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The effects of neuron heterogeneity and connection mechanism in cortical networks☆

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The mammalian cortices show an specific architecture close to the optimum, represented by the high clustering, short processing steps and short wiring length. What are the key factors that influence the layout of neural connectivity networks? Here a model to investigate the conditions leading to the small-world cortical networks with minimal global wiring is presented. The essential factors in this model are the introductions of the unequal number distribution of heterogeneous neurons and two connection mechanisms, the preferential attachment to neurons with large spatial coverage (PANLSC) and distance preference. Outcomes show that the specific architecture close to the optimum can only result from the PANLSC when the number distribution of neurons with diverse spatial coverage is highly unequal. This suggests the PANLSC may be an important connection mechanism in cortical systems.

1. Introduction

Mammalian brains show a highly specific structural organization, constrained by multiple limits placed by physical and chemical laws to diverse functional requirements. In particular, great efforts have been devoted to identify factors influencing the layout of neural connectivity networks. One prominent idea is that wiring length should be globally minimized in neural systems due to the metabolic cost [1,2], which places strong constraints on the design of neural networks [3–6]. Another idea has been suggested recently that neural systems are not exclusively optimized for minimal global wiring, but for the minimization of processing steps [7], i.e. the topological path length in neural networks.

It has been demonstrated that the drop of topological path length can be caused by the introduction of a few long-range edges, which may result in the small-world networks [8]. Previous studies have reported that the small-world properties (i.e. high clustering and short average path length), in both structural and functional brain networks [9–12], confer a capability for both specialized or modular processing in local neighborhoods and distributed or integrated processing over the entire network [13,14]. What are the key factors that lead the cortical networks to small-world graphs? Some recent works have demonstrated that the spatially preferential attachment mechanism plays a major role in determining the network evolution [15–18]. Since these models embrace the topologically preferential attachment introduced by Barabsi and Albert [19], it would result in the fact that the nodes added to the network in the early time have larger probability to become the highly connected ones. Such mechanism, however, appears unsuited as a general explanation for growing cortical systems with newly forming nodes and connections [9].

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In cortical systems, the generation mechanism of synaptic connectivity is still unclear. With the constraint of minimal global wiring, neurons may synaptically connect with the nearest ones, which results in the high local clustering and the long topological path length in cortical networks. On the other hand, due to their responsibility for the shortcuts in the cortical network, neurons with large spatial coverage may be preferentially synaptically connected to minimize the processing steps, leading to a large global wiring. Considering for the minimization of both global wiring and processing steps, there may be a compromise between the distance preference and the preferential attachment to neurons with large spatial coverage (PANLSC). Moreover, the apparently inverse relationship between number of neurons in the various interneuron classes and the spatial extent of their axon trees [20] may be an alternative solution. The larger population of local neurons insures a short global wring, while the existence of a small subpopulation of neurons with large spatial coverage reduces the processing steps by the long-range edges.

Although there are other factors that can result in the small-world graphs in cortical systems, such as the specific spatial arrangement of the components [7,21], we focus on the neuron heterogeneity and connection mechanism, which can influence the layout of neural connectivity networks on global wiring and processing steps. In this paper, we present a simple model to investigate the conditions leading to the small-world cortical networks with minimal global wiring.

2. Spatial network model

The model is considered as an undirected and unweighted network, in which a node i is likely to connect with a node j only as one of the two is in the other's interaction range that corresponds to the spatial extent of the axon tree. Here, the power-law relationship between spatial coverage and the number of neurons in a given class, hypothesized in the previous study [20], is adopted.

2.1. Basic principles for network generation

The basic principles underlying our network generation algorithms are the following.

(1) Number distribution of the nodes with different interaction ranges. The nodes have their own interaction range R_v, and the probability of the interaction range of a node to be r_i can be calculated by

$$P(r_i) = r_i^{-\alpha} / \sum_j r_j^{-\alpha},$$

where the heterogeneity parameter α serves to regulate the proportions of the nodes with different interaction range.

(2) Geographical constraints. A new node i must be placed near a preexisting node j according to the cell division, that is $d(i, j) \leq r_{\max}$, but not too close to all the preexisting ones for the spatial need of neuron growth, with the distance larger than $r_{\min}$.$d(i, j)$ denotes the linear distance between the node i and j.

