Simulation of an anatomic ally defined local circuit: The cone-horizontal cell network in cat retina

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Abstract

The outer plexiform layer of the retina contains a neural circuit in which cone synaptic terminals are electrically coupled and feed back through a GABAergic synapse to cones. In cat this circuit's structure is known in some detail, and much of the chemical architecture and neural responses are also known, yet there have been no attempts to synthesize this knowledge. We constructed a large-scale compartmental model (up to 50,000 compartments) to incorporate the known anatomical and physiological facts. The goal was to discover how the various circuit components interact to form the cone receptive field, and thereby what possible function is implied. The simulation reproduced many features known from intracellular recordings: (1) linear response of cone and horizontal cell to intensity, (2) some aspects of temporal responses of cone and horizontal cell, (3) broad receptive field of the wide-field horizontal cell, and (4) outer-surround cone receptive field (derived from a "decorrelation model"). With the network calibrated in this manner, we determined which of its features are necessary to give the cone receptive field a Gaussian center-surround shape. A Gaussian-like center that matches the center derived from the ganglion cell requires both optical 'blur' and cone coupling: blue alone is too narrow, coupling alone gives an exponential shape without a central dome-shaped peak. A Gaussian-like surround requires both types of horizontal cell, the narrow-field type for the deep, proximal region and the wide-field type for the shallow, distal region. These results suggest that the function of the cone-horizontal cell circuit is to reduce the influence of noise by spatio-temporally filtering the cone signal before it passes through the first chemical synapse on the pathway to the brain.

Keywords: Retina, Receptive field, Feedback, Computer simulation, Compartmental model

Introduction

As a visual signal travels from a cone outer segment to the brain, it passes through a complex circuit intrinsic to the outer retina. The hub of this circuit is the cone axon terminal ("pedicle"), and its basic plan is strikingly similar across vertebrate species (Lazansky, 1973, 1977; Kolb, 1970, 1975). After traversing the neural circuit, the visual signal is transmitted through a chemical synapse, which, due to biological constraints, limits the signal's range by adding distortion and noise (Laughlin et al., 1983). It has been postulated that the cone pedicle circuit filters the signal to reduce its dynamic range, lessening the effect of these limitations (Artwell, 1986). Since the filter provides inputs to the rest of the visual system, how and why it transforms signals is of considerable interest. In mammals and some other vertebrates the cone pedicle forms electrical synapses with its neighbors (Kolb, 1977; Revelo & Gillo, 1975, Smith et al., 1986), and chemical synapses with generally two types of horizontal cell, known in cat and rabbit as HA and HB (Fig. 1; Fisher & Boycott, 1974; Kolb, 1974; Boycott et al., 1978; but see Peichl & González-Soriano, 1994). HA and HB cells differ by a factor of 2 in dendritic-field width and number of cone contacts (Wassle et al., 1978). Both are coupled electrically to neighbors of their own type, though to different extents (Kolb, 1977; Vaney, 1991, 1993), and both types are GABAergic (Chew & Wässle, 1980; Sarthy & Fu, 1989; Vardi et al., 1994). In salamander, fish, and turtle the evidence for negative feedback onto the pedicle is direct, from intracellular recordings (Artwell et al., 1983; Baylor et al., 1971; Tachibana & Kano, 1984; Mozakami et al., 1982; Piccolino et al., 1981; Skrzypek & Werblin, 1983; Werblin, 1974; Wu, 1991; but see Lazansky, 1981; Burkhart, 1993). The feedback is mediated through chloride (Tachibana & Kano, 1984; Artwell et al., 1987; Wu, 1991). In mammals, the evidence is indirect and includes the demonstrations that depolarizing a horizontal cell antagonizes the light response of both on- and off-center ganglion cells (Mangel, 1991) and that oscillations at 40-50 Hz can be elic-
Fig. 1. A: Cone array in cat retina superficial, 1 μm section stained with toluidine blue near 1-deg eccentricity, showing regular pattern of cone spacing. Density ~24,000/m2. Neuronal circles represent diameter (1/10 peak) of Gaussian approximations to optical and receptive-field components. Point-spread function of cat's optics (PSF) includes about ten cones. Receptive-field center of one cone (RFC) includes about 50 cones, and receptive-field surround (RFS) includes about 1200 cones. B: A parasagittal view of cat horizontal cell arrays near 1-deg eccentricity stained with antibody to calbindin. Strongly stained cells (lightest gray) are type A, plex cells are type B. Gray scale of both images is inverted the black background represents no stain. Tissue prepared by S. Kimura and photographed by P. Arshavsky.

In the horizontal cell that almost certainly arise from feed-back from the GABA-R and GABA, (1981).

Thus, the circuit looks like a spatial bandpass filter (Fig. 2): cone coupling would remove high spatial frequencies and horizontal cell feedback would remove lower spatial frequencies. An estimate of the cone center-surround profile derived from photoreceptor measurements suggests that the cone surround should be weak (Smith & Stirling, 1969). However, less detailed measurements have been made of the spatiotemporal properties of the cone receptive field in mammals. Records by Nelson (1977) from the cat cone in vitro suggest, as might be expected from electrical coupling, a rather broad spatial repetition, consistent with evidence from lower vertebrates (Bayley et al., 1971; Detwiler & Hodgkin, 1979; Kraft & Burkhardt, 1986; Normann et al., 1984; Actaw & Berman, 1984). The inhibitory cone surround that would be expected from GABAergic feedback, observed in lower vertebrates, was not observed in cat. But the records were not of ideal quality and have never been repeated.

