

STRUCTURAL AND DYNAMICAL ASPECTS OF NEURAL
NETWORKS WITH ANISOTROPIC TISSUE GEOMETRY

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ABSTRACT

Non-random connectivity has been repeatedly reported in cortical networks, yet underlying connection principles of these patterns remain elusive. Proposing an abstract geometric network model reflecting stereotypical axonal and dendritic morphology of local cortical layer 5 networks, we here investigate in how far anisotropy in connectivity can constitute such an underlying connectivity rule. Using a combination of analytical considerations and numerical analysis, we find that while standard network measures and pair connectivity remain unaffected, higher order connectivity is strongly influenced by anisotropy, in many cases reflecting patterns found in local cortical circuits. Presenting an abstract network model featuring connectivity principles beyond distance-dependency, the results shown here not only make a strong case for morphology-induced rules as underlying connection principles of non-random patterns, but may provide another step towards a network archetype greatly improving upon the standard random model.

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INTRODUCTION

Brain network connectivity, the description of links between the brain's computational units, lies at the heart of many theories trying to explain the exceptionally diverse and robust functionality of the brain. As an essential component in the investigation of the emergence of the brain's unique cognitive abilities, connectivity is often associated with working memory and the remarkable performance in various perception tasks. Connectivity is, in its essence, intimately tied to mathematical concepts. Relying heavily on a graph theoretical framework for the analysis and discussion of network connectivity, this aspect of brain research constitutes an exciting and highly relevant example of applied mathematics.

In theoretical and computational neuroscience, neural network models are studied as a reflection of brain networks. Research in this field ranges from the modeling of single neurons to the simulation of large-scale networks. An area of particular interest lies in the dynamical aspect of neural networks; picking from a wide range of neuron models, a modeler can then investigate dynamical properties such as activity synchronization or oscillation. The standard network model for such considerations is that of a random graph, imposing completely random connectivity on the network (Brunel 2000). However, results over the last years have repeatedly shown that local cortical circuits display highly non-random connectivity features not present in random or even distance-dependent networks (Song et al. 2005; Perin et al. 2011). It is unclear how to incorporate such features in the common network models, as the underlying connection principles inducing the non-random patterns remain yet to be determined.

The search for such underlying principles is therefore an ongoing endeavor (cf. Klinshov et al. 2014). In an attempt to contribute to this effort, in this thesis anisotropy in connectivity is discussed as a morphology-induced connection principle. Condensing stereotypical anatomy of pyramidal cells in cortical circuits into a network model, the proposed connectivity rule may not only provide insight in the emergence of non-random patterns, but can potentially be a step towards a network archetype improving on the standard random network model.

1.1 OVERVIEW

Following the introduction and this outline, a short overview of the biological terms frequently appearing throughout this text is given as reference at the end of this chapter. The central mathematical objects in this study, various directed graph models, are then introduced and discussed in detail in Chapter 2. Building on these concepts, Chapter 3 introduces the anisotropic network model as the main object of investigation in this thesis. Next to an in-depth motivation of the anisotropic connectivity concept, the chapter also introduces the rewiring of networks and a measure for anisotropy, laying the groundwork for the analysis of structural features in anisotropic networks in Chapter 4. First investigating standard network attributes like degree distributions and small-world measures, analysis of higher order connectivity in the latter part of the chapter reveals the highly interesting emerging patterns in anisotropic networks. Closing the structural analysis with a critical discussion of the obtained results, the last chapter of this work provides an outlook on how anisotropy in connectivity may influence dynamical aspects.

1.2 BIOLOGY OF NEURAL NETWORKS

The fundamental computational units in brain networks are neurons, electrically excitable cellular elements that process and transmit information by a cell type dependent regime of electrical and chemical signals. Neurons are linked through synapses, forming together an expansive, interconnected network of different neuron types, dividing into functionally and anatomically distinct areas. The number of neurons in the average human brain is estimated at about 86 billion, connected by $10^{14} - 5 \times 10^{15}$ synapses (Herculano-Houzel 2009; Drachman 2005). Among the different brain areas studied, the multilayered cerebral cortex stands out as a region of particular interest with many studies analyzing its structural and dynamical features.

The principal excitatory neuron type in cortical networks are pyramidal cells. Connection between those neurons are mainly of chemical nature, in the synaptic contacts between cells the release and consequent reception of neurotransmitters transmits electrical signals. While cortical networks are considered sparse, pyramidal cells typically receive tens of thousands excitatory and several thousand inhibitory inputs, making up for an overall connectivity of about 10% in local networks (Spruston 2009). Such synaptic contacts are inherently asymmetric; signals travel from the cell body of a neuron along the axon to be transmitted

at a synapse contacting the dendritic tree of the post-synaptic neuron. Morphology of axon and dendrite are characteristically different; it is this difference that is taken up in this study and serves as a basis for the network model introduced in Chapter 3.

To enable the definition and critical discussion of such models, the next chapter introduces in detail the underlying mathematical concepts of network connectivity.

2

GRAPH THEORY

A review of graph theory lays the foundation for the mathematical considerations in this work. Following the discussion of directed graphs as a basis for the networks introduced in this work, common network measures are reviewed. Random graph models are integral to this work and are discussed in Sections 2.3 and 2.4, the latter introducing geometric random graphs and performing geometric, probabilistic computations essential for the analytical discussions in later chapters.

2.1 DIRECTED GRAPHS

Here we introduce the various categories of directed graphs. The main reference for this section is [Bang-Jensen and Gutin \(2008\)](#), for the formal definition below however, we follow [nLab \(2014\)](#).

Definition 2.1 (Directed graphs). A *directed pseudograph* G consists of two finite sets $V(G)$, the *set of vertices* of G , and $E(G)$, the *set of edges* of G , and two maps $s, t : E \rightarrow V$, the *source* and *target functions* of G . A *directed multigraph* is a directed pseudograph without loops, that is the map $d = (s, t) : E \rightarrow V^2$ already maps to $V^2 \setminus \Delta_V$, where $V^2 = V \times V$ denotes the cartesian product and $\Delta_V = \{(x, x) \mid x \in V\} \subseteq V^2$ the diagonal. Similarly, a *directed loop graph* is a directed pseudograph where d is injective. Finally, a *simple directed graph* can be defined as a directed pseudograph where d is both injective and already maps to $V^2 \setminus \Delta_V$.

short:
 $V(G)$ vertex set
 $E(G)$ edge set

Thus, in simple directed graphs, neither parallel edges nor loops (edges between the same vertex) are allowed, whereas directed multigraphs and directed loop graphs admit one of them respectively. We refer to any of the four graph types simply as a directed graph and only specify the type when needed.

A **morphism** $\phi : G \rightarrow H$, between two directed graphs $G = (V_G, E_G, s_G, t_G)$ and $H = (V_H, E_H, s_H, t_H)$, consists of a pair of maps $\phi_V : V_G \rightarrow V_H$ and $\phi_E : E_G \rightarrow E_H$, such that

$$s_H \circ \phi_E = \phi_V \circ s_G \quad \text{and} \quad t_H \circ \phi_E = \phi_V \circ t_G,$$

that is such that the following diagram commutes:

$$\begin{array}{ccc} E_G & \xrightarrow{\phi_E} & E_H \\ s_G \downarrow t_G & & \downarrow s_H t_H \\ V_G & \xrightarrow{\phi_V} & V_H \end{array}$$

A morphism $\varphi : G \rightarrow H$, between two directed pseudographs G and H is an **isomorphism**, if the maps $\varphi_V : V_G \rightarrow V_H$ and $\varphi_E : E_G \rightarrow E_H$ are bijections. Two directed pseudographs are called *isomorphic* if there exists an isomorphism inbetween them.

Remark. The last definition implies that, if there exists an isomorphism $\varphi : G \rightarrow H$, an isomorphism $\psi : H \rightarrow G$ can be found. This isomorphism is, of course, easily constructed via $\psi_V : V_H \rightarrow V_G, v \mapsto \varphi_V^{-1}(v)$, $\psi_E : E_H \rightarrow E_G, e \mapsto \varphi_E^{-1}(e)$.

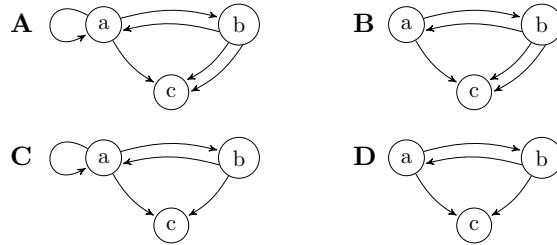


Figure 2.1: Examples of the directed graph types **A)** directed pseudograph **B)** directed multigraph **C)** directed loop graph **D)** simple directed graph.

The subobjects in the directed graph category are subgraphs. Containing only a subset of the vertices of the original graph, it may contain any number of eligible edges from G .

Definition 2.2 (Subgraph). Let G be a directed graph. A *subgraph* H of G is a directed graph with vertex set $V(H) \subseteq V(G)$ and edge set $E(H) \subseteq E(G)$ with source and target functions from G restricted to $E(H)$, such that for every $e \in E(H)$ the source and target $s(e), t(e)$ are in $V(H)$. We call the subgraph *full* if

$$E(H) = \{e \in E(G) \mid s(e), t(e) \in V(H)\}.$$

that is if H contains all edges of G with source and target in $V(H)$.

A **motif** H in G is then a full, connected subgraph of G , that is a subgraph such that every vertex in H is source or target of at least one edge in $E(H)$. An n -motif then refers to a motif H with $|V(H)| = n$. Usually

motifs with only few vertices are considered and are often understood as the “building blocks” of graphs. In neuronal networks, specific connection patterns are associated with specific dynamical functionality, making motifs an import aspect in the theory of neural network dynamics and a central object of interest in this thesis.

Definition 2.3 (Weighted directed graphs). An *edge-weighted directed graph* is a directed graph G along with a mapping $\omega : E(G) \rightarrow \mathbb{R}$, called the *weight function*. Similarly, a *vertex-weighted directed graph* is a directed graph with a mapping $\nu : V(G) \rightarrow \mathbb{R}$.

Remark. A directed graph G can be equivalently defined as a pair of finite sets V , the *set of vertices* of G , and $E \subseteq V^2$ the *set of edges* of G . For an edge $(x, y) \in E$, we call x the *source* and y the target of the edge (x, y) . Source and target functions are then uniquely determined as the projections on the first and second component,

$$s = \text{pr}_1, t = \text{pr}_2 : E(G) \rightarrow V.$$

Conversely, the edge set $E(G) \subseteq V^2$ can be determined from the source and target functions as $E := \{(s(e), t(e)) \mid e \in E\}$. The trivial identities $(x, y) = (\text{pr}_1(x, y), \text{pr}_2(x, y))$ and $\text{pr}_1(s(e), t(e)) = s(e)$ with $\text{pr}_2(s(e), t(e)) = t(e)$ quickly verify the equivalence of the definitions. Given a directed loop graph G , we often assume the graph to be given in this form and write edges as $e = (x, y)$. Note that this concept is more complicated to introduce for directed pseudographs, since parallel edges e and e' should be differentiated in the egde set of G , establishing the need for $E(G)$ to be a multi- or indexed set, notions we are trying to avoid in this document.

Equivalent
definiton for
directed loop
graphs

From now on any directed graph is assumed to be a directed loop graph. Although most, if not all, concepts work for directed pseudographs just as well, we want to start to heavily use the canonical edge representation, which when talking about pseudograpgs makes problems as mentioned before.

For a pair of vertex sets $X, Y \subseteq V(G)$ of a directed graph G we write

$$(X, Y)_G = \{(x, y) \in E(G) \mid x \in X, y \in Y\}$$

for the set of edges with source in X and target in Y . Specifically we write $T(x) = (x, V(G))_G$ for the set of *targets* for edges originating from the vertex x and $S(x) := (V(G), x)_G$ for the set of *sources* for edges projecting to x .

Notation for
target and source
sets

Definition 2.4 (In- and out-degree). For a directed graph G the **in-degree** $d_G^-(x)$ of a vertex x is defined as the number of edges of G with target x , that is

$$d_G^-(x) = |S(x)|.$$

Similarly, the **out-degree** $d_G^+(x)$ of x is defined as

$$d_G^+(x) = |T(x)|,$$

the number of edges in G with source x .

A basic property of the in- and out-degree in directed graphs is that number of in-degrees of every vertex, as well the sum of every out-degree, equal the total number of edges:

Proposition 2.5. *In every directed graph G , we have*

$$\sum_{x \in V(G)} d^-(x) = \sum_{x \in V(G)} d^+(x) = |E(G)|.$$

Proof. Since $(V(G), x)_G \cap (V(G), y)_G = \emptyset$ for $x \neq y$, we can write

$$\sum_{x \in V(G)} d^-(x) = \left| \bigcup_{x \in V(G)} (V(G), x)_G \right| = |(V(G), V(G))_G| = |E(G)|.$$

Analogously for the out-degree. \square

2.2 NETWORK MEASURES

Let G be a (simple) directed graph. A **walk** W in G is an alternating sequence $(x_1, e_1, x_2, e_2, x_3, \dots, x_{n-1}, e_{n-1}, x_n)$ of vertices x_i and edges e_i from G , such that

$$s(e_i) = x_i \quad \text{and} \quad t(e_i) = x_{i+1}, \quad \text{for } i = 1, \dots, n-1,$$

that is, such that the vertices are connected by the edges inbetween them. We denote the set of vertices (x_1, \dots, x_n) of W as $V(W)$ and the sequence of edges (e_1, \dots, e_{n-1}) as $E(W)$.

The vertices x_1 and x_n are called the *end vertices* of W and we also say that W is an (x, y) -walk. The **length** of W is defined as the length of the sequence of edges; a walk consisting of only one vertex has length zero.

Definition 2.6 (Distance). The **distance** of two vertices x, y in a directed graph G , is defined as the minimum length of an (x, y) -walk, if any such walk exists, otherwise $\text{dist}(x, y) = \infty$. In short,

$$\text{dist}(x, y) = \inf\{|E(W)| \mid W \text{ is } (x, y)\text{-walk}\}.$$

Proposition 2.7. *The distance function $\text{dist} : V(G) \times V(G) \rightarrow \mathbb{N}$ of a directed graph G satisfies the triangle equality,*

$$\text{dist}(x, z) \leq \text{dist}(x, y) + \text{dist}(y, z), \quad \text{for } x, y, z \in V(G).$$

Proof. Let x, y, z be vertices in G . If either no (x, y) -walk or (y, z) -walk exists, the inequality holds by definition. Otherwise, let W be an (x, y) -walk of minimal length and let U be a (y, z) -walk of minimal length. Certainly, by concatenating W and U we obtain an (x, z) -walk of length $|E(W)| + |E(U)| = \text{dist}(x, y) + \text{dist}(y, z)$, proving that

$$\text{dist}(x, z) \leq \text{dist}(x, y) + \text{dist}(y, z). \quad \square$$

Note, however, that although the distance of two vertices displays a triangle inequality, it does not constitute a metric on a directed graph G as symmetry fails, in general

$$\text{dist}(x, y) \neq \text{dist}(y, x).$$

The average distance or average path length in a directed graph G measures how efficiently information can be transported in the network.

Definition 2.8 (Average path length). The *average path length* of a directed graph G with $V(G) = n$ is defined as

$$l = \frac{1}{n(n-1)} \sum_{x \neq y \in V(G)} \text{dist}(x, y).$$

In practice, vertex pairs with $\text{dist}(x, y) = \infty$, that is pairs that are not connected by a walk, are disregarded in the computation and the average path length is determined in the connected components of the graph, ensuring that l is finite.

The concept of a small-world property in graphs was introduced by [Watts and Strogatz \(1998\)](#). Networks associated with the property are characterized by a small average path length, while however most nodes are organized in “cliques”, connecting to nodes that are themselves neighbors. A measure capturing this property is the (local) clustering coefficient:

Definition 2.9 (Clustering coefficient). The *clustering coefficient* of a vertex x in a directed graph G is defined as ratio of realized and possible edges between the neighbors of x . If N_x is the neighborhood of all vertices reciprocally connected to x ,

$$N_x = \{v \mid v \in T(x) \wedge v \in S(x)\},$$

then the clustering coefficient is given by

$$\text{clust}(x) = \frac{|(N_x, N_x)_G|}{|N_x|(|N_x| - 1)}.$$

Small-worldness is then described by a low average path length and high clustering coefficient, usually considered as the mean of all vertices.

2.3 RANDOM GRAPH THEORY

*focus on labeled,
simple directed
graphs*

From this chapter on, as it is common and practical when talking about random graph models, we move away from the abstract notion of graphs and their equivalence classes and consider *labeled graphs*, where the vertex set of a graph with n vertices takes the form $V = \{1, \dots, n\}$. Simple directed graphs constitute the fundamental mathematical object underlying the concepts developed in this work and if not specified otherwise, all graphs are assumed to be labeled and simple directed.

The concept of a random graph was first formally introduced by Erdős and Rényi (1959) for undirected graphs. In their $G(n, N)$ model, an undirected graph with n vertices and N edges is randomly and with equal probability selected from the set of such possible graphs. In the same year Gilbert (1959) independently introduced his $G(n, p)$ model, realizing edges between vertex pairs with a fixed probability p . The two models are closely related (Luczak 1990) and overlap in literature, both at times being referred to as *Erdős-Rényi graphs*. Here we focus on the $G(n, p)$ model, as it is closer in concept to a computational implementation of a random graph. Defining it in detail in 2.10 for directed graphs, we will refer to the random graph model as the *Gilbert random graph model*.

In general, a random graph model is a probability space over a set of graphs (Janson et al. 2000). Rather than specifying the sample space and probability measure explicitly, random graph models are often defined by a random process that generates such graphs, leaving probability measure and sample space implicit (Bollobás 2001). The term *random graph*, in the graph theoretical context, refers to the random graph model itself. However, as it is common in many probabilistic concepts, a random graph often refers to a single graph generated by a random process. Here we try to avoid this ambiguity and strictly refer to the mathematical object as a random graph model.

Keeping in mind that the term *graph* now refers to labeled, simple directed graphs if not otherwise specified we define \mathcal{G}^n to be the set of simple directed graphs with n vertices,

$$\mathcal{G}^n := \{G \mid G \text{ graph}, |V(G)| = n\}.$$

We first introduce Gilbert's random graph model $G(n, p)$ by explicitly defining a probability space over \mathcal{G}^n and show later how the model may be realized as a random process.

Definition 2.10 (Gilbert random graph model). Let $n \in \mathbb{N}$ and $0 \leq p \leq 1$. The *Gilbert random graph model* $G(n, p)$ is a discrete probability space over \mathcal{G}^n with event space $\mathcal{P}(\mathcal{G}^n)$ and probability measure

P , such that every graph G with $|E(G)| = k$ edges appears with equal probability

$$P(G) = p^k(1-p)^{n(n-1)-k},$$

for $0 \leq k \leq n(n-1)$.

Remark. Clearly $G(n, p)$ is well-defined, as there exist $\binom{n(n-1)}{k}$ distinct labeled graphs with n vertices and k edges and thus

$$\sum_{G \in \mathcal{G}^n} P(G) = \sum_{k=0}^{n(n-1)} \binom{n(n-1)}{k} p^k (1-p)^{n(n-1)-k} = 1,$$

after the binomial theorem.

Equivalently, the Gilbert random graph model can be defined as a stochastic process; to an empty graph with n vertices, for each of the $n(n-1)$ vertex pairs an edge is added at random and independently with probability p . The probability to obtain a specific graph G with k edges is then obviously $p^k(1-p)^{n(n-1)-k}$, already proving the equivalence, since assuming a process as above with edge probability p' such that the induced probability measure on \mathcal{G}^n equals P from 2.10, already yields $p = p'$ in the choice of $n = 2$ and $k = 1$.

equivalent
definition as
random process

Proposition 2.11. *In- and out-degree distribution of vertices in the Gilbert random graph model are binomial.*

Proof. Let X be a random variable on the random graph model, mapping to the in-degree (out-degree) $d_G(v)$ of a vertex v of a graph $G \in \mathcal{G}^n$. There are $n-1$ other vertices that, with probability p , project to v (receive input from v), thus

$$P(X = k) = \binom{n-1}{k} p^k (1-p)^{n-1-k},$$

showing that $P^X = \mathcal{B}_{n-1,p}$. □

The Gilbert random graph model is therefore also often referred to as *binomial random graph*. As typical neuronal networks are large ($n \geq 10^3$) with sparse connectivity ($p \approx 0.1$), in- and out-degree distribution can be approximated by a Poisson distribution, $P^X(k) \approx \text{Pois}_\lambda(k)$, with $\lambda = (n-1)p$, after the Poisson limit theorem.

