Is the Development of Orientation Selectivity Instructed by Activity?

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Summary

Is the development of orientation selectivity in visual cortex instructed by the patterns of neural activity of input neurons? We review evidence as to the role of activity, review models of activity-instructed development, and discuss how these models can be tested. The models can explain the normal development of simple cells with binocularly matched orientation preferences, the effects of monocular deprivation and reverse suture on the orientation map, and the development of a full intracortical circuit sufficient to explain mature response properties including the contrast-invariance of orientation tuning. Existing experiments are consistent with the models, in that (1) selective blockade of ON-center ganglion cells, which will degrade or eliminate the information predicted to drive development of orientation selectivity, in fact prevents development of orientation selectivity; and (2) the spontaneous activities of inputs serving the two eyes are correlated in the lateral geniculate nucleus at appropriate developmental times, as was predicted to be required to achieve binocular matching of preferred orientations. However, definitive tests remain to be done to (1) firmly establish the instructive rather than simply permissive role of activity and (2) determine whether the retinotopically- and center-type-specific patterns of activity predicted by the models actually exist. We conclude by critically examining alternative scenarios for the development of orientation selectivity and maps, including the idea that maps are genetically pre-specified.

Keywords: Simple cells, orientation maps, LGN spontaneous activity, visual cortex, Hebbian synaptic plasticity

Introduction

Ocular dominance and orientation selectivity are two of the most striking response properties found in primary visual cortex. Their development provides a key set of test problems for understanding the principles underlying development of cortical responses.

Patterns of neural activity are widely regarded as instructing the development of ocular dominance segregation (Katz and Shatz, 1996), as manipulations of subcortical firing can profoundly alter segregation outcomes. Blockade of retinal activity during the time that segregation normally develops prevents segregation (Stryker and Harris, 1986). Imposition of artificial patterns of neural activities in the optic nerves or tracts yields either no segregation, or segregation, depending on whether the activities of the two eyes' axons are synchronous or asynchronous, respectively (Stryker and Strickland, 1984).

The role of activity in the development of orientation selectivity, which develops 1-2 weeks earlier than ocular dominance, remains more controversial. In this article, we discuss how the hypothesis of activity-instructed development of orientation selectivity can be tested. We begin by briefly reviewing existing evidence as to the role of activity. We then review how models propose that activity-instructed development of orientation selectivity can occur. Finally, we consider alternative scenarios for development of orientation selectivity and maps, and critically examine experiments that seek to determine whether maps are genetically "pre-specified". We begin by focusing on development of simple cells in cat layer 4, but will also address development in other systems.

What Do We Know About the Role of Activity in the Development of Orientation Selectivity?

In cats, some orientation selective cells are observed in deep layers as early as recording is possible, around P6 (postnatal day 6) (Tsumoto and Suda, 1982; Albus and Wolf, 1984; Braastad and Heggelund, 1985; earlier work reviewed in Movshon and Van Sluyters, 1981; Fregnac and Imbert, 1984). Binocularly matched orientation maps are observable in optical recordings by P12 (Crair, Gillespie and Stryker, 1997), roughly as soon as the upper layers (those observed in optical recordings) receive synaptic input from layer 4 (Callaway and Katz, 1992). Thus, it is unclear precisely when the major development of orientation selectivity and an organized orientation map begins, but it is well underway by P12. Orientation selectivity continues to increase over the ensuing weeks. This development appears to be largely independent of the presence or absence of visual experience until after P18 (Fregnac and Imbert, 1984; Crair, Gillespie and Stryker, 1997), except perhaps for an overall delay of a few days caused by absence of visual experience (Fregnac, 1979). Thus, any activity-instructed explanation of the initial development of orientation selectivity must rely on the

spontaneous patterns of neural activity that occur in the absence of vision. It has thus far not been possible to measure or interfere with this spontaneous activity in cats at these young ages. The same problem applies in monkeys, which are born with well-developed orientation selectivity (Wiesel and Hubel, 1974). Note that the lack of a role of visual experience in the initial development of orientation selectivity means that the many experiments examining whether orientation preferences can be modified by later visual experience (reviewed in Movshon and Van Sluyters, 1981; Fregnac and Imbert, 1984) do not bear on the role of activity in *establishing* orientation selectivity.

The role of activity in development of orientation selectivity has been better studied in ferrets, which are born at an earlier stage in cortical development. The normal development of orientation selectivity was charted by Chapman and Stryker (1993). Visual cortical responses can first be recorded at P23. At this time, about 25% of cells in all layers show some orientation selectivity, although it is not clear whether this represents the beginning of the mature organization of orientation selectivity or simply random biases that become rearranged when orientation maps develop. This state does not change until the period P30-P35, when a dramatic development of orientation selectivity occurs in layers 2/3, with 90% of cells becoming orientation selective over the ensuing week. The following week a similar development occurs in layers 5/6. Only 40% of the cells in layer 4 ever become orientation selective (this differs from cat, in which most layer 4 cells become orientation selective, and in which the first development of orientation selectivity has been reported to occur in layers 4 and 6: Albus and Wolf, 1984; Braastad and Heggelund, 1985; but see Tsumoto and Suda, 1982). Orientation maps as assessed by optical imaging are visible a few days after the increase in orientation selectivity begins in layers 2/3, and their development does not seem to depend on the presence of visual experience (Chapman et al., 1996). Chapman and Stryker (1993) showed that blocking all activity in cortex with TTX prevents the development of orientation selectivity beyond the initial state observed at P23, demonstrating that activity plays at least a permissive role in this development. More recently, Gödecke and Chapman (1998) demonstrated that blocking the visual responses of ON-center retinal ganglion cells with APB, leaving OFF responses intact, also prevents development of orientation selectivity beyond the initial state observed at P23. This experiment provides the strongest evidence to date that activity is instructive, rather than simply permissive, for the development of orientation selectivity. We further discuss this experiment below.

