Non-random network connectivity comes in pairs

Felix Z. Hoffmann[1,2,*] and Jochen Triesch[1]

[1]*Frankfurt Institute for Advanced Studies (FIAS), Johann Wolfgang Goethe University, Frankfurt am Main, Germany*
[2]*International Max Planck Research School for Neural Circuits, Max Planck Institute for Brain Research, Frankfurt am Main, Germany*

[*]*Email: hoffmann@fias.uni-frankfurt.de*

Overrepresentation of bidirectional connections in local cortical networks has been repeatedly reported and is in the focus of the ongoing discussion of non-random connectivity. Here we show in a brief mathematical analysis that in a network in which connection probabilities are symmetric in pairs, $P_{ij} = P_{ji}$, the occurrence of bidirectional connections and non-random structures are inherently linked; an overabundance of reciprocally connected pairs emerges necessarily when the network structure deviates from a random network in any form.

Introduction

Increasing evidence shows that cortical microcircuitry is highly structured [1, 2]. Not every connection is equally likely to be established, rather some pairs of neurons are more likely connected than others. In this context, the relative occurrence of bidirectionally connected pairs has been of particular interest. Using data obtained from paired whole-cell recordings in cortical slices, the amount of bidirectionally connected pairs was compared to the number of reciprocal pairs as one would expect in a random network with the same overall connection probability. Connectivity of layer 5 pyramidal neurons in the rat visual cortex [1] and somatosensory cortex [3, 2] was shown to have a significantly stronger reciprocity than expected.

The prevalence of bidirectional connectivity has since been established as an important measure for the non-randomness of a network. However, the exact relationship between non-randomness and relative reciprocity has not been explained. Here, we model cortical circuitry as random networks in which each possible connection has a separate probability to exist. Using this model we're able to show that any non-random connectivity, expressed as higher connection probabilities in some edges and lower probabilities in others, necessarily induces a relative overrepresentation of bidirectional connections as long as

1

connection probabilities remain symmetric within pairs. Quantitatively, we analyze reciprocity in networks with a discrete and a continuous distribution in connection probabilities to demonstrate that a relative occurrence of bidirectional connections as reported from experimental studies can be easily obtained in these models.

Results

The emergence of non-random connectivity patterns can be modeled by assigning each possible connection in a random graph a separate probability to exist. In such a model some connections are more likely to be realized than others, allowing for the encoding of patterns within the specific probabilities of each connection. In the limiting case each connection either exists or is absent with certainty, representing a blueprint for the network architecture.

To analyze the effect of non-random structures within a network, specifically on the statistics of bidirectionally connected pairs found in the network, we consider a random graph model of N neurons in which a connection from node i to node j exists with probability P_{ij}. Here the P_{ij}, with $i, j = 1, \ldots, N$ and $i \neq j$, are identically distributed random variables in $[0, 1]$, yielding a probability of connection for each ordered pair of nodes in the graph. We explicitly exclude self-connections in this model and assume at all times that $i \neq j$.

Given the distributions of connection probabilities, what is then the probability in this model for a randomly selected node to have a projection to another randomly selected node? As the random variables P_{ij} are identically distributed, we compute this overall connection probability μ easily as the expected value of P_{ij},

$$\mu = \mathbf{E}(P_{ij}). \tag{1}$$

For example, if the P_{ij} have a probability density function f with essential support in $[0, 1]$, we can compute the connection fraction as

$$\mu = \int_0^1 x f(x) \, dx. \tag{2}$$

In this work we are interested in the probability $P_{\mathbf{bidir}}$ of a bidirectional connection to exist in a random pair of neurons. We determine $P_{\mathbf{bidir}}$ as the

expected value of the product of P_{ij} and P_{ji},

$$P_{\textbf{bidir}} = \mathbf{E}(P_{ij}P_{ji}). \tag{3}$$

The relative occurrence ϱ of such reciprocally connected pairs compares $P_{\textbf{bidir}}$ with the occurrence of bidirectional pairs in an Erdős-Rényi graph, in which each unidirectional connection is equally likely to occur with probability μ [4, 5]. The probability of a particular bidirectional connection to exist in such a random graph is simply μ^2 and we obtain the relative occurrence as the quotient

$$\varrho = \frac{P_{\textbf{bidir}}}{\mu^2} = \frac{\mathbf{E}(P_{ij}P_{ji})}{\mathbf{E}\left(P_{ij}\right)^2}. \tag{4}$$

