STATISTICAL THEORY OF SYNAPTIC CONNECTIVITY
IN THE NEOCORTEX

A dissertation presented
by
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In partial fulfillment of the requirements for the degree of
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June, 2010
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ABSTRACT OF DISSERTATION

Submitted in partial fulfillment of the requirement
for the degree of Doctor of Philosophy in Physics
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Abstract

Learning and long-term memory rely on plasticity of neural circuits. In adult cerebral cortex plasticity can be mediated by modulation of existing synapses and structural reorganization of circuits through growth and retraction of dendritic spines.

In the first part of this thesis, we describe a theoretical framework for the analysis of spine remodeling plasticity. New synaptic contacts appear in the neuropil where gaps between axonal and dendritic branches can be bridged by dendritic spines. Such sites are termed potential synapses. We derive expressions for the densities of potential synapses in the neuropil. We calculate the ratio of actual to potential synapses, called the connectivity fraction, and use it to find the number of structurally different circuits attainable with spine remodeling. These parameters are calculated in four systems: mouse occipital cortex, rat hippocampal area CA1, monkey primary visual (V1), and human temporal cortex. The neurogeometric results indicate that a dendritic spine can choose among an average of 4-7 potential targets in rodents, while in primates it can choose from 10-20 potential targets. The potential of the neuropil to undergo circuit remodeling is found to be highest in rat CA1 (4.9-6.0 nats/μm³) and lowest in monkey V1 (0.9-1.0 nats/μm³). We evaluate the lower bound of neuron selectivity in the choice of synaptic partners and find that post-synaptic excitatory neurons in rodents make synaptic contacts with more than 21-30% of pre-synaptic axons encountered with new spine growth. Primate neurons
appear to be more selective, making synaptic connections with more than 7-15% of encountered axons.

Another plasticity mechanism is included in the second part of this work: long-term potentiation and depression of excitatory synaptic connections. Because synaptic strength is correlated with the size of the synapse, the former can be inferred from the distribution of spine head volumes. To this end we analyze and compare 166 distributions of spine head volumes and spine lengths from mouse, rat, monkey, and human brains. We develop a statistical theory in which the equilibrium distribution of dendritic spine shapes is governed by the principle of synaptic entropy maximization under a “generalized cost” constraint. We find the generalized cost of dendritic spines and show that it universally depends on the spine shape, i.e. the dependence is the same in all the considered systems. We show that the modulatory and structural plasticity mechanisms in adults are in a statistical equilibrium with each other, the numbers of dendritic spines in different cortical areas are nearly optimally chosen for memory storage, and the distribution of spine shapes is governed by a single parameter – the effective temperature. Our results suggest that the effective temperature of a cortical area may be viewed as a measure of longevity of stored memories. Finally, we test the hypothesis that the number of spines in the neuropil is chosen to optimize its storage information capacity.
Acknowledgments

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# Table of Contents

Abstract ....................................................................................................................... 3
Acknowledgments ......................................................................................................... 5
Table of Contents .......................................................................................................... 6

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Introduction .................................................................................. 8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Potential Connectivity ................................................................... 12</td>
<td></td>
</tr>
<tr>
<td>2.1</td>
<td>Potential synapses and models of potential connectivity ............... 12</td>
<td></td>
</tr>
<tr>
<td>2.2</td>
<td>Volume density of potential synapses ......................................... 14</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Potential of Neural Circuits for Structural Synaptic Plasticity ...... 21</td>
<td></td>
</tr>
<tr>
<td>3.1</td>
<td>The connectivity fraction ............................................................ 21</td>
<td></td>
</tr>
<tr>
<td>3.2</td>
<td>Selectivity of post-synaptic neurons in their choice of pre-synaptic partners ... 26</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Synaptic Entropy .......................................................................... 31</td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Entropic contribution due to structural synaptic plasticity .......... 31</td>
<td></td>
</tr>
<tr>
<td>4.2</td>
<td>Comparison of structural synaptic entropy in different cortical areas .. 39</td>
<td></td>
</tr>
<tr>
<td>4.3</td>
<td>Entropic contribution due to modulatory synaptic plasticity .......... 40</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Generalized Cost of Dendritic Spines ......................................... 45</td>
<td></td>
</tr>
<tr>
<td>5.1</td>
<td>Model of a dendritic spine ........................................................... 45</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

Neural network in the human cerebral cortex consists of around 10 billion neurons linked to one another by more than 10 trillion synaptic connections, made between axonal and dendritic terminals of the neurons [1]. Synaptic input gathered by the dendrites of a pre-synaptic neuron is integrated in the cell body of the neuron and it is transmitted through its axonal terminals towards post-synaptic targets. There are two major classes of neurons and synapses in the brain, inhibitory and excitatory. In the mammalian brain, a large majority of excitatory synapses is made between swellings on axonal branches, called boutons, and small protrusions on the dendritic membrane, referred to as dendritic spines [2].

Neurons have the capacity to create, modify, and eliminate these synapses, resulting on a change in the spines or boutons morphology. Many important brain functions, such as learning and long-term memory formation, are attributed to such changes in synaptic connectivity [3-5]. Several substrates for changes in synaptic connections, or synaptic plasticity, had been discovered experimentally. Some plasticity mechanisms act by modulating the properties of
existing synaptic connections [6-8], while others are responsible for structural modifications of circuits in the neural network [9, 10]. In this study, we examine two major plasticity mechanisms capable of altering synaptic connectivity in adult cerebral cortex with a single synapse resolution; modulation of strengths (potentiation and depression) of excitatory synapses on dendritic spines [11] and structural plasticity by means of growth and retraction of spines accompanied with the formation of new synapses and elimination of the existing ones [12, 13]. These plasticity mechanisms are expected to provide the major avenues for altering neural circuits in adult brain. Furthermore, due to their experience dependent nature, these mechanisms have been suggested to play essential parts in learning and long-term memory formation [9, 10, 14-16].

To quantify the potentials of modulatory and structural synaptic plasticity mechanisms for learning and memory, we developed a statistical theory which encompasses both contributions. Our theory is based on the premise that the strength of an excitatory synaptic connection on a spine is correlated with the volume of the spine head [17-24]. Thus, by analyzing the distribution of spine head volumes, one may infer the strengths of synaptic connections and calculate neuropil’s potential for modulatory synaptic plasticity. Similarly, the number of different connectivity diagrams that can be built with structural synaptic plasticity is dependent on the distribution of dendritic spine lengths [25]. Hence, the shapes of dendritic spines (spine head volumes and spine lengths) in different cortical areas may contain clues to the roles these areas play in learning and long-term memory storage.
**Figure 1.1.** Neuropil and model of the spine. Left: Schematic illustration of a neuropil volume of 3 μm in diameter. Densities of axons (blue segments), dendrites (red segments), axonal boutons (blue spheres), and dendritic spines (red protrusions) are based on data from mouse occipital cortex. Boutons and spines that are in contact form actual synaptic connections. Any axonal and dendritic segment pair is potentially connected if it can be bridged by a dendritic spine. Right: In this model, spines are assumed to extend perpendicularly to dendritic shafts, have straight necks and spherical heads.

**Structural synaptic plasticity**

In the first part of the present work we focused on the structural spine remodeling mechanism. Here, we described the capacity of cortical circuits to change with structural spine remodeling. We considered and compared two possible scenarios of structural plasticity: one where the initial synaptic contact can be made between a dendritic spine and a point on an axon, preceding bouton formation [16], and the other where the initial synaptic contacts are preferentially established with pre-existing synaptic boutons [26]. Locations in the neuropil where synaptic contacts between axonal and dendritic branches can be made with new spine growth are termed potential synapses. Such axo-dendritic oppositions occur at different relative distances between neurites and, as a result, can be bridged by spines of different lengths. Hence, the shape of spine length distribution function is expected to reflect the neuropil’s potential for
spine remodeling [25]. Longer spines can chose among a larger number of potentially pre-synaptic targets leading to a large number of possible circuits. We calculated the density of potential synapses in the neuropil for the two quantitative models of spine remodeling plasticity. We derived an expression for the probability of an actual synapse being present at a potential synaptic site. This probability, or the connectivity fraction (formerly referred to as the filling fraction [16]), was calculated as a function of distance between axonal and dendritic branches. We estimated the number of structurally different circuits that can be achieved by spine remodeling. This number, or structural synaptic entropy, is a measure of the neuropil’s potential for circuit reorganization. Furthermore, we evaluated the selectivity of cortical neurons in their choice of synaptic partners. This selectivity, or probability for one neuron to establish a synaptic connection with another neuron encountered with a new spine growth, gives a sense of the number of functionally different classes of excitatory neurons in a small cortical region.

**Modulatory synaptic plasticity**

In the second part of this thesis, we analyzed the contribution to plasticity due to changes in the strengths of existing synapses, or modulatory synaptic plasticity. Our theory is based on the premise that the strength of an excitatory synaptic connection on a spine is correlated with the volume of the spine head [17-24]. This is likely to result from the insertion/removal of ion channels in dendritic spines, increasing/decreasing the volume of the spine heads during potentiation/depression of synaptic connections. By analyzing the distribution of spine head volumes, we infer the strengths of synaptic connections and calculate neuropil’s potential for modulatory synaptic plasticity.
Chapter 2

Potential Connectivity

2.1 Potential synapses and models of potential connectivity

A potential synapse is a location in the neuropil where the distance $s$ between an axon and a dendrite is small enough to be bridged by a dendritic spine (Figure 2.1A). We made the definition of a potential synapse more precise by considering the following two models. In Model A (Figure 2.1B) we assumed that a spine can bridge the gap between the axon and the dendrite regardless of the presence of a bouton on the axon [16, 27]. As a result, all dendrites that lay within the reach of a dendritic spine from the given axon are potential to that axon. In this model it was assumed that spine outgrowth and spine-axon contact precede bouton and synapse formation. In model B (Figure 2.1C) we assumed that the pre-existence of a bouton on the axon is required for establishing a new synaptic connection [26, 28]. Hence, in this model we defined a potential synapse as proximity between a bouton and a dendritic branch. In other words, all the dendrites that lay within the reach of a dendritic spine from the given bouton are potential to that bouton.
Figure 2.1. Potential synapse. A. 3D reconstructions of a layer 4 spiny stellate cell axon (blue) and a layer 2/3 pyramidal cell dendrite (red) from the cat primary visual cortex. Potential synapses between the arbors are shown with small black circles. Modified from [29]. B and C illustrate two models of potential connectivity. In B a potential synapse is defined as a site in the neuropil where a dendritic branch (red) is located a distance $s$ away from an axon, shown in blue (model A). The presence of a synaptic bouton on the axon is not required. In C (model B) a potential synapse is defined as a location in the neuropil where a dendritic branch is within a distance $s$ from an existing synaptic bouton (blue sphere on the axon).
2.2 Volume density of potential synapses

In the following we calculate how many potential synapses are there per unit volume of neuropil, that is, the potential synapses density. We begin by calculating the probability $P^4(d)$ that two long straight segments of given orientations (making angle $\theta$ with each other) and lengths $l_a$ and $l_d$, randomly positioned inside a large volume $V$ will be within distance $d$ ($d = l_{a,d}$) of each other (Figure 2.2A).

![Image of Figure 2.2](image)

**Figure 2.2.** Probability of potential connection for line segments in Model A. A. The probability that a random line segment of a given orientation and length $l_d$ (red) is located within distance $d$ from another segment (blue) of length $l_a$ ($l_{a,d} \gg d$) is equal to the probability that the origin of the first segment falls inside the prism shown in B.

Clearly, the two segments are located within distance $d$ of each other if one segment penetrates the imaginary cylinder of radius $d$ surrounding the other segment. The probability of this event is equal to the probability for the origin of the first segment to fall inside the right
prism (2d by l_a by l_d and angle θ at the base) as shown in Figure 2.2B. Hence, \( P^A(d) \) is equal to the ratio of the prism’s volume and volume \( V \),

\[
P^A(d) = \frac{2dl_d \sin \theta}{V}.
\]  

Similarly, one can calculate the probability \( P^B(d) \) that a long straight segment of a given orientation and length \( l_d \), randomly positioned inside a large volume \( V \) will be located within distance \( d \) of a given point (Figure 2.3).

![Figure 2.3](image)

**Figure 2.3.** Probability of potential connection for a line segment and a point in Model B. The probability that a random line segment (red) of length \( l_d \) is located within distance \( d \) from a given point (blue dot) is equal to the probability that the origin of this segment falls inside the cylinder of length \( l_d \) and radius \( d \) as shown.

The segment is located within distance \( d \) of the point if it intersects an imaginary sphere of radius \( d \) centered at the point. The probability of this event is equal to the probability for the
origin of the segment to be located inside the cylinder of radius $d$ and length $l_d$ as shown in Figure 2.3B. As a result, $P^B(d)$ is equal to the ratio of the cylinder’s volume and volume $V$,

$$P^B(d) = \frac{\pi d^2 l_d}{V}.$$  \hspace{1cm} (2.2)

Now, we account for the fact that axons and dendrites have finite thickness. In model A, consider a straight axonal segment of length $l'_a$ and radius $r_a$ located inside a large neuropil volume $V$. A randomly chosen dendritic segment of length $l'_d$, radius $r_d$ and a given orientation in the neuropil (making an angle $\theta_j$ with the axon), would make a potential synapse that can be bridged by a spine in the $[0, s]$ length range, if the axis of this segment is located within distance $d$ from the axis of the axon, such that $r_a + r_d \leq d \leq s + r_a + r_d$, as shown in Figure 2.4.