Weliky and Katz (1997) also disrupted the normal pattern of input activity in ferrets during the period of development of orientation selectivity. Through stimulation of the optic nerve, they ensured that all inputs fired synchronously for 1.8 seconds out of each 20 seconds; however, during much of the remaining 90% of the time input activity was presumably normal. The result was a great diminution, but not elimination of orientation selectivity,

and formation of very weak but normally structured orientation maps. While this suggests an important role for normal input activity patterns in the development of orientation selectivity, it cannot decide the issue of whether activity instructs that development: aspects of both normal activity and normal organization survived, and we do not know whether eliminating the former would eliminate the latter.

Correlation-Based Models of Cortical Development

Models of the development of orientation selectivity typically involve three basic components, which appear more generally to be required for an explanation of cortical columnar development by activity-instructed processes (von der Malsburg, 1973; Miller et al., 1989; reviewed in Miller 1990, 1996a, 1996b):

1. There appears to be some rule of synaptic development by which "neurons that fire together, wire together". That is, neurons that fire in a correlated way tend to innervate common postsynaptic cells. Such a "correlation-based rule" can be instantiated by a variety of underlying mechanisms, including Hebbian LTP/LTD, activity-dependent release and uptake of diffusible modification or trophic factors, or synaptic sprouting and retraction with correlation-based synaptic stabilization (Miller, 1998).

2. The rule underlying biological development also appears to be *competitive*: in the end, only one group of co-firing neurons will wire onto a given postsynaptic cell, while other such groups are eliminated (Guillery, 1972; Miller, 1996b). Some mechanisms that could underly such a competition have recently been discovered (Colman et al., 1997; Davis and Goodman, 1998; Turrigiano et al., 1998).

3. To account for periodic columnar organization, *e.g.* as observed for ocular dominance, there must be some influence that leads nearby neurons to tend to develop correlated patterns of inputs, and that leads neuron pairs with larger tangential separations (*e.g.* 300-400 microns) to develop un- or anti-correlated patterns of inputs.

   - The linking of nearby neurons can arise through the lateral diffusion of trophic factors whose release and uptake are activity-dependent, or through the synaptic influences of lateral excitatory connections.
   - The unlinking of more widely separated neurons can be achieved either by assuming that each afferent with a given mean activity will support a roughly equal amount of synaptic strength onto postsynaptic neurons (so that increasing an afferent's synaptic projection onto some cortical cells requires its withdrawal from other cortical cells), or else by assuming that a net inhibitory trophic or synaptic influence exists between more widely separated locations.

We can call a model embracing these elements a "correlation-based model". Note that this definition is very general and embraces a wide variety of models often thought of as competing. For example, the BCM model (Bienenstock et al., 1982) fits the above definition. It is distinct in focusing on a particular means of achieving competition and on a particular form of the correlation-based plasticity rule.

Our work has focused on very simple versions of correlation-based models. We see the major task of such models as being to understand the basic developmental outcomes that correlation-based mechanisms can achieve, and to understand the biological conditions required to achieve these outcomes. Furthermore, it is important to focus on outcomes that are robust in the sense that they do not depend greatly on the many biological details of which we are ignorant; while this is difficult to establish definitively, one gains confidence if the modeling reveals a simple qualitative explanation of an outcome that does not depend on model details. For these purposes, we believe the simplest correlation-based models have thus far been the most powerful. However, in some particular cases, more complex correlation-based models using nonlinearities in cortical activation or interaction have demonstrated interesting modifications in outcome relative to the simpler models we study (Goodhill, 1993; Feidler et al., 1997; Piepenbrock and Obermayer, 1999).

Modeling Development of Simple Cells in Cat Layer 4

The vast majority of cells in cat layer 4 are orientation-selective simple cells (Gilbert, 1977; Bullier and Henry, 1979). By simple cells, we mean cells with receptive fields composed of one or more spatially segregated, elongated, aligned subregions, each giving exclusively ON (response to light onset/dark offset) or exclusively OFF (response to light offset/dark onset) excitatory input (Hubel and Wiesel, 1962). As originally proposed by Hubel and Wiesel (1962), spatial segregation of the ON-center and OFF-center LGN inputs received by a simple cell underlies its spatial receptive field structure (Tanaka, 1983; Ferster, 1988; Reid and Alonso, 1995; Hirsch et al., 1998).

Any explanation of the development of simple cell response properties must include an explanation of the segregation of the ON and OFF afferent inputs received by a simple cell. We have proposed a simple activity-instructed, correlation-based explanation for this segregation that also accounts for the development of orientation selectivity organized in continuous maps (Miller, 1994). The key element required is a specific pattern of correlated spontaneous activity among the inputs (Figure 1) that leads to development of this ON/OFF segregation. This pattern is simple: at small retinotopic separations, two like-center-type inputs (both ON-center, or both OFF-center) should tend to be more coactive than two opposite-center-type inputs; but this relationship should reverse at larger retinotopic separations, so that two opposite-center-type inputs at such a separation should tend to be more

coactive than two like-center-type inputs. Selection of a "most-correlated" or most-coactive set of inputs to a cell then yields ON/OFF segregation and a simple-cell receptive field (Figure 1). Note that no orientation bias is needed in these activity patterns: the patterns may be circularly symmetric, yet the drive toward ON/OFF segregation that they create can lead the ON and OFF subregions to "choose" a direction across the receptive field and thus endow the cell with orientation selectivity. The possibility of such "spontaneous symmetry breaking" in receptive field formation was first noted by Linsker (1986).

