Optimal Wiring Principle and Plateaus in the Degree of Separation for Cortical Neurons

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Scaling properties of a cortical network wired in a stochastic manner with a distance-dependent probability of a direct connection are considered. In the infinite network limit, an average degree of separation between neurons displays both universality and criticality. The latter feature manifests itself by appearance of a stairlike structure with numerous plateaus as a function of a connectivity exponent. It is suggested that these plateaus may be advantageous in the cortex design. Wiring principle incorporating minimization of both axonal length and the degree of separation is also discussed. This principle leads naturally to a trade-off between saving axons and saving energy required in the communication.

There exists a strongly held belief in the neuroscience community that the architecture of the cerebral cortex is designed in such a way as to save available resources [1], which include axons and dendrites. Since axons are very important in long distance communication between cortical areas, they have been a prime target of saving. As a consequence, several authors [2–5] have explored the principle of minimal axon length as a candidate for an optimal wiring. In this type of wiring, one assumes that the cortex has a volume or geometry that minimizes the average length of long-range axons. However, this principle, and those similar to it [6], do not take into account energetic constraints involved in the transfer of information over long distances.

In this paper, we address this additional aspect by studying a quantity characterizing the degree of separation between neurons. This quantity is a good measure of how fast information can be conveyed in a network. It is also proportional to the overall energy cost required in this communication, since it is directly related to the number of spikes fired by neurons. For efficient communication, one would expect that the degree of separation should be as small as possible. We show that, in fact, there is a trade-off between minimizing the energy cost and minimizing the biochemical resources, i.e., axonal length and number of synapses. This is because shorter axons require more steps in connecting remote cortical areas, and vice versa. Thus, we argue that the optimal wiring in the cortex should be achieved for some intermediate values of axonal length and the degree of separation.

We study a network of volume V_g with a geometry that mimics that of the gray matter of the cortex, i.e., with a surface area $W = R_\parallel^2$ and thickness $R_\perp$ ($V_g = WR_\perp$), with a condition $R_\perp/R_\parallel \ll 1$. (For technical reasons, we will think about the cortical surface not as a sphere but as a plane, with the same total area, which arises after stretching out the cortical sphere). We assume that neurons are sparsely connected in a stochastic manner, i.e., each neuron is directly connected to M_0 others of the total number of neurons M, where $M_0/M \ll 1$. We also assume that despite many classes of neurons, there can be defined some globally average probability of a direct connection $p(r)$, the same for each neuron, that is distance r dependent.

There are three basic densities in the cerebral cortex which are roughly constant across cortical regions and different species [7]: (i) surface density of neurons $\rho = M/W$, (ii) volume density of synapses MM_0/V_g, and (iii) total length of short-range (intracortical, i.e., contained exclusively in the gray matter) axons per volume ML_1/V_g, where L_1 is the total length of short-range axons per neuron. It is not clear experimentally how the total length of long-range (cortico-cortical, i.e., those leaving the gray matter) axons scale with the gray matter volume. However, if we assume that the cortical white matter is composed primarily of long-range axons and that average axonal width does not change with a brain size [7], then we have $ML_2 \sim V_w$, where L_2 is the total length of long-range axons per neuron and V_w is volume of white matter. Since the latter scales with the volume of the gray matter as $V_w \sim V_g^\gamma$, where exponent $\gamma = 1.22$–1.33 [8–10], we obtain for long-range axons that density ML_2/V_g^γ should be roughly constant (brain size independent).

Based on the above experimental facts, we can introduce the following new scale transformations

$$
\begin{aligned}
M &\mapsto M(s) = Ms, \\
M_0 &\mapsto M_0(s) = M_0 s f(s), \\
R_\parallel &\mapsto R_\parallel(s) = R_\parallel s^{1/2}, \\
R_\perp &\mapsto R_\perp(s) = R_\perp s f(s), \\
L_1 &\mapsto L_1(s) = L_1 s f(s), \\
L_2 &\mapsto L_2(s) = L_2 s^{2\gamma-1}[f(s)]^\gamma,
\end{aligned}
\tag{1}
$$

which leave the above four densities invariant. Notice that $R_\parallel$ and $R_\perp$ scale differently, which is a consequence of an anisotropy in the system. In general, scaling function

$f(s)$ can have an arbitrary form with the only requirement $f(1) = 1$. However, guided by experimental data [8,9,11–13], we choose $f(s) \mapsto s^{\alpha-1}$ for $s \gg 1$, where α is a scaling exponent, and we hypothesize that $f(s) \mapsto 1$ for $s \ll 1$. The latter conjecture yields a reasonable behavior for $p(r)$ at small r (see below).

