Chapter 13 A Model of the Directional Selectivity Circuit in Retina: Transformations by Neurons Singly and in Concert

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I. Introduction

Retina is a good candidate for exploring the relationship between neural computation and circuit, in particular given its physically *peripheral* location and its physiologically *central* status. One example of a spatial–temporal computation in the retina is directional selectivity. This computation may rely on interactions within the dendritic tree that are incrementally more complex than the basic *point integration* and fire neuronal response.

In this chapter, we discuss directional selectivity of neurons in the vertebrate retina, including an overview of key experimental findings and an analysis of a model for the underlying circuitry. This analysis will particularly focus on properties of the model that may distinguish it from other model types. Simulations of morphometrically and biophysically detailed cell models will demonstrate model performance, and recent electrophysiological data will be presented that addresses some model predictions. We discuss how this model may work in a developmental context and, finally, we discuss implications for more general multi-dimensional filtering within dendritic trees.

Single Neuron Computation
Neural Nets: Foundations to Applications

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ISBN 0-12-484815-X

II. Overview of Directional Selectivity and the Retina

A. *Directional Selectivity versus Directional Difference*

Directional selectivity (DS) is classically defined as the property of a cell that consistently fires more spikes for movement in a specific (preferred) direction as compared to (null) movement that differs only in sign. For our dissection of the DS circuitry, we also consider the broader *directional difference* (DD) response distinction, defined as *any* preferred/null difference in system/cell output. For example, preferred/null (P/N) waveforms with equivalent averages but different shapes would constitute DD, but, by implication from the classical definition, not DS.

The model described in this chapter includes predictions for (at least) DD signals within the circuit that underlie the DS output. These DD signals will identify where in the retina the specific computation of DS first appears. Such a DD finding may be used, in principle, to rule out experimentally models that predict that a strictly DD signal will *not* be found elsewhere in the circuit, under any conditions.

B. *Structure of the Retina*

The vertebrate retina is organized in several layers of cell bodies and their interacting processes. Signal flow is both direct (perpendicular to the image) and lateral (parallel to the image) at all levels. Light is transduced at the photoreceptor layer, which outputs to bipolar and horizontal cells within the outer plexiform layer. Bipolar cell output impinges on the mesh of amacrine and ganglion cell dendrites within the inner plexiform layer (IPL). Finally, ganglion cell axons form the optic nerve. Each major cell type has several subtypes, classified either anatomically (e.g., according to dendritic tree shape), neurochemically (e.g., cholinergic, GABAergic), or physiologically (e.g.,ON/OFF, directionally selective, red/green opponent).

C. *Theoretical Requirements for DS and DD*

Motion detection is a computation on *spatially separated* inputs *over time*. Detection of motion *direction* (DD) requires a spatial *asymmetry* in the circuit. Finally, as described by Poggio and Reichardt (1973), DS responses also require a *nonlinearity* in the circuit.

It is useful at this point to define two broad classes of DS models: *ganglionic* models, where the crucial nonlinear interaction occurs in the ganglion cell, and *pre-ganglionic* models, where the interaction occurs prior to the ganglion cell. (See review in Koch *et al.*, 1986. In this chapter, *postsynaptic* means ganglionic, and *presynaptic* means pre-ganglionic.)

Thus, the specific questions we are trying to answer here are:

- What is the anatomy and connectivity of the DS pathway?
- What is the crucial nonlinearity of the DS pathway?
- Where on the DS pathway is the nonlinearity, e.g., is it pre-ganglionic or ganglionic?

D. *Experimental Work on Retinal DS*

Over the past 30 years, a large body of work has accumulated investigating DS with a variety of preparations. DS retinal output was first described in amphibian (frog, e.g., Maturana *et al.*, 1960) and eventually characterized in insect (fly, e.g., Hausen, 1981), reptile (turtle, e.g., Lipetz and Hill, 1970), bird (pigeon, e.g., Maturana, 1962), and mammal (rabbit, e.g., Barlow and Hill, 1963). We shall now outline some of the key findings that are pertinent to this chapter.

1. Physiology. The early extracellular rabbit experiments of Barlow and Levick (1965) described several phenomena related to the DS response. Using both moving slits and apparent motion protocols, they showed:

- DS Subunits: Small regions within the slit–mapped receptive field that were DS consistent with the response to full field stimuli.
- Inhibitory Mechanisms: A stimulus at a given point in the receptive field inhibited the response to a stimulus at a second point in the receptive field, when the sequence of the two stimuli simulated null-direction motion.

The first finding suggested that the DS circuit elements for a given ganglion cell were replicated many times for that cell. Historically, the most explored interpretation of the second finding was that the DS computation relied on an asymmetric inhibitory pathway. However, these data cannot rule out a model in which excitation is asymmetric and inhibition is symmetric.

Apparent asymmetric inhibition was not the only phenomenon observed in DS; Barlow and Levick (1965) (and later, Grzywacz and Amthor, 1989) also showed:

- Facilitatory Mechanisms: A stimulus at a given point in the receptive field facilitated the response to a stimulus at a second point in the receptive field when the stimuli sequence simulated preferred-direction motion.

Additional spatial and temporal parameters for the DS network may be inferred by the velocity tuning and size of DS receptive fields (e.g., Wyatt and Daw, 1975; Grzywacz and Amthor, 1989a,b; Granda and Fulbrook, 1989). For instance, the maximum length of the facilitatory lateral path on the retinal surface near the visual streak is typically 100 to 200 micrometers, as derived from apparent motion protocols. The minimum path length for a detectable DS is very short, fewer than 10 μm (Amthor and Grzywacz, unpublished data). The velocity of effective DS stimuli ranges from approximately 0.01 to 10 μm/msec (0.1 to 100 degrees/sec in the visual field.

2. Neurochemistry. The neurotransmitters involved in the DS circuit have been investigated by pharmacological protocols, for example Caldwell *et al.* (1978), rabbit, and Ariel and Adolph (1985), turtle. From this work, we can conclude the following:

- Inhibitory Mechanisms: Blockage of GABAergic pathways reduces or eliminates DS.

This result would seem to support the class of models in which inhibition is asymmetric. As we shall see, however, this data is also consistent with models in which the inhibitory pathway is symmetric. In particular, recent results from Smith *et al.* (1991) with GABAergic antagonists in turtle show:

- Inhibitory Mechanisms: For about 50% of all DS cells, DS is maintained or *reversed* when GABAergic pathways are blocked.

This result is similar to that reported previously in fly (Bülthoff and Bülthoff, 1987).

3. Anatomy. Physiologically identified DS ganglion cells have been stained in both rabbit (Amthor *et al.*, 1984) and turtle (Jensen and DeVoe, 1983). A clear result of this work is that:

- DS Morphology: The dendritic trees of DS ganglion cells are not aligned with nor asymmetric along their P/N axes.

Thus, the morphometric substrate for DS is not immediately obvious from the histology.

E. Retinal DS Models

Inspired in part by the correlation models of Hassenstein and Reichardt (1956) for motion detection in fly, several models have been proposed for the spatial

asymmetry, and the sites and biophysical mechanisms for the time–dependent nonlinear interaction (Fig. 1).

Barlow and Levick (1965) considered both asymmetric lateral inhibitory and excitatory pathways in the outer plexiform layer, with a nonlinear interaction at bipolar cells provided (according to them) by the threshold mechanism of the spike (they assumed that bipolar cells were capable of generating spikes). Others, including Torre and Poggio (1978) and Koch *et al.* (1986), suggested that the lateral pathway might be mediated by amacrine cells, among other possibilities. They showed that the interaction between an asymmetric lateral synaptic inhibition of the silent shunting type and symmetric synaptic excitation, possibly on the ganglion cell membrane itself, could provide the necessary nonlinearity for DS. These models do not explicitly define the mechanism of the delay, other than to point out that a mechanism that has a low–pass filter characteristic, or slower inhibitory synaptic kinetics, might suffice.