The key experimental tests of this model are (1) that such a pattern of correlated spontaneous activity should be observed in LGN at appropriate developmental times and (2) that disruption of the instructive pattern of correlated activity should disrupt or prevent the development of orientation selectivity. The first experiment has not yet been undertaken (although Meister et al. (1995) observed such a pattern of spontaneous activity in salamander retina, consistent with the idea, discussed in Miller (1994), that such a pattern of spontaneous activity can arise naturally from the circuitry that induces retinal and/or LGN center-surround receptive field structure). As discussed above, the second experiment was recently carried out in ferrets by Gödecke and Chapman (1998), who infused APB into both retinae to selectively block the activity of ON-center retinal ganglion cells. They showed specificity of the block through recordings in LGN: OFF-responses (responses to dark flashes) were normal, while ON-responses (responses to light flashes) were absent. The result was as predicted by the model: orientation-selective cells and optically-observable orientation maps did not develop. However, there are problems with the result. If the APB infusion was initiated sufficiently early in development, the result was an unresponsive cortex, rather than a cortex that responds to OFF stimuli as might be expected. This raises the possibility of nonspecific effects, although later initiation of infusion also prevented development of orientation selectivity without causing the cortex to become unresponsive.

The choice of species raises an additional problem, because only 40% of cells in ferret layer 4 become orientation selective (Chapman and Stryker, 1993). Moreover, studies have not yet been done to determine whether these orientation-selective ferret layer 4 cells are simple cells, *i.e.* show ON/OFF subfield segregation. Thus, it is not yet clear whether development of simple cells – the scenario our model explains – plays a significant role in the development of orientation selectivity in this species. If it does, the development of these cells might be accounted for by one parameter regime of our model (Miller, 1994, Figure 11), in which only a minority of layer 4 cells develop ON/OFF input segregation and orientation selectivity. In this parameter regime, strong spatial segregation of ON and OFF afferents into ON and OFF cortical patches also occurs, as is observed in ferrets (Zahs and Stryker, 1988). The model predicts that, in this regime, the orientation-selective simple cells will lie along the borders between cortical ON-patches and OFF-patches. It would be very interesting to determine if

such spatial organization of orientation-selective simple cells exists in ferret layer 4.

Modeling the Development of Binocular Matching of Orientation Preferences

Binocularly matched orientation maps are visible in kittens by P12, and their development does not depend on visual experience (Crair, Gillespie and Stryker, 1997). How can binocular matching arise through an activity-instructed process in the absence of vision?

The obvious answer is that correlations must be induced in the LGN between the spontaneous activities of the two eyes. Furthermore we have predicted that these between-eye correlations should be locally specific for center type (Figure 2). This causes interocular correlations to be maximized by interocular alignment of ON- and OFF subregions, and this in turn yields alignment of preferred orientations (Erwin and Miller, 1996b, 1998). The presence of interocular correlations in spontaneous LGN activity has recently been confirmed in ferrets during the week before the major development of orientation selectivity (Weliky and Katz, 1999). These correlations were shown to be dependent on, and presumably are induced by, corticogeniculate feedback. On average, no center-type specificity was seen in these correlations, but the retinotopic location of cells was not determined; hence it remains possible that a retinotopically localized signal might exist. Thus, a direct test of our proposal must await future experiments.

One indirect test already exists, however. If interocular orientation preferences become matched through interocular alignment of ON and OFF subregions, this subregion alignment should persist in adults. As a result, most binocular cells in adults should be tuned for zero disparity, as is indeed reported experimentally in cats (Fischer and Krüger, 1979; Ferster, 1981; LeVay and Voigt, 1988). Most cells tuned for non-zero disparities in cats are monocular, receiving primarily inhibition from the non-dominant eye. These results would not be expected if ON and OFF subregions were located independently in the two eyes' receptive fields in binocular cells.

Alternatively, activity-instructed interocular matching of preferred orientations could conceivably arise based simply on the elongation of receptive fields along the preferred orientation. If such elongation arises in each eye's receptive field, then retinotopically localized correlations between the eyes that do not distinguish between center types could be sufficient to favor alignment of the two elongated receptive fields (so as to maximize interocular correlations). If the direction of elongation corresponds to (or has a fixed relationship to) the direction of preferred orientation, this in turn would align the preferred orientations of the two eyes. However, this explanation seems far less robust, as not all simple cell receptive fields show elongation along the preferred orientation (*e.g.* Mullikan et al., 1984).

Gödecke and Bonhoeffer (1996) showed that interocular similarity of orientation maps could be maintained even after monocular deprivation of one eye sufficient to largely (but not entirely: Crair, Ruthazer, Gillespie and Stryker (1997)) eliminate orientation maps of that eye, followed by reverse suture (opening of the previously closed eye, closing of the previously open eye) to allow redevelopment of that eye's map. The map that reappeared for the newly opened eye, after reverse suture, showed 75-90% correlation with the map that had been observed for the originally open eye after the initial deprivation, even though the two eyes lacked common visual experience. How can this be explained under a correlation-based developmental hypothesis? The key observation is that ocularly well-correlated maps exist, in the absence of visual experience, well before monocular deprivation has any effect on development (Crair, Gillespie and Stryker, 1997). Thus, the main question posed for the correlation-based hypothesis is how much synaptic loss through monocular deprivation can be tolerated without losing "memory" of the initially existing map; if sufficient "memory" is retained, the originally deprived eye, after reverse suture, will evolve back toward a map similar to that which existed before the initial deprivation.

