Connectional Constraints and Feed-Forward Inhibition Allow the Development of Robust Cortical Direction Selectivity from Sparse Initial Inputs

Master's Thesis

Presented to

The Faculty of the Graduate School of Arts and Sciences
Brandeis University
Interdepartmental Program in Neuroscience
Stephen D Van Hooser, Advisor

In Partial Fulfillment
of the Requirements for the Degree

Master of Science
in
Neuroscience

by
Benyamin Louis Meschede-Krasa

May 2017
Acknowledgements

I extend utmost gratitude to Dr. Stephen Van Hooser and Dr. Arani Roy. Steve answered any and every question I had during my three years learning and working in the lab and was always an extremely welcoming mentor. Thank you for teaching me so much and for your patient mentorship during my time at Brandeis. Arani showed me so much of what is at the current frontier of neuroscience and explained topics beyond what I could have ever learned from any of my classes. My time working on many different experiments with Arani and working on this modeling project with Steve has been an unbelievable learning experience that has defined my undergraduate experience.
ABSTRACT

Connectional Constraints and Feed-Forward Inhibition Allow the Development of Robust Cortical Direction Selectivity from Sparse Initial Inputs

A thesis presented to the Interdepartmental Program in Neuroscience

Graduate School of Arts and Sciences
Brandeis University
Waltham, Massachusetts

By Benyamin Louis Meschede-Krasa

The development of direction selectivity (DS) in the carnivore primary visual cortex (V1) requires visual experience, although the mechanisms by which visually-driven activity sculpts the cortical circuits are not fully understood. A previous modelling study by Van Hooser et al. (2014) proposed a mechanism for the development of direction selectivity based on changes in the pattern of feedforward inputs from the lateral geniculate nucleus (LGN) onto V1 cells. Recent experimental findings have called into question some of the assumptions that went into the previous model. In that model, prior to visual experience, inputs to V1 cells came from LGN units with a broad range of spatial positions and response latencies. However, recent intracellular recordings from our lab suggest that visually naïve V1 cells receive more narrowly localized input. Additionally, the previous model allowed for all inputs across all positions and latencies to grow, implying that the final input structure could be determined by the properties of the visual training stimulus used. In contrast to this hypothesis, Ritter et al. (2017) found that speed tuning of actual
V1 cells following visual training did not depend on the velocity of the training stimulus used. This implies that visual experience plays a permissive, and not instructive, role in the development of direction selectivity. Therefore, in a new model, we implemented a restriction allowing only specific inputs to grow. We also added an inhibitory interneuron that acquired similar tuning properties to the DS cell it connected to. Recent findings by Wilson et al. (2017) show that inhibitory interneurons in ferret V1 are direction-selective and have similar direction tuning to nearby cells, consistent with our new inhibitory paradigm. Thus, our model proposes new mechanisms for the development and sharpening of direction selectivity that agrees with the most recent data from live animal recordings.
Table of Contents

Abstract ................................................................. iv

Chapter 1: Foundation of Visual Processing in Mammalian Carnivores .... 1

Chapter 2: Modeling the Development of Direction Selectivity .......... 11

  Introduction .................................................................. 11

  Materials and Methods ............................................... 12

  Results ....................................................................... 16

  Discussion ................................................................. 30

References ................................................................. 35
List of Tables

Table 1: Parameters for simulations ...................................................... 16
List of Figures

Figure 1: Orientation and direction tuning curves from a ferret V1 neuron ........ 2

Figure 2: The spatial relationship between circular LGN cell receptive fields and the elongated receptive field of a functionally connected V1 simple cell .... 3

Figure 3: Orientation columns are organized in a patchy pattern with notable pinwheel structures ................................................................. 4

Figure 4: Development of direction and orientation selectivity in ferret visual cortex .......................................................... 6

Figure 5: Reichardt detector diagram ................................................. 8

Figure 6: Slanted spatiotemporal receptive field of V1 cells allows for summation of inputs according to the Reichardt detector model ......................... 10

Figure 7: Possible structure of circuitry underlying observed direction-selective responses: An excitatory feed-forward model ...................... 20

Figure 8: A feed-forward excitatory circuit with strong individual LGN→V1 synaptic weights and possible inputs restricted to specific spatial positions and latencies does not develop strong direction selectivity after bidirectional motion training .......................................................... 23

Figure 9: Adding feed-forward inhibition to a circuit with strong individual LGN→V1 synaptic weights and possible inputs restricted to specific spatial positions and latencies develops strong direction selectivity after bidirectional motion training that matches that predicted by the unrestricted spatial positions and latencies .......................................................... 27

Figure 10: Simulations of unidirectional training only induce the development of direction selectivity if the directionality of the training stimulus matches the direction predicted by the restriction ........................................ 29
Chapter 1: Foundation of Visual Processing in Mammalian Carnivores

The mammalian visual system is organized in a hierarchical fashion. This can be experimentally observed through the analysis of receptive fields of neurons at various steps in the visual processing pathway. Ferrets and cats share a similar organization with primates and humans that differs from other rodent species.

The first step in building receptive fields can be observed in the responses from the retinal ganglion cells which contain all neural output from the retina. The retina has a basic neural circuit to output a specialized receptive field known as center surround. Each ganglion cell has a circular center-surround receptive field marked by a central region and ring around that region that are responsive to opposite light/dark stimuli. For example, if light is shone on the center receptive field it can increase the firing rate of the cell, and is referred to as the ON region. But if light is shone on the surround region it decreases the firing rate of the ganglion cell, and is referred to as the OFF region. Ganglion cells also exist with an OFF receptive field center and an ON surrounding region.

