Chapter 1
Introduction to Dendritic Morphology

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Abstract Dendrites play an important role in neuronal function and connectivity. This chapter introduces the first section of the book focusing on the morphological features of dendritic tree structures and the role of dendritic trees in the circuit. We provide an overview of quantitative procedures for data collection, analysis, and modeling of dendrite shape. Our main focus lies on the description of morphological complexity and how one can use this description to unravel neuronal function in dendritic trees and neural circuits.

1.1 Introduction

Probably the most striking feature of a neuron is its characteristic morphology: dendritic and axonal processes sprout as intricate tree structures to enable connections with other neurons. Through their dendrites, neurons receive signals from

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other neurons, and via their axons they transmit signals to other neurons. Historically, research on neuronal morphologies has focused more strongly on dendrites because the larger diameters of their branches make them more amenable experimentally and dendrites cover a more restricted space compared to axons. Only recently, full reconstructions of long-ranging axons have become available (Oberlaender et al. 2011; Ropireddy et al. 2011). The increase in the quantity and quality of neuronal staining and microscopy methods sparked a revived interest in morphological analysis and anatomical circuits such as in the projects of the Blue Brain Project (Markram 2006), the cortical column in silico project by Bert Sakmann (Oberlaender et al. 2012), and the connectomics approach (Helmstaedter et al. 2011). In this chapter we summarize the methods of morphological analysis of dendritic tree structures and argue that knowledge obtained through these methods will be invaluable for resolving the circuitry and function of the nervous system.

Dendritic trees come in all shapes and sizes (Fig. 1.1). They range from a total length of a few tens of micrometers to a few millimeters. Some neurons have only one main dendritic branch, while others possess up to 15–20. Some branches meander strongly, while others are approximately straight. Dendritic morphologies vary significantly even within one neuronal class (Ramaswamy et al. 2012; Soltesz 2005). In addition to this morphological diversity, the molecular composition of ion channels in the membrane strongly differs along the stretch of one dendrite (Migliore and Shepherd 2002), and more pronounced differences even exist between neurons of different types. Why such a diversity?

To answer this question it is necessary to consider the functions pertaining to the dendritic tree. Dendrites clearly serve two pivotal roles in the process of signal integration. First, neuronal morphology defines and is defined by the circuitry. The major element of neuronal connectivity is the synaptic contact between the output axon of one neuron and the input dendrite of another. As such, a precise morphology is crucial to establish the connectivity required for the nervous system to operate normally. Secondly, the precise morphology of a dendrite and its membrane's ion channel composition set the computation that a neuron performs on its inputs, i.e., the propagation and integration of synaptic input signals along the dendritic membrane up to the axon initial segment, the location where the neuronal output is typically generated (Van Elburg and Van Ooyen 2010; Mainen and Sejnowski 1996; Silver 2010; Torben-Nielsen and Stiefel 2010).

Studying dendritic trees thus reveals mechanisms of function in a neuron in terms of its connectivity and computation. Neurons of different types serving different functions should therefore noticeably differ in the morphology and/or physiology of their dendrites. Indeed, as Ramón y Cajal already illustrated more than 100 years ago, dendritic morphology is a defining feature of neuronal classes upon which neurons can be categorized. Up to this day, dendrite morphology represents one of the main criteria for classification of neurons into individual types (Cannon et al. 1999; Migliore and Shepherd 2005). At the same time, due to its wide implication in neuronal functioning, dendritic morphology plays a role in many pathological cases. Neurodegenerative diseases, autism, epilepsy, Parkinson, Alzheimer, and many others have been linked to changes in dendritic and axonal morphology

