



Modelling the development of cortical systems networks

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Abstract

The brain shows a highly specific structural organization, also in its connectivity. How may genetic specification or epigenetic self-organization influence the layout of cortical systems networks? We developed a computational model of spatial network growth to investigate the conditions leading to similar network density and clustering as found in the cortical connectivity of cat and macaque monkey. An essential factor in the model was the introduction of spatial borders. We further compared metric aspects of wiring in the macaque brain and the simulated networks, which suggest that cortical networks may trade perfect minimal wiring length for shorter average shortest paths among cortical areas.

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1. Introduction

The mammalian brain shows remarkable differentiation of structure and function. In terms of cytoarchitecture, several types of neurons as well as a large number of cortical areas can be distinguished. Neurons and areas exhibit different functions, depending on incoming and outgoing connections as well as intrinsic processing. The variety of expressed functions is also related to the organization of cortical systems connectivity. Regions with similar function are located near to each other, tend to be connected and have similar afferent and efferent connections. Considering the structure of cortical connectivity, the question remains how much of it is determined genetically (e.g., through guidance by adhesion molecules and chemical gradients) and how much

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is due to self-organization by physical and timing constraints. We used a computational model to investigate essential factors of cortical development.

2. Methods and results

2.1. Spatial network growth

We simulated mechanisms of spatial growth, in such a way that connections among nearby nodes (i.e., areas) in the cortical network were more probable than projections to spatially distant nodes [15]. Such a distribution could, for instance, result from the concentration of unspecific factors for axon guidance decaying exponentially with the distance to the source [12].

It was found for cortical development in humans that growth occurs in lateral and anterior direction [7]. This was accommodated in our model by positioning the initial two areas at medio-posterior positions (0.4, 0.3) and (0.6, 0.3) of the two-dimensional embedding space (1×1.5 units) enabling growth in lateral and anterior directions.

At each step of the algorithm a new area was added to the network until reaching the target number of nodes (55 areas for simulated cat and 73 for simulated macaque cortical networks). New areas were generated at randomly chosen positions of the embedding space. The probability for establishing a connection between a new area u and existing areas v was set as

$$P(u, v) = \beta e^{-\alpha d(u, v)} \quad (1)$$

with $d(u, v)$ being the distance between the nodes and α and β being scaling coefficients. Areas that did not establish connections were disregarded. A more detailed presentation of the network growth model is given elsewhere [8].

2.2. Similarity of ASP and clustering coefficient

The resulting networks were investigated for three essential features of cortical connectivity. First, multiple distinct network clusters, as found in the organization of cat (55 nodes) and macaque monkey (73 nodes) cortical connectivity [6,13,17] should arise. Second, the clustering coefficient, that is, the percentage of neighbors of a node that are connected with each other [14], should be similar to the value for biological cortical networks. Third, the average shortest path (ASP), that is, the number of links that have to be crossed—on average—to go from one node of the network to another, should be similar, as well.

We generated 50 networks each for the two sizes of cat and monkey cortical networks, through limited spatial growth in a fixed modeling space, and using parameters $\alpha_{\text{cat}}=5$, $\alpha_{\text{macaque}}=8$ and $\beta=2.5$ for both networks. The spatial limits imposed during the simulations might represent internal restrictions of growth (e.g., by apoptosis [10]) as well as external factors (e.g., skull borders). The simulated networks yielded clustering coefficients and ASP (Table 1) similar to the cortical networks. Moreover, the degree distribution of cortical and simulated limited growth networks showed a significant

Table 1
Comparison of cortical and simulated networks

| | C_{brain} | C_{limited} | $C_{\text{unlimited}}$ | ASP_{brain} | ASP_{limited} | $ASP_{\text{unlimited}}$ |
|---------|--------------------|----------------------|------------------------|----------------------|------------------------|--------------------------|
| Cat | 0.55 | 0.50 ± 0.02 | 0.29 ± 0.05 | 1.8 | 1.70 ± 0.04 | 3.86 ± 0.47 |
| Macaque | 0.46 | 0.40 ± 0.02 | 0.29 ± 0.05 | 2.2 | 2.16 ± 0.08 | 4.12 ± 0.41 |

Shown are the clustering coefficient C_{brain} and ASP_{brain} of neural networks of cat (55 nodes) and macaque (73 nodes) as well as the average clustering coefficient and ASP of 50 generated *limited* and *unlimited* spatial growth networks with respective standard deviation.

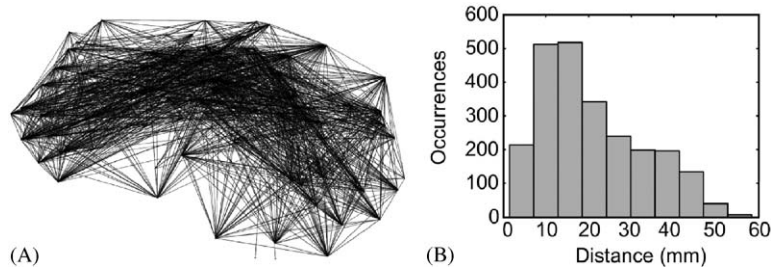


Fig. 1. (A) Analyzed macaque cortical network with 95 nodes and 2402 connections. (B) Distribution of fiber length approximated by the direct distances between connected areas.

correlation (Spearman's rank correlation $\rho = 0.77$ for the cat network, $P < 3 \times 10^{-3}$; and $\rho = 0.9$ for the macaque network, $P < 2 \times 10^{-5}$).

We also investigated an alternative growth model, using a developmental mechanism of growth and preferential attachment, in which new nodes were more likely to establish links to existing nodes that already had many connections [1]. This model was also able to yield density and clustering coefficients similar to those in cortical networks. However, it failed to generate multiple clusters seen in the biological systems, as only one main cluster could be generated by this approach.

