Synaptic Connectivity and Neuronal Morphology: Two Sides of the Same Coin

Viewpoint

Dmitri B. Chklovskii*
Cold Spring Harbor Laboratory
Cold Spring Harbor, New York 11724

Summary

Neurons often possess elaborate axonal and dendritic arbors. Why do these arbors exist and what determines their form and dimensions? To answer these questions, I consider the wiring up of a large highly interconnected neuronal network, such as the cortical column. Implementation of such a network in the allotted volume requires all the salient features of neuronal morphology: the existence of branching dendrites and axons and the presence of dendritic spines. Therefore, the requirement of high interconnectivity is, in itself, sufficient to account for the existence of these features. Moreover, the actual lengths of axons and dendrites are close to the smallest possible length for a given interconnectivity, arguing that high interconnectivity is essential for cortical function.

Introduction

The geometrical shapes of nerve cells are extraordinarily complex. Unlike most other cells of the body, neurons have long and branching processes: axons and (often spiny) dendrites (Figure 1). Numbers and dimensions of axonal and dendritic branches vary systematically between different neuronal classes. Such complexity and variability of neuronal structure raises a question about its function. Cajal argued that the shape of neurons reflects their role in communication: dendrites conduct signals from postsynaptic terminals to the integration site, which is often the cell body; axons conduct signals from the cell body to presynaptic terminals (Ramón y Cajal, 1899). One hundred years later, the role of axons and dendrites in communication is not in doubt, yet a quantitative theory of neuronal shape is still missing. Such a theory would establish how much of neuronal shape can be explained by communication requirements and how much it reflects signal processing, or computation, requirements. In particular, dendrites may perform nonlinear operations (Koch et al., 1982; Mel, 1993; Polsky et al., 2004), axons may serve as delay lines or frequency-dependent filters (Carr and Konishi, 1988; Debanne, 2004), and spines may be filtering compartments (Koch and Zador, 1993; Rose and Call, 1992; Svoboda et al., 1996; Yuste et al., 2000). Understanding of these and other physiological processes can benefit from a quantitative formulation of structure-function relationships.

Much progress in formulating structure-function relationships has been made by the wiring optimization approach, which is rooted in Cajal's laws of economy of space, time, and matter (Ramón y Cajal, 1899). In this

*Correspondence: mitya@cshl.edu

approach, brain design is viewed as a solution to an optimization problem, where the wiring cost is minimized for a given network functionality. Wiring optimization has been invoked to explain many aspects of brain design: why the brain is located in the head (Cherniak, 1994), why neocortex folds in a characteristic species-specific pattern (Van Essen, 1997), why gray and white matter segregate in the cerebral cortex (Murre and Sturdy, 1995; Ruppin et al., 1993), why there are separate visual cortical areas (Barlow, 1986; Mitchison, 1991), why the number of areas and neuron density scale with brain size (Changizi, 2001; Ringo, 1991), why cortical areas in mammals and ganglia in *C. elegans* are arranged as they are (Cherniak, 1994, 1995; Cherniak et al., 2004; Chklovskii, 2004; Klyachko and Stevens, 2003; Young, 1992), why topographic maps exist (Allman and Kaas, 1974; Chklovskii and Koulakov, 2004; Cowey, 1979; Nelson and Bower, 1990), why ocular dominance patterns (Chklovskii, 2000a; Chklovskii and Koulakov, 2000, 2004; Mitchison, 1991, 1992; http://arxiv.org/abs/q-bio.NC/0311027) and orientation preference maps are present in the visual cortex (Chklovskii and Koulakov, 2004; Durbin and Mitchison, 1990; Koulakov and Chklovskii, 2001; Mitchison, 1991), why axonal and dendritic arbors have particular dimensions (Cherniak et al., 1999; Chklovskii, 2000b; Chklovskii and Stepanyants, 2003; Hsu et al., 1998) and branching angles (Cherniak, 1992; Cherniak et al., 1999; Shefi et al., 2004), and why axons and dendrites occupy a certain fraction of the gray matter (Chklovskii et al., 2002; Stepanyants et al., 2002).

Making quantitative predictions with wiring minimization requires an expression for the wiring cost. This issue is complicated by the fact that the exact origin of the wiring cost has not been established unequivocally. Axons and dendrites take up valuable space (Cherniak, 1992; Hsu et al., 1998; Mitchison, 1991), introduce delays (Rushton, 1951) and attenuation (Rall et al., 1992), require material and metabolic energy (Attwell and Laughlin, 2001), and rely on genetic information for guidance in development (Dickson, 2002). Despite all that, there is growing evidence that the wiring cost can be approximated by the wiring volume. Indeed, pattern formation in the cortex (Mitchison, 1991), observed angles of dendritic branching (Cherniak, 1992; Shefi et al., 2004), differential axon diameters in rod and cone pathways (Hsu et al., 1998), and equipartition of volume between axons and dendrites in the cortical neuropil (Stepanyants et al., 2002) are best explained by the minimization of the wiring volume. Moreover, the wiring volume adds up linearly and can be conservatively exchanged between various axons and dendrites, making it a convenient approximation for the cost. Then the assumption that evolution minimized the wiring cost, while maximizing the network functionality, leads to the following optimal design problem. For a fixed functionality of the network, as specified by the synaptic connectivity, find the wiring design that minimizes the wiring volume.

