Reconstructing the connectome of a cortical column with biologically-constrained associative learning

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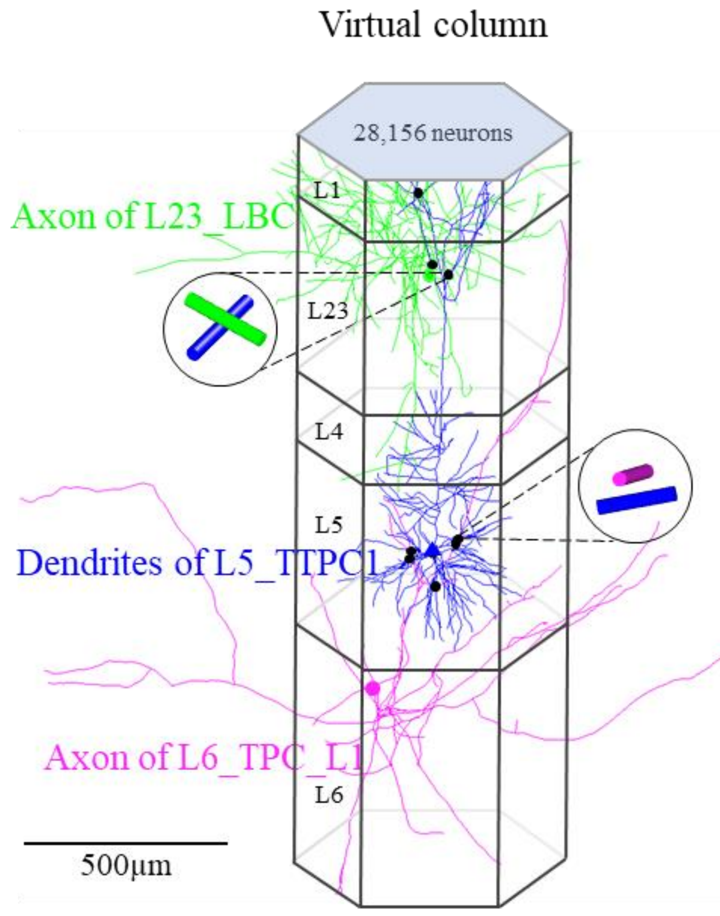
1. Introduction

The cortical connectome develops in an experience-dependent manner under the constraints imposed by the morphologies of axonal and dendritic arbors of numerous classes of neurons. In this study, we describe a theoretical framework which makes it possible to construct the connectome of a cortical column by loading associative memory sequences into its structurally (potentially) connected network.

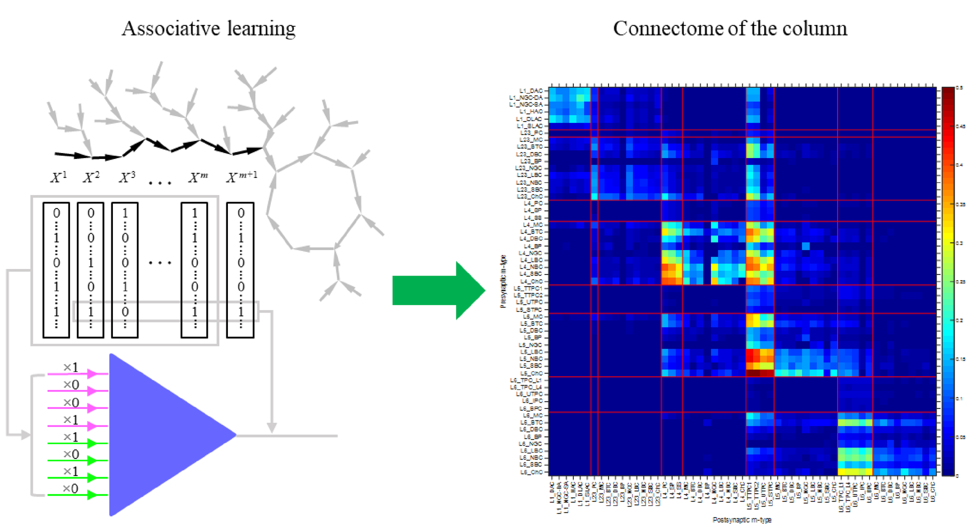
To generate the structural connectivity of the column, we put together axonal and dendritic arbors of 55 neuron classes reconstructed as part of the Blue Brain project [1,2] and created a network containing 28,156 neurons interconnected with 1.9×10⁸ potential synapses [3]. By loading associative memory sequences into this network [4,5], we generated its functional connectivity. Many properties of connectivity in the model column are in good agreement with the available experimental measurements. These include connection probabilities for 14 types of local excitatory and inhibitory projections, the dependence of connection probability on the distance between neurons, correlations between structural and functional connectivity, volume densities of inhibitory synapses in different cortical layers, and overexpression of specific excitatory and inhibitory 3-neuron motifs. Our results contain predictions regarding intra- and inter-laminar connectivity between specific neuron classes that can be tested in future experiments.

