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MAPS IN THE BRAIN: What Can We Learn from Them?

Dmitri B. Chklovskii and Alexei A. Koulakov
Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724;
email: mitya@cshl.edu, akula@cshl.edu

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Key Words cerebral cortex, visual processing, wiring economy, optimization, cortical map

■ **Abstract** In mammalian visual cortex, neurons are organized according to their functional properties into multiple maps such as retinotopic, ocular dominance, orientation preference, direction of motion, and others. What determines the organization of cortical maps? We argue that cortical maps reflect neuronal connectivity in intracortical circuits. Because connecting distant neurons requires costly wiring (i.e., axons and dendrites), there is an evolutionary pressure to place connected neurons as close to each other as possible. Then, cortical maps may be viewed as solutions that minimize wiring cost for given intracortical connectivity. These solutions can help us in inferring intracortical connectivity and, ultimately, in understanding the function of the visual system.

INTRODUCTION

Wiring distant neurons in the brain is costly to an organism (Ramón y Cajal 1999). The cost of wiring arises from its volume (Cherniak 1992, Mitchison 1991), metabolic requirements (Attwell & Laughlin 2001), signal delay and attenuation (Rall et al. 1992, Rushton 1951), or possible guidance defects in development (Tessier-Lavigne & Goodman 1996). Whatever the origin of the wiring cost, it must increase with the distance between connected neurons. Then, among various functionally equivalent arrangements of neurons, the one having connected neurons as close as possible is most evolutionarily fit and, therefore, likely to be selected. This argument is known as the wiring optimization principle, or the wiring economy principle, and is rooted in the laws of economy of space, time, and conductive matter postulated by Ramón y Cajal in the nineteenth century (Ramón y Cajal 1999). Since then, the wiring optimization principle has been used to answer many questions about brain organization: why there are separate visual cortical areas (Mitchison 1991), why neocortex folds in a characteristic species-specific pattern (Van Essen 1997), why ocular dominance patterns exist (Chklovskii & Koulakov 2000; Koulakov & Chklovskii 2003; Mitchison 1991, 1992), why orientation preference patterns are present in the visual cortex (Durbin

& Mitchison 1990, Koulakov & Chklovskii 2001, Mitchison 1991), why axonal and dendritic arbors have particular dimensions (Cherniak et al. 1999, Chklovskii 2000b, Chklovskii & Stepanyants 2003) and branching angles (Cherniak 1992, Cherniak et al. 1999), why gray and white matter segregate in the cerebral cortex (Murre & Sturdy 1995, Ruppin et al. 1993), why axons and dendrites occupy a certain fraction of the gray matter (Chklovskii et al. 2002, Stepanyants et al. 2002), and why cortical areas in mammals and ganglia in *C. elegans* are arranged as they are (Cherniak 1994, Cherniak 1995; Klyachko & Stevens 2003).

The circumstantial evidence in favor of wiring optimization is complemented by the smoking gun, which shows the principle in action. When neurons are grown in low-density culture, their shapes are often strikingly regular (Figure 1). Neurite branches are almost straight, similar to stretched rubber bands (Bray 1979). Because a straight line is the shortest trajectory connecting points on a plane, this is exactly what wiring optimization would predict. Straightness is not always a result of linear growth (Katz 1985) because, under some conditions, neurites straighten out only after they reach their targets (Shefi et al. 2002). A likely biophysical mechanism for straight segments and, hence, for wiring optimization is tension along neurites (Bray 1979). In addition to straightening neurites, tension pulls on cell bodies, resulting in effective attraction between synaptically connected neurons. Such attraction is difficult to counteract in cultures (Zeck & Fromherz 2001) and may be responsible for the formation of gyri and sulci in the cortex (Van Essen 1997). Although tension along neurites exists also in vivo (Condron & Zinn 1997), axons and dendrites are not always straight in dense neuropil. The reason for

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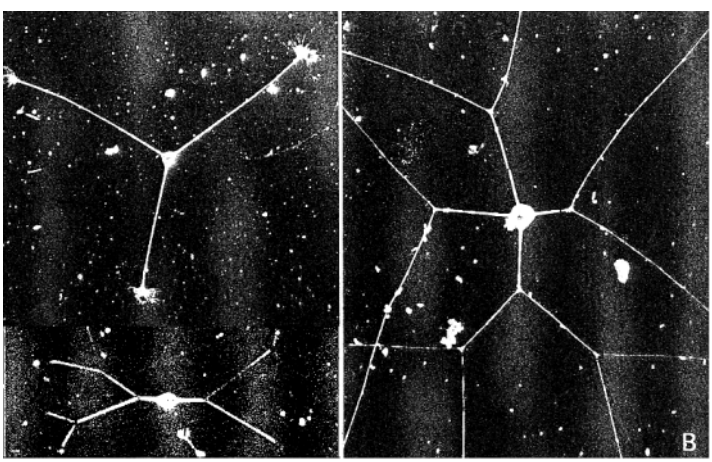

Figure 1 The smoking gun illustrating wiring optimization in action. Neurons grown at low density have regular shape with straight neurite branches consistent with wiring optimization. Reproduced neurons were taken from chick dorsal root ganglia and grown on a glass surface in culture medium with nerve growth factor (Bray 1979).

tortuous shapes is that optimization of different axons and dendrites comes into conflict owing to volume exclusion. Therefore, finding examples of neurons whose axons or dendrites are not straight (Young & Scannell 1996) does not disprove wiring optimization but rather emphasizes the importance of choosing an appropriate subset of the brain for applying wiring optimization.

In this review, we discuss the application of the wiring optimization principle to cortical maps. We stress the role of wiring optimization in establishing a link between the appearance of cortical maps and the connectivity of intracortical circuits. The review is organized as follows. First, we recapitulate classical explanations for the existence of retinotopic maps and multiple cortical areas, which rely on the wiring optimization principle. Second, we argue that wiring optimization may be a general principle of the cortical map organization and apply this principle to explain the appearance of ocular dominance patterns, orientation preference maps, and direction preference maps. Third, we address frequently asked questions about wiring optimization in the context of cortical maps.

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RETINOTOPY INDICATES THAT CORTICAL PROCESSING IS LOCAL IN VISUAL SPACE

A visual cortical area is called retinotopic (or said to contain a retinotopic map) if nearby cortical neurons receive inputs from nearby retinal neurons. Retinotopy is common among visual cortical areas and is even integral to their definition, with mirror reflection of a retinotopic map often being used to establish area boundaries. Why does retinotopic organization of cortical areas occur? One might think that retinotopy is inherited from the neuronal order in the retina and preserved by the axons in the optic nerve. However, experiments in adult cats (Horton et al. 1979) and in juvenile and adult rats (Simon & O'Leary 1991) show that axons from adjacent retinal ganglion cells are scattered in the optic nerve, yet they reassemble and project retinotopically in the lateral geniculate nucleus (LGN) and V1. Therefore, retinotopy requires another explanation.

The reason retinotopic maps exist is because "... visuotopic organization would permit neurons representing adjacent parts of the visual field to interact over short axonal and dendritic pathways" (Allman & Kaas 1974). The explanation goes as follows (see also Cowey 1979 and Nelson & Bower 1990). Because of spatial correlations in the external world, the early stages of the visual system combine information coming from the adjacent points in the visual field. For example, recognition of a face on a portrait (Figure 2) relies on exchanging information about facial features represented by neurons with adjacent receptive fields. Such processing requires connecting such neurons by costly wiring, i.e., axons and dendrites. To minimize the wiring length, neurons with adjacent receptive fields should be placed as close to each other as possible. This is exactly what an ordered retinotopic map (as defined above) accomplishes (Figure 2). Thus, the reason retinotopic maps exist is to minimize the total length of

intracortical connections that are required for processing local features of the visual space.

