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Review

# Contributions of Theoretical Modeling to the Understanding of Neural Map Development

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Theoretical/computational models have played an important role in developing our understanding of the fundamental mechanisms involved in neural map formation. I review models based on both chemospecific and activity-dependent matching of inputs to targets, with a particular focus on map development in the optic tectum and primary visual cortex.

## Introduction

Understanding neural map development means understanding how a set of neurons in a target structure acquire functional connectivity so as to represent their inputs in a "map-like" way. By "map-like" I mean a tendency for features of the input that are in some sense similar to be represented by nearby neurons in the target structure. An input "feature" can be, for instance, the spatial location of a ganglion cell in the retina or a touch receptor in the skin, a specific type of olfactory receptor, the preferred sound frequency of a hair cell in the cochlea, or a more abstract property, such as the orientation of an edge in a visual image (Figure 1A).

Explaining the appeal of neural map development for modelers highlights some of the crucial features of the underlying biological phenomena. Although the inputs may be complex, the output structure is usually a rather simple two-dimensional array of neurons. What is represented by these neurons that is relevant for the map (for instance, spatial location) is often fairly clear, as is how this changes when the system is perturbed. There is often abundant data available to challenge and constrain models, as it can be relatively straightforward (at least in principle) to alter the inputs and examine the effect on the resulting map. In addition, there are several plausible hypotheses for the kind of computational rules that could lead to neural map formation, and, remarkably, some of these really do seem to be relevant to map formation in biological nervous systems.

Most experimental work in neuroscience is driven by qualitative hypotheses, and the same has been true of neural map development. A seminal example is Sperry's chemospecificity hypothesis that the matching of molecular labels in the input and target structures might underlie map formation in some systems (Sperry, 1963). Such qualitative hypotheses can be instrumental in generating richly productive programs of experimental work (reviewed in Meyer, 1998). However, purely qualitative hypotheses also have limitations. First, they are inevitably imprecise. For any statement in words there are always a large number of different possible interpretations. Expressing a hypothesis in the form of mathematical equations forces precision, which can be a useful tool for identifying soft spots in the logic of the hypothesis. It is also important because subtly different interpretations can often have widely different outcomes. Working through the consequences of small changes in the mathematical assumptions can thus be important to delineate which of the many possible interpretations is the most relevant for understanding the biology. This prevents a qualitative hypothesis from remaining sufficiently vague so that it can be adapted to explain almost anything: it cuts down the "wiggle-room."

A second potential limitation of purely qualitative hypotheses is that they can become overwhelmed by the complexity of the observed phenomena and may not be capable of teasing apart the relative importance of different influences. This is certainly apparent for the case of map development. For instance, surgical, and more recently genetic, manipulations of retinotectal maps have produced a rich variety of results, with outcomes whose differences are sometimes more quantitatively than qualitatively distinct. The same is true for the data on the formation of multiple feature maps in primary visual cortex (both examples are discussed further below). In such circumstances, purely qualitative explanations may have limited power to eliminate possibilities or provide convincing arguments why one outcome should be observed over another.

Any model of the world, be it qualitative or quantitative, is a caricature. Just like a cartoonist sketching a politician, certain features deemed to be key are emphasized while others are ignored. The success of a model depends on making choices that allow progress to be made in understanding (at least some aspects of) the phenomena under consideration. A third way in which quantitative modeling can be advantageous is that it can allow a fully rigorous understanding of the particular caricature to be obtained. That is, the space of consequences of a particular set of assumptions can usually be explored to a greater level of detail than in qualitative approaches. Such quantitative explorations may lead to new insights and predictions.

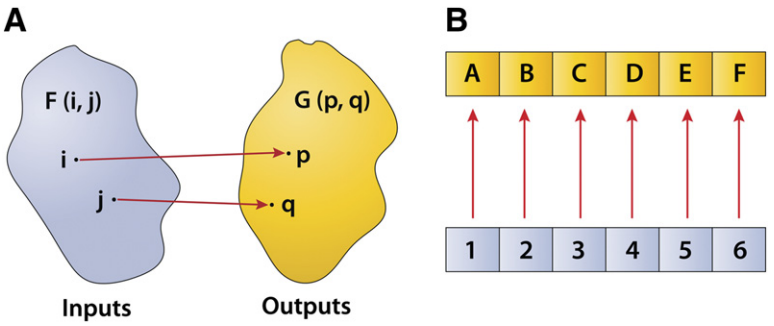


**Figure 1. Basic Principles of Topographic Mapping**

(A) In a very general characterization of topographic mapping (Goodhill and Sejnowski, 1997), the function F(i,j) specifies similarities between pairs of input points, and G(p,q) specifies similarities between pairs of output points. These similarities can be defined in different ways in different instances, including by molecular markers, physical connectivity, and correlations in neural activity.

(B) Simple topographic matching between a one-dimensional row of presynaptic neurons and a one-dimensional row of postsynaptic neurons. Prestige and Willshaw (1975) discussed two possibilities for how such a map might develop based on chemospecificity. In "type 1," there exist specific affinities between pairs of pre- and postsynaptic locations, so that for instance axons from location 3 are specifically attracted to location C. In "type 2," there exist graded affinities, so that location 3 maps to location C only because they occupy the same relative positions in the pre- and postsynaptic rows.

Some of these insights may ultimately be expressible in purely qualitative terms, but they required the initial sharpness of equations to become apparent (sometimes paraphrased as "equations are smarter than we are"). For an excellent review of the benefits of mathematical modeling in a more general biological context, see Mogilner et al. (2006).

In this review, I illustrate the above issues by highlighting some specific examples where mathematical models have helped clarify, explain, and guide experimental work in neural map formation. I focus particularly on visual map formation in the optic tectum and primary visual cortex, as this is where mathematical models have been most developed and where there has been the strongest interplay between theory and experiment. I first review some of the basic ideas underlying these two fields and then discuss in more detail some particular case studies. For reasons of space, this review is also merely a caricature, and much deserving work has had, unfortunately, to be omitted. For more complete reviews of mapping models, please see Erwin et al. (1995), Swindale (1996, 2003), Willshaw and Price (2003), and Goodhill and Xu (2005).

## Fundamental Principles of Map Formation

By the early 1970s, both chemospecific matching and correlated neural activity had been proposed as mechanisms that could lead to map formation (Gaze and Keating, 1972; Chung, 1974). Theoretical modeling in the later 1970s then rigorously demonstrated sufficient conditions for each of these mechanisms to actually work and along the way identified further necessary assumptions that had not been initially apparent from the qualitative statements of the hypotheses.

In chemospecific matching, similarity between input neurons is encoded by similarities in the molecules expressed (in a general sense) by those neurons, and likewise for output neurons. A simple way to do this is by molecular gradients, so that expression levels change systematically with distance in both the input and target structures. In activity-dependent matching, similarity between input neurons is encoded by correlations in activity, so that input features that tend to be coactive are "more similar" than features that do not tend to be coactive. The most prevalent hypothesis for the source of similarity between neurons in the output structure is that there exist lateral connections between them, with an efficacy that declines with distance. These influences are often assumed to be of the form of excitation at short range and inhibition at long range, a general profile known to have powerful pattern-forming abilities (e.g., Turing, 1952; Gierer and Meinhardt, 1972; Ermentrout and Cowan, 1979). An alternative idea is that neurons in the output structure release molecules in an activity-dependent manner, and it is the diffusion of these molecules that provides locality information in the target.

