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Local Circuit Inhibition in the Cerebral Cortex as the source of Gain Control and Untuned Suppression

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Abstract

Theoretical considerations have led to the concept that the cerebral cortex is operating in a balanced state in which synaptic excitation is approximately balanced by synaptic inhibition from the local cortical circuit. This paper is about the functional consequences of the balanced state in sensory cortex. One consequence is gain control: there is experimental evidence and theoretical support for the idea that local circuit inhibition acts as a local automatic gain control throughout the cortex. Second, inhibition increases cortical feature selectivity: many studies of different sensory cortical areas have reported that suppressive mechanisms contribute to feature selectivity. Synaptic inhibition from the local microcircuit should be untuned (or broadly tuned) for stimulus features because of the microarchitecture of the cortical microcircuit. Untuned inhibition probably is the source of Untuned Suppression that enhances feature selectivity. We studied inhibition's function in our experiments, guided by a neuronal network model, on orientation selectivity in the primary visual cortex, V1, of the Macaque monkey. Our results revealed that Untuned Suppression, generated by local circuit inhibition, is crucial for the generation of highly orientation-selective cells in V1 cortex.

Keywords

cerebral cortex; synaptic inhibition; automatic gain control; orientation selectivity; untuned suppression

INTRODUCTION

The aim of this review is to consider how cortical microcircuitry and inhibitory interactions lead to Untuned Suppression in the cerebral cortex, and also what are the functional consequences of Untuned Suppression.

Theoretical analysis of cortical models and cortical data have led to the concept that the operating point of the cortex is a balanced state in which synaptic excitatory and inhibitory currents across the cell membranes of cortical neurons are approximately equal (Brunel & Wang, 2003; Hamaguchi, Riehle, & Brunel, 2011; Hansel & van Vreeswijk, 2012; Rajan, Abbott, & Sompolinsky, 2010; Shelley, McLaughlin, Shapley, & Wiesel, 2002; van Vreeswijk & Sompolinsky, 1996). There is a growing body of experimental evidence in

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support of the balanced-state concept (Haider, Duque, Hasenstaub, & McCormick, 2006; Okun & Lampl, 2008; Poo & Isaacson, 2009; Shew, Yang, Yu, Roy, & Plenz, 2011; Stratford, Tarczy-Hornoch, Martin, Bannister, & Jack, 1996; Wehr & Zador, 2003; Zhang, Tan, Schreiner, & Merzenich, 2003). The concept of a balanced state has many implications for understanding how the cortex functions (Brunei & Wang, 2003; Hansel & van Vreeswijk, 2012; Isaacson & Scanziani, 2011; Rajan, et al., 2010; Shelley, et al., 2002; Shew, et al., 2011; van Vreeswijk & Sompolinsky, 1996). As we will show, a computational model of the cortex that operates in a balanced state reveals that cortical synaptic inhibition has dual functional roles: 1) inhibition controls the gain of the local circuit and 2) inhibition enhances feature selectivity through broadly-tuned or Untuned Suppression. Then we will draw on our own experimental work on Untuned Suppression in the visual cortex as an example of the functional importance of local circuit inhibition.

MODEL OF THE CORTICAL NETWORK

In order to understand the role of local circuit inhibition in the cortex we need to consider a neuronal network model for the cortex. We will discuss the framework of a large-scale model that was developed to understand the mechanisms of orientation selectivity in the visual cortex and also the diversity of selectivities, firing rates, and receptive field properties that are observed in the cortex (McLaughlin, Shapley, Shelley, & Wiesel, 2000). In order to produce a model that emulated cortical function, we were compelled to choose parameters for the model that placed the model in a balanced state. Then we were able to observe how the dynamics of the model were under the control of local circuit inhibition.

The model we discuss here was a model of VI cortex, constrained by biological measurements wherever possible (McLaughlin, et al., 2000). It was a model of a single layer of VI. As in the real cortex, the neuronal population of the cortical network model consisted of two kinds of neurons: excitatory and inhibitory. About 25% of the total number of model neurons were inhibitory. In the real cortex there are at least three different sub-types of inhibitory neuron (Markram, et al., 2004) but in the model there was only a single type of fast inhibitory neuron. As a first approximation, many models have treated excitatory and inhibitory cells as Integrate-and-Fire (IF) neurons, and so we did in this model too. The time evolution of the membrane potentials of E and I neurons can be described by a set of equations as follows:

$$\begin{aligned} dv_E^j/dt &= -g(v_E^j - V_R) - g_{EE}(t)(v_E^j - V_E) - g_{EI}(t)(v_E^j - V_I) \\ dv_I^k/dt &= -g(v_I^k - V_R) - g_{IE}(t)(v_I^k - V_E) - g_{II}(t)(v_I^k - V_I) \end{aligned} \quad (1)$$

where v_E^j is the membrane potential of the j -th excitatory neuron and v_I^k is the membrane potential of the k -th inhibitory neuron. When v_E^j (or v_I^k) exceeds a threshold $V_T = -55$ mV, the model neuron fires a nerve impulse and the potential is reset to the resting potential V_R . It is generally accepted that, approximately, $V_R = -70$ mV, $V_T = -55$ mV, $V_I = -80$ mV and $V_E = 0$ mV. In the original large-scale model $j = 1, 12,288$ and $k = 1, 4096$

