Why Have Dendrites? A Computational Perspective

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1. Introduction

This chapter concerns how dendritic trees may contribute to the information processing functions of individual neurons in the CNS. Before tackling this fascinating question, though, it is useful to address two background issues. First, could dendrites exist for reasons other than to enhance a cell's computing functions per se? If we focus on their spatial extent, we might infer that dendrites exist to increase the receptive surface area of a neuron, which they do by 10 or 20 fold. This makes room for a much larger number of synaptic connections between neurons, which seems advantageous. If we focus on their highly branched morphology, we might infer that dendrites are optimally shaped (per unit length) to extract information-bearing signals from the surrounding neuropil, analogous to root systems that are optimized for the extraction of water and nutrients from surrounding soil (Bejan 2000; Chklovskii, Schikorski et al. 2002). If we focus on their anatomically distinct subregions (e.g., apical vs. basal subtrees), we might infer dendrites exist so that different input pathways can be physically segregated on the surface of the cell (Shepherd 1998; McBain and Fisahn 2001). This could allow different classes of presynaptic terminals to be targeted by different modulatory substances (Patil, Linster et al. 1998), to be influenced by different classes of inhibitory interneurons (McBain and Fisahn 2001), or to be subjected to different synaptic learning rules (Golding, Staff et al. 2002; Froemke, Poo et al. 2005). Thus, at the very least, dendritic trees are likely to be multi-purpose devices which, apart from their information processing functions, play various physical roles in the early development and day-to-day operation of the neural circuit.

The second background issue pertains to the computing operations carried out within a single neuron. Before considering the role that dendrites may play, it is useful to clarify our expectations as to what an individual neuron lacking dendrites should be able to compute; this can serve as a baseline against which to measure the added value, if any, provided by a spatially extended dendritic tree. Historically, for lack of evidence to the contrary, it has been generally assumed that a neuron combines its excitatory and inhibitory inputs from across the cell in a relatively simple way, and the result of this process of "synaptic integration" determines the cell's overall firing rate and/or pattern. When expressed in mathematical terms, a neuron's integrative function has most often been modeled as a simple thresholded linear (TL) operation, that is, a weighted sum of its
excitatory and inhibitory inputs followed by a single output nonlinearity (Rosenblatt 1962; Hopfield 1982; Rumelhart, Hinton et al. 1986):

\[ y = g \left( \sum_i w_i x_i \right) \]  

(1)

where \( x_i \) is the firing rate of the \( i \)th pre-synaptic axon, \( w_i \) is the efficacy of the \( i \)th synapse (positive or negative), and \( g() \) is a function associated with the cell's output spiking mechanism—something like the F-I curve. In cases where a more biophysically realistic model of a neuron has been required, especially one that includes temporal dynamics, the "integrate and fire" (I&F) neuron has been the model of choice, consisting of a single-compartment RC circuit with an explicit spike generating mechanism superimposed. Given that TL and I&F neurons each contain only a single integrative node, and therefore lack any representation of dendritic space, they are sometimes called "point neurons". Point neurons are typically depicted in diagrams as circles or other simple shapes with multiple inputs and a single output representing the axon (Fig. 1). Despite various significant challenges detailed below, the point neuron hypothesis (PNH) has proven to be a remarkably durable one by virtue of its simplicity, and has remained the default view of the neuron for most experimental and computationally-oriented neuroscientists for the past hundred years. And given that it provides a reasonable answer to the question, "What should a neuron lacking dendrites be able to compute?", the PNH can also serve as our “null hypothesis” as we contemplate what the more exotic computing functions of dendritic trees may be.

Figure 1. Most neural models have explicitly or implicitly adopted the point neuron hypothesis, that is, have assumed the neurons have a single integrative zone. A. Hubel & Wiesel model with 4 simple cells feeding a complex cell in visual cortex (Hubel and Wiesel 1963). B. Subset of the stomatogastric ganglion circuit (Marder and Eisen 1984). C. Feedback connections from visual cortex to LGN (Murray Sherman, personal communication). D. Cerebellar circuit from (Raymond, Lisberger et al. 1996). E. Hopfield network (picture from http://www.elec.shonan.it.ac.jp/mizutanilab/syuusi/siratori/image/hopnn.gif). F. Usual mathematical abstraction of a point neuron involves global linear summation followed by a nonlinear thresholding operation. "Integrate and fire" models are closely related.
The nine lives of the point neuron hypothesis

Scratching just below the surface, the point neuron hypothesis with its underlying linear integration stage seems seriously underpowered to describe the behavior of a neuron with a large dendritic tree. In particular, a survey of the neurophysiological literature beginning in the 1980's reveals that the dendritic trees of many types of CNS neurons are far from linear devices, at least at the component level. They contain many types of voltage-dependent channels, including Na⁺, Ca²⁺, and NMDA currents capable of boosting synaptic inputs, and even of generating full-blown spikes that remain localized within the dendritic tree (see chapters 9 and 14). It is difficult to believe that this panoply of nonlinear membrane mechanisms would not somehow endow a neuron with powerful, general purpose computing capabilities.

