# 8

# Neuronal Morphology and Its Significance

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## Abstract

Since the days of Ramón y Cajal and Golgi, reconstruction of neuronal morphology has been a central element of neuroscience research. The cell body (soma) and dendrites receive and integrate synaptic input patterns from diverse neuronal ensembles. The axon, in turn, broadcasts the results of this integration process to a variety of neurons within and across brain regions. Morphological differences in the dendritic and axonal shapes are thus closely linked to a neuron's inputs, outputs, computations, and hence functions. Quantification of somatic, dendritic, and/or axonal properties by morphological reconstructions thus represents one of the major approaches to define brain areas and neuronal cell types therein. This chapter addresses some of the technical challenges involved in reconstructing neuronal morphologies and in linking morphology to other properties of the neurons, such as intrinsic physiology and synaptic connectivity. It discusses conceptual challenges involved in using morphological reconstructions for the definition of neuronal cell types, as well as for the identification of neural circuit structure and function.

## Introduction

The term "neuronal morphology" summarizes several of the structural properties of neurons. At the cellular level, somatic, dendritic, and axonal shapes—and the overlap between these post- and presynaptic neurites—determine which neurons can, in principle, be connected to each other. At the subcellular level, the shapes and density of spines and boutons along the dendrites and axons reflect the number and distributions of these contacts. Reconstruction and quantification of neuronal morphology, therefore, provide initial qualitative and quantitative insights into the structural organization of neuronal networks, and is one of the most widely used approaches in neuroscience research to delineate the borders between brain areas, to define neuronal cell types, and to identify neuronal circuits.

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Reconstructing the complete morphology of individual neurons remains, however, technically challenging due to:

1. the small dimensions of the neurites, which can have diameters as thin as 100 nm;
2. the elaborate and dense projection patterns, which can reach path lengths of several centimeters even locally within a cortical area; and
3. the large volumes that are innervated by a single axon, which can span from a few cubic millimeters in cortex to the entire brain.

The vast majority of what is known about neuronal morphology originates from incomplete, partial reconstructions acquired from acute or histological brain sections. For example, one predominant approach used to reconstruct a neuron's morphology is to label it *in vitro* with biocytin via patch-clamp recording pipettes in acute brain slices of typically 300–500 μm thickness. These neurons are then typically reconstructed at the resolution limit of light microscopy (LM) using either Camera Lucida based manual tracing software, automated reconstruction routines, or combinations of both.

In addition to the issue of varying tracing accuracy across humans or different algorithms, a major caveat when reconstructing *in vitro* labeled morphologies is the truncation of neurites. Because the brain is cut before the neuron is labeled, only neurites that are contained within the brain section and that remain attached to the soma can be reconstructed. Comparison with neuron morphologies that were labeled in the intact brain (*in vivo*) revealed that depending on the slicing angle, slice thickness, and cell type, approximately 30–50% of the dendrites and more than 90% of the axon will be missing in *in vitro* reconstructions. The issue of truncation also applies to reconstructions of sparsely or densely labeled tissue with electron microscopy (EM) approaches, where the sample and imaging dimensions are typically limited to a few hundred micrometers. As a result, the number of complete neuron reconstructions remains limited and originates primarily from sparse labeling methods (e.g., cell-attached recordings *in vivo*, virus injections, genetic targeting), which are either combined with slicing the brain into consecutive histological sections or with optical clearing methods that allow imaging of large brain volumes via light sheet fluorescence microscopy (reviewed in Kleinfeld et al. 2011).

## Variations in Neuronal Morphology Define Brain Areas

At each level, neuronal morphology displays an enormous variability. These variations are often systematic and correlated with each other. For example, more than a century ago, Brodmann described the variance in the shapes and diameters of neuron somata as a function of cortical depth. These differences correlate with systematic changes in neuron densities along the vertical cortex axis (i.e., from the pial surface toward the white matter), which gave rise

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to the concept of cytoarchitectonic layers (Brodmann 1909). The neocortex is typically subdivided into six layers (L1–6). However, the specific laminar organization (e.g., number and/or thickness of layers) differs between cortical areas, thus providing a structural criterion to define and delineate between them (Figure 8.1a).

