Origin of Orientation-Selective EPSPs in Simple Cells of Cat Visual Cortex

David Ferster

Department of Neurobiology and Physiology, Northwestern University, Evanston, Illinois 60201

According to current theory, orientation selectivity in cortical simple cells is critically dependent on intracortical synaptic inhibition. In particular, it is thought that IPSPs evoked by stimuli of the nonpreferred orientation are required to prevent a neuron from responding to a broadly tuned excitatory input at any but the preferred orientation. Yet EPSPs recorded in simple cells are in themselves highly orientation-selective. How is this possible, when excitation arises primarily from relay cells of the lateral geniculate nucleus (LGN), which are largely insensitive to orientation? In this paper, the properties of EPSPs are compared with the predictions of a model of geniculate excitation of simple cells. The model, which is derived from the suggestions of Hubel and Wiesel (1962), relies on the now familiar arrangement of the receptive fields of presynaptic geniculate cells into lines parallel to the axis of orientation of the postsynaptic cell. Several properties of the EPSPs observed in simple cells, and the orientation tuning of simple cells observed in extracellular experiments, can be accounted for without resorting to intracortical inhibition.

The receptive fields of relay cells in the lateral geniculate nucleus (LGN) of the cat are, to a first approximation, circularly symmetric; the neurons will respond almost equally well regardless of the orientation of a visual stimulus (Hubel and Wiesel, 1961). In the visual cortex, neurons are exquisitely sensitive to stimulus orientation; often, unless a bar or edge is turned to within 30° of the preferred orientation of a simple cell, the cell will not respond at all (Hubel and Wiesel, 1962). This change in spatial receptive-field properties occurring at the synapse between LGN and cortex represents a fundamental change in the neuronal representation of the retinal image, yet its origins remain obscure.

The central puzzle is this: The cortex derives a large amount of its information about the retinal image from the LGN. Cells, in particular the simple cells of layer 4, receive strong monosynaptic excitation from geniculate neurons, yet remain silent in response to an improperly oriented stimulus. How can the dramatic dependence of cortical responses on orientation be explained in light of the synaptic inputs from geniculate neurons, whose responses are largely invariant with orientation? Two broad classes of models have been proposed. In one, orientation

selectivity depends on the spatial organization of the geniculocortical connection. Hubel and Wiesel's (1962) serial-processing model, proposed when they first described orientation selectivity, falls into this class. In the other model, orientation selectivity depends upon specific intracortical connections. The cross-orientation inhibition model falls into this class (Bishop et al., 1971; Sillito et al., 1980; Morrone et al., 1982; Vidyasagar and Heide, 1984). These 2 models differ not only in the site of origin of orientation, but also in the synaptic mechanism responsible. The former relies principally on excitatory connections, while, in the latter, inhibition is central.

The serial model arose initially from the observation that the subregions of cortical simple cells resemble the receptive-field centers of geniculate neurons in their responses to flashing stimuli. Among the model's most powerful and enduring features is its account of how the elongated subregions of a simple cell arise from the monosynaptic excitation of a group of geniculate relay cells whose receptive fields are arranged in a line. ON regions would arise from excitation by ON-center geniculate neurons, OFF regions from OFF-center neurons (Hubel and Wiesel, 1962). The model thus predicts that all simple cells should receive monosynaptic excitation from neurons of the LGN, and intracellular records indicate that they invariably do (Ferster and Lindström, 1983; Martin and Whitteridge, 1984). Cross-correlation experiments show, in addition, that if an ON-center cell is presynaptic to a simple cell, its receptive-field center will overlap one of the simple cell's ON regions. Similarly, OFF centers overlap OFF regions (Tanaka, 1983).

That ON and OFF subregions are constructed from ON- and OFF-center geniculate cells may be well accepted, but Hubel and Wiesel's 1962 assertion that the subfields can account for the sensitivity of simple cells to stimulus orientation is less so. Perhaps the best evidence for this feature of the model comes from Jones and Palmer's (1987b) recent experiments, which show that orientation selectivity in simple cells can often be predicted quantitatively from 2-dimensional maps of sensitivity to small, flashing stimuli. But other features of cortical cells cannot be explained so easily in terms of ON and OFF subregions. The cross-orientation inhibition model was first proposed when Bishop et al. (1971) found that responses of cortical cells to an optimally oriented stimulus could be suppressed by a stimulus oriented 90° from optimal. They interpreted the suppression as evidence for the existence of inhibitory neurons with orientation preferences orthogonal to that of the cell being tested. Subsequently it was shown that removing synaptic inhibition by means of iontophoresis of GABA antagonists permitted cortical cells to respond to previously ineffective stimuli of the wrong orientation (Sillito et al., 1980).

Despite the evidence for cross-orientation inhibition, intra-

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Correspondence should be addressed to Dr. Ferster at the above address.

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cellular records from simple cells contain no trace of the IPSPs that null-oriented stimuli were predicted to evoke (Ferster, 1986). Instead, the excitatory drive to simple cells is in itself orientation-selective—indeed, sufficiently selective to account for the orientation tuning seen in extracellular studies of simple cells. But this observation only moves the original problem back one step: The orientation selectivity of the EPSPs must now be explained. And if cross-orientation inhibition is not present in the cortex and does not contribute to orientation selectivity, then an alternate explanation for the results that support it must also be found. In this paper, I have attempted to address both of these issues by comparing the visually evoked EPSPs recorded from simple cells with the predictions of a model based on the original proposals of Hubel and Wiesel (1962).

