Synaptic connectivity and neuronal morphology: two sides of the same coin

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Among the cells of the body, neurons stand out by the high number of inter-cell contacts, or synapses, and by the intricate shape of cell processes, or axonal and dendritic arbors. Are these two distinctive neuronal features related? I show that wiring up a neuronal network, such as a cortical column, in the allotted volume requires all the salient features of neuronal morphology: the existence of dendrites as well as axons, their branching and the existence of dendritic spines. Therefore, the neuronal morphology is an adaptation that makes high connectivity possible. This teleological argument should help in understanding brain evolution and in inferring synaptic connectivity from the arbor morphology.

INTRODUCTION

Brain functionality relies on large numbers of neurons and synaptic connections between them. A cubic millimeter of the mouse neocortex, for example, contains about 10^5 neurons and 10^9 synapses[1]. Building such a network is a formidable challenge because connections must be implemented in the physical world using biological wiring, i.e. axons and dendrites, which come at a considerable cost[2]. Axons and dendrites take up valuable space[3,4], introduce delays[5] and attenuation[6], require material and metabolic energy[7], and rely on genetic information for guidance in development[8]. Although we do not know the exact origin of the wiring cost, it may be approximated by the wiring volume[3,4,9-11]. 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 a network with all-to-all connectivity, where each neuron makes a synaptic connection onto every other neuron. I calculate the minimal physical size of the all-to-all connected network in terms of the number of neurons, N, and the wire diameter, d, Figure 1. The network size depends on the chosen wiring design. Starting with the simplest possible wiring design, non-branching (or point-to-point) axons, I add features of neuronal morphology, such as branching axons, branching dendrites, and dendritic spines, Figure 1. Inclusion of each feature 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 a cortical column, Figure 1. This calculation suggests that the neuronal morphology has evolved to implement high synaptic connectivity, necessary for brain function.

Figure 1. *Volume of network with all-to-all connectivity as a function of the number of units, N. Units correspond to cortical columns in the human cortical network (red line) or neurons in the mouse cortical column (other lines). Only branching axons and spiny dendrites (magenta line) give the correct volume (<1mm³) for the mouse cortical column, N=10⁵ neurons. This calculation*
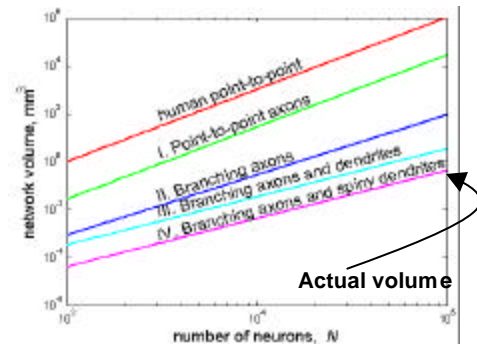
DESIGN I: POINT-TO-POINT AXONS

In the simplest wiring design, a synaptic connection between any pair of network units requires a dedicated axon, which I call a point-to-point axon, Figure 2. The term network unit is used instead of neuron, in this Section only, for the sake of generality: design I may approximate the neocortical network provided cortical columns (rather than individual neurons) are treated as network units[1]. In this approximation, the cortex is divided into N cortical columns, each containing N neurons[1]. Each neuron contains 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[1].

Figure 2. Neuronal network containing N units (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 unit are shown (blue lines originating from the gray sphere). The rest of the axons fill up the space between the units and determine the network size, R.

Imagine wiring up a neuronal network having only point-to-point axons at your disposal, Figure 2. Each unit has to make N connections, the average length of which scales as the network size, R. Therefore, the wiring length per unit, l, is given by

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

Since the brain consists mostly of wiring (almost all of the white matter and about 60% of the gray matter[1]) the neuronal network size can be estimated via the wiring volume. Assuming a fixed axon diameter, d, the wiring volume is given by

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

By substituting Eq.(1) into Eq.(2) I find that the network size, R, for point-to-point axon scales with the number of units, N, as

$$R \sim dN . \tag{3}$$

This scaling relation shows that the network size increases linearly in the number of units. For the human cerebral cortex, a rough estimate on the number of cortical columns[1] is $N = 10^5$, axonal diameter is $d = 1\mu m$. For these parameters, Eq.(3) yields brain size $R = 10cm$, which is not too far from reality[12] despite several simplifying assumptions made.