![Figure 2.4. Side view of a dendritic segment of radius $r_d$ (red circle) and an axonal segment of radius $r_a$ (blue circle), joined together by a dendritic spine of length $s$.](image)

This means that the surfaces of the axonal and dendritic cylinders must be at a distance $s$ or closer without touching each other. The probability of this happening is $P^A(s + r_a + r_d) - P^A(r_a + r_d)$, where subscripts are added in reference to segments $i$ and $j$. In
model B, a dendritic segment and a bouton of radius \( r_b \) can be bridged by a spine in the \([0, s]\) length range if the axis of the dendritic segment is located within distance \( d \) from the center of the bouton, such that \( r_b + r_d \leq d \leq s + r_b + r_d \). As a result, the probability of potential connection is

\[
P^B_{ij}(s + r_b + r_d) - P^B_{ij}(r_b + r_d).
\]

Using Eqs. (2.1) and (2.2) for models A and B, the probabilities of potential connection corresponding to spine lengths in the \([0, s]\) range reduce to,

\[
P^A_{ij}(s + r_a + r_d) - P^A_{ij}(r_a + r_d) = \frac{2s l^A_{i} l^A_{id}}{V} \sin \theta_{ij},
\]

\[
P^B_{ij}(s + r_b + r_d) - P^B_{ij}(r_b + r_d) = \frac{\pi \left[ s^2 + 2s \delta \right] l^B_{jd}}{V}.
\]

In the second equation \( \delta = r_d + r_b \) is the sum of dendritic and bouton radii (see Table 2.1). The expected cumulative number of potential synapses in the neuropil volume \( V \) that can be bridged by spines shorter than \( s \) is the sum of the probabilities in Eqs. (2.3) over all the dendritic segments (\( i \)) and potentially post-synaptic elements (\( j \), axonal segments in model A or boutons in model B):

\[
N^A_{pot}(s) = \frac{2s}{V} \sum_{i} l^A_{i} l^A_{id} \sin \theta_{ij},
\]

\[
N^B_{pot}(s) = \frac{\pi \left[ s^2 + 2s \delta \right]}{V} \sum_{i} l^B_{jd}.
\]
Due to the assumption of no correlation in the layout of axonal and dendritic branches (See Appendix A.2.), the sum in the first equation breaks down into a product of axonal and dendritic components. As a result, the cumulative number of potential synapses reduces to:

\[
N_{pot}^A(s) = \frac{2\sin \theta s L_a L_d}{V}
\]

\[
N_{pot}^B(s) = \frac{\pi \left( s^2 + 2s \delta \right) N_b L_d}{V}.
\]

In these expressions \(L_a\), \(L_d\) are the total axonal and dendritic lengths in the neuropil volume \(V\), \(N_b\) is the total number of boutons in the same volume, and \(\sin \theta\) is the average sine of angles between axonal and dendritic branches.

As \(L_a\), \(L_d\), \(N_b\), and the cumulative number of potential synapses, \(N_{pot}^{A,B}(s)\), are intensive quantities of volume, Eqs. (2.5) can be conveniently rewritten in terms of densities,

\[
n_{pot}^A(s) = 2\sin \theta \rho_a \rho_d
\]

\[
n_{pot}^B(s) = \pi \left( s^2 + 2s \delta \right) n_b \rho_d
\]

where \(\rho_{a,d}\) are the axonal and dendritic length densities (total length of axons or dendrites in a unit volume of neuropil) and \(n_b\) denotes the volume density of boutons. If relative orientations of axonal and dendritic branches are isotropically distributed (which is already true if either axonal or dendritic branches are isotropic), \(\sin \theta = \pi / 4\) [16]. This simplification is used later. Note that
models A and B result in different dependence of the cumulative potential synapse density on spine length \( s \).

In model A, the cumulative density of potential synapses in the neuropil, \( n_{\text{pot}}^A(s) \), depends on the product of axonal and dendritic length densities, \( \rho_a \) and \( \rho_d \), of excitatory neurons, due to the fact that a potential synapse was defined symmetrically with respect to axonal and dendritic branches (Figure 2.1B). In model B (Figure 2.1C) a potential synapse was defined as an opposition between a bouton and a dendrite, and thus \( n_{\text{pot}}^B(s) \) depends on the product of the volume density of boutons, \( n_b \), and the dendritic length density. Note that in model A the cumulative density of potential synapses depends linearly on the spine length, \( s \), while in model B the dependence is quadratic.

As the majority of excitatory synapses are made on dendritic spines [30] and the majority of spines bear a single excitatory synapse, the dendritic length density can be estimated as the product of the asymmetric synapse density and the average inter-spine interval along excitatory dendrites, \( \rho_d \approx n_s b_d \). The estimated values of \( \rho_d \) for four systems are shown in Table 2.1. Similarly, the axonal length density can be estimated as the product of the density of asymmetric synapses and the average inter-bouton interval on excitatory neuron axons, \( \rho_a \approx n_p b_a \). Due to the presence of multiple synapse boutons this expression may slightly overestimate the axonal length density.
Table 2.1. Anatomical parameters of synaptic circuits from mouse, rat, monkey, and human cortices. The data is shown in mean±std(sem) format. Details are provided in Appendix B and C.

<table>
<thead>
<tr>
<th>Species, brain area, age</th>
<th>Distribution of spine lengths, ( p(s) )</th>
<th>Average spine length, ( \bar{s} ) [(\mu m)]</th>
<th>Sum of the average dendritic and bouton radii, ( \delta ) [(\mu m)]</th>
<th>Inter-bouton interval along an axon, ( b_x ) [(\mu m)]</th>
<th>Spine density on a dendrite, ( 1/b_x ) [(\mu m^{-1})]</th>
<th>Density of asymmetric synapses, ( n_s ) [(\mu m^{-3})]</th>
<th>Dendritic length density, ( \rho_s \approx n_s \rho_d ) [(\mu m^{-2})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse occipital, layer 3, adult</td>
<td>[31]</td>
<td>0.99±(0.01)</td>
<td>0.70 [2]</td>
<td>4.5±1.4 [2, 32, 33]</td>
<td>1.94±0.42 [2, 34]</td>
<td>0.91±0.25 [2, 33]</td>
<td>0.48±(0.10)</td>
</tr>
<tr>
<td>Rat CA1, stratum radiatum, adult</td>
<td>[35]</td>
<td>1.08±(0.03) [36, 37]</td>
<td>0.50 [36-39]</td>
<td>3.7±0.6 [40]</td>
<td>3.41±1.05 [35, 38, 41]</td>
<td>2.0±0.30 [42]</td>
<td>0.59±(0.08)</td>
</tr>
<tr>
<td>Monkey V1, layer 3, adult</td>
<td>[16]</td>
<td>1.86±(0.05)</td>
<td>0.95</td>
<td>5.6±2.4 [43]</td>
<td>0.55±0.07 [44-47]</td>
<td>0.26±0.04 [48, 49]</td>
<td>0.47±(0.05)</td>
</tr>
<tr>
<td>Human temporal, layer 3, adult</td>
<td>[31]</td>
<td>1.42±(0.01)</td>
<td>1.35</td>
<td>-</td>
<td>2.62±0.34 [50]</td>
<td>1.07±0.31 [51]</td>
<td>0.42±(0.09)</td>
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</tbody>
</table>
Chapter 3

Potential of Neural Circuit for Structural Synaptic Plasticity

3.1 The connectivity fraction

Axo-dendritic oppositions can be bridged by spines of different lengths $s$, as shown by the spine length distributions (Figure 3.1). The probability of finding an actual synaptic connection at a potential synaptic site is described by the neuropil’s connectivity fraction $f$. The connectivity fraction is a measure of plasticity potential associated with spine remodeling. It reflects the number of structurally different circuits that can be realized in a given neuropil volume through spine reorganization. As the cumulative number of potential synapses depends on distance $s$, the connectivity fraction, in general, will be dependent on $s$ as well, $f(s)$. To calculate $f_{A,B}(s)$ (in Models A or B) we note that in a unit volume of neuropil, there are $\Delta n_{act}(s) = n_{spine} p_s(s) \Delta s$ actual synapses on spines in the $[s-\Delta s/2, s+\Delta s/2]$ length range. Here, $p_s(s)$ is the spine length distribution function (shown in Figures 3.1 for the studied systems) and $n_{spine}$ is the volume
density of spines. These $\Delta n_{\text{act}}(s)$ spines are distributed among $\Delta n_{\text{pot}}^{A,B}(s)$ potential synaptic sites (derived from Eqs. (2.6)).

![Figure 3.1](image.png)

**Figure 3.1.** Spine length distributions in: (A) mouse occipital cortex, (B) area CA1 of rat hippocampus, (C) monkey visual area V1, (D) human temporal cortex.

The connectivity fraction $f_{A,B}(s)$ can be obtained as the ratio of the numbers of spines and potential synapses in the $[s - \Delta s / 2, s + \Delta s / 2]$ interval:
In other words, the connectivity fraction is the fraction of potential synapses (for a given spine length, $s$) which had been converted into actual ones. According to this definition $f_{A,B}(s) \leq 1$ for all values of $s$. The above expressions are not convenient for making quantitative estimates of the connectivity fraction. This is because axonal and dendritic length densities are not typically measured in experiments. To get around this problem we note that the ratio $n_{\text{spine}}/\rho_d$ is equal to the average linear density of spines on the excitatory neuron dendrites, or the inverse of the inter-spine interval on a dendrite, $1/b_d$. Similarly, $\rho_a$ can be expressed as the product of the average inter-bouton interval on the excitatory neuron axons, $b_a$, and volume density of these boutons, $n_b$ ($\rho_a = b_a n_b$). Finally, denoting the ratio between the number of asymmetric synapses, $n_s$, and the number of boutons, $n_b$, on excitatory neuron axons as $m$ ($n_s = n_b m$), we arrive at the final expressions for the connectivity fractions in models A and B,

\[
\begin{align*}
 f_A(s) &= \frac{\Delta n_{\text{act}}}{\Delta n_{\text{pot}}} = \frac{n_{\text{spine}} p_s(s)}{2 \sin \theta \rho_a \rho_d}, \\
 f_B(s) &= \frac{\Delta n_{\text{act}}}{\Delta n_{\text{pot}}} = \frac{n_{\text{spine}} p_s(s)}{2 \pi (s + \delta) n_b \rho_d}.
\end{align*}
\]

(3.1)

All the components in these expressions are routinely measured with electron or light microscopy and are previously summarized in Table 2.1 for the given systems. For convenience,
in Eqs. (3.2) we had broken down the connectivity fractions into a product of two parts: dimensionless parameters $f_{dB}^*$, which depend on the anatomical details of neuropil organization, which is referred to as the connectivity parameter (Table 3.1), and a dimensionless part which is primarily dependent on the shape of the spine length distribution function. From now on, in this manuscript, we will take $m = 1$ and $\sin \theta = \pi / 4$ in Eqs. (3.2) (see Appendix A.3 for these approximations).

Table 3.1. Parameters of structural circuit remodeling in mouse, rat, monkey, and human cortexes. The data is shown in mean±sem format.

<table>
<thead>
<tr>
<th>Species, brain area, age</th>
<th>Connectivity parameter, $f^*$</th>
<th>Average connectivity fraction, $\bar{f}$</th>
<th>Maximum connectivity fraction, $f_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Mouse occipital, layer 3, adult</td>
<td>0.32 ±0.08</td>
<td>0.36 ±0.08</td>
<td>0.19 ±0.05</td>
</tr>
<tr>
<td>Rat CA1, stratum radiatum, adult</td>
<td>0.27 ±0.04</td>
<td>0.23 ±0.03</td>
<td>0.24 ±0.04</td>
</tr>
<tr>
<td>Monkey V1, layer 3, adult</td>
<td>0.14 ±0.04</td>
<td>0.10 ±0.01</td>
<td>0.10 ±0.03</td>
</tr>
<tr>
<td>Human temporal, layer 3, adult</td>
<td>-</td>
<td>0.20 ±0.05</td>
<td>-</td>
</tr>
</tbody>
</table>

A parameter similar to $f_d^*$ was initially introduced in [16] under the name of filling fraction. The values of $f_d^*$ for mouse neocortex (secondary motor area, MOs, and primary visual area, VISp), rat CA1 (based on CA3 to CA1 projection) and monkey V1 were there reported. In
spite of some differences in methodology and anatomical datasets used, those previous results are not significantly different from the results of this study. One difference being that in that earlier work spine length was measured between the tip of the spine head and the dendritic axis as opposed to the base of the spine. The value of this dimensionless parameter was estimated to be in the 0.1-0.3 range for many species and cortical areas consistent with the results of the present study (0.10-0.36).

Based on the published anatomical data (Figure 3.1) and the values of anatomical parameters (Table 2.1) we evaluated the connectivity fraction in mouse occipital cortex, rat CA1, monkey V1, and human temporal cortex. The results for models A and B are shown in Figure 3.2 and the values of the connectivity parameter and average connectivity fraction are summarized in Table 3.1 As it was expected from the definition of the connectivity fraction, $f(s) \leq 1$ for all values of $s$ in all numerical results.
Figure 3.2. Connectivity fraction as a function of spine length. Connectivity fraction is the ratio of the numbers of actual to potential synapses. Results based on model A are shown in red and those based on model B are shown in green.

3.2 Selectivity of post-synaptic neurons in their choice of pre-synaptic partners

Excitatory neurons in regions of the cerebral cortex differ in their functional properties. In the primary visual cortex, for example, neurons differ in their ocular dominance and orientation preference [52]. These neurons connect to each other based on the similarity of their functional
properties [5, 53, 54]. It is not entirely clear how many different neuron types are there in the visual cortex. In other words, what is the probability that two nearby randomly chosen excitatory neurons would establish a synaptic contact given the opportunity? One may think that this probability is quite small, less than 10% based on the dual intracellular recordings from nearby neuron pairs [55]. This view is also supported by the traditional Hubel and Wiesel model of the hypercolumn [56], which contains neurons with different ocular dominance and orientation properties. The question of selectivity of excitatory neurons becomes even more obscure in the non-primary cortical areas where functional classification of neurons is often unknown. We estimated the lower bound of selectivity of neurons in their choice of synaptic partners based on the shape of the spine length distribution function and average anatomical parameters of neuropil micro-architecture.

