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CHAPTER 20

Models of activity-dependent neural development*

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Introduction

In the development of many vertebrate neural systems, an initially rough connectivity pattern refines to a precise, mature pattern through activity-dependent synaptic modification or rearrangement (reviewed in Miller, 1990a; Constantine-Paton et al., 1990). What is known about these processes is generally consistent with a hypothetical rule first proposed by Hebb (1949): synapses are strengthened if there is temporal correlation between their pre- and postsynaptic patterns of activity. The development often appears to be competitive: for a given pattern of activation, a correlated group of inputs may lose strength when competing with a more strongly activated correlated input group, yet retain or gain strength when competitors are absent (Wiesel and Hubel, 1965; Guillery, 1972; Miller and MacKay, 1994).

The classic example of such correlation-based, competitive development is the formation of ocular dominance columns in the mammalian visual cortex (reviewed in Miller and Stryker, 1990; Shatz, 1990). Visual inputs from the lateral geniculate nucleus (LGN) to the visual cortex terminate in separate stripes or patches consisting largely or entirely of terminals serving a single eye (Fig. 1). There is a regular, periodic alternation across the cortex of patches dominated by each eye. This segregated projection develops in an activity-dependent manner from a diffuse, overlapping initial projection in which inputs serving the two eyes project roughly equally throughout cortical layer 4.

Orientation columns are another striking feature of visual cortical organization (Hubel and Wiesel, 1962; reviewed in LeVay and Nelson, 1991). Most cortical cells are orientation selective, responding selectively to light/dark edges over a narrow range of orientations. The preferred orientation of cortical cells varies regularly and periodically across the cortex. It has long been a popular notion that orientation columns, like ocular dominance columns, may develop by a process of activity-dependent synaptic competition. However, evidence has been lacking, because orientation selectivity generally develops before animals are born or have functioning vision (Wiesel and Hubel, 1974; Sherk and Stryker, 1976; Chapman and Stryker, 1993). This does not rule out activity-dependent development, because experiments have shown that there is spontaneous neural activity, locally correlated within each eye, in the absence of vision and in the fetus (Mastronarde, 1989; Maffei and Galli-Resta, 1990; Meister et al., 1991; Wong et al., 1993), and that this activity is sufficient to guide activity-dependent ocular dominance segregation (Shatz and Stryker, 1988; Shatz, 1990; Miller and Stryker, 1990).

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The rules of synaptic modification that drive cortical development are presumably local to the environment of each synapse and its pre- and postsynaptic cells. We would like to understand these rules, yet often what can be observed is only a large-scale developmental outcome, such as ocular dominance segregation. At the same time, we would like to understand the mechanisms underlying these large-scale outcomes: which synaptic plasticity rules could produce them, what other factors are required and how can alternatives be tested? To address these questions and others, various models have been devised for the development of columnar systems through local activity-dependent synaptic modification.

The Von der Malsburg model of column development

Von der Malsburg first formulated such a model for the development of visual cortical columns through 'self-organization' (Von der Malsburg, 1973; Von der Malsburg and Willshaw, 1976; Willshaw and Von der Malsburg, 1976) (see also related models developed at about the same time: Wilson and Cowan, 1973; Nass and Cooper, 1975; Perez et al., 1975; Grossberg, 1976). This model established many of the elements of current models, and so is worth examining in detail. Von der Malsburg assumed that synapses of LGN inputs onto cortical neurons are modified by a Hebbian rule, and that the process is competitive, so that some synapses are strengthened only at the expense of others. He enforced the competition by holding constant the total strength of synapses converging on each cortical cell (conservation rule). He assumed further that inputs tend to be activated in clusters or patterns, so that there are correlations in the firing of the inputs; and that cortical cells also tend to be activated in clusters due to the intrinsic connectivity of the cortex, e.g. short-range horizontal excitatory connections and longer-range horizontal inhibitory connections.

The results expected from this model were

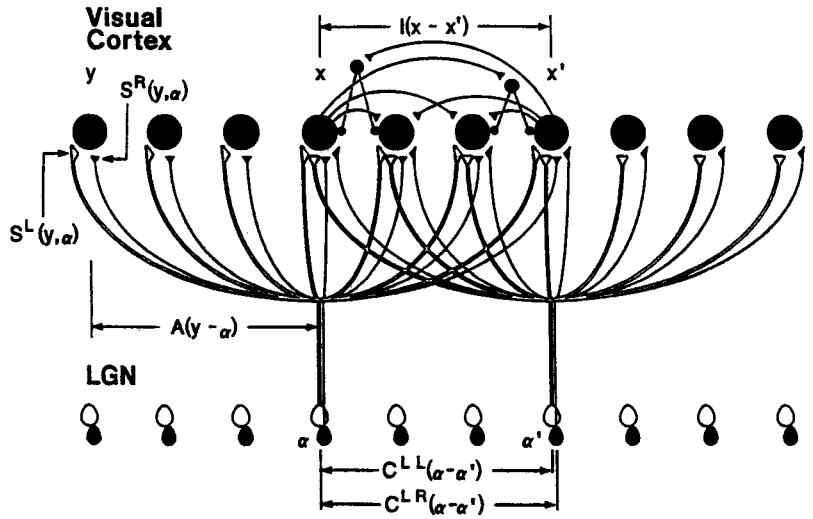


Fig. 1. Elements of the mature visual projection. Retinal ganglion cells from the two eyes project to separate laminae of the lateral geniculate nucleus (LGN). LGN neurons serving the two eyes in turn project to separate patches or stripes, known as ocular dominance columns, within layer 4 of the primary visual cortex. Binocular regions receiving inputs from both LGN layers are shown at the borders between ocular dominance columns; such binocular regions exist in some species, such as cats, but not in others, such as monkeys. The cortex is shown in cross-section, so that layers 1 through 3 are above and layers 5 and 6 below the layer 4 projection region. Reprinted by permission from Miller et al. (1989). © 1989 by the AAAS.

described as follows. The synaptic conservation rule should

'... (lead) to positive or negative interference between fibres connected to the same target cell. If such fibres are correlated in their activity ... their training effects are mutually reinforcing. On the other hand, synapses made on the same target cell by fibres which are anticorrelated never get reinforced.'

'After some time the modifiable synapses will have been rearranged so that each possible pattern of activity in the presynaptic sheet will evoke one of the possible patterns of activity in the postsynaptic sheet, thereby establishing associations between pairs of patterns. For discovering which patterns become linked together we use the crucial fact that each cell in a sheet belongs to several overlapping patterns. Under this condition the final projection has the property that overlapping stimuli will evoke overlapping responses and the responses to non-overlapping stimuli will not overlap. The geometrical interpretation of the resulting projections depends on the structure of the patterns of activity allowed.' (Von der Malsburg and Willshaw, 1976).

Von der Malsburg applied this model to the development of orientation columns (Von der Malsburg, 1973), the development of ocular dominance columns (Von der Malsburg and Willshaw, 1976) and, with Willshaw, to the development of topography (refinement of the retinotopic map) (Willshaw and Von der Malsburg, 1976). Computer simulations demonstrated that the models could work in each case. For orientation columns, inputs were activated in oriented patterns of all possible orientations. Individual cortical cells developed selective response to one such oriented pattern, with nearby cortical cells preferring nearby orientations. In the case of ocular dominance columns, inputs were activated in monocular patterns: each activation pattern was a localized cluster of cells from a single eye, and the two eyes were never simultaneously active. Individual cortical cells came to be driven exclusively by a single eye, and clusters of cortical cells came to be driven by the same eye. The tendency of overlapping cortical clusters to prefer the same eye resulted in a final arrangement of stripes of cortical cells preferring a single eye. 'The spacing between the stripes is determined by the range of inhibition' (Von der Malsburg and Willshaw, 1976), i.e. by the diameter of the intrinsic clusters of cortical activity.