We have found in simple models (Erwin and Miller, 1996a, 1999) that, even if orientation maps develop strictly through plasticity of geniculocortical connections (with no information stored in the intracortical connections), 80-90% of geniculocortical synaptic strength must be lost during deprivation before the deprived eye's map will fail to evolve, after reverse suture, to a map well correlated with that observed in the initially open eye (Figure 3b). Thus, the experimental observations of Gödecke and Bonhoeffer (1996) are natural outcomes of the hypothesis of correlation-based development of orientation selectivity. Interestingly, this result does not require that perfectly matching or even well-developed maps exist before the onset of deprivation. So long as the initial maps are sufficiently developed – a condition that can include very weak and noisy maps that show interocular correlation of only 70% – their fate under activity-instructed development is *dynamically determined* (Figure 3a). By this we mean the following: if, beginning from these weak and partially correlated maps, the two eyes' maps thereafter develop *completely independently* – the two eyes' maps no longer influence one another's development – then, in the absence of deprivation, the two eyes' maps will nonetheless converge upon the same final map, yielding high (95%) interocular map correlation (Erwin and Miller, 1998). If, beginning from the same initial state of weak maps with 70% correlation, we instead subject the eyes to monocular deprivation and reverse suture – again, with completely independent development of the two eyes' maps during these procedures – we find that the same dynamical fate determination can still yield an increase in interocular map correlation (Figure 3b). That is, the correlation between the map in the originally open eye and that in the subsequently opened eye can significantly exceed the original 70%. The initially deprived eye, even after drastic loss of synaptic strength in the

initial deprivation, develops after reverse suture along a trajectory very similar to that on which it was initially bound. That initial trajectory would have led to a nearly perfect match to the map in the initially open eye.

Development of Local Intracortical Circuitry Supporting Contrast-Invariant Orientation Tuning

The models discussed thus far deal only with development of geniculocortical connections amidst fixed intracortical circuitry. Can a correlation-based account be given of the co-development of geniculocortical and intracortical circuitry? We have recently shown (Troyer et al., 1998) that a mature circuit that we describe as "correlation-based intracortical circuitry" – excitatory connections between cells with well-correlated thalamocortical inputs, inhibitory connections between cells with well-anticorrelated thalamocortical inputs (Figure 4, top) – can, along with the aligned, segregated ON- and OFF-center thalamocortical input received by simple cells, account for the basic mature response properties of layer 4 cells, including the contrast-invariance of orientation tuning. In addition, this scheme is consistent with, and motivated by, extracellular and intracellular data (Palmer and Davis, 1981; Ferster, 1988; Hirsch et al., 1998) showing a "push-pull" organization of cortical connectivity: intracortical inhibition arises with opposite polarity to intracortical excitation (*e.g.*, a simple cell with an ON-subregion in a given visual field location would receive excitation from other cells with ON-subregions in the same location and inhibition from cells with OFF-subregions in that location).

The model of Troyer et al. (1998) did not discuss development of this model circuit. More recently, however, we have shown (Kayser and Miller, 1998) that this entire layer 4 circuit – the aligned, segregated ON- and OFF-center thalamocortical input to a simple cell, and the "correlation-based" intracortical connectivity between cortical cells – can codevelop through activity-instructed, correlation-based development (Figure 4, bottom), where we have extended the correlation-based plasticity rules to include plasticity of inhibitory synapses as in Komatsu (1996) as well as of excitatory synapses. As before, the main assumption needed is simply that the correlation structure of spontaneous activity in LGN must be as indicated in Figure 1. Given this LGN activity structure, along with biologically plausible constraints (details to be discussed elsewhere), the codevelopment of both intracortical and thalamocortical connectivity follows. Thus, the hypothesis of correlation-based development can potentially account for codevelopment of the complete, functional layer 4 circuit. Again, the major test of the developmental model is the existence of the postulated LGN correlation structure and the disruption of normal development if the information in this structure is eliminated; in addition, the mature circuit model has a number of independent tests (Troyer

et al., 1998).

The Development of Orientation Selectivity in Different Species: Alternative Scenarios

To the best of our knowledge, only two species have thus far been shown to have strong orientation selectivity in a large majority of the cells in the thalamic-recipient portion of layer 4: cat (Gilbert, 1977; Bullier and Henry, 1979) and galago (a nocturnal primate, also known as bush baby) (DeBruyn et al., 1993). It was not clear from the latter study whether or not most galago layer 4 cells are simple cells. In several other species, strongly orientation-selective cells constitute a minority (monkeys, Blasdel and Fitzpatrick (1984), Hawken and Parker (1984); ferret, Chapman and Stryker (1993)) or bare majority (tree shrew, Humphrey and Norton (1980)) of thalamic-recipient cells in layer 4.

In the model scenario outlined above, orientation selectivity develops as part of a process of segregation of ON and OFF subregions within the receptive fields of simple cells. This is based most obviously on the physiology of the cat. If the oriented cells in layer 4 of other species are simple cells, the same scenario might also apply to them (see discussion above, for the case of ferret, of the possible applicability of this scenario to cases in which only a minority of layer 4 cells are orientation selective). In addition, or alternatively, if non-oriented cells in layer 4 are ON and OFF cells, the same scenario might apply to formation of simple cells in upper layers based on segregation of ON and OFF inputs from layer 4. Another structure to which this scenario might apply is the avian Wulst, where ON- and OFF-center inputs also project to simple cells (Pettigrew, 1979).

What are alternative scenarios for development of orientation selectivity? One set of alternatives retains the idea that orientation selectivity arises through activity-instructed competition among inputs, but considers different patterns of activity than we postulated above. One possibility is that competition might occur among a wider variety of afferent types, yielding more complicated receptive field structures. For example, the monkey parvocellular system is color-selective, and so has multiple competing LGN input types – red-center/green-surround and green-center/red-surround of both ON- and OFF-center types, and similarly for blue-yellow cells (Derrington et al., 1984). A competition between these multiple input types is likely to lead to different outcomes than one between just the two types, ON-center and OFF-center. There are few orientation-selective cells in the parvocellular portion of layer 4 (Blasdel and Fitzpatrick, 1984; Hawken and Parker, 1984), but other chromatic preferences emerge there (Lennie et al., 1990), perhaps through competition among the LGN inputs. It is conceivable that competition among these diverse layer 4 inputs to upper layer cells could in turn yield orientation selectivity in upper layers. Similar con-

siderations apply to dichromat species (lacking blue-yellow cells), *e.g.* tree shrew and galago. It will be of great interest to determine the activity patterns among the various input types, which could serve as a basis for models that might account for the development of cortical receptive field structures in color-selective visual systems.