We consider a model in which creation of new synapses between axonal and dendritic branches requires the following three steps: First, the pre-synaptic axon has to be within the spine reach of the post-synaptic dendrite, i.e. the two branches must be in potential contact with each other; Second, a dendritic spine or filopodium has to find and establish an initial contact with the axon; Finally, based on the functional properties of the neurons this connection could be stabilized and transformed into a synapse or be eliminated.

Consider a potentially connected pair of axonal and dendritic branches. This potential connection may or may not contain an actual synaptic contact. The probability that potentially connected branches are synaptically coupled is given by the connectivity fraction, \( f(s) \).
According to the above model of synaptogenesis, this probability is equal to the product of the probability for a dendritic spine of length $s$ to find the axon, $p(find \mid s)$, and the probability for this initial contact to stabilize and transform into an actual synaptic connection, $p(stabilize \mid found)$. Hence,

$$f(s) = p(find \mid s) p(stabilize \mid found).$$  \hspace{1cm} (3.3)

Probabilities $f(s)$ and $p(find \mid s)$ depend on the distance $s$ between the branches. The conditional probability $p(stabilize \mid found)$ on the other hand is independent of the geometrical details of circuit organization. This probability is only dependent on functional properties of the neurons. It reflects the selectivity of cortical neurons in their choice of synaptic partners.

The fact that the probability $p(find \mid s)$ has to be less or equal to one for all values of the parameter $s$ allows us to obtain the lower bound for the probability $p(stabilize \mid found)$ in the following way,

$$p(stabilize \mid found) \geq f(s), \quad \forall s$$

$$p(stabilize \mid found) \geq f_{max}$$  \hspace{1cm} (3.4)

In the last expression $f_{max}$ is the maximum value of the connectivity fraction, $f(s)$, shown in Figures 3.2. We estimate the lower bound of $p(stabilize \mid found)$ based on the values of $f_{max}$ from Table 3.1 and Figures 3.2. The most salient feature of the results in Figures 3.2 is that the
average (or peak, $f_{\text{max}}$) connectivity fractions, $\bar{f}$, in rodents are significantly higher than those in the primates (p<0.05 for all pairwise comparisons, Student’s t-test for samples with unequal variance). Post-synaptic excitatory neurons in rodents make synaptic contacts with more than 21-30% of pre-synaptic targets (axons in model A, boutons in model B) encountered with new spine growth. Primate neurons appear to be more selective making synaptic connections with more than 7-15% of encountered targets. This estimate allows us to define the number of functionally different neuron classes in a given region of the cerebral cortex as the inverse of neuron selectivity. According to this measure, in the considered areas of rodent cortex there are at most 3-5 functionally different classes of neurons. In the primate cortical areas, the number of functionally different classes of neurons could be much higher. It is only limited from above by our estimate of 7-14 neuron classes.

There are no significant differences in $\bar{f}$ within rodent and primate groups. For example, in mouse occipital cortex the average connectivity fraction is 0.19 for model A (see Table 3.1) indicating that on average a spine can choose among $(0.19)^{-1} \sim 5$ potentially pre-synaptic axons. For model B $\bar{f} = 0.14$ which means that a single bouton can be contacted by about 7 potentially post-synaptic dendrites. In contrast, the average connectivity fraction in human temporal cortex is 0.072 in model B, which is significantly smaller (p<0.03). Here a single bouton can be contacted by an outstanding 14 different post-synaptic dendritic spines.

As our comparisons involved different species and cortical areas it is not clear whether these differences arise from differences between species, cortical areas, or are the result of the
combination. New experiments are needed to resolve these questions. The values of parameters of structural plasticity calculated in this study are only as good as the anatomical data that were used for the calculations. There is substantial variability in some anatomical measurements performed in different laboratories. One part of this variability is biological in nature. Parameters of cortical neuropil can be highly variable among individual animals (same species, age, and brain area). This inter-brain variability is reflected in the error bars reported in this study. We made conservative estimates of standard errors to the mean values of all the calculated parameters. As described in Appendix B section true standard errors are expected to be much smaller. Another part of variability in anatomical measurements, not captured by our error bars, is due to different biases introduced by different experimental procedures. To minimize the effect of experimental biases, when possible, we used results that are corrected for experimental artifacts (tissue shrinkage or hidden spines), are based on large numbers of animals, and results that are agreed upon by several experimental laboratories.
Chapter 4

Synaptic Entropy

4.1 Entropic contribution due to structural synaptic plasticity

In this chapter we calculate the structural entropy associated with all different possible connectivity patterns in the neuropil which can be attained with spine remodeling. This entropy can be viewed as the neuropil’s potential to form different circuits, but it is important to note that structurally different connectivity patterns in terms of individual synapses do not necessarily correspond to functionally different circuits at the level of individual neurons. For example, an axonal arbor of a pre-synaptic excitatory neuron in the neocortex typically makes several potential synapses with a dendritic arbor of a neighboring excitatory post-synaptic cell [29]. It is quite possible that different choices of actual synapses out of the potential ones do not result in functionally different connections between the two cells. Hence, the structural synaptic entropy only provides the upper bound of (but may be correlated with) the number of functionally different circuits that can be attained with structural spine remodeling.
The neuropil volume $V$ contains $\Delta n_{pot}^{A,B}V$ potential and $\Delta n_{act}^{A,B}V$ actual synapses in the $[s - \Delta s/2, s + \Delta s/2]$ range of spine lengths (quantities $\Delta n_{pot}^{A,B}$ and $\Delta n_{act}^{A,B}$ were previously defined in Chapter 3). In this range the number of ways to choose actual synapses out of the pool of potential ones is given by the binomial coefficient,

$$\Delta \Omega_{A,B}(s) = \binom{\Delta n_{pot}^{A,B}V}{\Delta n_{act}^{A,B}V}. \quad (4.1)$$

The structural synaptic entropy, $\Delta I_{struct}^{A,B}(s)$, of actual synapses in the $[s - \Delta s/2, s + \Delta s/2]$ range is defined as the natural logarithm of $\Delta \Omega_{A,B}(s)$. In the limit of large numbers of actual and potential synapses (large $V$) the binomial coefficient can be approximated using Stirling’s formula [57], and

$$\Delta I_{struct}^{A,B}(s) = \ln(\Delta \Omega_{A,B}(s))$$

$$= \ln \left[ \frac{(\Delta n_{pot}^{A,B}V)!}{(\Delta n_{act}^{A,B}V)!(\Delta n_{pot}^{A,B}V - \Delta n_{act}^{A,B}V)!} \right]$$

$$\approx V \left[ \Delta n_{pot}^{A,B} \ln(\Delta n_{pot}^{A,B}V) - \Delta n_{act}^{A,B} \ln(\Delta n_{act}^{A,B}V) - (\Delta n_{pot}^{A,B} - \Delta n_{act}^{A,B}) \ln \left( \left( \frac{\Delta n_{pot}^{A,B}}{\Delta n_{pot}^{A,B} - \Delta n_{act}^{A,B}} \right) \right) \right] \quad (4.2)$$

$$= V \Delta n_{pot}^{A,B} \left[ \ln(\Delta n_{pot}^{A,B}) - \frac{\Delta n_{act}^{A,B}}{\Delta n_{pot}^{A,B}} \ln(\Delta n_{act}^{A,B}) - \left( 1 - \frac{\Delta n_{act}^{A,B}}{\Delta n_{pot}^{A,B}} \right) \ln \left( \frac{\Delta n_{pot}^{A,B}}{\Delta n_{pot}^{A,B} - \Delta n_{act}^{A,B}} \right) \right]$$

Using the definition of connectivity fraction $f_{A,B}(s) = \frac{\Delta n_{act}^{A,B}}{\Delta n_{pot}^{A,B}}$ given in Eq. (3.1), we obtain
where,

\[
\Delta I^{A,B}_{\text{struct}} (s) = V \Delta n^{A,B}_{\text{pot}} \left[ \ln(\Delta n^{A,B}_{\text{pot}}) - f_{A,B} \ln(\Delta n^{A,B}_{\text{act}}) - \left( 1 - f_{A,B} \right) \ln\left( \Delta n^{A,B}_{\text{pot}} \left( 1 - f_{A,B} \right) \right) \right]
\]

\[
= V \Delta n^{A,B}_{\text{pot}} \left[ \ln(f_{A,B}) - \frac{1 - f_{A,B}}{f_{A,B}} \ln(1 - f_{A,B}) \right]
\]

\[
= - V \Delta n^{A,B}_{\text{act}} \left[ \ln(f_{A,B}(s)) + \frac{1 - f_{A,B}(s)}{f_{A,B}(s)} \ln(1 - f_{A,B}(s)) \right]
\]

\[
= - V n_{\text{spine}} p_{s}(s) \Delta S \left[ \ln(f_{A,B}(s)) + \frac{1 - f_{A,B}(s)}{f_{A,B}(s)} \ln(1 - f_{A,B}(s)) \right]
\]

\[
= - V i^{A,B}_{\text{struct}} (s) \Delta S
\]

\[
i^{A,B}_{\text{struct}} (s) = -n_{\text{spine}} p_{s}(s) \left[ \ln(f_{A,B}(s)) + \frac{1 - f_{A,B}(s)}{f_{A,B}(s)} \ln(1 - f_{A,B}(s)) \right]
\]

\[
\text{is the volume density of the structural synaptic entropy in terms of the corresponding connectivity fractions } f_{A,B}(s). \text{ Also, we will assume from now on that the volume density of spines } n_{\text{spine}} \text{ on excitatory neuron dendrites is equal to the volume density of asymmetric synapses } n_{s} \text{ (in both models A and B). This approximation is supported by generally low fractions of asymmetric synapses that are not made on dendritic spines of excitatory neurons (See Appendix A.3), therefore,}
\]

\[
\frac{i^{A,B}_{\text{struct}} (s)}{n_{s}} = -p_{s}(s) \left[ \ln(f_{A,B}(s)) + \frac{1 - f_{A,B}(s)}{f_{A,B}(s)} \ln(1 - f_{A,B}(s)) \right].
\]

\[
\text{The results of calculations based on this expression are shown in Figure 4.1.}
\]
Figure 4.1. Structural entropy density per spine as a function of spine length. The overall structural entropy per spine can be calculated as the area under these curves.

The units of this entropy are “nats”, that come from having taken natural logarithms in the calculation of the entropy, 1 nat = 1.44 bits. The shapes of the entropy density curves roughly follow the shapes of the spine length distribution functions. In mouse occipital cortex, the structural entropy density per spine peaks at about 2 nats/µm for 1 µm spines. This means that, for example, spines in the range of lengths from 0.95 µm to 1.05 µm contribute 2 nats/µm x
0.1 µm = 0.2 nats of entropy per spine to structural connectivity. The peak entropy density per spine is highest in rat CA1; 2 nats/µm in model A and 2.6 nats/µm in model B. For large values of spine length, \( s \), the entropy density per spine in model B is larger than that in model A. This trend, which is opposite to the trend in the connectivity fractions shown in Figures 3.2, is due to the fact that large connectivity fractions correspond to low entropy densities per spine and vice versa, as we can be seen in Eq. (4.5) or in Figures (4.2) where we had plotted the entropy densities as a function of the connectivity parameters \( f_{A,B}^* \), defined in Eqs. (3.2).

**Figure 4.2.** Structural entropy per spine as a function of connectivity parameter, \( f^* \). Panels A and B show the results based on models A and B for mouse occipital cortex (red), rat CA1 (blue), monkey V1 (green), and human temporal cortex (black). The dots in these figures indicate the connectivity parameters, \( f^* \) defined in the previous chapter, and the corresponding values of structural entropy per spine, \( i_{\text{struct}} / n_s \), shown in Table 4.1, calculated based on data from Tables 2.1.
Adding the entropic contributions arising from different spine length intervals, \( \Delta s \), we obtain the overall structural synaptic entropy per volume of neuropil, integrating Eq. (4.5) over spine lengths we arrived at the expression for the overall structural entropy per dendritic spine:

\[
\frac{i_{\text{struct}}}{{n}_s} = \frac{1}{{n}_s} \int_0^\infty i_{\text{struct}}^A(s) ds = -\int_0^\infty \left[ \ln\left(\frac{f_{A,B}(s)}{f_{A,B}(s)}\right) + \frac{1 - f_{A,B}(s)}{f_{A,B}(s)} \ln\left(1 - f_{A,B}(s)\right) \right] p_s(s) ds. \tag{4.6}
\]

In this expression \( i_{\text{struct}}^A(s) \) is referred to as entropy density distribution. The model dependence in this expression is contained in the connectivity fraction \( f_{A,B}(s) \), Eqs. (3.1). The structural synaptic entropy per volume scales with the volume density of spines, \( n_{\text{spine}} \) (replaced here by \( n_s \)), it is a functional of the spine length distribution function \( p(s) \) and depends on anatomical characteristics of neuropil micro-architecture through \( n_s, b_s, b_a, \) and \( m \). The results of this calculation (areas under the curves in Figures 4.1) are shown in Figure 4.3A and Table 4.1

In rodent cortex a single spine can contribute 2.5-3.1 nats of entropy to the patterns of synaptic connectivity. In monkey V1 and human temporal cortex the amount of entropy available to a single spine is significantly higher, 3.4-4.2 nats (p<0.04 for all pair wise comparisons). In addition, we did not detect any significant differences in structural entropy per spine within rodent and primate groups. The fact that a single spine in primate cortex has high entropy for structural plasticity seems satisfactory. Yet, in comparison, low 2.5-3.0 nats of entropy per spine in the rat CA1, an essential learning and memory area, could seem surprising. However, this lack of structural entropy per spine in rat CA1 is compensated by a large density of synapses.
Figure 4.3. Potential for structural plasticity. A. Structural entropy per spine in mouse occipital cortex, rat CA1, monkey V1, and human temporal cortex. Red bars show the results based on model A and green bars correspond to model B. B. Structural entropy per volume of cortical neuropil.