We note that in these circuit architectures the only directional signal available is strictly DS, under any circumstances. This is because the interaction between the asymmetric and symmetric pathways is immediately nonlinear. If the non-

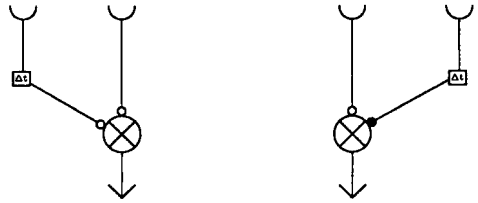

FIGURE 1. Correlation-type models for the computation of DS are typified by that proposed for the fly and vertebrate retina. Versions of this model have considered both an all-excitatory interaction (a) and an excitatory/inhibitory interaction (b) (e.g., asymmetric-veto or AND-NOT models). In the diagram, the nonlinear interaction between the direct and asymmetric delayed inputs is expressed as a multiplication, but this particular nonlinearity is not crucial to the model. In all figures, open and closed circles are excitatory and inhibitory inputs, respectively. Note that a position-dependent delay is applied before the nonlinearity. For both a and b, the preferred response is for motion to the right. For rightward motion in a, the delayed left-hand input is correlated with the undelayed right-hand input; for rightward motion, the delay amplifies the temporal separation at the nonlinearity. For rightward motion in b, the delayed right-hand input is correlated with the undelayed left-hand input, and the inversion of the right-hand input cancels out the left-hand input; for leftward motion, again the delay amplifies the temporal separation at the nonlinearity, in this case allowing passage of the left-hand input (assuming that the nonlinearity is not strictly multiplicative).

linearity is blocked (e.g., blocking inhibition for the inhibitory model), then no interaction can take place: There will be no DD signal at all.

Koch *et al.* (1982) (also O'Donnell *et al.*, 1985) examined the electrotonic structures of ganglion cell morphometrics in detail. They showed that the dendritic tree of the ganglion cell was well-suited for local interactions within the tree between an excitatory input and an inhibitory input that has a strong shunting component. The conclusion was that the computational substrate for subunit response was possible within the tree, supporting a ganglionic model.

Recently, Vaney and co-workers (Vaney *et al.*, 1989; Vaney, 1990) have expanded on ideas from Masland *et al.* (1984) and suggested a specific cell type in rabbit; the starburst cholinergic/GABAergic amacrine cell, as providing an asymmetric excitatory pathway for the DS circuit. They further suggested that starburst dendrites also mediate a lateral inhibitory pathway in the DS circuit, since these cells contain GABA and the tips of adjacent cells are in close proximity. In their *co-transmission* model, inhibitory connectivity from starburst cells is symmetrical, in contrast to the asymmetric excitation. On the other hand, the locus and biophysical mechanisms for the computation of DS are not specified in this model, although they mention both ganglionic and pre-ganglionic alternatives.

III. A Model of DS Output of Amacrine Cell Dendrite Tips

We now present a pre-ganglionic model for DS that is morphometrically similar to that of Vaney *et al.*, in that the lateral pathway is via individual branches of amacrine cells with tip outputs (Grzywacz and Borg-Graham, 1991). We find as well that given a plausible set of constraints on (a) the distribution and biophysics of synaptic input and output on the branches and (b) the intrinsic cable properties, the outputs of this pathway are at least DD and normally are DS. Thus, the necessary and sufficient conditions for the DS computation occur on the same substrate. The crucial DS element in this circuit is shown in Fig. 2, and the anatomy of the asymmetric pathway and the DS ganglion cell is shown in Fig. 3. We suggest, as Vaney, that multiple-oriented amacrine cell dendritic tips that converge on the DS ganglion cell form the basis for the observed subunit response and, as Torre and Poggio (1978), that the necessary nonlinearity is provided by the interaction of excitatory and inhibitory synaptic inputs. The directional properties of a cable with distributed synaptic conductance input has also been described by Grzywacz and Amthor (1989b). Likewise, Koch *et al.* (1982, Fig. 9a) suggested a similar (ganglionic) arrangement of locally symmetric

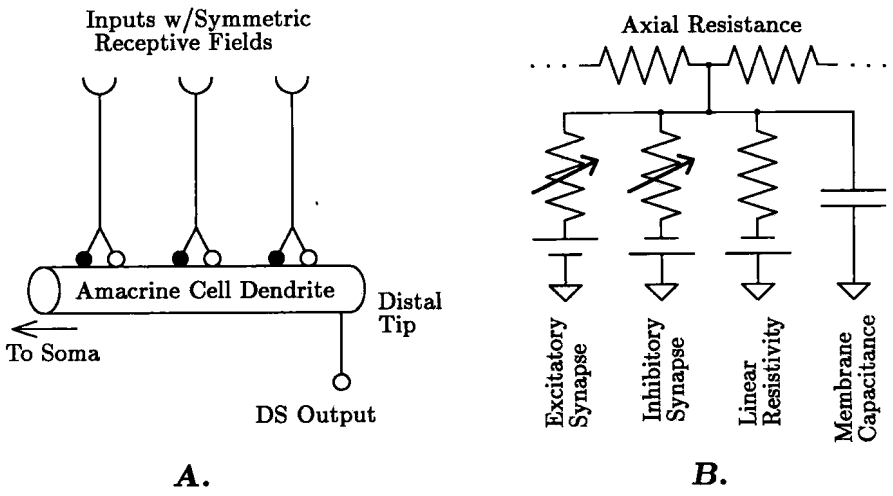

FIGURE 2. (a) Structure of cable model discussed here. In this model the time element is provided by the inherent kinetics of the input synapses, (Torre and Poggio, 1978; Koch *et al.*, 1983) and the nonlinearity by the distributed inhibitory synaptic conductance. Under certain conditions the location-dependent delay (phase shift) provided by the cable and an output nonlinearity may also be relevant (Sections IV.D and V.B). The preferred response of the tip output is for motion to the right in the model version analyzed here. (b) Equivalent circuit for a section of the dendrite cable, including the axial resistance, the linear resting membrane resistance and capacitance, and the synaptic inputs. Directionality of the distal tip output arises because in the null direction the delayed inhibition shunts subsequent excitatory input as the stimulus moves away from the tip. In the preferred direction, the inhibition is much less effective at attenuating the excitation.

excitatory and delayed inhibitory inputs along the branch of a putative asymmetric DS ganglion cell.

A. *Start by Finding the Asymmetry*

Histological data from retina does not immediately suggest the spatial asymmetry required for directional selectivity, as mentioned earlier. However, if we consider putative outputs on the dendritic tips of amacrine cells, the IPL becomes full of asymmetries, since for a large number of amacrine cells the tips are displaced with respect to the entire tree. This interpretation deviates from the assumption of *normal* neuronal polarity: Input to a neuron occurs in the dendritic tree, is conducted proximally, integrated by the soma membrane, and the output of the

cell is conducted out the somatic axon. Some retinal neurons challenge this dogma, and the distinction of dendrite versus axon becomes blurred. Many retinal cells do not have an axon at all *per se*, and single cell processes may have both input and output.

As Vaney pointed out, detailed studies of starburst amacrine cell dendrites support this potential asymmetry (Famiglietti, 1983a, b; Vaney, 1984; Tauchi and Masland, 1984). Small swellings in the outer third of the dendritic tree have