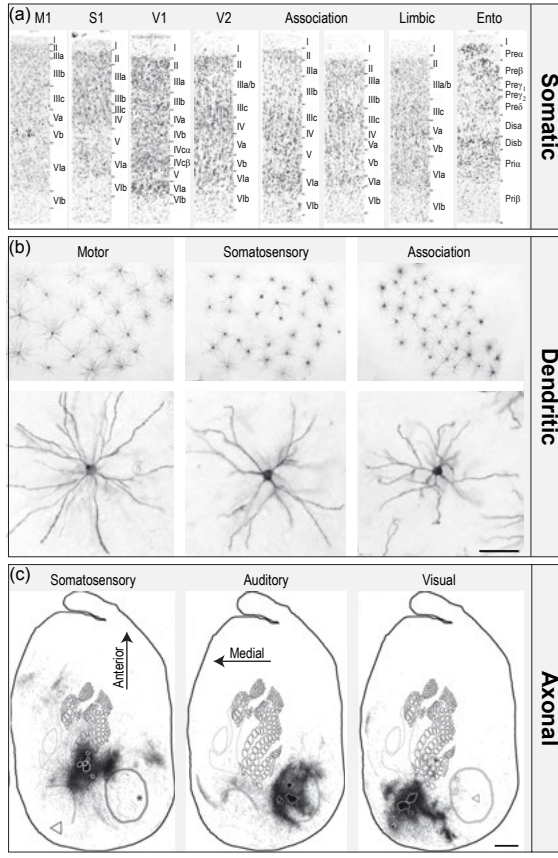


**Figure 8.1** Variations in soma, dendrite, and axon morphology define cortical areas. (a) Nissl-stained coronal sections from human cortex (left to right): primary motor cortex (M1), primary somatosensory cortex (S1), primary visual cortex (V1), secondary visual cortex (V2), association cortex of the inferior frontal gyrus and superior parietal lobule, limbic cortex of the cingulate gyrus, entorhinal cortex. Adapted from Palomero-Gallagher and Zilles (2017). (b) Tangential sections from mouse cortex. Dendritic fields of layer 3 pyramidal neurons (left to right): secondary motor cortex (M2), secondary somatosensory cortex (S2), lateral secondary visual cortex and association temporal cortex (V2L/TeA). Scale bar represents 60 µm. Adapted from Benavides-Piccione et al. (2006). (c) Distributions of intrinsic and extrinsic axons obtained from anterograde tract tracer injections into superficial layers of rat cortex (left to right): vibrissal part of rat primary somatosensory cortex (vS1; i.e., barrel cortex), auditory (A1) and visual (V1) cortex. Scale bar represents 2 mm. Adapted from Stehberg et al. (2014).

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At the somatic level, the laminar differences between cortical areas extend to the level of dendrites. In marmoset monkeys, for example, dendritic fields of L3 neurons are smallest in primary visual cortex (V1), increase progressively across the hierarchy of visual areas (e.g., V2, V4), and are largest in the prefrontal cortex (Elston et al. 1999). Similar area-specific differences in dendritic fields have also been reported in other species (Figure 8.1b), such as mice (Benavides-Piccione et al. 2006). Additional dendritic features, such as spine numbers or peak densities, were also shown to vary as a function of cortical area (Elston et al. 1999). Given that dendritic length and spine density reflect the number and subcellular distributions of synaptic contacts, it is likely that such regional variations in somadendritic morphology represent structural correlates of different functional capacities (reviewed in Elston 2003).

The relationship between neuronal morphology and brain area extends to the level axons, both for intrinsic (i.e., within a brain area) as well as extrinsic (i.e., across brain areas) connections. More specifically, long-range intrinsic axons, which can travel lateral distances of multiple millimeters without entry into the white matter (WM), are thought to interconnect neurons across several of the elementary functional units of cortex (cortical columns) in an area-specific manner (Figure 8.1c). For example, horizontal intrinsic axons in the vibrissal part of rodent primary somatosensory cortex (vS1) interconnect barrel columns that represent neighboring facial whiskers within the same row along the snout (Bernardo et al. 1990). In the motor cortex of the monkey (Huntley and Jones 1991), cat (Keller 1993), and rat (Weiss and Keller 1994), horizontal intrinsic axons link regions that activate related groups of muscles. The target regions of extrinsic axons (i.e., via the WM) also depend on the cortical area in which the neurons reside but vary considerably from cell to cell even within the same cortical area (reviewed in Harris and Shepherd 2015). For example, several recent studies revealed that neurons of the same cell type and cortical area can have different *in vivo* functions, which correlate with the specific target regions of their respective long-range axons (Chen et al. 2013; Lur et al. 2016; Rojas-Piloni et al. 2017).

