tree were a simple continuation of the parent branch (see Rall 1977). When a stimulus is applied to a thin branch that connects to a thick branch (c), then the voltage attenuation is exaggerated in the direction of the thick branch, since some of the charge that would have depolarized the thinner branch near the branch point is "sucked" into the relatively low resistance pathway offered by the thicker branch.

5. Voltage attenuation is directionally asymmetric in a dendritic tree, as illustrated for an idealized neuron in Figure 10A. If a constant current stimulus is applied at distal tip I, then the steady-state voltage response is strongly attenuated in the direction of the cell body (upper solid curve), whereas if the same stimulus is applied at the cell body, the voltage attenuation from the cell body to the distal tip is modest (lower dashed curve; figure from Rall and Rinzel 1973). This asymmetry is due to the difference in cable boundary conditions looking toward or away from the cell body, as discussed in item 4, and has been frequently treated in the literature, e.g. (Rall and Rinzel 1973; Koch *et al.* 1982; Brown *et al.* 1988). An excellent graphic representation of this asymmetry is provided by the morphoelectronic transform (MET) introduced by Zador (1993). As shown in Figure 10B for a hippocampal CA1 pyramidal cell, the length of each section of dendrite is scaled by the log steady-

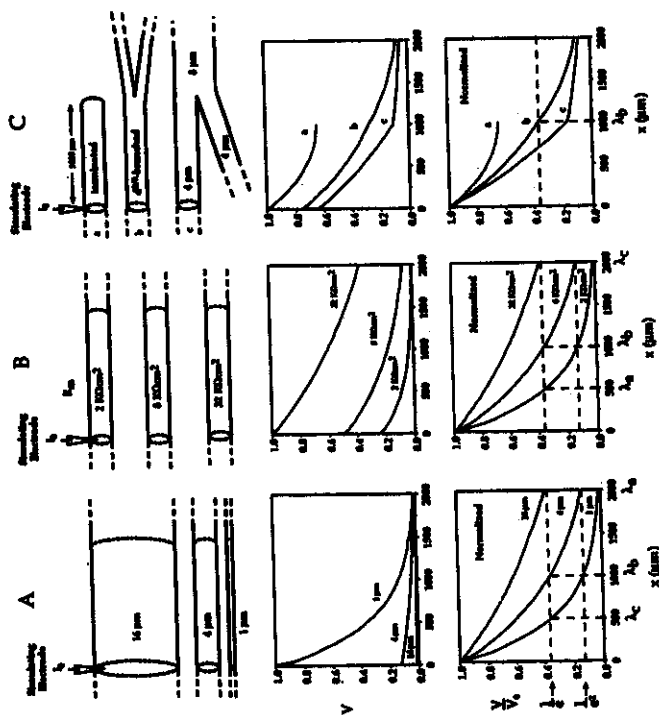


Figure 9: Steady-state spread of voltage from a stimulus origin (e.g., a voltage clamp at  $X = 0$ ) in an infinite cable, adapted from Shepherd and Koch (1990). Default cable parameters are  $R_m = 8000 \Omega - \text{cm}^2$ ,  $R_i = 80 \Omega - \text{cm}$ . Larger diameters (A) and higher specific membrane resistance (B) give longer space constants. (C) Steady-state spread of voltage under 3 branching conditions: (a) terminated, (b) connection to 2 or more daughter branches that satisfy the  $d^{3/2}$  law, and (c) connection at a branch point to one equivalent and one thicker branch. Adapted and extended from material in Shepherd and Koch (1990).

tially with distance, with  $\lambda = (r_m/r_i)^{1/2} = (d/2)(R_m/R_i)^{1/2}$ , where  $d$  is the branch diameter. Hence, voltage attenuation is more severe for thinner dendrites (Fig. 9A) and/or leakier membrane (Fig. 9B). The upper graphs in both A and B show the voltage at  $T \gg \tau$  along the length of the cable in response to a current step  $I_0$  at the origin; in the lower graphs the three curves are normalized to allow comparison of electrotonic lengths.

2. Voltage attenuation is more severe for high frequency components of an input waveform. For  $\omega \gg 1/\tau$ ,  $\lambda(\omega) \propto 1/\sqrt{\omega}$ . Thus, the peaks of signals that are fast relative to  $\tau$ , such as spikes or fast synaptic

state voltage attenuation from the soma to that section. (The *log-attenuation* is defined as  $L_{ij} = \log |A_{ij}|$ , where  $A_{ij} = V_i/V_j$  is the voltage attenuation from  $i$  to  $j$  for a stimulus at  $i$ ; see Zador 1993). The entire tree is highly reduced, particularly the basal dendrites and small apical side branches due to their closed-end boundary conditions. By contrast, in Figure 10C the distance from every point to the soma is made proportional to the log-attenuation from that point to the soma. In this case, small side branches and thin basal dendrites are exaggerated in length, reflecting the strong attenuation of voltage signals in the direction of the cell body.

6. Voltage and current attenuation are reciprocal: voltage attenuation from  $i$  to  $j$  is exactly equal to current attenuation from  $j$  to  $i$  in a passive dendritic tree (i.e.,  $A_{ij}^V = A_{ji}^I$ ), for any locations  $i$  and  $j$  (Koch *et al.* 1982). Thus, current attenuation from a distal site to the cell body can be modest, implying that a large fraction of the charge injected at a distal dendritic site flows to the cell body—compare responses at cell body due to somatic vs. distal stimulus in Figure 10A.

7. Speed, delay, and input synchronization. A transient input to a dendritic branch, such as a synaptic current, is reduced in size and smoothed out in time as it propagates away from the site of stimulation. In the case of an infinitely long unbranched passive dendrite, the centroid of the wave propagates at a speed of  $2\lambda/\tau$ , i.e., two space constants per time constant. More generally, the total signal delay is symmetric between any two points in a passive dendritic tree, and is independent of the shape of the input signal. Delays from dendrites to soma are on the order of one membrane time constant in morphologically realistic dendritic trees (Agmon-Snir and Segev 1993). Importantly, local charging times on thin dendritic branches may be an order of magnitude faster than the membrane time constant  $\tau$ . Consequently, distal dendritic arbors may function more as coincidence detectors for local synaptic inputs whereas the soma functions more as an integrator.

3.4 Compartmental Modeling. For all of their considerable conceptual appeal, analytic solutions to the cable equation become increasingly cumbersome to the extent that the case under study diverges from a passive unbranched uniform cable stimulated with a constant current or voltage source. When a cell has a complex irregular branching structure, nonuniform passive membrane properties, contains voltage- or concentration-dependent membrane channel conductances, or is driven by synaptic conductance changes in lieu of current inputs, then "compartmental" modeling is the technique of choice. Originally introduced

