Chapter 7
An Axonal Perspective on Cortical Circuits

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7.1 Introduction

How neurons connect in the complex circuits of neocortex is one of the fundamental problems in neuroscience. Anatomical techniques are used to trace the connection pathways involving axonal and dendritic trees, and electrophysiological recordings are applied to probe the connections between two or several neurons in the circuit. More recently, optical methods such as uncaging of glutamate and calcium imaging allow the functional circuit architecture to be explored on a larger scale, but the basic difficulty remains of establishing which neurons connect to which in a network consisting of several thousand of neurons. Neither is there a consentaneous theory about the basic function of a neocortical circuit, nor is there any unanimity about the principles by which the connections in the circuit are formed. The debate about the significance of the relative role of feedforward and recurrent processing for cortical function is still undiminished (Douglas and Martin, 2007a), as is the debate about the degree of randomness or specificity involved in wiring up the neurons (Ohki and Reid, 2007).

The most influential proposals about the overall circuit structure have therefore not come from direct experimental observations, but from building the circuit using the time-honoured assumption introduced by Ramón y Cajal that axons connect to dendrites whenever the two trees arborize (or overlap) in the same layer. We refer to this as the 'Cajal circuit' (Douglas and Martin, 2007b). What becomes clear from these studies is that our understanding of the neocortical circuits is intimately related to the precision with which we understand the organization of the dendritic and axonal branching patterns. This is particularly so for the axonal tree, which, with its complex and protruding branching pattern, is difficult to reveal and to characterize. The earliest attempts to construct an overall circuit diagram (Fig. 7.1a) were hampered by the incomplete staining of the axon of Golgi-impregnated neurons. The stained axons appeared as sparsely labelled trees and a connection had often to be
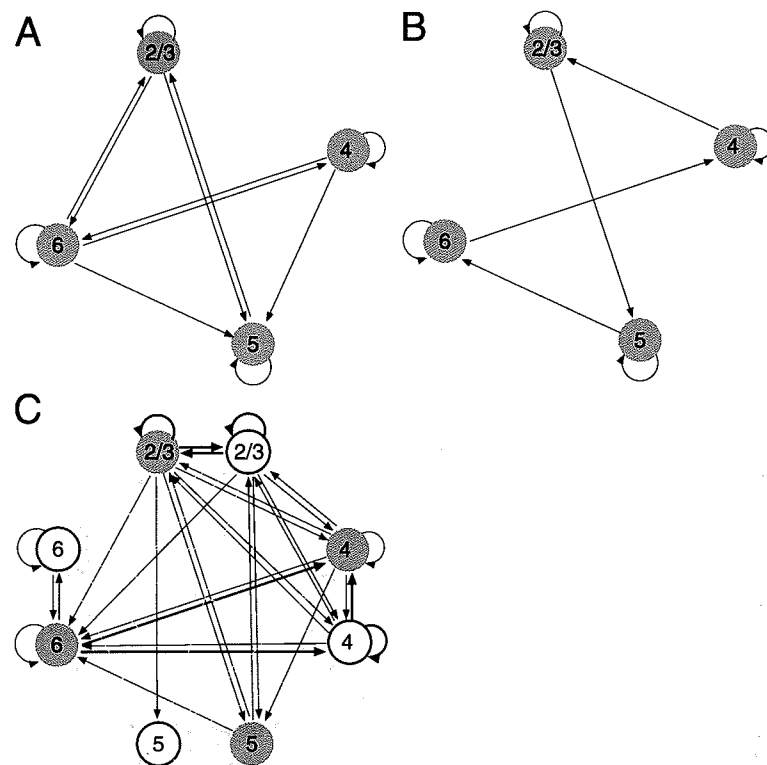
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Fig. 7.1 Local circuits of neocortex. (**a**) Qualitative circuit proposed by Lorente de Nó (1949), based on partially impregnated axons using the Golgi method. (**b**) Qualitative circuit proposed by Gilbert and Wiesel (1983) based on completely labeled axons using HRP. (**c**) Quantitative circuit proposed by Binzegger et al. (2004) based on digitized 3-D reconstructions of completely HRP labelled axons. Anatomical weights are indicated by *grayscale* and *line thickness* (*grey*: low weight, *thin black*: intermediate weight, *bold black*: large weight). *Grey-filled discs* indicate excitatory neurons, empty discs inhibitory neurons. Number in each disk indicates cortical layer

from earlier physiological studies of cortical receptive fields (Hubel and Wiesel, 1962, 1965).

The main problem with those early approaches of circuit modeling is that a large amount of subjectivity is involved in judging how much overlap is necessary for establishing a connection. In the case of the circuit diagram proposed by Lorente de Nó (1949) (Fig. 7.1a), connections were drawn between neurons for modest overlap, leading to a network with many recurrent connections between cortical layers. In contrast, the pathways in the circuit diagram of Gilbert (1983) (Fig. 7.1b) represent only the most complete overlap between axon and dendrite. Connections arising from an overlap of a given axon with the apical dendrites were also ignored. As a consequence, the diagram is simpler, essentially describing a big loop spanning cortical layers 2–6.

In order to avoid potential ambiguities, quantitative approaches have been used, both in order to have objective criteria when a connection is formed, and to give some measure of the strength of overlap between dendrites and axons. Early attempts to quantify these 'anatomical weights' in an overall circuit diagram had to rely on very crude approximation of neuronal morphology (Braitenberg and Lauria, 1960; Krone et al., 1986; Thomas et al., 1991). Axonal and dendritic trees were modelled as simple geometrical shapes (discs, rectangles, etc.) whose dimensions were estimated from 2-D drawings of Golgi-impregnated neurons. Fully labelled neurons reconstructed in 3-D offer unprecedented detail in the quantitative characterization of axonal trees. What the analysis of these new data shows is that axons have an intricate organization with salient structural features at many levels of detail ranging from the overall gestalt of the tree down to the level of how the branches are locally organized, wriggle through the neuropil, and form boutons in order to make synaptic contacts with targets. Here we review recent results from quantitative studies of axonal morphology. Using a simple connectivity principle based on the overlap rule ('Peters Rule'), we show that axonal complexity produces a circuit structure of exquisite complexity, and we provide a functional interpretation of this circuit.

