Synaptic Integration in an Excitable Dendritic Tree

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SUMMARY AND CONCLUSIONS

1. Compartmental modeling experiments were carried out in an anatomically characterized neocortical pyramidal cell to study the integrative behavior of a complex dendritic tree containing active membrane mechanisms. Building on a previously presented hypothesis, this work provides further support for a novel principle of dendritic information processing that could underlie the capacity for nonlinear pattern discrimination and/or sensory processing within the dendritic trees of individual nerve cells.

2. It was previously demonstrated that when excitatory synaptic input to a pyramidal cell is dominated by voltage-dependent N-methyl-D-aspartate (NMDA)-type channels, the cell responds more strongly when synaptic drive is concentrated within several dendritic regions than when it is delivered diffusely across the dendritic arbor. This effect, called dendritic "cluster sensitivity," persisted under wide-ranging parameter variations and directly implicated the spatial ordering of afferent synaptic connections onto the dendritic tree as an important determinant of neuronal response selectivity.

3. In this work, the sensitivity of neocortical dendrites to spatially clustered synaptic drive has been further studied with fast sodium and slow calcium spiking mechanisms present in the dendritic membrane. Several spatial distributions of the dendritic spiking mechanisms were tested with and without NMDA synapses. Results of numerous simulations reveal that dendritic cluster sensitivity is a highly robust phenomenon in dendrites containing a sufficiency of excitatory membrane mechanisms and is only weakly dependent on their detailed spatial distribution, peak conductances, or kinetics. Factors that either work against or make irrelevant the dendritic cluster sensitivity effect include 1) very high-resistance spine necks, 2) very large synaptic conductances, 3) very high baseline levels of synaptic activity, and 4) large fluctuations in level of synaptic activity on short time scales.

4. The functional significance of dendritic cluster sensitivity has been previously discussed in the context of associative learning and memory. Here it is demonstrated that the dendritic tree of a cluster-sensitive neuron implements an approximate spatial correlation, or sum of products operation, such as that which could underlie nonlinear disparity tuning in binocular visual neurons.

INTRODUCTION

Despite many decades of anatomic and physiological study, a basic understanding of the input-output behavior of the neocortical pyramidal cell is still lacking. What kind of "device" is a pyramidal cell, in the sense that one might ask of a transistor or a logic gate extracted from a computer circuit? How does it transform a complex pattern of synaptic input into an output firing rate? In short, what does a single neocortical pyramidal cell compute?

Experimental techniques do not yet exist that allow this question to be studied directly. Because dendritic branch diameters are commonly ≤1 μm, intradendritic recordings in neocortical pyramids have been extremely rare; those recordings that do exist have been taken only from thick apical trunks (Amitai et al. 1993; Pockberger 1991). Even as optical recording techniques grow increasingly sophisticated, allowing transmembrane voltage and/or intracellular ion concentrations to be imaged over large regions of a dendritic tree (Grinvald et al. 1981; Jaffe et al. 1992; Tank et al. 1988), it is not yet possible to selectively stimulate large numbers of afferent fibers that make synaptic contacts onto a dendritic tree at specific locations. Such precise stimulus control would be needed to directly probe mechanisms of spatiotemporal integration of synaptic input under "natural" stimulus conditions. Given the enormous technical hurdles that remain before direct experimental verification of hypotheses becomes possible, biophysically realistic compartmental modeling techniques remain the most powerful and flexible methodological approach to this question.

In early modeling work, dendritic trees were often conceptualized as electrically passive branched cablelike structures (see Jack et al. 1975; Rall 1977; Segev 1992; Mel, 1993). Both classical and more recent work on passive dendritic information processing has most often concerned 1) passive spatiotemporal integration of synaptic inputs (Borg-Graham and Grzywacz 1992; Koch et al. 1982; Poggio and Torre 1978; Rall 1964), 2) dendritic subunit structure (Koch et al. 1982; Miller and Bloomfield 1983; Woolf et al. 1991), or 3) the effects of synaptic background activity on passive cable structure (Bernander et al. 1991; Holmes and Woody 1989; Rapp et al. 1992; see also Laurent and Burrows 1989).

Other studies have considered possible roles of active membrane in dendrites or on spine heads in dendritic information processing (Miller et al. 1985; Perkel and Perkel 1985; Rall and Segev 1987; Rall and Shepherd 1968; Shepherd et al. 1985). For example, Rall and Segev (1987) modeled dendritic branches on which subsets of spines contained excitable membrane. Several different types of interactions were observed depending on the spatial distribution of active versus passive spine heads. It was suggested that the observed sensitivity to the distribution of active spine heads and input conditions could allow for a rich repertoire of logical operations among neighboring synapses. Indeed, others have demonstrated that appropriate localization of patches of voltage-dependent membrane could implement logical operations such as AND, OR, and XOR operations, with the suggestion that these "logic spots" might be strategically incorporated into dendritic membrane as needed to implement arbitrary logical computations in the dendritic tree (Shepherd and Brayton 1987; Shepherd et al. 1989; Zador et al. 1992). Although all of these studies have sources of valuable intuition as to the possibilities for infor-
FIG. 1. Sigma-pi unit is an abstract model neuron that sums contributions over independent multiplicative clusters of input synapses, $y = \sigma(\sum_{i=1}^{n} w_i \Pi x_i)$, where $i$ indexes the clusters and $\sigma$ is an optional sigmoidal nonlinearity applied to the sum of products. A single unit is thus a multilayered network in and of itself, where each multiplicative cluster acts as a nonlinear “hidden unit.”

**A motivating hypothesis**

The main goal of the current study, as for Mel 1992a, was to explore the validity of a simple, essentially statistical hypothesis as to the input-output behavior of a dendritic tree containing excitatory voltage-dependent conductances that depends little on the detailed geometry of the dendritic arbor, the precise strength or spatial distribution of active membrane conductances, their kinetics, or their voltage dependencies.

The initial hypothesis was derived from a simple abstract model neuron, called a sigma-pi neuron (Mel and Koch 1990; Rumelhart et al. 1986). A sigma-pi neuron computes its output as a weighted sum of contributions from a set of independent multiplicative clusters of synaptic inputs, in analogy with the weighted sum of multiplicative terms in a polynomial function (Fig. 1).

