

Invited review

Shape, connectedness and dynamics in neuronal networks

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ABSTRACT

The morphology of neurons is directly related to several aspects of the nervous system, including its connectedness, health, development, evolution, dynamics and, ultimately, behavior. Such interplays of the neuronal morphology can be understood within the more general shape–function paradigm. The current article reviews, in an introductory way, some key issues regarding the role of neuronal morphology in the nervous system, with emphasis on works developed in the authors' group. The following topics are addressed: (a) characterization of neuronal shape; (b) stochastic synthesis of neurons and neuronal systems; (c) characterization of the connectivity of neuronal networks by using complex networks concepts; and (d) investigations of influences of neuronal shape on network dynamics. The presented concepts and methods are useful also for several other multiple object systems, such as protein–protein interaction, tissues, aggregates and polymers.

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1. Introduction

The shapes of diverse biological entities are intrinsically related to constraints imposed by the geometry of the embedding space, such as distances and adjacencies (Thompson, 1917; Bookstein, 1991; Small, 1996; Dryden and Mardia, 1998; Lestrel, 2000; da F. Costa and Cesar Jr., 2001). A *shape* can be simply understood as any spatially limited and connected object (da F. Costa and Cesar Jr., 2001). Systems of multiple interconnected shapes will be understood as *networks*. Combinations of molecules give rise to multiple object systems such as materials, combinations of cells yield

organs, while combinations of organs and tissues give rise to living beings. Therefore, shapes extend spatially along a wide interval of scales.

The brain contains an impressive number of neurons, whose morphology is highly specialized to make *selective* connections capable of ensuring proper behavior and survival. This means that neurons do not connect indiscriminately between themselves, but form an intricate system of short to long-range connections with specific targets (Kandel et al., 1995; Gallos et al., 2011). To any extent, the neuronal milieu is a nice example of how thin prolongations (i.e. dendrites and axons) of cells are required in order to overcome the adjacency constraints imposed by the three-dimensional space. At the same time, the specific shape of a neuron – including its complexity and size – also influences the chances of that cell receiving incoming connections. As a consequence of such intertwined effects, neuronal cells tend to have a most diverse and

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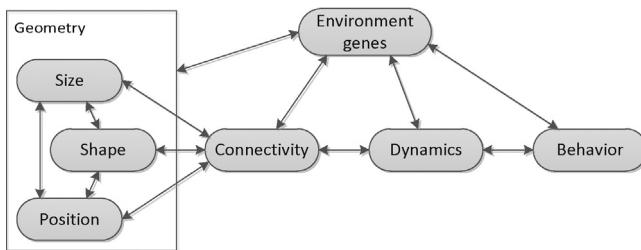


Fig. 1. The individual morphological features of neurons (including shape, size and position) may underlie the connectivity between such neurons and, subsequently, the overall dynamical properties of neuronal networks, which ultimately converges to the individual behavior. These influences are reciprocal, in the sense that the overall dynamics may also affect the connectivity and shape of the individual neurons. All these aspects are affected and affect the environment, which includes genes, stimuli, and other individuals.

specialized morphology, ranging from simple bipolar cells to highly elaborated Purkinje neurons.

The variety of neuronal morphology was understood by Ramon y Cajal, in the beginning of the 20th century, as being closely related to the complexity of human behavior and intelligence (Ramon y Cajal, 1989). Since then, several evidences about the relationship between neuronal shape and function have been unveiled, including the congruence between the electrophysiological (i.e. functional) and morphological classes of retinal ganglion cells (Boycott and Waessle, 1974) as well as the correlation between the structure of the receptive fields of those cells and the respective morphology (Peichl and Waessle, 1983). The mammalian brain therefore provides a most compelling illustration of a complex network whose dynamics is, to a great extent, related to the shapes of the individual components (da F. Costa, 1997, 2005b). Although complexity remains a somewhat elusive concept (Gell-Mann, 1995), the primate brain can be said to be characterized by different levels of complexity extending from the sophistication of the *shape* of its basic elements (i.e. the neuronal cells) to the complexity of the emerging *dynamics*, passing through the complexity of *connections* between such cells. As illustrated in Fig. 1, the geometrical properties of the individual neurons define their interconnectivity, which ultimately underlies a complex dynamics. At the same time, the activity of neurons is also known to influence the neuronal shape (Cuntz et al., 2010; Chklovskii, 2004). In this context it is worth mentioning the current efforts of two ambitious projects, named the human connectome (<http://www.humanconnectomeproject.org/>) and the blue brain project (<http://bluebrain.epfl.ch/>). The first aims at mapping the anatomical and functional connectivity between brain regions, while the second aims at reconstructing a synthetic brain taking into account all the levels of complexity explained above, an effort that if successful could represent a paradigm shift in neuroscience.

This article provides an overview of the important and relatively overlooked relationship between the shape and function of neuronal cells, with emphasis on developments from the author's group. The sections in this article address the main aspects depicted in Fig. 1.

2. Shape characterization

Given any shape, it is possible to map its morphological properties in terms of several measurements, which can be suitably represented as a *feature vector* (da F. Costa and Cesar Jr., 2001), namely a vector containing the measurements of the object under analysis. For instance, given the shape of a neuronal cell, it is possible to measure its volume, orientations of its processes (da F. Costa, 1995), its fractal dimension (da F. Costa and Velte, 1999; da F. Costa et al., 2002), lacunarity (Gefen et al., 1983; Mandelbrot, 1982; Allain

and Cloitre, 1991), wavelet features (da F. Costa et al., 1997; da F. Costa and Cesar Jr., 1998), Sholl's concentric spheres (Uylings et al., 1986), excluded volume and autocorrelations (da F. Costa et al., 2005a), as well as families of Minkowski shape functionals (Barbosa et al., 2003b), to name but a few among many other possibilities (Uylings and van Pelt, 2002; van Pelt and Uylings, 2007; Uylings et al., 1986). Several of the commonly used measurements can be easily calculated through the L-measure software (Scorcioni et al., 2008), which accepts as an input a neuronal shape, described by a.swc file (Cannon et al., 1998), and outputs many shape descriptors of interest.

Given such a plurality of alternatives to quantify shape, a fundamental question arises: what is the best set of measurements? The answer should take into account the purpose of the measurements. For instance, in case we are interested in quantifying the overall cell metabolism, a potentially useful measurement would be the total volume of the cell (Karbowski, 2007).

Two particularly relevant situations in neuromorphology concern the choice of measurements capable of: (a) distinguishing between neuronal cell classes (such as in diagnosis) and (b) provide a comprehensive representation of the cell geometry, in the sense that the cell shape could be statistically recovered (e.g., the only information we have is the number of branches) or even exactly recovered (e.g., we know the coordinates of all neuronal segments). However, even if the objectives are clearly stated in each of these cases, the choice of the optimal set of morphological features also has to take into account the specific types of neurons under analysis. For example, in case one wants to separate large from small cells, it may be enough to consider the *diameter* of the cells, namely the largest distance between any pair of points in the dendritic arbor of the cell. Yet, there are some properties of measurements which are generally desirable in both situations (a) and (b) mentioned above, especially invariance to translation and rotation. These properties are found in several features such as area, perimeter, curvature, among others (da F. Costa and Cesar Jr., 2001), and are important because often the shapes can appear translated and rotated and we do not want the measurement to be influenced by such transformations. Another relevant issue to be kept in mind is that the set of features should be kept minimal.

The measurements obtained for the neurons can be used for the purpose of shape discrimination or geometrical pattern recognition (see, for instance, Duda et al., 2001; da F. Costa and Cesar Jr., 2001). This task consists in, given one or more shapes, to organize them into classes such that an object inside each class tends to be more similar to other objects in that same class than to objects from the other classes. Note that we may or may not know the number of classes, and examples of objects from each class may be available or not. In case we do have examples of objects from all the classes, or information about the properties of those objects, we say we have a *supervised* pattern recognition problem; otherwise, it becomes an *unsupervised* pattern recognition (also called clustering) case (Duda et al., 2001; da F. Costa and Cesar Jr., 2001). Needless to say, the first type of problem is generally easier to be solved than the second type. An interesting problem in neuromorphology is to find subgroups inside known neuronal types, a problem that involves supervised classification followed by clustering.

There is also the case where the interest is in identifying the *archetypes* and *outliers* of a given neuron class or group (Zawadzki et al., 2012). By doing so, it is possible to find which shape characteristics are typical of the studied class, allowing the representation of the entire class by a few selected features. At the same time, the outlier cells can provide information that helps detecting eventual artifacts in the data acquisition process (e.g., microscope calibration) and even uncover morphological anomalies caused by diseases. Also, the same technique used in the archetype/outlier detection provides the means to estimate the possible shapes that

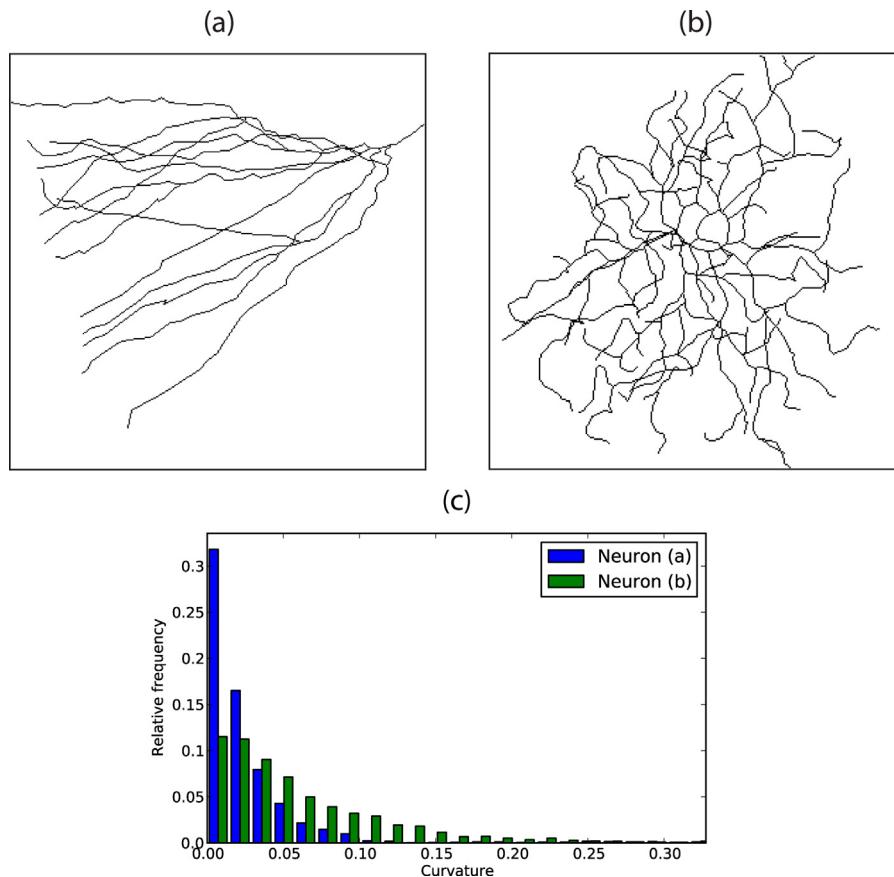


Fig. 2. Example of two neurons showing distinct values of curvature. (a) The dendrites are nearly straight segments. (b) The dendrites are curved. (c) Histogram of the curvature values obtained for each pixel of the two neurons. It is clear that the neuron shown in panel (b) has larger overall curvature. The files describing these neurons were obtained from the Neuromorpho repository (Ascoli et al., 2007).

a neuron can acquire, and compare them to those that occurs in nature (da F. Costa et al., 2010).

Unfortunately, the choice of features for pattern recognition is still largely subjective, in the sense that there are no definite guiding rules. The problem is further complicated by the fact that a larger number of measurements do not necessarily lead to better discrimination (da F. Costa and Cesar Jr., 2001). In practice, one has to rely on previous experiences, as well as with the intrinsic and distinguishing properties of each of the several available features.