In addition to providing an explanation for the existence of retinotopic maps, the wiring optimization principle possesses predictive power. For example, one may wonder whether processing within a given visual cortical area is local in visual space. It is difficult to answer such questions without direct knowledge of the intracortical neuronal connectivity. Yet, the wiring optimization principle suggests that the neuronal connectivity may be inferred from the spatial map of that cortical area. If the representation of the visual field in that cortical area is retinotopic, then by using the above wiring optimization explanation in reverse one can infer that the processing is likely local in the visual space. If the representation is nonretinotopic, then the processing is not likely local in the visual space. The utility of wiring optimization is not limited to visual cortical areas and applies to other topographic maps in the cortex: auditory, somatosensory, motor, and others. Just as in the visual cortex, wiring optimization provides a link between the topography of a cortical map and the locality of processing in a sensory space.

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EXISTENCE OF MULTIPLE VISUAL AREAS REFLECTS MODULARITY OF VISUAL PROCESSING

Visual cortex in primates contains almost 30 different visual areas, see e.g., Felleman & Van Essen 1991. Why do they exist in such numbers? Indeed, one could imagine a visual superarea (Barlow 1986) that combines the function of, say, both V1 and V2. In this hypothetical superarea, neurons from V1 and V2 would be finely intermingled but would preserve retinotopy. All the connections between neurons, and, hence, the function of the superarea, would be exactly the same as separate V1 and V2. Why do primates lack such a superarea? Mitchison (1991) argues that such a superarea would be detrimental, provided neurons have more connections with neurons of the same area (e.g., V1 to V1) than with neurons of the other (e.g., V1 to V2). His argument can be appreciated best if we first assume that neurons connect only with neurons of the same area. Then, inserting V2 neurons in between V1 neurons will push them farther apart from each other. In turn, longer distances between neurons of the same area lead to longer connections between them, hence increasing the wiring cost. Now, let us include the connections between V1 and V2 neurons. These connections would get shorter in the merger process because retinotopy is preserved. So, the result depends on the relative balance between intra- and inter-area connections. Mitchison (1991) predicted that for the typical numbers of connections in the mammalian brain, separate visual areas are advantageous from the wiring point of view. This explanation highlights a general principle of brain organization: If two sets of neurons connect mostly within their own set, they are better kept separate.

There is an alternative explanation for the existence of multiple cortical areas (Barlow 1986), which also relies on wiring minimization. This explanation

assumes that, because of different functional requirements, the connectivity in intracortical circuits is different from area to area. Then the optimal layouts are also different from area to area, leading to conflicting demands on spatial organization if the areas were combined into a superarea. Although this explanation seems plausible in principle, it is difficult to see how it applies to early levels of visual processing. Indeed, the most salient feature of spatial organization, retinotopy, is shared by all early visual areas.

In addition to explaining the existence of multiple visual areas, the wiring optimization principle can help us understand visual processing as illustrated by the following example. Theories based on the efficient coding hypothesis, together with statistics of natural images, predict orientationally selective receptive fields, similar to those observed in V1 (Bell & Sejnowski 1997, Olshausen & Field 1996). Unfortunately, the predictive power of these theories is limited because they do not specify why the orientationally selective receptive fields should exist in V1 but not in the LGN or V4. This shortcoming can be corrected by introducing an additional parameter, distinguishing different areas. Such a parameter should appear naturally in the wiring optimization approach because it explains the existence of multiple visual areas. This example illustrates how wiring optimization can help the construction of visual processing theories.

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WIRING OPTIMIZATION ESTABLISHES A LINK BETWEEN CORTICAL MAPS AND INTRACORTICAL CIRCUITS

Retinotopy and multiple visual areas are examples of how the spatial organization of cortical areas and the connectivity of neuronal circuits may be linked by the wiring optimization principle. In fact, the wiring optimization principle plays a unique role in establishing such links (Swindale 2001). Imagine taking a cortical area containing a map and scrambling neurons in that area, while preserving all the connections between neurons. Because the circuit is unchanged, the functional properties of the neurons remain intact. Then, the scrambled region without a map is functionally identical to the original one with the map. Thus, if we neglect possible interactions through nonsynaptic diffusion of messengers, the only remaining parameter that can differentiate candidate layouts for fixed neuronal connectivity is the length of wiring. If cortical maps are selected in the course of evolution to improve the fitness of the organism, they can only be chosen on the basis of the length of connections. Therefore, it is hard (if not impossible) to justify the existence of systematic cortical maps without invoking the cost of making long neuronal connections. This argument is not limited to maps and leads to the conclusion that "the principle of minimizing wire length appears to be a general factor governing the connections of nervous systems" (Allman 1999).

The link between cortical maps and circuits is significant for understanding the brain because data on spatial organization are often available, whereas data on neuronal connectivity are usually scarce and hard to obtain. In turn, knowledge

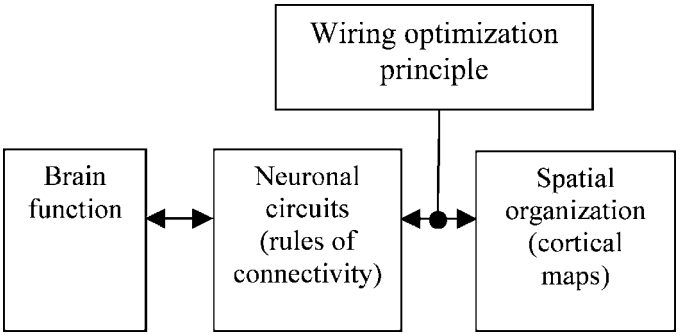

Figure 3 The wiring optimization principle helps establish a link between neuronal circuitry and spatial organization of neurons. This link allows one to infer neuronal circuitry, which is usually poorly understood, from the spatial organization of neurons, which is often better understood. Knowledge of neuronal circuitry is, in turn, essential for understanding brain function.

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of connectivity in neuronal circuits is essential for understanding brain function (Figure 3). To provide the link between intracortical connectivity and maps, the wiring optimization principle must be formulated in a rigorous quantitative manner. Next, we illustrate such formulation on several examples of cortical maps, starting with the simplest: the ocular dominance pattern (ODP).

OCULAR DOMINANCE PATTERNS ARISE FROM SAME-EYE BIAS IN CONNECTIVITY

What is the functional significance of the ocular dominance pattern (ODP), i.e., clustering of neurons based on their ocular dominance? Mitchison (1991) proposed that ODP is an adaptation that minimizes the length of intracortical connections involved in visual processing. The main idea is similar to the explanation for the existence of multiple visual areas. If there is bias in connectivity toward neurons with the same OD (i.e., the number of connections between neurons of the same OD exceeds the number of connections between neurons of different OD), the formation of OD clusters reduces the total length of connections. The original (Mitchison 1991) and more recent theories (Chklovskii & Koulakov 2000, Koulakov & Chklovskii 2003) explain why some mammals have ODPs and others do not, and why monocular regions have different appearances (stripes as opposed to patches) between different parts of V1 in macaque (Horton & Hocking 1996) and *Cebus* monkeys (Rosa et al. 1992) (Figure 4). In particular, wiring optimization predicts a transition from stripes to patches when the fraction of neurons dominated by one eye drops below 40%, in agreement with the ODP observed in macaque (Figure 4).