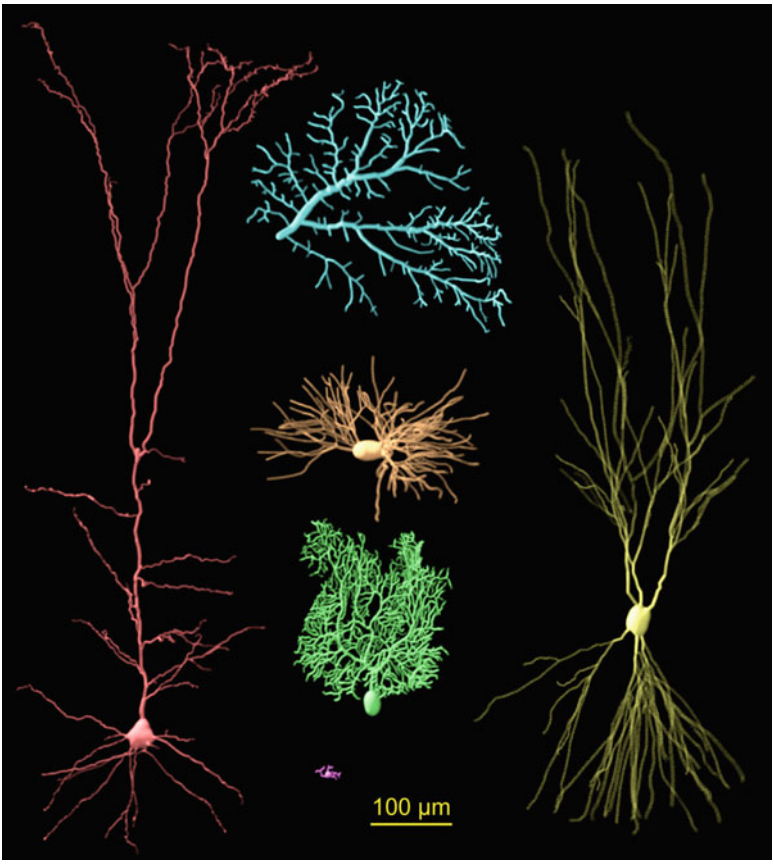

Fig. 1.1 Diversity of dendrite morphology. Different dendritic morphologies illustrating their wide diversity in neural systems. Dendrites are laid out on the same scale: (*red*) rat cortical pyramidal cell (Wang et al. 2002); (*cyan*) fly lobula plate HSN cell (Cuntz et al., 2008); (*orange*) rat thalamic relay neuron (Destexhe et al. 1998); (*yellow*) rat hippocampal pyramidal cell (Ishizuka et al. 1995); (*green*) rat cerebellar Purkinje cell (Vetter et al. 2001); (*pink*) rat neocortical neurogliaform cell (Furtak et al. 2007). Note the differences in size, overall shape, and diameters. Data downloaded from Neuromorpho.org (Ascoli et al. 2007) with reference to the works in which they originally appeared

(Kaufmann and Moser 2000; Moolman et al. 2004; Srivastava et al. 2012). Also, many genes and proteins involved in dendrite formation have recently been identified enabling the study of dendritic dysfunction in a more systematic manner (Jan and Jan 2010; Nagel et al. 2012). Different facets of neural function can therefore be studied directly taking advantage of knowledge of dendrite morphology: the role of different cell types, malfunctions in nervous tissue, development of neural function, and emergence of function in the single cell and in the circuitry. For all these reasons, neuronal morphology lies at the core of many studies in neuroscience. But are there really objective measures to quantify neuronal morphology per se?

1.2 Dendrite Reconstruction, the Data Collection Process

Ultimately, all quantitative measures of neurite morphology are extracted from microscopy data. After an initial stage in which neuronal tissue is prepared and neurons are stained or labeled, a neuron's most prominent features are accessible by visually inspecting it under the microscope. Some general features such as overall size, spatial embedding, and branching complexity can already be resolved at this stage.

However, for a thorough quantification of the dendrite structure, a reconstruction, i.e., a digital representation, of the morphology is required. Reconstructions can then be used in detailed multi-compartmental simulations to calculate the current flow within the tree structure (see chapter "Dendritic Computation") or, as discussed in this chapter, be used for detailed morphological analysis. Because the choice of method used for digitizing a neuronal morphology has consequences for the further analysis, we briefly describe the most common procedures. The very first digital reconstructions were obtained by controlling the microscope's focus with the computer using an electrical stepper (Capowski 1989; Glaser and Glaser 1990). Nowadays, three-dimensional image stacks obtained from confocal and multiphoton microscopes are standard to resolve the z-dimension in the tissue. Advances in staining methods, in particular using genetic tools, allow for staining distinct neurons or neural populations in different fluorescent colors (Lee and Luo 1999; Livet et al. 2007). In addition, novel algorithms and software packages have recently been developed to facilitate the reconstruction process of morphologies. These include the most popular commercial one called Neurolucida (Microbrightfield) and many freely available tools such as VAA3D (Peng et al. 2010), the Trees Toolbox (Cuntz et al. 2010), Neuromantic (Myatt et al. 2012), and the FIJI neurite tracer (Longair et al. 2011) amongst others. In principle, automatic reconstructions of morphologies from neural tissue preparations could provide objective criteria and relieve the human labor associated with manual reconstruction. However, none of the software packages available at present provide tools to flawlessly reconstruct the entire cell, and manual intervention is still required in most cases.

A recent technical development has led the connectome (i.e., the complete reconstruction of all neurons and their connections within a small chunk of neural tissue) to become experimentally accessible at histological scales. This is being made possible for example by combining the resolution of electron microscopy with ion beam or microtome sectioning (Denk and Horstmann 2004; Knott et al. 2008). It is important to note the different resolution of the current reconstruction techniques: while confocal and light microscopes achieve spatial resolutions of a fraction of a micrometer, electron microscopes reach a level of detail in the nanometer range. Dendritic spines or synaptic puncta can therefore hardly be resolved with a light microscope. Electron microscopes have a much higher spatial resolution, but the resulting amounts of data are huge. Obviously, the more detailed the analysis, the finer grained the reconstructions need to be.