In this paper, I consider the wiring up of a three-dimensional neuronal network inspired by the cortical column. Each neuron is assumed to make a synaptic
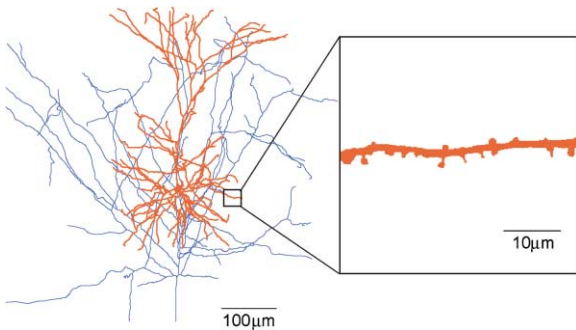
Figure 1. Reconstruction of a Pyramidal Neuron from Rat Neocortex

Axons are shown in blue, dendrites and cell body are shown in red. Spines are small protrusions on the dendrites shown in the inset. Image is courtesy of G. Shepherd, Jr. and K. Svoboda; inset is courtesy of A. Holtmaat and K. Svoboda.

connection onto every other neuron, or, in other words, network connectivity is all-to-all. This seemingly drastic assumption is justified below by using the concept of potential synapse. The minimal volume of the all-to-all connected network is calculated in terms of the number of neurons, N, and the wire diameter, d. The network volume depends on the chosen wiring design. I start with the simplest possible wiring design, nonbranching (or point-to-point) axons, and show that it occupies a prohibitively large volume. This means that evolution had to solve a difficult wiring problem. Adding features of neuronal morphology, such as branching axons, branching dendrites, and dendritic spines, reduces the size of the network, implying that neuronal morphology makes wiring more efficient. Moreover, only the final wiring design, including all the salient morphology features, yields the correct size of the cortical column. Therefore, if one assumes that cortical function requires high (potential) interconnectivity in a small volume, one need not look further to find a reason for the existence and total length of axons and spiny dendrites.

Results

Design I: Point-to-Point Axons

In the simplest wiring design, a synaptic connection between any pair of neurons requires a dedicated axon, which I call a point-to-point axon (Figure 2). The total volume of the network can be readily found by using a scaling estimate. In such an estimate, numerical coefficients of order one are ignored and the results apply when the number of neurons is large. The average length of each axon scales with the linear dimension of the network, R, e.g., with the width or height of a cubic volume. Each neuron has to send such an axon to every other neuron, meaning that there are N axons per neuron. Therefore, the wiring length per neuron, l, is given by

$$l \sim NR. \tag{1}$$

Since the brain consists mostly of wiring (about 60% of the gray matter [Braitenberg and Schüz, 1998]), the neuronal network volume can be estimated via the wiring volume. Assuming a fixed axon diameter, d, the wiring volume is given by
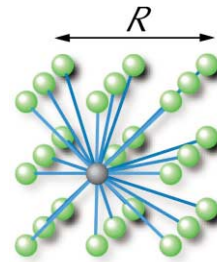

Figure 2. Design I: Point-to-Point Axons

Neuronal network containing N neurons (green spheres) with all-to-all connectivity implemented by point-to-point axons (design I). For the sake of illustration, only axons belonging to one neuron are shown (blue lines originating from the gray sphere). The rest of the axons fill up the space between the neurons and determine the volume of the network, R^3.

$$R^3 \sim Nld^2. \tag{2}$$

Substituting Equation 1 into Equation 2 gives the network volume

$$R^3 \sim d^3N^3. \tag{3}$$

Although this estimate works well for the global cortical network as a whole (see Appendix), it fails completely for a network of neurons *within* the cortical column. Initially, I compare theoretical predictions with data from mouse neocortex because of their relatively high quality, leaving interspecies comparison to the section on Comparison with Experiment. One cubic millimeter of mouse neocortex contains $N = 10^5$ neurons (Braitenberg and Schüz, 1998). Intracortical axons have an average diameter $d = 0.3$ μm (Braitenberg and Schüz, 1998). Substitution of these numbers into Equation 3 yields a column volume 30,000 times greater than in reality ($R = 3$ cm versus actual size of 1 mm). This result shows that point-to-point axons are insufficient to wire up the all-to-all connected network in the allotted volume.

What is missing here? One answer is that the cortical column is not an all-to-all connected network, but this is only a partial explanation. First, even including the observed connectivity sparseness of 0.01–0.1 (Holmgren et al., 2003; Markram et al., 1997; Mason et al., 1991; Sjöström et al., 2001; Thomson and Deuchars, 1997), this reduces the network size only to 3–10 mm, still significantly greater than the actual size of 1 mm. Second, as argued in the section on Comparison with Experiment, the functionality of the neuronal network may be specified by potential synaptic connectivity better than by actual synaptic connectivity (Stepanyants et al., 2002). In turn, the potential connectivity in the cortical column *is* close to all-to-all (A.B. Stepanyants et al., 2003, Soc. Neurosci., abstract). Therefore, to account for the cortical column size, I need to explore more sophisticated wiring designs.

Design II: Branching Axons

One redundancy in design I is that the same signal is carried from a given neuron along many point-to-point axons that run almost parallel to each other (Figure 2). Introducing axons that synapse on multiple neurons can
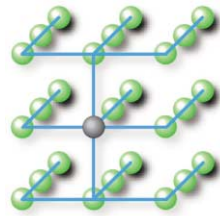
Figure 3. Design II: Branching Axons

Neuronal network wired up with branching axons (design II). Only the axonal arbor (blue lines), belonging to one neuron (gray sphere), is shown. The rest of the axons fill up the space between the neurons and determine the network volume. The volume of the branching axons network (design II) is smaller than that with the point-to-point axons (design I).
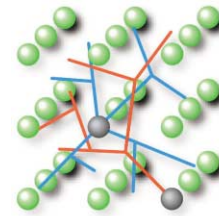

Figure 4. Design III: Branching Axons and Dendrites

Neuronal network wired up with branching axons and dendrites (design III). Only the axon (blue) belonging to one neuron (gray sphere in the center) and the dendrite (red) belonging to another (gray sphere in the corner) are shown. The rest of the axons and dendrites fill up the space between the neurons and determine the network size. Axons and dendrites form three-dimensional meshes that make contact with each other in the neuropil. The total network volume (design III) is smaller than that of the axons-only network (design II).

rectify such redundancy (Cherniak et al., 1999; Mitchison, 1991, 1992; Murre and Sturdy, 1995). Multiple synapse axons can make synapses along the way (en passant) and/or by adding branches (Figure 3). Both of these possibilities are encountered in cortical neurons (Braitenberg and Schüz, 1998). Since each en passant synapse may be viewed as a zero-length branch, in this paper, no distinction is made between these possibilities, and design II is referred to as branching axons.

