

# Dynamic Properties of Recurrent Inhibition in Primary Visual Cortex: Contrast and Orientation Dependence of Contextual Effects

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**Dragoi, Valentin and Mriganka Sur.** Dynamic properties of recurrent inhibition in primary visual cortex: contrast and orientation dependence of contextual effects. *J. Neurophysiol.* 83: 1019–1030, 2000. A fundamental feature of neural circuitry in the primary visual cortex (V1) is the existence of recurrent excitatory connections between spiny neurons, recurrent inhibitory connections between smooth neurons, and local connections between excitatory and inhibitory neurons. We modeled the dynamic behavior of intermixed excitatory and inhibitory populations of cells in V1 that receive input from the classical receptive field (the receptive field center) through feedforward thalamocortical afferents, as well as input from outside the classical receptive field (the receptive field surround) via long-range intracortical connections. A counterintuitive result is that the response of oriented cells can be facilitated beyond optimal levels when the surround stimulus is cross-oriented with respect to the center and suppressed when the surround stimulus is iso-oriented. This effect is primarily due to changes in recurrent inhibition within a local circuit. Cross-oriented surround stimulation leads to a reduction of presynaptic inhibition and a supraoptimal response, whereas iso-oriented surround stimulation has the opposite effect. This mechanism is used to explain the orientation and contrast dependence of contextual interactions in primary visual cortex: responses to a center stimulus can be both strongly suppressed and supraoptimally facilitated as a function of surround orientation, and these effects diminish as stimulus contrast decreases.

## INTRODUCTION

The emergent properties of cortical networks arise from specific features of the cortical circuitry. These properties are well described in the primary visual cortex (V1). A mechanistic description of how specific response properties arise in networks of V1 neurons is central to understanding cortical mechanisms of vision and of information processing by the cortex in general.

The basic functional architecture of the neocortex is dominated by local excitatory and inhibitory connections. Excitatory neurons project mainly to other excitatory neurons, but ~20% of their synapses are on inhibitory interneurons. Recent anatomic and immunohistochemical data (e.g., Kisvarday et al. 1993; Sik et al. 1995; Thomson and Deuchars 1997) demonstrate that inhibitory interneurons also project to excitatory neurons and to other inhibitory interneurons. Although this pattern of recurrent excitation and inhibition is ubiquitous in the neocortex and the hippocampus, its role in cortical function is far from being understood. Indeed, the majority of the models of cortical processing focus on the

role of recurrent excitation and ignore recurrent inhibitory connections (but see Traub et al. 1997; Van Vreeswijk et al. 1994). Inhibition in the neocortex has been long known to balance the effect of excitation (Sillito 1975; Toth et al. 1997), and complete blockade of inhibition with GABA antagonists leads to runaway excitation and epileptic seizure (e.g., Kamphuis and Lopez da Silva 1990). Theoretical considerations (e.g., Blomfield 1974; Koch and Poggio 1985) have suggested that inhibition could play a crucial vetoing role in the emergence and shaping of receptive field properties, such as direction (and possibly orientation) selectivity. More recently, Tsodyks et al. (1997) have suggested that interneuron-interneuron connections play a role in entraining the theta rhythm of hippocampal cells.

We have attempted to understand the functional role of recurrent excitatory and inhibitory connections by determining the dynamic properties of cortical networks in V1 that incorporate both these types of connections. The motivation for this analysis comes from specific phenomena in V1 that are likely to rely on such connections. Thus, it is well known that visual cortical neurons have both a center, or classical receptive field, where stimuli elicit spike responses, and a surround, or extra-classical receptive field, where stimuli modulate responses due to stimulation of the classical receptive field (Fig. 1A). However, despite the simplicity of this description, the way in which surround stimulation modulates responses elicited by a center stimulus is highly nonlinear. Thus, stimuli in the surround can either facilitate or suppress cortical responses depending on the relative orientation and contrast between the center and surround. The presence of a surround stimulus of orientation similar to the cell's preferred orientation suppresses the response to an optimal stimulus within the receptive field center (Gilbert and Wiesel 1990; Grinvald et al. 1994; Knierim and Van Essen 1992; Toth et al. 1996). On the other hand, stimulating the surround with a stimulus with an orientation that differs significantly from the cell's preferred orientation facilitates responses to optimal stimulation within the center (Levitt and Lund 1997; Sillito et al. 1995). In this case, the cell responds "supraoptimally"—i.e., beyond the level expected after stimulation with the optimal orientation (Fig. 1B). However, when the receptive field is presented with a low-contrast center stimulus, both the tuning and amplitude of the modulatory effects change so that the surround strongly suppresses responses at almost all orientations (Fig. 1C).

The key questions that we investigate in the current study are: 1) Why does a surround stimulus at nonpreferred orientations in conjunction with a center stimulus at the preferred orientation actually drive the cell beyond optimal responses

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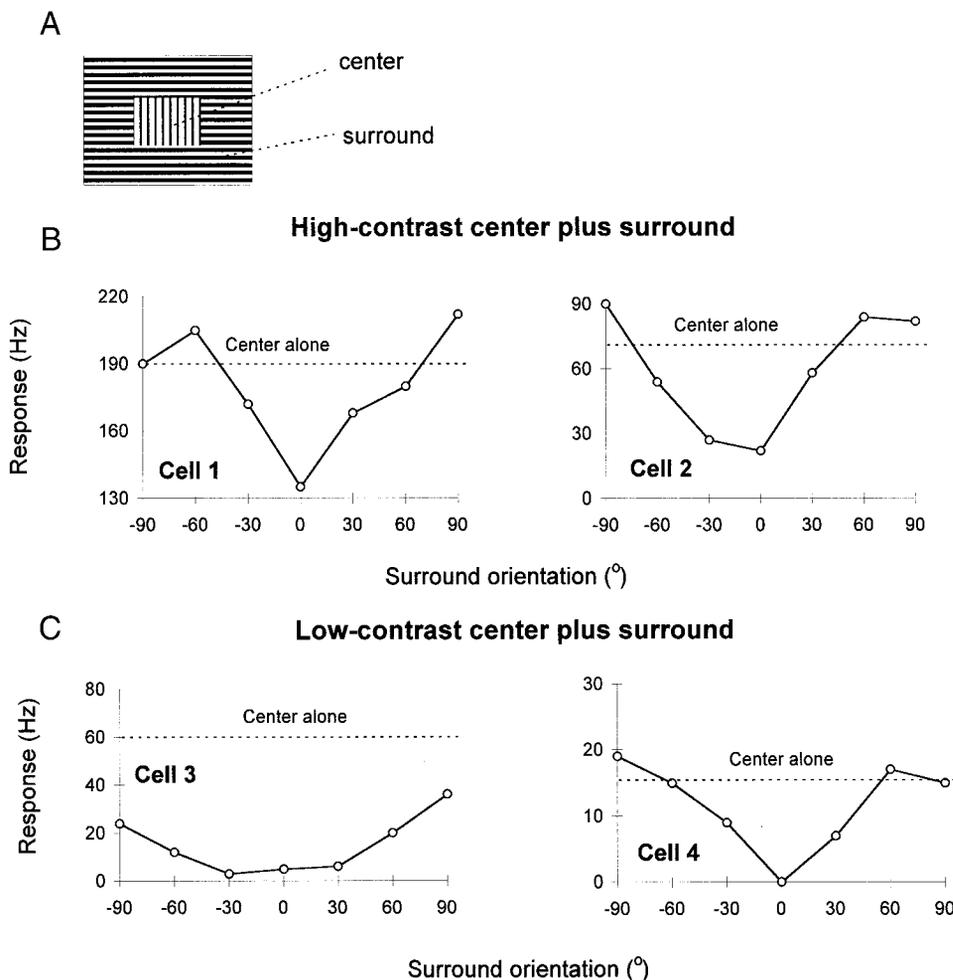


FIG. 1. *A*: spatial arrangement of the receptive field center and surround used to investigate contextual effects. The center grating stimulus is surrounded by a larger annulus field with the same mean luminance. *B*: responses to the high-contrast optimal center stimulus paired with high-contrast surround gratings of varying orientations. Cells 1 and 2 are adapted from Fig. 1, *A* and *D*, of Levitt and Lund (1997). *C*: responses to the low-contrast optimal center stimulus paired with high-contrast surround gratings of varying orientations. Cells 3 and 4 are adapted from Fig. 1, *D* and *E*, of Levitt and Lund (1997). Dashed lines in all panels indicate response to the optimal stimulus alone.

(obtained by presenting the preferred center stimulus alone), whereas a surround stimulus at the preferred orientation suppresses responses to the same center stimulus? 2) Why do the facilitatory effects diminish when the center is stimulated at low contrast?