Thus, a synaptic conservation rule was used that forced a Hebbian rule to become competitive. This led individual cells to become selective for a single correlated pattern of inputs. Combined with the idea that the cortex was activated in intrinsic clusters, this suggested an origin for cortical columns: coactivated cells in a cortical cluster would tend to become selective for similar, coactivated patterns of inputs.

A more general framework for analyzing cortical development

This model provided many of the elements of a model of cortical development, and it included a fundamental experimental prediction: the width of an ocular dominance column should be determined by measurable intracortical inhibition. But otherwise, the study of the model was largely a set of demonstrations that the ideas could work. The range of conditions under which the model *would* work, and the dependence of the model results on quantities a neurobiologist could measure, were largely unexamined. Such knowledge provides the means of testing a model or distinguishing it from alternative mechanisms.

Consider the model for ocular dominance columns: how do the results depend on the correlations in activities in the input layers? If the two eyes are sometimes coactivated, either because they are activated independently or because they are partially correlated by vision, can ocular dominance segregation occur? If inputs are correlated over a larger or smaller distance within an eye, how will this alter the outcome of development? How will the fact that inputs from the LGN have localized arborizations ('arbors') in

cortex affect development? Can the size of these arbors, or the distance over which inputs are correlated, influence the width of the final patches? Can columns develop under alternative patterns of intracortical connectivity, for example, if the intracortical inhibition is weak or non-existent during development? How would these same questions be answered under alternative models of column development?

To address questions like these, we developed a similar model of ocular dominance column development that allowed analytical characterization of the outcome of development (Miller et al., 1989; Miller, 1990a,b; Miller and Stryker, 1990). This analysis gives a general understanding of the framework for column formation proposed by Von der Malsburg, and extends this framework to include alternative plasticity mechanisms, alternative structures of connectivity and of correlation, and alternative implementations of the postsynaptic conservation rule that ensures a competition. A detailed discussion of the mathematical and biological assumptions necessary for this analysis is given in Miller, 1990b.

We showed that a large class of developmental models could be expressed in terms of three measurable elements (Fig. 2): (1) a set of correlation functions, describing the correlation between the activities of input pairs as a function of their eyes of origin and their retinotopic separation; (2) an arbor function that describes the spread of input arborizations in cortex allowed by retinotopy; (3) a cortical interaction function describing interactions within the cortex by which activity at one location influences the effectiveness of correlated synapses on different cortical cells at nearby locations. In the absence of such intracortical influences, the competition occurring at each cortical cell would be independent, and hence development of large-scale clustering of cortical properties, such as ocular dominance, would not be expected.

The cortical interaction function is particularly dependent on the biological mechanism proposed to underly plasticity. In a Hebbian mechanism, as used in Von der Malsburg's model, the cortical interaction function is determined by intracortical synaptic connections. It is positive over distances at which cortical cells tend to excite one another and negative over distances at which cortical cells tend to inhibit one another. For alternative mechanisms that involve the activity-dependent release and uptake of a trophic or modification factor, the cortical interaction function also incorporates the spread of influence across the cortex due to diffusion.

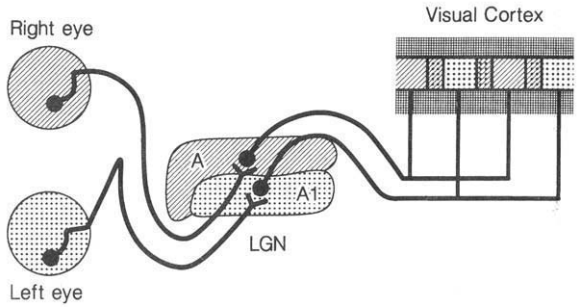


Fig. 2. Elements of a model of cortical development. Left (white) and right (black) input cells innervate cells in layer 4 of the visual cortex. α and α' label positions in the input layer (LGN) and x and x' label the retinotopically corresponding positions in the output layer (cortical layer 4); y labels an additional cortical position. The layers are taken to be two-dimensional, that is x, α, etc. are two-dimensional variables. The afferent correlation functions C^{LL} and C^{LR} measure, respectively, the correlation in activity between two left-eye afferents, and the correlation in activity between a left-eye and a right-eye afferent, as a function of the retinotopic separation of the two afferents. The arbor function A measures anatomical connectivity from a geniculate location to a cortical location, as a function of the retinotopic separation between the two locations. The cortical interaction function I measures the effect of neural activity at one cortical location (x') on the development of synapses at a lateral cortical site (x); in a Hebbian model, this function summarizes the effects of intracortical synaptic connections, by which activation at x' influences postsynaptic activation at x. The left-eye and right-eye synaptic strengths S^L and S^R represent the total physiological strength with which a given afferent activates a given cortical cell. These synaptic strengths are the dynamical (time-varying) variables in the model. The same framework can be applied to a competition between ON-center and OFF-center inputs from a single eye, rather than between left-eye and right-eye inputs: for example the correlation functions would then be $C^{ON\text{-}ON}$, $C^{ON\text{-}OFF}$, etc. Reprinted by permission from Miller et al. (1989). © 1989 by the AAAS.

Predicting the outcome of development

The outcome of development under mechanisms that can be expressed within this framework can be predicted as follows (Fig. 3) (Miller et al., 1989; Miller, 1990a; Miller and Stryker, 1990). We define the *arbor radius* as the radius of the arbor function, i.e. the radius of the retinotopically allowed arborization of an input to cortex. First, cortical cells tend to develop receptive fields consisting of a subset of inputs that are as correlated as possible (Fig. 3A). The most correlated subset is determined by the correlation functions but also by the arbor function, which restricts the set of inputs that can potentially innervate a cortical cell. This subset will be from a single eye, and hence cortical cells will tend to develop monocular receptive fields, provided that (1) inputs within each eye are locally correlated, and (2) at all separations within an arbor radius, inputs are better (or no worse) correlated with inputs from their own eye than with inputs from the opposite eye (Fig. 3A, top). Second, cortical cells tend to develop receptive fields that are as correlated as possible with other cortical receptive fields at excitatory distances across the cortex, but as anti-correlated as possible with other cortical receptive fields at inhibitory distances (Fig. 3B, top left). For ocular dominance, correlated receptive fields are those representing the same eye. Thus, as suggested by Von der Malsburg, cortical cells should be arranged in patches such that the patch width of a single eye corresponds approximately to the diameter of an excitatory region in cortex. More precisely, the width of a left-eye patch plus a right-eye patch corresponds to the spatial period that maximizes the Fourier transform of the cortical interaction function.

If intracortical inhibition is absent, then large clusters of cortical cells dominated by a single eye will form (Fig. 3B, top right). It is, however, possible for periodically alternating ocular dominance columns to develop in the absence of intracortical inhibition if an additional rule is invoked: the total synaptic strength made by each *input* cell must be approximately conserved (Fig. 3B, bottom). Note that this presynaptic conservation rule is distinct from the conservation rule that ensures competition, which is applied to each postsynaptic cell. The arbor function limits the synapses of each input to an arbor radius from its 'best' cortical location. Thus, presynaptic conservation limits the width of a patch of inputs from one eye to be no wider than the arbor radius, so that inputs from both eyes can form their synapses within the diameter of any arbor. In this sense, the presynaptic conservation rule has an effect similar to intracortical inhibition on a scale of about half an arbor radius. If inhibition is present on such a scale or finer, the rule does not alter the unconstrained course of development, but in the absence of such inhibition, the rule leads to development of ocular dominance columns with a width set by the arbors.

