Emerging feed-forward inhibition allows the robust formation of direction selectivity in the developing ferret visual cortex

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Van Hooser SD, Escobar GM, Maffei A, Miller P. Emerging feed-forward inhibition allows the robust formation of direction selectivity in the developing ferret visual cortex. J Neurophysiol 111: 2355–2373, 2014. First published March 5, 2014; doi:10.1152/jn.00891.2013.—The computation of direction selectivity requires that a cell respond to joint spatial and temporal characteristics of the stimulus that cannot be separated into independent components. Direction selectivity in ferret visual cortex is not present at the time of eye opening but instead develops in the days and weeks following eye opening in a process that requires visual experience with moving stimuli. Classic Hebbian or spike timing-dependent modification of excitatory feed-forward synaptic inputs is unable to produce direction-selective cells from unselective or weakly directionally biased initial conditions because inputs eventually grow so strong that they can independently drive cortical neurons, violating the joint spatial-temporal activation requirement. Furthermore, without some form of synaptic competition, cells cannot develop direction selectivity in response to training with bidirectional stimulation, as cells in ferret visual cortex do. We show that imposing a maximum lateral geniculate nucleus (LGN)-to-cortex synaptic weight allows neurons to develop direction-selective responses that maintain the requirement for joint spatial and temporal activation. We demonstrate that a novel form of inhibitory plasticity, postsynaptic activity-dependent long-term potentiation of inhibition (POSD-LTPi), which operates in the developing cortex at the time of eye opening, can provide synaptic competition and enables robust development of direction-selective receptive fields with unidirectional or bidirectional stimulation. We propose a general model of the development of spatiotemporal receptive fields that consists of two phases: an experience-independent establishment of initial biases, followed by an experience-dependent amplification or modification of these biases via correlation-based plasticity of excitatory inputs that compete against gradually increasing feed-forward inhibition.

feed-forward; Hebbian learning; unsupervised learning; Reichardt detector; logical AND-gate

Direction selectivity is the property of responding more strongly to visual motion stimulation in a preferred direction than any other. To exhibit direction selectivity, a cell not only must respond to a stimulus at a specific set of locations but must respond more strongly when the stimulus is moving in the appropriate direction. Thus direction selectivity depends on joint spatial and temporal stimulus characteristics that cannot be separated into independent components of space and time (Adelson and Bergen 1985; Barlow and Levick 1965; McLean et al. 1994; Reichardt 1961; Reid et al. 1987).

In ferrets, and possibly in humans (Ellemberg et al. 2002), direction selectivity in visual cortex is not present at the onset of visual experience but develops in the subsequent days/weeks. Visual experience with moving stimuli is required, as dark-reared animals (Li et al. 2006) or strobe-reared animals (Humphrey and Saul 1998) do not acquire robust direction selectivity. Brief experience with a motion stimulus that moves bidirectionally (back and forth) for 3–6 h is sufficient to cause the rapid emergence of direction selectivity in naive animals (Li et al. 2008). Weak initial directional biases that are present at the time of eye opening correlate with the final direction preference of cells, and likely provide the symmetry breaking necessary to allow cells to acquire a particular direction preference in response to bidirectional stimulation (Li et al. 2008). These biases form without visual experience (Van Hooser et al. 2012), but they are not immutable, as experience with motion in a single direction—unidirectional training—can override the initial biases, producing more cells that prefer the trained direction than would be expected otherwise (Van Hooser et al. 2012). The circuit mechanisms that underlie this development remain unclear and are explored here.

Unsupervised Hebbian models of development must address runaway excitation: inputs correlated with the output neuron are strengthened, causing more correlated activity, causing further strengthening and, eventually, unselective responses (von der Malsburg 1973). This problem is acute for spatiotemporal learning: the system must amplify appropriate inputs but not amplify them so much as to allow them to independently drive the circuit, which would violate the joint spatiotemporal activation requirement (Feidler et al. 1997). Theoretical treatments have employed multiplicative or subtractive normalization of synaptic weights to maintain circuit selectivity as input weights grow (Miller and MacKay 1994). Homeostatic synaptic scaling implements multiplicative normalization (Luz and Shamir 2012; Truigiano et al. 1998), but likely operates too slowly to underlie the rapid emergence of direction selectivity.

Here we show that a recently discovered form of inhibitory plasticity, postsynaptic activity-dependent long-term potentiation of inhibition (POSD-LTPi) (Garkun and Maffei 2014), can provide subtractive normalization for a feed-forward model of the development of direction selectivity. POSD-LTPi operates at the time of eye opening, overlapping with the period of the development of direction selectivity. Just as in ferret visual cortex, the POSD-LTPi model amplifies initial biases with bidirectional training to produce direction-selective cells, and
allows these biases to be overridden with unidirectional training.

MATERIALS AND METHODS

Computer simulations were performed in MATLAB (The MathWorks, Natick, MA). Integrate and fire neurons (Lapicque 1907; Abbott 1999) were updated with the following differential equation, using the Euler method with a time step of 1 ms or 0.1 ms (equivalent results):

$$\frac{dV_m}{dt} = -\frac{1}{\tau_m} (V_m - V_e) - \frac{R_m}{A_m \tau_m} \sum_i G_i(t)(V_m - V_{rev})$$

where $V_m$ is the membrane potential of the modeled cell, $V_e$ is the leak potential, $A_m$ is the membrane area, $\tau_m$ is the membrane time constant, $R_m$ is the membrane resistance, $G_i(t)$ is the synaptic current from synapse $i$, and $V_{rev}$ is the reversal potential of the current generated by synapse $i$. When $V_m$ reaches a voltage $V_{thresh}$, the model neuron generates a spike and $V_m$ is reset to $V_{reset}$ (see Table 1 for values).

Synapses were modeled with two time constants (Destexhe et al. 2000):$G_i(t) = \sum_j G_j[\exp(-\Delta t_j/\tau_j) - \exp(-\Delta t_j/\tau_1)]$

where $G_i$ is the peak conductance of the synapse, $\Delta t_j$ is the time between $t$ and the $j$th spike of the presynaptic neuron, and $\tau_j$ is the rising time constant and $\tau_1$ is the falling time constant. In some experiments, we reference the minimum $G_j$ necessary to produce an action potential; this value was determined by a binary search with 30 steps.

We implemented two forms of spike timing-dependent plasticity. The first we call “classic STDP.” Plasticity depended only on spike timing (Bi and Poo 1998; Markram et al. 1997), and we used the equation of Song et al. (2000):$
\frac{\Delta G_i}{G_{i,\text{max}}} = \begin{cases} 
A^+ \exp \left(-\frac{(t_{\text{post}} - t_{\text{pre}})}{\tau_1}\right), & t_{\text{post}} - t_{\text{pre}} > 0 \\
A^- \exp \left(-\frac{(t_{\text{pre}} - t_{\text{post}})}{\tau_1}\right), & t_{\text{post}} - t_{\text{pre}} < 0
\end{cases}
$

where $t_{\text{pre}}$ is the time of a presynaptic spike, $t_{\text{post}}$ is the time of the postsynaptic spike, $\tau_1$ and $\tau_2$ are the time constants that influence the spike-timing window, $A^+$ and $A^-$ determine the amplitude of the pre and post spikes, respectively, and $G_{i,\text{max}}$ is the imposed maximum (or “ceiling”) conductance that cannot be exceeded (see Table 1).

The second form of spike-timing-dependent plasticity is the “triplet rule” that depends jointly on both spike rate and spike timing (Bourjaily and Miller 2011; Gjorgjieva et al. 2011; Pfister and Gerstner 2006; Sjostrom et al. 2001):

$$\frac{\Delta G_i}{G_{i,\text{max}}} = \exp\left(-\frac{(t_{\text{post}} - t_{\text{pre}})}{\tau_1}\right)\{A^+_2 + A^-_2 \sum_j \exp\left(-\frac{(t_{\text{post}} - t_j)}{\tau_1}\right)\}$$

while if $t_{\text{post}} - t_{\text{pre}} < 0$,

$$\frac{\Delta G_i}{G_{i,\text{max}}} = \exp\left(-\frac{(t_{\text{post}} - t_{\text{pre}})}{\tau_1}\right)\{A^+_2 + A^-_2 \sum_j \exp\left(-\frac{(t_{\text{pre}} - t_j)}{\tau_1}\right)\}$$

The parameters for the synaptic plasticity rules were taken directly from Song et al. (2000) and Pfister and Gerstner (2006) (Table 1). The Pfister and Gerstner parameters were obtained by fitting the data of Sjostrom et al. (2001). Small variations in the plasticity parameters will not impact the conclusions of the present work.