The total axon length L per neuron can be defined as $L = \kappa L_1 + (1 - \kappa)L_2$, where κ is a fraction of neurons with short-range axons only. In the limit of large brains, L_1 and L_2 scale like $L_1 \sim s^\alpha$ and $L_2 \sim s^{\gamma(\alpha+1)-1}$ (or equivalently $L_1 \sim R_\perp \sim R_\parallel^{2\alpha}$, and $L_2 \sim R_\parallel^{2\gamma(\alpha+1)-2}$), which indicates that L is the exponentially growing function of the scaling exponent α (Fig. 1). The same is true for the number of synapses M_0 per neuron, which scales as $\sim s^\alpha$. Thus, the cost of biochemical resources increases very quickly with α.

We define a connectivity ratio $q \equiv M_0/M$, with a scaling relation $q(s) = qf(s)$, which is useful in the network classification for large brains. For $\alpha < 1$ the network becomes sparsely connected, $q(s) \mapsto 0$ for $s \mapsto \infty$. The case $\alpha > 1$ becomes not physical for large networks, since then $q(s) \mapsto \infty$ and the network becomes fully connected. We restrict our analysis below to the case $\alpha \leq 1$.

The relationship between the average "universal" probability $p(r)$ and the number of synapses M_0 per each neuron is given in the continuum limit by

$$\rho \int d^2r \, p(r) = M_0, \quad (2)$$

where r is 2D length measured along the cortical surface, with a scaling law $r(s) = rs^{1/2}$. The part of $p(r)$ with small values of r corresponds to a connection which uses a short-range axon that do not leave the gray matter. For large values of r, $p(r)$ describes a possible connection involving a long-range axon that leaves the gray matter, travels along the white matter, and again enters the gray
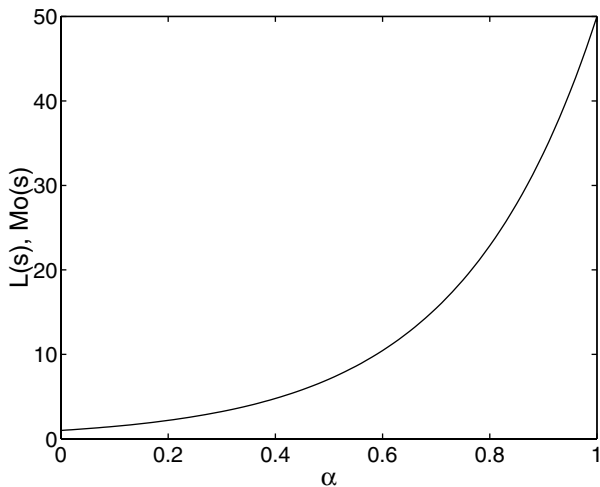

FIG. 1. Schematic dependence of the total axonal length L per neuron and the number of synapses M_0 per neuron on the exponent α. Note the exponential increase with α.

matter to connect a target neuron. Note that, in the continuum limit, $p(r)$ is a conditional probability of a direct connection between some primary neuron and another neuron, given that the latter is at distance r from the former. The probability of encountering another neuron at distance r is given by $\rho d^2r/M$.

