

RESEARCH ARTICLE | *Building Neural Circuits: Wiring and Experience*

Cortical amplification models of experience-dependent development of selective columns and response sparsification

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Submitted 10 March 2017; accepted in final form 11 May 2017

Christie IK, Miller P, Van Hooser SD. Cortical amplification models of experience-dependent development of selective columns and response sparsification. *J Neurophysiol* 118: 874–893, 2017. First published May 17, 2017; doi:10.1152/jn.00177.2017.—The development of direction-selective cortical columns requires visual experience, but the neural circuits and plasticity mechanisms that are responsible for this developmental transition are unknown. To gain insight into the mechanisms that could underlie experience-dependent increases in selectivity, we explored families of cortical amplifier models that enhance weakly biased feedforward signals. Here we focused exclusively on possible contributions of cortico-cortical connections and took feedforward input to be constant. We modeled pairs of interconnected columns that received equal and oppositely biased inputs. In a single-element model of cortical columns, we found two ways that cortical columns could receive biased feedforward input and exhibit strong but unselective responses to stimuli: 1) within-column recurrent excitatory connections could be strong enough to amplify both strong and weak feedforward input, or 2) columns that received differently biased inputs could have strong excitatory cross-connections that destroy selectivity. A Hebbian plasticity rule combined with simulated experience with stimuli weakened these strong cross-connections across cortical columns, allowing the individual columns to respond selectively to their biased inputs. In a model that included both excitatory and inhibitory neurons in each column, an additional means of obtaining selectivity through the cortical circuit was uncovered: cross-column suppression of inhibition-stabilized networks. When each column operated as an inhibition-stabilized network, cross-column excitation onto inhibitory neurons forced competition between the columns but in a manner that did not involve strong null-direction inhibition, consistent with experimental measurements of direction selectivity in visual cortex. Experimental predictions of these possible contributions of cortical circuits are discussed.

NEW & NOTEWORTHY Sensory circuits are initially constructed via mechanisms that are independent of sensory experience, but later refinement requires experience. We constructed models of how circuits that receive biased feedforward inputs can be initially unselective and then be modified by experience and plasticity so that the resulting circuit exhibits increased selectivity. We propose that neighboring cortical columns may initially exhibit coupling that is too strong for selectivity. Experience-dependent mechanisms decrease this coupling so individual columns can exhibit selectivity.

motion; thalamocortical input; recurrent connections; striate cortex; area 17

IN MANY SENSORY SYSTEMS, the neural connections that underlie receptive fields are initially established through molecular cues and are later refined via sensory experience such that selectivity to particular stimulus parameters is increased. At the onset of visual experience, neurons in visual cortex of carnivores already exhibit selectivity for stimulus orientation (Chapman et al. 1996; Hubel and Wiesel 1963) but lack strong selectivity for stimulus direction of motion. Direction selectivity forms in the days following eye opening via a process that requires visual experience (Li et al. 2006). Also during this period, sensory responses in visual cortex become sparser; that is, the number of neurons that are activated by a particular visual stimulus decreases as neurons become more selective (Griffen et al. 2012; Rochefort et al. 2011; Smith et al. 2015). The mechanisms that underlie the development of selectivity and the final structure of the mature, selective circuit are unknown.

We recently described a purely feedforward model of this process for a single cortical neuron (Van Hooser et al. 2014). Neurons in lateral geniculate nucleus (LGN) exhibited selectivity for different positions and latencies. Plasticity within the LGN-to-cortex connections and a nonspecific but activity-dependent increase in intracortical inhibition (Garkun and Maffei 2014) allowed a transition from an unselective circuit that responded about equally to two opposite directions to a selective circuit that responded exclusively to a single direction. When the model was provided with “experience” with opposite directions (“bidirectional training”), the cortical neuron became selective to the direction to which the cell was initially biased. When the model was trained with a single direction (“unidirectional training”), it acquired a preference for the trained direction. Thus the model could amplify initial biases or overwrite these biases by certain sensory experience. This model is related to other feedforward treatments of the development of direction selectivity (Blais et al. 2000; Buchs and Senn 2002; Feidler et al. 1997; Gjorgjieva et al. 2011; Sederberg and Kaschube 2015), and other feedforward models of this development rely on different mechanisms (Bednar and Miikkulainen 2006; Honda et al. 2011; Shon et al. 2004).

However, recent experiments have demonstrated that at least some of the circuit changes that underlie the development of

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direction selectivity must be purely cortical in origin. Preliminary experiments have shown that monocular stimulation with a bidirectional training stimulus was sufficient to produce direction selectivity through the untrained eye; that is, the development of direction selectivity exhibited ocular transfer (Corlew et al. 2010). Because signals from the two eyes are first merged in visual cortex, we can conclude that changes within cortical circuits must underlie the increase in selectivity through the untrained eye. In another experiment, Roy et al. (2016) provided optogenetic stimulation to the immature ferret visual cortex over several hours, causing an increase in direction selectivity. These experiments showed that the information about the direction preference that the neurons would eventually acquire was already present in the circuit before stimulation and that stimulation of the cortex alone (without natural activation of LGN) was sufficient to amplify initial biases.

Here we examine how families of cortical amplifier models (Douglas et al. 1995; Ernst et al. 2001; Rubin et al. 2015; Suarez et al. 1995) could transition from an initially responsive but unselective state to a selective state after experiencing either bidirectional or unidirectional stimulation. We identify several regimes of selectivity, some of which are compatible with biological experiments. One model that is consistent with experimental data is one in which the circuit initially responds unselectively because of strong initial excitatory connections between columns that receive opposite feedforward biases. Each column receives input that is biased for a particular stimulus, but the cross-column coupling causes both columns to respond to either stimulus. With experience, spike timing-dependent plasticity (STDP) mechanisms with a negative-dominated kernel cause this coupling to decrease, allowing the individual columns to respond selectively to their biased input. We suggest experiments that could support or refute these models.

MATERIALS AND METHODS

Computer simulations were run in MATLAB (The MathWorks, Natick, MA) on laboratory and Brandeis University High Performance Computing Cluster machines.

Cortical units, referred to here as columns, were modeled via the differential equation

$$\tau \frac{d\vec{r}}{dt} = -\vec{r} + f(W\vec{u} + M\vec{r})$$

where \vec{r} is the vector of columnar rates, \vec{u} is the vector of thalamic inputs that connect to cortical columns via matrix W , M is the recurrent connection matrix between cortical columns, and τ is the time constant (0.004 s). Input to each cortical column is summed and then run through an activation function, f .

Two different activation functions for the two models presented were used to ensure network stabilization. The coupled-pair model used a sigmoidal curve

$$f(x) = \frac{\alpha}{1 + e^{\beta(x_0 - x)}}$$

where x is the summed cortical input and α (100 Hz), $f(0.15)$, and x_0 (26) are constants that characterize the sigmoid function. The sigmoid curve was used to ensure that the network did not produce runaway excitation.

The models with separate excitatory and inhibitory neuron populations used a rectified supralinear curve

$$f(x) = [x^\vartheta]_+$$

where x is the summed cortical input and ϑ is a constant > 1 that characterizes the supralinear curve (Priebe et al. 2004; Priebe and Ferster 2005, 2008; Rubin et al. 2015). When both excitatory and inhibitory neurons were simulated, the power law was used instead of a sigmoid to ensure that network stabilization was a result of properties of the circuit (i.e., inhibition) and not simply through saturation of the activation function. Individual neurons in the developing cortex do not exhibit firing rates that are close to saturation, and so the firing of the column is also not near values that could be achieved with artificial stimulation. Therefore, it is more realistic for the network to self-stabilize, when both inhibitory and excitatory neurons are available.

Plasticity. Because both models are rate based, we adopted a continuous adaption of STDP (Bi and Poo 1998; Markram et al. 1997; Sjöström et al. 2001; Song et al. 2000) to simulate Hebbian modifications to synaptic weights:

$$\Delta M_{a,b} = \int_0^t \int_0^t r_a(t_1)r_b(t_2)K(t_1 - t_2)dt_1 dt_2$$

where $\Delta M_{a,b}$ is the change in connection strength from column a to column b , t is the time of the simulation, r_a and r_b are the respective rate functions for the corresponding columns at times t_1 and t_2 , and K is the kernel function simulated by piecewise exponential decay curves

$$K(\Delta t) = \begin{cases} a_p e^{-b_p \Delta t}, & \Delta t > 0 \\ -a_n e^{b_n \Delta t}, & \Delta t < 0 \\ 0, & \Delta t = 0 \end{cases}$$

where Δt is the change in time and a_p , b_p , a_n , and b_n are constants that characterize the curves corresponding to the sign of Δt . In Figs. 3 and 4, a_p and a_n were $5e-4$ and $6.4e-4$, respectively; in Fig. 8 and Fig. 9A, a_p and a_n were $5.5e-5$ and $5.0e-5$, respectively; in Fig. 9B, a_p and a_n were $5.0e-6$ and $5.2e-6$, respectively. In all figures, constants b_p and b_n were set to $2.7/s$, such that the “time constant” of the plasticity kernel was ~ 0.37 s.

Direction selectivity. For excitatory and inhibitory cortical columns the direction selectivity index (DSI) was the difference between responses in the preferred and null directions normalized by the sum of these responses:

$$DSI = \frac{(R_{\text{pref}} - R_{\text{null}})}{(R_{\text{pref}} + R_{\text{null}})}$$

Thresholds for plotting. To diagram selectivity for false-colored parameter-scan plots, we established several thresholds, chosen arbitrarily but in a manner that does not affect the qualitative conclusions. We first determined if the activity was oscillatory by examining the coefficient of variation for the last 100 ms of the response. When the coefficient of variation was < 0.05 , we declared the activity nonoscillatory; otherwise, we declared the activity oscillatory. For units that did not exhibit oscillations, responses were taken to be the steady-state activity at the end of stimulation. For units that exhibited oscillations, responses were taken to be the mean activity during the last 300 ms of stimulation.

For a column to be considered “responsive,” it needed to exhibit a response of at least 50 Hz. For a column to be considered “selective” or “direction-selective,” it needed to exhibit a DSI of at least 0.5. For a column to be considered “responsive but unselective,” it needed to exhibit activity of at least 50 Hz and a DSI < 0.3 . When E/I pair models were evaluated, only the activity of the E neuron was considered. Bicolumnar selectivity to opposite stimuli indicated that both

columns were selective for opposite stimuli. The threshold for labeling a model as exhibiting “bicolumnar selectivity to the same stimuli” was slightly lowered; both columns needed to be responsive and to exhibit a DSI of at least 0.4. Networks in which any unit exhibited firing above 1,000 Hz or in which responses failed to decline after the stimulus was removed were declared “unstable.”

RESULTS

The number of different ways that cortical circuits could produce direction selectivity is staggeringly large, and several approaches have been explored previously. Some models have accounted for the effect of retinotopic space within the cortex (or tectum), which can allow for a spatial amplification of selectivity via horizontal connections across columns (Honda et al. 2011; Shon et al. 2004; Wenisch et al. 2005), or inhibition of responses to the null direction (Adams and Harris 2014, 2015), as has been described in the retina (Barlow and Levick 1965; Briggman et al. 2011; Euler et al. 2002) but not in cortex (Jagadeesh et al. 1993, 1997; Priebe and Ferster 2005).

While there are many ways to construct a selective cortical circuit, we focused on cortical amplifier models (Ben-Yishai et al. 1995; Chance et al. 1999; Douglas et al. 1995; Somers et al. 1995) that receive input that is already biased for the feature of interest. This situation could apply to many sensory systems, as many systems begin with large receptive fields and become more selective with experience. In this work, we focus primarily on experimental comparisons to the development of direction selectivity in ferret visual cortex. Calcium imaging studies of naive ferret visual cortex have indicated that regions of the orientation map already exhibit very small but statistically significant biases for direction at the time of eye opening (Li et al. 2008; Van Hooser et al. 2012). At present, it is unknown whether these biases are due to the contributions of feedforward connections from retina/LGN or recurrent connections within the cortex, and here we treat them as feedforward in nature. Furthermore, amplifier models are relatively simple with relatively few parameters, which allowed us to explore a wide range of parameter space in several families of models.

We explored two families of cortical amplifier models. In the first, a “single-element” model, each cortical column was modeled by a single firing rate that represented the sum of the firing rates of all neurons in the column. Synaptic connections in the single-element model could be either positive or negative, indicating a net excitatory or inhibitory coupling across columns. One could similarly imagine this circuit element as a “unit” or “nucleus,” but we call it a column here.

In a second model, the “E/I pair” model, we divided each cortical column into two populations, an excitatory (E) population and an inhibitory (I) population. Both populations were modeled as a single rate that represented the sum of the firing rates of the neuronal population within the column. Synapses originating from E populations were constrained to be positive or 0, and synapses originating from I populations were constrained to be negative or 0. The E/I pair model can exhibit additional dynamics compared with the single-element model, such as inhibition-stabilized dynamics (Ernst et al. 2001; Ozeki et al. 2009; Rubin et al. 2015).

To focus exclusively on contributions of the cortical amplifier circuits, we did not allow any developmental changes in the feedforward “LGN” inputs to these columns. Instead, we modeled the feedforward input as a single number. One might

imagine that, in the actual animal, changes in both feedforward connections and intracortical connections might contribute to the development of selectivity. However, leaving the feedforward input fixed in this study allows us to isolate the behavior of the cortical models in order to understand the possible cortical contributions to the computation.