A related possibility is that orientation selectivity might be driven by patterns of input activity involving oriented or edge-like shapes. Much interest has focused on "waves" of spontaneous activity that occur in retina during the month preceding the development of orientation selectivity (Wong, 1999). We have argued elsewhere (Miller, 1994; Erwin and Miller, 1998) that these waves probably are not involved in the development of orientation selectivity, for three reasons. First, they disappear just before or about the time of the onset of orientation selectivity (between P0 and P7 in cats, between P23 and P30 in ferrets); second, they are wide compared to a receptive field width, and so would seem likely to correlate all inputs to a cell rather than to carve out an oriented subset of inputs; and third, their structure provides no explanation for ON/OFF segregation within simple cell receptive fields.

In spite of these problems, one might imagine that the waves could lead to an overall elongation of the receptive field, and that simple cell ON/OFF substructure would segregate later by a different mechanism. This scenario, or any scenario involving simple cells in which specification of preferred orientation via receptive field elongation precedes ON/OFF segregation, carries an additional problem: if ON and OFF stripes are carved out of an already-elongated, mixed ON/OFF receptive field, typical self-organizing mechanisms would lead the ON and OFF stripes to run parallel to the *short* axis of the elongated receptive field (because development of adjacent, segregated ON/OFF subregions within a receptive field suggests that there is a retinotopic separation at which interactions (*e.g.* correlations) between a pair of cells of opposite center-type are more favorable than those between a pair of the same center-type; and because running parallel to the short axis maximizes interactions between ON and OFF, and minimizes interactions between ON and ON or between OFF and OFF, at this separation). In fact, the ON and OFF stripes tend to run parallel to the long axis (*e.g.* Jones and Palmer, 1987; though exceptions exist, *e.g.* Mullikan et al., 1984). This seems more compatible with an explanation in which ON/OFF segregation arises first, determining preferred orientation; and elongation either arises through the development and lengthening of ON and OFF subregions, or arises subsequently – perhaps induced by intracortical circuitry (see below) and/or by visually-driven patterns of input activity.

Alternatively, orientation selectivity might develop by a fundamentally different mechanism. A prominently discussed candidate mechanism involves instruction from the pattern of long-range horizontal intracortical connections in layers 2/3, in systems in which the organization of orientation selectivity first arises in those layers (assuming such systems ex-

ist). In adults, these connections tend to connect regions of similar orientation preference (Malach et al., 1993; Weliky et al., 1995), and they are known in some species to show a greater retinotopic extension from a given site in directions corresponding to the preferred orientation at that site (Bosking et al., 1997; Schmidt et al., 1997). This raises the idea that initial retinotopic biases in these connections might instruct cells to become orientation selective. However, these connections show little obvious anisotropy and only very weak clustering at the time that orientation maps first emerge (Callaway and Katz, 1990; Durack and Katz, 1996; Ruthazer and Stryker, 1996), and they become functional in parallel with, rather than prior to, the emergence of orientation selectivity (Nelson and Katz, 1995). It will be of interest to document the degree of bias that exists when orientation selectivity develops in various species, and to theoretically explore whether scenarios exist in which this could suffice to instruct or seed development of orientation selectivity.

Determination of Map Structure

The question whether activity instructs the development of orientation selectivity is separable from the question of how, if orientation selectivity does form, the map of preferred orientations is determined.

In all correlation-based models, patterns of intracortical connections or lateral diffusible influences play an important role in shaping orientation maps. Short-range excitatory connections or influences lead nearby cells to develop similar preferences and account for map continuity. Longer-range influences that are effectively inhibitory, or limits on projection strengths of afferents, can lead more distant orientations to differ. The map self-organizes through the dynamical interactions among the developing synapses. A better understanding of the geometry of these early interactions is needed to understand the determination of orientation maps in correlation-based models (*e.g.*, see discussion in Miller (1994)).

The process of self-organization may occur in the presence of constraints. For example, boundary conditions may limit the patterns of preferred orientation that can develop near areal boundaries (Wolf et al., 1996). Similarly, pre-existing biases in cortex – *e.g.* retinotopic biases in the distribution of lateral connections, or distinguished points such as areas of constitutively higher activity (cytochrome oxidase blobs) (Jones and Leyton-Brown, 1998) or areas receiving special projections (areas of layers 2/3 receiving periodic, patchy connections from LGN C layers (cat) or K cells (monkeys)) – could bias or limit the possible arrangements of orientation maps that can develop. For all such biases, there are questions of priority – it is as yet unclear to what extent such biases exist prior to the orientation map, coevolve with it, or arise subsequently to or independently of map development. Furthermore the biases may themselves arise through processes of activity-instructed self-organization, so that in a deeper sense the entire map may be freely self-organized even if biases are visible

before maps. But, supposing there are factors that constrain map development, there is a continuum of possibilities, from such constraints having no influence on map development, to their limiting certain aspects of the form of the map (its period, whether isoorientation domains run parallel or perpendicular to boundaries, locations of singularities), to such constraints so tightly limiting map development that they largely determine or "instruct" the final map.

Much debate has focused on whether orientation maps are "genetically pre-specified" as opposed to "acquired" (*e.g.* Gödecke and Bonhoeffer, 1996). We feel that this question is poorly posed, because it is perfectly possible for orientations to be "acquired" through a process of dynamical self-organization, yet for those dynamics to be sufficiently constrained that aspects of final map organization can be well predicted from those constraints. Instead, we would propose that the question should be broken down as follows: first, is there a "pre-pattern", a set of prior structures from which aspects of the final map can be predicted? Second, what are the *mechanisms* driving (1) development of orientation selectivity and (2) selection of preferred orientations (map development)? These questions are separable, and an answer to one does not imply an answer to the others.

The Identical Twin Experiment

To illustrate the problems with the idea of "genetic pre-specification", we consider the following experiment which has been raised in informal discussions in the community: raise identical twin kittens and see if they have identical orientation maps. If so, the argument goes, this would show that genetics determines the map. While true at the surface level, the argument is incomplete: a positive result would not bear on the questions of whether activity instructs the map or even whether the map is self-organized.

