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Development of multi-cluster cortical networks by time windows for spatial growth

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Abstract

Many neural networks, such as the complex cortical networks of the mammalian brain, are organized in multiple clusters, with many connections within but few links between clusters. To generate this organization, we explored a wiring rule in which the establishment of a connection between two areas depended on the areas' distance as well as their respective time windows for connection establishment. The concept of time windows was based on the observation that the development of cortical areas partially overlaps in time. Our algorithm was able to generate multiple network clusters depending on the number and overlap of the time windows.
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1. Introduction

Cortical connectivity in mammalian brains forms intricately structured networks which consist of multiple network clusters. Clusters are groups of linked areas where areas within a group form more connections among each other that with areas in other parts of the network. It has been demonstrated that multiple distinct topological clusters exist in mammalian brain networks, such as visual, auditory, somatosensory-motor, and frontolimbic clusters in the cerebral cortex of the cat [3,4]. How does this organization arise during development? Whereas models have been put forward for the growth of axonal and dendritic processes at the cellular level [13], the formation of circuit clusters through inhibitory mechanisms [15], and the phylogenetic development of areas as well as the inheritance of connectivity [2,8], the formation of large-scale network clusters during the ontogenetic development of the brain is still poorly understood.

We previously proposed a simple spatial growth algorithm for the formation of neural and particularly cortical

networks [5,6]. In the algorithm, the probability for establishing a connection was higher for nearby than for distant nodes. Such an algorithm can generate networks that are similar to cortical networks in many respects. For example, the average shortest paths (or characteristic path length) and the clustering coefficient of the model networks were similar to those of cortical networks in the cat and the macaque monkey brain [6]. In addition, multiple clusters could occur (but only very infrequently) in the modelled networks. When a new node survives in a position that is remote from the existing network, candidate nodes in its vicinity are likely to establish a connection to such a *pioneer node*. However, the probability for the establishment of such remote nodes, requiring the formation of at least one long-distance connection to the existing network, is quite low. Therefore, there was no guarantee that multiple network clusters, as found in the cortical connectivity of the mammalian brain, would arise in the simple spatial growth model. Moreover, in cases where multiple clusters did occur, their size could not be controlled by the model parameters.

In order to explore the essential cluster feature of cortical connectivity, we modified the previous model and included one further factor of cortical development, the formation of cortical areas and their interconnections during specific,

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overlapping *time windows*. Time windows arise during cortical development [10,12], as the formation of many cortical areas overlaps in time but ends at different time points, with highly differentiated sensory areas (for example, Brodmann area 17) finishing last. Based on this experimental finding, we explored a modified wiring rule in which network nodes were more likely to connect if they were (i) spatially close and (ii) developed during the same time window.

2. Methods

The following algorithm was used for network growth depending on distance as well as time windows (cf. Fig. 1a). First, three seed nodes were placed at spatially distant locations (cf. Fig. 1b). New nodes were placed randomly in space. The time window of a newly forming node was the same as that of the nearest seed node, as it was assumed to originate from, or co-develop with, that node. Second, the new node u established a connection with an existing node v with probability $P(u, v) = P_{temp}(u) \times P_{temp}(v) \times P_{dist}(u, v)$. The dependence P_{dist} decayed exponentially with the distance between the two nodes (cf. [5]). Third, if the newly formed node failed to establish connections, it was removed from the network.

3. Results

The timed adjacency matrix shows the development of connections over time (Fig. 2a). Different grey levels represent the respective time windows of the nodes. The reordered matrix represents the original network with different node order, in such a way that nodes with similar connectivity were placed nearby in the adjacency matrix (Fig. 2b).

The inclusion of developmental time windows into the spatial growth algorithm generated multiple network clusters, with their number being identical to the number of different time windows that governed development. In addition to the number of clusters, the size of clusters could be varied by changing the width of the corresponding time window.

The network resulting from the developmental model exhibited both highly connected nodes and long-distance connections (Fig. 3), agreeing with observations for experimentally studied brain networks. Highly connected areas with more than 50 outgoing or incoming projection fibres were also found in neural networks in the macaque brain. Such areas occur both in the subcortical (Amygdala) as well as in the cortical domain (e.g., Lateral IntraParietal area—LIP, Area 7, Area 46) [9]. Moreover, the length distribution of projections in the model network is similar to that of the macaque monkey [6,7,11].