There is no model of cortical function to account for both orientation and contrast dependence of contextual interactions in V1. Although several studies (e.g., Somers et al. 1998; Stemmler et al. 1995) have investigated the involvement of long-range horizontal connections (that link cells with similar orientation preference over large regions of visual space) as the most likely candidate for explaining contrast-dependent context effects, the exact nature of the interaction between orientation and contrast dependency remains unresolved.

We show here how a model of cortical dynamics in V1 that relies on local interactions between excitatory and inhibitory neurons helps resolve the apparently puzzling shift between the context-dependent suppressive and facilitatory responses of pyramidal cells. We show first that by directly changing the level of the modulatory (long-range intracortical) input we can explain the emergence of both supra- and suboptimal context-dependent cortical responses that rely only on the dynamic interaction between inhibitory neurons. We subsequently explore the combined effect of

receptive field surround orientation and center contrast using a large-scale network model.

## METHODS

The model describes the processing of information at two sequential stages: lateral geniculate nucleus (LGN) and V1. A monocular patch of the visual field is divided into  $11 \times 11$  locations, where each location is represented by one hypercolumn—i.e., a full set of 72 orientation columns between 0 and  $180^{\circ}$  ( $2.5^{\circ}$  resolution). The model configures 8,712 LGN neurons arranged on the array of  $11 \times 11$  locations, with 72 cells per each location of the visual patch and 17,424 cortical neurons. For computational efficiency, we use equal numbers of pyramidal and smooth cells, despite anatomic evidence that cortical excitatory cells outnumber inhibitory interneurons by a factor of 4 (e.g., Gabbot and Somogyi 1986). This simplification speeds up simulations without altering the model's results.

Our strategy is to present input stimuli to LGN cells and then study the response properties of cortical excitatory and inhibitory neurons. The model (Fig. 2A) investigates the effect of two major types of input to cortical neurons: 1) thalamocortical input, labeled here “feedforward” input, and 2) intracortical input via lateral connections (short-range intracortical connections and long-range horizontal connections).

Model populations are activated directly by feedforward input stimuli that are presented in the classical receptive field and by long-range inputs from outside the classical receptive field (labeled

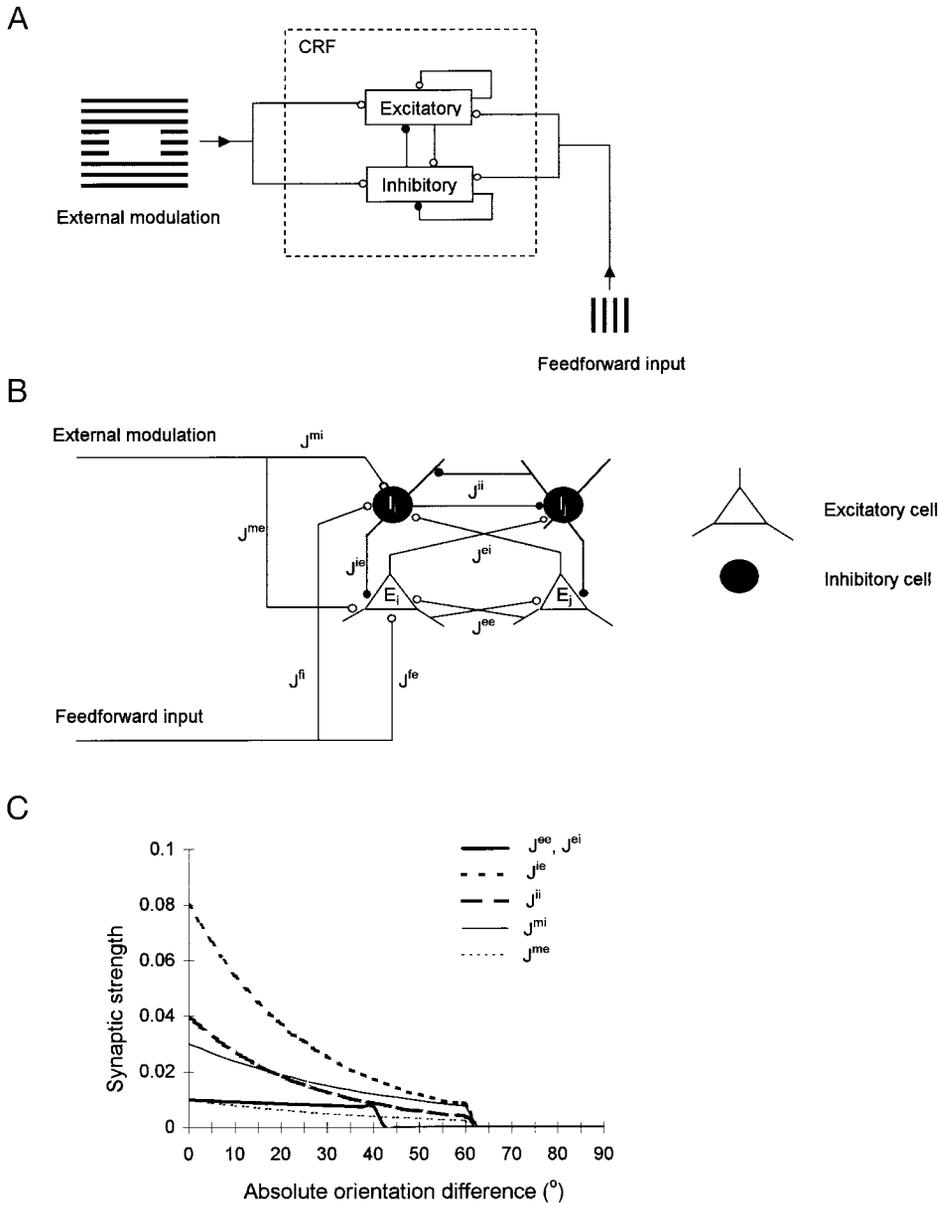


FIG. 2. **A**: simplified local population model. The feedforward input ( $90^{\circ}$  center stimulus) and the external modulatory input ( $0^{\circ}$  surround stimulus) excite both populations of excitatory and inhibitory cells in the classical receptive field (CRF). **B**: model description of synaptic connections.  $\circ$ , excitatory connections;  $\bullet$ , inhibitory connections;  $E_i, E_j$ , pyramidal cells;  $I_i, I_j$ , smooth cells;  $J^{ee}, J^{ei}$ , strengths of connections to excitatory ( $fe$ ) and inhibitory ( $fi$ ) cells;  $J^{ie}, J^{ii}$ , strengths of feedforward recurrent excitatory connections ( $ee$ ) and excitatory projections to inhibitory cells ( $ei$ );  $J^{ie}, J^{ii}$ , strengths of inhibitory projections to excitatory ( $ie$ ) and inhibitory ( $ii$ ) cells;  $J^{me}, J^{mi}$ , strengths of modulatory inputs to excitatory ( $me$ ) and inhibitory ( $mi$ ) cells. **C**: synaptic strengths of the various connection types implemented in the model as a function of the absolute orientation difference between pre- and postsynaptic cells. Connection labels are similar to those in **B**.

external modulatory drive), applied to both excitatory and inhibitory populations.

#### LGN cells

LGN cells are modeled as single units, with a mean rate of firing given by:

$$\frac{dLGN_i}{dt} = -0.01LGN_i + R_i(1 - LGN_i) \quad (1)$$

where  $LGN_i$  represents the lateral geniculate cell. The first term in the equation ( $-0.01LGN_i$ ) describes the spontaneous decay in the absence of any stimulation—i.e., the firing rate decreases to 0 if the total input to cell  $i$  becomes 0.  $R_i$  is the retinal input to each LGN cell. To ensure that thalamic responses increase linearly with the log of stimulus contrast, the retinal input is set to  $R_i = a \cdot \log(\% \text{ Contrast}) + b$ , where parameters  $a = 0.91$  and  $b = -0.81$  were chosen to generate realistic contrast response functions for LGN and cortical cells ( $R_i$  is constrained between 0 and 1). The

input stimuli consist of oriented bars applied to the receptive field (RF) center (RF size is idealized to 1 location). LGN cells receive input in a manner that corresponds topographically to the orientation preference of the cortical cell to which it projects. If the input stimulus is oriented at  $\theta$ ,  $R_i$  is maximal when the difference between  $\theta$  and  $\theta_i$  is zero ( $\theta_i$  is the preferred orientation of the cortical cell that corresponds topographically to  $LGN_i$ ).  $R_i$  decays exponentially to zero as  $|\theta_i - \theta|$  approaches  $20^{\circ}$ .

#### Cortical cells

The spread of geniculate inputs to the cortex ensures that each LGN cell synapses on a group of cortical cells with a broad range of orientations (with a spread of  $60^{\circ}$ ). Cortical cells receive center stimulation as an oriented input stimulus applied to the receptive field center of LGN cells and surround stimulation as oriented stimuli applied to the LGN of the surrounding hypercolumns (or locations).