## Variations in Neuronal Morphology Define Cell Types

In addition to defining and differentiating between brain areas, systematic and correlated variations in soma, dendrite, and/or axon morphology are also commonly used to classify neuronal cell types within (and across) brain areas. One of the first approaches to discriminate between cell types in cortex was by classifying their soma morphology. As introduced above, variations in soma shape and size—resembling pyramids, ovoids, or spheres—correlate with vertical changes in soma densities, and hence with a neuron's layer location. Grouping neurons by layers—a widely accepted approach—provides a first-order criterion to discriminate between neuronal cell types, and countless structural,

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functional, and genetic studies have hence reported their results in a layer-specific manner.

Within each cortical layer, neurons display a variety of dendritic shapes and subcellular dendritic morphologies. Neurons with large, pyramid-shaped somata (pyramidal neurons, PNs) typically represent excitatory cells. In contrast, small, spherical somata typically represent inhibitory cells (INs). PNs are characterized by the presence of an apical dendrite, which projects vertically from the soma across multiple layers toward the pial surface. Both apical and basal dendrites of PNs comprise spines (Figure 8.2a), whose density distributions and shapes can vary between different dendritic compartments and across different types of PNs. Dendrites of INs are more compact and less elaborate than those of PNs; they lack an apical dendrite and have no spines. Instead, INs display bead-like swellings along their dendrites, which often represent postsynaptic structures (Figure 8.2b). However, there are several exceptions to these general rules regarding PN versus IN dendrite morphology. For example, excitatory neurons, referred to as spiny stellates in layer 4, have small spherical somata and lack an apical dendrite. Moreover, INs can have spines along their dendrites.

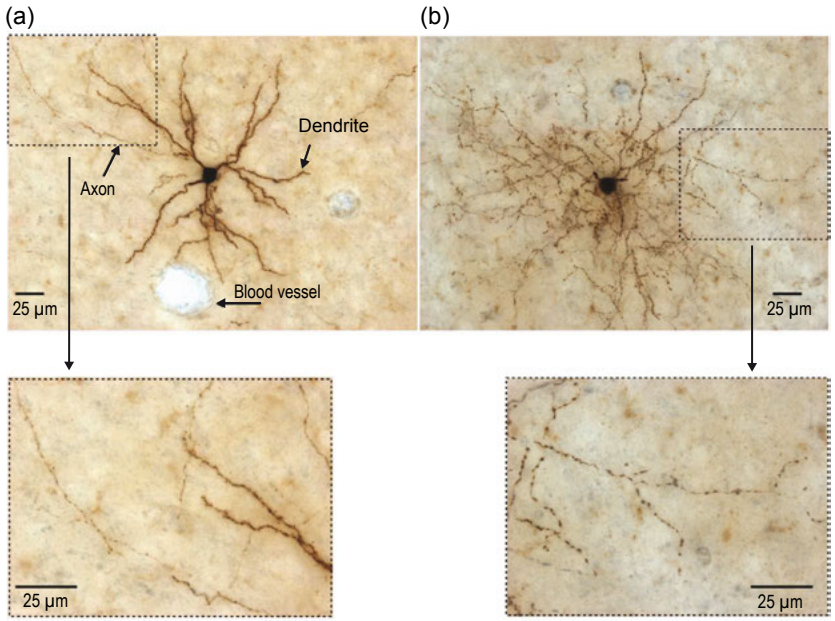


**Figure 8.2** Soma, dendrite, and axon morphology differ between pyramidal neurons (PNs) and inhibitory cells (INs). Brightfield microscope images of histological sections that were cut tangentially through the vibrissal part of rat primary somatosensory cortex (vS1) show one *in vivo* recorded, biocytin-labeled PN (a) and one fast-spiking IN (b). From Narayanan et al. (2014).