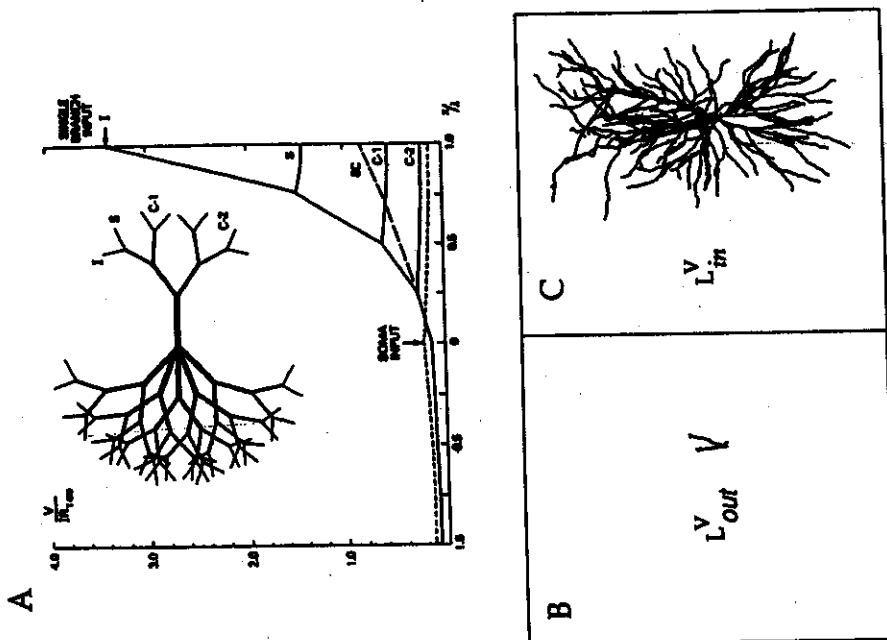


Figure 10: (A) Diagram of idealized neuron and plot of steady-state voltage for different stimulus conditions. Solid curve shows voltage profile in dendritic tree for constant current stimulus  $I$  at a single distal tip. Note steep voltage attenuation along trajectory to soma vs. gradual attenuation outbound along sister (S) and cousin (C-1,2) branches. Curve with short dashes shows voltage profile when same input  $I$  is delivered to soma. Reprinted with permission from Rall and Rinzel (1973). (B) Morphoelectronic transform (METs) of hippocampal CA1 pyramidal cell. Distance from cell body to every dendritic section is proportional to the log DC voltage attenuation  $L_{out}^V$  from the soma to that dendritic section. Reprinted with permission from Zador (1993); morphometric data courtesy Brenda Claiborne. (C) Different MET of same cell; now distance to cell body from each dendritic section is proportional to  $L_{in}^V$ , i.e., the log-attenuation from the dendritic section inward to the soma.

by Rall (1964), compartmental modeling represents a finite-difference approximation of the linear cable equation, or its nonlinear extensions. Compartmental modeling entails that the dendritic tree, axonal tree, or other cable-based structure be broken into a branched network of discrete isopotential compartments. Each compartment consists of a set of lumped circuit elements representing the biophysical properties of the corresponding length of neuronal cable, and the compartments are connected together via lumped axial resistances (Fig. 11). The time evolution of voltages and other variables within this "equivalent circuit" structure in response to an arbitrary pattern of synaptic or other input is computed using standard numerical integration techniques. The advantage of such a representation is that the biophysical properties of the membrane and the cytoplasm can vary arbitrarily from compartment to compartment if so desired, and the membrane or synaptic conductances within a compartment can be defined to have complex dependencies on voltage, time, and other variables—Hodgkin-Huxley channels are one example. The nuts and bolts of compartmental modeling are available elsewhere (for example, see Perkel *et al.* 1981; Segev *et al.* 1989; Claiborne *et al.* 1992 for various treatments of the method). See also Traub *et al.* (1991), Borg-Graham (1991), Brown *et al.* (1991b), and Mel (1993b) for examples including modeling of nonlinear membrane conductances, Mascagni (1989) for a lucid discussion of numerical issues, Shepherd (1992) for an interesting historical perspective, and De Schutter (1992) for an overview of currently available software for creating and running compartmental models.

#### 4 Computational Studies of Dendritic Function

A variety of modeling studies have been carried out over the past three decades to explore various aspects of dendritic function beyond simple summation of synaptic inputs. In the following, we discuss this work in the context of four main ideas that have dominated the conceptual landscape. These are,

1. The spatially extended nature of a dendritic tree permits useful spatiotemporal interactions among active synapses.
2. Dendritic trees can have multiple pseudoindependent processing subunits.
3. Passive dendritic structure may be modulated by external influences to alter the input-output behavior of the cell as a whole, or of individual subunits.
4. Nonlinear membrane mechanisms appropriately deployed can allow the dendritic tree of a single neuron to act as a powerful multilayer computational (e.g., logical) network.

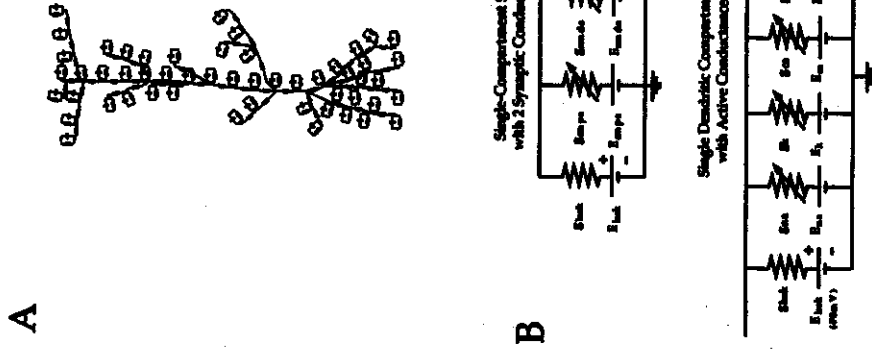


Figure 11: (A) Simplified compartmental representation of the dendritic tree of a hippocampal pyramidal cell (figure adapted from Brown *et al.* (1992)). (B) Blowup of equivalent circuit for a single dendritic compartment with attached spine. Main dendritic compartment is depicted with voltage-dependent  $Na^+$  and  $K^+$  conductances for fast Hodgkin-Huxley spiking, as well as a slow voltage-dependent  $Ca^{2+}$  conductance and a  $Ca^{2+}$ -dependent  $K^+$  channel.

**4.1 Spatiotemporal Integration.** Wilfred Rall (1964) first demonstrated that a passive dendritic branch, by virtue of its spatial extension, can act as a spatiotemporal filter that selects for specific temporal sequences of synaptic inputs. Since time is required for signals to propagate along a dendritic branch, it matters what part of the dendrite gets stimulated at what time. For example, the largest superposition of sig-

difference than in Rall's study case of excitation alone. Essentially, a large synaptic conductance increase whose reversal potential is close to the resting potential, usually called "silent" or "shunting" inhibition, acts like a hole in the membrane that shunts a large fraction of any passing current directly to the extracellular ground. While a shunting synapse cannot by itself alter the potential at the cell body, it can effectively short out the path to the cell body for any more distal depolarizing or hyperpolarizing influences (Poggio and Torre 1977; Koch *et al.* 1982, 1983); see Shepherd and Koch (1990) for an explanation of shunting inhibition.

In the simplest instance, the Koch-Poggio-Torre model for retinal direction selectivity entails that photoreceptors are topographically mapped onto each ganglion cell dendrite, and each photoreceptor is assumed to activate both an excitatory and an inhibitory synapse at approximately the same dendritic locus (Fig. 12B). The inhibitory conductances are assumed to activate with slower kinetics than the excitatory conductances, however, such that the excitatory input has time to begin propagating toward the cell body before the colocalized shunting inhibition is sufficiently activated to exert its "veto" effect. Thus, if the photoreceptor-induced stimulus sweeps along the branch *toward* the cell body, the slowly activating inhibitory conductances consistently exert their influence *distal* to the snowballing excitatory wave bound for the cell body, and are therefore ineffective at blocking it. If the photoreceptor stimulus sweeps along the branch *away* from the cell body, then the inhibitory conductances consistently exert their influence on the direct path to the cell body for all subsequently activated more distal excitatory inputs. This elemental nonlinear synaptic interaction was shown to produce strongly direction selective responses in a modeled retinal ganglion cell (Koch *et al.* 1986; Fig. 12C).