Ganglion cells synapse onto neurons in the Lateral Geniculate Nucleus (LGN) of the thalamus in an organized fashion such that a retinotopic map is retained. Additionally, a center surround receptive field is maintained in LGN cells (Hubel and Wiesel, 1965).
From the LGN, most cells project to layer 4 of the primary visual cortex (V1) in the occipital lobe. The response properties of V1 cells are markedly different from the LGN inputs. While LGN receptive fields are circular, V1 cells have elongated receptive fields that are oriented. These cells respond best to bars of light oriented at a specific angle and are therefore orientation-selective (Figure 1A). For example, if an orientation-selective cell fires most in response to a vertically oriented bar of light, then that cell will have little or no responses when presented with a horizontal bar of light (Figure 1A). This elongated structure is a result of the organization of LGN inputs. The circular inputs for regions along a line in visual space synapse onto a single V1 neuron (Figure 2) (Chapman et al, 1991; Reid and Alonso 1995).

![Figure 1](image)

**Figure 1:** Orientation and direction tuning curves from a ferret V1 neuron. **A**) A V1 simple cell in a ferret that has orientation-selective responses. Responses are greatest for vertical bars and are at baseline for other orientations. **B**) The same V1 simple cell demonstrates direction selectivity for rightward motion after the animal has gained visual experience.

Locations of orientation-selective cells within the cortex are highly organized. Cells that respond to the same orientation from the same region in space are clustered together and form a column of cells that have similar response
properties. (Hubel and Wiesel 1962, 1968; Swindale et al. 1987). These columns are also organized by orientation preference. Across the cortical surface orientation columns are situated based on their preferred angle and form a pinwheel pattern with columns of similar angles situated near one another (Figure 3) (Swindale et al. 1987; Bonhoeffer and Grinvald 1991). Additionally, retinotopy is also maintained in V1 (Cowey, 1964; Allman and Kaas 1971).

**Figure 2:** The spatial relationship between circular LGN cell receptive fields and the elongated receptive field of a functionally connected V1 simple cell is shown. ON receptive fields and sub regions are shown in red. OFF receptive fields and sub regions are shown in blue. Diameter of LGN receptive fields indicate relative receptive field size, thickness indicates strength of connection between the two cells based on correlation. LGN inputs align with their respective ON and OFF subregions in the V1 receptive field (from Reid and Alonso 1995)

Cells in V1 can be classified as either simple or complex based on their receptive field structure. While both maintain selectivity for oriented bars, they differ significantly in receptive field size and specificity of position. Simple cells respond to bars only in a localized area of the visual field and their receptive field has adjacent areas of excitation and inhibition, similar to the ON and OFF regions of
LGN cells. In contrast, complex cells respond to inputs over a broad area of the visual field (Hubel and Wiesel, 1962).

The orientation-selective neurons also display a related property called direction selectivity. A neuron is defined as direction-selective if it responds more strongly when a bar slanted at its preferred orientation moves in one of the two directions orthogonal to the orientation axis. For example, if a neuron tuned to vertically oriented bars responds equally when those bars are moving to the left or to the right, the neuron would be orientation-selective but not direction-selective (Figure 1A). However, if such a neuron responds more to the rightward motion as compared to the leftward motion then the neuron would be defined as both orientation-selective and direction-selective (Figure 1B).

Figure 3: Orientation columns are organized in a patchy pattern with notable pinwheel structures A) An image of section of V1 cortical surface imaged B) The organization of orientation preferences across this surface is shown. It seems patchy with pinwheel centers. C) Two examples of pinwheel centers are shown. At each pinwheel every orientation is represented (from Bonhoeffer and Grinvald, 1991).
In addition to being organized into orientation columns, V1 neurons are also organized into direction columns. Each orientation column is roughly divided down the middle with cells in either column responding to opposite orthogonal directions (Hubel and Wiesel 1962; Shmuel and Grinvald 1996).

Functional properties such as orientation selectivity and direction selectivity, and the neural circuits that underlie them, develop through a process that can be broadly divided into two main stages. The first stage occurs before the animal is exposed to any visual experience, usually defined as before the animal opens its eyes or before birth in animals born with open eyes. In this stage the development of neural circuits mostly proceed via genetically-specified mechanisms.

During this early stage, brain development is characterized by the formation of many synapses between brain regions. Axonal path finding is guided by various highly specific chemical gradients. In the visual pathway, thalamic projections are guided by Emx2 in order to correctly synapse with V1 neurons (Bishop et al., 2000; Bishop et al., 2002). Orientation selectivity maps are present before visual experience, although they are not fully mature yet (Figure 4) (Hubel and Wiesel, 1974). Orientation maps remain intact even after visual deprivation, although the maps do become less robust when the animal is visually deprived (Chapman and Stryker 1993; Chapman et al., 1999). Direction maps, however, are not present before visual experience and very little direction selectivity is observed in cortical cells before exposure to visual stimuli (Figure 4) (Li et al., 2006). Therefore, it is thought that while the orientation maps are largely specified by genetically-guided mechanisms, direction maps rely on subsequent visual experience for completion.
The second phase of development of the visual system involves exposure to visual experience. Although much of the underlying structure of visual maps has been organized before exposure to visual experience, the majority of synapses form after the animal begins to receive visual stimuli (Cragg 1975; Erisir and Harris 2003). Much of this synaptogenesis is a result of development of horizontal connections within the cortex, most of which form after exposure to visual stimuli (Callaway and Katz 1990; Durack and Katz 1996; Ruthazer and Stryker 1996).

**Figure 4: Development of direction and orientation selectivity in ferret visual cortex.** Normalized orientation selectivity index values (blue squares) and direction selectivity index values (orange circles) are plotted before eye opening and at multiple time points until both reach maturity. Orientation selectivity is present before visual experience though it is not fully matured. Direction selectivity is not preset before visual experience and requires visual experience to develop (from Li et al., 2006).
Visual experience drives development of both orientation maps and direction maps in V1. Although orientation maps already exist before eye opening, they do not reach full maturity until after visual experience is gained (Li et al., 2006). Development of direction selectivity seems to be entirely dependent on visual experience during a critical period right after eye opening. Ferrets dark-reared during this critical period do not develop direction selectivity maps, even if they are exposed to patterned visual experience later in life (Li et al., 2006).