Materials and Methods

The details of animal preparation and recording have been described in a previous paper (Ferster, 1986). Anesthesia was induced with ketamine, maintained with sodium thiopental, and monitored by recording blood pressure, heart rate, and EEG. Animals were paralyzed with gallamine triethiodide and artificially respired to keep end-expiratory $p\text{CO}_2$ between 3.5 and 4%. For intracellular recordings, cells were penetrated with 50–100 M Ω micropipettes filled with either K⁺-acetate or Cs⁺-acetate, the latter to block K⁺-channels and raise membrane resistance. Electrodes were introduced into area 17 through a small craniotomy. Warm agar over the craniotomy and a bilateral pneumothorax helped stabilize movements of the brain caused by respiration. Amplified intracellular potentials were digitized (at 4 kHz for visually evoked responses, 15 kHz for electrically evoked responses) and stored by computer, along with information about the amount of polarizing current injected through the electrode, the size, orientation, position, and speed of motion of visual stimuli, and the amplitude and frequency of electrical stimuli.

To separate EPSPs and IPSPs, cells were polarized by injected DC current. Hyperpolarizing current brought the membrane potential close to the reversal potential for IPSPs, reducing their amplitude while increasing the amplitudes of EPSPs. Depolarizing current suppressed EPSPs and enhanced IPSPs. The current was set to the 2 optimal levels while monitoring the response to electrical stimulation of the LGN. In these records, EPSPs could be easily identified by their characteristic latencies and shapes.

The LGN was stimulated electrically through an electrolytically sharpened tungsten electrode coated with lacquer to within 300 μm of its tip. Constant current stimuli of 0.2 msec duration were delivered at 2/sec. The electrode was placed so that its position in the geniculate retinotopic map matched the position of the cortical recording electrode in the cortical map.

Extracellular recordings from neurons of the LGN were made with lacquer-coated tungsten electrodes. Peristimulus time histograms for moving and flashing stimuli were constructed in the conventional manner. Visual stimuli consisted of high-contrast flashing or moving bars of light projected onto a dim photopic background. The eyes were focused on the tangent screen with contact lenses of the appropriate curvature. Each lens contained a 4 mm artificial pupil.

Results

Model of geniculocortical input to simple cells

Hubel and Wiesel (1962) predicted that a simple cell would derive its excitatory input from geniculate neurons whose receptive fields lay along a line parallel to its preferred orientation. The presence in simple cells of monosynaptic excitation from the LGN has been confirmed by cross-correlation analysis (Tanaka, 1983) and intracellular recording (Ferster and Lindström, 1983; Martin and Whitteridge, 1984), but whether the receptive fields of the presynaptic neurons arrange themselves according to prediction, or even whether such an arrangement can explain orientation selectivity, is uncertain. This portion of Results presents an implementation of Hubel and Wiesel's model—similar in some respects to the models of Rose (1979) and Daugman

(1980)—that will be used to test whether their idea is sufficiently powerful in predicting the properties of real simple cells and their synaptic inputs.

The model has been kept as simple as possible. The relationship between the frequency of action potentials in a presynaptic geniculate neuron and the depolarization produced in the modeled simple cell was taken to be linear, with a scaling factor identical for each presynaptic input. The number of inputs was kept as small as possible while remaining consistent with what is known about the size and shape of simple cell receptive fields. Finally, the temporal patterns of activity in the geniculate inputs were taken directly from recordings of neurons in the cat LGN. The stimuli applied to the model to evoke the geniculate responses matched in every respect the stimuli used to evoke EPSPs in simple cells. None of the model's parameters were varied in order to alter the final form of the model (e.g., to optimize orientation selectivity); they were chosen, before any calculations were made, on the basis of the known properties of simple and of geniculate cells.

Presynaptic geniculate neurons. Using this model, the specific goal in making calculations is to predict the synaptic input to a simple cell that will arise from a collection of presynaptic geniculate neurons whose receptive fields were stimulated with moving bars of different orientations. Two different aspects of the model are most critical to the results: (1) the relative positions of the receptive fields of the presynaptic cells, and (2) the responses of each presynaptic cell to the moving bar. The strict topographic organization of the geniculocortical projection dictates that the geniculate cells presynaptic to one simple cell lie close together in the LGN. Several geniculate neurons were therefore recorded within a small region of one lamina of the LGN, and peristimulus histograms of their responses to a long, narrow ($8^\circ \times \frac{1}{2}^\circ$) bar of light, both flashed in and swept across their receptive fields, were constructed. Pairs of cells, one ON-center and one OFF-center, were chosen from the sample for use in the model: they were matched closely in the sizes of their receptive-field centers and in the time courses of their responses to flashing stimuli.

One such pair of geniculate cells is illustrated at the top of Figure 1; their responses to the flashing stimulus are shown in Figure 1*a*, and to the moving stimulus in Figure 1*b*. In each case, the ON-center cell is above and OFF-center cell below. The upper curve in Figure 1*b* represents the responses of all the ON-center cells needed to model the simple cell in the lower parts of the figure. Similarly, the lower curve represents all OFF-center inputs. In real simple cells, each input no doubt varies slightly in the details of its response; it is hardly likely that any 2 geniculate neurons are exactly identical. I have assumed, however, that the effects of these variations are small. The curves in Figure 1*b* are intended to represent the averaged properties of a larger number of inputs. The 2 curves also represent the response of each geniculate neuron to stimuli of all orientations; perfect circular symmetry of each geniculate receptive field, or at least the absence of a net orientation bias in a population of inputs, is assumed, even if there are some random asymmetries among the individuals (see Discussion).