When ocular dominance segregation does occur, our analysis also allows prediction of the relative degree of segregation. In cats, where ocular dominance segregation in cortical layer 4 is not complete, there is some binocular overlap at the borders between the patches of the two eyes. In monkeys, where there is complete segregation in layer 4, there is no overlap. To understand such alternative outcomes, it is helpful to think of the development as a competition between monocular and binocular patterns of input. Because ocular dominance segregation does tend to occur, the fastest-growing pattern of inputs to a single cortical cell is a monocular pattern (Fig. 3A, top); but how much faster does it grow than a binocular pattern consisting of inputs from one eye in half of the receptive field, and inputs from the other eye in the other half (Fig. 3A, bottom right)? If the correlations within each eye are weak and occur only over input separations that are very small compared with an arbor radius, then the binocular pattern grows nearly as well as the monocular one. In this case the binocular pattern has slightly less total correlation than the monocular one because of the boundary between left-eye and right-eye inputs, but this loss is small because the correlations are weak and do not extend very far. Alternatively, if the correlations

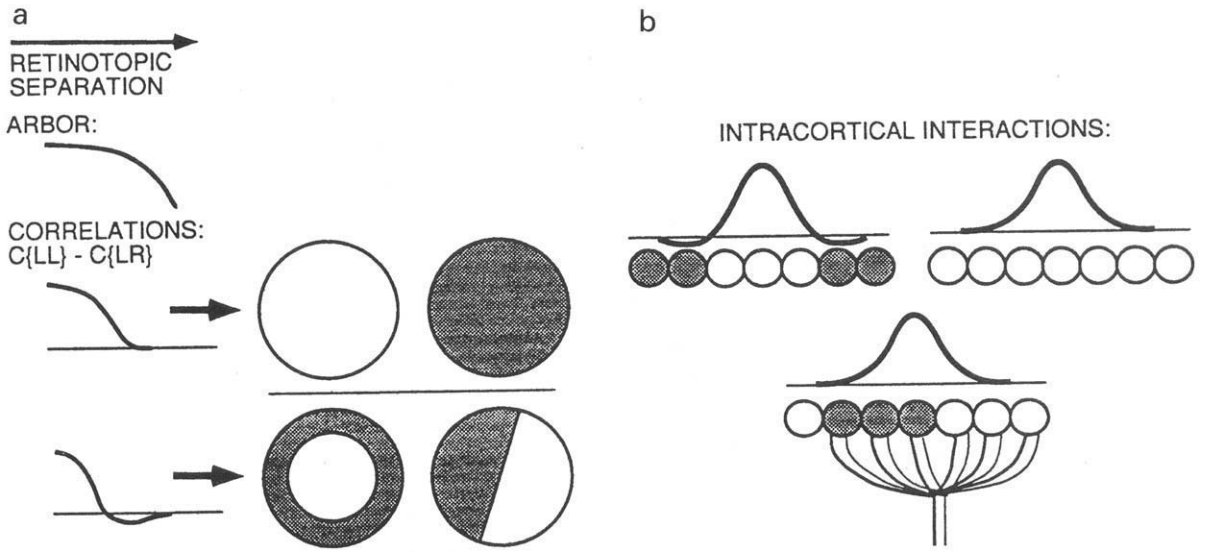


Fig. 3. Determinants of the outcome of cortical development as described by the model. (A) The correlations among input activities determine receptive field (RF) structure. Each large circle indicates the receptive field of a single cortical cell. White indicates left-eye inputs, shading indicates right-eye inputs. RF structure is determined by the degree to which two same-eye inputs with a given retinotopic separation are better correlated with one another than with an opposite-eye input at the same separation. This is described by the difference correlation function, $C^{D} \equiv C^{LL} - C^{LR}$, where we have assumed equality of the two eyes, $C^{LL} = C^{RR}$. TOP: If C^{D} is always positive within an arbor radius, ocular dominance segregation occurs: a cortical cell receptive field comes to receive only left-eye or only right-eye input. BOTTOM: If C^{D} were to change sign, so that at small separations same-eye inputs were best correlated, but at larger separations within the arbor radius opposite-eye inputs were best correlated, then receptive fields would develop segregated left-eye and right-eye subregions. Two alternative possible arrangements of such subregions are indicated. The correlation structure alone does not strongly distinguish between these; but the intracortical interactions lead to oriented arrangements, such as that at the lower right. The examples shown may be generalized: receptive fields tend to form with an alternation of left- and right-eye subregions whose spatial frequency maximizes the Fourier transform of C^{D}. (B) Intracortical interactions determine the arrangement of cortical cells. Only the case of ocular dominance segregation (A, top) is illustrated. TOP: Cells become arranged to best match the interactions. If the interactions are purely excitatory, arbitrarily large regions will become dominated by a single eye (top right). Note that interactions are assumed to be a function of distance, identical for every cell, although the figure shows them only for one cell. BOTTOM: If total synaptic strength is conserved over each presynaptic arbor, then ocular dominance columns can develop in the absence of intracortical inhibition. Initial arbors are shown stretching over six cortical cells. For each eye's inputs to retain approximately equal strength in the final arrangement, as a presynaptic conservation rule requires, eye patches can be no larger than half the arbor diameter (three cells wide); so patches of this size will develop in the absence of inhibition. This description of the determinants of development applies equally to a competition between ON- and OFF-center inputs from a single eye: in that case, $C^{D} \equiv C^{ON\text{-}ON} - C^{ON\text{-}OFF}$, white indicates ON-center inputs, shading indicates OFF-center inputs.

are strong and extend throughout the arbor, then inputs in one half of the receptive field cooperate with correlated inputs in the other half and the monocular pattern greatly outgrows the binocular one. In both cases ocular dominance segregation will occur, but in the first it will occur weakly: binocular patterns will develop on some cells, particularly those at the boundaries between the patches from the two eyes. In the second case, there will be complete segregation.

The method used to ensure competition can alter the outcome of development, by altering the minimal correlation structure needed for development of ocular dominance (Miller et al., 1989; Miller and MacKay, 1994). Recall that competition is modeled by conservation of total synaptic

strength over each cortical cell. If this conservation is subtractive, i.e. implemented by reducing each synaptic strength by the same amount, then ocular dominance can develop when the inputs from one eye are even slightly more correlated with their neighbors than with those from the other eye, as described above (Fig. 3A). If, however, this conservation is multiplicative (as was Von der Malsburg's), implemented by multiplying all synaptic strength by a renormalizing constant, then the tendency to develop ocular dominance can be spoiled if the two eyes sometimes fire together, even randomly. Thus, if conservation is multiplicative, the inputs must be strictly monocular in order for ocular dominance to develop (the exact requirement depends on details of the Hebbian rule but this is a reasonable intuitive characterization). Ocular dominance begins to develop in the fetus in some animals, and continues its development after birth in the presence of vision, despite the fact that the two eyes may fire together randomly in the fetus and in darkness (Mastronarde, 1989; Maffei and Galli-Resta, 1990; Meister et al., 1991) and are partially correlated by vision after birth. This suggests that subtractive rather than multiplicative mechanisms may be more appropriate for modeling the competitive nature of a Hebbian rule in the visual cortex.

Simulations have confirmed that this framework is sufficient to account for many aspects of visual cortical development, including the development of monocular cells and their organization into periodic ocular dominance patches, the degree of monocular segregation, the restriction of afferent arbors to periodic patches of cortical innervation, and the effects of monocular deprivation including a critical period (Miller et al., 1989; Miller, 1990a; Miller and Stryker, 1990).