In many versions of the models, we examine neighboring cortical columns that are linked by synaptic connections. At the time of eye opening, the visual cortical network of horizontal connections that links orientation columns across several millimeters has not yet been fully elaborated (Durack and Katz 1996; Ruthazer and Stryker 1996; White et al. 2001), so these modeled cross-column connections are intended to represent short-range connections within the same orientation column (or at most 1 orientation column away). Furthermore, we intend that these neighboring columns represent roughly the same locations within the map of visual space. Also, in the present work we do not examine direction-selective circuits with horizontal connections among cells or units that mediate different visual field locations, as models with these characteristics have been explored previously (Shon et al. 2004; Wenisch et al. 2005). We focus instead on the ability of neighboring columns to amplify feedforward input.

Single-element model. We began by examining the simplest case: a single column (*column A*) represented by a single model element (Fig. 1A). The column in the model is an abstracted column in cortex that sums feedforward input and amplifies this input through a recurrent self-connection. To simulate the biological saturation of response curves, and to maintain network stability, neuronal input was transformed into neuronal output firing rates through a sigmoidal activation function (Fig. 1A).

The model is capable of exhibiting selectivity in two ways. With the weight of the recurrent connection set to 0 (that is, no recurrent connections), and only feedforward input, the single-column model can exhibit selectivity with a large feedforward bias. That is, with strong feedforward input to the preferred stimulus (“up”) and weak feedforward input to the nonpreferred stimulus (“down”), the feedforward input dominates and the circuit is selective (Fig. 1B). Throughout the text and figures, we distinguish between parameters that are assigned to specific values with a “:=” sign and the resulting index values that are produced by simulations with a “=” sign.

If we allow moderately strong recurrent connections, then the system can also exhibit selectivity with only very weak feedforward input biases (Fig. 1C). If we increase the recurrent connection weight further beyond moderate values, the responses to the nonpreferred stimulus increase rapidly, and eventually the circuit enters an unselective regime (Fig. 1D). Responses to opposite directions (Fig. 1E) and direction selectivity (Fig. 1F) are plotted as a function of recurrent connection weight for a moderately strong feedforward input with a small bias. These curves demonstrate that selectivity gradually increases with increasing recurrent connection strength, until the recurrent weight allows the response in the preferred direction to enter into the sharp rise in the column’s activation function. As the recurrent weights increase further, the same behavior is seen to the nonpreferred stimulus, which makes the column unselective.

If we consider a single column in isolation, and if we maintain our constraint that we will only study changes within

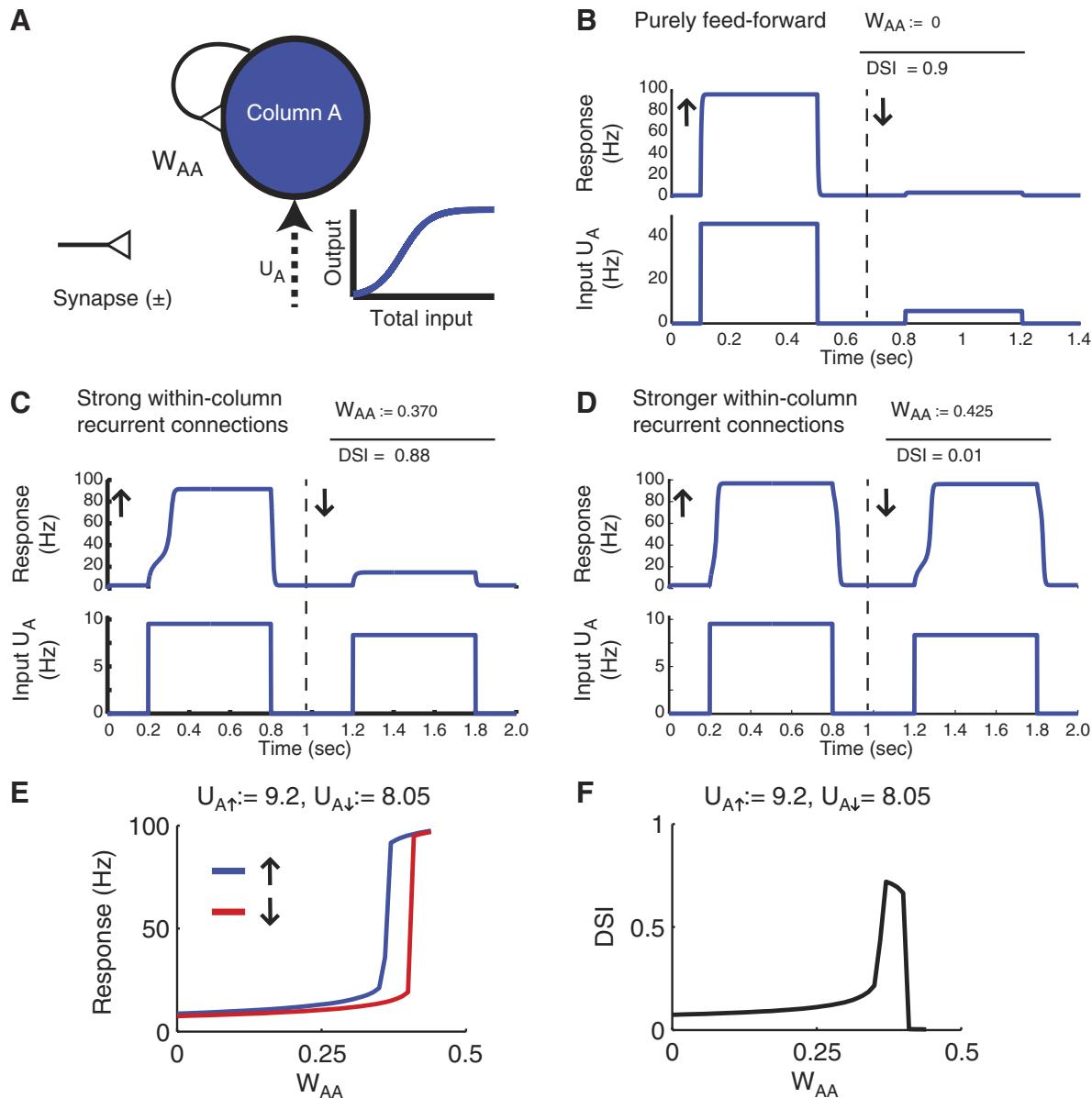


Fig. 1. Single element/column with feedforward and recurrent inputs. *A*: diagram of cortical column with feedforward input (U_A) and recurrent synapse (W_{AA}). Synapses are of the form $W_{Pre,Post}$. Inset: sigmoid that characterizes the activation function. *B*: response of a circuit without recurrent connections. The input to the model is shown at bottom, and the response of the element/column is shown at top. The “up” direction corresponds to the preferred stimulus, and the “down” direction corresponds to the nonpreferred stimulus. Model parameters are given above the solid black line; direction selectivity index (DSI) is given below the solid black line. “:=” denotes assignment of parameters; “=” indicates output results. This format recurs throughout this report. Without recurrent connections, the single element requires large feedforward input bias to achieve selectivity. Note different axis on input graph. *C*: recurrent connection allows for smaller feedforward input bias to achieve selectivity. *D*: too strong recurrent connections cause response saturation to either stimulus, and the circuit is not selective. *E*: responses to the preferred stimulus (up) and the nonpreferred stimulus (down) as a function of recurrent weight. *F*: relationship between recurrent connection strength and selectivity index with weak feedforward bias.

the cortex and not in feedforward input, then there is only a single way for the single-column model to transition from an initially responsive but unselective state into a selective state. We would have to imagine that the recurrent weight started out strong, such that the column responded strongly to both stimuli and then decreased until the column only responded strongly for the stimulus that matches its feedforward bias (recurrent connection weight of 0.344 in Fig. 1, *E* and *F*).

Coupled-pair model. We next investigated the interactions between two cortical columns with cross-connections, which we term the “coupled-pair” model (Fig. 2*A*). The two

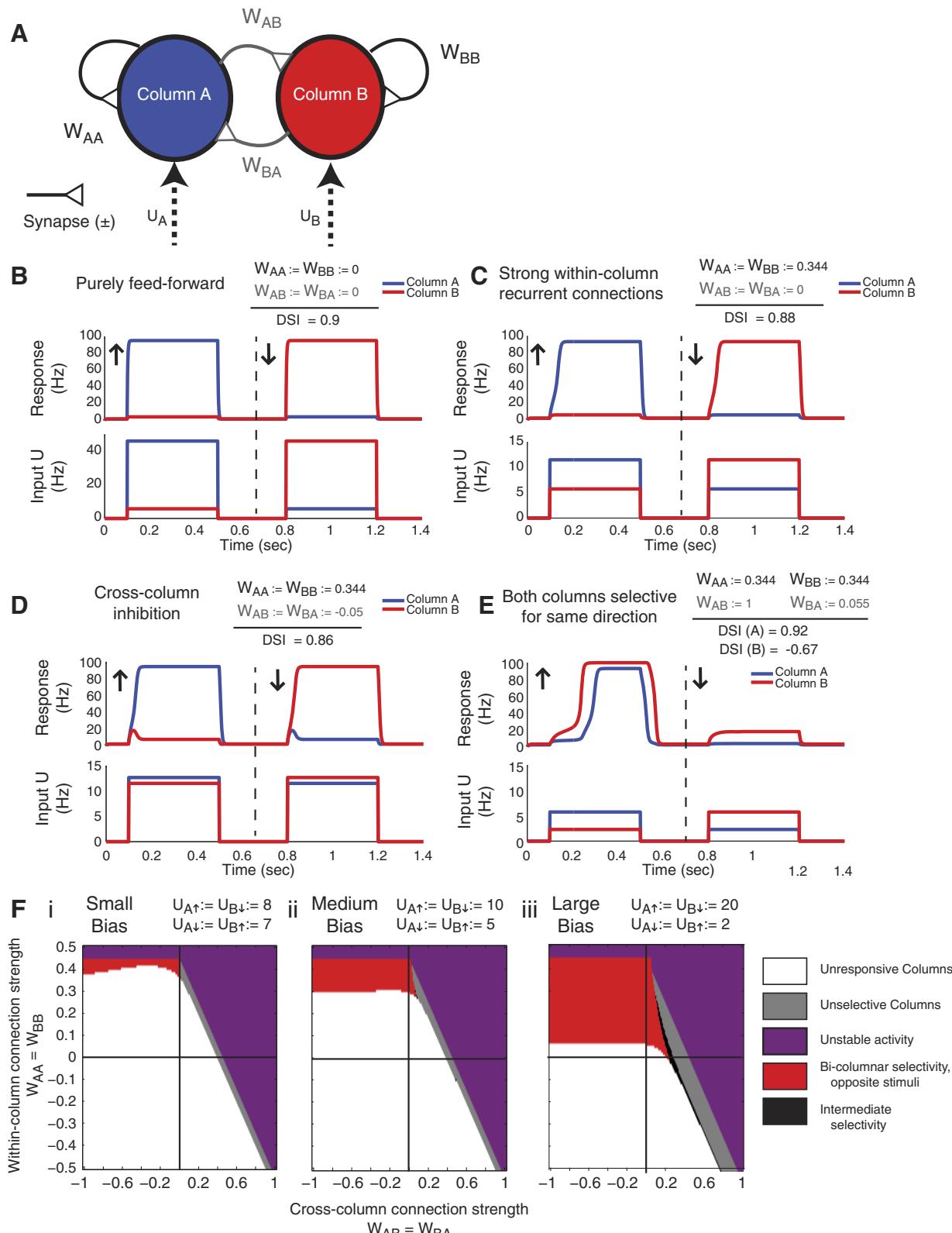
columns received equal but opposite feedforward input biases.

The coupled-pair model can exhibit selectivity in a variety of parameter regimes. If the cross connections are 0—that is, there are no cross-connections—then the model behaves as two independent columns (Fig. 2, *B* and *C*) and can achieve selectivity as in a single column (see Fig. 1, *B* and *C*). The model can also achieve robust bicolumnar selectivity to opposite stimuli with negative cross-connections (Fig. 2*D*). Strong negative cross-connection weights create a winner-take-all paradigm, where the only conditions required for direction

selectivity are 1) sufficiently strong feedforward drive that drives responses over the sigmoidal activation threshold and 2) a nonzero bias of this feedforward drive.

We examined the full parameter space for all “symmetric” models, where the two columns receive equal and opposite

input for preferred and null directions and $W_{AA} = W_{BB}$ and $W_{AB} = W_{BA}$. Figure 2F characterizes the behavior of the symmetric models for selected feedforward biases and input strength. We can draw several conclusions from this analysis. 1) As feedforward bias increases, so does the space for selec-



tivity. A goal of this model is to amplify input selectivity within the cortex, so the most interesting cases are those with weak input biases. 2) Cross-column inhibition provides the largest space for selectivity. 3) Selectivity can exist without cross or recurrent inhibition, but the cross-connection weights must be small.