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Figure 4 Appearance of the ODP in macaque visual cortex (Horton & Hocking 1996) is consistent with the wiring optimization theory (Chklovskii & Koulakov 2000, Koulakov & Chklovskii 2003). Gray regions show neurons dominated by the left eye, and white regions show neurons dominated by the right eye. This fragment shows extrafoveal representation in V1 (the large gray spot is the representation of the optic disc). The black line is the theoretical prediction for the location of the transition between *patchy* and *stripy* patterns, based on the fraction of left-eye neurons being about 40% (as averaged over an area of the size shown in the upper right corner). Visually, the transition from *stripy* to *patchy* patterns takes place near the black line, in agreement with the theory.

To illustrate how wiring optimization leads to these findings, we consider a simplified model. If the number of connections per neuron is small, solving the optimal layout problem does not require a computer. The problem is to find the layout of neurons, which minimizes the length of connections for given connection rules (Figure 5). Solutions shown in Figure 5 have been confirmed in computer simulations involving large numbers of connections per neuron (Chklovskii & Koulakov 2000, Koulakov & Chklovskii 2003). Such simulations are essential to establish a link with actual cortical circuits where each neuron receives thousands of inputs. In addition, for the large numbers of connections, the choice of the lattice does not affect the results.

As argued in the previous section, the only difference between various layouts with the same connectivity is the cost of wiring. Therefore, any theory of the map appearance must invoke wiring optimization. Hence, theories of the map

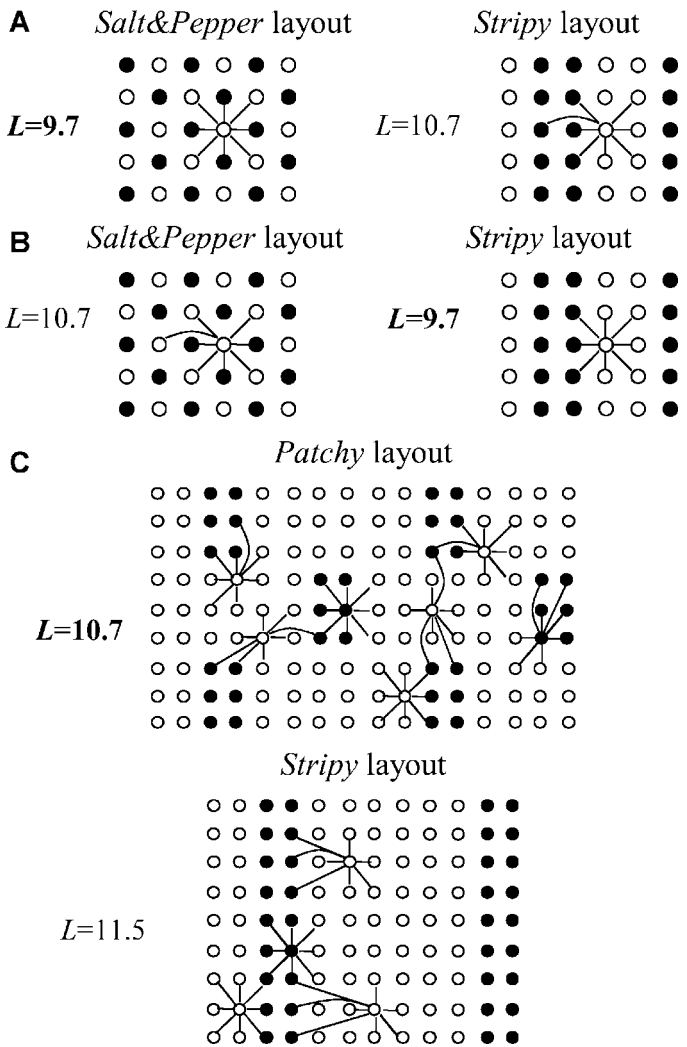

Figure 5 Wiring model of ODP. White circles are neurons dominated by the right eye, and black circles are neurons dominated by the left eye. (*A*) For equal numbers of same-eye and opposite-eye connections (four versus four) *Salt&Pepper* layout (*right*) gives a lower wire length per neuron, *L* (minimal lengths are in bold). (*B*) If there is a connectivity bias, i.e., same-eye connections are more abundant than the opposite-eye ones (five versus three), the ODP pattern, such as *Stripes*, provides a smaller wire length. (*C*) If left-eye neurons are less abundant, the same connection rules as in (*B*) result in a smaller wire length for *Patches*. For each layout, connections for all types of neurons are shown. All neurons in (*C*) satisfy the same (five versus three) connection rule as in (*B*) (Chklovskii & Koulakov 2000).

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formation that do not explicitly rely on wiring optimization invoke it implicitly, usually requiring the locality of intracortical connections. Here, we discuss the models that invoke explicitly the wiring cost.

Mitchison (1991) compared wiring cost between ODP and *Salt&Pepper* layout, assuming that interneuronal connections are determined both by ocular dominance and retinotopy. He found that the answer depends on the rules of axonal branching. If at branch points all axonal segments have the same caliber, ODPs are advantageous for some connectivity. However, if at branch points the total axonal cross-sectional area is conserved, the ODP do not save wiring volume relative to *Salt&Pepper*. The actual situation is probably somewhere in between the two cases (Chklovskii & Stepanyants 2003). Because the wiring optimization model presented here assumes separate connections for each neuron, it corresponds to the case of the cross-sectional area conservation. However, unlike Mitchison, we find that ODPs are more efficient than *Salt&Pepper*. This happens because, in accordance with experimental data (Katz et al. 1989), the intracortical connectivity rules do not rigidly enforce the retinotopy of connections. This assumption simplifies the theory, allowing us to map out the complete phase diagram and make experimentally testable predictions (Chklovskii & Koulakov 2000, Koulakov & Chklovskii 2003). The full theory of the ODP will require a more detailed analysis of axonal branching (Chklovskii & Stepanyants 2003).

Jones et al. (1991) proposed an explanation for why ODP have either *Stripy* or *Patchy* appearance. They assumed that neurons are already segregated into the ODP (by considering units whose size equals the width of monocular regions) and found that the difference between *Stripy* and *Patchy* appearances of the ODP could be due to the different shape of V1 in different species. Although the correlation between the shape of V1 and the ODP layout is observed, this model (Jones et al. 1991) does not explain why peripheral representation of macaque V1 has patchy ODP or why ocular dominance stripes run perpendicular to the long axis of V1 in some parts of V1 but not in others. Most important, unlike Jones et al. (1991), the wiring optimization theory presents a unified theory of ODP, including *Salt&Pepper*, *Stripy*, and *Patchy* layouts, and relates ODP appearance to the connectivity rules.

Another model related to wiring length minimization is the elastic net (Durbin & Mitchison 1990, Durbin & Willshaw 1987, Goodhill & Sejnowski 1997, Goodhill & Willshaw 1990). The original formulation of the model minimized the cost function, which penalized nearby placement of neurons whose activity was not correlated. This choice was justified by computational convenience. Unlike the wiring optimization theory, this penalty does not increase beyond a distance called cortical interaction. Because of this distance, the elastic net often has solutions, in which the cortical area is partitioned into two large monocular domains, although annealing procedure does not yield them. Later the elastic net model was generalized by the introduction of a C-measure (Goodhill & Sejnowski 1997). The wiring optimization theory presented here can be viewed as a subset of models described by C-measure. The virtue of wiring optimization is that it assigns a clear biological cost for placing neurons far from each other (the cost of wiring). Moreover,

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wiring optimization establishes a link between cortical maps and connectivity. Because both maps and connectivity can be obtained experimentally, the wiring optimization theory makes clear experimentally testable predictions.