7.2 Local Circuits

The primary visual cortex of the cat (area 17) has a surface area of about 2 cm² (Anderson et al., 1988) and a depth of about 2 mm. A typical cortical axon is confined to a vertical cylinder from pia mater to white matter whose volume occupies roughly 1% of the total volume of area 17. Within this cylinder the axon forms about 5,000 synapses, and although this seems an impressively large number, a cylinder of this size already contains about 100 times more neurons, each of which might be a potential target of the axon. Thus, we are confronted with the problem of establishing for every axon which targets are selected out of a large population of potential neurons in order to form the cortical circuit. Determining the targets for each single

inferred from a few axonal arbors overlapping with the dendritic trees (Lorente de Nó, 1949; Jones, 1975; Lund and Boothe, 1975; Szentágothai, 1975; Lund et al., 1979). A more confident assessment of overlap was made possible by injecting the label horseradish peroxidase (HRP) directly into the cell body (Gilbert and Wiesel, 1979, 1983; Martin and Whitteridge, 1984). Using this method, the axon could be labelled in glorious completeness, so that what had often appeared as an isolated axonal arbor in Golgi stain developed now into richly branching structures. Because the axons proved to be very layer specific in their arborization pattern, a salient diagram of pathways between cell types emerged from the overlap between axon and dendrites (Gilbert and Wiesel, 1981; Gilbert, 1983). The resulting circuit (Fig. 7.1b) was highly influential, particularly because it was consistent with that conjectured

cortical axon seems an impossible task. However, the regularity of the cortex makes this problem more approachable.

One of the main legacies from the Golgi era is the recognition that the morphologies of neocortical neurons are highly stereotypical. Each cortical layer consists of neurons forming a few anatomical types with distinctly different morphological features (Cajal, 1908; O'Leary, 1941; Lorente de Nó, 1949; Szentágothai, 1973; Szentágothai and Arbib, 1974; Lund et al., 1979). The ability to label axons in full using modern techniques resulted in refinements in the anatomical classification scheme, but in essence classification criteria remained the same (Martin and Whitteridge, 1984). Furthermore, it is generally assumed to be the case that while some cortical afferents may be distributed in a patchy fashion, the somata of a particular anatomical cell type are uniformly distributed within their layer of occurrence. In area 17, the Meynert cells of monkey area 17, which are readily distinguishable in layer 6 with conventional histological methods (Winfield et al., 1981), seem uniformly distributed. In general, however, direct inspection of the distribution or frequency of neurons belonging to the different anatomical cell types are, with a few exceptions, not possible due to the lack of appropriate markers which label exclusively a cell type.

Thus, the regularity in organization of area 17, and in cortical areas in general (Douglas and Martin, 2004), brings a great simplification. For any arbitrary position in a cortical area, the number of neurons and the composition of cell types in a vertical cylinder remains (statistically) the same. Each axon is confronted with the same mix of potential targets and will form synapses with a small subset of them. Thus, instead of being faced with an enormous, irregular wiring diagram between the millions of neurons in the area, the uniformity of the neuropil suggests that connectivity repeats itself statistically along the cortical surface (Szentágothai, 1975; Rockel et al., 1980; Hubel and Wiesel, 1972) and can be studied locally (a 'canonical' circuit). The assumption, of course, is that wiring rules are generic and do not change fundamentally across the cortical sheet.

7.3 Capturing Axon Morphology

Although the characteristic laminar gestalt of neurons observed in Golgi-impregnated slices has inspired many important ideas of how circuits are organized and function (Lorente de Nó, 1949; Jones, 1975; Szentágothai, 1975; Lund and Boothe, 1975; Lund et al., 1979), studies that explore the deeper intricacies of neuron-branching patterns, and in particular that of axonal trees, are still surprisingly rare, given how fundamental this is to neuronal circuits in general. Figure 7.2 shows examples of the most common cell types in cat area 17. The neurons are part of a large database of 39 neurons, each of which has been filled intracellularly with HRP during in vivo experiments. The neurons were digitized in 3-D using a computerized light microscope, that is, the spatial location of the boutons, axonal,
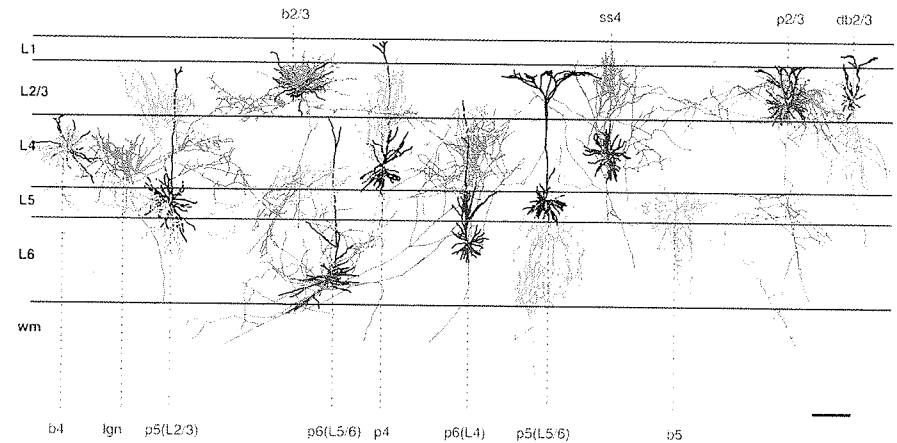
Fig. 7.2 Example neurons of the main cell types in cat area 17. The neurons were injected with horseradish peroxidase during in vivo experiments and subsequently reconstructed in 3-D using a computerized light microscope. *Dark blue* and *red* indicate dendrites, *light blue* and *yellow* indicate axons. Cell types are indicated at the *top* and *bottom*. Abbreviations: 'b2/3,' 'b4,' 'b5' basket cells in layers 2/3, 4, and 5; 'db2/3' double bouquet cell in layer 2/3; 'p2/3,' 'p4,' 'p5,' 'p6' pyramidal cells in layers 2/3, 4, 5, and 6. 'ss4' spiny stellate cells in layer 4. Spiny stellate cells and pyramidal cells were further distinguished by the preferred layer of the axonal innervation ('ss4(L4)' (not shown), 'ss4(L2/3),' 'p5(L2/3),' 'p5(L5/6),' 'p6(L4),' and 'p6(L5/6)'). 'X/Y' thalamic afferents of type X or Y. *Horizontal lines* indicate the approximate cortical layers L1, L2/3 (layer 2 and 3 were merged), L4, L5, and L6. Also indicated is the *white matter* ('wm'). Scale bar 300 μm

and dendritic segments are represented as a list of 3-D coordinates so that further sophisticated analyses were possible. What becomes clear from these examples is that axons and dendrites, but axons in particular, are complicated spatial structures. Branches curl through the neuropil in many different directions, they are topologically arranged in a tree and spatially in characteristic vertical and horizontal patterns that help distinguish and define the cell types. Summing the length of all branches together, the total length of an axon is of the order of 40 mm, for dendrites it is 4 mm. The number of 3-D coordinate points needed to describe the composite pattern formed by the axonal and dendritic trajectories to a reasonable accuracy requires of the order of 10,000 points. Yet, despite this apparent variation and complexity, a systematic analysis of the data shows that global principles do exist to explain spatial and topological aspects of the branching patterns. This raises the attractive possibility that only a minimal set of constructions rules are needed to form the cortical circuit.