Next, I calculate the volume of a neuronal network wired with branching axons (Figure 3). The axonal length per neuron is given approximately by the number of neurons, N, times the typical interneuron distance. In turn, the interneuron distance can be estimated under the assumption of the uniform spatial distribution (appropriate for cell bodies in the gray matter [Braitenberg and Schüz, 1998]) to be $R/N^{1/3}$. Then, the wiring length per neuron is

$$l \sim N^{2/3}R. \tag{4}$$

Substituting Equation 4 into Equation 2 gives the volume of the network

$$R^3 \sim d^3N^{5/2}. \tag{5}$$

This result was previously obtained by Murre and Sturdy (1995) and shows that the volume of the network with branching axons scales with the smaller power of N than that for the point-to-point axons, Equation 3. This implies that, in the limit of a large number of neurons, implementing a network with branching axons reduces the network volume. For example, the cortical column containing 10^5 neurons would increase 300-fold (or almost 7-fold in linear size) if point-to-point axons were used instead of branching axons. Of course, there may be other constraints on the wiring design. For example, the network of cortical columns, discussed in the Appendix, cannot utilize the branching axon design because each axon from a given cortical column belongs to a different neuron and, most likely, carries a different signal, appropriate only for the target column. However, other things being equal, evolution should prefer branching axons to point-to-point ones.

Although advantageous, wiring up a network with branching axons does not account fully for the cortical column size. Substitution of the intracortical axon diam-

eter $d = 0.3$ μm (Braitenberg and Schüz, 1998) into Equation 5 yields cortical column volume 90 times greater than in reality ($R = 4.4$ mm versus actual column size of 1 mm). This mismatch is primarily due to the existence of dendrites, which further reduce the network size, as I argue next.

Design III: Branching Axons and Dendrites
A shortcoming of the axons-only network is that each axon has to make its way to every cell body. Since all the signals received by a neuron are merged in the cell body, the same functionality can be achieved by a single process reaching out in the direction of axons and meeting them halfway (Chklovskii, 2000b). This process conducts signals from the synapses to the cell body and, hence, should be called a dendrite (Ramón y Cajal, 1899). Because a single dendrite takes up less volume than the many converging axons, this solution is more efficient. In reality, axons converge on a cell body from various directions, requiring several dendritic branches. Yet, in the limit of large convergence, adding dendrites to the wiring design lowers the wiring cost (Chklovskii, 2000b). This argument is consistent with correlations between convergence and dendritic complexity observed in ciliary ganglion (Purves and Hume, 1981; Purves and Lichtman, 1985; Purves et al., 1986) as well as the dimensions of dendrites and axons in the retina, cerebellum, and the olfactory bulb (Chklovskii, 2000b). Below, I show that adding dendrites to the all-to-all connected network, which possesses both high convergence and divergence, also improves the wiring efficiency.

In the all-to-all connected network, convergence and divergence are equal, suggesting a symmetry between axons and dendrites. This leads me to consider axons and dendrites built to the same design: a 3D mesh of wires with the constant caliber d uniformly spanning the volume of the network (Figure 4) (for axons and dendrites of different diameters, see below). The mesh size (diameter of the holes in the mesh) is uniquely related to the axonal (or dendritic) length. In turn, the axonal length follows from the condition that an axonal arbor must make contact with every dendritic arbor. In order to

calculate axonal length, an expression for the number of contacts is derived and set to one. The derivation neglects the topology of the arbors and correlations in the locations of branch segments (Stepanyants et al., 2002). First, the total volume, R^3, is divided into cubes of volume, d^3, i.e., into R^3/d^3 voxels. Then, the number of contacts between an axon and a dendrite is given by the number of voxels that contain them both. Each axon occupies l/d voxels, the same number as a dendrite. The fraction of voxels containing the axon is $(l/d)/(R^3/d^3)$, the same as the fraction containing the dendrite. Then, the fraction of voxels containing both the axon and the dendrite is the product of the two fractions, l^2d^4/R^6. By multiplying this fraction by the total number of voxels, I find the number of voxels containing axon and dendrite, l^2d/R^3. Then, the condition for having one contact is given by (Stepanyants et al., 2002)

$$l^2d/R^3 \sim 1. \qquad (6)$$

Combining Equations 6 and 2 and excluding l gives the following estimate for the volume of the network with branching axons and dendrites:

$$R^3 \sim d^3N^2. \qquad (7)$$

This result shows that adding branching dendrites (design III) to the axons-only network (design II) reduces the scaling exponent, implying that, in the limit of large N, this reduces the network volume. Substitution of the axonal diameter, $d = 0.3$ μm (Braitenberg and Schüz, 1998), and $N = 10^5$ into Equation 7 yields a cortical column size of $R = 0.7$ mm, which is smaller than for the axons-only network and close to actual size. This estimate is not right, however, because it ignores the fact that the dendritic diameter, $d_d = 0.9$ μm (Braitenberg and Schüz, 1998), is greater than axonal, $d_a = 0.3$ μm (Braitenberg and Schüz, 1998). Combining axons and dendrites with correct diameters yields an estimate for the column size $R = 1.6$ mm, which is still greater (four times by volume) than the actual size.

Design III can be improved by the addition of dendritic spines, which expand the reach of the dendrites without increasing their length (Sorra and Harris, 2000; Stepanyants et al., 2002; Swindale, 1981). Although this does not affect the scaling exponent in Equation 7, the prefactor is reduced. Then, dendritic spines reduce the size of the network and bring the size estimate in agreement with reality, as shown next.

Design IV: Branching Axons and Spiny Dendrites

Adding dendritic spines reduces the size of the branching axon and dendrite network (design III) because axons and dendritic shafts do not have to touch in order to make a synapse, but can pass within the spine length, s, of each other (Figure 5; Sorra and Harris, 2000; Stepanyants et al., 2002; Swindale, 1981). Then, the condition on the existence of a synapse between an axon and a dendrite, Equation 6, is replaced by (Stepanyants et al., 2002)

$$l^2s/R^3 \sim 1. \qquad (8)$$

Combining Equations 2 and 8, I find that the network volume scales with the neuron number as
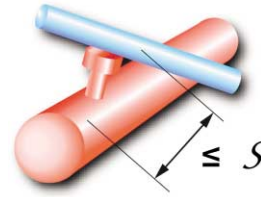

Figure 5. Design IV: Branching Axons and Spiny Dendrites
Dendritic spines (red mushroom-like object) can implement a synapse between a dendrite (red cylinder) and an axon (blue) that pass within the distance, s, of each other. Addition of spines increases the reach of the dendrites and reduces the network size (design IV) relative to the smooth dendrite network (design III).