POSf-LTPi was implemented by assuming that each “training stimulus” consisted of a sequence of several bars moving in a particular direction at a rapid repeat rate (such as 4 Hz) such that the cortical neuron would fire a train of action potentials in a brief period of time. This type of spike train, when generated in a pyramidal cell, produces POSf-LTPi in slice preparations (Garkun and Maffei 2014). The increase in the inhibitory synaptic weight was described by the equation $I = I_{\text{init}}(I_s)^N$, where $I$ is the inhibitory synaptic strength, $I_s$ is the multiplicative factor (>1) of increase with each train of stimulation, and $N$ is the number of trains of stimuli that have been given. $I$ was limited to a maximum value of $I_{\text{max}}$, such that the overall equation was $I = \min(I_{\text{init}}(I_s)^N, I_{\text{max}})$. Note that when $I$ is less than $I_{\text{max}}$, the incremental change in $I$ is $\Delta I = I \times I_s$, such that $I \to \min(I + \Delta I, I_{\text{max}})$.

**Direction selectivity.** A direction selectivity index (DSI) was defined as the normalized difference between the response to the preferred direction ($R_{\text{pref}}$) and the response to the direction opposite of the preferred ($R_{\text{null}}$):$\text{DSI} = \frac{R_{\text{pref}} - R_{\text{null}}}{R_{\text{pref}} + R_{\text{null}}}$

**Mathematical proof of relationship between inputs, response rates, and direction selectivity for a 2 $\times$ 2 network:** $|R_{\text{pref}} - R_{\text{null}}| < \alpha T$. How flexible is the four input single-layer circuit with excitatory
connections? Can it produce arbitrary $R_{up}$ and $R_{down}$ or is it restricted to a particular range? To examine this, let us assume that the input generated by the arrival of a synaptic input via one of the inputs $s_i$ produces some postsynaptic response $w_i$ that is converted to a firing rate by some nonlinear process $F$. Let us assume further that the circuit is being stimulated at its optimal velocity. Then

$$R_{up} = F(W_{11}) + F(W_{12} + W_{21}) + F(W_{22})$$

and

$$R_{down} = F(W_{12}) + F(W_{11} + W_{22}) + F(W_{21}).$$

For simplicity, let us assume that $F$ is a simple linear scaling with rectification above a threshold $T$: $F(W) = \alpha[W - T]$. (Note that $[\ ]$ indicates rectification above 0, ensuring $F(0)$ is never less than 0.) We also make the simplifying assumption that $W_{11} = W_{22} = W_y$ and $W_{12} = W_{21} = W_x$. Then we have

$$R_{up} = \frac{\alpha}{2} [W_y - T]_+ + [2W_x - T]_+$$

(1)

and

$$R_{down} = \frac{\alpha}{2} [W_y - T]_+ + [2W_x - T]_+$$

(2)

Our task is to produce a requested $R_{up}$ and $R_{down}$ given $T$ and $\alpha$ as properties of the system that we cannot change, while being free to change $W_x$ and $W_y$. We further assume that the circuit gives some response and arbitrarily assume that the response to “up” is greater than or equal to the response to “down” (one can rewrite the problem in the other direction if one prefers). The latter condition requires that $B > 0$, that is, $2W_y - T > 0$. Then, as we choose weights $W_x$ and $W_y$, we have eight possibilities for the terms $A$, $C$, and $D$ that are within the rectification terms. That is, we could potentially have every combination of $A$, $C$, and $D$ (defined in the brackets above) less than 0 or greater than 0:

- $[W_y - T] < 0$ and $[2W_y - T] < 0$ and $[W_x - T] < 0$ (000)
- $[W_y - T] < 0$ and $[2W_y - T] < 0$ and $[W_x - T] > 0$ (001)
- $[W_y - T] < 0$ and $[2W_y - T] > 0$ and $[W_x - T] < 0$ (010)
- $[W_y - T] < 0$ and $[2W_y - T] > 0$ and $[W_x - T] > 0$ (011)
- $[W_y - T] > 0$ and $[2W_y - T] < 0$ and $[W_x - T] < 0$ (100)
- $[W_y - T] > 0$ and $[2W_y - T] < 0$ and $[W_x - T] > 0$ (101)
- $[W_y - T] > 0$ and $[2W_y - T] > 0$ and $[W_x - T] < 0$ (110)
- $[W_y - T] > 0$ and $[2W_y - T] > 0$ and $[W_x - T] > 0$ (111)

There are two cases on this list of eight that cannot occur. We have assumed excitatory connections from thalamus to cortex such that the weights $W_x$ and $W_y$ need to be greater than 0. Therefore, if $[2W_y - T] > 0$ then it is necessary that $[W_x - T] > 0$, so cases 8 and 6 cannot occur. We consider the remaining cases in turn.

Under case 1, $R_{up} = \alpha [2W_y - T]$ and $R_{down} = 0$. We know $[W_x - T] < 0$, so $W_x$ can approach $T$ at its largest, so the largest value we can choose for $R_{up}$ can approach but not exceed $R_{up} = \alpha T$. So we have perfect direction selectivity, but we are not free to increase $R_{up}$ arbitrarily.

Under case 2, $R_{up} / \alpha = 2W_y - T$, so we must choose $W_y = 1/2 [R_{up} / \alpha + T]$. This leaves $R_{down} / \alpha = 2[W_x - T] = R_{up} / \alpha + T - 2T = R_{up} / \alpha - T$, so we can only create $R_{down}$ such that $R_{up} - R_{down} = \alpha T$.

Under case 3, $R_{up} / \alpha = 2W_y - T$ and $R_{down} / \alpha = 2W_x - W_y$. So we can create differences of $(R_{up} - R_{down}) / 2\alpha = W_x - W_y$. By the conditions of case 3, $T > W_y > T/2$ and $T > W_y > T/2$, so the difference we can create is limited by the largest value of $W_x$ and the smallest value of $W_y$ we can choose: $(R_{up} - R_{down}) / 2\alpha < T - T/2$ or $(R_{up} - R_{down}) \leq \alpha T$. So we can express $R_{up}$ values up to a maximum of $R_{up} = 2\alpha T$, but we have limited freedom to express $R_{down}$ we can only express differences such that $R_{up} - R_{down} \leq \alpha T$.

Under case 4, $R_{up} / \alpha = 2W_y - T$, so we must choose $W_y = 1/2 [R_{up} / \alpha + T]$. $R_{down} / \alpha = 2W_x - T + 2W_y - 2T = 2W_x + R_{up} / \alpha - 2T$, so that $R_{up} - R_{down} \leq 2\alpha(T - W_y).$ We are limited in our choice of $W_y$ here because $W_y < T$, so $W_x < T$, so $T/2 < W_x < T$. This means that we can choose $R_{up}$ arbitrarily, we are limited in specifying $R_{down}$, both $R_{up} - R_{down} \leq \alpha T.

Case 7 is symmetrical to case 4: $R_{down} / \alpha = 2W_y - T$, so we must choose $W_y = 1/2 [R_{down} / \alpha + T]$. This means that $R_{up} / \alpha = 2W_x - T + 2W_y - 2T = 2W_x + R_{down} / \alpha - 2T$, and that $R_{up} - R_{down} \leq 2\alpha(W_y - T)$. We are again limited in our choice of $W_x$, $W_y < T$, and $W_x < T$, so therefore $T/2 < W_x < T$. So while we can express any $R_{down}$ we want, we are limited in specifying $R_{down}$ such that $-\alpha T < R_{up} - R_{down} < \alpha T$. Note that in this case the preferred direction is restricted to the down direction.

The last case, case 8, does not exhibit any direction selectivity. Here, $R_{up} / \alpha = 2[W_y - T] + [2W_y - T] = 2W_x + 2W_y - 3T$ and $R_{down} / \alpha = 2[W_y - T] + [2W_y - T] = 2W_x + 2W_y - 3T$. So while we can pick arbitrarily high rates such that $R_{up} > 4\alpha T$, we are constrained so that $R_{up} = R_{down}$.

The conclusion of all of this is that the single excitatory layer circuit is limited in the direction selectivity it can provide. In the best of these cases, $0 \leq R_{up} - R_{down} \leq \alpha T$. We cannot produce arbitrary $R_{up}$ and $R_{down}$ with this circuit. The weights along the diagonals are activated simultaneously by stimuli that move at the optimal velocity. The distribution of the weights along the diagonals is not relevant, so without loss of generality we assume they are all equal.

$$\begin{array}{cccc}
 a & f & g & h \\
 b & a & f & g \\
 c & b & a & f \\
 d & c & b & a
\end{array}$$

The weights along the diagonals that run upper left to lower right are activated by a stimulus moving upward, and the weights along the diagonals that run upper right to lower left are activated by a stimulus moving downward.