The most salient feature of the overall gestalt of the axonal and dendritic trees is the laminar pattern when viewed in coronal view. Studying the dendrites of Golgi-impregnated neurons, Lorente de Nó (1949) marveled at the laminar precision with which dendrites arborized in the cortical layers. A systematic analysis based on the reconstructed neurons shows that each neuron forms most of its dendritic tree
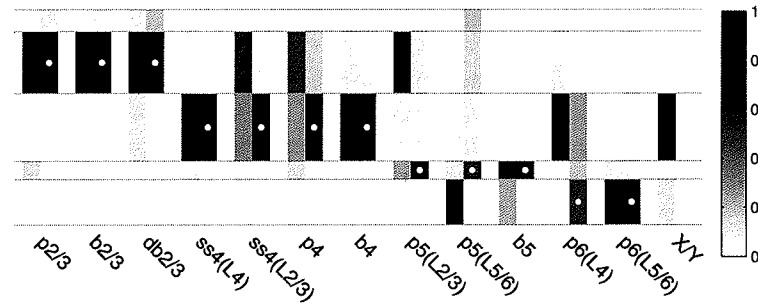
Fig. 7.3 Laminar innervation patterns of cortical cell types. Shown is for each cell type the fraction of synapses on boutons (*left column*) and the fraction of dendrites (*right column*) a typical neuron forms in each layer

(>75% of the total dendritic length) locally in the layer of soma, with some forming an additional richly branching apical tuft in a further layer (Fig. 7.3). HRP-labelled neurons show a similar laminar profile for the axon. Taken across all the main neuronal types, more than 40% of the boutons are formed in one layer, and more than 72% are formed in just two layers (Fig. 7.3).

The consequence of the laminar specificity of axonal and dendritic trees for network organization is that only particular subtypes of neurons have dendrites, which can overlap with an axon, which imposes a non-trivial structure that is far from random or all-to-all connectivity. Even with the least specific of all wiring rules, the diagram of the possible pathways between cell types is already rather intricate (Fig. 7.1c). Additional structure comes from the axonal arborization pattern within a layer. When a local population of neurons in the superficial layer are bulk injected with a label, a dense region of axon is labelled locally around the injection site, and additional labelled axon appears in more distal, isolated patches, giving the whole pattern the appearance of a 'daisy' (Douglas and Martin, 2004) with the distal patches forming the petals.

Although patch formation in the superficial layer of many cortical areas has been recognized as one of the most salient features of cortical organization, quantitative studies that explore and characterize their detailed organization are still rare and have mainly focused on the relationship of patches with the underlying functional maps in the visual cortex (Malach et al., 1993; Kisvárday et al., 1996; Bosking et al., 1997). The main conclusion from these studies is that patches arise from some need to connect neurons of similar receptive field properties, which explains the finding that patch organization reflects the underlying layout of the functional maps. However, the same studies invariably show that this correlation is not precise, and map layout characterizes patch organization only incompletely.

For example, in the visual cortex the local patch freely innervates all neighbouring orientation domains, and a significant proportion of axon in the distal patches is not located in the iso-orientation domains. Whenever patches have been analyzed quantitatively interesting principles of organization have emerged. The typical size

of the patches varies in different cortical areas, as do the basal dendritic field dendritic of superficial layer pyramidal cells, but their corresponding sizes always match (Rockland et al., 1982; Luhmann et al., 1986; Lund et al., 2003). Another scaling relationship holds for the separation distance (center-to-center) between the patches in the different areas, which is always about twice the typical diameter of the patches (Fig. 7.4).

The patchy axonal distribution of superficial layer neurons is most clearly observed for the individual axons of layer 2/3 pyramidal cells (Gilbert and Wiesel, 1983; Martin and Whitteridge, 1984) (Fig. 7.5). When a clustering algorithm is used to identify objectively the bouton patches of cortical axons in cat primary visual cortex (Binzegger et al., 2007), we found that clustered bouton clouds are common to
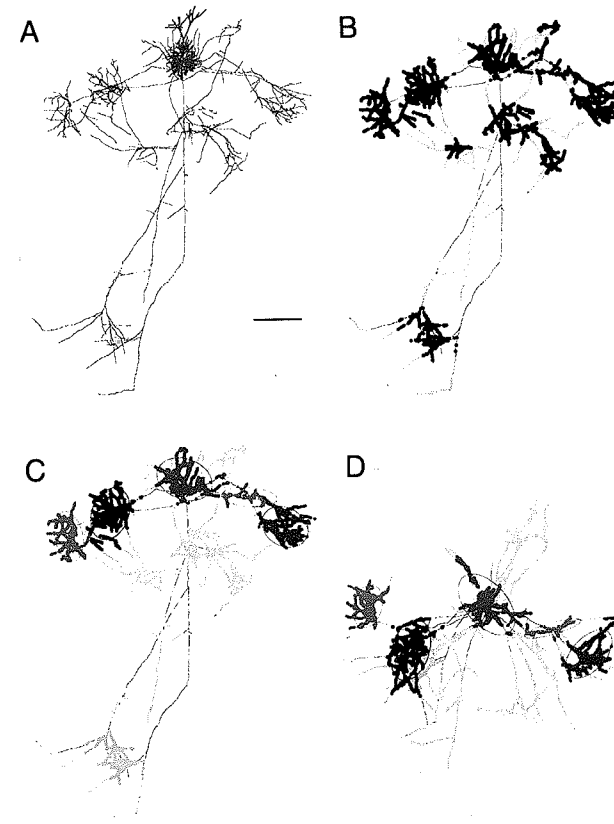