(3) Preferential attachment conditions. For a node i, its spatial neighbors (the nodes within its spatial coverage) are all assigned a preferential attachment index (PAI), which is defined for a given neighbor j by

$$PAI(i, j) = R_v^{\beta}(j)/d^{\gamma}(i, j),$$

where parameters β and γ, respectively, serve to adjust the effect of the PANLSC and distance preference. Then the node i preferentially connect to its neighbors with large PAI.

2.2. Network generation and parameters

The generation of a network involves two parts, i.e. the establishment of nodes and edges. In cortex networks, new neurons (nodes) are generated through cell division with the geographical constraints described as principle (2). The connections (edges) between neurons can be viewed as two sorts. The first are the necessary outcomes of the generation of new neurons, linking new neurons to their neighbors that already exist. The second are the new connections between the old existing neurons, whose generation is to meet more functional needs. This sort of connections can be established by linking some old neurons to one of their neighbors, respectively, or linking one randomly selected old neuron to some of its neighbors at each time step. In this paper, we adopt the latter.

Thus, our model network is generated as follow, similar with that by Xulvi-Brunet [22]. It starts from a preselected area in a two-dimensional Euclidean plane. In this area, we place at random m_0 nodes as initial nodes. At each time step a new node is added near a randomly selected preexisting node under the geographical constraints and connected to its m_1 neighbors with larger PAI. If its neighbors are fewer than m_1, the new node is connected to all of them. Additionally, once the new node is attached, m_2 new edges are added to the network by linking a randomly selected preexisting node to its m_1 neighbors with larger PAI but not yet connected to it. In case that the number of its neighbors, which are not yet connected to it, is $q < m_2$, then only q edges are added to the network.

We set 1000 as the final number of nodes in the growing network in this study. For other parameters, we adopt the following values considered by Xulvi-Brunet [22] in their models: $m_0 = 7$, $m_1 = 1$, $m_2 = 1$, $r_{\min} = 500$ m.u. and $r_{\max} = 1000$ m.u. (where *m.u.* stands for an arbitrary metric unit). Additionally, we choose a radius of 14 000 m.u. for our initially preselected disc area, and 1000 m.u. and 14 000 m.u. as the minimal and maximal values of the interaction range,

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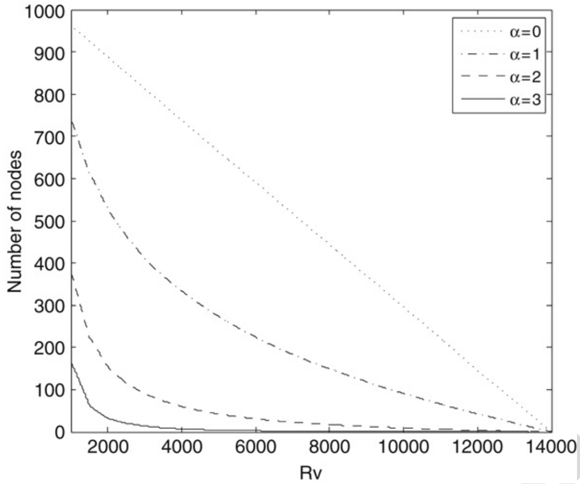

Fig. 1. Number distributions of nodes with coverage larger than R_v for $\alpha = 0, 1, 2, 3$.

respectively. The selected values of parameters are certainly arbitrary and are adopted in order to illustrate the effects of diverse preferential attachment conditions.

3. Properties of the model network

Since the small-world properties are the essential features of cortical connectivity and minimal global wiring is a primary constraint for the layout of neural connectivity networks, we focus on three important characteristics of the model networks: clustering coefficient, average path length, and average wiring length. In the following, we first investigate the influence of the unequal number distribution of heterogeneous neurons (UNDHN) on the cortical network, in which case random connection is adopted instead of the preferential attachments. Then, in the condition of the UNDHN, the effect of the preferential attachments, the PANLSC and distance preference, is studied.