There are reasons to be cautious, however, before dismissing a theory as parsimonious as the PNH: the presence of active (voltage-dependent) channels in pyramidal neuron dendrites does not automatically invalidate the point neuron idea. In fact, it is possible that certain biophysical properties of neurons may appear to introduce hard-to-model nonlinearities, but may in fact exist to simplify or regularize the overall input-output behavior of the cell. The issue of "synaptic democracy" is illustrative: according to passive cable theory, a dendritic tree could create such large location-dependent disparities among synapses, both in terms of their ability to influence the cell body (Rall and Rinzel 1973; Zador, Agmon-Snir et al. 1995), and in terms of their signal delay and temporal integration characteristics (Rall 1964; Agmon-Snir and Segev 1993), that the PNH would be stretched to the breaking point. Mitigating this, voltage-dependent currents in the dendrites could exist in part to boost and/or normalize the effects of distal synapses as seen at the cell body, and/or to help counteract classical synaptic sublinearities—leading in the end to a more linear, more point-neuron-like cell (Spencer and Kandel 1961; Shepherd, Brayton et al. 1985; Cauller and Connors 1992; Bernander, Koch et al. 1994; De Schutter and Bower 1994; Cook and Johnston 1997; Magee 1998; Cash and Yuste 1999; Williams and Stuart 2000). Similar arguments have been made to account for location-dependent scaling of synaptic efficacies (Magee and Cook 2000; London and Segev 2001; London and Hausser 2005). In yet another example, back-propagating action potentials (BPAPs) and the Na+ channels that support them could help to collapse a large dendritic tree down to a virtual point neuron, by broadcasting a trace of somatic firing activity to distal regions of the cell that would not be reached by passive voltage spread alone (Stuart and Sakmann 1994; Koester and Sakmann 1998; Schiller, Schiller et al. 1998; Larkum, Zhu et al. 1999). By extending the reach of the somatic AP into the dendrites, BPAP's could, for example, allow Hebb-type learning rules, which generally require that synapses "know" when the post-synaptic neuron has fired, to function in a large, non-isopotential neuron with widely scattered synaptic inputs (Magee and Johnston 1997; Markram, Luebke et al. 1997; Bi and Poo 1998; Dan and Poo 2004).
More difficult to dismiss: modeling studies suggest articulation

Historically, given the technical difficulties involved in recording voltage signals from dendrites, and of targeting multiple, specific synaptic sites for activation, much of our present understanding of the electrical functions of spatially-extended dendritic trees derives from computer modeling studies. Modeling studies dating to the 1980's had already mounted a challenge to the PNH, demonstrating that dendrites are capable of supporting highly articulated—i.e. multi-subunit—information processing tasks (Koch, Poggio et al. 1983; Rall and Segev 1987; Shepherd and Brayton 1987; Mel 1992aa; Mel 1992bb; Mel 1993). Rall and Rinzel (1973) provided a seminal early demonstration of the highly non-uniform voltage environment that is expected in a spatially extended dendritic tree. The effect derives from the pronounced distance-dependent attenuation of voltage signals in neural cables (see chapters 13 and 14); attenuation is especially severe when moving from high to low-input-resistance regions of the cell, such as when signals propagate from thin distal branches towards the main trunks and cell body (Zador, Agmon-Snir et al. 1995; Stuart and Spruston 1998; Golding, Mickus et al. 2005). In the first modeling study that explicitly addressed the compartmentalization of synaptic interactions, Koch et al. (1982) found that owing to its passive cable structure, a single large retinal ganglion cell could contain dozens of separate voltage compartments, or "subunits", defined by strong within-subunit voltage interactions and weak between-subunit interactions (Fig. 2A). Woolf et al (1991) and Segev et al (1992) came to similar conclusions using models of reconstructed olfactory and Purkinje cells, respectively. These early studies focused on voltage communication—or the lack thereof—between one stimulus and one recording site in a passive dendritic tree. Subsequent studies of both passive and active dendrites showed that a dendritic tree can maintain a significant degree of functional compartmentalization even when synapses are activated at a multitude of sites (Koch, Poggio et al. 1986; Rall and Segev 1987; Borg-Graham and Grzywacz 1992; Mel 1992a; Mel 1992b; Mel 1993) (Fig. 2B).

Figure 2. Early modeling studies weighing against the PNH. A. A compartmental modeling study showed a single retinal ganglion cell could support multiple independent subunits (Koch,
In the presence of voltage-dependent currents, excitatory synapses are most effective when activated in clusters of intermediate size—large enough to activate the voltage-dependent currents, small enough to avoid saturation. 100 excitatory synapses were used; output spikes were measured at the cell body (Mel 1993).