Fig. 7.4 Clustered bouton clouds of a layer 2/3 pyramidal cell. (a) Coronal view of axonal (*black*) and dendritic (*red*) arborization patterns. Cortical layers are indicated by *curved lines*. (b) Bouton cloud showing the linear regions (*gray dots*). These boutons were excluded from cluster analysis. (c) Bouton cloud showing the clusters (color coded) which were identified by the cluster algorithm. (d) *Top view* of bouton cloud with identified clusters. All figures are drawn to the same scale. Scale bar 0.5 mm
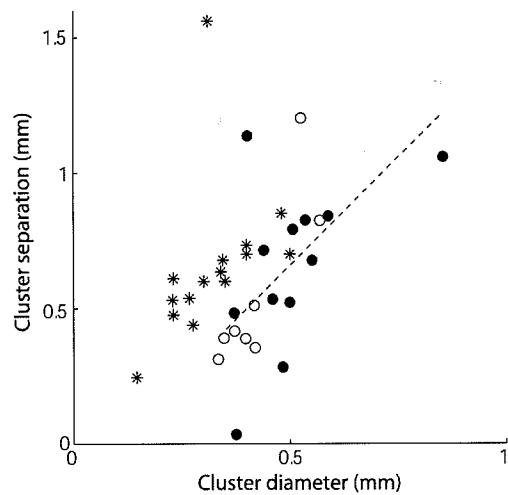
Fig. 7.5 Scaling relationship between cluster size and cluster separation for daisies in different cortical areas and species (*stars*), and for individual inhibitory neurons (*open circles*) and excitatory neurons (*closed circles*) of cat area 17. For the individual neurons, the distance of the proximal cluster to the next cluster was about one and a half diameters of the proximal cluster (*straight line*)

almost all cortical axons. Interestingly, the diameters of the identified clusters range over an order of magnitude, but nevertheless we found that single axons showed a similar scaling relationship between patch size and patch separation as was found at the population level. Thus, cluster formation is a fundamental organization principle which applies to most neurons, cell types, and cortical areas in most mammals. In this universal setting, the most basic structural role of a neuron's patchy axonal distribution is to innervate focally discrete sites of a cortical layer that are separated by a characteristic distance of roughly two patch diameters. In a network where neurons connect indiscriminately (overlap rule), spatial separation of local populations might be important to increase the functional complexity of the network. Cortical layers might play a similar role on a larger scale.

While the need for patch formation might be functionally related, the detailed organization might partly be a consequence of intrinsic growth mechanisms. A generic observation was that the number of clusters formed by an axon (1–7) is closely related to the diameter of the clusters (90–950 μm) and the number of boutons they contain (70–8,300), such that with increasing bouton number the clusters became more equal.

A simple growth model can account for the same relationship (Binzegger et al., 2007). The model works by starting with a fixed reservoir of boutons from which new patches are formed by allocating a constant proportion of boutons (20%) from the reservoir. If only two patches are formed (the remaining boutons in the reservoir and the newly formed patch), the number of boutons in the patches is unequal, and since bouton density per patch was found to be constant, there is also a significant

difference in patch diameter. In contrast, if seven patches are formed, the initial reservoir is depleted and all patches have roughly the same number of boutons and diameter.

Axonal trees have a highly heterogenous spatial distribution of branches, which is not easily cast into a simple mathematical characterization. The cluster analysis we performed is, however, a significant step into this direction and allows to approximate the gross vertical and horizontal distribution of cortical bouton clouds by a mixture of spherical normal distributions $\phi_{\mu,\Sigma}$, where the mean μ of the normal distribution codes for the spatial location of the cluster center and the covariance matrix Σ for the spatial extent of the cluster. While most boutons are involved in forming clusters, most axons form an additional sparse web of long isolated arbors which produce linear strings of boutons. These arbors often connect clusters, but they may also simply radiate outward. This diffuse component typically contains 15% of the boutons in the cloud, and its significance is unclear. If L stands for the distribution of the boutons in the diffuse component, we can represent the bouton cloud by the formula

$$B = \sum_{i=1}^{n} b_i \phi_{\mu_i, \Sigma_i} + L, \tag{1}$$

where b_i is the number of boutons in each cluster i and n is the number of clusters. What is not captured by this model is the heterogeneous distribution of the boutons within each cluster (Fig. 7.5). The axonal branches that form the clusters are only sparsely distributed in the patch volume and the boutons formed along the branches display correlations on a small scale determined by the exact branching geometry.

Detailed quantitative analysis of neuronal branching has focused mostly on the dendritic trees (Uylings and van Pelt, 2002). For the cortical axon, sporadic measurements such as branch number or branch length have been made for fully labelled reconstructions (Kisvárday et al., 1985, 1986). More systematic studies have been made for callosal and thalamic axons and different types of inhibitory cortical neurons in an attempt to quantify type specific differences in axonal branching (Tettoni et al., 1998; Gupta et al., 2000). Such differences can, perhaps not surprisingly, also be detected for the spiny and smooth cell types in the cat cortex (Binzegger et al., 2005). Branch number varied between 50 and 1,500, where smooth neurons generally form shorter branches than spiny neurons, but roughly twice as many branches. The surprising finding is that despite these differences, and the obvious differences in the overall gestalt of the different cell types, branch length and the logical or topological arrangement of the branches ('dendrogram') follow simple generic rules which are independent of cell type.

An example dendrogram is shown in Fig. 7.6, representing the logic structure a layer 2/3 pyramidal cell axon (Fig. 7.5). Only the branching structure and the branch length are represented, and spatial information such as the location of each branch, or the direction it takes in the neuropil, is ignored. For each tree it is possible to introduce generations of branches that determine an order when branches
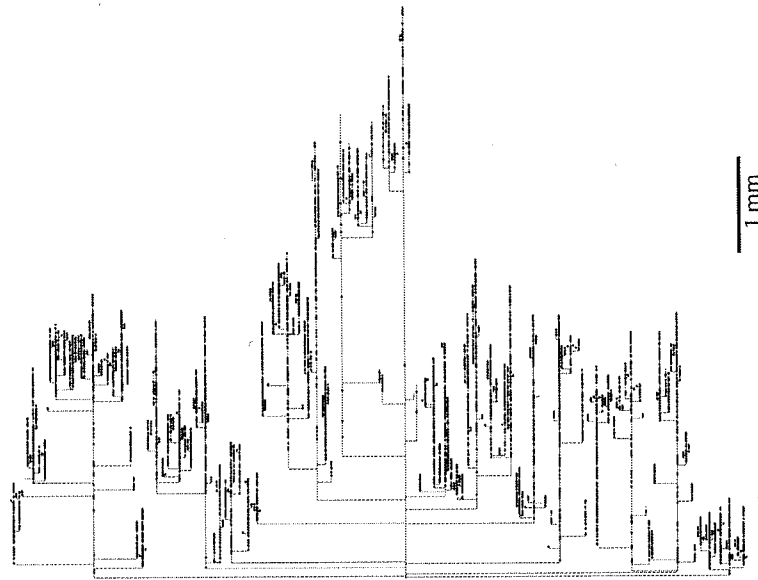
Fig. 7.6 Dendrogram of the pyramidal cell axon shown in Fig. 7.5. Axonal branches are indicated in *gray* and are drawn *vertically*. *Black circles* indicate boutons. Branch points are indicated by *horizontal gray lines*

have appeared during the growth of the tree. Clearly, it is not possible to infer the real growth order from the dendrogram, but even the introduction of hypothetical generations is useful to analyze how branch statistics changes with generation. There are several branch ordering schemes possible, but the one that is particularly attractive because of its natural appeal is to start with the full tree and deduct branch order be moving backward in 'time.' Thus, the terminal branches in the dendrogram are assigned order 1 and after removing these branches, the new terminal branches are of order 2, and so on, until the root of the tree is reached. Astonishingly, for every cortical axon analyzed, the number of branches tripled when moving distally from one branch generation to the other, indicating topological self-similarity. A similar scaling law was found for the mean branch length per generation, but only for the lower generations, that is, the branches, that presumably form the axonal patches. Moving distally from the third to the second, and from the second to the first generation, the average branch length shortened by 70% from one generation to the other.