Spatial arrangement of the geniculate receptive fields. After the properties of the individual geniculate inputs to the simple cell are determined, their number and spatial arrangement must be chosen. The simple cell modeled in Figure 1 was given a horizontal orientation axis and 3 subfields—1 central ON region and 2 flanking OFF regions (to match the receptive field of the

Figure 1. Model of the excitatory connections between neurons in the lateral geniculate nucleus (LGN) and a simple cell in the visual cortex. *a*, Responses of 2 geniculate neurons to a bar of light flashed in their receptive-field centers. An ON-center cell is *above*, an OFF-center cell *below*. Each histogram is the averaged response to 100 stimulus presentations. The 2 neurons were recorded close together within lamina A. *b*, Responses of the same 2 cells to a bar swept across their receptive fields at 5°/sec. *c*, Postulated arrangement of 18 neurons in the LGN, all of which monosynaptically excite the simple cell whose responses are to be calculated. A-F and M-N, OFF-center cells; G-L, ON-center cells. *d*, Synaptic input to the modeled simple cell from each of the 18 geniculate neurons, evoked when a vertical slit is swept across the receptive field. Letters labeling curves correspond to letters labeling geniculate receptive fields in *c*. The input from each ON-center cell is proportional to the upper curve in *a*; the input from each OFF-center cell is proportional to the lower curve. The relative displacement of the curves was calculated from the relative position of the receptive fields in *c* and from the initial position and orientation of the stimulus. *e*, Same as *d*, but for a horizontal stimulus. *f* and *g*, Point-by-point sums of the curves in *d* and *e*. These sums are taken to be the total excitation from the LGN to the simple cell for the vertical and horizontal stimuli. A high degree of orientation selectivity for the total geniculate excitation is predicted.

cell from which the records of Figure 7 were taken). Each subfield is assumed to arise from a row of geniculate cells of the appropriate center type, as originally suggested by Hubel and Wiesel (1962). Perhaps the best evidence in support of this arrangement is that of Tanaka (1983), who found connections (in cross-correlation studies) between a geniculate cell and a simple cell only when an OFF center overlapped the OFF region of the simple cell, or when an ON center overlapped an ON region.

The length of each subfield is one of the most critical parameters of the model. In choosing these lengths, I have relied on the quantitative data of Jones and Palmer (1987a). They measured the responses of simple cells to small light-and-dark stimuli flashed repeatedly throughout their receptive fields. Each stimulus lasted only a short period (50 msec), so that tens of thousands of stimuli could be presented in a few minutes. Through a reverse correlation between evoked spikes and the preceding stimuli, Jones and Palmer (1987a) constructed 2-dimensional receptive-field maps of unprecedented sensitivity and, equally important, of high resolution. The subfields studied ranged in length from 2 to 12 times their widths. If these subfields appear to be longer than those measured in previous experiments that used bars of light and more conventional averaging techniques, it is likely because of the greater sensitivity of the reverse-correlation technique.

For the simple cell modeled in Figure 1, an aspect ratio of 6 has been chosen for each subfield; the effects of changing this ratio will be examined below. As is shown in Figure 1c, to achieve an aspect ratio of 6:1, each subfield was constructed of 6 geniculate cells with colinear receptive fields, each field center just touching its closest neighbors. In reality, the alignment of the receptive fields along the orientation axis in each row is apt to be less than perfect. One might also place more than 6 receptive fields in each row by overlapping their centers, but the effects of these changes on the model are slight.

Thus, Figure 1c illustrates the relative positions of the 6 ON-center cells (G–L) and 12 OFF-center cells (A–F and M–R) that make up the monosynaptic geniculate input to the modeled simple cell. To calculate the synaptic drive on the simple cell resulting from these 18 inputs, several more assumptions need to be made. First, the relative strength of each input must be decided. For the sake of simplicity, each geniculate input was given equal weight. [In Jones and Palmer's (1987a) maps, the central portion of the receptive field was more sensitive than the periphery. The effect of this change on the model is slight.] Second, the time course of the input from each geniculate neuron must be decided. As stated above, the upper histogram in Figure 1b was used to model the input from each ON-center cell, while the lower histogram was used to model the input from each OFF-center cell. In other words, the depolarization evoked in the simple cell by a single input is taken to be proportional to the instantaneous frequency of the action potentials of the presynaptic cell, which in turn is modeled by the averaged response to many stimulus sweeps. Third, to combine the effects of the individual inputs on the postsynaptic cell, it was assumed that they interact linearly on the membrane of the simple cell.

The model's predictions

Calculating the response of the model simple cell to a vertical bar being swept across its receptive field is now a straightforward matter: The responses of the individual geniculate neurons to a bar being swept across their receptive fields are simply summed.

In Figure 1d, each lettered trace (A–R) reflects the synaptic input from the geniculate neuron whose receptive-field center is labeled with the corresponding letter in Figure 1c. A problem arises in that the sweep of the stimulus in the model, in order to cover the simple cell's entire receptive field, must be longer than the sweep of the actual stimulus used in Figure 1b. For use in Figure 1c, therefore, the curves in Figure 1b were extended in either direction by a horizontal line at the level of the cells' spontaneous activity, which was taken to be an average of the 10 bins at either end of the curve. During the collection of data into these bins, the stimulus was far from the receptive field, leaving only background illumination.

Clearly, a bar coming from the left toward the simple cell's receptive field first encounters the receptive fields of geniculate neurons A, G, and M; therefore, the stimulus-evoked changes in their activity reach the simple cell first. Similarly, neurons F, L, and R are encountered last and thus deliver their visual responses last. Each curve in Figure 1d, therefore, is merely a copy of the appropriate histogram in Figure 1b, displaced in time according to the position of its receptive field relative to the starting position and direction of motion of the bar. In Figure 1f, the total excitation from the LGN to the simple cell is calculated by summing the 18 individual contributions; i.e., the 18 curves of Figure 1c are scaled by a constant factor relating spike frequency to synaptic effect, and summed, point by point, to derive the total excitation evoked by the moving vertical bar.

The calculations of Figure 1, d and f, are repeated in Figure 1, e and g, for a horizontally oriented bar swept downward across the receptive field of the simple cell. The stimulus now encounters the receptive fields of the geniculate neurons in the first row (A–F) simultaneously. Traces A–F are therefore aligned with one another in Figure 1e. Similarly, traces G–L and M–R are aligned, though the traces in each row of 6 are displaced relative to those in the other rows. The point-by-point sum of traces A–R is shown in Figure 1g.