1.3 Digital Storage of Neuronal Morphologies

The de facto standard to describe neuronal morphologies is the SWC format (Cannon et al. 1998), where a neuronal morphology (be it dendrite or axon) is a set of connected nodes directed away from a root node. Since each node is attributed one diameter value, the segments in the graph each describes a frustum, i.e., a truncated cone, where the starting diameter of one frustum is the ending diameter of the parent frustum. The morphologies are encoded as plain ASCII text files that contain seven values to describe each node: (1) the node index starting at the value "1"; (2) a region code (or "type") describing whether a node belongs to the soma, the dendrite, or any other region of the neuron; (3–5) *x*-, *y*-, and *z*-coordinates; (6) the diameter at the node location; and (7) the index of the parent node where the root parent index is "−1." In principle, most neuronal structures (dendrites and axons) can be represented in sufficient detail although an accurate description of the soma and spines is hard to represent by connected frusta. Apart from the SWC format, digital reconstructions obtained by (recent) commercial software programs such as NeuroLucida (Microbrightfield) are provided in the software's internal proprietary file types, and they contain additional options to describe a morphology including metadata. For instance, the network context, e.g., laminar structures and tissue boundaries, can be annotated separately.

An entirely different way to represent neurons is to describe their shape as a mesh. A mesh is a detailed description of the surface of a body by means of a list of vertices that are connected to polygons (usually triangles). The level of detail can be adjusted by the number of vertices used to cover the surface and is generally much higher compared to the SWC description mentioned above. Consequentially, mesh representations of neurites are often used in simulations that require high spatial accuracy such as reaction–diffusion of molecules along and across membranes (Hepburn et al. 2012; Kerr et al. 2008).

In an effort to standardize neuroscientific models that span single neurons to entire networks the NeuroML initiative in the field of neuroinformatics has introduced its own formalism describing neuronal morphology, MorphML (Gleeson et al. 2010). The latest version, NeuroML 2.0, includes the possibility to describe functional characteristics of a model (e.g., the Hodgkin–Huxley equation), thereby making it possible to link morphological attributes with ion channel features and dynamics in one unified format.

Another development in the field of neuroinformatics is the advent of databases containing neuronal data and models that are open to the public. Thanks to this trend, reconstructed morphologies from different labs are widely shared in the scientific community. Several labs host their own databases that can be accessed through the Internet. The most complete database, NeuroMorpho.org (Ascoli et al. 2007), shares morphology files from a large number of different labs, standardizes them, and makes them available freely in the public domain. At the time of writing, the database contains almost 9,000 reconstructed morphologies in a standardized

SWC format. Among the available databases some also combine morphologies of single neurons with contextual circuit information, e.g., the standard brain databases for a large variety of insects (http://www.neurobiologie.fu-berlin.de/beebrain/Links.html). Some morphological reconstructions are also made available in combination with their electrical models, e.g., ModelDB (Migliore et al. 2003), allowing the morphology/function relations to be studied in detail.

1.4 Single-Neuron Morphometry and Quantification

Once digital reconstructions are obtained and stored, they can be used for further analysis and quantification. Quantitative analysis of neuronal morphologies can be used to address distinct research questions. One such question addresses the categorization of neurons into types. For this purpose, one discriminative measure can be sufficient. Another analysis strategy, however, is needed when investigating the differences in neuronal phenotype after genetic manipulation of a neuron. The latter might require a far more sensitive analysis likely involving multiple morphometric measures. Due to this diversity of scientific questions relying on morphometric analysis, not a single standard approach has yet emerged to quantify neuronal morphologies. In this section we discuss the possible methods to quantify morphologies.

However, before describing quantitative morphometric analyses in detail, we first introduce some terminology pertaining to morphometrics. The Petilla convention (Ascoli et al. 2008), a nomenclature specifically designed to describe the features of interneurons, sets a standard for some morphological features. However, a complete convention is still missing to our knowledge. As mentioned above, a neuron's morphology is described as a mathematical tree that is generally rooted at the cell body or the soma (Fig. 1.2). A tree is formally defined as a noncyclic graph. The dendritic stem segments (also know as "trunks" or "initial segments") sprout from this root, and each give rise to a branch. Branches in turn are composed of dendritic segments and branch points. Branch points are physical bifurcations at which a parent segment divides into two daughter segments. A branch has at least one termination point, the point at which the branch ends. In the terminology from graph theory, the root, branch, and termination points constitute the set of nodes in the tree, while the dendritic segments are the edges.

Morphometric measures can be divided into two main categories: topological and geometric morphometrics (Uylings et al. 1986; Verwer and van Pelt 1983). We further discuss functional measures that connect morphology directly to its function and measures to quantify similarity between neurons. The topological morphometrics deal with the branching structure of the tree independently of metric units (e.g., number of branch points and branch order). For geometric analyses, the topology is embedded in real space, thereby giving a shape to the topology. Associated measures consequently have metric or angular units. The functional measures refer to a morphology's function in the circuit and its ability to connect to other neurons and

