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The importance of metadata to assess information content in digital reconstructions of neuronal morphology

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Abstract

Digital reconstructions of axonal and dendritic arbors provide a powerful representation of neuronal morphology in formats amenable to quantitative analysis, computational modeling, and data mining. Reconstructed files, however, require adequate metadata to identify the appropriate animal species, developmental stage, brain region, and neuron type. Moreover, experimental details about tissue processing, neurite visualization and microscopic imaging are essential to assess the information content of digital morphologies. Typical morphological reconstructions only partially capture the underlying biological reality. Tracings are often limited to certain domains (e.g. dendrites and not axons), may be incomplete due to tissue sectioning, imperfect staining, and limited imaging resolution, or can disregard aspects irrelevant to their specific scientific focus (such as branch thickness or depth). Gauging these factors is critical in subsequent data reuse and comparison. NeuroMorpho.Org is a central repository of reconstructions from many laboratories and experimental conditions. Here we introduce substantial additions to the existing metadata annotation aimed to describe the completeness of the reconstructed neurons in NeuroMorpho.Org. These expanded metadata form a suitable basis for effective description of neuromorphological data.

Keywords

neuron morphology; metadata; digital reconstruction; data standards; completeness

Introduction

NeuroMorpho.Org is a central database of digital reconstructions of neuronal morphologies (Ascoli et al. 2007). The repository is freely accessible and allows unrestricted access to tracing files contributed by over 140 laboratories worldwide. Though the repository serves a growing need for public access to shared neuromorphological data, some limitations currently exist. To further increase the efficacy and impact of the repository in neuroscience we introduce new elements of its annotation system.

Every set of neurons in NeuroMorpho.Org was originally reconstructed to address particular questions, but is now available to different researchers for distinct scientific aims (Parekh and Ascoli 2014). When tracing neurons, researchers annotate the data with details relevant

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to their specific goals and often contextually to the experimental design. For optimal re-use of shared reconstructions, however, lack of metadata standardization may become a limiting factor. Each reconstruction in NeuroMorpho.Org is associated to essential metadata with which the database can be searched online, including information about the animal subject, experimental procedures, neuroanatomical details, and original data source. Nevertheless, due to absence of standards for reporting metadata of neuronal reconstructions, critical details often remain unreported in the publications and therefore are also absent in the repository.

Additionally, information about the "completeness" of reconstructions is seldom addressed in publications. This detail is especially important when re-using shared digital morphologies, as it pertains to the amount and type of data actually contained in the available files relative to the underlying biological reality. Neuronal tracings can vary broadly in this regard. On one end of the spectrum are complete reconstructions that constitute comprehensive and faithful digital representations of the corresponding neuron instances in the biological tissue. Examples of these are extremely rare if at all existing. On the opposite end are reconstructions that only record a limited subset of geometric characteristics of the branching geometry of neurons, thus capturing just a minimal description of the underlying biological structures. Most reconstructions in NeuroMorpho.Org fall in the middle of this spectrum. This issue is complementary to that of tracing accuracy (Horcholle-Bossavit et al. 2000; Kaspirzhny et al. 2002). Completeness relates to the focus and quantity of the data rather than its relative quality.

The scientific goal of the experiment typically determines reconstruction completeness. For example, if researchers are only interested in the axonal characteristics of a given set of neurons, they may knowingly choose not to reconstruct the dendrites (e.g. Lu et al. 2009). Similarly, in order to quantify specific differences between experimental conditions, a neuroscientist might decide to only sample a few sub-trees from many neurons rather than to trace full trees from fewer cells (Anderson et al. 1995). In many cases, neurons are reconstructed to establish or confirm the morphological identity after electrophysiological recording in the slice, therefore losing portions of the arbors to physical sectioning. Partial reconstructions still constitute invaluable data. However, they must be differentiated from those that are more or less complete as well as based on the type of their incompleteness.