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Differences in dendrite morphology within the group of PNs provide several structural criteria to subdivide them into nine major somadendritic types (reviewed in Harris and Shepherd 2015): pyramids in superficial layer 2 (L2py), in layer 3 (L3py) and layer 4 (L4py), star-pyramids in layer 4 (L4sp), thick-tufted (L5tt) and slender-tufted pyramids in layer 5 (L5st), corticothalamic (L6ct), and corticocortical pyramids in layer 6 (L6cc), which include a group of PNs with a variety of rare morphologies, such as those that have an "inverted" apical dendrite that projects toward the white matter (Figure 8.3a). Even though somata of these different somadendritic cell types intermingle within and across layers, the local axon morphologies of PNs display cell type-specific vertical (i.e., across layers) and horizontal (i.e., across columns) projection patterns (Narayanan et al. 2015). For example, L5st PNs in rat vS1 have axonal morphologies that remain largely confined to the dimensions of a single-barrel

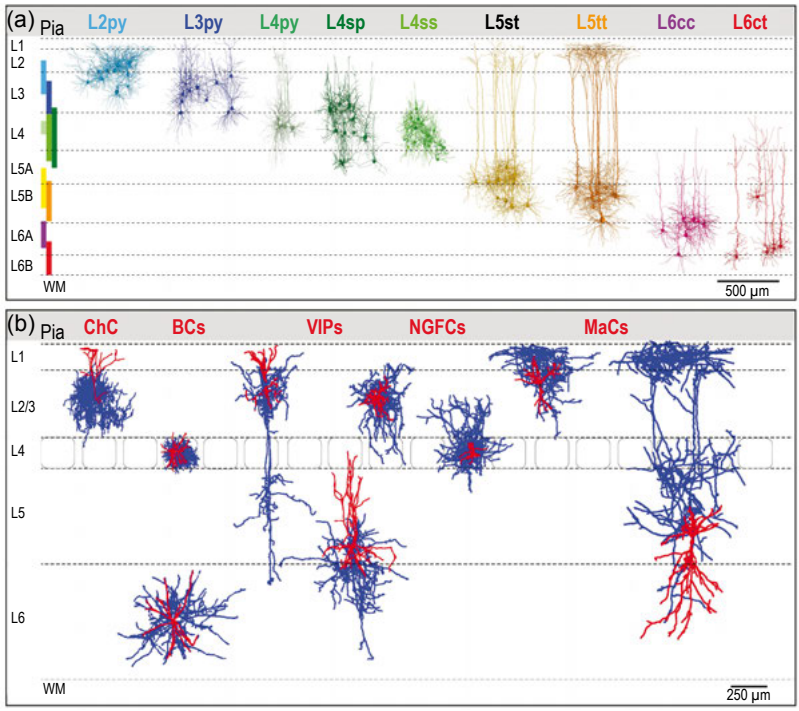


**Figure 8.3** Variations in soma, dendrite, and axon morphology define cell types. (a) Somadendritic morphologies of the major morphological pyramidal cell types in cortex. Colored bars represent the vertical extents of the respective cell type-specific soma depth distributions in the vibrissal part of rodent primary somatosensory cortex (vS1). Adapted from Oberlaender et al. (2012). (b) Dendritic (red) and axonal (blue) reconstructions of the five major morphological inhibitory cell types in cortex. Example reconstructions from different layers of rat vS1 represent: chandelier cells (ChC), basket cells (BCs), vasoactive intestinal polypeptide cells (VIPs), neurogliaform cells (NGFCs), and Martinotti cells (MaCs). Adapted from Feldmeyer et al. (2018).

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column in layer 5, and they project densely to several barrel columns in the superficial layers. In contrast, L5tt PNs have sparse and largely column-restricted axon projections to layers 2/3, but innervate multiple barrel columns in layer 5. The relationship between somadendritic cell type and intrinsic axon projection pattern extends to the long-range axonal targets of PNs (Harris and Shepherd 2015). For example, L5st PNs belong to the class of intratelencephalic neurons, which are defined by long-range extrinsic projections to other cortical (and striatal) areas. In contrast, L5tt PNs represent a class of pyramidal tract neurons defined by projections to subcortical regions.

In contrast to PNs, where soma depth location, dendrite morphology, local axon pattern, and long-range targets are closely related, different morphological types of INs are often exclusively defined by their axon projection patterns and/or specific axonal target structures (reviewed in Feldmeyer et al. 2018) (see Figure 8.3b). For example, chandelier cells (ChCs), typically found within the superficial layers (but also in layer 5), specifically innervate axon initial segments of PNs, which gives rise to their characteristic axon morphologies. In contrast, axons of Martinotti cells, typically found within layer 5, specifically project to layer 1, whereas axons of basket cells innervate somata and proximal dendrites of PNs largely within the vicinity of their own somata. However, because of the much larger variability of IN morphologies compared to those of PNs (even though INs represent less than 20% of all cortical neurons), objective criteria to define IN types and to differentiate between them remain controversial (Petilla Interneuron Nomenclature Group et al. 2008).