This modeling study depended critically, however, on a neuroanatomical assumption that has remained unsubstantiated—i.e., that inputs to retinal ganglion cell dendrites are precisely "wired" such that each inhibitory synapse is positioned to veto subsequently activated excitatory synapses when the stimulus sweep is in the "null" direction, but *not* when the stimulus sweep is in the preferred direction. An example of such an asymmetric wiring diagram is illustrated in Figure 13A. An interesting alternative source of the necessary asymmetry for DS responses is discussed by Borg-Graham and Grzywacz (1992; see also Vaney *et al.* 1989), that does not depend on precise asymmetric deployment of excitatory and inhibitory synapses onto the dendrites of retinal ganglion cells. The authors point out that even in the case of entirely symmetric, topographically mapped mixed excitatory and inhibitory input onto a circularly symmetric dendritic tree, the *tip* of each dendritic branch is direction selective when considered as an output, i.e., responds more strongly to photoreceptor sweeps toward the tip (Fig. 13B). Evidence that amacrine cells in the rabbit retina preferentially make contacts onto retinal ganglion cells via their branch tips has led these authors to the

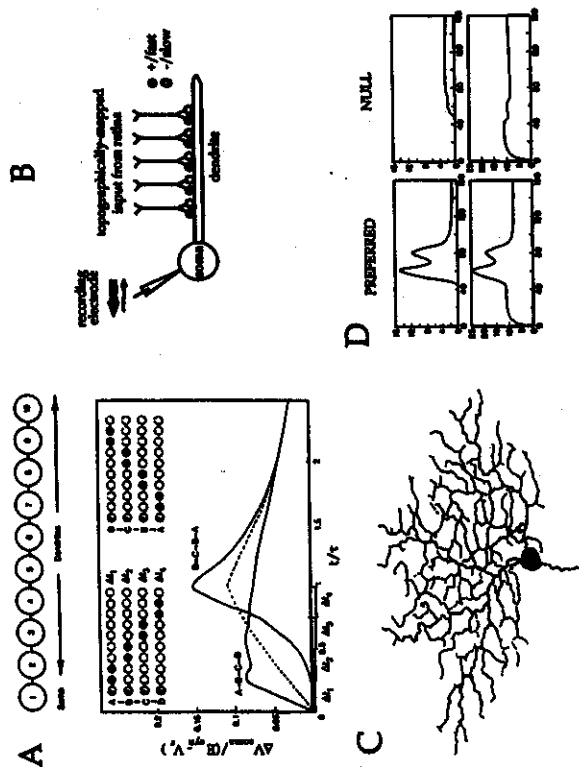


Figure 12: (A) Passive 10-compartment model demonstrates directional difference for input sequence ABCD vs. DCBA; reprinted with permission from Rall (1964). (B) Single branch schematic of Koch-Poggio-Torre (1983) model of direction selectivity as measured at the cell body. Fast acting excitatory inputs (black circles) are effectively "vetoed" by slow-activating shunting inhibition (open circles) only when the direction of sweep is away from the cell body. (C) Reconstructed direction-selective cell from the rabbit retina (reprinted with permission from Koch *et al.* 1986). (D) Cell in C was modeled assuming passive dendrites and on-path inhibition as schematized in B. Responses to preferred-direction stimulus are shown at left, null-direction at right. Lower traces include small DC current injection at cell body. Units are mV above rest (ordinate) vs. msec (abscissa).

nals at the cell body occurs when distal synapses are activated before proximal synapses. This principle is illustrated in Figure 12A: the peak of the voltage waveform at the cell body is twice as large when inputs are activated in a sweep toward the cell body (DCBA) than in a sweep away from the cell body (ABCD).

Poggio and Torre (1977) and Koch *et al.* (1982, 1983) pursued this basic idea further in the effort to explain direction-selective (DS) responses in retinal ganglion cells. They amplified on Rall's basic idea by showing that the relative placement and timing of excitatory and inhibitory synapses on the same dendrites could lead to a much more pronounced directional

ways more effective than asynchronous. When the number of activated synapses exceeds this threshold, then the saturating nonlinearity associated with excitatory synaptic action tips the balance gradually in favor of desynchronized inputs. With regard to precise timing of synaptic inputs, Softky and Koch (1992) and Softky (1993) have discussed the plausibility and consequences of submillisecond coincidence of synaptic inputs to dendritic trees that contain very large, very brief synaptic conductances and/or the potential for fast spike generation.

**4.2 Dendritic Subunits.** A second important idea relevant to dendritic information processing is that of "dendritic subunits," i.e., the idea that pseudo-independent computations can be carried out simultaneously in different dendritic subregions. An early discussion of dendritic subunits can be found in Linás and Nicholson (1971), where it was proposed that synaptic integration and consequent local spiking activity could occur pseudo-independently in different branches of the Purkinje cell dendritic tree. Koch *et al.* (1982) first formally defined a dendritic subunit as a region within which the voltage attenuation is small between any pair of synapses  $i$  and  $j$  in the subunit, but for which the voltage attenuation is large between any subunit synapse and the soma  $s$ . More precisely, a subunit consisted of any group of synapses such that  $A_{ij}^V/A_{ij}^V > c$ , ( $c > 1$ ) for all  $i$  and  $j$  in the subunit. (The original definition was expressed in terms of transfer resistances instead of attenuations.) For a particular choice of membrane parameters ( $R_m = 2500 \Omega \cdot \text{cm}^2$ ,  $R_i = 70 \Omega \cdot \text{cm}$ ,  $C_m = 2 \mu\text{F}/\text{cm}^2$ ) and the value  $c = 4$ , and under the assumption that subunits should not overlap, a set of subunits was determined as shown in Figure 14A for an  $\alpha$ -type retinal ganglion cell. The implication of this result is that an  $\alpha$ -type retinal ganglion cell does indeed have a considerable capacity for independent processing within its dendritic tree. A  $\beta$ -type ganglion cell with a much smaller dendritic tree ( $\sim 100 \mu\text{m}$ ) and relatively thick branches had very small subunits. The subunit boundaries of Figure 14A and B should not, however, be taken too literally, as they depend on  $c$ , which was arbitrarily chosen, on the cell morphology, on the algorithm used to grow subunits beginning at the dendritic tips, and on membrane parameters—they disappear almost completely when  $R_m > 8000 \Omega \cdot \text{cm}^2$ . It is also important to emphasize that the definition of dendritic subunits from Koch *et al.* (1982) stresses the electrotonic independence of subunits from the cell body, but not the electrotonic independence of subunits from each other.

Woolf *et al.* (1991) carried out a somewhat different analysis of subunit structure in granule cells of the olfactory bulb. In this case a subunit was defined to be a neighborhood in the dendrites about an arbitrarily chosen reference spine, for example, consisting of all spines at which the steady-state voltage attenuation was less than 5% relative to the stimulated reference spine (Fig. 14C). When the subunit criterion was changed to include all neighboring spines that were depolarized by more than

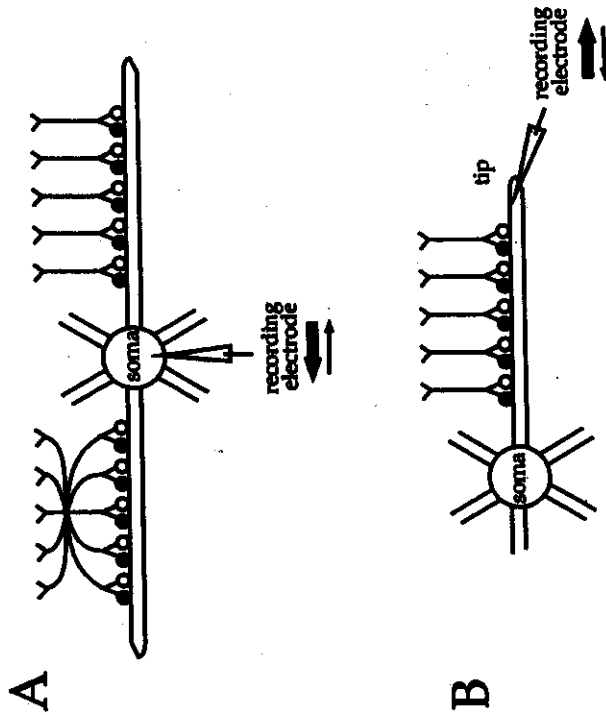


Figure 13: (A) One possible asymmetrical system of input connections giving rise to direction selectivity as measured at cell body (adapted from Koch *et al.* 1982). (B) Tip of long dendritic branch is always direction selective (adapted from Borg-Graham and Grzywacz 1992).

conjecture that the DS of retinal ganglion cells is due to DS inputs from amacrine cell branch tips rather than due to internal processing in retinal ganglion cells themselves. Consistent with this hypothesis, Borg-Graham and Grzywacz (1990) demonstrated that retinal ganglion cells remained direction selective even when their inhibitory inputs were blocked. For an elegant demonstration of the probably passive dendritic basis of direction selectivity in an invertebrate, the blowfly, see Haag *et al.* (1992).