Most results in the study of random graph models consider $n \rightarrow \infty$. In this study we are mostly interested in patterns of connectivity that arise in local circuits, leaving behind limit considerations and employ the Gilbert random graph model as a reference for the development of more detailed and specific random graph models.

2.4 GEOMETRIC GRAPHS

The theory of geometric graphs addresses the embedding of graphs in \mathbb{R}^d . Planar graphs are graphs that can be drawn on a surface with their edges drawn as straight lines between the vertices, such that no two lines intersect (Diestel 2000). Here we are interested in graphs embedded on surfaces. In the models introduced, connectivity then depends on geometric properties, such as distance between nodes or relative orientation between vertices. The basic graph type to allow for such connectivity rules is a geometric graph.

Definition 2.12 (Geometric directed graph). A *geometric directed graph* G_Φ is a directed graph G paired with a map

$$\Phi : V(G) \rightarrow [0, 1]^2,$$

representing vertex positions on the unit square.

This definition diverges from the usual notion of a geometric graph, which determines the existence of edges only between nodes within a spatial distance x in a specified norm (Penrose 2003). Moreover, geometric graphs are usually only discussed in the context of random graph models, a concept first introduced by Gilbert (1961). Denote the set of geometric graphs with n edges by \mathcal{G}_Φ^n . The spatial embedding of geometric graphs allows us to define (random) connectivity depending on vertex positions and inter-vertex distances. Central to this study is the distance-dependent random graph model, in which edges are added with probability $p(x)$ depending on the distance x between vertex pairs:

Definition 2.13 (Distance-dependent random graph model). Let $n \in \mathbb{N}$ and $C : [0, \sqrt{2}] \rightarrow [0, 1]$ a continuous map. A *distance-dependent geometric random graph model* $G_\Phi(n, C)$ is a random graph model over \mathcal{G}_Φ^n , generated by distributing uniformly at random the n vertices on the unit square and adding an edge from v to w for each vertex pair $(v, w) \in V(G_\Phi)^2 \setminus \Delta_{V(G_\Phi)}$ with a probability $C(x)$, depending on the distance $x = \|\Phi(v) - \Phi(w)\|$ between the vertices.

We call the function C the graph's *distance-dependent connection probability profile*. Note that the connection profile is *not* a probability density but gives a probability of connection between a vertex pair at distance x . Clearly, connectivity statistics in the distance-dependent graph model intrinsically depend on the profile C . To develop a thorough understanding of connectivity in the model however, mapping the distribution of inter-vertex distances is equally important. Here we calculate the distribution of the distance between two random points in

a square of side-length s . Being able to identify distributions of transformed random variables is integral to the calculation:

Lemma 2.14. *Let X, Y be independent continuous random variables with values in \mathbb{R} , denote with f_X and f_Y their probability distribution functions.*

- (1) *The distribution of the random variable $X + Y$ is given by the probability density function*

$$f_{X+Y}(x) = \int_{\mathbb{R}} f_X(z) f_Y(z-x) dz.$$

- (2) *The distribution of the random variable X^2 is given by the probability density function*

$$f_{X^2}(x) = \begin{cases} \frac{1}{2\sqrt{x}} (f_X(\sqrt{x}) + f_X(-\sqrt{x})) & x > 0 \\ 0 & x \leq 0 \end{cases}$$

- (3) *Let X only take positive values. Then the distribution of the random variable \sqrt{X} is given by the probability density function*

$$f_{\sqrt{X}}(x) = \begin{cases} 2x f_X(x^2) & x \geq 0 \\ 0 & x < 0 \end{cases}$$

Proof. These are well known identities. Distributions in (2) and (3) are easily verified by first considering the cumulative distribution function and subsequent derivation. \square

Theorem 2.15. *Let D be a random variable mapping to the distance of two random points in the square $[0, s]^2$ of side-length s . Then the distribution of D is given by the probability density function*

$$f(x) = \begin{cases} \frac{2x^4 - 8sx^3 + 2\pi s^2 x}{s^4} & x \in [0, s] \\ \frac{H(x)}{s^4} & x \in [s, s\sqrt{2}), \\ 0 & x \notin [0, s\sqrt{2}) \end{cases} \quad (2.1)$$

where

$$H(x) = 8sx\sqrt{x^2 - s^2} - 2x^3 - 4s^2x \left(1 + \arcsin \left(1 - \frac{2s^2}{x^2} \right) \right).$$

Proof. We follow the approach described by Moltchanov (2012). Consider two independently and uniformly distributed random points $p_1 = (x_1, y_1)$ and $p_2 = (x_2, y_2)$ in $[0, s]^2$. The distance between p_1 and p_2 is given as

$$\|p_1 - p_2\| = \sqrt{(x_1 - x_2)^2 + (y_1 - y_2)^2}.$$

As a first step we calculate the distribution for $\Delta_x = x_1 - x_2$. Denote with f_{Δ_x} its probability density. Then, since $f_{-x_2}(z) = f_{x_2}(-z)$,

$$f_{\Delta_x}(d) = f_{x_1+(-x_2)}(d) = \int_{\mathbb{R}} f_{x_1}(z) f_{x_2}(z-d) dz \quad (2.2)$$

after Lemma 2.14. Density functions for x_1 and x_2 are given by

$$f_{x_1}(z) = f_{x_2}(z) = \begin{cases} \frac{1}{s} & \text{for } z \in [0, s] \\ 0 & \text{otherwise.} \end{cases}$$

Thus we may only obtain non-zero values in (2.2) for $d \in (-s, s]$, as otherwise either one of the factors in the integrand is zero. In full we obtain the triangular distribution (Simpson 1755),

$$f_{\Delta_x}(d) = \begin{cases} 0 & d \notin (-s, s] \\ \frac{s+d}{s^2} & d \in (-s, 0] \\ \frac{s-d}{s^2} & d \in (0, s]. \end{cases}$$

Next we calculate the distribution for $\Delta_x^2 = (x_1 - x_2)^2$. Using Lemma 2.14 once again we obtain for $d > 0$

$$\begin{aligned} f_{\Delta_x^2}(d) &= \frac{1}{2\sqrt{d}} \left(f_{\Delta_x}(\sqrt{d}) + f_{\Delta_x}(-\sqrt{d}) \right) \\ &= \frac{1}{2\sqrt{d}} \left(\frac{s-\sqrt{d}}{s^2} + \frac{s+\sqrt{d}}{s^2} \right) = \frac{1}{s\sqrt{d}} - \frac{1}{s^2}, \end{aligned}$$

and $f_{\Delta_x^2}(d) = 0$ for $d \leq 0$. Note that of course, $f_{\Delta_x^2} = f_{\Delta_y^2}$ and we will refer to this density function as f_{Δ}^2 . Convolution yields again the probability density function for the sum of the random variables Δ_x^2 and Δ_y^2 ,

$$f_{\Delta_x^2 + \Delta_y^2}(d) = \int_{\mathbb{R}} f_{\Delta^2}(z) f_{\Delta^2}(d-z) dz.$$

Finally Lemma 2.14 lets us compute

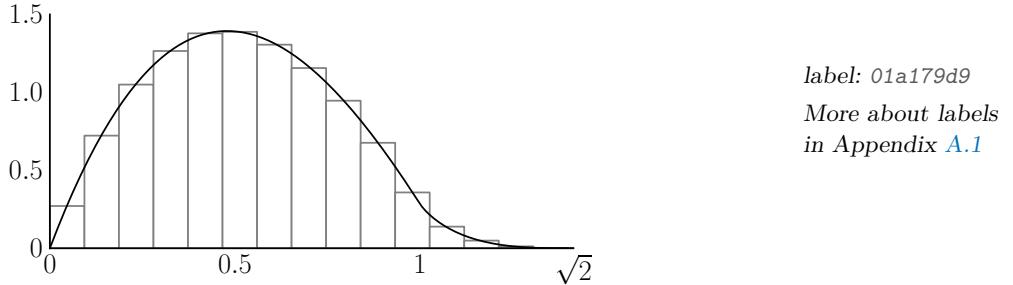
$$f_D(d) = f_{\sqrt{\Delta_x^2 + \Delta_y^2}}(d) = 2d f_{\Delta_x^2 + \Delta_y^2}(d^2),$$

for $d \geq 0$, yielding expression (2.1) for probability density function of D (Mathematica A.1). \square

The distribution for the distance between two random points in the unit square $[0, 1]^2$, is then obtained from (2.1) by setting $s = 1$. The probability density function f becomes

$$f(x) = \begin{cases} 2x^3 - 8x^2 + 2\pi x & x \in [0, 1) \\ 8x\sqrt{x^2 - 1} - 2x^3 & x \in [1, \sqrt{2}) \\ -4x - 4x \arcsin\left(1 - \frac{2}{x^2}\right) & x \in [\sqrt{2}, 1] \end{cases} \quad (2.3)$$

Plotting f in combination with the results of a numerical simulation (10000 points randomly distributed on unit square, extracted distances binned to a of width $\sqrt{2}/15$) verifies our calculation:



Density functions 2.1 and 2.3 are of high importance. Here we use 2.3 to compute the probability that a random pair of vertices in the distance-dependent random graph model is connected:

Corollary 2.16. *Let $v \neq w$ be vertices in an arbitrary realization of $G_\Phi(n, C)$. The probability p for an edge from v to w is given by*

$$p = \int_0^{\sqrt{2}} C(x) f(x) dx,$$

where $f(x)$ is the probability density function (2.3).

Example Let $C(x) = 1 - \frac{x}{\sqrt{2}}$. Then we compute the probability to find an edge between a random vertex pair in $G_\Phi(n, C)$ according to Theorem 2.16 as

$$p = \int_0^{\sqrt{2}} f(x) dx - \frac{1}{\sqrt{2}} \int_0^{\sqrt{2}} x f_D(x) dx = 1 - \frac{1}{\sqrt{2}} \mathbf{E}[D].$$

The expected distance between two random points on the unit square is computed as $\mathbf{E}[D] \approx 0.521405$ ([Mathematica A.1](#)), a result confirmed by [Philip \(2007\)](#). Thus we obtain the probability for connection of $p \approx 0.631311$

3

NETWORK MODEL

Motivated by anisotropic characteristics in connectivity in local cortical circuits found in the rat’s brain, a network model with anisotropic tissue geometry is developed. Employing both a graph theoretic definition and a numerical implementation, distance-dependent connectivity present in the model is exposed. The introduction of a rewiring algorithm and quantitative anisotropy measure lays the foundation for the analysis of structural aspects of the anisotropic network model in Chapter 4.

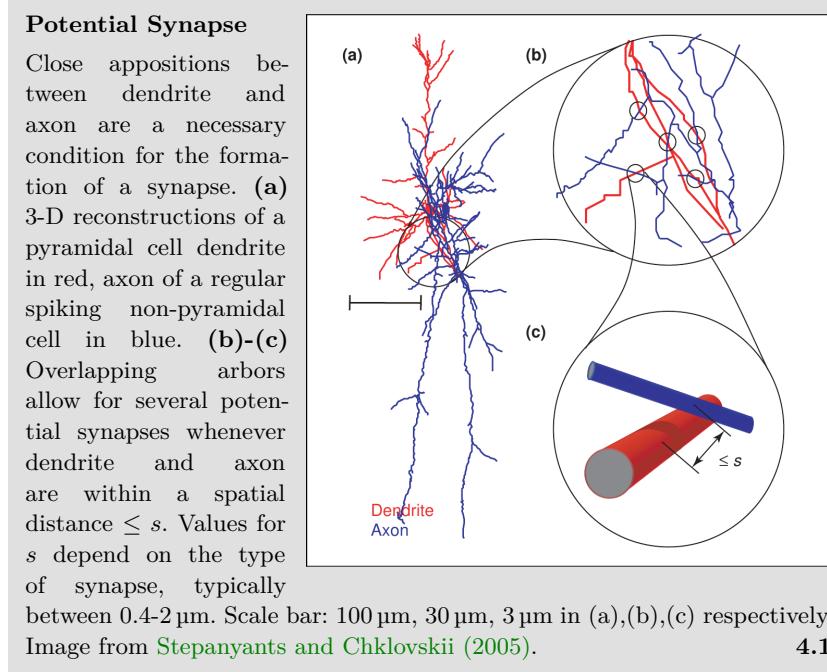
3.1 OVERVIEW

This chapter introduces the central object of this study, the *anisotropic network model*. Reviewing connectivity in local cortical circuits in Section 3.2, we identify anisotropy in connectivity in layer V pyramidal cells, inferred by their specific neuronal anatomy. Reducing the complex neuron morphology to characteristic axonal and dendritic profiles, we introduce the anisotropic network model in Section 3.3. While a graph theoretic definition allows for analytical considerations, a numerical implementation enables us not only to support the analytical observations but also gives access to results that go beyond. To fully harness this implementation we argue for the choice of a specific parameter set in Section 3.4, allowing us to generate a set of “sample graphs” to which we will refer through this study.

Using the analytical and numerical approach in conjunction, in our analysis of anisotropic networks we are most interested in identifying structural aspects that are due to the network’s anisotropy in connectivity and do not occur in similar, isotropic networks. To be able to make this distinction, in Section 3.5 we extract the distance-dependent connectivity of anisotropic networks, as it is imposed by the specific geometric relations present in the network. We then go on to introduce “rewiring” in Section 3.6, a method that allows us to manipulate the anisotropic networks to eventually display isotropy in connectivity. Finally then, Section 3.7 ties together the previous concepts by providing a measure for anisotropy and showing how rewiring is, in fact, providing the transition from anisotropic networks to networks with isotropy in connectivity.

3.2 ANISOTROPY IN NEURAL CONNECTIVITY

Neurogeometry addresses the problem of inferring synaptic connectivity from the geometric shapes of axon and dendrites. A fundamental concept in this field is that of a *potential synapse* (Stepanyants et al. 2002). Defined as the potential axonal-dendritic connection of two neurons, present whenever the axon of one neuron is within a spatial distance s of the dendrite of the other, it is a necessary, although not sufficient, condition for the formation of a synaptic connection (Figure 3.1). The existence of such close appositions solely depends on dendritic and axonal anatomy; identification of defining morphological characteristics in both axon and dendrite would therefore allow for a model of local network connectivity, assuming for example that a certain ratio r of potential synapses turn into active contacts independently. It is the hope that such a model, motivated from the geometry of a neuron's functional compartments, not only displays inherent patterns of connectivity similar to what has been observed in biological networks, but also proves itself as a testing ground for how this connectivity may affect network dynamics.



high variability in axonal morphology

Finding stereotypical anatomical characteristics however is difficult, as axonal morphology is, in general, highly diverse (Debanne 2004). Across different species, distinct regions in the central nervous system and different neuron types, axons display a wide variety of shapes characterized by morphometric parameters such as total length, branching complexity and axonal extent (Ropireddy et al. 2011). Typical exam-

ples of distinct morphology include the T-shaped axons of cerebellar granule cells branching only at a singular point (Ramon and Cajal 1911), and axons of hippocampal CA3 pyramidal cells, which, in stark contrast, may feature up to 40 branches resulting in a total length of axon collaterals of up to 12 mm (Ishizuka et al. 1990).

It is therefore imperative to confine this analysis to a specific brain region and neuron type. In this study, we set the focus on circuits of pyramidal cells in the mammalian cortex. More specifically, local circuits of thick tufted layer 5 pyramidal neurons in the rat's somatosensory cortex have been the target of advanced experimentation (Song et al. 2005; Perin et al. 2011; Romand et al. 2011; Ramaswamy et al. 2012), and will serve as a benchmark for results in neural morphology and network connectivity in this report.

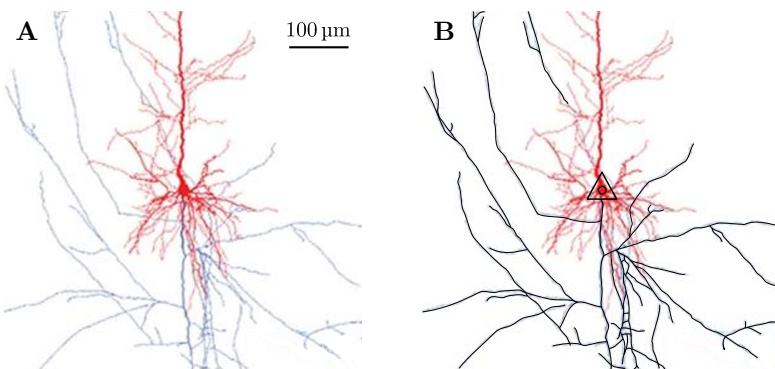


Figure 3.2: Tracing axonal branching of a pyramidal cell In a 3-D model reconstructed from biocytin-labeled thick-tufted layer 5 pyramidal cells in the somatosensory cortex of postnatal (day 14) Wistar rats, Romand et al. (2011) depict dendritic compartments in red, axonal compartments in blue. **A)** A 600 μm window centered on the soma of the pyramidal cell shows the main stem of the cell's axon projecting downwards in a straight line, collaterals branching at various angles. **B)** Using image manipulation software, axon morphology was manually traced and is emphasized in black.

Axonal morphology of pyramidal cells in the cerebral cortex is well described. From the soma the single main stem of the axon originates and projects downwards, describing a trajectory closely resembling a straight line (Braitenberg and Schüz 1998). At arbitrary points along this path, collaterals branch off at various angles and constitute themselves linear paths until they further ramify or terminate. Displaying a high degree of ramification, axonal trees of cortical pyramidal cells build, in general, complex structures (Petersen et al. 2003; Ramaswamy et al. 2012). Cortical slice experiments analyzing neural anatomy are typically constrained by a slice thickness of 300 μm . On this scale, 3-D reconstruction from labeled thick tufted layer 5 pyramidal cells reveals

cortical axons
form straight lines,
arborize profusely

characteristic morphology of the axonal tree (Figure 3.2). The downwards projecting, straight axon branches at several points, forming collateral branches that travel in linear path as well.

In a statistical view, this characteristic axonal morphology results in high axon branch densities along the main stem, whereas distant regions display a relatively low density (Figure 3.3). Specifically, axon collaterals do not cluster around the soma but align with the main stem's projection. As presence of an axonal branch constitutes a necessary condition for a potential synapse, a higher concentration of potential and, subsequently, realized synapses is expected in regions of high branch density. For a coherent picture of local connectivity profiles, however, dendritic morphology needs to be considered as well.

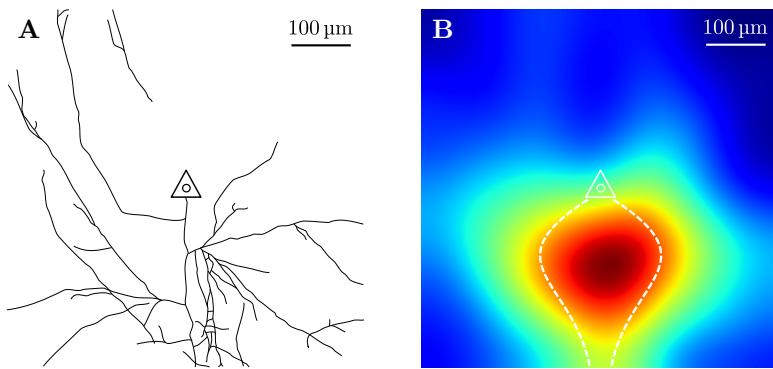


Figure 3.3: Illustrating axonal branch density In a sample of 5 reconstructions from thick-tufted layer 5 pyramidal cells (Romand et al. 2011), tracing axonal morphology illustrates characteristic branch density along the axon's main stem. **A)** Example of extracted axonal tree. Outline manually traced using image manipulation software. Soma indicated by triangle. Original data from Romand et al. (2011). **B)** Overlaying 5 axonal trees extracted as in A), applying a Gaussian filter and displaying high axon densities in warm colors, illustrates the characteristic higher branch densities along the axon's main stem.

basal dendrites dominate local connectivity

Dendritic anatomy of cortical pyramidal cells is inherently bipartite. From the soma several *basal dendrites* emerge and extend into arbitrary directions, branching profusely until they terminate. The single *apical dendrite* emerges from the apex of the pyramidal cell and ascends in a linear trajectory, forming occasional collateral branches until finally terminating into the apical tuft, where the dendrite branches several times to form a tree like structure (Feldman 1984). On the scale of typical cortical slice thickness, however, the apical dendrite is cut off and the basal dendrite dominates the dendritic morphology and potential of dendritic-axonal connections (Figure 3.4). The radial extension of dendritic branches results in a high concentration of dendritic branches

around the soma, much in the contrast to the findings of axonal branch densities before.