The Reichardt detector model suggests a possible mechanism by which neural circuits can build direction selectivity. This model consists of a series of spatial luminance detectors responding to light from varying positions in space, which then project on to an output cell (Figure 5). The connections from detectors have varying time delays, resulting in the signals summatiing on the output cell when a moving stimulus is presented in one direction but not in the opposite direction. For example, in figure 5 the time delays in the connections from detector to output cell allow for summation of signal in the leftward direction because the detector that gets stimulated first by leftward motion have the largest time delays associated with them. This allows for signals from all three detectors to simultaneously arrive at the DS output cell and push it above threshold. The effect of the time delays in response to rightward motion, however, would only be to separate each signal more in time, therefore arriving at spaced out intervals at the output cell and not activating it above threshold.
In the mammalian primary visual cortex, the inputs to the DS V1 cell can be thought of as the LGN and/or cortical inputs synapsing on the V1 cell. The varying time delays are built into these connections that all feed onto a direction-selective cortical cell. There is substantial evidence that the LGN contains excitatory neurons responding to different positions and latencies (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 neurons in carnivore species have classified LGN cells into two types based on response latency of the cell. The majority of cells are non-lagged, with latencies of less than 100ms but another group of lagged cells exist with response latencies greater than 100ms. It has been suggested that inputs from both classes could be the basis for a large range of direction selectivity in the cortex (Saul and Humphrey 1990; Wolfe and Palmer 1998), though the range of latencies within even the non-lagged group (40ms) could be enough to be the basis of direction selectivity (Feidler et al., 1997, Van Hooser et al., 2014).

**Figure 5: Reichardt detector diagram.** The circuitry for a simple Reichardt detector is shown with three spatial luminance detectors, each with a different latency. Motion in the leftward direction results in summation of detector responses onto the direction-selective output cell. Rightward motion, on the other hand, results in three temporally offset signals onto the direction-selective output cell.
The spatiotemporal receptive field (STRF) of a cortical direction-selective neuron displays the strengths of inputs at particular spatial positions and temporal latencies. The Reichardt detector model predicts that for a DS V1 neuron these inputs plotted by latency and position should have a slanted shape, allowing for summation of inputs over time if a stimulus is moving in the preferred direction (Figure 6A). In response to motion in the preferred direction, inputs with larger time delays are stimulated in earlier position, allowing for summation as described in the simple Reichardt detector in figure 5. The spatiotemporal receptive field shown in figure 6 would be selective for leftward motion because as in figure 5 the right most positions have the largest time delays, allowing for all signals to simultaneously arrive at the V1 output cell at the same time. Rightward motion would result in weak drive in the output cell. Intracellular recordings from primate visual cortex (Figure 6B) (De Valois et al., 2000) as well as cat visual cortex (McLean and Palmer, 1989) have found evidence for a slanted input structure to direction-selective cells which would agree with a Reichardt detector model. Intracellular recordings from our lab have corroborated these findings for DS cells in ferret V1.

This work focuses on how direction selectivity might arise during development as little is known about the details of this process. We propose a model that uses our best knowledge of the starting and ending conditions of the input structure in order to propose a mechanism that best describes current data on the
development of direction selectivity. We hope the proposed mechanism can generate experimental predictions on this topic to further our understanding of this circuit and brain development as a whole.

Figure 6: Slanted spatiotemporal receptive field of V1 cells allows for summation of inputs according to the Reichardt detector model. A) Each circle represents an input to a V1 cell, each with a different latency, plotted on the y axis, and position, plotted on the x axis. The red cells demonstrate the slanted pattern that is expected based on the Reichardt detector model. This representation of inputs is the spatiotemporal receptive field of the V1 cell. B) The spatiotemporal receptive field of a neuron from primate V1 is plotted with red ON regions and blue OFF regions (from De Valios et al., 2000).
Chapter 2:  
Modeling the Development of Direction Selectivity

Introduction

Direction selectivity is present when a neuron, in response to a moving stimulus, responds more strongly to one direction than any other. This response property is dependent on the space and time of the stimulus because a cell must respond to a stimulus’ specific location in space at particular times in order to compute motion. In ferrets, and possibly in humans as well (Ellemberg et al. 2002), neurons in primary visual cortex (V1) do not exhibit direction selectivity until after the animal has gained visual experience. Live animal recordings have demonstrated that an animal with no visual experience will develop strong direction selectivity after just 3-6 hours of exposure to a bidirectional moving stimulus (Li et al. 2008).

The Reichardt detector is a proposed mechanism thought to underlie direction-selective responses. However, the development of these responses is still not well understood. A feed-forward model has been proposed in which output V1 model neurons can be trained to become direction-selective using simulations of visual experience (Van Hooser et al., 2014). This model, however, relied on an initial set of inputs from a broad set of positions and latencies. Recent experiments have cast doubt on whether the initial set of inputs are broad or specific. For example, live animal intracellular recordings from our lab are inconsistent with this
assumption, and have instead shown that V1 neurons in visually naïve animals exhibit responses that are highly localized in spatial position and latency.

Additionally, experiments that provided artificial experience that was either slow or fast to naïve animals showed that experience could not influence the speed tuning of V1 cells (Ritter et al., 2017). This evidence suggests that the development of the spatiotemporal receptive field (STRF) of a V1 neuron is not flexible for different speeds and therefore the inputs to that cell are restricted to a subset of cells that fire at specific positions and specific latencies. This restriction could assure that each V1 cell could only learn to become direction-selective for a predetermined direction, not apparent before visual experience, which is supported by recordings from live animals (Van Hooser et al. 2012 and Roy et al. 2016). These joint requirements suggest that, initially, a small number of LGN neurons (perhaps one) are sufficient to drive the cortical cell, and that the STRF is restricted to grow according to specific positions and delays. In this paper we demonstrate a functional feed-forward model that exhibits all of these properties. This model shows that, in principle, these qualities are sufficient to account for present experimental data regarding the emergence of direction selectivity and speed tuning.