Since NeuroMorpho.Org's 2006 launch, the number of available reconstructions has increased from fewer than 1,000 at the first release to over 11,000 in May 2014 (v5.7). All reconstructions contributed to the repository undergo an extensive process of centralized curation and annotation aiming at maximal scientific impact (Halavi et al. 2008). The publications describing reconstruction data are also multiplying (Halavi et al. 2012) in parallel with the development of tools and resources (Parekh and Ascoli 2013) and data re-use (Parekh and Ascoli 2014). Although the field is thriving overall, continuous growth will eventually require development of adequate standards for reporting metadata details of digital reconstructions of neuronal morphologies. As a further step in this direction, here we present an expanded annotation system to categorize the completeness of reconstructions in terms of the represented aspects of the real neuron they were traced from. Furthermore, we report an initial status summary of the available reconstructions with respect to various

facets of completeness. Last but not least, we introduce the implementation of a new extension of the NeuroMorpho.Org search functionality, enabling users to effectively select neurons on the basis of several completeness dimensions.

NeuroMorpho.Org Metadata

Every reconstruction in NeuroMorpho.Org is currently annotated with metadata across four categories. The *animal* category includes details of the subject, such as species, strain, gender, weight, and age. In the *experiment* category, metadata include protocol (e.g. *in vivo*, slice, or culture), condition (control vs. experimental), label or stain used to visualize neurons, thickness of tissue section and slicing orientation, objective type and magnification, shrinkage, and reconstruction software. The *anatomy* category includes the brain region (and sub-regions) and neuron type (and sub-types) as identified by the authors. The fourth category, *source*, specifies the contributing laboratory, the reference publication, names of the individual neuron files, the original digital file formats, and the dates of receipt and website upload. At the time of data submission, authors are encouraged to provide as many of these details as possible (Table 1). Moreover, we extract any available information from the reference publication. When specific metadata are not available from the authors or the paper, they are indicated as “Not reported” in the corresponding repository entries. Neurons are searchable in NeuroMorpho.Org based on any combination of the above metadata.

Morphological Completeness

A perfectly complete digital reconstruction of a neuron would represent the branching geometry (including diameter and 3D coordinates) of the entire dendritic and axonal arbors stemming from the soma and fully traced to every terminal tip. Unfortunately, such ideal scenario rarely if ever materializes due to the need of researchers to optimize the balance between data content and the rate-determining labor intensity of neuronal tracing. The choice of experimental design does not simply translate into the classic trade-off between data quality and quantity, but rather implies complex consequences because of intertwined factors in the histological, imaging, and tracing procedures.

The most common experimental approaches to digitally reconstruct axonal and dendritic morphology involve tissue sectioning, labeling for visualization, microscopic imaging, and semi-manual tracing. Each of these separate manipulations implies a potential loss of data completeness. For example, many digital reconstructions miss branches that are cut off by slicing, incompletely stained, or simply fall below the limit of optical resolution. The reduced **physical integrity** of the digitally reconstructed morphology relative to the original biological neuron represents the most readily recognized aspect of tracing completeness, and we discuss it further below. Nonetheless, two other distinct facets are also fundamental to assess neuronal completeness when re-using shared reconstructions.

Specifically, it is first essential to determine which **domains** of a neuron the reconstruction includes, such as soma, dendrites (including apical and basal trees), and axonal arbor. While researchers may choose to trace morphology only in their domain of interest, the target neurons consist of whole biological entities with all their structural domains. The most important distinction related to reconstruction domain for NeuroMorpho.Org data is between

axonal and dendritic arbors. Other characteristics of the reconstruction, however, are also relevant to the domain aspect of completeness, such as the possible explicit inclusion of axonal varicosities or dendritic spines (e.g. Eyre et al. 2008) or the exclusive focus on terminal projections (e.g. Brown et al. 2012). It should be noted that physical integrity can also be domain-specific. For instance, it is not atypical for reconstructions to include nearly complete dendrites as well as a partial axonal tree.