Multiplying the entropy per spine, $i_{\text{struct}}^{A,B}/n_s$, with the density of asymmetric synapses, $n_s$, we obtain the structural synaptic entropy per volume of neuropil, $i_{\text{struct}}^{A,B}$ (see Figure 4.2 B and Table 4.1). This quantity reflects the number of structurally different circuits that can be achieved with spine remodeling in the unit volume of cortical neuropil.
Table 4.1. Structural Synaptic entropy results. The data is shown in mean±sem format.

<table>
<thead>
<tr>
<th>Species, brain area, age</th>
<th>Average entropy per spine, $i / n_s$ [nats]</th>
<th>Average entropy per volume, $i$ [nats/µm$^3$]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Mouse occipital, layer 3, adult</td>
<td>2.7 ±0.3</td>
<td>3.1 ±0.2</td>
</tr>
<tr>
<td>Rat CA1, stratum radiatum, adult</td>
<td>2.5 ±0.2</td>
<td>3.0 ±0.1</td>
</tr>
<tr>
<td>Monkey V1, layer 3, adult</td>
<td>3.4 ±0.3</td>
<td>4.1 ±0.1</td>
</tr>
<tr>
<td>Human temporal, layer 3, adult</td>
<td>-</td>
<td>3.9 ±0.2</td>
</tr>
</tbody>
</table>

With the exception of comparison between mouse and human in model B, all within-model differences in Figure 4.2 B are significant (p<0.05). Structural entropy per volume is highest in the rat CA1, 4.3-5.5 nats/µm$^3$ and lowest in the monkey V1, 0.9-1.1 nats/µm$^3$, primarily due to the high and low densities of asymmetric synapses in these cortical areas. The average structural entropy per spine, $i_{\text{struct}}^{A,B} / n_s$, according to Eq. (4.5) and Eq. (4.6), depends only on the shape of the spine length distribution function $p(s)$ and the connectivity parameter $f_{A,B}^*$. Figure 2.4 shows the dependence of $i_{\text{struct}}^{A,B} / n_s$ on $f_{A,B}^*$ in models A and B. The dots indicate the results of the calculations based on the data from Table 2.1, 3.1 and 4.1. For a given spine length distribution function, the structural entropy per spine is a decreasing function of the connectivity parameter.
4.2 Comparison of structural synaptic entropy in different cortical areas

In addition to the four spine length distributions shown in Figure 3.1, we calculated the entropy per spine (see Eq. (4.6)) in 96 distributions published in literature (See Appendix D, table D3.1) and shown in (Figure 4.4).

![Figure 4.4](image)

**Figure 4.4.** Spine length distributions ($n = 96$). Lines of different colors correspond to measurements done in dissociated or organotypic cultures and cortical slices from different areas of mouse, rat, monkey, and human brains.

The results, for the systems where spine lengths were measured reliably (see Appendix D), are shown in Figure 4.5. We used here only Model B, in which the spines target existing
boutons. Our results show that the synaptic entropy per dendritic spine in primary areas is higher than that in hippocampus.

Figure 4.5. Structural entropy per spine in mouse, rat, monkey, and human cortex. Numerals correspond to the system numbering in table D3.1 (see Appendix D). Error-bars indicate standard errors to the mean values. Abbreviations: BC – barrel cortex, V – visual, M – motor, L – layer.

4.3 Entropic contribution due to modulatory synaptic plasticity

As mentioned in the introduction, several plasticity mechanisms had been identified experimentally that can produce changes in the synaptic connectivity. One of them is the long-term potentiation and depression of existing synaptic connections [6-8]. The strengths of synaptic connections are correlated with the volumes of spine heads [11, 17-24, 58] and, thus, the number of synaptic connectivity patterns attainable with modulatory plasticity can be deduced from the distribution of spine head volumes.
Here we calculate the number of different connectivity diagrams that can be built by altering the strengths (but not the pattern) of existing synaptic connections (also see [58, 59] for similar calculations). Consider a large volume of neuropil containing $N_s$ excitatory synapses on dendritic spines (like the one shown in Figure 1.1). Each synapse can be in one of $n$ discrete states of synaptic strength. In statistical equilibrium, the states of individual synapses can change due to synapse potentiation or depression, but the distribution of synapses across different states remains the same. Hence, the number of synapses occupying the state of strength $i$, $N_i$, must remain constant. The entropy component from modulation of synaptic strengths is the natural logarithm of the number of different circuits that can be built from the population of $N_s = N_1 + \ldots + N_n$ synapses:

$$I_{mod} = \ln \left( \frac{N_1!}{N_1! N_2! \ldots N_n!} \right) = \ln(N_s!) - \sum_{i=1}^{n} \ln \left( N_i! \right)$$

$$\approx N_s \ln(N_s) - \sum_{i=1}^{n} N_i \ln \left( N_i \right)$$

$$= -N_s \sum_{i=1}^{n} P_i \ln \left( P_i \right)$$  \hspace{1cm} (4.7)

To arrive at the final expression in Eq. (4.7) we utilized the fact that numbers $N_i$ are typically very large in any biologically relevant unit of cerebral cortex (cortical area or column) and used the Stirling’s approximation for the factorials. Here $P_i = N_i / N_s$ is the probability that a given synapse is found in the synaptic state of strength $i$.

Because strength of a synaptic connection is proportional to the volume of a dendritic spine head, probabilities $P_i$ in Eq. (4.7) can be determined from experimental measurements of
spine head volumes. In particular, if $\Delta V$ is the change in the spine head volume associated with the unitary change in the synaptic strength, and $p_V(V_i)$ is the spine head volume probability density, $P_i = p_V(V_i)\Delta V$. $\Delta V$ is assumed to be a fundamental constant, independent of spine origin (animal age, cortical area, or species). Consequently, the upper bound of $\Delta V$ can be determined from the fact that the probabilities $P_i = p_V(V_i)\Delta V$ have to be less than 1 for all states of synaptic strengths, $i$. Hence, $\Delta V < 1/\max(p_V(V))$. The $\max[p_V(V)]$ for the systems where spine head volume was measured reliably (see Appendix D3) is 9.4 $\mu$m$^3$, leading to $\Delta V < 0.11$ $\mu$m$^3$. This upper bound on $\Delta V$ was used in Figure 5C. Without the knowledge of the precise value of $\Delta V$, the entropic contribution, $I_{\text{strength}}$, is ill defined in absolute terms. Yet, the relative (difference) values of $I_{\text{strength}}$ are informative, because they are independent of $\Delta V$.

For reasonably small $\Delta V$, summation in Eq. (4.7). can be replaced with integration:

$$I_{\text{mod}} = -N_s \int_0^\infty \ln \left( p_V(V)\Delta V \right) p_V(V)dV$$

(4.8)

$I_{\text{strength}}$ scales linearly with the number of dendritic spines and depends on the distribution of dendritic spine head volumes $p_V(V)$, like the ones shown in Figure 4.6. In what follows, we will use this continuous approximation of $I_{\text{strength}}$ in order to provide a unified description of the entropic contributions due to changes in synaptic strengths and patterns. However, our results are not dependent on this approximation. The same derivation can be carried out using Eq. (4.7), and will lead to the same conclusions.
From these 70 distributions we calculated the modulatory synaptic entropy, Eq. (4.8). The results for only 6 systems, in which the spine head volume was measured reliably (see Appendix D), are shown in Figure (4.7). Similar to the results for structural plasticity, the contribution from modulatory plasticity is the highest in temporal (human TE) and motor areas (mouse M2), while it is the lowest in the hippocampus (rodents CA1 and DG).

**Figure 4.6.** Distributions of spine head volumes \( n = 70 \). Lines of different colors correspond to measurements done in dissociated or organotypic cultures and cortical slices from different areas of mouse, rat, monkey, and human brains.
Figure 4.7. Entropy per spine in mouse, rat, monkey, and human cortex. Numerals correspond to the system numbering in table D3.1 in Appendix D. Error-bars indicate standard errors to the mean values. Abbreviations: BC – barrel cortex, V – visual, M – motor, L – layer.
Chapter 5

Generalized Cost of Dendritic Spines

5.1 Model of a dendritic spine

We model dendritic spines as protrusions extending along straight lines perpendicularly to the dendritic shafts (Figure 1.1). This is a reasonable simplification, motivated by inspection of light and electron microscopy images of dendritic spines. In reality, the entropy associated with different conformations of dendritic spine necks and deviations of dendritic spines from the normal direction, leading to new connectivity patterns, may not be negligible. This entropy, however, amounts primarily to a constant contribution and may be disregarded (See Appendix A.1) [25].

In our model, dendritic spines have straight necks and spherical heads with a synapse located at the furthest tip of the spine. This model is more appropriate for long spines and may not describe well short stubby spines, which were already disregarded due to their short length (see Appendix A.4). The spine length is calculated as the sum of the spine neck length and the
diameter of the spine head. The joint probability density for spines of head volume \( V \) and length \( s \), or spine shape probability density, is denoted with \( p(V,s) \). We recover the individual probability densities for \( V \), \( p_v(V) \) and for \( s \), \( p_s(s) \) by using the following expressions:

\[
p_v(V) = \int_0^\infty p(V,s)ds
\]

\[
p_s(s) = \int_0^\infty p(V,s)dV
\]

The spine shape, spine head volume, and spine length probability density functions are normalized to one:

\[
\int_0^\infty \int_0^\infty p(V,s)dVds = \int_0^\infty p_s(s)ds = \int_0^\infty p_v(V)dV = 1.
\]

5.2 \textbf{Hypotheses}

Our theory is based on two hypotheses that are supported by the experimental data. First, we hypothesized that the distribution of spine shapes, which change during the development of the brain, reaches a statistical equilibrium in adult. In this dynamic equilibrium, individual spines may change their shapes, new spines may appear, and the existing ones may be retracted, but the overall distribution of spine shapes remains the same. By drawing the analogy with the treatment of equilibrium statistical ensembles [60], we theorized that, for a fixed total “generalized cost” and number of dendritic spines in a given cortical region, the experimentally observed
equilibrium spine shape distribution maximizes the entropy associated with the number of different circuits that can be built with modulatory and structural synaptic plasticity mechanisms combined.

Second, we hypothesized that the generalized cost of a dendritic spine to the organism is a universal function of the spine shape, i.e. it is not dependent on the origin of the spine (different cortical areas or species). Though the exact nature of the dendritic spine cost is not known, below we deduce its functional dependence on the spine shape from the statistical equilibrium hypothesis. Our results, which are based on the analysis of 166 experimental distributions of spine head sizes and spine lengths (see Table D3.1 in Appendix D), measured in culture or slice preparations, in different cortical areas of mouse, rat, monkey, and human, are consistent with the statistical equilibrium and the universality hypotheses.

5.3 Total synaptic entropy

Consider a small volume of cortical neuropil (Figure 1.1 left). The strengths of synaptic connections in this volume are correlated with the volumes of spine heads, and, thus, the number of synaptic connectivity patterns attainable with modulatory plasticity can be deduced from the distribution of spine head volumes. New excitatory synaptic connections can only form between axonal and dendritic branches that can be bridged by dendritic spines (potential synapses [16, 27]), and hence the number of synaptic connectivity patterns attainable with structural synaptic plasticity is dependent on the distribution of spine lengths. It is not entirely clear if a spine
outgrowth precedes the formation of a postsynaptic bouton or if new dendritic spines preferentially contact existing boutons in the process of synaptogenesis [26]. Theoretical framework for these two models of synapse formation has been described in Chapters 2 and 3. As the two models are quantitatively very similar, in this section we will only consider the latter model, in which a potential synapse is an opposition between a bouton and a dendrite that can be bridged by a dendritic spine, see Section 2.2 and Figure 2.3.

Any change in the configuration of a neural network, such as a change in the size of a single spine head or a change in the location of a single spine, may alter the network’s functional connectivity. To quantify the number of possible connectivity configurations we introduce the notion of total synaptic entropy, $I$. This entropy is the natural logarithm of the number of different connectivity configurations attainable with modulatory and structural synaptic plasticity mechanisms combined:

$$I = I_{\text{mod}} + I_{\text{struct}}$$  \hspace{1cm} (5.3)

Where, $I_{\text{mod}}$ is given initially in Eq. (4.8) and can be rewritten in terms of the shape probability density $p(V,s)$ like

$$I_{\text{mod}} = -N_s \int_0^\infty \ln (p_V (V) \Delta V) p_V (V) dV = -N_s \int_0^\infty \ln (p_V (V) \Delta V) p(V,s) dV ds$$  \hspace{1cm} (5.4)

and $I_{\text{struct}}$ results from multiplying by the volume on both sides of Eq. (4.6), an expression that can be written also in terms of shape probability density $p(V,s)$ like this:
\begin{align}
I_{\text{struct}} &= -N_s \int_0^\infty \int_0^\infty \left[ \ln(f(s)) + \frac{1-f(s)}{f(s)} \ln(1-f(s)) \right] p(V,s) dV ds \tag{5.5}
\end{align}

Where \( f(s) = f_n(s) \) is given by Eq. (3.1). Longer spines can make larger contributions to \( I \) as they can chose among larger numbers of potential synapses. Similarly, wider distributions of spine head volumes, containing larger spine heads, can give rise to higher numbers of possible connectivity configurations. However, something prevents dendritic spines from growing beyond few micrometers in length or from having very large spine head volumes. We call this impeding factor the generalized cost of dendritic spines, \( \varepsilon(V,s) \). It is not known what contributes to the generalized spine cost. One part of the cost must be related to maintenance of dendritic spines and may be metabolic in nature [61] or functional, e.g. associated with molecular transport or signal attenuation in the spine neck. Another part of the cost must be related to synaptic plasticity, associated with new spine construction and potentiation, as well as depression and degradation of the existing spines. Though the exact composition of the generalized spine cost is not known, it is expected that both maintenance and plasticity related components are costlier for longer spines with larger spine heads and, thus, \( \varepsilon(V,s) \) must be an increasing function of \( V \) and \( s \).