**Materials and Methods**

A feed-forward model of thalamo-cortical circuitry has been developed to simulate development of direction selectivity based on plasticity rules (Van Hooser et al., 2014). In this paper we used the same base model and made specific modifications to it based on recent findings that call into question some of the
previous assumptions. Briefly, the basic structure of the model is as follows: In the model, an 8x8 matrix of model LGN neurons connect to a single V1 neuron with variable synaptic weights that can change following specified plasticity rules in response to sweeps of visual stimuli simulated by sequential activation of the LGN inputs. The direction selectivity of the cortical neuron was calculated according to a direction selectivity index (DSI) which 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 ($R_{\text{null}}$):

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

The LGN and cortical neurons were modeled as leaky integrate and fire (LIF) neurons (Lapicque 1907; Abbott 1999), which were updated via Euler’s method on the following differential equation at time steps of 1ms:

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

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 $V_{\text{rev}_i}$ is the reversal potential of the current generated by synapse $i$. In these model neurons, voltage changes according to this differential equation until $V_m$ reaches $V_{\text{thresh}}$ at which point
a spike is generated and \( V_m \) is set to \( V_{\text{reset}} \). In addition, we imposed an absolute refractory period of 2ms meaning the model neurons could not fire again until 2ms after the last spike (see Table 1 for values).

Synaptic connections between LIF neurons were modeled according to the following equation (Destexhe et al. 1994):

\[
G_i(t) = \sum_j G_i \left[ \exp\left(-\Delta t_j / \tau_2\right) - \exp\left(-\Delta t_j / \tau_1\right) \right]
\]

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 \( \tau_1 \) is the rising time constant and \( \tau_2 \) the falling time constant.

In order for the model to update the synaptic weights \( G_i \) from trial to trial, spike timing dependent plasticity (STDP) was introduced. Plasticity depended only on spike timing (Bi and Poo 1998; Markram et al. 1997), and we used the equation of Song et al. (2000):

\[
\frac{\Delta G_i}{G_i^{\text{cell}}} = \begin{cases} 
A^+ \exp\left(-\left(t_{\text{post}} - t_{\text{pre}}\right) / \tau^+, t_{\text{post}} - t_{\text{pre}} > 0 \right) \\
A^- \exp\left(\left(t_{\text{post}} - t_{\text{pre}}\right) / \tau^-, t_{\text{post}} - t_{\text{pre}} < 0 \right)
\end{cases}
\]

where \( t_{\text{pre}} \) is the time of a presynaptic spike, \( t_{\text{post}} \) is the time of the postsynaptic spike, \( \tau^+ \) and \( \tau^- \) are the time constants that influence the spike-timing window, \( A^+ \) and \( A^- \) determine the amplitude of the pre before post and post before pre plasticity, respectively, and \( G_i^{\text{cell}} \) is the imposed maximum (or “ceiling”) conductance that
cannot be exceeded (see Table 1). In all simulations the value of $G_{\text{ceil}}$ was the same as the minimum conductance $G_T$ necessary to produce an action potential in the cortical neuron. This was because all starting conditions of simulations had only one active input which therefore required the single input to have a conductance of $G_T$ in order for the initial conditions of the simulation to have spiking activity in both directions, a necessary prerequisite for development based on STDP. The $G_{\text{ceil}}$ and $G_T$ values for the excitatory cell were found by starting with a subthreshold value and gradually increasing it until the cell fired once. $G_{\text{ceil}}$ for connections to excitatory cortical cells was equal to 7nS. The $G_{\text{ceil}}$ and $G_T$ values for the inhibitory cell were found by starting at a subthreshold value and gradually increasing the value until a single input to the inhibitory cell was able to cause sufficient activity in the inhibitory cell in order to prevent a spike in the excitatory cell responding to a single active input. These were the conditions necessary to sufficiently drive down activity in the excitatory cell. $G_{\text{ceil}}$ for connections to inhibitory cortical cells was equal to 5.5nS.

Feed-forward inhibition was added with similar starting input structure as the inputs to the excitatory cell. The same 8x8 matrix of LGN cells also synapsed onto an inhibitory neuron. The inhibitory neuron synapsed onto the excitatory neuron with a fixed conductance of 3nS. The inputs were allowed to be trained according to the same STDP equations in response to simulations of visual stimuli. In order to prevent the inhibitory cell from growing at the same rate or faster than excitation, $\Delta G_i$ for the plasticity of inputs to the inhibitory cell were multiplied by 0.6 for simulations in figures 3 and 4.
Table 1: Parameters for simulations

<table>
<thead>
<tr>
<th>Default model parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leaky integrate and fire neuron</strong></td>
</tr>
<tr>
<td>$\tau_m = 10,\text{ms}$, $A_m = 0.1,\text{mm}^2$, $R_m = 10,\Omega$, $V_e = 75,\text{mV}$, $V_{\text{reset}} = -80,\text{mV}$, $V_{\text{thresh}} = -55,\text{mV}$</td>
</tr>
<tr>
<td><strong>Synapses</strong></td>
</tr>
<tr>
<td>$\tau_1 = 1,\text{ms}$, $\tau_2 = 20,\text{ms}$, $V_{\text{rev}} = 0,\text{mV}$ for excitatory synapses, $V_{\text{rev}} = -80,\text{mV}$ for inhibitory synapses</td>
</tr>
<tr>
<td><strong>Spike timing-dependent plasticity (STDP)</strong></td>
</tr>
<tr>
<td>$A^+ = 0.005$, $A^- = 0.00525$, $\tau^+ = 20,\text{ms}$, $\tau^- = 20,\text{ms}$</td>
</tr>
</tbody>
</table>