We wish to maximize the response to $R_{pref}$ while maintaining no response to $R_{null}$. Suppose we begin by using the longest diagonal with weights set to $a$ and let all other weights equal to 0. Then the response is $R_{pref} / \alpha = \alpha(Na - T)$. We do not want to activate in the null direction along any of the downward diagonals that include $a$, so we make sure that $a < T$.

Now we ask, can we do better by including some contribution from one of the lesser diagonals? Let us first consider the diagonal that is 2 offset from the $a$s, the $c$s. The response in the preferred direction is now $R_{pref} / \alpha = [Na - T] + [(N - 2)c - T]$. We do not want to add a contribution from the null direction diagonals that include $a$ and $c$, so we require that $a + c < T$. We will now show that no matter what value of $c$ we choose, we will actually reduce $R_{pref}$ and we are better off not using it at all. Suppose we choose a value $c$ such that we had suprathreshold contributions from both the $a$ and $c$ terms, so that $R_{pref} / \alpha = Na - T + (N - 2)c - T$. Now we know that $a + c < T,$
so let us examine the situation with the largest and smallest possible values of \( c, c < T - a \), and at most \( c \) can just approach \( T - a \). So we have \( R_{\text{out}} < \alpha = [N - T] + ([N - 1]b - T) \), which reduces to \( R_{\text{out}} < \alpha < 2a + NT - 4T \). We would like \( a \) to be as big as possible in this equation. Now, at most \( a \) can be just below \( T \), so \( R_{\text{out}} < \alpha < 2T + NT - 4T \), which reduces to \( R_{\text{out}} < \alpha < NT - 2T \). Using a nonzero value of \( c \) has made things worse than just using \( a \): \( R_{\text{out}} < \alpha = [N - T] + ([N - 1]b - T) \). So the diagonals that interact with the main diagonal in the null direction (\( c, c, d, e \)), do not help and should be set to 0 for maximum \( R_{\text{out}} \).

The first minor diagonal (with values equal to \( b \)) does not interact with the main diagonal in the null direction, so we can use nonzero values of \( b \). Similar to the above, we do not want to use nonzero values for diagonals that interact with the \( b \)s in the null direction. So we have \( R_{\text{out}} < \alpha = [N - T] + ([N - 1]b - T) \), and we require \( a < T \) and \( b < T \) (so we do not have null direction activation by these units alone). Therefore, assuming both contributions are above threshold: \( R_{\text{out}} < \alpha < [NT - T] + ([N - 1]T - T) \), which reduces to \( R_{\text{out}} < \alpha(TN - 3) \). If we add to these weights, we can increase \( R_{\text{out}} \) but at the cost of the same increase or a larger increase to \( R_{\text{out}} \).

Determining synaptic strength ceilings for feed-forward inputs of different sizes, latencies. When we examined the ability of classic STDP and triplet STDP to produce direction selectivity with unidirectional training, we limited the synaptic strengths as follows. We assumed that the “early” conductances activated before the main diagonal (values \( b, c, d, e \), and \( e \) in the \( 5 \times 5 \) matrix above), and those along the main diagonal (values \( a \) in the \( 5 \times 5 \) matrix above), would be the conductances that were strengthened by training in the upward direction. We wanted to limit these values so the response in the downward direction would never exceed 1 spike, which is the initial response to the downward direction. If POSD-LTP was employed, we increased \( W_{\text{pos}} \) by 1% of the product of \( W_{\text{pos}} \) and the response to the upward direction. If upward motion caused a response, we increased \( W_{\text{pos}} \) by 1% of the product of \( W_{\text{pos}} \) and the response to the downward direction. If POST-LTP was employed, we mimicked an increase in inhibition by increasing the threshold \( T \) of the cortical cell, using an increment of 0.2% (weak inhibition condition) or 0.4% (strong inhibition condition).

RESULTS

Construction of the feed-forward model. Our goals were to examine the ability of a simple feed-forward cortical circuit model to exhibit direction selectivity and to acquire direction selectivity from a naive state that lacks strong direction selectivity. We focused here on feed-forward models, both for simplicity and because of recent evidence that suggests that feed-forward models can, in principle, explain a majority of the basic receptive field properties in primary visual cortex (Chung and Ferster 1998; Ferster et al. 1996; Ferster and Miller 2000; Lien and Scanziani 2013; Priebe and Ferster 2012).

We represented the LGN as an \( R \times C \) matrix of units (Feidler et al. 1997). Each LGN unit responded, with a single action potential, to visual stimulation at a specific spatial location and with a specific latency. For example, the LGN unit at coordinate \( r, c \) responded to stimulation at position \( r \) and with latency of \( c \times \Delta t \). For simplicity, we assumed that the first column of units responded instantaneously, with 0 latency, but any number could be used for this baseline latency. The values \( \Delta t, R, \) and \( C \) were varied from simulation to simulation and are summarized in Table 1. The LGN units projected to a single area 17 (V1) cortical neuron that was modeled as a leaky integrate and fire neuron (Abbott 1999; Lapicque 1907). In the final, full model, there was a second V1 cortical neuron—an inhibitory integrate and fire neuron—that provided inhibitory input to the primary cortical neuron.

In this work, we focused on the ability of the circuit to express and learn direction selectivity, so we included only the elements necessary to explore these properties. For simplicity, we simulated a single spatial dimension, along the axis orthogonal to the orientation preference of the cortical neuron. Each simulated LGN unit in our model represents a set of approximately five real LGN cells—with colinear receptive fields—in the real animal, where the pattern of the LGN cell projections confers orientation selectivity (Chapman et al. 1991; Ferster et al. 1996; Hubel and Wiesel 1959; Reid and Alonso 1995).

Previous work has suggested that cortical neurons in the adult cat receive somewhere between 50 and 150 real LGN neuron inputs (Banitt et al. 2007; Troyer et al. 1998), and we model only 4–25 simulated LGN units here. Furthermore, we ignored the distinction between ON and OFF cells in the LGN; in a more realistic model, adding ON and OFF cells would essentially double the number of input LGN cells without greatly influencing response properties in other ways. We also ignored the complexities of spatial and temporal processing and response variability in LGN neurons because only a little is known about LGN cell responses to gratings in ferret visual cortex at the time of eye opening (Akerman et al. 2004; Krug et al. 2001; Ohshiro and Weliky 2006; Tavazoei and Reid 2000) and how these properties change during development (Akerman et al. 2004; Saul and Feidler 2002; Tavazoei and Reid 2000). We did not include any short-term synaptic dynamics like synaptic depression or facilitation (Buchs and Senn 2002; Chance et al. 1998), and we ignored differences between X and Y LGN cell types (Marr and Ullman 1981).

Structure of the feed-forward inputs to the model. One may ask whether there is an experimental basis for modeling the LGN as a set of excitatory neurons with different positions and latencies, and indeed the availability of these LGN inputs is supported by a wealth of experimental data (Feidler et al. 1997; Humphrey et al. 1998; Humphrey and Saul 1995, 1998; Maex and Orban 1991; Saul and Humphrey 1990, 1992; Wolfe and Palmer 1998). Studies of LGN in carnivores have documented two classes of LGN neurons, called nonlagged (latencies < 100 ms, a majority) and lagged (latencies > 100 ms, a minority) cells, and some have suggested that inputs from these two classes would allow a large range of direction selectivity to be expressed in cortex (Saul and Humphrey 1990; Wolfe and Palmer 1998). However, even if lagged cells are less common, there is still a large range (40 ms) of latencies within the class of nonlagged cells, and this variation by itself could provide a basis for forming direction-selective receptive fields (Feidler et al. 1997), if they could be connected to a cortical cell in an appropriate manner.

Even if there is a population of cells with different position preferences and latencies in the developing ferret LGN, it remains unclear whether or not each developing cortical layer...
4 neuron receives input from a broad range of these LGN cells, or rather from a restricted subset of LGN cells that is already highly specific in space and time. Cortical neurons exhibit orientation selectivity at the time of eye opening (Chapman and Stryker 1993; Li et al. 2006), so it is likely that cortical neurons receive input from a subset of LGN neurons with an elongated spatial bias. In this model, we assume that cortical neurons receive input from LGN units with a broad range of temporal latencies, and we are unaware of any experimental evidence that would help constrain this assumption.