OCULAR DOMINANCE STRIPES ALIGN WITH THE DISPARITY DIRECTION

ODP in primate V1 is not random: Orientation of the ocular dominance stripes on the cortical surface follows systematic trends found in macaque (Horton & Hocking 1996, LeVay et al. 1985) and *Cebus* monkeys (Rosa et al. 1992). These trends are easiest to describe when the ODP is transformed back into the visual field coordinates (Hubel & Freeman 1977, LeVay et al. 1985, Rosa et al. 1992, von Berg 1997) by dividing all cortical distances by the local magnification factor. [The magnification factor is defined as distance along the cortex (in millimeters), which corresponds to a 1° separation on the retina (Daniel & Whitteridge 1961).] The transformed ODP shows two major trends: In the parafoveal region stripes tend to run horizontally, whereas farther from the fovea, stripes follow concentric circles (Figure 6).

What is the functional significance of these trends in the orientation of ocular dominance stripes on the cortical surface? Chklovskii (2000a) proposed that the trends in the ODP reflect the properties of the binocular stereopsis circuitry as a result of wiring optimization. Visual information arriving through the two eyes is initially recombined in V1. Because V1 contains retinotopic maps, binocular disparity of a visual object leads to a separation between cortical representations of the same object (Figure 7). Therefore, recombining information coming from the two eyes requires horizontal intracortical connections (Gilbert et al. 1996). The length of such connections is minimized if the ocular dominance stripes are aligned with the direction of disparity (Figure 7*B*). The direction of disparity was determined for every point in the visual field by calculating the distribution of disparity and taking the dominant direction. Disparity being mainly horizontal in the parafoveal region and mainly cyclotorsional in the peripheral region (Figure 6) explains the main trends in stripe orientation (Chklovskii 2000a).

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ORIENTATION PREFERENCE MAPS REFLECT CONNECTIVITY BIAS

Cortical maps of orientation preference, as obtained by optical imaging, exhibit linear zones, whereas orientation preference changes smoothly, with occasional singularities such as pinwheels and fractures (Figure 8) (Blasdel 1992, Bonhoeffer & Grinvald 1991). Why these singularities exist has remained a mystery from the time they were discovered, which led some authors to suggest that pinwheels and fractures are developmental defects (Wolf & Geisel 1998). We show that,

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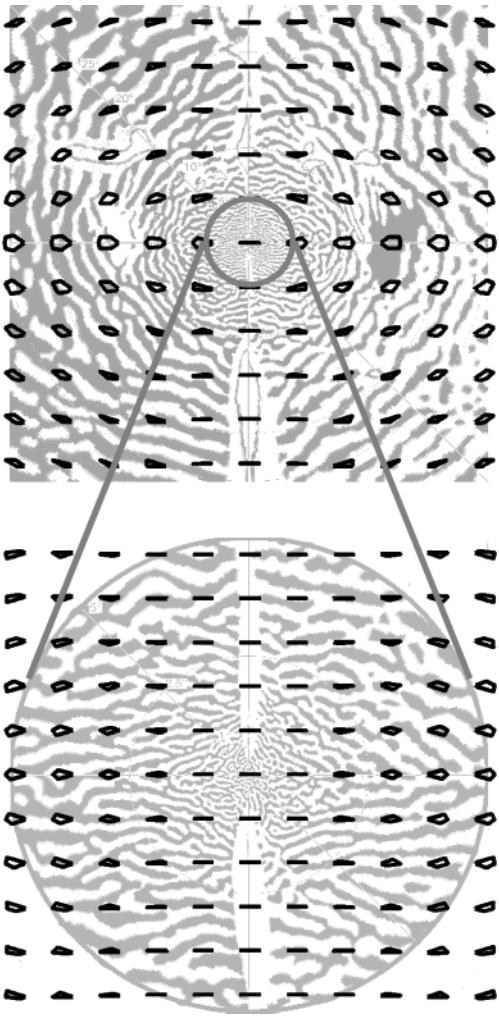

Figure 6 Global structure of the ODP is consistent with theoretical results (Chklovskii 2000a). Gray & white stripes show ODP (Horton & Hocking 1996) warped back into the visual field (von Berg 1997). (*Top*) Visual field up to 25° eccentricity. (*Bottom*) Magnification of the foveal region up to 5° eccentricity. Black polar plots show theoretically obtained frequency distributions of binocular disparity direction for corresponding locations in the visual field. The dominant direction of binocular disparity at each point of the visual field is given by the major axis (longest dimension) of the corresponding plot. Theory based on wiring optimization suggests that ocular dominance stripes should follow the dominant disparity direction. Experimental data are consistent with this prediction with the exception of the regions in the upper left and upper right corners of the top figure and the very center of the bottom figure (for possible reasons behind the discrepancy see Chklovskii 2000a).

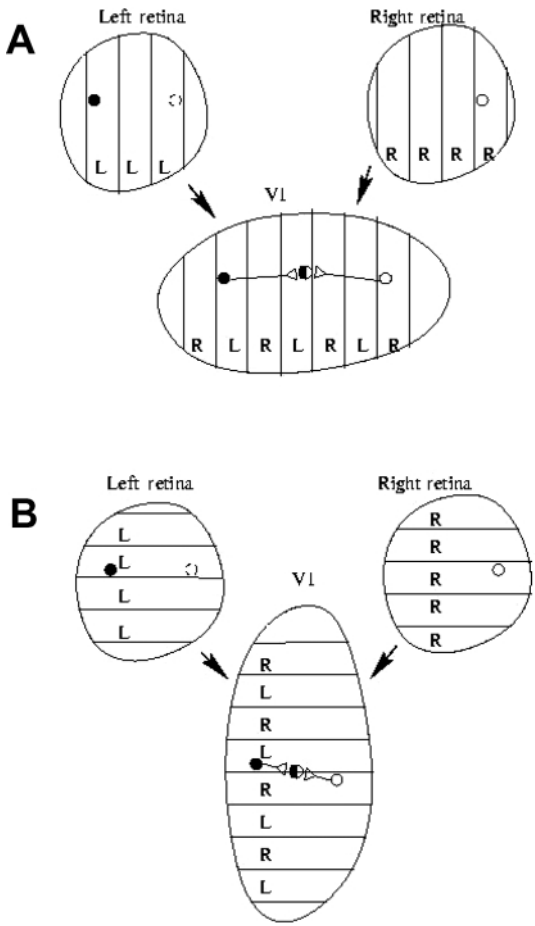

Figure 7 Schematic illustration showing a binocular neuron in V1 (*semifilled circle*) recombining corresponding information from the two eyes via long-range horizontal connections. Connections are longer if the ocular dominance stripes run orthogonally to the disparity direction (*A*) than if they run parallel to that direction (*B*). This finding suggests that the ocular dominance stripes should align with the dominant disparity direction (Chklovskii 2000a).

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for some intracortical circuits, singularities are needed to minimize the intracortical wire length, as previously surmised by Swindale (1996, p. 235). Therefore, we suggest that pinwheels and fractures are evolutionary adaptations that keep the cortical volume to a minimum. In addition, we propose that differences in map structure (both between species and within one animal) reflect differences in underlying intracortical neuronal circuits. The latter may be related to

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differences in natural scene statistics or in behavioral tasks solved by a particular animal.