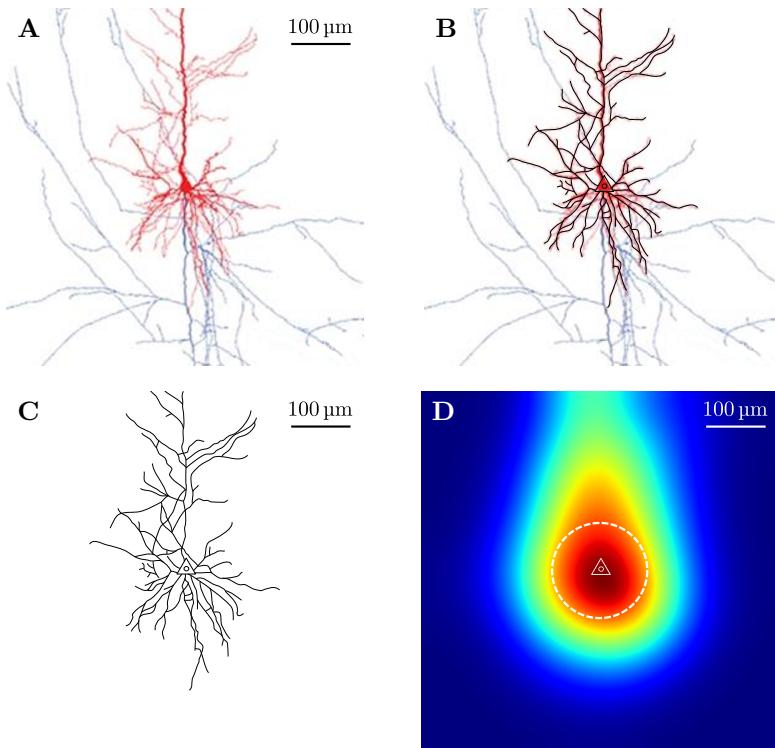


Figure 3.4: Dendritic morphology and branch density Using neuronal morphology of thick-tufted layer 5 pyramidal cells recorded by Romand et al. (2011), dendritic anatomy is traced and combined to illustrate high branch density around the soma. **A)** In a 600 μm window centered on the soma, basal dendrites (red) are visible extending around the soma. The ascending thick apical dendrite (red) is cut off and apical tuft is not shown. **B)-C)** Manual tracing of dendritic outlines in five samples (one shown), allows for clearer identification of stereotypical morphology and later analysis. **D)** Combining 5 dendritic outlines as shown in C) and subsequent Gaussian filtering reveals the relatively high dendritic branch density around the soma.

Combining the above results of dendritic and axonal branch densities in the light of neurogeometry, a clear concept of anisotropy of neural connectivity emerges. As dendritic branches of potential post-synaptic targets extend radially from the soma and do not display a preferred direction, target neurons for outgoing synaptic contacts originating from a single pyramidal cell, cluster around the downwards projecting axon (Figure 3.5). In their in-depth study, Stepanyants and Chklovskii (2005) confirm the overrepresentation of potential synapses along the axon for pyramidal cells. Consistent with the notion that stereotypical morphology of pyramidal cells is intrinsic to the local network's connectivity

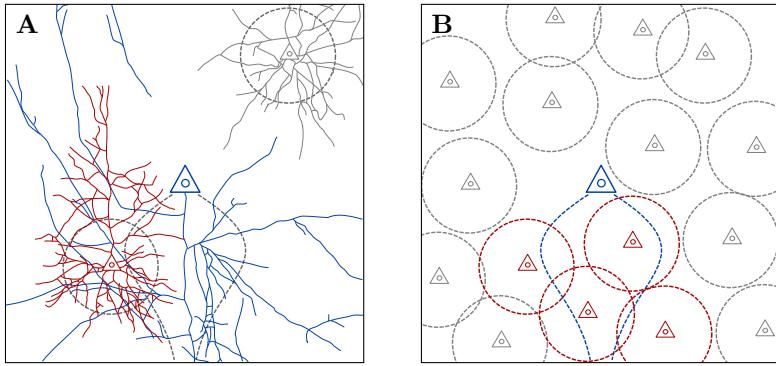


Figure 3.5: Connected neurons of a single pyramidal cell align with axonal projection Reducing the full axonal (blue, cf. Figure 3.2) and dendritic trees (red, gray, cf. Figure 3.4) as shown for two neurons in A) to their stereotypical axonal (blue) and dendritic profiles (red, gray) in B), demonstrates how connected neurons (red) tend to cluster around the pre-synaptic axon's profile, as spatial closeness constitutes a necessary condition for the formation of contacts. Unconnected neurons (gray) are found distant from the axon's projection, but not necessarily distant from the soma.

profile, they also find that anisotropy of this degree is *not* present in spiny stellate neurons located in lower-layer-4.

3.3 ANISOTROPIC GEOMETRIC NETWORK MODEL

Taking up the concept of anisotropy in neural connectivity introduced in the last section, we propose here, as basis for this study, a simple geometric network model featuring anisotropic connectivity. Constructing such a model, we're challenged with resembling the anisotropic aspects outlined in the last section as closely as possible, while at the same time basing the model on simple and abstract relations to allow for an analytical study of such anisotropic networks.

With this in mind, we propose the following model: On a square surface of side length s , a number of N point neurons are randomly, uniformly distributed. Connected neighbors are then calculated for each neuron separately and independently, by determining the randomly, uniformly distributed direction of the neuron's single axon. In this direction the axon traverses over the surface describing a straight path, terminating only when an edge of the surface is reached. Directed contacts are made with every neuron that is within a width $w(x)$ of the axon's trajectory, where in general w depends on the axon length x at this point (Figure 3.6).

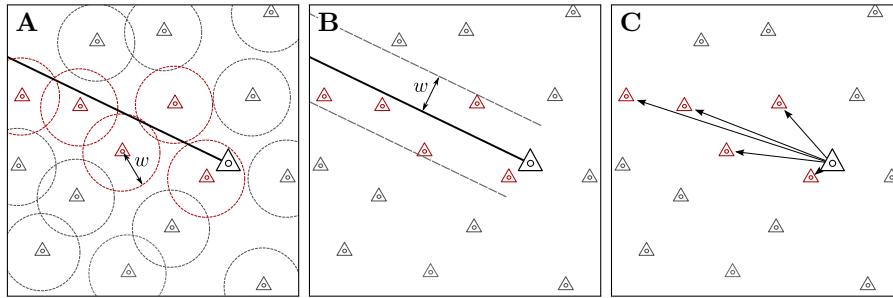


Figure 3.6: Anisotropic geometric network model and interpretations of width parameter w Illustrating the process of finding connections for one neuron (large triangle, black), the axon describes a linear trajectory in an arbitrary direction and until terminating on the surface's edge. Target neurons (red) are encountered along the path within a (here constant) distance w , which is in **A**) interpreted as a dendritic radius or, equivalently, in **B**) as a “bandwidth” of the axon. Connections to the encountered targets are then established as projections in **C**), consistent with the directed nature of synapses in biological networks (cf. Section 1.2).

The implementation of arbitrary axonal orientation is crucial to the model. Although cortical axons are described as consistently projecting downwards (Braitenberg and Schüz 1998, cf. Section 3.2), combining exclusively vertically aligned axons with the simplified axonal and dendritic morphological profiles would result in a “vertically staggered

random axonal orientation yields relevant connectivity

connectivity” - neurons could then only project to targets located below them. It is in fact not a vertical alignment of axon orientation, but the anisotropy in neural connectivity - the observation of neuronal targets aligning with the axonal projection - that we try to capture and analyze in this model.

We will refer to the model as the *anisotropic geometric network model*. Trying to provide a simple, abstract model isolating anisotropy in connectivity, in most of this study the width $w(x)$ is assumed to be constant, $w(x) = w$, a notable exception being the development of tuned networks in Section 4.5. In the graph theoretic context the anisotropic network model is a random graph model, in which a realization of the random process results in a geometric directed graph with a special mode of connectivity. We can formally define such realization as:

Definition 3.1 (Anisotropic geometric graph). Let $n \in \mathbb{N}$ and $w \in (0, \infty)$. An *anisotropic geometric graph* $G_{n,w}$ then consists of a tuple (G, Φ, a) , of a simple directed graph G with $|V(G)| = n$ vertices and the maps $\Phi : V(G) \rightarrow [0, 1]^2$ and $a : V(G) \rightarrow [0, 2\pi)$, such that for every vertex pair $v, v' \in V(G)$ and edge $e \in E(G)$ with $s(e) = v$ and $t(e) = v'$ exists if and only if the inequalities for scalar products

$$R_{-a(v)} (\Phi(v') - \Phi(v)) \hat{e}_x \geq 0 \quad \text{and} \quad \left| R_{-a(v)} (\Phi(v') - \Phi(v)) \hat{e}_y \right| \leq \frac{w}{2}$$

hold. Here R_φ is the rotation matrix of angle φ in the Cartesian plane and \hat{e}_x, \hat{e}_y are the standard unit vectors.

The anisotropic random graph model then is then giving the probability distribution over the set of anisotropic random graphs by describing a random process generating such graph.

Definition 3.2 (Anisotropic random graph model). Let $n \in \mathbb{N}$ and $w > 0$. The *anisotropic random graph model* $G(n, w)$ is a probability space over the set of anisotropic geometric graphs with a probability distribution induced by the following process: Let G be an empty graph with n vertices. Assign randomly and uniformly to every vertex $v \in V(G)$ a position $\Phi(v) \in [0, 1]^2$ and axonal orientation $0 \leq a(v) < 2\pi$. Then add edges such that (G, Φ, a) is an anisotropic geometric graph $G_{n,w}$.

*anisotropic model
independent of
scaling*

As with every geometric graph model introduced, we restrict the surface to be the unit square. This does not limit the model, as only the relative width of the axon band in regard to the surface’s side length is determining connectivity statistics - the expected number of connections is easily obtained by the quotient of the area covered by the axon and the surface area, making connectivity statistics in the anisotropic random graph model essentially “scale-free”.

The following maybe interpreted as a study of anisotropic geometric graphs in the light of a neuroscientific context. To enable such an analysis, a few more concepts are needed. The introduction of those concepts composes the rest of the chapter. A first important step is the numerical implementation of the anisotropic network model.

3.4 NUMERICAL IMPLEMENTATION

Numerical implementation of the anisotropic random graph model was achieved in Python¹. Relying on NumPy as part of the scientific Python library SciPy² for the more complex mathematical computations, the implementation also uses graph-tool³, to ensure convenient and efficient handling of the created networks.

The algorithm for the generation of anisotropic networks closely resembles Definition 3.1. After randomly distributing N neurons on the square of side-length s , for every neuron a random axon orientation $a \in [0, 2\pi)$ is chosen and an affine transformation, such that the current neuron is located at the origin and its axon projection aligns with the positive x-axis, secures a straightforward implementation of connectivity, using the the inequalities in Definition 3.1 as a rule for establishing connections.

To harness the numerical implemenation to generate networks, a set of parameters needs to be chosen. The network size N strongly influences the needed computational efforts in calculations based on the generated graphs and has thus been set to $N = 1000$. Choosing the surface side-length arbitrarily as $s = 100$, the axon width w determines connectivity in the network, the relation between width w and overall connection probability p being shown in Figure 3.7. In their analysis of connectivity of thick-tufted layer 5 pyramidal cells in neonatal rats (day 14), Song et al. (2005) report an overall connection probability of $p = 0.116$, consistent with prior reports of a cortical connection probability of $p \approx 0.1$. Choosing w to be constant, we determine the axon width such that overall connectivity matches the value report by Song et al. and obtain $w/2 = 12.6$ (Figure 3.7).

*parameter set
chosen to resemble
cortical circuits*

¹ Python Software Foundation. Python Language Reference, version 2.7. Available at <http://www.python.org>

² Eric Jones, Travis Oliphant, Pearu Peterson and others. NumPy version 1.6.1. Available at <http://www.scipy.org>

³ Tiago P. Peixoto. Efficient network analysis. Version 2.2.18. Available at <http://graph-tool.skewed.de/>

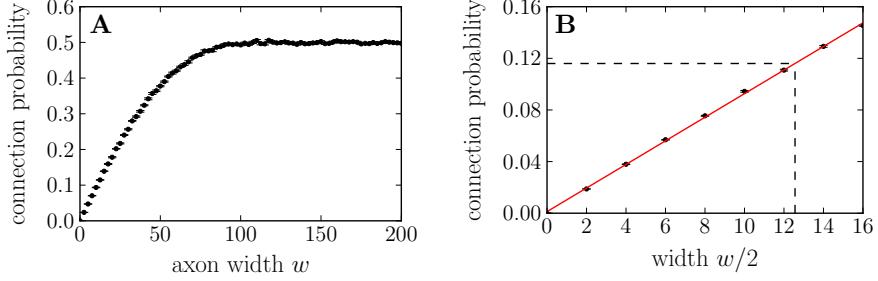


Figure 3.7: Axon width dependent connection probability determines parameter for numerical analysis Generating anisotropic networks with different axon widths w and extracting probability p of directed connection between two random nodes, demonstrates the dependency of p on the width parameter w . **A)** At an axon width of over $w = 100$, exceeding the square's side length, the connection probability saturates at $p = 0.5$, as axon bands are essentially “cutting” the square in a connected and unconnected half (c5b64f3e). **B)** For small w the connection probability is a linear function of w , allowing the width $w_S/2$ at which $p(w_S) = 0.116$ to be determined by a linear fit as $w_S/2 = 12.6$ (585a946f).

sample graphs as
reference for
structural analysis

Having determined a suitable set of parameters as $N = 1000$, $s = 100$ and $w = 25.2$, we generate 25 graphs with this parameter set⁴. This collection of sample graphs will serve as a reference for the following structural analysis. Extending the set by the (partially) rewired sample graphs (see Section 3.6) and by purely distance-dependent graphs best resembling the anisotropic networks (see Section 3.5) we obtain a resourceful reference for the analysis of structural features of anisotropic geometric graphs, that we will frequently employ to obtain quantitative and qualitative results in the structural analysis of anisotropic networks.

⁴ label: N1000w_ax126-flat_graph0-24

3.5 DISTANCE-DEPENDENT CONNECTIVITY

In Gilbert's random graph model $G(n, p)$, probability of connection p is independently chosen and a fixed value for all vertex pairs. The anisotropic geometric random graph model introduced in Section 3.3 is itself a random graph model - node positions as well as preferred directions of connection are uniformly at random distributed. In contrast to Gilbert's model however, neither is the probability of connection between a given vertex pair independent of the realization of other edges in the graph, nor is it a fixed value - probabilities strongly depend on internode distance in the anisotropic geometric graph model introduced.

random graph models in Section 2.3

Analyzing dependencies in the anisotropic model, specifically by identifying prevalent patterns of connectivity and relating these modes of non-randomness to biological findings, is the main focus of Chapter 4. However, such structural correlations may not necessarily be an inherent feature of the network's anisotropy - distance dependent connectivity alone, as imposed by the model's specific geometry, may be the cause for emerging dependencies. It is therefore a crucial initial task to map the anisotropic model's distance dependent connection probability. Inferring connection probability as a function of internode distance and comparing it with computational results, in this section we explore distance connectivity of the anisotropic network model, securing a vital component in the analysis of structural features.

Theorem 3.3. *Let $G_{n,w} = (G, \Phi, a)$ be an anisotropic random graph. Define $C : [0, \sqrt{2}] \rightarrow [0, 1]$ as the distance-dependent connection probability profile of (G, Φ) , that is such that $C(x)$ is the probability that for a vertex pair $(v, v') \in V(G)^2 \setminus \Delta_{V(G)}$ in distance $x = \|\Phi(v) - \Phi(v')\|$ the vertex v projects to vertex v' . Then*

$$C(x) = \begin{cases} \frac{1}{2} & \text{for } x \leq w/2 \\ \frac{1}{\pi} \arcsin\left(\frac{w}{2x}\right) & \text{for } x > w/2. \end{cases}$$

Proof. Let v, v' be a pair of vertices in $V(G)^2 \setminus \Delta_{V(G)}$ in Euclidean distance x of each other. The vector difference $\Phi(v') - \Phi(v)$ may then be written as $xe^{i\theta}$, with $0 \leq \theta < 2\pi$. We have

$$R_{-\alpha(v)} xe^{i\theta} = xe^{i(\theta - \alpha(v))}.$$

Only for suitable combination of θ and $\alpha(v)$ an edge from v to v' exists. Assuming $\alpha(v)$ fixed, we calculate the probability of connection depending on the random choice of θ . We can assume $\alpha(v) = 0$, otherwise the same argument holds for $\theta' = \theta - \alpha(v)$.

From 3.1 we obtain the necessary and sufficient conditions

$$x \cos \theta \geq 0 \quad \text{and} \quad |x \sin \theta| \leq \frac{w}{2}.$$

Choosing uniformly at random θ in the range of $[0, 2\pi)$, the first condition is satisfied with a probability of $\frac{1}{2}$. Consider for the second condition $\theta \in [0, \pi)$. We have

$$\sin \theta \leq \frac{w}{2x},$$

and for $x \leq \frac{w}{2}$ the inequality holds for all θ by definition of $\sin \theta$. In the case of $x > \frac{w}{2}$, we note that for the first condition to hold θ must already be in $[0, \frac{\pi}{2})$ and can thus write the second condition θ as

$$\theta \leq \arcsin \frac{w}{2x},$$

yielding $C(x)$ by combining the considerations above and using the symmetry of sine for θ in the third and fourth quadrant. \square

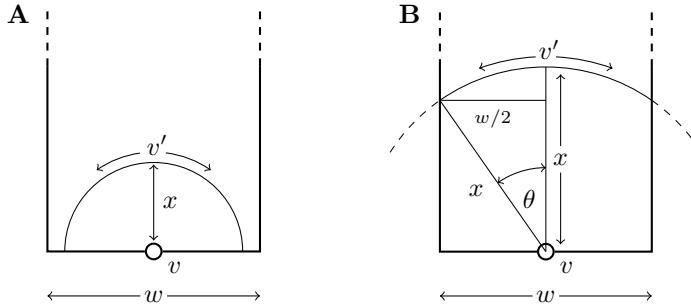


Figure 3.8: Illustrating the proof of Theorem 3.3 Distance-dependent connectivity profile $C(x)$ in an anisotropic geometric graph calculated from geometric dependencies. **A)** In the case of $x \leq w/2$, target v' may be located anywhere on the shown semicircle and therefore receives input from v with probability $1/2$. **B)** For $x > w/2$, suitable positions for target v' are dependent on x . The geometric relation $\sin \theta = w/2x$ leads to the distance-dependent connectivity profile as described in Theorem 3.3.

distance-dependent sample graphs as reference

We can verify this result by extracting the distance-dependent connection probabilities in the sample graphs created in Section 3.4. Combining data of all 25 graphs, we find that connection probabilities perfectly match the theoretical prediction (Figure 3.9). Additionally we're able to extend the reference sample graphs by distance-dependent networks (Definition 2.13). Using Theorem 3.3 in conjunction with the sample graph parameter set ($N = 1000$, $s = 100^5$, $w = 25.2$) we easily obtain the expected distance-dependent connectivity profile for the

⁵ The generalization of Theorem 3.3 to allow for arbitrary side-length s is trivial and omitted here

created sample graphs and, using this profile, generate purely distance-dependent networks⁶. Being highly interested in structural features not explained by distance-dependent connectivity, the numerical analysis in this work will heavily rely on these networks to identify aspects that are inherent to the anisotropy in connectivity.