$$R^3 \sim \frac{d^4}{s} N^2. \qquad (9)$$

Equation 9 shows that adding dendritic spines to the wiring design III, Equation 7, reduces the prefactor and, hence, the network volume. Assuming that the spine length $s = 2.5$ μm (Spacek and Hartmann, 1983) and accounting for the difference in axon and dendrite calibers (see below), I get the cortical column size, $R = 0.7$ mm. This is reasonably close to the actual size considering that wiring takes up about 60% of the 1 mm^3 cortical volume. Although neat, this agreement should not be overinterpreted. Scaling estimates presented here do not include numerical coefficients and are correct only by order of magnitude. Yet, I can still argue that the existing cortical column cannot be wired in the allotted volume if any of the salient morphological features are missing. For example, Equation 9 shows that elimination of spines from the actual cortical column would increase its volume several-fold. Finally, an effect similar to adding dendritic spine might be achieved by positioning synaptic boutons on short axonal branches, i.e., *terminaux* boutons.

Proof of Design Optimality

Can the network volume of design IV be reduced further? Not by order of magnitude. To demonstrate this, I estimate the minimum wire length, which determines the network volume if the wire diameter is fixed. Each dendrite has to be long enough for N axons to pass within distance s from it (Figure 6). Because of volume exclusion, the number of axons that can synapse on a dendrite is given by the cross-sectional area of dendritic arbor (from the point of view of axon), ls, times the maximum flux density of axons, $1/d^2$:

$$N \sim \frac{ls}{d^2}. \qquad (10)$$

Then the minimum dendritic length is given by

$$l \sim N\frac{d^2}{s}. \qquad (11)$$

This is the same expression as one gets for design IV by combining Equations 2 and 9. This proves that in design IV the dendrite volume and, by symmetry, the axon volume, are the smallest possible for an all-to-all connected network with N neurons. Therefore, design
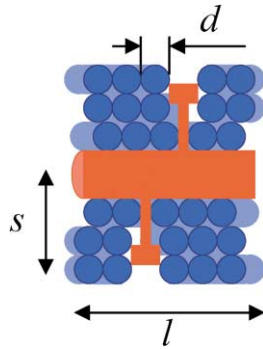
Figure 6. Cross-Section of a Dendrite with Adjacent Axons

Dendrites must be sufficiently long to ensure that every presynaptic axon can synapse with them. Because of volume exclusion among axons, the maximum number of available presynaptic axons, N, is given by the dendritic length, l, times the spine length, s, divided by the axon diameter, d, squared. Dendritic length estimated this way coincides with that in design IV, thus proving its optimality. The same argument relates minimum axonal length to dendritic diameter.

IV cannot be improved further, provided wire diameter and spine length are fixed.

Why could not spines be much longer? They could be, but then their volume should be counted toward the wiring cost, just as dendritic branches were. So far the spine volume has been excluded from the wiring cost because it depends weakly on the spine length. Indeed, the spine volume is dominated by its head, which does not scale with the spine length. Although the spine neck volume scales with the spine length, its cross-sectional area is rather small (Harris and Stevens, 1989). Presumably, much longer spines would require a thicker neck, which gives a large contribution to the volume. An integral treatment of dendrites and spines as wiring requires relaxing the constraint on the wire diameter, which leads to the next question.

If evolution attempts to minimize the wiring volume, why not make axons and dendrites thinner? The answer is that thinner wires impair brain functionality by adding to signal delay (Rushton, 1951) in axons and to attenuation (Rall et al., 1992) in dendrites and by reducing information transmission capacity in synapses (Hsu et al., 1998). Then, the trade-off between signal delay, attenuation, and information rate on the one hand and wiring volume on the other determines the wire diameter (Chklovskii et al., 2002; Chklovskii and Stepanyants, 2003; Hsu et al., 1998). This argument explains the observed difference in axonal diameters between different pathways (Hsu et al., 1998) across branch points (Chklovskii and Stepanyants, 2003) and explains the fraction of neuropil taken up by wiring (Chklovskii et al., 2002). In the present theory, the wiring cost is minimized for fixed functionality. Therefore, fixed axonal and dendritic diameters are assumed.

The difference in average diameter between axons, d_a, and dendrites, d_d, is easily incorporated into the theory by replacing Equation 11 with two separate expressions for axonal and dendritic length:

$$l_a \sim N \frac{d_d^2}{s} \qquad (12)$$

$$l_d \sim N \frac{d_a^2}{s}. \qquad (13)$$

Substituting these expressions into Equation 2 yields the following estimate for the network volume:

$$R^3 \sim N^2 \frac{d_a^2 d_d^2}{s}. \qquad (14)$$

This expression shows that when axons and dendrites have different diameters, Equation 9 contains their geometric mean. In addition, Equation 14 shows that axons and dendrites occupy approximately equal volume, a result consistent with anatomical data (Braitenberg and Schüz, 1998; Chklovskii et al., 2002; Nafstad and Blackstad, 1966; Stepanyants et al., 2002).

Comparison with Experiment

Equations 12 and 13 predict axonal and dendritic length, which can be compared with anatomical data from mouse neocortex (Braitenberg and Schüz, 1998). Substituting axonal diameter, $d_a = 0.3 \ \mu m$ (Braitenberg and Schüz, 1998), dendritic diameter, $d_d = 0.9 \ \mu m$ (Braitenberg and Schüz, 1998), and spine length, $s = 2.5 \ \mu m$ (Spacek and Hartmann, 1983), yields the total axonal length per neuron, $l_a = 4$ cm, and the total dendritic length per neuron, $l_d = 4$ mm. These results are in agreement with experimental data (Braitenberg and Schüz, 1998).