In summary, it is true that active channels in the dendrites of CNS neurons may help to equalize the effects of individual synaptic inputs independent of location, and may also help signals propagate more effectively from the soma outward; both effects are compatible with the PNH as with other theories. But two clear messages have emerged from compartmental modeling studies from their earliest days. First, the dendrites of many neuron types, by virtue of their passive cable properties, have a natural tendency to subdivide the cell into multiple integrative compartments. Second, neurons with active dendrites can exhibit integrative behaviors more complex than that of a point neuron. But if not a point neuron, what is the appropriate simplifying abstraction for a single nerve cell?

In the remainder of this chapter, we will trace a series of ideas about simplifying abstractions for complex neurons, with a focus on pyramidal neurons of the hippocampus and neocortex.

2. In search of simple abstractions for complex neurons

2-layer models

Most theories of nonlinear synaptic integration in dendritic trees can be cast in terms of an abstract 2-layer model. Common to these models, in the first layer of processing, a set of nonlinear terms is computed locally within a set of independent dendritic subunits. Subunit are generally assumed to correspond to spatially limited dendritic subregion, such as a branch or subtree. In the second layer of processing, the subunit outputs are summed, giving the cell's overall subthreshold activity level \( a \):

\[
a(x) = \sum_{\text{subunit } j} u_j s(x, w_j)
\]  

(2)

where \( x \) is the input vector, \( w_j \) are the parameters for the \( j \)th subunit, e.g. the weights on each input line, \( s() \) is the subunit nonlinearity, and \( u_j \) is the weight on the \( j \)th subunit. The activity \( a \) can be thought of as the result of all dendritic processing. An additional output nonlinearity \( g() \) may be included to describe the cell's firing rate, that is, \( y=g(a) \). If the subunit nonlinearity is a logical AND operation, and the second layer is set up to function as an OR gate by making \( g \) a Heaviside function with a low threshold, this leads to a 2-layer boolean logic network (Fig. 3A); if \( s() \) computes a product of its inputs, this leads to a polynomial (sigma-pi) model with each subunit corresponding to one monomial term (Fig. 3B); if \( s() \) is a sigmoid function, this leads to a classical 2-layer neural network (Fig. 3C), and so on. Thus, the primary difference between models of nonlinear dendritic computation boils down to what function is assumed for the subunit nonlinearity—
though the choice has almost always involved an expansive multiplication-like nonlinearity (Koch and Poggio 1992). Other differences include the sizes and physical locations of the nonlinear subunits within the dendritic arbor, whether the subunits are supposed to be entirely independent of each other or functionally overlapping, whether all subunits are governed by the same or different subunit functions, and as discussed above, how subunit outputs are pooled at the cell body.

![Figure 3](image-url) 2-layer networks. A. Logic network. B. Sigma-pi network. The “pi” units compute product of their inputs while the sigma represents a sum. Red circles indicate 2nd layer weights $w_j$, corresponding to the coefficients on each monomial (product) term. C. 2-layer neural network with sigmoidal hidden units. First layer weights are not shown.

In one of the first detailed models of nonlinear dendritic processing, the proposed subunit nonlinearity derived from the divisive interaction that arises when an excitatory and a shunting inhibitory synapse are co-activated near to each other. Owing to the veto-like effect that occurs when a large inhibitory conductance with reversal potential near the resting potential is activated on a branch, the authors dubbed the excitatory-inhibitory interaction as an AND-NOT operation (Koch, Poggio et al. 1982). Using compartmental simulations of a retinal ganglion cell, the authors showed that through proper targeting of excitatory and inhibitory synapse clusters to several different dendritic subregions, where each synapse was driven by a retinal input, the pooled voltage responses at the cell body were strongly direction-selective (Koch, Poggio et al. 1986). The authors did not, however, attempt to explicitly define the cell's subunit boundaries, or to quantitatively fit the model cell's responses with an explicit 2-layer analytical model.

Interestingly, (Borg-Graham and Grzywacz 1992) later proposed that individual dendritic branches of starburst amacrine (SA) cells in the retina could function as direction-selective (DS) subunits, based on biophysical mechanisms similar to those proposed by Koch, Poggio & Torre (1982). In a key difference, though, whereas the first layer of processing was proposed to occur in individual SA cell dendrites, analogous to the DS subunits of the Koch, Poggio & Torre model, the layer 2 pooling operation was proposed to take place—not in the SA neuron itself—but in a separate downstream neuron driven
by synaptic release from the tips of many similarly directionally-tuned SA dendrites. This proposal has since received experimental support (Euler, Detwiler et al. 2002), and attests to the variety of layered neuronal processing configurations in which dendritic subunits may be involved.

