Dendritic Control of Hebbian Computations

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INTRODUCTION

In his influential 1949 work, *The Organization of Behavior*, the Canadian psychologist Donald Hebb expressed the following postulate for synaptic modification:

> *When an axon of cell A is near enough to excite cell B, or repeatedly or consistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.*

The original idea underlying this proposal was that use-dependent synaptic modifications could form the substrate for cognitive learning and memory. More recently, it has been suggested that a similar process may also contribute to the self-organization of perceptual systems during development. Hebbian synaptic plasticity is interesting for at least two reasons. First, the idea has inspired many provocative theories and computational models of learning and self-organization (Linsker, 1990). Second, a process similar to what Hebb predicted has been shown to exist in the mammalian central nervous system (Kelso et al, 1986).

In contrast to this large body of work on artificial neural networks (see Linsker, 1990), relatively little is understood about the computations that might emerge in single neurons and neuronal circuits as a consequence of Hebbian synaptic plasticity. Here we outline some of the theoretical consequences of the interactions between

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Hebbian synapses and the physiology and morphology of individual neurons. We begin by reviewing the basic conceptual features of a Hebbian synapse. Next, we discuss the biological evidence for Hebbian modification and its biophysical properties. Finally, we illustrate an approach for examining the computations that might be performed by hippocampal neurons that possess Hebbian synapses on their dendrites.

FORMAL PROPERTIES OF HEBBIAN SYNAPSES

Hebb's basic proposal, now referred to as "Hebb's postulate" for learning (Stent, 1973), has been interpreted and cast into a variety of formalizations (reviewed in Brown et al, 1990). In Hebb's original statement, the term *efficiency* refers to what we would now call *efficacy* or *synaptic strength.* We will refer to a *Hebbian synapse* as one that strengthens when there is a co-occurrence of, or positive correlation between, pre- and postsynaptic activities.

Characteristics of Hebbian Plasticity

Three features characterize the modern concept of a Hebbian modification process (Brown et al, 1990). First, the process is *local,* by which we mean that all the information necessary for the change is available to the synapse as a consequence of ordinary synaptic transmission. This feature of Hebbian plasticity stands in sharp contrast to so-called "supervised" learning schemes, such as the perceptron learning rule (Rosenblatt, 1958) and the backpropagation algorithm (e.g. Rumelhart et al, 1986). Unlike these, Hebbian learning does not require an error or "external teacher" signal that instructs change on a synapse-by-synapse basis. Second, the process is *interactive* (cf Palm, 1982), in the sense that activity on both sides of the synaptic cleft is required to trigger strengthening. A mechanism that involves either pre- or postsynaptic activity alone, or a linear superposition of the consequences of pre- and postsynaptic activity, is called noninteractive. Finally, the mechanism is *time-dependent.* Synaptic strengthening only takes place if pre- and postsynaptic activity occur at about the same time.

These three features are the defining characteristics of a strictly Hebbian process. Note that without a mechanism for *decreasing* synaptic efficacy, all synaptic strengths could either increase without bound or saturate to some asymptotic value. Although Hebb did not discuss the conditions under which synaptic efficacy should decrease, a generalized Hebbian modification includes both Hebb's original enhancement process plus one or more processes that result in synaptic depression. Some examples of how these features are expressed in algorithmic form is discussed in the next section.

Hebbian Algorithms

Various formal representations of the features described above have been used in network models, and several of these have been reviewed elsewhere (Brown et al, 1990). The most general form of Hebbian algorithm is

$$\frac{dw_{ij}}{dt} = F\,[a_i(t), a_j(t), w_{ij}(t)] \qquad [1]$$

where t is time; $w_{ij}(t)$ is the connection strength (w stands for "weight") at time t from the *jth* (presynaptic) element to the *ith* (postsynaptic) element; $a_j(t)$ and $a_i(t)$ are some measures or functions of, respectively, presynaptic and postsynaptic activity; and $F[\bullet]$ is some functional of these activities. Although $F[\bullet]$ varies from model to model, in all cases it is designed to capture the interactive nature of the modification rule.