Experimental studies in local cortical circuits of rodents have repeatedly reported a relative occurrence of bidirectional connections $\varrho > 1$ [3, 1, 2]. To understand in which cases such an overrepresentations occurs, we consider two cases. In the first case, assume that the random variables P_{ij} and P_{ji} are independent. Then

$$\mathbf{E}(P_{ij}P_{ji}) = \mathbf{E}(P_{ij})\,\mathbf{E}(P_{ji}) = \mathbf{E}(P_{ij})^2, \tag{5}$$

and we expect to observe no overrepresentation of reciprocal connections, $\varrho = 1$. In the second case, assume that connection probabilities are symmetric in pairs, $P_{ij} = P_{ji}$. In this case,

$$P_{\textbf{bidir}} = \mathbf{E}(P_{ij}^2), \tag{6}$$

and the relative occurrence of reciprocal connections becomes

$$\varrho = \frac{\mathbf{E}(P_{ij}^2)}{\mathbf{E}\left(P_{ij}\right)^2}. \tag{7}$$

We note that now any distribution of P_{ij} with a nonvanishing variance will lead to a relative occurrence that deviates from the Erdős-Rényi graph, as

$$\mathbf{Var}(P_{ij}) = \mathbf{E}(P_{ij}^2) - \mathbf{E}\left(P_{ij}\right)^2. \tag{8}$$

Moreover, since $x \mapsto x^2$ is a strictly convex function, Jensen's inequality [6, 7] yields

$$\mathbf{E}(P_{ij}^2) \geq \mathbf{E}(P_{ij})^2, \tag{9}$$

and we find that $\varrho \geq 1$ in networks with symmetric connection probabilities. Jensen's inequality further states that equality in (9), and thus $\varrho = 1$, holds

if and only if P_{ij} follows a degenerate distribution, that is if all P_{ij} take the identical value μ. In the other case, where the P_{ij} take on more than one value with non-zero probability, we speak of a non-degenerate distribution.

As a central result of this study we thus find that any non-degenerate distribution of symmetric connection probabilities ($P_{ij} = P_{ji}$) necessarily induces an overrepresentation of bidirectional connections in the network, $\varrho > 1$. In other words, in a network where some pairs are more likely connected than others, the count of expected reciprocally connected pairs is strictly underestimated by the statistics of an Erdős-Rényi graph with same the overall connection probability $\mathbf{E}(P_{ij}) = \mu$.

Upper bound for ϱ

The overrepresentation of bidirectional connections ϱ is maximal when every connected pair in the network is already a reciprocally connected pair, that is when

$$\mathbf{E}(P_{ij}^2) = \mathbf{E}(P_{ij}). \tag{10}$$

In this case the overrepresentation is

$$\varrho = \frac{1}{\mathbf{E}(P_{ij})} = \frac{1}{\mu}. \tag{11}$$

Thus, in the local cortical circuits of L5 pyramidal neurons with a typical connection probability of $\mu = 0.1$ [8, 1] the maximal overrepresentation is $\varrho = 10$.

Two-point distribution

The simplest non-degenerate distribution of connection probabilities is a distribution that takes two values x, y with probability p and $1 - p$ respectively, as illustrated in Figure 1A. This distribution may be seen as a crude approximation to the connection probabilities recently observed in visual cortex as a function of the neurons' difference in orientation preference [9]. Formally, let $x, y \in [0, 1]$ with $x > y$ and $0 < p < 1$. A random variable X follows the two-point distribution $\mathcal{T}(p, x, y)$ if $P(X = x) = p$ and $P(X = y) = 1 - p$.

In our network model let then the P_{ij} be $\mathcal{T}(p, x, y)$ distributed. The overall

4

connection probability μ is

$$\mu = \mathbf{E}(P_{ij}) = px + (1-p)y. \tag{12}$$

Assume again that $P_{ij} = P_{ji}$. The relative occurrence of bidirectional connections is given by

$$\varrho = \frac{\mathbf{E}(P_{ij}^2)}{\mu^2} = \frac{px^2 + (1-p)y^2}{\mu^2}. \tag{13}$$