In considering dynamical, self-organized systems, two opposite kinds of results are commonly seen, often in the same system. First, many different initial states may converge on the same final state: each final state has a "basin of attraction", a set of earlier states that map onto it. In this case, even large differences between states in the same basin of attraction disappear under the dynamical development. This is what we referred to before as "dynamical fate determination". Second, very nearby initial states may diverge onto different final states, i.e. they lie on different sides of the divide between basins of attraction. In this case, even small differences between initial states will be amplified by the dynamical development. To the extent to which constraints limit the outcomes, they broaden the basins of attractions – larger groups of initial states are pooled into a more limited possible set of final outcomes.

If orientation map development is dynamically determined, then an identical twin experiment would simply be probing how robust the final state is to small stochastic variations in initial conditions, activity patterns, or other factors. In this case, a finding of identical

maps would simply indicate that the amount of variation generated, given identical genetics, is insufficient to dynamically divide the outcomes. A finding of different maps would, of course, indicate that something besides genes determines the map, and would suggest self-organization. However, whether this self-organization process involves activity, or perhaps simply involves molecules, would not be determined. In summary, this experiment, either for positive or negative results, does not address whether the maps are instructed by activity; and a positive result (identical maps) does not distinguish whether or not map development is self-organized.

It is instructive to consider the alternative experiment, which has already been done many times: animals with differing genes (sibling or unrelated kittens) do *not* develop the same orientation map. The situation is quite different for retinotopic maps, which, at least roughly, are quite consistent from animal to animal. This suggests that genetics determines retinotopy – it was something of significant evolutionary importance that the map became specified in a manner that is robust to the genetic differences from animal to animal (of course, genetics might achieve this result by a very noise-tolerant self-organization process). One might take the fact that this is not true for orientation maps as evidence in favor of self-organization.

Conclusion

For at least the cat visual system, simple models exist for the activity-dependent organization of binocularly matched orientation selectivity in layer 4. These models are likely to generalize to other species in which the first oriented cells (in the sense of serial order from the periphery) are simple cells, but this may not include all species. These models, and more generally any models of orientation development instructed by input activity patterns, have simple, direct tests: normal input activity patterns must have the information required to guide this development; and altering this input activity in such a way as to alter or eliminate this information should alter or block this development. Experiments thus far are consistent with the model predictions and with the hypothesis of activity instruction: blocking ON-center retinal ganglion cell development prevents map development; and significant between-eye activity correlations exist in the developing LGN. It now seems within reach for further experiments to decide the issue.

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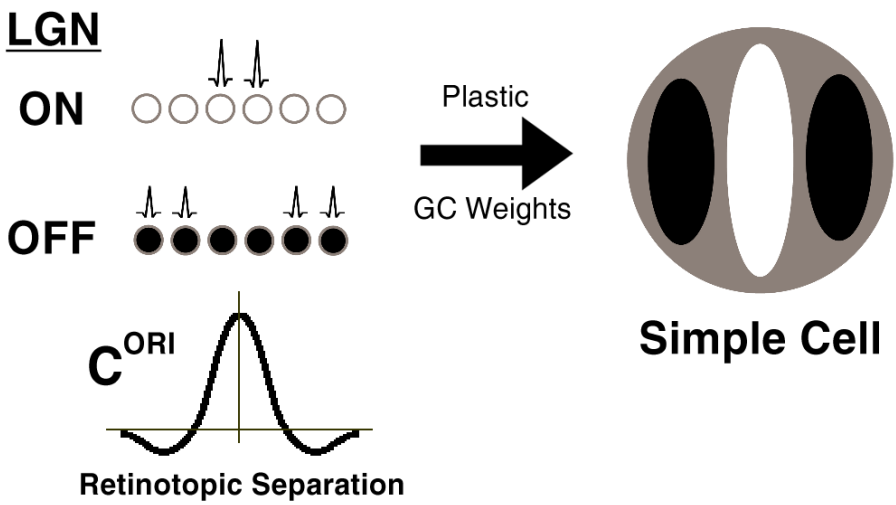

Figure 1:

Model requirements for development of simple cell receptive fields. Correlation-based mechanisms of synaptic development lead a cell to acquire a "most-correlated" set of inputs. For such a set to consist of ON-center inputs and OFF-center inputs from spatially segregated, adjacent regions, as in the simple-cell receptive field at right (white: ON inputs; black: OFF inputs), these inputs must tend to fire together. This is illustrated at top left: a local group of ON-center cells should statistically tend to fire together, and to be coactive with OFF-center cells in adjacent regions. This statistical tendency can be summarized by a correlation function, C^{ORI} (bottom left). C^{ORI} describes, for a given retinotopic separation between two inputs, the degree to which two inputs of the same center-type (both ON-center, or both OFF-center) tend to be more coactive than two inputs of opposite center types (one ON-center and one OFF-center). If, as illustrated, C^{ORI} is positive at smaller retinotopic separations (meaning that same-center-type pairs are more coactive than opposite-center-type pairs at those separations), but is negative at larger retinotopic separations (opposite-center-types more coactive than same-center-types), then simple cells will form under correlation-based development of geniculocortical (GC) weights.