Later in the 1980's, modelers began to ask whether active sodium channels could contribute additional power or flexibility to dendrite-based computations. (Shepherd and Brayton 1987) showed that certain arrangements of active spine heads on a dendritic branch could function as logical AND-gates and OR-gates. Based on these demonstrations, they speculated that multiple layers of logical operations might be implemented by a dendritic tree's multiple layers of branching, though they did not test this idea directly. It is worth pointing out that a 2-layer logic network consisting of a first layer of AND-gates feeding into a single OR-gate in the second (output) layer is already a completely general computing device (Fig. 3A) capable of representing any logic function\(^1\). This is to say that the Shepherd-Brayton idea would be interesting even if the dendritic tree were capable of providing only a single layer of AND-like operations feeding into the OR gate at the cell body.

Approaching a similar type of question from a different angle, (Rall and Segev 1987) ran simulations that included active and passive spine heads distributed over multiple dendritic branches, and found that complicated logic-like integrative behaviors could result. However, perhaps owing to the complexity of their results, no clear proposal resulted as to how the overall input-output behavior of such a cell should be modeled. Nonetheless, this study in conjunction with the Shepherd & Brayton study, demonstrated that active channels could indeed provide the local thresholding functions that underlie many forms of computation, and that dendritic trees by virtue of their compartmental structure are capable of supporting at least certain forms of multi-site active nonlinear processing.

In the early 1990's, we began to study synaptic integration in active dendritic trees, where the local subunit nonlinearities were provided either by NMDA channels (Mel 1992a), or by combinations of NMDA, Na+, Ca++, and anomalous rectifying K+ channels (Mel 1992b; Mel 1993). These compartmental modeling studies showed that in the presence of active channels, a fixed number of excitatory synaptic inputs generated the largest post-synaptic response when activated in clusters of intermediate size, as opposed to having the activated synapses diffusely scattered about the dendritic tree, or concentrated all at or near a single site. In contrast to this, a diffuse pattern of excitation is optimal for a passive dendritic tree (Rall 1964). The “cluster sensitivity” property of the cell arose from the local voltage thresholding provided by active membrane currents, and was modeled qualitatively by an abstract neuron-like unit called a “clusteron” (Mel 1992b). In the clusteron abstraction, dendritic subunits were continuously physically overlapping with each other, modeled by a sliding window of nonlinear interaction: any two inputs \(i\) and \(j\) separated by less than distance \(D/2\) were considered to lie within the same subunit, and gave rise to a multiplicative interaction term \(x_i x_j\) (Fig. 4). These terms were summed

\(^1\) This is strictly true only for an infinitely large first layer.
across the dendritic tree as a whole, so that the clusteron was in effect a "sigma-pi" unit (Fig. 3B) that was limited to include only pairwise product terms.

**Figure 4.** The clusteron was an early model for active dendritic integration. Overall response was \( y = g\left( \sum a_j \right) \), where \( a_j \) was the partial output of the dendritic region \( D_j \) surrounding synapse \( j \), with \( a_j = w_j x_j (\sum_{i \in D_j} w_i x_i) \). The clusteron was devised to capture the cluster sensitivity property illustrated in Fig. 2, and amounts to a 2-layer sigma-pi net (Fig. 3B) whose subunits have overlapping input sets. From Mel (1992b).

By providing an explicit 2-layer (quadratic) model of an active dendritic tree, including a specific, if simplistic, proposal as to how the cell's nonlinear subunits are physically mapped onto the dendritic tree, the clusteron provided a means to predict the responses of a biophysically detailed compartmental model using an explicit mathematical formula. In effect, the clusteron was a simple model of a complex model of a neuron. Its value would lie in its ability to provide a compact description of a cell's input-output behavior, expressed in the language of abstract computing operations rather than voltages and currents. The clusteron represented only a first step in this direction, however, in that it dealt only with the integration of excitatory inputs, provided no guidance as to the effects of dendritic branching on synaptic integration, and was used to predict compartmental model firing rates in only a crude, semi-quantitative way (Mel 1992bb).

**Linking dendritic computations to sensory computations**

Despite the clusteron's limitations, the idea that an active dendritic tree might crudely approximate a high-dimensional quadratic function suggested an intriguing possible connection between the "arithmetic" of dendritic processing and the arithmetic of sensory processing. Was it a coincidence that the nonlinear response properties of one of the principal cell types in primary visual cortex—the "complex cell" as defined by Hubel and Wiesel—had also been described by a 2-layer quadratic model, sometimes referred to as an "energy model" (Pollen and Ronner 1982; Ohzawa, DeAngelis et al. 1990; Heeger 1992)? Perhaps this 2-layer sensory computation could be carried out entirely within the dendritic tree of a single complex cell, rather than requiring the layer of "simple cells" as had generally been assumed by the Hubel-Wiesel-inspired models. Using a detailed
compartmental model of a pyramidal neuron with active dendrites, we found that when groups of ON- and OFF-center afferents corresponding to simple cell subunits formed excitatory contacts near to each other in the dendrites, the cell as a whole exhibited classical complex cell-like response, notably overlapping ON and OFF subfields, orientation tuning, etc. (Mel, Ruderman et al. 1998). In effect, though there was only a single neuron involved in the simulations, the complex cell behaved as if it were driven by multiple simple cells. This finding provided further support for the idea that an active dendritic tree can implement a 2-layer quadratic computation, even when hundreds of synapses and many different branches are simultaneously activated. However, given the probabilistic method used to map groups of functionally related inputs to nearby dendritic locations, as was done in earlier modeling experiments (Mel 1992a; Mel 1992b; Mel 1993), our understanding of the subunit structure of the pyramidal neuron remained limited to the vague notion that the multiplicative interactions between synapses "fall off with increasing distance". This lack of specificity regarding the mapping of abstract functional subunits onto the dendritic arbor precluded us from comparing the efficacies of different abstract 2-layer models in predicting compartmental model firing rates.