Solving (12) for p as

$$p = \frac{\mu - y}{x - y} \tag{14}$$

and inserting into equation (13) yields an expression for the relative overrepresentation depending on x, y and μ (see Supplementary Information SI1),

$$\varrho = \frac{x+y}{\mu} - \frac{xy}{\mu^2}. \tag{15}$$

In local cortical circuits, a single excitatory neuron is typically projecting to roughly 10% of the excitatory population. Fixing $\mu = 0.1$, we obtain the relative occurrence dependent on the two connection probability values x and y. Given $x \geq \mu$ it follows that $y \leq \mu$ (see Supplementary Information SI2) and the possible values for x and y are $0.1 \leq x \leq 1$ and $0 \leq y \leq 0.1$. Figure 1B shows contours of ϱ for the (x, y) pairings illustrating how different values for the relative overrepresentation of reciprocal connections can be induced by two-point distributed connection probabilities. We find that in such networks higher values of ϱ are easily obtained with reasonable network configurations. For example, a relative overrepresentation of $\varrho = 4$ could be achieved by a two-point distribution of connection probabilities where one group of neuron pairs is highly connected with probability $x = 0.7$, while the other group of neuron pairs is sparsely connected with probability $y = 0.05$. Collectively, the highly connected pairs then make up less than 8% of all neuron pairs, showing that it is sufficient to have a small subgroup of highly connected neuron pairs to induce a high overrepresentation of bidirectionally connected pairs in the network.
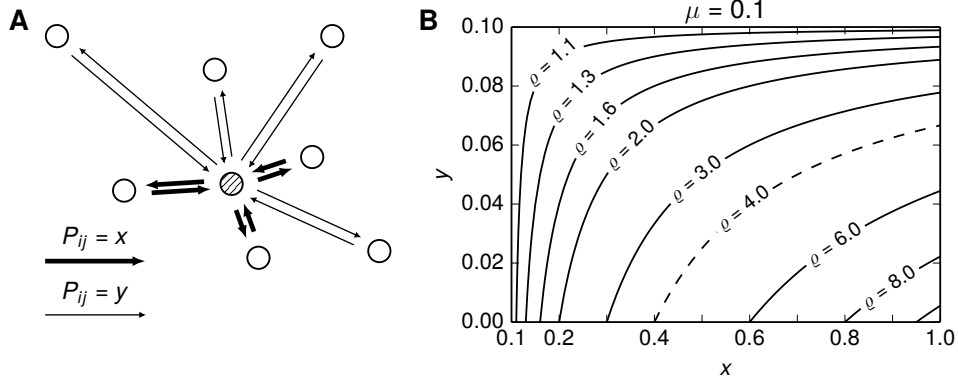
Figure 1: Relative overrepresentation ϱ of bidirectional connections in networks with a fraction of pairs connected with a high probability x and the rest of the pairs connected with a low probability y. **A** Diagram illustrating the targets connecting with a high chance x (thick arrows) and targets connecting with a low probability y (thin arrows) for a single source node (hatched). **B** Different pairings of x and y can induce a high relative overrepresentation ϱ in a network with two-point distributed connection probabilities, $P_{ij} \sim \mathcal{T}(\frac{\mu-y}{x-y}, x, y)$, and a fixed overall connection probability $\mu = 0.1$. The dashed line marks an overrepresentation of bidirectional connections of $\varrho = 4$ as observed for layer 5 pyramidal neurons in the rat visual cortex [1].

Gamma distribution

Next, we analyze the relative overrepresentation of bidirectional connections in a network with continuously distributed connection probabilities. The gamma distribution $\Gamma(\alpha, \beta)$ with probability density function

$$f_{\alpha,\beta}(x) = \begin{cases} \frac{1}{\beta^\alpha \Gamma(\alpha)} \, x^{\alpha-1} \, e^{-x/\beta} & x \geq 0 \\ 0 & \text{otherwise,} \end{cases} \tag{16}$$

allows the variation of the variance $\mathbf{Var}(X) = \alpha\beta^2$ of a gamma distributed random variable $X \sim \Gamma(\alpha, \beta)$, while keeping its mean $\mathbf{E}(X) = \alpha\beta$ constant [10]. The exponential distribution emerges as a special case of the gamma distribution ($\alpha = 1$).

To ensure that the randomly drawn connection probabilities lie within the interval $[0, 1]$, we here consider a modification to the traditional gamma distribution in the form of a truncated version. Let $\alpha, \beta > 0$. A random variable

X follows the truncated gamma distribution $\Gamma^T(\alpha, \beta)$ if it has the probability density function

$$
f_{\alpha,\beta}^T(x) =
\begin{cases}
K_{\alpha,\beta} \frac{1}{\beta^\alpha \Gamma(\alpha)} x^{\alpha-1} e^{-x/\beta} & 0 \le x \le 1 \\
0 & \text{otherwise.}
\end{cases}
\tag{17}
$$