Three factors have recommended this single-unit abstraction as the seed for a neurobiological model. First, direct monosynaptic connections between units with multiplicative input stages can implement a very general class of nonlinear associations (Durbin and Rumelhart 1989; Feldman and Ballard 1982; Koch and Poggio 1992; Mel and Koch 1990; Poggio and Girosi 1990). Second, the learning of such associations can be achieved with a simple Hebbian rule of a general type known to exist in the CNS (Bliss and Lomo 1973; Brown et al. 1988; Sejnowski and Tesauro 1989). Third, numerous suggestions have been made over the past decade that voltage-dependent membrane mechanisms in dendritic trees could afford the multiplicative interactions among neighboring synapses needed for this type of model neuron (Brown et al. 1988, 1991; Durbin and Rumelhart 1989; Feldman and Ballard 1982; Koch and Poggio 1987; Mel and Koch 1990; Poggio and Girosi 1990; Rall and Segev 1987; Shepherd and Brayton 1987; Shepard et al. 1989).

The theoretical appeal of the sigma-pi unit as a biological model thus motivated the main experimental paradigm used in this paper. Sigma-pi-like behavior in a real neuron might be evidenced by differential cell responses to patterns of synaptic input that differ in the degree of spatial clustering of the activated synapses. The present goal was to test whether biologically plausible distributions of voltage-dependent ionic conductances in a dendritic tree could render activation of synapses in clusters more effective than activation of the same number of synapses scattered diffusely across the dendritic tree.

**METHODS**

**Compartmental modeling**

A compartmental modeling program called NEURON was used to carry out the simulations reported in this work (Hines 1989). Anatomic data from a reconstructed layer 5 pyramidal cell from cat visual cortex was provided by R. Douglas and K. Martin. More than 3,000 measurements of branch length and diameter were consolidated into 163 connected dendritic branch sections, consisting of 10 basal dendrites leaving the soma culminating in 56 basal branch tips, and a main apical shaft terminating in an apical tuft with 31 apical branch tips (see Fig. 3). The cell used here was mapped into $\sim 500$ isopotential “compartments,” each representing a $\leq 40-\mu m$ segment of dendritic length. Because the available anatomic data did not encode the locations and structural parameters of dendritic spines, a scheme proposed by Stratford et al. (1989) was used to increment the length and diameter of each dendritic branch so that its area, input resistance, axial resistance, and effective electrotonic length mimicked those of a branch covered with spines at an assumed density of one spine per micron (see Douglas and Martin 1990; Larkman 1991). For each synapse that was to be explicitly activated during a simulation run, an additional compartment representing a cylindrical spine 1 $\mu m$ long and of 0.15 $\mu m$ diam was attached to the main dendritic branch compartment. The axon was not modeled, because its fine diameter represented a negligible conductance load relative to the much thicker dendritic processes. Passive membrane parameters are given in Table 1.

**Modeling N-methyl-D-aspartate and non-N-methyl-D-aspartate synaptic conductances**

Excitatory synapses onto neocortical pyramidal cells make up $\sim 85\%$ of the $>10,000$ synaptic contacts (Beaulieu and Colonnier 1983). The major component of excitatory synaptic action onto these cells is thought to be mediated by glutamate. Two broad classes of glutamate-sensitive receptor subtypes have been characterized, associated with $1)$ a voltage-independent fast $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type conductance and $2)$ a voltage-dependent long-lasting N-methyl-D-aspartate (NMDA)-type conductance (Mayer and Westbrook 1987).

The voltage-independent AMPA conductance was modeled as an alpha function (Fig. 2A)

$$G_A = g_A e^{-t/t_A}$$

(1)

with $g_A$, the peak AMPA conductance, $\epsilon = e/t_A$, and time to peak $t_A = 1 \text{ ms}$. The NMDA conductance depended exponentially on membrane voltage $V_m$ and on time, modeled as follows (Jahr and Stevens 1990a,b; Zador et al. 1990; Fig. 2B and C)

$$G_N = g_N e^{-t/t_1} e^{-t_2/t_2}$$

(2)

with $g_N$, the nominal peak NMDA conductance, $t_1 = 80 \text{ ms}$, $t_2 = 0.66 \mu s$, $\eta = 0.33/\mu \text{M}$, $[\text{Mg}^{2+}] = 1 \text{ mM}$, and $\gamma = 0.06/\mu \text{V}$. The exponential voltage dependence appearing in the denominator...
one of two conditions designed to span the range of possibilities: 

Table 2) and thus had little effect on these values. \( t_\gamma \) and \( t_\text{syn} \) synapses were assumed to be voltage independent. All parameters are summarized in Table 2.

Hodgkin-Huxley channels were essentially inactivated at rest (see Table 2) and thus had little effect on these values. \( \xi_N \), nominal peak NMDA conductance; \( \xi_A \), peak AMPA conductance; AMPA, \( \alpha\text{-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.} \) Input resistance, \( \tau \), and resting potential for entirely passive cell. Somatic Hodgkin-Huxley channels were essentially inactivated at rest (see Table 2) and thus had little effect on these values. \( \xi_N \) and \( \xi_A \) synapses were scaled to the local input resistance. Thus conductance triples given for high-NMDA and 0-NMDA conditions were typical values for peak synaptic conductances near the soma, on a distal dendritic tip, and averaged over the arbor.