Application to the development of orientation selectivity

In cats, the cortical cells in the layers receiving the LGN inputs are primarily 'simple cells' (Hubel and Wiesel, 1962; Bullier and Henry, 1979): orientation-selective cells whose receptive fields consist of oriented, spatially segregated subregions receiving exclusively ON-center or OFF-center excitatory input. The understanding we have achieved of the determinants of development raises the possibility that oriented cortical simple cells could result from a competition between ON-center and OFF-center inputs, very much as ocular dominance segregation results from a competition between left-eye and right-eye inputs (Miller, 1992, 1994).

The parameter regime in which ocular dominance segregation does not develop (Fig. 3A, bottom) results in receptive fields reminiscent of simple cells, with segregated subregions each receiving a different class of input. In particular, oriented receptive fields develop (as in Fig. 3A, lower right) if development occurs in the presence of intracortical interactions. For a competition between left- and right-eye inputs, the correlation structure that yields this outcome is not biologically reasonable, but this correlation structure, in which sign changes as a function of distance, is plausible for a competition between ON- and OFF-center inputs (Fig. 4).

Thus, orientation selectivity could develop through competition between ON-center and OFF-center inputs. The outcome of such competition is the formation of receptive fields like those of Fig. 3A, lower right, but with segregated subregions of ON-center and of OFF-center inputs rather than of left-eye and of right-eye inputs. Such receptive fields strongly resemble cortical simple cells. The parameter regime leading to this result (Fig. 3A, bottom) is that in which ON-center cells are best correlated with other ON-center cells at small retinotopic separations, but are best correlated with OFF-center cells at larger retinotopic separations within an arbor radius (Fig. 4). Experimental measurement will be necessary to determine whether such a correlation structure is actually present during development.

Simulations have demonstrated that competition between ON- and OFF-center inputs under these conditions leads both to the development of oriented simple cells and to their continuous ar-

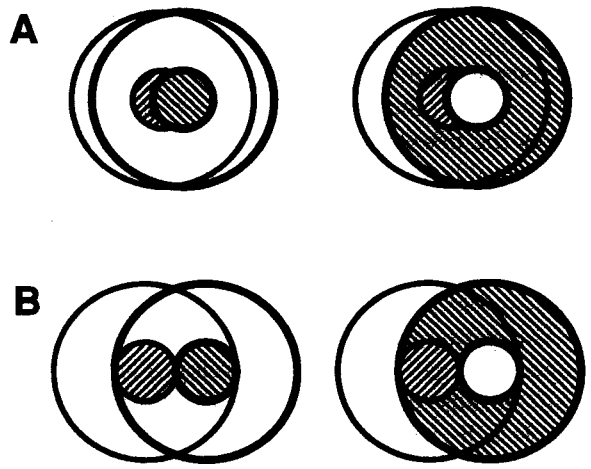


Fig. 4. Plausibility of a correlation structure between ON- and OFF-center inputs that would lead to development of orientation selectivity. Striped regions represent ON regions, and white regions represent OFF regions. Orientation selectivity develops in the dark (Wiesel and Hubel, 1974; Sherk and Stryker, 1976; Chapman and Stryker, 1993), so we consider correlations in spontaneous activity, in the absence of vision, due to common input from photoreceptors (Mastronarde, 1989). (A) Correlations at small retinotopic separations, where receptive field (RF) centers overlap. Left: Two ON-center RFs have overlapping ON-centers and overlapping OFF-surrounds, and hence would be expected to frequently receive common input and thus to be well correlated. Right: For an ON-center and an OFF-center RF at similar separations, ON-center overlaps OFF-center, and ON-surround overlaps OFF-surround, so anticorrelation is expected. Such correlations and anticorrelations at separations where centers overlap have been observed in dark activity of retinal ganglion cells (Mastronarde, 1989). (B) Correlations at larger retinotopic separations, where RF center overlaps RF surround. Left: Two ON-center RFs. The ON-center of each RF overlaps the OFF-surround of the other, and so the two would be expected to rarely receive common input, and thus to be poorly correlated or anticorrelated. Right: An ON-center and an OFF-center cell. The ON-center of one RF overlaps the ON-surround of the other, and similarly OFF-center overlaps OFF-surround, so better correlation might be expected than at left. While such correlations have not been observed, measurements have only been made in the retina; the LGN has stronger RF surrounds compared to the retina, so this effect might originate in or become enhanced in the LGN.

rangement in periodic orientation columns resembling those seen experimentally (Miller, 1992, 1994) (Fig. 5). The determinants of development follow the same general framework discovered for ocular dominance. The receptive fields consist of a subset of inputs that are as correlated as possible. Because of the change in correlations with distance, this subset consists of segregated, adjacent subfields of ON- and OFF-center inputs. For example, ON-inputs in an ON- subfield are, given this correlation structure, better correlated with OFF-inputs in an adjacent subfield than they would be with ON-inputs at that adjacent location. The intracortical interactions determine that the receptive fields of cortical cells are as correlated as possible at excitatory distances and as anticorrelated as possible at inhibitory distances. This both determines that individual receptive fields will be oriented (Fig. 3A bottom right rather than bottom left), and determines the arrangement of the orientation map. The determination of the width of the orientation columns by this mechanism is complicated, involving intracortical interactions, correlations and arbors. The fact that the width of orientation columns is determined somewhat differently than the width of ocular dominance columns is consistent with experiment: in both cats and monkeys, the periods of these two systems differ by 20–30% (Hubel et al., 1978; Loewel et al., 1988). A novel finding of the model is that the spatial phase of cortical simple cells — i.e. the spatial location within the receptive field of the ON-regions and of the OFF-regions — is a critical variable in determining the orientation maps. Hence, the maps of orientation and of spatial phase must be measured simultaneously to understand the origin of the orientation map alone.

Note that these ideas have diverged from those of Von der Malsburg. He conceived of orientation selectivity arising through a process by which competing oriented patterns of inputs become associated with different clusters of coactivated cortical cells. In the present model, there are no oriented patterns of inputs. Rather, competing ON- and OFF-center inputs converge onto cortical cells but become segregated within receptive fields. Given intracortical interactions, this leads to the emergence of orientation selectivity and its organization across cortex despite the absence of oriented patterns in the inputs.

These ideas demonstrate the potential power of modeling. We began with the belief, based on work in ocular dominance columns, that a Hebbian or similar mechanism is operating in the development of visual cortex. A general analysis of such competition demonstrated an unexpected outcome: convergence of two competing input populations onto postsynaptic cells but segregation within individual receptive fields. Previously, Hebbian competition between competing input populations was assumed to produce segregation between postsynaptic cells, as in ocular dominance segregation (but see Linsker, 1986a,b,c, discussed below). Identification of this novel parameter regime with cortical simple cells suggested an unexpected explanation for the origin of orientation selectivity in visual cortex. This explanation is testable: experiment can determine whether the postulated correlation structure is present during development, and experimental manipulations that would disrupt the ON/OFF correlation structure, for example forcing all inputs to fire in synchrony, should prevent the development of orientation selectivity if the hypothesis is correct.

Strengths and limitations of this approach

This framework allows understanding of the results of development based on the spatial arrangements of correlations, arbors, and intracortical interactions. This is the same level of detail as that studied in many experiments on column formation (Miller and Stryker, 1990): measurement or perturbation may be made of the correlations between competing sets of inputs, the arborizations of those inputs in the cortex, or the types and interconnections of cells in cortex, as well as of the biochemical mechanisms underlying plasticity. The model thus systematically connects experimentally measurable and perturbable quantities with expected developmental outcome at similar levels of detail. It also demonstrates that formulation of the problem at this level is sufficient to account for a wide range of observed phenomena, and it makes a number of novel predictions, for example, that the development of orientation selectivity may depend on the ON/OFF correlation structure.

