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Gamma frequency feedback inhibition accounts for key aspects of orientation selectivity in V1

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Abstract

There is now strong evidence that gamma frequency oscillations occur during the engagement of cortical region. These oscillations involve gamma frequency feedback inhibition. Thus, understanding the properties of this form of inhibition is critical to understanding how excitation and inhibition interact to determine which cells fire and, more generally, how cortex performs computations. In previous work, we argued that gamma frequency inhibition performs a type of winner-take-all computation that obeys simple rules: 1) cells fire if their excitation is within E% of the cell with maximum excitation; 2) E%max is determined by the delay of feedback inhibition and the membrane time constant. This framework was previously applied to the best-studied cortical computation, orientation selectivity of cells in V1. Measurements show that orientation tuning is insensitive to illumination contrast. We showed that this finding can be simply explained by the E%max model. Recently, a new property of orientation selectivity has been discovered: orientation tuning varies with the phase of the gamma oscillations. Here, we show that this too can be simply explained by the E%max model. These successes suggest that simple rules underlie the selection of which cells fire in cortical networks.

Cortex is one of the least understood parts of the brain. Notably, it remains unclear how different cell types and different cortical layers function together to produce specific computations. In most cortical regions, the computation being performed is not even known, so little progress can be made with regard to the underlying mechanisms. However, an important exception is V1. Here, a clear computation has been identified: the conversion of the representation from center surround organization, as seen in the input to V1, to a representation in V1 in which cells respond best to bars of a particular orientation (Hubel and Wiesel 1962). There has therefore been considerable experimental and theoretical interest in this computation (Priebe and Ferster 2012), an effort that takes on additional importance because of its potential implications for the general capability of cortical computation.

The question that I will address in this short article is the importance of gamma frequency oscillations in the computation of V1 orientation selectivity. Because gamma oscillations involve time-dependent inhibition (Soltesz and Deschênes 1993), an understanding of the role of these oscillations in producing orientation selectivity speaks to the fundamental mechanism by which excitation and inhibition interact to control cell firing (Isaacson and Scanziani 2011). Most fundamentally, the presence of gamma frequency oscillations, which

is a likely indicator of cortical engagement, implies that inhibition is dynamic; it changes within tens of milliseconds. It would thus be valuable to understand the rules of computation that are applicable to such dynamic inhibition.

Gamma oscillations are easily observed in field potential recordings from visual cortex. Such oscillations have now been seen in a wide range of organisms (Engel, Konig et al. 1990). Studies in both the hippocampus and V1 have demonstrated that gamma frequency oscillations can also be seen in intracellular recordings from principal cells (Soltesz and Deschênes 1993, Volgushev, Pernberg et al. 2003). Because the intracellular oscillations are due to periodic inhibition at gamma frequency (Soltesz and Deschênes 1993), firing tends to occur at the phases of gamma when inhibition is least. Given that gamma-mediated inhibition is synchronized over a relatively wide cortical area and thus similarly affects neurons in the region (Yu and Ferster 2010), it follows that different principal cells will tend to fire in a clustered (synchronized) way (Burns, Xing et al. 2010). Such synchronization is one of the major functions of gamma. Work in the hippocampus shows that cells that fire within a gamma cycle define the neural ensemble that represents a particular position in the environment (Dragoi and Buzsaki 2006, Lisman and Buzsaki 2008). Similarly, synchronization is highest for cells in V1 having the same orientation tuning (Engel, Konig et al. 1990). A somewhat controversial corollary (see below) is that the exact timing of firing of cells *within* a gamma cycle is not important (i.e., cells are part of the same ensemble even if they fire 10 msec apart). A second consequence of synchronization concerns communication between neurons: the synchronized output of cells within an ensemble will allow downstream neurons to detect the ensemble by coincidence detection mechanisms (Konig, Engel et al. 1996). The exact duration of the coincidence detection window probably depends on many details but certainly will be less than the membrane time constant (10–30 msec) (Leger, Stern et al. 2005, Waters and Helmchen 2006). Furthermore, given that an ensemble fires primarily within a 10 msec window (i.e., within about half of a gamma cycle), there is a paucity of firing for about 10 msec between the activity of sequential ensembles. This paucity has the desirable consequence of ensuring that the coincidence detector in downstream networks detects single ensembles rather than a combination of sequential ensembles (Lisman and Jensen 2013).