We have been interested in simple forms of Eq. 1 in which the terms can be mapped on to known biological processes. Consider a functional of the form

$$F\,[a_i(t), a_j(t)] = F\,[\alpha\,(a_j(t) - A_j)\,(a_i(t) - A_i)] \qquad [2]$$

where A_i, A_j and α are constants and $a_i(t)$ and $a_j(t)$ are defined as above. If we let $F[\bullet]$ be a linear functional, then Eq. 2 becomes

$$F\,[a_i(t), a_j(t)] = \alpha F\,[a_i(t)\,a_j(t)] - \beta F\,[a_i(t)] - \gamma F\,[a_j(t)] - \delta \qquad [3]$$

where the constants β, γ and δ depend upon A_i, A_j and α. In the special case where $F[\bullet]$ is the expectation value $E\{\}$, and A_j and A_i are, respectively, the average pre- and postsynaptic activities, then Eqs 2 and 3 represent the *covariance* of pre- and postsynaptic activities (Sejnowski, 1977).

Eq. 3 may be generalized to

$$F\,[a_i(t), a_j(t)] = \alpha\,[a_i(t)\,a_j(t)] - \beta\,[a_i(t)] - \gamma\,[a_j(t)] - \delta \qquad [4]$$

where $\alpha[\bullet]$, $\beta[\bullet]$, and $\gamma[\bullet]$ now represent distinct functions rather than constants and the other terms have their previous meanings.

The terms on the right hand side of Eq. 4 can be related to biological processes as shown in Table 1 (Kairiss et al, 1988). The first term on the right hand side could correspond to long-term potentiation (LTP, discussed below). It represents an interactive process for synaptic enhancement similar to that underlying the Hebbian synaptic potentiation described in the CA1 region of hippocampus (Kelso et al., 1986). The functional $\beta[a_i(t)]$ represents the contribution of heterosynaptic depression. The third term, $\gamma[a_j(t)]$ represents a noninteractive type of homosynaptic depression, while the constant δ represents a passive decay process.

Table 1. Terms in the Modification Equation and Possible Biological Counterparts

Formal Representation	Biological Correlate	Presynaptic Activity	Postsynaptic Activity	Synaptic Change
$\alpha[a_i(t)a_j(t)]$	Long-term potentiation	+	+	+
$\beta[a_i(t)]$	Heterosynaptic depression	-	+	-
$\gamma[a_j(t)]$	Homosynaptic depression	+	-	-
δ	Passive decay	-	-	-

Note: A (+) indicates presence of activity, or increase in synaptic strength, and (-) indicates lack of activity or decrease in synaptic strength.

NEUROBIOLOGY OF HEBBIAN SYNAPSES

Hebbian Forms of Long-Term Potentiation

As introduced above, long-term potentiation is a form of synaptic plasticity that seems ideally suited for storing certain kinds of information in the nervous system (reviewed in Brown et al, 1989, 1990). LTP is a rapid and persistent form of synaptic enhancement. First discovered in the hippocampus by Bliss and Lomo (1973), LTP is not unique to this structure. There are also several varieties of LTP, including one that resembles the synaptic modification proposed by Hebb.

LTP has been extensively studied at the Schaffer collateral/commissural (Sch/com) input to pyramidal neurons of hippocampal region CA1. The key features of LTP at these synapses include the following: (1) conjunctive pre- and postsynaptic activity is necessary for the enhancement; (2) this activity must co-occur within a certain time window; and (3) the change is specific to only the co-activated synaptic inputs.

The Hebbian nature of these synapses has been clearly demonstrated. Tetanic stimulation of an afferent input *during* postsynaptic depolarization induced LTP in the activated synapses (Kelso et al, 1986; Malinow and Miller, 1986; Wigström et al, 1986). In contrast, neither postsynaptic depolarization alone, nor synaptic activation while voltage clamping the postsynaptic neuron to negative potentials, resulted in LTP (Kelso et al, 1986).

The postsynaptic depolarization required for the induction of LTP can be supplied by several types of experimental manipulations. Stimulation of a strong afferent pathway can provide sufficient postsynaptic depolarization to induce LTP at synapses in that pathway. Alternatively, stimulation of a strong pathway can be paired with stimulation of a weak pathway (Barrionuevo and Brown, 1983; Kelso and Brown, 1986). In this case, the depolarization resulting from the weak input alone is not sufficient to induce LTP, but coactive stimulation of the strong pathway can provide sufficient depolarization to potentiate the weak pathway. Finally, the voltage dependence of LTP induction can be demonstrated directly by pairing synaptic activation with direct postsynaptic depolarization by intracellular current injection (Kelso et al, 1986).