Although negative cross-connections (that is, cross-inhibition) caused robust selectivity in the model, current evidence from experimental recordings of cortical direction-selective neurons does not support the idea that strong cross-inhibition exists in the cortex. Priebe and Ferster (2005) used *in vivo* whole cell recordings to examine the synaptic conductances of direction-selective cortical neurons and saw that both excitatory and inhibitory synaptic conductances were strongest in the preferred direction and weakest in the opposite direction; they observed no evidence of null-direction inhibition as a mechanism of direction selectivity in cortical neurons. However, the model columns with negative cross-connections would be expected to exhibit the largest inhibition in the null direction. Thus although the model parameters allow cross-inhibition it is unlikely to be realized in cortex, suggesting that the relevant parameter regime of this model is where cross-connections are positive but weak.

Bicolumnar selectivity for the same direction was very uncommon in the parameter space (Fig. 2E). The only regime in which it was found required weak recurrent weights and asymmetric cross-connections where one connection weight (say, W_{AB}) was large and the other weight (say, W_{BA}) was small but present. In Fig. 2E, the small weight W_{BA} is necessary to allow *column B* to be amplified by *column A* during upward stimulation, but it needs to be small enough to not activate *column A* when the network receives stimulation in the downward direction. Any small alterations from these parameters resulted in a model that was either unselective or unresponsive. Figure 2F shows that bicolumnar selectivity for the same direction does not exist within a symmetric model. This is not a problem for explaining experimental results, because, at present, there is no experimental evidence that cortex can achieve bicolumnar selectivity for the same direction. That is, there is no evidence that columns that are initially biased toward one stimulus can undergo a complete switch to prefer the opposite stimulus.

Influence of experience (bidirectional training). Experimental observations show that cortical responses to different directions are only weakly biased before eye opening and that direction selectivity develops with visual experience (Li et al. 2006, 2008). Laboratory experiments have shown that just a few hours of experience with bidirectional stimulation (gratings that move in alternating directions) is sufficient to

cause the rapid emergence of direction selectivity by amplifying these small initial biases (Li et al. 2008). Furthermore, if experience with only a single direction is provided (unidirectional training), then columns that were initially biased toward the trained direction exhibit a strong increase in direction selectivity while columns that were initially biased in the opposite direction exhibit little to no change in direction selectivity (Van Hooser et al. 2012).

To investigate the development of selectivity, we initially started the model in an unselective regime with high excitatory cross-connections and weak feedforward biases. We allowed the longer-range cross-connections (but not the local recurrent connections) to undergo synaptic plasticity. We applied a rate-based learning rule that was adapted from traditional STDP kernels (see MATERIALS AND METHODS). The total area under the plasticity kernel (Fig. 3A) was slightly negative, such that coactivated synapses would become weaker. This kernel has the property that it would generally help to maintain stable activity, as the excitatory synapses across the columns are unlikely to grow arbitrarily large.

When the unselective model was provided experience through bidirectional training, either with strict alternation between opposite directions (Fig. 3, B, C, and E) or random presentation of opposite directions as might occur in nature (Fig. 3F), the cross-connection weights decreased to nearly 0, and the model transitioned from an unselective state (Fig. 3B) to a selective state (Fig. 3C). Training with random stimuli where stimulus direction was randomized at several points during an individual stimulus run also became direction-selective, albeit with a slower time course (not shown). Thus the model's initial lack of selectivity was due to strong coupling across columns that weakened with experience, such that cortical responses become sparser and more selective, as in actual experiments (Griffen et al. 2013; Rochefort et al. 2009; Smith et al. 2015).

Asymmetric models and unidirectional training. Up to now, we have only considered symmetric models, in which the cross-column connections have equal strengths. One may ask whether other outcomes are possible if we allow connections to become asymmetric, such as might occur with unidirectional training. We sketched the selectivity of the coupled-pair model for asymmetric cross-column connection weights (Fig. 4A), for increasing values of local recurrent connections (W_{AA} , W_{BB}): nonexistent (Fig. 4Ai), weak (Fig. 4Aii), or moderate (Fig. 4Aiii). When recurrent weights (W_{AA} , W_{BB}) were low, strong asymmetries in cross-column weights could produce bicolumnar selectivity for the same stimulus (e.g., *columns A* and *B* might both respond selectively to "up," blue regions in Fig. 4A,

Fig. 2. Coupled-pair model and its selectivity properties. A: diagram of 2 cortical columns with oppositely biased inputs. B–E: responses of models with different parameters; format as Fig. 1B. B: with no recurrent or cross-connections, the model behaves as 2 independent columns requiring large feedforward biases to achieve selectivity. C: with recurrent connections but without cross-connections, the model still behaves as a pair of independent columns but requires weaker feedforward biases to achieve selectivity. Note different axis on input graph. D: negative/inhibitory cross-connections create a winner-take-all paradigm, allowing for the model to achieve robust selectivity with a very weak feedforward bias. E: bicolumnar selectivity to the same stimulus. This regime requires weak feedforward input and a strong bias in cross-connection strength. The cross-connection from *B* to *A* must be small but present. F: parameter space for symmetric model with cross-connection strength on the x-axis and recurrent connection strength on the y-axis for a small bias in feedforward input (i), a medium bias in feedforward input (ii), and a large bias in feedforward input (iii). White indicates unresponsive columns (all responses < 50 Hz). Gray indicates responsive but unselective models (that is, response > 50 Hz and selectivity index < 0.3). Red indicates bicolumnar selectivity for opposite stimuli (response > 50 Hz and selectivity index > 0.5). Purple indicates unstable activity (e.g., when the network is activated, its recurrent drive is so high that it does not deactivate). Black indicates an unclassified activity region that is intermediate between strong selectivity and weak selectivity. Strong selectivity requires negative or weak cross-connections.

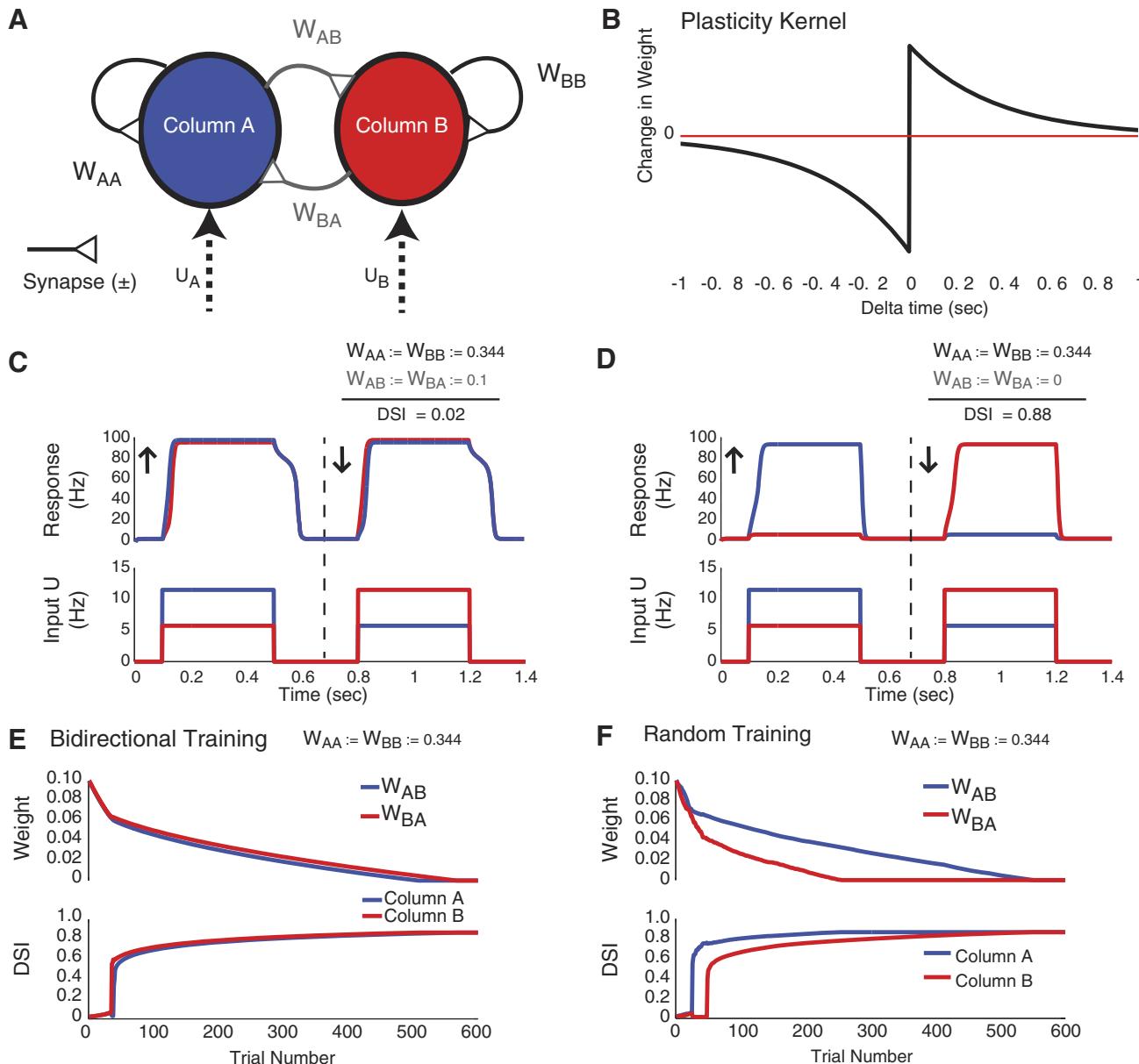


Fig. 3. Bidirectional training of the coupled-pair model with a negative weighted plasticity kernel allows for the development of selectivity. **A:** circuit diagram. **B:** the plasticity kernel that operates at cross-connections is a piecewise function of 2 exponential decays, with positive Δt signifying pre-before-post firing and negative Δt signifying post-before-pre firing. **C:** initial state of the model. Format as in Fig. 1B. During stimulation with the preferred stimulus for *column A*, *column A* exhibits a higher firing rate at an earlier time than *column B*, and the input from *B* to *A* will be weakened by the plasticity kernel. The reverse occurs during stimulation with the preferred stimulus for *column B*. **D:** state of the model after 600 trials of bidirectional training. Model now exhibits bicolumnar selectivity to opposite stimuli. **E:** cross-connection weights and DSI as a function of trial number for bidirectional training. Each trial consisted of a stimulus presentation in each of 2 opposite directions. Cross-connection weights have dropped to nearly 0, and the columns can respond independently to their feedforward inputs. **F:** cross-connection weights and DSI as a function of trial number for input that was randomly chosen to be 1 of 2 opposite directions on each trial. The progression of the change in weights depends upon the precise order of the sequence but eventually converges to the same state as in a circuit provided strictly alternating input.

i and *ii*). However, when recurrent weights were low, there was no set of cross-column weights that would produce bicolumnar selectivity for opposite directions, as normally occurs with bidirectional training. When local recurrent weights were moderately high (Fig. 4*Aiii*), as they would need to be to produce bicolumnar selectivity with a small feedforward bias (Fig. 1, *E* and *F*; Fig. 2*F*), then only two selective conditions were observed: bicolumnar selectivity to opposite directions (with near 0 cross-column weights) and a condition that we call unicolumnar selectivity (+) (1 column selective, the other

responsive but unselective). Thus, under the recurrent connection weights required here, bicolumnar selectivity to opposite directions and unicolumnar selectivity (+) are possible, but bicolumnar selectivity to the same direction cannot be observed.

We provided unidirectional training to the same initial model as before (Fig. 3*C*), employed the same plasticity rule (Fig. 3*B*), and found that the model also recapitulated the experimental results. When trained with a single direction (*column A*, “up”), the column that was biased toward the