What remains unclear is how the individual components of this circuit interact and why they are necessary. For example, the cone's receptive-field center is probably shaped by optical blur and cone coupling, but what are their respective contributions? Similarly, the cone's receptive-field surround is probably shaped by both wide-field and narrow-field cells, but why the two types? Such questions are not easily addressed by direct experiment. Where recording is easiest (lower vertebrates), neither the natural optics nor the overall structure of the circuit have been quantified. Where the optics and the circuit structure have been quantified (mammals), the physiological descriptions are incomplete. Even if all the information were available for a given species regarding optics, connections, and receptive fields, a dynamic model would be required to establish the key interactions.

We report here a biophysically based computer simulation of the circuit underlying the cone receptive field in the cat outer plexiform layer, starting with an "approximate correct" model incorporating basic facts such as the known optics, density of the three neuronal types, and their synaptic connect-
Each cone was coupled to its nearest eight neighbors (Smith et al., 1986). The cone array was square with a lateral extent of between 40 to 80 cones (240 to 480 µm).

### Horizontal cell model

Horizontal cells were given a square dendritic field. A separate dendrite connected the soma or each cone within the dendritic field, and all dendrites were given equal electronic length. Type A horizontal cells (HA) received input from 196 cones, whereas type B cells (HB) received input from 106 cones (Wässle et al., 1979a; Fig. 3). Leakage resistance was set to 20,000 Ohm-cm², and membrane capacitance (for cones as well) was set to 1 µF/cm². The product of this capacitance and total conductance (membrane leakage and tonic synaptic input) gave a time constant of about 15 ms (see Wässle & Copenhagen, 1988). Two arrays of horizontal cells were connected with the appropriate cell spacing to give cone coverage factors appropriate for the central cat eye (covFactr: A = 4, B = 6; Wässle et al., 1979).

Horizontal cells were coupled into synaptic arrays by gap junctions. HA cells were given relatively strong coupling conductances (100 nS), e.g., 1000 nS between horizontal cells to simulate the gap junctions (Kolb, 1977). HB cells were given weak coupling (30 nS). Our reasoning was that biochemically injected decorrelates synaptic conductances between HB cells but Lucifer Yellow does not (Vaney, 1991, 1993), and that gap junctions are not observed between HB cells by inspection at the EM level (Kolb, 1977).

### Synaptic model

A synaptic was represented by a conductance in series with a voltage source. The conductance was modulated by a function of voltage in the presynaptic terminal (Smith, 1992), based on the model of Bengtson and Copenhagen (1988) after Fark and Fatt (1972). The synaptic transfer function was sigmoidal, defined by parameters for threshold, slope, and saturation characteristics (Fig. 4, Table 1). Synaptic threshold was defined as the presynaptic voltage that produced a postsynaptic conductance of 2.5% of maximum. The function also included a temporal low-pass filter described by its time constant. The low-pass filters were disabled for the first 20 ms of the simulation to allow the feedback network to stabilize more quickly.

### Synaptic connections

Each cone in the simulation provided synaptic input to all horizontal cells whose dendrites extended to it (Wässle et al., 1979a). Synaptic weight (representing multiple anatomical contacts between cone and horizontal cell, see Kolb, 1974) was set to unity. Since the ratio of HB:HA coverage is about 3:2, the HB array gave stronger feedback to cones than the HA. Neuroromitted, released by cones was excitatory (depolarizing) with a postsynaptic reversal potential in the horizontal cell of -10 mV (Atwill et al., 1987). Synaptic threshold was set to -45 mV (cones) and -50 mV (horizontal cells), suggested by the activation voltage range for calcium channels (Atwill, 1986; see Table 1). Synaptic conductance was set at 200 pS/synapse, which produced a total feedback conductance of 1 nS, roughly the same as the light-modulated conductance in a cone outer segment (Eichler et al., 1990). Feedback reversal potential (i.e.,...
driving potential for the GABA channel in the cone pedicle) was set near ~65 mV (Attwell et al., 1983; Stryker & Werblin, 1983; but see Borkhardt, 1993). The requirement that the network should not oscillate constrained many combinations of synaptic gain, conductance, and membrane conductance (see below).

**Edg effect**

Initial simulations revealed both static and dynamic "edge" effects in the responses recorded from initial simulations, e.g., cones near the edge of the array were depolarized at rest from those in the center (Fig. 5). Such edge effects were due to mas-
Fig. 4. Synaptic transfer function used in simulation to relate presynaptic to postsynaptic conductance. An exponential relation function of the form Tw = exp(8) · V(Theta) has produced varying gains when supplied with different values for "exp(8)" (different traces). Note that all curves cross at the threshold of ~5 mV, the point at which the conductance is 2.5%. The released transmitter (Twr) was applied to a Michaelis-Menten saturation function, Twr = Twr (1 - Twr11), to produce the overall S-shaped function. Solid line shows that a presynaptic voltage of approximately ~77 mV relates on the "exon 2" plot to a normalized postsynaptic conductance of 0.5, the point at which the synaptic gain curve is most linear.