3.1. Influences of the UNDHN on the cortical network

In this model, the number distribution of heterogeneous neurons is regulated by the heterogeneity parameter α. As α goes larger, the small neurons increase and the large ones oppositely decrease. Yet, neurons with the threshold coverage exist, even at large α (see in Fig. 1). In addition, since the range of different neurons changes successively in our model, the numbers of neuron classes for different values of α can be considered the same. This makes comparisons reliable. It is noticeable that the selection of the threshold for the range of neurons depends on the size of the network. For the diameters of the model networks with 1000 nodes are about 30 000 m.u., 14 000 m.u. is suited for the threshold.

The increase of small neurons and the decrease of large neurons certainly bring the corresponding changes of short-range and long-range edges. As shown in Fig. 2, as the heterogeneity parameter α increases, the direct consequence of these changes is the decrease of the average wiring length (AWL), defined as the average metric length of all the edges. This indicates that the UNDHN helps to minimize the wiring length and then economize the metabolic cost. Furthermore, the decrease of long-range edges leads to the increase of the average path length (APL), the number of links that have to be crossed-on average-to go from one node of the network to another, which is an indication of information processing steps in cortical networks. A short APL is of significance in avoiding the additional noise, shortening the signaling delay and increasing synchrony [23]. Additionally, the structural and functional robustness of neural systems increases when processing pathways (chains of nodes) are shorter [7]. Apparently, the UNDHN makes against the minimization of processing steps. Note that the data in Fig. 2 have been normalized by the values at $\alpha = 0$, respectively, where the number distribution of heterogeneous neurons is equal. This makes the comparison more meaningful.

The clustering coefficient is an important characteristic that can reflect some local information of complex networks. The clustering of a node is defined as the percentage of neighbors of the node that are connected with each other [8]. The clustering coefficient C of a network is obtained by averaging clustering over all the nodes in the network. Since the clustering coefficient is a good approximation of the local efficiency [24], which shows how efficient the communication is between the first neighbors of a node when it is removed, cortical networks with high clustering are robust in local information processing even if some neurons languish or suffer attack. Note that this is different from the robustness mentioned in some other papers about brain networks [25], where the authors consider the response of the entire network to the removal of nodes. As shown in Fig. 2, the clustering coefficient of the model network increases with the parameter α. This suggests that the UNDHN is in favor of local information processing.

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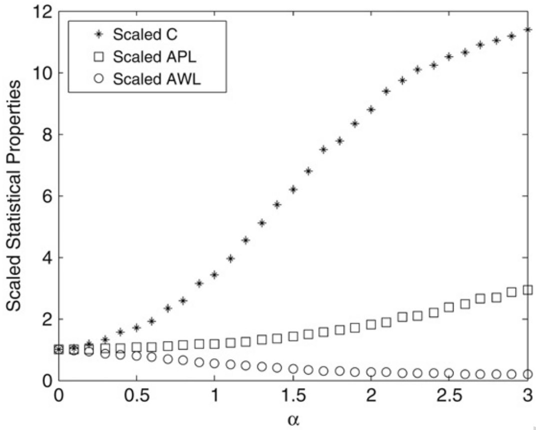

Fig. 2. Collective dynamics of the model networks with random connection in terms of the average path length (APL), the average wiring length (AWL) and the clustering coefficient (C). α serves to regulate the proportions of the nodes with different interaction range. The data of APL, AWL and C are normalized by the values at $\alpha = 0$, respectively.

As analyzed above, without any preferential attachment condition, the UNDHN works for minimizing the wiring length and increasing the clustering coefficient, but makes against minimizing the processing steps. However, the cortical networks show both minimal global wiring and the small-world properties. The shortage of the UNDHN in minimizing the processing steps may be complemented by some special connection mechanism.

3.2. *Effects of diverse connection mechanisms on the cortical network*

We consider three cases of the model networks according to preferential attachment conditions. Case (i), $\beta = 1$ and $\gamma = 0$, corresponding to the cortical network with the PANLSC. Case (ii), $\beta = 1$ and $\gamma = 1$, an integrative case. Case (iii), $\beta = 0$ and $\gamma = 1$, for which edge formation is based on the distance preference.