We conclude that basic properties of connectivity in the cortical column may have resulted from biologically-constrained associative learning in a morphologically constrained neural network.

2. Associative learning model for a cortical column



- The cortical column consists of 28,156 excitatory and inhibitory neurons, belonging to 55 morphologically defined classes of cells in six layers.
- Structural connectivity of the column was calculated based on the neuron positions within the column and the morphologies of their axonal and dendritic arbors.
- A structural (potential) connection between two neurons was defined as an apposition of their axonal and dendritic branches at less than 2.0 μm for excitatory-to-excitatory connections and less than 0.7 μm for the remaining three connection types.
- We applied soft thresholds to remove connections with few potential synapses. A threshold of 2 was used for excitatory-to-excitatory connections and 1 for other connection types.



- The structural column was loaded with associative sequences of network states, $X^1 \to X^2 \to \ldots X^{m+1}$, by training individual neurons (e.g. neuron *i*) to independently associate a given network state, vector X^μ, with the state at the following time step, $X_i^{\mu+1}$.
- Several biologically-inspired constraints were imposed on the learning process. These include sign constraints on excitatory and inhibitory connection weights, hemostatic l_1 norm constraints on presynaptic inputs to each neuron, and noise robustness constraints. Note that connection weights of structurally unconnected neurons remain zero throughout learning.

$$\theta\left(\sum_{j=1}^{N} J_{ij} X_j^{\mu} - h + \eta_i\right) = X_i^{\mu+1}; \quad i = 1,\ldots,N; \quad \mu = 1,\ldots,m$$

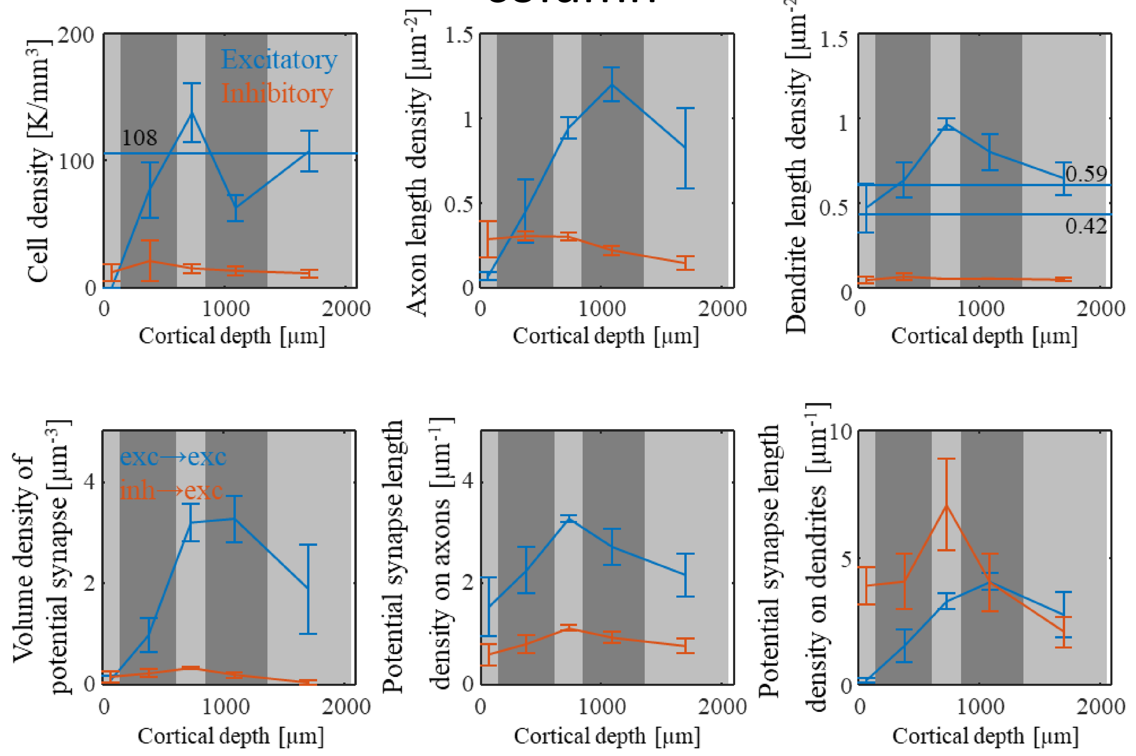
$$J_{ij} g_j \geq 0; \quad j = 1,\ldots,N$$