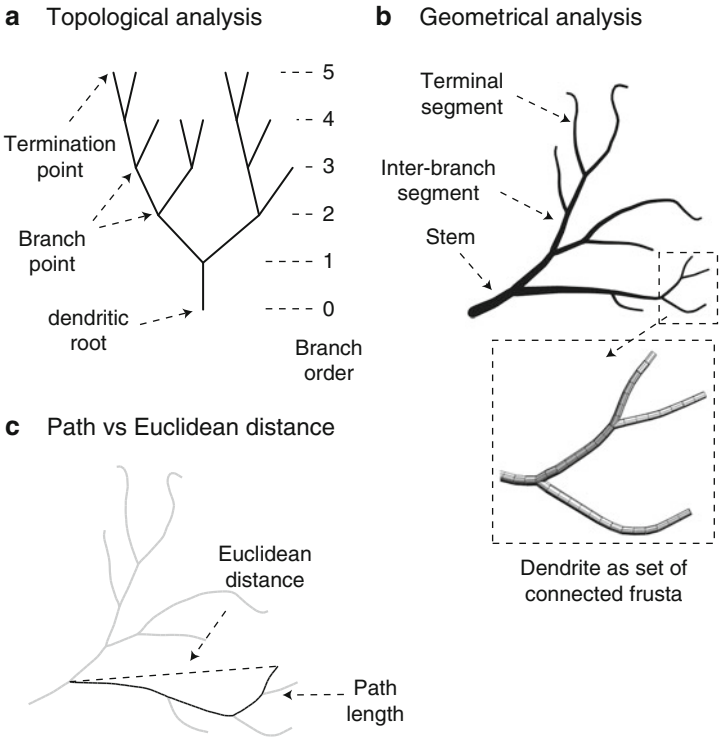

Fig. 1.2 Morphometric analysis of dendrite morphology. (**a**) Topological analyses disregard the metric features and describe the connections in the graph underlying the dendritic tree structure. Terminology shown for an idealized representation of a neuronal tree. (**b**) For a geometrical analysis, the tree is embedded in space and length values, as well as angles play a role. *Inset* shows the frustum-based representation of the dendritic structure in space. (**c**) An important geometric morphometric is the path length in a tree. Path lengths are always longer than the Euclidean distances, and many other morphometrics are calculated as a function of one of these two measures

to integrate inputs. Many other distinctions between types of morphometrics exist, such as the distinction between global/scalar and local/vector morphometric features. An example for the latter is the distinction between total length of a neuron and the individual lengths of all segments in a neuron. The total length is a global, scalar value while the individual lengths are local values. Table 1.1 summarizes the geometric and topological measures presented below.

1.4.1 Topological Measures

Intuitive topological measures are the *number of stems* defined as the number of edges leaving the dendritic root, the *number of branch points*, and the *number of*

Table 1.1 List of frequently used morphometric measures to quantify neuronal morphologies

Property	Brief description
Number of stems[a]	Total number of segments leaving from the dendritic root
Number of branch points[a]	Total number of branch points in the tree
Branch order	Topological distance from the dendritic root. The root has order 0, and the order of a segment in the tree equals the number of branch points along the path to the root + 1
Maximum branch order[a]	Maximum branch order in a neuron
Degree	Number of termination points downstream of the node under investigation
Maximum degree[a]	Maximum degree in a tree. By definition the degree at the dendritic root
Total length[a]	Summed segment lengths of all segments in a tree (see next)
Segment length	Path length of the incoming segment toward a node
Stem length	Path length between a branch point with order = 1 and the dendritic root
Interbranch length	Path length between branch points
Terminal segment length	Path length between the termination point and the last branch point
Euclidean distance	Can be applied in a similar fashion as the path length. Often used to measure the distance between the soma and the termination points
Dimension[a]	Width, height, and depth of the bounding box
Taper rate[a]	The uniform decrease in diameter across a dendritic branch
Somatofugal tropism[a]	Quantification of the preference of a neurite to grow away from the soma. Defined as the ratio of a segment's path length and the Euclidean distance between its starting and end point
Fractal dimension[a]	Fractal dimension used as a measure of space-filling
Contraction	Quick proxy of the fractal dimension: the Euclidean length of a branch divided by the path length
Partition asymmetry[a]	Topological complexity of a tree. A completely asymmetric tree has PA = 1, symmetric has PA = 0
Lacunarity[a]	A measure of "holes" in a volume spanned by a tree. See Sect. 1.4.2
Horton–Strahler index	Measure of topological complexity of a tree relating the order and asymmetry in that tree. Computed for each branch point. See Sect. 1.4.1
Strahler number[a]	The Horton–Strahler index associated with the root of the tree

Light shading—topological measures
Medium shading—geometrical measures
Dark shading—compound measures
[a]Global measure as opposed to distribution of local measures. However, often derived features are used as global feature. For instance, to describe the branch order in a tree, a distribution of all orders can be given, or the distribution can be characterized by considering the maximum branch order, the average branch order, etc. This holds for all local measures

termination points. For the sake of correctness, we use the term "dendritic root" rather than "cell body" or "soma" because in certain neuronal types (for instance many insect neurons) the dendrites do not sprout from the soma. However, in most cases, the soma is the root of the dendritic tree. The number of stems is sometimes