Synchronization, however, is not the only important function of gamma. An altogether different function relates to gamma's role in selecting which cells fire (de Almeida, Idiart et al. 2009). This analysis built on the generally accepted ideas regarding the mechanism of gamma generation by feedback inhibition (Buzsaki and Wang 2012): 1) that active principal cells provide convergent excitation to fast-spiking interneurons (basket cells and chandelier cells); 2) that interneurons of this type are electrically coupled to each other, thus approximating one giant interneuron; and 3) that these interneurons rapidly inhibit a large population of principal cells because of the highly divergent connections from the interneuron to the principal cells. It was proposed (de Almeida, Idiart et al. 2009) that circuits that involve such feedback inhibition perform a type of winner-take-all process (termed E%max) and that this process has certain lawful properties. These are reviewed in the following paragraph.

A key concept for understanding the winner-take-all process organized by gamma-frequency inhibition is that the decay of this inhibition during a gamma cycle forms a positive-going ramp, the function of which is to “hunt” for the most excitable principal cells in the local network. Simply put, the most excited cells in the population will be the first to reach threshold as inhibition declines (for a related idea regarding the role of theta frequency inhibition, see (Mehta, Lee et al. 2002)). The resulting firing produces strong feedback inhibition in all principal cells in the region, diminishing the probability of further firing. Indeed, this inhibition will organize the “hunting” process to find the winners on the next gamma cycle. However, this type of winner-take-all process is not perfect; not only does the most excited cell fire, but also somewhat less excited cells fire (many poorly excited cells will not fire). The reason is that, after the most excitable cell fires, there is a delay (d) before feedback inhibition arrives at other principal cells. During this delay, the inhibitory ramp continues to decline. It follows that somewhat less excited cells will fire during this delay. It is possible to derive a simple equation that describes what fraction of cells will fire (de Almeida, Idiart et al. 2009). This provides a simple approximation: cells will fire if their excitation is within $E\%$ of the excitation of the most excited cell, where $E\%_{\max} = d/\tau$ (τ is the time constant of the decline of the IPSP, which will generally be determined by the membrane time constant). Experiments show that d is 2–3 msec (Miles 1990), and τ is 10–30 msec (Waters and Helmchen 2006, Schmidt-Hieber, Jonas et al. 2007). Thus, $E\%_{\max}$ is on the order of 0.1. This means that the cells having the top 10% of excitation will fire; the others will not. The $E\%_{\max}$ framework is different than the k -winner-take-all framework that has been most commonly used in computational neuroscience. According to the latter, there are k cells that fire in each competition. In contrast, within the $E\%_{\max}$ framework, the number of cells that fire is not fixed but, rather, depends on the particular distribution of excitation. For instance, if only one cell in the network had strong excitation, only that cell would fire; conversely, if all cells had excitation within 10% of each other, they would all fire.

Application of the $E\%_{\max}$ framework to orientation selectivity

The winner-take-all concept described above provides a simple explanation of properties of orientation selectivity in V1. A key finding has to do with the effect of stimulus contrast on the tuning of orientation selectivity. In this type of analysis, a tuning curve is constructed by giving lines or gratings at different orientations and plotting the firing rate as a function of orientation. If excitation were tuned in this way and interacted with fixed inhibition, then reducing the excitation by decreasing contrast should narrow the range of orientations that evoke spikes; this is because cells less well tuned to the orientation of the stimulus would cease to fire because they could not overcome the fixed inhibition (Fig. 1A). However, contrary to this line of thinking, orientation tuning was found to be little affected by changes in stimulus contrast (Sclar and Freeman 1982, Anderson, Carandini et al. 2000). This insensitivity of orientation tuning to stimulus contrast can be simply explained by a gamma-mediated winner-take-all process (de Almeida, Idiart et al. 2009). On the assumption that changing contrast just scales the excitation to all cells, it follows that the cells that are most excited at one contrast level will also be the most excited at another. This concept is

illustrated in Fig. 1B,C. Thus, over a wide range of contrasts, orientation selectivity will be contrast invariant.