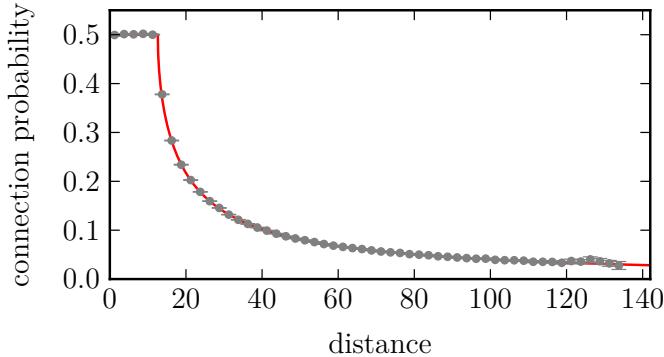


Figure 3.9: Predicted distance-dependent connection probability profile is matched by numerical results Averaging distance-dependent connection probabilities over the 25 sample graphs, we find the expected profile calculated in Theorem 3.3 is matched perfectly by the numerical results. (dbffa88e)

More about labels
in Appendix A.1

3.6 REWIRING

Distance-dependency as identified in the last section may already account for many of the structural features present in anisotropic networks. A central question of this study is: What structural aspects in the network are truly features of the anisotropy in connectivity? Although a quantitative measure for anisotropy will only be introduced in the next section, already here we are able to qualitatively observe the strong directionality in connectivity - edges originating from one node “point in the same direction”, effectively aligning with the orientation of the axonal projection of the source node (cf. Figure 3.6). To answer the question above, we need to introduce a method that eliminates this directionality, making networks essentially isotropic in connectivity. Then, structural features present in the original anisotropic networks, but not in their rewired, isotropic counterparts may be attributed to anisotropy.

eliminate
anisotropy to
identify affected
structural features

Rewiring as introduced here, provides the transition from anisotropic connectivity to networks isotropic in connectivity, closely resembling purely distance-dependent networks. Applying this process only partially then allows us to analyse structural features as they change with

⁶ label: N1000-dist_depend-flat_graph-00-24.xml.gz

a varying degree of isotropy, asserting the importance of this process to our study. In designing the specific rewiring algorithm we identify two requirements that our implementation should satisfy:

1. elimination of anisotropy in connectivity
2. preservation of distance-dependent connectivity

The second point is especially important to us, as we want to impose isotropy on the network at “minimal cost”, that is by changing as little as possible about the other characteristics of the network’s connectivity. The following process respects both of the points above:

For every edge between vertices v and v' with inter-vertex distance x , identify neurons with distance to v in the range of $(x - \varepsilon, x + \varepsilon)$ as potential new targets. Then pick at random one of these vertices (including v') as a new target for the current edge, if such an edge doesn’t already exist ([Figure 3.10](#)).

In the graph theoretic context we formally define a rewiring as follows:

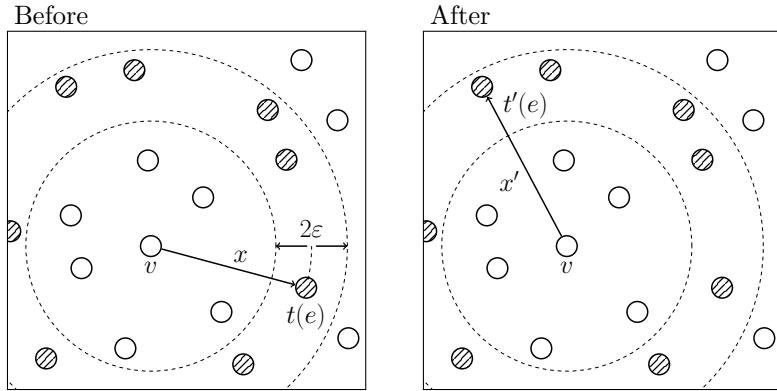


Figure 3.10: Rewiring transforms anisotropic geometric graphs to networks with isotropic connectivity For a given edge e with a distance x from its source vertex v to its target vertex $t(e)$, potential new targets (striped) are found in within a distance $(x - \varepsilon, x + \varepsilon)$ of v . The rewired edge then projects from v to a new target $t'(e)$, randomly chosen from the set of vertices within in this range. Inter-vertex distance between v and $t'(e)$ differs by less than ε from x , ensuring that for small ε the original distance-dependent connectivity is preserved. (Note that all targets within range are eligible for rewiring as no other edges exist. In general this is not the case.)

Definition 3.4. Let G be an anisotropic geometric graph with $|V(G)| = n$ and $\varepsilon > 0$. Then we define a *rewiring* R_ε of G to be probability space over G_Φ^n , induced by the following process: For every edge $e \in E(G)$

uniformly at random pick a potential new target $t'(e)$ from the set $M_e = T_e \setminus K_e$, where T_e is the set of all vertices that differ in their distance to $s(e)$ less than ε from the distance of $s(e)$ to $t(e)$,

$$T_e = \{v \in V(G) \setminus s(e) \mid |\text{d}(s(e), v) - \text{d}(s(e), t(e))| < \varepsilon\}$$

and K_e the set vertices that already are connected to $s(e)$ by another rewired edge,

$$K_e = \{v \in V(G) \mid \exists e' \in E'(G) : s(e') = s(e), t(e') = v\},$$

where $E'(G)$ is the set of all edges that have been rewired already.

Note that in the way Definition 3.4 is formulated, it is possible for M_e to be empty for some edge e . In this case no new edge is realized and the resulting rewired network has $|E(G)| - 1$ edges. In practice this happens negligibly often, on average only 25.68 (4.51 standard deviation) edges, accounting for roughly 0.02% of the rewired edges, are “lost” in this process (4afc2727).

We formulated Definition 3.4 in such a way, that distance-dependent connectivity is preserved; the rewiring margin ε thus simultaneously governs how many new targets are available for each edge and how well distance-dependency is preserved. Setting $\varepsilon = 1.25$ and applying the rewiring algorithm to the 25 sample graphs, we find that distance-dependent connectivity of the original graphs is matched (Figure 3.11) while at the same time ensuring that for any edge e sufficiently many new rewiring targets are available (Figure A.2).

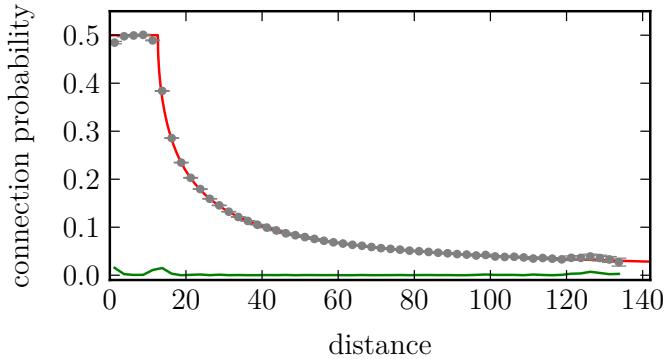


Figure 3.11: Rewiring with $\varepsilon = 1.25$ preserves distance-dependent profile in sample graphs Comparing the distance-dependent connection probabilities of the original graph (Theorem 3.3) in red with extracted of probabilities from the rewired ($\varepsilon = 1.25$) sample graphs in gray (errorbars SEM⁷) we verify that distance-dependent connectivity is preserved when rewiring. The green curve shows the absolute difference between the original profile and distance dependent probabilities found in the rewired network. (4f4dfcf1)

As a generalization of Definition 3.4, we define a partial rewiring $R_{\varepsilon,\eta}$, finding new targets only for a fraction η of all edges:

Definition 3.5. Let $\varepsilon > 0$ and $0 \leq \eta \leq 1$. A *partial rewiring* $R_{\varepsilon,\eta}$ of an anisotropic geometric graph $G_{n,w}$ with *rewiring factor* η is then a rewiring R_ε of $G_{n,w}$, in which every edge is rewired with a probability of η , otherwise it remains. To avoid the occurrence of multiple edges, K_e is then extended to include the targets of all edges originating from $s(e)$ that will not be rewired.

Clearly, as with full rewiring, partial rewiring also preserves distance-dependent connectivity. Using the algorithm we extend our set of sample graphs once more by adding rewired versions of each graph. Choosing a rewiring margin of $\varepsilon = 1.25$, with fractions $\eta = 0.25$, $\eta = 0.5$,

rewiring of sample graphs

and $\eta = 0.75$ and $\eta = 1$ we obtain through rewiring five stages of the sample graphs, from complete anisotropy in connectivity in the original graphs to the isotropic, fully rewired graphs⁸. By introducing a measure for anisotropy and applying it to the rewired and original version of the sample graphs, we're able to solidify this notion and tie together the concepts introduced through this chapter in the next section.

3.7 ANISOTROPY MEASURE

A measure for anisotropy in connectivity in geometric graphs can be adapted from concepts in the field of directional statistics. The *mean direction* of a set of unit vectors in \mathbb{R}^2 is the sum of the vectors, divided by the cardinality of the set (cf. Mardia and Jupp 2000). The resulting vector gives a preferred direction of the sample, pointing towards a clustering of the set. The length of the mean direction measures the vectors dispersion, with a length of close to one implying tight clustering. Here we adapt the length of the mean direction to provide a measure of anisotropy in connectivity for each vertex in a geometric graph:

Definition 3.6 (Anisotropy degree). Let $G_{n,\Phi}$ be a geometric graph. For each vertex v in $G_{n,\Phi}$, the anisotropy degree of v is defined as

$$\lambda(v) = \frac{1}{|T(v)|} \sum_{w \in T(v)} \frac{\Phi(w) - \Phi(v)}{\|\Phi(w) - \Phi(v)\|}$$

if the target set $T(v)$ of v is non-empty, otherwise we set $\lambda(v) = 0$.

By the triangle inequality, the anisotropy degree $\lambda(v)$ takes values from 0 to 1. If targets of v mostly align along a projection from v , the degree

⁷ SEM = standard error of the mean

⁸ labels: N1000w_ax126-flat_graph0-25-rewired_frac025, -50,-75,-100

$\lambda(v)$ is close to 1. On contrast, if targets are widely dispersed, $\lambda(v)$ is almost 0. Note however that $\lambda(v) = 0$ does *not* necessarily imply even distribution of directions, examples for this are easily constructed (cf. Mardia and Jupp 2000).

Considering the distribution of vertex anisotropy degrees in a geometric graph, the profiles provide an appropriate measure for anisotropy in connectivity. Recording values for each vertex in anisotropic networks and their rewired counterparts, we find that rewiring does indeed eliminate anisotropy (Figure 3.12). In fact, distributions in fully rewired networks resemble anisotropy degrees in distance-dependent graphs, suggesting that rewired networks can be considered equivalent to distance-dependent networks in terms of their structural aspects. This, however, turns out not to be true. In Section 4.2 we find strongly varying out-degree distributions in the two network types. Therefore both network models remain highly relevant as a reference for the analysis of structural features in anisotropic networks.

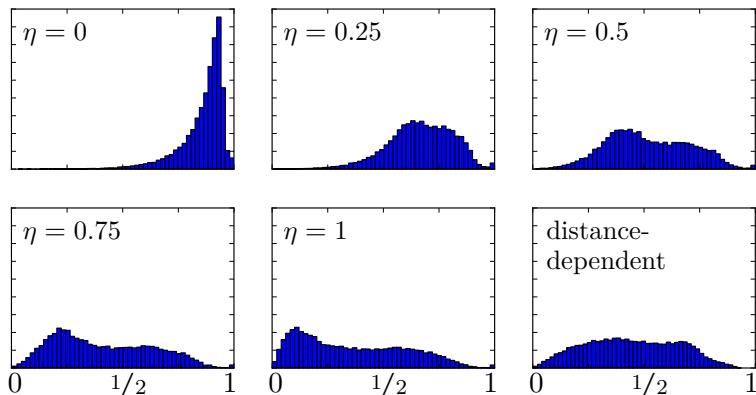


Figure 3.12: Rewiring significantly reduces anisotropy Analyzing vertex anisotropy degrees in the 25 sample graphs (Section 3.4) and their rewired versions, we find that the mean anisotropy degree decrease with increasing rewiring factor η . In completely rewired graphs ($\eta = 1$), anisotropy degree distribution resembles those of distance-dependent networks. (038f5b8c, 9893ab1f, 0c429f3c, 400a41bc, a5f54cb4, a5b674f0)

3.8 SUMMARY AND DISCUSSION

This chapter introduced and discussed the following network types:

1. random networks
2. distance-dependent networks
3. rewired anisotropic networks
4. anisotropic networks

While random and distance-dependent networks were formally defined as graphs in Sections 2.3 and 2.4, this chapter introduced the concept of anisotropy. Built upon it, anisotropic graphs were defined as a geometric graphs with a specific connectivity rule. Identifying a parameter set reflecting local cortical networks, samples of anisotropic networks and of the other graph types were created. For this we extracted the distance-dependent connectivity profile in anisotropic networks and introduced rewiring as a method to eliminate anisotropy while keeping other connectivity parameters unaltered. Finally, by introducing the a measure for network anisotropy, we are able to relate the concepts of distance-dependency and anisotropy, finding that rewiring does indeed significantly reduce anisotropy while keeping the distance-dependent connectivity intact.

The network types discussed span a spectrum of completely random connectivity to networks with specific connectivity rules. Investigating in how far such a specific rule is able to produce non-random connectivity, reflecting findings in local cortical circuits, is the main task of Chapter 4. For the analysis we will heavily recruit all of the network models above as well as their computational implementations. While rewired networks are most closely related to anisotropic networks and provide a reference for features directly caused by anisotropy, comparison with distance-dependent and random networks reveals indirectly affected features and provides insight to structural features present in anisotropic networks not found in the standard network types.

4

STRUCTURAL ASPECTS

Subjecting the anisotropic network model to a critical examination of its structural features, we identify prevalent patterns of connectivity and relate theoretical and computational results to findings from experiments in the rat's cortex.

4.1 INTRODUCTION

Investigation of the brain's connectivity is an ongoing endeavour. Concurrent collaborative efforts like the Human Connectome Project, the Open Connectome Project and the Allen Brain Atlas, intent on mapping the 'wiring' of the brain, as well as the continued development of experimental techniques and computational resources, demonstrate the great interest in advancing this field.

Research in brain connectivity spreads over the whole scale of the brain; from the mapping of fiber pathways between brain regions at the macroscopic level, to the synaptic connections of individual neurons on the microscale, researchers are trying to identify the links that enable the brain its characteristic cognitive abilities. Connections, these links are of anatomical nature. However, statistical dependencies and causal relationships between the distinct computational units in the brain are being researched with equal emphasis (Sporns 2007). Connectivity in the context of the anisotropic network model introduced in Section 3.3, refers in this chapter to structural links. So far, we have only briefly mentioned that the network's nodes should be interpreted as individual neurons; to allow for a discussion of functional relationships between nodes, we have yet to provided a physical description of a neuron's function. Here we explore the network's structural connectivity, modeling synaptic contacts between axon and dendrites of individual neurons.

In the local cortical circuits the anisotropic geometric model was derived from, synaptic connectivity is a major mode of configuration. In those networks, connectivity has been determined to be neither completely random nor exclusively specific; recurring patterns of connectivity have been identified by several reports (Sporns and Kötter 2004; Song et al. 2005; Perin et al. 2011).

HUMAN
Connectome
PROJECT

humanconnectome.org

Open Connectome
Project

[openconnectome-
project.org](http://openconnectome-project.org)

ALLEN BRAIN ATLAS

brain-map.org

synaptic
connectivity

The impact of this structural specificity discovered in local networks is shown to be significant; while linking network structure to network dynamics remains an active field of research, several studies were able to employ computational and theoretical models to establish such a connection. A study by Zhao et al. (2011), for example, demonstrates how second order connectivity statistics affect a network's propensity to synchronize. In the same year, Alex Roxin reported on the influence of in- and out-degree distributions on dynamics of neural network (Roxin 2011). Later, Pernice et al. were able to link structural connectivity to spike train correlations in neural networks (Pernice et al. 2011).

mapping synaptic connectivity in experiments

Experimentally, paired intracellular recordings are used to determine synaptic connectivity in cortical slices. Using two electrodes, one inserted in the cell and one outside the cell, a single intracellular recording allows for measurement of a cell's membrane potential (Brette and Destexhe 2012, Chapter 3; Weckstrom 2010). Simultaneous recordings from multiple neurons are then able to infer synaptic connectivity by evoking an action potential through current injection in one neuron and observing the change of membrane potential in the other cells (Song et al. 2005).

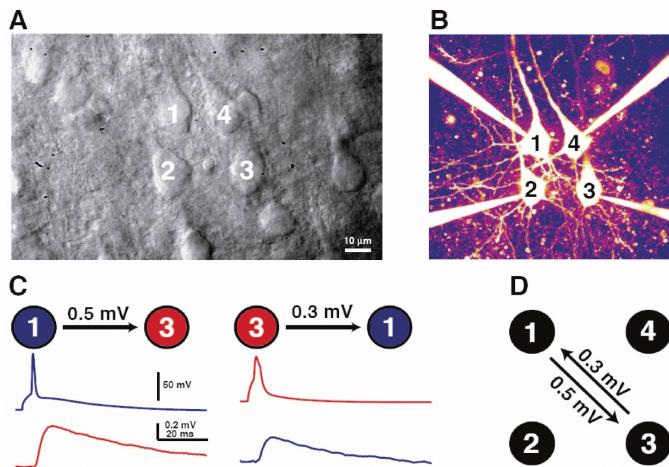


Figure 4.1: Song et al. use quadruple whole-cell recordings, observing simultaneously the membrane potential of four neurons. **A)** Contrast image showing four thick-tufted L5 neurons **B)** Fluorescent image of the same cells after patching on **C)** Evoking an action potential in the presynaptic neuron causes characteristic membrane potential change in the postsynaptic neuron **D)** Inferring synaptic connectivity from the EPSP waveform observed in C). Image from Song et al. (2005).

While techniques for paired intracellular recordings are rapidly developing, their ability to capture connectivity patterns of large networks is yet very limited. To this date, the connectome of *C. Elegans* remains

the outstanding exception of a connectivity configuration that has been fully mapped (White et al. 1986). Even in the state-of-the-art experiment conducted by Perin et al., using a setup capable of recording up to twelve neurons simultaneously, the authors note that an investigation of degree distribution was not carried out, due to lack of sufficient data (Perin et al. 2011).

Working with a geometrical network model and its computational implementation, such restrictions disappear; the full information about the network, in form of its connectivity matrix, is given at point in time and can be easily queried for. Experiments that may take days to perform *in vivo*, can be completed in a matter of seconds *in silico*. As such, geometrical models lend themselves to extensive examination of their structural aspects. In trying to exploit these advantages, two approaches present themselves. One may construct a network model that extrapolates the known biological configuration; a full structural examination of these networks could possibly expose relevant patterns not yet observed. For this approach a sophisticated understanding of the biological configuration is critical. Neuron morphology, however, is difficult to describe and extract. For this analysis we suggest a reductionist approach. Having motivated an abstract model reflecting a cortical network's anisotropy in connectivity, we distinguish emerging structural patterns, specific to anisotropic networks, from results, that only indirectly stem from the network's anisotropy, in the hopes to be able to characterize the significance of directional heterogeneity in structural connectivity of cortical circuits.

In this chapter we subject the anisotropic network model introduced in Section 3.3 to a critical analysis of its structural aspects. General network topology, as well as specific modes and patterns of connectivity, are to be identified and laid out for comparison with findings in biological neural networks. In an effort to identify structural features that can be directly associated with the network's anisotropy in connectivity, it is crucial to differentiate such findings from results that are only indirectly caused by the network's anisotropy. To this end we are recruiting the different network types introduced in the previous chapter throughout this analysis. Having shown a decreasing degree of anisotropy in rewired and distance-dependent networks, both models will serve as reference to compare against for structural features found in anisotropic networks. Analyzing standard graph measures in the first two sections, we quickly move on to towards neuronal network specific connectivity and anisotropy's role in being able to model such highly non-random patterns in the later sections.

*exploiting the
benefits of a
geometrical model*

*rewired and
distance-depen-
dent networks as
reference*

4.2 DEGREE DISTRIBUTION

The in- and out-degree of a vertex in a directed graph describes the number of incoming and outgoing connection from and to other vertices. *cf. Definition 2.4* As a fundamental concept in graph and network theory, the degree distribution is integral in the categorization of networks and allows for the estimation of graph properties.

Node degree distribution was shown to have strong impact on the dynamics of neuronal networks models commonly used in computational neuroscience research (Roxin 2011; Pernice et al. 2013). Increasing in-degree variance for example could be connected to the appearance of oscillations in the network. Extracting degree distributions from biological networks however, remains a challenge as many neurons need to be tracked simultaneously to obtain enough data to confidently estimate degree distributions.