The wiring model of the orientation preference patterns is an extension of the model for ODPs described in the previous section. Instead of having just two categories of neurons (left-eye dominated and right-eye dominated) we introduce several categories of neurons differing by their preferred orientation. This idea is illustrated on a toy model that includes four different orientation preference categories (Figure 9). As in the OD model, functionality of the network requires each neuron to make certain numbers of connections with neurons of other categories. But instead of there being only two numbers in the OD model, now there are as many numbers as there are categories. We refer to these numbers collectively as the connection function. The results of layout optimization with fifteen categories of orientation preference are shown in Figure 10.

Maps presented in Figure 10 reflect bias in connectivity toward neurons of similar orientations (Koulakov & Chklovskii 2001). This bias favors layouts in which neurons of close orientation reside next to each other, thus resulting in smooth maps. If the connectivity bias is strong, as in Figures 10*C–F*, the corresponding maps are completely smooth and free of singularities (pinwheels or fractures). As the bias decreases in strength, as in Figures 10*G–J*, singularities appear in the orientation maps, thus leading to *Pinwheels* or *Fractures* layouts (Figures 10*H* and *J*, respectively). The emergence of singularities is related to the unbiased, or uniform, component in the connection function, which favors close placement of neurons with dissimilar orientation. If the connection function contains only the unbiased, or uniform, component (Figure 10*A* and *B*), singularities proliferate, and the *Salt&Pepper* layout becomes optimal.

These results imply that for each shape of the connection function (*left column*) there is a layout that minimizes wiring length (*right column*). Therefore, interspecies differences in orientation maps or variations in the layout within a single map could be traced back to the intracortical connectivity. This hypothesis can be tested experimentally. For example, the connection function for the pinwheel layout (Figure 11*A*) should be of the form shown in Figure 11*B*. This is consistent with experimental data (Yousef et al. 1999) (Figure 11*C*,*D*). Another prediction is based on the observation that the rodent V1 has *Salt&Pepper* layout (Girman et al. 1999). Theories based on wiring optimization suggest that the connection function in rodents is different from the one in cats and monkeys, despite the similarity in cell tuning properties (for details see Koulakov & Chklovskii 2001).

Another approach to inferring intracortical connectivity from orientation maps is based on the locality of connections (Das & Gilbert 1999, Schummers et al. 2002). To determine the origin of intracortical inputs to a neuron, one draws a circle around that neuron and counts the numbers of neurons in that circle with various orientation preferences. This procedure implicitly relies on wiring optimization because it assumes that connections are made with neurons within a certain distance only. In fact, the set of connected neurons in the wiring optimization

theory presented here is usually close to a circle (Koulakov & Chklovskii 2001). One virtue of the circle procedure is its prediction of the difference in connectivity for neurons located in pinwheels and orientation domains (Schummers et al. 2002). This result does not contradict the wiring optimization theory because the uniformity of connection function among neurons is a simplifying assumption, not a conclusion, of the theory. It is relatively straightforward to generalize the wiring optimization theory by including an additional category of neurons with different connection function. The circle procedure does not render the wiring optimization theory useless. First, the result of this procedure depends strongly on the radius of the circle. Whereas using a circle with a short radius produces a strongly biased connection function, long radius produces a uniform connection function. Because the radius of the circle must be guessed, arbitrariness is introduced into the procedure. Second, this procedure does not explain the existence of the maps. The connectivity is determined from maps and not the other way around.

There is an important difference between wiring optimization and related theories such as the locality principle (Das & Gilbert 1999, Schummers et al. 2002) and the elastic net (Durbin & Mitchison 1990, Goodhill & Cimponeriu 2000). These theories make rigid assumptions about intracortical connectivity, such as requiring connections within a circle or with the nearest neighbors. Conversely, in the wiring optimization approach, the intracortical connectivity can vary from case to case. In an attempt to establish a link between maps and connectivity, we consider as many connection functions as needed to explain the variability of observed maps (the most up-to-date database of connectivity and corresponding layouts is maintained at http://koulakovlab.cshl.edu/anneal). The only assumption made in these models is that the link between connectivity and maps is established through wiring optimization.

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DIRECTION OF MOTION PREFERENCE MAPS

In addition to being selective to stimulus orientation, many neurons in visual cortex show preference for a particular direction of motion. Spatial organization of neurons according to preferred direction is reflected in direction preference maps (DPMs), which have been studied electrophysiologically (Albright et al. 1984, Diogo et al. 2003, Swindale et al. 1987) and optically (Kim et al. 1999, Malonek et al. 1994, Shmuel & Grinvald 1996, Weliky et al. 1996). The organization of the DPMs differs between visual areas and species. In some cases, such as ferret area 17 (Weliky et al. 1996) and cat area 18 (Shmuel & Grinvald 1996, Swindale et al. 1987), DPMs contain clusters of neurons with the same direction preference. These clusters are correlated with the orientation maps present in these areas: The preferred direction of motion is orthogonal to the preferred orientation. In other cases, such as cat area 17, no robust directional clustering is observed (Bonhoeffer et al. 1995; but see Swindale et al. 1990), despite the presence of directionally selective cells (Hubel & Wiesel 1962).

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As with the orientation preference maps, the differences in the DPMs could be due to the differences in the intracortical circuitry. The link between maps and connectivity is established through wiring optimization. Some preliminary considerations (Koulakov & Chklovskii 2001, 2002) show promising results in explaining map diversity. Although solving layout optimization problems for direction maps is very similar to the case of orientation maps discussed above, the parameter space of direction-sensitive connection functions is larger. Thus, we limit ourselves to a few examples, which show reasonable similarity to DPMs observed in visual cortices. The connectivity is characterized by the connection function similar to that used for orientation maps, but it depends on the difference in direction preference. According to experimental data (Roerig & Kao 1999), the connection function has two peaks: One is around 0° direction difference (connections with neurons of similar preferred direction), and another is around 180° direction difference (connections with neurons of opposite preferred direction). We vary the relative amplitude of the two peaks and search for the optimal layout, which minimizes the total length of connections.

First, we use the connection function with two peaks of the same magnitude (Figure 12*A*). In this case the direction map (Figure 12*A*, center) is disordered, i.e., a *Salt&Pepper* layout is formed. At the same time, the orientation map, obtained by assuming orthogonality between direction and orientation preference (Swindale et al. 2003), shows a regular lattice of pinwheels, surrounded by areas with smooth orientation. This finding implies that the direction map is not entirely random: The neurons with similar orientation form clusters where neurons of opposite direction preference are intermixed. Intrinsic optical imaging of such a map should show a weak direction signal because it averages responses over a small cortical area. Because in the *Salt&Pepper* layout such an area is expected to contain an equal mixture of units with opposite preferred directions (same orientation), no robust direction map results. At the same time the orientation map is well defined. These features are consistent with observations in cat area 17 (Bonhoeffer et al. 1995, Hubel & Wiesel 1962). Although this explanation seems plausible, we cannot rule out the possibility that the direction preference signal could be weaker than orientation preference because direction tuning is weaker than orientation tuning.

Next, we use the connection function with reduced second peak, where the ratio between the magnitudes of the same direction and opposite direction peaks is about 5 to 1 (Figure 12*C*). We find that in the optimized layout, neurons form an axis of motion clusters (Figure 12*C*). These clusters segregate into several regions of opposite direction preference. Boundaries between these regions zigzag through clusters. In the cortical plane, direction preference changes frequently by 180°, whereas the axis of motion remains more continuous. This feature is similar to electrophysiological measurements done in macaque area MT (Albright et al. 1984). In optical imaging experiments, such maps should result in extended areas, where direction signal is weak, intermixed with the areas where direction is well defined. Whether intrinsic optical imaging supports these results in animals, such

as owl monkey (Malonek et al. 1994), where MT is readily accessible on the brain surface, would be interesting.

