

Successes and Rewards in Sharing Digital Reconstructions of Neuronal Morphology

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Abstract The computer-assisted three-dimensional reconstruction of neuronal morphology is becoming an increasingly popular technique to quantify the arborization patterns of dendrites and axons. The resulting digital files are suitable for comprehensive morphometric analyses as well as for building anatomically realistic compartmental models of membrane biophysics and neuronal electrophysiology. The digital tracings acquired in a lab for a specific purpose can be often re-used by a different research group to address a completely unrelated scientific question, if the original investigators are willing to share the data. Since reconstructing neuronal morphology is a labor-intensive process, data sharing and re-analysis is particularly advantageous for the neuroscience and biomedical communities. Here we present numerous cases of “success stories” in which digital reconstructions of neuronal morphology were shared and re-used, leading to additional, independent discoveries and publications, and thus amplifying the impact of the “source” study for which the data set was first collected. In particular, we overview four main applications of this kind of data: comparative morphometric analyses, statistical estimation of potential synaptic connectivity, morphologically accurate electrophysiological simulations, and computational models of neuronal shape and development.

Keywords Neuronal morphology · Digital reconstructions · Electrophysiological simulations

Introduction

In digital reconstructions of neuronal morphology, dendrites and/or axons are semi-manually traced with the aid of a computer interface (e.g. mouse and monitor overlay) from a microscope feed or a previously acquired image stack. In this process, visual volumetric information (a set of three-dimensional voxels, each with an intensity value) is reduced to an ordered set of vectors and respective diameters and links, representing the arbor as interconnected cylinders or truncated cones (reviewed in Ascoli 2006). This technique, exemplified by the popular NeuroLucida system (<http://www.microbrightfield.com>), is gaining widespread adoption. Neurons are often reconstructed during intracellular electrophysiological recordings to identify the morphological phenotype. Researchers also reconstruct neurons in the course of pharmacological, developmental, behavioral, or genetic manipulations to characterize the structural consequences of specific experimental conditions.

Dendritic and axonal digital reconstructions can be directly employed to extract a nearly unlimited number of morphometric measures and to implement anatomically realistic computational models of neuronal electrophysiology based on compartmental simulations of membrane biophysics. Therefore, they constitute a useful format in the investigation of the structure–activity relationship in single neurons. Moreover, vector-based representations are much more compact to store and exchange than the corresponding raw microscopic images. This versatility implies that neurons reconstructed in one lab for a given purpose (for example, to investigate dendritic pruning and retraction during aging) can be also used by other investigators with a different aim (e.g., to examine the influence of branching symmetry on spike back-propagation by compartmental modeling).

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Although computer-assisted neuronal reconstruction systems are becoming increasingly automated, the process is still fairly labor-intensive, thus emphasizing even more the positive impact of digital morphology sharing and re-use. However, not all neuroscientists are yet aware of the importance and potential of these data files. This issue regards both data owners, who may not be willing to invest any additional effort to make their reconstructions available to others without a reason or benefit for science, and prospective users, who might not realize the value of incorporating available morphologies in their own investigations. This mini-review addresses both stakeholding parties by presenting several success stories of sharing and re-use in digital reconstructions of neuronal morphology. Virtually all data overviewed here are publicly available for download at <http://www.NeuroMorpho.Org>, a centrally curated repository of more than 1,000 cells from a wide variety of animal species, brain regions, and morphological classes (Ascoli 2006).

The presented use cases are far from a comprehensive coverage of the peer-reviewed literature and/or ongoing projects. Instead, they represent selected examples (biased towards, but not limited to, the author's direct experience) in each of four main areas of application: comparative morphometric analyses, statistical estimation of potential synaptic connectivity, morphologically accurate electrophysiological simulations, and computational models of neuronal shape and development. This brief outline focuses on studies in which the application of shared reconstructions was independent of the original project for which the data were first acquired, involving independent labs, addressing different scientific questions, and leading to distinct peer-reviewed publications.

Comparative Morphometric Analyses

A straightforward application of shared digital neuronal reconstructions is the comparative morphometric analysis of previous, different, independent, or combined data sets. For example, Costa and Velte (1999) used a large collection of ganglion cells from the salamander retina already reconstructed and characterized by a separate lab (Toris et al. 1995) to develop an automated classification method based on morphometric cluster analysis. Interestingly, sharing these data did not prevent the original owners from pursuing their own later reanalysis, when they investigated the influence of dendritic architecture on signal propagation in these cells by compartmental models (Fohlmeister and Miller 1997). The scripts for these simulations are also publicly shared on ModelDB (<http://senselab.yale.med.edu>).