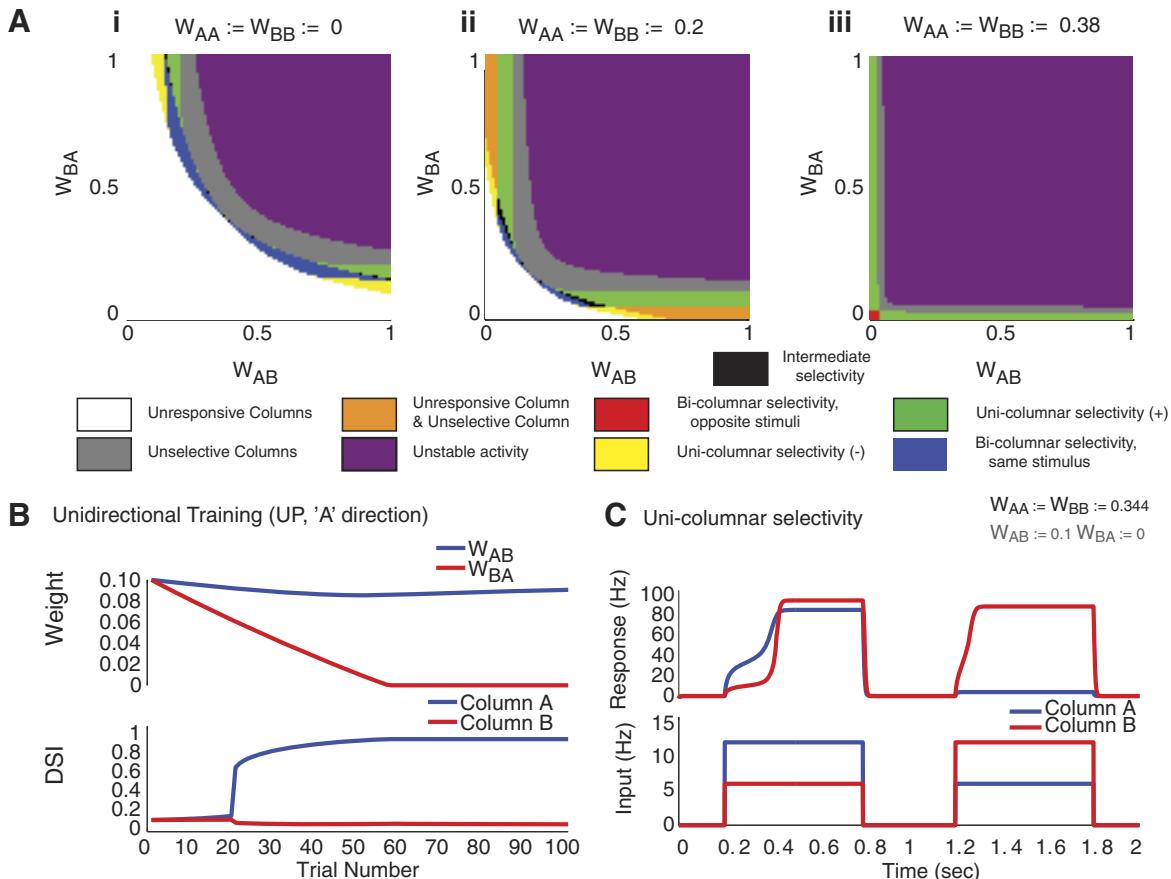


Fig. 4. Training with a single stimulus causes selectivity in the column that is biased for that stimulus. **A:** parameter analysis of selectivity of coupled-pair model with asymmetric cross-connections for weak (i), moderate (ii), and moderately strong (iii) recurrent connections. White area indicates unresponsive models. Gray indicates responsive but unselective models. Orange indicates that one column is unselective and the other column is unresponsive. Purple indicates unstable activity (e.g., when the network is activated, its recurrent drive is so high that it does not deactivate). Red indicates bicolumnar selectivity for opposite stimuli. Yellow indicates that one column is selective while the other is unresponsive, a condition we term unicolumnar selectivity (-). Green indicates that one column is selective while the other is responsive but unselective, a condition we term unicolumnar selectivity (+). Blue indicates bicolumnar selectivity for the same stimulus. For moderately strong recurrent connections (where selectivity exists with weak feedforward biases and nonnegative cross-connections), bicolumnar selectivity for the same stimulus is not observed. **B:** cross-connection weights as a function of trial number for unidirectional training in “up” direction (column A’s biased direction). **C:** state of the model after 100 trials of unidirectional training. Format as in Fig. 1B. Initial state shown in Fig. 3C. Column A is now selective, while column B remains responsive and unselective.

trained direction (A) became selective while the column that was biased for the opposite direction (B, “down”) remained unselective (Fig. 4, B and C). That is, the model exhibited unicolumnar selectivity (+).

The timing of the stimulus response, together with the STDP rule, determined the resulting cross-connection weights. During unidirectional training, the column that was biased toward the trained direction (A) responded slightly earlier than the column that was biased toward the opposite direction (B), and the two columns responded together during most of the stimulation. During the time that A responds before B, there was an increase to the cross-connection from A to B; when A and B respond together, there was a small decrease in the cross-connection from A to B. On balance, the increase and decrease were approximately equal, so the cross-connection from A to B undergoes little net change and maintains its initial strong value (Fig. 4B). Conversely, early in the stimulation column B fired after column A, so there was a decrease in the connection from B to A; later B and A fired equally, so there was again a decrease in the connection from B to A. As a result, the connection from B to A slowly dropped to 0,

allowing column A to exhibit selectivity only to upward motion (Fig. 4, B and C).

E/I pair model. The coupled-pair model allowed us to examine the impact of recurrent excitation and cross-column connectivity on the amplification of biased selectivity, but it lacks the ability to exhibit other dynamics that have been observed in column models with separate E/I populations that have differential cross-column inputs onto these populations (Fig. 5A). First, in the coupled-pair model the stability of each single element was artificially imposed by a sigmoidal response function, whereas E/I populations can be self-stabilizing through sufficiently strong inhibition (Fig. 5B). Second, E/I networks can operate as inhibition-stabilized networks (ISNs) (Ernst et al. 2001; Ozeki et al. 2009; Rubin et al. 2015).

In the ISN regime (Fig. 5, D and F), recurrent excitation is set to be so strong that the network activity would become arbitrarily large with moderate feedforward input, and inhibition is set to be strong enough to stabilize this powerful recurrent excitation. Under this regime, most of the drive to the activated cortex arises within the cortex itself; the cortex is like an engine, and the feedforward input like a throttle. In the ISN

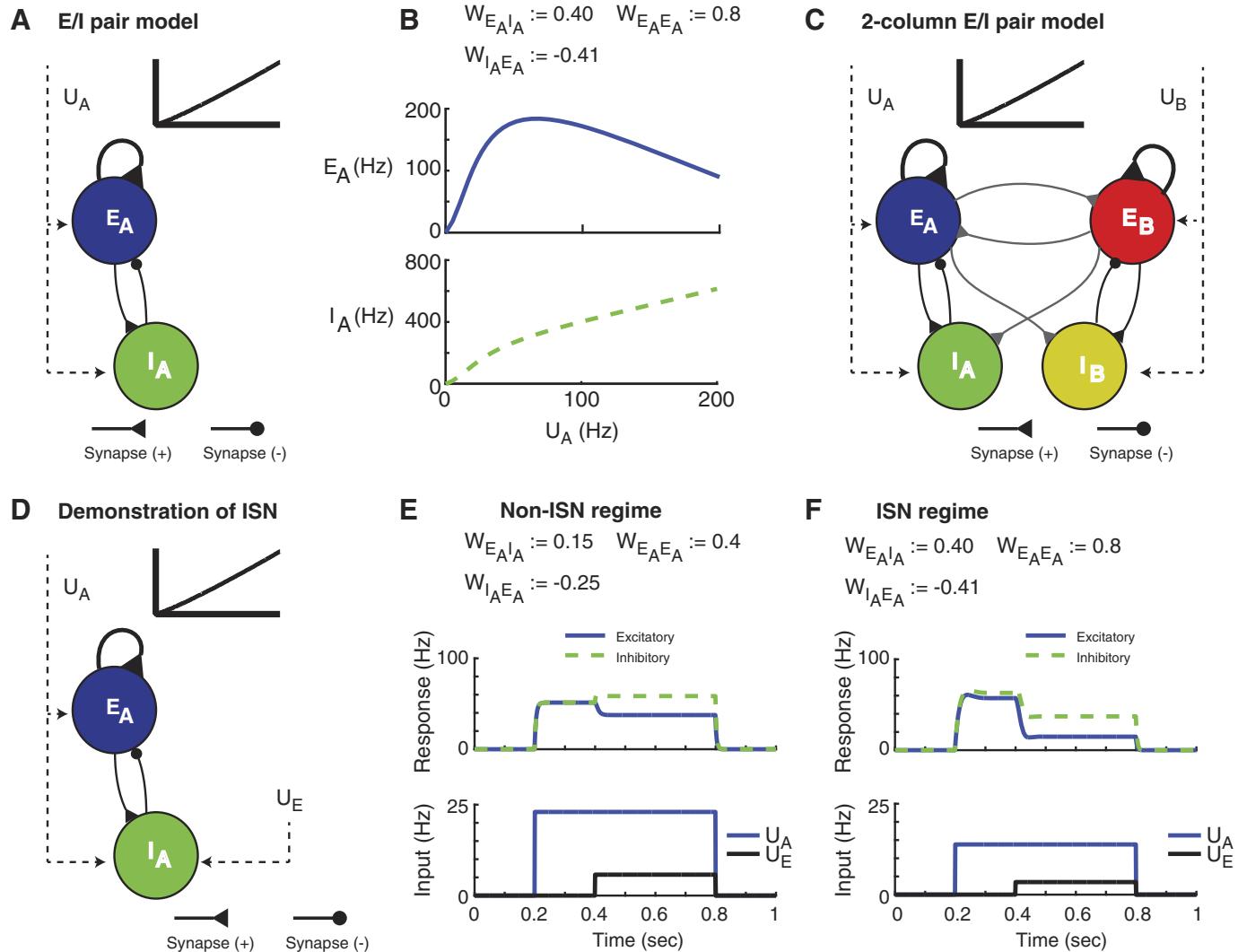


Fig. 5. Columnar model with separate E/I populations. *A*: diagram of E/I populations and connections among them. Response function of individual populations is shown in *inset*. *B*: response of E/I pair to increasing feedforward input. The system remains stable, even under very large inputs. The E unit reaches a maximum firing rate for increasing input and then is finally slowed by the I population, which can ultimately control the E cells at high response rates. Note separate firing rate axes. *C*: diagram of the 2-column E/I pair model with *columns A* and *B* and respective excitatory units (E), inhibitory units (I), and feedforward input (U). Synapses are of fixed signs within the model. *D–F*: demonstration of non-ISN (*E*) and ISN (*D* and *F*) regime. *D*: single column with E/I populations that receives an external input U_E to I population. *E*: in non-ISN regime, extra inhibition directly causes the reduction of firing rates. Inhibitory population firing rate increases, and coupled excitatory column firing rate decreases. *F*: in ISN regime, activity in cortex is primarily recurrent. Extra input to inhibitory column causes a reduction in both inhibitory and excitatory population responses due to a reduction in recurrent excitatory drive.

regime, the E and I cell activity rise and fall together (Fig. 5*F*), rather than E cell activity falling as I cell activity rises (Fig. 5*E*). The input/output relationship of an E/I pair in the ISN regime is supralinear but is less supralinear than the saturating input/output curve used in the coupled-pair model (Fig. 1*E*).

It is important to note that the ISN regime is an operating mode of the circuit that occurs for certain values of the synaptic connections in conjunction with sufficient external drive. It does not automatically occur for a given set of connection parameters. The same model could produce non-ISN behavior if the input drive is not sufficiently strong or is too strong (Ozeki et al. 2009; Rubin et al. 2015).

Two-column E/I pair model. We extended the E/I pair model into a two-column model (Fig. 5*C*). It is important to note that two-column E/I pair model retains much of the potential functionality of the coupled-pair model; it can still exhibit increases and then decreases in selectivity through

increases in recurrent excitatory connections (Fig. 1*E*), albeit with a weaker supralinearity (Fig. 5*B*), and reductions in cross-column coupling could still enhance selectivity with bidirectional training as in Fig. 3 or unidirectional training as in Fig. 4.

However, the two-column E/I pair model can achieve selectivity in different ways, as first shown by Ernst et al. (2001). In a model that lacks excitatory cross-connections but has excitatory-to-inhibitory cross-connections, the model can exhibit a null-direction suppression that is not possible in the coupled-pair model (Fig. 6*A*). Here the opposite column provides excitation onto the inhibitory unit, which in turn causes a reduction in the activity of both the excitatory and the inhibitory unit in the column. Responses are suppressed, but without an increase in inhibitory conductance, as necessary to be compatible with the experimental measurements of Priebe and Ferster (2005).

One of the largest regimes is a type of unicolumnar selectivity where the other column is unresponsive (Fig. 6B; Fig. 7), which we term unicolumnar selectivity (−). This occurs when the cross-column E-to-I weights are significantly strong and stronger for one column than the other, which in effect shuts

down all responses of the other column. Figure 6C demonstrates another regime, unicolumnar selectivity where the other column is responsive but unselective, which we term unicolumnar selectivity (+). Note that the data from unidirectional training experiments in ferret visual cortex are consistent with unicolumnar selectivity (+) (Van Hooser et al. 2012).

We examined the parameter space of the two-column E/I model (Fig. 7). We were particularly interested in capabilities of the cross-column E-to-I connections, which were not present in the coupled-pair model. To reduce the number of variables in the model, the intracolumn weights ($W_{E_A E_A}$, $W_{E_B E_B}$, $W_{I_A I_A}$, $W_{I_B I_B}$) were fixed to values that were capable of generating ISN dynamics for moderate inputs. We imposed symmetry between excitatory cross-connections but explored asymmetries of the E-to-I cross-connections. By these restrictions, the number of variables was reduced to three ($W_{E_A E_B} = W_{E_B E_A}$, $W_{E_A I_B}$, $W_{E_B I_A}$), and we were able to map the parameter space for a range of input parameters, as shown in Fig. 7.

The network exhibited strong selectivity when feedforward inputs were of moderate strength. When feedforward inputs were weak, the network could not respond until the cross-column E-to-E weights were very strong, which produced unstable responses that grew arbitrarily high (Fig. 7A). When feedforward inputs were strong, asymmetries in the E-to-I weights produced an unselective “winner-take-all” dynamic, where a stronger (but unselective) column always suppressed the opposite column, which became unresponsive (Fig. 7C). When moderate feedforward inputs were used, the network exhibited many selective and partially selective modes (Fig. 7B). When the cross-column E-to-I connections were roughly symmetric, a majority of models exhibited robust direction selectivity as in Fig. 6A. If cross-column E-to-I connections were asymmetric, then one column commonly exhibited selectivity while the other was suppressed and thus unresponsive; that is, most models exhibited unicolumnar selectivity (−) as in Fig. 6B. Only small regions of the parameter space exhibited strong but unselective responses or unicolumnar selectivity (+) (Fig. 7D), and bicolumnar selectivity for the same stimulus was not observed (Fig. 7).