We have also assumed that these LGN units do not exhibit any direction selectivity at this stage in development. Is this a reasonable assumption in ferret? Recent studies have identified abundant direction-selective neurons in the adult mouse LGN (Marshel et al. 2012; Piscopo et al. 2013; Scholl et al. 2013). It remains unclear whether the direction selectivity that is present in mouse LGN represents a species difference, or whether strong direction selectivity is present in the LGN of most mammals. Direction selectivity in cat LGN is much weaker than in cat visual cortex (Thompson et al. 1994a, 1994b), and only weak direction selectivity has been reported in tree shrew LGN and visual cortex (Van Hooser et al. 2013).

At present, it remains unknown whether cells in the developing or adult ferret LGN respond to drifting sinusoidal gratings in a direction-selective manner, so we are assuming that these LGN cells exhibit no strong direction selectivity (similar to cat). If future recordings discover otherwise, then the model would need to be revised.

Direction-selective ganglion cells in the retina (Barlow and Levick 1965; Briggman et al. 2011; Euler et al. 2002; Reichardt 1961) can be explained by a half-Reichardt detector model of direction selectivity, with feed-forward excitation opposed by delayed directional feed-forward inhibition. In mammals, this delayed null-direction feed-forward inhibition is implemented via dendritic synapses from specific branches of starburst amacrine cells onto direction-selective ganglion cells (Briggman et al. 2011; Euler et al. 2002). Such cells experience null-direction inhibition, as predicted by the model, which is capable of producing arbitrary responses to the preferred and null directions (Adelson and Bergen 1985; Reichardt 1961). However, null-direction inhibition has not been observed in visual cortex (Priebe and Ferster 2005), and projections from the LGN to cortex are purely excitatory. The model under investigation here is an excitatory half-Reichardt detector, with only the directional feed-forward excitation represented.

Running the model. The model’s principle of operation can be demonstrated by consideration of just four LGN unit inputs to a cortical cell, as illustrated in Fig. 1. The four LGN inputs are arranged in two rows (positions) and two columns (latencies) as shown in Fig. 1A. We assume that neurons with delayed responses to stimulation are found in the LGN, but they could also reside in cortex without altering the underlying behavior of the circuit (Fig. 1B). An unselective circuit configuration is shown in Fig. 1C. The individual synaptic weights from the LGN units have been set, for illustration, at 75% of the amount needed to drive a single action potential in the cortical neuron. In the simulation, a stimulus moves upward and then downward. The stimulus moves at the “optimal” velocity for the circuit, such that it arrives at position 2 exactly $\Delta t$ after it arrived at position 1. That is, the stimulus arrives at position 2, and activates neuron $u_{21}$, at exactly the same time that neuron $u_{12}$ responds to the stimulus at position 1. When these neurons are activated simultaneously, the cortical neuron is driven to fire action potentials. Because the synaptic weights are symmetrical, the circuit responds similarly to upward and downward motion.

This model circuit is also capable of exhibiting selective responses to stimulus direction, as shown in Fig. 1D. Here the weights of the input units that produce a preference for downward motion have been set to 0 nS, and the output cell only fires action potentials for the upward direction.

Actual firing rates of ferret visual cortical neurons and capabilities of the excitatory feed-forward model. When synaptic weights are small (Fig. 1D), the cortical neuron can only be driven by the simultaneous activation of multiple inputs, which helps to constrain the response of the cortical neuron to stimuli with particular joint spatial and temporal characteristics; mere activation at a single location at a particular time cannot, by itself, produce action potentials in the cortical cell. If synaptic weights are made larger, however, this requirement of joint activation is lost. This fundamental limit of the circuit is demonstrated in Fig. 1E, where the weights of the LGN unit inputs that support the response to upward motion have been increased so they are individually suprathreshold (110% of threshold). This modified circuit is no longer purely selective for upward motion but also responds weakly to downward motion. If the circuit has more than four LGN unit inputs, then the weight requirements become more complicated, as one wants to prevent the driving of responses by inappropriate combinations of inputs, in addition to single inputs as in Fig. 1E.

Before examining the limitations in the responses and the direction selectivity that can be expressed in the feed-forward excitatory model, it is reasonable to examine real responses in the developing ferret visual cortex. Spiking responses of cortical neurons in ferret visual cortex to drifting sinusoidal gratings for three groups of animals—those with closed eyes that were opened during the experiment, those with ~2 days of visual experience through naturally opened eyes, and those with many days of experience—were reanalyzed from a previous experiment (Clemens et al. 2012) and plotted in Fig. 2.

Firing rate responses to stimulation in the preferred and null directions are relatively low, and the raw differences between the responses to the preferred and null directions are also relatively low (Fig. 2, B and C). Furthermore, high direction selectivity co-occurs with low responses to the null direction, and we do not see any examples of cells with strong direction selectivity and large responses to both the preferred and null directions (compare Fig. 2C).

To determine whether the feed-forward model was flexible enough to capture the spiking responses observed in ferret visual cortex, we explored the space of the response rates and DSI values that the excitatory feed-forward model could achieve if one were completely free to set the synaptic weights. To do this, we developed a simplified linear-threshold model of the output of the cortical neuron (see Materials and Methods). This analysis revealed that, in this circuit, the difference in the cortical response to the preferred direction and the response to the opposite direction is constrained to be less than a particular constant. This constant depends on the number of LGN units and the input-output properties of the cortical cell. If we assume that the number of positions represented in the LGN is
Fig. 1. An excitatory feed-forward model of direction selectivity. A: a model circuit with 4 lateral geniculate nucleus (LGN) inputs in a $2 \times 2$ configuration; the LGN units in each row respond to different stimulus positions, while the units in each column respond to different stimulus latencies (1st column latency is 0, 2nd column latency is $\Delta t$). These units project to a cortical neuron $V$ with the synaptic conductances indicated. B: while this paper posits that units with different latencies are in the LGN, if the cells with longer-latency responses reside in the cortex, then the behavior of the circuit is the same.

C: a simulation with all synaptic weights equal to 75% of the amount necessary to produce an action potential in cortical cell $V$. The bar stimulus first moves upward and then downward. The bar first arrives at the lower stimulus position, which immediately activates unit $u_{11}$. The bar next arrives at the upper stimulus position at time $\Delta t$; at that time, unit $u_{12}$ responds to the stimulus at the lower position (because it has a latency of $\Delta t$) while unit $u_{21}$ responds to the stimulus in its receptive field. The simultaneous activation of units $u_{12}$ and $u_{21}$ drives cortical cell $V$ to fire action potentials. The process is reversed for downward motion. DSI, direction selective index; $V_m$, membrane potential.

D: a selective model. Only units $u_{12}$ and $u_{21}$ have nonzero synaptic conductances; the cortical cell fires only for upward motion.

E: synapses that are too strong cause reduced selectivity. The weights of $u_{12}$ and $u_{21}$ have been increased to 110% of threshold; the cortical neuron’s selectivity is reduced, as activation of either $u_{12}$ or $u_{21}$ is sufficient to drive $V$; joint activation of $u_{12}$ and $u_{21}$ is no longer required.

F: a model with a $5 \times 5$ LGN matrix, demonstrating that additional inputs allow increased firing rates of $V$ with maintained selectivity. Conductances that are activated before the set of 5 LGN neurons that comprise the “upward diagonal” are indicated as $G_{early}$, and those activated after are indicated as $G_{late}$.
FEED-FORWARD METHODS FOR LEARNING DIRECTION SELECTIVITY

Output curve slope independently; if one raises the threshold $T$ for constant injected current is decreased so the product

$$\text{slope of the spike input-output curve of the cortical neuron}$$

response to the opposite direction, $R$ where

$$R$$

is the threshold of spike activation

$$T$$

and

$$K$$

is the product of the slope of the spike input-output curve of the cortical neuron $\alpha$ in units of input. Note that $\alpha$ and $T$ in general do not vary independently; if one raises the threshold $T$, then the input-output curve slope $\alpha$ (which is a measured property of the cell) for constant injected current is decreased so the product $\alpha T$ is almost the same (exactly the same if there are no nonlinearities in the cell beyond the spike threshold).