Another issue relevant to dendritic spatiotemporal integration is the question as to whether synchronously activated synapses scattered about a dendritic tree are more effective at driving a cell than the same number of inputs activated asynchronously—as has been commonly postulated (e.g., Abeles 1982). This question has been investigated in Bernander *et al.* (1994) for passive dendrites (though NMDA synapses were considered in one condition), where it was shown that when the number of active synapses is less than the number of fully-synchronized inputs needed to fire a single action potential, then synchronous inputs are al-

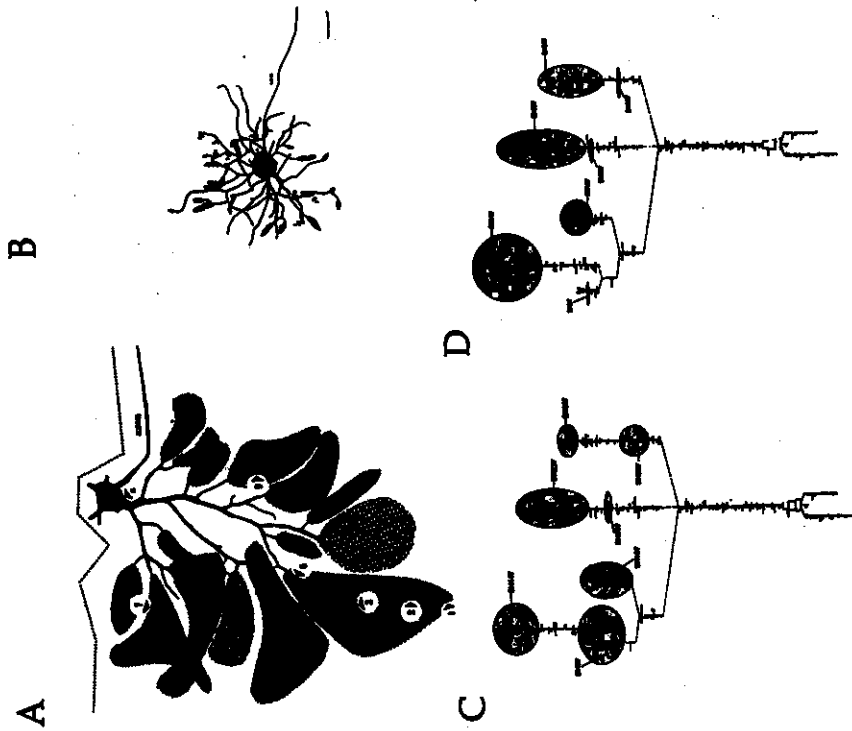


Figure 14: (A,B) Subunit structure of two types of retinal ganglion cells based on passive cable properties (reproduction of Figs. 2, p. 240 and 3, p. 241, with permission from Koch *et al.* 1982). (A) Large subunits in an  $\alpha$  retinal ganglion cell. (B) Much smaller subunits are seen in  $\beta$  ganglion cell in same study. C,D. Study of subunit structure of granule cell of the mouse olfactory bulb (reprinted with permission from Woolf *et al.* 1991). (C) Subunits around 7 reference spines are illustrated, where subunit is defined as region around input spine with no more than 5% steady-state voltage attenuation. (D) Same cell, where subunit criterion is region of greater than 10 mV depolarization in response to 4 nS input at reference spine.

10 mV in response to a 4 nS transient synaptic conductance input at the reference spine, some subunits remained essentially unchanged, oth-

ers grew dramatically, and still others essentially disappeared (Fig. 14D). When the EPSP rise time was slowed from 0.2 to 1 msec, subunits grew so large as to encompass the entire dendritic tree.

In these two subunit studies, the observed sensitivity of subunit structure to biophysical parameter assumptions and to subunit definitions has double-edged significance. Though the concept of dendritic subunits is heuristically useful, and has guided important questions as to the passive integrative properties of dendritic trees, the marked sensitivity of subunit size to changes in modeling assumptions makes their explicit graphic enumeration less informative than it might be hoped. Any attempt to characterize a dendritic tree in terms of the locations of a fixed number of discrete subunits is thus necessarily misleading. On the other hand, the sensitivity of subunit size to parameters and assumptions in these studies is informative in and of itself, as it makes explicit the notion that the effective electrotonic structure of a dendritic tree depends strongly on both biophysical membrane parameters (see next section), and on the specific type of intradendritic voltage communication under consideration. In this latter case, for example, synaptic interactions that have sharp voltage thresholds may be expected to operate within a radially different virtual subunit structure than those that depend smoothly on voltage (Fig. 14C,D).

Given the virtual impossibility of counting discrete subunits or assigning their boundaries in a meaningful way, an alternative statistical approach may be used to quantify the relative electrotonic independence of dendritic synapses from each other. In a study of the input-output behavior of neocortical pyramidal cell dendrites, a histogram was generated to quantify the steady-state voltage and current attenuation between randomly chosen pairs of synapses in the passive dendritic tree (Fig. 15); from Mel 1992c). The histogram shows that the average steady-state attenuation factor for voltage or current between randomly chosen synapse pairs is nearly 70; for about half the pairs of synapses in the dendritic tree, the attenuation factor is greater than 25. The histogram representation of a dendritic tree is weak in that it quantifies the electrotonic independence of each dendritic locus from each other in only a probabilistic sense, but it is immune to the dramatic parameter sensitivity characteristic of efforts to define and discretely label dendritic subregions.

**4.3 Modulation of Passive Membrane Properties.** The fact that dendritic subunit structure is sensitive to biophysical membrane parameters leads directly to the suggestion that intradendritic information processing could be modulated by any outside influence acting on passive membrane properties. A third idea relevant to dendritic integration thus entails that outside modulating influences can act to alter the cable properties of part of all of a dendritic tree, thereby changing its integrative behavior in response to patterns of synaptic input.



### Voltage/Current Attenuation Dendrite to Dendrite

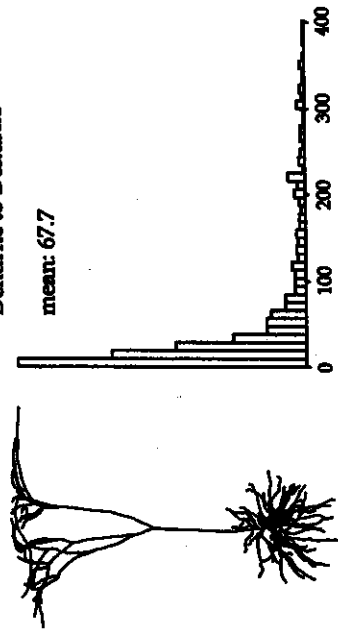


Figure 15: Voltage or current attenuation histogram for DC current inputs to electrically passive pyramidal cell dendritic tree, with  $R_m = 10,000 \Omega - \text{cm}^2$ ,  $R_i = 200 \Omega - \text{cm}$ ,  $C_m = 1 \mu\text{F}/\text{cm}^2$ . Pairs of input and recording locations were chosen at random, uniformly in dendritic length. Average steady-state attenuation factor was 67.7. Pyramidal cell morphology courtesy of Rodney Douglas and Kevan Martin.