Table 1. Standard parameters for simulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light-modulated conductance</td>
<td>1.4 nS, -8 mV driving force</td>
</tr>
<tr>
<td>Retinal cell</td>
<td>20,000 Ohm-cm²</td>
</tr>
<tr>
<td>Bipolar cell</td>
<td>200 Ohm-cm (Sprurton &amp; Johnston, 1992)</td>
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<tr>
<td>Amplitude conductance</td>
<td>1 µF/cm²</td>
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<tr>
<td>Gap junction conductance</td>
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<tr>
<td>Coefficient from H2 cells</td>
<td>100 nS</td>
</tr>
<tr>
<td>Feedforward synapses</td>
<td>1 mV/Hz/cell</td>
</tr>
<tr>
<td>Neuron/retina action</td>
<td>Depolarizing</td>
</tr>
<tr>
<td>Gain parameter</td>
<td>2 mV/ν-fold increase</td>
</tr>
<tr>
<td>Threshold</td>
<td>~45 mV</td>
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<tr>
<td>Reversal potential</td>
<td>~10 mV</td>
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<tr>
<td>Time constant</td>
<td>0.4 ms</td>
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<tr>
<td>Conductance</td>
<td>100 pS</td>
</tr>
<tr>
<td>Morphology</td>
<td>Sphere, diameter 16 µm</td>
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<tr>
<td>Orientation</td>
<td>Length 30 µm, diameter 1.5 µm</td>
</tr>
<tr>
<td>Axon</td>
<td>Sphere, diameter 5 µm</td>
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<tr>
<td>Pedicle</td>
<td>Number of horizontal cell synapses</td>
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<td>Coverage factor, HA</td>
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</tr>
<tr>
<td>Coverage factor, HB</td>
<td>6</td>
</tr>
<tr>
<td>Topology</td>
<td>Core array size</td>
</tr>
<tr>
<td>Core spacing</td>
<td>60 x 60, square</td>
</tr>
<tr>
<td>Horizontal cells</td>
<td>20,000 Ohm-cm²</td>
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<tr>
<td>Retinal cell</td>
<td>200 Ohm-cm (Sprurton &amp; Johnston, 1992)</td>
</tr>
<tr>
<td>Bipolar cell</td>
<td>1 µF/cm²</td>
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<tr>
<td>HA gap junction conductance</td>
<td>100 nS</td>
</tr>
<tr>
<td>HB gap junction conductance</td>
<td>5 nS</td>
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<tr>
<td>Conductance from cone synapse</td>
<td>200 pS/spine</td>
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<tr>
<td>Feedback synapses</td>
<td>Hyperpolarizing</td>
</tr>
<tr>
<td>Neuron/retina action</td>
<td>Gain parameter, HA</td>
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<tr>
<td>Gain parameter, HB</td>
<td>2 mV/ν-fold increase</td>
</tr>
<tr>
<td>Hyperpolarizing</td>
<td>2 mV/ν-fold increase</td>
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<td>Rectification potential</td>
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<td>Time constant</td>
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<tr>
<td>Conductance</td>
<td>200 pS</td>
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<tr>
<td>Morphology</td>
<td>84 µm, square</td>
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<tr>
<td>Size of HA dendritic tree</td>
<td>60 µm, square</td>
</tr>
<tr>
<td>Size of HB dendritic tree</td>
<td>Size of HA dendritic tree</td>
</tr>
<tr>
<td>Stimulated H2 cells contain all cones within dendritic field.</td>
<td>Number of cones contacted, HA</td>
</tr>
<tr>
<td>Number of cones contacted, HB</td>
<td>196</td>
</tr>
<tr>
<td>Topology</td>
<td>Coverage factor, HA</td>
</tr>
<tr>
<td>Coverage factor, HB</td>
<td>6</td>
</tr>
<tr>
<td>Stimulus</td>
<td>Latent spot, convolved with 22 µm</td>
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<tr>
<td>(diameter at 1/∞ Gaussian point-</td>
<td></td>
</tr>
<tr>
<td>spread function.</td>
<td>spread function.</td>
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</table>
Receptive-field measurements

A receptive field is normally mapped in vivo by recording the response of a neuron to a stimulus moved across space. However, to compute a simulated receptive field in this manner would be extremely costly in computation time. Instead, we centered the stimulus on the network and recorded simultaneously the responses of many cones and horizontal cells across a radius of the network. A plot of peak responses of these cells plotted against their spatial locations was equivalent to the receptive field of one cell. Thus, receptive fields of all three cell types were measured simultaneously from the response to a single flash (see Fig. 8). Since the stimulus in most cases was a radially symmetric spot, the receptive field had approximate radial symmetry and could be described in the form of a Bessel function of radius. However, since a Bessel function approaches the corresponding one-dimensional exponential (function measured with an extended bar) as radius increases, we informally describe slowly decaying receptive-field profiles as "exponential" in form to differentiate them from the quickly decaying "Gaussian" form (see Results).