This response limit imposes straightforward limitations on the maximum amount of direction selectivity that can be expressed in this circuit. If we assume that $R_{\text{null}}$ is the response to the direction opposite the preferred, then at most $R_{\text{pref}} = R_{\text{null}} + K$, and so DSI would be at most

$$\text{DSI}_{\text{max}} = \frac{R_{\text{pref}} - R_{\text{null}}}{R_{\text{pref}} + R_{\text{null}}} = \frac{K}{2R_{\text{null}} + K}$$

We verified the results of this analysis by comparing the expected range of responses in the preferred and opposite directions and DSI for the linear-threshold analysis with those obtained from 8,000 models with $2 \times 2$ LGN input configurations with random synaptic weights (Fig. 3, A–C) and for 20,000 models of a $5 \times 5$ configuration (not shown). The integrate and fire model used in the actual simulations exhibits some nonlinearities that are not captured by the linear-threshold analysis, and so a few models exceeded the expected limits, but the linear-threshold analysis produced a good approximation to the constraints of the actual biophysical models. We calculated the limits of responses and direction selectivity that would be expected for cells with additional LGN inputs in Fig. 3, D–F. With a $4 \times 4$ LGN, output cells can exhibit DSI values of up to 0.5 as long as the response to the null direction remains less than $\sim 10$ Hz.

When analyzed on a spikes per bar basis, responses in the actual ferret visual cortex are compatible with the excitatory feed-forward model with $2 \times 2$ or $4 \times 4$ inputs (compare Fig. 2B and Fig. 3D). Furthermore, we did not observe examples of high direction selectivity co-occurring with high fire rates in the null direction (compare Fig. 2C and Fig. 3F). On the basis of these comparisons, we conclude that the feed-forward model is capable of representing the types of responses observed in ferret visual cortex at the time of eye opening.

Learning direction selectivity with the feed-forward model. The results presented so far describe the type of direction selectivity that the feed-forward circuit could achieve if one were able to manually choose the synaptic weights, free of any restrictions of synaptic plasticity rules. In the ferret visual cortex at the time of eye opening cells are, at most, only weakly selective to direction but develop a direction preference after several hours or days of experience with a moving visual stimulus. In the typically developing animal, this experience is presumably based on the motion of natural scenes (Li et al.)
transiently. Eventually, if the maximum conductance allowed sponse to the upward direction increases, and the DSI increases into Fig. 2, A (Fig. 4 B). Initially, as these inputs are strengthened, the re-
tances that support the upward direction will be strengthened stimulated with upward motion, then the synaptic conduc-
(2011; Pfister and Gerstner 2006) (see MATE-
and Poo 1998; Song et al. 2000) and “triplet STDP”
timing-dependent rules that we refer to as “classic STDP” (Bi
in ferret visual cortex at this stage of development, we simu-
lated and compared the effects of two different common spike
inocclusion experiments (Cooke and Bear 2010; Ehrlich and
appear to exhibit “ceilings,” such as those described in LTP
This mechanism is biophysically plausible, as real synapses
cannot grow so strong that any one LGN unit could drive a
cortical neuron begins responding to stimulation in both direc-
tions, and the DSI drops back to 0.
A simple solution to this problem of loss of selectivity with
further training is to constrain the range of possible synaptic strengths by setting a maximum conductance value, or a
conductance “ceiling,” on the synapses that cannot be ex-
ceeded (Fig. 4B) (Linsker 1986a, 1986b, 1986c). With an
appropriate value for the maximum conductance, the synapses
cannot grow so strong that any one LGN unit could drive a
cortical neuron individually, and the increased DSI is stable.
This mechanism is biophysically plausible, as real synapses
appear to exhibit “ceilings,” such as those described in LTP
occlusion experiments (Cooke and Bear 2010; Ehrlich and
So far, we have only considered networks with a $2 \times 2$
LGN, where selectivity can be maintained by forcing individual
synaptic weights to remain below the threshold for driving
action potentials. What if the LGN is larger, such as a $5 \times 5$
configuration? What if the latency step values $\Delta t$ are small,
such that the synaptic potentials will sum together across time?
We explore these conditions in a family of $5 \times 5$ models that
vary in their latency step $\Delta t$ (Fig. 5). Each model network was
started with equal synaptic weights chosen so that the cortical
neuron fires a single action potential in response to stimulation

![Fig. 3. Capabilities of the excitatory feed-forward model. A–C: limitations of models with $2 \times 2$ LGN configurations. Red and green bars indicate the boundaries of combinations of $R_{\text{pref}}$ and $R_{\text{null}}$ that can exist in a linear threshold (LT) simplification of the computational model. The maximum difference between $R_{\text{pref}}$ and $R_{\text{null}}$ is constrained to be $\leq$ a constant (see text). Shaded area indicates region where model can operate. Dots indicate computational models with randomly generated synaptic conductances. Note that these dots largely fall within the predicted region; some models slightly exceed the bounds because the response of an integrate and fire (I+F) neuron to input is nonlinear (see text). Blue lines indicate maximum direction selectivity; direction selectivity is constrained to be less than or equal to the blue line (shaded region). C is a zoomed-in view of B. D–F: response combinations and direction selectivity possible for $N \times N$ LGN configurations, where $N$ is the number indicated on each curve. D: red lines indicate maximum $R_{\text{pref}}$ that is possible for each value of $R_{\text{null}}$. Green line indicates the minimum value of $R_{\text{null}}$ as equal to $R_{\text{null}}$. E and F: blue lines indicate maximum direction selectivity that is possible. F is a zoomed-in view of E. Compare to Fig. 2, B and C.](http://jn.physiology.org/)}
in either direction (binary search, 30 steps). The maximum synaptic conductance was determined by the procedure described in MATERIALS AND METHODS. In brief, we determined (by hand) the maximum synaptic conductances that would maintain 1 spike per bar in the opposite direction (such that the circuit would never increase its firing above 1 spike per bar in response to the opposite direction). We assume that, in the actual animal, the approximate number of LGN inputs, the corresponding initial weights, and the limits of those weights would be determined independent of experience, through evolution.

With unidirectional stimulation, networks with a broad range of latencies (25 ms to 200 ms shown here) for LGN neurons can develop strong selectivity for the trained direction (upward direction shown with classic STDP (Fig. 5, A–C) or triplet STDP (Fig. 5, D–F). The enhancement of directional selectivity in the classic STDP case is a result of both increases in the conductances that are activated early in a single sweep of a bar and decreases in the conductances that are activated late in the single sweep. In the triplet case, the increase in direction selectivity is primarily through decreases in the conductances that are activated late, owing to the low firing rates in our model network (the triplet model requires at least moderate presynaptic/postsynaptic firing rates to exhibit synaptic potentiation) (see also Gjorgjieva et al. 2011).

Initial biases and bidirectional motion training. In the real animal, neurons must develop a direction preference without the benefit of unidirectional stimulation. Natural visual scenes include motion in all directions. We have mimicked this situation in the laboratory by training for several hours with a bidirectional motion stimulus that moves back and forth. Training with a bidirectional motion stimulus produces strong direction selectivity, and each cell whose orientation preference matches that of the stimulation acquires a preference for one of the two trained directions. There is no information in a bidirectional stimulus as to which direction a cell should ultimately prefer; instead, previous experimental evidence suggests that initial directional biases that are already present at the time of eye opening predict the eventual direction preference that will emerge with experience for a given cell (Li et al. 2008).

The classic STDP rule is not capable of supporting the development of strong direction selectivity with bidirectional stimulation. If we provide bidirectional training to a circuit projecting to a single cortical cell that is initially equally selective to upward and downward stimulation (i.e., its DSI = 0), the cortical cell’s response to each direction is increased equally (Fig. 6A). Even if the cortical cell commences with a strong directional bias (e.g., its DSI = 0.5), the main effect of motion training is to increase the cell’s response to the nonpreferred direction, such that the direction selectivity is reduced by training (Fig. 6B).