A complementary aspect of completeness ascertains which **attributes** of neuronal morphology a reconstruction captures in a biologically realistic manner. Certain studies do not require accurate measurement of branch diameter, for example if only focusing on arbor length (Rihn and Claiborne 1990). Likewise, when the identification of neuron type based on peculiar shape is the sole goal of tracing, the two-dimensional projection is often sufficient, avoiding the painstaking recording of branch depth (e.g. Banke and McBain 2006). Branching angles are similarly irrelevant to other applications of digital reconstruction, such as the accurate characterization of electrotonic structure, for which dendrograms provide adequate information (Bannister and Larkman 1995). At the same time, some researchers record anatomical boundaries or reference landmarks, providing a useful spatial registration of the traced morphology (Ishizuka et al. 1995).

Domain and attribute completeness largely depend on experimental *design* and can be directly assessed by visual inspection of the reconstruction together with simple morphometric measures (Figure 1). In contrast, the physical integrity of reconstructed neurons is greatly affected by the experimental *conditions*. Several parameters are particularly critical for gauging the likely degree of physical integrity. The *slice thickness* determines the extent of neuronal arbor retained in the tissue section. For example, the vast majority of the axonal length is lost when cortical pyramidal cells or other projection neurons are traced from typical electrophysiological preparations in vitro. The *staining* used for visualization often determines which parts of the neuron are fully labeled. For instance, myelinated axons go undetected by Golgi impregnation. In optical microscopy, the *objective type* and *magnification* affect the minimum discernable resolution, below which following the thinnest branches becomes impossible.

Structural domain, physical integrity, and morphological attributes constitute complementary (though not always independent) aspects of data completeness in digital reconstructions of neuronal morphology (Figure 1). In order to allow NeuroMorpho.Org users to consider these crucial factors when searching and examining available data, we extended the existing metadata annotation in the repository to include an assessment of each of these distinct facets of neuronal completeness.

Completeness of digital reconstructions in NeuroMorpho.Org

To evaluate reconstruction completeness, we undertook a systematic review of the available NeuroMorpho.Org content (v5.7 release). Specifically, we mined all 226 publications describing the shared neuronal morphologies for relevant information. Moreover, we sampled a random subset of neurons from each publication for visual inspection and analysis. As a first step, we estimated the structural domains, physical integrity, and

morphological attributes at the level of individual datasets, defined as collections of reconstructions from a single publication and sharing the same metadata. The underlying assumption is that all neurons within a given dataset are typically reconstructed in a similar manner and hence are likely to share a comparable level of completeness. Assigning the same completeness descriptors to all the neurons in each dataset, however, only constitutes a first approximation, as it is not uncommon for reconstruction to vary considerably by physical integrity even within the same experiment. Thus, we plan to gradually refine the information of this new metadata category in future NeuroMorpho.Org releases to specify completeness at the level of individual reconstructions.

The determination of structural domains was usually straightforward. For each dataset, we first evaluated whether the reconstructions included soma, axons, and/or dendrites, specifying apical and basal where applicable (e.g. Jacobs et al. 2001), by extracting elementary morphometric characteristics (e.g. surface area) for each domain (these measurements are available under Search by Morphometry in NeuroMorpho.Org). We then confirmed this evaluation by directly inspecting sampled digital morphologies. Similarly, identifying the morphological attributes of each dataset simply required noting if the reconstructions were captured in 2D or 3D and whether the distributions of branch diameters and angles displayed a coefficient of variation within an order of magnitude from unity. The initial assessment based on automated morphometric measurements was validated by direct inspection of sampled reconstructions as well.

Gauging the extent of physical integrity was substantially more challenging. Even a rather coarse distinction between “complete”, “moderate”, and “incomplete” required considerable depth and breadth of domain expertise across brain regions and neuron types as well as critical inferences based on sectioning, visualization, and imaging details reported in the individual publications. We additionally relied on careful qualitative assessments of the sampled reconstructions in each dataset to glean further clues about their physical integrity.