There are several ways to represent the morphology of neurons, including: (i) its bitmap image; (ii) its contour extracted as a list; (iii) hierarchical descriptions such as those used in the swc format (Cannon et al., 1998). Each of these formats is potentially more suitable for obtaining specific types of measurements. For instance, the fractal dimension and lacunarity can be more easily obtained from the bitmap representation, while the curvature and angles of the processes can be derived more directly from the contour representation. One problem with the latter type of format is the crossings between processes that often appear in 2D images (projections). The problem of obtaining contour descriptions in such cases has been addressed by using several heuristics, such as good continuation of tangent (Leandro et al., 2009).

The remainder of this section presents some remarks about more comprehensive shape measurements and their specific interpretation and characteristics. We note that throughout the paper we will consider the neuron as a 2D structure, but most characterizations presented here have a straightforward extension to the 3D case.

Hierarchical angles and lengths: Provided a shape can be organized along hierarchical levels, namely as a branching pattern, an

interesting set of measurements can be obtained by taking into account the angles and arc lengths of the subsequent constituent segments (Coelho and da F. Costa, 1997; da F. Costa and Coelho, 2002). Hierarchical decomposition, which is more viable for the analysis of branching patterns, can be obtained by applying skeletonization approaches as discussed in da F. Costa (1999), da F. Costa and Estrozi (1999), da F. Costa et al. (2000), Falcão et al. (2002), da F. Costa (2000), da F. Costa et al. (2003d), Chen et al. (2005) or by curvature-based methods as described in da F. Costa and Cesar Jr. (1999). In the case of neuronal cells or shapes that have a body, it is important to detect such a body (Chen et al., 2005) in order to have the correct identification of the beginning of each type of processes (i.e. a dendrite or an axon).

Curvature: Quantifying the rate of change of the tangent angle along a given curve, the curvature provides invariance to translation and rotation and is complete (i.e. invertible) up to such transformations. The identification of high curvature points provides valuable resources for identifying the extremities of shapes (da F. Costa, 1995; da F. Costa and Cesar Jr., 1999). An effective approach to numerical curvature estimation has been described (Cesar Jr. and da F. Costa, 1996, 1997; da F. Costa and Cesar Jr., 1999, 2001; da F. Costa and Velte, 1999; da F. Costa et al., 2003c) which estimates the shape derivatives required for curvature calculation by using the derivative property of the Fourier transform, combined with Gaussian regularization (i.e. low-pass filtering). The histogram of curvatures of a shape, as well as its respective statistical moments, may also provide valuable information for shape characterization and discrimination. In Fig. 2 we give an example of the potential of using curvature to distinguish between two shapes.

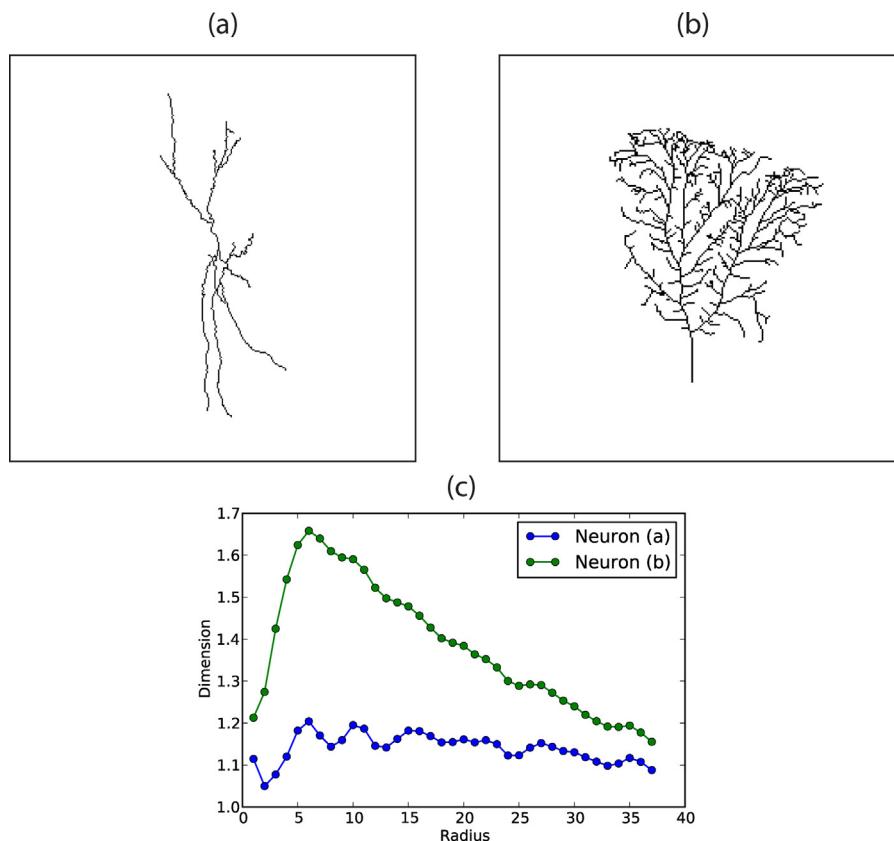


Fig. 3. Example of multiscale fractal dimension curves for two neurons. (a) The neuron shape is mostly elongated in one direction. (b) The dendrites cover a good portion of the 2D plane in all directions. This means that the fractal dimension of (b) is much closer to two than in case (a). In panel (c) we show the curves obtained for the two neurons, where radius is the scale being considered to calculate the dimension (see text for explanation). It is common to define the typical dimension of the shape as the maximum of this curve. The files describing these neurons were obtained from the Neuromorpho repository (Ascoli et al., 2007).

Bending energy: Given a two-dimensional shape, its bending energy can be shown to be proportional to the sum of the squared curvature values (Young et al., 1974; Bowie and Young, 1977). Therefore, the more intricate a shape is, the higher its bending energy. The bending energy has been used with encouraging success for classification of neuronal cells (Cesar Jr. and da F. Costa, 1997).

Fractal dimension: The several available definitions of fractal dimension (Falconer, 2003) provide an interesting alternative for quantifying the ‘complexity’, spatial distribution or spatial coverage of a given shape (see, for instance, da F. Costa and Cesar Jr., 2001; da F. Costa et al., 2002). For example, if we draw a line in a 2D space, the line will have a dimension of 1, but if we fold this line many times, so as to create a plane, the shape will be 2-dimensional. Anything that is in the middle of these two extreme cases has a dimension between 1 and 2. However, depending on the scale that we look at the shape, we can obtain different values for the dimension. If we look very closely to any point in the contour of an object, or in our case to any point of a dendrite, we will arrive at the conclusion that we are looking at a line, because locally any curve looks like a line. This is the motivation for the definition of the multiscale fractal dimension (e.g., da F. Costa and Cesar Jr., 2001), where a typical dimension is defined for each scale that we look at the shape. In Fig. 3 we give an example of a multiscale fractal curve of two neurons.

Lacunarity: Introduced in order to complement the fractal dimension (Gefen et al., 1983; Mandelbrot, 1982; Allain and Cloitre, 1991), the lacunarity quantifies the degree of translational invariance of a shape. Typically, the higher the lacunarity, the less translational invariant the shape is (see Fig. 4). The traditional way to calculate the lacunarity involves sliding a window along

the whole image while estimating the mass comprised by the window. Several sizes of windows are usually considered, yielding the lacunarity as function of the windows size. This window plays the same role as the observed scale in the fractal dimension, which means that for a very small window we simply have the lacunarity of a line segment. A recent study (Rodrigues et al., 2005) has shown that translational and rotational invariance can be achieved by using circular windows centered only at the object points, not indiscriminately throughout the whole embedding space.

Minkowski functionals: As implied in the name, shape functionals are maps from a given shape to scalar values. Minkowski functionals are a special class of functionals which are additive, motion invariant and continuous (de Raedt et al., 2000; Michielisen and de Raedt, 2001; Mecke, 1998). In the plane, such functionals comprise the perimeter, area and Euler number, corresponding to the number of holes in the object under analysis. Minkowski functionals have been successfully applied to the characterization of neuronal shape (Barbosa et al., 2003a,b).

Critical percolation densities: Given a shape and an empty embedding space, the progressive superposition of this shape at uniformly distributed random positions along the space eventually leads to percolation, which can be identified by looking for a cluster of shapes extending from side to side of the embedding space (da F. Costa and Monteiro, 2003). The average density of shapes observed when percolation occurs is called the critical percolation density. This feature has been suggested (da F. Costa and Monteiro, 2003) as one of the most direct measurements of the capacity of an axon arbor to establish new connections, or of a dendritic arbor to receive new connections. Interesting previous investigations of percolation in neuronal systems, where the neuronal shape was simplified as circles, have been reported in van Ooyen et al. (1995).

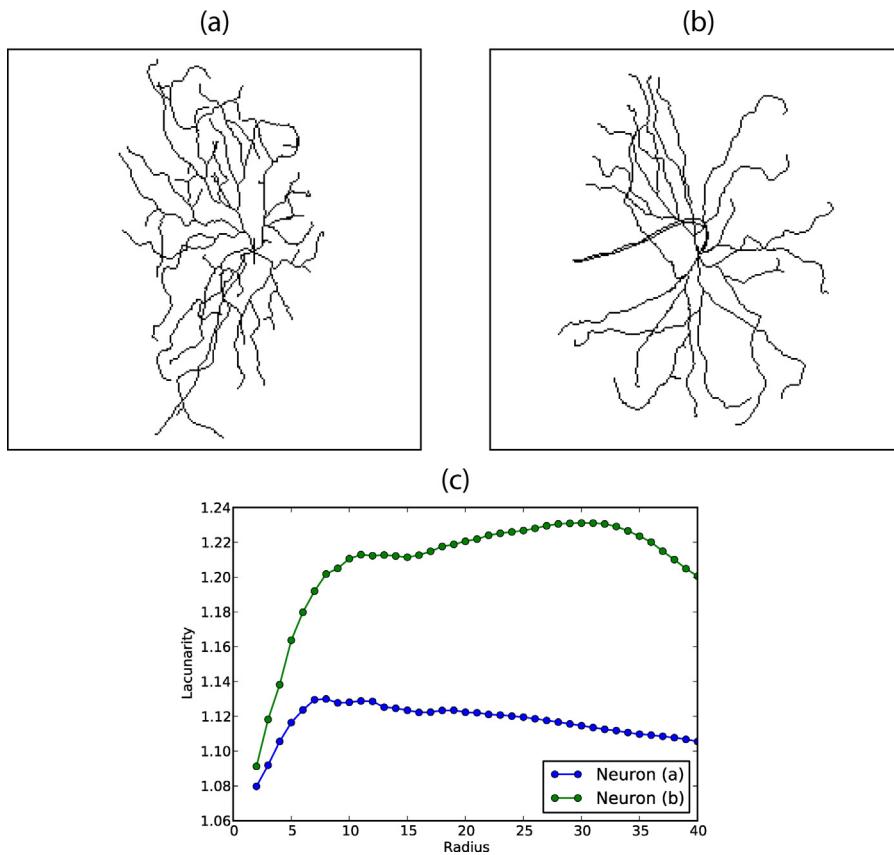


Fig. 4. Example of neurons showing different lacunarity values. (a) There are big empty spaces in the dendritic arborization. (b) Empty spaces are well distributed along the shape. Thus, the lacunarity of (a) is smaller than (b). In panel (c) we show the multiscale lacunarity obtained for the two neurons. The radius is related to the scale at which the lacunarity is being calculated. The files describing these neurons were obtained from the Neuromorpho repository (Ascoli et al., 2007).