Biophysics of LTP Induction

A critical step in the induction of LTP at Sch/com synapses involves a transient, localized increase in postsynaptic [Ca^{2+}] (Dunwiddie and Lynch, 1979). This increase, which is thought to result from Ca^{2+} influx through channels associated with the N-methyl-D-aspartate (NMDA) subclass of glutamate receptor, triggers a sequence of biochemical events that leads to the induction of LTP (reviewed in Brown et al, 1988a,b).

The NMDA receptor-iontophore complex can respond to the conjunction of presynaptic activity and postsynaptic depolarization that is characteristic of a Hebbian synapse. The channel allows Ca^{2+} influx when there is (1) binding of ligand—glutamate or an analog such as NMDA—and (2) depolarization of the postsynaptic membrane (Nowak et al, 1984; Mayer and Westbrook, 1987; Jahr and Stevens, 1987). The requirement for postsynaptic depolarization arises from block of the NMDA receptor channel by extracellular Mg^{2+} at negative membrane potentials. This block is gradually relieved with membrane depolarization. Thus, the NMDA receptor-iontophore complex can act as a "coincidence detector" for pre- and postsynaptic activity.

Although most of our knowledge of the biophysical mechanism of LTP induction is based on studies of the Sch/com system in CA1, this mechanism is not universal. For example, the induction of LTP at mossy fiber synapses is governed by a different mechanism (reviewed in Brown et al, 1989). There may therefore be several different biophysical mechanisms underlying the induction of LTP at Hebbian synapses (Jaffe and Johnston, 1990).

Biophysical Model of LTP Induction

Many of the synaptic inputs onto pyramidal cells are on dendritic spines. We suspect that the neurophysiology of the spine may play a role in the induction of LTP. To appreciate this possible role, it is useful to simulate the biophysical processes that occur at a synapse during synaptic activation. Zador et al, (1990) have developed a model of Ca^{2+} influx, transport, and buffering following activation of NMDA receptor-gated channels located on a spine head. The amount of synaptic potentiation is assumed to be proportional to the concentration of free Ca^{2+} or Ca^{2+} bound to substrates such as calmodulin. The model accounts for the three key aspects of the phenomenology of LTP induction that were mentioned above: the conjunctive requirement, temporal specificity, and input specificity. A simplified version of the model was used in the simulations of hippocampal neurons presented below.

HEBBIAN COMPUTATIONS IN SINGLE NEURONS

A large body of theoretical work has explored the properties of networks of highly simplified "processing elements", in which the connections between elements are modified according to Hebbian algorithms (Anderson, 1985; Hopfield, 1984; Kohonen, 1989; Linsker, 1990; reviewed in Brown et al, 1990). These simple systems have the advantage of mathematical tractability. Despite their simplicity, they have been quite successful at solving many "difficult" real-world tasks (e.g. Sejnowski and Rosenberg, 1986).

Neurons vs Processing Elements

In connectionist networks, the processing elements are represented as summation nodes whose output is passed through a transfer function. A general representation of a processing element is

$$a_i^{t+1} = \theta\left(\sum_{j=1}^{N} w_{ij}^t a_j^t\right) \qquad [5]$$

where the output a_i of the *ith* element at time $t+1$ is equal to the sum of N inputs a_j at time t weighted by associated "connection weights" w_{ij}. This sum is then passed through the transfer function $\theta(\bullet)$, which may be a threshold (step) function or a continuous function such as sigmoid.

Clearly, the processing element model lacks most of the temporal, spatial and stochastic complexity inherent in neurons. The properties of voltage- and ligand-gated channels, when combined with the passive electrotonic behavior of neurons, produce complex spatiotemporal dynamics. A limited amount of dynamics could be introduced into Eq. 5 by redefining $\theta(\bullet)$ as a time-varying functional. Similarly, the highly branched tree structure of real neurons adds spatial complexity by enabling local interactions between subsets of inputs. Some aspect of this complexity might be captured by including higher-order interactions between the inputs (e.g. the sigma-pi units of Durbin et al, 1989). Finally, synaptic transmission is a quantized, probabilistic process, which gives rise to a stochastic complexity that is not represented in Eq. 5.