Although the absolute physical integrity of a neuronal reconstruction can hardly ever be definitively established, we tentatively deemed as complete morphologies for which we found no indication otherwise (e.g. Tamamaki and Nojyo 1993; Wittner et al. 2007). Reconstructions clearly truncated due to tissue sectioning, but essentially complete within the slice, were marked as ‘moderate’ (e.g. Glickfeld and Scanziani 2006; Yu et al. 2013). Reconstructions of axonal fragments (Santiago et al. 2010) or limited to the initial portion of the axonal arbor (e.g. Kole et al. 2004) were marked as ‘incomplete’. When the physical integrity of reconstructions from within a single dataset ranged all the way from clearly incomplete to essentially complete, we marked the whole collection as ‘moderate’ (Wang et al. 2002). These cases will clearly benefit from future refinement of completeness from the dataset level to the individual neuron level.

Several studies describe measures taken to maximize the physical integrity of the reconstruction. For example, useful selection criteria for the morphologies to be traced include thorough staining of the neuronal arbors with clear contrast against the background, ability to follow branches unobtrusively through the following bifurcation or natural termination, and central position of neurons in the tissue (Jacobs et al. 1997; Li et al. 2005;

Golding et al. 2005; Brunjes et al. 2011; Marx and Feldmeyer 2012). Gentle or progressive taper can often distinguish real dendritic terminals from slicing truncations or interrupted dye penetration. Other reports include post-hoc analyses to estimate the extent of physical integrity, such as quantifications of the proportion of axon terminals corresponding to a varicosity (Wittner et al. 2007) or ending more frequently than expected close to the slice edges (Ascoli et al. 2009). At the same time, known instances of partial physical integrity are also occasionally indicated in some publications (Takemura et al. 2013; Hayes and Lewis 1996).

The above annotation procedure yields a broad distribution of reconstruction completeness across NeuroMorpho.Org in terms of structural domains, physical integrity, and morphological attributes (Figure 2). With respect to domains, more than half of the datasets (126 out of 226, accounting for 6,063 reconstructions) include soma, axons, and dendrites. Approximately another third (79 datasets, 3,529 reconstructions) included soma and dendrites but lacked axons. The remaining tenth (21 datasets, 1,743 reconstructions) lacks dendrites, soma, or both (Figure 2A).

Of the 132 datasets with both axonal and dendritic reconstructions, less than a quarter (31 datasets accounting for 762 reconstructions) is deemed reasonably complete in regard of physical integrity. An additional 36 datasets, with 948 reconstructions, have complete dendrites but moderate or incomplete axons. The remaining half of the datasets is split between having moderate axons and dendrites (29 for 1,857 reconstructions), and having incomplete axons, dendrites, or both (Figure 2B). Including the datasets with only dendritic or axonal reconstructions in the analysis of physical integrity further corroborates these trends (Figure 2B inset): about half of the datasets have essentially complete dendritic reconstructions and only one tenth have clearly incomplete dendrites. In contrast, the datasets with clearly incomplete axonal reconstructions exceed in number those with reasonably complete axons, and approximately one third falls in the moderate category.

Lastly, with respect to morphological attributes, more than two thirds of the datasets (8,194 reconstruction) include branch diameter, angles, and depth (Figure 2C). Approximately one quarter of the datasets (2,635 reconstructions) lack diameter information, and a small minority are traced as 2D projections (13 datasets, 475 reconstructions), or as dendrograms (4 datasets, 290 reconstructions).

Enhanced search functionality of NeuroMorpho.Org by metadata completeness

Current search options in NeuroMorpho.Org allow users to filter data in the repository by combining multiple selection criteria across four main metadata categories, namely *animal*, *experiment*, *anatomy* and *source*, each of which we described above. The new annotation of reconstructions based on distinct aspects of completeness introduced in the present work is now implemented as a new metadata category in NeuroMorpho.Org. Under the Search by Metadata option, users can specify the selection of reconstructions by structural domain (soma, dendrite, axon), physical integrity (complete, moderate, incomplete), and morphological attributes (depth, diameter, angles). For example, users can restrict their

search for reconstructions of neurons that include complete axons traced in 3D (in v5.7 this query returns 1,598 hits out of 11,335 available reconstructions).