4. Discussion

The brain, like many other biological and technical networks, extends in space [5]. However, most current
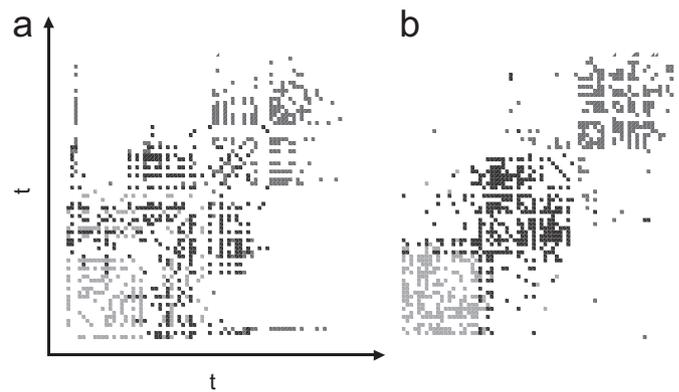
Fig. 2. (a) Timed adjacency matrix (the first nodes are in the left lower corner). (b) Clustered adjacency matrix. The matrix is the same as in (A), but nodes with similar connections are arranged more adjacent in the node ordering.
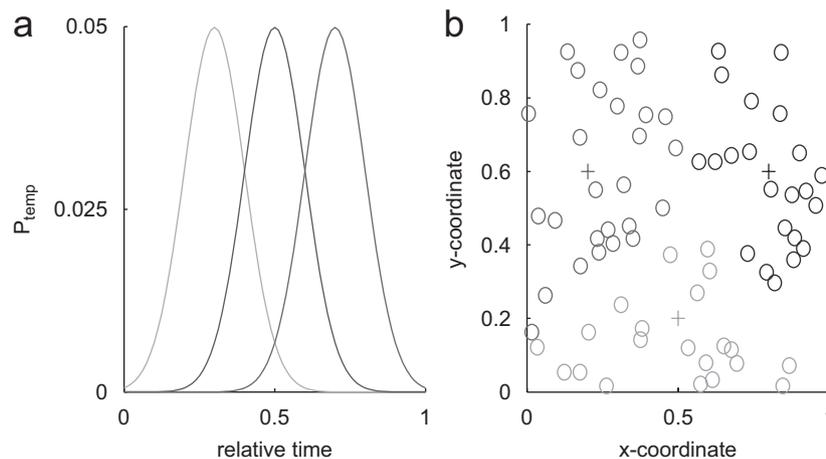
Fig. 1. Time windows and initial seed nodes. (a) Temporal dependence P_{temp} of projection establishment depending on node domain. Relative time was normalized such that '0' stands for the beginning of development and '1' for the end of network growth. The three seed nodes had different time windows which were partially overlapping. (b) Two-dimensional projection of the 73 three-dimensional node positions. The grey level coding represents the time window corresponding to one of the three seed nodes (+).
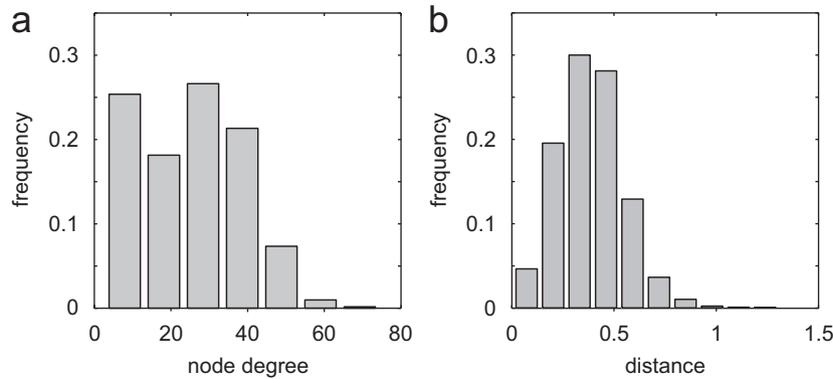
Fig. 3. Network properties after spatial growth with time windows (73 nodes, 100 runs). (a) Degree distribution. Whereas most nodes had fewer than 40 (incoming or outgoing) connections, highly connected nodes also existed. (b) Distribution of 'fibre' lengths, as approximated by the Euclidean distance between the three-dimensional node positions, in the generated networks. While most connections were formed among nearby nodes, a small number long-distance connections also occurred.

algorithms for network generation do not take into account the spatial position of nodes, but only consider topological properties of the nodes or edges of the network.

We previously suggested a simple spatial growth model that could reproduce basic features of neural networks [5]. By modifying this algorithm so that spatial growth was combined with developmental time windows, we were able to generate multiple network clusters, an important feature found in cortical networks in the mammalian brain [3,4]. The number of clusters was controlled through the number of different time windows that governed development, while the size of clusters could be varied by changing the width of the corresponding time window.

The design of our model is supported by experimental studies. One assumption of the model was that clusters can arise independently of network activity. Indeed, a comparable cortical structure and fibre tract organization arises in the mouse brain independent of whether neurotransmitter release at synapses is intact or blocked during development [14]. The formation of local, intrinsic connectivity may also be partly independent from neural activity, as studies on the development of ocular dominance columns have shown [1].

Additional experimental information about the timing of cortical development as well as the spatial layout of nodes and area clusters in the cortex will have to be included in more specific future models, in order to verify the simulation results against the detailed organization of biological cortical networks. However, the present model can already be used to derive a number of experimentally testable predictions: (1) a small overlap in the developmental time windows of two regions should result in fewer fibre tracts between those regions compared to other regions with larger overlap, (2) regions with wider time windows should possess a larger number of connections, (3) artificially prolonging synaptogenesis in vivo within a region should result in a larger number of connections, and (4) early-forming regions that are available throughout a longer period of ontogenetic development should acquire more connections than later forming regions.

Acknowlededgment

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