As previously mentioned, comparison of the all-to-all network with the cortical column may seem artificial because connectivity in the cortical column is sparse. This is not a problem, however, if the brain functionality is specified by the potential synaptic connectivity. Potential synapse (Stepanyants et al., 2002) means a location in the neuropil where an axon and a dendrite come within a spine length of each other (Figure 6). The potential synapse is a necessary although not sufficient condition for the actual one. Its significance derives from the observation of the structural plasticity in adult neocortex (Trachtenberg et al., 2002): longitudinal in vivo imaging shows that dendritic spines constantly extend and retract, forming and eliminating actual synapses. At the same time, axonal and dendritic branches do not change (Mizrahi and Katz, 2003; Trachtenberg et al., 2002), meaning that the potential synapses remain stable. Therefore, it may be more appropriate to characterize the cortical column by its potential connectivity. Although potential connectivity depends on the cortical layer and cell type, it remains close to all-to-all over several hundred micrometers (A.B Stepanyants et al., 2003, Soc. Neurosci., abstract). For the purposes of the scaling estimate, the actual volume of the cortical column has been rounded off to 1 mm³. Possible overestimate of the column volume is compensated, to some extent, by neglecting the fact that a pair of neurons can make more than one potential synapse. The ratio between the numbers of actual and potential synapses is called the filling fraction, f (Stepanyants et al., 2002). Its value is typically much smaller than one (Stepanyants et al., 2002), as would be expected from the sparseness of local cortical connectivity.

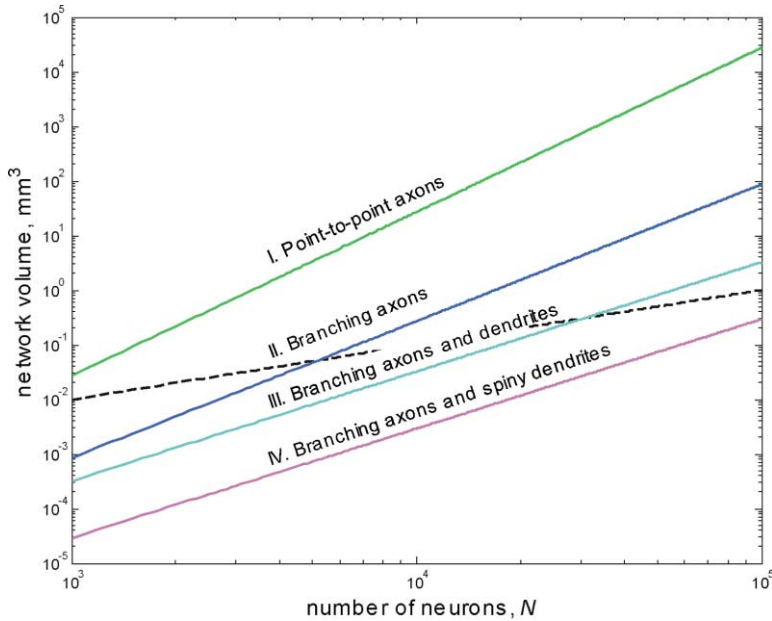Given that the cortical column has all-to-all potential

Figure 7. Volume of Network with All-to-All Connectivity as a Function of the Number of Neurons, N

Out of all wiring designs (solid lines), only branching axons and spiny dendrites (magenta line) give the correct volume (<1 mm^3) for the mouse cortical column, $N = 10^5$ neurons. Dashed line gives the actual network volume provided neuron density is that of the mouse cortex. Differences in slope reflect differences in scaling exponents. Note that log-log scale underemphasizes the actual reduction in volume. This calculation assumes a fixed wire diameter, $d_a = 0.3$ μm for axons and $d_d = 0.9$ μm for dendrites.

connectivity, its volume can be calculated using Equations 3, 5, 7, and 9 (see Figure 7). Different wiring designs yield very different volumes (notice log-log scale), while different slopes reflect different exponents. Predicted network volume can be compared with the actual cortical network, which is calculated assuming that the density of neurons is fixed. If the cortical column includes $\sim 10^5$ neurons, then only the final design fits into the volume allotted for the cortical column (Figure 7), meaning that all the morphological features are necessary to implement observed high interconnectivity. It is possible that the number of neurons in the cortical column is smaller. Then, depending on how many neurons there are, some of the features may not be needed (Figure 7). Similar considerations may explain why smaller neuronal networks (Okada et al., 2001; White et al., 1986) can be implemented without some morphological features, such as dendrites or spines.

These results apply to cortical design of various mammalian species and can be used for comparative (allometric) analysis. To demonstrate this, I calculate the density of synapses in the optimally wired neuropil (design IV). In the cortical column with volume R^3, there are fN^2 synapses, where f is the filling fraction. Then, by using Equation 9, the density of synapses (ignoring the difference between axonal and dendritic diameter) is

$$\rho_s \sim \frac{fs}{d^4}. \tag{15}$$

According to existing data, there is little variation in the average diameter of local axons and dendrites (Schüz and Demianenko, 1995), spine length (Schüz and Demianenko, 1995), or filling fraction (Stepanyants et al., 2002) between mammalian species. Then, Equation 15 predicts that the density of synapses does not vary significantly either. This prediction is consistent with available data (Schüz and Demianenko, 1995). Another consequence of Equation 9 is the expression for the density of neurons:

$$\rho_n \sim \frac{s}{Nd^4}. \tag{16}$$

According to Equation 9, the size of the cortical column $R \sim N^{2/3}$. Then, by combining this with Equation 16, I get $R \sim \rho_n^{-2/3}$. If the density of neurons decreases by a factor of 4 from mouse to human (Schüz and Demianenko, 1995), the cortical column size must increase by a factor of 2.5. This is consistent with existing data (Schüz and Demianenko, 1995) if the cortical column scales with the size of pyramidal neuron dendrites. However, the density variation between mouse and human may be much greater than 4 times (Tower, 1954), and the extent of the cortical column (as defined by potential connectivity domain) (A.B. Stepanyants et al., 2003, Soc. Neurosci., abstract) is more likely to scale with axons rather than dendrites. Therefore, a conclusive experimental test of these relations will require quantitative anatomical measurements using the same techniques in different species.

Discussion

This paper studies wiring up a neuronal network with all-to-all potential connectivity inspired by the cortical column. Inclusion of each morphological feature of cortical neurons such as branching axons, dendrites, and spines into the wiring design significantly reduces the network volume. Only the final wiring design, including all the salient features of the neuronal morphology, gives a correct order-of-magnitude estimate for the cortical column volume. This means that the existence of dendrites as well as axons, their branching, and the presence of dendritic spines are necessary to wire up the cortical column sufficiently efficiently to fit within the known volume. In addition, the optimal total lengths of axons and dendrites are of the same order of magnitude as actual, suggesting that the cortical column is optimized for high interconnectivity in a small volume.