## Models of Chemospecific Map Development

Besides addressing the formation of a spatial map under normal circumstances, modeling of chemospecific map development has also attempted to explain alterations to the map following surgical manipulations such as removal or translocation of parts of the retina and tectum (reviewed in Udin and Fawcett, 1988) and, more recently, alterations due to misexpression of Eph/ephrins (reviewed in McLaughlin and O'Leary, 2005; Lemke and Reber, 2005; Flanagan, 2006).

Prestige and Willshaw (1975) developed the first mathematical model of Sperry's chemospecificity hypothesis. They introduced a distinction between "type I" matching, where each presynaptic cell has an affinity for just a small neighborhood of postsynaptic cells, with peak affinity for the topographically matching cell in the postsynaptic sheet, and "type II" matching, where all pre(post)-synaptic axons (cells) have maximum affinity for cells (axons) at one end of the post(pre)-synaptic sheet (Figure 1B). Prestige and Willshaw showed through simulations that, while type I matching is sufficient to form a map under normal conditions, it is too rigid to easily account for the map plasticity observed in fish and frogs when, for instance, parts of the retina or tectum are rotated or removed (reviewed in Udin and Fawcett, 1988; Goodhill and Xu, 2005). Type I matching was subsequently investigated further in the model of Gierer (1983) (re-expressed in a simpler form in Gierer, 1987), who confirmed that by itself type I matching

had difficulties explaining observed map plasticity. A slightly modified form of type I matching enjoyed a brief resurgence of interest in the late 1990s, when early results concerning Eph/ephrin gradients in mice were interpreted in these terms (e.g., Nakamoto et al., 1996; Honda, 1998). However, subsequent experiments genetically manipulating Eph/ephrin levels suggested again that such matching by itself is an insufficient explanation for all but map formation under normal circumstances (reviewed in Goodhill and Richards, 1999; Goodhill and Xu, 2005; see also Honda, 2003).

Type II matching is somewhat closer to what has subsequently been discovered about the role of Eph/ephrin gradients in the tectum (albeit with maximum disaffinity rather than affinity for one end of the postsynaptic sheet). In simulating this type of mechanism, Prestige and Willshaw (1975) gained the key insight that *competition* for postsynaptic sites is crucial to prevent all axons from clustering at one end of the postsynaptic sheet. Prestige and Willshaw introduced the competition via normalization, limiting both the number of postsynaptic sites an axon may contact simultaneously and the number of axon branches that can contact a postsynaptic cell. More recently, competitive mechanisms (reviewed in van Ooyen, 2001) have also been invoked to explain ephrin gene manipulation experiments (e.g., Feldheim et al., 2000).

Following this, models were proposed based primarily on sorting mechanisms, whereby pairs of presynaptic axons reverse their position in the postsynaptic sheet if they are determined to be in the wrong order (Hope et al., 1976), and marker induction, whereby neighborhood information in the postsynaptic sheet comes from the local diffusion of presynaptic molecular markers that are transported from the pre- to postsynaptic sheet (von der Malsburg and Willshaw, 1977; Willshaw and von der Malsburg, 1979). Because data from surgical manipulations of the retinotectal system of frogs and fish cannot readily be interpreted in terms of just one type of mechanism (reviewed in Udin and Fawcett, 1988), a particular concern has been to understand how influences such as weak chemospecificity, competition for target space, fiber-fiber interactions, and activity-dependent effects, while working seamlessly together during normal development, can produce a variety of outcomes under subtly different experimental perturbations (e.g., Fraser, 1980, 1985; Fraser and Perkel, 1990; Whitelaw and Cowan, 1981; Cowan and Friedman, 1990; Weber et al., 1997; Overton and Arbib, 1982; Tsigankov and Koulakov, 2006). For example, Fraser and Perkel (1990) modeled the process of retinotectal map formation as attempting to minimize the value of an "energy function" consisting of the sum of several terms representing specific types of constraints. They showed quantitatively how the competition between these constraints could reproduce map plasticity following retinal or tectal ablation, and experiments where pieces of tectum are grafted into ectopic locations.

A more recent stimulus for modeling has been the increasingly quantitative data emerging from experiments manipulating Eph and ephrin levels in mouse retina and superior colliculus (reviewed in McLaughlin and O'Leary, 2005; Lemke and Reber, 2005; Flanagan, 2006). For instance, Lemke and colleagues (Brown et al., 2000; Reber et al., 2004) characterized the variety of maps formed when levels of Eph expression are changed in just a subpopulation of retinal ganglion cells. They proposed first qualitatively and then quantitatively a model explaining these altered maps in terms of "relative signaling," where it is only the ratio of Eph expression levels between subpopulations that determines the structure of the resulting map. This idea was challenged by Koulakov and Tsigankov (2004), who proposed an alternative model based only on absolute differences in Eph expression levels. In contrast, Willshaw (2006) showed how a revised version of the marker induction model (Willshaw and von der Malsburg, 1979) could explain the same data and predicted that one should see corresponding changes in ephrin expression levels. Recent modeling has also addressed the role of Eph/ephrin-controlled branch formation in map formation (Yates et al., 2004).

## Models of Activity-Dependent Map Formation

Modeling of activity-dependent mechanisms has been most applied to understanding the development of the functional architecture of V1 (reviewed in Horton and Adams, 2005; Fitzpatrick, this issue) and how this depends on visual experience (reviewed in Sengpiel and Kind, 2002).

Sufficient parameters for activity-dependent mechanisms to form spatial, orientation, and ocular dominance preference maps were rigorously explored by von der Malsburg (1973), Willshaw and von der Malsburg (1976), and von der Malsburg and Willshaw (1976). They considered a sheet of presynaptic cells totally connected, with synapses of variable strengths, to a two-dimensional sheet of postsynaptic cells (a "high-dimensional" model; see Figure 2). Initial connectivity was random, with a small initial bias in the spatial map case to model an initial chemospecific matching mechanism. Neighborhood information in the postsynaptic sheet was communicated via lateral connections, excitatory at short range and inhibitory at long range. Simple patterns of activity were presented to the presynaptic sheet: unstructured blobs in the spatial mapping model, oriented edges for the orientation preference model, and activity blobs anticorrelated between the two eyes for the ocular dominance column model. All postsynaptic cells with activity above a certain threshold then had their connection strengths updated according to a Hebbian-type rule (Hebb, 1949). In order to prevent connection strengths from growing without bound, the total sum of strength for each postsynaptic unit was normalized to a constant value by dividing each connection strength by the total sum (analyzed in Wiskott and Sejnowski, 1998). An elegant mathematical analysis of a nonlinear model closely related to that of Willshaw and von der Malsburg's was presented by Takeuchi and Amari (1979) and Amari (1980).