Distinctive features of our model (McLaughlin, et al., 2000) that were incorporated in all subsequent versions include:

- Local lateral connectivity in the cortex that is nonspecific and isotropic in cortical space, with lateral monosynaptic inhibition acting at shorter length-scales than excitation.
- An ordered map for orientation preference of cortical neurons laid out as pinwheel patterns across the model's cortical surface, based on experimental results from

optical imaging experiments of preference in V1. Orientation preference is conferred on the model's cortical cells from the convergence of input from many LGN cells, laid out as segregated subregions of On-and Off-center cells.

- A disordered map of spatial phase preference with a broad distribution of spatial phase preference. The convergent input from LGN cells sets a spatial phase preference that varies widely across the population of model cortical neurons.
- Strong cortico-cortical inhibition.

Membrane potential changes are induced by conductance changes in such a conductance-based IF model. Conductance changes are induced in target neurons by nerve impulses in all of the target neuron's source neurons. The cortico-cortical synaptic conductances g_{EE} , g_{EI} , g_{IE} , g_{II} couple the neurons to each other. Each neuron's synaptic conductance is the sum of single conductance shots evoked by nerve impulses coming from all the source neurons in the network connected to that neuron. The synapses have their own characteristic temporal impulse responses, respectively $G_E(t)$ for excitatory synapses or $G_I(t)$ for inhibitory synapses. Excitatory synapses are modeled as glutamate AMPA type synapses with a time to peak of 3 msec, while inhibitory synapses are of the GABA_A type with time to peak of 5 msec. It is important to know that the inhibitory synapses are fast but not as fast as the excitatory. More elaborate, more realistic, models should include in addition slower glutamate excitatory synapses with NMDA postsynaptic receptors and slower inhibitory synapses with GABA_B receptors, in order to account completely for the response dynamics of cortical cells. Later versions of the model did include NMDA receptors (Tao, Cai, McLaughlin, Shelley, & Shapley, 2006) but have achieved reasonable agreement with data without GABA_B receptors in the model.

Spatial summation of cortico-cortical synaptic excitation and inhibition is crucial for relating a network model to the function of the real cortex. Each synaptic conductance is assumed to have a spatial point-spread function determined by the spatial spread of axon terminals and target-cell dendrites. These spatial point-spreads can be derived from neuroanatomical measurements. What we are considering in this paper are the local circuits of the cortex and for these we can approximate the point-spread function for the excitatory conductances g_{EE} and g_{IE} as Gaussian functions with a spread of 200 μm while the inhibitory conductances g_{EI} and g_{II} have spatial spreads of 100 μm , approximately (Figure 1). In the original paper on the large-scale model (McLaughlin, et al., 2000) full justification was given for the choices of spatial scales for the excitatory and inhibitory conductances, based on neuroanatomical observations.

Balanced State

Many different models with different connection rules can be constructed based on the network described by equations 1. By trial and error with many simulations, we found that in order to simulate the behavior of the real cortex, the network needs to be in a balanced state, meaning that the excitatory and inhibitory synaptic currents must be approximately balanced, averaged over time (Shelley, et al., 2002; Wieleaard, Shelley, McLaughlin, & Shapley, 2001). The criteria for judging that the model simulated the real cortex was that it successfully emulated the real cortex's distribution of spike rates, and neuronal dynamics of responses to stimuli, and receptive field properties like orientation selectivity. The only regime that enabled the model to work like the real cortex was an approximately balanced state. Based on the approximation that the membrane potential is on average near the resting potential V_R , if the time average of excitatory and inhibitory synaptic currents are approximately equal, then the following equation applies:

$$\langle g_{EE}(t)(V_E - V_R) \rangle_t = \langle g_{EI}(t)(|V_I - V_R|) \rangle_t \quad (2)$$

where the notation $\langle \dots \rangle_t$ denotes time average. The balance described by eq. 2, together with the relative values of the two electromotive forces in eqn. 2, $V_E - V_R \gg |V_I - V_R|$, implies a much larger average inhibitory than excitatory conductance; for instance for excitatory neurons,

$$\langle g_{EI}(t) \rangle_t = [(V_E - V_R)/(V_I - V_R)] \langle g_{EE}(t) \rangle_t \gg \langle g_{EE}(t) \rangle_t \quad (3)$$

The modeling result, that to emulate the real cortex, excitatory and inhibitory currents need to be approximately balanced, is consistent with many experimental measurements in different cortices and different species (e.g. Haider, et al., 2006; Okun & Lampl, 2008; Poo & Isaacson, 2009; Shew, et al., 2011). The consequence -- that inhibitory conductance has to be much bigger than excitatory conductance -- is therefore also confirmed by the experimental evidence for balanced currents.