that the voltage dependence of the NMDA channel is such that the actual NMDA conductance peak achieved during synaptic stimulation falls considerably short of the nominal peak value. For example, at a depolarized membrane potential of \( 30 \text{ mV} \) (Fig. 2C), the denominator of Eq. 2 is \( \sim 3 \), such that the NMDA conductance actually achieved is only one third of the nominal peak conductance. For the cell and parameters used in this study, the input resistance measured at a spine head varied by almost a factor of 17 depending on its dendritic location (roughly 2,200 \text{ M\Omega} on a distal apical dendrite vs. 133 \text{ M\Omega} near the soma) and was on average approximately three times greater for apical versus basal dendrites. In the experiments presented here, therefore, peak synaptic conductance was scaled to the input resistance measured locally at the spine head. This scaling procedure forced a rough but convenient correspondence between the size of a cluster of active synapses and the size of the local peak depolarization due to the clustered synaptic activity—indeed of dendritic locus. Although on its face this procedure implies that synapses on thick proximal trunks are much stronger than those on thin distal branchlets, a strong synapse may be viewed as consisting of a group of weaker synapses in close proximity without loss of generality in any of the following results or discussions. In a typical high-NMDA test condition, the \( \xi_N \) value ranged from 3.6 \text{nS} near the cell body to 0.2 \text{nS} on a distal apical tip, with an average value of 0.95 \text{nS}, as compared with peak AMPA conductance values one tenth as large, i.e., 0.36, 0.02, and 0.095 \text{nS}. In zero-NMDA runs, peak AMPA conductance values ranged from 1.5 \text{nS} near the soma to 0.09 \text{nS} on a distal apical tip, with an average of 0.48 \text{nS}. For the AMPA channels, the \( \xi_A \) value is achieved during each synaptic event, independent of the local membrane voltage.

Dendritic spiking mechanisms

The motivation to study the effects of dendritic spiking mechanisms comes primarily from intradendritic and other recording experiments in hippocampal pyramidal cells (Andersen et al. 1987; Benardo et al. 1982; Mayakawa and Kato 1986; Poolos and Kocsis 1990; Turner et al. 1989; Wong et al. 1979), and most recently intradendritic recordings in neocortical pyramids (Amiati et al. 1993; Pockberger 1991). In both types of cells, intradendritic current injections were shown to give rise to complex superpositions of fast and slow dendritic spikes. In hippocampal pyramids, fast dendritic spikes were found to be mediated by sodium, on the basis of their sensitivity to tetrodotoxin (TTX) (Benardo et al. 1982; Wong et al. 1979), whereas slow spikes were inferred to be calcium mediated on the basis of their elimination in zero-Ca\(^{2+}\) solution (Poolos and Kocsis 1990). A recent optical recording study used Ca\(^{2+}\)- and Na\(^+\)-sensitive dyes simultaneously, confirming the participation and interaction of both ionic species in the generation of spikes in the dendrites of CA1 hippocampal pyramidal cells (Jaffe et al. 1992).

FAST-SPIKING MECHANISM. In the present simulations, a fast-spiking mechanism was used in the cell body and in some cases in the dendritic membrane. This mechanism consisted of a fast inward sodium current \( (I_{\text{Na}}) \) and an outward current carried by a delayed rectifier \( (I_{\text{DR}}) \) (Fig. 2D). A modified Hodgkin-Huxley formalism (O. Benard, unpublished data) was used to compute the currents as a function of voltage and time (Fig. 2D). Each "gating" term (e.g., \( m, h \)) obeyed first-order kinetics, with steady-state values of the form \( m_g = 1/[1 + e^{(V - V_{1/2})/k}] \), where \( V_{1/2} \) and \( K \) were the half-activation voltage and slope of the sigmoidal voltage dependence, respectively. The time constants \( t_m \) and \( t_h \) were assumed to be voltage independent. All parameters are summarized in Table 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_m )</td>
<td>10,000 \text{ \Omega cm}(^2)</td>
</tr>
<tr>
<td>( C_m )</td>
<td>1.0 \text{ \uS cm}^{-2}</td>
</tr>
<tr>
<td>( R_s )</td>
<td>200 \text{ \Omega}</td>
</tr>
<tr>
<td>Input resistance at soma*</td>
<td>24 \text{ \Omega}</td>
</tr>
<tr>
<td>( \tau )</td>
<td>10 \text{ ms}</td>
</tr>
<tr>
<td>Resting potential</td>
<td>-70 \text{ mV}</td>
</tr>
<tr>
<td>Dendritic spine</td>
<td>( l = 1.0 \mu m, d = 0.15 \mu m )</td>
</tr>
<tr>
<td>Synaptic stimulation</td>
<td>100 Hz with randomized interspike interval</td>
</tr>
<tr>
<td>Active synapses</td>
<td>100, stimulated asynchronously</td>
</tr>
<tr>
<td>High-NMDA condition†</td>
<td>( \xi_N = 3.6/0.2/0.095 \text{nS}, \xi_A = 0.1 \xi_N )</td>
</tr>
<tr>
<td>0-NMDA condition†</td>
<td>( \xi_N = 1.5/0.09/0.48 \text{nS} )</td>
</tr>
<tr>
<td>NMDA Parameters</td>
<td>( \eta = 0.33/\text{mM}, [\text{Mg}^{2+}] = 1 \text{ mM}, \gamma = -0.06/\mu \text{V} )</td>
</tr>
<tr>
<td>time constants</td>
<td>AMPA: ( \tau = 1 \text{ ms}, \text{NMDA:} t_\gamma = 80 \text{ ms}, t_\text{syn} = 0.66 \text{ ms} )</td>
</tr>
<tr>
<td>Synaptic reversal potential</td>
<td>0 \text{ nV} (both AMPA and NMDA)</td>
</tr>
<tr>
<td>Compartments</td>
<td>473 plus 1 per activated dendritic spine</td>
</tr>
<tr>
<td>Compartment length</td>
<td>40 \mu \text{m}</td>
</tr>
<tr>
<td>Integration time step</td>
<td>0.1 \text{ ms}</td>
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**SYNAPTIC INTEGRATION IN EXCITABLE DENDRITES**

1. **Voltage-Independent AMPA Synapse**: A voltage-independent α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) synapse is modeled as a fast-rising alpha function with $t_r = 1$ ms and peak AMPA conductance ($g_A$) = 1 nS.

2. **NMDA Synapse**: An N-methyl-D-aspartate (NMDA)-type synapse has a long-duration (compare with A) voltage-dependent conductance waveform, shown under simulated voltage clamp for nominal peak NMDA conductance ($g_N$) = 1 nS. Bottom trace is at holding potential of -70 mV. Conductance waveform is repeated at 20-mV depolarizing increments.

3. **Voltage-Dependent NMDA Channel**: As membrane is depolarized (under voltage clamp) from resting potential of -70 to -30 mV, peak injected current grows by a factor of 3. Each fast-spiking conductance pair is variant of Hodgkin-Huxley mechanism.