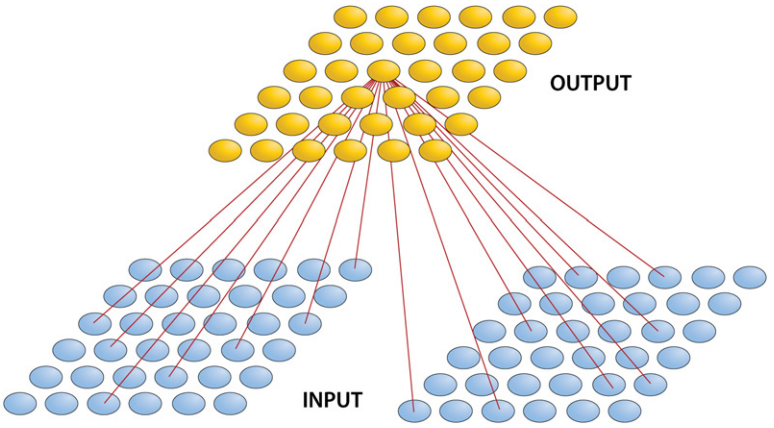


**Figure 2. Basic Framework of High-Dimensional Models**

One or more sheets of input neurons project to a sheet of output neurons. Some initial pattern of connectivity is assumed, either random, roughly topographic, or finely topographic (for clarity, only connections to one output neuron are shown in the figure). Patterns of activity are applied to the input layers, and the resulting activity of neurons in the output layer is calculated. Output neurons are usually assumed to be connected by short-range excitation and long-range inhibition, though direct evidence for this in visual cortex is lacking (reviewed in Swindale, 1996; Carreira-Perpiñán and Goodhill, 2004). Connection strengths are then updated, usually with some form of Hebbian learning rule.

However, subsequent work showed that ocular dominance and orientation (though not spatial topography) could still form in simplified linear models, allowing further mathematical analysis of the role of particular parameters. Linsker (1986) showed that a linear network with several layers, loosely modeled on the first few layers of visual processing in the retina, LGN and V1, required only a simple Hebbian learning rule to produce receptive fields roughly matching those found biologically at each layer, including an orientation map in V1. MacKay and Miller (1990) performed an eigenvector analysis of this model, which further established the role of particular parameters in determining the types of receptive fields that emerged. Linsker's model showed that completely unstructured "spontaneous" input activity in the first layer was sufficient to drive structured receptive field development in later layers, establishing that complex correlations in the input are not required for complex structure to emerge at later stages of processing. Miller and colleagues developed related modeling ideas for the formation of ocular dominance maps (Miller et al., 1989), orientation maps (Miller, 1994), and the joint formation of both (Erwin and Miller, 1998), and Berns et al. (1993) for the formation of disparity selectivity. Again, the linearity of these models allowed a thorough characterization of the dependence of the results on the parameters (see also Dayan and Goodhill 1992; Piepenbrock et al., 1997).

Meanwhile, high-dimensional nonlinear models continued to be developed and were found to have some interestingly different properties from linear models (Obermayer et al., 1990; Goodhill, 1993; Barrow et al., 1996; Bauer et al., 1997; Riesenhuber et al., 1998; Scherf et al., 1999; Woodbury et al., 2002), including models that also allow plasticity of lateral connections (Sirosh and Miikkulainen, 1997; Bednar and Miikkulainen, 2006). More recently, models have been proposed that can "interpolate" smoothly between the linear and nonlinear regimes (Piepenbrock and Obermayer, 1999, 2000; Dayan, 2001). In addition, it has been shown that more complex rules for modifying synaptic strengths, such as spike-timing-dependent plasticity (STDP) (Song and Abbott, 2001; Young et al., 2007) and information-theoretic approaches (Linsker, 1989, 1990; Hyvärinen and Hoyer, 2001; Hyvärinen et al., 2001; Osindero et al., 2005), can also lead to map formation. Models have also begun to be developed that address the laminar structure of V1, particularly the role of the subplate in map formation, rather than treating it as just a two-dimensional sheet (Grossberg and Seitz, 2003; Kanold and Shatz, 2006). Lateralization effects between map development in opposite hemispheres have also been explored (Levitan and Reggia, 2000).

## Low-Dimensional and Other Models

In parallel to high-dimensional models, several authors have proposed an alternative framework based on a "low-dimensional" formulation of the mapping problem (Durbin and Mitchison, 1990; Goodhill and Willshaw, 1990; Obermayer et al., 1992). Here, inputs are simplified, from patterns of activity in an array of input cells, to points in a space of just a few dimensions, each dimension representing the complete range of values of a "prepackaged" feature (Figure 3). For instance, two dimensions for visual field position, one for ocularity, one for spatial frequency, and so on. The receptive fields of postsynaptic neurons can then be represented as points in this low-dimensional feature space, their location in the feature space indicating their preferred stimuli. These models are generally based on either the elastic net (Durbin and Willshaw, 1987) or Kohonen (1982, 2000, 2006) algorithms, both of which can be interpreted as particular mathematical instantiations of Hebbian learning. They trade off principles of "coverage" (Swindale, 1991), which matches cortical receptive fields to the input features that need to be represented, and continuity, which ensures that neighboring postsynaptic neurons represent similar features (Durbin and Mitchison, 1990). Such continuity can be motivated by the idea of "minimal wiring," i.e., keeping intracortical connections short (Cowey, 1979; Durbin and Mitchison, 1990; Mitchison, 1995; Koulakov and Chklovskii, 2001; Chklovskii and Koulakov, 2004). Low-dimensional models give a remarkably good fit to experimental data on the geometrical properties of maps in V1 (Figure 4), including subtle changes in these properties following various forms of visual deprivation (e.g., Erwin et al., 1995; Swindale and

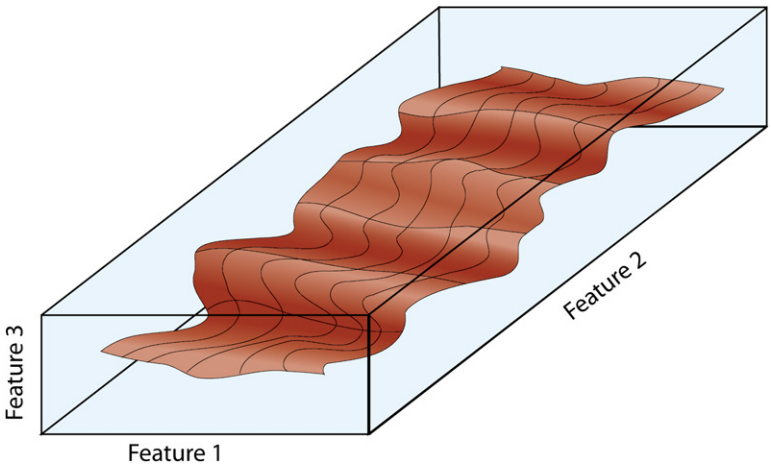


**Figure 3. Basic Framework of Low-Dimensional Models**

The box represents the space of input features. Only three are shown (representing for instance azimuth, elevation, and ocular dominance), though there can be many more. The receptive fields of output neurons are represented by points in the input space. The position of each point represents the combination of features to which it is most responsive (the degree of selectivity, or size of receptive field, is not drawn). These positions are unrelated to physical positions in the array of output neurons. To convey information about physical position, the points representing the receptive fields of physically neighboring output neurons are connected by lines, forming the folded sheet drawn in the input space. This gives a visual impression of the degree of distortion of the map along each feature dimension. Learning generally consists of choosing points in the feature space and then "pulling" the cortical sheet toward those points.

Bauer, 1998; Swindale, 2000, 2004; Yu et al., 2005; Carreira-Perpiñán et al., 2005; Farley et al., 2007). They have also proved amenable to extensive mathematical analysis (e.g., Durbin et al., 1989; Hoffsümmer et al., 1996; Wolf et al., 2000; Goodhill and Cimponeriu, 2000). In addition, it has been demonstrated that models that appear different superficially can actually be at root quite similar (e.g., Yuille et al., 1996; Goodhill and Sejnowski, 1997).