We found that a simple three-parameter tree growth model (Galton–Watson branching process) can produce the same scaling relationship for branch number and branch length (Binzegger et al., 2005). This suggests that all cortical axons might be constrained by similar growth rules, and that they configure themselves in the 3-D space to satisfy further constraints imposed by connectivity or functional requirements.

7.4 The Problem of Choice

Simply from inspection of the vertical and horizontal gestalt of the axonal and dendritic morphology, it is evident that selectivity must exist in the choice of the postsynaptic cell type and in the horizontal position of the neurons of these cell types. That such specificity exists is therefore not challenged. The point of debate is if, and to what extent, an axon preferentially targets particular neurons or neuronal types beyond those implied by the gross vertical and horizontal morphology. The volume of an axonal patch (about 300 μm in diameter) contains potential target cell bodies and dendritic branches (or fragments thereof) originating from neurons of many different cell types, and the exact composition changes with vertical position of the patch (Binzegger et al., 2004). A rule needs therefore to be in place that assigns synapses formed by the axon with the dendritic segments or cell bodies in the patch volume. But what is the exact composition in the first place?

While it is possible to determine the total number of neurons for each cortical layer (Beaulieu and Colonnier, 1983), the fraction that are excitatory (80–85% in each layer) or inhibitory (15–20%) (Gabbott and Somogyi, 1986), a detailed breakdown of the neuropil (cell number, axon, and dendrite) according to cell type is not possible by direct experimental observation. It is possible, however, to derive estimates based on published cell number counts and by multiplying this number with the laminar distribution of the dendrites and axons presented in Fig. 7.3. What such a quantitative estimate shows is that each layer consists of dendrites and axons originating from a unique mixture of cell types and intensity profiles (Fig. 7.7).

The contribution of inhibitory cell types to each layer can be estimated from quantitative labeling studies. Inhibitory neurons are immunoreactive for parvalbumin (basket cells and chandelier cells) or calbindin (double bouquet cells, Martinotti cells, and neurogliaform cells). From these estimates it is clear that basket cells dominate in most layers, both in terms of the number of cell bodies and total length of dendrites.

For the excitatory cell types no such markers exist, and estimates must be made by other means. In layer 6, for example, two types of pyramidal cells are encountered (Fig. 7.2). The subclass p6(L5/6) are characterized by an ascending axon which innervates almost exclusively the upper layers (mostly layer 4, p6(L4)), while the subclass p6(L5/6) has an axon which is contained to the deep layers 5 and 6. The subclass p6(L5/5) forms an efferent to the claustrum and can therefore be labeled exclusively by injecting a retrograde label into the claustrum. Using this method, Katz (1987) estimated that the subclass p6(L5/6) forms 25% of the total population of pyramidal cells in layer 6, and the remaining 75% is formed by the subclass p6(L4) (Fig. 7.7b). But because individual pyramidal cells p6(L5/6) tend to form most of their dendrites in the deeper layers, they contribute almost half of the dendrites in layer 6 (Fig. 7.7b). The subclass p6(L4) spreads the dendrites over several layer, contributing considerably to layers 4 and 5.

A similar breakdown can be made for the boutons (or synapses) formed by the different cell types (Fig. 7.7c). The important point that follows from this analysis is that the neuropil supports an architecture where signals from many different sources
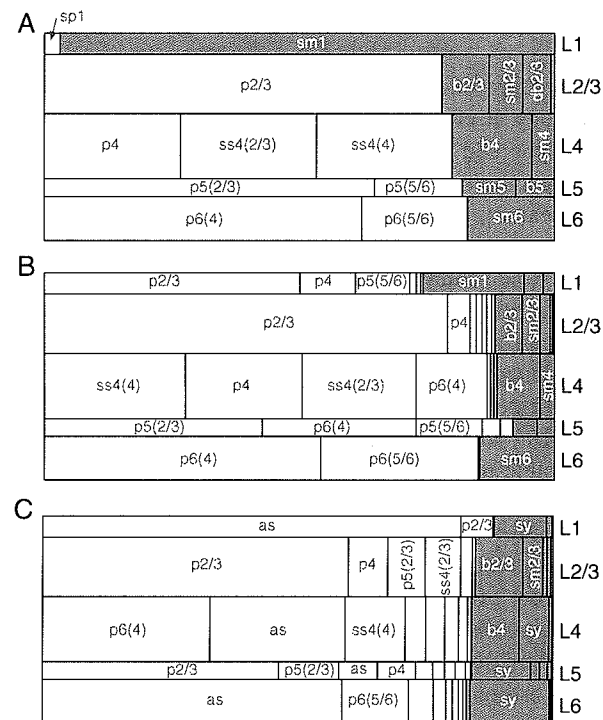
Fig. 7.7 Breakdown of the neuropil by layer and cell type. **a** Fraction of neurons of a given cell type. *Gray-shaded areas* indicate inhibitory cell types. **b** Fraction of dendrite formed by a given cell type. (Fraction of synapses on boutons formed by a given cell type. Included in the estimates are the proportion of synapses from sources outside the area ('sy' symmetric synapses, 'as' asymmetric synapses)

can be mixed, even on a local level. An axonal patch located anywhere in area 17 has the possibility to simultaneously influence different cell types each of which has different physiological properties (Gupta et al., 2000) and communicates with different extrastriate areas and subcortical regions (Gilbert and Kelly, 1975). Similarly, a dendritic tree, whose branches typically span a similar volume as the axonal patch, can receive synapses from many of those cell types.