Holmes and Woody (1989) first demonstrated that different spatially nonuniform patterns of background synaptic activity impinging onto a modeled cortical pyramidal dendritic tree give rise to different nonuniform resting membrane potential distributions, various distortions in the effective length constants of dendritic branches, location-dependent changes in the ability of distal synapses to influence the cell body, and pronounced changes in membrane time constants (see Fig. 16). Essentially, the spontaneous low-frequency openings of 10,000–20,000 synapses in the dendritic tree of the modeled cell yielded, in the aggregate, a significant change in effective membrane resistivity which in turn induced the observed changes in electrotonic structure and time constants of the cell. Though these authors considered only the passive membrane case, the straightforward inference could be made from this work that induced inhomogeneities in the dendritic voltage environment under variable patterns of background synaptic activity could lead to variable operating regimes for any voltage-dependent membrane mechanisms residing in the dendritic tree.

Bernander *et al.* (1991) further explored the effects of background synaptic activity on the passive cable structure of a layer 5 neocortical pyramidal cell. A fixed spatial distribution of 4000 excitatory and 1000

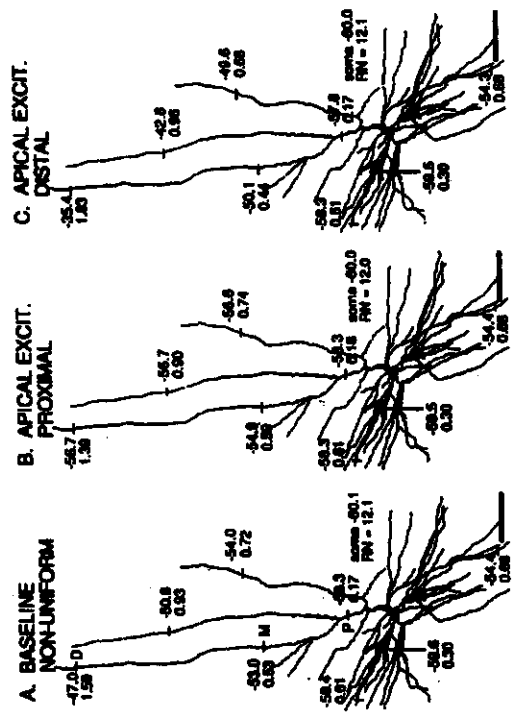


Figure 16: Steady-state response of passive neuron for different synaptic activity distributions. The resting potential (upper number) and electrotonic distance (lower number) to selected dendritic locations in the cortical pyramidal cell were computed for each of the three conditions (reprinted with permission from Holmes and Woody, 1989).

inhibitory synapses was modeled, while frequency of background activity was varied from 0 to 7 Hz. Over this range, the time constant and input resistance of the cell measured at the cell body were reduced by a factor of 10, while the electrotonic length of the cell grew by a factor of 3 (Fig. 17). The authors further demonstrated that the reduction in membrane time constant associated with more vigorous background activity could lead to an increased selectivity for synchronous vs. asynchronous activation of other synaptic inputs (see also Bernander *et al.* 1993; Rapp *et al.* 1992). This study thus demonstrates that the activity of the intrinsic cortical network is likely to exert a powerful influence on the integrative behavior of individual neurons.

In a different vein, Laurent and Burrows (1989) and Laurent (1990) have proposed that nonspiking interneurons in the metathoracic ganglion of the locust may have independently modulable input-output regions within their dendritic trees. In these invertebrate neurons, input and output synapses intermingle along the same dendritic branches (Fig. 18A), in contrast to most vertebrate neurons for which dendrites are input structures exclusively (see Shepherd 1990 for rules and exceptions). A

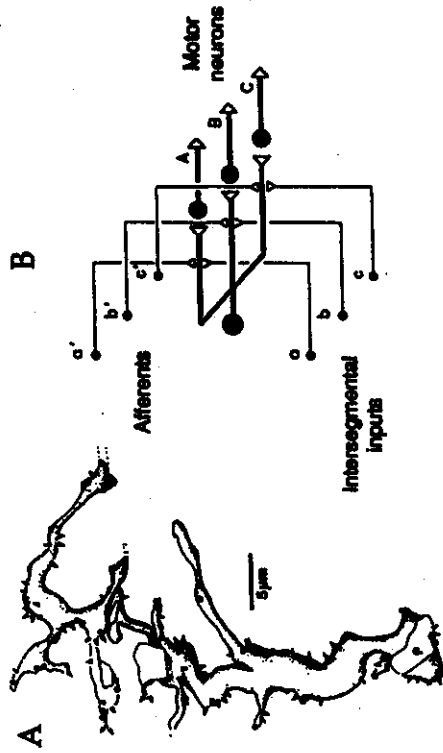


Figure 18: Possible input-output function of intersegmental interneuron dendritic tree in locust. (A) Reconstruction of portion of a nonspiking local interneuron in thoracic nervous system of locust. Twenty-two input (circles) and 64 output (triangles) synapses are spatially intermingled. Reprinted with permission from Watson and Burrows (1988). (B) Model of a nonspiking interneuron that receives input from 3 local afferents (a', b', c') and from 3 intersegmental interneurons (a, b, c); output connections (A, B, C) project to three motor neurons. In this model, the 3 local circuits (a', a, A), (b', b, B), and (c', c, C) can be modulated separately. Reprinted with permission from Laurent and Burrows (1989).

**4.4 Nonlinear Processing in Dendrites.** One of the questions of greatest interest in the study of neuronal information processing regards the limits of computational power of the single neuron. In this vein, the fourth idea we consider here is that nonlinear membrane mechanisms, if appropriately deployed in a dendritic tree, can allow the single neuron to act as a powerful multilayer computational network. The most common instantiation of this idea has been the proposal that individual neurons may implement a hierarchy of logical operations within their dendritic trees, consisting of AND, OR, AND-NOT, and XOR operations (Lorenz de N6 and Condouris 1959; Llinás and Nicholson 1971; Poggio and Torre 1977; Koch *et al.* 1982, 1983; Shepherd *et al.* 1985, 1989; Rall and Segev 1987; Shepherd and Brayton 1987; Zador *et al.* 1992; see Fig. 19).

**4.4.1 Synaptic Nonlinearities.** One version of this idea was based on the mathematical observation that synaptic conductance changes interact in a nonlinear way on a dendritic branch (Rall 1964; Poggio and Torre 1977);

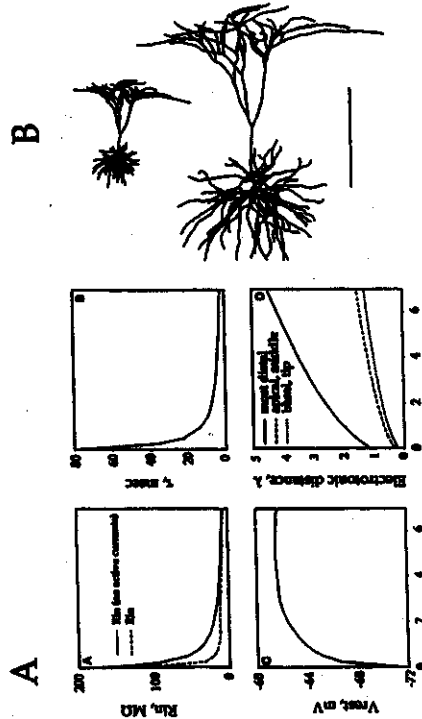


Figure 17: (A) Impact of synaptic background firing frequency from 0 to 7 Hz on cell parameters, including input resistance (upper left), time constant (upper right), resting potential (lower left), and electrotonic length (lower right). (B) Electronic size of cell at two levels of synaptic background activity: 0 Hz (upper cell), representative of conditions in a slice, and 2 Hz (lower cell), representative of condition of low-level background activity. Reprinted with permission from Bernander *et al.* (1991).

biophysical mechanism was proposed whereby a system of intersegmental control axons could modulate a sensorimotor reflex arc. In the reflex circuit of Figure 18B, afferent inputs from mechanosensory receptors on the legs are spatially intermingled with outputs to motor neurons in the dendrites of a nonspiking interneuron. Intersegmental control inputs make additional synaptic contacts onto these same branches. While their precise function is unknown, these inputs seem capable of locally modulating membrane properties in such a way as to enhance or suppress the afferent-to-motor reflex connection within a restricted region of the dendritic tree. One putative mechanism involves large shunting synaptic conductances activated by intersegmental inputs that simply lower the local input resistance, reducing the size, spread, and effectiveness of afferent EPSPs (Laurent and Burrows 1989). The subunit structure of the dendritic tree has also been shown in modeling studies to permit the input resistance to be pseudoindependently modulated in different dendritic regions (Laurent and Haiyun 1993), consistent with the idea that different reflex arcs may indeed be controllable by different intersegmental inputs.