Tuning the network parameters

After initial calibration, the network parameters were adjusted to give a cone receptive field that approximated in amplitude and spatial extent a difference-of-Gaussians template derived from the convolution model (Fig. 7a; see Smith & Stirling, 1990). Although the network when tuned in this manner reasonably matched the template, there were several degrees of freedom: membrane resistance, coupling conductances, synaptic conductance, gain, and threshold. Within this parameter space many tradeoffs were possible. For example, the effect on the normalized cone receptive field of small increases in feedback gain were equivalent to decreases in cone coupling (Fig. 7c). Since there was no way to decide which particular combination was biologically correct, we amplified comparisons by settling on a set of parameters that matched ganglion cell physiology as a standard "central set" (Table 1). Our goal was to assess which parameters are both sufficient and necessary to generate a difference-of-Gaussians cone receptive field.

In most cases parameters were constrained, sometimes in several ways, by biophysical limits or by the function of the circuit. Several important constraints were that:

1. The resting potentials should be appropriate, for example, within the range of -10 to -70 mV.
2. The network should not oscillate. This limited overall voltage gain for the loop to less than 1. This relation limited feedback gain to the inverse of feedback gain:
3. Feedforward gain (i.e. the ratio of cone to horizontal cell responses) was constrained to be in the range of 1-2 with full-field flash (Beltgen & Cynader, 1988).

4. The ratio of synaptic to membrane conductance in the horizontal cell contributes to feedforward gain, and the range of these conductances was limited by biophysical assumptions. Input resistance of a cone affected feedback gain and input resistance varied with membrane properties and degree of electrical coupling in the cone network.
5. The cone synapse should operate around the midpoint of its input/output function. This is necessary for the cone to impact equal gain to signals greater than and less than the mean level.

Results

Summary of simulation
We selected for simulation a square array of 60 x 60 cones which was large enough to capture the function of cone center and surround without much edge effect (see Methods). The light stimulus was usually a small spot, presented to the center of the array through a convolution filter that simulated optical blur (see Fig. 3). The simulation included arrays of horizontal cells (7 x 7 type A, 15 x 15 type B: Fig. 3) and were interconnected with the cone array by reciprocal synapses. Reciprocal fields were measured by recording from multiple sites in each array the responses to a single light flash.

Reversing potentials
As an isolated neuron, the cone sits at a dark potential of about -20 mV, and the horizontal cell sits near -70 mV. When the complete network is turned on, their synaptic interactions within 20 ms of “neural” time produce a stable cone potential of -37 mV and horizontal cell potentials of -45 mV (Fig. 5). Reversing potentials of cones and both types of horizontal cells are uniform (to 0 mV) across the network except near the edge. As noted in Methods, the network includes compensatory feed-back onto the cones near the edge, but this method left vestiges of depolarization in the cones and Hb cells near the edge.

Reversing potentials were affected by several parameters including synaptic threshold, synaptic gain, synaptic conductance, and membrane resistance. For most of these combinations, the cone array rested between -44 and -55 mV, and horizontal cells between -50 and -30 mV, consistent with published records (Foerster et al., 1977; Steinberger, 1969). With high values of synaptic gain and/or input resistance (see Methods), reversing potentials were unstable (i.e., they oscillated).

Light responses
When a small spot of light (5 μm diameter, but with blur added) is flashed (1 ms) at the center of the cone array, the cones and horizontal cells hyperpolarize, the response peaking at 60 ms (Fig. 5). The peak responses vary across the cone array, and there were used to plot receptive fields. Responses across the HA array are low in amplitude and essentially uniform, but across the HB array they are larger and nonuniform. This suggests an important difference between the two types that we explored further with stronger stimuli.

A large spot covering the full dendritic field of the central horizontal cells (Figs. 1a and 1b) evokes in all three cell types a marked transient plus sustained hyperpolarization with a modulated poststimulus depolarization. This pattern resembles recordings from mammalian horizontal cells (Steinberg, 1969; Nelson, 1977; van de Grind & Grünser, 1981; Lankheter et al., 1990; Bloomfield & Miller, 1982; Daubech & Ravizza, 1982).

A plot of response vs. intensity from the network shows the response of an HB cell is greater than either the cone or HA to a spot that matches the HB receptive-field extent (Fig. 6). Simulated light responses showed a “S” shape typical of published responses (Nelson, 1977; Bloomfield & Miller, 1982; Lankheter et al., 1991) except that the range of linear response in the simulated network was narrower. This difference may be related to the fact that the transduction element of the simulated cone, although designed to produce a realistic response to different intensity flashes (Smith, 1992), did not possess “photosensitive adaptation” that is thought to occur in the outer segments of cones (Tranchina et al., 1991).