Excitatory and inhibitory cortical neurons are modeled separately as single units whose mean rate of firing is given by:

Excitatory cells

$$\frac{dE_i}{dt} = -0.01E_i + (J^{fe}F_i + \sum_j J_{ij}^{ee}E_j + \sum_j J_{ij}^{me}E_j)(1 - E_i) - \sum_j J_{ij}^{ie}I_j \quad (2)$$

Inhibitory cells

$$\frac{dI_i}{dt} = -0.01I_i + r(J^{fi}F_i + \sum_j J_{ij}^{ei}E_j + \sum_j J_{ij}^{mi}E_j)(1 - I_i) - \sum_j J_{ij}^{ii}I_j \quad (3)$$

where  $E_i$  represents excitatory and  $I_i$  represents inhibitory cells. In agreement with experimental evidence (Connors et al. 1982; McCormick et al. 1985) we chose  $r = 3$  to ensure that inhibitory cells have a higher firing rate than excitatory cells (by a factor of 2).

The first inhibitory term in each equation (i.e.,  $-0.01E_i$  and  $-0.01I_i$ ) describes the spontaneous decay in the absence of any stimulation. The stimulus-specific feedforward input to each cell,  $F_i$ , is given by the summed response of LGN cells centered at  $i$  with a spread of  $60^\circ$ .  $J^{fe}$  and  $J^{fi}$  are the strengths of feedforward connections and are equal for excitatory ( $fe$ ) and inhibitory ( $fi$ ) cells (we use the value 0.04 for these connection strengths; however, model predictions hold for a larger range of parameter values).  $J_{ij}^{ee}$  and  $J_{ij}^{ei}$  are the strengths of recurrent excitatory connections ( $ee$ ) and excitatory projections to inhibitory cells ( $ei$ ).  $J_{ij}^{ie}$  and  $J_{ij}^{ii}$  are the strengths of the inhibitory projections to excitatory cells ( $ie$ ) and inhibitory cells ( $ii$ ).  $J_{ij}^{me}$  and  $J_{ij}^{mi}$  are the strengths of long-range (modulatory) inputs to excitatory cells ( $me$ ) and inhibitory cells ( $mi$ ).

Figure 2B shows the model synaptic connections as described in Eqs. 2 and 3 by presenting an expanded diagram of four interconnected cortical neurons: two excitatory cells and two inhibitory cells. The connectivity pattern includes both intracolumnar (feedforward:  $J^{fe}$  and  $J^{fi}$ , and intracortical:  $J^{ee}$ ,  $J^{ei}$ ,  $J^{ie}$ , and  $J^{ii}$ ) and extracolumnar (external modulatory:  $J^{me}$  and  $J^{mi}$ ) connections. To simplify Fig. 2B, we do not represent indices  $i$  and  $j$  from Eqs. 2 and 3.

Our approach in constructing the model V1 microcircuits is based on implementing the basic circuit infrastructure as revealed by existing anatomic and neurophysiological data. However, although these data offer sufficient information regarding, for instance, the spread of excitatory and inhibitory connections and the specificity of long-range horizontal connections, the lack of complete information on the strength of the various connections implemented in the model makes detailed comparison with anatomic-physiological data difficult. Therefore, in specific instances (e.g., choosing peak synaptic conductances) we had to settle for a set of parameters that were held fixed throughout simulations, and the model's robustness was tested by varying these parameters and comparing the new predictions with the initial ones (see RESULTS).

### Short-range intracortical connections

Members of the excitatory population are interconnected by recurrent excitatory synapses (Martin 1988; Peters and Payne 1993), and members of the inhibitory population are interconnected by recurrent inhibitory synapses (Beaulieu and Somogyi 1990; Kisvarday et al. 1995; Sik et al. 1995). In addition, local excitatory cells excite neighboring inhibitory cells, which in turn inhibit excitatory cells (Anderson et al. 1994; Beaulieu and Somogyi 1990; McGuire et al. 1991).

Cortical cells have short-range excitatory and inhibitory connections within each hypercolumn, with the strength of connections decreasing as cortical neurons become more widely separated in orientation (Fries et al. 1977; Miller 1992; Nelson and Frost 1981). The strength of excitatory connections decays exponentially from 0.01 at distance 0 to 75% of the peak value at the  $40^\circ$  orientation difference between pre- and postsynaptic cells; the strength is 0 beyond  $40^\circ$ . The spread of excitatory connections that we use is motivated by cross-correlation data: Toyama et al. (1981) state that

"cells with orientation preferences up to  $40^\circ$  apart shared common excitatory input."

Consistent with evidence from cross-correlation studies (Hata et al. 1988; Michalski et al. 1983; Toyama et al. 1981) and from combined imaging and intracellular recording (Tucker and Katz 1998), intracortical inhibitory connections arise from cells with a broader distribution of orientation preferences than do intracortical excitatory connections. Recent evidence (Roerig and Katz 1998) suggests that although the majority of inhibitory inputs that a cell receives are from cells that lie within  $500 \mu\text{m}$ , excitatory inputs are restricted even closer, to  $300 \mu\text{m}$ . However, earlier studies (e.g., Ferster 1988; Hirsch and Gilbert 1991) had suggested that inhibitory connections may not spread further than excitatory ones. Taking these data together, we conservatively set the spread of inhibitory inputs to an orientation difference of  $60^\circ$  between pre- and postsynaptic cells. (The model generates qualitatively similar predictions if the spread of inhibitory connections is made larger than  $60^\circ$ ; conversely, reducing the spread of inhibition below  $50^\circ$  orientation difference yields incorrect predictions). Inhibitory connection strengths decay exponentially with distance, from a maximum value at distance 0 to 10% of the peak value at  $60^\circ$  orientation difference between pre- and postsynaptic cells. The strength of inhibitory connections is 0 beyond  $60^\circ$ .

Consistent with the experimental data reporting an asymmetry between the strength of excitatory and inhibitory synapses in V1 (e.g., Komatsu et al. 1988; Thomson and Deuchars 1994; Thomson and West 1993), peak inhibitory connection strengths were chosen stronger than excitatory ones (we use 0.08 for inhibitory-to-excitatory projections and 0.04 for inhibitory-to-inhibitory projections). More recent evidence for the bias toward inhibition in neocortical circuits was presented by Galarreta and Hestrin (1998). Their data suggest that over time neuronal activity is able to shift the balance between the strength of excitatory and inhibitory synapses to favor inhibition. For instance, after sustained synaptic activation at 20 Hz, the postsynaptic currents (PSC) of excitatory synapses were much more depressed than inhibitory ones. The average steady-state PSC levels were 4.2% for connections from excitatory to excitatory neurons and 6.6% for excitatory to inhibitory synapses, whereas the steady-state inhibitory PSC (IPSC) level of connections from inhibitory to excitatory neurons was 28.9% (the PSC levels were calculated relative to the current amplitudes before stimulation). These values suggest that, at steady state, inhibitory synapses could be at least 5 times more effective than excitatory synapses (similar results were reported under different stimulation patterns e.g., burst, as well as under a broad range of stimulation frequencies). Given that the center-surround stimulation protocol employed in our analysis requires continuous stimulation for many minutes and that in these conditions the neuronal discharge rates are usually high, we have incorporated the steady-state asymmetry between the strength of excitatory and inhibitory synapses without specifically modeling synaptic depression.

### Long-range intracortical connections

Long-range horizontal connections (Gilbert and Wiesel 1979; Livingston and Hubel 1984; Martin and Whitteridge 1984; Rockland and Lund 1982) link cells across distinct regions of the visual field and spread across four orientation hypercolumns (or locations) in the model. Although the spread of long-range connections is larger in primates, because our model is designed to explain data across species, the extent of horizontal connectivity was restricted to four orientation hypercolumns. Model long-range horizontal connections are excitatory and originate from pyramidal cells in the surround (cf. Gilbert and Wiesel 1989). These cells contact other pyramidal cells, as well as nearby inhibitory cells that are locally interconnected within a range of  $\pm 60^\circ$  (Kisvarday et al. 1986; McGuire et al. 1991). Model

activation of horizontal connections evokes direct iso-orientation excitatory and multisynaptic inhibitory responses from local pyramidal cells in an orientation-dependent fashion: stronger activation of iso-orientation domains and gradually weaker activation of cross-orientation domains. The strengths of model long-range horizontal connections are chosen in agreement with experimental evidence by Weliky et al. (1995) and Weliky and Katz (1994). They showed that the amplitude of synaptic inputs onto single cells evoked from distant cortical sites is modulated by a cyclical pattern of large- and small-amplitude responses, with the maximum correlation for neighboring cells and gradual shifts toward minimum correlation with increasing distance (see also Gilbert and Wiesel 1989; Malach et al. 1993). Thus, we set the strengths of model long-range horizontal connections as being maximal when they connect cortical cells with the same orientation preference; the strengths gradually decrease with increasing relative orientation between cells.