However, the estimate based on point-to-point axons, Eq. (3), fails completely for a network of neurons *within* a cortical column. Because measurements on the human neocortex are hard to come by, I use anatomical data from the mouse neocortex. One cubic millimeter contains $N = 10^5$ neurons[1]. Intra-cortical axons have average diameter $d = 0.3\mu m$[1]. Substitution of these numbers into Eq.(3) yields a column size of $R = 3cm$, much greater (thirty thousand times by volume, Figure 1) than the actual size of 1mm. 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 a cortical column is not an all-to-all connected network, but this is beyond the point. First, even including the observed connectivity sparseness of 0.01-0.1[13-17], reduces the network size only to 3-10mm, still significantly greater than the actual size of 1mm. Second, as I argue in the Discussion, the functionality of the neuronal network maybe better specified by potential rather than by actual synaptic connectivity[10]. In turn, the potential connectivity in a cortical column *is* close to all-to-all[18]. Therefore, to account for the cortical column size, I need to explore more sophisticated wiring designs.

DESIGN II: BRANCHING AXONS

Point-to-point axons (design I) may be an appropriate model for a network of cortical columns because axons are myelinated, and, therefore, cannot make synapses along the way (*en passant*). However, the majority of axons in the cortical gray matter are non-myelinated and make *en passant* synapses at a high rate[1]. Since each *en passant* synapse may be viewed as a zero-length branch, non-myelinated axons can be viewed as branching axons in a broad sense.

Figure 3. 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 network size with branching axons (design II) is smaller than that with the point-to-point axons (design I).
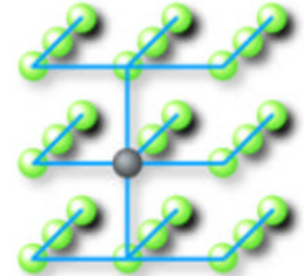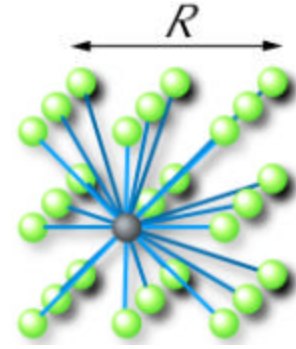
Imagine wiring a neuronal network with branching axons, Figure 3. The axonal length per neuron is approximately given by the number of units, N, times the typical inter-unit distance. In turn, the inter-unit distance can be estimated under the assumption of the uniform spatial distribution (appropriate for the cell bodies in the gray matter[1]) to be $R/N^{1/3}$. Then the wiring length per neuron:

$$l \sim N^{2/3}R. \qquad (4)$$

By substituting Eq.(4) into Eq.(2) I find the size of the network[19]

$$R \sim dN^{5/6}. \qquad (5)$$

This result shows that the size of the network with branching axons scales with the smaller power of N than that for the point-to-point axons, Eq.(3). This implies that, in the limit of large number of units, implementing a network with branching axons reduces the network size. For example, a cortical column containing 10^5 neurons would be almost seven times bigger in linear size (or three hundred times in volume, Figure 1) 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 previous Section, 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 intra-cortical axon diameter $d = 0.3\mu m$[1] into Eq.(5) yields cortical column size $R = 4.4mm$, which is significantly greater (about ninety times by volume, Figure 1) than the actual column size of 1mm. 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[20]. This process conducts signals from the synapses to the cell body and, hence, should be called a dendrite[2]. 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[20]. This argument is consistent with correlations between convergence and dendritic complexity observed in ciliary ganglion[21-23] and the dimensions of dendrites in the retina[20]. 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.