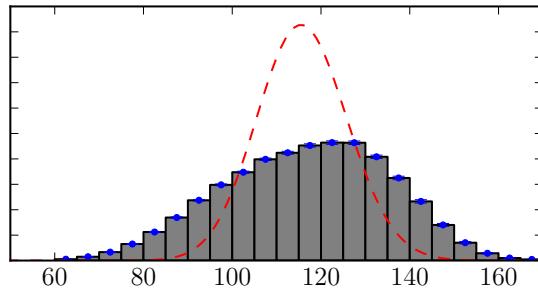


Figure 4.2: In-degree distribution in anisotropic networks shows comparably high variance and is skewed to the left From 250 anisotropic networks in-degree distributions were extracted and are shown in a normed histogram plot, errorbars SEM. Comparison with the binomial degree distribution (red) of a Gilbert random graph model with matching parameter set ($N = 1000$, $p = 0.116$) shows higher variance of in-degrees in anisotropic networks (sample variance = 344.54, variance of binomial distribution $Np(1 - p) = 102.44$.) Skewness to the left of the sample is -0.1763 . (9326138e)

Here we analyze in- and out-degrees in the anisotropic network model. First we find that compared to the binomial in-degree distribution of a Gilbert random graph model, in-degrees of vertices in anisotropic networks display higher variance and their distribution is skewed to the left (Figure 4.2). However, this specific in-degree profile is not an intrinsic property of anisotropy, as the distribution remains stable under manipulation of the anisotropy degree and closely matches the profile of a purely distance-dependent network (Figure 4.3). This result agrees

with findings of Perin et al. (2011, Fig. S3), who were able to recreate degree distributions from their experiment with layer 5 thick-tufted pyramidal cells in neonatal rats from the extracted distance-dependent connection profiles alone.

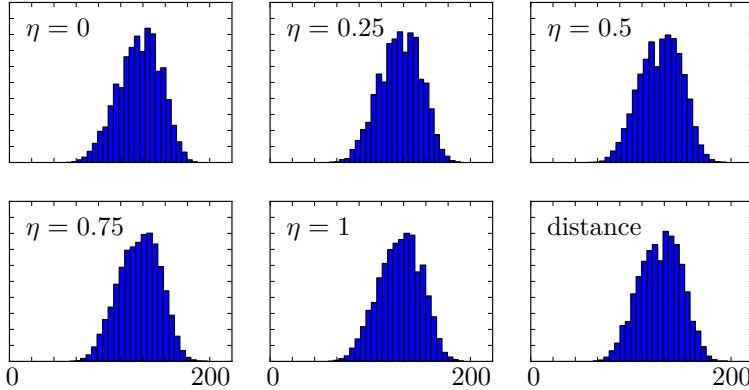


Figure 4.3: In-degree distribution not affected by varying degrees of anisotropy In-degree distributions from the 25 sample graphs and their rewiring stages are plotted in normed histograms and listed from rewiring factor $\eta = 0$ (original anisotropic) to $\eta = 1$ (completely rewired, maximal isotropy). Comparison shows that varying degrees of anisotropy do not influence the degree distribution, in fact in-degree distributions match with the degree distribution of an equivalent distance-dependent network shown bottom-right (77995b6b).

While the out-degree distribution of vertices in the anisotropic network also shows itself stable under rewiring, its distribution is drastically different from the out-degree distribution in a comparable distance-dependent network (Figure 4.4). The asymmetric, long-tailed distribution is identified as an artifact of the anisotropic network's spatial confinement; a neuron, closely located near a surface edge, might have an axon projection out of the square causing minimal out-degree or, projecting through the entire length of the surface, may have maximal out-degree. Approximating the expected number of outgoing connections for a vertex in an anisotropic network of size N , side-length s and axon width w as

$$N \frac{wl}{s^2},$$

with parameters $N = 1000$ and $\frac{w}{s} = 0.252$, we obtain an upper bound for the expected out-degree,

$$N \frac{wl}{s^2} \leq N \frac{w}{s} \sqrt{2} \approx 350.$$

If $f(l)$ is the probability density function to find axon length l for a random node v in the anisotropic network model, the out-degree distribution is then approximated by

$$\mathbf{P}(d_{\text{out}}(v) = N \frac{wl}{s^2}) = f(l), \quad (4.1)$$

see also [Figure 4.5](#).

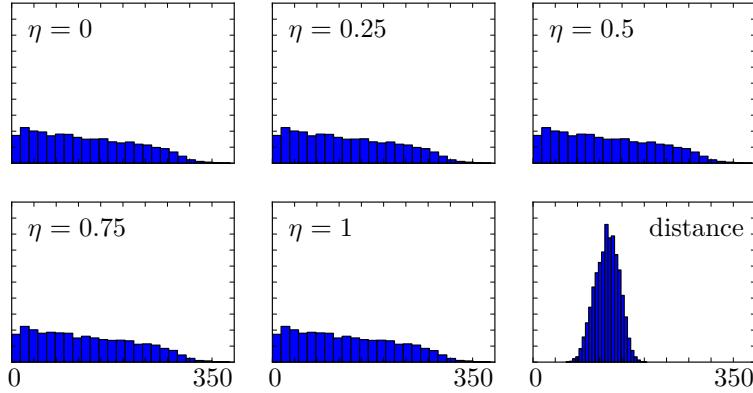


Figure 4.4: Out-degree distribution not affected by varying anisotropy but highly different from distance-dependent networks Out-degree distributions from the 25 sample graphs and their rewiring stages are plotted in normed histograms and listed from rewiring factor $\eta = 0$ (original anisotropic) to $\eta = 1$ (completely rewired, maximal isotropy). While varying degrees of anisotropy do not influence the degree distribution, the characteristic out-degree profile is drastically different from the distribution found in equivalent distance-dependent networks (77995b6b).

Steep incline for small out-degree cut off due to binning (cf. [Figure A.3](#))

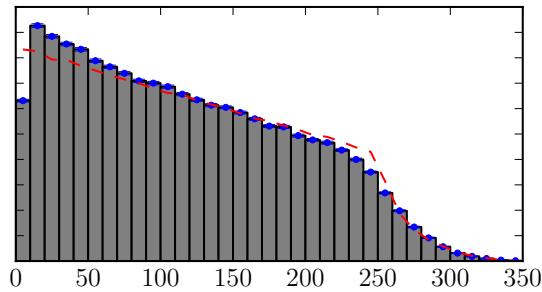


Figure 4.5: Characteristic out-degree distribution as an artifact of network's boundaries From 250 anisotropic networks out-degree distributions were extracted and are shown in a normed histogram plot, errorbars SEM. The characteristic distribution is identified as an artifact of the network's spatial confinement; using equation 4.1 the out-degree profile is approximated (red) by the distribution of axon lengths in the anisotropic network (019555b0).

4.3 SMALL WORLD PROPERTIES

Small-world networks, as described in Section 2.2, are characterized by a small average path length and comparably high clustering coefficient. In brain networks, combining advantages of sparse connectivity with mostly local and only few long-range projections, small-world properties are frequently discussed as a way of achieving high efficiency in the parallel processing of information (cf. Achard and Bullmore 2007). While most often reported on the macroscale (Sporns and Zwi 2004; Bassett and Bullmore 2006), small-worldness is also found in local cortical networks (Perin et al. 2011, SI).

Here we are interested in exploring the question whether anisotropy in connectivity influences the small-worldness of geometric networks. First we find that at a network size $N = 1000$, anisotropic networks display a relatively high clustering coefficient, $c = 0.1581 \pm 0.0008$ compared with $p = 0.116$ in random networks, and a comparable path length, $l_{\text{aniso}} = 1.937 \pm 0.002$ and $l_{\text{random}} = 1.8820 \pm 0.0001$, ascertaining a small-world property in the anisotropic network model.

*in random
networks from
independence
clustering = p*

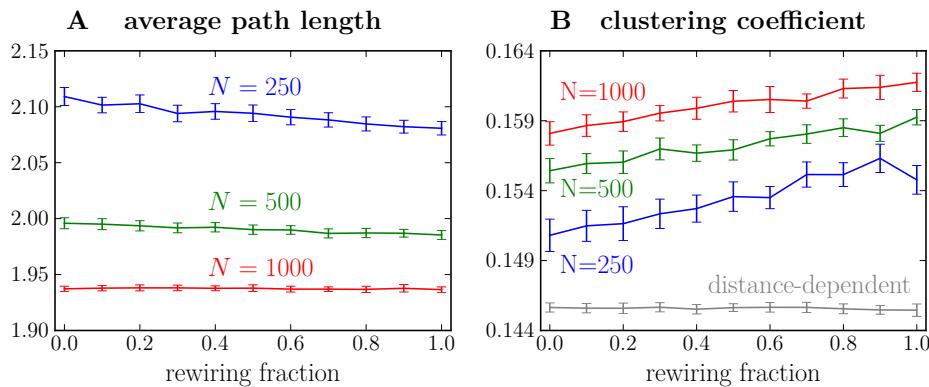


Figure 4.6: Anisotropy does not contribute to small-worldness In increasingly rewired networks, trends show a decreasing average path length and rising clustering coefficient and thus possibly a higher degree of small-worldness in the rewired, isotropically connected networks. **A)** Average path lengths for network sizes $N = 250$, 500 and 1000, where vertex pairs with no existing are discarded. Individual value pairs are obtained by averaging over a trial size of 20, 15 and 5 respectively; errorbars are SEM. **B)** Network configuration as in A), additionally showing clustering coefficients for distance-dependent networks. (064f9b10)

However, is this degree of small-worldness inferred by anisotropy in connectivity? Using distance-dependent networks as a reference, we find that successively eliminating anisotropy through rewiring contributes

positively to the small-world property; with rising isotropy in the network, the characteristic path length declines in small networks and remains unchanged in larger networks, while the clustering coefficient increases regardless of network size, resulting together in rewired networks to display a higher degree of small-worldness ([Figure 4.6](#)).

In distance-dependent networks the average path length is generally smaller than in (rewired) anisotropic networks ([Figure A.4](#)), matching those of a random network as reported above. At the same time also the clustering coefficient is smaller than in anisotropic networks ([Figure 4.6](#)), resulting overall in a comparable degree of small-worldness in distance-dependent networks¹ and leading to the conclusion that the observed small-worldness in the anisotropic networks is due to the imposed distant-dependent connectivity rather than the anisotropy in connectivity.

4.4 TWO NEURON CONNECTIONS

Connectivity in local cortical circuits exhibits a salient feature: Examining the occurrence of connections in neuron pairs, studies have repeatedly found that bidirectionally connected neuron pairs appear much more frequently than expected from the network's overall connection probability. In layer 5 of the somatosensory cortex studies from [Markram \(1997\)](#) and [Perin et al. \(2011\)](#) have found an overrepresentation of reciprocally connected pairs of thick tufted pyramidal cells, an observation that has also been reported in layer 2/3 ([Holmgren et al. 2003](#)) and layer 5 ([Song et al. 2005](#)) of the visual cortex. The overrepresentation of bidirectionally connected pairs is significant, Song et al. for example found such pairs represented four times the expected amount.

The underlying connection principle imposing this overrepresentation on the network however remains unclear. Song et al. discuss the possibility of known learning rules to explain their findings, leaving a definitive answer open to further investigation. More recent studies find overrepresentation of reciprocally connected pairs *in vitro* resulting from functional specificity ([Ko et al. 2011](#)) and *in silico* from dense neuron clustering rules ([Klinshov et al. 2014](#)), identifying specific network characteristics that may contribute to the reported overrepresentation *in vivo*.

¹ Differences in the absolute values of both path length and clustering coefficient presumably relates to difference in the out-degree distribution ([Figure 4.4](#))

Here we examine anisotropy in connectivity as a possible candidate for an underlying principle explaining the characteristic two neuron connection distribution. In random networks, the chance to encounter a specific mode of connection in a random pair of neurons can easily be computed from the overall connection probability p . For this let X be the random variable of the number of edges between two different vertices in a Gilbert graph $G(n, p)$ with $n \geq 2$. As the edges are independently realized, resulting in a simple directed graph, we have

$$\begin{aligned}\mathbf{P}(X = 0) &= (1 - p)^2 && \text{unconnected pair,} \\ \mathbf{P}(X = 1) &= 2p(1 - p) && \text{single connection,} \\ \mathbf{P}(X = 2) &= p^2 && \text{reciprocal connection;}\end{aligned}\tag{4.2}$$

in short $\mathbf{P}(X = k) = \mathcal{B}_{2,p}(k)$ for $k \in \{0, 1, 2\}$ and $\mathbf{P}(X = k) = 0$ otherwise. Using this probability distribution as the expectation for connectivity of neuron pairs in the various network types, a numeric analysis of the anisotropic sample graphs reveals that bidirectionally connected pairs appear almost twice as often as expected from the overall connection probability ($p = 0.116$) and equations 4.5, similarly as reported by Song et al. (Figure 4.7 A). However, comparing the pair probabilities in anisotropic networks with the probabilities in their rewired counterparts, we find that anisotropy does not influence the occurrence of two-neuron motifs (Figure 4.7 B) In fact, expected connections in neuron pairs are identical in distance-dependent and rewired anisotropic networks (Figure A.5).

We further support this observation by computing the probability distribution for the expected number of edges between two random vertices in the anisotropic graph model. For this we assume that only the distance-dependent connection probability $C(x)$ determines the occurrence of edges in vertex pairs in the anisotropic graph model. Then, using the probability distribution $f(x)$ for the a random neuron pair to be at distance x , we calculate

$$\begin{aligned}\mathbf{P}(X = 0) &= \int_0^{\sqrt{2}} (1 - C(x))^2 f(x) dx, \\ \mathbf{P}(X = 1) &= \int_0^{\sqrt{2}} 2C(x)(1 - C(x))f(x) dx \quad \text{and} \\ \mathbf{P}(X = 2) &= \int_0^{\sqrt{2}} C(x)^2 f(x) dx.\end{aligned}$$

Inserting the distance-dependent connection probabilities $C(x)$ in the anisotropic graph model as computed in Theorem 3.3 and the probability distribution $f(x)$ from Theorem 2.15 we obtain

$$\begin{aligned}\mathbf{P}(X = 0) &= 0.791336 & 0.7907 \pm 0.0008 \\ \mathbf{P}(X = 1) &= 0.184151 & 0.1846 \pm 0.0007 \\ \mathbf{P}(X = 2) &= 0.024513 & 0.02462 \pm 0.00009,\end{aligned}$$

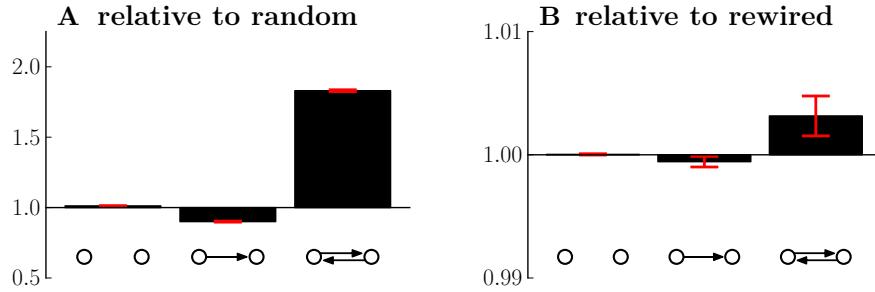


Figure 4.7: Overrepresentation of reciprocal connections in anisotropic networks due to distance-dependent connectivity Extracting the counts of unconnected, one-directionally and bidirectionally connected neuron pairs in the anisotropic sample graphs, overrepresentation of reciprocally connected pairs is identified as a feature of the network's distance dependency as opposed to anisotropy in connectivity. **A)** Showing the quotient of the counts for the three pair types, extracted from the set of sample graphs, with the number of expected pairs in Gilbert random graphs $G(n, p)$, where $n = 1000$ and $p = 0.116$ were matched to the sample graph parameters. While single connections appear less often than in Gilbert random graphs, reciprocal connections are significantly overrepresented. Errorbars SEM. **B)** Comparing appearance of connection pairs in the anisotropic sample graphs with their respective appearance in the rewired sample graphs, we find that eliminating anisotropy does not significantly change the counts for the connection types, indicating that anisotropy does not influence two neuron connection probabilities. Errorbars SEM. (c5f1462b)

perfectly matching the probabilities extracted from anisotropic sample graphs in the right column (error SEM, c5f1462b). Noting that distance-dependency alone is sufficient to accurately predict edge probabilities in neuron pairs in the anisotropic network model and combined with the observations in Figure 4.7, we conclude that varying degrees of anisotropy do not affect the occurrence of neuron pair motifs.

4.5 TUNING DISTANCE-DEPENDENCY

The discussion in the last section focused on the effect of anisotropy in connectivity on the occurrence of neuron pair motifs. Could distance-dependency itself, as imposed by the specific geometry, be a decisive factor in the distribution of edge counts in neuron pairs? Song et al. (2005), as well as Perin et al. (2011), report an overrepresentation of reciprocal connections independent from distance-dependent connectivity, opposing the observations made in the last section (Figure 4.7 A). Furthermore, the connectivity profile in the anisotropic graph model, as identified in Section 3.5, follows purely from abstract geometry rather than being motivated by connectivity found in cortical circuits. In an attempt to rectify this and to allow for a more differentiated examination of two neuron connections, in this section we step away from simplistic geometry and “tune” the anisotropic networks to display a distance-dependent connectivity as reported by Perin et al. by adjusting the width $w(x)$ at any point x along the axon’s projection.

For this we introduce anisotropic networks tuned to reflect a given distance-dependent connection profile $C(x)$. We are facing the following problem: Given $C(x) : [0, \sqrt{2}] \rightarrow [0, 1]$, find $w : [0, \sqrt{2}] \rightarrow [0, \infty)$ such that the probability to have a connection from v_1 to v_2 for arbitrary vertices $v_1 \neq v_2$ in an anisotropic graph $G(n, w)$ with distance $d(v_1, v_2) = x$ is $C(x)$. The problem is in general highly complex when nothing can be assumed about $C(x)$. We find an approximate solution to the problem considering the following geometric relation:

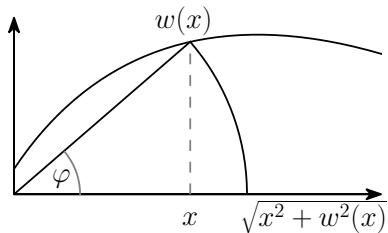


Figure 4.8: Computing connection probability $C(x)$ from non-constant $w(x)$

From Figure 4.8 we have the relation

$$C\left(\sqrt{x^2 + w^2(x)}\right) = \frac{1}{\pi} \arctan \frac{w(x)}{x}. \quad (4.3)$$

In order to solve for $w(x)$ we first consider a linear approximation, expanding

$$C\left(\sqrt{x^2 + w^2(x)}\right) \approx C(x) + \left(\sqrt{x^2 + w^2(x)} - x\right) C'(x).$$

The resulting transcendental equation

$$C(x) + \left(\sqrt{x^2 + w^2(x)} - x \right) C'(x) = \frac{1}{\pi} \arctan \frac{w(x)}{x}$$

is however still too complex in the context of this work. Instead we propose the approximation $\sqrt{x^2 + w^2(x)} \approx x$, which inserting into 4.3 yields

$$C(x) \approx \frac{1}{\pi} \arctan \frac{w(x)}{x}. \quad (4.4)$$

Under the assumption that $C(x) < \frac{1}{2}$ for all x we obtain the identity

$$w(x) = x \tan(\pi C(x)), \quad (4.5)$$

being aware that it only holds as well as approximation 4.4 does.

Here we use relation 4.5 to generate anisotropic networks reflecting the distance-dependent connectivity profile as found by Perin et al. (2011). For this we finally need to adjust the before arbitrarily determined side length of the network's surface. Perin et al. mapped connectivity in layer 5 of the rat's somatosensory cortex up to a distance of 300 µm. Using this reported distance connectivity to generate anisotropic networks via 4.5, the chosen side length s determines the networks overall connectivity (Figure 4.9 A). We determine $s = 296$ µm to match the overall connection probability of $p = 0.116$ as used before and reported by Song et al. (Figure 4.9 B). The obtained value for s is consistent with the slice thickness of 300 µm used in Perin et al.'s experiment.