Receptive fields
The cone receptive field mapped from the standard network has a relatively broad, Gaussian-like center whose space constant (≈25 μm) is more than twice the diameter of the optical event spread function (Figs. 7, 8, and 11). The receptive field also has a Gaussian-like surround. The convolution of 37 such receptive fields appropriately matches the beta-gamma-cell center and surround Gaussian (Fig. 7b) except that the surround produced is somewhat lower in amplitude. This is consistent with evidence of additional sources of lateral inhibition on the pathway to ganglion cells, including GABA input to the bipolar dendrites (Vardi & Sclarberg, 1994), bipolar axons (Poucho & Owczarek, 1989; Suzuki et al., 1990; Yeh et al., 1990), and ganglion cell (Freed, 1992). When mapped with a bar, the receptive-field surround appears twice the center diameter is almost unchanged (Fig. 7b). This is consistent with actual receptive fields of ganglion cells plotted with narrow bars (Cleland et al., 1975; see Smith & Sclarberg, 1990).

In one sense, that relatively broad, center-surround cone receptive field is not a true “result” because, as noted, the standard values in the model were deliberately chosen to produce it. Furthermore, the parameter values that produce this receptive field are not unique. For example, an essentially identical result is obtained when the cone coupling conductance is reduced while the HB gain is increased (Fig. 7c). On the other hand, the center-surround cone receptive field is a “result” because the parameter values are all plausible and the network is sufficient.

Fig. 8. Receptive fields of the cone, HA, and HB cells with standard network parameters. Note that HA receptive field decays exponentially with radius but HB has surround which truncates its center relatively sharply.
to produce it. Furthermore, the same values reproduce other important features such as details of horizontal cell receptive fields that were not tuned into the model.

**Horizontal cell receptive fields**

The HA receptive field from the standard network has a skirt of approximately "exponential" form as would be expected from gap junction coupling (Fig. 8, Latham & Simon, 1988). The space constant is about 100 µm, almost three times greater than the radius of the dendritic field (~25 µm in the simulation), and there is no surround. This is similar to the actual receptive fields reported by Nelson (1977) and Lankheet et al. (1990). Under some conditions (e.g., when mapped by spot displacement), however, cat and rabbit HA receptive fields are much larger, on the order of 50 times greater than the dendritic reach (Lankheet et al., 1990; Bloomfield & Miller, 1982).

The HB receptive field appears more Gaussian than exponential and has a smaller space constant (~50 µm) (Fig. 8), about 50% greater than the dendritic reach. The HB receptive field also exhibits a definite inhibitory surround. This is an emergent feature of the network that has not been reported for mammalian cells corresponding to the HB. However, an inhibitory surround has been demonstrated for the homologous narrow-field horizontal cells in turtle (Piccolino et al., 1981), and also in salamanders (Skraypek & Werblin, 1983).

**Function of components in circuit**

**Origin of the receptive-field center**

Cone coupling and optical blur both contribute to the standard-cone receptive field (Fig. 9). When optical blur is omitted from the simulations, the cone center has a sharp peak due to exponential decay from cone-coupling. The inclusion of optical blur widens the central peak into a smooth dome. In a simulation with optical blur and cone-coupling but without horizontal cells, the central dome decays exponentially beyond the radius of optical blur (11 µm) (Fig. 10).

**Cone-coupling**

The two main effects of cone-coupling are to widen the cone receptive-field center (due to lateral spread of current) (Figs. 10b and 11a), and to reduce its amplitude (lateral path of current shunts the cone response) (Figs. 10a and 11a). In the complete network, the effect of increased coupling in the normalized cone receptive field is to expand the receptive-field center and reduce the proximal surround (Fig. 11b). Removal of cone-coupling narrows the center to match the optical blur function, increases the absolute center amplitude, and reduces surround strength relative to the center (Fig. 11b).

**Horizontal cell coupling**

The strength of electrical coupling between horizontal cells modulates their receptive-field amplitudes and diameters (Fig. 12).

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**Fig. 9.** Standard cone RF compared to cone RF without coupling or without optical blur. Main effect of gap junctions is to broaden size of center. When coupling is absent, receptive field generated by Gaussian optical blur without coupling (dotted line) is not visible in plot because receptive field was sampled at 1-µm intervals in adjacent cones (see "Receptive field measurement" in Methods).

**Fig. 10.** Effect of different cone-coupling gap junction conductances on cone receptive field in network without horizontal cell feedback but including optical blur. A: Gap junction coupling reduces amplitude of response due to lateral current spread. B: Normalized plot; coupling produces exponential-type receptive field whose space constant varies with conductance.
Fig. 11. Contribution of cone coupling and optical blur to standard cone receptive field. A: Amplitude of cone response. Over a wide range of coupling, responses reduced in millivolt range. B: Response normalized to emphasize lateral extent. Modulation of coupling affects center shape and proximal surround amplitude.

Increased coupling reduces the peak amplitude and expands the receptive field center. Over a wide range of coupling strengths, the HB has an antagonistic surround which originates in the cone surround generated by neighboring horizontal cells (Figs. 12c and 12d). When HB cells are given strong coupling, their receptive-field center expands at the expense of the surround, producing a receptive field similar to the HA (Figs. 12c and 12d). A further increase in HB coupling eliminates its surround but this happens only at levels of coupling where the HB receptive-field diameter approaches that of the HA.