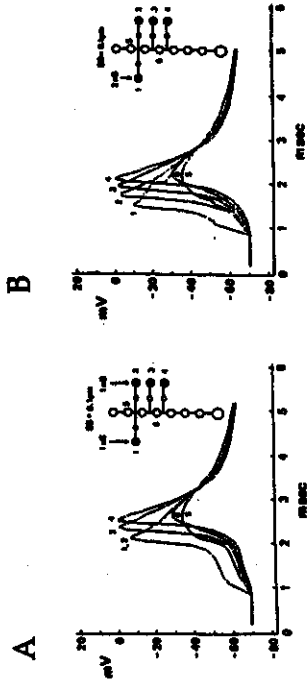


Figure 20: Dendritic implementation of two input logic functions. (A) A group of 4 neighboring spine heads contained active (Hodgkin-Huxley) membrane. Synaptic conductances were chosen such that a single synaptic input was insufficient to fire any of the spines, whereas simultaneous activation of spines 1 and 2 led to firing of all 4 spine heads (voltage traces for each spine head are numbered). This thresholding behavior was likened to a two-input logical AND (this and part B reprinted with permission from Shepherd and Brayton 1987). (B) When synaptic conductances were doubled, input to spine 1 alone led to firing of all 4 spine heads. This condition was likened to a logical OR.

head, a single presynaptic event could be made to trigger suprathreshold activity in all four spines; this was termed an OR-gate, since only one of many possible inputs was needed to generate an output for the region (Fig. 20B). While the existence of Hodgkin-Huxley membrane in spine heads has not been demonstrated experimentally, results of this kind generalize well when the excitable membrane resides instead on dendritic shafts (Shepherd *et al.* 1989), or when altogether other excitatory voltage-dependent mechanisms are assumed (Mel 1992b, 1993b).

In analogy to a logical XOR function, Zador *et al.* (1992) have demonstrated that a combination of two voltage-dependent membrane mechanisms could produce a nonmonotonic output from a dendritic region in response to monotonically increasing synaptic input (Fig. 21). Thus, low levels of synaptic input to dendritic sites A and B (corresponding to a logical 0, 0) were insufficient to cause a somatic spike. At intermediate levels of net synaptic input delivered to the two sites (corresponding to logical 1, 0 or 0, 1), action potentials could be elicited. However at higher levels of combined synaptic input to A and B (corresponding to logical 1, 1), membrane depolarization in the dendritic tree was sufficient to activate voltage-dependent calcium channels, leading to an influx of calcium ions, followed by activation of calcium-dependent potassium

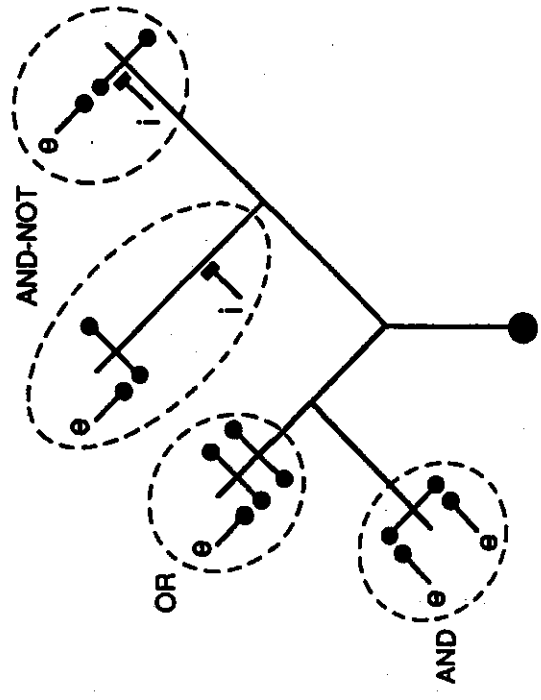


Figure 19: Representation of a Boolean network within a dendritic tree; reprinted with permission from Shepherd (1990).

the emphasis of this latter study was on the second-order multiplicative interaction between excitatory and shunting inhibitory synapses underlying the so-called AND-NOT operation (Koch *et al.* 1982, 1983, 1986); see Koch and Poggio (1987, 1992) for discussions of multiplicative and other nonlinear mechanisms in neuronal computation.

**4.4.2 Voltage-Dependent Membrane and Logic Operations.** A number of other modeling studies have further pursued the neuron-as-logic-network metaphor, primarily by demonstrating that dendrites appropriately configured with voltage-dependent membrane can approximately implement two-input logical operations, such as AND, OR, and XOR. For example, Shepherd and Brayton (1987) showed that simultaneously synaptic input to two neighboring spines with excitable Hodgkin-Huxley spine heads could, once both spines fired action potentials, result in sufficient depolarization in the underlying dendritic branch as to fire off two additional nearby spines; a single synaptic input was presumably insufficient (Fig. 20A). They argued that this behavior was AND-like in that the output of the dendritic region, signaled by the activation of the entire cluster of four spines, depended on the simultaneous activation of two inputs. By increasing the synaptic conductance onto each spine

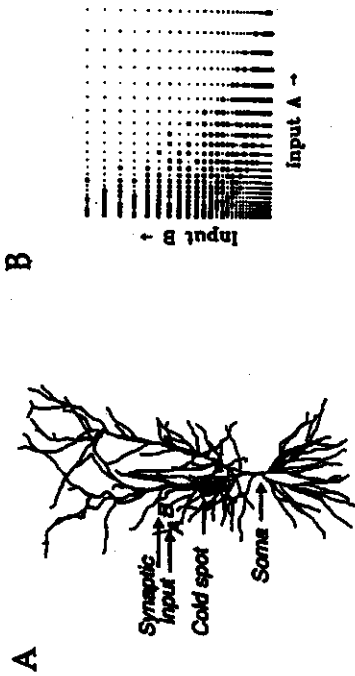


Figure 21: (A) In a reconstructed hippocampal pyramidal cell, a "cold spot" was placed in the dendritic membrane, consisting of a high density of  $\text{Ca}^{2+}$ -dependent K channels, and a low-density of voltage-dependent  $\text{Ca}^{2+}$  channels. Synapses were activated on dendritic branches A and B. Nonmonotonic responses at the cell body with increasing input at branches A and B are shown in plots B (bold dot for single spike); the nonmonotonicity was likened to that of a logical XOR. Reprinted with permission from Zador *et al.* (1992).

channels that gave rise to a strong inhibitory (outward) current. In this case, action potentials at the cell body were suppressed (Fig. 21B).

In an attempt to explore the complexity of interactions among many synaptic inputs in a dendritic tree, Rall and Segev (1987) tested the input-output behavior of dendritic branches containing passive and excitable dendritic spines (Fig. 22). Several synaptic input conditions are shown at left, where black spines are excitable and white spines are passive. The corresponding output condition shows all those spines that fired action potentials as a result of the given synaptic input. The resulting somatic depolarization is also given for each case. Based on the complexity of interactions seen in these demonstrations, the authors concluded that dendritic trees with excitable spine clusters (and presumably other varieties of excitable membrane nonlinearities) afford rich possibilities for pseudoindependent logic-like computations (Rall and Segev 1987).