The factor $K_{\alpha,\beta}$ is the inverse of the cumulative probability that $x \le 1$ of the untruncated gamma distribution,

$$
K_{\alpha,\beta} = \left(\int_0^1 f_{\alpha,\beta}(x)\, dx \right)^{-1},
\tag{18}
$$

and is needed to ensure that

$$
\int f_{\alpha,\beta}^T(x)\, dx = 1.
\tag{19}
$$

Consider then the above network model in which the connection probabilities P_{ij}^T are $\Gamma^T(\alpha, \beta)$ distributed. We compute the relative overrepresentation ϱ numerically from

$$
\mu = \mathbf{E}\left(P_{ij}^T \right) = \int_0^1 x f_{\alpha,\beta}^T(x)\, dx,
\tag{20}
$$

$$
\mathbf{E}\left(P_{ij}^{T^2} \right) = \int_0^1 x^2 f_{\alpha,\beta}^T(x)\, dx.
\tag{21}
$$

Pairings of the shape parameter α and the scale parameter β were chosen such that the overall connection probability reflects connectivity statistics in local cortical networks, $\mu = 0.1$. Probability density functions and resulting relative overrepresentation of reciprocal connections ϱ for four representative α, β pairs are shown in Figure 2A. Here, β was determined to yield $\mu = 0.1$ for the given α, following the relationship shown in Figure 2B (solid curve).

In the sparse networks we modeled, the truncated gamma distribution can be well approximated by the untruncated version, $K_{\alpha,\beta} \approx 1$. Assuming connection probabilities to be standard gamma distributed, $P_{ij} \sim \Gamma(\alpha, \beta)$, we have

$$
\mathbf{E}(P_{ij}^2) = \mathbf{Var}(P_{ij}) + \mathbf{E}(P_{ij})^2 = \alpha\beta^2 + \alpha^2\beta^2,
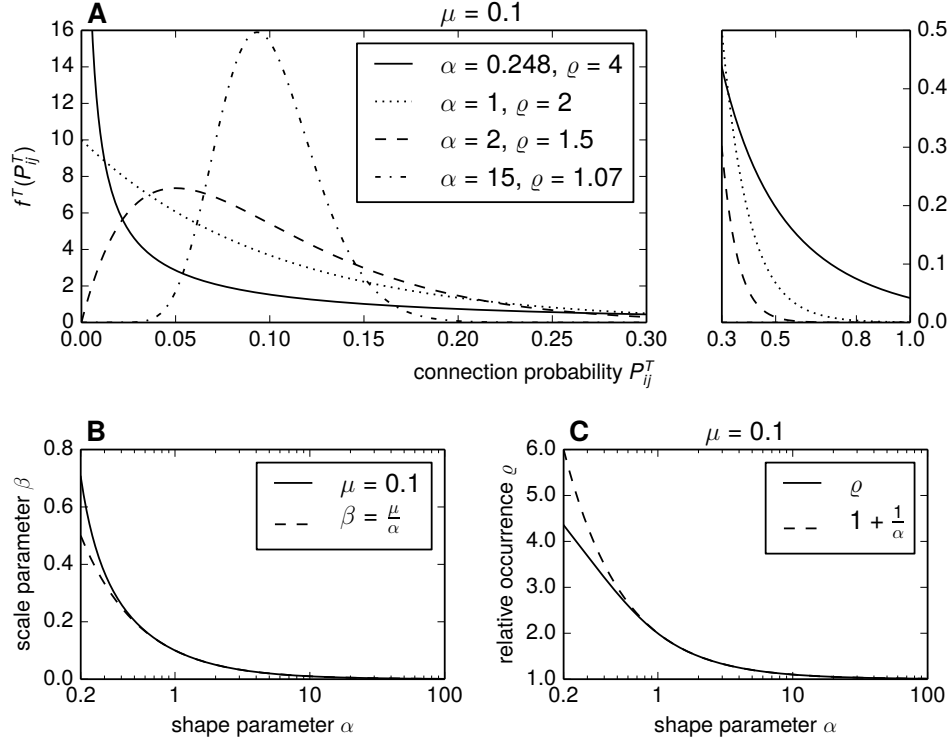\tag{22}
$$