$$\frac{1}{N}\sum_{j=1}^{N} \left|J_{ij}\right| = w$$

$$|\eta_i| \leq \kappa; \quad \mathrm{Prob}\left(X_i^{\mu}\right) = \begin{cases} 1 - f_i, & X_i^{\mu} = 0 \\ f_i, & X_i^{\mu} = 1 \end{cases}$$

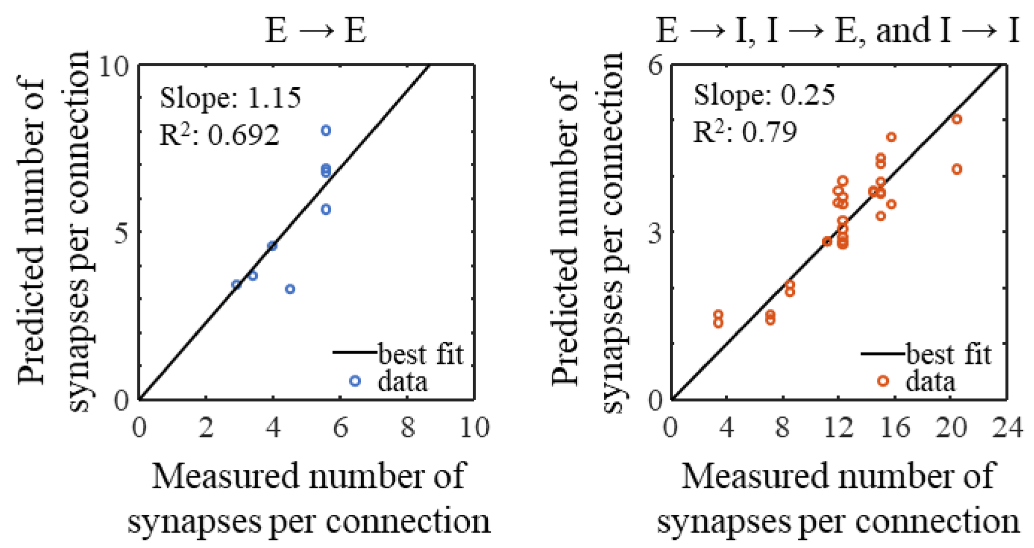
- We solved the associative learning problem with the replica method in the limit of $N \to \infty$ and with convex optimization for finite *N*.
- The values of parameters governing the model were inferred by comparing experimentally measured structural and dynamical properties of local cortical networks with the results of the associative learning model [5].