## Relating Neuronal Morphology to Function

The difficulty involved in reconstructing complete neurons represents just one of the challenges in trying to assess the significance of neuronal morphology necessary for understanding the basic principles of cortical circuit organization. Several additional properties are involved in determining a neuron's cellular and/or network functions, and need to be measured alongside the reconstruction of its morphology. For simplicity, these properties may be grouped into four categories: intrinsic physiology, *in vivo* activity, synaptic wiring, and genetic profile.

### Morphology versus Intrinsic Physiology

One of the standard approaches to measure the intrinsic physiological properties of individual neurons is to perform somatic, dendritic, and/or axonal whole-cell patch-clamp recordings in acute brain slices *in vitro*. By injecting currents of different shape, amplitude, and/or frequency through the recording pipette, and/or modifying the solution within which the slice is embedded, one can identify which ion channels are expressed in the different morphological

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compartments and in different cell types. Following the recording, the neurons are labeled and reconstructed as introduced above. Accordingly, a rich literature on the intrinsic physiological properties of morphologically identified neurons was generated and has revealed a variety of relationships between the neurons' "electrical" and morphological cell types. For example, as reviewed by Ramaswamy and Markram (2015), L5tt PNs were shown to possess a $Ca^{2+}$ channel dense region around the first bifurcation point of the apical tuft. Current injections into this $Ca^{2+}$ hot spot can trigger dendritic $Ca^{2+}$ spikes, which in turn can trigger bursts of somatic action potentials (APs)—referred to as BAC firing—when coinciding with a backpropagating AP (bAP). In contrast, L5st PNs typically lack the intrinsic (and morphological) properties to support BAC firing. As a result, L5tt and L5st PNs are often referred to as burst (BS) and regular spiking (RS) cells, respectively. However, not every BS cell in layer 5 has a thick-tufted morphology, nor does every thick-tufted PN elicit bursts (Harris and Shepherd 2015). This example thus illustrates one general caveat of *in vitro* recording/labeling: it is difficult to differentiate between biological variability and variability that is caused by the experimental approach itself. More specifically, truncation of the apical dendrites can result in false morphological classification of L5st and L5tt PNs. Truncation of the axon can transform a BS into a RS cell (Kole 2011).

## Morphology versus *In Vivo* Activity

In contrast to *in vitro* studies, which relate a neuron's intrinsic physiological properties to its morphological properties, measurements of *in vivo* activity patterns for morphologically identified neurons and cell types remain scarce. One standard approach to achieve these measurements is to perform whole-cell or cell-attached patch-clamp recordings from single neurons *in vivo* and to label the recorded neurons (e.g., with biocytin) for post hoc reconstruction. Such studies in the V1 of cat (Binzegger et al. 2004) and mouse (Vélez-Fort et al. 2014) have revealed several relationships between a neuron's morphological cell type and specific *in vivo* functions. Moreover, *in vivo* recording/labeling approaches were recently combined with injections of retrograde tracer agents, which provide additional information about the input populations (Vélez-Fort et al. 2014) and/or target structures (Rojas-Piloni et al. 2017) of the recorded and reconstructed neurons. *In vivo* recording/labeling approaches are thus capable of providing information about a neuron's soma location, dendrite morphology, local axon projection pattern, long-range axonal targets, input populations, intrinsic physiology (i.e., current injections during whole-cell *in vivo* recordings), and *in vivo* functions (e.g., during sensory stimulation). However, the number of neurons that can be recorded per animal is limited to just a very few within the same brain area. Hence, alternative approaches aim to link morphological properties to *in vivo* functions by combining population $Ca^{2+}$ imaging with EM reconstructions (Bock et al. 2011). Similar to the

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*in vivo* electrophysiology approaches described above, $Ca^{2+}$ imaging has also recently been combined with retrograde tracer injections (Chen et al. 2013). Thus, in principle, $Ca^{2+}$ imaging, when combined with post hoc EM reconstructions, can yield structure-function measurements similar to those from *in vivo* recording/labeling approaches, but for larger populations and with synaptic resolution.