The three preferential attachment conditions firstly show their differences in the effect on the AWL. As shown in Fig. 3(a), the AWL in the network with the PANLSC drops sharply with the parameter α, resulting from that numbers of long-range edges are replaced by short-range ones. In the case of distance preference, the AWL is small throughout with slightly decrease, which supports that distance preference rejects the long-range edges. Besides, the AWL in the integrative case shows an inverse U-shape change, corresponding to the increase of long-range edges followed by the decrease later. This distinct change results from the interaction between the PANLSC and distance preference. By comparison, the networks with distance preference have the fewest long-range edges leading to the most economical wiring, while the networks with the PANLSC own the most long-range edges but get the similar wiring length when α is large. The integrative case gets an intermediate result.

The larger the wiring length is, the more the long-range edges and then the fewer the processing steps are. In other words, there is an inverse relation between the AWL and the APL. As shown in Fig. 3(b), the APL in the networks with distance preference and the PANLSC are, respectively, longest and shortest. The results are consistent with our speculation that distance preference helps to minimize the global wiring and the PANLSC makes for the global information processing.

Fig. 3(c) shows the relations between the clustering coefficient and the parameter α. The distance preference holds the large clustering coefficient throughout, while the PANLSC leads to a U-shape change. The effect of parameter α is to regulate the proportion of the nodes with large interaction range and further adjust the percentage of long-range edge. In the case of distance preference, preferential attachment to the close nodes results in short-range edge always in the largest quantity. Although the number of long-range edge changes with α, it is too weak to significantly influence the clustering coefficient of the network. However, in the PANLSC case, the parameter α greatly affects the proportion of the short-range and long-range edges. At $\alpha = 0$, nodes tend to connect to those with large R_v that are connected with each other, and long-range edge is dominant; while at $\alpha = 3$, nodes prefer to linking to the closely connected nodes in their neighborhood, resulting in the dominant short-range edge. At the two thresholds, the networks own large clustering coefficient. However, in the transition of dominance from long-range edges to short-range ones, there are balanced states of two classes of edges, where the nodes with small R_v are in majority but not closely connected, and the nodes with large R_v are closely connected but not dominant in number, which lead to the small clustering coefficient of the network. Note that when the parameter α is large, the PANLSC can lead to the similar clustering coefficient with that in the case of distance preference.

In mammalian cortical systems, an optimal architecture should be represented by the high clustering, short average path length and short wiring length. High clustering means robust local information processing and promotes functional overlap of densely connected neuronal elements, which are functionally segregated from one another and constitute building blocks (topological modules) of the cortical architecture [13]. A short APL is of significance in avoiding the additional noise, shortening the signaling delay and increasing synchrony. Besides, a short AWL is beneficial to economize the metabolic