Our analysis focuses on predictions that are independent of the details of biological non-linearities, because the nature of these is largely unknown. We accomplish this by concentrating on the initial development of a pattern of the difference between two similar input projections; this difference is initially small, allowing linearization of the equations (Miller, 1990b). We restrict our analysis to elements that develop in the early, linear regime of the model and thus are very robust to implementation details. These include the column width, and the very facts that cortical cells become monocular or orientation-selective. We do not address questions like the detailed layout of ocular dominance columns (i.e. long straight stripes vs. irregular patches), that depend on non-linearities and hence may vary with details of model implementation. The results must also be robust to noise, meaning that they develop from essentially any randomly chosen initial condition. Similarly, we respect biological constraints such as the exclusively excitatory nature of the LGN input to cortex.

This framework does not address the details of neuronal structure or the temporal structure of activation and plasticity. The conjunctions of activation that lead to Hebbian plasticity depend in a complex way on the temporal and spatial distributions of input activities, on interactions through the dendritic structure of the postsynaptic cell, and on the biophysical and learning mechanisms at the synapse. Yet in our model this is expressed simply through a correlation function that summarizes the ability of inputs to cooperate in achieving Hebbian plasticity on any postsynaptic cell, and the postsynaptic cell is collapsed to a point without dendritic structure. In a sense we are begining with the answer: we know that the competition ultimately leads an entire cell to become dominated by a single pattern of inputs. Thus, competition is ultimately integrated over the cell as a whole, so we ignore finer levels of competition.

Our framework also ignores cell- and cell-type specific connectivity. Given the complexity and

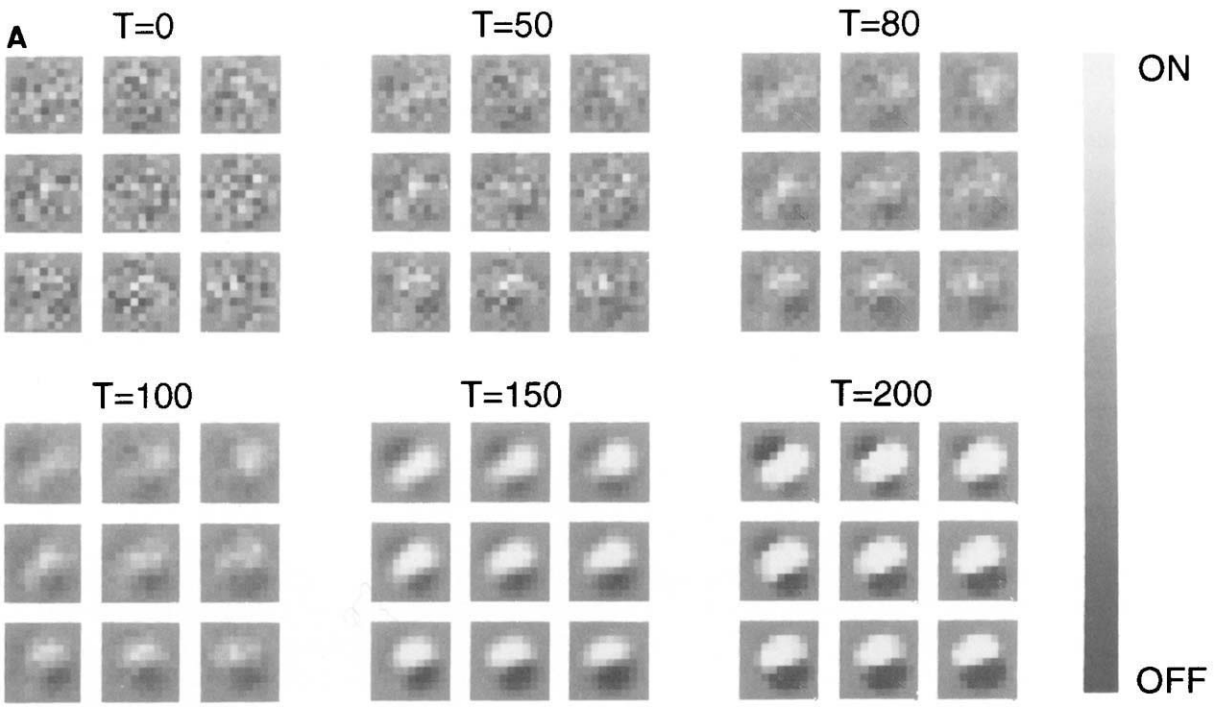
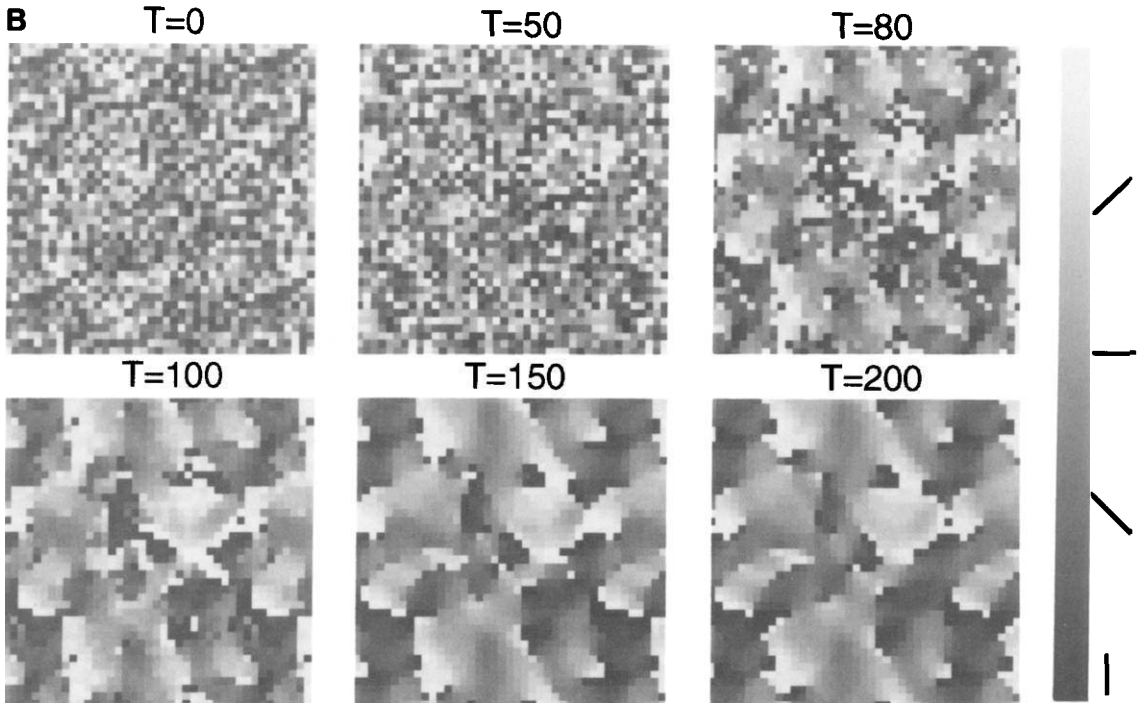


Fig. 5. Development of orientation selectivity through competition between ON- and OFF-center inputs. Results from simulation of development in a 31 by 31 array of cortical cells. (A) Development of orientation selectivity in receptive fields of a 3 by 3 group of cortical cells. Difference between ON-center and OFF-center synaptic strength at each point in each receptive field is shown, at six time steps ranging from a randomly assigned initial condition ($T = 0$) to the final state. (B) Time development of map of preferred orientation from the same simulation. Each pixel shows the 'best' orientation of one cortical cell. Orientation selectivity

specificity of cortical connections, why should the intracortical interactions be described simply as a function of the horizontal separation of two cortical sites? There is at present no compelling answer for this question based on realistic models of cortical circuitry, although simplified circuits with this property can be constructed (Von der Malsburg, 1973; Wilson and Cowan, 1973; Pearson et al., 1987), and there are bits of evidence for the real cortex (Miller and Stryker, 1990). Again, we begin with the solution: without an interaction function that depends on separation, it is difficult to account for such regular spatial properties as periodic columns. Should the cortical interaction function and correlation functions be independent of one another? It may be that the average distance over which intracortical interactions are excitatory depends on the average size of a coactivated set of inputs, and not simply on intrinsic circuitry in cortex. By beginning with the separate role of each of these functions, we reach an understanding that will serve us even if it turns out that one function partly determines the other.