## Morphology versus Synaptic Wiring

In addition to the dense EM approaches introduced above, several other methods are commonly used to study synaptic wiring between morphologically identified neurons. Most prominently, simultaneous patch-clamp recordings *in vitro* from multiple (up to eight) neurons are combined with post hoc reconstructions and identification of putative synaptic contact sites at the resolution limit of LM. In some cases, the putative contacts are confirmed as synapses by correlating LM and EM reconstructions. However, the impact of truncating dendrites and axons on such connectivity measurements will increase with the number of recorded neurons. Another important aspect for linking connectivity patterns and morphology to a neuron's function is the measurement of spatiotemporal synaptic input patterns during *in vivo* conditions. Recent technical advances that allow imaging of $Ca^{2+}$ hot spots (putative synapses) at several dendritic locations, while simultaneously measuring the somatic response to different sensory stimuli (Jia et al. 2010), have provided remarkable structural and functional data in a variety of sensory systems and species. Here, dendritic events were generally found to be more broadly tuned than the somatic responses, and that inputs with different stimulus preferences intermingle both spatially and temporally along the dendrites. These measurements hence provide the first direct insight into how neuronal function arises from a complex interplay of parameters at subcellular, cellular, and network scales; that is, between intrinsic physiology, dendrite morphology, synaptic wiring, and population activity.

## Morphology versus Genetic Profile

In recent years, the focus of classifying neurons has shifted from their morphological and physiological properties toward their genetic and/or molecular profiles. For example, neurons expressing three markers—the $Ca^{2+}$-binding protein parvalbumin, the neuropeptide somatostatin, and the ionotropic serotonin receptor 5HT3a—were shown to label three disjoint populations of cortical INs (Rudy et al. 2011). This discovery provided access to study and manipulate IN circuit function *in vitro* and *in vivo* via optogenetic approaches. However, several recent studies revealed that an IN's molecular marker correlates only weakly, if at all, with its morphological and electrical properties (see Tremblay et al. 2016). Revealing the significance of a molecular marker

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for an IN's cellular and circuit function thus remains a highly active field of research. For PNs, such a "standard set" of genetic or molecular markers has not been established so far. However, several markers exist that are capable of labeling subsets of neurons that share similar structural and/or functional properties. Moreover, gene sequencing and bioinformatics approaches applicable to morphologically and physiologically characterized neurons have recently become available. Thus far, however, these approaches have failed to reveal sets of genetic markers that, for example, correlate with a PN's long-range axonal target (Sorensen et al. 2015).

## Significance of Neuronal Morphology

To discover the structural and functional organizational principles of the nervous system, it is essential to reconstruct neuronal morphologies for the following reasons. First, a neuron's soma location, dendritic shape, and axonal projection pattern determines the pre- and postsynaptic populations to which a neuron can, in principle, be connected. Second, its morphology combined with its intrinsic properties—as defined by a variety of voltage- and ligand-gated ion channels that are expressed differently in the soma, dendrites, and axon, and which are often restricted to specific dendritic and/or axonal subdomains—determine how a neuron integrates, transforms, and transmits synaptic input patterns. Third, its morphology and intrinsic properties combined with the specific spatiotemporal organization of synaptic input patterns—as defined by the wiring diagram and (stimulus- and state-dependent) population activity—determine how a neuron computes, for example, during sensory stimulation.

Consequently, the significance of neuronal morphology for neuronal and network functions can only be revealed once reconstructions of complete morphologies are complemented with measurements of their genetic, intrinsic, and functional properties as well as with dense reconstructions of their synaptic in- and output patterns. As discussed above, approaches that would allow us to measure all of these properties simultaneously are presently unavailable. Therefore, the major significance of morphological reconstruction for neuroscience research at the moment may be to provide a way to correlate measurements of different cellular and network properties—and at different scales—in a cell type-specific manner. Several collaborative efforts and large-scale initiatives, such as the MindScope Project of the Allen Brain Institute, aim to collect across-scale structural and functional data systematically and consistently for a particular sensory modality, such as the mouse visual system.