used to classify cell types (e.g., bipolar cells in the retina), while the number of branch and termination points represent the extent of branching in a tree. Since branch points typically are bifurcations in all neurons, the number of termination points is the number of branch points plus one. Furthermore, the *branch order* (or "centrifugal order") for each node is computed as follows: the dendritic root has by convention an order of zero so that the order of a node becomes one plus the number of branch points encountered on the path between the inspected node and the dendritic root (Fig. 1.2a). The reciprocal property is the *degree*, which is defined as the number of termination points in the sub-tree rooted at the node under investigation. The distribution (count) of the order and degree of branch points in a tree can be used for classification and description of morphologies (Verwer and van Pelt 1983). Order and degree are often used as auxiliary properties in combination with other morphometric features. For instance, any local morphometric measure can be plotted against order or degree to create a conditional distribution (see Sect. 1.4.4). The order and degree are also used in composite morphometrics. One such composite, topological measure is the *partition asymmetry* that assesses the topological complexity of a neuronal tree based on the normalized difference between the degree of two daughter branches at a branch point. The partition asymmetry index ranges from 0 (completely symmetric) to 1 (completely asymmetric) (van Pelt et al. 1992; van Pelt and Schierwagen 2004). Another composite morphometric based on order and degree is the *Horton–Strahler (HS) index* that relates the asymmetry in a tree with the depth of the tree (Binzegger et al. 2004; Toroczkai 2001). The HS index is computed at each branch point and equals $k+1$ when both daughter branch points have equal HS index of k or as $\max(k_1,k_2)$ when the HS indexes of its daughters k_1 and k_2, respectively, are not equal. The *Strahler number* is defined as the Horton–Strahler index associated with the root of the tree.

1.4.2 Geometric Measures

In contrast to topological properties that have no metric interpretation, geometric properties consider the spatial embedding of a tree. The segment length values and diameters are among the main properties in this category and give rise to a multitude of related morphometric properties. The most basic one is the *total dendritic length*. Distinct parts of the tree can be described in terms of their length as well, e.g., *stem length, interbranch point length,* and *terminal segment length* (Fig. 1.2b). Also, relations between any location in the tree can be described by a length metric in terms of the Euclidean distance or the path length between those locations (Fig. 1.2c).

The (somatofugal) tropism factor relates the segment length to the Euclidean distance from the dendritic root (Marks and Burke 2007; Samsonovich and Ascoli 2003). The ratio between length and distance is 1 for a segment that grows radially away from the dendritic root and 0 for a segment growing concentrically in relation

to the dendritic root. Spatial extent and its associated spatial embedding can be quantified in a number of ways. Most straightforward is the *dimension*: the raw bounding box in three dimensions. The *fractal dimension* is a measure of self-similarity and is often used as a measurement of space-filling (Smith et al. 1996). By definition, a straight line has a dimension of 1, a square has 2, and a cube has 3, but dendrites can be associated with fractional dimensions since the space that they cover is not fully filled. However, the interpretation of the fractal dimension is arbitrary and strongly depends on the method used to calculate it. In the "calliper method" (Fernández and Jelinek 2001), the fractal dimension represents the level of meandering of a dendrite, where a straight line has a dimension of 1 and more meandering dendrites receive slightly higher values. Since the validity of the fractal dimension is disputed in the analysis of neuronal morphologies (Cannon et al. 1999; Jelinek and Fernández 1998), *contraction* of a dendrite might be used as a proxy of the fractal dimension (when the fractal dimension is computed using the calliper method). Contraction is defined for a stretch of dendrite between two points as the ratio of the Euclidean distance and the associated path length between those points. A straight line has a contraction of 1, while a meandering dendrite has a slightly lower value. Intuitively, the relation between contraction and the fractal dimension can thus be approximated as fractal dimension $\approx (2 - \text{contraction})$ for planar dendrites. Both contraction and fractal dimension quantify space-filling. The reciprocal morphometric is a measure of "holes" in a morphology and is defined by the *lacunarity* (Smith et al. 1996). Apart from the overall dimension, locally the spatial embedding can be assessed by the angles in three dimensions between parent and daughter branches. Different variants are in use: the amplitude of the angle between the daughters can be measured as well as the angle between the parent segment and the daughters (Scorcioni et al. 2008). Recently, the perceived planarity of dendritic branch points (Kim et al. 2012; Uylings and Smit 1975) has received renewed attention as it was linked to optimal wiring principles and led to the development of detailed morphometrics quantifying the angles of branch points (van Pelt and Uylings 2011).

The diameter can be specified in relation to its change along the neuronal processes, i.e., tapering. Typically diameters reduce along a dendritic cable and can thus be approximated by a *tapering rate:* the linear or the nonlinear rate at which the diameter decreases per unit of length. Discontinuities in the tapering rate occur at branch points and can be referred to by the *child–parent ratio*, the ratio between the diameters of the parent and the child segments.

1.4.3 Functional Measures

Most morphometric properties inherently have some influence on the function and electrotonic structure of that neuron: with longer and/or thinner dendritic segments, input signals are more attenuated than with shorter and/or thicker segments. Hence, distal inputs, all things being equal, contribute less to the electrical activity at the

site of action potential initiation compared to proximal inputs. On the other hand, some morphological features do not impact on certain aspects of neural computation: angles in the dendrite do not matter for a current traveling through a dendrite. In some cases, morphometric measures are directly inspired by the function of neurons. An exemplary measure for this is *Rall's power*, a measure relating the diameters of a parent branch and its daughters at the branch point. Wilfrid Rall studied the power relation between parent (D) and daughter branch diameters (d_1 and d_2), $D^r = d_1^r + d_2^r$, with "r" now coined Rall's power (Scorcioni et al. 2008). Rall calculated that for the specific power $r = 3/2$, there is continuity in the impedance sensed by centrifugal signal flow at branch points such that a dendritic tree can be collapsed to a non-tapering, non-branching cable piece useful for applying analytical solutions of the cable equation to more complex dendrites (Rall 1959).