Results

A feed-forward model was used to explore possible mechanisms underlying the development of direction selectivity based on the most recent data from live animal recordings. This work refines and modifies a previous model of this process. Some basic aspects of the previous model are preserved here. The previous model and the current model both posit that a matrix of LGN inputs, with each element responding to a different position and different latency, provides feed-forward input to a V1 cortical cell (Figure 7A). All simulations used an 8x8 matrix of LGN inputs, simulating LGN units responding to 8 different positions in space with 8 different response latencies. Visual experience is simulated by modeling LGN responses to sweeping visual bars, either bidirectional or unidirectional, similar to stimuli used to provide visual experience to animals during live recordings (Li et al., 2008). The amount of lag between the visual stimulus hitting adjacent positions was 50ms and the differences in response latency values was also 50ms. Positions with a latency of zero fired immediately in response to a visual stimulus though a baseline latency
could be added to all units without affecting the results of the model. Spike timing
dependent plasticity at the LGN-to-cortex synapses was used to recalculate weights
after each trial of the stimulus. A ceiling was imposed on these LGN-to-cortex
synapses in order to prevent runaway synaptic growth (Van Hooser et al., 2014).

The focus of the model was to address the question of how the circuit could
learn direction selectivity and therefore only included the simplest features needed
to explore a potential mechanism of learning. Simulations of visual stimuli were only
in two directions along a single spatial axis, referred to as upward or downward
motion. Each LGN input represents a set of approximately 5 real LGN cells – with
colinear receptive fields – in the real animal. The pattern of the LGN cells confers the
orientation selectivity of the cortical cell (Chapman et al. 1991; Ferster et al. 1996;
Hubel and Wiesel 1959; Reid and Alonso 1995). Experimental evidence shows that
cortical neurons in adult cat receive input from between 50 and 150 LGN individual
neurons (Banitt et al. 2007; Troyer et al. 1998). Our simulations consisted of a
matrix of 64 LGN units, though only 8 units were allowed to connect to the cortical
cell. Additionally, we did not differentiate the LGN inputs as ON or OFF cells, though
the addition of this distinction to our model would theoretically only serve to double
the number of inputs without substantially affecting the behavior of the model.
Another way we simplified the model was to assume that LGN units responded
reliably and without complex spatial or temporal processing because little is known
about these details in ferrets at eye opening (Akerman et al. 2004; Krug et al. 2001;
Ohshiro and Weliky 2006; Tavazoie and Reid 2000) or how these properties change
during development (Akerman et al. 2004; Saul and Feidler 2002; Tavazoie 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).

Recent experiments that were motivated in part by the previous model indicate that revisions are needed in order to better reflect the circuit that is present in the developing ferret. First, the previous model assumed that the initial LGN inputs to the cortical cell were widespread and weak. However, recent data suggests that the initial inputs to cortical neurons may be very compact. Live animal intracellular recordings from our lab have shown that V1 neurons in naïve animals exhibit responses that are highly localized in spatial position and latency. Both possible initial states in Figure 7A demonstrate alternative possible input structures that agree with these recent findings. These initial input structures allow for unselective initial responses typical of naïve V1 neurons because activity in both directions is driven by the same strong localized input (Figure 7B) (Li et al. 2008).

Second, the model posited that these synaptic connections were very flexible, such that synapses from LGN cells at all positions and response latencies were able to grow in strength (Possible Initial State I, Figure 7A). However, recent experiments that provided artificial experience that was either slow or fast to naïve animals showed that experience could not influence the speed tuning of V1 cells (Ritter et al., 2017). This evidence suggests that the development of the STRF of a V1 neuron is not flexible for different speeds, implying that some LGN inputs are restricted in their growth. In the new model, we now restrict the LGN inputs to a subset of cells that fire at specific positions and specific latencies. This restriction
assures that each V1 cell could only learn to become direction-selective for a predetermined direction, not apparent before visual experience, which is supported by recordings from live animals (Van Hooser et al., 2012; Roy et al., 2016).

Therefore we rejected Possible State I in favor of Possible State II which includes a restriction allowing only those inputs along one diagonal axis to grow (Figure 7A).

The Reichardt detector model of direction selectivity predicts that an input structure slanted in space and time can produce direction-selective responses in an output cell. Figure 7C, where inputs grow along one diagonal axis in space and time, is an example of the input structure predicted by the Reichardt detector model. This allows for the temporal alignment of early position, high latency inputs and later position, low latency inputs and therefore a summation of responses from motion in the preferred direction (Figure 7D). A moving stimulus in the opposite direction, however, will result in separate, independent inputs and little overall response (Figure 7D). Intracellular recordings in primate (De Valois et al., 2000) and cat (McLean and Palmer, 1989) visual cortex have demonstrated that the STRF of direction-selective V1 cells are slanted in space and time. Our lab’s own intracellular recordings in ferret visual cortex have corroborated these results. The input structure in Figure 7C demonstrates a possible organization of LGN units that would produce such a STRF.
Figure 7. Possible structure of circuitry underlying observed direction-selective responses: An excitatory feed-forward model.