The role of realistic models

Realistic modeling may help bridge the gap between biophysically realistic neuronal properties and the level at which our modeling begins. If the plasticity rule is coupled to local postsynaptic voltage, why should the competition on a single cortical cell result in the left eye or right eye winning the entire cell, rather than in an independent competition for each dendrite? The answer will ultimately be determined by detailed single-cell modeling (Lytton and Wathey, 1992), which is



corn(preference for best orientation) is initially extremely slight, as seen in (A). Note that, because orientation is a circular variable, black and white extremes both represent vertical. If one grid interval is regarded to represent about 100 μm, the final map shows reasonable resemblence to maps measured in cats. This scale is biologically plausible, corresponding for this simulation to arbor diameters of about 1 mm, purely excitatory intracortical interactions over about 200 μm, and a change in sign in ON/OFF correlations (Fig. 3A bottom) at a retinotopic separation corresponding to about half an arbor radius.

just beginning to be used to explore synaptic plasticity (Holmes and Levy, 1990; Zador et al., 1990; Brown et al., 1991). Using realistic but linear membrane biophysics, realistic synaptic conductances, and a Hebbian plasticity rule that depends on local postsynaptic voltage, it has been found that there are conditions in which one or a small number of patterns of synaptic inputs 'takes over' an anatomically detailed hippocampal pyramidal cell (Brown et al., 1991). The parameters that give this result are still under investigation, but are difficult to characterize due to the complexity of the model. Should intracortical interactions be described simply as a function of intracortical separation? This could be investigated by constructing biophysically and anatomically realistic models of activation in cortical networks, using methods like those described in Traub and Miles (1992), in order to determine the cortical interactions that emerge on a time scale appropriate to affect plasticity in a correlated group of inputs.

Such piece-by-piece use of biophysical modeling to evaluate or alter key assumptions in a simplified model should be contrasted with an attempt to directly attack a developmental problem using a biophysically detailed simulation. The latter approach faces two major hurdles. First, it must necessarily use a very simplified version of the biophysics, for practical reasons. It is at present computationally impossible to simulate detailed model networks like those, say, of Traub and Miles (Traub and Miles, 1992) for the hours or days of real time that are the minimum needed

to study development. Second, despite such simplification a biophysically detailed model of plasticity necessarily has a large number of parameters that are not constrained by experimental knowledge. Some means of managing this complexity must be found.

Inclusion of biophysical detail does not necessarily render a model more realistic (see related discussion in Sigvardt and Williams, 1992). For example, one recent model of development in somatosensory cortex (Pearson et al., 1987) used a plasticity rule involving hypothetical receptors with complicated kinetics and 14 arbitrary parameters, and rules for cortical cell activation requiring specification of 10–15 additional parameters. But, under the conditions studied, the plasticity rule reduced to a Hebbian rule in which plasticity occurs only when the postsynaptic cell is depolarized, and the pattern of cortical activation was simply short-distance excitation and longer-distance inhibition (Miller and Stryker, 1990). Thus, our analysis could be applied so that the results could be understood from the correlations in the input patterns used, the arbors, and the intracortical interactions as specified by the range of excitation and inhibition (Miller and Stryker, 1990). Interesting developmental results were obtained, but understanding was obscured rather than enhanced by using biologically unconstrained complexity to implement a very simple model. In particular, because the authors did not understand what determined the width of the cortical patches that developed in their model, they did not realize that certain aspects of their results could be ruled out by existing physiological observations (Miller and Stryker, 1990).

In sum, models must be informed and constrained by biological knowledge at their particular level of realism or abstraction. An increase in detail does not imply an increase in realism; unrealistic or unconstrained details may obscure rather than enhance understanding. Genuine study of the problem of plasticity at deeper levels of biological realism will extend and transform our knowledge, but this will likely need to be guided by, and will in turn guide, the understanding we gain at a more simplified level of description.

Abstract models of activity-dependent development

Models of development may also be formulated at an abstract level. These models explore dynamical or optimization principles that may lead to patterns like those observed in development. The elements of these models cannot readily be identified with biologically measurable quantities; but the simplified setting may expose principles that can carry over to a biological setting.

One set of models characterizes the Fourier transforms of biological patterns, either directly (Rojer and Schwartz, 1990) or by positing developmental rules that are simple in Fourier space (Swindale, 1980, 1982). Swindale proposed that ocular dominance at one cortical site influences the growth of ocular dominance at another cortical site according to a simple function of distance, and that these influences add linearly; the biological nature of the influence was not specified (Swindale, 1980). Such a rule selects periodic patterns of ocular dominance whose spatial period corresponds to the peak of the Fourier transform of the influence function. A similar rule, proposing that orientations influence one another's growth according to a function of distance (Swindale, 1982), selects a periodic pattern of preferred orientations in the same way.

The strength of these models is that they accurately describe observed maps of orientation and ocular dominance in a very simple way. Furthermore, the simplicity of the models allows interesting reasoning about issues such as monocular deprivation (Swindale, 1980) or the spacing of orientation singularities (Swindale, 1982). The problems with these models are that they cannot obviously be distinguished from more complex models that would yield a similar final distribution of power in Fourier space, and they do not propose a biological mechanism by which the posited influences might be exerted.

In the case of the ocular dominance model, there is a simple bridge to a biologically identifiable model. In the limit in which each eye fires as a unit, so that correlations are completely specified by eye of origin without need to specify retinotopic position, the model we proposed for ocular dominance reduces to one in terms of an influence function. The influence function is then specified in terms of biologically identifiable factors: correlations, arbors, cortical interactions, and presynaptic conservation rules if any. However, in the case of orientation selectivity our model does not provide such a connection: in our model, the interaction between two cells of the same orientation can vary from maximally positive to maximally negative depending on the spatial phases of the two receptive fields, so an influence function cannot be derived that depends on orientation difference alone.

Another set of models posit simplified versions of Hebbian rules. Linsker used linear Hebbian rules with synapses that could be either positive or negative, and a constraint that fixed the total percentage of positive and of negative synaptic strength in a receptive field (Linsker, 1986a,b,c; analyzed in Miller, 1990b; MacKay and Miller, 1990a,b). Variation of those percentages and of the input correlations revealed circumstances in which interesting receptive field structures arise. Correlations that oscillate led to spatially structured receptive fields with segregated regions of positive and negative synaptic input. Symmetry could spontaneously break, so that circularly symmetric inputs and arbors led to oriented receptive fields. However, the orientation-selective cells developed only when the constraint was finely tuned, and then only in the non-linear regime of development (MacKay and Miller, 1990a). Most of the results similarly depended on the constraint and its tuning, on the ability of synapses to become either positive or negative (or more generally, on the assumption of complete indistinguishability of positive and negative synapses (Miller, 1990b)), and on the particular choice of saturating synaptic non-linearities (Miller, 1990b; MacKay and Miller, 1990a,b). Thus, this model demonstrated previously unknown dynamical outcomes that could arise from Hebbian rules, but it did not demonstrate biologically plausible or robust ways to achieve those outcomes.