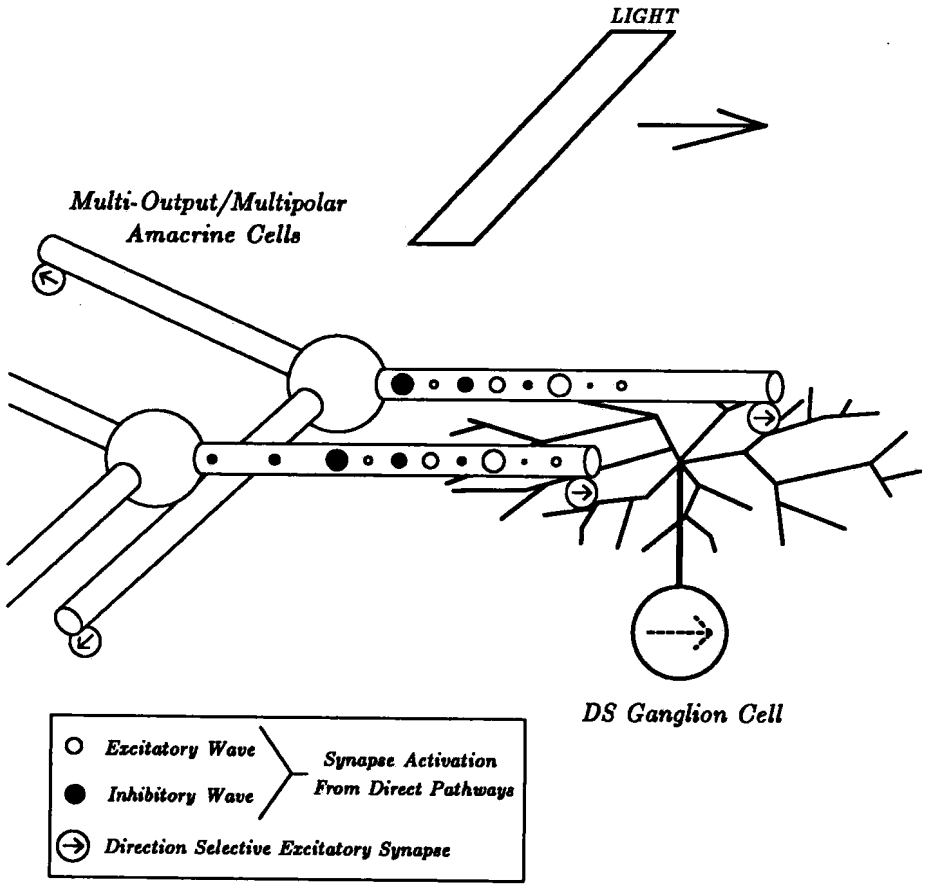

FIGURE 3. Relationship between the asymmetric pathways in the cable model and the target DS ganglion cell with a preferred direction stimulus. Input onto the asymmetric amacrine cell dendritic paths are from symmetric (direct) pathways (either via bipolar cells or amacrine cells). The DS ganglion cell also receives direct symmetric input from bipolar and amacrine cells (not shown). Note that the inhibition kinetics lag behind the excitation.

been described, and electron micrographs show that synapses with ganglion cells occur in the swellings' zone (Brandon, 1987). In contrast, the general distribution of synaptic inputs along the dendrites is apparently uniform.[1]

B. *Add Location Dependence*

The morphometric asymmetry is necessary for directional selectivity, but not sufficient. If the dendrite branch is isopotential, then there is no location dependence of branch input, precluding any sort of motion selectivity, much less directional selectivity. When we add the intracellular resistance of the cable, then location dependence results (Koch *et al.*, 1983).

C. *Directional Difference for the Linear Case*

Let us now examine the response of the cable tip to moving inputs. We begin with the simplest case: distributed excitatory synaptic input onto the (linear) cable. If the synapses are modeled as current sources, e.g., the excitatory synapse injects a depolarizing current, then the tip response can be obtained by the appropriate superposition of responses to individual inputs. The resulting waveforms for motion in the two directions will have different shapes but, since the system is linear, equal areas.

We now have in the dendrite cable the prerequisites—location dependency and asymmetry—for DD (but not DS)—see also Rall (1964). Accentuating the difference is the location–dependent delay of the cable (due to the cable time constant). This tends to increase the output amplitude for motion towards the tip; the EPSPs arriving at the tip are more correlated, since the delay (phase shift) cable counters the motion delay. Otherwise, the two waveforms would simply be reversed in time. We shall return to this phenomenon later in the simulations section.

Now we assume that at each point on the cable there is a paired excitatory/inhibitory input, with the inhibitory kinetics slower than that of the excitation (Torre and Poggio, 1978). Again, if the inhibitory synapse is modeled as a

[1] It should be pointed out that there is conflicting support for the starburst amacrine cell specifically in the DS circuit. For example, Linn and Massey (1990) suggest that cholinergic release from starburst cells is not inhibited directly by GABA, which is contrary to the model prediction. However, cable inhibition might be mediated by another system on the starburst cells, and other amacrine cells may have the necessary input–output relationship. Later, we shall show simulations of a cell whose morphometry is based on the starburst cell; despite the evidence against the starburst cell specifically, we feel that the conclusions from this tree geometry are applicable to other amacrine cells.

hyperpolarizing current source, the (linear) responses for the two directions will have equal area. The DD response holds, still without DS.

D. *Synaptic Nonlinearities and Cable Directionality*

Synaptic input, however, is more accurately modeled by a conductance change in series with a battery. The circuit is now a nonlinear one; the variable conductance input means that the motion responses cannot be derived from the superposition of a sequence of point responses, and the area for the two directions is generally *not* conserved.

The effect of the inhibitory input is particularly important on the directionality of the cable tip response. Assuming that the reversal potential for the inhibition is close to the cell's resting potential, then the main effect of the inhibition will be to *shunt* locally any excitatory current to the extracellular space. The effect of the shunt on the tip response strongly depends on the relative location of the excitatory and inhibitory inputs with respect to the output. As Rall (1964) and Koch *et al.* (1982, 1983) showed, inhibition is most effective when it is *on the path*, that is, interposed between excitation and the output. Conversely, if the excitation is closer to the output, then the inhibitory shunting is much less effective (Fig. 4).

The inhibitory shunting now supplies the necessary nonlinearity for the DS response. This prediction is in concert with the experimental evidence as to the importance of inhibitory mechanisms for DS, and with evidence that shunting inhibition might mediate DS in rabbit (Amthor and Grzywacz, 1991).

We also note that, while the efficacy of the inhibitory synapse with respect to DS is mainly due to its shunting component, it is also true that the precise value for the inhibitory reversal potential is not crucial (as long as it is in the neighborhood of the resting potential). Locality of interaction is strongest when the inhibitory reversal potential equals the resting potential, but this is not relevant for the geometry of the model presented here.

E. *Considering Tip Output Nonlinearity, Facilitation, and the Sign of the Output*

Inhibition onto the cable suffices to make the towards-tip response larger than the opposite direction, so a linear output function would preserve the distinction. It is more likely, though, that the output synapse has a threshold. The resulting supralinear region only amplifies the DS distinction.

The experimental evidence of preferred–direction facilitation data mentioned earlier supports placing a facilitatory mechanism on the DS pathway, as opposed

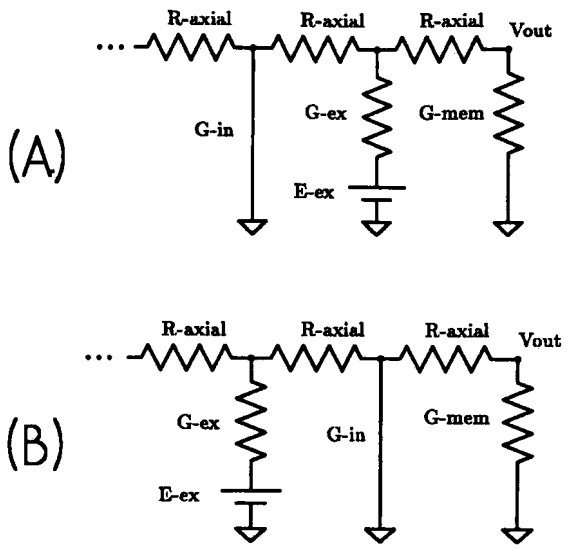

FIGURE 4. The effect of inhibition on tip output is dependent on the relative position of the excitation and the inhibition with respect to the output. To illustrate, we use an extreme case in which the inhibitory battery is equal to the resting potential, and the activated inhibitory conductance is infinite. In a, the excitatory input is closer to the tip than the inhibitory input. Although the membrane potential at the site of inhibition is clamped to the resting potential (short-circuited), the axial resistance of the cable partially isolates the excitatory location, and the tip (V_{out}) is depolarized. In b, the interposed inhibitory input clamps the cable between the excitatory input and the output to the resting potential, so that the output stays at rest. Adding membrane capacitance, a finite conductance to the activated inhibitory synapse, or making the inhibitory reversal potential not exactly equal to the resting potential does not change the basic interaction. However, a nonzero axial resistance *is* crucial.

to only a symmetric location (e.g., on the ganglion cell soma). We postulate that this could be accounted for by various mechanisms located at the amacrine cell tip. For example, facilitatory mechanisms intrinsic to the synaptic output might suffice. Likewise, we may consider a time- and voltage-dependent K^+ channel at the tip that is normally open at rest but inactivates with depolarization, similar to the I_D channel identified in hippocampal pyramidal cells. (See review by Storm, 1990.) The characteristics of this channel would cause the tip output to be *primed* by distant cable input, such that subsequent excitation near the tip would be unopposed by the now–inactivated K^+ shunt.