### 5.4 Determining the generalized cost of dendritic spines from the entropy maximization principle

The total cost of \( N_s \) dendritic spines to the organism can be obtained by integrating \( \varepsilon(V,s) \) with the spine shape distribution function:
\[
E = N_0 \int_0^\infty \int_0^\infty \epsilon(V, s) p(V, s) dV ds .
\]  

(5.6)

For a fixed value of \( E \), Eq. (5.6) constraints the possible shapes of \( \epsilon(V, s) \).

According to the first hypothesis, the spine shape distribution function, \( p(V,s) \), in adult brain maximizes the synaptic entropy of neuropil. The maximization is subject to two constraints. First, \( p(V,s) \) has to be normalized according to Eq. (5.2). Second, the total cost of dendritic spines to the organism, \( E \) in Eq. (5.6), is kept constant. Such constrained optimization problem is typically solved by maximizing the Lagrange function which combines the two contributions to the synaptic entropy with the constraints weighted by the Lagrange multipliers [60]

\[
L = I_{mod} + I_{struct} - \frac{1}{T} N_0 \int_0^\infty \int_0^\infty \epsilon(V, s) p(V, s) dV ds + \frac{\mu}{T} N_0 \int_0^\infty \int_0^\infty p(V, s) dV ds .
\]  

(5.7)

Due to the analogy between this optimization problem and the treatment of non-equilibrium Fermi and Boltzmann gases in statistical physics [60], we had chosen (without loss of generality) to denote the Lagrange multipliers in Eq. (5.7) with \(-1/T\) and \(\mu/T\). Parameter \( T \), or the effective temperature, controls the relative contributions of the dendritic spine cost and the synaptic entropy to the Lagrange function \( L \). As the generalized cost of dendritic spines is always detrimental to the organism, the effective temperature must be non-negative, \( T \geq 0 \). Parameter \( \mu \) is referred to as the effective potential. It is analogous to the chemical potential. This parameter describes the contribution of a single spine to the objective function, \( L \), and can be positive or
negative. It follows from Eq. (5.7) that the effective temperature, the effective potential, and the
generalized spine cost must have the same units. These units are referred to as arbitrary cost units
or [cu]. Because the experimentally measured spine shape distribution function, \( p(V,s) \), is
precisely the one that maximizes the Lagrange function, Eq. (5.7), the functional derivative of
the that function with respect to \( p(V,s) \) must be zero,

\[
\frac{\delta L}{\delta [p(V,s)]} = \frac{\delta I_{\text{mod}}}{\delta [p(V,s)]} + \frac{\delta I_{\text{pattern}}}{\delta [p(V,s)]} - \frac{1}{T} N_s \varepsilon(V,s) + \frac{\mu}{T} N_s = 0. \tag{5.8}
\]

Using Eqs. (5.4) we have:

\[
\frac{\delta I_{\text{mod}}}{\delta [p(V,s)]} = -N_s \ln \left( p_r(V) e^{\Delta V} \right). \tag{5.9}
\]

In the same way, using equation (5.5) and remembering that \( f(s) \) also depends on the spine length
distribution through Eq. (3.2), we obtain:

\[
\frac{\delta I_{\text{pattern}}}{\delta [p(V,s)]} = \frac{\delta I_{\text{pattern}}}{\delta [f(s)]} \frac{\delta [f(s)]}{\delta [p(V,s)]}
= -N_s \frac{\delta}{\delta [f(s)]} \left[ \ln(f(s)) + \frac{1-f(s)}{f(s)} \ln(1-f(s)) \right] f(s) \left( \frac{f_B s^2}{s + \delta} \right) \frac{\delta [f(s)]}{\delta [p(V,s)]}
= N_s \frac{\delta}{\delta [f(s)]} \left[ f(s) \ln(f(s)) + (1-f(s)) \ln(1-f(s)) \right] \left( \frac{f_B s^2}{s + \delta} \right) \left( \frac{s + \delta}{f_B s^2} \right)
= -N_s \left[ 1 + \ln \left( f(s) \right) - 1 - \ln \left( 1 - f(s) \right) \right]
= N_s \ln \left( \frac{1-f(s)}{f(s)} \right) \tag{5.10}
\]
Replacing these two results in (5.8) we arrive at:

\[-\ln(p_v(V)e\Delta V) + \ln\left(\frac{1}{f(s)} - 1\right) - \frac{1}{T} \varepsilon(V, s) + \frac{\mu}{T} = 0.\]  

(5.11)

As a result, the generalized cost of dendritic spines is:

\[\varepsilon(V, s) = \mu + T \left[ -\ln(p_v(V)e\Delta V) + \ln\left(\frac{1}{f(s)} - 1\right) \right].\]  

(5.12)

Here we see that the generalized cost of dendritic spines splits into spine head volume and spine length related contributions, and Eq. (5.12) can be re-written in the form:

\[\varepsilon(V, s) = \mu + T \left[ \tilde{\varepsilon}_v(V) + \tilde{\varepsilon}_s(s) \right],\]  

(5.13)

where \(\tilde{\varepsilon}_v(V)\) and \(\tilde{\varepsilon}_s(s)\) are dimensionless functions given by

\[\tilde{\varepsilon}_v(V) = -\ln(p_v(V)e\Delta V)\]

\[\tilde{\varepsilon}_s(s) = \ln\left(\frac{1}{f(s)} - 1\right).\]  

(5.14)

These functions are entirely dependent on experimentally measurable parameters, Figure 5.1.
In a slightly different, but more general, formulation of the above optimization problem we assign different effective temperatures, $T_V$ and $T_s$, to the volume and length dimensions of dendritic spines and minimize the neuropil’s grand potential [60]:

$$
\Phi = N_s \int_{0}^{\infty} \varepsilon(V, s) p(V, s) dV ds - (T_V I_{mod} + T_s I_{struct}) - \mu N_s \int_{0}^{\infty} p(V, s) dV ds.
$$

This way the theory can be generalized to the situations where the two degrees of freedom are not in thermal equilibrium with each other, $T_V \neq T_s$. For example, in a system with
no structural synaptic plasticity, the contribution of $I_{\text{pattern}}$ to the objective function can be frozen out by setting $T_s$ to zero.

In this formulation, the generalized cost of dendritic spines in Eq. (5.13) has the form:

$$\varepsilon(V, s) = \mu + T_v \tilde{\varepsilon}_v(V) + T_s \tilde{\varepsilon}_s(s).$$

(5.16)

This expression can be broken down into two independent contributions again, assuming that $\mu$ can be separated too: $\mu = \mu_v + \mu_s$, then,

$$\varepsilon(V, s) = \varepsilon_v(V) + \varepsilon_s(s)$$
$$\varepsilon_v(V) = \mu_v + T_v \tilde{\varepsilon}_v(V)$$
$$\varepsilon_s(s) = \mu_s + T_s \tilde{\varepsilon}_s(s)$$

(5.17)

The effective temperatures, $T_v$ and $T_s$, and the effective potentials, $\mu_v$ and $\mu_s$, determine the scale and the offset for the generalized costs, $\varepsilon(V, s)$, in Figure 5.1.

### 5.5 Universality of the generalized spine cost

According to the second hypothesis in section 5.2, the generalized spine costs, $\varepsilon(V, s)$, and therefore its components $\varepsilon_v(V)$ and $\varepsilon_s(s)$, are the same in different cortical systems. As a result, appropriate choice of parameters $T_{V,s}$ and $\mu_{V,s}$ should make the $\varepsilon_v(V)$ and $\varepsilon_s(s)$ curves calculated for different systems collapse on top of each other. Parameters of the theory $T_v$ and $T_s$, are referred to as the effective spine head volume and spine length temperatures. These temperatures
depend on the shapes of dendritic spines and can differ across systems. Parameters $\mu_V$ and $\mu_s$ specify the offsets of the corresponding dendritic spine cost components and are called the effective potentials. The effective temperatures and potentials should not be confused with the physiological temperature of the brain and the chemical potential, regardless of the similarities in the theoretical treatment.

It is evident that the choice of such parameters $T_{V,s}$ and $\mu_{V,s}$ is not unique. This is because all the effective temperatures can be rescaled by two arbitrary positive multiplicative factors, one for $T_V$ and one for $T_s$. Fixing these factors defines the two effective temperature scales. Similarly, the effective potentials, $\mu_{V,s}$, are defined up to two arbitrary additive constants, which combined specify the absolute energy scale. In choosing the absolute effective temperature and energy scales we used mouse dentate gyrus as a reference system, (system #8 in table D3.1 in Appendix D). The choice of this system as the reference was motivated by several considerations. First, this system contains the largest number of measured dendritic spines ($n = 10,677$). Second, measurements were performed in adult brain (12-14 months) and both spine head areas and spine neck length were measured, making accurate estimates of spine head volumes and spine lengths possible. Finally, due to continued neurogenesis [62], connectivity in the dentate gyrus (DG) remains very plastic even in adult. Hence, this system may have a better chance of reaching the statistical equilibrium.

With no loss of generality we set $T_V^{\text{ref}} = T_s^{\text{ref}} = 1 \text{cu}$ for the reference system. Here, “cu” denotes arbitrary cost units used in describing $T, \mu$, and $\epsilon$. Parameters $\mu_V$ and $\mu_s$ were chosen in
such a way that the generalized costs $\varepsilon_V(V)$ and $\varepsilon_s(s)$ would have straight line asymptotes passing through the (0,0) points. Because dendritic spine costs appear to be linear in the limit of large $V$ and $s$, the reference costs $\varepsilon_V(V)$ and $\varepsilon_s(s)$ were linearly extrapolated onto the larger $V$ and $s$ values. The resulting reference costs are shown in Figures 5.2 A and 5.2 B. The values of the parameters $T_{V,s}$ and $\mu_{V,s}$ for all the systems from table D3.1 in appendix D, were determined according to the last two expressions in Eqs. (5.17).

![Figure 5.2](image-url)

**Figure 5.2.** Reference cost. Volume (A) and length (B) related components of the reference cost of dendritic spines were created by linear extrapolation (dashed lines) of $\tilde{\varepsilon}_V(V)$ and $\tilde{\varepsilon}_s(s)$ from adult mouse dentate gyrus (system #8 in Table D3.1 (Appendix D), blue lines).
The reference costs were used in the left sides of these expressions, and the right sides contained $\tilde{c}_V(V)$ and $\tilde{c}_s(s)$ of a particular system. This formulation is equivalent to a linear regression problem [63]. Best fit values of $T_{V,s}$ and $\mu_{V,s}$, and the corresponding 95% confidence intervals were obtained from the fitting procedures, where the points corresponding to spine head volumes of less than 0.05 $\mu$m$^3$ and spine lengths of less than 1.0 $\mu$m were ignored (as mentioned above).

Next, by substituting the best fit values of $T_{V,s}$ and $\mu_{V,s}$ in Eqs. (5.17) we calculated the generalized spine costs, $c_V(V)$ and $c_s(s)$, for every system. Consistent with the second hypothesis, the dendritic spine cost curves collapse on top of each other, Figures 5.3A and 5.3B. The goodness of this collapse can be described by the adjusted $R^2$ coefficient, which was $0.93 \pm 0.05$ (mean $\pm$ SD, $n = 70$) in the case of $c_V(V)$ and $0.95 \pm 0.06$ ($n = 96$) in the case of $c_s(s)$. In agreement with the idea of volume being a major resource, limiting the number of possible synaptic connectivity configurations [58, 64-66], the generalized spine cost $c(V,s)$ in different systems increases linearly with the volume of spine head. In addition, $c(V,s)$ appears to be linear in $s$ for spines longer than about 1 $\mu$m. For shorter spines, the dependence on $s$ is non-linear. This non-linearity could result from the non-uniformity of space in the vicinity of dendritic shafts, inhibitory shaft synapses, and glial cells. It is also likely that systematic undercounting of short spines due to the limited optical resolution and the effect of short spine shadowing by dendritic branches contributes to the non-linearity.
5.6 Effective temperatures and statistical equilibrium in adult cerebral cortex

In this section we analyze the values of the effective temperatures, $T_V$ and $T_s$, which led to the collapse of the generalized spine cost curves (Figures 5.3A and 5.3B). First we study their dependence on age, because progressive changes in the shapes of dendritic spines occur in the course of development, and $T_V$ and $T_s$ are expected to change as well. In younger animals, dendritic spines are longer and have smaller heads and, as a result, $T_s$ is high and $T_V$ is low at early ages, Figure 5.4. Figure 5.4 shows that $T_s$ progressively decreases and $T_V$ increases with
development, and in adult rodents (by the end of the first postnatal month) both temperatures appear to stabilize.

**Figure 5.4.** Effective temperatures in development. Effective temperature $T_s$ decreases in the course of development while $T_V$ increases. These temperatures in rodents appear to stabilize roughly at the end of the first postnatal month. Numerals correspond to the system numbering in table D3.1 (Appendix D). Only the relative measurements (ratios) of $T_V$ within individual groups are reliable.

In adult cerebral cortex, the modulatory and structural synaptic plasticity mechanisms would be in statistical equilibrium with each other, if the effective temperatures $T_V$ and $T_s$ within different cortical systems were nearly equal. So we plotted $T_V$ vs. $T_s$ for adult rodents in Figure 5.5. We took only set of data in which the volume was measured reliably. We see that most of the values for wild type animals lie close to the diagonal, supporting the statistical equilibrium hypothesis. In contrast, the statistical equilibrium is perturbed in transgenic (APP/PS1) model Alzheimer’s disease mice [67] (red points with error bars in Figure 5.5).
Figure 5.5. Evidence of statistical equilibrium in adult cerebral cortex. Effective temperatures $T_V$ and $T_s$ are close to the diagonal, hence, the modulatory and structural synaptic plasticity mechanisms are in equilibrium with each other in different areas of wild type adult cerebral cortex. This equilibrium is perturbed in transgenic (APP/PS1) model Alzheimer’s disease mice (red dots with error bars). Numerals correspond to the system numbering in table D3.1 (Appendix D).