The potential for multiple interactions is not restricted to cell types, but is also found for individual neurons, such that within a local population every neuron can form a synapse with every other neuron in the population. Labeling nearby layer 5 pyramidal cells in the rat slice revealed that the 3-D reconstructed axonal and dendritic trees always had close appositions between axons and dendrites (Kalisman et al., 2005). This local 'all-to-all' layout matches, of course, the qualitative observations of early investigators who likened the processes of Golgi-stained cortical neurons to tangled thickets like Ramon y Cajal (1989) where no structure could be

observed. This is the source for the notion that cortical networks are random or diffuse (Sholl, 1959; Braitenberg and Schüz, 1998). However, an all-to-all network of synaptic connections is not realized, because the fraction of pairs of nearby layer 5 pyramidal cells that actually form synaptic connections are only 15% (Kalisman et al., 2005). More generally, experimental evidence indicates that less than 50% of axo-dendritic appositions form synapses, even if there is virtually no separation between the axonal and dendritic branches (Tamás et al., 1997).

Even on the smallest scale choice exists. The density and axonal spread of thalamic afferents are such that any point in layer 4 overlaps with at least 400–800 X-axons and five times more Y-axons (Freund et al., 1985; Friedlander and Martin, 1989), and a theoretical argument shows that every point along an axon is in close apposition to more than one dendritic branch (Stepanyants et al., 2002).

7.5 Wiring Neurons

The gross morphological features of the neuron morphology defined by the vertical and horizontal patchy distribution of the axon determine the main focal innervation sites. How an axonal patch connects to the various targets at those sites is regulated by the cortical connectivity rule. The rule investigated here is that the axon connects indiscriminately to the various targets. This is the quintessence of the overlap rule that has been traditonally applied to derive circuit diagrams, that is, whenever axon and dendrite overlap a connection is formed. The quantitative version of this rule adopts different forms, depending on the level of detail.

The version that has been studied in most detail is termed Peters' Rule (Braitenberg and Schüz, 1998) and has its roots in experimental observations of how the thalamic afferents connect to the spiny and smooth neurons in layer 4 of the rat cortex. Studying the postsynaptic targets of the asymmetric synapses formed by thalamic boutons, Peters and Feldman (1976) found that about 85% of the synapses were on spines (presumably from excitatory neurons) and 15% on dendritic shafts (presumably from inhibitory neurons). This proportion is similar to the spines and shafts in layer 4 which are able to receive asymmetric synapses, as can be inferred from inspecting the targets of an arbitrary selection of boutons forming asymmetric synapses in layer 4 (Peters and Feldman, 1976). The hypothesis put forward which might explain this correspondence is that '... their [the boutons of thalamic afferents] distribution with respect to postsynaptic targets may be essentially random, in the sense that no specific types of neurons receive the afferents' (Peters and Feldman, 1976). Indeed, if the thalamic synapses are distributed randomly (i.e., indiscriminately) over the pool of possible postsynaptic targets, the thalamic afferents connect in direct proportion to the occurrence of the type-specific synaptic targets in the neuropil. It is important to note that Peters' Rule characterizes the overall connectivity between population of neurons. The pooled synapses of all afferents innervating layer 4 (or all afferents innervating a more localized volume) distribute randomly over the dendrites of all spiny or smooth neurons in the same volume.

No further assumption is made about how the individual afferents distribute their synapses over the target neurons.

Peters' Rule is easily extended to cortical axons and is shown to predict the correct proportions of spines and shafts contacted by the axons of spiny and smooth neurons in the mouse cortex (Braitenberg and Schüz, 1998). We extended it further to all cortical axons and derived predictions about the number of synapses ('anatomical weight') the axons of a particular cell type form with the dendrites of any other cortical cell type (Binzegger et al., 2004). The anatomical weights were estimated from the breakdown of the neuropil (Fig. 7.7). In essence, if a layer contains a total length of D_i dendrites of cell type i, the fraction of dendrites this cell type forms in the layer are

$$q = \frac{D_i}{\sum_k D_k},$$
(2)

where the sum is over all cortical cell types and is the total length of dendrite contained in the layer. If the axonal patch forms s synapses, Peters' Rule dictates that the dendrites of type i in the volume receive sq of those synapses. In order to obtain all synapses the axon forms with the dendrites of type i, one has to sum over all layers where the axon forms synapses. A diagram summarizing the resulting circuit of pathways is shown in Fig. 7.1c.

Peters' Rule is feasible because the cloud of synapses formed by a population of axons is to a good approximation 'thoroughly mixed' (Braitenberg and Schüz, 1998) with the dendrites of the target population, such that a random distribution of synapses over the dendrites is conceivable. For individual axons this is obviously not true. The branches of an axonal patch are organized in tree-like structures, and the boutons formed by these branches do not form a homogenous cloud. So what does it mean to connect indiscriminately between individual neurons in a local population? Synapse formation between neurons is constrained to the axo-dendritic appositions between neurons, which suggests the rule to distribute randomly the pool of synapses formed by an individual axon onto the various apposition it forms with the neurons in the local population. Network connectivity is then largely determined by the cloud of axo-dendritic apposition whose organization has been extensively studied (Uttley, 1954; Liley and Wright, 1994; Stepanyants et al., 2002; Kalisman et al., 2003; Stepanyants et al., 2007).

A difficulty with this approach is the need to introduce a critical distance between axonal and dendritic branches such that synapse formation is possible for branch separation smaller than the critical distance and that no synapse can be formed for a larger separation. Electron microscopy shows that the pre- and postsynaptic parts of a synapse are separated by only several nanometers (Palay, 1956), but the formation of spine necks and bouton terminaux of various lengths can significantly increase the critical distance for synapse formation. In practice, the critical distance is set globally, i.e., 2 μm for appositions between spiny neurons (Stepanyants et al., 2007), which leads to a linear dependence of the number of appositions with critical

distance (Stepanyants et al., 2004; Kalisman et al., 2003). Despite these inherent ambiguities, this approach is useful because conceptually it separates the necessary aspect of synapse formation (appositions) from the actual formation of a synapse.

The mapping of synapses onto the appositions has not been investigated in detail. However, because boutons appear at the synapse forming appositions of an axon, inspection of the bouton arrangement along axonal branches can indicate conspicuous clustering which would not be expected under the random setting. A systematic study of reconstructed cortical axons shows that the linear bouton arrangement along a strand of axon is not clustered, but is essentially random (homogenous Poisson process) with spiny neurons forming a bouton every 8 μm and smooth neurons every 5 μm (Anderson et al., 2002). Deviations from randomness occurred only at two places. First, there was a lack of very short interbouton distances, which can be trivially explained by the physical size of a bouton, which requires that there be a minimum center-to-center distance between neighbouring boutons formed along the same strand of axon. Second, axonal arbors involved in vertical projections or horizontal projections connecting two patches were often sparsely populated with boutons (Figs. 7.5 and 7.6). However, for the more distal branches which form the axonal patches, bouton density was constant.