A) The model circuit is composed of a matrix of LGN inputs (circles), here 25 cells in a 5x5 configuration. Each row of LGN cells responds to a different position in visual space and each column responds with a different stimulus latency. These LGN cells provide input to a V1 cell (red triangle) with independent synaptic weights. The initial input structures both consist of one strong synapse at G_{cell} (red circle) with all other inputs starting at a connection strength of zero (gray and white circles). One could imagine two potential possibilities for the addition of new synapses to the initial connections. In Possible State I all inputs from any position and latency are able to grow equally well (gray circles). In Possible State II learning is restricted for all inputs (white circles) except for those along one diagonal shown in gray. Previous experiments have found evidence for Possible State II. B) The theoretical response of the output cell at starting conditions to motion in both directions is shown in red as well as the timing of firing of each LGN input (black squares). In both directions there is only one active input (red circle) which is sufficient to drive the output cell to fire once in each direction. C) The possible adult state is shown with all inputs along one diagonal strengthened. D) The theoretical response of the output cell at final conditions to motion in both directions is shown in red as well as the timing of firing of each LGN input (black squares). The slanted input structure results in summation of synchronously active inputs (red circles) in the preferred direction (downward) causing a large response, but results in separate, individual responses in the null direction (upward).
**Feed-forward excitatory input with constrained position and latency preferences is insufficient to produce strong direction selectivity**

As a first pass towards implementing the requirements motivated by our recent experiments, we created a new input structure that aligns with more recent findings. To simulate small, localized inputs we chose to only have one input be active initially (Figure 7A). This represents the most extreme possible localization of inputs, though an organization of more delocalized inputs should behave similarly. Additionally, we added a restriction on which inputs could form synapses to the V1 cell. This restriction was designed such that only inputs along one diagonal axis can grow while all other inputs are unable to increase in synaptic strength (Figure 7A, gray inputs). The design of the restriction was based on predictions of the Reichardt detector model in order to allow for summation of inputs in response to motion on one direction but separate weak responses in the other direction (Figure 7D).

With these revisions, the model was able to develop into the final input structure shown in Figure 8A from starting conditions resembling Possible State II after bidirectional training. All white inputs had a synaptic strength of zero and did not increase because they were completely restricted from growing. All red inputs grew to the synaptic ceiling because they were aligned on the unrestricted diagonal axis (Figure 8A). With this configuration the V1 cell responded as expected in the preferred direction with a summation of inputs causing a large burst of spiking in the V1 cell (Figure 8B).
The model still fails to develop DSI values that agree with data from live animal recordings. There is still a significant amount of activity in the null direction because each input that has developed along the diagonal axis is able to independently cause the V1 cell to spike (Figure 8B). This results in a final DSI value of 0.24 which is not the level of direction selectivity expected in a visually experienced cortical cell (Li et al., 2008; Van Hooser et al., 2012). Furthermore, when one observes responses over the course of the simulation’s development, DSI rises to much higher values, reaching a maximum of 0.86 (Figure 8D), but this value decreases steeply towards the end of the training. This decrease in DSI is the result of increases in null direction responses when the other inputs along the diagonal have increased in synaptic strength to the point that they can independently drive the output cell (Figure 8B, downward direction). The unrestricted inputs grow to such high values because the ceiling imposed on synaptic growth must be large enough to drive spiking in order for the initial conditions to generate responses from just one active input. This increase in null direction activity causes a large decrease in DSI towards the end of training (Figure 8D).
Figure 8. A feed-forward excitatory circuit with strong individual LGN→V1 synaptic weights and possible inputs restricted to specific spatial positions and latencies does not develop strong direction selectivity after bidirectional motion training. 

A) An 8x8 LGN input model that began from Possible Initial State II ended with the input structure shown. Inputs only along the unrestricted diagonal axis were allowed to develop and each one grew to the maximum weight possible. B) The bidirectional response trace of the model in its final state is shown in red. The response time of each LGN input is plotted in black beneath the trace. The inputs highlighted by red circles correspond to strong inputs shown in A. In the upward direction all strongly connected LGN neurons fire simultaneously and result in a burst of activity. In the null direction, the active inputs respond asynchronously and activate the output cell at different times. Because the inputs are so strong, individual inputs drive spiking and therefore there is considerable activity in the null direction. C) Responses in the preferred (red) and null (green) directions are plotted for each trial over the course of training. Just before trial 150, there is a large increase in activity in the null direction as all other inputs have increased sufficiently to be able to independently drive spiking. D) Direction selectivity is plotted for each trial over the course of training. A large decrease in DSI is seen just before trial 150 corresponding with the large increase in null direction spiking observed in C.
Feed-forward excitatory and inhibitory input with constrained position and latency preferences is able to produce strong direction selectivity

We hypothesized that the introduction of an inhibitory interneuron could drive down responses in both directions and therefore increase the DSI of the final state. We added an inhibitory cell receiving input from the same matrix of LGN inputs responding to varying latencies and positions with independently determined weights, also following the same STDP learning rules throughout training. The changes in synaptic weight were multiplied by 0.6 in order to prevent the inhibitory neuron from growing faster than the excitatory cell which could make responses go to zero. Additionally, these inputs have the same restriction applied to them, allowing inputs only along one diagonal to grow. The inhibitory cell then synapses onto the excitatory cell with a constant synaptic weight (Figure 9A). The amount of inhibition onto the excitatory cell depends on how much the LGN inputs drive spiking in the inhibitory cell.

After the addition of inhibition, the final input structure to the excitatory cell develops similarly to the previous trial, with inputs along one diagonal growing while all other inputs are restricted from growth (Figure 9A). The same pattern was replicated in the inputs to the inhibitory cell which were also subjected to a restriction that allowed only inputs along one diagonal to grow. Again, this configuration of inputs caused the V1 cell to respond as expected in the preferred direction with a summation of inputs causing a large burst of spiking in the V1 cell (Figure 9B, red trace, downward motion). A similar burst in activity was also observed in the inhibitory cell which had an analogous input structure (Figure 9B,
blue trace, downward motion). In the null direction, however, the addition of inhibition caused the excitatory cell responds far less (Figure 9B, red trace, upward motion) resulting in a much higher final DSI value of 0.83. At first, excitatory responses in the preferred and null direction grow similarly to the uninhibited model. A similar sharp increase in null direction activity is observed towards the end of training when all unrestricted inputs reach the maximum synaptic value. In subsequent training trials, however, increasing inhibition causes null direction activity to decrease to just one spike in the null direction (Figure 9C, green). This pattern is mirrored in the development of DSI in the excitatory cell, where DSI is gradually increasing for most of the training, decreases sharply when inputs reach their maximum values, and then increases again as inhibition continues to grow. This increase in excitatory DSI occurs concurrently with increases in null direction activity in the inhibitory cell (Figure 9E). The inhibitory cell also develops weak direction selectivity because its inputs are restricted to grow only along a diagonal axis, resulting in a Reichardt detector pattern of inputs (Figure 9F).
Figure 9: Adding feed-forward inhibition to a circuit with strong individual LGN→V1 synaptic weights and possible inputs restricted to specific spatial positions and latencies develops strong direction selectivity after bidirectional motion training that matches that predicted by the unrestricted spatial positions and latencies.