In addition to statistical equilibrium of modulatory and structural synaptic plasticity mechanisms ($T_V \approx T_s$) in individual cortical systems, there appears to be equilibrium among different synaptic domains within the systems as well. Figure 5.6 shows that $T_V$ and $T_s$ are not statistically different between layers 2/3 and 5/6 of adult rat motor cortex. The average effective temperature $T_V$ is the same on apical and basal dendrites in mouse V1, as well as mouse CA1. In the latter system, however, $T_V$ increases with distance from the cell body along apical dendrites and is significantly higher on very distal apical branches (but not basal branches). In this figure,
we can only compare the values of effective temperatures within individual groups. For example, the values for the effective temperatures $T_s$ and $T_V$ in rat motor cortex (first 4 bars in Figure 5.6) cannot be compared to each other because the values of volume heads for this system were calculated from head diameters measurements [68], while the spine lengths were measured directly.

![Figure 5.6](image)

**Figure 5.6.** Evidence of statistical equilibrium in adult cerebral cortex. In rodents, effective temperatures $T_V$ and $T_s$ are not statistically different in different layers of a given cortical area, as well as on apical and basal dendritic branches. With the exception of very distal apical branches (asterisks, $p < 0.01$ two-tailed Student’s t-test for samples with unequal variances), $T_V$ on CA1 neurons remains constant with spine distance to the soma. Numerals correspond to the system numbering table D3.1 (Appendix D). Only the relative measurements (ratios) of $T_V$ within individual groups are reliable.

### 5.7 Statistical traces of long-term memories stored in different cortical areas
Though the modulatory and structural synaptic plasticity mechanisms appear to be in statistical equilibrium within individual cortical systems, different cortical systems can have vastly different effective temperatures. In Figure 5.7A, we show the values of the effective temperatures grouped by species. The result suggests that the effective temperature decrease from primary sensory areas to association areas in the neocortex to hippocampal areas (CA1 and dentate gyrus). For example, the effective temperature of monkey V1 (primary visual) is more than 2-fold higher than those in areas V2, V4, TE, and 7a, and the average effective temperature in rodent hippocampus is about 3-fold lower than that in the neocortex. This finding is consistent with the fact that CA1 synapses are typically much smaller than their neocortical counterparts (see e.g. [69, 70]).

Knowledge of the effective temperatures in different systems makes it possible to calculate the average volume and length related components of the generalized costs per dendritic spine in these systems. Figure 5.7B shows these costs measured from the corresponding minimal cost levels, $\Delta E_{V,s}/N_s = E_{V,s}/N_s - \varepsilon_{V,s}^{\text{min}}$ (see Figures 5.2A and 5.2B).
Figure 5.7. A. Effective temperatures $T_V$ (green) and $T_s$ (blue) in hippocampal areas are much lower than those in the neocortical areas. B. Both volume and length related components of the generalized cost per dendritic spine, $\Delta E_V/N_s$ and $\Delta E_s/N_s$, in hippocampus are lower than the corresponding cost components in neocortex ($\Delta E_{V,s}/N_s = E_{V,s}/N_s - \varepsilon_{V,s}^{\min}$, see Figures 5.2 A and 5.2 B). Abbreviations: TE – temporal, V – visual, M – motor, BC – barrel cortex, DG – dentate gyrus, A – auditory, FS – forelimb somatosensory.

Due to the universality of the dendritic spine cost, $\varepsilon(V,s)$, the average cost per spine is well correlated with the effective temperature. This cost in rodent hippocampus is several-fold lower than in neocortical areas. We suggest that the generalized cost of dendritic spines, and in particular its plasticity related component, may be the limiting factor defining the plasticity rate of synaptic connectivity. Because, this cost is correlated with the effective temperature, the latter can be viewed as a measure of circuit plasticity rate and, consequently, is related to the longevity
of stored memories. Higher effective temperature areas containing longer and larger dendritic spines, should have lower motility rates, and, hence, are expected to store longer-lasting memories. Such “hard-wired” systems should include primary areas (e.g. sensory and motor), where there is no clear necessity to change synaptic connectivity in normal adulthood. Consistent with this argument, the highest effective temperatures belong to monkey and rat V1, and rat and mouse motor and barrel cortical areas. In contrast, the effective temperatures of mouse and rat hippocampus are the lowest, which is in agreement with temporary storage and relatively fast turnover of hippocampal (declarative) memories [71-74]. An experimentally falsifiable prediction of this theory is that the in vivo motility rate in rodent hippocampus must be much higher than those in primary neocortical areas.

5.8 Equilibrium distributions of spine head volumes and spine lengths

Because the generalized spine costs $\varepsilon_V(V)$ and $\varepsilon_s(s)$ for different systems are universal, in the following we will denote these costs with $\varepsilon^u_V(V)$ and $\varepsilon^u_s(s)$, where the superscript $u$ stands for the universality. In addition, due to the thermodynamic equilibrium between the spine head volume and the spine length degrees of freedom, $T_V = T_s$, we will use a single effective temperature, $T$. 
As a result of the above universality and thermodynamic equilibrium, the functional forms of the probability densities of dendritic spine volumes and spine lengths, as well as the connectivity fraction in any given cortical area are determined by only few parameters (see Eqs. (3.1) and (5.14)):

\[
p_{V}(V) = \frac{1}{e^{\Delta V}} e^{\frac{\mu_{V} - e^{\gamma_{V}(V)}}{\tau}}
\]

\[
p_{s}(s) = 2\pi\rho_{d}(s + \delta) f(s) = \frac{2\pi\rho_{d}(s + \delta)}{e^{\gamma_{s}(s) - \mu_{s}} + 1 + e^{\frac{\gamma_{s}(s) - \mu_{s}}{\tau}}}
\]

(5.18)

The effective potentials, \(\mu_{V,s}\), in Eq. (5.18) are determined from the normalization conditions Eq. (5.2). Consequently, in the presented model of synaptic plasticity, the equilibrium state of the neuropil is completely described with only four parameters, e.g. \(T, \rho_{d}, \delta, \) and \(\Delta V\).

Parameters, \(\Delta V, \rho_{d}, \) and \(\delta\), do not change dramatically from one cortical region to another and only have a limited effect on the shapes of \(p_{V,s}\) (as will be shown in Chapter 6), leaving the effective temperature, \(T\), as the main determinant of the spine shape. To show how well the effective temperature predicts the distribution of dendritic spine shapes, we performed simultaneous single parameter fits of the experimental spine head volume and spine length distributions with Eqs. (5.18). Figure 5.8 illustrates goodness of the fits for four systems [31, 75] in which both spine head volume and spine length measurements were made reliably (systems 1-3 in table D3.1 on Appendix D). In addition, separate \(p_{V}(V)\) and \(p_{s}(s)\) single parameter fits of all distributions from this table yielded adjusted \(R^{2}\) of 0.93 ± 0.10 (mean ± SD, \(n = 70\)) for \(p_{V}(V)\) and 0.94 ± 0.10 (\(n = 96\)) for \(p_{s}(s)\).
Figure 5.8. Distributions of spine head volumes and spine lengths (for large dendritic spines) in adult cortical areas are completely determined by a single parameter – the area’s effective temperature. A1 and A2. Experimental distributions of spine head volumes and spine lengths (blue bars) were fitted simultaneously (red lines) with Eqs. (5.18) containing a single free parameter, $T$. Spine head volumes of less than 0.1 $\mu$m$^3$ and spine lengths of less than 1.0 $\mu$m were ignored during fitting (shaded areas). The areas under the best fit lines are normalized to 1. The experimental distributions were scaled along the y-axes to match the areas under the best fit lines in the non-shaded regions. The best fit effective temperature and the adjusted $R^2$ coefficient are shown in the figure caption. Similar results are obtained for mouse cortical areas V1 (B1 and B2) and A1/S2 (C1 and C2).
Chapter 6

The numbers of synapses in different cortical areas are nearly optimally chosen for memory storage

One of the implications of the universality of the generalized spine cost $\varepsilon(V,s)$ is that the state of cortical neuropil is completely specified by only four parameters. One choice of such parameters is $[E/N_s, \rho_d, \delta, \Delta V]$, which consists of the average generalized cost per spine, the dendritic length density, the sum of the average bouton and dendrite radii, and the unitary change in spine head volume. The first parameter is correlated with the effective temperature and can differ among cortical regions (Figure 5.5A). Parameters $\rho_d$ and $\delta$ can be easily measured experimentally. These parameters and $\Delta V$ do not change dramatically from one cortical region to another and have little effect on the results of this study (see Appendix D2 and Figures 6.2). The four parameters completely define the distribution of spine shapes, $p(V,s)$. For example, comparison of the experimental and theoretical spine shape distributions yielded adjusted $R^2$ of $0.92 \pm 0.10$ (mean ± SD, $n = 70$) in the case of $p_V(V)$ and $0.94 \pm 0.10$ ($n = 96$) in the case of $p_s(s)$ (points corresponding to spine head volumes of less than $0.05 \mu m^3$ and spine lengths of less than
1.0 µm were ignored for the comparison). The four parameters in a given system also define the connectivity fraction, $f(s)$ [25], the effective temperature and potential, $T$ and $\mu$, and the average synaptic entropy per spine, $I/N_s$.

Consider a cortical system with a fixed amount of total generalized cost, $E$, available to $N_s$ dendritic spines. Assume that the number of spines may vary, and the question is what value of $N_s$ maximizes the synaptic entropy? To answer this question we made another selection of parameters: the number of dendritic spines per unit cost, $N_s/E$ (in place of $T$), $\Delta V$, $\rho_d$ and $\delta$. Other quantities describing the system can be expressed in terms of these four parameters with the help of Eqs. (3.1), (4.8), (5.5) and (5.6). These equations are summarized below:

\[
\frac{I_{\text{mod}}}{N_s} = -\int_0^\infty \ln(p_r(V))p_r(V) dV - V \ln(\Delta V)
\]

\[
\frac{E_r}{N_s} = -\int_0^\infty e_r^s(V)p_r(V)dV
\]

\[
\frac{I_{\text{struct}}}{N_s} = -2\pi\rho_d \int_0^\infty \left[f(s)\ln\left(1 - f(s)\right) + (1 - f(s))\ln\left(1 - f(s)\right)\right] (s + \delta)d
\]

\[
\frac{E_s}{N_s} = -\int_0^\infty e_s^s(s)p_s(s)ds
\]

The total synaptic entropy per spine, $I/N_s = (I_{\text{mod}} + I_{\text{struct}})/N_s$, can be expressed in terms of these four parameters as:

\[
\frac{I}{N_s} = g\left(\frac{E}{N_s}, \rho_d, T, \delta\right) - \frac{1}{\Delta V} \ln(\Delta V)
\]
Notice, that the dependence of this expression on $\Delta V$ is trivial.

The functional form of $g$ in Eq. (6.2) cannot be deduced analytically due to the empirical nature of the universal spine costs, $\varepsilon_r^e(V)$ and $\varepsilon_s^a(s)$. Yet, the shape of this function can be obtained numerically. Here, this was done by using the Newton’s method for solving non-linear systems of equations [63].

We are going to use an alternative form of Eq. (6.2) here:

$$\frac{I}{E} = h \left( \frac{N_s}{E}, \rho_d, \delta \right) - \ln(\Delta V) \frac{N_s}{E}$$

(6.3)

This equation clearly shows that for a constant value of the total cost of dendritic spines, $E$, and the experimentally observed values of $\Delta V$, $\rho_d$, and $\delta$, the total synaptic entropy is only a function of the number of spines, $N_s$. Function $h$ in this expression is completely defined by the shape of the universal dendritic spine cost, $\varepsilon(V,s)$. The shape of the curve in Eq. (6.1) is shown in Figure 6.1 (solid line).

To understand this shape consider a cortical system with a fixed amount of total generalized cost, $E$, available to $N_s$ dendritic spines. For small $N_s$, spines must be large and long on average in order to accommodate the fixed total dendritic spine cost constraint. In this limit the effective temperature is high, and the average synaptic entropy per spine increases logarithmically as $N_s$ decreases.
Figure 6.1. Cortical neuropil is nearly optimally designed for storing information in strengths and patterns of synaptic connections. For a fixed total cost of dendritic spines, $E$, the dependence of the synaptic entropy on the spine number is shown with the black line. The values of $I/E$ vs. $N_s/E$ in different cortical systems are shown with red and blue dots.

However, the total synaptic entropy decay to zero as it is in addition proportional to the number of spines. In the limit of large numbers of dendritic spines, increase in $N_s$ must be accompanied with a decrease in the generalized cost of individual spines. Hence, spines will assume shapes for which the generalized cost is minimal. This is the low effective temperature limit. At certain value of $N_s$ the distribution of spine lengths becomes so narrow that spines occupy all the available potential synaptic sites in that range of spine lengths. At this point there is only one possible connectivity pattern, and $I_{\text{struc}}$ is zero. Similar argument shows that $I_{\text{mod}}$ is zero in this limit as well. This abrupt transition occurs at a value of $N_s/E = 1/\epsilon^{\text{min}} \approx 0.15 \text{ cu}^{-1}$,
where $\varepsilon_{\text{min}}$ denotes the minimal dendritic spine cost of the reference system ($\varepsilon_{\text{min}} = \varepsilon_V^{\text{min}} + \varepsilon_s^{\text{min}} \approx 6.7 \text{ cu}$, see Figures 5.2A and 5.2B).

Figure 6.1 also shows the values of $I/E$ and $N_s/E$ calculated for individual cortical systems (points). In all the considered systems, the observed neuropil states are near the maximum of the synaptic entropy curve. The maximum of the $I/E$ curve is so broad that, for the relatively large effective temperature range (1-5 cu) encountered in different cortical systems, the numbers of dendritic spines in these systems are nearly optimally chosen for storage of memories in strengths and patterns of synaptic connections. As it is often the case in biological systems, getting to the optimal solution may be too costly and unnecessary. “Good enough” solutions to biological problems usually suffice. These solutions are responsible for the diversity of organization observed in individual animals [76].