Figure 2: Relative occurrence of bidirectional connections ϱ in networks with gamma distributed connection probabilities. **A** Probability density functions of the truncated gamma distribution $\Gamma^T(\alpha, \beta)$ for different shape parameters α and the induced relative overrepresentation ϱ in a network with such distributed connection probabilities P_{ij}. For a given α, the scale parameter β was chosen such that $\mu = 0.1$. Plot to the right continues the density functions on a different scale. **B** Contour of α, β pairings that yield an overall connection probability of $\mu = 0.1$. **C** Relative occurrence ϱ in dependence on α for fixed $\mu = 0.1$. For $\alpha \geq 1$ this relationship is well approximated by $\varrho \approx 1 + \frac{1}{\alpha}$.

and thus

$$\varrho = \frac{\mathbf{E}\left(P_{ij}^{T\,2}\right)}{\mathbf{E}\left(P_{ij}^{T}\right)^2} \approx \frac{\mathbf{E}\left(P_{ij}^{\,2}\right)}{\mathbf{E}\left(P_{ij}\right)^2} = \frac{\alpha^2\beta^2}{\alpha^2\beta^2} + \frac{\alpha\beta^2}{\alpha^2\beta^2} = 1 + \frac{1}{\alpha} =: \tilde{\varrho}. \qquad (23)$$

The approximation $\varrho \approx \tilde{\varrho} = 1 + \frac{1}{\alpha}$ works well for $\alpha \geq 1$ as shown in Figure 2C.

To induce a high overrepresentation of reciprocal pairs in the network, the

8

gamma distribution of connection probabilities takes a highly skewed shape. In order to obtain $\varrho = 4$, only 57% of pairs have a higher connection probability than 0.01 ($\alpha = 0.248$, $\beta = 0.487$). In other words, almost half of all neuronal pairs have a vanishingly small chance to be connected at all. Such a situation could be likely if, e.g., the connection probability strongly depends on the spatial separation of the neurons such that only nearby neurons are likely to be connected, as it was found in layer 5 excitatory circuits of the rat somatosensory cortex [2].

Discussion

Experimental evidence suggests that any pair of excitatory cells within a cortical column has contact points between axon and dendrite close enough to support a synaptic connection between the cells [11, 12]. Despite this potential "all-to-all" connectivity, only a small fraction of the contacts are realized as functional synapses. Uncovering the underlying principles of which contact points get utilized for synaptic transmission is crucial for our understanding of the structure and function of the local cortical circuits in the mammalian brain.

The emerging local networks in the visual and somatosensory cortex have been shown to feature non-random structure and much attention was given to bidirectionally connected neuron pairs, which are occurring more often than expected from random connectivity. In this study we have shown that non-random network structure and the occurrence of reciprocally connected pairs are inherently linked; a relative overrepresentation of bidirectional connections arises necessarily in networks with a non-degenerate distribution of symmetric connection probabilities. Absence of an overabundance of reciprocal pairs on the other hand, as for example found in the intra-layer connectivity of the mouse C2 barrel column [13], points towards either a truly random network or an asymmetry in the connection probabilities.

Quantitatively, a network in which connection probabilities take on one of two values is easily able to account for even the highest values of overrepresentation reported. A network with such a two-point distribution of connection probabilities might occur naturally, where the probability of connection depends on whether a given pair of neurons shares a certain feature, for example has a similar orientation preference or not [9].

A continuous distribution in connection probabilities on the other hand might occur when pair connectivity depends on a continuous parameter such as the

inter-neuron distance or the neurons' age. We showed that networks in which connection probabilities follow a gamma distribution can as well have a high relative occurrence of reciprocally connected pairs, however in this case a larger fraction of pairs remain unconnected with a very high probability.

It is likely that a combination of such effects determines the connection probabilities in local cortical networks. Importantly, we showed that as long as this probability is symmetric for pairs, any such effect that creates a non-degenerate distribution of probabilities will cause an increase of the reciprocity in the network.

Our results confirm the intuitive notion that reciprocity is favored in symmetric networks, whereas asymmetric probabilities of connection inhibit the occurrence of bidirectionally connected pairs. Network models with symmetric connectivity such as Hopfield nets generally excel at memory storage and retrieval through fixed point attractor dynamics [14], while asymmetric network models such as synfire chains are suitable for reliable signal transmission [15, 16]. This suggests the intriguing possibility that one may be able to infer the nature of the computations in a neural circuit based on certain statistics of its connectivity such as the abundance of bidirectionally connected pairs.

In conclusion, the present study puts the overrepresentations bidirectional connections found in local cortical circuits in a new light. If connection probabilities are symmetric in pairs, the overrepresentation emerges as a symptom of any form of non-random connectivity. It is thus crucial for both future experimental and modeling studies to develop a more refined view of non-random network connectivity that goes beyond simple pair statistics. Focusing on higher order connectivity patterns and taking into account the actual synaptic efficacies seem promising avenues for future research into the non-random wiring of brain circuits.