Finally, if the second peak in the connection function is very weak or nonexistent (Figure 12*D*), the direction preference map is continuous with occasional fractures. These fractures terminate at pinwheels. When going around a pinwheel, direction preference changes gradually by 180° and jumps by 180° at the fracture (Swindale et al. 1987). Because preferred orientation is orthogonal to preferred direction, the orientation map is continuous across the fracture. The orientation map contains only one type of singularity: 180° pinwheels. These results are consistent with observations in ferret area 17 (Weliky et al. 1996) and cat area 18 (Shmuel & Grinvald 1996).

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FREQUENTLY ASKED QUESTIONS ABOUT WIRING OPTIMIZATION AND MAPS

Q: If wiring optimization is so important, why does not brain size shrink to zero, presumably, the most economical solution?

A: Although decreasing brain volume to zero would reduce the wiring cost, it would also reduce brain's functionality. Because functionality and cost contribute to fitness with different signs, such a radical solution is not favored by animal evolution. In the wiring optimization approach, functionality is fixed by considering various layouts with the same connectivity.

Q: The minimization of wiring cost in the course of evolution proceeded in parallel with functionality maximization. That said, why is it correct to minimize wiring cost for fixed functionality?

A: From the mathematical point of view, fitness is a function of many variables including wiring cost and circuit functionality. Evolution tends to maximize this multivariable function. Yet, to explore that maximum varying only one variable, the wiring cost, while fixing functionality by specifying neuronal connectivity is a valid approach. This approach permits one to answer many questions of brain design. When a quantitative description of brain functionality is available, it can be included in the optimization approach, along with the wiring cost.

Q: If wiring volume is so costly, why not make all the wires infinitesimally thin?

A: Thinner axons and dendrites are detrimental for brain functionality because they conduct signals slower and with more attenuation. If brain functionality is fixed, then wires can be made thinner only if they get shorter as well. This solution would be possible if the brain contained only wiring components. However, when the brain contains nonwire components (i.e., those that do not shrink with brain size), such as synapses, cell bodies, and blood vessels, its

cost is minimized when nonwire components compose 40% of the volume (Chklovskii et al. 2002).

Q: If two candidate layouts have a small difference, say 10%, in wiring cost, should one layout be favored?

A: In principle, an animal with a suboptimal layout with 10% more wiring than the existing one could exist if brain's functionality is reduced. However, if brain's functionality is exactly the same the existence of such an animal is close to impossible. Indeed, imagine that an external object, such as a blood vessel, is introduced in a certain area of the gray matter. In this case some of the neuronal connections would have to go around the vessel and, therefore, become longer. If the nerve pulses are to be delivered at the original speed and intensity, the elongated axons and dendrites have to be made thicker, to increase the pulse propagation speed and decrease dendritic attenuation. This procedure leads to more obstacles for other neuronal connections and so on. Thus, introduction of a new blood vessel leads to an infinite series of axonal and dendritic reconstructions. Such an infinite series can diverge, which implies that the connection volume increases indefinitely. In this case the new blood vessel can never be inserted without sacrificing significantly the brain function. Mammalian cortex is on the verge of this so-called wiring catastrophe (Chklovskii et al. 2002) so that it becomes increasingly more difficult to accommodate excess volume in the nerve tissues. Thus, even 10% increase, resulting from wasteful neuronal positioning, may be important.

Q: Many theories produce realistic ocular dominance and orientation preference maps. What is special about the wiring optimization theory?

A: Most theories of map formation generate maps by repetitive application of postulated learning rules that emulate development (Swindale 1996). Although understanding development is clearly important, our current level of knowledge is, in most cases, insufficient to formulate mechanistic theories of map formation, on the level required for testing these theories experimentally. Conversely, the wiring optimization theory bypasses development and provides a link between map structure and intracortical connectivity, both experimentally measurable quantities.

Q: If the wiring optimization theory does not predict the outcome of developmental manipulations, how can it be tested?

A: The role of theory is to make predictions and ask questions; these predictions and questions make further experimental work more effective. By using an assumption of wiring optimization, we predict that the difference in cortical map appearance reflects the difference in intracortical connectivity. These predictions can be tested by comparing maps and connectivity in different animals or in different parts of the same animal. For example, despite a similarity in the orientation tuning, the intracortical connectivity in cats and rats should be different. Testing these predictions will provide necessary feedback for further development of the theory, which will, in turn, generate new predictions.

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Q: What can wiring optimization say about developmental mechanisms?

A: The wiring optimization principle aids studies of development by imposing a constraint on the possible forms of the mechanisms. Indeed, to produce an evolutionarily fit organism, developmental rules should, if possible, respect the wiring constraint. A link between wiring optimization and developmental rules can be illustrated with the following example. In the theory of ocular dominance patterns (Chklovskii & Koulakov 2000), formation of ocular dominance columns minimizes wiring length for certain neuronal circuits. In addition, by performing a gradient descent on the wiring length cost function we derive a learning rule that has a "Mexican hat" appearance. Such a learning rule has been used to model development of ocular dominance patterns (Swindale 1980) and also appears in a more biologically realistic model (Miller et al. 1989). Therefore, "Mexican hat" developmental rules can minimize wiring length. A nice bonus of the wiring minimization approach is that the exact shape of the Mexican hat can be derived without any ad hoc parameters.

Q: Why do wiring optimization theories of maps in V1 involve intracortical connections only? Is not ODP set up by thalamic afferents, and is not feedback from V2 important?

A: The current wiring optimization theory considers intracortical connections only because they constitute the majority of wiring in the cortex. Inclusion of the extracortical connections should yield only small corrections. Also, the wiring optimization theory bypasses development: Whatever the developmental mechanism, it should strive to maximize the fitness of an organism. Therefore, wiring optimization results are immune to the exact developmental mechanism responsible for ODP, whatever it turns out to be.

Q: Does not existence of singularities in the orientation map follow from dimension reduction? Specifically, neurons in V1 represent retinotopic coordinates and the orientation variable. But the mapping from a three-dimensional (3D) feature space onto a two-dimensional (2D) cortical sheet cannot be accomplished continuously. Therefore, singularities in orientation maps, such as pinwheels and fractures, are inevitable.

A: Although a mapping from 3D to 2D cannot be accomplished continuously, this is not sufficient to explain singularities in orientation maps because any two coordinates of the 3D space can be mapped continuously in 2D. For example, imagine an ensemble of neurons, each characterized by a 2D position of the receptive field (X and Y coordinates) and the preferred orientation (θ). These neurons can be arranged in 2D so that the X coordinate increases continuously along one axis, while orientation increases continuously in the other direction. Of course, the Y coordinate cannot be mapped continuously in this case. Therefore, dimension reduction is not sufficient to explain singularities in orientation maps. Moreover, experimental observations of continuous orientation maps (see Figure 10 or Shmuel & Grinvald 2000) prove that the presence of singularities is not necessary. That the wiring optimization principle yields

orientation maps with and without singularities depending on the connection function is one of the theory's virtues (Figure 10).

Q: Many theories of orientation maps assume the locality of connections based on the distance along the cortical sheet. What is the advantage of wiring optimization compared to such theories?