In several cases, the whole body of shared data from multiple studies is greater than the sum of the individual

components. A large repository of hippocampal neurons has been available for nearly a decade in the so-known "Southampton Archive," constituting one of the earlier and bolder efforts to foster data sharing in cellular neuroscience. It pools data from several studies on CA3 and CA1 pyramidal cells, dentate granule cells, and interneurons, by two laboratories (Pyapali and Turner 1994, 1996; Turner et al. 1995; Mott et al. 1997). A third group, collaborating with one of the original data owners, mined these collections in a statistical analysis (technically similar to the approach employed in the previous example) to demonstrate that dendrites of classes of hippocampal neurons differ in structural complexity and branching patterns (Cannon et al. 1999). Once again, the original owners also went back to the data sets after making them available, and produced a meta-comparison between in vivo and in vitro techniques (Pyapali et al. 1998).

In a logical and technical extension of this study, Scorcioni et al. (2004) paired all CA3 and CA1 pyramidal cells from the Southampton Archive with cells of the same type and regions from several other labs and experimental preparations (Ishizuka et al. 1995; Henze et al. 1996; Carnevale et al. 1997; Megias et al. 2001). The goal was to assess the differences between anatomical classes and reconstructing laboratories across a large number of morphometric parameters, including the most common neuroanatomical measurements. As expected, several parameters differed significantly between CA3 and CA1, but approximately the same number of parameters was also found that discriminated among cells within the same morphological class, but reconstructed in different labs. These inter-laboratory differences far outweighed the differences between experimental conditions within a single lab, such as aging or preparation method. Interestingly, the sets of morphometrics separating anatomical regions and reconstructing laboratories were almost entirely non-overlapping, and corresponded respectively to global quantities (e.g. branch order and Sholl distance) and local variables (e.g. branch diameter and bifurcation angles). Compartmental models of electrophysiological activity showed that both differences between anatomical classes and reconstructing laboratories could dramatically affect the simulated firing rate of these neurons under different experimental conditions. A conceptually similar investigation, limited to CA1 pyramidal cells and including one additional data set (Bannister and Larkman 1995) independently confirmed these conclusions (Ambros-Ingerson and Holmes 2005).

A final success story in comparative morphometry consists of the discovery of morphological homeostasis in cortical dendrites entirely based on reanalysis of shared digital reconstructions (Samsonovich and Ascoli 2006). An initial examination of hippocampal pyramidal cells from the data sets described above showed that the dimension of

cortical dendrites exhibits significantly higher stability than if individual trees and their parts developed independently. In particular, if a part of a neuron (e.g. a subtree) randomly happens to be bigger (or smaller) than expected based on the population average, other parts of the same neuron systematically compensate in the opposite direction. This is contrary to what one would anticipate if size were genetically and/or environmentally regulated (e.g. people with big hands tend to have big feet). Instead, it suggests the action of direct intracellular competition for resources. The results are statistically robust across scales (from whole arborizations to individual branches) and size measures (bifurcation count, length, membrane area, dendritic volume). The availability of additional shared data sets allowed the extension of these findings from pyramidal to granule cells (Rihn and Claiborne 1990), rat to monkey, and hippocampus to prefrontal cortex (Duan et al. 2003).

Potential Synaptic Connectivity

As a particular usage case of morphometric analysis, shared digital reconstructions have been often adopted as testbeds to develop new measures and approaches. In a recent example, Costa and Manoel (2003) employed the retinal ganglion cells mentioned above (Toris et al. 1995) as well as motoneurons generated in a separate computational study (Ascoli et al. 2001) to introduce, define, and assess the potential of the concept of critical percolation to characterize, classify, and quantify neuronal morphology with respect to its effect on network connectivity. An earlier and more direct effort to estimate circuit connectivity from neuritic structure was introduced for the cricket nervous system (Jacobs and Theunissen 1996). More recently, a complete mathematical framework was developed directly linking digital reconstructions of dendritic and axonal morphologies with the probability of establishing a synaptic contact, starting with data from the rat somatosensory cortex (Kalisman et al. 2003; Chklovskii 2004).