Supplementary Material

The supplementary information document for references SI1 and SI2 is available online at DOI: 10.6084/m9.figshare.3501860. Python code for the numerical computations is available as a GitHub repository and was archived at DOI: 10.5281/zenodo.154007. A website documenting the code is found at https://non-random-connectivity-comes-in-pairs.github.io/.

References

[1] S. Song, P. J. Sjöström, M. Reigl, S. Nelson, and D. B. Chklovskii. Highly Nonrandom Features of Synaptic Connectivity in Local Cortical Circuits. In: *PLoS Biol* 3.3 (2005), e68. DOI: 10.1371/journal.pbio.0030068.

[2] R. Perin, T. K. Berger, and H. Markram. A Synaptic Organizing Principle for Cortical Neuronal Groups. In: *Proceedings of the National Academy of Sciences* 108.13 (2011), pp. 5419–5424. DOI: 10.1073/pnas.1016051108.

[3] H. Markram, J. Lübke, M. Frotscher, A. Roth, and B. Sakmann. Physiology and Anatomy of Synaptic Connections between Thick Tufted Pyramidal Neurones in the Developing Rat Neocortex. In: *The Journal of Physiology* 500.Pt 2 (1997), pp. 409–440.

[4] E. N. Gilbert. Random Graphs. In: *The Annals of Mathematical Statistics* 30.4 (1959), pp. 1141–1144. DOI: 10.1214/aoms/1177706098.

[5] P. Erdős and A. Rényi. On Random Graphs, I. In: *Publicationes Mathematicae (Debrecen)* 6 (1959), pp. 290–297.

[6] J. L. W. V. Jensen. Sur les fonctions convexes et les inégalités entre les valeurs moyennes. In: *Acta Mathematica* 30.1 (1906), pp. 175–193. DOI: 10.1007/BF02418571.

[7] T. M. Cover and J. A. Thomas. *Elements of Information Theory 2nd Edition*. 2 edition. Hoboken, N.J: Wiley-Interscience, 2006.

[8] A. M. Thomson, D. C. West, Y. Wang, and A. P. Bannister. Synaptic Connections and Small Circuits Involving Excitatory and Inhibitory Neurons in Layers 2–5 of Adult Rat and Cat Neocortex: Triple Intracellular Recordings and Biocytin Labelling In Vitro. In: *Cerebral Cortex* 12.9 (2002), pp. 936–953. DOI: 10.1093/cercor/12.9.936.

[9] K.-S. Lee, X. Huang, and D. Fitzpatrick. Topology of ON and OFF Inputs in Visual Cortex Enables an Invariant Columnar Architecture. In: *Nature* 533.7601 (2016), pp. 90–94. DOI: 10.1038/nature17941.

[10] R. V. Hogg and A. T. Craig. *Introduction to Mathematical Statistics*. 4th ed. New York: Macmillan, 1978.

[11] A. Stepanyants, G. Tamás, and D. B. Chklovskii. Class-Specific Features of Neuronal Wiring. In: *Neuron* 43.2 (2004), pp. 251–259. DOI: 10.1016/j.neuron.2004.06.013.

[12] N. Kalisman, G. Silberberg, and H. Markram. The Neocortical Microcircuit as a Tabula Rasa. In: *Proceedings of the National Academy of Sciences of the United States of America* 102.3 (2005), pp. 880–885. DOI: 10.1073/pnas.0407088102.

[13] S. Lefort, C. Tomm, J. C. Floyd Sarria, and C. C. H. Petersen. The Excitatory Neuronal Network of the C2 Barrel Column in Mouse Primary Somatosensory Cortex. In: *Neuron* 61.2 (2009), pp. 301–316. DOI: 10.1016/j.neuron.2008.12.020.

[14] J. J. Hopfield. Neural Networks and Physical Systems with Emergent Collective Computational Abilities. In: *Proceedings of the National Academy of Sciences of the United States of America* 79.8 (1982), pp. 2554–2558.

[15] M. Abeles. *Local Cortical Circuits an Electrophysiological Study*. Berlin, Heidelberg: Springer Berlin Heidelberg, 1982.

[16] M. Diesmann, M.-O. Gewaltig, and A. Aertsen. Stable Propagation of Synchronous Spiking in Cortical Neural Networks. In: *Nature* 402.6761 (1999), pp. 529–533. DOI: 10.1038/990101.