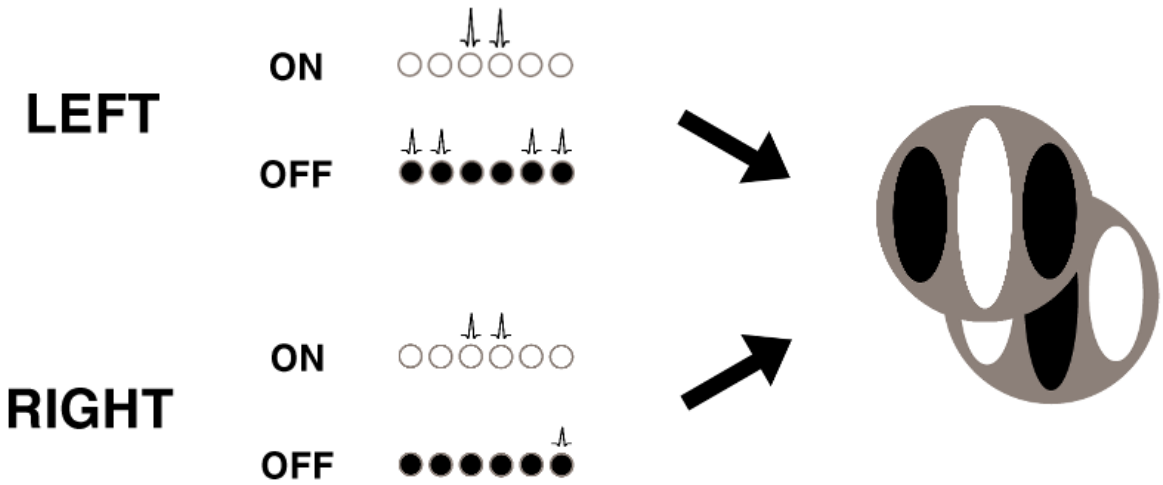

Figure 2:

Model requirements for binocular matching of the preferred orientations of simple cells: between-eye correlations in the LGN must differentiate between center types. The reason for this requirement is as follows. A correlation-based mechanism does not directly "know" about preferred orientation; rather, it maximizes the total correlation among the activities of the synaptic inputs received by a cell. If (1) LGN between-eye activity correlations did not differentiate between center types (*e.g.* so that an ON-center cell serving one eye were equally correlated with an ON or an OFF cell serving the other eye at the same retinotopic position); and (2) each eye's receptive field were circular (not elongated), then this total input correlation would not be altered if one eye's receptive field were rotated relative to the other, and so orientations could not become aligned. Therefore, between-eye correlations must differentiate between center types. A simple example is illustrated at left: a tendency of ON-center cells in one eye to be coactive with ON-center cells at the corresponding location in the other eye, and similarly for OFF-center cells. This causes total input correlation to be maximized if ON-subregions in one eye tend to overly ON-subregions in the other eye, and similarly for OFF-subregions; this in turn forces the preferred orientations of the two eyes to become aligned. Other factors might lead to shifts in the overall positions of each eye's receptive field, as illustrated, but in the region of binocular overlap, subregions would be appropriately aligned.

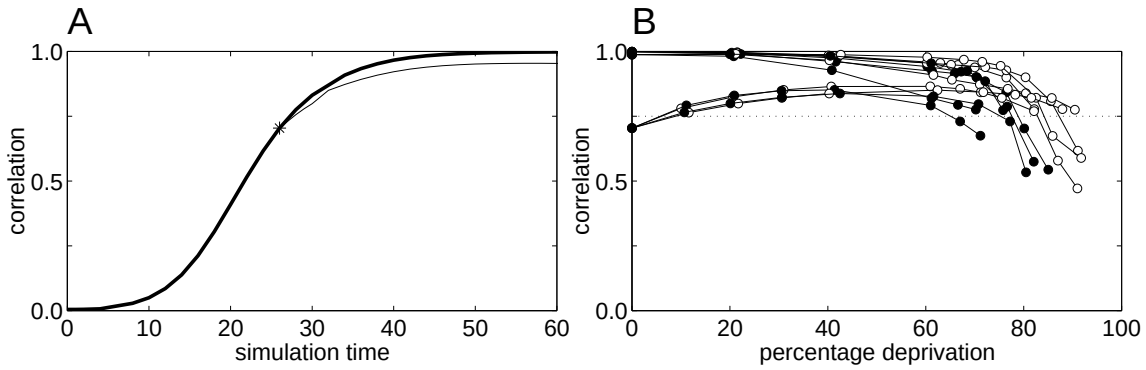

Figure 3:

Interocular correlation of orientation maps in normal development (A) and after monocular deprivation and reverse suture (B). (A) "Dynamic fate commitment". Heavy line: time course of development in a simulation with input activity correlations like those in Figure 2. Over time, the two eyes' orientation maps become 100% correlated. Light line: simulation was identical to that of the heavy line up to the asterisk (interocular map correlation 70%); but thereafter, interocular activity correlations were set to zero. Although the two eyes' maps were developing completely independently, the correlation between them continued to increase, from 70% to 95%. Once each eye's map is sufficiently developed, the dynamics lead them each independently to converge upon a common fate. (B) Results of simulations of monocular deprivation, followed by reverse suture, across multiple parameters. Plot shows degree of correlation between the map in the initially open eye at the end of the initial deprivation, and that in the subsequently opened eye at the end of the reverse deprivation. Monocular deprivation continued until the total synaptic strength in the deprived eye was decreased by the percentage indicated on the horizontal axis; then reverse deprivation was carried out until the newly deprived eye's total strength was reduced to this same level. Each line indicates a single parameter set; open and closed balls indicate data points. For most parameters, loss of more than 80% of strength in the initially deprived eye is needed before the interocular correlation falls below 75% (dotted line); experimentally observed correlations were 75%–90% (Gödecke and Bonhoeffer, 1996). Lines beginning from 70% correlation represent deprivation initiated at the asterisk in (A); due to dynamic fate determination, interocular correlation can rise despite massive deprivation. Lines beginning from 100% correlation represent deprivations initiated later in development. White circles: deprived eye has zero activity (representing TTX infusion); black circles: deprived eye has reduced and unstructured activity. Interocular activity correlation was always zero during deprivations.

(A) replotted from (Erwin and Miller, 1998, Figure 12). Interocular correlation measured as in (Gödecke and Bonhoeffer, 1996): correlation coefficient is measured between cortical response patterns to stimulation of each eye by a grating of one orientation; interocular correlation is average of these coefficients over multiple (18) orientations ($0^o - 170^o$ by 10°).