Hebbian Plasticity in a Realistic Neuron Model

What kinds of dendritic computations might take place when Hebbian synapses interact with the temporal, spatial, and stochastic dynamics of biological neurons? How do the morphology and dynamics of dendritic membrane influence the interactions among modifiable synaptic inputs? To explore these possibilities, we have begun to investigate the behavior of a neuron model that includes some of the spatiotemporal complexity associated with hippocampal neurons. A hippocampal CA1 neuron was modeled on a Sun workstation using a customized version of NEURON, a compartmental simulator developed by Michael Hines (Hines, 1989). Our studies divided the parameter space into three components: the neuron morphology and membrane properties; the spatial and temporal relations among the inputs to the neuron; and the properties of the synaptic modification algorithm.

MODEL PARAMETERS Anatomical measurements were obtained from three-dimensional reconstructions of CA1 neurons (Mainen et al, 1990; Claiborne et al, in preparation). Each cell was described by a tree structure consisting of a set of 3000-4000 short cylinders specified by a three dimensional location and a diameter. The compartmental model was built from the morphometric data collapsed by a factor of 10 (to 300-400 compartments, but with branching structure and diameter changes preserved). Estimates for electrical constants were $C_m = 1\ \mu F/cm^2$ and $R_i = 200\Omega$-cm. The true value of R_m for hippocampal pyramidal cells is not known. Estimates based on whole-cell patch clamp recordings are significantly higher than those derived from conventional intracellular methods (Spruston and Johnston, 1990). We explored the effects of letting R_m vary from 15 to 150kΩ-cm^2. No voltage-dependent conductances were included in the simulations reported here.

SYNAPTIC INPUT Synapses were distributed with a uniform density across the apical and basal dendrites of the neuron. Groups of synapses were selected for activation in user-definable patterns, and the computed voltage dynamics and synaptic strengths were viewed on a color graphics display. A Hebbian rule (described below) was used to modify peak synaptic conductances in an activity- and time-dependent fashion.

Synaptic transmission in the Sch/com synapses involves both NMDA and non-NMDA (specifically, AMPA) conductances. In the model, synaptic input was represented by a current with separate NMDA and AMPA components on the head of a two-compartment spine. For each simulation, a subset of synapses was selected randomly from the total synaptic distribution. Simulations were run in 100 ms epochs during which a single subset of synapses was activated synchronously or near synchronously. Inputs consisted of 3 stimuli at intervals of 3 ms. Each of the patterns was presented sequentially until synaptic strengths stabilized. The statistical relations of the synaptic activities within and among patterns constituted the nature of the environment to which the neuron was exposed. In addition to the spatial distribution of synapses for each pattern, the effects of variations in number of patterns, pattern size, and overlap among patterns were examined.

SYNAPTIC PLASTICITY A generalization of Eq. 4 (Brown et al, 1991) was used to model synaptic plasticity. The synaptic strength was represented by the peak conductance of the AMPA component, and was modified individually for each synapse at the end of a simulation epoch. The conductance range was constrained with a sigmoid function to lie between 0.1 and 1.0 nS. The peak NMDA conductance was set initially to 0.2 times the peak AMPA conductance. This value was either fixed to the initial value or modified to remain at a uniform fraction of peak AMPA conductance. A simplified form of the single-spine model of Ca^{2+} dynamics (Zador et al, 1990) was used to compute Ca^{2+}influx and the resulting level of synaptic potentiation. Homosynaptic depression (proportional to the level of presynaptic activity) was computed as a function of the time integral of the AMPA conductance. Heterosynaptic depression (proportional to the postsynaptic activity) was computed as a function of the difference between the cell's resting potential and the local potential at the subsynaptic membrane. Because of the complex electrotonic structure of the neuron, the spatial distribution of postsynaptic potential depended on the precise electrotonic relationships among the active synapses.

Simulation Results

The interactions among neuron architecture, environment, and synaptic modification algorithm result in a very complex parameter space. For example, the depolarization that results from a single input pattern depends on the particular combination of membrane resistance, pattern size, and peak synaptic conductances (as well as many other parameters). The following results were robust over a broad range of this parameter space.