Figure 4. *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. The total network volume (design III) is smaller than that of the axons-only network (design II).*
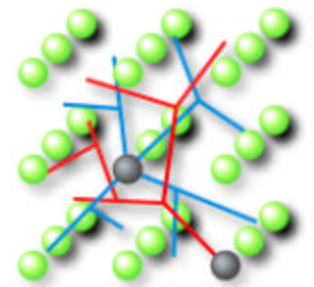
In the all-to-all connected network, convergence and divergence are equal, suggesting a symmetry between axons and dendrites. This leads me to consider axons and dendrites built to the same design: 3D mesh of wires with caliber d uniformly spanning the volume of the network, Figure 4. The mesh size (diameter 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 a contact with every dendritic arbor. In order to calculate axonal length, I derive an expression for the number of contacts and set it to one. The derivation neglects the topology of the arbors and correlations in the locations of branch segments[10]. 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, same number as a dendrite. The fraction of voxels containing the axon is $\dfrac{l/d}{R^3/d^3}$, 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, $l^2 d^4 / R^6$. By multiplying this fraction by the total number of voxels, I find the number of voxels containing axon and dendrite, $l^2 d /R^3$. Then, the condition for having one contact is given by[10]:

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

By combining Eqs.(6,2) and excluding l, I find the following estimate for the size of the network with branching axons and dendrites:

$$R \sim dN^{2/3}. \qquad (7)$$

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 size. Substitution of the axonal diameter, $d = 0.3\mu m^1$, and $N = 10^5$ into Eq. (7) yields cortical column size of $R = 0.7$mm, which is smaller than for axons-only network and close to the actual size. This estimate is not right, however, because it ignores the fact that the dendritic diameter, $d = 1\mu m^1$, is greater than axonal, $d = 0.3\mu m^1$. Combining axons and dendrites with correct diameters yields and estimate for the column size $R = 1.6$mm, which is still greater (four times by volume, Figure 1) than the actual size.

Can this wiring design be improved further? It is possible to show that Eq. (7) gives the smallest possible network size, provided only smooth dendrites are used. This follows from the fact that dendrite length in design III is the smallest possible. To see this, notice that because of volume exclusion by axons coming in contact with the dendrite, the length of the dendrite cannot be less (by order of magnitude) than the number of axons, N, times the axon diameter, d:

$$l \geq Nd. \qquad (8)$$

At the same time, the dendrite length in design III can be found by combining Eqs.(7,2):

$$l \sim Nd. \qquad (9)$$

This proves that 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 III cannot be improved further, provided only smooth dendrites are used.

Interestingly, the limitation on the dendrite length, Eq.(8) can be circumvented by the addition of dendritic spines, which expand the reach of the dendrites without increasing their length[10,24]. Although this does not affect the scaling exponent in Eq.(7), the pre-factor is reduced. Then, dendritic spines reduce the size of the network and bring the size estimate in agreement with reality, as I show 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 don't have to touch in order to make a synapse, but can pass within the spine length, s, of each other[10,24], Figure 5. Then the condition on the existence of a synapse between an axon and a dendrite, Eq.(6), is replaced by[10]

$$l^2 s/R^3 \sim 1. \qquad (10)$$

Figure 5: 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).
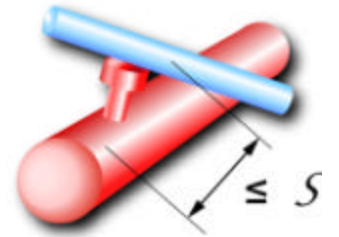
Combining Eqs. (2,10), I find that the number of synapses per axon (or dendrite) is $N \sim ls/d^2$ and the brain size scales with the neuron number as:

$$R \sim \frac{d^{4/3}}{s^{1/3}} N^{2/3} . \tag{11}$$

Eq.(11) shows that adding dendritic spines to the wiring design III, Eq.(7), reduces the pre-factor and, hence, the network size. Assuming that the spine length, $s = 2.5\mu m$[25], and, accounting for the difference in axon and dendrite calibers, I get the cortical column size, $R = 0.8$mm. This is reasonably close to the actual size considering that wiring takes up about 60% of the 1mm³ cortical volume. Although neat, this agreement should not be overemphasized. Scaling arguments 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 allotted volume if any of the salient morphological features are missing. For example, Eq. (11) shows clearly that elimination of spines from the actual cortical column would increase its volume several-fold. I should also note that an effect similar to adding dendritic spine might be achieved by positioning synaptic boutons on short axonal branches, i.e. *terminaux* boutons.

If spines extend the reach of the dendrites, why aren't they counted towards the wiring volume? Spine volume may be 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 very small. An integral treatment of dendrites and spines as wiring requires relaxing constraint on the wire diameter, see Discussion.

DISCUSSION

In this paper, I show that including each feature of the neuronal morphology into the wiring design significantly reduces the size of the all-to-all network. Only the final wiring design, including all the salient features of the neuronal morphology, gives a correct estimate for the cortical column size. This means that the existence of dendrites as well as axons, their branching, and the presence of dendritic spines are necessary to wire up a cortical column. Although my argument suggests the evolutionary *raison d'etre* for axonal and dendritic arbors, it does not rule out their other uses such as non-linear interactions between input currents and compartmentalization in dendrites and spines (see e.g. [26] and references therein).

As previously mentioned, the comparison of the all-to-all network with a cortical column may seem artificial because connectivity in a cortical column is sparse. This is not a problem, however, if the brain functionality is specified by the potential synaptic connectivity. By potential synapse[10], I mean a location in neuropil where an axon and a dendrite come within a spine length of each other, Figure 5. The potential synapse is a necessary but not a sufficient condition for the actual one. Its importance is emphasized by the observation of the structural plasticity in adult neocortex[27]: longitudinal *in vivo* imaging shows that dendritic spines constantly extend and retract, forming and eliminating actual synapses. In the same time, axonal and dendritic branches do not change, meaning that the potential synapses remain stable. Therefore, it may be more appropriate to characterize a cortical column by its potential connectivity. In turn, potential connectivity remains close to all-to-all over several hundred microns[18], thus supporting my model.

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[5] in axons and to attenuation[6] in dendrites. Then, the trade off between signal delay and attenuation on the one hand, and the wiring volume, on the other, determines the wire diameter[9,11]. The difference in conduction mechanisms between axons and dendrites (active vs. primarily passive) tilts the cost balance, and leads to the difference in their cross-sectional area. Having this in mind, I assumed fixed axonal and dendritic diameters for the purposes of this paper. The above trade off will be included into the present theory elsewhere.

If neuronal shape is a solution of the optimal design problem, why do different neurons have different shapes? The main reason is that not all neuronal networks have all-to-all connectivity. Different connectivity requirements for different neurons lead to different solutions to the optimal design problem, yielding a variety of neuronal shapes. For example, I have shown previously that different convergence-divergence ratios in a topographic projection favor different arbor sizes[20]. Another reason for different design solutions is the existence of other constraints, which could affect neuronal shape. 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 constraints on brain

design. Finally, it is possible that the neuronal shape is sub-optimal. Yet, the explanatory and predictive power of the wiring optimization, as demonstrated here and elsewhere[3,4,9-11,20,28-32], suggests that this is a productive approach to understanding principles of brain design.

Future progress will require solving wiring optimization problems for networks other than the all-to-all connected or the topographic projection[20]. Finding optimal designs for various networks would establish a mapping between the synaptic connectivity and the neuronal morphology, which should help inferring the former from the latter. In turn, establishing the synaptic connectivity is crucial for understanding brain function.

In conclusion, I have shown that the neuronal arbor morphology and the synaptic connectivity are the two sides of the same coin, currency being the evolutionary fitness.

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