The critical percolation density can also be estimated for ballistic deposition, as investigated in da Silva et al. (2005). In the case the shapes change with time, as is the case with growing neurons, it is possible to define a critical percolation density which is a direct consequence of the growth dynamics and spatial distribution of the cells (da F. Costa and Coelho, 2005). In the case of a collection of not necessarily connected and static objects, it is still possible to force percolation through some imposed growth dynamics, such as parallel dilation (da F. Costa, 2004a, 2005a; da F. Costa et al., 2005b). In Section 5 we give an example of percolation density calculation for four real neurons.

3. Stochastic shape modeling and synthesis

In this section we discuss the problem of how to computationally synthesize artificial instances of neuronal shapes of a given category. For instance, one may be interested in obtaining a collection of neuronal cells which are statistically equivalent to those of a certain biological class (e.g. alpha cat retinal ganglion cells). By *statistical equivalence* we mean that the synthesized cells will yield the same statistical distribution of values of geometrical measurements as those considered as reference. Two important situations arise: (i) the original shapes evolve without influences from the environment and (ii) the shapes are affected by the environment. The problem of stochastic shape synthesis in these two situations is discussed in the following subsections.

3.1. Absence of environmental influences

In this case, the shapes are the result of a growing dynamics which takes into account only internal constraints imposed by

the physics/biology of the object (e.g. its genes or molecular differentiation). In the following we illustrate this kind of strategy with respect to the simulation of neuronal outgrowth (Coelho and da F. Costa, 1997; da F. Costa and Coelho, 2002). Other approaches include the stochastic evolution of the growth cone (Koene et al., 2009; Pelt et al., 2001), methods adopting differential equations to model cytoskeleton outgrowth (Hentschel and Fine, 1994; Hentschel et al., 1998; da F. Costa et al., 2003b; Bianchi et al., 2001), methods based on Hillman's (Hillman, 1979) set of quantitative anatomical correlations (Ascoli and Krichmar, 2000; Ascoli et al., 2001), activity and competition during process outgrowth (van Ooyen et al., 1995, 2001; van Ooyen and Willshaw, 1999; Graham and van Ooyen, 2004), L-systems (Lindenmayer, 1968; Hamilton, 1993), as well as hidden Markov models (Samsonovich and Ascoli, 2005).

Although our discussion is limited to 2D neuronal shapes (several neuronal types, such as retinal ganglion cells, are largely planar), the extension to 3D is immediate. The image of the neuronal cell can then be processed in order to identify the points belonging to the cell and the points belonging to the background. The contour of such cells is particularly important and can be obtained by using edge detection and contour following algorithms (da F. Costa and Cesar Jr., 2001). The particularly important points of the neuronal ramification, namely the extremity and branching points, can be obtained by applying a curvature-based procedure (Cesar Jr. and da F. Costa, 1995; da F. Costa and Cesar Jr., 1999) or skeletonization algorithms (da F. Costa et al., 2000; da F. Costa and Cesar Jr., 2001).

The angles and arc lengths along each segment along the hierarchies of the ramifications can then be obtained by applying simple analytical geometry concepts and methods, so that conditional probability densities of the angles and lengths can be inferred.

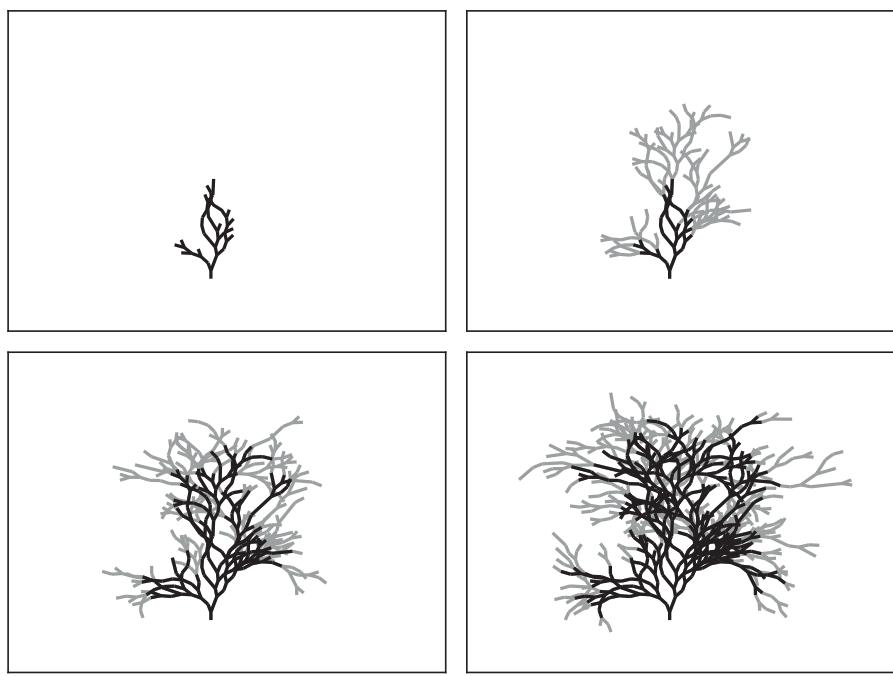


Fig. 5. An example of artificial neuronal growth. Given a single initial segment, a bifurcation is placed at one end of the segment. The angle of the bifurcation and the lengths of the segments are chosen according to distribution functions that are similar to the ones observed for real neurons. Then, for the two generated segments the process is repeated and two new bifurcations are generated. This continues until a desired number of segments is reached. Each new segment has a fixed probability of being deleted before going through a bifurcation.

As discussed in the previous section, such measurements provide an inherently suitable characterization of the neuronal geometry. Finally, the conditional densities can be sampled by using the Monte Carlo method (Newman, 1999) in order to produce a virtually infinite number of synthetic cells whose geometrical features will have statistical densities equivalent to the original cells used as prototypes.

In Fig. 5 we present 4 growth steps of a neuron created with such a procedure. In order to create the neuron, we sample the bifurcation angles and segment lengths from a Gaussian and a power distribution, respectively. The parameters of both distributions are chosen according to the measured values of a large set of real neurons. Additionally, each segment has a probability of being deleted before generating a bifurcation. It was shown that

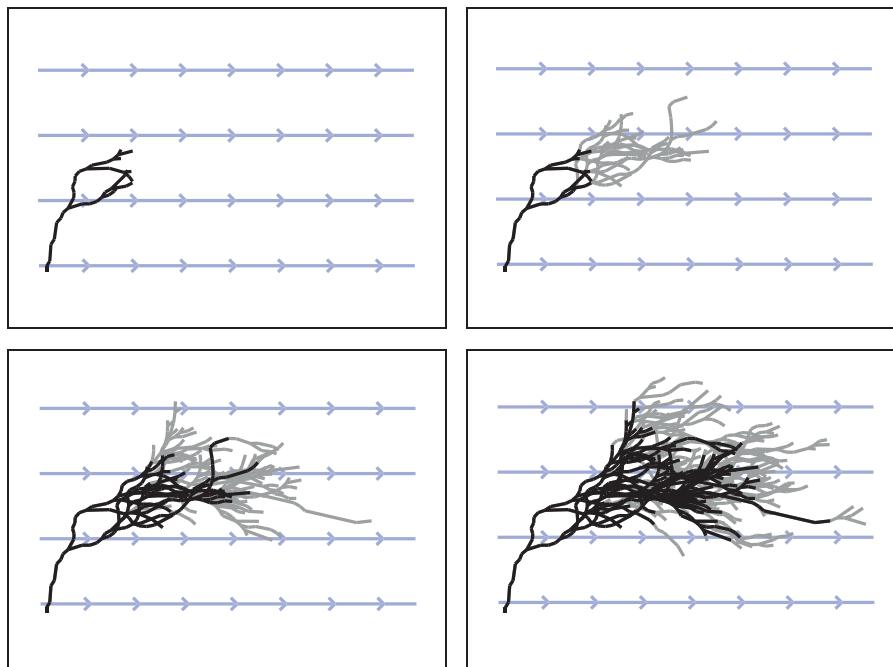


Fig. 6. An example of an artificial neuron growing in the presence of an external field, here represented by the arrows. The dendrites tend to follow the direction of the field. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

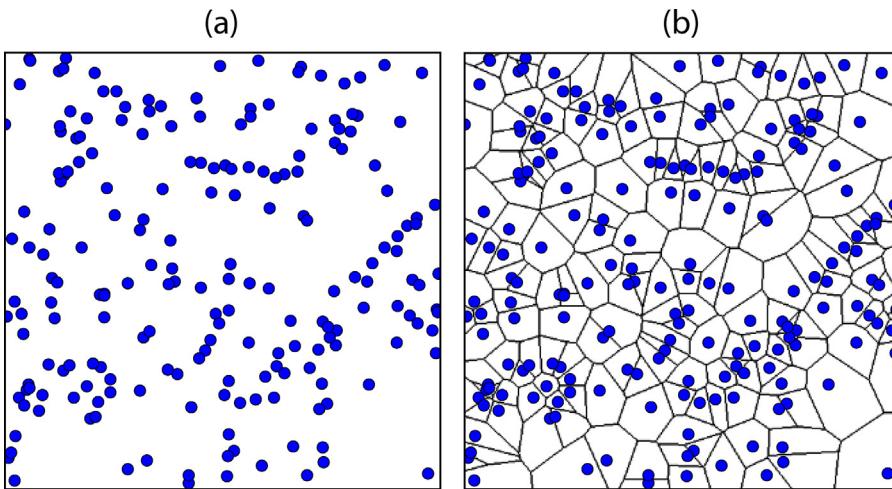


Fig. 7. Example of Voronoi tessellation. (a) Points randomly distributed in an embedding space. (b) The respective boundaries of the Voronoi cells for each point.

such procedure can generate neurons with many features having distributions close to the real cases (da F. Costa et al., 2010).

3.2. Presence of environmental influences

The more realistic situation of shapes developing under environmental influences requires a modeling approach capable of integrating *both* internal and external influences, because the former are always present in physical and biological systems. Often, external influences manifest themselves in terms of *fields* or *waves*. For instance, the growth cones (namely the tips of growing axons) are known to follow gradient fields derived from neurotrophic growth factors, ionic concentrations, electric, and even gravitational fields (Berg, 1984; McCaig and Rajnicek, 1991; Dowell-Mesfin et al., 2004). Therefore, it is reasonable to incorporate the effect of such fields in neuronal outgrowth by adding to the instant growth velocity (implied by internal influences) a vector component parallel to the external field (da F. Costa and Consularo, 1998; Bianchi et al., 2001; da F. Costa et al., 2003b), as exemplified in Fig. 6. It has been verified (Samsonovich and Ascoli, 2003) that the incorporation of a vector component pointing away from the cell soma also accounts for biological realism in neuronal outgrowth.

Because the neuronal activity during neuronal development can also have effects in shaping the neuronal morphology, it is interesting to consider such dynamics in simulations. We can use the recently introduced Sznajd complex networks (da F. Costa, 2005c), whose topology is determined by correlations between the neuronal connectivity/activity, in order to reflect Hebbian dynamics, where the most active connections are reinforced. Another effect to be considered is the fact that waves of ionic concentration have been verified to induce neuronal spikes (da F. Costa et al., 2001). Therefore, it would be interesting to include such waves in neuronal outgrowth simulations.

4. Spatial characterization

It is not only the shape that can be intrinsically related to function, the relative position of neurons also affects the underlying dynamics. It is clear that if neurons are far apart, the shape will have diminished effect in the collective dynamics. If neurons are near each other, their position can dictate the topological regularity of the network of interactions created by them (Scholl et al., 2000; Curtis and Wilkinson, 1997; Jun et al., 2007; Jungblut et al., 2009; da F. Costa and Rodrigues, 2009). For instance, it can be expected that the connectivity of neurons placed in a lattice-like

configuration will be more regular than if the neurons are randomly placed.