Influence of experience (training) with plastic E-to-I connections Having established a wide parameter space that exhibited robust direction selectivity, we examined the influence of experience. We chose initial parameters that reflected biological observations to be unselective or weakly biased (Fig. 8C). To move along the parameter planes in Fig. 7, the excitatory cross-connection weights were fixed and the inhibitory cross-connections were plastic. In contrast to the negatively weighted plasticity kernel we employed in the coupled-pair model, we used a plasticity kernel weighted toward positive values (Fig. 8B). This serves to increase the cross-column E-to-I connections, which promotes network stability by in-

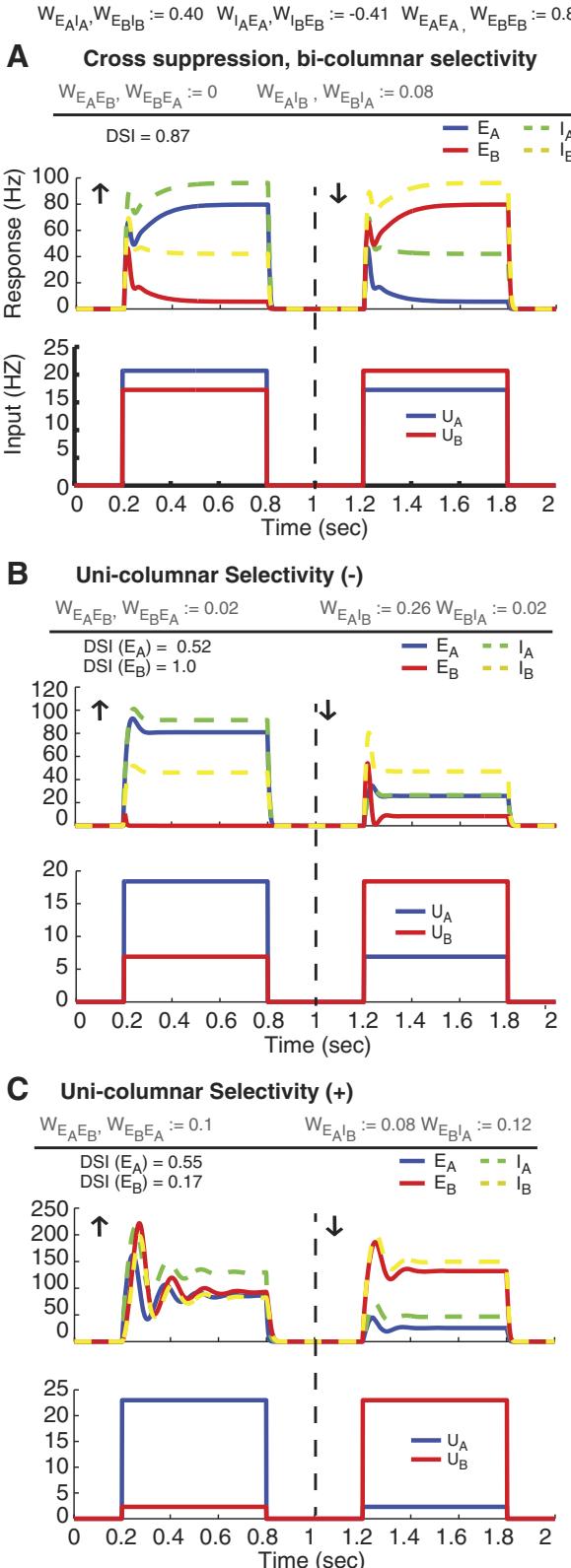


Fig. 6. Example responses of 2-column E/I network in ISN regime. Common parameters are indicated at top. A: example set of parameters that demonstrate cross-suppression that results in bicolumnar selectivity to opposite stimuli in the ISN regime. The cross-excitation onto the inhibitory populations ($W_{E_B I_A}$, $W_{E_A I_B}$) causes activity in the opposite column to be decreased, but without direct nonpreferred stimulus inhibition. B and C: demonstration of unicolumnar selectivity where the opposite column is silent (−) and where the opposite column is unselective (+). B: column A is selective, while column B does not cross response threshold. C: column A is selective, while column B is unselective. Note that the experimental data with unidirectional training are consistent with unicolumnar selectivity (+).

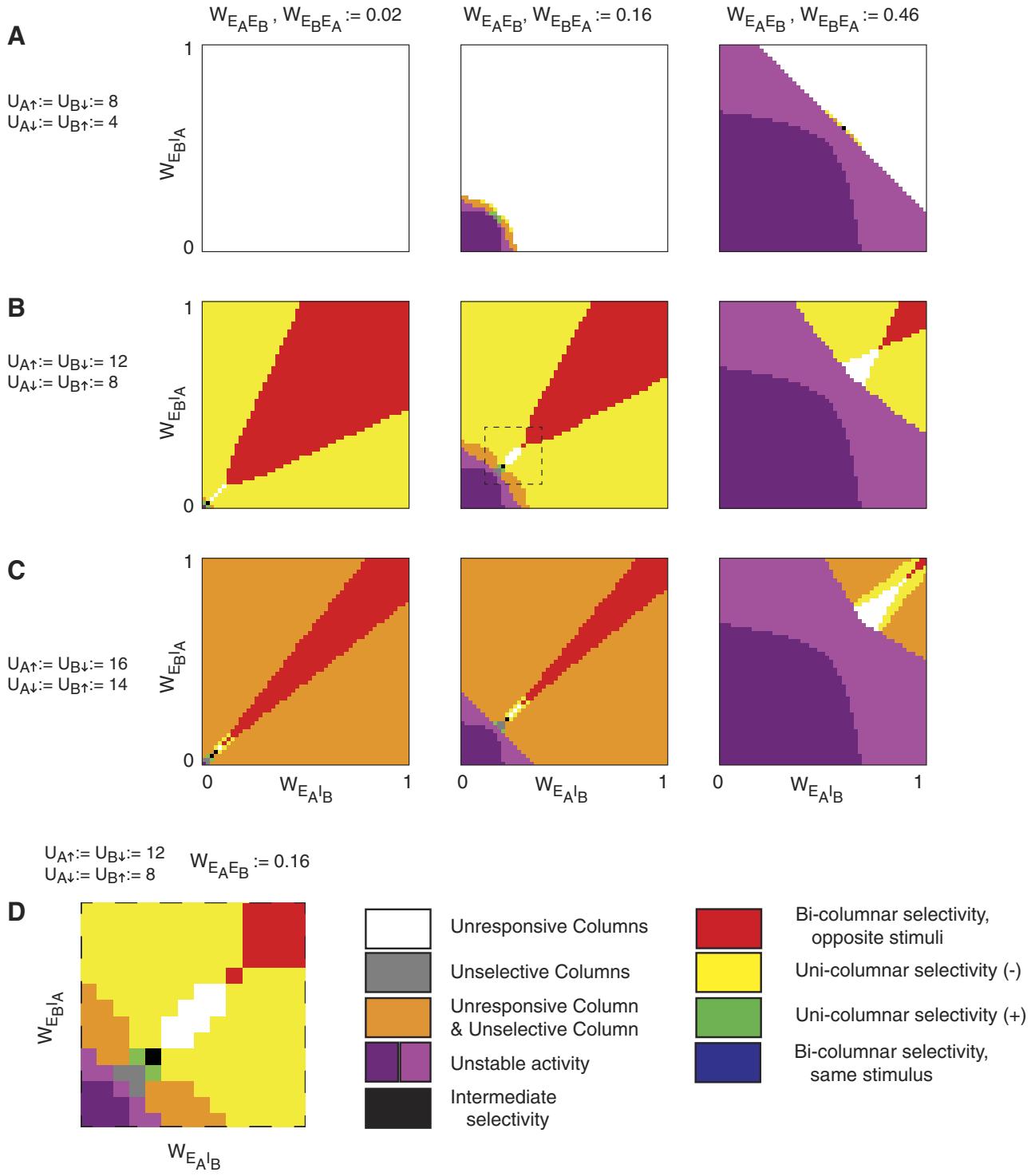


Fig. 7. Parameter space of 2-column E/I network for symmetric excitatory cross-connections (W_{EAE_B} , W_{EBE_A}) and asymmetric inhibitory cross-connections (W_{EAI_B} , W_{EBI_A}). Internal columnar weights were fixed (same as Fig. 6). Increasing values of excitatory cross-connections (W_{EAE_B} , W_{EBE_A}) were used in each column. Increasing feedforward bias values were used in each row. Each individual plot shows a parameter sweep of W_{EAI_B} and W_{EBI_A} from 0 to 1. *A*: when feedforward inputs were weak, most models did not exhibit above-threshold responses until cross-column E-to-E connection strength was high, a condition that caused the network to exhibit oscillations or unstable firing rates (arbitrarily large). *B*: with moderate inputs, many selective regimes were apparent. Robust bicolumnar selectivity for opposite stimuli (red) was observed when E-to-I cross-connections were roughly symmetric. When E-to-I cross-connections were asymmetric, networks exhibited strong selectivity for one column while the opposite column was suppressed, as in Fig. 6*B* [unicolumnar selectivity (-)]. Dashed box, *center*, shown in *D*. *C*: if feedforward inputs were increased further, symmetric E-to-I cross-connections could still produce selective models. When E-to-I cross-connections were asymmetric, “winner-take-all” dynamics were observed, with the strong column responding to both stimuli and the opposite column suppressed for both stimuli. *D*: expansion of dashed box in *B*, *center*. When cross-connection weights were low, there were small regions of parameter space that exhibited unselective responses or unicolumnar selectivity (+). Note that the experimental data from ferret visual cortex after unidirectional training are consistent with unicolumnar selectivity (+). Classification criteria are the same as Fig. 3 and Fig. 4, except that, in addition, unstable oscillatory activity (see MATERIALS AND METHODS) is denoted by pink.

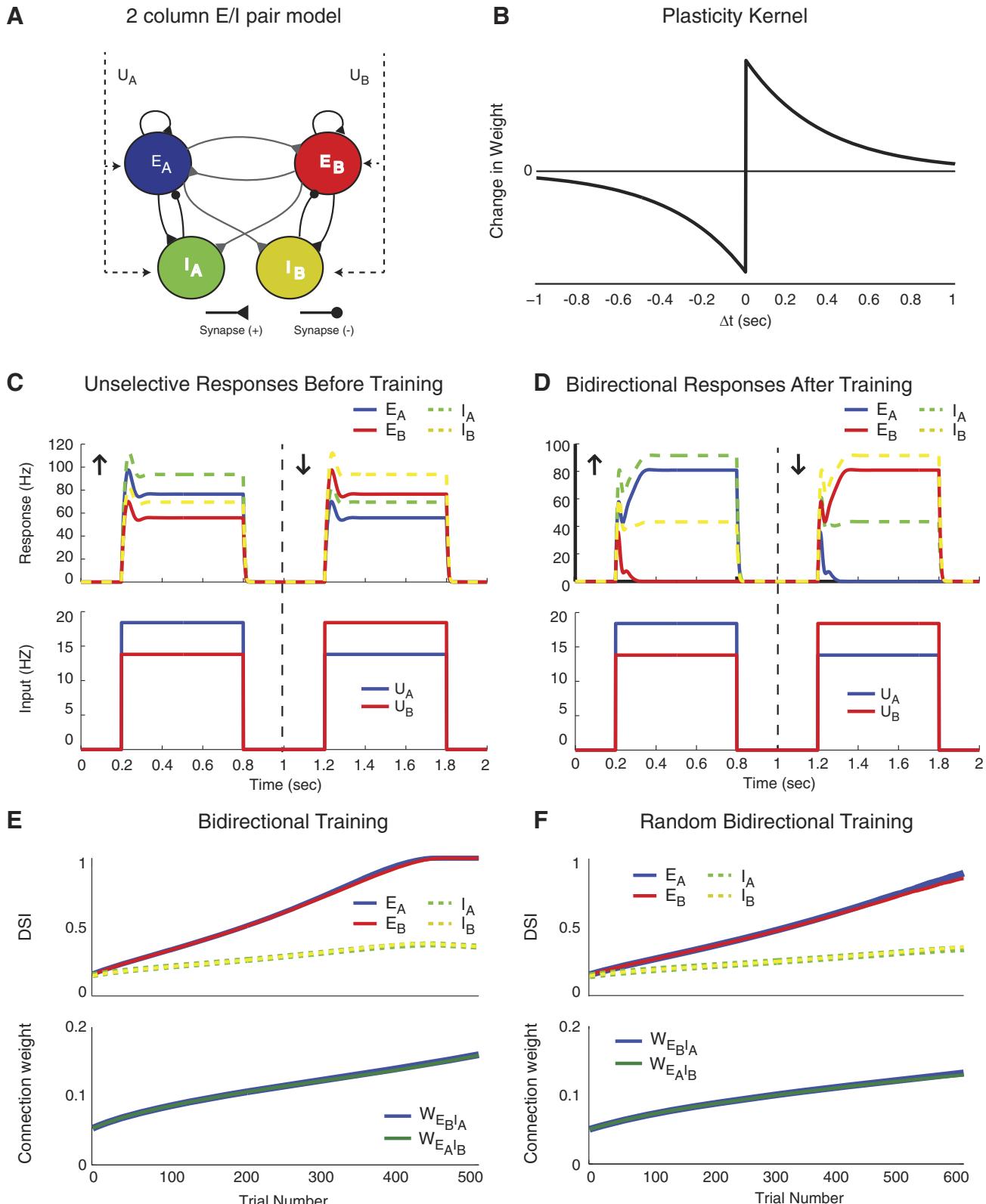


Fig. 8. Bidirectional training with opposite stimuli for the 2-column E/I pair model allows for the development of selectivity. *A*: diagram of 2-column E/I pair model. Within-column connections are represented by black lines; cross-column connections are represented by gray lines. *B*: the plasticity kernel that operates at cross-connections from E-to-I populations is a piecewise function of 2 exponential decays with a net positive weight. *C*: responses before training were responsive but unselective. *D*: responses after bidirectional training showed bicolumnar selectivity to opposite stimuli. *E*: for bidirectional training, relationship between trial number and columnar direction index (*top*) and inhibitory cross-connection strength (*bottom*). *F*: same relationship for training with randomly altering stimuli.

creasing drive to I cells. After bidirectional or randomized bidirectional training (Fig. 8, E and F) the model was able to achieve bicolumnar direction selectivity. In our simulations (Fig. 8, E and F) the inhibitory synapses grow without bound, but in a real network these synapses would need to have a reasonable ceiling, as those observed in long-term potentiation experiments (i.e., synaptic strengthening can be occluded) (Cooke and Bear 2010; Ehrlich and Malinow 2004; Heynen et al. 2003; Stein et al. 2003). Furthermore, if one were to measure the inhibitory conductance produced in either E unit in response to a preferred or null stimulus, one would observe a smaller inhibitory conductance in the null direction compared with the preferred direction, as Priebe and Ferster (2005) found in actual neurons (Fig. 8D).