The other main function of neurons is to connect to other neurons in order to receive input. Specific measures directly relate a morphology to connectivity. The *critical percolation density* relates the dendritic morphology to the ability to connect to other neurons in the network (Costa and Manoel 2003). To calculate this property one populates a volume with instances of one particular morphology. Then, the percolation density is the average density at which a path suddenly emerges that leads from one side of the volume to the other along dendritic branches. The *excluded volume* (Costa et al. 2005; Wassle et al. 1981) is a related measure that quantifies the part of a dendritic tree's spanning volume that is not easily reachable for axons to make contacts with. The excluded volume is likely at the center of a dendritic structure when surrounded by dense branching.

An overarching metric and first approximation of connectivity can be derived from Peter's rule, which states that the number of synapses is proportional to the overlap between an axon and a dendrite (Binzegger et al. 2004; Peters and Payne 1993). Therefore, the allowed distance between dendrite and axon at which structural appositions are thought to occur can be used as a first approximation of connectivity. Note that Peter's rule associates two morphologies, a dendritic and an axonal one, while the percolation density and the excluded volume are single-neuron metrics.

1.4.4 Similarity

The aforementioned morphometric measures can be used to categorize morphologies and rank them on their similarity. Morphometrics can thus be used as a metric to quantify similarity between morphologies. In a straightforward fashion, the Euclidean distance between scalar morphometrics provides a measure of (dis)similarity. Vector morphometrics comprise a one-dimensional distribution, and hence the similarity between two such distributions can be quantified using hypothesis tests, of which the Student's test (t-test) is the most popular parametric test and the Kolmogorov–Smirnov test and ranksum tests are well-known nonparametric alternatives.

An issue is that morphometric measures are often not independent from each other. Thus, morphometric measures can be seen independent from each other (=univariate) or conditioned on other measures (=multivariate). For instance, the segment length might be independent of any other feature of the neurite tree (univariate description), or, might be dependent on the topological order of the segment (conditional, bivariate description), and so forth. Sholl was the first to perform such a two-dimensional analysis as he counted the number of intersections between the dendritic segments and imaginary concentric circles at increasing Euclidean distance from the cell body (Sholl 1953). As briefly mentioned before, any bivariate morphometric can be plotted against another, and this is generally referred to as a Sholl-like analysis. As an example, one can argue that the segment length changes depending on the branch order (Burke et al. 1992; Nowakowski et al. 1992). Such higher order relations surely exist in neurons, but the application of multivariate measurements remains restricted due to limited amount of data (a large sample size is needed to uncover higher order relations).

In addition to comparisons of morphometrics there are dedicated measurements to quantify similarity. A first similarity measure is the *tree edit distance* and formalizes how many operations ("tree edits") have to be made to morph one tree into another (Heumann and Wittum 2009). Another measure of similarity between neurite morphologies is the *shape diffusion index* (Luczak 2010). While technically a bit more complex, intuitively it can be seen as a measure of how easily a morphology can be synthesized using the diffusion-limited aggregation approach (see next section and Chap. 5). Luczak found that some classes of neurons were "easy" to approximate, while others were "harder." This difference can then be used to express similarity.

1.4.5 Further Quantification

The review we presented here is by no means exhaustive; it rather reflects a choice of morphometric measures most commonly used to quantify morphology and link morphology to connectivity. Graph theory itself has many ways to describe tree structures and network topologies. These descriptions, however, often have little or no biological interpretation. A good introduction into more exotic measures to quantify neuronal morphologies is provided by Rocchi et al. (2007). Also, a lot of ad hoc measures are in use. These measures are often proposed to study a particular trait in a particular neuronal type. For instance, somatofugal tropism was first used to quantify the preference of a dendritic tree to direct away from its soma in pyramidal cells. Ad hoc measures have the intrinsic drawback that there is no standard definition of how to compute them, which makes their evaluation and their comparison to well-defined morphometrics harder. Nevertheless, when picked up by others, as in the case of the measure for tropism, these ad hoc measures can make it into the standard repertoire of measures and extend the standard battery of useful measures.

1.5 Algorithms to Synthesize Dendrites

Since morphometric measures are so numerous, variable, and dependent on many factors like context and age, it is difficult to extract principles of dendritic structure directly from these measures. In the last two decades, generative approaches were developed to study dendritic morphologies by synthesizing (parts of) dendritic morphologies in the computer. The rationale behind this approach is that by generating dendrites according to a particular principle, resulting synthetic morphologies may share morphological traits with real dendrites. This finding then can corroborate the initial hypothesis about the underlying principle. In a sense, it is the computational neuroanatomy interpretation of Lord Kelvin's maxim: "I am never content until I have constructed a mechanical model of what I am studying. If I succeed in making one, I understand; otherwise I do not."