The triplet STDP rule (Gjorgjieva et al. 2011; Pfister and Gerstner 2006) is sensitive to both the timing and the rate of presynaptic/postsynaptic spikes and is analogous to the purely rate-based Bienenstock, Cooper, Munro (BCM) model (Bienenstock et al. 1982). This feature allows the triplet STDP rule to reduce the rate at which synaptic weights are allowed to grow large. The conductances that support the upward direction ($G_{12}$, $G_{21}$) increase with each presentation of the stimulus. During stimuli 6–8, the cortical cell exhibits moderate direction selectivity. However, as the weights continue to increase, activations of units $u_{12}$ or $u_{21}$ alone are sufficient to drive activity in cortical cell $V$ and joint activation of $u_{12}$ and $u_{21}$ is no longer required. After stimulus 9, the responses to the downward direction increase and DSI falls back to 0. B: training with classic STDP but with an imposed ceiling of 6.64 nS on the maximum synaptic conductance. The cell exhibits moderate direction selectivity that is stable. Note that the smaller weight changes per trial and the larger amount of stimulation necessary to induce direction selectivity in B are a result of the classic STDP equation, which produces, after each pre-post spike pairing, a conductance increase that is in proportion to the maximum allowable conductance.
that a competitive mechanism could allow a feed-forward circuit with small initial biases to develop robust direction selectivity with bidirectional training for both classic and triplet STDP. Recently, Garkun and Maffei (2014) discovered a form of activity-dependent plasticity at inhibitory synapses onto excitatory neurons that could in our model produce competition between the inputs to the excitatory cortical cell (Fig. 7A). At the time of eye opening, local inhibitory-to-excitatory synapses are weak but exhibit potentiation whenever the excitatory cell fires a burst of 10 or more action potentials. This potentiation does not depend on the activity of interneurons themselves but rather only depends on the postsynaptic excitatory cell. For this reason, we call this plasticity postsynaptic activity-dependent long-term potentiation of inhibition, which we abbreviate POSD-LTPi. POSD-LTPi exists for only a brief time in development, from the time of eye opening until the beginning of the critical period for ocular dominance plasticity. This is precisely the time window in which direction selectivity develops in ferret visual cortex, so POSD-LTPi exists at the right time to provide increases in inhibition.

Note that POSD-LTPi is distinct from another form of long-term potentiation of inhibition, called LTPi (Maffei et al. 2006), which depends on the joint activation of the presynaptic inhibitory neuron and the postsynaptic excitatory neuron (Bourjaily and Miller 2011; Luz and Shamir 2012; Vogels et al. 2011). POSD-LTPi only requires activity in the postsynaptic excitatory cell.

**Fig. 5.** Constrained synaptic weights and STDP allow the development of direction selectivity during unidirectional motion training. **A:** results of simulations for circuits with a $5 \times 5$ LGN, $\Delta t$ as indicated, and where the output cell initially responded unselectively, with 1 spike to each direction. **Top:** final DSI achieved. **Bottom:** responses in the preferred direction after training. **B:** the initial and final values of synaptic conductances from the $5 \times 5$ LGN with classic STDP and a latency step size of 0.25 s. The "early" LGN synaptic conductances that are activated before the "upward diagonal" are highlighted in yellow, while the "late" LGN synaptic conductances that are activated after the "upward diagonal" are highlighted in orange (see Fig. 1E). C: the early conductances exhibit increases with training, while the "late" synaptic conductances typically decrease as a result of training, particularly for short lags ($\Delta t < 100$ ms). Dashed blue lines indicate calculated $G_t^{\text{ceil}}$, dashed red lines indicate initial $G_t$. **D–F:** same as A–C, for triplet STDP rule.
We implemented POSD-LTPi by inserting a feed-forward interneuron in our network. It is most reasonable to assume that this is a fast-spiking interneuron, as evidence strongly suggests that these cells receive direct input from LGN (Zhuang et al. 2013). The initial inhibitory-to-excitatory synapse value was small, and this value increased by a multiplicative factor with each episode of visual stimulation until it reached a maximum (Fig. 7B). We implemented a model training protocol that was similar to the protocol used in vivo (20 bar sweeps over 5 s, at a rate of 4 Hz, with a 5 s pause), so the excitatory neurons could fire several bursts over a single training sweep. POSD-LTPi could cause the strength of the inhibitory-to-excitatory synapse to gradually increase across multiple sweeps. We found that we could set the initial inhibitory synaptic strength to any arbitrary number, as long as we adjusted the feed-forward excitatory weights to the cortical neuron to compensate for the initial inhibition (data not shown). The feed-forward interneuron received broadly tuned excitation from all LGN units such that the inhibitory cell fired tonically at a rate of 10–11 Hz.

Fig. 6. Constrained synaptic weights and classic STDP (A–D) and triplet STDP (E–H) do not permit the development of robust direction selectivity with bidirectional training. A: bidirectional training (upward followed by downward) in a cell that initially exhibited no directional bias. DSI has a sign; positive values indicate that the response in the upward direction is greatest, while negative values indicate that the response in the downward direction is greatest. The responses to both the upward and downward directions increase as a result of bidirectional training, but direction selectivity does not increase. B: bidirectional training in a cell that initially exhibits a suprathreshold directional bias for the upward direction. The response to the downward direction increases, while the response to the upward direction, which was already near its ceiling, decreases slightly. Direction selectivity weakens as a result of bidirectional training. C and D: summary of the impact of bidirectional training and unidirectional training with constrained synaptic weights and classic STDP. y-axis indicates initial directional bias. Symbols S+2 and S−2 indicate subthreshold directional biases in the upward direction, where initial conditions were set to those obtained with 27 and 55 upward directional sweeps such that the cortical cell fired 1 spike in each direction (shown in Fig. 4B); S+ and S− indicate subthreshold biases in favor of the downward direction, similarly defined. y-axis indicates final DSI values obtained or change in DSI values from initial conditions. Bidirectional training cannot produce robust direction selectivity, although unidirectional training produces strong direction selectivity for the trained stimulus. E: for some initial conditions, such as S+2, bidirectional training with triplet STDP can produce full direction selectivity in the biased direction. F: other initial biases are not amplified by bidirectional training, and full direction selectivity is not achieved. G and H: summary of the impact of bidirectional training and unidirectional training with constrained synaptic weights and triplet STDP.
The synapses from the LGN to the interneuron were not plastic.

How does adding this broad, untuned feed-forward inhibition impact the operation of the circuit? Feed-forward inhibition does not alter the fundamental limits of the direction selectivity that the circuit can express (Fig. 7). Instead, it is functionally equivalent to changing the threshold $T$ (which also alters $\Delta t$) in the linear-threshold model that was explored earlier. In Fig. 7, $C$ and $D$, we show the effect of increasing the threshold $T$ in a linear-threshold model from an initial condition plotted as point "a." As the threshold increases, the responses in both directions decrease. This has the effect of pulling the output of the circuit into a range where changes in the excitatory weights have a big impact on the direction selectivity that is expressed. The circuit is still restricted to responses and DSI values that fall within the shaded areas (as in Fig. 3), but the raised threshold moves the circuit into regions where the expression of high direction selectivity is possible. We can see this another way by examining the effect of increasing inhibition (or threshold) on a direction tuning curve (Fig. 7E). An increase in overall inhibition or threshold causes the relative height of the portion of the tuning curve that is suprathreshold to become larger, increasing direction selectivity.

The modified circuit with POSD-LTPi produces robust direction selectivity in a cell with a small initial bias (Fig. 8). A circuit with classic STDP and equal LGN weights increases the cell’s responsiveness, but the cell does not become more selective for either direction (Fig. 8A). If the synaptic conductances from LGN cells to the cortical cell are slightly different, they can produce an initial response bias. Bidirectional training can amplify this bias and produce robust direction selectivity, regardless of whether the initial bias is subthreshold (Fig. 8B) or suprathreshold (Fig. 8C). Just as in the experimental animal, these initial biases are not immutable; unidirectional training in the upward direction can modify the direction preference of a neuron that is initially biased to prefer downward stimulation such that, after training, the neuron responds exclusively to upward stimulation.

Thus the model, when modified with feed-forward inhibition and POSD-LTPi, can mimic the major findings in the developing ferret. When bidirectional training is employed, weak initial directional biases are amplified into strong selectivity (Fig. 8E). When unidirectional training is used, cells develop a

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**Fig. 7.** A feed-forward circuit with postsynaptic activity-dependent long-term potentiation of inhibition (POSD-LTPi). 

A: modification of the model in Fig. 1 to include feed-forward inhibition. LGN units provide input to a feed-forward inhibitory interneuron, which in turn provides inhibition to the cortical excitatory neuron that is monitored as the output of the circuit. 

B: POSD-LTPi is present around the time of eye opening and increases with burst activation of the postsynaptic excitatory cell; activation of the interneuron is irrelevant to the increase in inhibition (Garkun and Maffei 2014). We model this as a small increase in inhibition with each training stimulation. 

C and D: illustration of the impact of increasing spike threshold (equivalent to increasing broad inhibition) on the circuit. Circles labeled a–e denote the level of threshold, which increases from a to e. The firing rate combinations $R_{up}$ and $R_{down}$ and the direction selectivity DSI that are achievable do not change; as before (Fig. 3), the circuit can only produce activity within the shaded reasons. However, starting from position $a$, increasing threshold brings the circuit into a region where it is capable of expressing a wide variety of DSI values. 