Two versions of this model include either that the amacrine DS output forms an excitatory connection with a DS ganglion cell, or the connection is inhibitory. It is also possible to include plausible voltage- and time-dependent nonlinearities

in the cable so that the preferred direction for the branch output is *away* from the tip. Also, the tip output may pass through bipolar cells or amacrine cells before the ganglion cell.

While any combination of the preceding polarities will yield a ganglion cell DS response, the fact that directional responses have been recorded in the absence of GABAergic inhibition (Section II.D.1) suggests that the DS pathway has an excitatory component at every junction. Further, data described later in this chapter from turtle ganglion cells with local block of GABAergic inhibitory input supports the excitatory connectivity version. Also, simulations of model cells with likely membrane parameters favor the preferred-towards-tip orientation for the cable output (Section V and unpublished data).

IV. Predictions of the Model

We now consider testable predictions, namely, those for somatic recordings of amacrine and target ganglion cells.

A. *DS Somatic Recordings?*

With respect to amacrine cells, the model predicts that moving stimuli centered on the somatic receptive field would not elicit a directionality, assuming a symmetrical dendritic tree. If either the stimuli or the dendritic tree was asymmetric with respect to the soma, then a directional response would result, perhaps similar to the pre-ganglionic DS/DD recordings of DeVoe *et al.* (1989). While this result supports the proposed mechanism for DS, it does not link the mechanism to an identified DS ganglion cell.

From the point of view of the DS ganglion cell, the model predicts that the input waveforms to the cell are themselves DS; any ganglionic computational mechanisms will be inherently symmetric and serve only to refine the P/N response properties. This result is in contrast with the ganglionic model class, in which the inputs are not DS by themselves.

B. *DS Dependence on Ganglion Cell Membrane Potential*

Differences in P/N EPSPs are predicted by the ganglionic model, but since the differences arise from ganglionic interaction of conductances with different reversal potentials, this model predicts that the relationship between the preferred and null EPSPs will depend on the membrane potential.

For example, let us consider the ganglionic AND-NOT circuit: Null direction

response reflects a temporal overlap of the excitatory input with inhibitory (mainly shunting) input at the ganglion cell. Since the inhibitory reversal potential might be near the resting potential, there would be few negative portions in either the preferred or null response. A negative portion would result if the membrane potential is artificially raised by injecting current. The *unmasked* IPSP would be expected to be more correlated with the control EPSP in the null direction as compared to the preferred direction (e.g., Marchiafava, 1979). If the ganglion cell was hyperpolarized by the electrode, the *unmasked* inhibitory input would now contribute a component to the EPSP. With sufficient hyper/depolarization (at least such that the entire response stays below the inhibitory reversal potential), the *amplitude* of the null response could become greater than that of the preferred response.

This result is in clear contrast to a pre-ganglionic model. The single reversal potential of the directionally-selective circuit inputs imply that the ratio of the preferred and null EPSPs is *independent* of the membrane potential: Manipulating the membrane potential will not reverse the P/N axis.

C. *Comparing Total Synaptic Input for the P/N Responses*

The preceding result is related to measuring the somatic input conductance, $G_{\text{In}}(S(x,t))$, of the ganglion cell during a motion stimulus S. For a lumped cell approximation and no voltage-dependent membrane, predictions about $G_{\text{In}}(S(x,t))$ are simple. In the ganglionic model, the only difference in the inputs for the preferred versus null responses is in their timing. Thus, the model predicts:

$$\int G_{\text{In}}(S(x,t)) = \int G_{\text{In}}(S(-x,t)).$$

On the other hand, for the pre-ganglionic model, there is more synaptic input for one direction versus the other; therefore (assuming the lumped cell without voltage dependencies):

$$\int G_{\text{In}}(S(x,t)) > \int G_{\text{In}}(S(-x,t))$$

for a pre-ganglionic excitatory DS input model, and

$$\int G_{\text{In}}(S(x,t)) < \int G_{\text{In}}(S(-x,t))$$

for a pre-ganglionic inhibitory DS input model, where $(S(x,t))$ is a stimulus moving in the preferred direction. It can be shown (Borg-Graham, in preparation[a]) that under some constraints on the ganglion cell and the experimental protocol, similar relationships are testable even with distributed inputs on dendritic trees and voltage-dependent membrane.

D. *Dynamic Range of Cable Mechanisms: Saturation and DS Reversal*

Real biophysical mechanisms saturate; e.g., a supralinear transfer function will not stay supralinear for unbounded inputs. We now consider possible implications of saturation on the performance of the model.

Saturation of input synaptic conductance onto the cable will not change the basic distinctions between the preferred and null waveforms. Saturation (strictly speaking, a sublinear region) of the output nonlinearity can have quite different effects: For strong enough cable excitation, the null waveform, with its greater temporal support, will eventually yield a final *integrated* output that is equal to the preferred output, despite the larger amplitude of the preferred waveform. Increasing excitation further could cause a *reversal* of the P/N orientation, after the output nonlinearity. This might be observed, for example, with a stimulus contrast that is normally DS, but with inhibition reduced or blocked (e.g., with pharmacological manipulations). Whether DS would be entirely eliminated or reversed would be dependent on circuit and stimulus parameters.

This result is unique to models in which the DS asymmetry includes distributed excitatory input with relative delays along the P/N axis. Such models have been explored theoretically for the interpretation of DS reversal in fly (Ögmen, 1991), and in Section V.B. we show simulations that demonstrate this effect.

V. Simulations of Morphometrically and Biophysically Detailed Amacrine Cell Models

To investigate neuronal properties that are pertinent to the cable model, we have run simulations of amacrine cells. The model parameters are as constrained as possible; morphometry is obtained from histological data in the literature, and membrane properties are either inferred from experimental data and/or supported by theoretical studies of other cells (Borg-Graham, 1987).

An important aspect of these simulations is that dynamic retinotopic stimuli may be used as input to the model circuit. Since the simulator maintains the three-dimensional structure of the cells, it is straightforward to interpret model response to realistic arbitrary stimuli (Borg-Graham, in preparation[b]).

A. *Simulations of Asymmetric Responses from Symmetric Cells*

In Figs. 5 through 7, we show a simulation of an amacrine cell whose morphometry is taken from a rabbit starburst amacrine cell. All membrane and cable properties are uniform, including specific capacitance (C_m), membrane resistivity (R_m), intracellular resistivity (R_i), excitatory synaptic density (G_{ex}), and inhibitory

synaptic density (G_{in}). R_m and R_i are fixed at 100 KΩcm^2 and 200 Ωcm (R_i from Shelton, 1985), respectively. C_m is set to 1.0 μFcm^{-2} (τ_m = 100 mS), G_{in} is set to 100 pS μm^{-2}, and G_{ex} to 1 pS μm^{-2}. The resting potential for the cell is -70 mV. The reversal potentials for the excitatory and inhibitory synapses are 50 and -70 mV, respectively. No voltage-dependent membrane is included.