Other simplified Hebbian models use the self-organizing feature maps of Kohonen (Kohonen, 1989) or similar algorithms (Durbin and Mitchison, 1990) to model the development of ocular dominance and orientation columns (Durbin and Mitchison 1990; Obermayer et al., 1990, 1991, 1992). The Kohonen mappings are an abstraction of a Hebbian rule. The major abstractions are that, for any given input pattern, the output of cortical cells is determined without intracortical interactions, and reinforcement of active inputs then occurs only on the most activated cortical cell and its near neighbors, a representation of localized clusters in cortical activation. Multiplicative constraints conserve the sum of squares of the synaptic weights over each cortical cell. These mappings are amenable to analysis and have a number of interesting features. They lead to continuous maps in which all inputs gain equal representation in cortex if activated equally often, nearby inputs develop nearby cortical representations, and a constant distance across the cortex corresponds to a roughly constant distance in 'input space'. If the input space has more than the cortex's two dimensions — for example, the five-dimensional space of ocular dominance, preferred orientation, orientation selectivity, and 2D retinotopic position — this means that, when one feature is changing rapidly across cortex, the others will be changing slowly. The algorithms produce realistic maps of orientation (Durbin and Mitchison, 1990; Obermayer et al., 1990) and of ocular dominance (Kohonen, 1989; Obermayer et al., 1991, 1992), and reproduce many of the experimentally observed relationships between orientation and ocular dominance columns (Obermayer et al., 1991, 1992).

These mapping algorithms have several problems as biological models: they do not predict the column widths in any straightforward way from biologically identifiable parameters; as implemented thus far, they cannot break symmetry to

develop oriented responses from non-oriented input patterns, and more generally, the biological interpretations of the various abstractions used are not clear. But these models demonstrate simple rules that can account for complicated aspects of cortical maps, and their formal closeness to Hebbian rules suggests that they may serve as a guide for more biologically based models.

The abstract models demonstrate that differing dynamical mechanisms may converge on similar results resembling those seen biologically. Conversely, very different biological mechanisms may hide similar underlying dynamics. Furthermore some aspects of the results of a model may vary with details of implementation and thus not be firmly tied to the mechanism being studied. Thus, resemblance of model and biological results should not be viewed as a validation of a proposed model; rather it is a demonstration that a proposed mechanism can be involved, under some circumstances, in achieving results like those found biologically.

Summary and conclusions

What makes a useful model of neural development? One important contribution of modeling is to demonstrate that proposed biological mechanisms can be sufficient to account for experimental results. The Von der Malsburg model is a classic example. But such demonstrations alone do not provide tools to experimentally distinguish one mechanism from another. To draw such distinctions, the connection between measurable biological quantities and developmental outcomes must be established.

Perhaps the most important task for the future of developmental modeling is to deepen the connection between theory and experiment. Experimentally, this requires detailed and difficult measurements or experimental perturbations of the correlations among inputs and the intracortical connectivity existing during development. Simultaneous measurement of the maps of spatial phase and orientation of mature simple cells will provide important information for the understanding of orientation column development.

Theoretically, the number of open problems is enormous. How will inclusion of additional plasticity mechanisms, such as sprouting and retraction of synapses or plasticity of intracortical connections, alter the analytical understanding thus far achieved? What precisely determines the width of orientation columns in the model presented here? Can the relationship between ocular dominance and orientation columns be understood from developmental rules in a testable way? The existing framework may be extended to a three-dimensional cortex and to more complex models of intracortical connectivity. It may also be applied to other developmental phenomena including the development of lamination in the LGN (Shatz and Stryker, 1988; Hahm et al., 1991), the formation of visual maps in experimentally altered auditory cortex (Roe et al., 1990, 1992), and the mapping of visual and auditory maps in the optic tectum (Knudsen and Brainard, 1991; Brainard and Knudsen, 1993). For each system the goal is to develop testable predictions as to the patterns of activity and connectivity that could or could not lead to the results observed given a proposed mechanism of plasticity. Incorporation of deeper levels of biophysical realism will extend, deepen, and perhaps fundamentally alter the framework presented here. An important goal for the future will be to understand the computational and functional significance of developmental rules.

Activity-dependent, competitive mechanisms of synaptic plasticity appear to play an important role in many processes of late neural development, where an initially rough connectivity pattern refines to a precise, mature pattern. A prominent example is the formation of ocular dominance columns in the visual cortex of many mammals. These processes may be modeled at several levels. Simple models use abstract neurons and assume synaptic modification according to a Hebbian or similar correlation-based rule. These models incorporate biological constraints and attempt to predict large-scale developmental

patterns from the combination of synaptic-level plasticity rules and measurable biological patterns of activation and connectivity. More detailed models attempt to incorporate various levels of biophysical realism, including membrane and channel properties and dendritic geometry. Abstract models examine the connectivity patterns that may result if biological development follows certain dynamical or other abstract rules, without concern for how such rules might be implemented at the synapse. The strengths and weaknesses of these approaches have been examined in the present review through study of models for the development of ocular dominance and of orientation selectivity in the visual cortex.

References

Brainard, M.S. and Knudsen, E.I. (1993) Experience-dependent plasticity in the inferior colliculus: a site for visual calibration of the neural representation of auditory space in the barn owl. *J. Neurosci.*, 13: 4589–4608.

Brown, T.H., Zador, A.M., Mainen, Z.F. and Claiborne, B.J. (1991) Hebbian modifications in hippocampal neurons. In: J. Davis and M. Baudry (Eds.), *Long Term Potentiation: A Debate Of Current Issues,* MIT Press, Cambridge, MA, pp. 357–389.

Bullier, J. and Henry, G.H. (1979) Laminar distribution of first-order neurons and afferent terminals in cat striate cortex. *J. Neurophysiol.*, 42: 1271–1281.

Chapman, B. and Stryker, M.P. (1993) Development of orientation selectivity in ferret visual cortex and effects of deprivation. *J. Neurosci.*, 13: 5251–5262.

Constantine-Paton, M., Cline, H.T. and Debski, E. (1990) Patterned activity, synaptic convergence and the NMDA receptor in developing visual pathways. *Annu. Rev. Neurosci.*, 13: 129–154.

Durbin, R. and Mitchison, G. (1990) A dimension reduction framework for understanding cortical maps. *Nature,* 343: 644–647.

Grossberg, S. (1976) On the development of feature detectors in the visual cortex with applications to learning and reaction-diffusion systems. *Biol. Cybern.*, 21: 145–159.

Guillery, R.W. (1972) Binocular competition in the control of geniculate cell growth. *J. Comp. Neurol.*, 144: 117–130.

Hahm, J.O., Langdon, R.B. and Sur, M. (1991) Disruption of retinogeniculate afferent segregation by antagonists to NMDA receptors. *Nature,* 351: 568–570.

Hebb, D.O. (1949) *The Organization of Behavior,* John Wiley, New York.

Holmes, W.R. and Levy, W.B. (1990) Insights into associative long-term potentiation from computational models of NMDA receptor-mediated calcium influx and intracellular calcium concentration changes. *J. Neurophysiol.*, 63: 1148–1168.

Hubel, D.H. and Wiesel, T.N. (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J. Physiol.*, 160: 106–154.

Hubel, D.H., Wiesel, T. and Stryker, M.P. (1978) Anatomical demonstration of orientation columns in macaque monkey. *J. Comp. Neurol.*, 177: 361–380.

Knudsen, E.I. and Brainard, M.S. (1991) Visual instruction of the neural map of auditory space in the developing optic tectum. *Science,* 253: 85–87.

Kohonen, T. (1989) *Self-Organization and Associative Memory,* Springer-Verlag, Berlin, 3rd edition.