Finally, we note that the conclusions drawn from Figure 6.1 do not depend strongly on the values of the parameters $\varepsilon_{\text{min}}, \rho_d, \Delta V, \delta$. Figures 6.2 B and 6.2 C show that the position of the reference system (system #8) with respect to the maximum of the $I/E$ curve does not change substantially if the values of the above parameters are varied in the biologically plausible range (See Appendix D.2). With the exception of very low values of $\varepsilon_{\text{min}}$ (less than 1 cu) the deviation from the optimum remains within 15%.
Figure 6.2. Relative deviation of $I/E$ for the reference system from the maximum of the curve in Figure 6.1. The deviation is small for all biologically plausible values of parameters $\epsilon_{\text{min}}$, $\rho_d$, $\Delta V$ and $\delta$. Asterisks show the default parameter values used throughout this study.
Chapter 7

Conclusions and Outlook

We constructed a geometrical model of connectivity in the brain. Cortical circuits continuously change during learning and memory formation. This plasticity, along with a very large number of synapses in the brain, makes it possible to utilize methods of statistical physics in describing the equilibrium connectivity configurations.

We calculated and compared the potential for structural spine plasticity in different cortical areas. Our numerical results are based on experimental distributions of spine lengths, as well as other neuroanatomical parameters, measured in mouse, rat, monkey, and human brains. We found that a single spine in the primate cortex can choose among many more potential targets than that in the rodent cortex. The total structural synaptic entropy per volume of neuropil is highest in rat CA1 and lowest in monkey V1.

Next, we extended our theory to include modulatory circuit plasticity contributions coming from synapse potentiation and depression. In this theory, the shapes of dendritic spines
are governed by the generalized cost and two (spine length and spine head volume related) effective temperatures. We found that the generalized spine cost universally depends on spine head volume and spine length, i.e. the dependence is the same in all the 166 systems we considered. Our results show that this dependence is roughly linear for large spines. The effective temperatures in a given cortical area change in development but reach the same equilibrium point in adult, suggesting that the modulatory and structural plasticity mechanisms in adult are in a statistical equilibrium with each other. We show that the diversity of dendritic spine shapes across different areas of adult cerebral cortex is governed by a single parameter – the effective temperature, and that the numbers of synapses in these areas are nearly optimally chosen for memory storage.

Knowledge of neuron morphology and the functional shape of the dendritic spine cost, combined with the idea of statistical equilibrium in the adult, can lead to biologically realistic modeling of synaptic connectivity on the level of a large cortical network. For example, such model can be based on the following three steps. First, to establish a synaptic connection, the pre-synaptic axon has to be within the spine reach from the post-synaptic dendrite (potential synapse). Second, a dendritic spine or a filopodium has to find and establish an initial contact with the axon. Finally, based on the cost of the dendritic spine and functional properties of the two neurons, the initial connection is either stabilized and transformed into a synapse or is eliminated. For this model, a realistic potential connectivity matrix of a cortical system can be generated from dendritic and axonal arbors of neurons reconstructed in 3D. This matrix will contain information about the numbers of potential synapses between all pairs of neurons, as
well as the spine lengths required to transform these potential synapses into actual. Because the potential connectivity matrix in the adult cerebral cortex does not generally change in time, it serves as a major biological constraint. Spines will be randomly placed in potential synaptic sites in a Monte Carlo simulation and will be either stabilized or retracted using the Metropolis algorithm. The latter procedure will take in account the cost of dendritic spines and differences in the functional properties of neurons. The resulting numbers of synapses between synaptically coupled neurons and the probability of finding such neurons in the artificial network can be compared to the experimental data [77] to validate the model.
APPENDIX A

Assumptions and approximations

Our method relies on several realistic assumptions and approximations. In the following we provide a list of assumptions specifying with A or B the model of potential connectivity for which these assumptions are needed.

A.1. Dendritic spines as straight segments

The first approximation made in our model is treating dendritic spines as straight segments that extend perpendicularly from pre-synaptic dendritic branches connecting them to post-synaptic targets. Though by and large dendritic spines in light microscopy images appear to be quite straight and extend predominantly perpendicularly to dendritic shafts, our results underestimate the amount of structural synaptic entropy. This is because we did not account for the excess entropy associated with spine conformations which could result in new connectivity patterns. The number of potential synapses accessible to spines in the \([s - \Delta s / 2, s + \Delta s / 2]\) length range is proportional to \(\Delta A_A = 2h_s\Delta s\) in model A, the cross-sectional area per spine of a cylindrical shell surrounding an axon where the pre-synaptic dendritic branches are located (see Chapter 2). In model B this number is proportional to \(\Delta A_B = 2\pi(s + \delta)\Delta s\), which is the cross-sectional area of a spherical shell surrounding a bouton. With new spine conformations these cross-sectional areas increase to \(\tilde{A}_{A,B}\), leading to a proportional increase in the number of potential synapses and a
decrease in the connectivity fraction, \( \tilde{f}_{A,B}(s) = f_{A,B}(s) \Delta A_{A,B} / \tilde{A}_{A,B} \). To estimate the increase in structural entropy per spine due to this effect, we note that in the limit of small connectivity fractions, the second term in Eq. 4.6 can be neglected and
\[
\tilde{i}_{A,B} / n_s \approx -\int_0^\infty \ln(\tilde{f}_{A,B}(s)) p(s) ds = i_{A,B} / n_s + \int_0^\infty \ln(\tilde{A}_{A,B} / \Delta A_{A,B}) p(s) ds.
\]
Hence, due to different spine conformations, structural entropy per spine increases in the amount equal to the average logarithm of \( \tilde{A}_{A,B} / \Delta A_{A,B} \), and can be large in absolute terms. However, the role of this term in comparing structural entropy per spine between different systems is much smaller. To illustrate this point consider comparison between two systems, with spine length distribution functions \( p_1(s) \) and \( p_2(s) \), in model A. Difference in the conformational entropy terms in these systems is
\[
\int_0^\infty \ln(\tilde{A}_A / \Delta A_A)[p_1(s) - p_2(s)] ds.
\]
Due to the fact that the spine length distribution functions are normalized to unity this expression reduces to
\[
\int_0^\infty \ln(\tilde{A}_A)[p_1(s) - p_2(s)] ds.
\]
It is not clear how \( \tilde{A}_A \) depends on \( s \) but, because of the slow nature of the logarithm function, the resulting integral is small (fraction of one bit for the considered systems) for all reasonable dependences. Moreover, as \( \tilde{A}_A \) is expected to increase with \( s \), accounting for conformational entropy of dendritic spines only enhances the difference in structural entropy per spine between rodent and primate groups.

A.2. Approximations related to dendritic and axonal branches

- The average axonal (A) and dendritic (A, B) branch lengths were assumed to be much longer than the average spine length. Branch here was defined as a neuron process
extending from soma or a bifurcation point to a successive bifurcation or an end point. This approximation ignores the corrections to the potential synapse count due to branch tips and bifurcation points. This approximation is certainly valid for the excitatory neurons in the cerebral cortex.

- We made a simplifying assumption that axonal (A) and dendritic (A, B) branches of excitatory neurons are randomly distributed in the neuropil. Inhomogeneous distributions of branches would lead to spatial variations in the values of the calculated parameters. Yet, this should not affect the average values calculated in this study. This is justified in part by the absence of correlations between the positions of axonal and dendritic branches (axons on average are not “attracted to” or “repelled from” dendrites) [78].

- We assumed that synaptic contacts can occur anywhere along axonal (A) and dendritic (A, B) branches. In other words, there are no hot-spots for spine and bouton formation. The presence of hot-spots on dendritic branches would not change the results of our calculations because the average inter-spine interval is already smaller than the average spine length.

- Even though the results for model A were derived for an arbitrary distribution of angles between axonal and dendritic branches in the neuropil, in all numerical results we made a simplifying assumption that this distribution is isotropic. This assumption had been verified on the dataset of cortical excitatory neurons reconstructed in 3D [29]. It is already valid if the orientation of either axonal or dendritic branches is isotropic. Anisotropic distribution of angles could lead to slightly different numerical values (see below).
A.3. Number of synapses, spines and boutons

- We made a simplifying approximation in which the number of asymmetric synapses is approximately equal to the number of boutons on excitatory neuron axons (A, B). This is because the majority of boutons on excitatory axons contain only a single asymmetric synapse. This approximation is supported by low fractions of multiple synapse boutons: 0.026 in cat primary visual cortex [30, 79], 0.16 in rat motor cortex [80], 0.18-0.24 in rat hippocampus [81, 82], and 0.14 in mouse barrel cortex [26]. The average asymmetric synapse to bouton ratio is 1.08 in mouse neocortex [2]. For asymmetric synapse to bouton ratios much larger than one, it would be necessary to use the general expressions given in Eq. (3.1) and (3.2) with $m \neq 1$ and $\sin \theta \neq \frac{\pi}{4}$.

- Another simplifying approximation made in the main text (Chapter 4 onwards) is that the volume density of spines of excitatory neuron dendrites is equal to the volume density of asymmetric synapses (for models A and B). This approximation is supported by generally low fractions of asymmetric synapses that are not made on dendritic spines of excitatory neurons. For example, in mouse neocortex this fraction is estimated at 0.13 [2]. For large fractions of such synapses it would be necessary to use Eqs. (3.1) and (4.4) in the calculations. In general, asymmetric synapse to bouton ratio is greater than one and it would proportionally increase the connectivity parameter, Eqs. (3.2), and decrease the structural synaptic entropy per spine. However, this change is expected to be small due to
the slow dependence of the structural synaptic entropy on the connectivity parameter in the 0.1-0.4 range (see Figures 4.2).

A.4. Other approximations

- We did not take into consideration volume exclusion effects in the neuropil (A, B), assuming that neurites are flexible and can be easily deformed to accommodate synaptic connections. Such effects could be important near the dendritic shafts where the space is partly occupied by inhibitory axons and their shaft synapses. This may effectively push the excitatory axons farther out. Hence, our results may not be accurate for small values of the parameter $s$ (less than 0.5\(\mu\)m).

- Optical measurements of spine length distribution functions may not be accurate. First, due to the limited resolution, spine lengths shorter than 0.5\(\mu\)m cannot be measured accurately. Second, some dendritic spines can be overshadowed by the dendrite. Third, spines that do not lie entirely in the focal plane will appear shorter, shifting the spine length distribution function to the left. In the experimental data used in this study the last two effects were minimized by only measuring spines which lie in the focal plane on both sides of the dendritic branch.
APPENDIX B

Estimation of error-bars

In this study we compared parameters of structural synaptic plasticity in different systems. Such comparisons are hindered by generally large variability in anatomical measurements, and significant differences (if any) can only be observed on the level of the mean values. Hence, it is necessary to provide quantitative estimates of the standard errors to the mean values (sem). As the raw experimental data for the citations in Table 2.1 were not available to us, our strategy here was to estimate the upper bounds of the sem’s from the reported standard deviations (std) and the numbers of measurements.

Consider an experiment where a statistical measurement is performed in $n$ brains from multiple samples per brain. The samples are then pooled together and the mean and total variance ($\text{var} = \text{std}^2$) are reported as results of the experiment. Table 2.1 shows a number of such experiments where the inter-bouton interval along an axon, the spine density on a dendrite, and the density of asymmetric synapses in different systems were measured. To access inter-brain variability we would like to estimate the variance in the average measurements for different brains. For this we note that the total variance is equal to the sum of the average within-brain variance and variance in the averages for different brains. Hence, variance in the averages for different brains is always less or equal to the total variance. Then the upper bound of the standard
error to the mean is equal to the square root of the total variance divided by \( n \),
\[
\text{sem} \leq \sqrt{\text{var}/n} = \text{std}/\sqrt{n}.
\]
Standard deviation of all measurements pooled together divided by the square root of the number of brains provides a conservative estimate of inter-brain sem.

When calculating the product of two or more measured variables we propagated their sem’s using the Monte Carlo procedure. Here, we took advantage of the central limit theorem [57] and for each variable generated a set of 10,000 elements from a Gaussian distribution with the measured mean value and the sem estimated as described above. Next, we calculated the product between all members of the sets and obtained the mean and the sem for the product. This is how the mean and the sem values were estimated for all the calculated quantities, including the dendritic length density \( \rho_d \) from Table 2.1 and all the parameters from Table 3.1 and Table 4.1.

To test for the pairwise difference in the means of the calculated parameters and to obtain the corresponding p-values we used the Student’s t-test for samples with unequal variance.
APPENDIX C

Anatomical data used in Chapters 3 and 4

To evaluate the connectivity fraction and the capacity of neural circuits to undergo structural remodeling, we used previously published anatomical data from some of the best-studied cortical systems. Our choice of the cortical systems was primarily restricted by the availability of the spine length distribution function and we confined our analysis to mouse occipital cortex, rat CA1, monkey V1, and human temporal cortex. The anatomical parameters of circuit micro-architecture in these areas are provided in Table 2.1. Below we give a detailed account of how these parameters were selected. Unless stated otherwise, the numerical values are shown in the mean±std(sem) format.