High Inhibitory Conductance and Gain Control in the Cortical Model

The high inhibitory conductance causes the cortex to be in a high conductance state (Destexhe, 2010; Destexhe, Rudolph, & Pare, 2003; Shelley, et al., 2002). There are many functional implications of the high conductance state. Here we point how one can use the existence of the high conductance state to conclude that local circuit inhibition acts like a local gain control signal. In the limit of high synaptic conductance, one can simplify eq. 1. Let us consider only the excitatory neurons. In a high conductance state we can approximate $dv_E^j/dt=0$ meaning that if the conductance is high enough, the membrane reaches its equilibrium value instantaneously. Also we need to calculate $v_{ER}^j(t) = v_E^j(t) - V_R$, the modulation of the membrane potential from the resting potential—it is this $v_{ER}^j(t)$ that controls spike rate and neural communication. Then eq. 1 becomes

$$g(v_{ER}^j) + g_{EE}(t)(v_{ER}^j - [V_E - V_R]) + g_{EI}(t)(v_{ER}^j - [V_I - V_R]) = 0 \quad (4)$$

We make the approximation that the leakage term $g(v_{ER}^j)$ is negligibly small. Then one obtains the membrane potential modulation as,

$$v_{ER}^j(t) = (g_{EE}(t)[V_E - V_R] + g_{EI}(t)[V_I - V_R]) / (g_{EE}(t) + g_{EI}(t)) \quad (5)$$

As we concluded above, for the balanced state the inhibitory conductance has to be the largest conductance, so that means that $g_{EI}(t) \gg g_{EE}(t)$. This leads to the result:

$$v_{ER}^j(t) = [V_E - V_R](g_{EE}(t)/g_{EI}(t)) + [V_I - V_R] \quad (6)$$

Equation 6 means in words that the temporal modulation of the membrane potential (minus the resting potential) is proportional to the ratio of the (time-modulated) excitatory and inhibitory synaptic conductances. Thus, inhibitory conductance will act as an automatic gain control on the excitatory input to each excitatory neuron (Shelley, et al., 2002; Zhu, Xing, Shelley, & Shapley, 2010).

In the noisy real cortex (Destexhe, 2010) the impulse firing rate of excitatory neurons will be approximately proportional to the membrane potential modulation calculated in eqn. 6 (Chance, Abbott, & Reyes, 2002; Shelley, et al., 2002). Therefore, the function of inhibition as a gain control of synaptic excitation will be evident also in the firing rate of cortical neurons.

The conclusion that local circuit inhibition is a local gain control emerges naturally from the large-scale network model of V1 in eq. 1 as a recurrent network that settles into a high conductance state. Thus network modeling justifies the assumption of a contrast gain control or normalization mechanism that has been used to fit data in V1 cortex (Heeger, 1992). But the cortical architecture that generates local circuit inhibition in V1 cortex is found throughout the cerebral cortex, and therefore inhibition's role as a gain control is likely to apply to the entire cortex. The modeling indicates that local circuit inhibition has a second function, to increase selectivity for input features.

Untuned (or broadly tuned) Inhibition and Orientation Selectivity in the Cortical Model

Cells in the sensory areas of cerebral cortex are more selective for stimuli than are their thalamic inputs. Understanding the mechanisms of enhanced cortical selectivity is necessary for understanding the function of the cortex. Many investigators have concluded that inhibitory or suppressive mechanisms are involved in feature selectivity. A key experimental observation in support of inhibition's role, from work on the visual cortex, is that orthogonal-to-preferred stimulus orientations reduce the impulse firing rate below the spontaneous level in those cortical visual cells that have high enough spontaneous firing rate to observe the reduction (e.g. Celebrini, Thorpe, Trotter, & Imbert, 1993; De Valois, Yund, & Hepler, 1982; Ringach, Shapley, & Hawken, 2002). The firing rate reduction is a clear sign of inhibition. There is experimental evidence from other cortical areas for role of suppression in feature selectivity (reviewed by Isaacson & Scanziani, 2011). For instance, cortical inhibition seems to play an important role in tonotopic tuning in the primary auditory (A1) cortex (Sadagopan & Wang, 2010; Wu, Arbuckle, Liu, Tao, & Zhang, 2008). Also, olfactory cortical neurons in the piriform cortex have tuning curves for odorants that are sharpened by inhibition (Franks, et al., 2011; Poo & Isaacson, 2011). Furthermore, cortical inhibition has been shown to shape the directional selectivity of neurons in macaque M1 motor cortex (Merchant, Naselaris, & Georgopoulos, 2008).