Concluding Remarks

Technical advances in histological processing, image acquisition and automated tracing are jointly contributing to the accelerating pace of data collection. High-throughput generation is accompanied by a welcomed trend towards open data sharing with the neuroscience community (Mizuseki et al. 2014). If active steps are not taken to standardize metadata annotation, however, the wealth of data may easily become an unmanageable deluge. Establishment of common annotation standards is particularly critical to maximize the impact of shared data. When contributors submit digital reconstructions to NeuroMorpho.Org, we ask them to provide specific details about the reconstructions using a semi-structured metadata form. For all data received in the future, we have now modified the metadata request form (http://NeuroMorpho.Org/neuroMorpho/Metadata_Form.xls) based on the new annotation system for reconstruction completeness introduced here (asterisks in Table 1).

The enabling nature of rich metadata descriptors, however, is not restricted to the purview of digital reconstructions, but can rather benefit all fields of neuroscience investigating neuronal properties at large, including electrophysiology (Gibson et al. 2009) and neurochemistry. A useful step forward would be for scientific journals to request analogous metadata information from authors upon accepting manuscripts for publication.

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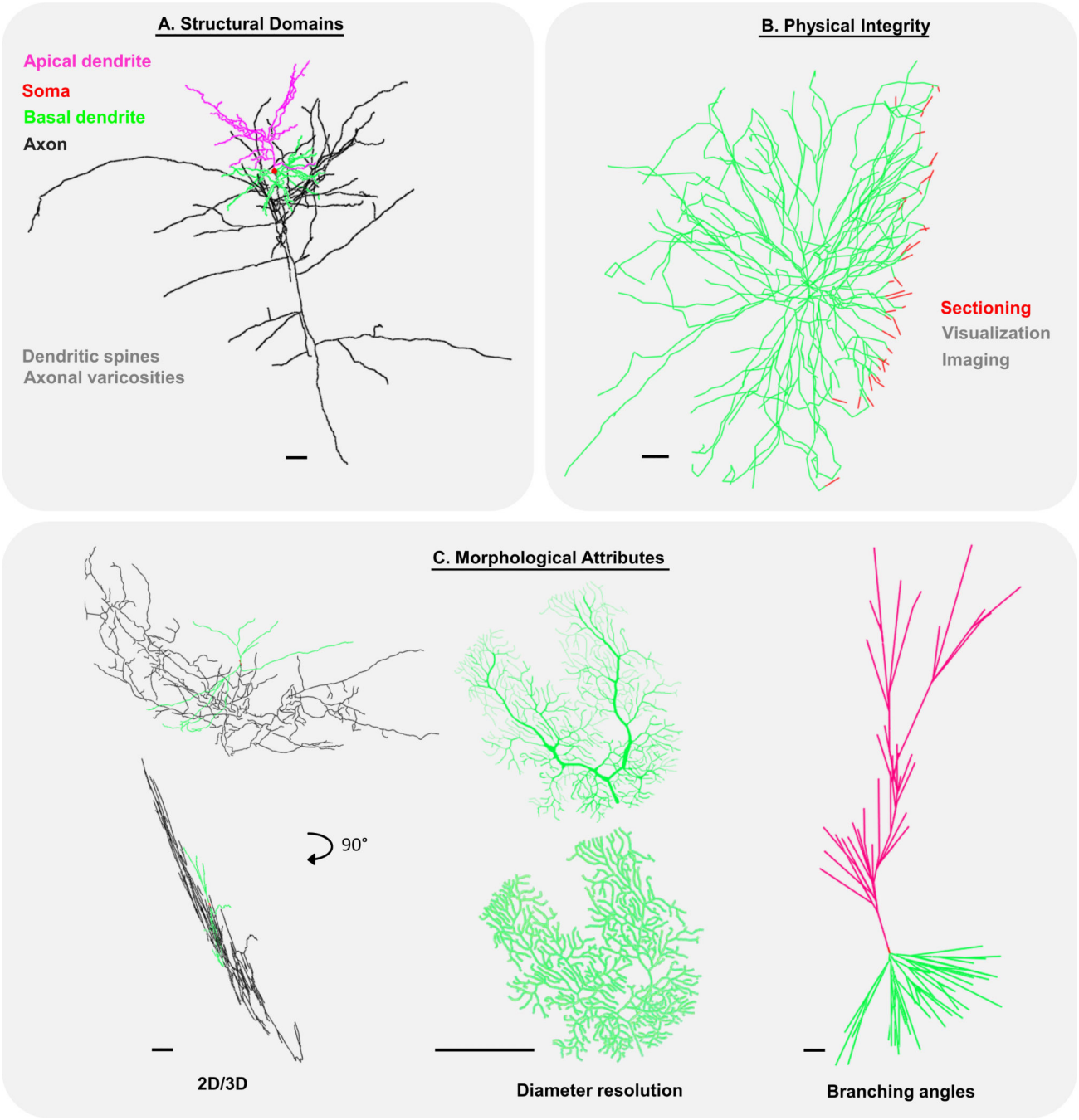