E: illustration of increasing inhibition (a to δ) on a direction tuning curve. Increasing inhibition causes increased selectivity and increased competition among the feed-forward excitatory synapses that support the 2 peaks.

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**Fig. 8.** A feed-forward circuit with postsynaptic activity-dependent long-term potentiation of inhibition (POSD-LTPi). 

A: modification of the model in Fig. 1 to include feed-forward inhibition. LGN units provide input to a feed-forward inhibitory interneuron, which in turn provides inhibition to the cortical excitatory neuron that is monitored as the output of the circuit. 

B: POSD-LTPi is present around the time of eye opening and increases with burst activation of the postsynaptic excitatory cell; activation of the interneuron is irrelevant to the increase in inhibition (Garkun and Maffei 2014). We model this as a small increase in inhibition with each training stimulation. 

C and D: illustration of the impact of increasing spike threshold (equivalent to increasing broad inhibition) on the circuit. Circles labeled a–e denote the level of threshold, which increases from a to e. The firing rate combinations $R_{up}$ and $R_{down}$ and the direction selectivity DSI that are achievable do not change; as before (Fig. 3), the circuit can only produce activity within the shaded reasons. However, starting from position $a$, increasing threshold brings the circuit into a region where it is capable of expressing a wide variety of DSI values. 

E: illustration of increasing inhibition (a to δ) on a direction tuning curve. Increasing inhibition causes increased selectivity and increased competition among the feed-forward excitatory synapses that support the 2 peaks.
preference for the trained direction regardless of their initial biases (Fig. 8F).

Model robustness—sensitivity to parameters. While we have demonstrated that a particular set of model parameters replicates the major experimental findings in ferret visual cortex for both classic and triplet STDP, one may reasonably ask whether the region of the parameter space that replicates the experimental findings is large or small. Presumably, the model only makes biophysical sense if the range of parameters can vary by some reasonable amount, perhaps 20%. To examine this, we systematically varied the two major parameters in the model—the maximum value of the LGN synaptic conductances (\(G_{\text{cell}}\)), and the maximum value of the inhibitory conductance (\(I_{\text{max}}\))—and evaluated the ability of the model cortical cell to acquire direction selectivity after bidirectional training when the cell possessed either an initial direction selectivity of 0.5 or a subthreshold bias. The model was most sensitive to the value of the maximum conductance of the LGN inputs (Fig. 9). When the initial bias was 0.5 and POSD-LTPi was excluded, strong selectivity could only develop over a 12% range of \(G_{\text{cell}}\).
(Fig. 9, A and B). With POSD-LTPi, the model could tolerate a wide (35%) range in $G_{i,ceil}$. When the initial bias was subthreshold (Fig. 9, C and D), POSD-LTPi was required to develop selectivity with classic STDP. Furthermore, POSD-LTPi greatly expanded the range of $G_{i,ceil}$ over which triplet STDP could achieve direction selectivity from bidirectional training. Therefore, the presence of POSD-LTPi greatly enhances the ability of the model to acquire direction selectivity across a wide range of parameters.

**POSD-LTPi implements subtractive normalization.** The behavior of our model resembles simple models of a single neuron that performs Hebbian learning on its inputs, but with subtractive normalization (Hertz et al. 1991; Linsker 1986a, 1986b, 1986c; Miller et al. 1989; Miller and MacKay 1994; von der Malsburg 1973). In such simple models, the weight update function, which determines changes in synaptic strengths, is in the form

$$\frac{d}{dt}w(t) = Cw - e(w)$$

where $w$ is a vector of the feed-forward synaptic input weights, $C_{ij}$ is the correlation between inputs $i$ and $j$, among input neurons, and $e(w)$ is a subtractive normalizing factor that depends on the weights. Our model appears similar if we treat the untuned inhibition as a negative contribution to the feed-forward input weights, yielding the related equation

$$\frac{d}{dt}w_{eff}(t) = STDP(Inp, w_{eff}, Out) - \Delta I$$

where STDP is the spike timing-dependent change in weights that depends on each input of the input vector $Inp$, the effective synaptic weights $w_{eff}$, and the cell’s output $Out$. $\Delta I$ is the change in inhibition, which, under POSD-LTPi, varies as a function of experience. When $I$ has not reached its maximum and is still growing, $\Delta I = I_{init}(I_+)^N(I_+ - 1)$, so $I$ grows exponentially with $N$, the number of episodes of stimulation that result in cortical excitatory neuron firing (and provides a constant negative contribution to the effective weights with respect to time). In this formulation, the subtractive normalizing factor (the inhibition) and the weights are not explicitly a function of one another but are indirectly correlated because as the synaptic input weights that are most correlated increase with each epoch of stimulation, so too does the inhibition grow with each epoch of stimulation. When $I$ reaches $I_{max}$ then $\Delta I = 0$, and the dynamics proceed according to standard STDP.

We can gain further insight into how POSD-LTPi affects the dynamics of the feed-forward model by examining how the effective synaptic weights are altered in the simplified, 2 x 2 LGN model that was used for the mathematical proof in MATERIALS AND METHODS. In this illustration, we use a version of classic STDP to simulate synaptic strengths (see MATERIALS AND METHODS). We examine unidirectional training and bidirectional training in turn.

Fig. 9. The model is robust over a moderate region of parameter space. Plot of final direction selectivity after 1,000 iterations of bidirectional training. For A and B, the model was started with an initial direction selectivity value of 0.5. A: classic STDP. B: triplet STDP. Color indicates the final DSI value achieved, according to the scale at right. The $G_{i,ceil}$ and $I_{max}$ parameters were varied relative to the parameters used in Fig. 8 with the scale factors shown. The model acquires direction selectivity for a wide range of parameter values. The model is most sensitive to the value of $G_{i,ceil}$. When no POSD-LTPi is used ($I_{max} = 0$), the model can tolerate a 12% variation of $G_{i,ceil}$ (red region in left column of each graph). When sufficient POSD-LTPi is present, the model can acquire strong direction selectivity over a range of $G_{i,ceil} > 35\%$ (red region, right columns). C and D: same as A and B, but for an initial direction selectivity of $S^+$ (see Figs. 6 and 8). For classic STDP (C) the model was very sensitive to the parameters, achieving full direction selectivity over a narrow range of $G_{i,ceil}$ and POSD-LTPi, while the triplet model (D) was less sensitive for this subthreshold initial bias.
Under the unidirectional training paradigm without POSD-LTPi, synaptic weights will increase as long as the weights are strong enough so the cortical cell responds to the unidirectional training stimulus (Fig. 10A). If the cortical cell does respond to the training stimulus, the synaptic weights that support the response to the training stimulus ($W_s$) will increase until the synaptic weight ceiling is reached, as indicated by the arrows in Fig. 10A. With POSD-LTPi, inhibition increases after each bout of cortical stimulation. The amount of the increase in inhibition is proportional to existing inhibition that is currently provided to the cortical cell. At the onset of training, inhibition is relatively weak (Fig. 7B), so increases in inhibition are also effectively weak, similar to Fig. 10A. As inhibition increases, more inhibition is added during each bout of cortical stimulation, which modifies the effective change in synaptic weights during unidirectional training (Fig. 10B) such that direction selectivity is increased over a wider range of synaptic weights (more arrows point to the region of high direction selectivity). As training continues, the increase in inhibition becomes stronger (Fig. 10C), and weights are further pushed into a regime where the cortical cell will respond strongly to the unidirectional stimulus. Finally, inhibition reaches its ceiling, and the dynamics return to those depicted in Fig. 10A.

Under the bidirectional stimulation paradigm without POSD-LTPi, responses to both directions are amplified (Fig. 10D). With POSD-LTPi, the system begins in a state where increases in inhibition are relatively weak (Fig. 7B), and so the dynamics resemble the case without POSD-LTPi. As inhibition increases, the effective synaptic weights are altered so that initial biases are selectively amplified (arrows point off the diagonal in Fig. 10E). As inhibition increases further, these biases are amplified further (Fig. 10F). Finally, as inhibition hits its ceiling, the dynamics return to those in Fig. 10D.

**DISCUSSION**

The newly discovered inhibitory plasticity mechanism POSD-LTPi, which operates in the developing cortex, allows a simple feed-forward network with spike timing-dependent plasticity of excitatory inputs to develop robust direction se-
lectivity. Similar to cells in developing ferret visual cortex (Li et al. 2008), model cells with small initial directional biases develop strong selectivity for their direction of initial bias during exposure to a bidirectional motion stimulus. Furthermore, cells that are trained with unidirectional motion acquire a robust preference for the trained direction regardless of any small initial biases, similar to cells in real developing ferrets (Van Hooser et al. 2012).