3. Structural statistics of the cortical column



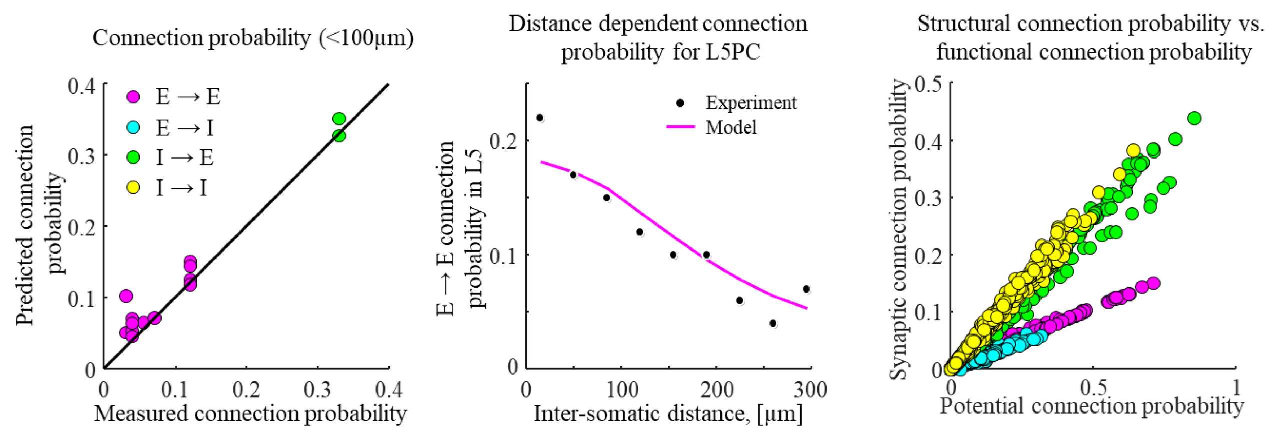
- Neuron densities in the model column are consistent with the experimental measurements [1,6].
- Dendrite length densities agree with the measurements from two cortical systems [7,8]. However, the length densities of excitatory neuron axons in the model are far below the experimental values (~5μm⁻²) due to the absence of long-range projections originating from neurons outside the column [9].
- Volume densities of potential synapses are much larger than the experimentally measured densities of synapses, which is indicative of high structural plasticity potential of cortical networks.

4. Number of synapses per connection



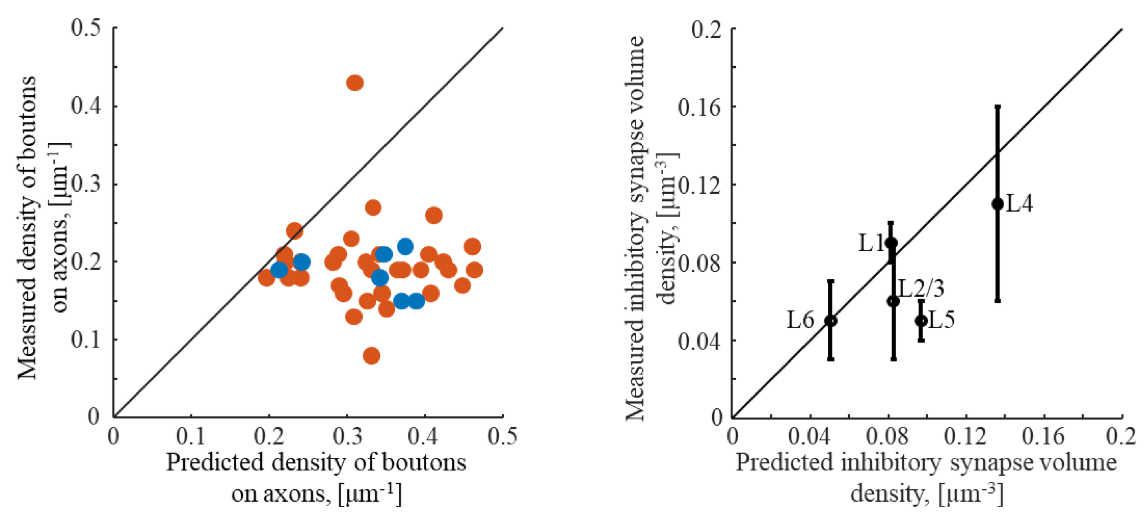
- The average number of synapses between potentially connected excitatory neurons matches well with experimental data.
- The average number of synapses for E → I, I → E, and I → I connections obtained in the model are about 4 times smaller than that reported in experimental studies. We think that this may be due to a bias in the identification of synapses based on light microscopy images.