NON-ISOPOTENTIALITY OF PYRAMIDAL NEURONS Steady-state voltage gradients along the dendritic tree decrease as R_m increases (Jack et al, 1975). However, the frequency-dependent nature of cable transmission implies that *transient* signals will behave differently than the steady-state case. We began by studying the response of the model to single synaptic inputs at selected locations throughout the dendritic tree. Specifically, we examined the effects of letting R_m vary from 15 to 150kΩ-cm^2 on the signals that result from synaptic activity.

In the simulation depicted in Figure 1, a synaptic input was applied to four locations on the dendritic tree of the model neuron. The voltage transient that appeared at the soma was, in all cases, a small fraction of that generated at the site of the synaptic input. Evidently, large voltage gradients can exist under simulated synaptic input and current clamp conditions, even for R_m as high as 150kΩ-cm^2.

In voltage clamp studies of synaptic activity, the soma of the neuron is clamped to a desired potential, and the conductance waveform of activated synapses is derived from the current measured by the clamp. What are the consequences of the nonisopotentiality observed above for the interpretation of these measurements? The simulation shown in Figure 2 illustrates that significant differences between the actual synaptic current and the current measured at the soma can result from the gradients between the voltage-clamped soma and the dendritic loci of synaptic input. This ob-

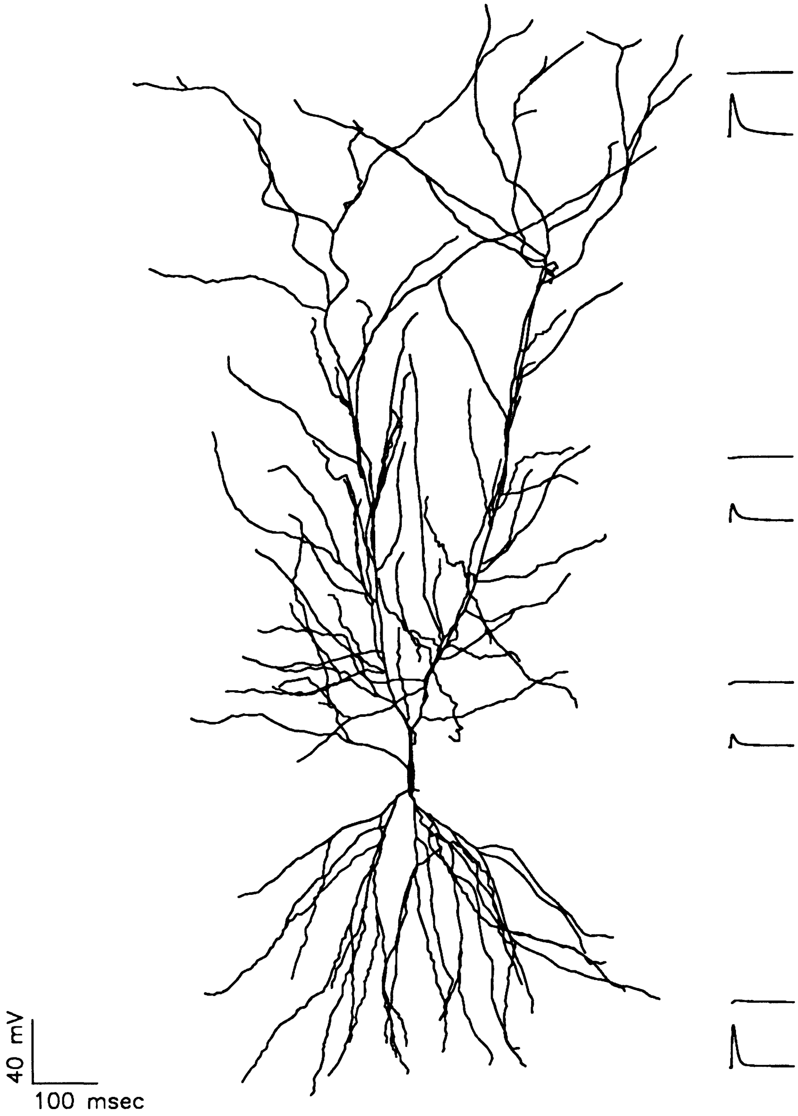

Figure 1. Response to synaptic input at four dendritic locations. Each pair of traces shows post-synaptic potential measured at the soma (top) and at the subsynaptic membrane (bottom). Membrane resistance was set to 150kohm-cm^2. In each case the cell received 5 nS peak synaptic conductance.