A: Although some theories of map formation may not explicitly mention the wiring optimization principle, they use it implicitly, usually in requiring the locality of intracortical connections. The locality of connections is likely to be a consequence of wiring minimization. In most cases the locality of connections and the wiring optimization principle yield the same predictions. A notable exception is the existence of long-range horizontal connections (Gilbert et al. 1996, Gilbert & Wiesel 1989), which cannot be accounted for by the locality. Yet, the wiring optimization approach leads naturally to the appearance of long-range horizontal connections. Indeed, imagine that the composition of intracortical circuits is dominated by the connections between neurons with adjacent receptive fields, with a few connections between neurons with remote receptive fields. Then, the optimal layout includes a retinotopic map with local connections and a few long-range horizontal connections. A hypothetical rearrangement of neurons that minimizes the long-range projections would not save wiring because it would elongate the local connections. Therefore, wiring optimization seems more fundamental than locality of connections.

Q: How can one prove that the wiring is optimal in the brain?

A: Although evolution is known to optimize many aspects of animal design (Alexander 1996, Weibel 2000), the claim of design optimality is fraught with caveats. For example, animals may have been optimized for a lifestyle different from the one they lead today, or many design features are inherited from the ancestors; also, the role of chance in evolution cannot be excluded. However, the goal of the wiring optimization approach is not to prove the wiring is optimal, but rather to use the idea of optimality to understand as much brain architecture as possible (Parker & Maynard Smith 1990) without resorting to "historical accident" explanations, which often have an agnostic flavor. Understanding of brain design based on optimization satisfies our scientific curiosity and helps build a harmonic and self-consistent view of neurobiology.

Q: Wiring cost may play some role in brain design, but it cannot be the only factor. In view of this, how can one make any predictions based on wiring optimization alone?

A: Wiring optimization does not insist that wiring cost is the only constraint. It suggests that, other things being equal, evolution prefers the layout with minimum wiring cost. That this cost can be expressed quantitatively allowing one to generate experimentally testable predictions is a virtue of this theory. In those cases, where these predictions are confirmed, wiring optimization is likely to be the crucial factor. In other cases, where wiring optimization predictions disagree with the experimental results, some other factors may be more important.

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To differentiate these cases, it is crucial to solve the optimal layout problems and compare their solutions with the experiment results. Therefore, wiring optimization is only the first step in the program of unraveling principles of brain design. Structural plasticity is another factor that has emerged already in this program (Stepanyants et al. 2002).

Q: If wiring optimization is so important, why is V1 in the back of the brain, as far as possible from the eyes?

A: Sensory input to the cortex (with the exception of olfaction) is required to pass through the thalamus, which is located roughly in the center of the head. Because all the locations on the cortex are roughly equidistant from the thalamus, placing V1 in the occipital lobe is not particularly detrimental. Moreover, the extreme posterior location of V1 may make sense because it connects with fewer visual areas (Felleman & Van Essen 1991).

Q: Could the length of connections be maximized (rather than minimized) by evolution?

A: One could imagine a task, such as binaural sound localization, that requires detecting short time intervals by introducing conduction delays. In such a system, the dynamic range would be broader if wires were longer. Although this may suggest wiring maximization, there is no contradiction with the wiring optimization theory. This theory optimizes wiring length among various functionally identical layouts, meaning the dynamic range should be fixed from the outset.

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CONCLUSION

In this review, we argue that cortical maps reflect the connectivity properties of intracortical circuits as a consequence of wiring optimization. By formulating and solving optimal layout problems, we show that wiring optimization may account for the existence of cortical maps. The variety of map appearances follows naturally from the differences in intracortical connectivity. Therefore, the wiring optimization approach may provide a general unifying framework, which will help organize the multitude of experimental facts about cortical architecture. Although predictions of the wiring optimization theory are mostly consistent with experimental data, further testing is desirable. Detection of mismatches between the wiring optimization theory and experiment results will help investigators discover other principles of brain design.

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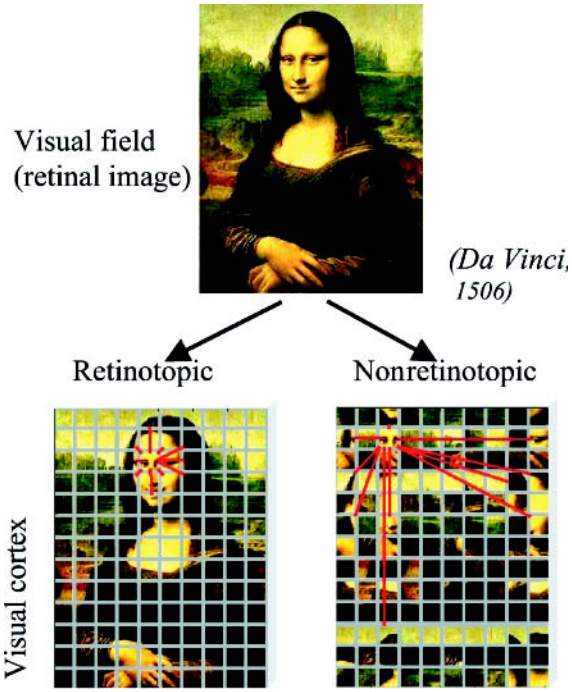

Figure 2 A retinotopic map minimizes the cost of connecting neurons that have adjacent receptive fields. (*Top*) Retinal image. (*Bottom*) Two candidate layouts of cortical neurons: retinotopic (*left*), nonretinotopic (*right*). *Squares* represent receptive fields of cortical neurons at corresponding cortical locations. Retinotopic layout minimizes the length of intracortical connections (*red*) that are required for processing local features of the image.

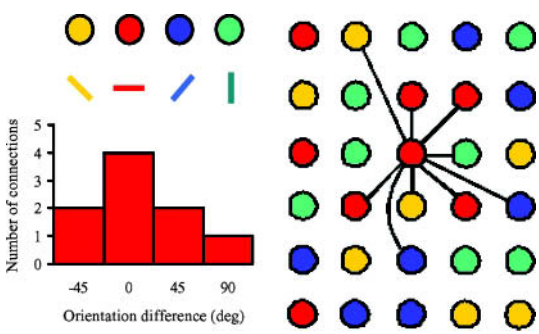

Figure 9 The wiring optimization model of orientation preference maps in a simplified case of only four different orientation values.

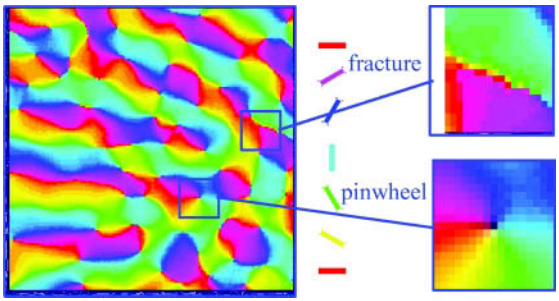

Figure 8 An orientation preference map in tree shrew primary visual cortex (Bosking et al. 1997). Colors code for orientation preference according to the legend. Orientation preference changes smoothly along the cortex with the exception of singularities: pinwheels and fractures (*right*). Notice a pinwheel-free region in the left part of the map. Based on our wiring optimization theory, we predict that the connectivity rules in intracortical neuronal circuits are different between that region and the rest of the map.