The current work builds on several important insights gained from the study of the retina. Description of the neuronal arbor as a space-filling mesh has been put forward and validated for ganglion cells in the retina (Panico and Sterling, 1995). The concept of potential (as opposed to actual) convergence and divergence has been used previously for retinal neurons (Sterling et al., 1988). The wiring optimization approach to the two-dimensional topographic network explains the correlation between the dimensions of axonal and dendritic arbors with the convergence/divergence ratio that has been observed experimentally (Chklovskii, 2000b). The current work is essentially an extension of that approach to a three-dimensional all-to-all connected network.

In combination with previous results, the present work strongly suggests that neuronal morphology is largely a reflection of synaptic connectivity. Specifically, dimensions of axonal and dendritic arbors are correlated with divergence and convergence factors. Evidence for this comes from neuronal networks from various brain regions and convergence/divergence ratios. In the rabbit ciliary ganglion, for example, the complexity of dendritic arbors is correlated with the numbers of innervating axons (Purves and Hume, 1981; Purves and Lichtman, 1985; Purves et al., 1986). In the retinal neurons, as mentioned in the previous paragraph, the size of dendritic and axonal arbors is explained by the convergence/divergence ratio in agreement with wiring optimization of a two-dimensional topographic projection (Chklovskii, 2000b). Similar observations hold for the parallel fiber to Purkinje cell projection in the cerebellum and for the mitral to granule cell projection in the olfactory bulb, although the quasi-two dimensionality of these projections requires further analysis (Chklovskii, 2000b). As shown in the current paper, in pyramidal cells of the cortex, the total length of dendrites and axons reflects high convergence and divergence, correspondingly. Because convergence and divergence must be the same (averaged over all cortical neurons), the volume of the axonal arbor approximately equals that of the dendritic arbor (Stepanyants et al., 2002). These observations coming from various brain structures, when taken together, point to a general relationship between morphology and connectivity.

The quantitative relationship between neuronal morphology and synaptic connectivity is established by the wiring optimization approach. In this approach, the differences in neuronal morphology arises naturally because the wiring optimization problem yields different solutions for different connectivity requirements. In those cases, where the wiring optimization problem has been solved, its solutions are consistent with anatomical data (see previous paragraph). Therefore, it is likely that the wiring optimization approach will lead to a general theory explaining the variability in axonal and dendritic arbors among different neurons and brain structures. Completing this theory will require solving the wiring optimization problem for remaining network connectivities and comparing solutions with observed neuronal morphology. Eventually, this general theory will establish a mapping between neuronal shape and synaptic connectivity. Such mapping can be used to predict the latter from the former. In turn, knowing synaptic connectivity is essential to understand brain function.

Although the present theory successfully predicts the total length of axons and dendrites, it does not account for the number and length of individual branches. Indeed, within the current framework, designs II-IV work equally well with axons that have several long branches as with axons that snake through the neuropil and make only zero-length branches, i.e., en passant synapses. Explanation of axonal and dendritic branching requires extending the current theory, for example, by including signal delay and attenuation (Chklovskii and Stepanyants, 2003) or information transmission capacity of synapses (Hsu et al., 1998) into the cost function. Trade-off between the wiring volume cost and other contributions can account for variations in branch diameters and spine dimensions. In turn, including variations in branch diameter is crucial to explain the existence and the geometry of branching arbors (Cherniak, 1992; Cherniak et al., 1999; Mitchison, 1991, 1992).

Another challenge is to understand the architecture of the cortical network as a whole. Presumably, there is a limit on the number of neurons that can be wired in the all-to-all manner. Circumventing this limit while preserving small network diameter requires adopting the small-world architecture (Changizi, 2001; Karbowski, 2003). An example of such architecture is sketched in the Appendix. Sparse long-range interconnections integrate cortical columns, each having dense local interconnections. Experimental measurements suggest that the long-range connections make a small contribution to the cortical column volume (Anderson et al., 1998; Anderson and Martin, 2002), justifying ignoring them in the main text. Next, we need to understand how the total brain volume is partitioned between the gray (mostly local connections) and the white (mostly long-range connections) matter.

Although the current work suggests the evolutionary raison d'etre for axons, dendrites, and spines, it does not rule out their other uses such as nonlinear operations in dendrites (Hausser and Mel, 2003; Koch et al., 1982; Mel, 1993; Polsky et al., 2004), delay lines in axons (Carr and Konishi, 1988), and signal filtering in spines (Koch and Zador, 1993; Rose and Call, 1992; Svoboda et al., 1996; Yuste et al., 2000). These functional requirements are not needed to explain the existence and the total lengths of the processes in cortical pyramidal neurons. In other parts of the brain, these or some other functional constraints may be important. For example, as discussed above, myelinated axons cannot make en passant synapses, thus becoming point-to-point axons (design I). Also, making synaptic connections between distant neurons requires active signal propagation and, hence, the use of axons rather than dendrites (design II). Detecting mismatches between the wiring optimization predictions and anatomical data will help discover other functional and structural constraints on brain design.

Appendix

Here the volume of long-range interconnections (white matter) in the global cortical network is estimated. For this purpose, each cortical column (rather than each neuron) is treated as a network node. How many neurons are there in one column? Assuming that the density of neurons among mammalian species scales with the

brain volume as $\rho_n \sim V^{-1/3}$ (Prothero and Sundsten, 1984; Tower, 1954), the number of neurons in a column scales as $N \sim V^{1/3}$, according to Equation 16. How many columns are there? According to Equation 9, the volume of the column, $R^3 \sim N^2 \sim V^{2/3}$, meaning that the total number of columns scales as $V^{1/3}$. Then the number of columns in the brain scales the same way as the number of neurons in a column. This argument rationalizes "the square root compartments" model for the global cortical network (Braitenberg and Schüz, 1998). In this model, the cortex is divided into N cortical columns, each containing N neurons (Braitenberg and Schüz, 1998). Each neuron gives off an axon, which passes through the white matter and makes synapses with neurons in a target column. If every axon from a given column targets a different column, the resulting network of N columns has all-to-all connectivity (Braitenberg and Schüz, 1998) and small network diameter (Changizi, 2001; Karbowski, 2003). Because most axons originate from different neurons and are mostly myelinated, this network must be wired by using design I (point-to-point axons). For the human cerebral cortex, a rough estimate of the number of cortical columns (Braitenberg and Schüz, 1998) is $N = 10^5$, axonal diameter is $d = 1$ μm. For these parameters, Equation 3 yields brain size $R = 10$ cm, which is not too far from reality (Blinkov and Glezer, 1968) despite several simplifying assumptions made.