It is known that the arrangement of ganglion cells in the mammalian retina can accurately represent the visual field with little overlap (Hubel and Wiesel, 1965; Wandell et al., 2007). Moreover, the relative position between neurons and other structures (e.g. blood vessels, glia, etc.) is also relevant. The spatial relationship between neurons and vessels is of fundamental importance in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), which considers that increased blood flow is associated, in a coarse-grained way, with neuronal activity (Buxton, 2009; Bailey et al., 2003).

Traditional approaches to quantify spatial order take into account nearest neighbor distances between cells (Cook, 1996; Rockhill et al., 2000; Wassle and Riemann, 1978), while others consider the Voronoi tessellation (Okabe et al., 2000; Stoyan and Kendall, 2009) of the embedding space and count the number of sides of each Voronoi cell (Nishi and Hanasaki, 1989; Pigatto et al., 2004). For a given set of points (or seeds), the Voronoi tessellation can be understood as a partition of the embedding space according to Voronoi cells. Each Voronoi cell is related to a seed and defined as all points in the embedding space that are closer to the given seed than to any other seed. An example of Voronoi tessellation for a random set of points is given in Fig. 7.

Another compelling way to quantify the arrangement of points is called polygonality (da Fontoura Costa et al., 2006). This measurement uses the neighborhoods defined by the Voronoi tessellation to quantify the *angular regularity* of the arrangement. This means that it complements features related to neighboring distances, as the angles are not directly influenced by the distances. The polygonality is calculated with respect to a particular regular structure. If one chooses a lattice as a reference, then the polygonality is used to compare the angles with the value 90 deg. In case a hexagonal lattice is used as reference, the polygonality is commonly called hexagonality and the angles are compared with 60 deg. In Fig. 8 examples of hexagonality values, H , are shown. In this figure, we start with a hexagonal lattice and apply random perturbations to the points, according to a Gaussian distribution with a fixed standard deviation. When the perturbation is negligible, the hexagonal lattice is preserved and the measurement has the maximum value. As the perturbation increases, the distribution of the points start to resemble a uniformly random placement, and the hexagonality decreases. This means that it is also possible to compare the value obtained for the hexagonality with the random case. The procedure is to randomly place the same number of points as the real system in a space with the same area and find the hexagonality.

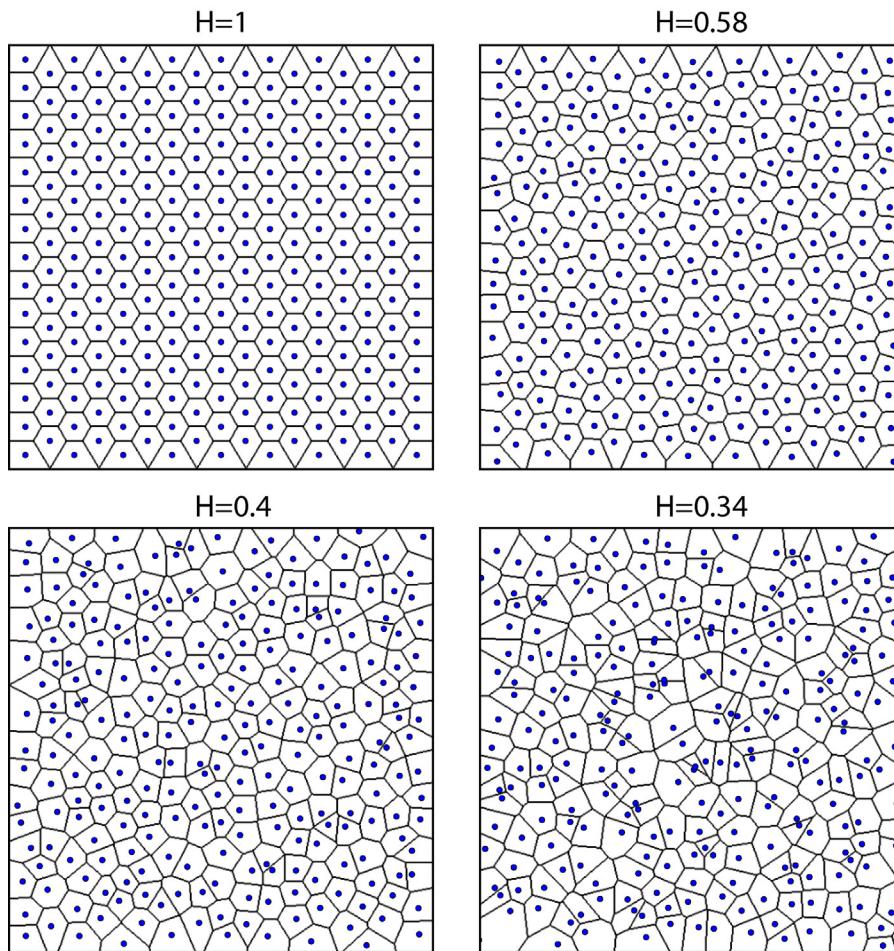


Fig. 8. Example of hexagonality values. Upper left panel shows a hexagonal lattice with the respective Voronoi tessellation. In the other panels a random perturbation was applied to each point, changing the Voronoi boundaries and the respective hexagonality. Note that points at the border are not considered in the calculation.

After repeating for many realizations, the average of the distribution represents the value that one would obtain if the points were randomly placed.

As for the interaction between neurons and other systems such as vessels, the distance between elements is also commonly used as a means to quantify the relationship (Enright et al., 2007; Casper et al., 2003). Usually, the distances between the center of mass or the mains axis of the objects are considered. Also, there is the possibility to study the spatial relationship while also considering the shape of the objects. One way to do this is by using one class of objects as reference and calculate the distance of the points that belong to the second class to the borders of the first class (Travencolo et al., 2007), obtaining a more informative quantification of the spatial arrangement.

5. Synthesis of morphological networks

Provided we have implemented the means to grow individual shapes, they can be combined in order to produce networks. We start with N seeds distributed spatially according to some desired statistical density. In the case of neurons, it is often reasonable to assume a uniform distribution of cells, see da F. Costa et al. (2005c) for a discussion on the measurement of spatial dispersion in neuronal mosaics. An example of such organization is shown in Fig. 9(a).

The connections between neurons can be defined according to the desired characteristics being studied. One approach is to connect neurons that are overlapping. In this case the system can be

represented by an undirected network, where neurons are nodes and an edge connects two nodes whenever the respective neurons are in contact. In Fig. 9(b) we show the network generated from the set of neurons in Fig. 9(a). Another approach is to connect only the neurons whose dendrites are touching the soma, creating a directed network where each edge follows the direction soma → dendrite. The generated network is sparser (i.e., has fewer connections) than the previous case, but is more biologically representative. An example of such network is shown in Fig. 9(c). We note that the most biologically plausible model would be to consider, besides somadendritic connections, axon-dendritic connections. But we will not enter in detail about this matter because the tracing of complete axons is a difficult task. Consequently, axon data is scarce and not always reliable, making it difficult to define a proper set of parameters for modeling axonal growth. Usually, the simulation decisions end up being specific to the particular problem being studied. Nevertheless, the other two connectivity schemes presented here are well capable of characterizing the connectivity of a given neuronal shape.

The procedure to generate a network can consider static neurons, i.e., the neurons placed in the considered space are already in its final growth form, or the connections can be made as the shape of the neurons grow along time. In Fig. 10 we show an example of the first approach, where neurons are successively added to the embedding space. In this case the same neuron is used and on each addition the neuron is rotated by a random angle. With this arrangement it is possible to quantify non-trivial characteristics of the neuron through measurements applied to the generated network.

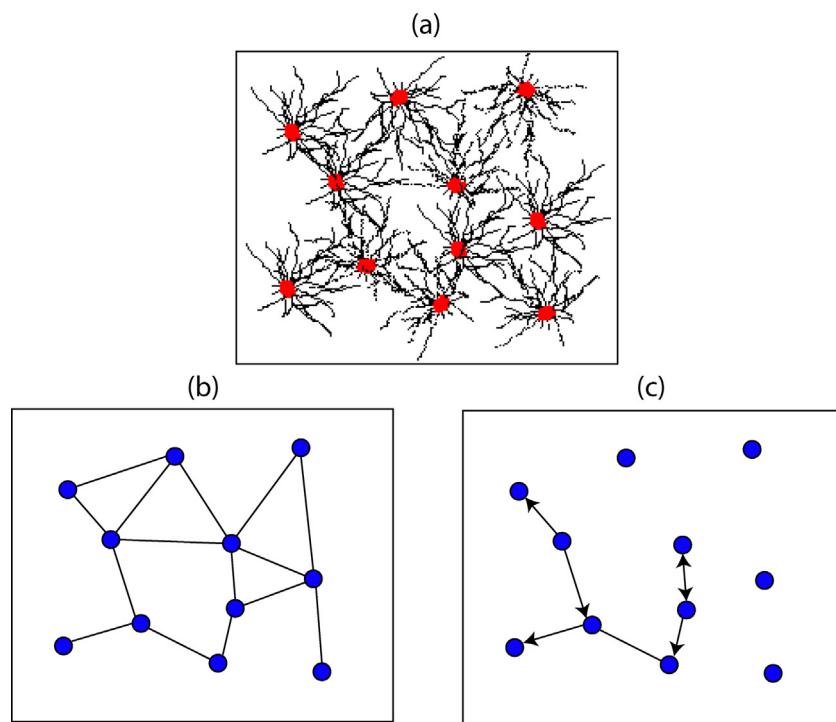


Fig. 9. Illustration of network creation. (a) Neurons are placed in a given space and connect through (b) the dendrites and (c) the dendrites and soma. In the latter case the connection has a fixed direction, giving rise to a digraph.

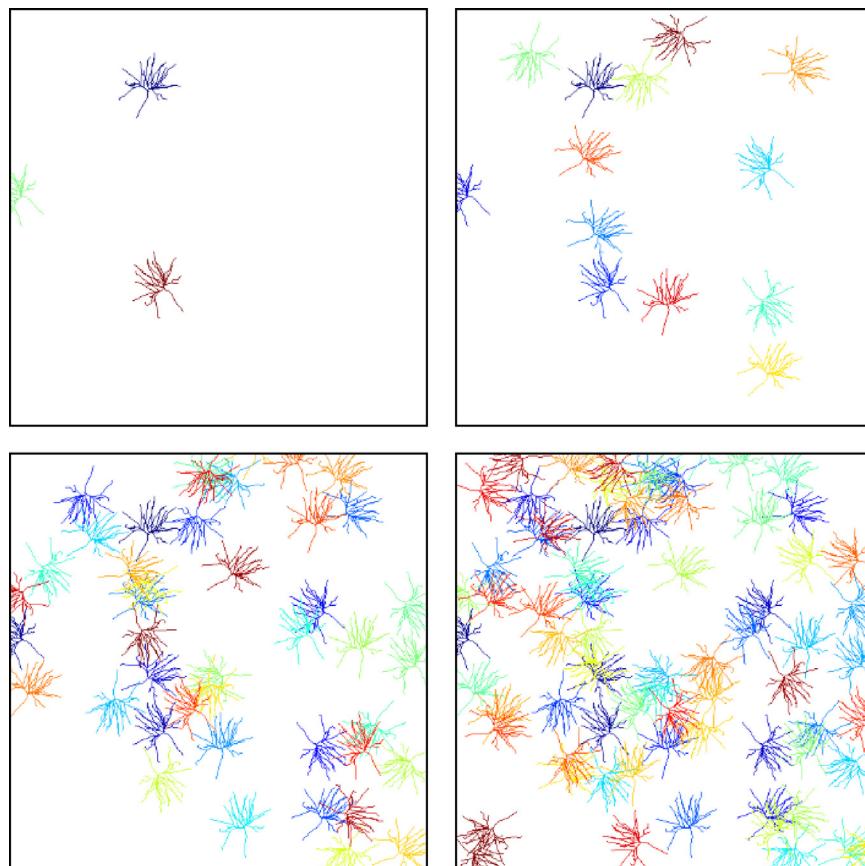


Fig. 10. The procedure used to generate a neuronal network. A given neuron is rotated by a random direction and successively placed in an embedding space. The picture shows four stages of the procedure.