Synaptic transfer functions are fixed. Excitatory response is given by the half-wave-rectified convolution of the light stimulus by the difference of two alpha functions, $\alpha(t)$,

$$\alpha(t) = \frac{t}{\tau^2} e^{-t/\tau},$$

the first with a τ of 10 mS and the second with a τ of 60 mS. This transient response is typical of retinal ON response to a flashing stimulus. The inhibitory response is the half-wave-rectified convolution of the light stimulus with a single alpha function of unit area and τ = 100 mS. This sustained ON response approximates the time course for inhibition to various stimuli (Amthor and Grzywacz, 1988). Adding an OFF component to the transfer functions does not change

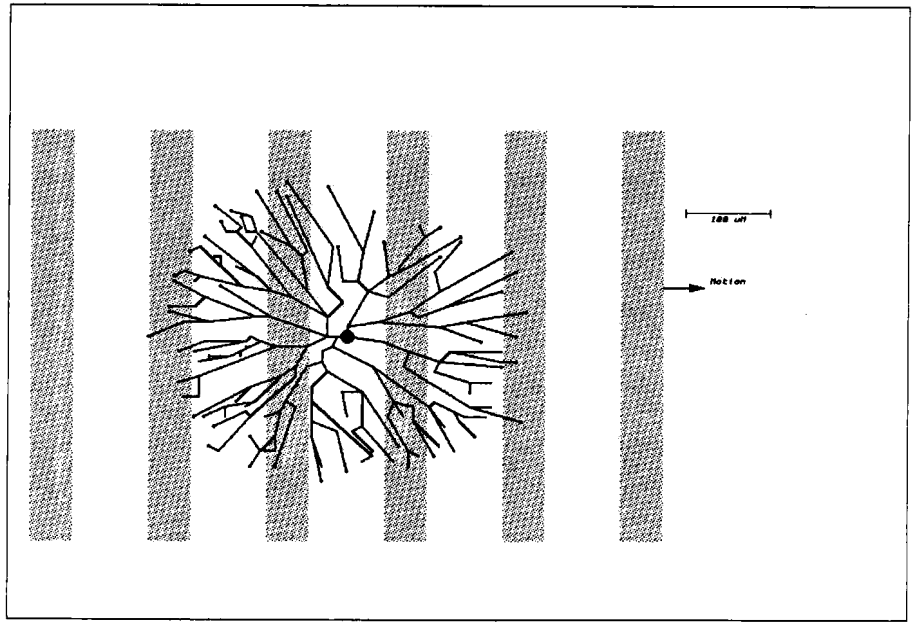

FIGURE 5. Simulations were done of a model cell based on the morphometry of a rabbit starburst amacrine cell, taken from Tauchi and Masland (1984). Shown here is a flat mount view of cell, with snapshots of the trajectory of the stimulus slit. Node 32211 referred to in Fig. 6 is the distal tip farthest to the right.

the motion-dependent behavior. For simplicity, the spatial impulse response for both synapse types is $\delta(x,y)$. Although the receptive field of candidate bipolar or amacrine cell inputs to the DS dendrite is probably on the order of tens to hundreds of micrometers wide, we were interested in an upper bound on the intrinsic spatial discrimination of the DS dendrite structure.

The large value for R_m is consistent with values measured in our lab and others in various neurons using the whole-cell patch technique (Coleman and Miller, 1989). Synaptic conductance densities and kinetics are less constrained as far as the literature is concerned; the range of values we have chosen produce synaptic potentials that are consistent with available data.

In Fig. 6, we show the response of the soma and a distal node to a bar moving across the entire field of the cell. The soma response is almost identical for opposite motions, while the tip response is highly DS. In Fig. 7, we have plotted the integrated response of each dendritic tip of the cell, scaled by stimulus speed, as a function of angle off the soma, for a slit traveling across the entire breadth of the cell. Despite the overall symmetry of the cell, this functional is highly directional.

B. *Parametric Simulations of Cable Mechanisms*

In this section, we present a series of simulations on a simple cell model to illustrate how the different mechanisms in the dendrite cable interact. The basic structure is a one-dimensional symmetrical cell with two opposing unbranched processes (Fig. 8). Cell membrane and synaptic parameters are identical to the simulated cell in Fig. 5, except as follows: We shall vary C_m (1.0 and 1.0^{-5} μFcm^{-2}, or τ_m = 100 mS and 0.001 mS),* and G_{in} (100, 10, 1, 0.1, and 0 pS μm^{-2}). The goal here is to see how directionality depends on the inhibitory input versus the intrinsic cable properties.

As before, the stimulus is a moving slit, 50 μm wide, now with velocities of 0.5, 1, 2, 4, 8, and 16 μm/msec. The response waveforms from the right-hand distal tip for rightward and leftward motion will be compared. In particular, we shall compute a directional index (*DI*) (after Grzywacz and Koch, 1987) for both the linear integral of the waveforms and the integral of the waveforms after being passed through a sigmoidal nonlinearity (representing synaptic transmission):

*A cm of 0 μF_{cm}^{-2} was not possible due to the integration technique of the simulator.

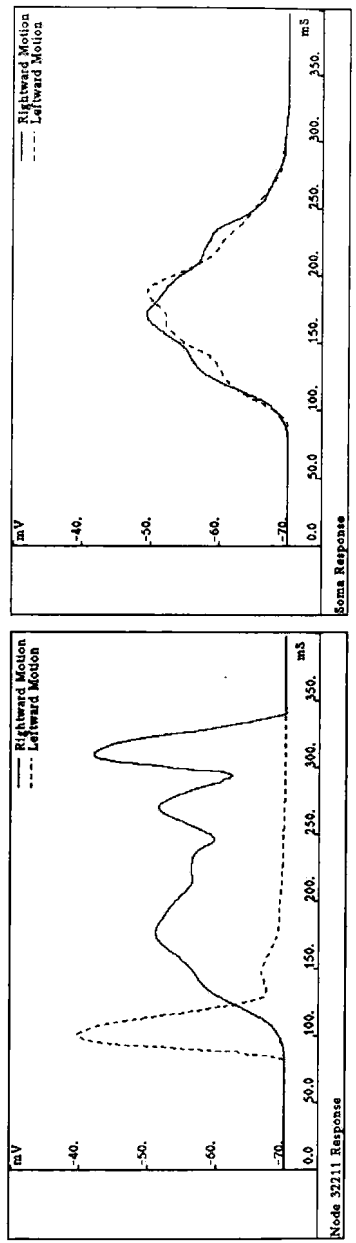

FIGURE 6. Responses of cell in Fig. 5 to 50 μm slit moving from left to right and back again at 2 μm/msec. The voltage at the rightmost distal tip in Fig. 5 (Node 32211) is highly DS, whereas the soma response is barely DD. Model parameters are given in the text. Simulations also show that inclusion of a K^+ conductance that inactivates with depolarization can both facilitate the preferred-direction response and attenuate the null-direction response. (See Section III.E.)