The way the cortex generates high selectivity for stimulus features is well illustrated by the emergence of neurons in the visual cortex that are highly selective for visual stimulus orientation. One of the main problems the visual cortex needs to solve, to generate high orientation selectivity, is the reduction of responses to non-preferred orientations (Ben-Yishai, Bar-Or, & Sompolinsky, 1995; Sompolinsky & Shapley, 1997; Troyer, Krukowski, Priebe, & Miller, 1998). Information-theory analysis by Kang, Sompolinsky and Shapley (2004) showed that a pedestal of response to non-preferred orientations degrades orientation discrimination by the V1 population. The original feed-forward model provided by Hubel and Wiesel (1962) is supported by several studies (e.g. Ferster, Chung, & Wheat, 1996; Reid & Alonso, 1995) and it provides the bias for the preferred orientation in most models of visual cortex. However feed-forward excitation alone cannot provide the inhibition at non-preferred orientations that has been observed (Celebrini, et al., 1993; De Valois, Yund, et al., 1982; Ringach, Shapley, et al., 2002) and that is the basis for high selectivity.

The large-scale cortical model we have been discussing predicts that cortical synaptic inhibition should be untuned or very broadly tuned for orientation. This modeling result was not intentionally put into the model but instead was a result of cortical architecture and connectivity. The reason for the low orientation selectivity of inhibition is two-fold: 1) inhibitory neurons in the model tend to be more broadly tuned than excitatory neurons and

2) the convergence of many inhibitory neurons onto excitatory neurons produces an untuned inhibitory signal (Zhu, et al., 2010). The broader tuning characteristics of inhibitory neurons in the model was in part a consequence of their higher spontaneous firing rates and also their higher firing rates in response to visual stimulation (McLaughlin et al., 2000; Zhu, Shelley and Shapley, 2009), as well as to their denser intra-cortical connectivity. The existence of inhibitory neurons in visual cortex that are broadly-tuned (or untuned) (but see Hirsch, et al., 2003) for orientation has been found in experiments on visual cortex (Cardin, Palmer, & Contreras, 2007; Nowak, Sanchez-Vives, & McCormick, 2008), consistent with model results. But in the model it was mostly the convergence of many inhibitory neurons with different orientation preferences onto excitatory neurons that made the orientation tuning of intracellular inhibition in model neurons almost constant with orientation. Experiments have recently found such dense inhibitory convergence of inhibitory neurons onto excitatory cortical neurons in many cortical areas (Fino & Yuste, 2011; Levy & Reyes, 2012; Oswald & Reyes, 2008; Packer & Yuste, 2011).

The dependence of synaptic inhibition on orientation in the model is illustrated in Figure 2 (Tao, et al, 2006). The figure illustrates intracellular voltages and conductances from many example neurons from the model, and in all of them the orientation selectivity of inhibitory conductance is weak or non-existent. In the model, as also illustrated in Fig. 2, the (untuned) inhibitory conductance causes the firing rate orientation selectivity to be much greater than that of the excitatory conductance, by means of suppression of responses to non-preferred orientations below the threshold for nerve impulse firing. In what follows we present evidence from our own experiments on Macaque visual cortex that such untuned inhibition causes Untuned Suppression that greatly enhances orientation selectivity, and then we will discuss supporting evidence from other experiments on the visual cortex and from other sensory cortices for the same idea, that untuned inhibition increases feature selectivity.

Experiments on the existence of Untuned Suppression in primary visual cortex

While theoretical work (McLaughlin, et al., 2000; Troyer, et al., 1998) predicted that there should be Untuned Suppression as a consequence of local circuit inhibition, and that the Untuned Suppression should play an important role in sharpening orientation selectivity, experimentally it has been hard to obtain convincing evidence about the orientation tuning of cortical inhibition.

Intracellular measurements in cat V1 implied the existence of broadly-tuned cortical inhibition (Anderson, Carandini, & Ferster, 2000; Gillespie, Lampl, Anderson, & Ferster, 2001; Lampl, Anderson, Gillespie, & Ferster, 2001; Monier, Chavane, Baudot, Graham, & Fregnac, 2003; Volgushev, Pei, Vidyasagar, & Creutzfeldt, 1993). Solving the problem of inhibition's contribution to orientation selectivity would be easy if one could intracellularly record neural activity from every neuron and estimate precisely the excitatory and inhibitory conductances. However technically it is difficult to record neuronal activity intracellularly for the long time needed to complete all the measurements to estimate inhibition's orientation tuning. Therefore, although intracellular studies demonstrated the existence of inhibition, up to now estimating the amount of inhibition and its tuning characteristics for every neuron has been too technically difficult.