4. **Slow-Spiking Complex**: It contains a high-threshold, noninactivating voltage-dependent calcium channel, a calcium- and voltage-dependent potassium channel, and calcium buffering, diffusion, and extrusion. Resulting spike is 10–20 ms in width.

5. **Calcium Spike Complex Generation**: Pictured are inward calcium current, internal calcium concentration, and outward potassium current (in a ball and stick model) during the generation of the spike in E. G: HH-type spike waveform with slowed kinetics and raised threshold, used as control for parameter uncertainty in slow-spiking mechanism of E and F. Spiking channel parameters are shown in Table 2.

**TWO SLOW-SPIKING MECHANISMS.** Two different mechanisms were used to generate slow dendritic spikes. The first was a calcium spiking mechanism based on 1) an inward current through a high-threshold non-inactivating calcium channel, similar to an L channel, 2) an outward current through a calcium- and voltage-dependent potassium channel, and 3) calcium diffusion, buffering, and extrusion. The calcium channel was implemented using parameters as in Table 2. The potassium channel was taken from Moczydlowski and Latorre (1983), as included with the nmodl package within NEURON. Diffusion was one-dimensional and radial ($D = 0.6 \mu m^2/ms$) and discretized in four concentric compartments (as provided in NEURON). Longitudinal diffusion was ignored. Buffering kinetics within each diffusion shell $i$ were as follows:

$$Ca_i + Buf_i \rightarrow BoundBuf_i$$

with $k_i = 100/mM/ms$, $k_R = 0.1$ per millisecond. Total buffer was $\sum_i = 30 \mu M$. Calcium extrusion was modeled as simple exponential decay of calcium concentration in the outer shell, with a time constant of $\sim 60$ ms.

A spike generated by this mechanism is shown in Fig. 2F. The fast rising phase is driven by the activation of the voltage-dependent calcium channel; rapid increases in voltage and calcium concentration then activate the voltage- and calcium-dependent potassium current, causing the membrane to be repolarized over 10–20 ms. Given the considerable uncertainty in the many parameter settings used in this channel complex, including those associated
fopen m2h translation to dendritic integration in the way studied here.

Other of these very different slow-spiking mechanisms in the dendritic tree were modified according to the modified Hodgkin-Huxley formalism as described here. The second slow-spiking mechanism was implemented to act as a form of control. It was reasoned that if two functionally distinct slow-spiking mechanisms gave rise to very similar dendritic responses in a wide variety of dendrites, then the biophysical details of either should be of reduced importance—at least with respect to the questions being investigated here. The second slow-spiking mechanism was implemented according to the modified Hodgkin-Huxley formalism as described above, with slowed kinetics to give a 10-ms spike width, and a modified voltage dependence to give a raised firing threshold from -50 mV to approximately -40 mV (Fig. 2G; see slow-in and slow-out in Table 2). In numerous simulation experiments using one or the other of these very different slow-spiking mechanisms in the dendrites, no functionally significant differences were observed in relation to dendritic integration in the way studied here.

**TABLE 2. Modified Hodgkin-Huxley parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( I_{N_A} )</th>
<th>( I_{DR} )</th>
<th>( I_{Ca} )</th>
<th>( I_{K_{Ca}} )</th>
<th>( I_{slow-in} )</th>
<th>( I_{slow-out} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f_{open} ), mV</td>
<td>(-40, -42)</td>
<td>(-35)</td>
<td>(-25, -30)</td>
<td>(-20)</td>
<td>(-3, 3)</td>
<td>(-3)</td>
</tr>
<tr>
<td>( V_{th}, ) mV</td>
<td>(-45)</td>
<td>(-3)</td>
<td>(-2, 2)</td>
<td>(-0, 6, 0)</td>
<td>(-12)</td>
<td></td>
</tr>
<tr>
<td>( \tau, ) ms</td>
<td>(0.05, 0.5)</td>
<td>(2, 2)</td>
<td>(-95, 115)</td>
<td>(-95, 40)</td>
<td>(-95, 40)</td>
<td></td>
</tr>
<tr>
<td>Dendritic</td>
<td>( g (S/cm^2) )</td>
<td>(0.1, 0.05)</td>
<td>(0.001)</td>
<td>(0.008)</td>
<td>(0.05)</td>
<td>(0.02)</td>
</tr>
<tr>
<td>Somatic</td>
<td>( g (S/cm^2) )</td>
<td>(0.4)</td>
<td>(0.2)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

Double entries (separated by commas) are for activation and inactivation particles. Peak dendritic conductances \( g \) were for conditions with only a single spiking complex in dendrites. When both spiking complexes were present, peak conductances were usually reduced. Rate and time constants for \( I_{K_{Ca}} \) were both voltage and calcium dependent, and were thus handled differently (see text).

The fast and slow spiking mechanisms were inserted directly into the dendritic shaft membrane rather than on spine heads, and were randomly located clusters of k spines each. The probability of each cluster site was uniform in dendritic length. Spines within a cluster were generally attached to the same isopotential dendritic compartment representing 40 \( \mu m \) of dendritic length. It is important to reiterate that the term “cluster” as used here (see also Rall and Segev 1987) does not refer to anatomic clumping of spines along a stretch of dendrite; spines were in fact assumed in these experiments to be uniformly distributed across the dendritic arbor (a simplification; see Larkman 1991). Instead, a cluster designates a dendritic neighborhood where the density of synaptic activation is increased relative to other parts of the dendritic arbor. A 100-Hz spike train was delivered asynchronously to each of the 100 preselected synapses. The train delivered to each synapse was generated by adding a random perturbation between -5 and +5 ms (half the average interspike interval) to the arrival time of each spike. The number of action potentials generated at the cell body was then counted over the first 100 ms of synaptic stimulation. Passive soma response measures were also used with similar results, including peak somatic potential and time integral of somatic potential. Cluster sizes were systematically varied, ranging from size 1 (unclustered) to size 15. The cell responses for each cluster size were averaged across a number of randomized runs to control for the variation from run to run in the locations of the activated synapses relative to the cell body.