From Eqs. (1) and (2), it follows a scaling relation for the probability of connection $p[r(s), s] = f(s)p[r(1), 1]$, where $p(x, 1) \equiv p(x)$. This relation is crucial for determining the degree of separation between neurons in the network. In order to achieve this, we define probability $S_k(r)$, which represents the probability of connection, between neurons separated by r, along at least one of the shortest paths that use k steps (k synapses). Note that this definition forbids paths with loops. The probability $S_k(r)$ has the following form in the discrete limit

$$S_k(r) = 1 - \prod_{\langle i_1, i_2, \dots, i_{k-1} \rangle}^{N_k} [1 - P^{(k)}(r; \vec{r}_{i_1}, \dots, \vec{r}_{i_{k-1}})], \quad (3)$$

where $N_k = \binom{M-2}{k-1}(k-1)!$ is the number of all possible paths connecting two neurons through k synapses ($N_k \approx M^{k-1}$ for $k \ll M$), and

$$P^{(k)}(r; \vec{r}_{i_1}, \dots, \vec{r}_{i_{k-1}})$$
$$= p(|\vec{r}_{i_1}|)p(|\vec{r}_{i_2} - \vec{r}_{i_1}|) \cdots p(|\vec{r} - \vec{r}_{i_{k-1}}|) \quad (4)$$

is the probability of a k-synapse connection for neurons separated by r via a given path $i_1, i_2, \dots, i_{k-1}$, where subscript i_l denotes the neuron's number (because loops are not allowed, subscripts along the path must be different). One can justify the formula for $S_k(r)$ by noting that the product involving probabilities $P^{(k)}$ on the right hand side of Eq. (3) represents the probability of not having k-synapse connection via either path.

We simplify further the form for $S_k(r)$ by using an identity $\prod_{\{i\}} x_i = \exp(\sum_{\{i\}} \ln x_i)$, obtaining in the continuum limit

$$S_k(r) = 1 - e^{-p_k(r)}, \quad (5)$$

where functions $p_k(r)$ are given by

$$p_k(r) = -\rho^{k-1} \int d^2r_1 \cdots \int d^2r_{k-1}$$
$$\times \ln[1 - P^{(k)}(r; \vec{r}_1, \dots, \vec{r}_{k-1})]. \quad (6)$$

In this limit, $S_k(r)$ becomes a conditional probability, similar to $p(r)$, of connection between two neurons along at least one of the shortest paths that use k synapses, given that the connected neuron is separated by r from the original neuron. Note that for $k = 1$ we have $p_1 = -\ln[1 - p(r)]$, and hence $S_1(r) = p(r)$, as should be.

The complicated dependence of the probability $S_k(r)$ on k for fixed r simplifies in the limit $s \mapsto \infty$, and this is due to the scaling properties of $p_k[r(s), s]$. From the scaling law for $p[r(s), s]$ and Eq. (6), we obtain

$$p_k[r(s), s]_{s \mapsto \infty} \longmapsto \begin{cases} 0, & \alpha < 1/k, \\ p_k^{(1)}(r), & \alpha = 1/k, \\ \infty & \alpha > 1/k, \end{cases} \quad (7)$$

where $p_k^{(1)}(r)$ is the first term of the series for $p_k(r)$ after expanding the logarithm and reads

$$p_k^{(1)}(r) = \rho^{k-1} \int d^2 r_1 \cdots \int d^2 r_{k-1}$$
$$\times P^{(k)}(r; \vec{r}_1, \ldots, \vec{r}_{k-1}). \quad (8)$$

Notice that in this limit, i.e., the limit of very large brains, the rescaled probability $S_k[r(s), s]$ in Eq. (5) becomes distance independent and additionally displays a step-like behavior as a function of k, assuming value 0 for $k < 1/\alpha$ (lack of connection), and value 1 for $k > 1/\alpha$ (complete connection); see Fig. 2. The former feature is a form of the universality, while the latter is a signature of the critical behavior. Thus the smallest number of steps $N_{s \mapsto \infty}$ required to connect two arbitrary neurons in the limit of the infinite network is given by the smallest integer satisfying $N_{s \mapsto \infty} > 1/\alpha$.