To gain intuition about why bidirectional training succeeds, it is useful to examine the trajectory of these models through state space. Figure 9 shows how increasing the cross-column E-to-I connections causes increases in selectivity for varying fixed values of the cross-column E-to-E synapses. For moderate E-to-E weights (Fig. 9Bi), the network is capable of

exhibiting several response properties: unselective but responsive, high selectivity to opposite directions, intermediate selectivity, and unicolumnar selectivity. If we start the network in an unselective state, and provide bidirectional training that causes the E-to-I connections to increase, the circuit moves to a highly selective state (Fig. 9, B and C).

In contrast to results with bidirectional training, unidirectional training with plasticity on the inhibitory connections was unable to produce an enhancement of the selectivity of the column that was biased to the trained direction. An examination of Fig. 7, B and D, shows that the parameter regimes that produce this response property (shown in green) are very small. Furthermore, these regimes are located away from any natural ceilings or floors of parameter values, so it would be very difficult to construct a reasonable plasticity mechanism that would allow the network to settle into these regimes in a stable manner. To illustrate the difficulty of driving the circuit into the unicolumnar selectivity (+) regime, we trained the unselective network with two plasticity kernels, one that would promote stability (positively weighted) and one that would promote instability (negatively weighted).

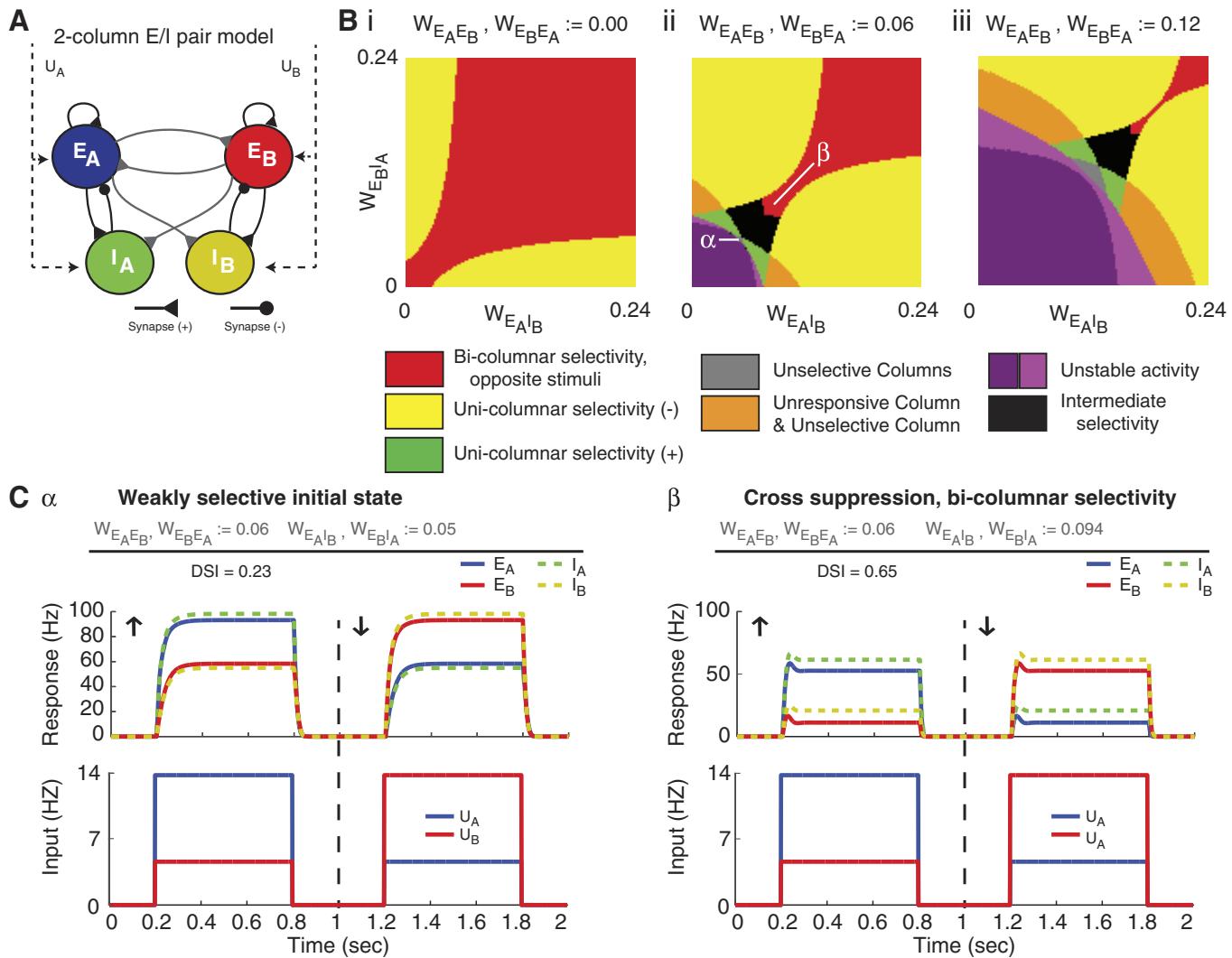
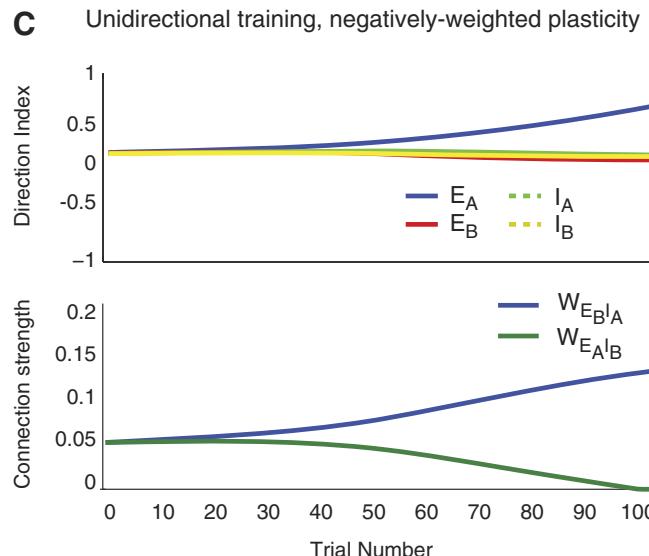
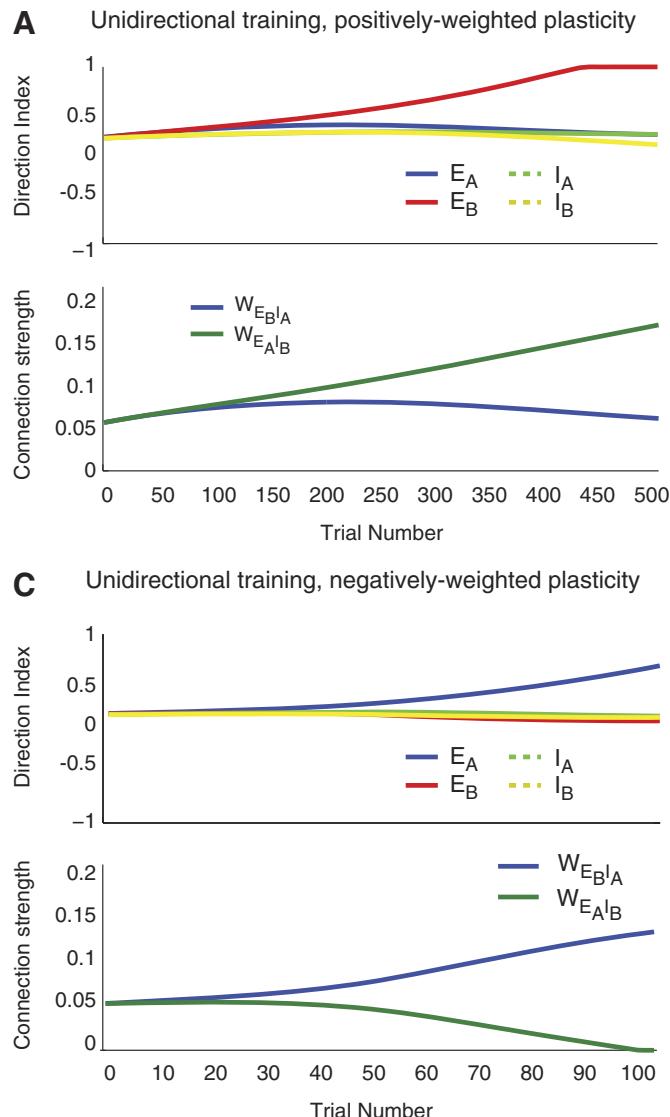


Fig. 9. State space of 2-column E/I pair model with varied cross-column E-to-I connection weights. A: circuit diagram of 2-column E/I pair model. B: false-color diagrams of response properties of circuit for 3 fixed values of cross-column E-to-E connections (i, zero; ii, moderate, iii, strong) and varied cross-column E-to-I connections. For moderate cross-column E-to-E connection values, the circuit can transition from a responsive but unselective state α to a selective state β with an increase in cross-column E-to-I strength. Note increased zoom and different input biases compared with Fig. 7B. C: responses of circuit models α and β .

With a positively weighted plasticity kernel and training in the direction that matched *A*'s bias (Fig. 10, A and B), the coactivation of E_A and I_B caused the weight of synapse $W_{E_A I_B}$ to increase. Even though the direction selectivity of *column A* increased, *column B* became unresponsive, suppressed by the activity of *column A*. With a negatively weighted plasticity kernel and training in the direction that matched *column A*'s bias (Fig. 10, C and D), *column A* became relatively unresponsive and *B* remained unselective. Neither of these situations matches what occurs in ferret visual cortex, where the column that is biased toward the training direction exhibits an increase in direction selectivity while the opposite column exhibits little change (Van Hooser et al. 2012).

In hindsight it is perhaps unsurprising that the two-column E/I pair model cannot transition from a responsive but unselective network to the unicolumnar selective (+) regime.



Because the input/output relationship of each column is less supralinear than in the coupled-pair model (Fig. 1E vs. Fig. 5B), more of the nonlinearity that contributes to selectivity must arise from interactions between the columns. That is, selectivity requires either a very large feedforward bias or selective input from the opposite column. Furthermore, if one column is selective, then it provides a bias to the opposite column, which means the opposite column is also likely to be selective or unresponsive.