One of the ideas that kick-started the generative approach stems from the seminal work of Hillman who described a set of *fundamental parameters* sufficient to generate dendritic morphology (Ascoli and Krichmar 2000; Hillman 1979). Many generative algorithms are based on this idea by iteratively constructing a dendritic tree while sampling from statistical descriptors (Burke et al. 1992; Tamori 1993). One of the first publicly available tools is L-Neuron (Ascoli and Krichmar 2000), which relies on an L-system in combination with stochastic sampling to generate synthetic dendrites. An L-system or a Lindenmayer system (Prusinkiewicz and Lindenmayer 1990) is a formalism that can recursively generate branched structures, such as plants and neurons, from a parsimonious representation. The geometry, however, is sampled from statistical descriptors based on morphometric measures. The differences between existing sampling algorithms mostly lie in the statistical descriptors used: the number and selection of parameters as well as their statistical descriptions as a parametric model (Ascoli and Krichmar 2000; Eberhard et al. 2006) or a non-parametric model (Lindsay et al. 2007; Torben-Nielsen et al. 2008).

A different approach, inspired by principles of neuronal development, has been developed over the years by van Pelt and colleagues (van Pelt et al. 1992; van Pelt and Schierwagen 2004). They followed a generative approach that could be used to synthesize dendritic topology constrained by the branch order and the number of simultaneously developing segments. By adjusting the rate of growth to the number of developing growth cones, a basic interpretation of competition over resources is included. Their work led to the development of a tool, NETMORPH (Koene et al. 2009), that can generate large networks of interconnected synthetic morphologies by addition of a geometric component to the developing branched structures (see Chap. 4).

Note that the aforementioned tools synthesize morphologies without (or to a limited extent) considering the interactions with other parts of the tree, with other neurons, or with physical boundaries within the circuit. Because neurons do not grow in isolation, it can be assumed that not all natural factors are captured by these algorithms. A number of recently developed approaches overcome these limitations in various ways.

One approach that explicitly takes other neurons into account during the generation process is proposed by Luczak (2006) (see Chap. 5) and is based on diffusion-limited aggregation (Hentschel and Fine 1996; Witten and Sander 1981): "neurotrophic particles" are distributed into a bounded space where they randomly move. Then, upon colliding with an n-particle aggregate, the moving particle will stick and form an $n+1$-particle aggregate. Some extra rules are needed to constrain the aggregates to biologically relevant structures, but such an aggregation process yields realistic synthetic dendritic structures. By using several seeds, i.e., initial 1-particle aggregates, at the same time within the same bounded space, virtual morphologies under construction effectively compete over resources and hence a biologically plausible form of interaction is captured in the algorithm.

Recently another approach was proposed by Memelli et al. (2013) where a virtual morphology is grown under the presence of environmental influences. A branching rule determines when a dendritic tree branches, but the direction of growth is solely determined by environmental cues. Cues act as biases on the direction of growth. Additionally, the virtual morphologies are constrained to a bounded space. As a proof of principle, highly realistic morphologies were synthesized by solely taking self-referential (i.e., stiffness, soma tropism, and self-avoidance) cues into account. So far the environmental interaction is thus limited to the neuron's own guidance cues. However, a cue coming from another neuron is conceptually identical to a cue coming from the neuron itself: it is a bias on the direction of growth. Therefore, this approach can be directly used to investigate hypotheses about various environmental cues shaping the final dendrite morphology.

A different approach to generate dendritic morphologies is based on the functional implication of the structure of neural trees, the influence of diameter values on voltage propagation, and circuit connectivity (Cuntz et al. 2007, 2008, 2010; see Chap. 6). Target points are distributed in a volume of interest and connected iteratively to a growing tree in a competitive manner to minimize total wiring cost and conduction times. In a post-processing step, diameters are assigned according to the propagation dynamics, and a synthetic morphology is created. One advantage of using this approach is that it is far less data intensive compared to standard sampling methods: the only statistical descriptor in use is a two- or a three-dimensional density function of the target points. Indeed, no detailed statistics about branching angles, segment length, etc. are used, and hence the algorithm is less prone to researcher-induced biases. It also permits to draw direct conclusions about the connectivity principles in the circuit. Optimization principles of wiring constraints such as the ones used for these models have traditionally been successful at directly predicting scaling relationships in branching statistics (Chklovskii and Koulakov 2004; Klyachko and Stevens 2003; Wen et al. 2009; Wen and Chklovskii 2008). This is described in great detail in Chap. 7.

Beyond the constraint of connectivity, the hypothetical computational function of a neuron can also constrain the morphology. This idea is explored by Torben-Nielsen and Stiefel (2010) and is coined the "inverse approach" (see Chap. 9). In the inverse approach, morphologies are synthesized with a straightforward sampling algorithm. However, the parameters defining the statistical distributions from which

they are sampled are not based on biological data. Rather, the parametric distributions are optimized using evolutionary algorithms so that a model neuron endowed with the optimized morphology successfully performs a predefined neuronal computation. The inverse approach can be used in a twofold manner: as a hypothesis tester and a hypothesis generator. In case it is hypothesized that a neuron performs a computation, a synthetic morphology can be optimized to perform the same function. When the resulting morphology resembles the real counterpart, this result can corroborate the hypothesis. On the other hand, morphologies can be optimized to perform a computation of interest. If neurons in the brain then resemble the synthesized morphology, a hypothesis about the function of these neurons can be proposed.