References

Allman, J.M., and Kaas, J.H. (1974). The organization of the second visual area (V II) in the owl monkey: a second order transformation of the visual hemifield. Brain Res. 76, 247–265.

Anderson, J.C., and Martin, K.A. (2002). Connection from cortical area V2 to MT in macaque monkey. J. Comp. Neurol. 443, 56–70.

Anderson, J.C., Binzegger, T., Martin, K.A., and Rockland, K.S. (1998). The connection from cortical area V1 to V5: a light and electron microscopic study. J. Neurosci. 18, 10525–10540.

Attwell, D., and Laughlin, S.B. (2001). An energy budget for signaling in the grey matter of the brain. J. Cereb. Blood Flow Metab. 21, 1133–1145.

Barlow, H.B. (1986). Why have multiple cortical areas? Vision Res. 26, 81–90.

Blinkov, S., and Glezer, I. (1968). The Human Brain in Figures and Tables (New York: Plenum Press).

Braitenberg, V., and Schüz, A. (1998). Cortex: Statistics and Geometry of Neuronal Connectivity, 2nd Edition (Berlin: Springer).

Carr, C.E., and Konishi, M. (1988). Axonal delay lines for time measurement in the owl's brainstem. Proc. Natl. Acad. Sci. USA 85, 8311–8315.

Changizi, M.A. (2001). Principles underlying mammalian neocortical scaling. Biol. Cybern. 84, 207–215.

Cherniak, C. (1992). Local optimization of neuron arbors. Biol. Cybern. 66, 503–510.

Cherniak, C. (1994). Component placement optimization in the brain. J. Neurosci. 14, 2418–2427.

Cherniak, C. (1995). Neural component placement. Trends Neurosci. 18, 522–527.

Cherniak, C., Changizi, M., and Won Kang, D. (1999). Large-scale optimization of neuron arbors. Phys. Rev. E Stat. Phys. Plasmas Fluids Relat. Interdisc. Topics 59, 6001–6009.

Cherniak, C., Mokhtarzada, Z., Rodriguez-Esteban, R., and Changizi, K. (2004). Global optimization of cerebral cortex layout. Proc. Natl. Acad. Sci. USA 101, 1081–1086.

Chklovskii, D.B. (2000a). Binocular disparity can explain the orientation of ocular dominance stripes in primate primary visual area (V1). Vision Res. 40, 1765–1773.

Chklovskii, D.B. (2000b). Optimal sizes of dendritic and axonal arbors in a topographic projection. J. Neurophysiol. 83, 2113–2119.

Chklovskii, D.B. (2004). Exact solution for the optimal neuronal layout problem. Neural Comput. 16, in press.

Chklovskii, D.B., and Koulakov, A.A. (2000). A wire length minimization approach to ocular dominance patterns in mammalian visual cortex. Physica A 284, 318–334.

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

Chklovskii, D.B., and Stepanyants, A. (2003). Power-law for axon diameters at branch point. BMC Neurosci. 4, 18.

Chklovskii, D.B., Schikorski, T., and Stevens, C.F. (2002). Wiring optimization in cortical circuits. Neuron 34, 341–347.

Cowey, A. (1979). Cortical maps and visual perception: the Grindley memorial lecture. Q. J. Exp. Psychol. 31, 1–17.

Debanne, D. (2004). Information processing in the axon. Nat. Rev. Neurosci. 5, 304–316.

Dickson, B.J. (2002). Molecular mechanisms of axon guidance. Science 298, 1959–1964.

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

Harris, K.M., and Stevens, J.K. (1989). Dendritic spines of CA 1 pyramidal cells in the rat hippocampus: serial electron microscopy with reference to their biophysical characteristics. J. Neurosci. 9, 2982–2997.

Hausser, M., and Mel, B. (2003). Dendrites: bug or feature? Curr. Opin. Neurobiol. 13, 372–383.

Holmgren, C.D., Harkany, T., Svennenfors, B., and Zilberter, Y. (2003). Pyramidal cell communication within local networks in layer 2/3 of rat neocortex. J. Physiol. 551, 139–153.

Hsu, A., Tsukamoto, Y., Smith, R.G., and Sterling, P. (1998). Functional architecture of primate cone and rod axons. Vision Res. 38, 2539–2549.

Karbowski, J. (2003). How does connectivity between cortical areas depend on brain size? Implications for efficient computation. J. Comput. Neurosci. 15, 347–356.

Klyachko, V.A., and Stevens, C.F. (2003). Connectivity optimization and the positioning of cortical areas. Proc. Natl. Acad. Sci. USA 100, 7937–7941.

Koch, C., and Zador, A. (1993). The function of dendritic spines: devices subserving biochemical rather than electrical compartmentalization. J. Neurosci. 13, 413–422.

Koch, C., Poggio, T., and Torre, V. (1982). Retinal ganglion cells: a functional interpretation of dendritic morphology. Philos. Trans. R. Soc. Lond. B Biol. Sci. 298, 227–263.

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

Markram, H., Lübke, J., Frotscher, M., Roth, A., and Sakmann, B. (1997). Physiology and anatomy of synaptic connections between thick tufted pyramidal neurones in the developing rat neocortex. J. Physiol. 500, 409–440.

Mason, A., Nicoll, A., and Stratford, K. (1991). Synaptic transmission between individual pyramidal neurons of the rat visual cortex in vitro. J. Neurosci. *11*, 72–84.

Mel, B.W. (1993). Synaptic integration in an excitable dendritic tree. J. Neurophysiol. *70*, 1086–1101.

Mitchison, G. (1991). Neuronal branching patterns and the economy of cortical wiring. Proc. R. Soc. Lond. B. Biol. Sci. *245*, 151–158.

Mitchison, G. (1992). Axonal trees and cortical architecture. Trends Neurosci. *15*, 122–126.