Orientation selectivity of the model's response. The response of the simple cell calculated in Figure 1 is critically dependent on the orientation of the stimulus. The null-oriented stimulus evokes a long, low-amplitude potential in the simple cell; the optimally oriented stimulus evokes a short, high-amplitude potential and a second, lesser peak. Two properties of the model are responsible for this result: (1) For the optimally oriented stimulus, the responses of the ON-center cells of the central ON subregion are stimulated simultaneously; the peaks in their individual responses sum to form a peak 6 times the size of one individual response. At the null orientation, these 6 responses occur sequentially. Their summed response is 6 times as long as any one of them, but no higher than any one. The same is true of the responses of the 6 OFF-center cells in the top row and of the 6 in the bottom row. Any increase or decrease in the aspect ratio of the subfields will increase or decrease the degree of orientation tuning observed (see below). (2) For the optimally oriented stimulus, the positions of the rows are such that the increase in activity of the OFF-center cells A–F, evoked as the bar leaves their receptive-field centers, occurs simultaneously with the increase in activity of the ON-center cells G–L, evoked as the bar enters their receptive-field centers. By contrast, for the null-oriented stimulus, the bar always encounters the receptive-field centers of an ON-center cell simultaneously with those of 2 OFF-center cells. The decrease in activity of the latter partially offsets the increase in activity of the former. This an-

Figure 2. *a*, Excitation from the LGN to the model simple cell of Figure 1, evoked by stimuli of 7 different orientations. Curves were each calculated in the same way as those in Figure 1, *f, g*. The stimulus orientation is indicated to the right of each curve. Vertical, 0°; horizontal, 90°. *b*, Peak amplitude of the geniculate excitation as a function of stimulus orientation. Horizontal line (BACKGROUND) marks the sum of the spontaneous activity of the 18 individual inputs.

tagonism between the increase in excitation by ON-center cells and the withdrawal of excitation by OFF-center cells will contribute to the orientation selectivity of a postsynaptic simple cell, particularly in cases where the OFF-center neurons have high spontaneous activity and a correspondingly large decrease in that activity as the center is stimulated by the bar. But, as seen below, antagonism between ON and OFF inputs is not required for orientation selectivity.

Because each of the individual inputs to the simple cell is taken to be completely insensitive to orientation, the total amount of excitation evoked in the simple cell by the horizontal stimulus must be identical to that evoked by the vertical stimulus; the total number of spikes evoked in each of the inputs is taken to be the same for any orientation of the stimulus. The consequence for the model is that the area under the curve in Figure 1*f* must be identical to that in Figure 1*g*: The same 18 individual responses are used to make up each curve. As for any function that is the sum of a number of other functions, the integral of the sum is equal to the sum of the integrals of the components. It is merely the relative timing of the inputs that determines whether ON- and OFF-center cells reinforce or cancel one another or whether the excitatory contributions from different inputs occur simultaneously or sequentially. The timing, in turn, is determined by the orientation of the stimulus.

In Figure 2*a*, the responses of the model to stimuli of 7 different orientations are shown. The top and bottom curves are scaled copies of those in Figure 1, *f, g*. The intermediate curves were calculated in the same way, but with the different stimulus orientations (indicated to the left of each curve). To obtain a complete orientation-tuning curve, the response of the simple cell to stimuli at 180 different orientations was calculated. In Figure 2*b*, the *peak* value of each of these curves is plotted as a function of orientation. The level marked "background" represents the excitatory input to the simple cell in the absence of a stimulus, equal to the value near the ends of any one of the curves in Figure 2*a*.

It is important to note that Figure 2*b* does not represent the orientation selectivity of the simple cell as it would be recorded extracellularly, but rather the peak excitatory input the cell would receive from the array of geniculate relay cells diagrammed in Figure 1*c*. Other excitatory inputs, such as neurons in layer 6

or in the visual claustrum, or inhibitory inputs originating from within the cortex, are not represented. Yet the curve in Figure 2*b* shows considerable orientation tuning; the sharp central peak has a half-width of less than 30°, comparable to the sharpest half-widths of orientation-tuning curves for simple cells recorded in area 17 of both cat (Henry et al., 1974) and monkey (Schiller et al., 1976). It is therefore possible to derive the extracellularly recorded behavior of real simple cells from the curve of Figure 2*b* simply by adding a threshold mechanism. The figure indicates that the excitatory input evoked at every orientation is above background, i.e., at least a small response is evoked by all stimuli, even those perpendicular to the optimal orientation. But by giving the cell a high enough threshold, the cell can be prevented from responding to any stimulus oriented more than 30° from optimal.

The sharpness of the central peak in Figure 2*b* (see also Dugman, 1980), in addition to giving the cell sharp orientation tuning, makes the orientation tuning, within limits, rather insensitive to variations in threshold. As long as the threshold remains above the sharp break at the bottom of the central peak, the large slope of the curve within the central peak predicts that, under normal circumstances, the width of orientation tuning will not be severely affected by significant changes in a cell's excitability. But if the threshold were to sink below the base of the central peak, the shallow slope of the curve outside the peak would ensure that orientation selectivity deteriorated catastrophically. The number of spikes elicited by stimuli at 0° and 90° would be determined by the relationship between EPSP amplitude and spike frequency, but the cell would begin to respond to all stimuli that, earlier, were completely ineffective. There is no apparent stable intermediate level of excitability that would leave the orientation tuning width at a value between normal and 180°.

Thus, the curve in Figure 2*b* indicates that, by adjusting the threshold, the cell can be put into 2 distinct states: (1) When threshold is above the base of the central peak, the cell will be well tuned, responding only to stimuli oriented within 30° of optimal; (2) when threshold is below the base of the central peak, the cell will respond to almost any stimulus, though it could maintain some orientation bias. Were the curve in Figure 2*b* not to have a sharp break, but instead descend more uni-

formly from its peak down to the value it assumes at 90°, adjusting the cell's threshold could give the simple cell almost any width of orientation tuning.