A different approach to the simplification of high-dimensional models was taken by Swindale (1980, 1982). This model eliminates an explicit representation of the inputs entirely and focuses instead on how center-surround patterns of lateral connectivity in the postsynaptic layer cause some spatial patterns of synaptic strengths to increase at the expense of others (see also Rojer and Schwartz, 1990; Grossberg and Olson, 1994). Realistic-looking maps can be produced within a very simple framework, which again can be analyzed mathematically. Tanaka's model (Tanaka, 1991a, 1991b; Miyashita and Tanaka, 1992) took a "thermodynamic" approach based on an analogy with well-established models for the self-organization of certain physical systems. Again it was shown how minimizing a biologically motivated objective function can be an effective means for producing patterns closely resembling maps in V1.

Others have modeled map formation driven by diffusion of neurotransmitters (Montague et al., 1991), by intracortical competition for limiting supplies of neurotrophins (Elliott and Shadbolt, 1996, 1998, 1999; Harris et al., 1997), and how cortical growth might affect map structure (Oster and Bressloff, 2006). A particular recent concern has also been symmetry considerations and the coupling of spatial and orientation preference maps (Lee et al., 2003; Thomas and Cowan, 2004; Wolf, 2005). Neuromorphic hardware has begun to be developed which forms maps in silicon with some of the properties of those seen in V1 (Taba and Boahen, 2003; Merolla and Boahen, 2004, Boahen, 2005). An open-source software package (http://topographica.org) has also recently been introduced that allows simulations of some of the above models to be easily constructed (Bednar et al., 2004).

## Some Examples of How Visual Mapping Models Have Illuminated Specific Issues in Map Development

### *Models Have Suggested Reasons Why Overall Map Structure Has Species-Specific Biases*

A notable difference between species in maps in V1 is their degree of global order. For instance, macaque ocular

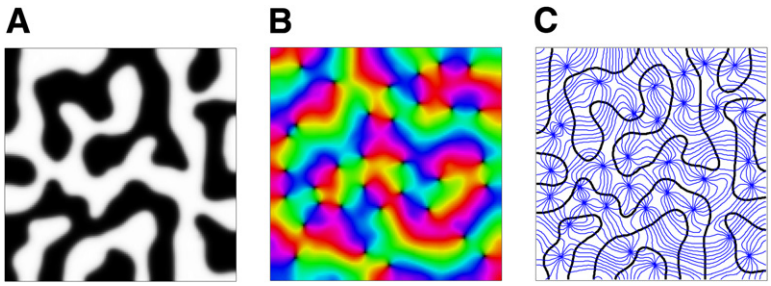


**Figure 4. Simulation of the Simultaneous Formation of Maps of Spatial Topography, Ocular Dominance, and Orientation Preference in Visual Cortex Using a Low-Dimensional Model (in This Case the Elastic Net)**

(A) Ocular dominance map. White represents regions of cortex dominated by one eye, and black by the other.

(B) Orientation preference map for the same part of cortex as in (A). Colors represent preferred orientation on a periodic color wheel. Note the presence of orientation singularities (pinwheels).

(C) Contours of ocular dominance (black) and orientation (blue). As in experimental data, the two sets of contours tend to intersect at steep angles, and pinwheels tend to lie at the center of ocular dominance columns. For further details, see Carreira-Perpiñán et al. (2005).

dominance columns tend to form parallel stripes (LeVay et al., 1985; Horton and Hocking, 1996), while cat ocular dominance columns are more disordered (e.g., Kaschube et al., 2003). Following an initial suggestion of LeVay et al. (1985), theoretical models have shown that these differences could arise purely from the shape of the V1, which is much more elongated in the macaque than the cat. Jones et al. (1991) demonstrated in a nondevelopmental model that optimization of a simple measure of map continuity produced disordered ocular dominance stripes when mapping two circles, representing the retinae, to a circle, representing cat V1, but much more parallel stripes when mapping to an ellipse, representing macaque V1. The same was then shown in developmental models (Goodhill and Willshaw, 1994; Bauer 1995), which were also extended to account for more subtle features of overall ocular dominance organization in macaque V1 (Goodhill et al., 1997). The idea was applied to the case of orientation columns in cat V2 in Wolf et al. (1996), who argued that the strong geometrical constraints in this case could explain the alignment of orientation maps between the two eyes in cats, even in the absence of binocular visual experience (Gödecke and Bonhoeffer, 1996; see also Shouval et al., 2000). Wolf et al. (1994) also introduced the notion that purely geometrical constraints could underlie the formation of the topographic field discontinuities and islands that are observed in some cases. While more recent experimental work has suggested a strong influence of molecular cues competing with activity-dependent self-organizing effects on map development in V1 (e.g., Weliky and Katz, 1997; Crowley and Katz, 2002; Kaschube et al., 2002, 2003), the modeling work described above has played an important role in both stimulating particular types of experiments and characterizing the surprisingly reproducible order that can be obtained from purely self-organizing mechanisms.

### *Models Have Suggested Specific Dynamics for the Development of Maps*

Optical imaging studies have shown that, from as soon as functional maps in V1 can be recorded, their global structure is essentially stable, though they can disappear again without adequate visual stimulation (Crair et al., 1998). This however does not address the question of how their structure develops initially, before functional maps are obtainable with current recording techniques. Certain theoretical models have made some intriguing predictions regarding the dynamics of this early development. For instance, Hoffsümmer et al. (1996) and Goodhill and Cimponeriu (2000) showed that final column width in the elastic net model is closely related to the rate of column development, and predicted that if the periodicity of the final orientation map is greater than the periodicity of the final ocular dominance map then orientation columns must have developed before ocular dominance columns, and vice versa. Given experimental measurements of final periodicities in cats (Löwel et al., 1998) and monkeys (Obermayer and Blasdel, 1993), the prediction becomes that orientation columns form first in cats, but that ocular dominance columns form first in monkeys. Related to this, Giacomantonio and Goodhill (2007) suggested that the variability in angioscotoma representation observed in squirrel monkey V1 by Adams and Horton (2002, 2003) could be due to variations in the progress of ocular dominance column development at the time of birth in these animals. A more boldly controversial claim by Wolf and Geisel (1998) was based on a very general mathematical analysis of the pattern-formation processes underlying all physical structures resembling orientation maps (Wolf and Geisel, 2003). They predicted that, to be consistent with the relatively low final density of orientation map pinwheels compared to orientation map periodicity observed experimentally, pinwheels of opposite chirality must be moving, colliding, and annihilating during development. While as yet there is no direct experimental evidence to support these predictions, it is unclear whether current technologies probing functional maps in V1 in very young animals are adequate to test them. The examples discussed above provide useful illustrations of the kinds of predictions that would be unlikely to arise from purely qualitative reasoning.

### *Models Have Provoked Experimental Tests of Hypotheses for the Factors that Control the Width of Cortical Columns*

Maps such as ocular dominance and orientation preference are characterized by a very regular periodicity. Theoretical models have played an important role in refining our understanding of which biological variables control this periodicity. Although not thoroughly analyzed in the original studies of von der Malsburg (1973) and von der Malsburg and Willshaw (1976), the primary determinant of periodicity in those models is the extent of intracortical connections. Swindale (1980, 1982), and Miller et al. (1989) addressed this issue more systematically in their models and showed that this periodicity is largely determined by the position of peak power in the Fourier transform of the cortical interaction function (pattern of lateral connections). A similar influence of lateral connections was subsequently shown in nonlinear models (e.g., Goodhill, 1993; Dayan, 1993). To test this hypothesis experimentally requires disrupting the normal pattern of intracortical connections. This was finally achieved by Hensch and Stryker (2004), who showed they could indeed influence ocular dominance column periodicity by perturbing GABA-mediated intracortical inhibition.