This shortcoming was addressed in part using a simplified ball-and-sticks model of a pyramidal neuron with a minimal complement of active dendritic channels (Archie and Mel 2000). We tested whether the long, thin terminal branches of the basal dendritic tree could function as independent half-squaring subunits (i.e. quadratic to the right of the origin and zero to the left), as called for by the energy model (Fig. 5). The hypothesis that terminal basal branches function as independent subunits was motivated in part by the fact that the terminal thin basal and apical oblique branches contain most of a pyramidal neuron's spines (Beaulieu and Colonnier 1985; Elston and Rosa 1998; Megias, Emri et al. 2001), and are electrically well isolated from each other by the main trunks and/or cell body. In fact, the responses of the ball-and-sticks model showed that its subunits were not perfectly independent, that is, significant crosstalk between branches was found. Crosstalk was defined as any deviation from linear summation of the subunit outputs as measured at the cell body. Nor was the input-output relation of each thin-branch perfectly quadratic when individually tested. Despite these non-ideal properties, in experiments resembling those of Mel et al. (1998), we found that the compartmental model cell with four basal branch-subunits could carry out the 2-layer computation that leads from monocular center-surround inputs to an orientation- and disparity-tuned binocular complex cell. In particular, the pattern of nonlinear binocular interactions generated by the compartmental model cell in response to light and dark bars presented at varying receptive field positions was strikingly similar both to the neurophysiological data (Ohzawa et al. 1997) and to those generated by an abstract quadratic subunit model (Fig. 5E)—though fits using other subunit nonlinearities such as cubics or exponentials were also quite good.
Figure 5. Binocular disparity model from (Archie and Mel 2000). A. Ball and sticks with 4 basal branches receiving inputs corresponding to monocular simple cells. Black dots on branches correspond to synapses from oriented rows of monocular center-surround cells with ON and OFF-center receptive fields as shown in four insets. B. Optimally oriented (vertical) grating activated synapses that were concentrated primarily on one branch. This led to a relatively strong spiking response (inset). Small black dots indicate locations of 16 center-surround RFs providing input to the compartmental model. C. Orientation tuning curve derived from stimuli as in B and D. D. Orthogonal orientation led to a diffuse activation, and a reduced response. E. Binocular interaction map. Axes represent position of a light/dark bar in the left/right RF respectively. Diagonal positive region indicates superlinearity when same-color bars are at zero disparity over a range of positions. Negative flanks show nonlinear suppression when bars are spatially offset in the two eyes.
As a side note, we found that the inhibitory synapses used in these simulations impacted on firing rates very differently depending on their locations relative to the cell body. In particular, we observed that distal inhibition exerted a more divisive influence, while proximal inhibition exerted a more subtractive influence, on output firing rates. However, given that the excitation and inhibition were not independently manipulated in these experiments, and that the spatial pattern of excitation and inhibition varied from stimulus to stimulus, it was not possible to draw reliable conclusions regarding the form of the excitatory-inhibitory interaction. Overall, the firmest conclusions that could be drawn were that (1) a thin basal branch containing active channels can function as an integrative subunit governed by some form of accelerating nonlinearity, (2) summation in the second layer, i.e. at the cell body is roughly linear but includes some crosstalk between subunits, and (3) when active dendrites are in play, distal inhibition appears to be divisive in nature while perisomatic inhibition appears more subtractive in nature.

Quantitative predictions of compartmental model firing rates

Based on this study using a simplified ball-and-sticks model, an unresolved issue was whether a realistic pyramidal neuron morphology, outfitted with a realistic complement of voltage-dependent currents, would continue to conform to such a simple mathematical description as an idealized 2-layer network. In other words, would a 2-layer model with quadratic subunits corresponding to whole branches continue to at least roughly describe the cell's mean firing rate? Two potential concerns were that (1) the actual subunit nonlinearity must inevitably saturate at the high end for biophysical reasons; this would seem to rule out any simple accelerating nonlinearity such as a quadratic function, and (2) the mixing of voltage signals originating simultaneously within many different branches could compromise the cell's ability to maintain functional independence among all of its thin-branch subunits. This latter concern was partly addressed by earlier work in which pyramidal neuron models could be driven by large numbers of synapses across the dendritic arbor, and yet maintain the basic cluster sensitivity property (Mel 1992a; Mel 1992b; Mel 1993; Mel, Ruderman et al. 1998). However, the locations of the synapses in these simulation studies were never maintained in any fixed relation to any specific dendritic structure(s), and the spike rates produced by the compartmental models used in these studies had never been compared quantitatively to the outputs of an abstract model on a stimulus by stimulus basis.