2.3. Comparison of cortical and simulated wiring lengths

We compared the wiring length of networks generated with our model in three dimensions with the wiring length of cortical systems connectivity in one hemisphere of the macaque monkey. Connectivity among cortical areas was obtained from three studies [2,5,11], for which data was available in the CoCoMac-database (<http://www.cocomac.org>). Average spatial positions of cortical areas were estimated based on surface coloring using the CARET software (van Essen Lab, <http://brainmap.wustl.edu/caret>). The length of connections was approximated as the direct Euclidean distance between the geometric centers of two connected areas. The resulting network consisted of 95 cortical regions and 2402 connections (Fig. 1A). The distribution of distances between nodes, that is, the length of connections showed that also long-range connections occurred (Fig. 1B). Long-distance connections existed, for example, between areas

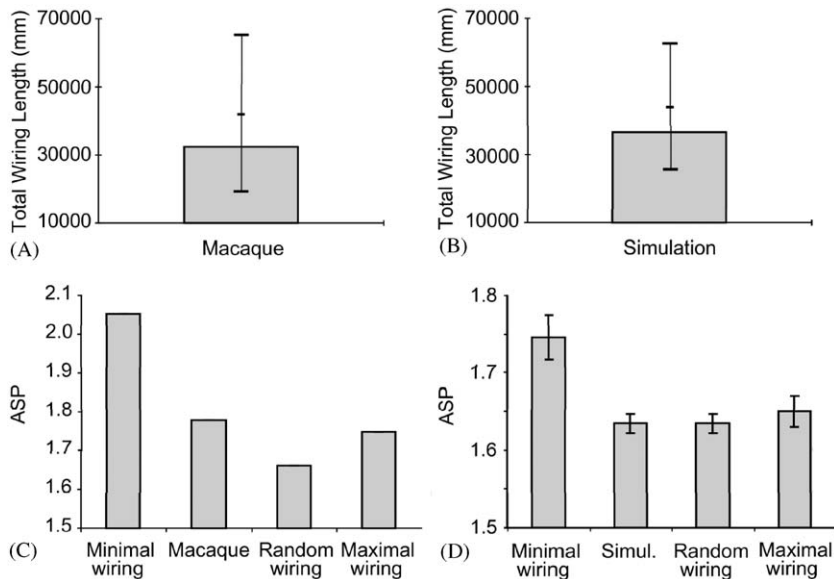


Fig. 2. (A) Total wiring length cortical network. (B) Total average wiring length of 50 generated networks. (C) ASP in cortical network. (D) Average ASP in generated networks.

10o and 7a, V2 and 46, and V3 and 46. These connections give a cautioning to predictors of connectivity that are based on close proximity of cortical areas [16] or criteria of optimal wiring [9].

A component placement approach has been used previously to demonstrate optimal wiring for *C. elegans* and cerebral cortex (using adjacency of areas instead of metric distances) [3,4,9]. In the component placement concept, connections remain fixed and the positions of nodes are evolved. We used a complementary method, in which the positions of areas were invariant, and their connections could be rearranged.

For the macaque cortical network (Fig. 2A) as well as comparable generated networks (Fig. 2B, length scaled to account for different embedding space), the total length of all connections is shown as a bar. The horizontal marks represent the range of possible wiring lengths. The lowest mark in the diagram represents minimal wiring, in which nodes were linked in the order of the shortest distances between them. The upper mark, on the other hand, stands for maximal wiring, in which nodes were connected via the largest-possible distances. The average value of random wiring is indicated by the middle mark. In this case, the distance between nodes was not taken into account for their wiring, resulting in an intermediate outcome between minimal and maximal wiring. For both the cortical as well as the generated networks, the total length was positioned between minimal and random wiring, therefore indicating a general preference for short-distance connections.

In addition, we compared a central topological network measure, the average shortest path (ASP), for different metric wiring setups. Both for cortical (Fig. 2C) as well as

simulated growth networks (Fig. 2D, length scaled for different embedding space), the ASP for minimal wiring was larger than for the actual networks. A low ASP, that is, a low number of intermediate nodes in cortical paths, might be important for several reasons: first, intermediate nodes carry out additional signal transformations and may introduce noise and, second, additional areas and synapses add to the signaling delay in the path. Moreover, without long-range connections, synchronous processing in proximal and distant areas might be impossible. Therefore, preserving a low ASP may be an important constraint for the evolution of cortical wiring.

3. Conclusions

Using a simple spatial growth model, we found that spatial borders as limits of growth are required to produce network properties comparable to those in real cortical systems. The importance of growth limits has also been demonstrated experimentally for the mouse cortex by eliminating apoptosis [10], resulting in a distorted cortical topology. Importantly, structural properties of cortical networks in the current study could be generated without assuming specific growth factors and receptors.

In a complementary approach to component placement optimization, we found that the total wiring length characteristics of the generated networks were similar to the macaque cortical network. The existence of long-range connections in these networks increased total wiring length, but also led to a shorter ASP. As the ASP in cat as well as in the extended macaque dataset was at a low value of 1.7, the conservation of a low ASP, that is, a low number of intermediate nodes in cortical pathways, might be a more important constraint than minimizing total ‘cable’ length.

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Marcus Kaiser studied biology at the Ruhr-University Bochum and continues studies of computer science at the distance university Hagen. He did an internship at the University of Newcastle upon Tyne where he worked on Bayesian spike train analysis and properties of cortical networks. His master thesis was experimental work about visual perception during saccadic eye movements. He is pursuing his Ph.D. degree in neuroscience at the International University Bremen. His research is about the development, robustness, and structure-function relationships in biological (cortical and biochemical) networks.



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