However, simulations and analysis of nonlinear models have demonstrated an additional possible influence on ocular dominance column periodicity besides the structure of lateral connections: the degree of correlation between the two eyes (Goodhill and Willshaw, 1990; Dayan, 1993; Goodhill, 1993; Sirosh and Miikkulainen, 1997; Elliott and Shadbolt, 1998; Wolf et al., 2000; Scherf et al., 1999). To test this requires disrupting the normally positive correlations between the two eyes, and in particular Goodhill (1993) predicted that strabismic cats should have wider ocular dominance columns than normal cats. A subsequent experiment directly testing the strabismus idea

found results consistent with the prediction (Löwel, 1994). The hypothesis that the statistics of retinal activity could affect not just local cortical structure (as in for instance the shifts of column borders with monocular deprivation [Shatz and Stryker, 1978]) but also the large-scale periodicity of V1 (Goodhill and Löwel, 1995) proved a fruitful, though controversial, stimulus for further work. In support, analogous increases in ocular dominance column width were reported in cats raised with alternating monocular occlusion (Tieman and Tumosa, 1997) and in amblyopic monkeys (A.W. Roe et al., 1995, Soc. Neurosci., abstract), and very broad columns were reported in strabismic squirrel monkeys (Livingstone, 1996). At the same time, it became apparent that the prediction was a robust feature of several different models, and a deeper analytical understanding of why the effect occurs in some models was obtained. However, other experimental studies challenged the hypothesis. No systematic changes were reported in periodicity in macaque V1 with strabismus (Murphy et al., 1998; Crawford, 1998), and a study of strabismic squirrel monkeys was inconclusive (Adams and Horton, 2006). Furthermore, a subsequent analysis by Löwel and colleagues of a much larger number of normal and strabismic cats (Kaschube et al., 2003) found no differences in periodicity on average. This line of enquiry helped stimulate two important discoveries. First, that there exists large "natural" variability in column periodicities between individuals of the same species (e.g., Horton and Hocking, 1996; Rathjen et al., 2002; Adams and Horton, 2006). Second, genetic background exerts a strong influence on the overall structure of V1, in particular the periodicity of orientation (Kaschube et al., 2002) and ocular dominance (Kaschube et al., 2003) columns, a factor that was not controlled for in Löwel (1994). Thus, to definitively establish whether strabismus causes wider ocular dominance columns, differing rearing conditions would need to be applied to genetically identical cats. This example illustrates that theoretical predictions do not necessarily have to be immediately proven correct to be useful: they can still play an important role in stimulating new directions for research.

## Conclusions and Future Directions

Basic modeling principles established in the 1970s are still highly relevant today. Several different types of mathematical caricatures of neural map formation have been explored, both by simulation and (in some cases extensive) mathematical analysis. These models have had a strong influence on our general understanding of mechanisms for neural map formation, and in some cases have directly motivated and guided experimental work. However, the dramatic recent increase in our knowledge of the molecular mechanisms underlying map formation suggests many avenues for future work. These include understanding more about how chemospecific and activity-dependent cues conspire and compete in map formation, how chemospecific mechanisms alone might produce feature as well as spatial maps, and the mechanisms underlying the similarity of overall map structure between genetically related individuals. Additionally, there is great potential for new imaging technologies to produce more quantitative characterizations of map structure for comparison with model predictions. More generally, it will also be important to understand better the relevance of models of visual mapping to mapping in other modalities.

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## REFERENCES

Adams, D.L., and Horton, J.C. (2002). Shadows cast by retinal blood vessels mapped in primary visual cortex. Science *298*, 572–576.

Adams, D.L., and Horton, J.C. (2003). The representation of retinal blood vessels in primate striate cortex. J. Neurosci. *23*, 5984–5997.

Adams, D.L., and Horton, J.C. (2006). Ocular dominance columns in strabismus. Vis. Neurosci. *23*, 795–805.

Amari, S. (1980). Topographic organization of nerve fields. Bull. Math. Biol. *42*, 339–364.

Barrow, H.G., Bray, A., and Budd, J.M.L. (1996). A self-organizing model of color blob formation. Neural Comput. *8*, 1427–1448.

Bauer, H.-U. (1995). Development of oriented ocular dominance bands as a consequence of areal geometry. Neural Comput. *7*, 36–50.

Bauer, H.-U., Brockmann, D., and Geisel, T. (1997). Analysis of ocular dominance pattern formation in a high-dimensional self-organizing-map model. Network *8*, 17–33.

Bednar, J.A., and Miikkulainen, R. (2006). Joint maps for orientation, eye, and direction preference in a self-organizing model of V1. Neurocomputing *69*, 1272–1276.

Bednar, J.A., Choe, Y., De Paula, J., Miikkulainen, R., Provost, J., and Tversky, T. (2004). Modeling cortical maps with Topographica. Neurocomputing *58*, 1129–1135.

Berns, G.S., Dayan, P.S., and Sejnowski, T.J. (1993). A correlational model for the development of disparity selectivity in visual cortex that depends on prenatal and postnatal phases. Proc. Natl. Acad. Sci. USA *90*, 8277–8281.

Boahen, K. (2005). Neuromorphic microchips. Sci. Am. *292*, 56–63.

Brown, A., Yates, P.A., Burrola, P., Ortuno, D., Vaidya, A., Jessell, T.M., Pfaff, S.L., O'Leary, D.D.M., and Lemke, G. (2000). Topographic mapping from the retina to the midbrain is controlled by relative but not absolute levels of EphA receptor signaling. Cell *102*, 77–88.

Carreira-Perpiñán, M.Á., and Goodhill, G.J. (2004). The influence of lateral connections on the structure of cortical maps. J. Neurophysiol. *92*, 2947–2959.

Carreira-Perpiñán, M.Á., Lister, R., and Goodhill, G.J. (2005). A computational model for the development of multiple maps in primary visual cortex. Cereb. Cortex *15*, 1222–1233.

Chklovskii, D.B., and Koulakov, A.A. (2004). Maps in the brain: what can we learn from them? Annu. Rev. Neurosci. *27*, 369–392.

Chung, S.H. (1974). In search of the rules for nerve connections. Cell *3*, 201–205.

Cowan, J.D., and Friedman, A.E. (1990). Development and regeneration of eye-brain maps: A computational model. In Advances in Neural Information Processing Systems, II, D.S. Touretzky, ed. (San Francisco, CA: Elsevier), pp. 92–99.

Cowey, A. (1979). Cortical maps and visual perception. Q. J. Exper. Psychol. *31*, 1–17.

Crair, M.C., Gillespie, D.C., and Stryker, M.P. (1998). The role of visual experience in the development of columns in cat visual cortex. Science *279*, 566–570.

Crawford, M.L.J. (1998). Column spacing in normal and visually deprived monkeys. Exp. Brain Res. *123*, 282–288.

Crowley, J.C., and Katz, L.C. (2002). Development of cortical circuits: lessons from ocular dominance columns. Nat. Rev. Neurosci. *3*, 34–42.

Dayan, P.S. (1993). Arbitrary elastic topologies and ocular dominance. Neural Comput. *5*, 392–401.

Dayan, P. (2001). Competition and arbors in ocular dominance. In Advances in Neural Information Processing Systems, 13, T.K. Leen, T.G. Dietterich, and V. Tresp, eds. (Cambridge, MA: MIT Press), pp. 203–209.