C.1. Mouse occipital cortex: Anatomical data for the mouse occipital cortex was based on measurements from adult mice. The distributions of spine neck lengths and spine head areas were measured on basal dendrites of layer 3 pyramidal cells of 2 mice [31]. As there is no correlation between spine neck length and spine head area [31], these distributions were used to generate the spine length (neck length + head diameter) distribution. This was done with the following Monte Carlo procedure. 10,000 spine neck lengths and head areas were sampled from their corresponding distributions. The average spine head diameters were calculated for each spine head. These diameters were randomly associated with different spine neck lengths to
generate the spine length distribution function (Figure 3.1A). The average spine length obtained from this distribution is 0.99±(0.01)µm (n=2 mice, 1226 spines). The correction for hidden spines (spines above and below the dendrite) was deemed unnecessary, as only lateral spines were reconstructed in the above study. Parameter δ was estimated at 0.70µm which is the sum of the average radius of dendritic branches, 0.45µm [2], and the average radius of synaptic boutons, 0.25µm [2]. Though, this value of the parameter δ was based on several cortical regions and does not contain error bars, it does not affect strongly the results of our theory. This parameter is only present in model B, Eqs. 8, and has only an effect on our results in the region of small spine lengths. The average inter-bouton interval was estimated to be 4.5±1.4(0.47)µm (n=9 mice, 20 cells) based on measurements in layers 2-4 of different cortical areas [2, 32, 33]. As no significant variations in b across cortical areas is reported [32], we used this value to represent the inter-bouton interval in the mouse occipital cortex. Based on [2, 34] the average spine density along a dendrite, 1/b, is 1.94±0.42(0.24)µm⁻¹ (n=3 mice, 10 cells). The volume density of asymmetric synapses in layer 3 of mouse occipital cortex is 0.91±0.25(0.15)µm⁻³ (n=3 mice, 3 blocks of tissue). This value was calculated as the product of the total synapse density, 1.05±0.29(0.17)µm⁻³, and the 0.87 fraction of asymmetric synapses [2, 33]. We would like to mention that a significantly higher estimate of the average density of asymmetric synapses, 2.2µm⁻³ (n=1 mouse), was reported in [51]. We did not use this measurement as it is based on a single animal and is averaged across all cortical layers. However, the discrepancy in the densities of asymmetric synapses may have resulted from methodological differences. This point is further addressed in the discussion section. The dendritic length density calculated as the product of the
inter-spine interval and the density of asymmetric synapses is $0.48 \pm (0.10) \mu m^{-2}$, implying that one cubic micrometer of neuropil in layer 3 of adult mouse occipital cortex contains on average $0.48 \mu m$ of dendritic length.

C.2. Rat CA1: Anatomical data for the rat hippocampus was based on measurements in stratum radiatum of CA1 region in adult Long-Evans and Wistar rats. Here, the spine length distribution function (Figure 3.1B) was derived from the work of [35] (n=2 rats, 485 spines). In this work the cumulative distribution is scaled to the median spine length of $1 \mu m$. Hence, in generating the distribution in Figure 3.1B we differentiated the original cumulative distribution and rescaled it to the average spine length of $1.08 \pm (0.03) \mu m$ (n=4 rats, 351 spines). This value of spine length was determined by averaging the results from [36], $0.95 \pm 0.42 \mu m$ (n=3 rats, 100 spines), and [37], $1.21 \pm 0.43 \mu m$ (n=1 rats, 251 spines). The value of the average radius of dendritic branches in stratum radiatum, $0.30 \mu m$, was obtained by averaging the results from [36], $0.28 \mu m$ (n=3 rats, 7 dendritic segments), [37], $0.36 \mu m$ (n=3 rats, 3 cells), and [38], $0.25 \mu m$ (n=7 rats, 26 dendritic segments). This value was added to the average radius of synaptic boutons, $0.2 \mu m$ (n=2 rats, 224 varicosities) [39], resulting in $\delta = 0.5 \mu m$. The average inter-bouton interval in stratum radiatum of rat CA1, $3.7 \pm 0.6 (0.3) \mu m$ (n=5 rats, 1909 varicosities), was based on measurements for CA3 axons projecting to CA1 [40]. This value of inter-bouton interval is consistent with the value of $3.0 \pm 1.4 \mu m$ reported in [39] which has to be corrected for tissue shrinkage by an estimated 10-25% [39]. The density of spines on a dendrite, $1/b_d$, in stratum radiatum of rat CA1, $3.41 \pm 1.05 (0.40) \mu m^{-1}$ (n=7 rats, 20 cells), was obtained from the work of [38]. This value is
roughly in the middle between the two other reported measurements of spine density, 3.03±0.83(0.59)µm⁻¹ (n=2 rats, 15 dendrites) [41], and 3.80±0.76(0.54)µm⁻¹ (n=2 rats, 26 dendrites) [35]. Pooling all the data together would not result in a significant change in the density of spines. Using the density of asymmetric synapses of 2.0±0.30(0.13)µm⁻³ (n=5 rats, 5 blocks of tissue) [42] we estimated that the dendritic length density in stratum radiatum of rat CA1 is 0.59±(0.08)µm⁻². This result is similar to that in the mouse occipital cortex.

C.3. Monkey V1: This data was based on measurements from layer 3 of adult Macaque monkey primary visual cortex. Here, the distribution of spine lengths on basal dendrites was obtained from the work of [16], where the spine length was measured between a point on the dendritic axis closest to the base of the spine and the tip of the spine head. As in the present work spine length was measured from the dendritic surface, the original distribution was shifted to the left by 0.70µm, the amount corresponding to the average radius of basal dendrites [16]. The resulting distribution (Figure 3.1C) has the average spine length of 1.86±(0.05)µm (n=3 monkeys, 233 spines). Parameter δ was estimated as the sum of the average radius of basal dendritic branches, 0.70µm, and the generic average radius of synaptic boutons, 0.25µm. As stated above, this parameter does not strongly affect the results of our calculations. We obtained the average inter-bouton interval in layer 3 of monkey V1 from the work of [43]. The inter-bouton histogram in this study is consistent with an average inter-bouton interval of 5.6±2.4(1.2)µm (n=4 monkeys, 400 varicosities) reported as 180 boutons/mm. To estimate the average spine density on basal dendrites we pooled together data from four different studies [44-47] performed in Macaque primary visual cortex. Our estimate of 1/b₃, which was based on the reported measurements of
spine density and the number of branches as a function of distance from soma, resulted in 0.55±0.07(0.03)µm⁻¹ (n=5 monkeys). The volume density of asymmetric synapses was calculated as the product of the volume density of all synapses in layer 3 of adult Macaque monkey V1, 0.34±0.04(0.02)µm⁻³ (3 monkeys, 9 blocks of tissue) [48], and the fraction of asymmetric synapses, 0.76±0.09(0.06) (n=2 monkeys, 5 blocks of tissue) [49], resulting in 0.26±0.04(0.03)µm⁻³. This estimate lead to the average dendritic length density of 0.47±(0.05)µm⁻².

C.4. Human temporal cortex: The spine length distribution function was derived from the work of [31]. Here the distributions of spine neck lengths and spine head areas were measured on basal dendrites of layer 3 pyramidal cells in temporal cortexes of 2 adult male patients. The spine length distribution (Figure 3.1 D) was generated in the same way as for mouse occipital cortex, resulting in the average spine length of 1.42±(0.01)µm (n=2 humans, 2768 spines). The value of parameter δ, which in this case is equal to the sum of the average radii of second order dendritic branches and synaptic boutons, was estimated as 1.1µm +0.25µm. The former number was based on the analysis of published neuron images [31] and the latter is the generic value of the average bouton radius. We did not find a reliable estimate of the average inter-bouton interval in human temporal cortex and thus, we provided results for model B only. The value of the average spine density on basal dendrites of layer 3 pyramidal cells in human temporal cortex, 2.62µm⁻¹ (n=1 human, 73 dendrites), comes from the work of [50]. This type of data is very difficult to come by with and in this study we used measurements from only a single human subject. We did not use the measurements of the spine density reported in [31] for 2 human patients, as in that
comparative study no correction was made for hidden spines, i.e. spines located directly above or below the dendrite. To have an estimate of the extent of inter-subject variability we applied the variability observed in the monkey spine density to the human data. This estimate is justified in part by the fact that a similar coefficient of variation had been observed in human data from [31]. This resulted in a spine density of $2.62 \pm 0.34(0.34)\mu m^{-1}$. The volume density of asymmetric synapses in layer 3 of human temporal cortex was calculated by multiplying the density of all synapses with the reported fraction of asymmetric synapses resulting in $1.07\pm0.31(0.18)\mu m^3$ ($n=3$ humans, 60 blocks of tissue) [51]. As a result, the dendritic length density calculated as the product of the inter-spine interval and the density of asymmetric synapses was $0.42\pm(0.09)\mu m^2$. 
D1. Distributions of dendritic spine head volumes and spine lengths

The data set used in Chapters 5 and 6 was compiled from a number of published articles reporting the distributions of dendritic spine shape measurements such as: spine length, spine neck length, spine head diameter, spine head area, and spine head volume (see Table D3.1 in Appendix D3). A custom made MatLab algorithm was used to extract accurate quantitative information from high resolution digital images of these distributions.

Our theory utilizes the distributions of spine head volumes and spine lengths. However, in some studies these parameters were not reported directly. In these instances we generated the necessary distributions from the reported data with Monte Carlo sampling algorithms. For example, if an article reported a distribution of spine head diameters, this distribution had to be converted into the distribution of spine head volumes. To this end, we sampled 10,000 spine head diameters, and for each diameter calculated the corresponding spine head volume, assuming spherical geometry. We note that because this procedure greatly amplifies systematic errors, only the relative values of spine head volumes can be considered reliable. Such data were only used in Figures 4.6 and 5.1 A to illustrate the universality of the volume related component of the generalized spine cost, and in Figures 5.4 and 5.5 to illustrate the increase of the effective temperature $T_r$ with age. No quantitative conclusions were made in these cases.
In cases where neck length and head diameter distributions were reported, these distributions were combined to generate the spine length (neck length + head diameter) distribution. Here we assumed that there is no correlation between the two measurements [31], sampled 10,000 spine neck lengths and head diameters from their corresponding distributions, and randomly paired them with each other to generate the spine length distribution.

Due to the limited resolution of optical microscopy, dendritic volume measurements of less than 0.05 µm³ (diameter of about 0.5 µm) were deemed unreliable and were ignored. Because the fraction of spine head volumes below 0.05 µm³ is very low (see Figures 4.6, 5.1A, and 5.3A), this approximation does not affect the conclusions of our theory. Similarly, spine length measurements of less than 1 µm were thought unreliable (see Figures 4.4, 5.1B, and 5.3B). This assumption is based on the limited resolution of confocal microscopy, as well as the fact that short spines are often shadowed by dendritic branches (about 1 µm in diameter), resulting in an underestimate of the number of short spines.

D.2. Anatomical parameters

For this part we consider several systems. In mouse barrel cortex we find that $\rho_d = 0.51 \, \mu m^{-2}$. This result was calculated using the reported values of $n_s = 0.92 \, \mu m^{-3}$ (L2/3, postnatal day 16) [83] and $f_d = 1.8 \, \mu m^{-1}$ (L2/3, postnatal day 15) [84]. In mouse visual cortex we estimate that $\rho_d = 0.66 \, \mu m^{-2}$; calculated based on $n_s = 0.66 \, \mu m^{-3}$ (all layers, adult) [85] and $f_d = 1 \, \mu m^{-1}$ (L3,
postnatal day 60) [31]. In rat motor cortex we find that \( \rho_d = 0.3 \, \mu m^{-2} \); based on \( n_s = 0.47 \, \mu m^{-3} \) (L5, 4-6 months old) [80] and \( f_d = 1.55 \, \mu m^{-1} \) (L5/6, 3 months old) [86]. Direct ultrastructural measurements in layer 1 of young monkey visual and prefrontal cortices resulted in \( \rho_d = 0.35 \, \mu m^{-2} \) [87] and 0.5 \( \mu m^{-2} \) [88]. Because the exact values of \( \rho_d \) in different systems are unknown, and because the conclusions of this study are not very sensitive to the values of \( \rho_d \) in a biologically plausible range (0.1 – 1.0 \( \mu m^{-2} \), see below and Figure 6.2A), we used the value of \( \rho_d = 0.5 \, \mu m^{-2} \) for all the considered systems.

Parameter \( \delta \), which is the sum of the average radius of dendritic branches and axonal boutons, was estimated to be in the range of 0.5-0.7 \( \mu m \) in mouse and rat and 0.95-1.35 \( \mu m \) in monkey and human cerebral cortices [25]. Again, because exact values of this parameter are not known in all the considered systems, and because the conclusions of our theory do not depend strongly on the values of \( \delta \) in the 0.5-1.5 \( \mu m \) range (see e.g. Figure 6.2 B), we used \( \delta = 0.7 \, \mu m \) throughout this part of the study.

Parameter \( \Delta V \) is the change in the spine head volume corresponding to the unitary change in the synaptic strength. We assume that this parameter fundamentally depends on the molecular composition of synaptic machinery, which is expected to be the same in different species or cortical areas. Hence, in all calculations \( \Delta V \) is treated as a fundamental constant. Because conclusions of our theory are not sensitive to the values of \( \Delta V \) in the biologically plausible range of this parameter (0.01 – 0.11 \( \mu m^3 \), see below and Figure 6.2 B), we set \( \Delta V = 0.05 \, \mu m^3 \).
D3. **Anatomical measurements of dendritic spine lengths and head sizes.** Experimental studies reporting distributions of dendritic spine shapes are referenced in Table D3.1. All datasets in the table were used to generate Figures 4.4, 4.6, 5.1–5.3 of the main text. Highlighted entries show control/wild type experiments used to generate Figures 4.5, 4.7, 5.4–5.8. Estimates of $T_V$ were performed only if spine head volumes or areas were measured. Abbreviations: TE – temporal, V – visual, A – auditory, S – somatosensory, M – motor, DG – dentate gyrus, BC – barrel cortex, Hipp. – hippocampus, FS – forelimb somatosensory cortex, ha – spine head area, hv – spine head volume, hd – spine head diameter, nl – spine neck length, sl – spine length.

Table D3.1.

<table>
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<th>#</th>
<th>Species</th>
<th>Brain area</th>
<th>Layer (L) Apical (A) Basal (B)</th>
<th>Age</th>
<th>Slice or culture</th>
<th>Spine number</th>
<th>Spine head measurement</th>
<th>$T_V$</th>
<th>Spine length measurement</th>
<th>$T_s$</th>
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<td>L3 B</td>
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References