Length of the subfields. How critical are the parameters chosen for the model in obtaining the sharp orientation sensitivity of the geniculate input? The effect of changing the relative dimensions of each subfield is illustrated for a second modeled simple cell in Figure 3. (The simple cell from which these curves were derived is illustrated further in Figs. 4 and 5.) The curve labeled " $n = 6$ " is similar to that in Figure 5*b*. To calculate the curve labeled " $n = 4$," the inputs A, F, G, and L in Figure 4 were eliminated to bring the length-width ratio of each row of inputs to 4. Note that background activity and the peak response evoked by an optimally oriented stimulus will be reduced by this procedure to $\frac{2}{3}$ of their original sizes. Therefore the " $n = 4$ " tuning curve and corresponding background level have been magnified by $\frac{3}{2}$ for comparison with the original tuning curve (" $n = 6$ "). The width of the sharp central peak has increased slightly in response to the decrease in the length of the subfields, but the main features of the curve have not changed. Only when the number of inputs underlying each subfield is reduced further (" $n = 2$ "), is the orientation tuning severely affected. The width of tuning has substantially increased and the depth of modulation of the response (referred to the background level) has decreased. Were the antagonism between ON and OFF regions (see above) not present, the orientation tuning would be even more severely affected by the reduction in subfield length.

That the sharpness of orientation tuning should decrease when the subfields are shortened is no surprise (Daugman, 1980). In the limiting case, with each subfield constructed from only one geniculate neuron, orientation selectivity would depend only on the weak antagonism between ON and OFF subfields. Experimental evidence for the effects of the length of subregions comes from Jones and Palmer (1987*b*), who found wide variations among simple cells in the subfield aspect ratio. As it does in the model, the width of orientation tuning decreased as aspect ratio increased.

Number of subfields. Just as well-oriented simple cells with varying numbers of subfields can be found in the cortex, the number of subfields used in the model has little effect on the derived orientation tuning. The simple cell in Figures 4 and 5, which was constructed with only 2 subfields, one ON and one OFF, is no less well oriented than one with 3 subfields (Figs. 1 and 2). Furthermore, Rose (1979) and Daugman (1980) have shown that orientation selectivity can arise from a single row of ON-center geniculate-like inputs. That orientation selectivity in these models is relatively independent of the arrangement of subfields suggests an experiment similar to one performed on real simple cells. 4-Amino-2-phosphonobutyric acid (APB) suppresses activity in ON-center retinal ganglion cells when injected into the vitreous humor of the eye. In the presence of the drug, however, cells in the visual cortex of both monkey (Schiller, 1982) and cat (Sherk and Horton, 1984) do not lose their orientation specificity, prompting Schiller's (1982) suggestion that interactions between ON and OFF channels do not produce orientation selectivity, but that ON and OFF channels each have independent access to the mechanism responsible for orientation.

An APB experiment is illustrated in Figure 6, which contains 2 orientation-tuning curves derived from the simple cell modeled in Figures 4 and 5. The unlabeled curve is copied from

Figure 3. Orientation-tuning curves predicted by the model for the simple cell of Figure 4, with different numbers (n) of presynaptic geniculate neurons making up the 3 subfields. For $n = 6$, the curve is identical to that in Figure 2*b*. For $n = 4$, the individual inputs AFGL have been eliminated from the calculation. For $n = 2$, BEHK have also been eliminated. Curves are scaled for comparison to match the spontaneous activity and peak amplitudes. Orientation-tuning width is increased slightly for $n = 4$ and much more for $n = 2$.

Figure 4*b*. Curve "APB" was calculated after the ON-center cells (G-L, Fig. 4*c*) were silenced. Despite the absence of ON-center cells, the width of orientation tuning does not change significantly from the control, though the amplitude of the excitatory input from the LGN is reduced. The lower curve is an almost perfect replica of the upper one, scaled down by a factor of 2 (largely because of the similarity in the size and shape of the responses of presynaptic ON- and OFF-center cells). In these 2 effects on the excitatory input to simple cells, the removal of ON-center input in the model exactly mimics the effects of APB, which reduced the responsiveness of cortical simple cells but left orientation tuning largely unaffected in both cat and monkey.

Comparison with intracellular records

The most significant prediction of the model is that the excitatory drive to simple cells is highly orientation-specific, although a small input should be evoked by a null-oriented stimulus. Records from simple cells (Ferster, 1986) confirm that EPSPs are highly orientation-specific, but that no EPSPs at all were detected in response to the null-oriented stimulus. If, however, there were slowly varying potentials with amplitudes more than 5–10 times smaller than the peak response, they could have been obscured by noise and slow drift in the records. Figure 7 represents an attempt to detect the null-oriented input in a simple cell of layer 4. Three factors contribute to an improved signal-to-noise ratio. First, the resting potential of the cell is greater than that of previously recorded simple cells. Second, cesium ions injected into the cell have increased the membrane resistance by blocking K^+ -channels, and have possibly increased the amplitude of synaptic potentials. That the injected Ce^{+} has affected the membrane resistance is indicated by the increase in the membrane time constant: The decay of electrically evoked IPSPs lasted almost 100 msec (not shown). Third, individual records were digitized and averaged by computer.

Figure 4. The predicted behavior of the EPSPs generated in a second model simple cell by monosynaptic input from the LGN. Conventions as in Figure 1. Only 2 subfields are modeled, one ON and one OFF.

In interpreting the records of Figure 7, it is important to consider what the changes in potential evoked by the stimulus represent, whether hyperpolarizations are caused by an increase in inhibition or a decrease in ongoing excitation, and whether depolarization represents an increase in excitation or a decrease in inhibition. The resting membrane potential of the cell in Figure 7 was near 60 mV. At this potential, the only visible response to electrical stimulation of the LGN was a monosynaptic EPSP (Fig. 8). A disynaptic IPSP was visible only when the cell was depolarized with current injected through the microe-

lectrode (not shown). If the resting potential, then, is close enough to the IPSP reversal potential to make IPSP amplitudes too small to see, the visually evoked responses of Figure 7 must consist almost entirely of EPSPs. Depolarizations must reflect an increase in excitation, and hyperpolarizations a decrease in background excitation, rather than an increase in synaptic inhibition.