Influence of plastic cross-column E-to-E connections and fixed cross-column E-to-I connections. Having established the capabilities of cross-column E-to-I plasticity in isolation, we next sought to examine the capabilities of cross-column E-to-E plasticity. In the coupled-pair model, reductions in cross-column E-to-E connections produced increases in either bico-

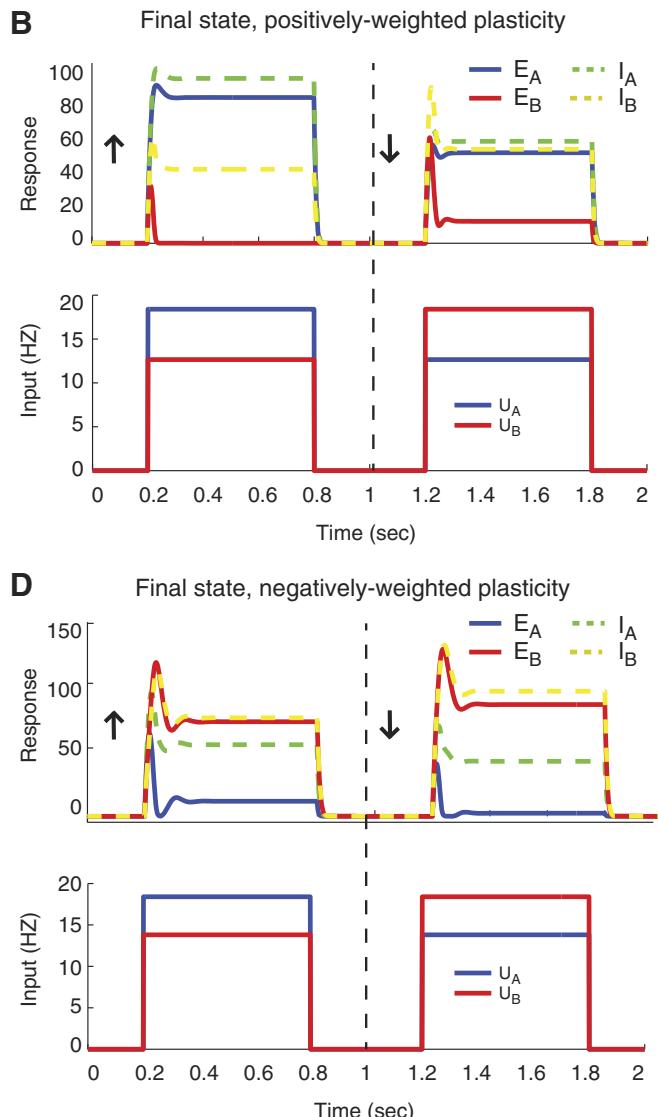


Fig. 10. Unidirectional training for the 2-column E/I pair model for 2 plasticity rules yields results that are incongruent with experiments in ferret. **A:** training with the same positively weighted plasticity kernel as in Fig. 8. Direction indexes of columns and cross-connection weights from E-to-I populations. **B:** responses after training. The column with the same preference as the training direction (*column A*) remains unselective because the opposite column (*column B*) never provides strong suppressive input to the I population of *column A*. *Column B* becomes unresponsive because *column A* provides a robust signal to the inhibitory population of *column B*. The lack of selectivity in *column A* and the lack of responsiveness in *column B* are inconsistent with unidirectional training results in ferret. **C:** as A, but with a negatively weighted plasticity kernel (as in Fig. 3) operating at the cross-column E-to-I connections. **D:** responses after unidirectional training with negatively weighted plasticity kernel. *Column A* becomes suppressed by *column B*; *column B* remains responsive but does not develop strong selectivity, while *column A* becomes unresponsive. The lack of selectivity and responsiveness in *column A* is inconsistent with unidirectional training results in ferret.

lumbar direction selectivity (with bidirectional training, Fig. 3) or unicolumnar selectivity (+), where the column that was biased to the trained stimulus became selective and the opposite column remained unselective (with unidirectional training, Fig. 4). Here we show that a similar principle applies in the two-column E/I pair model, but with some modifications when cross-column E-to-I connection weights are substantially greater than zero. Again, we employed a negatively weighted plasticity kernel to ensure stability of the network.

The response space of the two-column E/I pair model with variable cross-column E-to-E connections is shown in Fig. 11. If synaptic plasticity causes both cross-column E-to-E connections to decrease, then bicolumnar direction selectivity emerges (Fig. 11, *B* and *C*, *state* β). If E-to-E connections from *column A* to *B* decrease (asymmetrically, with no change in *column B*-to-*A* connections), then *column A*'s selectivity increases (Fig. 11, *B* and *C*, *states* γ and ε). However, if E-to-E connections become too small in the presence of nonzero cross-column E-to-I connections (Fig. 11, *B* and *C*, *state* ζ), then *column A*'s response magnitudes become very small, despite being selective. If a brain circuit were to exhibit cross-column E-to-I connections, and were to gain selectivity exclusively by modifying cross-column E-to-E connections in an asymmetric fashion, then a nonzero E-to-E floor would be necessary to keep the system in the vicinity of the unicolumnar selective (+) model in Fig. 11, *B* and *C*, *state* ε , and away from the unicolumnar selective (−) model in Fig. 11, *B* and *C*, *state* ζ . If cross-column E-to-I connections were very large (Fig. 11*Biii*), then only limited selectivity is possible if these constraints are placed on E-to-E cross-connections.

Mixtures of plastic cross-column E-to-E, E-to-I connections. In the previous analyses, we showed that Hebbian plasticity in cross-column E-to-I connections could produce a bicolumnar selective circuit that amplifies initial biases in the case of training with opposite stimuli (bidirectional training; Fig. 8, Fig. 9) but would produce only a weakly responsive circuit in the case of training with a single stimulus (unidirectional training; Fig. 10, Fig. 9). Furthermore, we showed that plasticity in cross-column E-to-E connections could enhance bicolumnar selectivity to opposite stimuli or unicolumnar selectivity to a single stimulus (Fig. 4, Fig. 11). Here we consider whether employing mixtures of plasticity in these two classes of synapses offers additional functionality.

A parameter scan of mixed changes in cross-column E-to-I or E-to-E connections shows that a single plasticity mechanism in E-to-I connections is incompatible with both bicolumnar and unicolumnar selectivity (+). Figure 12 shows the results of altering $W_{E_B F_A}$ and $W_{F_A I_B}$ while leaving $W_{E_A F_B}$ and $W_{F_B I_A}$ fixed, as might occur with Hebbian plasticity under unidirectional training (see Fig. 4, Fig. 10). To transition from an unselective state to a strongly unicolumnar-selective state, decreases in both $W_{E_A I_B}$ and $W_{E_B F_A}$ are required. However, to transition from an unselective state to bicolumnar direction selectivity, experience must produce increases in $W_{E_A I_B}$. Therefore, one would have to construct a plasticity mechanism that would somehow provide increases in cross-column E-to-I connections in the case of bidirectional stimulation and decreases in those same connections in the case of unidirectional stimulation. We cannot imagine a plasticity mechanism that would provide opposite plasticity under these different stimulus conditions.

Therefore, it is unlikely that concomitant plasticity in cortical cross-column E-to-E and E-to-I connections—in the absence of other mechanisms operating at the same time—could produce the selectivity changes that are observed in ferret visual cortex.

DISCUSSION

We explored families of cortical amplifier models to determine the parameter regimes under which these models could support selectivity, and to determine how such circuits could transition from a responsive but unselective regime to a selective regime with simulated experience.

The coupled-pair model was only capable of high selectivity when the connections across columns were very weak or negative. Studies in cortex have not observed strong null-direction inhibition, so it is likely that coupling across cortical columns in mature circuits is weak or involves cross-column suppression of ISN circuits, as in the two-column E/I pair model (Fig. 6*A*).

Bidirectional and unidirectional experience. The development of direction selectivity in ferret visual cortex requires visual experience. Animals raised in the dark or with strobe illumination during a critical period after eye opening never develop direction selectivity (Humphrey and Saul 1998; Li et al. 2006).

Around the time of eye opening, experience with either a bidirectional training stimulus (Li et al. 2008) or a unidirectional training stimulus (Van Hooser et al. 2012) causes a rapid increase of direction selectivity. Regions of the naive cortex exhibit very slight but significant biases for different directions, and with bidirectional training these biases are amplified and determine the direction preference that cells will acquire as direction selectivity emerges (Li et al. 2008). With unidirectional training, the amount and quality of direction selectivity that is acquired vary with position within the evolving direction map. In areas already biased toward the trained direction, there is a substantial increase in direction selectivity. In areas that exhibit biases for the opposite direction, there is no statistical change in selectivity. Areas in between, with more neutral biases, tend to change slightly to favor the trained direction (Van Hooser et al. 2012).

With bidirectional training, models that reduced cross-coupling among excitatory neurons (both frameworks) or increased E-to-I neuron cross-coupling (2-column E/I pair model) could amplify initial biases to become strongly selective.

With unidirectional training, models that asymmetrically reduced cross-coupling among excitatory neurons developed unicolumnar direction selectivity: the column whose initial bias matched the training stimulus would acquire selectivity, while the opposite column would remain unselective. These results agree nicely with the experiments (Van Hooser et al. 2012), though we did not consider intermediate columns in this work.

However, there are two circuits that are not compatible with unidirectional training experiments. If we imagined isolated columns that initially had high recurrent connections (Fig. 1, *E* and *F*) that became weaker with activation, then these columns would acquire selectivity for their biased directions regardless of the quality of experience. That is, they would exhibit the same end point as bidirectional training, which is inconsistent

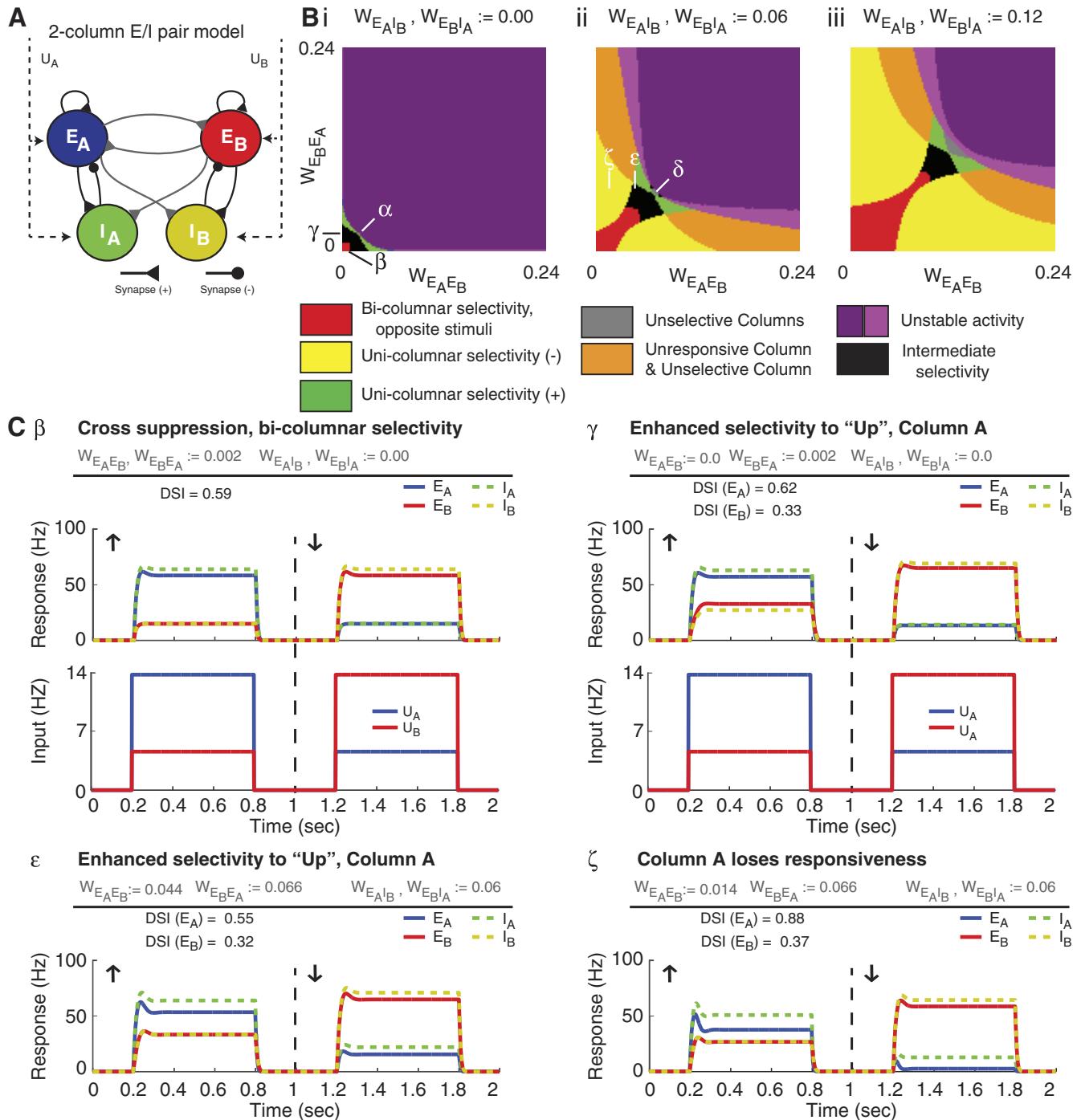


Fig. 11. State space of 2-column E/I pair model with varied cross-column E-to-E connection weights. **A:** circuit diagram of 2-column E/I pair model. **B:** false-color diagrams of response properties of circuit for 3 fixed values of cross-column E-to-I connections (*i*, zero; *ii*, moderate, *iii*, strong) and varied cross-column E-to-E connections. When cross-column E-to-I connections are zero, then the circuit exhibits a similar state space as the coupled-pair model (Fig. 3, Fig. 4): the model can switch from an unselective state α to a bicolumnar selective state β when both E-to-E weights are reduced, or the model can switch from the unselective state α to a unicolumnar selective (+) state γ by an asymmetric reduction of 1 cross-column E-to-E weight. (State γ is in the intermediate selective black region.) For moderate cross-column E-to-I connection values, the circuit can transition from a responsive but unselective state δ to a moderately unicolumnar selective (+) state ϵ with a moderate asymmetric decrease of cross-column E-to-E weight, but larger decreases cause the selective column to become very weakly responsive as in state ζ . If this mechanism were to be relied upon exclusively for increasing selectivity, then one would need to impose an artificial "floor" value for the cross-column E-to-E weights. **C:** responses of circuit models β , γ , ϵ , and ζ .