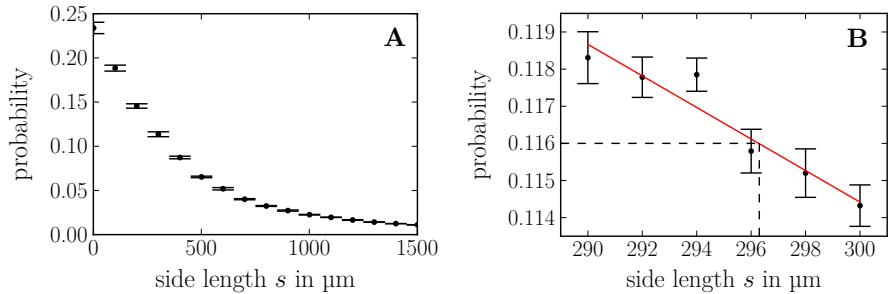


Figure 4.9: Network side length adjusted to match overall connection probability Side length of the network's surface determines the overall connection probability in the network when axon width function $w(x)$ is fixed. **A)** Connection probability declines with rising side length **B)** Determining side length as $s = 296$ µm to match $p = 0.116$ as reported by Song et al. (2005). (6154302f, ef0e785d)

Having determined the network's side length s , we're extending the quiver of generated sample networks for the numerical analysis once more by the “tuned anisotropic graphs”, in which the axon width $w(x)$

was determined such that the networks reflect Perin's connectivity profile. Analyzing the obtained axon width function we note that $x \gg w(x)$ holds for most x , justifying the approximation

$$\sqrt{x^2 + w^2(x)} \approx x$$

a posteriori (Figure 4.10). From the 25 generated networks overall connection probability is extracted as $p = 0.1160 \pm 0.0006$ (SEM), as expected from the choice of s (f11dca65).

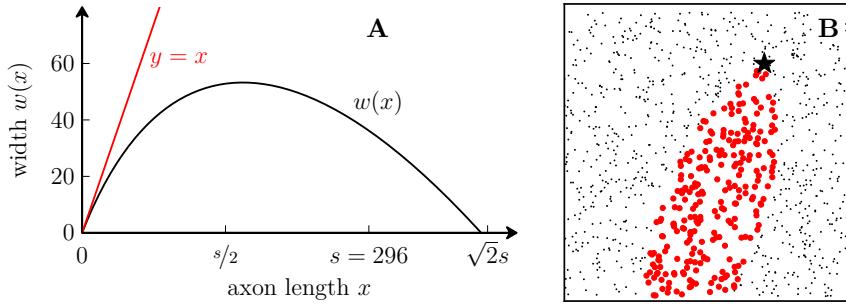


Figure 4.10: Anisotropic network model with tuned axon width $w(x)$ **A)** Resulting axon width function $w(x)$ from tuning to distance-dependent connection profile as reported by Perin et al. (2011), see also Figure 4.11. Note that $x \gg w(x)$ for most x , supporting approximation 4.4. **B)** Showing for a single neuron (star) connected (red) and unconnected (gray) neurons in the tuned anisotropic network, revealing the characteristic axon shape. (d45c02e4, 8f0d65e4)

Overall distance-dependent connection probabilities in the tuned anisotropic graphs clearly match the profile of Perin et al. (Figure 4.11 A), presenting strongest the argument in support of the chosen approximation. Analyzing two neuron connections in the tuned networks, we affirm the findings of the last section. In their experiment, Perin et al. were able to show an overrepresentation of reciprocal connections at any inter-neuron distance (Figure 4.11 B-C). Rather than matching these profiles, we find that occurrences of one- and bidirectionally connected pairs in the anisotropic graphs align with probabilities obtained from the distance-dependent overall connection probability $p(x)$ under the assumption of independence (cf. Equation 4.5),

$$\begin{aligned} \mathbf{P}_{X=1}(x) &= 2p(x)(1-p(x)) && \text{single connection,} \\ \mathbf{P}_{X=2}(x) &= p(x)^2 && \text{reciprocal connection.} \end{aligned}$$

Thus, in comparison with Perin et al.'s findings, we find that anisotropy in connectivity cannot account for the overrepresentation in reciprocal connections. While results in Section 4.4 still indicated such an overrepresentation due to distance-dependency, examining the occurrence of two neuron connections at any inter-neuron distance in anisotropic

revisiting two
neuron
connections

networks, tuned to a distance-dependent connection profile matching experimental findings from cortical circuits, imply complete unrelatedness of anisotropy and two-neuron connection distributions.

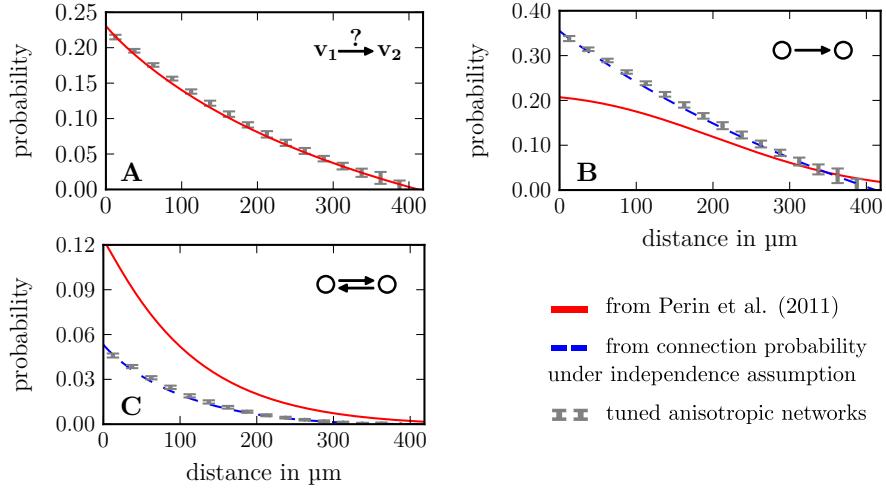


Figure 4.11: Distance-independent overrepresentation of reciprocal connections Comparison of occurrences of one- and bidirectionally connected neuron pairs in the tuned anisotropic networks (gray) with profiles found by Perin et al. (red), shows that overrepresentation of bidirectional pairs is distance-independent and not connected to anisotropy. **A)** Overall connection probability in the tuned anisotropic networks was successfully adjusted to reflect connection probability found by Perin et al. **B)-C)** Showing in blue the probabilities to obtain a neuron pair motif (single edge in B, two edges in C) calculated under independence assumption from the overall probability from A), we find that counts in the tuned anisotropic networks (gray) match the independence assumption and do *not* show the overrepresentation present in Perin et al.'s experiment. (875505b0)

4.6 MOTIFS

Non-random connectivity in local cortical circuits extends well beyond specific connection probability in neuron pairs: As one of their main results, [Song et al. \(2005\)](#) report a characteristic occurrence of motifs of three neurons, while [Perin et al. \(2011\)](#) find patterns in the number of connections appearing in clusters of up to 8 neurons. Motifs have been shown to have a significant influence on network dynamics, with patterns affecting dynamical correlations ([Pernice et al. 2011](#)) and network synchrony ([Zhao et al. 2011](#)).

Finding no correlation between two-neuron connection probabilities and anisotropy in connectivity prior, does anisotropy influence the occurrence of neuron motifs? In this section we analyze higher order connectivity in the different network types and observe a surprisingly strong impact of anisotropy on patterns of connected neurons, promoting the concept as an underlying principle for non-random network connectivity.

Three-neuron patterns

We first investigate the occurrence of three-neuron patterns in anisotropic networks. Song et al. (2005) reported a characteristic, highly non-random motif distribution of pyramidal cells in the rat's visual cortex layer 5, a result later confirmed by Perin et al. (2011) in their experiment in the rat's somatosensory cortex layer 5. Repeating the experiment *in silico* for the different networks subject to this study, we find similar, characteristic motif distributions strongly influenced by anisotropy in connectivity.

There are 13^2 non-isomorphic 3-motifs in simple directed graphs. In reference to Song et al.'s result, the patterns are labeled 4 to 16,



Let X be a random variable that maps three random vertices $v_1 \neq v_2 \neq v_3$ in a graph G to the $n \in \{4, 5, \dots, 16\}$ labeling the isomorphism class of the full subgraph with vertex set $\{v_1, v_2, v_3\}$ in G as above if the subgraph is connected, and let X map to $n = 0$ otherwise. A first idea of how to compute the distribution of X is by inferring the probabilities of motif occurrence from the two-neuron connection probabilities from Section 4.4. In anisotropic networks we found that the probabilities of occurrence are

$$\begin{aligned} p_u &= 0.791336 && \text{for unconnected pairs,} \\ p_s &= 0.184151 && \text{for single connections and} \\ p_r &= 0.024513 && \text{for reciprocal connections.} \end{aligned}$$

From these we may, for example, calculate the probability of occurrence for motif 8,

$$\mathbf{P}(X = 8) = 6 p_u p_s p_r,$$

² There are 16 non-isomorphic simple directed graphs with 3 nodes. Three of those graphs are unconnected (cf. Davis 1953, N. J. A. Sloane. The On-Line Encyclopedia of Integer Sequences, <http://oeis.org>. Sequence A000273).

where the factor 6 is determined by the number of different *labeled* graphs belonging to the isomorphism class. The distribution of X for the remaining motifs is given by

$$\begin{aligned}\mathbf{P}(X = 4) &= 3p_s^2 p_u & \mathbf{P}(X = 9) &= 3p_r^2 p_u & \mathbf{P}(X = 13) &= 6p_s^2 p_r \\ \mathbf{P}(X = 5) &= 3p_s^2 p_u & \mathbf{P}(X = 10) &= 6p_s^3 & \mathbf{P}(X = 14) &= 3p_s^2 p_r \\ \mathbf{P}(X = 6) &= 6p_s^2 p_u & \mathbf{P}(X = 11) &= 2p_s^3 & \mathbf{P}(X = 15) &= 6p_s p_r^2 \\ \mathbf{P}(X = 7) &= 6p_s p_u p_r & \mathbf{P}(X = 12) &= 3p_s^2 p_r & \mathbf{P}(X = 16) &= p_r^3.\end{aligned}$$

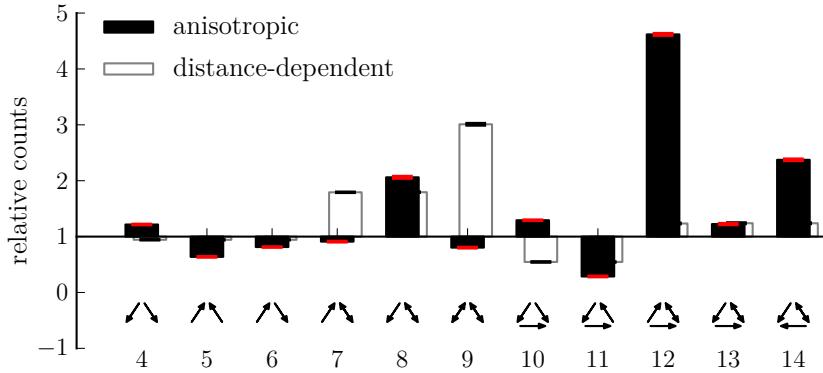


Figure 4.12: Relative occurrence of three-neuron patterns Extracting the counts of three-node motifs in anisotropic (filled bars) and distance-dependent networks (unfilled bars), the quotient of the obtained count with the number of occurrences expected from the two-neuron connection probabilities in the networks (cf. Section 4.4) shows the over- and underrepresentation of specific motifs in the network (red and black errorbars are SEM). In anisotropic networks pattern 12, for example, appears around five times more often than we would expect from the occurrence two-neuron connections. The relative counts for anisotropic networks resemble the findings of Song et al. (2005) and differ significantly from the counts in distance-dependent networks, implying that anisotropy has a strong influence on the relative occurrence of three-neuron patterns. (4839ce41)

distribution from
neuron-pairs as
reference

Does this distribution accurately reflect the occurrences of three-neuron motifs in anisotropic or even distance-dependent networks? Here we take the distribution determined from the two-neuron probabilities as a reference to analyze occurrences of three-neuron motifs in our sets of sample graphs. Counting the occurrences of patterns in we find that there are significant over- and underrepresentations in anisotropic as well as distance-dependent networks, relative to our expectation (Figure 4.12). We find, for example, that in anisotropic graphs pattern 12 occurs almost 5 times as often as we would have expected from the two-neuron probabilities, whereas the counts for pattern 11 only make up less than 30% of the occurrences expected.

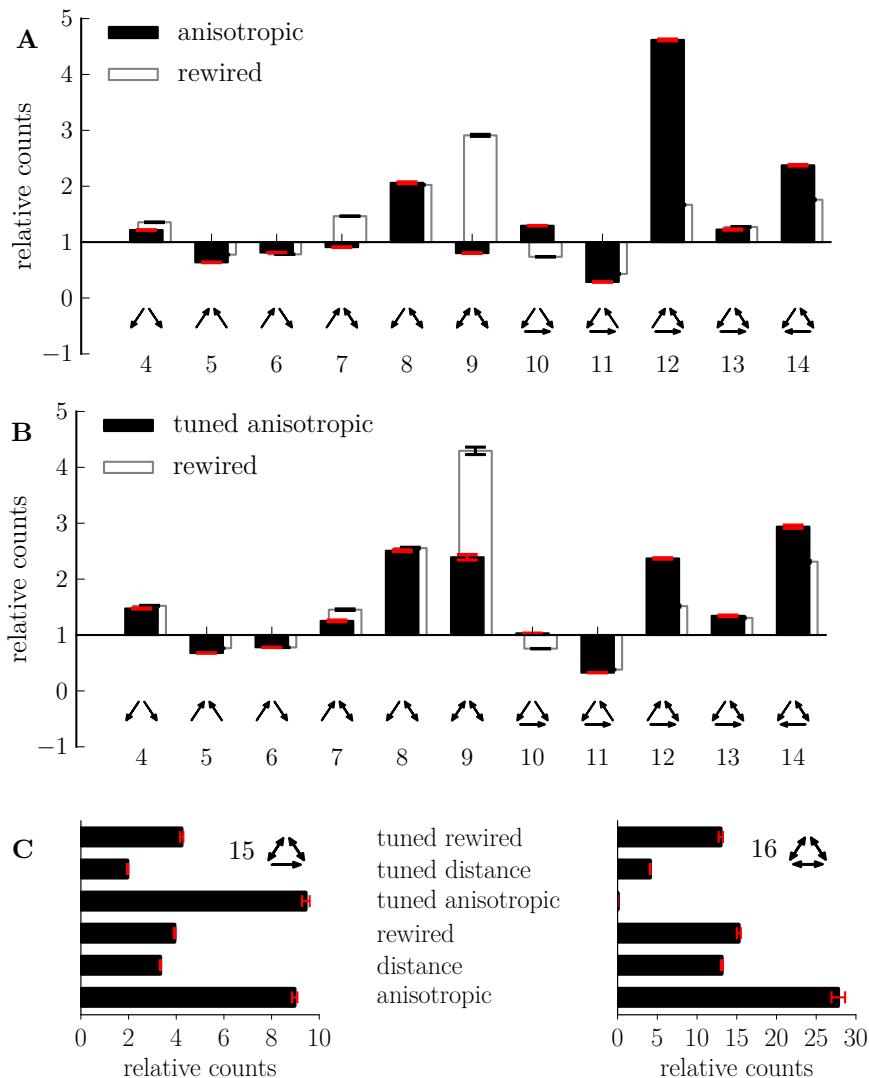


Figure 4.13: Three-neuron motif occurrence in different network types **A)** Comparing counts in anisotropic sample graphs with their rewired counterparts. **B)** Three-neuron motifs occurrence in tuned anisotropic networks (cf. Section 4.5) with their rewired counterparts. For this two-neuron connection probabilities were extracted as in Section 4.4 and motif probabilities were calculated analogously to anisotropic networks. **C)** Relative counts for the high edge count motifs 15 and 16 for different network types, errorbars SEM. (4839ce41)

Comparing the relative counts for motifs in anisotropic graphs with those in comparable distance-dependent networks, we identify a strong influence of anisotropy in connectivity on three-neuron motif occurrence (Figure 4.12). In their experiments, Song et al. and Perin et al. find an overrepresentation of motifs 4, 10, 12 and 14. In anisotropic networks increased counts of motifs 4, 8, 10, 12, 13 and 14 were recorded. However, motifs 8 and 13 are overrepresented in distance-dependent

*anisotropy
strongly affects
3-motif occurrence*

networks as well, leaving the reported motifs 4, 10, 12 and 14 as motifs that are overrepresented due to anisotropy. To analyze this effect closer, we also compare three-neuron counts before and after rewiring in anisotropic networks ([Figure 4.13](#)).

Considering motif occurrences in anisotropic as well as tuned anisotropic networks, we once again confirm the overrepresentation of motifs 4, 10, 12 and 14. However, increased counts of pattern 4 are observed in the rewired networks as well, leading to the conclusion that increased occurrence in this motif is only implicitly affected by anisotropy. Motifs 10, 12 and 14 however show significant overrepresentation even over their rewired counterparts in anisotropic as well as in tuned anisotropic networks.

The overall motif distribution shows itself stable under changes in the distance-dependency with the notable exception of motif 9, that shows underrepresentation only in anisotropic but not in tuned anisotropic or any distance-dependent network type. Analyzing the occurrences of motifs 15 and 16 with a high edge counts ([Figure 4.13 C](#)) we find that anisotropy has strong influence on both motifs, with motif 15 being significantly overrepresented in anisotropic networks. Motif 16 shows a highly increased occurrence in anisotropic networks, however tuning causes the loss of this feature in the network connectivity.

results summary

Summarizing the above observations, we find that anisotropy in connectivity induces increased occurrence of motifs 10, 12, 14 and 15 in the network, reflecting experimental results in the rat's cortex. While over- and underrepresentation observed in local cortical circuits can be indirectly linked to anisotropy for some motifs (4, 9), it does not accurately reflect observed counts for other motifs (8) and shows instability under manipulation of distance-dependency in some patterns (9, 16).

On motif occurrence in networks

In obtaining and discussing the previous results, we closely followed the approach described by [Song et al. \(2005\)](#). Here, relying on analytical considerations, we submit these results to a critical analysis and identify potential caveats when dealing with motif distributions in distance-dependent networks.

For this consider for example the motifs 9, 15 and 16 as labeled above. In distance-dependent networks we find that each of the patterns is overrepresented, observing that the motifs occur about 3, 3 and 12 times more often than expected from the two-neuron connection probabili-

ties, respectively (Figure 4.12). Thus, in distance-dependent networks, triplets in which two of the pairs are reciprocally connected appear more often than expected, regardless of the connectivity in the third pair. This is surprising, as probabilities for the first two neuron pairs in a triplet should be independent and the probabilities of obtaining a certain connectivity should reflect the product of two-neuron probabilities. The overrepresentation found in these motifs may thus not necessarily be an inherent feature of the network connectivity but rather an artifact of triplet selection.