### Stimulus/recording paradigm

As motivated by the sigma-pi hypothesis, the stimulus paradigm was designed to test for differences in the steady-state input-output behavior of the pyramidal cell as a fixed number of activated excitatory synapses was increasingly spatially clustered in the dendritic arbor. Because intracortical network properties were not the object of this investigation, the neuron was as if dissociated from the brain and studied in isolation. Neither background synaptic activity nor inhibitory input due to local circuit interneurons was modeled in these studies.

Each simulation run was parameterized by a single variable \( k \), the cluster size (Fig. 4). At the outset of each simulation run, the entire cell was set to a resting potential of 70 mV. One hundred synapses to be activated were then placed on 100 \( \mu m \) randomly located clusters of \( k \) spines each. The probability of each spine within a cluster was generally attached to the same isopotential dendritic compartment representing 40 \( \mu m \) of dendritic length. It is important to reiterate that the term “cluster” as used here (see also Rall and Segev 1987) does not refer to anatomic clumping of spines along a stretch of dendrite; spines were in fact assumed in these experiments to be uniformly distributed across the dendritic arbor (a simplification; see Larkman 1991). Instead, a cluster designates a dendritic neighborhood where the density of synaptic activation is increased relative to other parts of the dendritic arbor. A 100-Hz spike train was delivered asynchronously to each of the 100 preselected synapses. The train delivered to each synapse was generated by adding a random perturbation between -5 and +5 ms (half the average interspike interval) to the arrival time of each spike. The number of action potentials generated at the cell body was then counted over the first 100 ms of synaptic stimulation. Passive soma response measures were also used with similar results, including peak somatic potential and time integral of somatic potential. Cluster sizes were systematically varied, ranging from size 1 (unclustered) to size 15. The cell responses for each cluster size were averaged across a number of randomized runs to control for the variation from run to run in the locations of the activated synapses relative to the cell body.

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A single cluster of size 100 \( mod \ k \) was also included when \( k \) did not divide evenly into 100.
FIG. 3. Voltage-dependent membrane mechanisms were spatially distributed in one of 3 different ways. A: when NMDA channels were present, they were restricted to activated spine heads. B and C: when spiking channel complexes were present, they were usually distributed in 1 of 2 spatial configurations. B: “distal” configuration, in which channels were uniformly spread throughout the dendritic membrane except the main apical trunk and the proximal basal dendrites (shown in gray). Apical branches were labeled distal where their diameters fell <2 mm (shown in black). C: in the “branch point” configuration, channels were confined to 40-μm segments at each distal branch point and branch tip (shown in black).

RESULTS

Passive cell baseline

The first block of simulation runs served as an experimental baseline, consisting of an electrically passive dendritic tree, driven by 100 voltage-independent AMPA-type synapses. The results averaged over 100 runs are shown in Fig. 5. As cluster size increased from 1 to 15, average cell responses decreased monotonically. This result is due to the well-known saturating nonlinearity associated with summation of conductance inputs: as clusters grow larger, the membrane under each cluster is progressively depolarized by the increased local synaptic activity, but the driving force at each synapse is correspondingly reduced as the local membrane potential approaches the synaptic reversal potential. Each synapse thus becomes a less effective current injector as clusters grow larger. In the passive case, the optimal stimulus configuration is one in which the activated synapses are distributed as widely as possible throughout the dendritic arbor (Bush and Sejnowski 1992; Koch et al. 1982; Rall 1964, 1967).

NMDA SYNAPSES

The next block of simulation trials was a replication of the main effect reported in Mel 1992a. The dendritic tree was again electrically passive, but unlike the baseline case, synapses were deployed in the high-NMDA condition. Peak conductances were as shown in Table 1. Figure 6 exemplifies cell behavior for clusters of size 1 (A) and size 10 (B). As seen in Fig. 6A1, subsynaptic voltage traces are relatively little depolarized from rest, because each of the 100 synapses acts “alone.” The NMDA channels remain relatively polarized and thus relatively inefficient. Average NMDA conductance (A2) and current (A4) remain modest. The somatic voltage trace (A3) shows that no action potentials were generated during this run. By contrast, when synapses are clustered in groups of 10 (Fig. 6B), subsynaptic voltage traces are boosted into a more favorable voltage range for the NMDA channels (B1) and average NMDA conductance (B2) and current (B4) are correspondingly increased. In this case, two action potentials are generated at the cell body (B3).

Averaged responses from 50 randomized runs at several cluster sizes are shown in Fig. 7B. In opposition to the passive case reproduced in Fig. 7A, the NMDA-rich cell at first shows an average increase in cell response as cluster size is increased. At larger cluster sizes, the attenuating effects of synaptic saturation begin to offset the excitatory effects of the NMDA voltage-dependence. Note that the specific cluster size at which the cell response peaks depends on a number of variables including the elemental peak synaptic conductance, the afferent firing frequency, the number of active synapses, and the proportion of NMDA to non-NMDA conductance at each synapse. The average firing

FIG. 4. In each simulation run, 100 synapses were activated in randomly distributed clusters. Each active synapse is designated by a black dot. Shown are representative runs with cluster sizes 1, 5, and 10.
tered synaptic input, proved to be extremely robust under wide-ranging parameter variations. As reported in Mel 1992a, parameter variations tested in the high-NMDA/passive-dendritic case included membrane resistivity from 10,000 to 100,000 Ω/cm², membrane capacitance from 0.9 to 7.0 μF/cm², cytoplasmic resistivity from 100 to 362 Ω/cm (several configurations were taken from Stratford et al. 1989); synaptic conductance waveforms in either saturating or nonsaturating conditions, spine membrane correction used or not, and count of activated synapses varied from 80 to 200. Most runs in this earlier study were carried out with peak synaptic conductances assigned uniformly across the dendritic tree, rather than scaled to local input resistance as was done here. Spine neck resistance was increased in one run from 173 MΩ six-fold to 1,038 MΩ, which led to a significant reduction, but did not abolish the cluster sensitivity (i.e., there persisted a 50% increase in average cell response as clusters grew from size 1 to size 3). Finally, in a pilot study on a smaller layer 3 pyramidal cell, cluster sensitivity was seen at stimulus frequencies of 20 and 100 Hz, or when only a single spike was delivered to each synapse.