The response to an optimally oriented bar swept across the receptive field at 2°/sec is shown in Figure 7b. As in Figure 1, the bar was chosen to be $8^\circ \times \frac{1}{2}^\circ$ in size. Four individual responses

Figure 5. *a*, Excitation from the LGN to the model simple cell of Figure 4, evoked by stimuli of 7 different orientations. Curves were each calculated in the same way as those in Figure 4*f,g*. Stimulus orientation is indicated to the right of each curve. Vertical, 0°; horizontal, 90°. *b*, Peak amplitude of the geniculate excitation as a function of stimulus orientation. Horizontal line marks the sum of the spontaneous activity of the 18 individual inputs.

to 4 stimulus sweeps are shown above an average of those 4, together with 3 others not shown. The 4 phases of the responses reflect the presence of 3 discrete subfields, one central ON region flanked by 2 OFF regions: As the bar enters the first OFF region, the membrane is hyperpolarized; as the bar enters the central ON regions, the cell is depolarized; a second hyperpolarization indicates a second OFF subfield; a small depolarization is evoked as the bar leaves the second OFF region. This fourth phase of the response is not easily recognized in the individual traces because of its small size, compared to the noise. Each of the regions revealed by the sweeping stimulus responded appropriately to flashing stimuli. In the ON regions, a light increment evoked a depolarization; in the OFF regions, a light decrement evoked a hyperpolarization (not shown).

The 4 phases of the responses in Figure 7*b* are easily explained in terms of the current model. As in Figure 1, each subregion would derive its existence from presynaptic geniculate neurons of the corresponding center type. The hyperpolarizations and depolarizations seen in the simple cell would reflect the rise and fall of activity evoked in the presynaptic neurons as the bar entered and left their receptive fields. These changes in intracellular potential evoked by an optimally oriented stimulus correspond exactly to changes in spike frequency recorded extracellularly from simple cells. In extracellular experiments, however, a null-oriented stimulus evokes no response at all, while the model predicts a small synaptic excitation from the LGN that may remain below threshold. A small excitatory input that resembles the model's prediction is present in Figure 7*a*.

The traces of Figure 7*a* show the EPSPs evoked in the simple cell by a moving stimulus 90° from optimal. Here, as in Figure 7*b*, 4 individual records are shown above an average of 7. Clearly, the EPSPs are highly tuned to orientation. In some individual traces, no response at all can be discerned. In others, both a small, graded depolarization and an increase in the frequency of action potentials are present, but their exact amplitude and duration are difficult to measure against the background noise. In the averaged trace, the response becomes more distinct. The amplitude of the graded response is 1–2 mV, as compared to the peak-to-peak amplitude of the optimal response of over 10 mV. The exact point at which the response begins and ends is

still difficult to determine accurately, since it rises slowly out of the noise; but the duration of the response appears to be just over 1 sec, which makes the receptive field over 2° in length along the axis of orientation.

The calculated curves in Figure 1*f,g*, and the averaged traces in Figure 7*a,b*, resemble each other in several important ways. First, the ratio between the peak amplitudes of the optimal and null responses in each case is similar: between 7 and 10. Also, the durations of the optimal and null responses are comparable; together, the 4 phases of the optimal response last almost as long as the response to sweeping across the entire length of the subfields in the null direction. Finally, the overall shape of the calculated traces for the 2 stimulus conditions closely conforms to that of the intracellular traces. These similarities emerged

Figure 6. Two orientation-tuning curves calculated for the cell in Figure 4. Unlabeled curve is for the receptive field, as pictured in Figure 1*c*. Curve APB was calculated from the OFF-center inputs A–F alone. The 2 curves were scaled to matched the background activity. The removal of ON-center input results in a decrease in the total excitation, but no loss of orientation tuning.

Figure 7. Intracellular records from a simple cell in layer 4 of area 17, showing the response of the cell's excitatory inputs to a bar of light swept across its receptive field at 2 different orientations. *a*, Preferred orientation for the EPSPs; *b*, 90° from preferred. Top 4 traces of each panel show responses to 4 different stimulus sweeps (calibration bar, 10mV); the bottom trace (*A*) shows an average of 8 individual responses, including the 4 shown above. Averaged traces are shown at twice the gain of the individual traces (calibration bar, 5 mV). Resting potential of the cell was 60 mV. The velocity of motion of the bar was 2°/sec.

even though the only features of the model specifically chosen to resemble the cell in Figure 7 were the number and type of subfields. All other decisions that contributed to the model were arrived at independently.

Convergence in the geniculocortical pathway

One essential property of the model is the large number of geniculate neurons that converge on each simple cell. The minimum number for a simple cell with 2 subfields, each with an aspect ratio of 2, is 4, or 8 if the cell is binocular. For most simple cells with longer subfields, however, a larger convergence is predicted, and any overlap between the receptive fields of geniculate neurons making up a single subfield would increase the number yet again. Though some authors have suggested that cortical neurons receive excitatory input from only a single geniculate neuron (Creutzfeldt et al., 1974; Sillito et al., 1980; Heggelund and Moors, 1983; Vidyasagar and Heide, 1984), evidence for multiple geniculate inputs to simple cells comes from both anatomical and physiological experiments. Freund et al. (1985) labeled single geniculate axons with HRP and found that each axon could account for only a small fraction of the synapses of geniculate origin on a single Golgi-impregnated cortical cell. Tanaka (1983), while recording from a single simple cell, sampled cells in the retinotopically corresponding part of the LGN,

finding up to 5 cells that, from their correlograms, appeared to excite the simple cell monosynaptically.