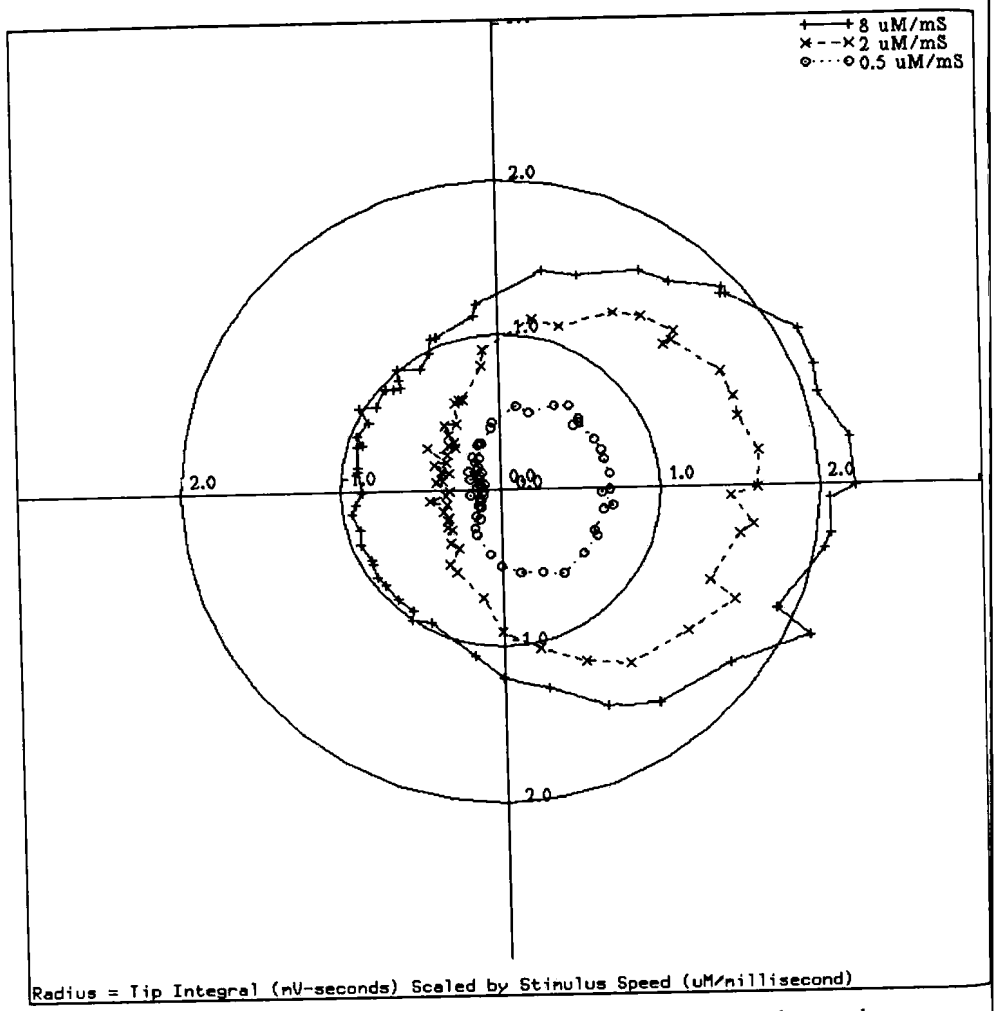

FIGURE 7. Polar plot of integral of distal tip voltages scaled by the stimulus speed versus angle of tip with respect to the soma, relative to the slit trajectory shown in Fig. 5. Slit speeds include 0.5, 2, and 8 μm/msec. Despite the overall symmetry of the cell, the tip outputs respond asymmetrically to motion.

$$DI = \frac{\int f(V_P) - \int f(V_N)}{\int f(V_P) + \int f(V_N)}$$

$DI = -1$	$DI = 0$	$DI = 1$
Strongly Selective for Motions Away from the Tip	No Directionality	Strongly Selective for Motions Towards the Tip

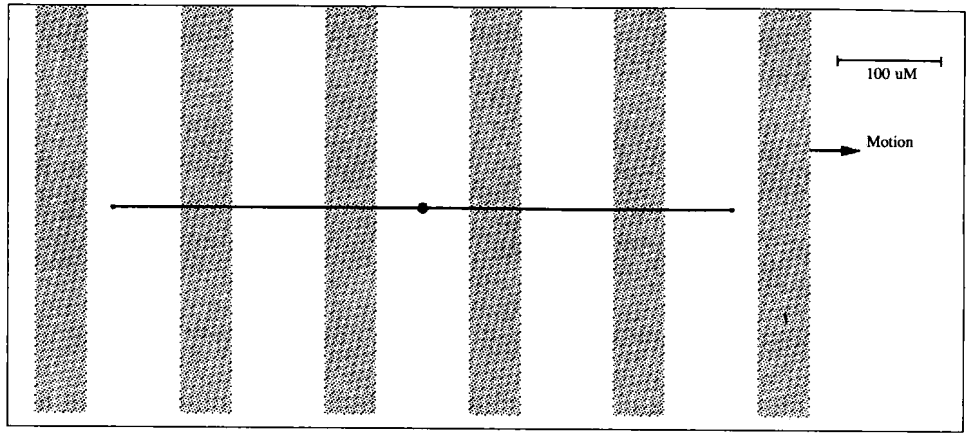

FIGURE 8. Model cell with two opposing dendrites whose diameters taper linearly from 1.0 to 0.2 μm (proximal to distal). The output used in the later figures is from the right-hand distal tip.

where $f()$ is either the identity ($\Rightarrow DI$(Average)), or the sigmoidal nonlinearity shown in Fig. 11 ($\Rightarrow DI$(Sigmoid Average)). V_P is the voltage waveform for the distal tip for light moving toward the tip, and V_N is the waveform for the opposite direction.

As shown in Fig. 10 and 11, the *normal* directionality of the tip outputs ($DI > 0$) is strongly dependent on the presence of inhibition. However, if a nonlinear functional is applied to the tip waveform, the distributed nature of the cable *without* inhibition generates a directional response, although it is much weaker than the control case. In addition, the particular nonlinearity in Fig. 11 causes a DI reversal. As illustrated in Figs. 9 and 11, the ability of a nonlinear integrator to make this distinction depends on the delay provided by the cable capacitance. This prediction is consistent with the experimental results cited earlier.

VI. Intracellular DS Recordings with Local Block of Inhibition

We now present recent data from turtle retina that address some of the model predictions.

Interpretation of the ganglion cell membrane potentials may be complicated by inhibitory input onto the cell that might not have a direct link to the directional properties. For this reason, we have recorded from ganglion cells in the intact isolated turtle retina (Borg-Graham and Grzywacz, 1990), using whole-cell patch

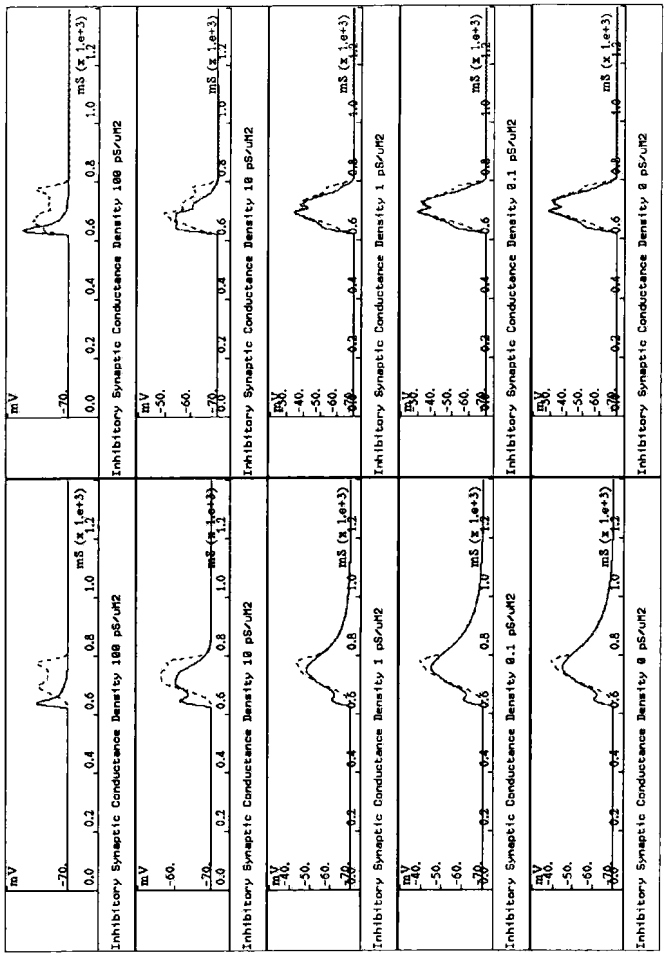

FIGURE 9. Example set of simulations for cell in Fig. 8 for a stimulus moving at 4 μm/msec at various values for G_{in} and C_m. On the left, C_m = 1.0 μFcm^{-2}, and on the right, C_m = 1.0^{-5} μFcm^{-2}. Tip output is from the right-hand distal tip in Fig. 8, and the solid and dashed waveforms are for leftward and rightward motion, respectively. When inhibition is absent (bottom simulations), the cable capacitance distorts the equal area waveforms so that a nonlinear integrator may distinguish them (bottom left). If the nonlinearity saturates, then the *fatter* leftward response yields a larger total output than the higher amplitude rightward response (DS reversal). With no inhibition and very low capacitance (bottom right), the waveforms become mirror-symmetric.