A) A feed-forward inhibitory interneuron has been added to the circuit (blue triangle). The final input structure, after training, is shown in the matrix of LGN cells. Inputs only along the unrestricted inputs grew and each one grew to the maximum weight possible. The final structure of inputs to the excitatory and inhibitory cells are the same. B) The bidirectional responses of the model in its final state are shown. The membrane voltage trace of the excitatory output cell is shown in red and the trace of the inhibitory cell is shown in blue. The response time of each LGN input is shown in black beneath the traces. The inputs for both the excitatory and inhibitory cells summate synchronously in the downward direction (red circles), but are asynchronous and dispersed in the upward direction. The inhibitory responses to single inputs provide sufficient inhibition to prevent most spiking in the excitatory cell’s response to the upward direction. C) The excitatory output cell responses in the upward and downward directions are plotted for each trial. Again we see an increase in null direction spiking around trial 150 as inputs to the excitatory cell become strong enough to drive individual spiking. In subsequent trials, however, inhibitory responses increase and drive null direction spiking down again. D) DSI of the excitatory output cell is plotted for each trial based on spiking responses in the preferred and null directions. Direction selectivity gradually rises until null direction spiking increases around trial 150, where DSI rapidly decreases. Inhibition of null direction responses increases DSI in subsequent trials. E) Inhibitory spiking responses in the preferred and null directions are plotted per trial. Null direction inhibition does not increase until after trial 150 F) DSI of the inhibitory cell is plotted for each trial based on spiking responses in the preferred and null directions.
Unidirectional training simulations only induce the development of direction selectivity when stimulus direction matches prediction of restriction.

Unidirectional visual training in live animal recordings has had different results from bidirectional training, giving some information about the mechanism underlying the development of direction selectivity. Van Hooser et al (2012) demonstrated that in cells with a low DSI before training, some cells develop strong direction selectivity, but some remain unselective.

We simulated unidirectional training for two situations: one in which the restriction only allowed growth along the diagonal axis matching the training direction, and one in which they did not match. When the training stimulus direction matched the direction predicted by the restriction, development followed the same course as during bidirectional training. The final input structure reached the same values as bidirectional training simulations (Figure 10a). Additionally, responses in the preferred and null direction developed as during bidirectional training (Figure 10b). This resulted in the development of strong direction selectivity in the response to unidirectional training.

Next, we used the same unidirectional training stimulus, but the restriction only allowed growth of cells along the other diagonal axis. Therefore, the direction predicted by the restriction was opposite the training direction. If direction selectivity did develop in this simulation, we expected it to have a negative value, meaning selectivity increases for the opposite direction as the previous trial. After the same amount of training, the final input structure had not developed at all. All inputs remained at their initial values (Figure 10c). Additionally, responses to
either direction did not change throughout the simulation and DSI did not change (Figure 10d). These results agree with the findings of Van Hooser et al (2012) as we only focused our simulations on unidirectional training of initially unselective cells.

Figure 10: Simulations of unidirectional training only induce the development of direction selectivity if the directionality of the training stimulus matches the direction predicted by the restriction.

A) First we simulated unidirectional training that matches the direction predicted by the restriction. The initial and final input structures to the excitatory cell are shown. The initial input structure again started with only one active LGN input shown in red. Only inputs shaded in gray were unrestricted from growth. The direction preference predicted by these unrestricted inputs matches the training stimulus direction, and therefore all inputs along the diagonal axis grow to their maximum synaptic weight after training. The input structure to the inhibitory neuron mirrors this same pattern of development. B) The spiking responses of the excitatory cell are plotted. A similar pattern of development is seen as bidirectional training. DSI development also matches the course of development during bidirectional training. C) The same stimulus direction was used for the next simulation but the restriction was changed to only allow the development of the other diagonal axis. The initial input structure is the same as the previous simulation, just the restriction predicts the opposite direction. The same amount of unidirectional visual training results in no development of the initial input structure. The input structure to the inhibitory neuron mirrors this same pattern of development. D) The spiking responses and direction selectivity index values throughout development are plotted. Spiking responses do not change throughout development because the input structure remains unchanged. DSI remains zero as well.
Discussion

Here we updated a model of the development of direction selectivity based on recent experimental data which called for the initial inputs to be redesigned and for the addition of a restriction on which inputs could grow, allowing only inputs along one diagonal axis of the matrix of possible LGN inputs to grow. The addition of these two revisions to the model were insufficient to produce DSI values that are observed in V1 neurons of mature animals, so feed-forward inhibition was added to sharpen direction selectivity tuning. This inhibitory interneuron also received input from the same matrix of LGN inputs at varying position and responses latencies, though the synaptic weights to the inhibitory cell were allowed to grow independently from all feed-forward connections to the excitatory cell. The inhibitory cell also had the same restriction imposed on its inputs resulting in a similar final input structure for both the inhibitory and excitatory cells as well as weak direction tuning in the inhibitory responses. The addition of the feed-forward inhibition resulted in the development of sharp direction tuning in the excitatory cortical cell from a non-selective starting state that now aligns with the most recent findings on the development on direction selectivity.