Figure 1. Features of neuronal reconstructions that determine its "completeness"

A) Structural domains currently represented in NeuroMorpho.Org include soma, axon, dendrites (possibly divided into apical and basal), and spines (the NeuroMorpho.Org ID for this reconstruction is NMO_05815). B) The **physical integrity** of a reconstruction is affected by the combined experimental conditions of sectioning (illustrated here), visualization, and imaging (NMO_00609). C) The **morphological attributes** of each reconstruction specify if the neuron was traced in 2D or 3D (NMO_07888) and whether the

diameter (NMO_00865) and branching angles (NMO_0871) were meaningfully measured. Scale bars: 100 μm.

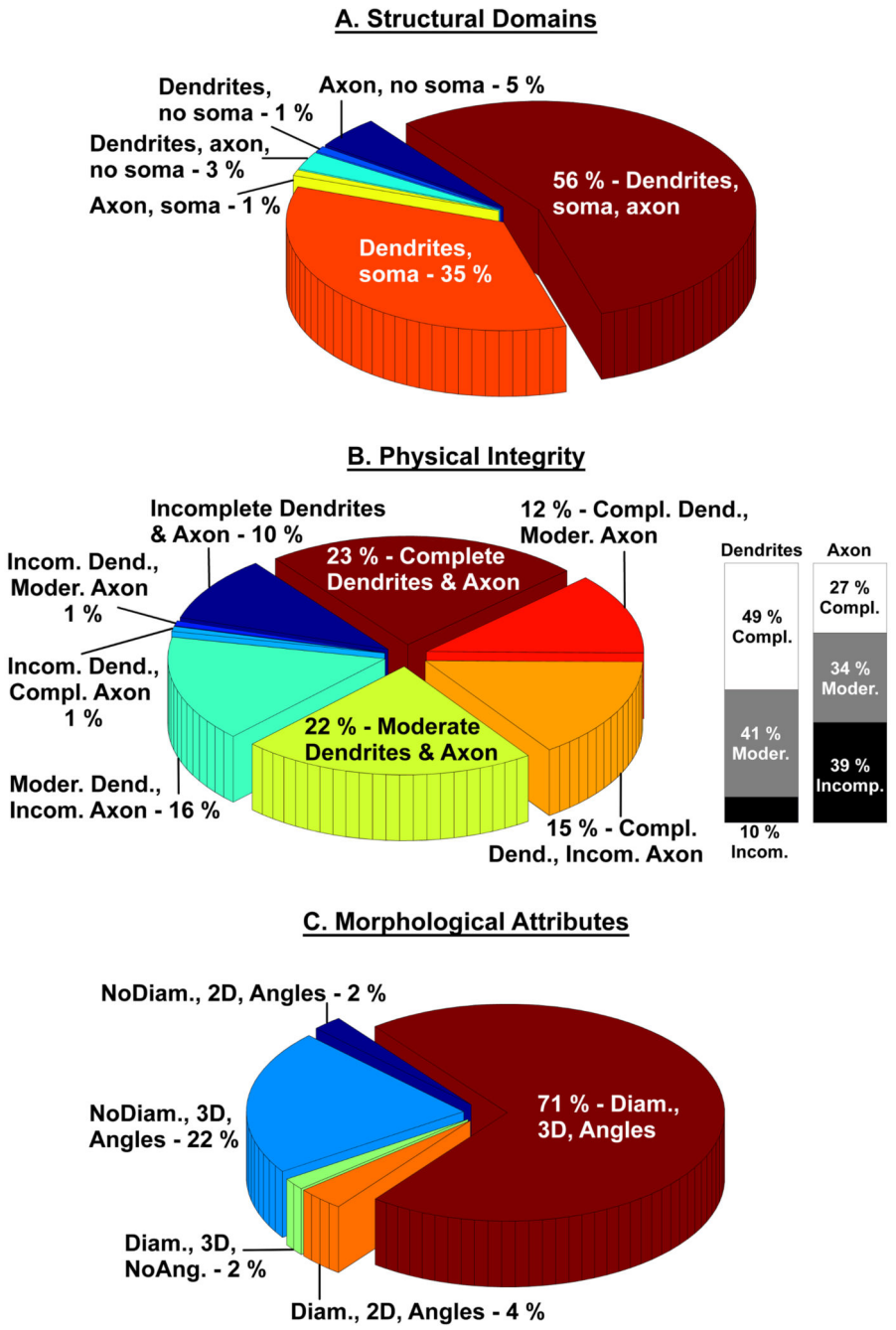

Figure 2. Completeness of NeuroMorpho.Org data with respect to structural domains, physical integrity, and morphological attributes

A) Proportion of publications corresponding to the indicated structural domains. B) Distribution of dendritic and axonal physical integrity when both domains are present. The insets indicate the physical integrity for each separate domain independent of the completeness of the other. **C)** Proportion of publications corresponding to the indicated morphological attributes.

Table 1