That multiple geniculate afferents excite a single cortical cell is supported by the experiment illustrated in Figure 9. The experiment is based on the assumption that each of the geniculate neurons presynaptic to the cortical cell from which the records were taken has a slightly different threshold of electrical activation. As the intensity of geniculate stimulation is gradually increased from 0, the afferent with the lowest threshold must be recruited first, followed by those with higher and higher thresholds. As each afferent begins to respond to the stimulus, the amplitude of the EPSP evoked in the cortical cell will increase by a discrete amount, equal to the size of the unitary EPSP produced by that afferent. The total number of discrete steps in amplitude recorded as the stimulus intensity is gradually raised should then reflect the number of presynaptic cells. One step from 0 to maximal would indicate 1 presynaptic component, 2 steps 2 components, and so on.

The 40 traces superimposed in Figure 9a were evoked by a series of geniculate stimuli that were graded in amplitude. The later portions of the traces, 2 or more milliseconds following the stimulus, contain some polysynaptic components, as well as an underlying field potential; but prior to 2 msec, only the monosynaptic EPSP is present. While individual traces are not

Figure 8. Response to electrical stimulation of the LGN, recorded in the simple cell of Figure 7. A monosynaptic EPSP (latency, 1.7 msec) is visible.

labeled with the corresponding stimulus intensity, the response amplitude consistently increased with stimulus intensity. In this case, however, the discrete steps in amplitude are difficult to discern, since they are so small compared to the noise. Noise can be estimated from the traces of Figure 9*b*, each of which was evoked by a supramaximal stimulus that should reliably activate all presynaptic cells. Given the variability observed in Figure 9*b*, noise can account for less than 10% of the variability observed in Figure 9*a*. The minimum number of presynaptic cells must therefore be at least 10. There could equally well be more, however: The ratio of the largest to the smallest responses measured in Figure 9*a* at 2 msec latency is well over 20. In either case, convergence in the geniculocortical pathway is extensive enough not to rule out the model of orientation selectivity proposed by Hubel and Wiesel (1962).

Discussion

The model used in this report to mimic the excitatory input from the LGN to cortical simple cells is a quantitative version

of Hubel and Wiesel's original model (1962). It was motivated by observations that EPSPs themselves are highly orientation selective and that IPSPs in simple cells do not have the properties required to contribute to orientation selectivity. Several important properties of EPSPs in simple cells can be explained solely on the basis of the spatial organization of the receptive fields of geniculate neurons presynaptic to a cortical simple cell: the width of tuning of EPSPs, the relative amplitudes of optimal and null responses, the relative durations of optimal and null responses, the overall shape of the responses, and the loss of responsivity and maintenance of orientation selectivity produced by application of APB.

In comparing the model's results (Fig. 1) with intracellular records from simple cells (Fig. 7), I have made the implicit assumption that the intracellular records reflect almost entirely excitation from the LGN. Simple cells in layer 4 do receive projections from several other sources besides the LGN, including neurons in layer 6 (McGuire et al., 1984; Ferster and Lindström, 1985) and in the visual claustrum (LeVay and Sherk, 1981). The input from layer 6 is potentially a very powerful excitatory projection; when layer 6 neurons are activated antidromically from the LGN, layer 4 cells are strongly driven. But the EPSPs evoked in layer 4 cells appear only if the frequency of stimulation is raised above 10 Hz. Since layer 6 cells are often poorly responsive in the heavily anesthetized animals used in the intracellular experiments, they likely contribute little to the intracellular records. The close agreement between the predictions of the model and the intracellular records is in itself an argument that excitation from the LGN determines orientation selectivity and spatial organization of the receptive field. Layer 6 neurons may be more important for determining length selectivity or summation (Ferster and Lindström, 1985; Bolz and Gilbert, 1986).

While inhibition evoked by a stimulus at the null orientation is not present in most cortical cells, inhibition evoked by an optimally oriented stimulus is. The role of this inhibition will not be discussed in detail here, though its spatial organization

Figure 9. *a*, EPSPs evoked in a layer 4 cell by electrical stimulation of the LGN at a range of stimulus intensities between 0 and 800 μ A. Forty traces are superimposed. Amplitude of the monosynaptic component of the response, measured at 2.5 msec after the shock artifact, varies from less than 1 mV to more than 20 mV. *b*, Ten superimposed traces evoked by stimulation of the LGN at 1000 μ A. Variation in the amplitude of the response is small compared to that in *a*. For all records, the cell was hyperpolarized by 3 nA of DC current.

in simple cells indicates that it may be important for enhancing contrast sensitivity. In ON regions, excitation evoked by a light increase is often accompanied by inhibition evoked at light decrease, the former evoked directly from monosynaptic geniculate input, the latter indirectly via cortical interneurons. In OFF regions, excitation is evoked by light decrease and inhibition by light increase (D. Ferster, unpublished observations). IPSPs with the described spatial organization can contribute little to orientation selectivity if the neurons that mediate it are all but silent at the null orientation.

Alternative models of orientation selectivity

It has been assumed by some that very few geniculate neurons excite any one simple cell (Creutzfeldt et al., 1974; Heggelund and Moors, 1983; Vidyasagar and Heide, 1984). Heggelund and Moors (1983) suggested that one geniculate neuron might excite a simple cell monosynaptically, while another with an opposite receptive-field type (ON instead of OFF, for example) might inhibit the simple cell. If the 2 geniculate receptive fields were slightly displaced from each other, the response of the simple cell would acquire an orientation bias perpendicular to the direction of displacement. So far, little evidence for direct inhibition from the LGN has been found from intracellular experiments (Toyama et al., 1974; Ferster and Lindstrom, 1983) or from cross-correlation experiments (Tanaka, 1983).

In Vidyasagar's and Heide's (1984) model, a single geniculate afferent excites each simple cell, but the simple cell's orientation selectivity depends initially on the intrinsic orientation bias that is observed in geniculate receptive fields. This bias would then be sharpened by inhibition from other cortical cells with orthogonal orientation preferences. The first feature of the model, a low geniculocortical convergence, is supported by neither the experiment of Figure 9 nor Tanaka's (1983) cross-correlation experiments. Nevertheless, evidence for the second feature of the model, a role of intracortical inhibition in generating orientation selectivity, is not lacking. Such evidence is, in fact, what made the failure to find intracellular cross-orientation inhibition so surprising (Ferster, 1986). It derives primarily from 2 independent experiments.