Dendritic spiking mechanisms

It was necessary to establish whether the cluster sensitivity seen in the passive-dendrite/high-NMDA case was an inherent property of a dendritic arbor containing any form of excitatory voltage-dependent conductance in sufficient quantity, or whether the behavior was particular to some aspect of the kinetics, voltage-dependence, peak conductance, or sparse pattern of activation of NMDA synapses in particular. Simulation experiments were thus repeated using various combinations of dendritic spiking mechanisms in the dendritic arbor, both with and without NMDA synapses. Figure 7, C–E, shows the results for three representative cases. In case C, the dendrites contained the slow-spiking calcium channel complex in the distal dendritic configuration (Fig. 3B). Zero-NMDA synapses were used. In case D, the dendrites contained only the fast-spiking conductance complex in the distal configuration, again with zero NMDA. In case E, a combination of all three voltage-dependent mechanisms was used: NMDA synapses, the slow-spiking mechanism in the distal configuration, and the fast-spiking mechanism in the branch-point configuration. In all three of these test cases, cell responses showed pronounced sensitivity to the degree of spatial clustering of the synaptic activation pattern.

A number of other cases were studied. In general, sufficient criteria for cluster sensitivity were 1) a high proportion of synaptic current due to NMDA channels or 2) a spiking conductance complex over most of the dendritic tree. Thus a configuration with a spiking conductance complex only at branch points, and with no NMDA channels at activated synapses, led to cell responses with no initial cluster-sensitive regime (Fig. 7F). No qualitative differences were seen in the cluster-sensitive behavior of the dendritic tree when the full calcium-mediated slow-spiking mechanism was replaced with the simpler voltage-mediated slow-spiking mechanism, suggesting that the signaling intermediary between inward and outward currents, whether voltage or calcium concentration, was not of primary functional importance for the effects studied here.

Variations in number of active synapses

Cell responses also depend on the number of active synapses, or similarly, the total stimulated synaptic conductance. We contrast the range of cell responses seen under variations in cluster size with the range of cell responses seen under variations in the number of active synapses with cluster size fixed at 1. This comparison is important: if the total number of active synapses varies significantly from moment to moment, then changes in cell responses due to differential clustering of synaptic inputs could be washed out. If this were the case, then the cluster-sensitivity property could not be used to establish the selectivity of cell responses.

Figure 8B shows the averaged results for 30 runs in a cell biophysically configured as in Fig. 7E (reproduced in A). The number of active synapses was varied from 50 to 200; the runs at 100 active synapses were equivalent to those of plot A at cluster size 1. Beginning with 100 active synapses, increases in synapse number of ~25–50% cause increases in cell responses comparable to the maximum response increase observed due to clustering alone. This result indicates that optimal sensitivity to changes in the degree of synaptic clustering can only be accomplished under conditions of relatively tight control on the number of active afferents impinging on a cell’s dendrites from moment to moment. It is also crucial that the total excitatory synaptic conductance applied to the dendritic tree is not so large as to produce very strong or maximal cell responses for unclustered layouts, because this would preclude further signif
FIG. 6. A: response of cell to 100 active synapses in high-NMDA condition with cluster size 1. 100 subsynaptic voltage traces are shown in A1; because each synapse acts “alone,” synapses remain relatively polarized. As a result, average NMDA conductance (A2) and current (A4) remain modest. No somatic spike is generated in this case (A3). B: same stimulus conditions, except synapses are grouped in clusters of 10. Subsynaptic voltage traces are much elevated (B1 vs. A1), as are NMDA average conductance (B2 vs. A2) and current (B4 vs. A4). Two somatic spikes are generated in this case (B3). Total peak synaptic conductance allocated to 100 active synapses was 8% less in case B than in case A.
Passive Dendrites

NMDA Synapses

Ca++ spikes over all distal dendrites

Na+ spikes over all distal dendrites

NMDA, Ca++ over distal tree, Na+ at BP's

No initial cluster sensitivity

**FIG. 7.** A: response of passive dendrites and AMPA synapses as cluster size is increased (reproduced from Fig. 5). B: in high-NMDA condition, direction of effect is reversed: cell displays an initial increasing responsiveness to clustered synaptic stimuli, with a subsequent falloff due to saturation as in A. C: with slow-spiking complex in the distal configuration but no NMDA, initial “cluster sensitivity” is pronounced. D: with fast-spiking complex in distal configuration (i.e., dendrite is made to look like an axon), strong cluster sensitivity remains. E: combination of high NMDA, slow spiking distributed distally, and fast spiking distributed at branch points. Cluster sensitivity is among strongest of all studied cases. F: in 2 cases when no NMDA was present, and dendritic spiking conductances were sparse as in branch-point configuration, cluster sensitivity was abolished.

Dendritic cluster sensitivity

The foregoing results support the conclusion that the responses of neocortical pyramidal cells, if endowed with a significant complement of voltage-dependent excitatory membrane mechanisms, will be strongly dependent on the spatial pattern of synaptic activation across the dendritic arbor. The dependence is simple and is essentially statistical in nature: when synaptic input is relatively clustered, cell responses tend to be large. When synaptic input is relatively diffuse, cell responses tend to be small.

How much greater is the actual current injection per synapse in clustered versus unclustered stimulus conditions? The answer is complicated by the fact that the net current flowing into the cell is not a steady-state quantity, because it depends on the time-changing channel activity across the entire dendritic tree. The average current flowing into the cell may be measured over an extended interval, but this quantity is not simply related to the cell’s output firing rate during that interval. Other quantities are crucial, such as time spent above firing “threshold,” but are more poorly defined.

Two results nonetheless shed light on this question. First, in a previously reported simulation experiment (Mel 1992a), total injected charge at the passive cell body was measured in a passive-dendrite/high-NMDA condition for varying cluster sizes. The maximum increase in average somatic current injection relative to an unclustered stimulus condition was 40% for basal dendrites and 18% for apical
Cell Response vs. Cluster Size for 100 Synapses

Cell Response vs. Number of Active Synapses

Varying Baseline Levels of Synaptic Activity

FIG. 8. Plot of cell responses (spikes/100 ms) as a function of cluster size (A) and number of active synapses (B). In C, number of active synapses is increased from 100 (as in A) to 1,000 to see effect of response saturation on cluster sensitivity. Same synaptic strengths were used in all 4 cases; values were those optimal for case of 100 active synapses. Only a weak initial regime of cluster sensitivity is thus conserved when baseline level synaptic drive is increased by an order of magnitude. Parameters were as in Tables 1 and 2.

dendrites. The larger percentage increases typically seen in the number of somatic spikes produced in clustered versus unclustered conditions—e.g., see range in Fig. 7B–E—is due to the thresholding nonlinearity of the somatic spiking mechanism. In another run with 1) high-NMDA synapses, 2) fast spiking in the distal basal dendrites, and 3) slow spiking in the distal apical dendrites, average current injection at the passive soma showed a maximum increase of 70% for clustered versus unclustered stimuli (using parameters as in Tables 1 and 2).