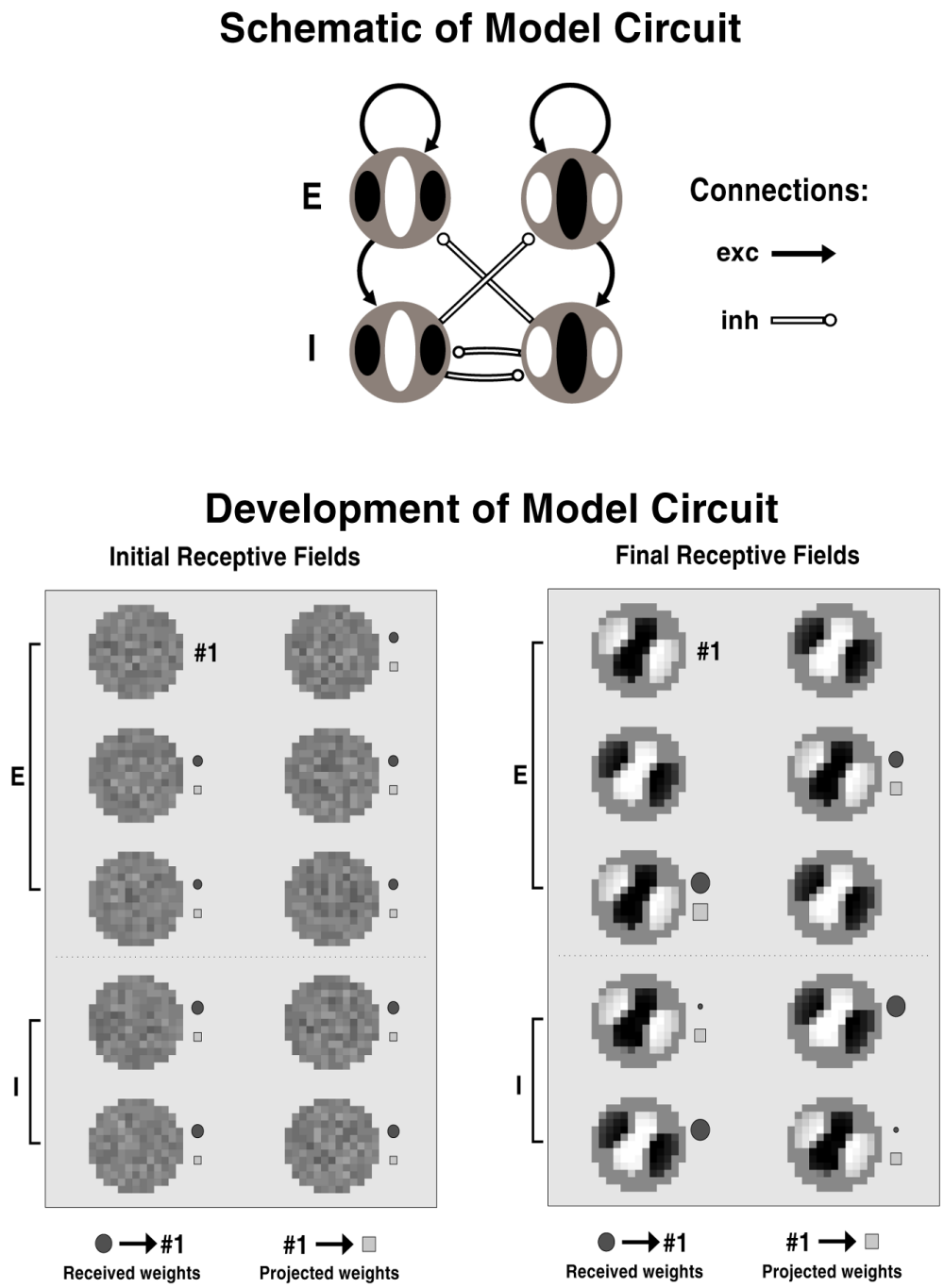
Schematic of Model Circuit
E
I
Connections:
exc
inh
Development of Model Circuit
Initial Receptive Fields
Final Receptive Fields
#1
E
I
#1 → #1
Received weights
#1 → #1
Projected weights

Figure 4:

Figure 4:

Development of a full layer 4 intracortical circuit. Top: schematic illustration of model cortical circuit (Troyer et al., 1998). Excitatory cells (E) connect to other cells with well-correlated receptive fields; inhibitory cells (I) connect to other cells with well-anticorrelated receptive fields. Thus, connections are onto cells having similar preferred orientation, and similar (E projections) or roughly opposite (I projections) retinotopic locations of ON subregions and of OFF subregions. ("Self-connections" of excitatory cells represent connections among a population of similar cells, not of a single cell onto itself). Though the schema shows connections between identical or perfectly opposite receptive fields, it is sufficient that connections be made statistically, with probability of an E (I) connection between two cells increasing strongly with their degree of receptive field correlation (anticorrelation). Provided inhibition dominates excitation, this circuit achieves contrast-invariant orientation tuning and other response properties of the mature cortical circuit. Bottom: development of the model circuit. We consider development of 10 cortical cells, 6 E and 4 I cells, receiving inputs from a diameter-13 circle of LGN cells. Initial connections (left) are all-to-all and nonspecific. Circles show ON-center minus OFF-center synaptic strength from each LGN location to a given cell, on a scale from black (all OFF) to white (all ON). Intracortical projections to and from cell #1 (top left cell) are indicated by symbols to side of each receptive field. After correlation-based development (right), LGN inputs to each cell have segregated to form simple-cell receptive fields, while intracortical connections instantiate the model circuit: cell #1 projects to well-correlated cells (both E and I), while receiving inputs from well-correlated E cells and well-anticorrelated I cells. Projections to and from other cells are similarly appropriate. When initial condition includes retinotopic jitter, a greater diversity of simple cell receptive fields emerges.