with experiments. Another circuit that is incompatible with unidirectional training experiments is the two-column E/I pair model with experience-dependent changes in cross-connections from E-to-I neurons (Fig. 8E). Because both columns are initially activated by the stimulation, both E-to-I cross-connec-

tions grow, allowing the activity of one column to shut down the other column (Fig. 10). That is, increases in cross-suppression can account for the enhancement of selectivity to both directions in bidirectional training but cannot account for the unidirectional training results. It is possible that this plasticity

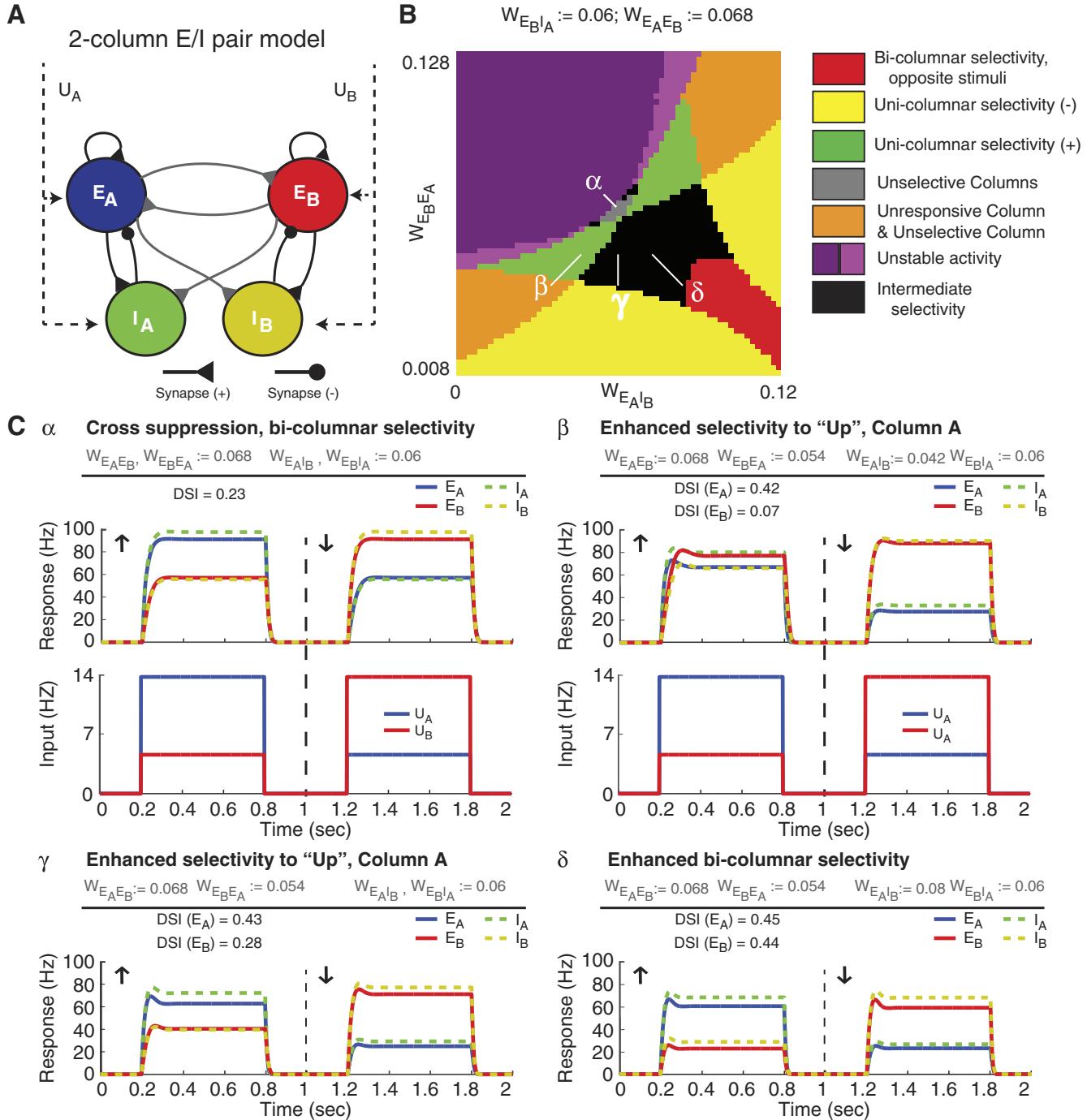


Fig. 12. State space of 2-column E/I pair model with asymmetric cross-column E-to-I and E-to E connection weights. *A*: circuit diagram of 2-column E/I pair model. *B*: false-color diagrams of response properties of circuit for moderate fixed values of $W_{E_B|I_A}$ and $W_{E_A|E_B}$ and varied $W_{E_A|I_B}$ and $W_{E_B|E_A}$. To transition from an unselective state α to a unicolumnar selective (+) state β , it is necessary to decrease $W_{E_A|I_B}$ and to decrease $W_{E_B|E_A}$. However, to transition from the unselective state α to a moderately bicolumnar selective state δ , then it is necessary to increase $W_{E_A|I_B}$ and to decrease $W_{E_B|E_A}$. It is highly unlikely that a plasticity mechanism operating at cross-column E-to-I connections could exhibit opposite behaviors depending upon the stimulus that was encountered, so we conclude that jointly varying cross-column E-to-I and E-to-E plasticity is not a good strategy for allowing experience-dependent trajectories to bicolumnar (bidirectional experience) or unicolumnar (unidirectional experience) selectivity. *C*: responses of circuit models α , β , γ , and δ .

could be employed in the actual animal, but one would have to imagine that plasticity in other connections would also be required.

These models provide only limited comparisons to experiments involving visual deprivation. If we consider dark-rearing experiments, visual experience is removed. Under the dark-

rearing condition, where input to the network is zero or greatly reduced, the pre/post activity needed to drive the STDP mechanisms would not be present, and the circuit would remain responsive but unselective, which is exactly what is observed in animal experiments (Li et al. 2006; Van Hooser et al. 2012). On the other hand, deprivation by lid suture strongly impacts

orientation tuning (White et al. 2001). In these models, the orientation-tuned signal is embedded into the simple feedforward input signal. Changes to the input signal are beyond the scope of the present model, and therefore the model does not provide insight into lid suture experiments.

Sparsification. Both models are consistent with sparsification of neuronal responses during development of mice (Rochefort et al. 2009) and ferrets (Smith et al. 2015). Authors in both experiments used calcium imaging to investigate receptive field properties during development of the visual system. They recorded from V1 while showing directional grating stimuli and found that responses become sparser as the animals gained more visual experience.

At a mechanistic level, Griffen et al. (2013) observed an experience-dependent decrease in columnar coupling over the first weeks of visual experience in rats. In brain slices from experienced animals, electrical stimulation of V1 layer 4 produced smaller propagating waves of activity than in animals lacking visual experience, and these differences were explained by both decreases in excitatory synapses and increases in inhibitory synapses. This decrease in columnar coupling is similar to that observed in simulations of the coupled-pair model.

Experimental predictions. Our analysis of the coupled-pair model suggests that direction selectivity could develop via a transition from an initial state where there is strong coupling across columns to a state where the cross-column coupling is much weaker. If this were true, then one could perform an experiment in the ferret much like that Griffen et al. (2013) performed in the rat. We would expect that a larger area of cortex would be recruited via focal stimulation of the naive cortex compared with mature cortex, and that excitatory synaptic connections across these columns (as assessed by glutamate uncaging) would be reduced.

Our analysis of the two-column E/I pair model suggests that a different way that selectivity could be enhanced is through suppression of inhibition-stabilized responses by columns with opposite preferences. This prediction could be tested by examining selectivity (with an extracellular or intracellular recording) in a column “A” in the presence and absence of a precise optogenetic “kick” to a neighboring column “B” that exhibits opposite selectivity preferences. If cross-column suppression is present, then the increased activity in the neighboring *column B* should suppress activity in the measured *column A*. Furthermore, if measurements of synaptic conductances could be made in *column A*, we would predict that the suppression should co-occur with a reduction of both excitatory and inhibitory conductances (Ozeki et al. 2009). This experiment may not be feasible with present optogenetic methods and may require vectors that direct expression to cell somas (Baker et al. 2016; Grubb and Burrone 2010), so that very spatially precise manipulations of *column B* could be made, as direction preferences can change abruptly across 100 μm of cortical space (Li et al. 2008; Ohki et al. 2005; Weliky et al. 1996).

Another feature of the two-column E/I pair model is that the inhibitory units in each column acquire direction selectivity that matches the column’s direction preference. In fact, a new experiment has found that inhibitory neurons in ferret visual cortex are, in fact, direction selective, and the direction preferences of these inhibitory neurons match the selectivity of their nearby excitatory neighbors (Wilson et al. 2017). It

should also be noted that in the coupled-pair model each unit represents the summed activity of excitatory and inhibitory neurons in the actual cortex, so this model, too, is consistent with the idea that local inhibitory neurons are direction selective.

If cross-column suppression existed, then we might also expect that cortical contributions to direction selectivity should increase with stimulus contrast, as the suppression would be stronger for higher firing rates. Experimentally, direction selectivity is slightly higher on average at low contrasts rather than high contrasts, although it is unclear whether feedforward contributions or cortical contributions are responsible for this overall effect (Peterson et al. 2006).

A permissive influence of visual experience on direction selectivity? While the development of direction selectivity requires visual experience, is the experience instructive, in that the parameters of the direction selectivity that is acquired are determined by the parameters of visual stimulation? Or is the experience permissive, allowing expression of tuning parameters that are fully seeded at the onset of visual experience?

Our previous feedforward model of the development of direction selectivity described a mixed permissive/instructive process that was influenced jointly by initial biases and experience (Van Hooser et al. 2014). With balanced visual experience (bidirectional training), cortical cells acquired the direction preference that matched their initial biases (even if these biases were subthreshold). But if these cells were stimulated repeatedly with an arbitrary spatiotemporal sequence, such as in unidirectional training, these biases would be overcome, and the cortical cells would acquire selectivity to the trained stimulus.

The cortical amplification models described here are permissive. Bidirectional training causes the two columns to become uncoupled, allowing the initial biases to dominate the responses. Unidirectional training in the coupled-pair model causes one column to become uncoupled from the other, allowing that column to be selective while the other column remains unselective.

Experiments also suggest that the tuning parameters of direction-selective neurons are already determined at eye opening. Calcium imaging of the naive ferret cortex showed that different regions of the cortical surface already exhibited small biases for different directions and that bidirectional motion training amplified these initial biases (Li et al. 2008). Furthermore, direct optogenetic stimulation of the developing cortex has shown that patterned or unpattered stimulation is sufficient to cause the emergence of direction selectivity (Roy et al. 2016). The parameters can be altered slightly, as unidirectional training experiments showed that regions that exhibited the weakest net biases for direction altered their tuning to match the trained direction but cells in regions that were biased for the direction opposite the trained direction did not acquire selectivity (Van Hooser et al. 2012). These experiments strongly suggest that the parameters of direction selectivity, including direction preference, are largely determined at the time of eye opening and merely need sufficient cortical activation to be fully expressed by the circuit.

Rate models vs. spiking models. In this study, we have employed a rate model of cortical columns, where a single rate represents the sum of activity in an entire cortical column. Spiking models of ISNs/supralinear-stabilized networks ex-

hibit all the same behaviors as their corresponding rate models in broad regions of the parameter space in which neural spiking is fluctuation driven (Ahmadian Y, Miller KD, Obeid D, private communication). Although the fine details of the stability and parameters would certainly be altered if the model were implemented in a spiking network, the precise impacts of converting an ISN or supralinear-stabilized network to a spiking network is still an active topic of research.”

Future models. While many of the recurrent models described here can account for a variety of experimental observations regarding the development of direction selectivity, real cortical neurons exhibit higher orders of spatiotemporal selectivity, such as velocity tuning. Indeed, direction selectivity can vary with stimulus speed/velocity (Moore et al. 2005). The models described here do not account for velocity tuning, which may provide a useful constraint on future circuit models. To assess such velocity tuning in the context of plasticity, the time-dependent amplitude of the stimuli will be necessary and the model circuit may need to include spiking model neurons to incorporate appropriate variants of STDP.

Summary. Here we have shown that cortical amplifier circuits—by themselves—are capable of exhibiting transitions from responsive but unselective states to highly selective states. The majority of the models that we explored that seem most consistent with present neural data are those in which initial circuits exhibit selectivity in feedforward inputs that is blurred by too-strong recurrent connectivity within the cortex. This inherent selectivity can then be revealed by plasticity mechanisms that reduce these cross-column connections with experience.

A majority of the model state-space trajectories from responsive but unselective states to highly selective states are “permissive.” These circuits exhibit little ability to overcome feed-forward biases in a manner that reverses the selectivity of individual columns from that of its biased input. New experiments will be required to assay whether the mechanisms modeled here are found in actual brain circuits.

ACKNOWLEDGMENTS

We thank members of the Van Hooser lab for comments.

GRANTS

This work was funded by National Institutes of Health Grants EY-022122 (S. D. Van Hooser) and DA-033463 and used the Brandeis High Performance Computing Cluster.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

I.K.C. and S.D.V.H. analyzed data; I.K.C., P.M., and S.D.V.H. interpreted results of experiments; I.K.C. and S.D.V.H. prepared figures; I.K.C. and S.D.V.H. drafted manuscript; I.K.C., P.M., and S.D.V.H. edited and revised manuscript; I.K.C., P.M., and S.D.V.H. approved final version of manuscript; P.M. and S.D.V.H. conceived and designed research.

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