The interaction of 2 visual stimuli presented simultaneously in the receptive field of cortical cells yielded the first evidence for cross-orientation inhibition; that a null-oriented conditioning stimulus suppresses the response to an optimally oriented test stimulus has been taken as evidence that the null-oriented stimulus evokes orientation-specific inhibition, originating in the cortex (Bishop et al., 1971; Morrone et al., 1982). The 2 stimuli, however, interact not only in the receptive field of the simple cell being tested, but in the receptive fields of presynaptic geniculate cells as well. In preliminary experiments, conditioning stimuli reduce the magnitude of the response to the test stimulus and raise the level of background activity in geniculate neurons. The resulting reduction in the signal-to-noise ratio of the geniculate response, when applied to the current model, can explain the effects of the conditioning stimulus on the responses of cortical cells.

Binocular conditioning experiments also point to the LGN as the site of action of the conditioning stimulus. In cortical cells, a null-oriented stimulus presented in the receptive field of the eye contralateral to the test stimulus has no effect on the response to the test stimulus (Ferster, 1981; Ohzawa and Freeman, 1986). If cross-orientation inhibition is to explain this result,

all of the inhibitory interneurons tuned to the null orientation must be monocular. Furthermore, within the dendritic tree of the postsynaptic cell, the effects of inhibitory input from one eye must be electrically isolated from the excitatory input of the other eye. A more parsimonious explanation would be that the effect arises in the LGN, where receptive fields are strictly monocular.

Independent evidence for cross-orientation inhibition comes from experiments in which GABA antagonists are applied to the cortex iontophoretically or systemically in order to block intracortical inhibition. That orientation selectivity is reduced or abolished by the drugs has been interpreted as a sign that intracortical IPSPs evoked by null-oriented stimuli are required to prevent a neuron from responding to stimuli of inappropriate orientation (Tsumoto et al., 1979; Sillito et al., 1980). This interpretation implies that the excitatory drive to these cells is in itself poorly oriented.

The appearance of a response to a stimulus that was ineffective in the absence of a GABA antagonist may, in fact, be the result of the removal of a specific inhibitory input that previously prevented the cell from responding. But GABA antagonists could also produce nonspecific increases in the excitability of a neuron. These drugs are often used to induce seizures in the studies of epileptogenesis, and a low rate of spontaneous activity appears in some of the published records of bicuculline-treated cells. Iontophoresis of bicuculline, after all, may remove all inhibition not only from the cell being studied, but from hundreds or thousands of surrounding cells, many of which certainly make excitatory connections with one another and with the cell under study. A nonspecific increase in excitability, in combination with the normally subthreshold EPSPs evoked in simple cells by a null-oriented stimulus (Figs. 1*f*; 7*b*), could as easily explain the effects of bicuculline analogs as the suppression of cross-orientation inhibition.

That glutamate, which clearly does produce a nonspecific excitation, does not have the same effect on orientation as bicuculline would contradict this interpretation of the bicuculline experiments, though perhaps the synapses affected by the glutamate adapt to the steady application, or the adaptive mechanisms of the cortical circuit (Ohzawa et al., 1986) prevent its having a large effect. A nonspecific increase in excitability may explain the behavior of spike frequency in Figure 7. While simple cells normally fire no action potentials in response to a null-oriented stimulus, the cell of Figure 7 does; it has clearly been rendered hyperexcitable in a way that could resemble a cell exposed to GABA antagonists. The agent in this case is Ce^+ , which, in blocking potassium channels, may cause a depolarization (perhaps along with the electrode penetration itself) and an increase in membrane resistance. Spontaneous activity is present where none usually is. And the small, slow EPSPs evoked by the null stimulus clearly increase the frequency of those action potentials. There is no doubt that, in both the model and in Figure 7, the size of the EPSPs evoked by the null-oriented stimulus is smaller than those evoked by the optimal stimulus. In the bicuculline experiments, then, one would still expect some orientation bias in the spikes evoked by these 2 stimuli. The low maximal firing rates of cortical cells, as well as adaptation to visual stimulation, might well compress the relationship between EPSP amplitude and spike frequency, making the orientation bias that is observed in the presence of the drug slight.

These arguments, presented in an attempt to reconcile the

seemingly contradictory intracellular experiments and bicuculline experiments, represent an extreme position. Alternatively, it may be argued that inhibition and excitation share the responsibility for creating orientation selectivity, or that different mechanisms operate in different cells. One may also take the viewpoint opposite to the one argued here: that, for technical reasons, intracellular records fail to reveal the cross-oriented IPSPs, which are present nonetheless. It has been argued, for example, that the cross-oriented IPSPs are of the so-called shunting type or are located remote in the dendritic tree and so do not produce potentials visible to an electrode in the cell soma. While there is little direct evidence for such mechanisms being present in mammalian cells, conclusively proving the negative that undetectable IPSPs do not operate in simple cells and that cross-oriented IPSPs are not present in any form, is difficult. The purpose of the model, therefore, has been to show that the generation of orientation selectivity is at least plausible in the absence of inhibition.

The model's results are consistent with the notion that orientation selectivity is established by the connections between a cortical neuron and its presynaptic geniculate afferents. Preliminary evidence from stimulation of the optic nerves indicates that the same will be true for binocularity as well, i.e., that binocular cells in layer 4 are binocular by virtue of their monosynaptic input from geniculate neurons of laminae A and A1, not from other cortical neurons (see also Ito et al., 1977). One of the remarkable features of the neocortex is the complexity of interconnections among its neurons; yet 2 distinguishing physiological properties of cortical neurons, orientation and binocularity, seem hardly to depend on these interconnections at all. Instead, the seemingly random arborizations of geniculocortical axons and of stellate cell dendrites within layer 4 must possess some hidden order, the effects of which are propagated throughout the cortical columns.

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