We set out to address these shortcomings by systematically studying the integrative behavior of a realistic CA1 pyramidal neuron model. We generated 1,000 stimulus patterns involving from 32 to 63 excitatory synapses activated on from 4 to 37 apical oblique terminal branches, including patterns that were diffuse, clustered, and heterogeneous (Fig. 6). For simplicity, we treated entire terminal branches as monolithic subunits, that is, we distributed all synapses assigned to a branch uniformly and did not explore sub-branch spatial effects. All synapses on all branches were equal in strength and were driven with 50 Hz Poisson trains, and output spikes were counted over the 600 ms stimulus period. We compared the firing rate of the compartmental model, which ranged from 0 to more than 60 Hz, to firing rates predicted by several different 2-layer
Figure 6. Predicting firing rates using a 2-layer model. 1,000 synaptic activation patterns each consisting of from 32 to 63 excitatory synapses were delivered to from 4 up to 37 thin apical branches of a model CA1 pyramidal cell. Spatial patterns ranged from diffuse (left column) to clustered (right column), including intermediate cases that were partly clustered and partly diffuse (middle column). Three 40-synapse cases are shown here. A 2-layer model with sigmoidal hidden units provided best predictions of the cell’s output (somatic) firing rate. From (Poirazi, Brannon & Mel, 2003b).
models on a pattern by pattern basis. The abstract models differed only in the form of the subunit function, which was either linear, quadratic, cubic, square root, or sigmoid. Given the monotonic nature of all of the subunit functions tested, all of the abstract models were fairly good at predicting firing rates for stimuli that varied primarily in overall "power". In other words, all models could predict that a stimulus consisting of 60 excitatory synapses in a diffuse pattern would generate larger responses than would 40 synapses spread in a diffuse pattern. In contrast, for stimulus sets that were equated for power, but varied mainly in spatial configuration, i.e. including diffuse patterns, clustered patterns, and everything in between, the 2-layer model with sigmoid subunits significantly outperformed all others. Quantitatively, the model with sigmoidal subunits captured 67% of the variance in the compartmental model's spike rate vs. 36% for quadratic subunits, 21% for cubic subunits, 11% for linear subunits (corresponding to the point neuron hypothesis), and -15% for square-root subunits (representing an anticorrelation). The superiority of the sigmoidal branch nonlinearity in predicting firing rates was consistent with pre-existing evidence that synaptic input to an individual thin dendrite can trigger a regenerative local spike that remains confined within the activated branch (Schiller, Major et al. 2000; Wei, Mei et al. 2001).

The hypothesis that the perisomatic domain of a pyramidal neuron functions as a 2-layer network with sigmoidal thin-branch subunits lends itself to experimental validation. In the simplest experiment, two synaptic stimuli A and B are applied separately and together, either to the same branch or to two different branches, and the resulting depolarization is measured at the cell body. The 2-layer model with sigmoidal subunits predicts that when A and B are delivered to the same branch, summation of somatic EPSPs will be subject to the sigmoidal subunit nonlinearity, that is, summation will be approximately linear when A and B are weak, superlinear when A and B together just push the subunit past its threshold, and sublinear when A and B are both individually strong enough to cross the local threshold. In contrast, when A and B are delivered to two different branches, their combined response should always be a sum of their individual responses, regardless of their magnitudes. These predictions were borne out both in a compartmental modeling study using the same detailed CA1 pyramidal cell model as in Fig. 6 (Poirazi, Brannon et al. 2003a), as well as in experiments carried out in neocortical slices (Polsky, Mel et al. 2004). Superlinear summation has also been reported in the apical oblique branches of CA1 pyramidal cells, mediated there primarily by a fast sodium spiking mechanism that. Unlike layer 5 pyramidal cells however, the superlinear response in CA1 pyramidal cells requires synchronization of the multiple synaptic inputs within a few-millisecond time window (Losonczy and Magee).