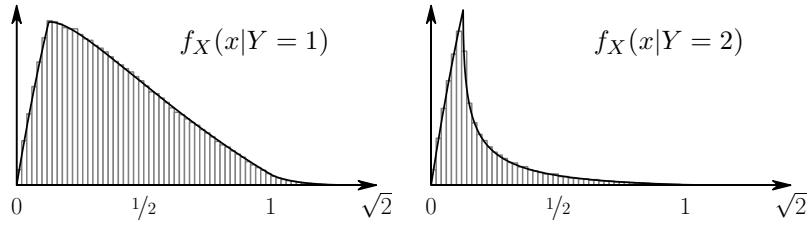
To analyze this further, we compute the relative probabilities of occurrence for motifs 9, 15 and 16. Formulated differently, given a triplet with two reciprocally connected pairs, what is probability of connection in the third pair? For this we first find the probability density function of the distance between a random neuron pair, given that we know its connectivity, meaning the existence of either 0, 1 or 2 edges between the neurons. Let X be the random variable mapping a random neuron pair of neurons to the distance between them and Y the random variable mapping to the number of edges between the pair. By the relation

$$f_X(x|Y = n) = \frac{f_{X,Y}(x,n)}{\mathbf{P}(Y = n)},$$

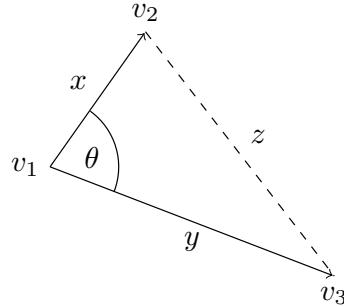
for $n = 0, 1, 2$, the probability density function f_X of the continuous variable X conditioned on the discrete variable Y , are then computed as the quotients

$$\begin{aligned} f_X(x|Y = 0) &= \frac{f(x)(1 - C(x))^2}{\int_0^{\sqrt{2}} f(x)(1 - C(x))^2 dx} \\ f_X(x|Y = 1) &= \frac{f(x)2C(x)(1 - C(x))}{\int_0^{\sqrt{2}} f(x)2C(x)(1 - C(x)) dx} \\ f_X(x|Y = 2) &= \frac{f(x)C(x)^2}{\int_0^{\sqrt{2}} f(x)C(x)^2 dx}, \end{aligned} \quad (4.6)$$

where $f(x)$ is the probability density function of the distance between two random in the unit square the found in Theorem 2.15 and $C(x)$ the distance-dependent connectivity from Theorem 3.3. Values for the denominator in Equation 4.6 have already been determined in Section 4.4. Evaluating the products in the numerator, we find that the expected probability density function is perfectly match by the distance distributions found in the simulated distance-dependent network model (38c11969):



Consider then a triplet with vertices v_1, v_2 and v_3 , the pairs (v_1, v_2) and (v_1, v_3) being reciprocally connected. With the density function $f_X(x|Y=2)$ we then have a distribution for the distances $x = d(v_1, v_2)$ and $y = d(v_1, v_3)$. In the triangle spanned by the positions of the vertices, the distance $z = d(v_2, v_3)$ is then determined by the angle θ between x and y :



By the law of cosines, between x, y, z and θ we have the relation

$$z = \sqrt{x^2 + y^2 - 2xy \cos \theta}. \quad (4.7)$$

From this we can, extensively using Lemma 2.14, calculate the probability density of z in the triplet (v_1, v_2, v_3) from the densities $f_X(x|Y=2)$ of x and y , similar to the proof of Theorem 2.15. Here, however, it suffices to find the expected value of z . The expected values for x and y are

$$r := \mathbf{E}[x] = \mathbf{E}[y] = \int_0^{\sqrt{2}} x f_X(x|Y=2) dx.$$

Finding the expected value of z is then the well known problem of determining the length of a chord between two random points on the circle (cf. Weisstein 2014). For $x, y = r$, Equation 4.7 becomes

half-angle formula,
Abramowitz and
Stegun (1964)

$$z(\theta) = r \sqrt{2 - 2 \cos \theta} = 2r \left| \sin \frac{\theta}{2} \right|.$$

Using the symmetry of the problem, we then find the expected value

for z by integration,

$$\begin{aligned}\mathbf{E}[z] &= \int_0^{2\pi} \frac{1}{2\pi} z(\theta) d\theta \\ &= \int_0^{2\pi} \frac{r}{\pi} \left| \sin \frac{\theta}{2} \right| d\theta \\ &= \frac{2r}{\pi} \int_0^{\pi} \sin \frac{\theta}{2} d\theta = \frac{4r}{\pi}.\end{aligned}$$

With the expected distance z we can finally calculate the relative probabilities to obtain either motif 9, 15 or 16 from the distance-dependent connectivity profile $C(x)$. If Z is the random variable mapping given a triplet (v_1, v_2, v_3) with reciprocal connections between v_1 and v_2 , as well as v_1 and v_3 to the labels of the possible motifs 9, 15 or 16 describing the triplet, the distribution is (Mathematica A.2)

$$\begin{aligned}\mathbf{P}(Z = 9) &= (1 - C(\mathbf{E}[z]))^2 &= 0.697628 \\ \mathbf{P}(Z = 15) &= 2C(\mathbf{E}[z])(1 - C(\mathbf{E}[z])) &= 0.275227 \\ \mathbf{P}(Z = 16) &= C(\mathbf{E}[z])^2 &= 0.0271455.\end{aligned}\tag{4.8}$$

What relative occurrences would be expect from the two-neuron connection probabilities? For this we take the probabilities to find motifs 9, 15 and 16 under all motifs,

$$\mathbf{P}(X = 9) = 3p_r^2 p_u, \quad \mathbf{P}(X = 15) = 6p_s p_r^2, \quad \mathbf{P}(X = 16) = p_r^3,$$

and normalize the probabilities by their sum. Building the quotient of the calculated relative probabilities \mathbf{P} from (4.8) with the expected relative frequency \tilde{F}_2 , inferred from two-neuron connectivity, we find the relative overrepresentation in the family of triplets with two reciprocal connections.

	\tilde{F}_2	\mathbf{P}/\tilde{F}_2	$k\mathbf{P}/\tilde{F}_2$	F_2
9 	0.677625	1.0295	3.2408	2.9852
15 	0.315379	0.8727	2.7471	3.2810
16 	0.006997	3.8797	12.2126	12.9001

(label: b5e4ed3e)

We note that amongst triplets with two reciprocal connections, motif 16 appears about four times as often as expected, while motifs 9 and 15 are not significantly over- or underrepresented. How do these numbers relate to the absolute overrepresentation F_2 amongst all three-motifs? We find that triplets with two reciprocal connections appear $k = 3.1478$

as often amongst all three-motifs as expected (b5e4ed3e); multiplying the quotient P/F_2 with k then yields an absolute overrepresentation as found in the simulated distance-dependent networks.

summary & discussion

In distance-dependent networks, independence in the connectivity of the first two neuron pairs was expected. From our simulations, however, we clearly find that all triplets with at least two reciprocally occur more frequently than expected. This is due to boundary effects - neurons located close to the border or even a corner have drastically different distribution of distances to all other neurons as node located close to the center. Thus, rectifying for this bias, the “true” overrepresentation was calculated in (4.8), finding only motif 16 with an increased occurrence relative to the expectation.

Fortunately, results in anisotropic networks remain unaffected by this problem. As only statements relative towards rewired or distance-dependent networks were made, both containing this bias, overrepresentation due to anisotropy could still be accurately identified. Song et al.’s three-motif distribution also does not immediately show this problem. While, for example, motifs 9, 15 and 16 are all reported as overrepresented, it is well in the error margin of their experiment to have triplets with at least two reciprocal connections appearing overall as expected. However, the analysis shown here may well be important for further studies in brain connectivity, testing results against potential biases, or, gaining new insights on neuronal connectivity, finding without doubt that such overrepresentations do occur.

Edge counts in neuron clusters

In motifs consisting of 3 to 8 neurons, Perin et al. (2011) reported a striking statistic from their experiment with pyramidal cells in the rat’s somatosensory cortex, layer 5: Counting the number of edges appearing in a cluster of n neurons, they find that clusters with relatively high edge counts appear significantly more often than expected from the network’s distance-dependent connection probabilities alone. Do anisotropic networks exhibit a similar feature?

Recruiting the collection of sample graphs once again we analyze the occurrence of edge counts in clusters of n neurons in the different network types. In the main process, after randomly sampling n pairwise different vertices S_n , the motif H in G with vertex set $V(H) = S_n$ is identified and its number of edges $|E(H)|$ is recorded. Repeating this sufficiently often (order 10^6) we obtain edge counts for clusters of 6,8 and 12 neurons in the anisotropic- and tuned anisotropic networks

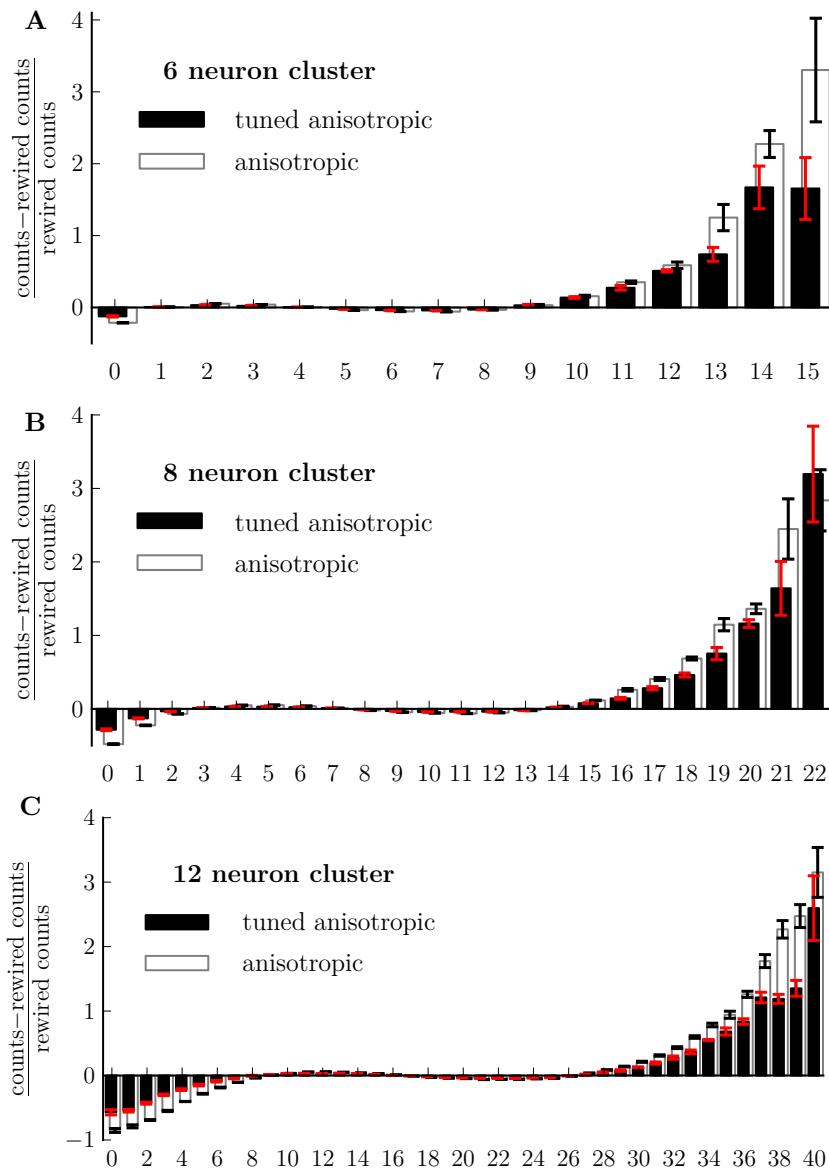


Figure 4.14: High edge counts are overrepresented in networks with anisotropy Normalized difference between number of edges in clusters of 6, 8 and 12 randomly selected neurons in anisotropic networks and rewired networks shows an overrepresentation of high edge counts in networks with anisotropy in connectivity. Errorbars SEM. (76cc6fa0, smtcite987992b0, 54329cf4)

as well as in their rewired counterparts. Then, showing the difference between counts in the anisotropic networks and counts in the rewired networks, normalized by the rewired counts, we identify an overrepresentation of high edge counts in the neuron similar to Perin et al. (Figure 4.14).

In anisotropic networks an overrepresentation of high edge counts is found consistently through clusters of 6, 8 and 12 neurons, with the

highest counts appearing up to four times as often as expected. Low edge counts occur less frequently than expected and an increasing number of connections shows an oscillation around the expectation. These findings are consistent with the report of Perin et al, which however indicates a higher maximal overrepresentation in clusters of 8 neurons.

Tuning the network's distance-dependency appears to not affect the overrepresentation as edge counts in anisotropic and tuned anisotropic essentially match (Figure 4.14). Anisotropy in connectivity therefore presents itself as an important factor in the occurrence of increased high edge counts in cortical networks, possibly fully reflecting the findings of Perin et al., as the overrepresentation effect is found to be even stronger when comparing edge counts to distance-dependent networks as opposed to rewired versions (Figure 4.15).

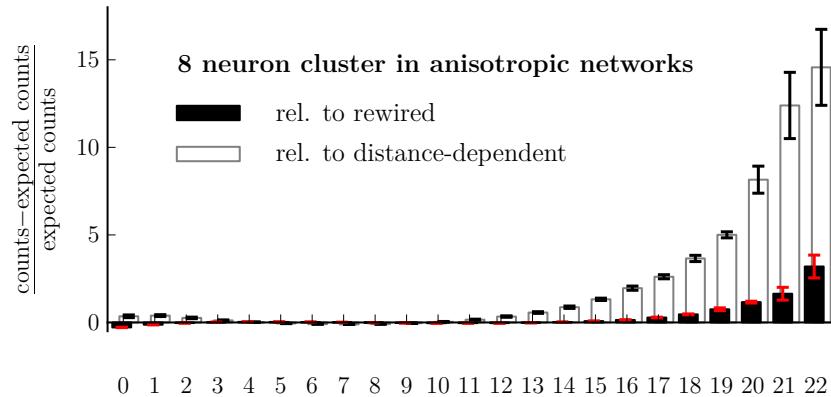


Figure 4.15: Stronger overrepresentation of clusters with high edge counts with distance-dependent networks as reference

Showing the occurrence of edge counts in clusters of 8 random neurons, we find that the overrepresentation of motifs with high edge counts is stronger when taking distance-dependent networks as a reference as opposed to rewired networks. (7c826e10)

4.7 COMMON NEIGHBOR RULE

common neighbor rule as underlying principle?

In their study, Perin et al. follow their report of increased edge counts in neuron clusters with the observation of a “common neighbor rule”: Relying once again on their data in the rat's somatosensory cortex, Perin et al. find that not only do neuron pairs with a high number of common neighbor count appear significantly more often than expected, but also that such pairs display a higher probability of being connected. In fact, the relationship between pair connectivity and number of common neighbors appears to be linear. Perin et al. also report that this effect

is most pronounced when only considering common in-neighbors, that is other neurons that are projecting to both neurons in the pair.

Here we also investigate our networks for the existence of such a common neighbor relationship. Simultaneously recording connection probabilities and the number of common neighbors between pairs of neurons, we find inherent dependencies between the two quantities in all network types (Figure 4.16).

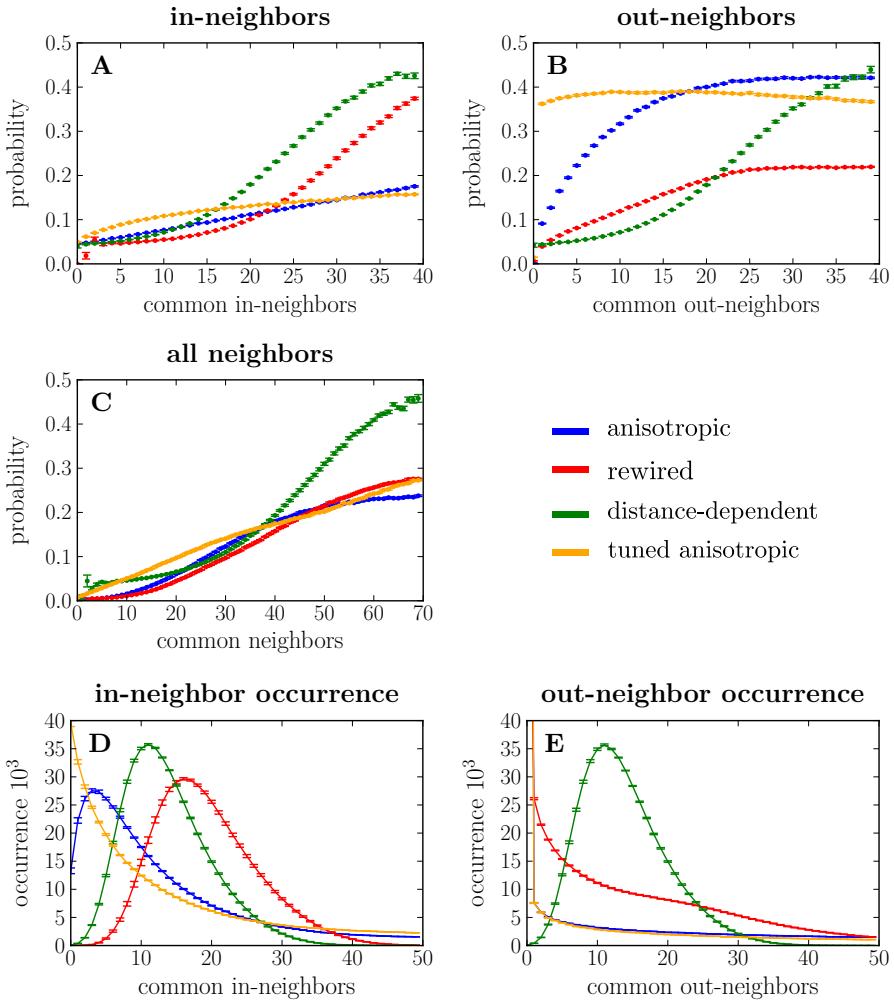


Figure 4.16: Common neighbor rules in the different network types

Showing the dependency of connection probability on the number of shared neighbors for random neuron pairs, characteristic curves for the network types (see legend) arises. High error margins (errorbars SEM) for small number of common neighbors in distance-dependent networks is induced by vanishingly low occurrence of a small common neighbor count. (5841710e)

Analyzing the results, we immediately note the sharp difference between in- and out-neighbors in their effect on connection probabili-

ties in anisotropic networks, as well as in rewired networks. Only in distance-dependent networks it appears that in- and out-neighbors can be considered equivalent in their influence on connection probabilities ([Figure 4.16 A-B](#)). Furthermore, while the distribution of the number of common neighbors is consistent in distance-dependent networks, the other network types display a characteristic distribution of common out-neighbors ([Figure 4.16 D-E](#)). While the latter observation clearly also relates to the differences in out-degree distributions found in [Section 4.2](#), finding differences between common inputs and outputs in neuron pairs is consistent with the observations of Perin et al., who report a significant difference in effect of the common neighbor rule. In trying to model the inherently asymmetric axonal-dendritic connections between pyramidal cells in cortical circuits with the anisotropic networks, finding such disparity is not only expected but gives the model further validity as an approach to obtain network connectivity going beyond the distance-dependent archetype, which here fails to produce diverging connectivity statistics for in- and outputs.

Both for in- and out-neighbors, we find characteristic curves describing their influence on connection probabilities. The in-neighbor profiles split into two categories: While networks with anisotropy in connectivity (blue, orange) display a constant increase, distance-dependent network types (red, green) show a sigmoidal shared input-connection probability curve ([Figure 4.16 A](#)). We thus find a strong influence of anisotropy on the shared input relationship, inducing a common neighbor rule characteristically different from isotropic, distance-dependent networks.

Does this anisotropy-induced rule reflect the findings in cortical networks? Perin et al. report a linear common neighbor relationship, finding a stronger effect when considering only in-neighbors. Imposing the common neighbor rule on *in silico* networks reflecting a distance-dependency as determined *in vivo*, Perin et al. were then able to reproduce the observed overrepresentation of high edge counts in neuron clusters, identifying the common neighbor effect as an underlying connection principle inducing increased high edge counts in clusters comparable to the profiles shown in [Figure 4.14](#). Showing not only the presence of such an edge count overrepresentation in anisotropic networks, but also finding that only networks featuring anisotropy display an approximately linear relationship between common inputs and connection probability, we identify anisotropy in connectivity as a candidate for an underlying connection principle motivated from neuronal morphology, to induce a common neighbor rule, that may be at the heart of many of the non-random connectivity statistics observed in local cortical networks.

*anisotropy induces
characteristic
common neighbor
rule*

*anisotropy as
underlying
connection
principle!*

Extending the analysis of shared inputs in the different network types, we further observe that anisotropy affects the number of common in-neighbors typically observed itself (Figure 4.16 D). We specifically find that increases anisotropy in connectivity induces an increased variance in the distribution of common inputs of a random neuron pair Figure 4.17). Such increased variance may provide an important advantage in the processing of information, allowing a heightened functional specificity in the network, where many neurons do not share many common inputs, enabling a high variety of functionality, and where few neuron pairs have a high number of shared inputs, strengthening their correlation and thus their capacity to relay related information.