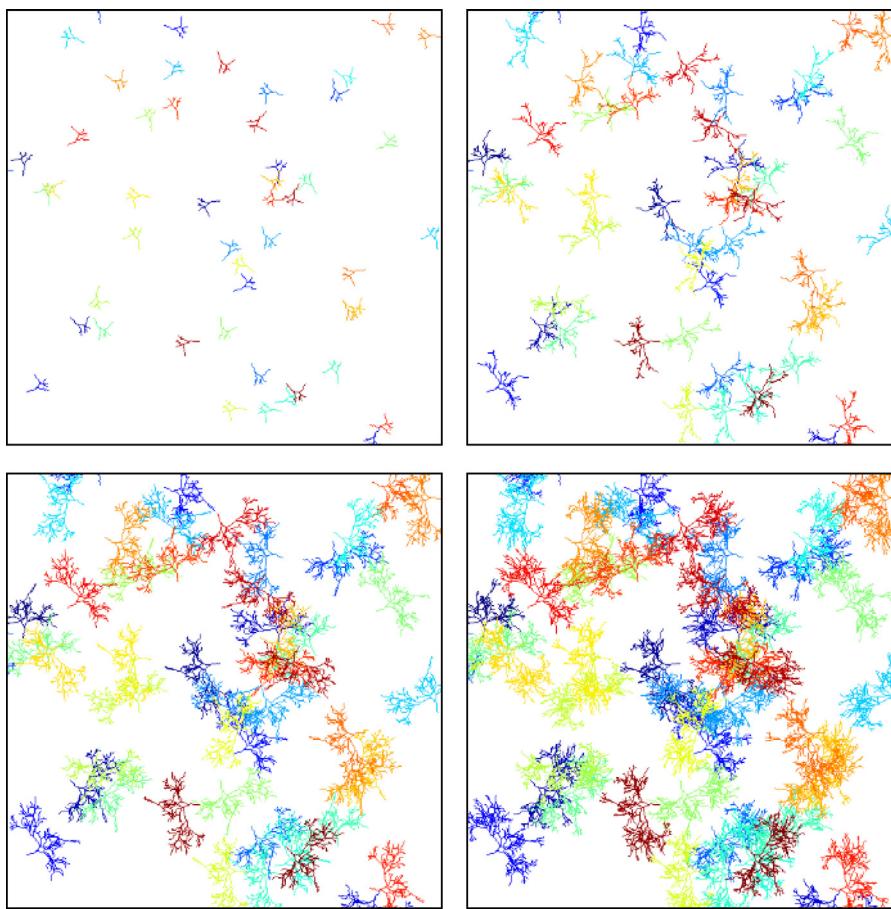


Fig. 11. The procedure used to generate a growing neuronal network. A number of copies of a given neuron are rotated by a random direction and placed in an embedding space. The neurons make connections as they grow. The picture shows four stages of this procedure.

Another approach can be applied to obtain artificial neuronal networks. First, a number of young neurons are placed in the embedding space. Then, the neurons are grown by using the technique described in Section 3. At each growth step new connections are made. An example of such a procedure is given in Fig. 11. There is also the possibility of taking into account the cost involved to build the network, usually reflecting the connections length (Wen and Chklovskii, 2008; Wen et al., 2009; Bullmore and Sporns, 2012).

6. Representation and characterization in terms of complex networks

One particularly interesting perspective to apply complex network measurements regards obtaining each measurement as a function of time or development epochs. For instance, traditional complex network measurements such as the node degree and clustering coefficient in terms of time can provide valuable information about the local connectivity of the objects as the system evolves. More global information about the system connectivity can be gathered by using the recently introduced hierarchical versions of the node degree and clustering coefficient, as well as several new hierarchical measurements (da F. Costa, 2004b; da F. Costa and Silva, 2006; da F. Costa and da Rocha, 2006) and wiring lengths between neuronal modules (da F. Costa and Luis, 2005). The application of community finding algorithms (Lancichinetti and Fortunato, 2009) can add complementary information with implications to the functional dynamics of the system under analysis, such as the evolution of synchronization and attractors formation. Another promising perspective is the quantification of the cycles of several lengths in the growing networks, which can

also have important implications for the system dynamics (Varier and Kaiser, 2011; Kaiser and Hilgetag, 2006).

Here we illustrate the kind of information one can gather from network characteristics. Using the real neurons shown in Fig. 12, 10 networks were created for each neuron. The process to create each network was the same as the one previously presented in Fig. 10. We note that we consider two neurons as connected if any part of their bodies are in contact, this is not biologically realistic, but it is still useful to characterize the overall connectivity potential of the neuron. In addition, so as to give a fair comparison between the cases, the neurons were normalized to have the same diameter. The measurements chosen to characterize the networks were the mean degree (the mean number of connections of the nodes), the mean clustering (basically, the number of triangles in the network) and the number of connected components (where a component is composed by nodes that can reach each other by following the connections). For an in-depth explanation of the adopted measurements, please refer to (da F. Costa et al., 2007).

Every time a neuron was added, the network was characterized, and the values were averaged over the 10 networks related to each neuron. The result is shown in Fig. 13. The mean degree of the generated network is a useful measure of the overall reach of the neuron. As we see in Fig. 13(a), each shape is related to a distinct mean degree, this means that neuron 4 can easily make new connections, while neuron 2 originates a network with many isolated nodes. We note that while it is clear that the mean degree must be correlated with the length of the dendrites, they are not the same. For example, an elongated neuron will originate a different network than a circular neuron with the same length.

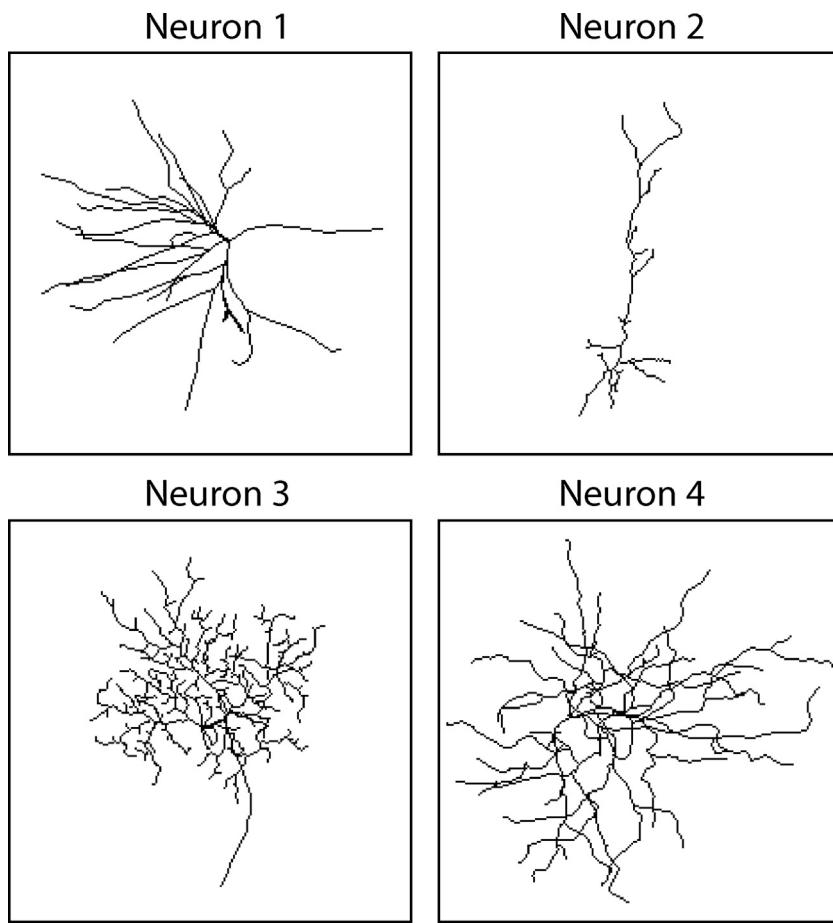


Fig. 12. The four real neurons used during our examples. They were obtained from the Neuromorpho repository ([Ascoli et al., 2007](#)).

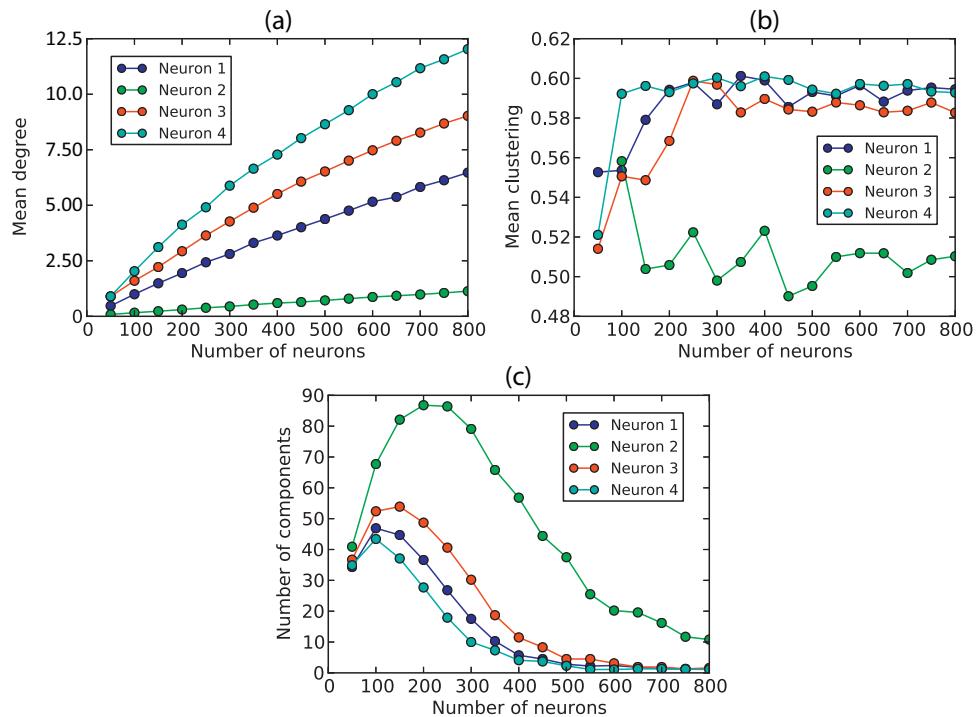


Fig. 13. Characterization of the networks generated by the four neurons of Fig. 12. (a) Mean degree of the nodes, (b) mean clustering coefficient and (c) number of disconnected components.

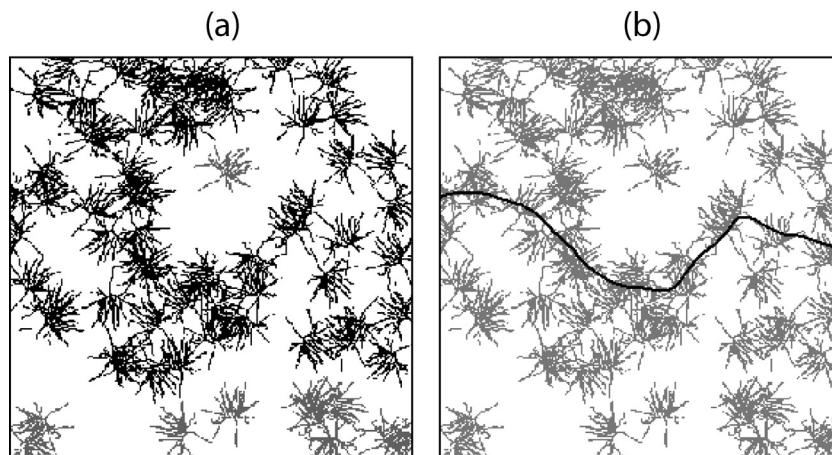


Fig. 14. The two types of percolation considered. (a) When the size of the largest component (black neurons) is comparable to the system size. (b) When it is possible to go from one edge of the space to the other following the connections between neurons, as represented by the black path.