**Horizontal cell feedback gain**

A perturbation in feedback gain from either HA or HB modulates its influence on the cone receptive field. For example, an increase in HB feedback increases the depth of the cone's proximal surround (Fig. 13), and an increase in HA feedback increases the depth of the distal surround. In this respect, the action of an horizontal cell type on the cone receptive field is related to the horizontal cell's receptive-field profile (see Fig. 8).

However, a perturbation in synaptic gain produces an additional effect on the cone receptive field not directly proportional to the horizontal cell's receptive-field profile. Synaptic gain controls resting potentials throughout the network which induce nonlinear effects (see "Balance of feedback" below). For example, a decrease in HB feedback gain increases the distal surround amplitude (Fig. 13), and a decrease in HA feedback increases the proximal surround.

Entirely removing one of the horizontal cell types amplifies the effect of a change in feedback gain. Without HA feedback, the distal surround of the cone is reduced and the near surround strengthened. Without HB (HA restored) the proximal cone surround is reduced and the distal surround strengthened (Fig. 14). In both cases the reduction in feedback allows the cone resting potential to depolarize significantly towards the driving potential of the light-modulated outer segment conductance. This "saturation" effect reduces the cone's light response, so to demonstrate the spatial differences in this case, we partially compensated for the saturation by increasing the remaining feedback two-fold. When both horizontal cell types are removed (Figs. 10 and 14), the cones depolarized to ~14 mV, not illustrated, reducing the amplitude of light responses (compare Fig. 1ta with Fig. 11a). This suggests one function for horizontal-cell feedback might be to maintain the cone resting potential in a non-saturated state (see Discussion).

Modulating gap junction coupling between either HA or HB affects cone receptive-field profiles throughout the network but does not affect resting potentials. For example, an increase in HB coupling directly reduces the HB receptive-field amplitude and increases the diameter (Figs. 12c and 12d). These effects in turn reduce the cone's proximal surround and increase its distal surround (not illustrated).

**The action of negative feedback**

The cone resting potential in the network is hyperpolarized from the resting potential of an isolated cone due to negative feedback. Depending on the synaptic loop gain, the feedback tends to "clamp" the resting potentials of both cone and horizontal cell to several millivolts depolarized from their respective synaptic thresholds (see Figs. 5 and 15 and Table 1). An hyperpolarizing perturbation in the cone decreases transmitter release and hyperpolarizes horizontal cells, which in turn decreases the horizontal cells' transmitter release and causes a depolarization of the cone, opposing the original perturbation. Thus, negative feedback maintains a nearly constant synaptic activation.

Nonlinearities in synaptic transfer functions affect the operation of the feedback circuit. Since synaptic gain is dependant on the presynaptic voltage level, gain tends to be low at hyperpolarized and depolarized voltages, and high at intermediate voltages. An hyperpolarization of the cone pedicle reduces gain in the forward cone–horizontal cell synapse because the spike of its transmitter release curve diminishes at threshold (Fig. 4). Such a modulation of gain can arise from either an injected current or a cone's resting light (e.g., see Fig. 15). The overall loop gain is dependent on the "operating point" in a complex way because several factors (stimulus, synaptic gains, other
membrane conductances) control presynaptic voltages (see Methods).

Effect of feedback on gain for two signals
A further complexity is introduced into the cone-horizontal feedback circuit because its neurons reduce their transmitter release with light. During a light response, negative feedback tends to decrease the cone’s chloride conductance. The decrease in conductance disinhibits the cone, opposing the original hyperpolarization to light, but under some conditions it also increases the gain for light stimuli. When the change in shunt conductance causes a large enough increase in synaptic gain at the cone pedicle, it leads to instability (e.g., Fig. 15b). Such an effect is fairly direct when there is one stimulus, because negative feedback can only oppose it. However when two stimuli are given, their feedback effects tend to interact. For example, a depolarizing current injected into all cones (e.g., mimicking the effect of turning off a rod stimulus) depolarizes the cones and horizontal cells, which increases feedback and also may increase loop gain. However, the increased feedback also shunts the cone, decreasing its input resistance, and decreasing its tonic response to light (Figs. 15a and 15b). This “positive feedback” effect is similar in sign and magnitude to the “suppressive rod-cone interaction” measured in horizontal cells (Pflug et al., 1990; Lankheet et al., 1993), therefore a similar feedback mechanism may be responsible.

Effect of resting potentials
Resting potentials are an important determinant of network function because they control synaptic gains. When resting poten-
tials in the network lie in the central linear portion of both feedforward and feedback synapses' input range (i.e. 5-10 mV above threshold), synaptic gains are maximal and the network loop gain behaves in an "additive" fashion, i.e. a reduction in synaptic gain (or an hyperpolarization of resting potential) reduces loop gain in the network.

However, when resting potentials are offset from the middle linear portion of the transfer curve (e.g. hyperpolarized due to increasing the synaptic feedback conductance parameter), synaptic gains are less than maximal. In this case the loop gain of the network is affected by negative feedback, i.e. a reduction in synaptic gain causes a shift in resting potential that tends to restore the original level of gain (not illustrated).