Figure 2. Response to synaptic input at four dendritic locations, under somatic voltage clamp. Each pair of traces shows post-synaptic current measured at the soma (top) and at the subsynaptic membrane (bottom). Membrane resistance was set to 150kohm-cm^2. In each case the cell is under somatic voltage clamp to -80mV and receives 5 nS peak synaptic conductance.

servation emphasizes the fact that errors associated with inadequate space clamp can be substantial, even if R_m is very large.

These results have two important implications for the role of dendrites in electrical signalling as well as plasticity. First, a single compartment can not accurately represent the electrical properties of a neuron, even one with high R_m. Synaptic inputs can generate steep voltage gradients within dendritic trees. Therefore, a model that contains a biologically accurate representation of dendritic branching and electrotonic structure is necessary to study the computational aspects of dendritic structure. Second, because Hebbian synaptic plasticity depends critically on postsynaptic voltage, the electrotonic structure of the postsynaptic cell will play an important role in synaptic modifications. The fact that different parts of a neuron may be at different potentials suggests that *differential* modification of synapses can take place across the space of the dendritic tree. In our simulations described in the following section, coactive synapses that were electrotonically close to one another experienced greater subsynaptic depolarization than did coactive but electrotonically separate inputs.

DEVELOPMENT OF FEATURE MOSAICS Brown et al (1988) suggested that "...[a Hebbian synaptic mechanism] could cause the formation of spatial domains (mosaics) of enhancement among electrotonically proximal and functionally related synapses." The voltage sensitivity of the Hebbian synaptic mechanism enables electrotonically related groups of synapses to cooperate in such a way as to promote their potentiation. Our simulations support this idea: synapses that are electrotonically close to one another, and whose activity is correlated, sometimes achieve similar final weights. We refer to these groups of synapses as "clusters".

The formation of inhomogeneous synaptic weights across neurons results from the operation of the interactive rule for enhancement in conjunction with the two rules for depression. This effect is possible because of the voltage gradients in the dendrite. If the whole cell were isopotential—in which case it could be represented electrically as a single compartment—all of the synapses within a pattern would change uniformly. The homosynaptic depression term tends to depress those synapses that are active but electrotonically remote from other coactive inputs. The heterosynaptic term tends to depress those synapses that are electrotonically nearby to synapses with activity that is anticorrelated (i.e. synapses participating in different patterns). When the entire input space was considered, the pattern of self-organization formed a "feature mosaic" across the dendritic tree.

PATTERN SELECTION Despite identical initial number and strengths of synapses, some patterns within a simulation experienced a net increase in synaptic efficacy ("winners"), while others experienced a net decrease ("losers"). Effectively, the neuron became selective to a particular subset of its total input space. It might be that "winners" are those patterns where the synapses have a favorable electrotonic location, in the sense that active synapses within the pattern are electrotonically near each other. A losing pattern may result from several factors. The active synapses could be electrotonically distant from each other. Alternatively, they may be close to a winning pattern, in which case they are weakened by heterosynaptic depression. Although pattern selection was highly sensitive to the initial spatial distribution of synapses, analytical methods will be required to understand all of the factors that determine whether a pattern will win or lose.

Implications For Computation

The fact that synaptic activity can generate voltage gradients in the CA1 neuron model provides some clues about the computational significance of dendrites. The electrotonic structure of the neuron creates a class of synaptic interactions that do not readily lend themselves to implementation by connectionist-style processing elements. The latter cannot use the spatial dimension to extract higher-order information from the input environment. The self-organization of synaptic weights into feature mosaics provides a specific examples of how a realistic neuron model can exhibit behavior that is much more complex than that of a processing element. Thus, the Hebbian synapse takes on a greater computational significance when embedded in the context of dendritic electrotonus.

The full significance of this self-organization may only become apparent when dendritic voltage-dependent channels are included in our model. Evidence is accumulating for the heterogeneous distribution of voltage-gated Ca^{2+} and possibly other channels in the dendrites of hippocampal neurons (Jones et al, 1989; Regehr et al, 1989). The local nonlinearities introduced by these channels could allow regions of a dendrite to make decisions about subsets of the inputs previously organized into a feature mosaic. We are currently investigating the computational consequences of such nonlinearities in dendritic membranes.

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