The general agreement between these data and detailed biophysical models regarding the form of nonlinear summation in thin dendrites containing active channels has provided the strongest support yet for the idea that a pyramidal neuron can function as a 2-layer processing device, and that the thin basal and apical oblique terminal branches are good candidates for the cell's integrative subunits. Important differences may exist however in different subtypes of pyramidal neurons. For example, the rules governing nonlinear summation do not depend in any obvious way on the relative locations of the inputs to an
apical oblique branch in a CA1 pyramidal cell, suggesting that terminal branches may be equivalent to functional subunits (Losonczy and Magee 2006). In contrast, in the basal dendrites of layer 5 pyramidal cells summation evidently does depend on location, in a way that suggests those branches may not act as monolithic, functionally homogeneous subunits (see fig. 5 in Polsky et al. 2004). In particular, the strength of the nonlinear interaction between two inputs to a layer 5 basal dendrite fell off as the distance between the two inputs increased (Polsky et al. 2004). This finding could signify that a terminal branch should be represented as a set of continuously overlapping subunits with sliding boundaries (see clusteron discussion above). Alternatively, the regression towards linear summation for more distantly separated inputs could reflect a non-uniform distribution of ion channel properties, such as the NMDA-AMPA ratio, along the length of the basal dendrites in these cells. Resolution of this issue awaits further studies.

Figure 7. Compartmental modeling study of spatial interactions between excitation and inhibition on thin terminal branches. A. Contour plot of firing rate over the E vs. I plane when excitation and inhibition were mixed on the same thin terminal branch of a model layer 5 pyramidal cell. E and I represent number of excitatory vs. inhibitory synapses activated on the branch (at 50 Hz), respectively. Diagonal structure of 3-D plot indicates a linear (subtractive) interaction prior to the sigmoidal subunit nonlinearity. B. Same as A, except E and I synapses are activated on two different branches. Function contours are now nearly parallel to I axis (compare to A), indicating inhibition on branches lacking excitation has relatively little effect on firing rate.

What role for inhibition?

One of the earliest proposals for a spatial nonlinear interaction between excitation and inhibition was that of Koch, Poggio, and Torre (1982), who pointed out that inhibition with a reversal potential near the resting potential would act divisively on subthreshold EPSPs. What role might inhibition play in active—rather than passive—synaptic integration, and in a firing rather than subthreshold mode? The issue has received
relatively little attention (Holt and Koch 1997; Archie and Mel 2000). While inhibitory synapses had been included in the compartmental simulations discussed above, they had not been manipulated systematically, either in location or in number in relation to the excitatory synapses, as would be needed to support a quantitative model of inhibition's effects.

The most parsimonious hypothesis as to how inhibition figures into an abstract 2-layer model with sigmoidal subunits would be to assume that inhibitory synapses simply carry a negative sign but are otherwise treated like excitatory inputs. This is the conventional artificial neural network assumption, and at first blush would seem to indicate that inhibition has a linear subtractive influence on the subunit response. However, if the subunit nonlinearity has an accelerating regime that approximates a rising exponential, such as the rising phase of a quadratic or sigmoidal function, then within this regime, a subtractive influence on the input side translates into a divisive influence at the subunit's output. A second observation is that, as long as the subunit function is always greater than or equal to zero (as in the above examples), then inhibition within a branch-subunit can only suppress the subunit's response down to zero (by definition), and not below. Therefore, inhibition delivered to a branch lacking any excitatory input should in principle have no effect on the cell's response. This aspect of the model is supported by a recent experiment in hippocampal culture in which the integration of one excitatory and one inhibitory stimulus was studied (Liu 2004).

To systematically investigate the issue of excitatory-inhibitory interactions in an active dendritic tree, we placed from $E=0$ to 9 excitatory and from $I=0$ to 9 inhibitory synapses either on the same or different thin terminal branches of a layer 5 neocortical pyramidal cell model (Archie 2004), whose AMPA and NMDA conductances had been adjusted to reproduce the NMDA-spike data of Schiller et al. (2000). When excitatory and inhibitory synapses were intermixed on the same terminal branches, the firing rate of the model cell rose/fell sigmoidally on the principal E and I axes, respectively, with approximately diagonal contours in the (E, I) plane (Fig. 7A). This meant that the cell's firing rate could be roughly described as a sigmoidal nonlinearity applied to a subtractive (linear) combination of E and I, i.e. firing rate $y = \text{sigmoid}(E-kI)$ with constant $k$ representing the relative potency of one E vs. one I synapse. When $E$ was held fixed, increments in $I$ pushed the firing rate backwards down an accelerating curve parallel to the $I$ axis, so that the net effect of the inhibition could be called roughly divisive. (This assumes that the $F$-$I$ curve at the cell body corresponding to $g$ in eq. 1 was approximately linear over the range in question). In contrast to the same-branch case, when $E$ and $I$ were varied on different branches, the firing rates were much less dependent on $I$ (compare Fig. 7B to 7A). This led to an overall firing rate of roughly $\text{sigmoid}(E)$. Taken together, these two experiments support a 2-layer model in which excitatory and inhibitory influences combine linearly within each subunit, followed by a sigmoidal subunit nonlinearity. This model in turn supports the idea that inhibition delivered more distally on the thin terminal branches of a pyramidal neuron's basal or apical oblique dendrites can have an overall roughly divisive effect on firing rates.
What about apical-basal interactions?