Recently, an important new property of orientation tuning has been discovered: that this orientation tuning broadens as a function of phase during a gamma cycle (Womelsdorf, Lima et al. 2012) (see also related findings by (Konig, Engel et al. 1995, Vinck, Lima et al. 2010)). Here, I will argue that this is an expected consequence of the E%max winner-take-all mechanism. As noted earlier, the decline of inhibition during a gamma cycle is a process that “hunts” for the most excited cell. Thus, the cell that fires first will be one that is tuned to stimulus orientation being presented. Once this occurs, feedback inhibition is set in motion, but there is a finite time ($d=2-3$ msec) before this inhibition. During this delay, the inhibitory ramp will continue to decline. This allows cells to fire that are not perfectly tuned to the stimulus, as observed (Vinck, Lima 2010). For a cell to fire, there are two orientations at which it will have substantial but suboptimal excitation: one clockwise of its preferred orientation and one counterclockwise. Thus, as shown in Fig. 2, the orientation tuning curve of these late-firing cells will be broader than that of cells that fire early in the gamma cycle.

Concluding Remarks

Although E%max model provides insight into qualitative aspects of the data, notably the contrast invariance of orientation tuning and the variation of orientation tuning within gamma phase, the model is much too simple to account for many aspects of the data. For this, a much more elaborate model would be required. Some of the complexities relevant to the E% process are enumerated in Table 1. Several laboratories have developed rich models of orientation selectivity (see below). The fact that orientation selectivity varies with gamma phase and correlates with gamma power (Womelsdorf, Lima et al. 2012) makes the strong case that gamma-frequency inhibition is integral to the mechanism of orientation selectivity and thus should be part of any correct model. Surprisingly, several advanced models of orientation tuning do not simulate oscillations (Pugh, Ringach et al. 2000, Palmer and Miller 2007). Thus, unless gamma can be introduced into these models, they are unlikely to account for orientation selectivity in the way that it is actually computed. Two recent models do produce gamma (Folias, Yu et al. 2013, Rangan and Young 2013). The analysis presented here suggests that these models will be able to reproduce the findings of (Womelsdorf, Lima et al. 2012).

At the experimental level, the role of gamma oscillations in cellular computation has been difficult to assess. Disabling inhibition may eliminate gamma but may also generate epileptiform activity through recurrent excitation, complicating interpretation. Approaches that eliminate both recurrent excitation and feedback inhibition (Lien and Scanziani 2013) may provide a way around this difficulty. In a different approach, fast-spiking interneurons can be optogenetically stimulated at different frequencies. The results show the greatest effect when stimulation is done at gamma frequency, consistent with the importance of these cells in producing gamma (Cardin, Carlen et al. 2009). However, proving a causal role of a specific class of interneurons in gamma will require the demonstration that inhibiting these cells prevents gamma, a demonstration that has not yet been achieved. With regard to testing the E%max model of orientation selectivity presented here, one strategy would be to

lengthen the time constant (τ) of the decline of the IPSP. It may be possible to achieve this using benzodiazepines, which are known to increase the IPSC duration and decrease gamma frequency (Whittington, Jefferys et al. 1996, Scheffzik, Kukushka et al. 2013). If these drugs in fact increase the IPSP duration, the E%max model predicts that a sharpening of orientation selectivity will occur.

As noted at the beginning of this article, the elucidation of orientation selectivity has importance far beyond that of understanding vision; it is perhaps our best opportunity for understanding the fundamental principles of cortical computation. What could such fundamental principles be? I suggest the following:

1. That gamma frequency inhibition is a general feature of cortical computation and that the E%max rule provides an approximate description of the network processes that determine which cells fire.
2. That an ensemble is defined by the group of cells that fire within a gamma cycle. It is important to emphasize that this definition of an ensemble implies that cells that fire a few milliseconds apart within the same gamma cycle are part of the same ensemble. This means that, even though such cells may have somewhat different representations, as indeed they do in V1 (discussed above), these differences are just a byproduct of the imperfections in the winner-take-all mechanism and are not important functionally; their input will fall within the coincidence window of target cells and will thus be summed together with input from the other inputs that occur during that gamma cycle.