7.6 Improving Peters' Rule

The concept of unspecific wiring is attractive, not least because it implies a simplicity in the rules of how to connect neurons. This simplicity contrasts strongly with the assumption that there are detailed connectivity rules. The resulting circuits are interesting because they represent the least specific connectivity structures consistent with the known quantitative neuroanatomy. But how realistic is the circuit diagram predicted by unspecific wiring?

The existence of pathways between anatomical cell types can be directly tested by recording pairs of neurons that are subsequently labelled and identified anatomically. With this method, the majority of the pathways predicted by Peters' Rule do exist (e.g., Stratford et al., 1996; Thomson and Bannister, 2003). There are a few exceptions, however. For example, no functional connection could be demonstrated from layer 3 pyramidal neurons to the upper layer 5 pyramidal cells (p5(L2/3)) and layer 4 pyramidal cells (Thomson and Bannister, 2003). While these connections may well be demonstrated in future studies (it is much harder to show the non-existence of a pathway), the clearest exception comes from anatomical studies which show that the chandelier cells form symmetric synapses exclusively with the axon initial segment of pyramidal cells (Somogyi et al., 1982). This example demonstrates two kinds of specificities that violate the assumption of indiscriminant wiring. First, chandelier cells should form synapses with smooth neurons as well, but typically no such connections are formed. Second, synapses should be distributed randomly along the dendritic branches (or soma), but the axons of chandelier cells target a specific substructure (the initial axonal segment). Similar

substructure specificity is found for other axons of smooth neurons. For example, basket cells innervate the proximal regions of an excitatory neuron and inhibitory neurons, and double bouquet cells form synapses more distally along the dendrites of the target neuron (Tamás et al., 1997, 1998). Further substructural specificity may yet emerge from detailed maps of synapses on identified neurons.

Peters' Rule is easily adapted to incorporate this kind of specificity by allowing each cell type to specify 'contactable regions' on their dendrites or axons (Binzegger et al., 2004). For example, the region on pyramidal cells contactable by the chandelier cells is the initial axonal segment, and there is no region on smooth neurons which is contactable by the chandelier cells. Similar, the region on pyramidal cells contactable by the basket cells is the proximal part of the dendrites, and the region contactable by the chandelier cells is the distal part of the dendrites.

Peters' Rule predicts the existence of pathways between cell types, but it also predicts the anatomical weight associated with each pathway. For the spiny stellate cells and basket cells in layer 4 of cat area 17 the anatomical weights of their presynaptic cell types have been estimated based on experimental observations and, importantly, without the assumption that synapses distribute randomly over the contactable targets (Ahmed et al., 1994, 1997). A comparison with the weights predicted by Peters' Rule showed good agreement (Fig. 7.8), in particular in the case of the spiny stellate cells. This suggests that Peters' Rule, or the modified version thereof, is a very good
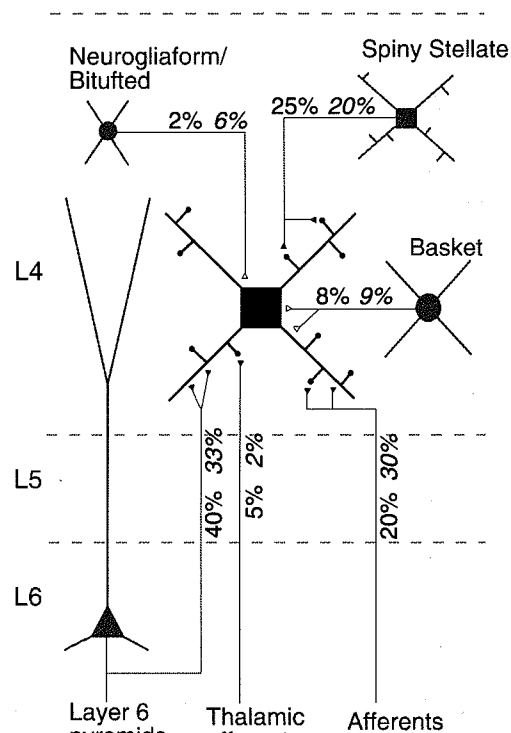

Fig. 7.8 Input map of a spiny stellate cell in layer 4. Shown are the proportions of synapses on the spiny stellate dendrite (*black*) arising from the different cell types (*gray*). Estimates made by Ahmed et al. (1994) are shown in *black*. For comparison, independent estimates based on Peters' Rule are indicated

first approximation to the cortical circuit that is formed by pathways between cell types.

How might deviations from Peters' Rule originate from the local interaction of the axonal and dendritic branches? One possibility is that axonal growth is in itself specific, that is, branches avoid dendritic segments of certain subregions or types of neurons such that particular axo-dendritic combinations simply do not occur in close apposition. At the same time branches might be attracted by other types of segments, with the result that these axo-dendritic appostions occur more frequently. Thus, even if synapses are distributed randomly over the appositions, there will be a bias in the synaptic connections toward certain substructures, neurons, or cell types. For excitatory axons there is no evidence for a biased growth toward or away from dendrites. Nearby pairs of pyramidal cells in layer 5 of the rat cortex had the same number of axo-dendritic appositions, irrespectively of being functionally connected or unconnected (Kalisman et al., 2005). Similarly, in a theoretical study based on pairs of neighbouring 3-D reconstructed superficial layer neurons, the number of formed appositions was determined before and after the axon was 'decorrelated' from the dendrites by shifting it randomly by a small distance (Stepanyants et al., 2004). For axons from excitatory neurons no difference was detected in the number of appositions, suggesting that axons and dendrites were spatially uncorrelated. However, for the axon of inhibitory neurons the number of appositions was significantly larger than expected if the pair was functionally connected, indicating a bias in axonal growth. Inhibitory neurons form smaller axonal branches than excitatory neurons, which might enable them to correlate their trajectories more easily with the dendrites of the selected neuron. Another possible deviation from Peters' Rule might occur if the synapses are formed only at appositions between the axon and selected dendritic segments. This does not have to result in non-random bouton placement along axons as long as the selected targets are homogeneously distributed (Anderson et al., 2002).

In general, a definite validation or rejection of Peters' Rule is difficult because computing the anatomical weights involves an accurate characterization of the composition of the neuropil and the axonal and dendritic morphology. For example, increasingly sophisticated imaging methods allow the determination of spatial input maps to a specific neuron (Dantzker and Callaway, 2000; Kozloski et al., 2001; Yabuta et al., 2001; Schubert et al., 2003; Morishima and Kawaguchi, 2006) revealing connection specificity in the sense that two different cell types within the same region receive differential input from the various sources whose axons innervate this region. These findings may reflect genuine deviations from Peters' Rule which would have to be addressed, but systematic differences in the dendritic morphology of the target types might also be an explanation (Schubert et al., 2003).