Dayan, P.S., and Goodhill, G.J. (1992). Perturbing Hebbian rules. In Advances in Neural Information Processing Systems, 4, J.E. Moody, S.J. Hanson, and R.P. Lippman, eds. (San Mateo, CA: Morgan Kaufmann), pp. 19–26.

Durbin, R., and Willshaw, D.J. (1987). An analogue approach to the travelling salesman problem using an elastic net method. Nature *326*, 689–691.

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

Durbin, R., Szeliski, R., and Yuille, A. (1989). An analysis of the elastic net approach to the traveling salesman problem. Neural Comput. *1*, 348–358.

Elliott, T., and Shadbolt, N.R. (1996). A Mathematical model of activity-dependent, anatomical segregation induced by competition for neurotrophic support. Biol. Cybern. *75*, 463–470.

Elliott, T., and Shadbolt, N.R. (1998). Competition for neurotrophic factors: ocular dominance columns. J. Neurosci. *18*, 5850–5858.

Elliott, T., and Shadbolt, N.R. (1999). A neurotrophic model of the development of the retinogeniculocortical pathway induced by spontaneous retinal waves. J. Neurosci. *19*, 7951–7970.

Ermentrout, G.B., and Cowan, J.D. (1979). A mathematical theory of visual hallucination patterns. Biol. Cybern. *34*, 137–150.

Erwin, E., and Miller, K.D. (1998). Correlation-based development of ocularly matched orientation and ocular dominance maps: determination of required input activities. J. Neurosci. *18*, 9870–9895.

Erwin, E., Obermayer, K., and Schulten, K. (1995). Models of orientation and ocular dominance columns in the visual cortex: a critical comparison. Neural Comput. *7*, 425–468.

Farley, B., Yu, H., Dezhe, J., and Sur, M. (2007). Alteration of visual input results in a coordinated reorganization of multiple visual cortex maps. J. Neurosci. *27*, 10299–10310.

Feldheim, D.A., Kim, Y.I., Bergemann, A.D., Frisén, J., Barbacid, M., and Flanagan, J.G. (2000). Genetic analysis of ephrin-A2 and ephrin-A5 shows their requirement in multiple aspects of retinocollicular mapping. Neuron *25*, 563–574.

Flanagan, J.G. (2006). Neural map specification by gradients. Curr. Opin. Neurobiol. *16*, 59–66.

Fraser, S.E. (1980). A differential adhesion approach to the patterning of neural connections. Dev. Biol. *79*, 453–464.

Fraser, S.E. (1985). Cell interactions involved in neural patterning. In Molecular Bases Of Neural Development, G.M. Edelman, W.E. Gall, and W.M. Cowan, eds. (New York: Wiley), pp. 481–507.

Fraser, S.E., and Perkel, D.H. (1990). Competitive and positional cues in the patterning of nerve connections. J. Neurobiol. *21*, 51–72.

Gaze, R.M., and Keating, M.J. (1972). The visual system and "neuronal specificity". Nature *237*, 375–378.

Giacomantonio, C.E., and Goodhill, G.J. (2007). The effect of angioscotomas on map structure in primary visual cortex. J. Neurosci. *27*, 4935–4946.

Gierer, A. (1983). Model for the retinotectal projection. Proc. R. Soc. Lond. B. Biol. Sci. *218*, 77–93.

Gierer, A. (1987). Directional cues for growing axons forming the retinotectal projection. Development *101*, 479–489.

Gierer, A., and Meinhardt, H. (1972). A theory of biological pattern formation. Kybernetic *12*, 30–39.

Gödecke, I., and Bonhoeffer, T. (1996). Development of identical orientation maps for two eyes without common visual experience. Nature *379*, 251–254.

Goodhill, G.J. (1993). Topography and ocular dominance: a model exploring positive correlations. Biol. Cybern. *69*, 109–118.

Goodhill, G.J., and Willshaw, D.J. (1990). Application of the elastic net algorithm to the formation of ocular dominance stripes. Network *1*, 41–59.

Goodhill, G.J., and Willshaw, D.J. (1994). Elastic net model of ocular dominance: Overall stripe pattern and monocular deprivation. Neural Comput. *6*, 615–621.

Goodhill, G.J., and Löwel, S. (1995). Theory meets experiment: correlated neural activity helps determine ocular dominance column periodicity. Trends Neurosci. *18*, 437–439.

Goodhill, G.J., and Sejnowski, T.J. (1997). A unifying objective function for topographic mappings. Neural Comput. *9*, 1291–1304.

Goodhill, G.J., and Richards, L.J. (1999). Retinotectal maps: molecules, models, and misplaced data. Trends Neurosci. *22*, 529–534.

Goodhill, G.J., and Cimponeriu, A. (2000). Analysis of the elastic net model applied to the formation of ocular dominance and orientation columns. Network *11*, 153–168.

Goodhill, G.J., and Xu, J. (2005). The development of retinotectal maps: a review of models based on molecular gradients. Network *16*, 5–34.

Goodhill, G.J., Bates, K.R., and Montague, P.R. (1997). Influences on the global structure of cortical maps. Proc. Biol. Sci. *264*, 649–655.

Grossberg, S., and Olson, S.J. (1994). Rules for the cortical map of ocular dominance and orientation columns. Neural Netw. *7*, 883–894.

Grossberg, S., and Seitz, A. (2003). Laminar development of receptive fields, maps and columns in visual cortex: the coordinating role of the subplate. Cereb. Cortex *13*, 852–863.

Harris, A.E., Ermentrout, G.B., and Small, S.L. (1997). A model of ocular dominance column development by competition for trophic factor. Proc. Natl. Acad. Sci. *94*, 9944–9949.

Hebb, D.O. (1949). The Organization of Behaviour (New York: Wiley).

Hensch, T.K., and Stryker, M.P. (2004). Columnar architecture sculpted by GABA circuits in developing cat visual cortex. Science *303*, 1678–1681.

Hoffsümmer, F., Wolf, F., Geisel, T., Löwel, S., and Schmidt, K. (1996). Sequential bifurcation and dynamic rearrangement of columnar patterns during cortical development. In Computational Neuroscience: Trends in Research 1995, J. Bower, ed. (San Diego, CA: Academic Press), pp. 197–202.

Honda, H. (1998). Topographic mapping in the retinotectal projection by means of complementary ligand and receptor gradients: a computer simulation study. J. Theor. Biol. *192*, 235–246.

Honda, H. (2003). Competition between retinal ganglion cell axons under the servomechanism model explains abnormal retinocollicular

projection of Eph-overexpressing or ephrin-lacking mice. J. Neurosci. *23*, 10368–10377.

Hope, R.A., Hammond, B.J., and Gaze, R.M. (1976). The arrow model: retinotectal specificity and map formation in the goldfish visual system. Proc. R. Soc. Lond. B. Biol. Sci. *194*, 447–466.

Horton, J.C., and Hocking, D.R. (1996). Intrinsic variability of ocular dominance column periodicity in normal macaque monkeys. J. Neurosci. *16*, 7228–7239.

Horton, J.C., and Adams, D.L. (2005). The cortical column: a structure without a function. Philos. Trans. R. Soc. Lond. B. Biol. Sci. *360*, 837–862.

Hyvärinen, A., and Hoyer, P.O. (2001). A two-layer sparse coding model learns simple and complex cell receptive fields and topography from natural images. Vision Res. *41*, 2413–2423.