**4.4.3 Problems with the Logic-Network Metaphor.** The dendritic-tree-as-logic-network metaphor has been a useful concept that has motivated a variety of analyses of the nonlinear computational properties of single neurons. However, two issues may be raised that suggest a potential misfit between logical computation and dendritic computation. First, logical computation is inherently "ill behaved"—changes in any and every input variable must in general be capable of altering or not altering

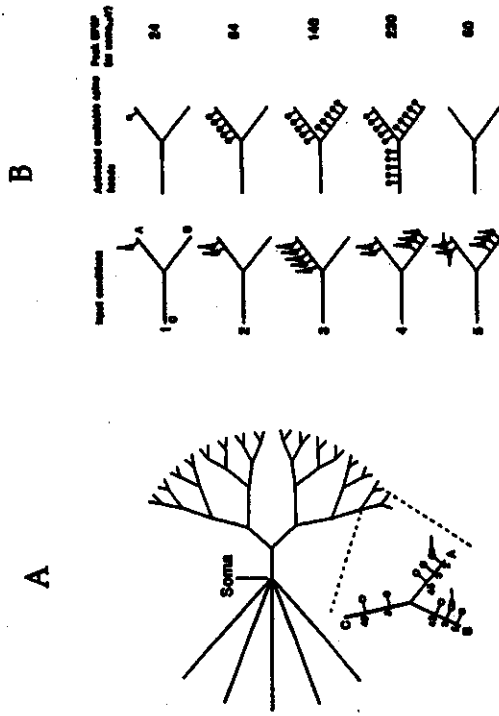


Figure 22: Summary of 5 different cases with active spine heads on distal dendritic branches; reprinted with permission from Rall and Segev (1987). (A) Location of subtree relative to soma of passive cell; each branch had 50 spines, 45 passive (open), 5 active (filled). (B) Left column shows spines receiving synchronous excitatory (open synapses) or inhibitory (filled) synaptic input. Center column shows active spine heads that fired action potentials. Right column shows peak of passively propagated wave as measured at cell body.

the output of the logic function depending on the values of all other inputs. Second, inputs to a logic function are in general unrelated to each other in terms of their effects on the output. Both of these aspects of logical computation are at odds with the fact that the electrotonic structure of a dendritic tree gives rise to extensive voltage sharing and smooth neighborhood relations among synaptic inputs (see Figs. 9 and 10A). Furthermore, logic functions require precise wiring diagrams, where a single erroneous input connection or malfunctioning computational element can corrupt the input-output behavior of an entire circuit. A crucial accompaniment of any logic-network theory of dendritic processing, therefore, is a mechanism, such as some form of learning, that can drive the appropriate microorganization of individual dendrites, synapses, and membrane channels. Such a process would, for example, need to explain the development of the precise spatial juxtaposition of each afferent synapse both with other specific afferent synapses and with the appropriate type of nonlinear membrane as suggested by Figure 19. Such a theory must also cope with accumulating evidence that significant dendritic remodeling

occurs in the mammalian brain, even during adulthood (Greenough and Bailey 1988), implying that a dendritic logic circuit must continuously adapt to "on line" changes in its basic computing architecture.

A literal interpretation of the dendritic-tree-as-logic-network metaphor would be significantly bolstered by a demonstration in which a biologically relevant nontrivial (e.g., multiple input) logic function is mapped onto a realistically modeled dendritic tree, such that the output of the cell follows the specified truth table. The case would be particularly strong if accompanied, as suggested above, by a biologically plausible account for the establishment of the dendritic logic circuit. No such demonstration has yet appeared in the published literature.

**4.4.4 Low-Order Polynomial Functions.** An alternative metaphor for nonlinear dendritic computation, which may be viewed as a smooth, analog version of the "logical dendrites" hypothesis, is the idea that a dendritic tree acts as an approximative low-order polynomial function with many terms—in short, a big sum of little products. A number of authors have fielded conjectures along these lines (Poggio and Torre 1977; Feldman and Ballard 1982; Durbin and Rumelhart 1990; Mel 1990; Mel and Koch 1990; Poggio and Girosi 1990), where the requisite multiplicative nonlinearity has typically been assumed to derive from some nonlinear membrane mechanisms of an excitatory nature. The Hodgkin-Huxley thresholding mechanism previously used in demonstrations of AND-like synaptic interactions is one example (Shepherd and Brayton 1987; Shepherd *et al.* 1989); NMDA channels and a variety of other mechanisms have also been considered good candidates (see Koch and Poggio 1992; Wilson 1992; Mel 1992a,b, 1993a,b). As a nonlinear approximator, the low-order polynomial representation is highly constrained in that (1) only two levels of computation are involved—a sum of products, (2) only the simplest nonlinear interaction is allowed—multiplication, and (3) the number of terms in each product is small—e.g., 2 or 3. An example of a biologically relevant computation of this order of complexity is a correlation between two high-dimensional input patterns.

An abstract model neuron called a "clusteron" has recently been introduced that maps low-order polynomial functionality onto a dendritic tree in a way that is directly testable within a detailed biophysical model (Mel 1992a, 1993a,b). The clusteron consists of a "cell body" where the global output of the unit is computed, and a dendritic tree, which for present purposes is visualized as a single long branch attached to the cell body (Fig. 23). The dendritic tree receives a set of  $N$  excitatory weighted synaptic contacts from a set of afferent "axons." The output of the clusteron is given by

$$y = g \left( \sum_{i=1}^N w_i a_i \right) \quad (4.1)$$

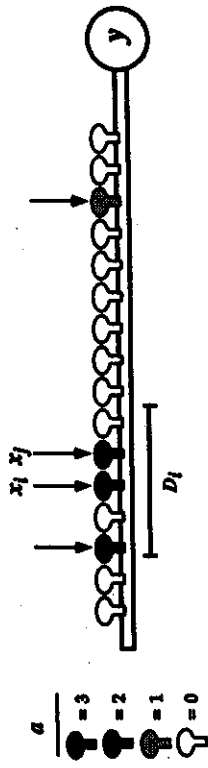


Figure 23: The clusteron is a limited second-order generalization of a thresholded linear unit, in which the excitatory effect of each synaptic input depends on the activity of other synapses in the neighborhood (active inputs designated by arrows). A cluster-sensitive Hebb-type learning rule says that synapses that are frequently coactivated with their neighbors should be stabilized; those that tend to act alone are destabilized and allowed to reestablish connections at new dendritic loci.

where  $a_i$  is the net excitatory activity due to synapse  $i$ ,  $w_i$  is its weight, and  $g$  is an optional thresholding nonlinearity. Unlike the thresholded linear unit, in which the net input due to the  $i$ th synapse is  $w_i x_i$ , the net input at the  $i$ th clusteron synapse is its weight  $w_i$  times its activity  $a_i$ , where

$$a_i = x_i \left( \sum_{r \in \mathcal{D}_i} w_r x_r \right), \quad (4.2)$$

$x_i$  is the direct input stimulus intensity at synapse  $i$ , and  $\mathcal{D}_i = \{i, r, \dots, i, \dots, i + r\}$  represents the neighborhood of radius  $r$  around synapse  $i$ . The clusteron as defined includes only pairwise interactions among synapses in the same neighborhood, denoted by the  $x_i x_j$  terms in equation 4.2. Thus, the underlying "biophysical" assumption implicit in clusteron "physiology" is that the output of a dendritic neighborhood grows quadratically, i.e., expansively, with increasing input.