Arguably, one of the major challenges for such integrative approaches lies in the classification and identification of neuronal cell types, which ideally represent the canonical elements that are sufficient to describe a circuit and its functions. The large biological variability and differences in fundamental

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neuronal properties between species (Kalmbach et al. 2018), however, renders the definition of "meaningful" structural and functional features that can be used by classification algorithms as challenging. For example, classification of dendritic cell types is often based on a variety of custom-defined morphological (e.g., path length), topological (e.g., branch depth), and/or shape parameters (e.g., bounding box). Such differences in how morphological reconstructions are parameterized, as well as differences between the methods used to cluster the resultant branching statistics, hamper objective definitions and comparisons of morphological cell types across studies. Similarly, a standard set of intrinsic physiological features for the classification of electrical cell types has not been established. To overcome such inconsistencies, and to establish sets of "meaningful" parameters that reliably distinguish between cell types, generative models that produce synthetic morphologies (e.g., that preserve electrotonic properties of the dendrite) are currently being developed (Cuntz et al. 2010).

To reach a consensus for classification, one promising way is to generate publically available databases, such as NeuroMorpho.org which presently comprises thousands of single-neuron morphologies acquired in different species and labs. The International Neuroinformatics Coordinating Facility, Human Brain Project, Allen Institute, and others are also in the process of generating similar "big data" neuroinformatics platforms. At present, however, these large-scale efforts are based primarily on *in vitro* measurements. As discussed above, experiments in acute brain sections are hampered by severe truncation of dendrites and axons, and thus introduce variability to measurements of neuronal morphology, intrinsic properties, and synaptic connectivity which may exceed, or at the very least increase, the true biological variability. Moreover, depending on the dendritic and axonal extents of the investigated cell types, the effects of truncation may vary substantially across experiments in a largely unpredictable manner. It thus remains to be seen whether large-scale databases of *in vitro* acquired data will facilitate or hamper the identification of the elementary building blocks of neuronal circuits.

Even if the variability caused by truncation could be minimized (e.g., by *in vivo* recording/labeling), direct clustering of morphological, intrinsic physiological, and/or connectivity features may still be unsuitable for the definition of cell types. More specifically, some evidence suggests that the various cellular and network properties which can be used to parameterize neurons are related to each other (Marder and Goaillard 2006). For example, homeostatic mechanisms could compensate for morphological differences across neurons by adjusting their intrinsic properties (Figure 8.4a), so that all neurons of a particular cell type show similar functions. A cell type would thus be defined by a set of specific functional behaviors that arise from complex relationships between morphological, intrinsic physiological, and synaptic properties in high-dimensional parameter spaces (Figure 8.4b). Thus, reliable measurements of variability across neurons—and of parameter distributions in general—represent

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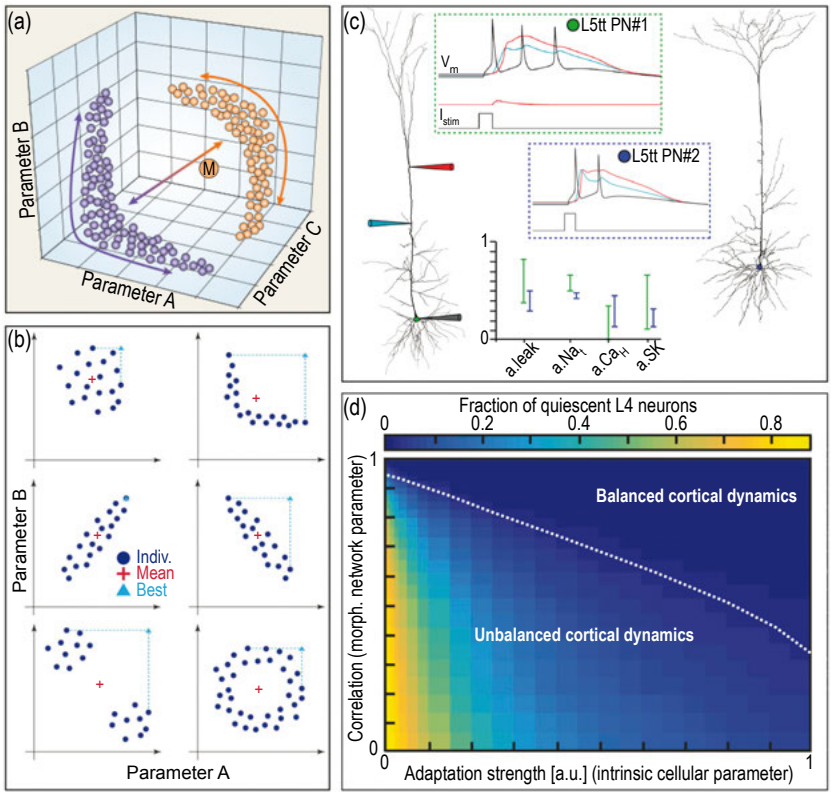