The last approach to be mentioned here is the most elaborate one and is proposed by Zubler and colleagues (Zubler et al. 2011; Zubler and Douglas 2009). They developed a phenomenological growth simulator in which growing neurons can migrate and interact with structural boundaries as well as other cells within the simulated environment. Each growth cone contains the growth rules for this neuron encoded in a gene-like format (Zubler et al. 2011). The growth rules can use environmental cues such as secreted substances or laminar information. In addition a growing neurite can also secrete substances and switch on or off growth rules depending on its environment. With this setup, many of the environmental complexities of cortical circuitry can be modeled (at least in a phenomenological way).

1.6 Future Perspectives

A major problem with studying dendritic morphology is that the shape of a neuron is not a perfect instance of a general blueprint. In the nervous system, individual cells have to compete with others as well as with different structures such as glia cells and blood vessels. Reconstructed morphologies are always mere snapshots of a particular neuron in time and contain the combined effects of development and learning. As a result, large variation exists in their morphology. Variation is commonly seen as the difference in morphology between members of the same type, while diversity is the distinction between different classes (Soltesz 2005). In general, the description of diversity is easier than the description of variation. For instance, it is straightforward to differentiate a motor neuron from a pyramidal neuron. Sometimes, however, the variation within a class is larger than the diversity between classes. Purely based on the morphology it is fairly hard to tell apart a layer five (L5) pyramidal neuron from a layer six (L6) one. It is even harder to tell the difference between L5 pyramidal neurons at different ages. In general, the more detailed the research question becomes, the more sophisticated the quantitative analysis needs to be. The presented morphometric quantification helps considerably: it provides hard numbers to describe neuronal morphologies. But, how to cope with the variance?

Here, we sketch three future strategies that will be useful to quantify and understand variation. Let us for example consider the rat sensorimotor cortex that is

roughly 2,000 μm thick and layer 5 (in 2-week-old animals) is 650–700 μm thick. L5 pyramidal cells have an apical dendrite growing to the pia where it branches extensively. A large variation in total length occurs when a neuron's cell body is located deeper in layer 5 and has to extend further to reach the pia (Oberlaender et al. 2012; Ramaswamy et al. 2012). Because the current standard to represent morphological reconstructions (e.g., the aforementioned SWC format) only includes the geometry of a single morphology, there is no direct way of taking the location of the cell body into account. Hence, no statistical model will capture the fact that L5 pyramidal cells closer to the pia have a shorter apical dendrite. This example illustrates a pitfall in the quantification of morphologies: as long as they are considered in isolation, simple biophysical explanations for morphometric variation will be overlooked.

The first strategy to overcome the outlined issue is to include metadata such as laminar position and 3D spatial context in the description of a neuron. This strategy is adopted in the cortical column model by the group of Oberlaender and colleagues. This is summarized in Chap. 8, where the 3D context is stressed in the reconstruction of the rat vibrissal cortex.

A second strategy is a pragmatic approach to investigate the natural variation in neuronal types and relies on the fact that a good statistical model should be able to generalize and infer morphometrics as long as the sample size is large enough. By using larger samples, the statistical models can better generalize. This strategy is adopted by Costa and his colleagues. They analyze morphologies from the complete NeuroMorpho.org database to investigate morphological outliers and archetypes (Costa et al. 2010; see Chap. 3).

A final strategy we discuss here to alleviate the issue of variance and the lack of metadata is to actually study the biophysical mechanisms that underlie neurite morphologies. Our understanding of cell biological mechanisms resulting from genetics is increasing rapidly. In Chap. 2, Tavosanis concisely summarizes some of the prominent molecular mechanisms of morphological differentiation that underlie not only basic properties as branching and elongation but also more complex behaviors requiring interaction between developing dendrites as required for tiling and self-avoidance. If the underlying mechanisms can be expressed as phenomenological rules, morphometrics do not need to be used to deduce morphological traits, because the traits and associated hypothesized rules can be studied using the generative approach. First attempts to generate morphologies according to developmental rules include reports by Memelli et al. (2013) and Zubler and Douglas (2009). In the future, generative approaches in general coupled with better molecular understanding of morphological differentiation will allow us to explain differences in sizes as in the example of the L5 pyramidal cell. Combined with rigorous morphometric analysis, it would then be possible to attribute highly varying morphometric features not to diversity or variation but to, for instance, avoidance of capillaries or the repulsion away from another neuron of a specific class.

In conclusion, morphology of neurons plays a fundamental role in brain functioning. Using morphometric quantification we are currently able to classify some types of neurons. Moreover, rigorous quantification allows us to study morphological traits and their connection to the brain circuit at large. In the future, we

expect a synergy between the big data projects generating detailed statistics of neurite morphology and their connections (e.g., connectomics), genetic studies revealing local interaction rules governing dendritic growth, and generative approaches to link large-scale data and local interactions. Please enjoy the following chapters covering the state of the art in the quantitative studies of dendritic morphology.

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