There were many earlier studies (Bonds, 1989; Carandini, Heeger, & Movshon, 1997; Nelson & Frost, 1978; Ringach, Shapley, et al., 2002; Sato, Katsuyama, Tamura, Hata, & Tsumoto, 1996; Volgushev, et al., 1993) that suggested that suppressive or inhibitory cortical mechanisms might be involved in the cortical emergence of orientation selectivity and contrast gain control. However, more recent studies (Finn, Priebe, & Ferster, 2007; Freeman, Durand, Kiper, & Carandini, 2002; Koelling, Shapley, & Shelley, 2008; Priebe & Ferster, 2006) suggested that the suppressive effects studied in earlier experiments that used

plaids and drifting gratings as stimuli (e.g. Carandini, et al., 1997) might be due to pre-cortical non-linearities in the retina and/or LGN. These re-examinations of the neuronal mechanism of orientation selectivity motivated us to link the dynamics of orientation selectivity to more conventional measurements with drifting gratings, and to make a quantitative assessment of Untuned Suppression's contribution, as presented below.

One experimental fact that was important for our experiments is that many V1 cells have a low or zero spontaneous impulse firing rate (cf Ringach, Shapley, et al., 2002). Furthermore, synaptic excitation and inhibition co-exist in all cortical neurons (Borg-Graham, Monier, & Fregnac, 1998; Volgushev, et al., 1993). These two experimental facts make it technically difficult to obtain an estimate of inhibition from extracellular measurements. To overcome the technical difficulties in estimating inhibition's contribution to feature selectivity, we and our colleagues developed a new kind of stimulus and new data analysis techniques (Ringach, Hawken, & Shapley, 1997). We used a rapid sequence of flashed visual stimuli to elevate the average spike rate and employed reverse correlation to measure dynamic responses from each neuron. Then we dissected inhibition from excitation based on their dynamic properties. This approach made it possible to measure Untuned Suppression in every V1 cell studied with extracellular recordings (Ringach, Hawken, & Shapley, 2003; Xing, Ringach, Hawken, & Shapley, 2011; Xing, Shapley, Hawken, & Ringach, 2005).

Fig. 3 illustrates the reverse correlation method in the orientation domain (Ringach, et al., 1997; Xing, et al., 2005). Sinusoidal gratings of 18 different orientations equally spaced from 0 to 180 deg, plus "blanks" (defined as uniform frames having the same luminance as the mean luminance of the grating images) were used. Each stimulus in a sequence was randomly chosen from the 152 types of stimuli (18 orientation times 8 different phases plus 8 identical blanks) with replacement and flashed to a cell for 20ms. Fifteen minutes (~300 repetition of each stimulus) of experiment time allowed us to measure dynamic responses to different stimulus orientations and to see Untuned Suppression in most neurons.

In order to see the Untuned Suppression, the key is to compare a neuron's dynamic response at its preferred orientation, $R_{pref}(t)$, and at the orthogonal-to-preferred orientation, $R_{orth}(t)$. Population averages of the time course of responses at preferred and orthogonal orientations (Figure 4) illustrate that $R_{orth}(t)$ was usually biphasic while $R_{pref}(t)$ was usually monophasic. That the dynamics difference between $R_{pref}(t)$ and $R_{orth}(t)$ (Figure 4) is caused by cortical mechanisms is indicated by the data in Figure 5 from experiments on lateral geniculate nucleus (LGN) cells in macaque. The experiments depicted in Fig. 5 measured the reverse correlation of LGN response with stimulus spatial phase. There was no dependence of response time course on spatial phase. The LGN results imply that the dynamics differences seen in Fig. 4 are not a result of pre-cortical nonlinearities like retinal contrast gain control or response saturation (Koelling, et al., 2008; Priebe & Ferster, 2006). Rather, the difference in response dynamics seen in Fig. 4 can be explained by a consequence of cortical Untuned Suppression's time course being slightly slower than excitation's, causing later responses to be more suppressed than earlier responses. This explanation of orientation dynamics (Fig. 4) demands a quantitative estimation of Untuned Suppression's time course, which is what we present next.

Estimate Untuned Suppression for each neuron

To estimate the strength and time-course of suppression we used a two-component (Tuned Enhancement and Untuned Suppression) descriptive model to account for V1 orientation dynamics (below, Equation 8; Ringach, et al., 2003; Xing, et al., 2005). A V1 cell's orientation dynamics had strong Tuned Enhancement ($E(\theta, t)$ in equation 8) and Untuned Suppression ($U(t)$ in equation 8) when the stimulus was of optimal size (Xing, et al., 2005).