The fundamental idea in this type of application is that a spatial overlap between the axonal and dendritic arborizations is a necessary condition for inter-neuronal communication. In particular, the branch of a dendrite must fall within the distance of a “spine length” (or shaft diameter) from an axon. On the one hand, positive synapse identification requires ultrastructural analysis by electron microscopy. On the other, in plastic cerebral regions, spines can twitch in and out and synapses can be formed and pruned within minutes. Thus, axo-dendritic apposition is sufficient to determine the *potential* for the presence of a synapse. The concept of “potential synaptic connectivity” is directly linked to the assessment of network memory capacity, or the number of independent states that it can represent (Stepanyants et al.

2002). Thus, the derivation of this information from digital morphologies constitutes a particularly exciting step in understanding neural computation.

This development has recently led to several successful collaborations between theoretical and experimental neuroscientists. Stepanyants et al. (2004) compared the calculated density of potential synapses within a cortical column with the number of contacts between the corresponding reconstructed cells verified by paired intracellular recordings, and demonstrated selective discrimination between excitatory and inhibitory circuitry. A similar approach was used to determine the layer-specificity of thalamocortical connections in the rodent barrel complex (Shepherd et al. 2005). Most recently, this technique allowed the probabilistic characterization of local potential connectivity in the cat primary visual cortex (Stepanyants et al. 2007).

The recent simplified formulation for computing the statistics of axo-dendritic connectivity from 3D reconstructions, which discretizes the exact integral derivation into a computationally inexpensive expression (Stepanyants and Chklovskii 2005) opens new avenues to create cellular-level atlases of neural circuits. In digital morphologies reconstructed from intracellular staining, the somatic location is often known relative to standard anatomical references (e.g. bregma and lambda for in vivo recordings) or histological boundaries (typically visible in vitro). In regions with fairly stereotypical neuronal orientation (such as the cerebellum, neocortex, and hippocampus), this allows in practice the construction of a long-range connectivity map if the corresponding 3D reconstructions are available. This exciting idea was recently demonstrated for the fly olfactory system (Jefferis et al. 2007), and as a proof of principle for the rat dentate gyrus (Scorcioni et al. 2002).

Anatomically Accurate Electrophysiological Simulations

Perhaps topping the usage of shared digital reconstructions of neuronal morphologies is their application to implement compartmental simulations of neuronal electrophysiology. In these cases, the vector based representation of dendritic (or axonal) arbors is divided in sufficiently small sections to be considered isopotential (i.e., with a negligible voltage gradient between the two ends). This format is suitable for the numerical solution of active (Hodgkin–Huxley) channel dynamics on top of passive membranes (cable equation). In one of the first such treatments, De Schutter and Bower (1994) implemented a complex model of cerebellar Purkinje cell biophysics based on morphologies reconstructed by Rapp et al. (1994). These simulations, which led to a number of testable hypotheses, remain among the most successful, cited, and re-used/updated in computational neuroscience.

All popular simulation environments in computational neuroscience now enable the direct incorporation of neuronal reconstructions, and all shared morphological files available at <http://www.NeuroMorpho.Org> can be downloaded in simulation-ready format. The number of peer-reviewed publications based on this type of application is far too great to be reviewed comprehensively, and range from computational models of sub-threshold synaptic integration to simulations of the structure–activity relationship in spiking and bursting cells. Here we only offer selected examples from the more seminal or recent literature. A much more extensive (though still not complete) coverage is provided by the bibliographies maintained by the simulators NEURON (<http://www.neuron.yale.edu/neuron/bib/usednmr.html>) and GENESIS (<http://www.genesis-sim.org/GENESIS/pubs.html>).

Two logical applications of digital reconstructions to compartmental models are the investigations of the influence of dendritic morphology (from local branching to whole arborizations) on neuronal electrophysiology (e.g. firing rate and regularity), and of the interaction of dendritic structure and membrane biophysics in shaping neural computation (e.g. non-linear summation, coincidence detection, etc.). In both cases, the use of the same simulation parameters with different reconstructions enables a realistically controlled condition to tease out the net functional effect of neuronal morphology. A landmark and often referenced example showed that one and the same biophysical model and stimulation condition, applied to various types of cortical cells (layer 2 and layer 3 pyramidal, stellate, etc.) could result in a variety of firing patterns covering the wide range typical of those morphological classes (Mainen and Sejnowski 1996). A similar approach demonstrated that, even within a single neuronal family (CA3 pyramidal cells), the natural morphological variability was sufficient to educe the whole span of observed electrophysiological behaviors, from low- and high-frequency spiking to irregular firing and bursting (Krichmar et al. 2002).