Any viable abstract model of a pyramidal neuron's integrative behavior requires that the role of the distal apical tuft be addressed. Numerous experimental studies support the view that the distal apical tree represents a separate integrative center (Schiller, Schiller et al. 1997; Golding and Spruston 1998; Schwindt and Crill 1998; Rhodes and Llinas 2001; Gasparini, Migliore et al. 2004) whose role may be to modulate the cell's overall firing rate or pattern (Cauller and Connors 1992; Kepecs, Wang et al. 2002; Larkum, Senn et al. 2004). This idea is represented pictorially in Fig. 8, where the cell's basic output level is determined by the perisomatic 2-layer network. In turn, input to the distal integrative zone sets a gain factor that multiplies the cell's basic rate up or down (Larkum et al. 2004). Fig. 8 also includes the more speculative proposal that the apical tuft is in itself a 2-layer subunitized network. This idea has no direct experimental support, but is consistent with one modeling study showing that the tuft branches in an active dendritic tree can exhibit the cluster sensitivity property, which is essentially a 2-layer behavior (Mel et al 1998).

Figure 8. Speculative 3-layer model of a pyramidal neuron. Output of apical tuft network sets gain factor for cell that multiplicatively modulates output of basal network (see text for discussion). Figure adapted from (Spruston and Kath 2004) and (Hausser and Mel 2003).
Non-pyramidal neurons

The 2-layer or 3-layer models that have so far been used to describe pyramidal neurons may or may not apply to other neurons such as Purkinje cells, spinal motor neurons, or striatal spiny neurons, or to the large number of inhibitory neuron subtypes found in cortical and subcortical regions. Just as differences may exist in the integrative behavior of the same dendrites in different subclasses of pyramidal neurons, or between different dendritic subregions of the same neuron, the dramatically different morphologies and ion channel distributions found in neurons from different brain areas could lead to wide range of integrative behaviors. For example, it is entirely possible that some classes of neurons are designed to act as linear point neurons, while others, such as Purkinje cells with their fantastically articulated terminal arbors, may follow some radically different integrative plan. Coordinated experimental and modeling studies will be needed in each case to determine which simplifying abstractions apply to what neurons. Perhaps it will be discovered that only a few basic models will be needed to cover all neuron types.

Conclusions

In this chapter we have discussed various simple models aimed at compactly describing a pyramidal neuron's integrative behavior. Given its historical importance, we began with the point neuron hypothesis, which holds that a pyramidal cell contains only a single integrative zone. We then reviewed data from both experimental and modeling studies that are inconsistent with the PNH, supporting instead various more articulated 2-layer and 3-layer models of dendritic integration. The process of abstracting away from the biological details at the single neuron level requires that we (1) define what the cell's integrative subunits correspond to physically within the cell's dendritic arbor, (2) define the subunits' nonlinear input-output functions in simple mathematical terms, and (3) describe how the subunits interact to determine the cell's overall output.

Given that experimental validation of these simplified models has become possible only recently, and only to a limited extent, we have in the past relied on two main strategies for validating models. First, a detailed compartmental model of a pyramidal neuron is developed, with the goal to faithfully reproduce the passive and active electrical signaling properties of a real pyramidal neuron. Then, we have (1) characterized the compartmental model's "receptive field" properties in response to simulated sensory input, and compared them to data and models from the sensory neurophysiology literature, or (2) stimulated the biophysically detailed model cell with various systematic patterns of synaptic input, and compared its responses to those generated by simple, explicit mathematical models. The first strategy leads to predictions regarding the role dendrites may play in the various nonlinear sensory computations that take place in the brain. The second strategy is more one of system identification.

Why is it important to arrive at the proper simple model for a pyramidal (or other) neuron? If we accept the premise for the sake of argument that multi-layered models of
pyramidal cells are on the right track, then the cost of not realizing this could be enormous from a neuroscientific perspective. The first pitfall is a matter of sheer numbers: an investigator looking under the microscope and seeing only point neurons would be overlooking 95% of the neural circuit, and would thus massively underpredict the circuit's raw processing power. The second point relates to algorithms and architectures: to overlook a layer (or more) of nonlinear processing elements in a complex circuit would very likely prevent one from understanding how the circuit works.

Given this complexity, the most promising path to refining our abstract models of pyramidal and other neurons in the long run will be a highly interdisciplinary one. Cooperation between modeling and experimental approaches is clearly needed as always. Perhaps even more importantly, however, it will be essential to attack the single neuron problem at multiple levels of analysis. In the short run, advances in our understanding of the circuit-level functions of neural tissue, including sensory feature extraction, cue combination, gain control, and attentional modulation, to list a few examples, should directly inform our theories of single neuron function. It seems likely that in the future, the molecular level may play an equally important role in helping to decipher the computing functions of individual neurons.

References