We label the inputs through long-range projections as external modulatory inputs (because these inputs are unable to activate cortical cells, their effect is made effective only when the classical receptive field is stimulated). Long-range connection strengths decay exponentially from  $J_i^{mi} = 0.03$  and  $J_i^{me} = 0.01$  at distance 0 to 25% of the peak value at  $60^\circ$  orientation difference between pre- and postsynaptic cells. Figure 2C represents the spatial spread of the various model connections types—i.e., intracortical excitatory and inhibitory synapses and long-range excitatory synapses.

## RESULTS

## Analysis of recurrent inhibition

To explain the contextual modulation of cortical responses, we have examined how neuronal activity is shaped by changes in the gain of local circuits induced by the concurrent stimulation of the classical and extraclassical receptive field. These changes occur through alterations of the balance between local excitation and inhibition. However, the asymmetry between the firing rates of inhibitory and excitatory cells and between the synaptic strengths of inhibitory and excitatory connections suggest that at high center contrast levels this balance is biased toward inhibition. Therefore, we hypothesize that the mechanism that explains the emergence of supra- and suboptimal cortical responses relies heavily on context-dependent modulation of recurrent inhibition. Specifically, when the surround and center stimuli are presented at the same optimal orientation, cortical responses become suboptimal due to the *increase* in local inhibition relative to the center-alone condition. Contrarily, when the surround and center stimulus orientations are orthogonal, cortical responses become supraoptimal because of the *decrease* in local inhibition level.

To test this hypothesis we first model the behavior of two

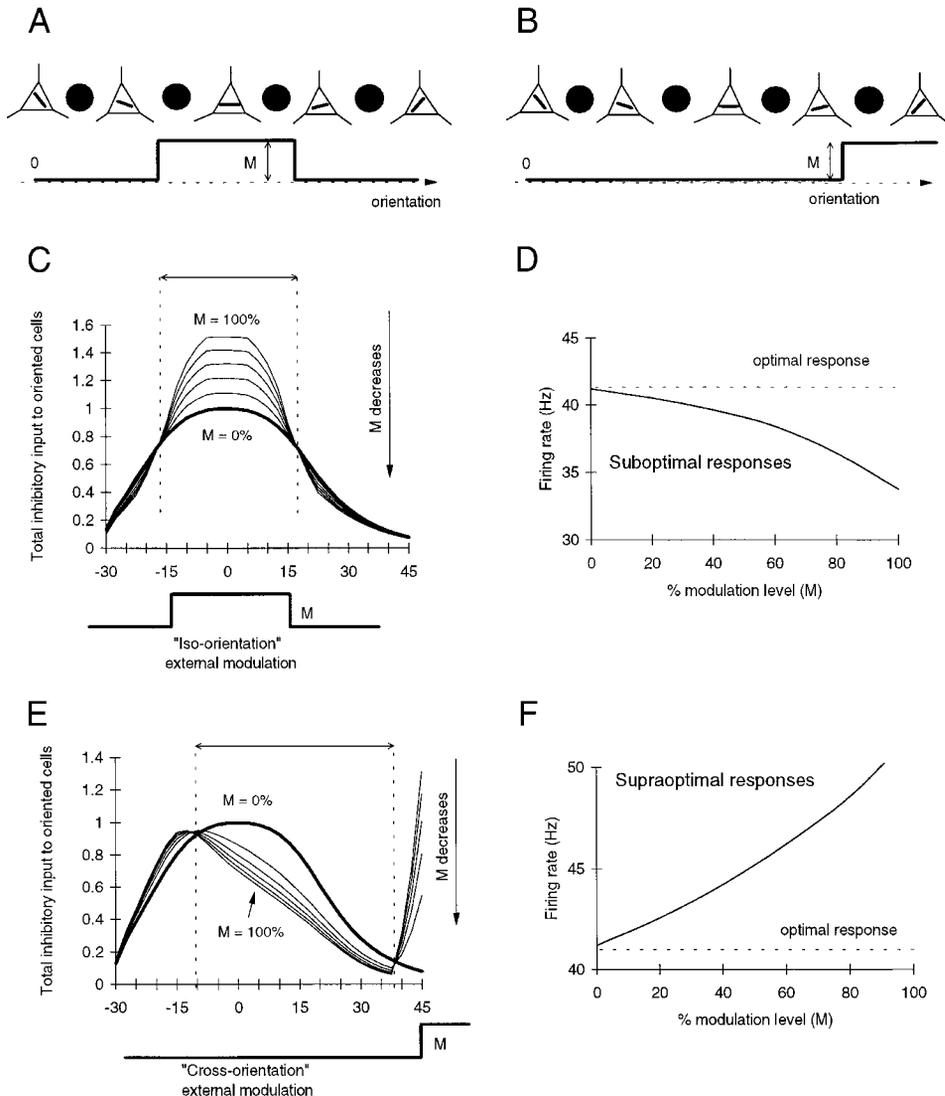


FIG. 3. Analysis of the facilitation-suppression effects induced by the external modulatory drive. *A*: external drive is applied only to iso-oriented neurons within the range  $0 \pm 15^\circ$ ; *B*: external drive is applied to cross-oriented neurons with orientation preferences differing by more than  $60^\circ$  counter-clockwise from the center stimulus orientation. Maximum amplitude of the external drive is  $M$ . External modulation is applied to both excitatory and inhibitory neurons according to their orientation difference with respect to the horizontal. *C*: total inhibitory input to oriented cells in the same hypercolumn. External modulation is applied to iso-oriented cells within an orientation range of  $0^\circ \pm 15^\circ$ . Bold line represents the center-alone condition ( $M = 0$ ), and thin lines represent center + external modulation. Thin lines (from top to bottom) correspond to  $M = 100, 80, 60, 40,$  and  $20\%$ . Below the x-axis is the geometric shape of the modulatory input (as a function of orientation). *D*: average firing rate of the cell tuned to  $0^\circ$  as a function of the external modulation level ( $M$ ). Dashed line: response level to the  $0^\circ$  center stimulus; thin line: response to center + modulatory input. *E*: total inhibitory input to oriented cells in the same hypercolumn. External modulation is applied to cross-oriented cells with orientation preferences in the range  $60 \pm 15^\circ$ . Bold line: center-alone condition ( $M = 0$ ); thin lines (from top to bottom) correspond to  $M = 100, 80, 60, 40,$  and  $20\%$ . *F*: average firing rate of the cell tuned to  $0^\circ$  as a function of the external modulation level ( $M$ ). Dashed line: response level to the  $0^\circ$  center stimulus; thin line: response to center + modulatory input.

intermixed populations of excitatory and inhibitory cells exposed to a fixed feedforward input and a variable modulatory input. The rationale for using such a configuration is that the fixed feedforward input is similar to a fixed oriented stimulus presented in the receptive field center, whereas the variable modulatory input is similar to the long-range effect of a stimulus of variable orientation presented outside the receptive field. The most interesting aspect of this analysis emerges when comparing the influence of a modulatory input applied to iso-oriented excitatory and inhibitory neurons (Fig. 3A), without affecting other parts of the network, with the effect of a modulatory input applied only to cross-oriented neurons (Fig. 3B). These types of external modulation resemble the effect of different kinds of long-range inputs to cortical cells.

The population of 72 excitatory and 72 inhibitory neurons is externally activated by two types of input: 1) a fixed feedforward input stimulus that is always presented in the center of the receptive field at  $0^\circ$ , and 2) a variable modulatory input that selectively activates excitatory and inhibitory subpopulations of neurons (Fig. 3, A and B). Each neuron from the two subpopulations can either be modulated by a signal of amplitude  $M$  or 0, according to the profile of the modulatory input. We examine the consequences of increasing  $M$  from 0 to maximum (100%) and applying it to: 1) iso-oriented excitatory and inhibitory neurons within the range  $0 \pm 15^\circ$  centered around the cell that prefers the  $0^\circ$  orientation (Fig. 3A), and 2) cross-oriented excitatory and inhibitory neurons with orientation preferences differing by  $60^\circ$  counterclockwise from the center stimulus orientation. In this case, the modulatory input was applied to neurons within the orientation preference range  $60 \pm 15^\circ$  (Fig. 3B). (Because network connectivity is symmetric we use only a counterclockwise stimulation; clockwise stimulation yields similar results).