Hyvärinen, A., Hoyer, P.O., and Inki, M. (2001). Topographic independent component analysis. Neural Comput. *13*, 1527–1558.

Jones, D.G., Van Sluyters, R.C., and Murphy, K.M. (1991). A computational model for the overall pattern of ocular dominance. J. Neurosci. *11*, 3794–3808.

Kanold, P.O., and Shatz, C.J. (2006). Subplate neurons regulate maturation of cortical inhibition and outcome of ocular dominance plasticity. Neuron *51*, 627–638.

Kaschube, M., Wolf, F., Geisel, T., and Löwel, S. (2002). Genetic influence on quantitative features of neocortical architecture. J. Neurosci. *22*, 7206–7217.

Kaschube, M., Wolf, F., Puhlmann, M., Rathjen, S., Schmidt, K.-F., Geisel, T., and Löwel, S. (2003). The pattern of ocular dominance columns in cat primary visual cortex: intra- and interindividual variability of column spacing and its dependence on genetic background. Eur. J. Neurosci. *18*, 3251–3266.

Kohonen, T. (1982). Self-organized formation of topologically correct feature maps. Biol. Cybern. *43*, 59–69.

Kohonen, T. (2000). Self-Organizing Maps, Third Edition (Berlin: Springer).

Kohonen, T. (2006). Self-organizing neural projections. Neural Netw. *19*, 723–733.

Koulakov, A.A., and Chklovskii, D.B. (2001). Orientation preference patterns in mammalian visual cortex: a wire length minimzation approach. Neuron *29*, 519–527.

Koulakov, A.A., and Tsigankov, D.N. (2004). A stochastic model for retinocollicular map development. BMC Neurosci. *5*, 30.

Lee, H.Y., Yahyanejad, M., and Kardar, M. (2003). Symmety considerations and the development of pinwheels in visual maps. Proc. Natl. Acad. Sci. USA *100*, 16036–16040.

Lemke, G., and Reber, M. (2005). Retinotectal mapping: new insights from molecular genetics. Annu. Rev. Cell Dev. Biol. *21*, 551–580.

LeVay, S., Connolly, M., Houde, J., and Van Essen, D.C. (1985). The complete pattern of ocular dominance stripes in the striate cortex and visual field of the macaque monkey. J. Neurosci. *5*, 486–501.

Levitan, S., and Reggia, J.A. (2000). A computational model of lateralization and asymmetries in cortical maps. Neural Comput. *12*, 2037–2062.

Linsker, R. (1986). From basic network principles to neural architecture (series). Proc. Natl. Acad. Sci. USA *83*, 7508–7512, 8390–8394, 8779–8783.

Linsker, R. (1989). How to generate ordered maps by maximizing the mutual information between input and output signals. Neural Comput. *1*, 402–411.

Linsker, R. (1990). Perceptual neural organization: some approaches based on network models and information theory. Annu. Rev. Neurosci. *13*, 257–281.

Livingstone, M. (1996). Ocular dominance columns in New-World monkeys. J. Neurosci. *16*, 2086–2096.

Löwel, S. (1994). Ocular dominance column development: strabismus changes the spacing of adjacent columns in cat visual cortex. J. Neurosci. *14*, 7451–7468.

Löwel, S., Schmidt, K.E., Kim, D.-S., Wolf, F., Hoffsümmer, F., Singer, W., and Bonhoeffer, T. (1998). The layout of orientation and ocular dominance domains in area 17 of strabismic cats. Eur. J. Neurosci. *10*, 2629–2643.

MacKay, D.J.C., and Miller, K.D. (1990). Analysis of Linsker's application of Hebbian rules to linear networks. Network *1*, 257–297.

McLaughlin, T., and O'Leary, D.D.M. (2005). Molecular gradients and development of retinotopic maps. Annu. Rev. Neurosci. *28*, 327–355.

Merolla, P., and Boahen, K. (2004). A recurrent model of orientation maps with simple and complex cells. In Advances in Neural Information Processing Systems, 16, S. Thrun and L. Saul, eds. (Cambridge, MA: MIT Press), pp. 995–1002.

Meyer, R.L. (1998). Roger Sperry and his chemoaffinity hypothesis. Neuropsychologia *36*, 957–980.

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

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

Mitchison, G. (1995). A type of duality between self-organizing maps and minimal wiring. Neural Comput. *7*, 25–35.

Miyashita, M., and Tanaka, S. (1992). A mathematical model for the self-organization of orientation columns in visual cortex. Neuroreport *3*, 69–72.

Mogilner, A., Wollman, R., and Marshall, W.F. (2006). Quantitative modeling in cell biology: what is it good for? Dev. Cell *11*, 279–287.

Montague, P.R., Gally, J.A., and Edelman, G.M. (1991). Spatial signalling in the development and function of neural connections. Cereb. Cortex *1*, 199–220.

Murphy, K.M., Jones, D.G., Fenstemaker, S.B., Pegado, V.D., Kiorpes, L., and Movshon, J.A. (1998). Spacing of cytochrome oxidase blobs in visual cortex of normal and strabismic monkeys. Cereb. Cortex *8*, 237–244.

Nakamoto, M., Cheng, H.J., Friedman, G.C., Mclaughlin, T., Hansen, M.J., Yoon, C.H., O'Leary, D.D.M., and Flanagan, J.G. (1996). Topographically specific effects of ELF-1 on retinal axon guidance in vitro and retinal axon mapping in vivo. Cell *86*, 755–766.

Obermayer, K., and Blasdel, G.G. (1993). Geometry of orientation and ocular dominance columns in monkey striate cortex. J. Neurosci. *13*, 4114–4129.

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

Osindero, S., Welling, M., and Hinton, G.E. (2005). Topographic product models applied to natural scene statistics. Neural Comput. *18*, 381–414.

Oster, A.M., and Bressloff, P.C. (2006). A developmental model of ocular dominance column formation on a growing cortex. Bull. Math. Biol. *68*, 73–98.

Overton, K.J., and Arbib, M.A. (1982). The extended branch-arrow model of the formation of retino-tectal connections. Biol. Cybern. *45*, 157–175.

Piepenbrock, C., and Obermayer, K. (1999). The role of lateral cortical competition in ocular dominance development. In Advances in Neural Information Processing Systems, 11, M.S. Kearns, S.A. Solla, and D.A. Cohn, eds. (Cambridge, MA: MIT Press), pp. 139–145.

Piepenbrock, C., and Obermayer, K. (2000). The effect of intracortical competition on the formation of topographic maps in models of Hebbian learning. Biol. Cybern. *82*, 345–353.

Piepenbrock, C., Ritter, H., and Obermayer, K. (1997). The joint development of orientation and ocular dominance: role of constraints. Neural Comput. *9*, 959–970.

Prestige, M.C., and Willshaw, D.J. (1975). On a role for competition in the formation of patterned neural connexions. Proc. R. Soc. Lond. B. Biol. Sci. *190*, 77–98.

Rathjen, S., Schmidt, K.E., and Löwel, S. (2002). Two-dimensional analysis of the spacing of ocular dominance columns in normally raised and strabismic kittens. Exp. Brain Res. *145*, 158–165.

Reber, M., Burrola, P., and Lemke, G. (2004). A relative signalling model for the formation of a topographic neural map. Nature *431*, 847–853.

Riesenhuber, M., Bauer, H., Brockmann, D., and Geisel, T. (1998). Breaking rotational symmetry in a self-organizing map model for orientation map development. Neural Comput. *10*, 717–730.