We assumed that the dynamics of orientation tuning were controlled only by an excitatory process we called Tuned Enhancement $E(\theta, t)$ that was a function of orientation and time, and by Untuned Suppression $U(t)$ defined to be independent of orientation. We (Xing, et al., 2011) made the approximation that Tuned Enhancement $E(\theta, t)$ was separable in orientation and time, i.e. the product of an orientation tuning curve and a time dependence:

$$E(\theta, t) = E_\theta(\theta) E_T(t). \quad (7)$$

In other words, the orientation-tuning curve of excitation was assumed to be independent of time, an assumption based on experimental data (Anderson, et al., 2000; Gillespie, et al., 2001; Sharon & Grinvald, 2002). We defined the (time-independent) ratio of the excitatory responses at the orthogonal to preferred orientations as $\alpha = E_\theta(\theta_{orth})/E_\theta(\theta_{pref})$; α could be calculated from the measured orthogonal/preferred response ratio at short times less than 40 ms (Xing, et al., 2005). The two-component descriptive model is written in Equation 8.

$$R(\theta, t) = E(\theta, t) - U(t) \quad (8)$$

Eqn. 8 indicates that inhibition subtracts from excitation while we showed previously in eqn. 6 that inhibition acts as divisor of excitation. There is no contradiction. In eqn. 8 we are making the approximation that division acts like subtraction for small perturbations around an operating point. The goodness of fit of the two-component model with experimental data supported the idea that orientation selectivity and its dynamics could be understood in terms of the two components, Tuned Excitation and Untuned Suppression (Xing, et al., 2011).

The measurable responses $R_{pref}(t)$ and $R_{orth}(t)$ were expressed in terms of Tuned Excitation and Untuned Suppression in Equations 9 and 10, by following Eq. 8, and substituting the re-scaled $E(\theta_{pref}, t)$ for $E(\theta_{orth}, t)$. Then algebraic re-arrangement led to Equation 11 that expresses $U(t)$ in terms of the measured $R_{pref}(t)$ and $R_{orth}(t)$.

$$R_{pref}(\theta, t) = E(\theta_{pref}, t) - U(t) \quad (9)$$

$$R_{orth}(\theta, t) = \alpha E(\theta_{pref}, t) - U(t) \quad (10)$$

$$U(t) = (\alpha R_{pref}(t) - R_{orth}(t)) / (1 - \alpha) \quad (11)$$

Equation 11 was used to estimate Untuned Suppression from $R_{pref}(t)$ and $R_{orth}(t)$ for each cell. In Fig. 6 the estimation procedure is illustrated with orientation dynamics data of one representative V1 cell.

Using eqs. 9–11, we took orientation dynamics data and estimated the time-courses of the underlying processes, E and U . Fig. 6 shows the time-course of the estimated Untuned Suppression $-U(t)$. This was the goal of eqn.'s 7–11. Fig. 6 shows that Untuned Suppression that is slightly delayed with respect to excitation can explain the different time courses of $R_{pref}(t)$ and $R_{orth}(t)$ in Fig. 4

In our descriptive model, Untuned Suppression is constant as a function of orientation. However, McLaughlin et al. (2000), Marino et al. (2005) and Tao et al (2006), using computational models of V1, have suggested that the inhibitory effect on some V1 cells may be tuned with a bandwidth similar to tuned excitation (see for example Fig. 2). However, inhibition is predicted always to have a pedestal of response at non-preferred orientations. If

the models were correct and the inhibitory tuning and excitatory tuning were similar around the peak of the tuning curve, we would be unable to dissect the tuned part of the local suppression process from excitation using the curve-fitting procedure we employed. Thus we cannot exclude the possibility that so-called Untuned Suppression may also have a tuned component. But the data require that inhibition also must have a pedestal of suppression across all orientations.

Untuned Suppression appears to be a cortical process, because it is too slow to be a retinal or LGN effect, but too rapidly decaying to be consistent with synaptic depression at thalamocortical or corticocortical synapses. Synaptic depression is also ruled out as an explanation from the experimental results of Boudreau and Ferster (2005). Convincing evidence for the cortical locus of Untuned Suppression comes from Sato et al. (1996) in which cortical GABA-ergic inhibition in Macaque V1 was weakened by application of bicuculline to the cortex. Sato et al. (1996 cf their Fig. 8) found that bicuculline reduced orientation selectivity by decreasing Untuned Suppression: the response to all orientations grew stronger during bicuculline administration. Recently, Attalah et al (2012), using genetic and optogenetic techniques, have confirmed and quantified Sato et al.'s (1996) results and extended them to the mouse visual cortex (see Fig. 3 in Attalah et al, 2012).

Untuned Suppression is a local neural mechanism

Theoretical work (McLaughlin, et al., 2000; Troyer, et al., 1998) not only predicted that there should be Untuned Suppression--as a result of local circuit inhibition-- but also suggested that the Untuned Suppression should come from a local cortical region, because anatomically, inhibitory connections have a small footprint ($<200\mu\text{m}$). This is confirmed by our experimental results -- Untuned Suppression is the same for stimuli of optimal size and for stimuli 2–4 times larger (Xing, et al., 2005). Such size-invariance of Untuned Suppression suggests that it is a process mainly due to local circuitry in V1.