Figure 3, C–F, illustrates quantitatively the effect of adding iso-oriented (Fig. 3, C and D) and cross-oriented (Fig. 3, E and F) external modulatory inputs. We investigate how the total inhibitory inputs to different oriented cells from the population of 72 excitatory neurons varies as a function of the strength of external modulation, with the feedforward input fixed and oriented at  $0^\circ$ . We show that the iso-oriented external modulatory drive *increases* the total inhibitory input to cortical cells that respond to the center stimulus (Fig. 3C, facilitation of inhibition), whereas the cross-oriented external modulatory drive *decreases* the total inhibitory input to cortical cells that respond to the same center stimulus (Fig. 3E, suppression of inhibition). The maximum facilitation and suppression of inhibition are obtained for maximum strength of the modulatory input ( $M = 100\%$ ).

Explanation for this behavior follows from the dynamic gain change at the local circuit level that results from the interaction of local inhibitory neurons modulated by the external drive. Thus, when the modulatory stimulus is applied to iso-oriented neurons, within the range  $0 \pm 15^\circ$ , both local iso-orientation excitatory and inhibitory cell populations receive strong excitation. However, because inhibitory cells typically fire at a higher rate than excitatory cells (McCormick et al. 1985), the net effect of the iso-orientation modulatory drive is biased toward inhibition. Figure 3C illustrates this effect (facilitation of inhibition) showing that when the amplitude of the modulatory drive ( $M$ ) is varied from 0 to 100% the total inhibitory input to oriented cells increases in magnitude above the center-

alone level (bold line). Thus as a consequence of increasing the local inhibition level, the responses of cells that prefer the  $0^\circ$  orientation are strongly suppressed (Fig. 3D); responses become suboptimal.

In contrast, when the modulatory stimulus is applied to cross-oriented neurons that prefer orientations differing by more than  $60^\circ$  counterclockwise from the center stimulus orientation, the more distant inhibitory cells located in the vicinity of cross-orientation domains are activated strongly by the modulatory drive (see the increase in inhibition for the cross-oriented cells in Fig. 3E). At the same time, the inhibitory cells near the iso-orientation domains fire at a lower rate because they do not actually receive the modulatory input (see the curves below the bold line in Fig. 3E). Because of this asymmetry in the firing rates of iso- and cross-oriented inhibitory cell populations, inhibitory cells near the iso-orientation domains are suppressed by the inhibitory cells near the cross-orientation domains. This effect is quantified in Fig. 3E, which shows that when  $M$  is increased from 0 (no external modulation) to 100%, the total inhibitory input to iso-oriented cells decreases in magnitude below the center-alone level (suppression of inhibition), and the tuning of suppression becomes narrower. This interaction further removes tonic inhibition from pyramidal cells in the vicinity of local iso-orientation inhibitory neurons, and thus the disinhibited target pyramidal cells fire supraoptimally in response to the  $0^\circ$  stimulus (Fig. 3F).

Figure 3, C–F, also shows that the strength of facilitatory and suppressive effects depends on the magnitude of the external drive  $M$ . If  $M$  is decreased in amplitude, the modulatory effect on local inhibitory cells diminishes because these neurons suppress only weakly the inhibitory interneurons to which they project. Thus, the normal receptive field balance between local excitation and inhibition is restored (Fig. 3, D and F).

We conclude from our analysis of recurrent inhibition that the response of oriented cells can be supraoptimally facilitated when the external modulation is applied to cross-orientation domains and suppressed when the external modulation is applied to iso-orientation domains. These effects are due to changes in the gain of the local circuitry that selectively regulates the local inhibition level depending on whether the modulatory inputs are applied to iso-orientation or cross-orientation subpopulations. We next use large-scale model simulations to explain the orientation and contrast dependence of contextual interactions in V1.

#### Large-scale model simulations

We have performed simulations to evaluate neuronal responses to oriented stimuli that covered 1) the classical receptive field alone (center stimulus), or 2) the classical and extraclassical receptive fields (center + surround stimuli). When the center stimulus is presented alone at the optimal orientation, Fig. 4A shows the model contrast response function. The response increases rapidly with increasing contrast and then saturates at high-contrast levels. The shape of this function is useful because it allows us to define the low- and high-contrast stimulus levels used in the center-surround simulations. Thus, we chose the low-contrast level at 15% because it produces cortical responses near the middle of the cell's dynamic range (in agreement with Levitt and Lund 1997), whereas the high-

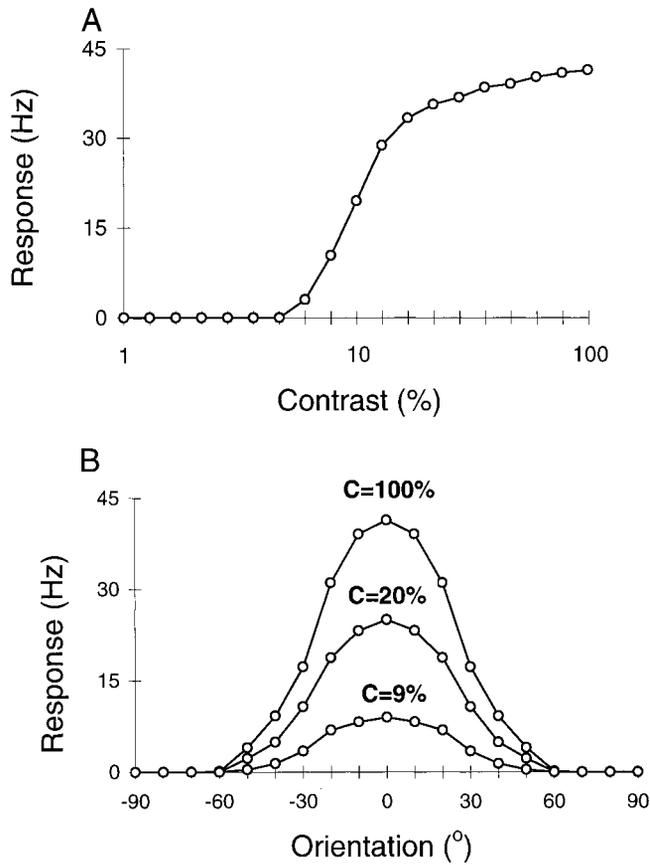


FIG. 4. Model responses to center stimulation alone. *A*: contrast response function obtained by center stimulation at the optimal orientation. *B*: tuning curves of a cell that prefers the  $0^\circ$  orientation as a function of contrast. The selectivity remains constant at center contrast levels of 100, 20, and 9%.

contrast level was chosen at 100% because it elicits the maximum response from the cell. As shown in previous models using recurrent excitation (e.g., Ben-Yishai et al. 1995; Somers et al. 1995), the orientation tuning of the receptive field center remains invariant with stimulus contrast. Figure 4*B* displays typical model orientation response curves at three different contrasts. As stimulus contrast is increased from 9 to 100%, cortical responses increase without losing their orientation selectivity—i.e., the model generates sharp orientation tuning curves across a broad range of stimulus contrasts. This contrast invariance of orientation tuning is consistent with experimental data (e.g., Sclar and Freeman 1982).

Our goal in the subsequent simulations was to understand how neuronal responses are modulated by changes in the balance between local excitation and inhibition as a result of surround stimulation. Therefore, we repeated the same experimental manipulations used by Sillito et al. (1995) and Levitt and Lund (1997). The receptive field center was always stimulated at the optimal orientation, whereas surround orientation was varied systematically from  $0$  to  $180^\circ$  to fully investigate the orientation dependence of contextual effects. The center stimulus was either presented at high (100%) or low (15%) contrast levels, whereas surround stimuli were presented only at high contrast (100%). The results mainly show the firing rate of cells receiving optimal center stimulation when the center contrast and surround orientation covary.

Figure 5, *A* and *B*, illustrates the effect of the disinhibitory

mechanism that we propose. Figure 5*A* shows that responses to the center stimulus are suppressed by an iso-oriented surround. However, responses to the same center stimulus become supraoptimal in the presence of an orthogonal or oblique surround. These results should be compared with the experimental data obtained in similar conditions (Levitt and Lund 1997) (our Fig. 1*B*). When the center stimulus is presented at low contrast, the facilitatory effects induced by cross-oriented surround stimuli disappear or become very small (Fig. 5*B*), and this determines a broader tuning of the suppressive effects (Levitt and Lund 1997) (Fig. 1*C*).