Mizrahi, A., and Katz, L.C. (2003). Dendritic stability in the adult olfactory bulb. Nat. Neurosci. *6*, 1201–1207.

Murre, J.M., and Sturdy, D.P. (1995). The connectivity of the brain: multi-level quantitative analysis. Biol. Cybern. *73*, 529–545.

Nafstad, P.H., and Blackstad, T.W. (1966). Distribution of mitochondria in pyramidal cells and boutons in hippocampal cortex. Z. Zellforsch. Mikrosk. Anat. *73*, 234–245.

Nelson, M.E., and Bower, J.M. (1990). Brain maps and parallel computers. Trends Neurosci. *13*, 403–408.

Okada, T., MacIsaac, S.S., Katsuyama, Y., Okamura, Y., and Meinertzhagen, I.A. (2001). Neuronal form in the central nervous system of the tadpole larva of the ascidian *Ciona intestinalis*. Biol. Bull. *200*, 252–256.

Panico, J., and Sterling, P. (1995). Retinal neurons and vessels are not fractal but space-filling. J. Comp. Neurol. *361*, 479–490.

Polsky, A., Mel, B.W., and Schiller, J. (2004). Computational subunits in thin dendrites of pyramidal cells. Nat. Neurosci. *7*, 621–627.

Prothero, J.W., and Sundsten, J.W. (1984). Folding of the cerebral cortex in mammals. A scaling model. Brain Behav. Evol. *24*, 152–167.

Purves, D., and Hume, R.I. (1981). The relation of postsynaptic geometry to the number of presynaptic axons that innervate autonomic ganglion cells. J. Neurosci. *1*, 441–452.

Purves, D., and Lichtman, J.W. (1985). Geometrical differences among homologous neurons in mammals. Science *228*, 298–302.

Purves, D., Rubin, E., Snider, W.D., and Lichtman, J. (1986). Relation of animal size to convergence, divergence, and neuronal number in peripheral sympathetic pathways. J. Neurosci. *6*, 158–163.

Rall, W., Burke, R.E., Holmes, W.R., Jack, J.J., Redman, S.J., and Segev, I. (1992). Matching dendritic neuron models to experimental data. Physiol. Rev. *72*, S159–S186.

Ramón y Cajal, S. (1899). Textura del Sistema Nervioso del Hombre y de los Vertebrados. (Texture of the Nervous System of Man and the Vertebrates), Vol 1 (New York: Springer).

Ringo, J.L. (1991). Neuronal interconnection as a function of brain size. Brain Behav. Evol. *38*, 1–6.

Rose, G.J., and Call, S.J. (1992). Evidence for the role of dendritic spines in the temporal filtering properties of neurons: the decoding problem and beyond. Proc. Natl. Acad. Sci. USA *89*, 9662–9665.

Ruppin, E., Schwartz, E.L., and Yeshurun, Y. (1993). Examining the volume efficiency of the cortical architecture in a multi-processor network model. Biol. Cybern. *70*, 89–94.

Rushton, W.A. (1951). Theory of the effects of fibre size in medullated nerve. J. Physiol. *115*, 101–122.

Schüz, A., and Demianenko, G.P. (1995). Constancy and variability in cortical structure. A study on synapses and dendritic spines in hedgehog and monkey. J. Hirnforsch. *36*, 113–122.

Shefi, O., Harel, A., Chklovskii, D.B., Ben Jacob, E., and Ayali, A. (2004). Biophysical constraints on neuronal branching. Neurocomputing *58–60*, 487–495.

Sjöström, P.J., Turrigiano, G.G., and Nelson, S.B. (2001). Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. Neuron *32*, 1149–1164.

Sorra, K.E., and Harris, K.M. (2000). Overview on the structure, composition, function, development, and plasticity of hippocampal dendritic spines. Hippocampus *10*, 501–511.

Spacek, J., and Hartmann, M. (1983). Three-dimensional analysis of dendritic spines. I. Quantitative observations related to dendritic spine and synaptic morphology in cerebral and cerebellar cortices. Anat. Embryol. *167*, 289–310.

Stepanyants, A., Hof, P.R., and Chklovskii, D.B. (2002). Geometry and structural plasticity of synaptic connectivity. Neuron *34*, 275–288.

Sterling, P., Freed, M.A., and Smith, R.G. (1988). Architecture of rod and cone circuits to the on-beta ganglion cell. J. Neurosci. *8*, 623–642.

Svoboda, K., Tank, D.W., and Denk, W. (1996). Direct measurement of coupling between dendritic spines and shafts. Science *272*, 716–719.

Swindale, N.V. (1981). Dendritic spines only connect. Trends Neurosci. *4*, 240–241.

Thomson, A.M., and Deuchars, J. (1997). Synaptic interactions in neocortical local circuits: dual intracellular recordings in vitro. Cereb. Cortex *7*, 510–522.

Tower, D.B. (1954). Structural and functional organization of mammalian cerebral cortex: the correlation of neuron density with brain size. J. Comp. Neurol. *101*, 19–51.

Trachtenberg, J.T., Chen, B.E., Knott, G.W., Feng, G., Sanes, J.R., Welker, E., and Svoboda, K. (2002). Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature *420*, 788–794.

Van Essen, D.C. (1997). A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature *385*, 313–318.

White, J.G., Southgate, E., Thomson, J.N., and Brenner, S. (1986). The structure of the nervous system of the nematode *Caenorhabditis elegans*. Philos. Trans. R. Soc. Lond. B Biol. Sci. *314*, 1–340.

Young, M.P. (1992). Objective analysis of the topological organization of the primate cortical visual system. Nature *358*, 152–155.

Yuste, R., Majewska, A., and Holthoff, K. (2000). From form to function: calcium compartmentalization in dendritic spines. Nat. Neurosci. *3*, 653–659.

Note Added in Proof

After this work was completed, it was learned that Braitenberg (2001) had previously estimated the volume of the network built according to Design I. He concluded that such an estimate is reasonable in the case of long-range interconnections between cortical columns (see Appendix) and prohibitively big in the case of the wiring within the cortical column.

Braitenberg, V. (2001). Brain size and number of neurons: an exercise in synthetic neuroanatomy. J. Comput. Neurosci. *10*, 71–77.