In Fig. 13(b) we see the effect of the elongated shape of neuron 2. The clustering coefficient of this neuron is the smallest, meaning that it does not connect neighbors in an efficient manner. That is, if neuron i is connected with neurons j and k , then j and k have a low probability of being connected between themselves, when compared to the other neurons. Another interesting behavior is that the three other neurons have nearly the same clustering coefficient, i.e., although they have distinct shapes, the networks they generate have strong similarities. The clustering coefficient is a widely used measurement to characterize the small-world behavior of networks (Watts and Strogatz, 1998), and have been found to have fundamental importance to the brain (Sporns et al., 2004).

Finally, the number of connected components shows how well the communication of the network is. If a given number of neurons constitute a large number of components, no information can be passed between them. On the other hand, if the network corresponds to a single component, all neurons can send signals to all other neurons. In Fig. 13(c) we see that initially the network is composed by many isolated neurons, i.e., the number of components is almost the same as the number of neurons. The value increases as neurons are added, until it reaches a maximum value, which is the stage where the components start to connect between themselves, up to a point where a single component spans the entire network.

A direct quantification of the overall connectivity of the system can be obtained in terms of its percolation (Pérez-Reche et al., 2010; Handford et al., 2011). It is possible to define two kinds of percolation. In the first, we follow the size of the largest component as neurons are added, the percolation occurs when this component has a size comparable to the total number of neurons added, i.e., the system is almost entirely connected. An example is shown in Fig. 14(a). In the second case we define that a percolation occurs when it is possible to start from one edge of the space and cross to the other side by following the connections between neurons, as shown in Fig. 14(b). The average number of neurons where percolation takes place corresponds to the critical percolation density.

The size of the largest components generated by the four neurons of Fig. 12 is shown in Fig. 15. Each neuron has a characteristic curve indicating how many elements are needed in order to generate a network where the communication is global, i.e., each node can send information to all others.

We have applied static and dynamic, natural and forced percolations (da F. Costa, 2004a) in order to investigate the influence of the individual shape of neurons to the overall connectivity (da F. Costa and Monteiro, 2003; da F. Costa and Coelho, 2005). In investigations considering alpha and beta cat ganglion cells with

normalized sizes, we observed that more complex cells tend to percolate sooner. However, the critical percolation density or time (in the case of growing systems with constant density) has been verified to be a function of several other parameters, such as the neuronal cell elongation, the excluded volume, as well as the straightness of the neuronal processes. Further investigations are required in order to establish a clear relationship between the individual object properties, as well as their growth dynamics, with the final overall network connectivity.

7. Consequences on the overall system dynamics

Because morphological features of neurons have been found to strongly correlate, jointly with their size and spatial distribution, with both local and global connectivity (Ahnert et al., 2009), they will also be inexorably related to the emerging dynamics and behavior of the system.

After investigating the effect of using scale free connectivity in Hopfield networks (Stauffer et al., 2003; da F. Costa and Stauffer, 2003), we investigated how the individual neuronal shape can affect neuronal dynamics (da F. Costa et al., 2003a). We have also quantified the memory capacity of neuronal systems in terms of the overlap measurement, which is related to the number of

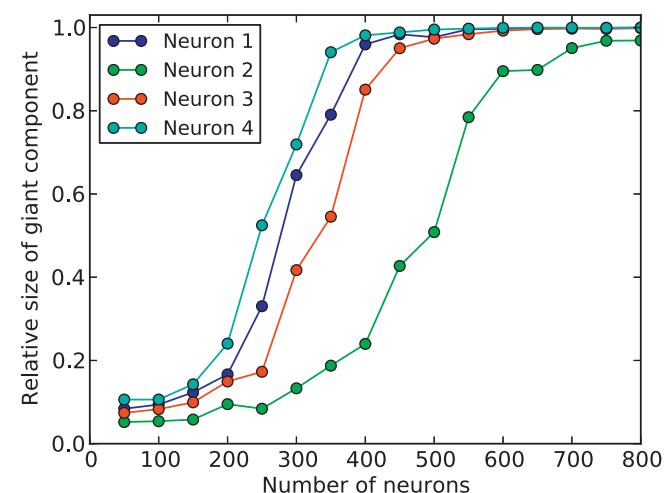


Fig. 15. Size of the largest component of the neuronal network divided by the number of neurons added to the system. It is clear that the four networks have a distinct percolation threshold.

correct recovered bits, between the originally trained pattern and the pattern recovered (starting from a perturbed version of the original pattern) after other patterns had been trained into the neuronal system. Considering small neurons with the same area, we have found (da F. Costa and Barbosa, 2004) that the memory capacity is highly dependent on the individual neuronal shape, with shapes exhibiting ramified and broader distribution of mass (i.e. neuron-like) tending to perform substantially better than simple shapes such as bars and crosses. The distribution of complex eigenvalue of the adjacency matrices obtained with neuron-like cells have resulted less degenerated, which is known to be associated with better recall capabilities (Haykin, 1999).

There have been many studies in the literature linking the heterogeneity of a system with dynamical properties. Pérez-Reche et al. (Pérez-Reche et al., 2010; Handford et al., 2011) provides a good theoretical argument linking the complexity of the morphology with heterogeneities on the resulting network of connections, which in turn makes the population less susceptible to epidemic outbreaks. Ahnert et al. (Ahnert et al., 2009) generated artificial networks with simplified neurons in order to study the influence of the morphology on an integrate-and-fire dynamics. By representing the network through hierarchical components he showed that it is possible to predict the onset and intensity of avalanches of activation for the resulting structure.

Another approach to study the relationship between shape and dynamics is by developing models for the electrophysiological evolution of the neural network (e.g. Gerstner and Kistler, 2002; Izhikevich, 2004). Many of these studies are more suitable to use when a single neuron is involved, as they not only have a large number of parameters, but also have a high cost to implement in a computer. Nevertheless, in the context of networks of neurons, many simple models have also been defined (Kaiser and Hilgetag, 2010; Perc, 2007; Roxin et al., 2004). These models take an information-theoretic approach of the neuronal dynamics, which is not concerned with the particular shape of the neuron signals, but with the times and intervals of neuronal spikes. The most traditional dynamics that follows this approach is the integrate-and-fire model (Lapicque, 1907; Brunel and van Rossum, 2007; Comin et al., 2012, 2013), which treats the neuron as an integrator with a hard threshold limit, T . If one is not interested in studying the dynamics *per se*, but use it as a tool to study the effects of the morphology, it is possible to use a simplified discrete integrate-and-fire dynamics given by

$$V_i(t+1) = \begin{cases} V_i(t) + \sigma \sum_{j=1}^N \sum_f A_{ij} \delta(t - t_j^f) & \text{if } V_i(t) < T \\ \sigma \sum_{j=1}^N \sum_f A_{ij} \delta(t - t_j^f) & \text{if } V_i(t) \geq T, \end{cases} \quad (1)$$

where $V_i(t)$ is the membrane potential of neuron i at time t , t_j^f the instant of the f th spike of neuron j , $\delta(x)=1$ when $x=0$ and $\delta(x)=0$ otherwise and σ the coupling strength. A is the adjacency matrix that describes the connectivity of the network, which means that $A_{ij}=1$ if neuron i is connected with neuron j and $A_{ij}=0$ otherwise. In this simplified scheme the relevant dynamical parameter is T/σ , and so, without loss of generality, it is possible to set $\sigma=1$. When V_i reaches the threshold T , the neuron fires a unitary signal to all its neighbors and V_i is reset to zero. Note that the time scale of the dynamics only matters for the typical interspike interval of the neuron.

For the four neurons shown in Fig. 12, we used the random placement method illustrated in Fig. 10 and the whole cell body connectivity presented in Fig. 9 to generate 10 random networks. Then, the integrate-and-fire dynamics was applied to

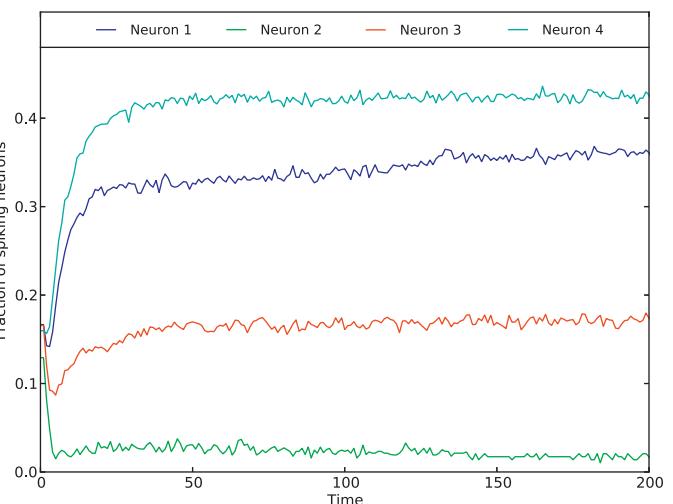


Fig. 16. Integrate-and-fire dynamics taking place in the generated neuronal networks. The neurons used for the simulation are shown in Fig. 12. After a short transient time, the number of neurons spiking in each network approach a distinct fixed value. This plot shows how the morphology of a neuron can drastically influence the overall dynamics of the system.

each network. The initial condition of the dynamics was to randomly draw the values of the membrane potential with uniform probability inside the interval $[0, T]$, where $T=5$ (note that T is non-dimensional). The result is shown in Fig. 16. Each curve of the plot represents the average number of spiking neurons in a given time, divided by the number of neurons in the network. It is clear that besides having different transient evolutions (for example, neuron 3 has a large drop followed by an increase in activity), the asynchronous state of the system reaches distinct limiting values depending on the morphology of the neuron.

8. Conclusions and future works

The present text reported an integrated review and discussion of the problem of relating shape and function through connectivity, with emphasis on developments from the author's group. The focus of the work was on the fact that shape, position, connectivity, function and the environment are all interrelated and influence each other.

We showed that when studying individual shapes, the main objective is to have the most *complete* and yet synthetic description of the object. To this end, many measurements were presented, each one aimed at quantifying a particular characteristic of a shape, and more specifically, of neurons. Some of the measurements, like size and curvature, originate from simple concepts, while others, like fractal dimension and lacunarity, are built upon a vast physical and mathematical background. By applying such measurements to real neurons, one can gather enough information to synthesize artificial structures with predefined characteristics. Many techniques used for such task were presented here, especially L-systems and Monte Carlo sampling based on observed measurements in real neurons.

Having defined the tools to analyze and create individual neurons, it is possible to start looking at the *emergent* behavior of a set of neurons. In order to do so, one can represent the neurons by nodes and its connections by edges, and draw on the extensive knowledge offered by the field of complex networks. Such knowledge is then used to characterize the effect of the individual shape on the connectivity of the overall system. Among the many characterizations presented, special attention was given to the critical percolation density, as it can quantify how well the neurons can communicate inside the system. Finally, the influence of the shape

on the system dynamics was presented, showing that shape can potentially affect the dynamics.

Although the present article reviewed many methods to study neuronal shapes, a series of important problems remain open to investigation. Among the most important advancements in the area is the expansion of the Neuromorpho repository. Currently incorporating almost 9000 neurons, it is already a great database to apply pattern recognition methods and obtain rich statistical distributions of neuron characteristics, among many other possibilities. The problem is that this base is still not very comprehensive. For example, rat, mouse and human neurons correspond to more than 85% of the available neurons, while many other species do not have any neuron included in the database. A similar situation holds also for different brain areas and types of neurons.

Still on the topic of data availability, the human connectome project (<http://www.humanconnectomeproject.org/>) is expected to make publicly available anatomical and functional brain mappings of a large number of carefully chosen individuals. Such initiative would be of critical importance in studying biologically realistic networks, ultimately allowing the comparison between models of network creation with real networks.