5. Cell-type specific connectivity



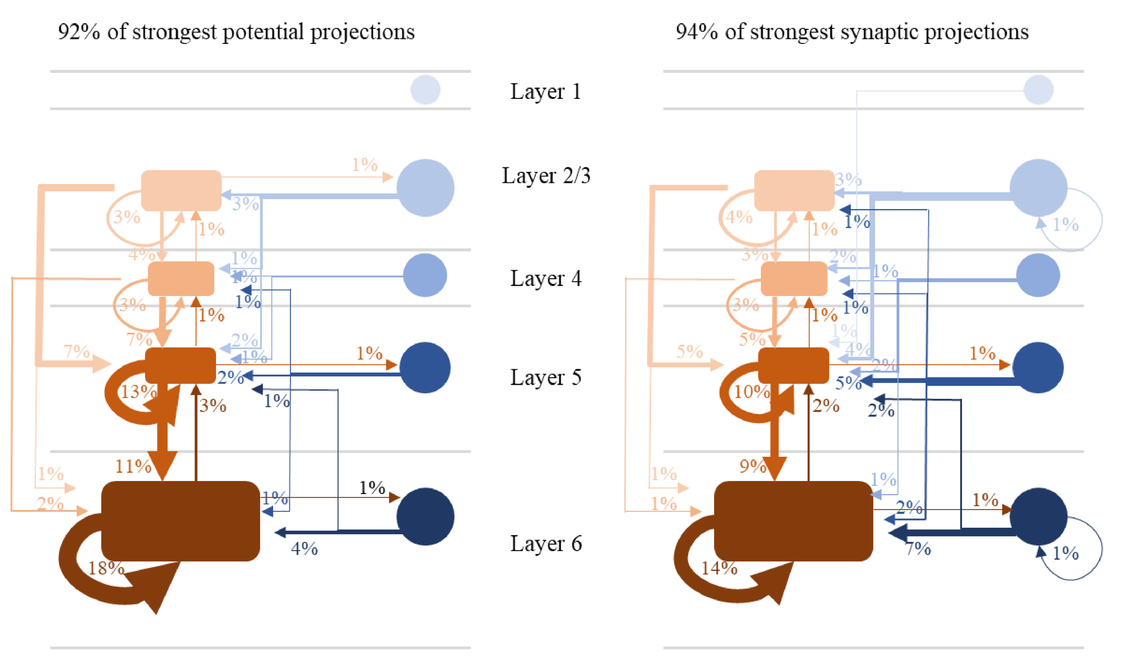
- Synaptic connection probabilities for 14 projections between different excitatory and inhibitory neuron classes in the model column are in good agreement with the experimental data [1].
- Distance-dependent synaptic connection probability between L5PCs in the model also agrees with the experimental measurements [13].
- Functional connectivity in the model column is proportional to structural connectivity [10].

6. Bouton densities on axons and inhibitory synapse volume densities



- Bouton densities in the model are significantly higher than the experimentally measured values.
- Volume densities of inhibitory synapses in the model are generally consistent with the densities of symmetric synapses measured with electron microscopy in different cortical layers.

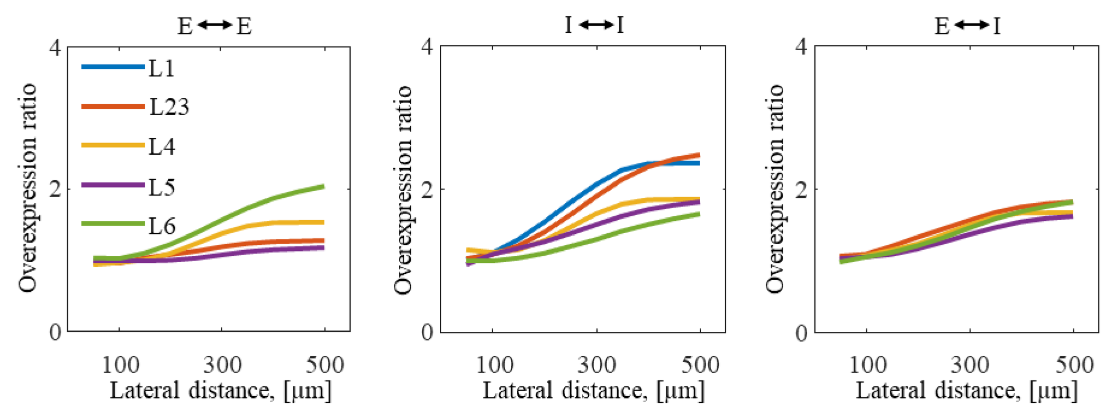
7. Structural and functional connectomes