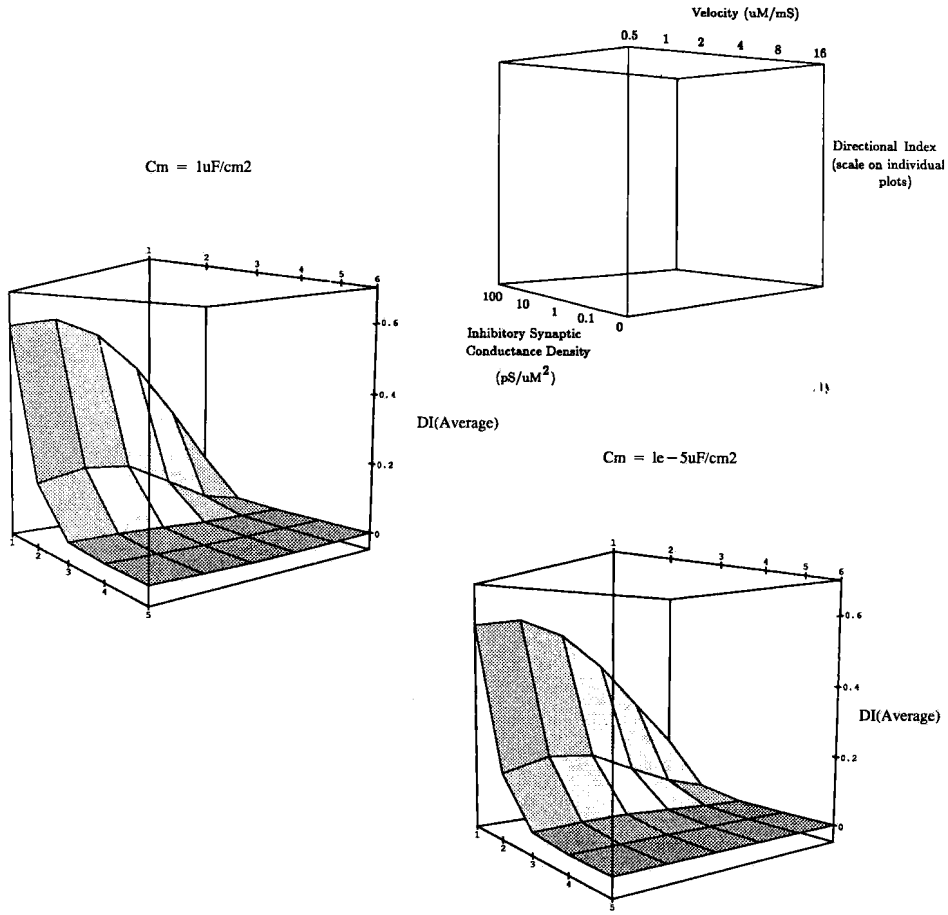

FIGURE 10. *DI* for the linear average of distal tip waveforms obtained from simulations of cell in Fig. 8, over a range of inhibitory synaptic conductance densities and stimulus velocities, for C_m = 1.0 μFcm^{-2} (middle left) and 10^{-5} μFcm^{-2} (lower right). Axes are shown in the upper right. For this linear functional, DS is eliminated as inhibition is lowered, independent of C_m. Furthermore, cable capacitance does not seem to have a significant effect on DS when inhibition is present.

electrodes in which the electrode solution is free of ATP and Mg^{2+}. Given the large bore of the electrode (1–2 μm), it is likely that the cell contents are dialyzed by the electrode solution within several minutes after the start of recording. It has been reported in hippocampus that such conditions block the response of $GABA_A$ receptors (Stelzer *et al.*, 1988); thus, this technique offers a method for selectively blocking an inhibitory component of the synaptic input to the cell being recorded from, without disturbing the rest of the network.

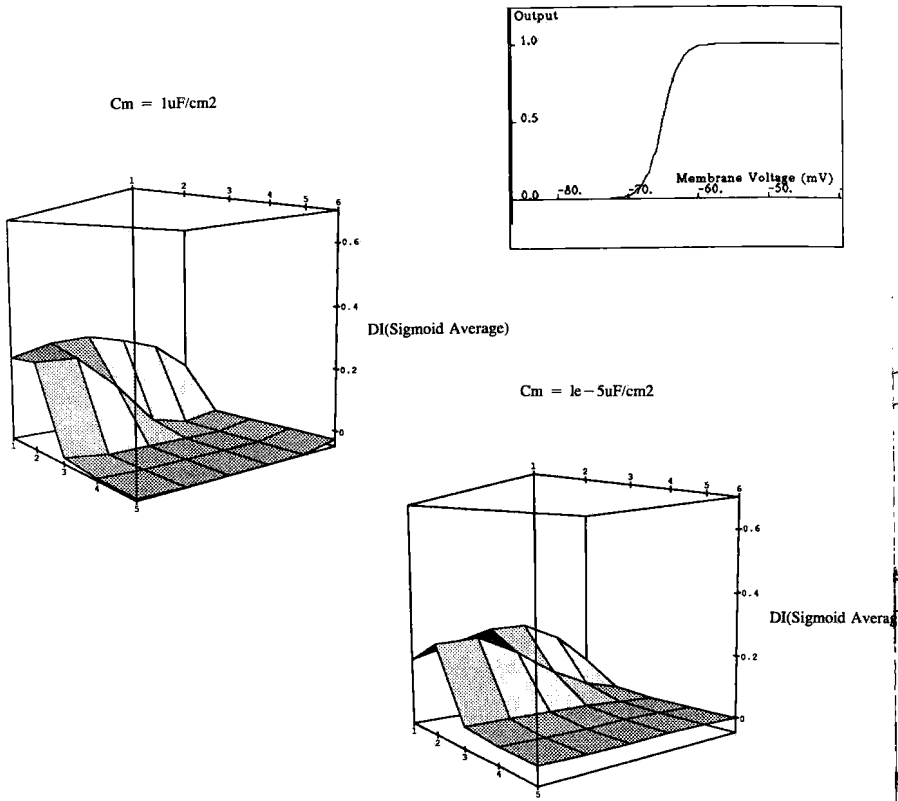

FIGURE 11. *DI* for the same simulations as in Fig. 10, but taken of the average of distal tip waveforms after being passed through the sigmoid shown in upper right. With normal C_m (middle left), the directionality *reverses* ($DI < 0$) as inhibition is lowered. When C_m and inhibition are both small (lower right), this reversal is dramatically reduced. Axes are as in Fig. 10.

With this technique, ganglion cells show clear light-evoked IPSPs and EPSPs at normal resting potential at the onset of the recording. Within, typically, 10 minutes of recording, light-evoked IPSPs disappear while EPSPs are maintained, suggesting the block described previously. Removal of direct inhibitory input to these cells was verified by depolarizing the cells: Negative synaptic potentials were not observed despite large depolarizations (30 mV above the resting potential). Hyperpolarizing potentials were observed, however, in conjunction with action potentials, suggesting preservation of voltage-dependent hyperpolarizing mechanisms.

In some of these cells, we observe clear directional responses (Fig. 12 and 13), despite the lack of significant inhibitory input onto the ganglion cell. P/N

distinctions were stable with respect to both hyperpolarizing and depolarizing current. These results suggest that some turtle ganglion cells receive excitatory input that is already DS (Borg-Graham and Grzywacz, 1991).

VII. Development of DS: The Problem of Coordination of Asymmetries

A problem for any model of DS is how to break symmetry on a scale significantly larger than that predicted by random distributions of local asymmetries. In the retina, the DS response is correlated over multiple subunits, and several directions

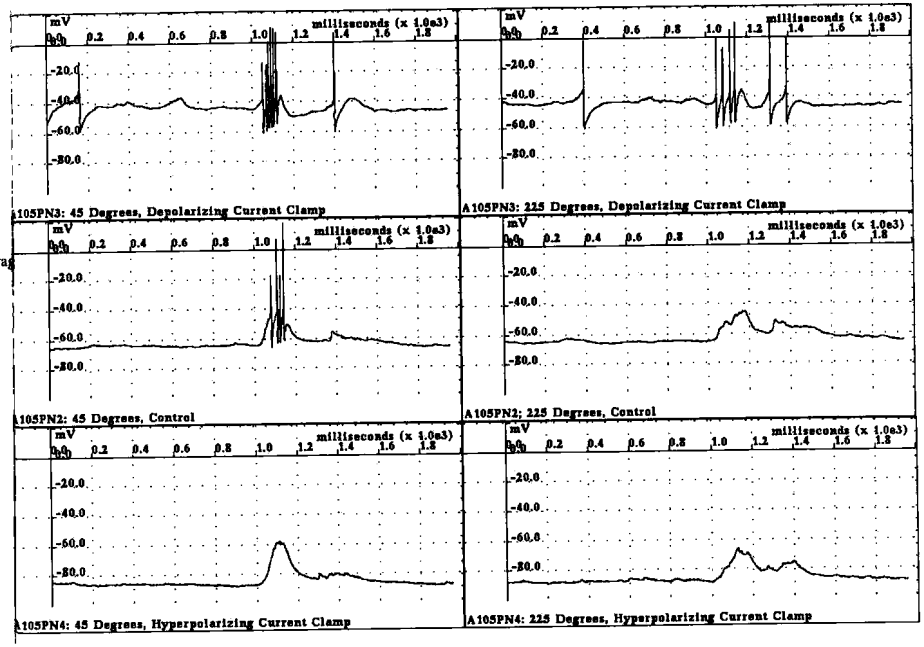

FIGURE 12. DS intracellular (whole-cell patch) data from an on/off ganglion cell (A105) in isolated intact turtle retina. The response to motion at a 45° orientation (in terms of either the number of spikes or the size of the EPSP) is larger than that for the opposite (225°) orientation, independent of the holding current. IPSPs are not observed, even with depolarizing current, suggesting that the DS response does not require inhibitory input to the recorded cell.