Untuned suppression improves orientation selectivity

It is conceivable that Untuned Suppression increases orientation selectivity by reducing the vertical offset of the orientation tuning curves. This is illustrated for a single representative V1 neuron and for a V1 population in Figure 7. However the magnitude of suppression's contribution to tuning selectivity is not yet determined. This question is also important to answer in multiple cortical areas where it has been reported that suppressive mechanisms are involved in feature selectivity (Franks, et al., 2011; Isaacson & Scanziani, 2011; Poo & Isaacson, 2011; Sadagopan & Wang, 2010; Wu, et al., 2008). We used the dynamic measurements to assess the contribution of Untuned Suppression to orientation selectivity. Across the population of V1 neurons we carried out an analysis on a cell-by-cell basis as follows: 1) first we estimated Untuned Suppression from an individual cell's orientation dynamics; 2) we then computed the cell's steady-state orientation tuning based on an LN model; 3) finally we computed what the cell's steady-state orientation tuning should be when its Untuned Suppression was removed.

Nearly all cells showed a positive change of Orthogonal/Preferred (O/P) ratio with removal of Untuned Suppression (points above the diagonal line in Fig. 8, indicating that the effect of Untuned Suppression on V1 cells' responses to non-optimal orientations is general across the population. On average, Untuned Suppression decreases V1 cells' O/P ratios from 0.38 to 0.26.

It is especially noticeable that many sharply-tuned cells ($\text{O/P} < 0.2$) are strongly affected by the removal of Untuned suppression. The largest increase of O/P ratio as a result of Untuned Suppression's removal happens to cells with an original O/P ratio less than 0.2. On average,

Untuned Suppression reduces the O/P ratio for these cells from 0.25 to 0.08. This suggests that the most highly selective cells are greatly affected by Untuned Suppression (changes of O/P ratio are 0.17 for neurons with O/P ratio < 0.2 and 0.12 for the whole population). Overall the results suggest that the receptive fields of neurons with high orientation selectivity are not just formed by their excitatory input but that Untuned Suppression plays an important role in increasing these cells' orientation selectivities.

Correlations

Another indication of the importance of local circuit inhibition for feature selectivity is the strong correlation between orientation and spatial frequency selectivity observed in Macaque V1 (De Valois, Yund, et al., 1982; Xing, Ringach, Shapley, & Hawken, 2004; Zhu, et al., 2010). De Valois et al. (1982) and Xing et al. (2004) found correlations between orientation and spatial frequency selectivity in Macaque V1 populations. The strong correlation between response attenuation of non-optimal stimuli in the two domains of orientation and spatial frequency led to the suggestion that there was a common mechanism: cortical response suppression (Xing, et al., 2004) as a result of local circuit inhibition (Zhu et al, 2010). Experimental results on the dynamics of orientation and spatial frequency selectivity (Bredfeldt & Ringach, 2002; Malone & Ringach, 2008; Ringach, Bredfeldt, Shapley, & Hawken, 2002) support the idea that suppression of non-preferred stimuli is the neural mechanism for the correlations.

Conclusions

Our experimental results support the modeling discussed earlier in finding that Untuned Suppression, presumably caused by local circuit inhibition, is the main neuronal mechanism involved in producing high orientation selectivity in cortical neurons. However, theorists have suggested that recurrent cortico-cortical excitation is needed for cortical orientation tuning (Ben-Yishai, et al., 1995; Somers, Nelson, & Sur, 1995). Our data do not need a cortical amplification process to explain orientation selectivity in V1. Perhaps cortical amplification in V1 is very fast (so it is absorbed into what we called Tuned Enhancement, $E(\theta, \tau)$ and cannot be distinguished from feed-forward input). Future work will be needed to dissect cortical recurrent amplification from other sources of excitation. Our results suggest that feature selectivity throughout the cortex could be controlled by local circuit inhibition.

The other main conclusion is that feature selectivity and gain control are linked through their dependence on synaptic inhibition in the local cortical circuit. Others have noted the importance of cortical inhibition for these two functions of the cortex, based on extensive experimental evidence (e.g. Isaacson & Scanziani, 2011). What we have presented in this review article is the theoretical underpinning for the linkage, based on a cortical model, a network of conductance-based, IF neurons (McLaughlin, et al., 2000; Shelley, et al., 2002) that is in a state of (approximate) excitation-inhibition balance. The model's design was based on existing knowledge of the functional properties of single neurons and the micro-anatomy of neural connectivity. The theory suggests that feature selectivity and gain control are naturally occurring properties for a balanced neural network with feature-biased inputs. And we have also offered powerful evidence from the dynamics of orientation tuning in Macaque V1 that the linkage of gain and selectivity by local circuit inhibition agrees with our data on orientation dynamics.