The previous examples used simulated somatic current injection to elicit spike trains. A complementary goal is to investigate the morphological modulation of dendritic back- and forward-propagation of single action potentials. These characteristics are heavily affected by the level of membrane excitability, expressed e.g. as a ratio between the densities of voltage-dependent sodium and potassium conductances. Different morphological classes (from dentate granule to cerebellar Purkinje cells) were shown to require vastly different ratios to obtain the same behavior (Vetter et al. 2001). The individual (sub-)trees of certain dendritic arbors are considerably independent of each other, such as in the case of the oblique branches stemming from the apical tuft of CA1 pyramidal cells. Using a collection of 3D reconstructions from several sources and experimental protocols (e.g. Ishizuka et al. 1995; Pyapali et al. 1998), Migliore et al.

(2005) investigated oblique signal propagation ortho- and anti-dromically. The two conditions were found to be differentially controlled by the local branch diameter mismatch and the distribution of active potassium channels, respectively. Moreover, in an intriguing interplay, the potassium conductance in the oblique dendrites modulated spike conduction in the main shaft.

Several comparisons of shared neuronal reconstructions from various archives showed that simulated electrophysiological behavior can vary considerably in compartmental models using different anatomical sources (Scorcioni et al. 2004; Szilagy and De Schutter 2004; Ambros-Ingerson and Holmes 2005). On the one hand, this fact implies that particular attention should be exercised when fitting experimental data to models (Holmes et al. 2006), an issue also related to the effect of reconstruction errors (Jaeger 2000). On the other hand, it suggests the need to verify the robustness and generality of the conclusions derived from computational simulations by using several available digital reconstructions for a given neuronal type. For instance, in relating the frequency of synaptic inputs to the resulting spiking output, use of a sufficiently large number of individual morphologies enables the establishment of the standard deviation, in addition to the mean, of the observed phenomena (Li and Ascoli 2006).

Shape and Developmental Models

A different family of computational models tackles the simulation of neuronal structure itself. Some approaches aim at quantitatively describing the adult structure, independent of the underlying developmental mechanisms, whereas others address the dynamics of the growth process directly (Ascoli 2002). Digital reconstructions of neuronal morphology constitute fundamental data for all these models, as they provide rich sources of experimental measures to constrain the simulation parameters and/or validate the results. Here we only offer selected examples of this application, without providing a truly representative coverage of the available literature (for a more comprehensive review, see Donohue and Ascoli 2005a).

In an early effort to model the reconstructed morphology of cat spinal motoneurons (from Cullheim et al. 1987); Burke et al. (1992) developed a parsimonious algorithm based on a local rule of extension, bifurcation, or termination on the basis of branch diameter. This approach was also applied to the description of Purkinje cells and further compared to a different simulation scheme in which subsequent phases of branch attachment were implemented in parallel over an entire population of cells (Ascoli et al. 2001). A simplified version of the diameter-based strategy was later extended to CA1 pyramidal cells, with different

success for separate dendritic regions: tree size was better captured in basal than in apical trees, but the opposite held for topological asymmetry (Donohue and Ascoli 2005b).

An alternative model of dendritic morphology makes the virtual growth behavior dependent on path distance from the soma instead of on diameter. As in the previous examples, the stochastic implementation of this function can be statistically constrained by distributions extracted from experimental data. Such an approach was applied to all principal cells of the rat hippocampus (Samsonovich and Ascoli 2005a, b). Interestingly, the model succeeded in capturing the essential morphological features of granule cells, the basal dendrites of CA3 and CA1 pyramidal cells, and the CA3 apical trees, but initially failed on the CA1 apical arbors. However, even this dendritic class was successfully simulated when a portion of the subtrees, corresponding to the oblique branches, was described based on the distance from the main trunk rather than from the soma. This finding provided support for the previously hypothesized mechanism of interstitial branching (as opposed to terminal growth cone splitting), while at the same time allowing an estimate of the proportion of branches following each of the two developmental processes.