The general solution for the smallest number of steps or equivalently the average degree of separation $\langle N \rangle_s$ valid at arbitrary scale s can be obtained by calculating the expected number of minimal steps, which are necessary to connect two neurons. In the interval $0 < \alpha < 1$, and in the limit $s \mapsto \infty$, this solution can be written in the form

$$\langle N \rangle_{s \mapsto \infty} = \text{int} \left[\frac{1}{\alpha} + 1 \right] + \zeta(\alpha) + O(s^{-\epsilon}), \quad (9)$$

where $\text{int}[x]$ denotes an integer part of x, ϵ is some positive exponent (it depends on α) controlling the contribution coming from finite-size effects, and $\zeta(\alpha) = \lim_{W \mapsto \infty} \frac{1}{W} \int d^2 r \exp[-p_k^{(1)}(r)]$ for $\alpha = 1/k$, and $\zeta(\alpha) =$

0 otherwise. The function $\zeta(\alpha)$ is only marginally important, for it is nonzero and smaller than one only at the discontinuity points. We display the dependence of $\langle N \rangle_{s \mapsto \infty}$ on α, in the interval $0 < \alpha < 1$ in Fig. 3. For $\alpha = 1$ we have $\langle N \rangle_{s \mapsto \infty} = 2 - M_0/M$, and for $\alpha < 0$ we have both $S_k[r(s), s]_{s \mapsto \infty} = 0$ (for every k) and $\langle N \rangle_{s \mapsto \infty} = 0$, which implies that the network is completely disconnected in this case.

Equation (9) is our major result. It basically shows that the average degree of separation between neurons displays numerous plateaus and discontinuous jumps at points for which $\alpha = 1/k$, for $k = 1, 2, 3, \ldots$. This critical behavior ("phase transitions") associated with a stairlike structure (Fig. 3) is a consequence of Eq. (7). Similar structures appear also in phenomena involving fractals [14]. The stairlike structure gradually becomes smooth and eventually disappears as finite-size effects are included. However, the decaying trend of $\langle N \rangle_s$ with the exponent α remains unchanged.

The average degree of separation $\langle N \rangle_{s \mapsto \infty}$ and the total axonal length L per neuron depend differently on the exponent α (compare Figs. 1 and 3). The former decreases with α or exhibits plateaus, while the latter increases continuously with α. These two quantities are related, respectively, to the energy consumption during communication and to the use of biochemical resources in a wiring design. In the case of an optimal wiring, one wants to have both $\langle N \rangle_{s \mapsto \infty}$ and L, M_0 as small as possible, which turns out to be impossible to satisfy simultaneously. Thus, there is a trade-off between minimizing energetic and biochemical costs suggesting that an optimal situation should arise somewhere for intermediate values of the exponent α. It was determined based on the data for larger corticies of different species with sizes spanning a few orders of magnitude [8,9,11–13], that $\alpha_{\text{ex}} \approx 0.10$. If one
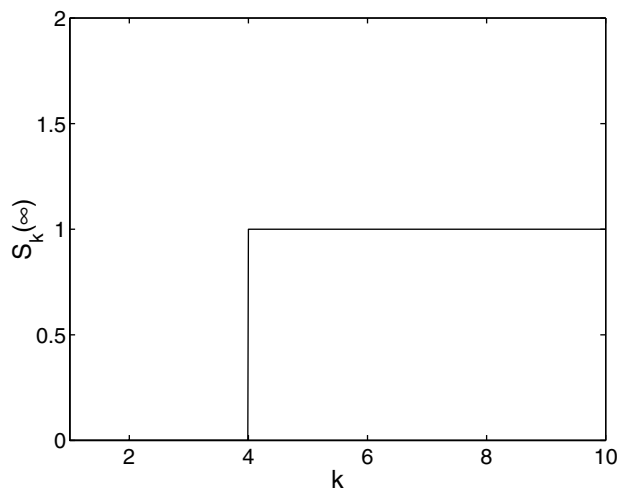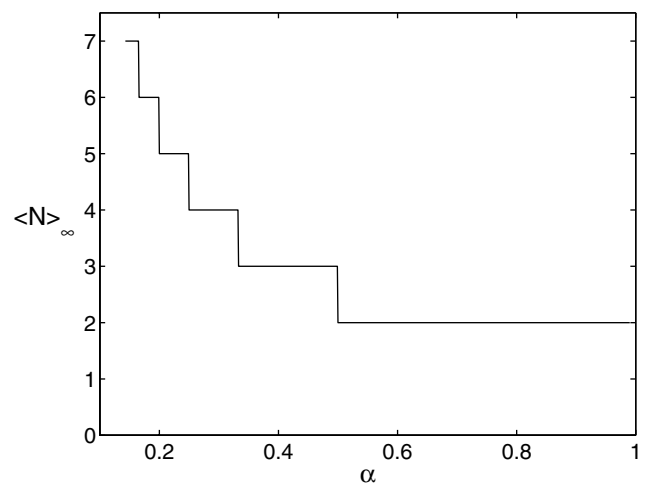
FIG. 2. Dependence of the probability of k-steps connection $S_k(\infty)$ via at least one of the shortest paths between two neurons on the number of steps k in the limit of the infinite network. Note a critical behavior at $k = 4$, which corresponds to the case with $\alpha = 0.25$.