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Figure 1. Schematic of a model layer 4Cα hypercolumn (Left), with axonal (gray circle) and dendritic (dark circle) arbor widths indicated for excitatory (E) and inhibitory (I) cells. The neuron along the ray at angle 2θ (emanating from the pinwheel center) in the cortex inherits its orientation preference on the basis of convergent feedforward input from a distribution of ON and OFF lateral geniculate nucleus (LGN) cells (Upper Right). The distribution's orientation at angle θ in the visual field sets the orientation preference. OFF LGN cells are indicated by filled circles. The Lower Right graph shows the LGN temporal kernel. (From McLaughlin et al, 2000)

Figure 2.

Tuning properties for V1 model cells (a–d) near the pinwheel center of an orientation column vs. cells (e–f) from iso-orientation domains. For six sample excitatory cells from the V1 model, plotted as functions of stimulus orientation within the five panels for each cell are (from Top to Bottom): firing rates (spikes per second) for medium contrast (solid lines) and low contrast (dot-dashed lines) stimuli; membrane potential; excitatory conductances from lateral geniculate nucleus (LGN) inputs; cortico-cortical excitatory conductances; and cortico-cortical inhibitory conductances. (Conductances are measured in units of sec^{-1} .) All quantities are time-averaged, with the dashed curves showing the mean ± 1 SD. For LGN excitation, the SD illustrates the tuning of its F1 component. With the exception of the topmost panels, all are at medium contrast. (a, b, and e) Simple. (c, d, and f) Complex cells. (From Tao et al 2006).

Figure 3.

Dynamic orientation tuning measured by reverse correlation. A: The reverse correlation method. Stimuli with different orientations plus a blank were flashed for 20 ms in a random sequence. Each cell's spike time was recorded with 1ms resolution. B: dynamics of orientation tunings of two example cells. Tuning curves are plotted every 10 ms, starting at 30 ms after stimulus onset and ending at 130 ms after stimulus onset. Red points represent cells' responses to orientation at 90° deg (preferred orientation) and blue points are cells' responses to orientation at 180° (orthogonal to preferred). For convenience, each cell's tuning curves were shifted by a fixed value, so that its preferred orientation is around 90° . Dash-dot lines in B represent cells' responses to blank stimulus. (From Xing et al 2011)

Figure 4.

Dynamic responses in V1. Population averaged dynamic responses to their preferred orientations (R_{pref} , red curve) compared with dynamic responses to their orthogonal orientations (R_{orth} , blue curve) for V1 cells. The dashed curve is a rescaled version of R_{pref} by α (≈ 0.27) in order to match the early part of R_{orth} . The intersections of vertical lines and horizontal line represent T_{dev} and T_{dec} , the times at which R_{pref} equals half its peak value. (From Xing et al 2011).

Figure 5.

Dynamic responses in LGN. Population averaged dynamic responses to their preferred spatial phases (R_{pref} ; red curve) compared with averaged dynamic responses to all spatial phases (R_{aver} ; blue curve) for LGN cells. Dashed curve is a rescaled version of R_{pref} by α ($=0.17$) in order to match the early part of R_{aver} . Note that in the LGN unlike the cortex, the re-scaled preferred response fits the response averaged over all phases (including non-preferred responses) very well.

Figure 6.

Untuned suppression is needed to fit the dynamics of orientation tuning for individual V1 cells. A: shows the time courses of R_{pref} (red curves), R_{orth} (blue curves) from a V1 cell. Both R_{orth} and R_{pref} have positive responses at early time. At early time (prior to 45ms after stimulus onset), R_{orth} has a time course similar to R_{pref} but is rescaled by α , 0.25 (dashed curve). At later times, the blue and dashed curves are different because of Untuned Suppression. B shows estimated time-course of Untuned Suppression for this cell. What is plotted is $-U(t)$ to illustrate that Untuned Suppression is subtracted from Tuned Excitation. (From Xing et al, 2011).

Figure 7.

Change of orientation tuning curves with removal of untuned suppression. A and B show the change of the orientation tuning curve of an example cell, before and after its untuned suppression was removed. C. The population (cells with $O/P < 0.2$) averaged orientation tuning (black curve; $O/P = 0.08$) compared with the population average orientation tuning without untuned suppression (red curve; $O/P = 0.25$). (From Xing et al, 2011).

Figure 8.

The effect of untuned suppression on O/P ratio estimated across the V1 population. A. Distribution of the measured O/P ratio of V1 cells from experiments with drifting gratings as stimuli. B. Distribution of the O/P ratio of V1 cells estimated from dynamics experiments that include untuned suppression. C. Distribution of the O/P ratio of V1 cells without untuned suppression, estimated from dynamics experiments. D. A scatter plot, for $N=140$ cells recorded in V1, of predicted O/P ratio (x-axis) versus O/P ratio without untuned suppression (y-axis). The distance of each point from the unit line, drawn as the diagonal, is the amount that untuned suppression contributed to orientation selectivity. (From Xing et al, 2011).