LeVay, S. and Nelson, S.B. (1991) The columnar organization of visual cortex. In: A.G. Leventhal (Ed.), *The Neural Basis of Visual Function,* CRC Press, Boca Raton, pp. 266–315.

Linsker, R. (1986b) From basic network principles to neural architecture: emergence of orientation columns. *Proc. Natl. Acad. Sci. USA,* 83: 8779–8783.

Linsker, R. (1986a) From basic network principles to neural architecture: emergence of orientation-selective cells. *Proc. Natl. Acad. Sci. USA,* 83: 8390–8394.

Linsker, R. (1986c) From basic network principles to neural architecture: emergence of spatial-opponent cells. *Proc. Natl. Acad. Sci. USA,* 83: 7508–7512.

Loewel, S., Bischof, H.-J., Leutenecker, B. and Singer, W. (1988) Topographic relations between ocular dominance and orientation columns in the cat striate cortex. *Exp. Brain Res.*, 71: 33–46.

Lytton, W.W. and Wathey, J.C. (1992) Realistic single-neuron modeling. *Semin. Neurosci.*, 4: 15–25.

MacKay, D.J.C. and Miller, K.D. (1990a) Analysis of Linsker's applications of Hebbian rules to linear networks. *Network,* 1: 257–298.

MacKay, D.J.C. and Miller, K.D. (1990b) Analysis of Linsker's simulations of Hebbian rules. *Neural Comput.*, 2: 173–187.

Maffei, L. and Galli-Resta, L. (1990) Correlation in the discharges of neighboring rat retinal ganglion cells during prenatal life. *Proc. Natl. Acad. Sci. USA,* 87: 2861–2864.

Mastronarde, D.N. (1989) Correlated firing of retinal ganglion cells. *Trends Neurosci.*, 12: 75–80.

Meister, M., Wong, R.O.L., Baylor, D.A. and Shatz, C.J. (1991) Synchronous bursts of action-potentials in ganglion cells of the developing mammalian retina. *Science,* 252: 939–943.

Miller, K.D. (1990a) Correlation-based models of neural development. In: M.A. Gluck and D.E. Rumelhart (Eds.), *Neuroscience and Connectionist Theory,* Lawrence Erlbaum Ass., Hillsdale, NJ, pp. 267–353.

Miller, K.D. (1990b) Derivation of linear Hebbian equations from a non-linear Hebbian model of synaptic plasticity. *Neural Comput.*, 2: 321–333.

Miller, K.D. (1992) Development of orientation columns via competition between ON- and OFF-center inputs. *NeuroReport,* 3: 73–76.

Miller, K.D. (1994) A model for the development of simple cell receptive fields and the ordered arrangement of orientation columns through activity-dependent competition between ON- and OFF-center inputs. *J. Neurosci.,* 14: 409–441.

Miller, K.D. and MacKay, D.J.C. (1994) The role of constraints in Hebbian learning. *Neural Comput.,* 6: 98–124.

Miller, K.D. and Stryker, M.P. (1990) The development of ocular dominance columns: mechanisms and models. In: S.J. Hanson and C.R. Olson (Eds.), *Connectionist Modeling and Brain Function: The Developing Interface,* MIT Press/Bradford, Cambridge, MA, pp. 255–350.

Miller, K.D., Keller, J.B. and Stryker, M.P. (1989) Ocular dominance column development: analysis and simulation. *Science,* 245: 605–615.

Nass, M.M. and Cooper, L.N. (1975) A theory for the development of feature detecting cells in visual cortex. *Biol. Cybern.,* 19: 1–18.

Obermayer, K., Ritter, H. and Schulten, K. (1990) A principle for the formation of the spatial structure of cortical feature maps. *Proc. Natl. Acad. Sci. USA,* 87: 8345–8349.

Obermayer, K., Schulten, K. and Blasdel, G.G. (1991) A neural network model for the formation and for the spatial structure of retinotopic maps, orientation- and ocular dominance columns. Theoretical Biophysics Technical Report TB-91-09, The Beckman Institute, University of Illinois Urbana-Champaign.

Obermayer, K., Blasdel, G.G. and Schulten, K. (1992) A statistical mechanical analysis of self-organization and pattern formation during the development of visual maps. *Phys. Rev. A,* 45: 7568–7589.

Pearson, J.C., Finkel, L.H. and Edelman, G.M. (1987) Plasticity in the organization of adult cerebral cortical maps: a computer simulation based on neuronal group selection. *J. Neurosci.,* 7: 4209–4223.

Perez, R., Glass, L. and Shlaer, R. (1975) Development of specificity in the cat visual cortex. *J. Math. Biol.,* 1: 275–288.

Roe, A.W., Pallas, S.L., Hahm, J.-O. and Sur, M. (1990) A map of visual space induced in primary auditory cortex. *Science,* 250: 818–820.

Roe, A.W., Pallas, S.L., Kwon, Y.H. and Sur, M. (1992) Visual projections routed to the auditory pathway in ferrets: receptive fields of visual neurons in primary auditory cortex. *J. Neurosci.,* 12: 3651–3664.

Rojer, A.S. and Schwartz, E.L. (1990) Cat and monkey cortical columnar patterns modeled by bandpass-filtered 2D white noise. *Biol. Cybern.,* 62: 381–391.

Shatz, C.J. (1990) Impulse activity and the patterning of connections during CNS development. *Neuron,* 5: 745–756.

Shatz, C.J. and Stryker, M.P. (1988) Tetrodotoxin infusion prevents the formation of eye-specific layers during prenatal development of the cat's retinogeniculate projection. *Science,* 242: 87–89.

Sherk, H. and Stryker, M.P. (1976) Quantitative study of cortical orientation selectivity in visually inexperienced kitten. *J. Neurophysiol.,* 39: 63–70.

Sigvardt, K.A. and Williams, T.L. (1992) Models of central pattern generators as oscillators: the lamprey locomotor CPG. *Semin. Neurosci.,* 4: 37–46.

Swindale, N.V. (1980) A model for the formation of ocular dominance stripes. *Proc. R. Soc. London B.,* 208: 243–264.

Swindale, N.V. (1982) A model for the formation of orientation columns. *Proc. R. Soc. London B.,* 215: 211–230.

Traub, R.D. and Miles, R. (1992) Modeling hippocampal circuitry using data from whole cell patch clamp and dual intracellular recordings in vitro. *Semin. Neurosci.,* 4: 27–36.

Von der Malsburg, C. (1973) Self-organization of orientation selective cells in the striate cortex. *Kybernetik,* 14: 85–100.

Von der Malsburg, C. and Willshaw, D.J. (1976) A mechanism for producing continuous neural mappings: ocularity dominance stripes and ordered retino-tectal projections. *Exp. Brain Res.,* 1(Suppl.): 463–469.

Wiesel, T.N. and Hubel, D.H. (1965) Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J. Neurophysiol.,* 28: 1029–1040.

Wiesel, T.N. and Hubel, D.H. (1974) Ordered arrangement of orientation columns in monkeys lacking visual experience. *J. Comp. Neurol.,* 158: 307–318.

Willshaw, D.J. and Von der Malsburg, C. (1976) How patterned neural connections can be set up by self- organization. *Proc. R. Soc. London B.,* 194: 431–445.

Wilson, H.R. and Cowan, J.D. (1973) A mathematical theory of the functional dynamics of cortical and thalamic nervous tissue. *Kybernetik,* 13: 55–80.

Wong, R.O., Meister, M. and Shatz, C.J. (1993) Transient period of correlated bursting activity during development of the mammalian retina. *Neuron,* 11: 923–938.

Zador, A., Koch, C. and Brown, T.H. (1990) Biophysical model of a Hebbian synapse. *Proc. Natl. Acad. Sci. USA,* 87: 6718–6722.