**Dynamic balance of feedback**

To discover the effect of nonlinear feedback, some simulations were run with resting potentials near synaptic threshold but with higher synaptic conductance to maintain loop gain. In this circumstance, negative feedback tends to reduce HA and HB feedback gains (by hyperpolarizing the entire network), so gain is dynamically controlled. Cone center and surround space constants are not controlled by a preset level of feedback but by the balance between HA and HB feedback gains (Fig. 16). The explanation for this is that both circuits include the same cone pedicle and synapse. An increase in synaptic gain from HA to the cone terminal causes the cone terminal to hyperpolarize, which opposes the original increase in feedback. The cone hyperpolarization, however, also affects HB, nonlinearly reducing its influence (i.e. gain) on the cone.

**Discussion**

The model's standard set of parameters reproduces the basic properties known from intracellular recordings in cat, including stable resting potentials at the appropriate magnitude, light responses of the appropriate amplitude and time course, and the appropriate receptive field of the HA horizontal cell (Steinberg, 1969; Nelson, 1977; Lankheet et al., 1990). The model also produces other properties anticipated from studies on other species: an HB receptive field smaller than the HA and with an inhibitory surround (Piccolino et al., 1981), and for a wide variety of parameter values, a broad center and antagonistic surround in the cone (see Hsu & Smith, 1994).
Fig. 15. Response of the network to a large spot (150 mm) of 200 ms duration. Shaded parameters, except feedforward conductance 200 pS; synapse that hyperpolarizes cones through feedback. Records from 21 cones and 1 Hb horizontal cells taken along a radial line from center; central red opaque was hyperpolarized (see Fig. 3). Cones rest at -39 mV; horizontal cells at -45 mV. Hyperpolarizing "noise" is due to delay in feedback loop, which includes feedforward synaptic delay, horizontal cell time constant, and feedback synaptic time constant (20 ms). Biphasic response in cones near edge results from current spread through cone gap junctions coupling added to delayed feedback from horizontal cells. A: Light stimulus only. B: Effect of 20 nA current injected into each cone, starting at 20 ms. Noise is increased but tonic response to light is decreased due to feedback effect of injected current. Slight ringing occurs at end of noise in feedback because feedback loop gain is greater. When gain parameters (feedback vs feedforward) are slightly larger, entire network becomes unstable (not illustrated).

Our simulations suggest several conclusions regarding the assembly of the cone receptor field. (1) A broad cone receptive-field center survives, its optical blur and cone-cone coupling because when either of these factors was omitted from the simulation, the cone center shrunk; (2) the cone surround is related to the HA and HB receptive-field amplitude and extent, and to the strength of feedback, and (3) the cone receptive field's approximate "difference-of-Gaussian" shape (i.e., broad dome-shaped center decaying rapidly with radius to weak wide surround) evidently is an emergent property of the network.

Fig. 16. Effect of setting gain parameters so resting voltage is nonlinear "low" region of synaptic transfer curve. With high HB feedback gain (expt 3), cone surround is narrow and deep, corresponding well with HB receptive field. Lower HB feedback gain causes cones surround to be "HA-like," i.e., shallow and wide.

A major reason for amplifying the visual signal at an early stage in its pathway is likely to be lens vulnerability to noise at later stages. The first synapse from the cone pedicle to bipolar cells likely has relatively high gain for this reason (Herkenham & Copenhagan, 1989). However, high gain has a consequence: the synapse saturates (i.e., it distorts the signal) on the maximum and minimum ends of its range (Fig. 4). As a result, the range of voltage over which neurotransmitter release can be usefully modulated is relatively narrow (Bellem & Copenhagan, 1988; Atwill, 1996; Werblin, 1977).

Function of the cone surround
Our simulations suggest that a surround for the cone pedicle would perform two distinct functions to maintain high gain for the cone signal. First, the pedicle's light-driven signal is opposed by horizontal cell feedback, which disambiguates the cone pedicle, tending to drive the pedicle voltage towards its initial resting voltage, near the "middle" of the synaptic transfer function where gain is highest (Fig. 4; see Laughlin et al., 1987; Burkhardt, 1993). This conclusion follows from the result that the cone's weak but wide antagonistic surround (Figs. 5, 13, and 14) originates in negative feedback from horizontal cells. Subtracting the horizontal cell signal (i.e., the light signal tends to eliminate "residual" i.e., transmitted by more than one cone) low spatial-frequency components of cone signals (Strinivasan et al., 1982). Such a system allows signals from bright and dark objects to be coded equally well both by the synapse (Fig. 4), and reduces distortion.

The second function performed by negative feedback from the surround is related to transfer of the cone's signal from the outer segment to pedicle. When some cone outer segment channels close in response to light (E_0 = -10 mV), negative feedback closes some of the pedicle's GABA-sensitive chloride channels (E_0 = -67 mV) in response. These conductances of the cone can
be approximated as a resistive voltage divider and the small signal response of such a circuit is optimal when the resistances are equal, i.e., when the voltage reset at the middle of its range (see Appendix), near to the voltage (+38 mV) maintained by negative feedback (Figs. 5 and 15). Therefore negative feedback also tends to maintain optimal transfer of low contrast signals from outer segment to inner segment, and a tonic chloride-based feedback would imply some sort of chloride pump to maintain osmotic balance inside the cyst.