Stimulus is 200 μm square spot, moving at 4 μm/ms, with a path length of 1200 μm. Spot motion is timed so that the spot passes over the receptive field center at 1000 ms for both orientations. The receptive field, mapped with a stationary flashing spot, is approximately 500 μm in diameter. Whole-cell electrode solution lacks ATP and Mg^{++}, which contributes to the attenuation of IPSPs.

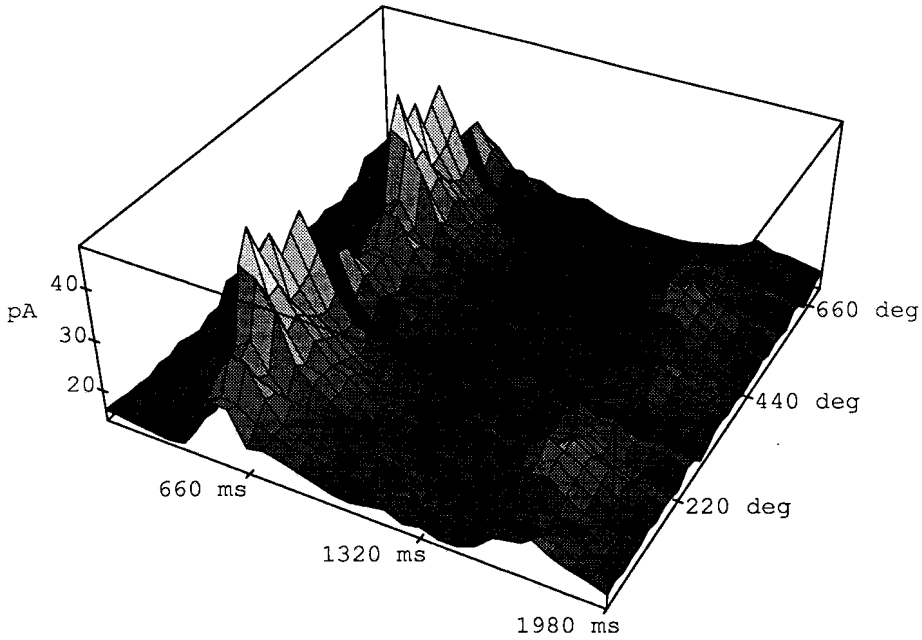

FIGURE 13. DS voltage clamp data from an ON ganglion cell (A56) in turtle, under the same experimental conditions as Fig. 12. Stimulus is 1 hz grating with a spatial period of 800 μm and a 100 μm square aperture, centered on the spot-mapped receptive field. Grating is presented at 16 orientations (22.5° steps), 1980 ms per orientation. There are 2 averaged trials per orientation, and in this plot the 16 clamp current waveforms are repeated in order to show more clearly the directional selectivity. Holding potential is −80mV, and the clamp current is low pass filtered (f_c = 20 hz) and inverted, so that a positive output represents an inward (or excitatory) current. For all orientations, the stimulus phase was adjusted so that an ON edge appeared at the side of the dark aperture at 0 ms. Extracellular (ON cell patch) recordings of this cell with similar stimuli prior to whole-cell access showed a DS response with a preferred direction of 135°. The strong directionality of the voltage clamp inward current (best at 157.5°) and the low holding potential suggest that the excitatory input to this cell is already DS.

are represented. For the model presented here, this translates into determining how a ganglion cell could selectively connect to amacrine dendrite tips of similar orientation. One solution that seems natural for this model is to postulate a Hebbian correlational process (Hebb, 1949) similar to long-term potentiation in the hippocampus. (See review by Brown *et al.*, 1990). A Hebbian type process strengthens active synapses when the pre- and postsynaptic cells fire simultaneously and may weaken synapses when activity is not correlated.

The initial symmetry in the retina may then be broken as follows: Assume that at an early stage of synaptogenesis, initial DS amacrine connections to a proto-DS ganglion cell have a range of orientations, but overall there is a slight orientation bias. If this bias is strong enough, then a Hebbian mechanism could reinforce it. The connectivity of subsequent synapses would then become stronger or weaker depending on their dendrite's alignment relative to the initial (weak) orientation.

A Hebbian mechanism, at least in this simple form, is suited for a preganglionic DS model because the mechanism requires signals that can be correlated; the postsynaptic cell tends to collect correlatable inputs. Ganglionic computation of DS loses this advantage, since there is no motion asymmetry intrinsic in the ganglion cell afferents.

VIII. Retinal Directional Selectivity: Exemplar of a Canonical Computational Mechanism?

Thus far, we have discussed the directional properties that may arise intrinsically whenever dendrites have distributed excitatory and inhibitory input, at least in terms of the waveforms at the dendrite end. The key to this property is the asymmetric distribution of the inputs with respect to the output, and we have demonstrated how this sort of asymmetry may be especially effective when the output synapse is on the dendrite tip. Since in retina the salient stimuli features are retinotopic, it is very important to consider the exact geometry of the amacrine cells' dendritic trees.

However, in the more general case, we may consider the cascade of inputs along a dendritic branch of a generic central neuron. The performance of the retinal DS model suggests that a similar directionality will exist under some conditions for non-retinal neurons, with respect to the afferents along each branch. We suggest that with plausible biophysical parameters, the soma of a more general cell, which is asymmetric with respect to each dendritic branch, will see a *directional* response from its branch inputs. Specifically (at least with the version of the model discussed here), for a given set of inputs over time along a branch, the soma EPSP will be greatest when the temporal order of the inputs is from distal to proximal, i.e., stepping in time toward the soma. Conversely, the same set of inputs, only reversed in time, may be much less effective in depolarizing the soma.

As with retinal DS, the net result would be that the dendritic branch functions as more than just a time–independent integrator of inputs. Rather, the branch functions as a nonlinear *spatio*–temporal filter.

IX. Conclusions

In summary, we have presented a model for directional selectivity in retina whose anatomical structure and simulated performance is consistent with the data. The crucial elements for directionality are as follows:

- Asymmetric input-to-output distribution on the DS dendrite.
- Intracellular resistivity of the dendrite cable allowing on-the-path interactions that depend on stimulus direction.
- Inhibitory nonlinear shunting of sufficient duration to mask subsequent proximal excitation of the distal tip output.

Further, we have showed that other cable mechanisms may generate testable predictions unique to this model.

Acknowledgments

We would like to acknowledge Prof. Tomaso Poggio for his initial suggestion to investigate this problem, and his continuing support of this work. We also thank Randy Smith, John Wyatt, John Lisman and Frank Amthor for their comments.

This chapter describes research done within the Center for Biological Information Processing in the Department of Brain and Cognitive Sciences and at the Smith-Kettlewell Eye Research Institute. This research is sponsored by the grant, EY08921-01A1, from the National Eye Institute; by the grant, BNS-8809528, from the National Science Foundation; a grant from the Office of Naval Research, Cognitive and Neural Sciences Division; the Alfred P. Sloan Foundation; and a grant from the National Science Foundation under contract IRI-8719394. Tomaso Poggio is supported by the Uncas and Helen Whitaker Chair at the Massachusetts Institute of Technology, Whitaker College.

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