Existing and additional (*) metadata annotation of neuromorphological reconstructions in NeuroMorpho.Org

The examples listed here are not intended to refer to any specific dataset but are provided for illustration purposes only as representative instances from miscellaneous repository content.

Categories	Features	Examples
Dataset	Archive name	Jacobs
	Number of data files	100
	Format of data files	Neurolucida.dat
	PMID	19496174
Subject	Species	Mouse
	Scientific name	Mus musculus
	Strain	C57B6/SJL
	Gender	Male
	Development	Adult
	Age	P80–P90
	Weight	20–25 grams
Anatomy	Brain region	Neocortex
	Sub-region	Somatosensory
	Sub-region	Barrel cortex
	Sub-region	Layer V
	Cell type	Principal
	Sub-type	Pyramidal cell
	Sub-type	Star-pyramidal
Processing	Experimental condition	Control
	Preparation protocol	In vitro
	Stain	Biocytin
	Fixation method*	4% paraformaldehyde
	Slice thickness	350 μm
	Slicing direction	Coronal
	Tissue shrinkage	10%, uncorrected
	Objective type	Oil
	Objective magnification	100x
	Reconstruction software	Neurolucida
	Notes	Thionin counterstain
Domain	Soma	Yes
	Axon	Partial
	Dendrites	Yes
	Apical dendrites	Yes
	Basal dendrite	Yes

Categories	Features	Examples
	Spines	No
	Other (e.g. contours)	Neocortical layers
Attributes*	Angles	Yes
	2D or 3D	3D
	Diameter resolution	0.2 μm–5.0 μm
Physical Integrity*	Axon	Moderate
	Dendrites	Complete