Function of the two horizontal cell types

The fact that horizontal cells are not heterotypically coupled (Kolb, 1977; Vaney 1993) suggests that their receptive fields might differ in some way. Indeed, our simulations suggest that while both types of horizontal cell are involved in computing the cone's surround, they perform slightly different functions because the extent of their coupling may differ. The HA, being large and well coupled, has a large receptive field (>200 μm, see Laikehet al., 1993). In our simulations the HB, being smaller and not well coupled, has a small receptive field (10 μm) and a more local effect (Figs. 8, 12, and 14). In simulations with only one horizontal cell type, either one alone produced an exponential receptive-field surround in the cone (Fig. 14), but the action of both types in the complete network was more complex.

Our results suggest that the two types of horizontal cell together produce a surround in the cone that neither could produce alone. Although we do not know the exact properties of HA and HB feedback onto cones, our simulations show that tuning their feedback gains would modify the cone surround profile but only over the range in which both types influence the cone (Figs. 13 and 14). A large disparity in gain between HA and HB feedback seems likely because there would then have essentially no function in the circuit. Therefore it seems likely that both HA and HB feedback contribute to the surround, which would thereby contain a mixture of wide and narrow components, reminiscent of a Gaussian (Figs. 8 and 14). Thus, it appears that the function of the two types of horizontal cell is to fashion a Gaussian-like surround in the cone. Since the dome shape of a receptive-field center is optimal for increasing signal to noise ratio (Takahamote et al., 1990), it is likely that a similar shape is optimal as well for the surround.

Modulation of surround

Another possibility is that a differential modulation of synaptic gain in the two types could be important for the circuit's function. If the circuit was modulated (e.g. by light through the action of dopamine) so that feedback from one type was weak and the other strong, the weak one would be effectively eliminated from the circuit because of nonlinear properties of the feedback, and the surround from the strong one would remain. Thus, the two horizontal cell types might provide dynamic control over spatial properties of the cone surround.

Laikehet al. (1990) found HA receptive field size to vary depending on stimulus configuration and intensity. They found that (1) low intensity or spot displacement measurements (a which minimizes light falling on a neuron's receptive field) gave larger receptive fields, and (2) high intensity or spot size measurements gave smaller receptive fields. In our simulations (not illustrated) as well as physiological recordings in lower vertebrates (e.g. Bel-

Conclusion

Our results suggest that the cone pedicle circuit generates a center-surround receptive field that performs several closely related functions. The center is shaped by optical blur and electrical coupling, and to a lesser degree by feedback. In serve at

Function of the receptive-field center

The receptive-field center of the cone is the result of several factors, the most important being optical blur and electrical coupling between cones but also including feedback from horizontal cells (Figs. 9 and 14). Although these factors produce a smooth center profile that approximates a Gaussian (Fig. 9), they serve different functions. In cat area striate, the optical blur func-

tion is wider (22 μm diameter, Robinson & Enroth-Cugel, 1978) than cone spacing (66 μm at 1 deg eccentricity, Smith & Sertling, 1990), so it reduces aliasing in the cone array (Levitan & Buch baum, 1993). Electrical coupling between cones, since it oper-

ates on the image already sampled by the cone outer segment, cannot reduce aliasing noise that (if not for optical blur) might appear in cone sampling, but can reduce aliasing noise from sampling in the next array (bipolar cells). If aliasing were the only problem, the simplest solution would be to blur the image optically down to the spatial-frequency cut-off of higher-order neurons such as the beta ganglion cell. Yet it is apparent that optical blur is held to just over the minimum needed to prevent aliasing in the cone array. This permits addi-

tional blur required by the cone-to-cell array to be accomplished by electrical coupling between cones (Levitan & Buchbaum, 1993). The advantage is that electrical coupling also reduces noise (Leith & Simon, 1976) that originates in Poisson photon fluctuation, channel fluctuation, and the biochemical cascade in the outer segment (Hanks et al., 1987; Schnapf et al., 1990).

A cone receives signals from its neighbors through two pathways: non-inverting (gap junctions) and inverting (from hori-

zontal cells). The spatial extent of the two signals overlaps to a large extent so it might appear that over this extent they can cancel each other (see Figs. 8 and 9), which would imply a compro-
mise in function between center and surround. Such a compromise is resolved by the observation that feedback from the horizontal cell is indirect and slow, and electrical coupling, being direct and fast, serves a different function (i.e. noise reduc-
tion) which does not directly compete with feedback. This obser-
vation is consistent with the expression of the N ganglion cell receptive-field center at high temporal frequency (Frishman et al., 1987).
References


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This result implies that the maximum transfer of a low-contrast signal to the pedicle occurs when the membrane resistance of the cone and pedicle is equal to the outer segment membrane resistance. Although in reality cones are more complex than this, a more realistic derivation that includes factors for axonal and membrane resistance of the cone axon gives a similar conclusion (Hsu et al., 1994).