To quantify the tuning strength of the modulatory effects induced by the surround we calculated an orientation suppression index. For this analysis we considered the response suppression values  $R(\theta_i)$  obtained at surround orientations  $\theta_i$  in the range ( $-90^\circ$  to  $+90^\circ$ ), calculated by subtracting the response during center + surround conditions from the response when

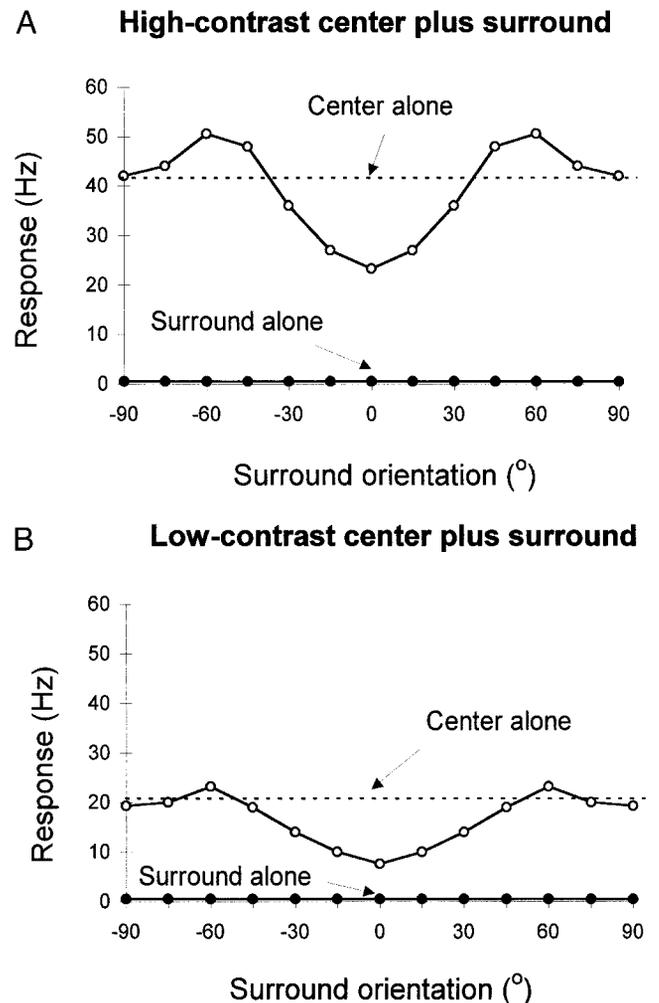


FIG. 5. Orientation- and contrast-dependent suppression and facilitation. *A*: responses to high-contrast optimal center stimulus (contrast 100%) paired with high-contrast surround of varying orientation ( $\circ$ ) and to surround stimulus alone ( $\bullet$ ). Center contrast and surround orientation values are identical with those used by Levitt and Lund (1997). *B*: responses to the low-contrast optimal center stimulus (contrast 15%) paired with a high-contrast surround of varying orientation ( $\circ$ ) and to the surround stimulus alone ( $\bullet$ ). Center contrast and surround orientation values are identical with those used by Levitt and Lund (1997). Dashed lines: response to the optimal stimulus alone (high center contrast value is 100% in *A*; low center contrast value is 15% in *B*).

the center is presented alone (surround orientation step is  $\Delta\theta = 15^\circ$ ). The suppression index is calculated using Fourier analysis, where the second harmonic is extracted from the set of response suppression values and then normalized by dividing by the mean response suppression values in the range ( $-90^\circ$  to  $+90^\circ$ ).

$$\text{Suppression Index} = \sqrt{a^2 + b^2} / (\text{MeanResponse}),$$

where

$$a = \sum_{i=1}^N R(\theta_i) \cos(2\theta_i)$$

and

$$b = \sum_{i=1}^N R(\theta_i) \sin(2\theta_i)$$

(Wörgötter and Eysel, 1991).

For the data displayed in Fig. 5, *A* and *B*, when the suppression index is calculated for both high- and low-contrast center + surround conditions we found a 78% decrease when the center stimulus is presented at low contrast (high-contrast index = 3.01; low-contrast index = 0.67). Thus, changing the contrast of the center stimulus modulates not only the amplitude of the suppressive effects but also the tuning of surround suppression.

#### Analysis of contrast effects

To further investigate the mechanism that produces the results shown in Fig. 5, *A* and *B*, we have analyzed numerically the changes in the response of excitatory and inhibitory neurons in a representative population of cells with orientation preferences in the range ( $-30$  to  $+75^\circ$ ), with the surround stimulus being presented either at  $0^\circ$  or  $60^\circ$  (Fig. 5). These values for surround orientation are representative for our study because they are exactly the conditions in which cortical responses are maximally suppressed ( $0^\circ$  surround orientation) and maximally facilitated ( $60^\circ$  surround orientation). In all simulations, the center stimulus is presented at  $0^\circ$ , and the

contrast level is fixed either at 100% or 15%. We explain first how responses become supraoptimal when the surround is oriented at  $60^\circ$  and suboptimal when the surround is oriented at  $0^\circ$ . We then show that the facilitatory effect of the cross-oriented surround disappeared at low-contrast center stimulation.

**HIGH-CONTRAST CENTER STIMULATION.** When the surround is oriented at  $60^\circ$  it yields a stronger activation of inhibitory cells in the vicinity of iso-orientation domains (e.g.,  $60^\circ$ ) and weaker activation of inhibitory cells in the vicinity of non-iso-orientation domains (e.g.,  $0^\circ$ ; iso and non-iso-orientation are considered with respect to surround orientation). For example, Fig. 6 represents key intermixed populations of excitatory and inhibitory cells that receive long-range inputs from one pyramidal cell in the surround. Although the projection from the surround targets both excitatory and inhibitory neurons (e.g., Gilbert and Wiesel 1989; Weliky and Katz 1994; Weliky et al. 1995), the strength of long-range connections is orientation-dependent: 1) stronger projections to iso-orientation domains (e.g., the projection to the pyramidal cell on the *left* in Fig. 6) and to the inhibitory cells in the vicinity of iso-orientation domains and 2) weaker projections to non-iso-orientation domains (e.g., the projection to the pyramidal cell on the *right* in Fig. 6 that is tuned to horizontal orientation) and to the inhibitory cells in the vicinity of non-iso-orientation domains.

We have calculated the changes in activity level for inhibitory and excitatory cells relative to the center-alone condition (Fig. 7, *A* and *B*). Because of their higher firing rates, inhibitory cells with orientation preference close to that of the surround (i.e., the cells with orientation preferences near  $60^\circ$ ) are able to fire continuously in response to the center and surround stimuli and thus exert tonic inhibition on their postsynaptic targets (i.e., inhibitory and excitatory cells with orientation preferences near  $0^\circ$ ). The effect of this interaction can be seen in Fig. 7*A*, where the activity of inhibitory cells is represented for the population with orientation preference range between  $-30^\circ$  and  $75^\circ$ . This figure shows that the activity of inhibitory cells oriented away from the surround orientation (e.g., the  $0^\circ$  cells) diminishes below the center-alone condition. The net effect of this removal of tonic inhibition, or disinhibition, from pyramidal cells in the vicinity of the  $0^\circ$  domain is an increase in the strength of excitation relative to the center-alone condition (Fig. 7*B*). This explains the supraoptimal responses obtained when the surround is cross-oriented with respect to the center stimulus (Fig. 5*A*).

However, when the surround is iso-oriented at  $0^\circ$ , there is an overall increase in the activity of inhibitory cells above the center-alone condition (Fig. 7*A*). The effect of this increase of tonic inhibition is a decrease in the strength of excitation relative to the center-alone condition (Fig. 7*B*), thus explaining the suboptimal responses obtained when the surround is iso-oriented (Fig. 5*A*).

**LOW-CONTRAST CENTER STIMULATION.** Although the mechanism that relies on the local interaction between inhibitory interneurons is reliably strong when the receptive field is stimulated at high contrast, it breaks down when the center is presented with a low-contrast stimulus. We consider the case in which the surround orientation is maintained fixed at  $60^\circ$ , whereas the center orientation is  $0^\circ$  at a contrast level of 15%. In this case, the response of inhibitory cells that are

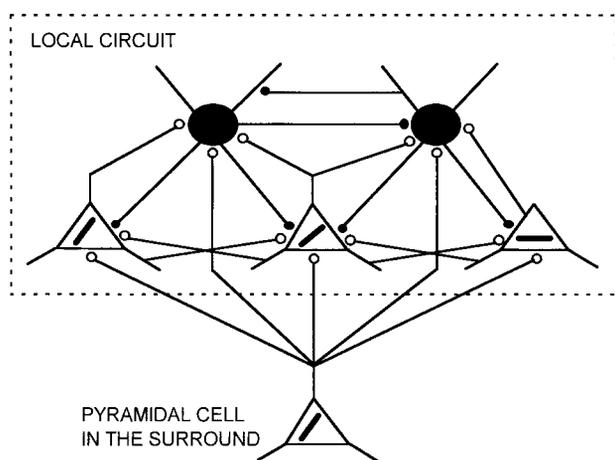


FIG. 6. Interactions between representative cells in the superficial layers of V1 embedded in their local circuit (dashed rectangle). Pyramidal cells in the surround project to both excitatory (triangles) and inhibitory (filled circles) neurons. ○, excitatory connections; ●, inhibitory connections.