FIG. 3. Dependence of the average degree of separation $\langle N \rangle_{s \mapsto \infty}$, on the exponent α in the limit of the infinite network. Note the stairlike structure with infinitely many plateaus, and a decaying trend of $\langle N \rangle_{s \mapsto \infty}$ as α grows.

considers only smaller nonconvoluted corticies [9,12], then α_{ex} is larger, namely $\alpha_{\mathrm{ex}} \approx 0.25$. From Eq. (9) these values yield the following estimates of the average degree of separation: $\langle N \rangle_\infty = 10-11$ for $\alpha_{\mathrm{ex}} \approx 0.10$, and $\langle N \rangle_\infty = 5$ for $\alpha_{\mathrm{ex}} \approx 0.25$. The fact that α_{ex} is closer to zero than to one may suggest that for the corticies, especially bigger, it is more advantageous to save axons and synapses than to save energy used in the long distance communication between cortical areas.

The appearance of the plateaus in the degree of separation may be an advantageous feature in the cortex design, because it allows one to save axonal fibers at the same energetic cost required in the communication. Although in the regime relevant for bigger brains, i.e., for small α, the plateaus become shorter and consequently the savings of axonal length per neuron becomes tiny; the total axonal length in the cortex can be reduced significantly. This is because the total number of neurons in the cortex is immense.

For finite brains, it follows from Eq. (5) that in order to reach remote neurons in the cortex in just few steps, it is required that $p_k(r)$ have a long-range tail. This condition is satisfied only when the original probability $p(r)$ has a long-range tail. One can produce such behavior naturally by imposing a homogeneity condition on $p(r(s), s)$, i.e., $p(r(s), s) = p(r(s)/s^\beta, 1)$ with some homogeneity exponent β. This condition can be justified by noting that different corticies look roughly alike anatomically at sufficiently large spatial scales. Combining the two scaling laws for $p(r(s), s)$, we obtain $p(r) \sim (r/\sigma)^z$ for $r/\sigma \gg 1$, i.e., the power-law decay for large distances with $z = -2(1 - \alpha)/(1 - 2\beta)$ [note that β must satisfy $\beta < 1/2$ in order $z < 0$], and $p(r) \mapsto 1$ for $r \mapsto 0$. The quantity σ denotes a microscopic length characterizing neuron's size or an extent of local, intracortical connections ($\sigma/R_\parallel \ll 1$), and has a scaling law $\sigma(s) = \sigma s^\beta$. At short distances ($r/\sigma \ll 1$), that is, in the regime relevant for local connections, we expect that $p(r)$ decays faster, such as a Gaussian [15]. Finally notice that theoretically the minimal separation between neurons is reached for $\alpha = 1$, corresponding to $z = 0$, which is the case with the longest possible tail of $p(r)$.

The approach presented in this paper can be generalized to other situations with different geometry and different invariants. It is somehow related to the approaches taken in the so-called "small-world" networks [16–19]. The main difference between the two is that in the present approach, the probability of a direct connection is distance dependent, contrary to most of the small-world models, with one very recent exception [20].

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