The second result relevant to the magnitude of the cluster sensitivity effect was discussed earlier: In contrasting the plots in Fig. 8, A and B, it was seen that the maximum increase in cell response due to synaptic clustering (from 0 to 4 spikes over 100 ms) was comparable to that associated with a 25–50% increase in total synaptic conductance input to the dendritic tree. For an additional point of reference, in the case of passive dendrites, a 33% increase in direct somatic current injection (0.6–0.8 nA) can account for an increase in somatic spiking rate from zero spikes to four spikes in a 100-ms stimulus period for the somatic fast-spiking parameters as in Table 2. We conclude that substantial percentage increases in somatic current injection can be due to synaptic clustering alone, in the range of 20–70% depending on assumptions.

It is important to note that the family of stimuli used in these experiments, parameterized by cluster size, is only a crude abstraction of the continuum of distributions of synaptic activity in a dendritic tree that ranges from uniform to clumpy. Although this particular family of stimuli is well suited to the generation of large numbers of randomized stimulus patterns, the magnitude of the cluster sensitivity effect, as represented in Fig. 7, could be considerably increased if the stimulus family were specifically tailored to the electrotonic structure of the dendritic tree under study (unpublished observations).

**Different biophysics, similar behavior**

Although the four cases summarized in Fig. 7, B–E, are all highly cluster sensitive, the biophysical conditions that hold within the dendritic trees in these four cases are very different from each other. The difference is particularly salient when comparing the NMDA-only case in B with the NMDA/fast/slow-spiking combination shown in E. Subsynaptic and somatic voltage traces for these two runs may be compared in Fig. 9 for 100 active synapses in clusters of 5. In the NMDA-only case, the subsynaptic voltage traces achieve smooth steady-state values, whereas in the combination case the subsynaptic voltage traces reveal a chaotic jumble of fast and slow spikes throughout the dendritic arbor. Direct intradendritic current injections in this latter cell configuration, as shown in Fig. 10, confirm the complex nature of the voltage activity in the dendritic tree under these distributions of active membrane and synaptic conductances; the inset shows an intradendritic spiking trace recorded from a real neocortical pyramid for purposes of qualitative comparison (Amitai et al. 1993).

**Dendritic spike propagation**

If most or all of a dendritic tree contains excitatory conductances in sufficient quantity for the generation of action potentials (e.g., the distal condition described above), then it would appear that any accidental concentration of synaptic input at a single dendritic locus could "light up" the entire tree, and thereby effectively destroy the cell's selectivity for the global spatial pattern of synaptic activation. In the apical tree of the cell used in this study, a single concentrated synaptic action can in fact "ignite" the entire apical tree, because the apical tree structure is qualitatively similar to a branched axon. An action potential initiated in a distal dendritic tip can propagate first proximally, and then dis-
FIG. 9. **A**: dendritic and somatic voltage traces for clusters of size 5, in high-NMDA condition. Dendritic voltage traces are relatively placid (except when interrupted by somatic spiking). **B**: in contrast, with addition of slow- and fast-spiking conductances to the dendritic tree (condition as in Fig. 7E), chaotic dendritic spiking ensues that is invisible in somatic voltage traces. Despite their biophysical differences, both cases show strong cluster sensitivity. Bursting in somatic voltage trace in **B** is due to presence of slow-spiking channels in basal dendrites (see Traub and Llinas, 1979).

In the basal tree, the situation is quite different. The cell body acts as a large current sink, isolating voltage fluctuations in one basal dendrite from all of the others. An individual basal dendrite can therefore spike freely without igniting the other basal dendrites. This is made possible by the strong attenuation of dendritic voltage peaks when propagated to the soma and beyond (Fig. 11). Only when a dendritic spike happens to push the soma over spiking threshold can it have a more global effect within the basal arbor, synchronously firing all of the basal dendrites antidromically. In general, the stellate structure of the basal dendritic tree is electrotically better suited than the branched apical tree to permit numerous simultaneous but independent local processing operations, such as that which underlies cluster sensitivity.

**Visibility of dendritic spikes at soma**

In a related observation, distal dendritic spiking is likely to be essentially invisible in somatic recordings in cells of this or similar construction. The smooth somatic voltage trace in Fig. 9 **B**, interrupted only by somatic action potentials, supports this conclusion. Additional control experiments were carried out to confirm that individual dendritic spikes are in fact strongly filtered in somatic recordings because of their large high-frequency components. The table in Fig. 11 shows the voltage attenuation for fast spikes, slow spikes, and steady-state current injections at four dendritic loci. For fast spikes, the peak voltage attenuation was never less than a factor of 8, which occurred when the spiking membrane patch was only 15 μm from the cell body (**A**). For a spiking patch at the top of the main apical trunk 370 μm from the cell body (**B**), the attenuation factor for fast spikes was 20, giving a peak somatic depolarization only 4 mV in height. A fast spike on the tip of a basal dendrite (**C**), 200 μm from the cell body, is attenuated by a factor of 180, giving a peak somatic depolarization of only 0.5 mV in height. Attenuation of spike height is still greater for a more distal apical locus (**D**), where a 350-fold attenuation leads to somatic deflections of only 0.24 mV. Slow-spike and
steady-state attenuation were much less for all four loci; steady-state voltage attenuation values varied from 1.9 for locus A to 30 for locus D.

These results suggest that an absence of clear, miniature action potentials in somatic voltage traces should not be taken as evidence for dendritic passivity. Rather, superpositions of fast and slow spikes at multiple dendritic sites are compatible with relatively smooth voltage traces at the cell body. This is consistent with the failure to see complex spikes of the kind seen intradendritically when recording from the cell body (Amitai et al. 1993).