7.7 Computation in Daisy Architectures

At the heart of cortical computation is the local cortical circuit. While feedforward input to an area may drive a neuron to fire, and feedback input may modulate this

connections arising from within an area. The quantitative analysis of the number of synapses in area 17 suggests that no more than 30% of the asymmetric synapses on spiny dendrites are from these afferents, and that the vast majority of synapses are used in the local circuits (Binzegger et al., 2004). The local circuit forms the big loop described by Gilbert and Wiesel (1981), but the total number of synapses involved in forming the loop amounts to only 21% of all the asymmetric synapses in the circuit. An even larger number of asymmetric synapses (34%) are involved in forming connections between neurons in the same layer. More generally, the local circuit is dominated by a small number of pathways involving a large proportion of the synapses. In addition there are a large number of pathways which involve only a small number of synapses. The functional significance of such a long tail distribution of anatomical weights is not understood, but it is interesting to note that a similar distribution was also found for the functional synaptic weights between individual neurons (Song et al., 2005).

The superficial layers are singled out by their position in the cortical network. They receive afferent feedback input from other cortical areas and are driven, via layer 4, by the feedforward input from the lateral geniculate nucleus. In addition, the quantitative circuit diagram (Fig. 7.1c) shows that no other layer contains so many synapses arising from the neurons within the layer itself. More than two-thirds of all excitatory synapses formed with superficial layer pyramidal cell dendrites originate from other superficial layer pyramidal cells. This suggests that the superficial layers receive peripheral sensory information as well as processed information from other cortical areas and that the massive network in the layer integrates and processes this information using the prominent system of patchy horizontal connections ('the daisy architecture'). While these properties distinguish layer 2/3 from other layers, a wealth of anatomical studies suggest that these organizational principles are not unique to area 17, but are common to the superficial layer of all higher mammals (Douglas and Martin, 2004).

We have speculated that a basic computational role of the patchy daisy architecture is to enable rich mixing of information between small population of neurons while limiting signal redundancy and spike correlation between the neurons in the network (Binzegger et al., 2007). The intuition is as follows. A population of neurons within a target patch C receives input spike trains from, say, two source populations (A and B) that are well separated spatially, and whose patchy axonal projection 'petals' spatially overlap with the target patch. In this way statistically independent information from A and B can be combined in population C using spike time-dependent synaptic mechanisms. If, however, populations A and B are not well separated, so that the primary bouton arborizations overlap with each other or with the petals, then the interactions between the two populations of neurons will induce correlations between their output spike trains and so reduce the efficacy of the spike time-dependent processing in C (Fig. 7.9). We consider that the conspicuous separation between the proximal patch of superficial layer neurons and the next closest patch might be a mechanism to avoid this scenario, by limiting unwanted spike correlation in the network.
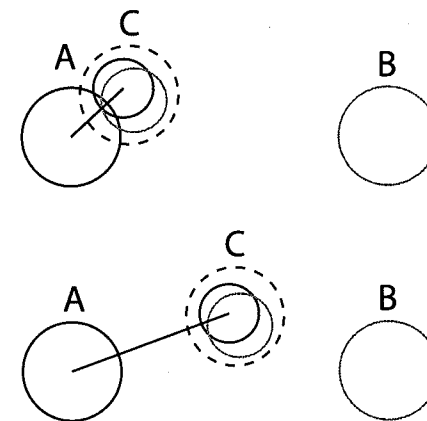
Fig. 7.9 The separation of patches limits unwanted spike correlation in a network of spiking neurons. Depicted is the situation where a population C (*stippled line*) receives projection petals (*small black* and *grey circles*) from two independent source populations A (*large black circle*) and B (*large grey circle*). In the first scenario (*top*), the petal formed by population A is not well separated from A, ultimately leading to an increase in correlated firing between the neurons in A and B. In the second scenario (*bottom*), the petal formed by A is well separated from both A and B, which does not increase correlated firing between the neurons in A and B

How the axonal patches of the individual neurons in the local source populations are mapped onto the petals in the daisy determines the degree of redundancy in the target population. One possibility (large redundancy) is that each neuron in the local population forms as many patches as there are petals and each patch is mapped onto one petal. However, the clustering study of the bouton clouds (Binzegger et al., 2007) suggests a scenario with less redundancy. The number of identified clusters per axon varied considerably in the study, even if the neurons were restricted to a single cell type such as the layer 2/3 pyramidal cells (1–7 patches). What this suggests is that patches are mapped irregularly onto the petals of the daisy, such that the patches of nearby neurons might overlap with entirely different petals. Depending on the active neurons in a local source population, information might therefore be routed to different combinations of target populations, thereby increasing the possibility to mix signals in the network in various combinations.

Thus, the patchy horizontal connections in 2/3 suggest a sophisticated mechanism by which local populations of neurons exchange and mix signals. Each local population processes information from a large variety of independent signals originating from various distal sites within the layer. The local network that processes this information is in character distinctly different from the strongly structured pathways on the larger scale. The rich arborizations of the axons and dendrites of the neurons generate a diffuse architecture where any two neurons have the potential to connect, and many different circuit instantiations are possible.

Both modeling and experimental data suggest that a chief signature of this network is the abundance of recurrent excitatory connections (Douglas et al., 1995;

Holmgren et al., 2003), that is, a neuron has a high probability to receive synaptic connections from its local excitatory targets. The interplay of these recurrent connections with the local inhibitory neurons generates competitive processing such that subgroups of recurrently connected excitatory neurons tend to amplify the initial input they receive, and at the same time each subgroup uses inhibitory neurons to increasingly suppress all other subgroups in the population. Which subpopulation wins the contest for dominance depends on the initial input to each group, and which neurons form a subgroup depends on the detailed wiring and synaptic weight of the local connections (Hahnloser et al., 2000; Xie and Song, 2002). More specifically, the basic function of the local network might be to select competitively the subgroup of neurons whose a priori expectation encoded in their local weight matrix best matches the input (Hahnloser et al., 2000; Douglas and Martin, 2007a) and feed this solution back to the horizontal network until some mutual consent in form of an overall steady state in layer 2/3 is achieved. In this way, the superficial layer might evolve from a variety of potentially conflicting local inputs from a wide range of sources to the most consistent overall response. This response is fed to layer 5, the primary output layer to the subcortical areas involved in motor action.

The functional model presented here is general enough so that its principles might apply universally to all cortical areas. But it is also detailed enough to give justice to the anatomical circuit complexity which exists at every spatial scale. On close inspection of the neuron geometries one finds that many aspects of circuit structure result from generic principles of organization. This suggests that quite simple construction rules might generate cortical circuit structure and the sophisticated function it subserves.

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