Much remains to be learned about gamma oscillations. For instance, we still do not know the relative role of different types of fast-spiking interneurons. What is clear, however, is that these oscillations do control cell firing and strongly influence orientation selectivity. Although complex models of cellular interactions in V1 will no doubt be needed to explain the details of cortical processing, very simple considerations about gamma frequency inhibition appear sufficient to explain the contrast insensitivity of orientation tuning and the gamma-phase dependence of orientation tuning.

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Fig. 1. The E%max model provides an explanation of why orientation tuning is not dependent on contrast

A. Conditions under which orientation tuning curves depend on contrast. Lower curve shows orientation tuning of excitation relative to threshold (dashed line). As shown in the lower curve, the width of the tuning of firing (double arrow) can be quite narrow because only a few orientations are above threshold (the iceberg effect). However, if the overall level of excitation is scaled up (higher curve), as would occur if image contrast is enhanced, then the tuning becomes broader, contrary to experimental observations. B. Tuning of excitatory input as a function of orientation (same as in A) at two different levels of contrast. C. Orientation tuning of firing during gamma oscillations, as computed using E%max model. Curve fits to data show no effect of increasing contrast on orientation selectivity. Reprinted with Permission Figs.5 and 6 of (de Almeida, Idiart et al. 2009).

Fig. 2. The E%max model provides an explanation for why orientation selectivity becomes lower with time during a gamma cycle

Positive-going ramps are due to decline of inhibition from previous gamma cycle. Blue corresponds to vertical stimulus that is well tuned to the orientation selectivity of the cell. On other trials, the stimulus (green) is slightly less well tuned and thus has lower excitation and will lead to firing later in the gamma cycle. The lower excitation may be due to either a clockwise or counterclockwise shift in orientation relative to the optimal orientation. Consequently, the orientation selectivity (bottom) becomes lower, as observed by (Womelsdorf, Lima et al. 2012). With more strongly mistuned orientation (red), the cell will not fire because it does not reach threshold before the arrival of the feedback inhibition initiated by the best tuned cell.

TABLE 1

Properties of a “Full Model” relevant to the E%max computation

1	The signal-to-noise ratio for detecting gamma oscillations is not high; thus, the assignment of the gamma phase to spikes is not accurate, and the resulting smearing must be taken into consideration in accounting for how orientation tuning varies with gamma phase.
2	In our simple model, there is only a single interneuron. This assumption is motivated by the fact that fast-spiking interneurons are electrically coupled (Galarreta and Hestrin 1999, Gibson, Beierlein et al. 1999, Bartos, Vida et al. 2001), but this assumption must certainly be only an approximation.
3	In our model, the circuitry is homogeneous, but recent work suggests that important aspects of the local circuitry may vary quantitatively from cell to cell (Folias, Yu et al. 2013). It remains unclear whether this results from variability in wiring or whether such variation stems from the fact that different types of cells have been lumped together. The latter possibility is suggested by recent work using large-scale optical imaging of V1. This work demonstrates that, just as orientation is spatially mapped on the surface of V1, spatial frequency is also mapped; indeed, the two are mapped orthogonally (Nauhaus, Nielsen et al. 2012). It seems possible that orientation tuning will become much less variable if only cells having a given spatial frequency tuning are considered.
4	Although Hubel and Wiesel’s original work on orientation tuning used non-moving stimuli, most subsequent work has used moving gratings. This is perhaps unfortunate because it means that any quantitative account of the data must take into consideration the mechanisms of directional selectivity, an altogether different computation, the mechanism of which remains unclear.
5	Many V1 cells have an orientation tuning curve that appears to rest on a basal rate. This basal rate would not be predicted by the E% model without further assumptions.
6	Although in the simplest E%max model, inhibition is global, this is unlikely to be the case for V1 as a whole, given the fact that the activity of inhibitory neurons shows orientation selectivity. Thus, a more realistic model would be that inhibitory cells were driven by several nearby orientation columns and thus have a broad but not completely uniform orientation selectivity, as observed in some fast-spiking interneurons (**Nowak; but see Cardin). This condition would be sufficient to produce the competition between orientations that underlies the E% model.