A natural extension of most methodologies presented here is the consideration of correlations between geometrical and topological features. That is, a neuron with a large number of branches might be more likely to have a large fractal dimension, so one question that can be asked is what are the differences between neurons having similar fractal dimensions but different number of branches. In the same way, it is known that the length or volume of dendrites naturally yield well-connected networks. One could try to isolate the effect of the length and study what other features influence the edge density. A similar consideration was used in Section 6 to normalize the neurons by the overall width in order to achieve a fair comparison between the networks generated by them.

We believe that the relationship between different scales of neuronal systems should be addressed more systematically in the literature, as they cannot be completely understood if treated isolatedly. Computational power is advancing at a fast pace, making possible the simultaneous development of new observations and models in an unprecedented manner. This synergy will be of fundamental importance in answering one of the main questions of current research: what is the role of geometry and connectivity on the emergent behavior of an organism?

Acknowledgments

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References

- Ahnert SE, Travencolo BAN, da F. Costa L. Connectivity and dynamics of neuronal networks as defined by the shape of individual neurons. *New J Phys* 2009;11:103053.
- Allain C, Cloitre M. Characterizing the lacunarity of random and deterministic fractal sets. *Phys Rev A* 1991;44:3552–8.
- Ascoli GA, Donohue DE, Halavi M. Neuromorpho.org: a central resource for neuronal morphologies. *J Neurosci* 2007;27:9247.
- Ascoli GA, Krichmar JL. L-neuron: a modeling tool for the efficient generation and parsimonious description of dendritic morphology. *Neurocomputing* 2000;32:1003–11.
- Ascoli GA, Krichmar JL, Scorcioni R, Nasuto SJ, Senft SL. Computer generation and quantitative morphometric analysis of virtual neurons. *Anat Embryol (Berl)* 2001;204:283–301.
- Bailey DL, Townsend DW, Valk PE, Maisey MN. *Positron emission tomography: basic sciences*. London: Springer; 2003.
- Barbosa MS, da F. Costa L, Bernardes ES, Ramakers G, van Pelt J. Characterizing neuromorphologic alterations with additive shape functionals. *Eur Phys J B* 2003a;37:109–15.
- Barbosa MS, da F. Costa L, de S, Bernardes E. Neuromorphometric characterization with shape functionals. *Phys Rev E* 2003b;67:061910.
- Berg DK. New neuronal growth factors. *Annu Rev Neurosci* 1984;7:149–70.
- Bianchi AGC, Santos MF, Britto DEH, da F. Costa L. How do neurons grow. In: *Proceedings of the World Congress on neuroinformatics*; 2001. p. 386–94.
- Bookstein FL. *Morphometric tools for landmark data*. Cambridge: Cambridge University Press; 1991.
- Bowie JE, Young IT. An analysis technique for biological shape. II. *Acta Cytol* 1977;21:455–64.
- Boycott B, Waessle H. The morphological types of ganglion cells of the domestic cat's retina. *J Physiol* 1974;240:397–419.
- Brunel N, van Rossum MCW. Quantitative investigations of electrical nerve excitation treated as polarization. *Biol Cybern* 2007;97:341–9.
- Bullmore E, Sporns O. The economy of brain network organization. *Nat Rev Neurosci* 2012;13:336–49.
- Buxton RB. *Introduction to functional magnetic resonance imaging: principles and techniques*. Cambridge: Cambridge University Press; 2009.
- Cannon RC, Turner DA, Pyapali GK, Wheal HV. An on-line archive of reconstructed hippocampal neurons. *J Neurosci Methods* 1998;84:49–54.
- Casper D, Finkelstein E, Goldstein IM, Palencia D, Yunger Y, Pidel A. Dopaminergic neurons associate with blood vessels in neural transplants. *Exp Neurol* 2003;184:785–93.
- Cesar RM Jr, da F. Costa L. Piecewise linear segmentation of digital contours in $O(N \cdot \log(N))$ through a technique based on effective digital curvature estimation. *J Real-Time Imaging* 1995;1:409–17.
- Cesar RM Jr, da F. Costa L. Towards effective planar shape representation with multiscale digital curvature analysis based on signal processing techniques. *Pattern Recogn* 1996;29:1559–69.
- Cesar RM Jr, da F. Costa L. Application and assessment of multiscale bending energy for morphometric characterization of neural cells. *Rev Sci Instrum* 1997;68:2177–86.
- Chen Q, Chen TJ, Letourneau PC, da F. Costa L, Schubert D. Moca regulates n-cadherin-mediated cell–cell adhesion and neurite outgrowth. *J Neurosci* 2005;25:281–90.
- Chklovskii DB. Synaptic connectivity and neuronal morphology: two sides of the same coin. *Neuron* 2004;43:609–17.
- Coelho RC, da F. Costa L. Morphologically realistic neural networks. In: IEEE – III international conference on engineering of complex systems; 1997. p. 223–8.
- Comin CH, Batista JLB, Viana MP, da F. Costa L, Travencolo BAN, Kaiser M. Structure and dynamics: the transition from nonequilibrium to equilibrium in integrate-and-fire dynamics. *Int J Bifurcat Chaos* 2012;22:1250174.
- Comin CH, Viana MP, da F. Costa L. The relationship between structure and function in locally observed complex networks. *New J Phys* 2013;15:013048.
- Cook JE. Spatial properties of retinal mosaics: an empirical evaluation of some existing measures. *Vis Neurosci* 1996;13:15–30.
- Cuntz H, Forstner F, Borst A, Häusser M. One rule to grow them all: a general theory of neuronal branching and its practical application. *PLoS Comput Biol* 2010;6:8.
- Curtis A, Wilkinson C. Topographical control of cells. *Biomaterials* 1997;18:1573–83.
- da F. Costa L. Computer vision based morphometric characterization of neural cells. *Rev Sci Instrum* 1995;66:3770–3.
- da F. Costa L. New perspectives in neuromorphometry and computational neuroscience. In: X Simpósio Brasileiro de Computação Gráfica e Processamento de Imagens; 1997. p. 1–6.
- da F. Costa L. Multidimensional scale-space shape analysis. In: Proceedings of the international workshop on synthetic-natural hybrid coding and three dimensional imaging; 1999. p. 214–7.
- da F. Costa L. Robust skeletonization through exact Euclidean distance transform and its application to neuromorphometry. *J Real-Time Imaging* 2000;6:415–31.
- da F. Costa L. Actively-induced percolation: an effective approach to multiple object systems characterization; 2004a. arXiv:cond-mat/0404310 cond-mat.dis-nn.
- da F. Costa L. The hierarchical backbone of complex networks. *Phys Rev Lett* 2004, August;93:098702.
- da F. Costa L. Biological sequence analysis through the one-dimensional percolation transform and its enhanced version. *Bioinformatics* 2005a;21:608–16.
- da F. Costa L. Morphological complex networks: can individual morphology determine the general connectivity and dynamics of networks? 2005b. arXiv:q-bio/0503041 q-bio.MN.
- da F. Costa L. Szajndj complex networks. *Int J Mod Phys C* 2005c;16:1001.
- da F. Costa L, Barache D, Antoine JP, Cesar RM Jr. Shape characterization with the wavelet transform. *Signal Process* 1997;62:265–90.
- da F. Costa L, Barbosa M, Coupe V. On the potential of the excluded volume and autocorrelation as neuromorphometric descriptors. *Physica A* 2005a;348:317–26.
- da F. Costa L, Barbosa MS. An analytical approach to neuronal connectivity. *Eur Phys J B* 2004;42:573–80.
- da F. Costa L, Barbosa MS, Coupe V, Stauffer D. Morphological hopfield networks. *Brain Mind* 2003a;4:91–105.
- da F. Costa L, Barbosa MS, Schierwagen A, Alpár A, Gartner U, Arendt T. Active percolation analysis of pyramidal neurons of somatosensory cortex: a comparison of wildtype and p21h-rasval12 transgenic mice. *Int J Mod Phys C* 2005b;16:655–67.
- da F. Costa L, Bianchi AGC, Santos MF, Hamasaki-Brito DE. Inferring shape evolution. *Pattern Recogn Lett* 2003b;24:1005–14.
- da F. Costa L, Campos AG, Estrozi LF, Rios Filho LG, Bosco A. A biologically-motivated approach to image representation and its application to neuromorphology. In:

- Lecture Notes in Computer Science 1811 – international workshop on biologically motivated computer vision; 2000. p. 407–16.
- da F. Costa L, Cesar RM Jr. Neural cell classification by wavelets and multiscale curvature. *Biol Cybern* 1998;79:347–60.
- da F. Costa L, Cesar RM Jr. Computer-vision-based extraction of neural dendograms. *J Neurosci Methods* 1999;93:121–31.
- da F. Costa L, Cesar RM Jr. Shape analysis and classification: theory and practice. Boca Raton: CRC Press; 2001.
- da F. Costa L, Coelho RC. Realistic neuromorphic models and their application to neural reorganization simulations. *Neurocomputing* 2002;48:555–71.
- da F. Costa L, Coelho RC. Growth-driven percolations: the dynamics of connectivity in neuronal systems. *Eur Phys J B* 2005;47:571–81.
- da F. Costa L, Consularo A. The dynamics of biological evolution and the importance of spatial relations and shapes. In: Proceedings of the 3rd international workshop on human and machine perception: emergence, attention and creativity; 1998. p. 1–14.
- da F. Costa L, da Rocha LEC. A generalized approach to complex networks. *Eur Phys J B* 2006;50:237–42.
- da F. Costa L, Estrozi LF. Multiresolution shape representation without border shifting. *Electron Lett* 1999;35:1829–30.
- da F. Costa L, Estrozi LF, Rios Filho LG, Campos AG, Cesar RM Jr. 1D and 2D Fourier-based approaches to numeric curvature estimation and their comparative performance assessment. *Digit Signal Process* 2003c;13:172–97.
- da F. Costa L, Luis D. Topographical maps as complex networks. *Phys Rev E* 2005, February;71:021901.
- da F. Costa L, Manoel ETM, Faucereau F, Chelly J, van Pelt J, Ramakers G. A shape analysis framework for neuromorphometry. *Network: Comput Neural Syst* 2002;13:283–310.
- da F. Costa L, Monteiro ETM. A percolation approach to neural morphometry and connectivity. *Neuroinformatics* 2003;1:65–80.
- da F. Costa L, Mutinari G, Schubert D. Characterizing width uniformity by wave propagation. *Phys Rev E* 2003d;68:056704.
- da F. Costa L, Rios Filho LG, Tanaka JS, Manoel ETM. Ch. Morphofunctional roles of simulated neurons in volume transmission. In: Biophysical neural networks: foundations of integrative neuroscience. New York: Mary Ann Liebert; 2001. p. 43–74.
- da F. Costa L, Rocha F, de Lima SMA. Statistical mechanics characterization of neuronal mosaics. *Appl Phys Lett* 2005c;86:093901.
- da F. Costa L, Rodrigues FA. Seeking for simplicity in complex networks. *Europ Phys Lett* 2009;85:48001.
- da F. Costa L, Rodrigues FA, Travieso G, Boas PRV. Characterization of complex networks: a survey of measurements. *Adv Phys* 2007;56:167–242.
- da F. Costa L, Silva FN. Hierarchical characterization of complex networks. *J Stat Phys* 2006;125:841–72.
- da F. Costa L, Stauffer D. Associative recall in non-randomly diluted neuronal networks. *Physica A* 2003;330:37–45.
- da F. Costa L, Velte T. Automatic characterization and classification of ganglion cells from the salamander retina. *J Comp Neurol* 1999;404:33–51.
- da F. Costa L, Zawadzki K, Miazaki M, Viana MP, Taraskin SN. Unveiling the neuro-morphological space. *Front Comp Neurosci* 2010;4:150.
- da Fontoura Costa L, Rocha F, de Lima SMA. Characterizing polygonality in biological structures. *Phys Rev E* 2006;73:011913.
- da Silva LC, Barbosa MS, Oliveira ON, da F. Costa L. Percolation and roughness in ballistic deposition of complex shapes; 2005. arXiv:cond-mat/0501020 cond-mat.ds-nn.
- de Raedt H, Hams AH, Michielsen K, de Raedt K. Quantum computer emulator. *Comput Phys Commun* 2000;132:1–20.
- Dowell-Mesfin N, Abdul-Karim MA, Turner AM, Schanz S, Craighead HG, Roysam B, et al. Topographically modified surfaces affect orientation and growth of hippocampal neurons. *J Neural Eng* 2004;1:78–90.
- Dryden IL, Mardia KV. Statistical shape analysis. Chichester: Wiley; 1998.
- Duda RO, Hart PE, Stork DG. Pattern classification. New York: Wiley; 2001.
- Enright LE, Zhang S, Murphy TH. Fine mapping of the spatial relationship between acute ischemia and dendritic structure indicates selective vulnerability of layer V neuron dendritic tufts within single neurons *in vivo*. *J Cereb Blood Flow Metab* 2007;27:1185–200.
- Falcão AX, da F. Costa L, Cunha BS. Multiscale skeletons by image foresting transform and its application to neuromorphometry. *Pattern Recogn* 2002;35:1571–82.
- Falconer K. Fractal geometry: mathematical foundations and applications. Chichester: Wiley; 2003.
- Gallos LK, Makse HA, Sigman M. A small world of weak ties provides optimal global integration of self-similar modules in functional brain networks. *PNAS* 2011;108:2825–30.
- Gefen Y, Meir Y, Mandelbrot BB, Aharony A. Geometric implementation of hypercubic lattices with noninteger dimensionality by use of low lacunarity fractal lattices. *Phys Rev Lett* 1983;50:145–8.
- Gell-Mann M. The quark and the jaguar. New York: St. Martin's Griffin; 1995.
- Gerstner W, Kistler WM. Spiking neuron models. Cambridge: Cambridge University Press; 2002.
- Graham BP, van Ooyen A. Transport limited effect in a model of dendritic branching. *J Theor Biol* 2004;230:421–32.
- Hamilton P. A language to describe the growth of neurites. *Biol Cybern* 1993;68:559–65.
- Handford TP, Pérez-Reche FJ, Taraskin SN, da F. Costa L, Miazaki M, Neri FM, et al. Epidemics in networks of spatially correlated three-dimensional root-branching structures. *J R Soc Interface* 2011;8:423–34.
- Haykin S. Neural networks and learning machines. New Jersey: Prentice Hall; 1999.
- Hentschel HGE, Fine A. Instabilities in cellular dendritic morphogenesis. *Phys Rev Lett* 1994;73(December):3592–5.
- Hentschel HGE, Fine A, Samuels D. Instabilities during the dendritic and axonal development of neuronal form. *Physica A* 1998;254:46.
- Hillman DE, Ch. Neuronal shape parameters and substructures as a basis of neuronal form. In: The neurosciences, Fourth Study Program. Cambridge: The MIT Press; 1979. p. 477–98.
- Hubel DH, Wiesel TN. Receptive fields and functional architecture in two non-striate visual areas (18 and 19) of the cat. *J Neurophysiol* 1965;28:229–89.
- Izhikevich EM. Which model to use for cortical spiking neurons? *IEEE Trans Neuron Netw* 2004;15:1063–70.
- Jun SB, Hynd MR, Dowell-Mesfin N, Smith KL, Turner JN, Shain W, et al. Low-density neuronal networks cultured using patterned poly-L-lysine on microelectrode arrays. *J Neurosci Methods* 2007;160:317–26.
- Jungblut M, Knoll W, Thielemann C, Pottköt M. Triangular neuronal networks on microelectrode arrays: an approach to improve the properties of low-density networks for extracellular recording. *Biomed Microdev* 2009;11:1269–78.
- Kaiser M, Hilgetag CC. Non-optimal component placement, but short processing paths, due to long-distance projections in neural systems. *PLoS Comput Biol* 2006;2:e95.
- Kaiser M, Hilgetag CC. Optimal hierarchical modular topologies for producing limited sustained activation of neural networks. *Front Neuroinfo* 2010;4:1–14.
- Kandel ER, Schwartz JH, Jessel TM. Essentials of neural science and behavior. New York: McGraw-Hill; 1995.
- Karbowski J. Global and regional brain metabolic scaling and its functional consequences. *BMC Biol* 2007;5:18.
- Koene RA, Tijms B, van Hees P, Postma F, de Ridder A, Ramakers GJA, et al. Netmorph: a framework for the stochastic generation of large scale neuronal networks with realistic neuron morphologies. *Neuroinformatics* 2009;7:195–210.
- Lancichinetti A, Fortunato S. Community detection algorithms: a comparative analysis. *Phys Rev E* 2009;80:056117.
- Lapicque L. Recherches quantitatives sur l'excitation électrique des nerfs traitée comme une polarization. *J Physiol Pathol Gén* 1907;9:620–35.
- Leandro JJG, Cesar RM Jr, da F. Costa L. Automatic contour extraction from 2D neuron images. *J Neurosci Methods* 2009;177:497–509.
- Lestrel PE. Morphometrics for the life sciences. Singapore: World Scientific; 2000.
- Lindenmayer A. Mathematical models for cellular interactions in development. I. Filaments with one-sided inputs. *J Theor Biol* 1968;18:280–99.
- Mandelbrot BB. The fractal geometry of nature. New York: W. H. Freeman and Company; 1982.
- McCaig CD, Rajnicek AM. Electrical fields, nerve growth and nerve regeneration. *Exp Physiol* 1991;76:473–94.
- Mecke KR. Integral geometry in statistical physics. *Int J Mod Phys B* 1998;12:861–99.
- Michielsen K, de Raedt H. Integral-geometry morphological image analysis. *Phys Rep* 2001;347:461–538.
- Newman MEJ. Monte Carlo methods in statistical physics. New York: Oxford University Press; 1999.
- Nishi O, Hanasaki K. Automated determination of polygonality of corneal endothelial cells. *Cornea* 1989;8:54–7.
- Okabe A, Boots B, Sugihara K, Chiu SN. Spatial tessellations: concepts and applications of Voronoi diagrams. Chichester: Wiley; 2000.
- Peichl L, Waessle H. The structural correlate of the receptive field centre of alpha ganglion cells in the cat retina. *J Physiol* 1983;341:309–24.
- Pelt JV, Ooyen AV, Uylings HBM. Computational Neuroscience: Realistic Modeling for Experimentalists. Boca Raton: CRC Press; 2001. p. 179–208, Ch. 7.
- Perc M. Stochastic resonance on excitable small-world networks via a pacemaker. *Phys Rev E* 2007;76(December):066203.
- Pérez-Reche FJ, Taraskin SN, da F. Costa L, Neri FM, Gilligan CA. Complexity and anisotropy in host morphology make populations less susceptible to epidemic outbreaks. *J R Soc Interface* 2010;7:1083–92.
- Pigatto JA, Andrade MC, Laus JL, Santos JM, Brooks DE, Guedes PM, et al. Morphometric analysis of the corneal endothelium of yacare caiman (caiman yacare) using scanning electron microscopy. *Vet Ophthalmol* 2004;7:205–8.
- Rámón y Cajal S. Recollections of my life. Cambridge: The MIT Press; 1989.
- Rockhill RL, Euler T, Masland RH. Spatial order within but not between types of retinal neurons. *PNAS* 2000;97:2303–7.
- Rodrigues EP, Barbosa MS, da F. Costa L. Self-referred approach to lacunarity. *Phys Rev E* 2005;72(July):016707.
- Roxin A, Riecke H, Solla SA. Self-sustained activity in a small-world network of excitatory neurons. *Phys Rev Lett* 2004;92(May):198101.
- Samsonovich AV, Ascoli GA. Statistical morphological analysis of hippocampal principal neurons indicates cell-specific repulsion of dendrites from their own cell. *J Neurosci Res* 2003;71:173–87.
- Samsonovich AV, Ascoli GA. Statistical determinants of dendritic morphology in hippocampal pyramidal neurons. A hidden Markov model. *Hippocampus* 2005;15:166–83.
- Scholl M, Sprössler C, Denyer M, Krause M, Nakajima K, Maelicke A, et al. Ordered networks of rat hippocampal neurons attached to silicon oxide surfaces. *J Neurosci Methods* 2000;104:65–75.
- Scorcioni R, Polavaram S, Ascoli GA. L-measure: a web-accessible tool for the analysis, comparison and search of digital reconstructions of neuronal morphologies. *Nat Protoc* 2008;3:866–76.
- Small CG. The statistical theory of shape. New York: Springer; 1996.
- Sporns O, Chialvo DR, Kaiser M, Hilgetag CC. Organization, development and function of complex brain networks. *Trends Cogn Sci* 2004;8:418–25.

- Stauffer D, Aharony A, da F. Costa L, Adler J. Efficient hopfield pattern recognition on a scale-free neural network. *Eur J Phys B* 2003;32:395–9.
- Stoyan D, Kendall WS. *Stochastic geometry and its applications*. Chichester: Wiley; 2009.
- Thompson DW. *On growth and form*. Cambridge: Cambridge University Press; 1917.
- Travencolo BAN, Debat CM, Beletti ME, Silveira JRS, Ehrlich R, da F. Costa L. A new method for quantifying three-dimensional interactions between biological structures. *J Anat* 2007;210:221–31.
- Uylings HBM, Ruiz-Marcos A, van Pelt J. The metric analysis of three-dimensional dendritic tree patterns: a methodological review. *J Neurosci Methods* 1986;18:127–51.
- Uylings HBM, van Pelt J. Measures for quantifying dendritic arborizations. *Netw Comput Neural Syst* 2002;13:397–414.
- van Ooyen A, Graham BP, Ramakers GJA. Competition for tubulin between growing neurites during development. *Neurocomputing* 2001;38–40:73–8.
- van Ooyen A, van Pelt J, Corner MA. Implications of activity dependent neurite outgrowth for neuronal morphology and network design. *J Theor Biol* 1995;172:63–82.
- van Ooyen A, Willshaw DJ. Competition for neurotrophic factor in the development of nerve connections. *Proc R Soc Lond B* 1999;266:883–92.
- van Pelt J, Uylings HBM. Modeling neuronal growth and shape. In: *Modeling biology – structures, behaviors, evolution*. Cambridge: The MIT Press; 2007. p. 195–215.
- Varier S, Kaiser M. Neural development features: spatio-temporal development of the *C. elegans* neuronal network. *PLoS Comput Biol* 2011;7:e1001044.
- Wandell BA, Dumoulin SO, Brewer AA. Visual field maps in human cortex. *Neuron* 2007;56:366–83.
- Wassle H, Riemann HJ. The mosaic of nerve cells in the mammalian retina. *Proc R Soc Lond B* 1978;200:441–61.
- Watts DJ, Strogatz SH. Collective dynamics of small-world networks. *Nature* 1998;393:440–2.
- Wen Q, Chklovskii DB. A cost–benefit analysis of neuronal morphology. *J Neurophysiol* 2008;99:2320–8.
- Wen Q, Stepanyants A, Elston GN, Grosberg AY, Chklovskii DB. Maximization of the connectivity repertoire as a statistical principle governing the shapes of dendritic arbors. *PNAS* 2009;106:12536–41.
- Young IT, Walker JE, Bowie JE. An analysis technique for biological shape. I. *Inform Control* 1974;25:357–70.
- Zawadzki K, Feenders C, Viana MP, Kaiser M, da F. Costa L. Morphological homogeneity of neurons: searching for outlier neuronal cells. *Neuroinformatics* 2012;10:379–89.