Feed-Forward Inhibition that is tuned for direction

The previous model also incorporated an inhibitory interneuron though it was designed differently. The inhibitory paradigm in the previous model was based on a method of inhibitory plasticity called postsynaptic activity-dependent long-term potentiation of inhibition (POSD-LTPi) (Garkun and Maffei 2014). It was
modeled as exponentially increasing synaptic weight at the inhibitory synapse to the excitatory neuron with constant spiking activity in the inhibitory cell. It received input from all LGN cells and was therefore untuned. That is, it provided equal inhibition in both the preferred and null directions.

The broad inhibitory paradigm was rejected due to new experimental evidence showing that inhibitory input to excitatory cells is tuned for direction selectivity. Specifically, intracellular recordings of direction-selective cortical cells showed that inhibitory input to mature cells had a slanted STRF. These receptive fields matched the ones for excitatory input to the same cells meaning excitatory input and inhibitory input to the direction-selective cell have the same direction tuning (Priebe and Ferster, 2005). Additionally, a recently published paper imaged inhibitory cells in ferret V1 and found that inhibitory cells exhibited robust direction tuning. The inhibitory neurons were also found to be less direction-selective than nearby excitatory neurons (Wilson et al., 2017). The inhibitory cell proposed in the model also has direction-selective responses that are smaller in magnitude than the excitatory cortical cell, agreeing with these recent findings.

Elongation of Spatiotemporal Receptive Field During Learning

From our lab’s intracellular recordings of V1 cells, the STRF of naïve and mature cells were calculated. It was these recordings that altered our proposed initial input structure for a naïve cell. Recent analyses of the STRFs has shown that they become elongated and larger in space time. These findings agree with the STRF development of the cortical output cell in our model. Specifically, the analysis found
the STRFs grow such that response latencies at some positions are earlier in time. Our model of development allowed equal growth of both early and later inputs, meaning the STRF would elongate in both directions equally. A future improvement of the model could alter the learning mechanism in order to prefer growth of early inputs.

Convergence of Inputs from LGN

Our model assumes the basis of direction selectivity is the convergence of patterned inputs from the thalamus, specifically from the LGN. There is substantial evidence that the LGN contains excitatory neurons responding to different positions and latencies (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 neurons in carnivore species have classified LGN cells into two types based on response latency of the cell. The majority of cells are nonlagged, with latencies of less than 100ms but another group of lagged cells exist with response latencies greater than 100ms. It has been suggested that inputs from both classes could be the basis for a large range of direction selectivity in the cortex (Saul and Humphrey 1990; Wolfe and Palmer 1998), though the range of latencies within even the nonlagged group (40ms) could be enough to be the basis of direction selectivity (Feidler et al., 1997, Van Hooser et al., 2014).

Though there is evidence that LGN cells exist in accordance with the assumptions of the model, it is still unknown if these LGN cells connect with cortical cells in V1 in the same pattern as is proposed in the model. In a visually naïve
animal, cortical neurons respond with robust orientation selectivity (Chapman and Stryker 1993; Li et al. 2006) which suggests that cortical cells receive input from a set of LGN cells that respond to parts of an elongated spatial region. Little is known about the range of temporal latencies of LGN inputs to cortical cells.

Predictions based on the model

The revisions made to the previous model have introduced new predictions that could be tested to further lend support to this hypothesis as part of the mechanism underlying the development of direction selectivity. Though it has recently been shown that direction tuned inhibitory cells do exist in ferret V1, the direction tuning of these cells before visual experience is still unknown. This model predicts that inhibitory cells should also be unselective for direction before visual experience. Additionally, it predicts that direction tuned inhibitory cells should have the same direction tuning as the cortical cells it synapses on to.

The introduction of the restriction on which inputs can grow suggests that the role of visual experience on the development of direction selectivity is permissive rather than instructive. This proposes that exposure to visual stimuli allows for the development direction selectivity, but the properties of the direction stimulus does not necessarily instruct the cell how to become direction-selective. This notion is supported by Ritter et al. (2017) who found that the speed tuning of V1 cells in ferrets was not significantly different between two groups trained with different stimulus speeds. Additionally, Roy et al. (2016) found that unpatterned direct optogenetic stimulation of naïve ferret visual cortex was sufficient to produce
an increase in direction selectivity which also supports the permissive theory of learning. The restriction used in the model represents one possible mechanism for how visual experience could permit the development of direction selectivity without serving an instructive role. The restriction we implemented would predict that if ferrets were trained with a scrambled motion stimulus instead of smooth motion, the cells would still become selective for smooth motion as opposed to becoming selective for the scrambled motion.
References


Erisir, A. and J. L. Harris (2003). "Decline of the critical period of visual plasticity is concurrent with the reduction of NR2B subunit of the synaptic NMDA receptor in layer 4." J Neurosci 23(12): 5208-5218.


Hubel, D. H. and T. N. Wiesel (1962). "Receptive fields, binocular interaction and

Very Young, Visually Inexperienced Kittens." J Neurophysiol 26: 994-1002.

in Two Nonstriate Visual Areas (18 and 19) of the Cat." J Neurophysiol 28: 229-
289.

Hubel, D. H. and T. N. Wiesel (1968). "Receptive fields and functional architecture of

Humphrey AL, Saul AB. (1995). "Strobe rearing alters the spatiotemporal structure

Krug, K., et al. (2001). "Responses of neurons in neonatal cortex and thalamus to
patterned visual stimulation through the naturally closed lids." J Neurophysiol

631-644.


Li, Y., et al. (2008). "Experience with moving visual stimuli drives the early

threshold accounts for cortical direction selectivity." Proc Natl Acad Sci U S A
88(9): 3549-3553.

Markram, H., et al. (1997). "Regulation of synaptic efficacy by coincidence of


field structure to velocity selectivity of simple cells in area 17 of cat." Vision Res