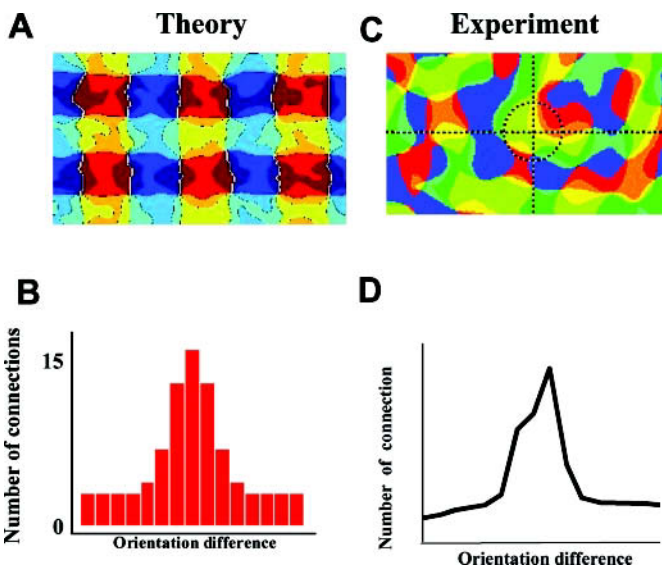

Figure 11 Results of wiring optimization are consistent with experimental data. (*A*) Orientation map obtained by wiring minimization from the connection function shown in (*B*). (*C*, *D*) Experimentally obtained orientation map and anatomically measured connection function (Yousef et al. 1999). Although the theoretical map is more orderly, it contains all the main features of the experimental data: linear regions and pinwheels. Similarity between the theoretical and the anatomically measured connection functions supports our approach and suggests using wiring optimization to infer connectivity from map appearance.

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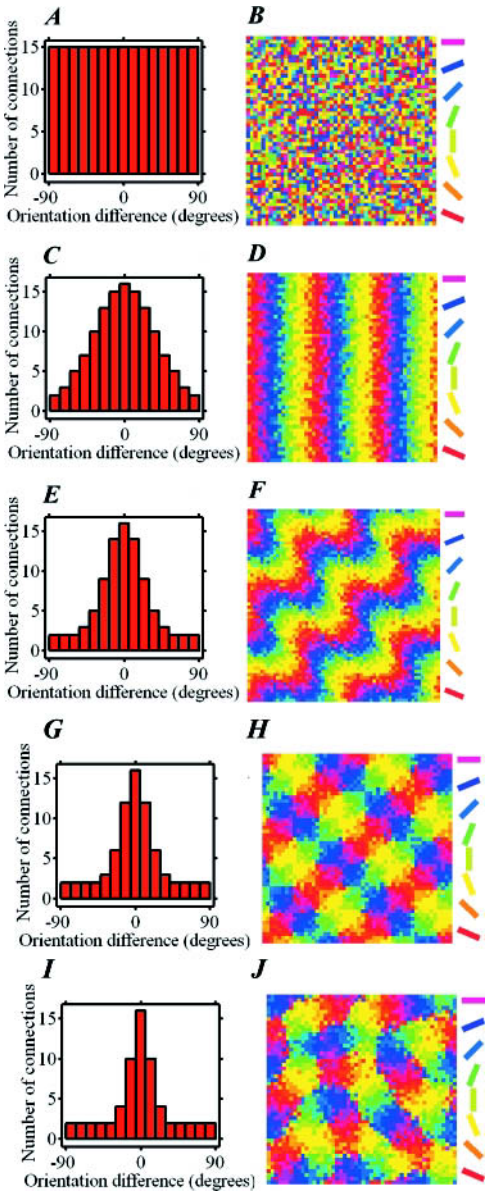

Figure 10 Numbers of intracortical neuronal connections in the visual cortex (*left column*) and corresponding orientation preference patterns (*right column*) obtained by minimizing the length of these connections (Koulakov & Chklovskii 2001). Based on these results, we propose that the differences in orientation preference patterns [within one animal (Figure 10) and between species] reflect the differences in the connectivity rules of intracortical circuits. In addition, we suggest that the functional significance of pinwheels and fractures may be in minimizing wiring length for certain intracortical connection rules.

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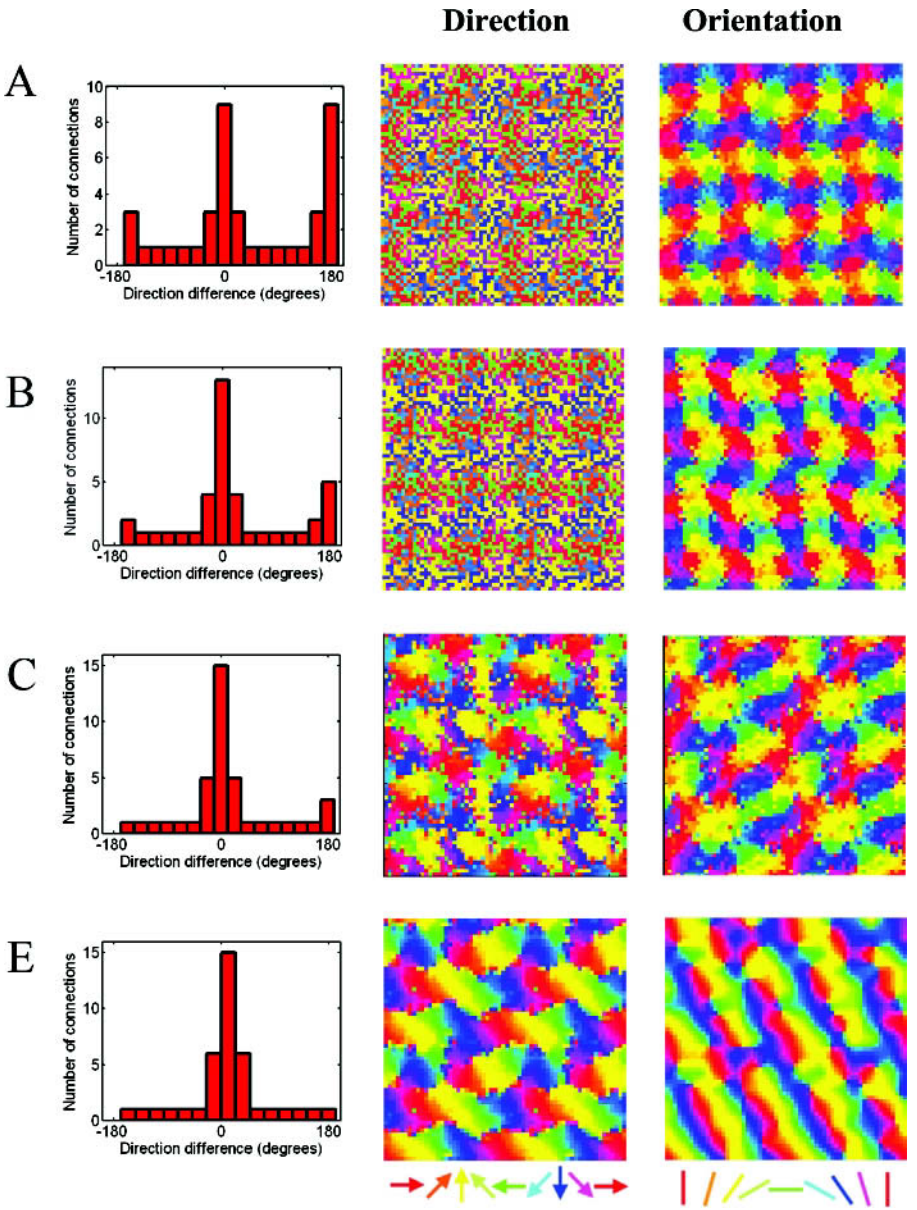

Figure 12 Wiring optimization relates intracortical connectivity (*left* column) to direction and orientation preference maps (*middle* and *right* columns, respectively). Different connection functions correspond to different direction and orientation preference maps (*A–D*).

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