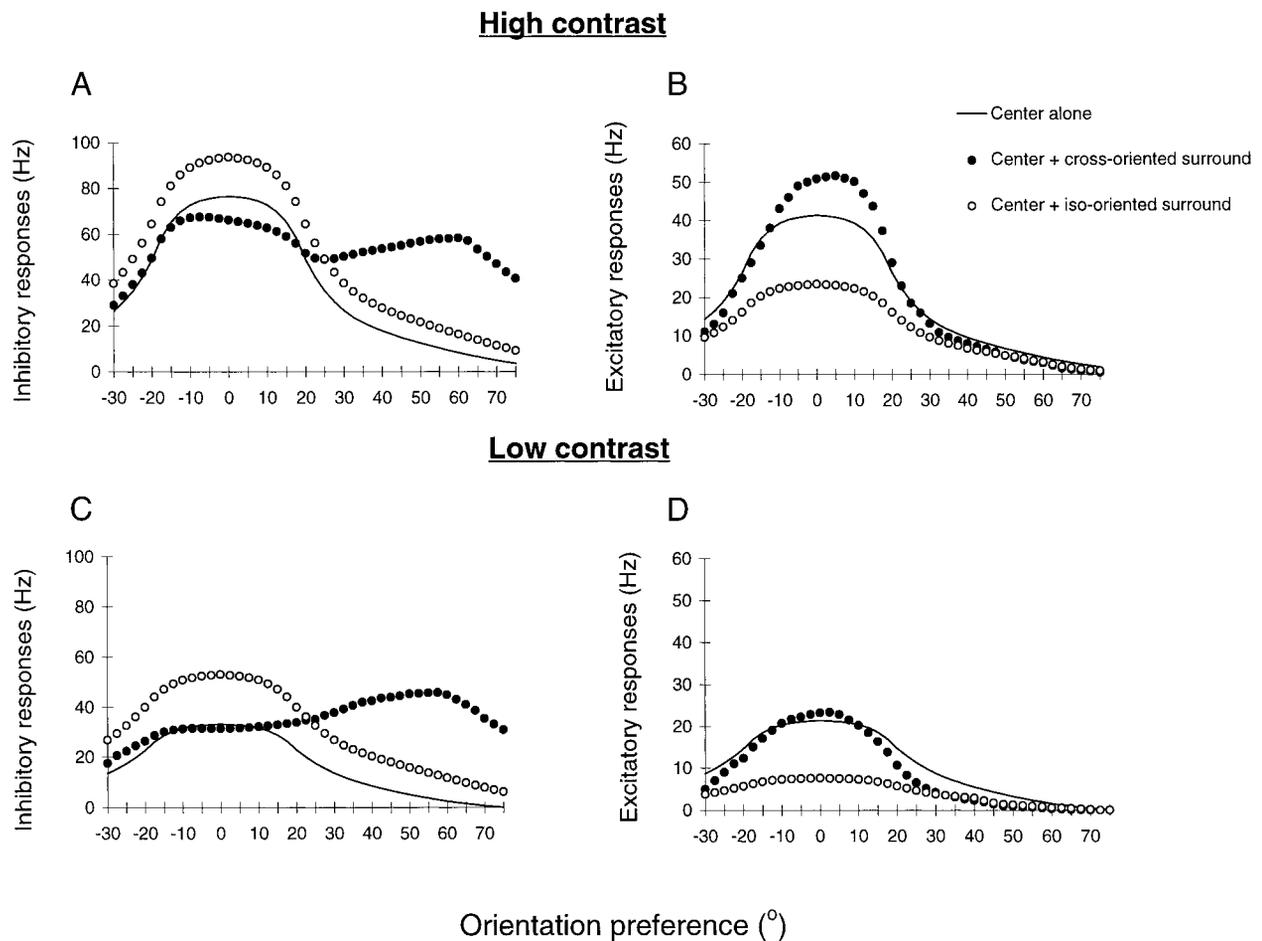


FIG. 7. Analysis of contrast-dependent center-surround interactions. *A, B*: high-contrast center stimulation; *C, D*: low-contrast center stimulation. *A*: response of inhibitory cortical cells with orientation preferences between  $-30^{\circ}$  and  $75^{\circ}$ . When the surround is cross oriented at  $60^{\circ}$  ( $\bullet$ ), cells oriented away from the surround orientation are released from local inhibition relative to the center-alone condition (solid line). When the surround is iso-oriented at  $0^{\circ}$  ( $\circ$ ) there is an overall increase in the local inhibition level. *B*: response of excitatory cortical cells with orientation preferences between  $-30^{\circ}$  and  $75^{\circ}$ . When the surround is cross-oriented, the net effect of the removal of tonic inhibition from pyramidal cells in the vicinity of the  $0^{\circ}$  domain is an increase in the strength of excitation relative to the center-alone condition. When the surround is iso-oriented, there is a decrease in the response of excitatory cells relative to the center-alone condition. Center stimulus: 100% contrast level, orientation is fixed at  $0^{\circ}$  (*A, B*). *C*: response of inhibitory cortical cells with orientation preferences between  $-30^{\circ}$  and  $75^{\circ}$ . When the surround is cross-oriented, inhibitory responses are suppressed to a lesser extent than in the high-contrast case. *D*: response of excitatory cortical cells with orientation preferences between  $-30^{\circ}$  and  $75^{\circ}$ . When the surround is cross-oriented, the total excitatory input to cortical cells does not differ substantially from the center-alone condition. Center stimulus: 15% contrast level, orientation is fixed at  $0^{\circ}$  (*C, D*).

iso-oriented with respect to the surround (i.e., the inhibitory cells tuned to  $60^{\circ}$ ) diminishes relative to the center-alone condition, and these cells therefore suppress only weakly their postsynaptic targets, including other inhibitory cells. Figure 7C shows that, relative to the center-alone condition, inhibitory responses are suppressed to a lesser extent than in the high-contrast case. Thus, at low contrast, the iso-oriented inhibitory cells are no longer capable of sustaining the release from inhibition of the non-iso-oriented excitatory cells. This results in a total excitatory input to cortical cells which does not differ substantially from the center-alone condition (Fig. 7D). The net effect of this interaction is that the facilitatory effects induced by cross-oriented surround stimuli disappear or become very small (Fig. 5B). This also determines a broader tuning of the suppressive effects (see the suppression index analysis). Indeed, Fig. 7, C and D, predicts that the disinhibitory effect from Fig. 7, A and B,

will become ineffective at low contrast. Thus, Fig. 5B shows that for a large range of surround orientations, the response to the low-contrast center stimulus is suppressed.

The model therefore demonstrates that orientation-dependent long- and short-range connections can have bi-phasic modulatory effects, depending on the relative orientation and contrast between center and surround.

#### Model parameters

To demonstrate that the effects investigated in our model are not caused by particular arrangements of parameters but constitute emergent properties of the basic principles implemented here, we varied selected parameter values that control the strengths of key synaptic connections involved in the center-surround interactions. Thus, Fig. 8 illustrates the parametric effects of varying the amount of local (short-range) inhibition,