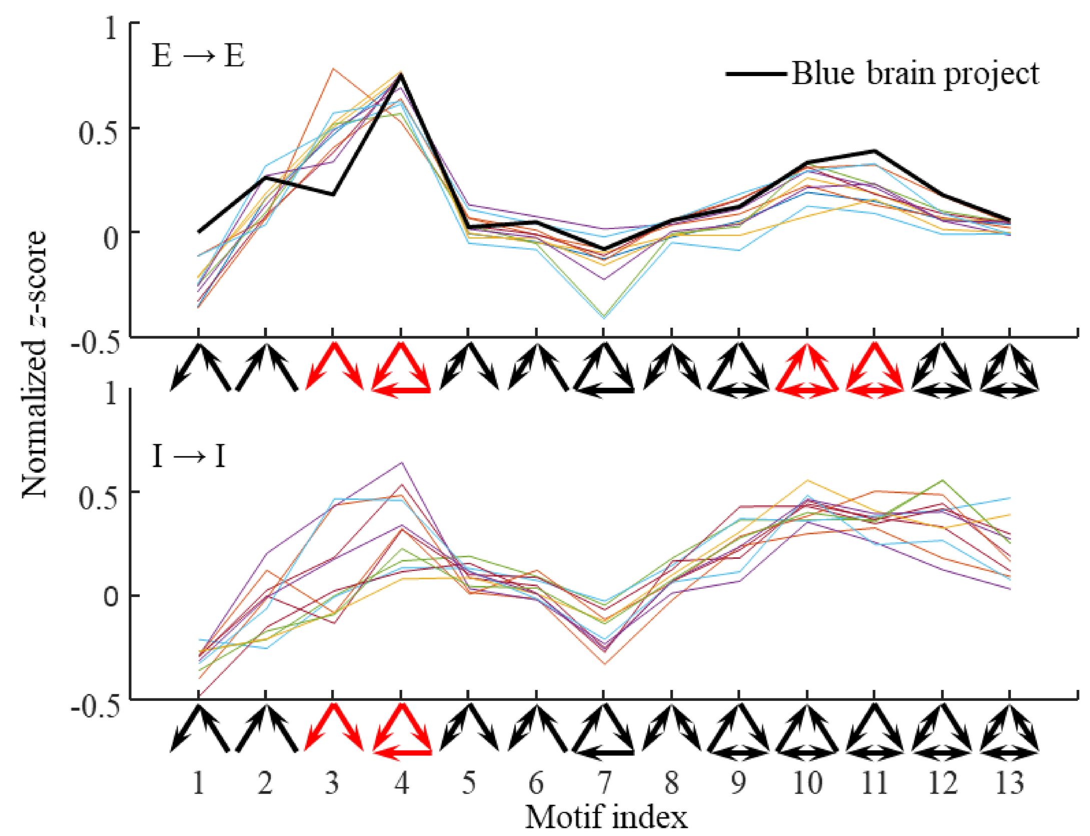
- Projections contributing less than 1% of the total synapse numbers were eliminated to avoid clutter.
- Overall, the connectome of the model cortical column exhibits a small world topology with abundant intra-layer interactions and sparse inter-layer projections.

- The model connectome shows that L5 excitatory neurons receive inputs from all layers, including a strong excitatory projection from L2/3. These and many other features of the model connectome are ubiquitously present in many cortical areas (see e.g., [11,12]).

8. Two- and three-neuron motifs



- Overexpression of bidirectional synaptic connections increases with the lateral distance between neurons. Overexpression is negligible for neurons separated by less than 100 μm.
- Experimentally observed overexpression of bidirectional connections between excitatory neurons may be caused by correlations in associative memory patterns [4,5].



- Overexpressions of excitatory and inhibitory three-neuron motifs observed in the model are in general agreement with various experimental measurements.
- Overexpressions of motifs 3, 4, 10, and 11 were detected in excitatory L5TTPC subnetworks [13], while overexpressions of motifs 3 and 4 in inhibitory subnetworks were reported in [14].

9. References

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