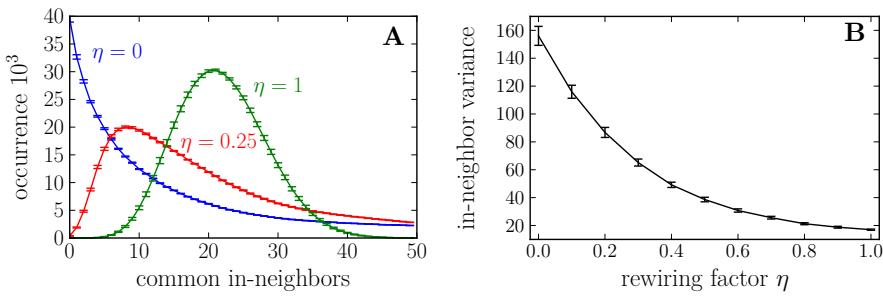


Figure 4.17: Anisotropy increases variance of common input distribution

Recording common in-neighbor counts for random neuron pairs in tuned anisotropic networks and their rewired versions reveals increased variance in networks with a high degree of anisotropy. **A)** Common in-neighbor distribution for original tuned anisotropic networks ($\eta = 0$, blue) and rewired versions with 1/4 of all edges rewired ($\eta = 0.25$, red) and completely rewired ($\eta = 1$, green). (5841710e) **B)** Variance of the common in-neighbor distributions declines with increasing rewiring factor η ; highest variance is found in networks with the highest degree of anisotropy ($\eta = 0$). Errorbars SEM. (ffcefef9b)

4.8 DISCUSSION

The structural analysis of anisotropic networks revealed connectivity characteristically different from comparable distance-dependent or even rewired networks. Such differences however only occur when considering patterns in connectivity of three or more neurons, pair connections and standard network measures remain unaffected.

Accordingly, vertex degree distributions in anisotropic networks were found to have increased variance and skew, but as rewired and distance-dependent networks also show this feature, this is only indirectly caused by network anisotropy. Similarly, while anisotropic networks display a small-world property, short path lengths and high clustering coefficients are not due to anisotropy, but stem from the network's distance-dependency. In fact we find that eliminating anisotropy in the network can lead to even shorter path lengths and higher clustering, strengthening the small-worldness of the network. Finally, we were able to present conclusive evidence that anisotropy is not able to reproduce overrepresentation of reciprocally connected neuron pairs, reported repeatedly in cortical networks.

In terms of higher order connectivity however, anisotropy yields highly interesting results. Three-neuron motif occurrences are not only strongly influenced by anisotropy, but resulting overrepresentations resemble in many aspects the profiles found by [Song et al. \(2005\)](#). Furthermore, anisotropy in connectivity induces an increased frequency of high edge counts in neuron clusters, matching results from experiments in the rat's cortex ([Perin et al. 2011](#)). In their study, Perin et al. were able to relate such edge count overrepresentations to a *common neighbor rule* - a specific relationship between shared in- or outputs of a neuron pair and the probability of connection in the pair. Being able to reproduce increased high edge counts by imposing such relation on distance-dependent networks, the common neighbor rule was identified as an underlying organization principle. By the interpretation of the authors, stereotypically connected clusters arising from this rule then constitute “building blocks” of cortical networks to be molded by experience.

In this study, anisotropy was recruited as a connection principle for the generation of geometric networks, reflecting the dimensions of typical cortical slices. Capturing stereotypical axonal and dendritic morphology of pyramidal cells in the cortex, those anisotropic networks inherently feature connectivity going beyond distance-dependency. Indeed, not only do anisotropic networks display non-random patterns as found in local cortical circuits, but we were here able to show that a common neighbor rule itself is highly affected by anisotropy. Together, these

findings promote the concept of anisotropy as an important underlying connection principle.

The results presented here provide new insight in how non-random connectivity in cortical circuits may arise from morphological characteristics inherent to cells in cortical networks. Employing an abstract model, capturing stereotypical axonal and dendritic morphology, allowed for an analytical and numerical analysis, revealing the strong impact of anisotropy on structural aspects in neural networks. Certainly such an oversimplified model brings caveats; as a consequence of the chosen axon shapes, for example, directions of axonal projections had to be chosen at random, while statistics from the cortex imply alignment of axons. Also, the choice of positioning of the neurons on a surface risks the loss of information contained in three-dimensional, spatial networks. However, basing the analysis on comparisons with otherwise identical networks lacking anisotropy, the chosen abstractions serve the aim of this report in identifying the role of anisotropy in determining structural aspects of geometric neural networks as precisely as possible.

With anisotropy likely being only one amongst many potential morphology-induced connectivity principles, the results here make an important case for the study and inclusion of morphological aspects in future of networks models. The presented connectivity principle may provide a first step towards a network archetype better resembling non-random connectivity features found in cortical circuits. As such patterns of connectivity were found to strongly affect network dynamics (Pernice et al. 2011; Zhao et al. 2011), development in this direction is crucial. Furthermore, underlying principles may reveal unexpected, not yet reported connectivity statistics. Here we found that the distribution of the number of common inputs for a random neuron pair shows a drastically higher variance in networks with a high degree of anisotropy, potentially enabling an increased functional specificity in the networks.

As continuously evolving experimental techniques and efforts provide more and more information on brain connectivity, identification of connection principles will become ever more important. This work provides an important aspect in the discussion and identification of such underlying principles, implying that neuronal morphology may play a crucial role in network connectivity. Countering arguments focusing heavily on plasticity as connection principles, the observations here may contribute to a differentiated discussion of underlying principles including various aspects of brain networks, in the hopes of finding consistent models for connectivity in the different areas of the brain.

5

OUTLOOK: DYNAMICAL ASPECTS

So far the focus of this study lay in uncovering how anisotropy affects structural aspects of geometric neural networks. Finding that higher order connectivity is indeed strongly influenced by anisotropy, the question arises if and how anisotropy affects dynamical aspects as well. The answer to the first question was heavily implied throughout this thesis; referencing once again the convincing evidence of network structure affects various dynamical aspects (Pernice et al. 2011; Zhao et al. 2011), we expect that anisotropy does in fact display a strong influence on network dynamics. The second question, however, is not as easily answered and opens up a whole new direction of study, which goes beyond the scope of this report.

However, as an outlook on what surprising results one might find investigating this topic we further, we here show how anisotropy in connectivity affects network dynamics in a linear rate model. Considering a system of n neurons receiving some external input \mathbf{s} , in such model the rate vector $\mathbf{r}(t)$, describing the activity for each neuron at time t , is governed by the differential equation

$$\dot{\mathbf{r}} = -\mathbf{r} + W\mathbf{r} + J_S\mathbf{s}, \quad (5.1)$$

where W is the weight matrix of the network, reflecting its connectivity (Sadeh et al. 2014). Each column in the $n \times n$ matrix corresponds to a neuron in the network, determining the cell to either be of inhibitory or excitatory nature. The weight matrix then carries positive, non-zero entries in the columns of excitatory neurons wherever an edge exists in the network, i.e. $W_{ij} \neq 0$ is a necessary and sufficient condition for the existence of an edge e with $s(e) = j$ and $t(e) = i$. The columns of inhibitory neurons carry non-zero, negative entries.

Without examining the equation in detail, we note how solutions of (5.1) are determined by the eigenvalue spectrum of W . We therefore here analyze the eigenvalue spectrum of the weight matrix for anisotropic networks. For this we choose the following, typically used parameters resembling an *inhibition dominated network* (Brunel 2000; Sadeh et al. 2014). First we determine randomly $f = 0.2$ of all neurons to be of inhibitory nature, the rest being excitatory. Weights for existing edges are then given as $J = 0.136$ mV in the excitatory case and $-gJ$ in the

inhibitory case, making up with a factor $g = 8$ for the smaller inhibitory population.

Analyzing the eigenvalue spectrum of weight matrices of anisotropic and rewired networks, we find that the spectrum in anisotropic graphs clusters more tightly around the origin. While the estimated radius of the bulk of the spectrum (computed as described by [Rajan and Abbott \(2006\)](#)) is not affected, eigenvalue density peaks close to the origin in anisotropic networks, whereas rewired networks show a much flatter distribution ([Figure 5.1](#)). Interestingly, eigenvalue densities in anisotropic and rewired networks match perfectly with their tuned counterparts, implying that while anisotropy does strongly affect the density distribution, varying distance-dependency has no effect at all.

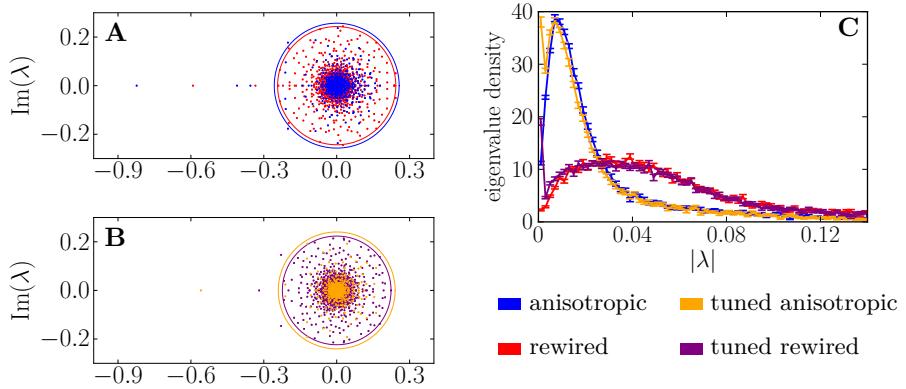


Figure 5.1: Anisotropy in connectivity reduces spread of eigenvalues

The complex eigenvalue spectra of weight matrices (additionally normed by $V_{\text{reset}} = 20 \text{ mV}$) of anisotropic and rewired graphs (**A**), and their tuned versions (**B**), show a higher clustering in anisotropic networks. Circle indicates the radius of the bulk spectrum, computed as described by [Rajan and Abbott \(2006\)](#). The density of eigenvalues λ decreases characteristically with rising $|\lambda|$. Note that the two anisotropic networks and the two rewired networks have perfectly matching density distributions (**C**), implying that while anisotropy strongly affects the density distribution, varying distance-dependency does not at all. Errorbars SEM. (65552fe9)

In the dynamical context, radius and density of the bulk spectrum are closely associated with the network's stability under perturbations. Therefore, using a linear rate model for a dynamical investigation of anisotropic networks, we here find a first hint of dynamical aspects directly influenced by anisotropy in connectivity, establishing a promising prospect for a more detailed dynamical analysis in the future.

A

APPENDIX

A.1 REPRODUCIBILITY OF COMPUTATIONAL RESULTS

Computational implementations of network models and numerical analysis of their features are an integral part of this study. In order to ensure the reproducibility of this part of the analysis, *Sumatra*¹, a software for provenance capture of computational projects, was used. As a “lab notebook for computational researchers”, the software combines version control of code with the capture of inputs and outputs, as well as the used parameter sets, for each computational process (Davison 2012). Providing a database and various interfaces, the tool allows not only direct management of simulations and data but provides a platform to make the computational reproducible and accessible to others.

In this study, for every computational result referenced in the text, a label was cited, referring to the record of the process in Sumatra’s database. Code and produced data are understood as part of the work of this thesis; giving references to computational processes in which the results were obtained, allows the reader at any point to see the exact implementation of the described process or to look up a parameter not explicitly mentioned in the text (Figure A.1). Through this, the work presented here displays reproducibility and transparency of the described methods and results, meeting this important requirement in all scientific work.

Sumatra labels

Further contributing to the reproducibility of this work is the exclusive use of free and open source software. With the single exception of *Mathematica*², all tools used to create this work are freely available and can be modified as their source code is openly accessible. The list of software used in this thesis includes, additionally to the programs mentioned throughout the text, *GNU Emacs*³, *Inkscape*⁴, *GNU Image*

use of free, open source software

¹ Sumatra: Automated tracking of scientific computations. Available at <http://neuralensemble.org/sumatra/>

² Wolfram Mathematica Version 7.0.1.0. See <http://www.wolfram.com/mathematica/>

³ GNU Emacs Version 24.3. Free Software Foundation. Available at <http://www.gnu.org/software/emacs/>

⁴ Inkscape Version 0.48.3.1. Available at <http://www.inkscape.org>

*Manipulation Program*⁵ and *TeX Live*⁶. The document's layout is based on an adapted version of *Classicthesis*⁷.

```
-----
Label      : com_inp_N500-trials5-step010
Timestamp  : 2014-06-06 17:29:39.663398
Reason     : common input variance
Outcome    :
Duration   : 1087.83452988
Repository : GitRepository at /users/hoffmann/research
Main_File  : comp/common_input_variance.py
Version    : 10690e97199851f08955ed7944f7eadfe71b4bf2
Script_Arguments : com_inp_N500-trials5-step010 <parameters>
Executable  : Python (version: 2.7.3) at /usr/bin/python
Parameters  : rew_frac_min = 0.1
              : n_trials = 5
              : rew_margin = 1.25
              : Torus = False
              : l_ax = 1000
              : rew_frac_max = 1.0
              : N = 500
              : ed_l = 296
              : rew_frac_step = 0.1
              : save_the_graph = True
              : comp_label = "common_input_variance/"
              : self_loops_allowed = False
              : parallel_edges_allowed = False
Input_Data  : []
Launch_Mode : serial
Output_Data : [common_input_variance/com_inp_N500-trials5-step010.p
              : (1aacdd2202ba8ce6a419b6e8cf5d241c2ef37454)]
User       : Felix Hoffmann <Felix11H@github.nomail>
Tags       : clustering
-----
```

Figure A.1: Example Sumatra record entry Showing the label, parameter set and outputs, Sumatra record entries display the full information required to reproduce referenced results. The version number is here of critical importance; it refers to a snapshot of the code base at the time of simulation. Through it the exact code at this point can be recovered and used to reproduce results.

⁵ GNU Image Manipulation Program Version 2.8.8. Available at <http://www.gimp.org/>

⁶ Tex Live 2012. D.E. Knuth. Available at <https://www.tug.org/texlive/>

⁷ Classicthesis 4.1. André Miede. Available at <http://www.ctan.org/pkg/classicthesis>

A.2 MATHEMATICA

```

In[1]:= f[d_] = Piecewise[{{1 / (s * (d)^(1/2)) - 1 / (s^2), 0 < d < s^2}, {0, d > s^2}}]
Out[1]= 
$$\begin{cases} -\frac{1}{s^2} + \frac{1}{\sqrt{d}} & 0 < d < s^2 \\ 0 & \text{True} \end{cases}$$


In[2]:= g[x_] := Convolve[f[d], f[d], d, x, Assumptions -> {d ∈ Reals, x ∈ Reals}]
Simplify[g[x], {s > 0, x ∈ Reals}]
Out[2]= 
$$\begin{cases} \frac{\pi s^2 - 4 s \sqrt{x+x}}{s^4} & x > 0 \&& s^2 \geq x \\ -\frac{2 s^2 + x + \frac{4 \pi^3}{\sqrt{-s^2+x}} - \frac{4 \pi x}{\sqrt{-s^2+x}} - 2 s^2 \operatorname{ArcTan}\left[\frac{s}{\sqrt{-s^2+x}}\right] + i s^2 \operatorname{Log}\left[s-i \sqrt{-s^2+x}\right] - i s^2 \operatorname{Log}\left[s+i \sqrt{-s^2+x}\right]}{s^4} & s^2 < x \&& 2 s^2 > x \\ 0 & \text{True} \end{cases}$$


In[3]:= h[x_] := g[x^2] * 2 * x
In[4]:= Simplify[h[x], {s > 0, x ∈ Reals, x > 0}]
Out[4]= 
$$2 x \begin{cases} \frac{\pi s^2 - 4 s x + x^2}{s^4} & s \geq x \\ -\frac{2 s^2 + x^2 + \frac{4 \pi^3}{\sqrt{-s^2+x^2}} - \frac{4 \pi x^2}{\sqrt{-s^2+x^2}} - 2 s^2 \operatorname{ArcTan}\left[\frac{s}{\sqrt{-s^2+x^2}}\right] + 2 s^2 \operatorname{ArcTan}\left[\frac{\sqrt{-s^2+x^2}}{s}\right]}{s^4} & s < x \&& \sqrt{2} > x \\ 0 & \text{True} \end{cases}$$


In[5]:= (*For s == 1, h becomes*)
In[6]:= Simplify[h[x], {s == 1, x ∈ Reals, x > 0}]
Out[6]= 
$$2 x \begin{cases} \pi + (-4 + x) x & x \leq 1 \\ -2 - x^2 + 4 \sqrt{-1 + x^2} - 2 \operatorname{ArcCot}\left[\frac{1}{\sqrt{-1+x^2}}\right] + 2 \operatorname{ArcTan}\left[\frac{1}{\sqrt{-1+x^2}}\right] & 1 < x < \sqrt{2} \\ 0 & \text{True} \end{cases}$$


In[7]:= (*Expected Value*)
s := 1.
Integrate[x * h[x], {x, 0, Sqrt[2]}]
Out[7]= 0.521405

```

Mathematica A.1: Computation of probability density function for distance between two random points in square of side length s as supplement to proof of Theorem 2.15. Note that form of final result Out[7] differs from solution given in 2.15 for $1 < x < \sqrt{2}$. While proof of equivalence could not be achieved analytically, expressions given are numerically equivalent.

```

In[200]:= (*Expected distance between reciprocally connected pairs*)
r = NIntegrate[x * w[x] * c[x]^2 / 0.02451, {x, 0, Sqrt[2]}]
Out[200]= 0.20001

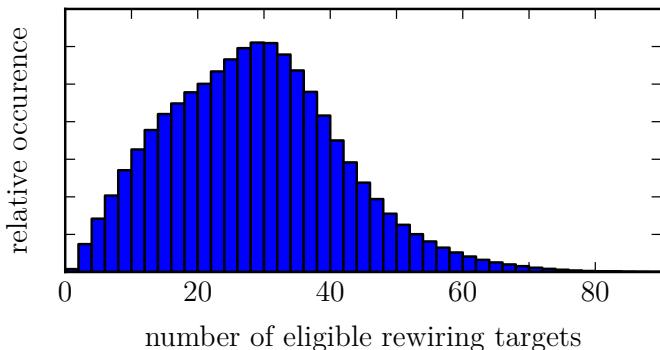
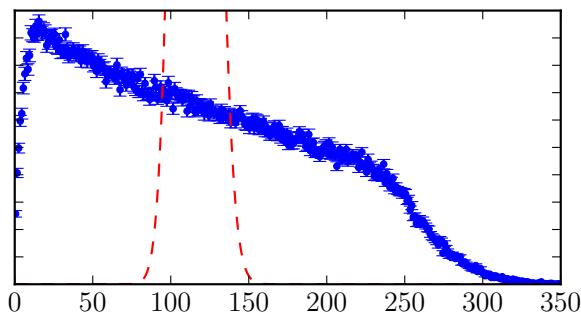
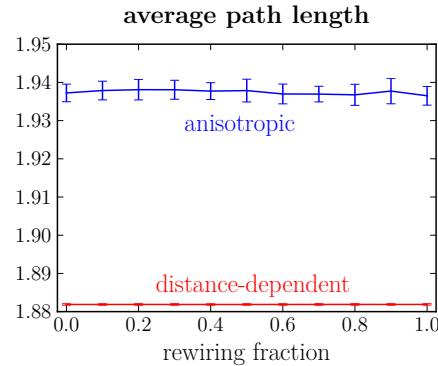
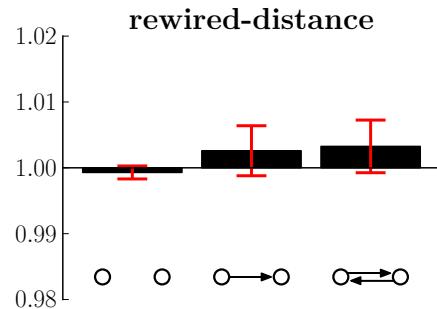
In[201]:= (*Probability of connection in third pair when other two are reciprocally connected*)
p = c[4 / Pi * r]
Out[201]= 0.164749

In[202]:= (*Probabilities for motif 9, 15 and 16 are then*)
(1 - p)^2
2 * p * (1 - p)
p^2
Out[202]= 0.697643
Out[203]= 0.275214
Out[204]= 0.0271424

```

Mathematica A.2: Computation of three motifs for Section 4.6. Function $c[x]$ is the distance-dependent probability distribution from Theorem and $w[x]$ the probability density function for distance between two random points in a box (cf. Mathematica A.1, Moltchanov 2012).

A.3 SUPPLEMENTARY FIGURES

**Figure A.2:** (4afc2727)**Figure A.3:** (c7ee86d7)**Figure A.4:** Average path length for anisotropic and distance-dependent networks, $N = 1000$. (064f9b10)**Figure A.5:** Probabilities for connections in neuron pairs are identical in distance-dependent and rewired anisotropic networks. (c5f1462b)

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ERKLÄRUNG

Hiermit versichere ich, dass ich diese Arbeit selbständig verfasst und nur die angegebenen Quellen und Hilfsmittel benutzt habe.

Freiburg, 17. Juni 2014

Felix Hoffmann