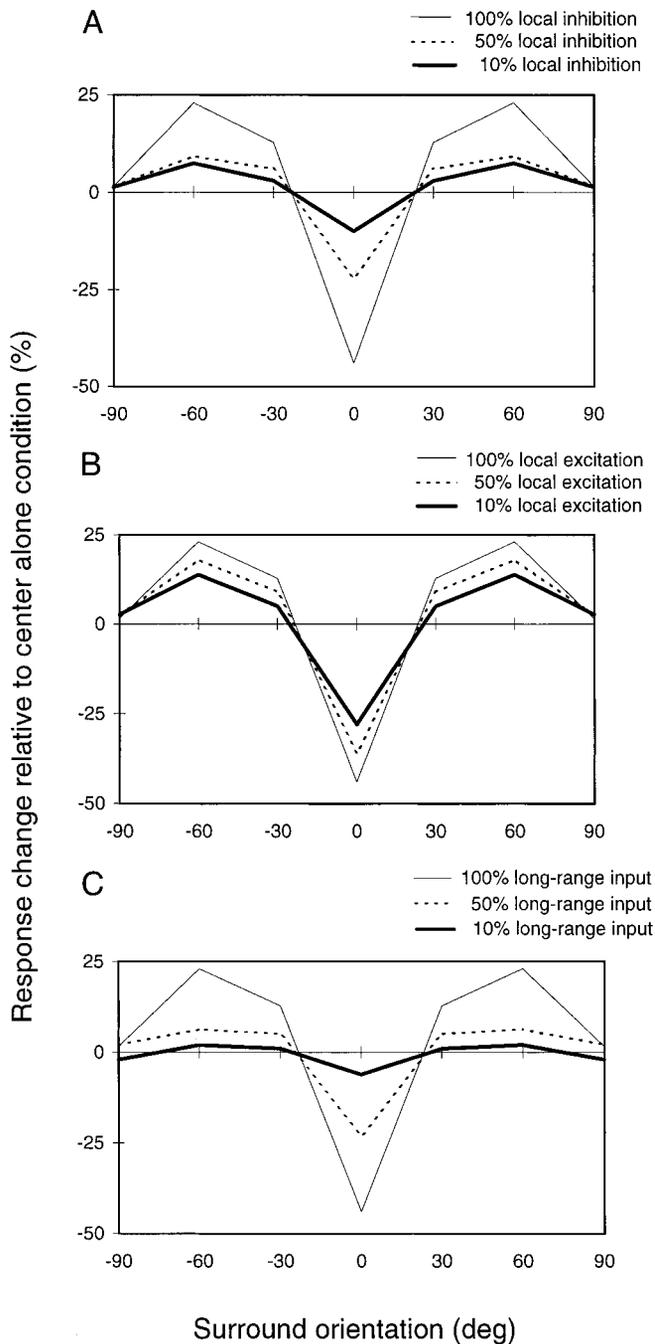


FIG. 8. Comparison of orientation-dependent suppression and facilitation effects when the total input to cortical cells is varied. *A*: response change relative to center-alone condition when the strength of local inhibition is reduced (short-range parameters  $J_{ij}^{ie}$  and  $J_{ij}^{ii}$  are decreased (see Eqs. 2 and 3)). *B*: response change relative to center-alone condition when the strength of local excitation is reduced (short-range parameters  $J_{ij}^{ee}$  and  $J_{ij}^{ei}$  are decreased). *C*: response change relative to center-alone condition when the strength of long-range input is reduced [connection strengths  $J_{ij}^{me}$  and  $J_{ij}^{mi}$  are decreased (see Eqs. 2 and 3)].

local (short-range) excitation, and long-range input to cortical neurons, by comparing the magnitude of orientation-dependent suppression and facilitation effects when the optimal center stimulus (contrast 100% and orientation  $0^\circ$ ) is paired with a surround orientation varying between  $-90^\circ$  and  $+90^\circ$ . Figure 8A shows the change in response relative to the center-alone condition when the strength of local inhibition is reduced

(short-range parameters  $J_{ij}^{ie}$  and  $J_{ij}^{ii}$  are decreased; see Eqs. 2 and 3). In this case, as the response of inhibitory interneurons is reduced by a factor of 10, the magnitude of both suppressive and facilitatory effects diminishes. Figure 8B illustrates the change in response when the strength of local excitatory input is reduced (short-range parameters  $J_{ij}^{ee}$  and  $J_{ij}^{ei}$  were decreased). Similar to the effect of reducing local inhibition level, both facilitatory and suppressive surround effects diminished in strength when the short-range excitatory input to both excitatory and inhibitory cells varies from 100 to 10%. Finally, a similar effect can be seen in Fig. 8C, which shows the response change when the strength of long-range input is reduced (connection strengths  $J_{ij}^{me}$  and  $J_{ij}^{mi}$  are decreased; see Eqs. 2 and 3). All simulations are performed under conditions similar to those in which the basic surround effects were investigated (Figs. 5 and 7).

Two conclusions can be drawn from Fig. 8. First, large variations in the strength of local inhibition and excitation (from 100 to 10%), and long-range input (from 100 to 50%) do not abolish the shift between supra- and suboptimal responses of cortical cells. This demonstrates that the effects illustrated in Fig. 5 constitute emergent properties that result from the model's principles. Second, the strengths of short-range inhibition and long-range input to cortical cells are critical for producing the shift between supraoptimal and suboptimal cortical responses. As Fig. 8A shows, reducing the strength of local inhibition by a factor of 10 reduces the magnitude of both supra- and suboptimal responses, but the reduction is much weaker if the strength of local excitation is reduced by the same amount. However, decreasing the total long-range input by a factor of 10 (Fig. 8C) completely abolishes the modulatory effects due to the surround. These results confirm our initial hypothesis: the local interaction between inhibitory interneurons modulated by the presence of surround stimuli constitutes the key requirement for explaining orientation and contrast dependence of contextual effects.

## DISCUSSION

The context-dependent removal of inhibition through local disinhibition that we propose here is an intricate process that yields an orientation-dependent dynamic gain control mechanism: an oriented surround increases the responsiveness of cross-oriented pyramidal cells via a disinhibitory mechanism, whereas iso-oriented pyramidal cells are strongly suppressed. Thus, our model incorporates principles that depend strongly on interneuron-interneuron interactions, a ubiquitous feature of neural connectivity in the mammalian brain. Disinhibitory interactions, although underinvestigated models of visual processing, were first hypothesized to be involved in the excitation induced in Deiters neurons when presynaptic cerebellar Purkinje cells are inhibited (Ito et al. 1968). Disinhibitory circuits have been observed in the pericruciate cortex of the cat (Kelly and Renaud 1974) and have been implicated in the initiation (Getting and Dekin 1985) and generation (Hultborn et al. 1971) of rhythmic activities in neuronal populations. More recently, Toth et al. (1997) have suggested that the septal projection to the hippocampus mediates the disinhibition of hippocampal pyramidal cells. However, despite their role in other brain systems, the function of disinhibitory mechanisms in the visual cortex has always been neglected in favor of recurrent excita-

tion (Ben-Yishai et al. 1996; Douglas et al. 1995; Somers et al. 1995). This omission may be one of the reasons why the assumptions of other models of extraclassical receptive field effects in V1 (e.g., Somers et al. 1998; Stemmler et al. 1995) were insufficient to explain the emergence of orientation-dependent supraoptimal cortical responses and the contrast regulation of the shift between supra- and suboptimal responses. These models of cortical function were only able to explain the influence of center contrast on the sign of contextual effects.

The key finding of our study is that under some center-surround configurations the responses of inhibitory interneurons can be completely reversed: iso-oriented stimuli in the surround increase the firing rate of local inhibitory cells that further suppress their postsynaptic pyramidal cells, and cross-oriented stimuli in the surround decrease the firing rate of local inhibitory cells that further disinhibit their postsynaptic pyramidal cells. In addition, the magnitude of the disinhibitory effect decreases with reductions in the center contrast level. Thus, the model advances a clear-cut prediction: Measuring the total intracellular excitatory and inhibitory synaptic responses during in vivo presentations of different center-surround configurations would yield inhibitory responses below the center-alone condition and excitatory responses above the center-alone condition when the surround is cross-oriented, and inhibitory responses above the center-alone condition and excitatory responses below the center-alone condition when the surround is iso-oriented.

The large-scale model with which we have examined the specificity of contextual influences in V1 implements several types of connections between cortical neurons. However, only one assumption is critical. As shown in our initial analysis, recurrent inhibition is the key assumption responsible for the disinhibitory mechanism that controls the contrast-regulated shift between supra- and suboptimal responses. Nonetheless, the disinhibitory mechanism acts only when the local balance between excitation and inhibition is changed by the presence of cross-oriented surround stimuli. Therefore the results reported here depend strongly on the anatomic substrate for surround integration—i.e., long-range horizontal connections. These connections are known to target neurons with similar orientation preferences (Gilbert and Wiesel 1989; Malach et al. 1993; McGuire et al. 1991) and constitute a property of the connectivity pattern in the superficial layers of V1. But cells sensitive to contextual influences have also been found in layers 4 and 6 (in addition to layer 2–3) (Levitt and Lund 1997), where long-range horizontal connections do not appear to exist. Therefore, in an extension of our model (unpublished results), we added interlaminar connections (layer 4 → layer 2–3 → layer 6) as a possible substrate for surround effects in other layers of V1. A surprising prediction of our model is that contextual effects similar to those seen in the superficial layers of V1 (as shown in Fig. 5) can also be generated in layer 4 and layer 6. Furthermore, by modeling the corticogeniculate feedback (V1 layer 6 to LGN), we were able to show that LGN cells become sensitive to extraclassical receptive field stimuli (cf. Cudeiro and Sillito 1996). These effects are due to the cortical feedback that propagates neuronal activity resulting from the disinhibitory mechanism in the superficial layers of V1 to layer 4 and the LGN, thus making these neurons sensitive to visual context despite the absence of anatomic substrate for surround integration. Moreover, by incorporating cortical

feedback, the orientation-dependent facilitatory (or disinhibitory) effect of the surround is able to bring pyramidal cells to almost three-fold supraoptimal response levels (cf. Levitt and Lund 1997; Sillito et al. 1995).

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