We speculate that the development of spatiotemporal receptive fields proceeds in two steps. In an initial step that is independent of experience, neurons develop weak biases. In a second step that depends on visual experience, these biases are strengthened or modified by spike timing-dependent processes. Selectivity is maintained by increasing feed-forward inhibition via a process like POSD-LTPi.

Unsupervised learning with limited weights and POSD-LTPi. Hebbian learning rules that operate on feed-forward inputs, including rules based on pure correlation or spike timing, cause enhanced responsiveness to stimuli that drive the neuron. Unchecked, this process causes runaway excitation that ultimately reduces selectivity (Miller and MacKay 1994; van Rossum et al. 2000; von der Malsburg 1973). This problem is acute for spatiotemporal selectivity, where one must increase the weights of appropriate synapses without allowing them to increase so much that they fire the output neuron independently (Blais et al. 2000; Feidler et al. 1997). Several mathematical solutions have been proposed, including normalization with multiplicative or subtractive factors (Miller et al. 1989; Miller and MacKay 1994; Oja 1982), which allow competition among synaptic inputs so as to maintain selectivity during learning.

POSD-LTPi provides subtractive normalization and enhances the selectivity of a feed-forward pattern detector. In this model, selectivity is initially broad, but because feed-forward inhibition increases, excitatory feed-forward synapses must also be strengthened—as they are by STDP—in order to maintain a suprathreshold contribution to the neuronal output.

Comparisons with other models of development of direction selectivity. This feed-forward model with POSD-LTPi offers a biophysically plausible modification to previous feed-forward models, which demonstrated that Hebbian learning could produce direction selectivity if learning rules were modified to allow synaptic competition. However, in previous models, synaptic competition was either limited to two LGN cells (Feidler et al. 1997) or relied on purely rate-based learning rules (Blais et al. 2000).

Another family of feed-forward models relies on an array of LGN neurons with different receptive field positions but a single common latency (Gjorgjieva et al. 2011; Shon et al. 2004). Each LGN cell sends a postsynaptic excitatory postsynaptic potential (EPSP) and, with a delay, an inhibitory postsynaptic potential (IPSP), to the cortical neuron. The asymmetry of the STDP window allows the inputs from the array to develop selectivity with unidirectional training: synapses that fire early in the stimulus are potentiated, while those that fire later in the stimulus are de potentiated. When stimulated in the preferred direction, the potentiated EPSPs can sum to an amount greater than the feed-forward IPSPs; when stimulated in the null direction, the depotentiated EPSPs cannot overcome the feed-forward IPSPs, and so inhibition dominates in the null direction. However, cortical neurons in such a circuit would not exhibit the space-time slant in spatiotemporal receptive field maps generated by reverse correlation as is found in real cortical neurons (McLean and Palmer 1989; Priebe and Ferster 2005; Reid et al. 1991), so this circuit configuration may not describe visual cortex.

The recurrent models of Suarez et al. (1995), Wenisch et al. (2005), Rao and Sejnowski (2003), Shon et al. (2004), and Honda et al. (2011) produce direction selectivity by amplifying small feed-forward directional biases with excitatory recurrent connectivity. These circuits are effective at learning direction selectivity. If the recurrent connectivity were too strong, neurons in such a model would be unable to exhibit the position-sensitive responses of visual cortical simple cells; when the input of simple cells is combined in a recurrent manner with high gain, position sensitivity is lost and complex cell receptive fields result (Chance et al. 1999). It remains unclear experimentally whether recurrent circuitry is involved in the development of direction selectivity, although it could play a role in addition to or instead of feed-forward mechanisms.

Predictions. The feed-forward model makes several experimental predictions. First, the model assumes synaptic mechanisms that should be present in the actual animal: 1) geniculo-cortical synapses should exhibit spike timing-dependent plasticity when examined in LGN/cortex stimulation experiments in developing animals (such as Fregnac et al. 2010; Heynen and Bear 2001), and 2) ferret visual cortex should exhibit broad increases in intracortical inhibition in response to visual cortex activation, as in rat (Garkun and Maffei 2014). Furthermore, 3) if we could block these increases in inhibition pharmacologically, we should reduce the ability of the circuit to learn direction selectivity.

The model also makes predictions about the result of future visual training experiments in naive animals. In previous experiments, we always presented gratings moving smoothly in phase. This feed-forward model, which includes STDP and input from LGN cells with a range of latencies, predicts that 4) training with an arbitrary grating phase sequence that activates the naive cortex should produce selectivity to that sequence. For example, if a progression of phases of 1-2-3-4-5 produces upward motion and 5-4-3-2-1 produces downward motion, one might imagine training with an arbitrary sequence, such as 1-3-5-2-4. The feed-forward model predicts that the circuit would amplify selectivity to this sequence just as it would a unidirectional training stimulus. Similarly, 5) training with a counter-phase grating stimulus should yield a cortex that responds more strongly to the counter-phase training stimulus than either single direction. If these experiments were to fail to show the expected modifications of visual selectivity, then it would be highly likely that some aspect of the feed-forward model—such as the ability of a cortical cell to amplify input from a broad range of LGN cells, or thalamocortical STDP itself—is not found in developing visual circuits.

Another experiment that could provide evidence in support of the model (but not falsify it) is to examine the velocity sensitivity of training. Velocity tuning in a neuron could in principle be the result of the feed-forward projection of LGN neurons with different sets of latencies, or it could reflect integration of a feed-forward and recurrent projections. If motion training at a single velocity produced direction selectivity only at the trained velocity, but did not generalize, then it is likely that the feed-forward model described here is at least partially correct. However, if it were to generalize, then we
would not know whether velocity tuning was simply formed by input from a single set of feed-forward inputs (that were trained) or rather from recurrent input.

Four observations in adult animals are consistent with the feed-forward model. Experiments in which correlations between cortical neurons and a visual stimulus were artificially induced by cortical stimulation showed that cortical neurons become more selective to the trained stimulus in a spike timing-dependent manner (Meliza and Dan 2006; Schuett et al. 2001). This includes experiments that have enhanced or suppressed ON/OFF subunits of simple cells, which might be the result of manipulating thalamocortical synapses (Debanne et al. 1998). The model predicts the absence of strong null-direction inhibition, as in experimental measurements (Priebe and Ferster 2005). Furthermore, the model posits the existence of feed-forward interneurons that are unselective for direction; such cells have been observed (Hirsch et al. 2003). Finally, transiently blocking inhibition reduces direction selectivity (Murthy and Humphrey 1999), consistent with the idea that inhibition opposes excitatory input that is driven by both directions.

Formation and amplification of initial biases. This work does not address how the initial directional biases form. These biases are critical for acquiring selectivity for either of two directions during bidirectional training. Experience is not necessary for the formation of either the initial directional biases or orientation selectivity, as dark-reared animals exhibit both (Li et al. 2006; Van Hooser et al. 2012). Possibly, both features arise during the period of spontaneous retinal waves (Meister et al. 1991), though the mechanisms remain unknown. It is also possible that the small initial biases are simply the result of random heterogeneity in the numbers and strengths of inputs that any cortical cell receives, and so require no additional mechanism.

In previous studies we noted that nearby neurons exhibited similar biases, and that the structure of the eventual direction selectivity map was present at the time of eye opening (Li et al. 2008; Van Hooser et al. 2012). Whether the direction map is primarily determined by recurrent connectivity or feed-forward connectivity remains unknown. One can hypothesize that local cortical mechanisms could amplify these biases, as they do in models of ocular dominance plasticity (Miller et al. 1989). However, an original hypothesis about the existence of orientation maps was that they minimized the wiring length of the feed-forward inputs to cortex from LGN (Hubel and Wiesel 1963). If the initial map structure were a feed-forward phenomenon, the present work shows that nearby neurons do not need to influence their neighbors in order to amplify the initial selectivity biases (thus becoming similar to their neighbors) but such amplification can arise through purely feed-forward processes, without recurrent circuitry.

Species differences. In the mouse visual cortex, direction selectivity is present at the time of eye opening and does not depend on visual experience (Rochezefort et al. 2011). Furthermore, the mouse retina has several classes of direction-selective retinal ganglion cells that project to LGN (Huberman et al. 2009; Marshall et al. 2012). It remains unclear at present whether LGN cells in the developing ferret exhibit strong direction selectivity. If LGN neurons exhibited strong direction selectivity, then feed-forward learning of direction selectivity from non-direction-selective neurons as proposed here would not be necessary. Future studies of ferret LGN will be needed to clarify these issues.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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