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

Scherf, O., Pawelzik, K., Wolf, F., and Geisel, T. (1999). Theory of ocular dominance pattern formation. Phys. Rev. E *59*, 6977–6993.

Sengpiel, F., and Kind, P.C. (2002). The role of activity in development of the visual system. Curr. Biol. *12*, R818–R826.

Shatz, C.J., and Stryker, M.P. (1978). Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation. J. Physiol. *281*, 267–283.

Shouval, H.Z., Goldberg, D.H., Jones, J.P., Beckerman, M., and Cooper, L.N. (2000). Structured long-range connections can provide a scaffold for orientation maps. J. Neurosci. *20*, 1119–1128.

Sirosh, J., and Miikkulainen, R. (1997). Topographic receptive fields and patterned lateral interaction in a self-organizing model of the primary visual cortex. Neural Comput. *9*, 577–594.

Song, S., and Abbott, L.F. (2001). Cortical development and remapping through spike-timing dependent plasticity. Neuron *32*, 339–350.

Sperry, R.W. (1963). Chemoaffinity in the orderly growth of nerve fiber patterns and connections. Proc. Natl. Acad. Sci. USA *50*, 703–710.

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

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

Swindale, N.V. (1991). Coverage and the design of striate cortex. Biol. Cybern. *65*, 415–424.

Swindale, N.V. (1996). The development of topography in the visual cortex: a review of models. Network *7*, 161–247.

Swindale, N.V. (2000). How many maps are there in visual cortex? Cereb. Cortex *10*, 633–643.

Swindale, N.V. (2003). Development of ocular dominance stripes, orientation selectivity, and orientation columns. In Modeling Neural Development, A. Van Ooyen, ed. (Cambridge, MA: MIT Press), pp. 245–271.

Swindale, N.V. (2004). How different feature spaces may be represented in visual cortex. Network *15*, 217–242.

Swindale, N.V., and Bauer, H.U. (1998). Application of Kohonen's self-organizing feature map algorithm to cortical maps of orientation and direction preference. Proc. R. Soc. Lond. B. Biol. Sci. *265*, 827–838.

Taba, B., and Boahen, K. (2003). Topographic map formation by silicon growth cones. In Advances in Neural Information Processing Systems, 15, S. Becker, S. Thrun, and K. Obermayer, eds. (Cambridge, MA: MIT Press), pp. 1163–1170.

Takeuchi, A., and Amari, S. (1979). Formation of topographic maps and columnar microstructures in nerve fields. Biol. Cybern. *35*, 63–72.

Tanaka, S. (1991a). Theory of ocular dominance column formation - mathematical basis and computer simulation. Biol. Cybern. *64*, 263–272.

Tanaka, S. (1991b). Phase transition theory for abnormal ocular dominance column formation. Biol. Cybern. *65*, 91–98.

Thomas, P.J., and Cowan, J.D. (2004). Symmetry induced coupling of cortical feature maps. Phys. Rev. Lett. *92*, 188101.

Tieman, S.B., and Tumosa, N. (1997). Alternating monocular exposure increases the spacing of ocularity domains in area 17 of cats. Vis. Neurosci. *14*, 929–938.

Tsigankov, D.N., and Koulakov, A.A. (2006). A unifying model for activity-dependent and activity-independent mechanisms predicts complete structure of topographic maps in ephrin-A deficient mice. J. Comput. Neurosci. *21*, 101–114.

Turing, A.M. (1952). The chemical basis of morphogenesis. Phil. Trans. R. Soc. Lond. B Biol. Sci. *237*, 37–72.

Udin, S.B., and Fawcett, J.W. (1988). Formation of topographic maps. Annu. Rev. Neurosci. *11*, 289–327.

van Ooyen, A. (2001). Competition in the development of nerve connections: a review of models. Network *12*, R1–R47.

von der Malsburg, C. (1973). Self-organization of orientation sensitive 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. (*Suppl 1*), 463–469.

von der Malsburg, C., and Willshaw, D.J. (1977). How to label nerve cells so that they can interconnect in an ordered fashion. Proc. Natl. Acad. Sci. USA *74*, 5176–5178.

Weber, C., Ritter, H., Cowan, J., and Obermayer, K. (1997). Development and regeneration of the retinotectal map in goldfish: A computational study. Phil. Trans. R. Soc. Lond. B Biol. Sci. *352*, 1603–1623.

Weliky, M., and Katz, L.C. (1997). Disruption of orientation tuning in visual cortex by artificially correlated neuronal activity. Nature *386*, 680–685.

Whitelaw, V.A., and Cowan, J.D. (1981). Specificity and plasticity of retinotectal connections: a computational model. J. Neurosci. *1*, 1369–1387.

Willshaw, D.J. (2006). Analysis of mouse EphA knockins and knockouts suggests that retinal axons programme target cells to form ordered retinotopic maps. Development *133*, 2705–2717.

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

Willshaw, D.J., and von der Malsburg, C. (1979). A marker induction mechanism for the establishment of ordered neural mappings: its application to the retinotectal problem. Phil. Trans. Roy. Soc. B Biol. Sci. *287*, 203–243.

Willshaw, D.J., and Price, D.J. (2003). Models for topographic map formation. In Modeling Neural Development, A. Van Ooyen, ed. (Cambridge, MA: MIT Press), pp. 213–244.

Wiskott, L., and Sejnowski, T. (1998). Constrained optimization for neural map formation: A unifying framework for weight growth and normalization. Neural Comput. *10*, 671–716.

Wolf, F. (2005). Symmetry, multistability, and long-range interactions in brain development. Phys. Rev. Lett. *95*, 208701.

Wolf, F., and Geisel, T. (1998). Spontaneous pinwheel annihilation during visual development. Nature *395*, 73–78.

Wolf, F., and Geisel, T. (2003). Universality in visual cortical pattern formation. J. Physiol. (Paris) *97*, 253–264.

Wolf, F., Bauer, H.-U., and Geisel, T. (1994). Formation of field discontinuities and islands in visual cortical maps. Biol. Cybern. *70*, 525–531.

Wolf, F., Bauer, H.-U., Pawelzik, K., and Geisel, T. (1996). Organization of the visual cortex. Nature *382*, 306–307.

Wolf, F., Pawelzik, K., Scherf, O., Geisel, T., and Löwel, S. (2000). How can squint change the spacing of ocular dominance columns? J. Physiol. (Paris) *94*, 525–537.

Woodbury, G.A., van der Zwan, R., and Gibson, W.G. (2002). Correlation model for joint development of refined retinotopic map and ocular dominance columns. Vision Res. *42*, 2295–2310.

Yates, P.A., Holub, A.D., McLaughlin, T., Sejnowski, T.J., and O'Leary, D.D.M. (2004). Computational modeling of retinotopic map development to define contributions of EphA-ephrinA gradients, axon-axon interactions, and patterned activity. J. Neurobiol. *59*, 95–113.

Young, J.M., Waleszczyk, W.J., Wang, C., Calford, M.B., Dreher, B., and Obermayer, K. (2007). Cortical reorganization consistent with spike timing-but not correlation-dependent plasticity. Nat. Neurosci. *10*, 887–895.

Yu, H., Farley, B.J., Jin, D.Z., and Sur, M. (2005). The coordinated mapping of visual space and response features in visual cortex. Neuron *47*, 267–280.

Yuille, A.L., Kolodny, J.A., and Lee, C.W. (1996). Dimension reduction, generalized deformable models and the development of ocularity and orientation. Neural Netw. *9*, 309–319.