**Figure 8.4** Relationships between morphology, intrinsic physiology, and synaptic connectivity define cell type-specific functional behaviors. (a) Individual neurons that display two different types of functional behaviors are shown in purple and orange, respectively. Both populations comprise neurons with widely different values of three parameters (e.g., conductance values for three different ion channels). Neuromodulators could move neurons from one behavior to another (gradient arrow). Adapted from Marder and Goaillard (2006). (b) Example distributions of parameters for neurons that share a common behavior or set of behaviors. Adapted from Marder and Taylor (2011). (c) Morphologies of two thick-tufted (L5tt) pyramidal neurons (PNs) from the vibrissal part of rodent primary somatosensory cortex (vS1). Both L5tt PNs show qualitatively the same set of functional behaviors, for example BAC firing (dashed boxes). Morphological differences across L5tt PNs result in different active dendritic properties, as illustrated by the respective ranges of four exemplary conductance values (i.e., normalized) along the apical dendrites (a) that represent acceptable models that reproduced BAC firing of neuron #1 (blue) and #2 (green), respectively. Adapted from Hay et al. (2011). (d) Example of how relationships between morphology-related network properties (here: correlations in synaptic connectivity) and intrinsic cellular mechanisms (here: spike-frequency adaptation) can assure a circuit's proper behavior. Breakdown of balance is reflected by unrealistically sparse and temporally regular firing. Adapted from Landau et al. (2016).

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an additional requirement for the definition of cell types. Alternatively, numerical simulations of biophysically detailed multi-compartmental (MC) neuron models, when combined with algorithmic approaches that allow exploration of large multidimensional parameter spaces (Marder and Taylor 2011), may also provide the general relationships between parameter distributions required to assure a specific cellular and/or circuit function.

The need for such multidimensional structure-function approaches for cell type classification can be illustrated by two examples. First, in a study by Hay et al. (2011), L5tt PNs from rat S1 were physiologically characterized in response to a set of somatic and/or dendritic current injections. These neurons were then reconstructed and converted into MC models (Figure 8.4c). The conductance values of the various ion channels along the MC model were then tuned until numerical simulations reproduced both responses to somatic and dendritic current injections. The conductance value distributions that were obtained differed substantially across L5tt PNs. Thus, despite very similar input-output behaviors, the morphological differences between L5tt PNs needed to be compensated by differences in their intrinsic properties. Second, simulations of morphologically simpler models, consisting of networks of integrate-and-fire point neurons, have recently been shown to reveal some of the general relationships between cellular and network properties that are required to assure a circuit's proper dynamics (Landau et al. 2016). Specifically, Landau et al. showed that a specific morphology-related feature, heterogeneity in incoming connectivity, has a significant qualitative impact on cortical dynamics and that the circuits' proper function depends on the interplay between connectivity structure and single-neuron intrinsic properties (Figure 8.4d).

## Conclusion

As efforts are made to elucidate the general significance of neuronal morphology and to understand the basic principles that underlie the structural and functional organization of cortical circuits, we must confront an array of issues:

- Is there a canonical circuit for the networks in different cortical areas and species?
- Is the concept that cortical columns represent elementary functional modules justified?
- Do cortical layers reflect different computational functions?
- Are there overarching principles of how noncortical processors are connected to the cortex?

In this chapter I have presented background information necessary to approach these questions. First, I introduced how systematic and correlated variations in soma, dendrite, and axon morphology allow us to define and delineate between different cortical areas and cell types. Second, I discussed some of the

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present technical limitations for reconstructing individual and complete neuronal morphologies. Finally, I argued that revealing the significance of neuronal morphology requires complementing neuron reconstructions with measurements of intrinsic physiology, *in vivo* activity, and (dense) synaptic wiring.

At present, experimental approaches to measure all of these properties at once are not available. Thus, consideration was given to the challenge of creating integrative approaches capable of combining data from different experimental approaches in a cell type-specific manner. In conclusion, numerical across-scale simulations provide a promising venue to explore how and to what extent the details of neuronal morphology, intrinsic physiology, and synaptic connectivity are related to each other, and how these relationships affect the dynamics and functions of cortical circuits.

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