An opposite strategy consists of optimizing the algorithmic parameters to maximize the fit of the resulting structures to the digital reconstructions. One such example was applied to neocortical pyramidal cells (Schaefer et al. 2003), but the general idea was previously developed in an extensive family of models by Van Pelt et al. (reviewed in Van Ooyen and Van Pelt 2002). Their successive implementations included both interstitial and terminal branching as well as dependencies of bifurcating probability on branch order and tree size, yielding a realistic correspondence between simulated age and known developmental stages. Another approach of this type recently assumed non-parametric estimates of uni- and multi-variate probability densities, independent of dendritic location, to simulate the morphology of lamina II/III interneurons of the spinal dorsal horn (from Olave et al. 2002) based again on local dendritic diameter (Lindsay et al. 2007).

The models described so far in this section are limited to specific aspects of neuronal morphology, namely the branching patterns, lengths, and diameters. These properties characterize the so-called dendrogram, and are necessary and sufficient for compartmental electrophysiological simulations. A complementary set of features regards the three-dimensional embedding of dendrograms, i.e. the spatial orientation and meandering of each branch. These characteristics give rise to the familiar appearance of individual neurons, and underlie potential network connectivity. Despite its apparent complexity, the 3D arrangement of hippocampal dendrites can be reproduced by a surprisingly simple two-parameter model (Samsonovich and Ascoli 2003). In particular, the tendency

to grow radially away from the soma (measured relative to the “null-hypothesis” of straight elongation) and a random deflection angle, extracted by Bayesian analysis from each morphological class, are enough to generate accurate and realistic basal, apical, and granule arborizations.

The above study demonstrated that no additional propensity to grow in a constant, “external” direction beyond the initial stem orientation is necessary to reproduce the observed neuronal polarity in the rat hippocampus. Moreover, it suggested testable developmental hypothesis to explain the apparent (and quantified) phenomenon of somato-dendritic repulsion. An analogous approach was recently reported, with similar findings, on spinal motoneurons (Marks and Burke 2007). A complementary proposal relied instead on diffusion-limited aggregation process to model the 3D shapes of several morphological classes by tuning the available spatial extent (external boundaries), the concentration of virtual neurotrophins, and the rate of pruning (Luczak 2006).

Concluding Remarks

This sparse overview of success stories in re-using digital neuronal morphology illustrates the versatility of this kind of data, and thus the potential long-term scientific benefit of making 3D reconstructions publicly available. The general topic of data sharing has been stirring considerable debate in neuroscience (Koslow 2000, 2002). Scientific data should be exploited for all their worth in the pursuit of biomedical advancement, transcending perceived ownership by labs or investigators (Gardner et al. 2003; Insel et al. 2003). At the same time, relative to mainstream bioinformatics, neuroscience data present heterogeneous challenges, such as lack of standards, privacy protection, commercial interests, and complexity of annotation (Eckersley et al. 2003). From these standpoints, neuronal morphology represents an almost ideal case in which major benefits of sharing/reuse come at a comparatively minor costs to providers (Ascoli 2006). A relevant parallel can be drawn with microarrays (several neuroinformatics aspects of which are exposed in the Mini-Review by Wan and Pavlidis, in this issue). Microarray data sharing initially met considerable resistance (Geschwind 2001), but is now recognized to also benefit the original owners in addition to the end users (Piwowar et al. 2007).

Neuroanatomists sometime feel that the experimental data they acquired are only valid for the original scientific intent, and any application beyond that specific purpose constitutes an unwarranted stretch without adequate quality control. For example, neurons coarsely reconstructed to identify their morphological class (e.g. pyramidal vs. granule cell) may not be sufficiently accurate to investigate a sensitive outgrowth mechanism. Similarly, electrophysiological simu-

lations can safely disregard errors in the exact 3D position of branches, as long as diameter and length are precisely determined, whereas almost the opposite holds for the computation of potential synaptic connectivity. Nevertheless, new ideas, methods and techniques are developed continuously, and data owners should remain open to the possibility that novel and future usages may emerge which they had not previously imagined or expected.

The introduction of proposed metadata standards for digital reconstructions (Crook et al. 2007) may help data providers to clearly state the limits of their sets to facilitate informed usage. Ultimately, however, the responsibility of ensuring that any data is appropriate for its intended employment always belongs to the end user, never to the original provider. After all, authors are not held responsible for how their articles are cited by peers, and do not refrain from publishing in order to avoid being misrepresented or misunderstood. In conclusion, our warm recommendation regarding digital reconstructions of neuronal morphology is “share enthusiastically, use carefully.”

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