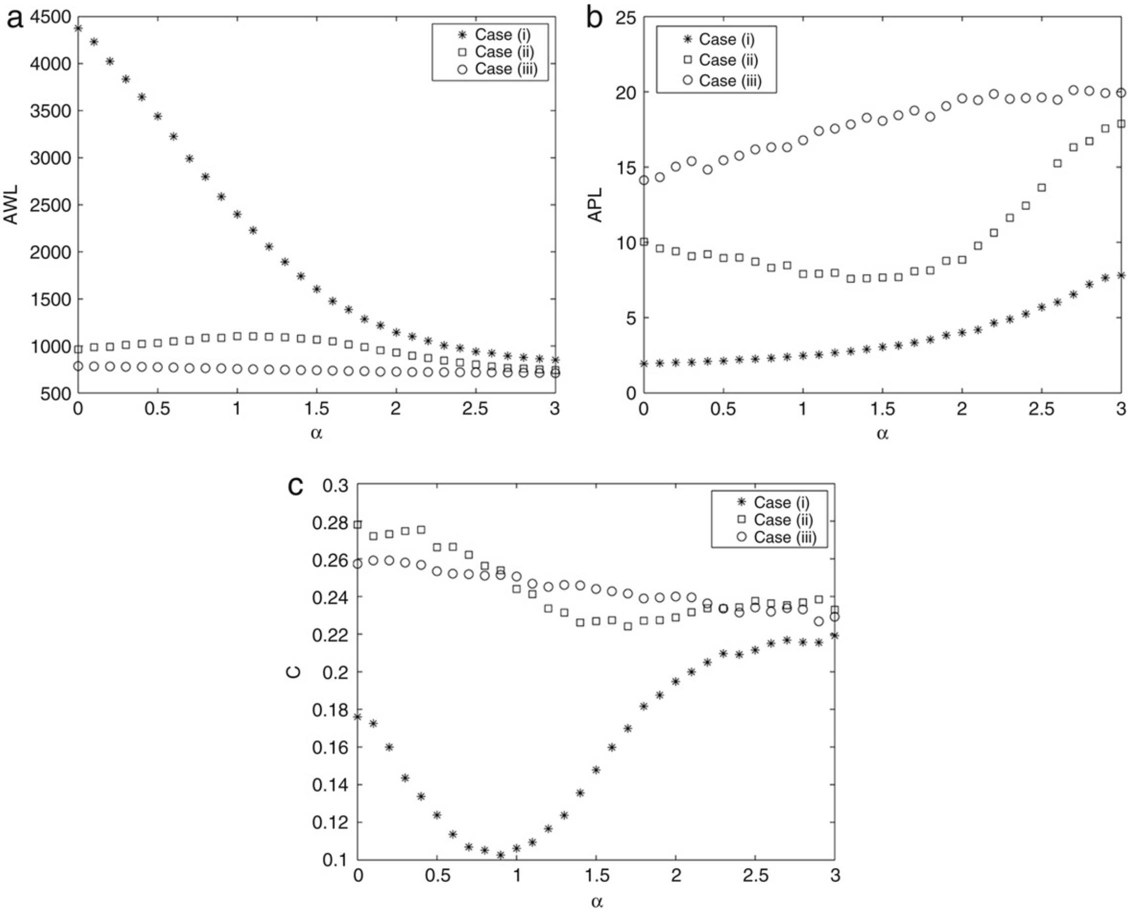

Fig. 3. Plots of (a) the average wiring length, (b) the average path length and (c) the clustering coefficient versus the parameter for the model networks with the three preferential attachments, respectively.

cost. Results show that this architecture can be only obtained by the PANLSC when the number distribution of neurons with diverse spatial coverage is highly unequal, i.e. the parameter α is large. This is an indication that the PANLSC may be an important connection mechanism in cortical networks.

4. Discussions and conclusions

In mammalian cortices, the majority of neurons are the various interneurons, which are exceptionally diverse in their morphological appearance and functional properties [26–28]. Previous study suggested there is an apparently inverse relationship between number of neurons in the various interneuron classes and the spatial extent of their axon trees [20]. In this paper, we have investigated the effect of this unequal number distribution of heterogeneous neurons (UNDHN) on cortical networks. Results show that the UNDHN helps to increase the clustering coefficient of the cortical networks, which means more local circuits (triangles) are generated. This is beneficial to more complex and more diversiform functions. Additionally, the large population of local neurons insures a short global wiring.

In this model, what's the threshold of the coverage range R_v is an important question. We suggest that the maximal value of R_v should increase with the size of model network N. This is consistent with the fact that the number of different neuron types is actually increasing for complex brains and especially larger brains (e.g. from rats to human).

Further, a recent study suggests that the ratio of interneurons with local and distant connections also increases for larger brains [20], i.e. for a large N there should be a large α which is corresponding to a network with large clustering coefficient, small wiring and large processing steps. Then, if without any preferential attachment, large brains seem to be superior in local information processing and economizing metabolic cost, but relatively inferior in information integration. This is not consistent with the fact. A possible interpretation is that tiny long-distance projections can provide "just-enough" to guarantee a significant effect on their targets [29,30]. Although the neurons with long axons relatively decrease, they may be still enough for the transmission of global information. The alternative solution is that neurons in large brains connect to others with some preferential attachment mechanism. In this paper, we propose that neurons with large spatial coverage should be preferentially connected. Results show that this preferential attachment mechanism can reduce the topological path length in neural networks greatly, which is beneficial to information integration, while retaining a high local efficiency and economic wiring.

In conclusion, the UNDHN and PANLSC together lead to a cortical network with a large clustering coefficient for local integration, a short APL for efficient global processing and a short wiring length for metabolic cost economy. Apparently, as the complement of the UNDHN, the PANLSC is one appropriate connection mechanism for the optimal architecture.

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