**Predictions**

The simulation results presented in this paper justify the prediction, subject to several conditions discussed below, that the dendrites of neocortical pyramidal cells are selectively responsive to spatially inhomogeneous patterns of synaptic activation. This prediction depends primarily on a strong presence of excitatory voltage-dependent membrane mechanisms in the dendrites, for which there is good evidence (e.g., Amitai et al. 1993; Fox et al. 1990; Miller et al. 1989; Pockberger 1991). Given the relative insensitivity of the simulation results presented here (and in Mel 1992a) to manipulation of biophysical membrane parameters, synaptic waveforms, type, distribution, or kinetics of excitatory synaptic and membrane conductances, frequency of synaptic activation, or details of dendritic morphology, it seems unlikely that this single-cell phenomenon is an artifact of some aspect of the compartmental modeling approach. These results are likely to hold essentially as well for other types of vertebrate CNS neurons that contain active con-
ductances in their dendrites, including hippocampal pyramidal cells, and cerebellar Purkinje cells.

Several circumstances could, however, either invalidate or render irrelevant the prediction of dendritic cluster-sensitivity. These are 1) a general paucity of excitatory voltage-dependent inward currents in comparison with voltage-dependent outward currents in the dendritic tree, 2) extremely high-resistance spine necks that prevent effective voltage communication among neighboring synapses, 3) peak synaptic conductance values of such a magnitude that any single postsynaptic event saturates the synaptic driving force, making cooperativity among neighboring synapses moot, 4) very high levels of synaptic drive onto pyramidal cells (when stimulated), such that cell outputs are saturated, and therefore insensitive, to modest changes in the voltage communication among neighboring synapses, 5) a high degree of variability in the average level of synaptic activation onto pyramidal cells during periods of stimulation, such that changes in cell response due to differences in the spatial configuration of active synapses are occluded, or 6) malign network effects, such as a highly disruptive role for local circuit inhibition, or large fluctuations in spontaneous synaptic background activity.

Direct experimental verification of dendritic cluster sensitivity may require the ability to image voltage and/or calcium concentration over a large portion of a dendritic tree during normal synaptic activation of the cell. The standard experimental method for "orthodromic" stimulation, i.e., via a shock to an afferent synaptic pathway, is inappropriate in this case because it affords no control over the fine spatial distribution of activated synapses on a postsynaptic dendrite. Even when laminar specificity of orthodromic stimulation is achievable, it would remain inadequate because afferents projecting to the same dendritic lamina may actually make synaptic contacts onto electrotonelectronically remote regions of a dendritic arbor. Cells grown onto electrode arrays would be one possible means to achieve more precise multiafferent stimulus control. Alternatively, a preparation that leaves a sensory input pathway intact might also allow complex patterned stimuli to be delivered to a pyramidal cell's dendrites under experimental control. In this case, a cell's output firing rate in response to randomly generated complex stimulus patterns would be predicted to be correlated with the instantaneous spatial pattern of dendritic activity—i.e., strong responses associated with cluster stimulus patterns, visualized for example via calcium-, sodium-, or voltage-sensitive dyes.

**Functional significance of dendritic cluster sensitivity**

The functional significance of dendritic cluster sensitivity was first 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. In a subsequent study, it has been estimated that a 5 x 5-mm slab of neocortex has the capacity to represent on the order of 100,000 input-output pattern associations with high accuracy (unpublished data). We consider here a related computation provided directly by the biophysics of cluster-sensitive dendrites: a correlation operation. It is shown that nonlinear disparity selectivity in a binocular visual cell, for example, could arise purely through an intradendritic correlation of inputs from left- and right-eye receptive fields.

The underlying idea is that groups of frequently coactivated afferent axons represent significant 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 case of stereopsis, a significant 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. A zero-disparity visual stimulus would thus 1) contain many of these higher-order "correspondence" features, 2) activate many clustered pairs of synapses in an appropriately configured dendritic tree, and hence 3) produce a much stronger cell response than a non-corresponding stereo stimulus. This idea is illustrated schematically in Fig. 12. The global response of such a cell is...
nonlinear because the response to a matched stereo pair is greater than the response to an unmatched stereo pair of the same stimulus intensity. 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).

To test this idea in practice, a developmentally inspired learning procedure called “clusteron learning” (Mel 1992b) was used here to sort the afferent fiber projection onto our modeled pyramidal cell; after learning, corresponding inputs from simulated left- and right-eye receptive fields gave rise to neighboring synaptic connections with high probability. As suggested by the schematized “visual system” configuration of Fig. 12, zero-disparity stereo pairs gave rise to relatively clustered patterns of synaptic activation within the dendritic tree. To assess the degree of nonlinear response selectivity possible under these circumstances, test stimuli were delivered to the modeled pyramidal cell that consisted of either 1) randomly generated matched stereo pairs consisting of the same stimulus to left- and right-eye receptive fields or 2) randomly generated nonmatched stereo pairs. In all test cases, exactly 100 synapses were activated, 50 driven by each eye. The dendritic tree was biophysically configured as for the run of Fig. 7E.

Average cell responses are shown in Fig. 13. Zero-disparity stereo pairs generated responses about three times greater than those due to noncorresponding stimulus pairs. Because the average amount of afferent drive to the cell was equivalent for both categories of test stimuli, the cell’s strong preference for zero-disparity pairs was necessarily based solely on the spatial ordering of afferent synaptic contacts.

This demonstration must be interpreted with caution, because it concerns the input-output behavior of a single model pyramidal cell isolated from the cortical network in which it normally functions. Nor can the schematic of Fig 12 be presently defended as a realistic model for the anatomic substrate of disparity-selective binocular cell responses. The demonstration is nonetheless of interest in that the ability of the cluster-sensitive neuron to represent the second-order nonlinearity associated with binocular disparity selectivity—entirely internal to its dendritic tree—is highly suggestive of a possible neurobiological basis for this type of nonlinear cell response. It is interesting to note that the sum-of-products type of computation evidenced here has been proposed in various forms as a 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 intriguing possibility of low-order polynomial computation within the dendrites of neocortical pyramidal cells may thus be worthy of further consideration.

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