We note that as a fixed number of synaptic inputs are delivered to a clusteron, first in a diffuse spatial pattern, and then in progressively more clustered spatial patterns, the response of the clusteron steadily increases. Experiments of exactly this kind were carried out in a detailed biophysical model of a layer 5 neocortical pyramidal cell containing various complements of excitatory voltage-dependent mechanisms in its dendrites (Mel 1992a, 1993a; Fig. 24). Under a variety of conditions in which either NMDA synapses, slow calcium spikes, fast sodium spikes, or combinations of the three were placed in the dendrites in differing spatial distributions, an initial positive-slope regime in response to increasingly clustered synaptic input was indeed observed (Fig. 24);

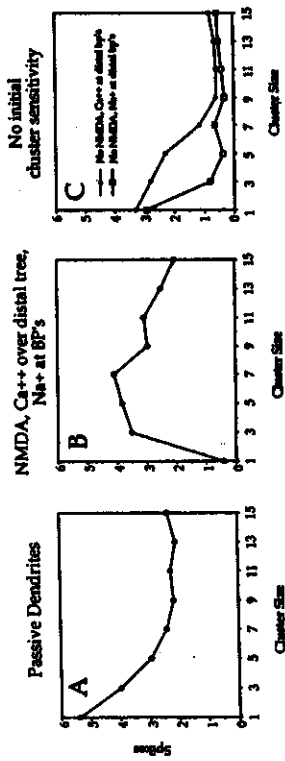


Figure 24: Plots of average cell response vs. cluster size under three biophysically conditions (from Mel 1993a). 100 synapses were activated at 100 Hz for 100 msec and resulting somatic spikes were counted. (A) Response of cell with passive dendrites and AMPA synapses falls off monotonically due to classical synaptic (saturation) nonlinearity as cluster size is increased from 1 to 15. (B) Combination of high-NMDA, slow-spiking membrane distributed distally, and fast-spiking membrane distributed at branch points gave strong cluster sensitivity. (C) In two cases when no NMDA was present, and dendritic spiking conductances were sparse (at branch-points only), cluster sensitivity was abolished. Reprinted with permission from Mel (1993).

results for a passive dendritic tree as control condition are shown in A. Since the biophysically modeled cell was subject to saturation effects, unlike its abstract clusteron counterpart, responses to highly clustered synaptic input patterns were gradually diminished. The positive-slope "cluster-sensitivity" regime was observed to be present as long as the dendrites contained a sufficiently powerful and widely distributed complement of expansive nonlinear membrane mechanisms. No significant dependence on the kinetics, voltage dependence, or localization of the voltage-dependent membrane channels was observed in these steady-state stimulus-response experiments. Figure 24C shows two conditions in which a sparse, patchy distribution of either sodium or calcium spikes was insufficient to yield a cluster-sensitive regime.

**4.4.5 Functional Significance of Dendritic Cluster Sensitivity.** The functional significance of dendritic cluster sensitivity was demonstrated in Mel (1992a), where it was shown that the nonlinear input-output behavior of an NMDA-rich dendritic tree could provide a capacity for nonlinear pattern discrimination (Fig. 25A). In a subsequent study, it was estimated that a 5 x 5 mm slab of neocortex containing cluster-sensitive cells has the capacity to represent on the order of 100,000 sparse input-output pattern associations with high accuracy (Mel 1993a). Another recent study

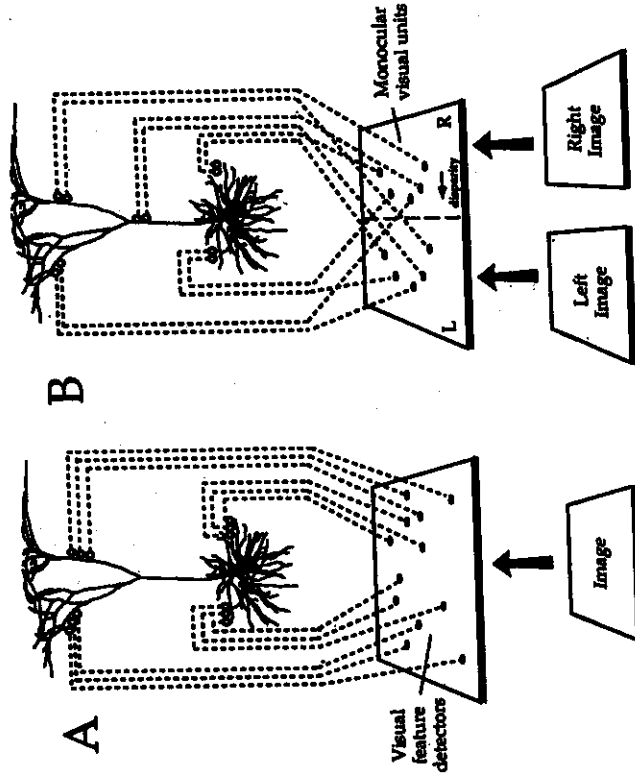


Figure 25: (A) Discriminating familiar patterns within a cluster-sensitive dendritic tree. Visual input patterns drive a layer of visual feature-selective cells whose axons terminate on the cluster-sensitive dendrites. Patterns that drive synapses in clusters elicit relatively strong cell responses. Reprinted with permission from Mel (1992a). The spatial ordering of afferent synaptic connections onto the dendritic tree may thus be of crucial importance for information storage. (B) Implementation of a "tuned excitatory" disparity-selective binocular cell in a schematized visual cortex. Axons from corresponding left and right monocular units, which are strongly correlated during normal vision, make synaptic connections onto neighboring patches of the binocular dendritic tree. Zero-disparity binocular images thus tend to activate synapses in pairs, a relatively effective (i.e., clustered) stimulus condition. Nonmatching inputs to the left and right receptive fields activate synapses diffusely, and are thus relatively ineffective stimuli. Reprinted with permission from Mel (1993b).

has shown that a cluster-sensitive neuron can implement an approximate correlation operation entirely internal to its dendritic tree, with possible relevance to the establishment of nonlinear disparity tuning in binocular visual cells (Fig. 25B; see Ohzawa *et al.* 1990). Interestingly, a sum-of-products computation has been proposed in various forms as a

progress in the development of optical recording methods portends an unprecedented period in which modeling techniques and experimental hypothesis testing can proceed in concert. The secrets of dendritic information processing may then be fully told.

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crucial nonlinear operation in other types of visual cell responses, including responses to illusory contours (Peterhans and von der Heydt 1989), responses to periodic gratings (von der Heydt *et al.* 1991), and velocity-tuned cell responses (Nowlan and Sejnowski 1993).

The underlying idea in both examples of Figure 25 is that groups of frequently coactivated afferent axons represent prominent higher-order "features" in an input stream. These features may be encoded as groups of neighboring synaptic contacts onto a cluster-sensitive dendritic tree (see Brown *et al.* 1991 for discussion of related ideas).

In the context of pattern memory, a "prominent" higher-order feature is any group of frequently coactivated input lines corresponding to a frequently observed conjunction of elemental sensory features in the input stream. If the prominent higher-order features accumulated from a set of training patterns are dendritically encoded in this way, then training patterns, which contain relatively many of these higher-order features, will (1) activate relatively many clustered pairs of synapses in the dendritic tree, and, hence, (2) produce stronger cell responses than unfamiliar control patterns. The memory capacity of a cluster-sensitive dendritic tree is studied empirically in Mel (1993a).

In the case of stereopsis, a prominent higher-order feature is any pair of afferents from corresponding locations in the left- and right-eye receptive fields, which have a high probability of being coactivated during normal visual behavior. As illustrated in Figure 25B, if these features are dendritically encoded, a zero-disparity visual stimulus contains relatively many higher-order "correspondence" features, activates many clustered pairs of synapses in the dendritic tree, and produces a stronger cell response than a noncorresponding stereo stimulus. Such a preference for stimuli at fixed disparity across the receptive field is a characteristic of many binocularly drivable complex cells in the primate visual system (Ohzawa *et al.* 1990).

Both of the scenarios of Figure 25 entail that the ordering of synaptic connections onto a dendritic tree be manipulated by some form of learning process, such that frequently coactivated input lines tend ultimately to form neighboring synaptic connections. An abstract learning rule with these properties is discussed in detail elsewhere (Mel 1992a, 1993a). Biophysically detailed modeling studies of Hebbian learning mechanisms in dendritic trees have also been carried out (Holmes and Levy 1990; Brown *et al.* 1991a; Pearlmutter 1994).

#### 5 Conclusions

We are at present in an awkward period, where many of the new ideas relating to dendritic function are the products of modeling studies, but where limited experimental access to dendritic trees means that modeling work proceeds mostly without direct experimental support. Recent

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