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Morphological analysis and modeling of neuronal dendrites

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Abstract

Morphological data on two classes of neurons from mammalian midbrain have quantitatively been analyzed for dendritic shape parameters. Their frequency distributions were used to optimize the parameters of a dendritic growth model which describes dendritic morphology by a stochastic growth process of segment branching. The model assumes randomness with respect to both the selection of the branching segment out of the tree segments and the occurrence of the branching event in time. Model-generated trees have shape properties closely matching the observed ones. The dendritic trees of each of the two classes of neurons are represented by a specific set of growth model parameters, thus achieving morphological data compression.

Keywords: Neuronal dendrites; Shape parameters; Stochastic growth model; Cat superior colliculus neurons; Parameter optimization

1. Introduction

Neuronal architecture is characterized by elongated neurites of which two kinds can be differentiated, i.e. axons and dendrites which often built widely branching structures. The morphological complexity of dendritic and axonal arborizations to a large extent determines their functional properties. An interesting phenomenon in studying arbor morphologies is the large variability of their shapes both within and between different cell types and species. This variability is reflected in metrical shape parameters (dimensions of soma size, diameters and lengths of the

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constituting segments, surface area and volume of the arbor) and correlations between them, as well as topological characteristics (the number and the connectivity pattern of the segments).

The development of arbor shape is partly determined by genetic factors and partly by interactions with the surrounding tissue (e.g. [1]). Since a large number of (in many cases scarcely understood) mechanisms is involved, it is reasonable to consider arbor pattern formation as a stochastic process.

In this study, the focus is on topological aspects of dendritic tree shape. There are several methods for describing trees topologically (for review, see [2]). We used topological measures and parameters of a stochastic model for dendritic growth to compare dendrites of neurons from cat superior colliculus (SC) previously published [3–5]. The SC is a part of the midbrain involved in eye movement control [6].

2. Parameters of dendritic shape

The study was done on a data set obtained from SC neurons stained with HRP [3,4]. The sample of cells selected for analysis comprised a triplet of neurons each from superficial (SLNs) and deep (DLNs) SC layers (Fig. 1). The dendritic arborization of the SC neurons is described as a set of hierarchically arranged segments. A segment is defined as a portion of dendrite extending between two ramification nodes (intermediate segments), or between a node and a tip (terminal segments). On the whole, the sample contained all dendritic trees of the six SC neurons reconstructed (26 trees from DLNs, and 12 trees from SLNs).

Categorizing dendritic trees according to topological type depends on the patterning of segments, and is independent of metrical and orientation features. The following parameters have been used to characterize the trees (Fig. 2):

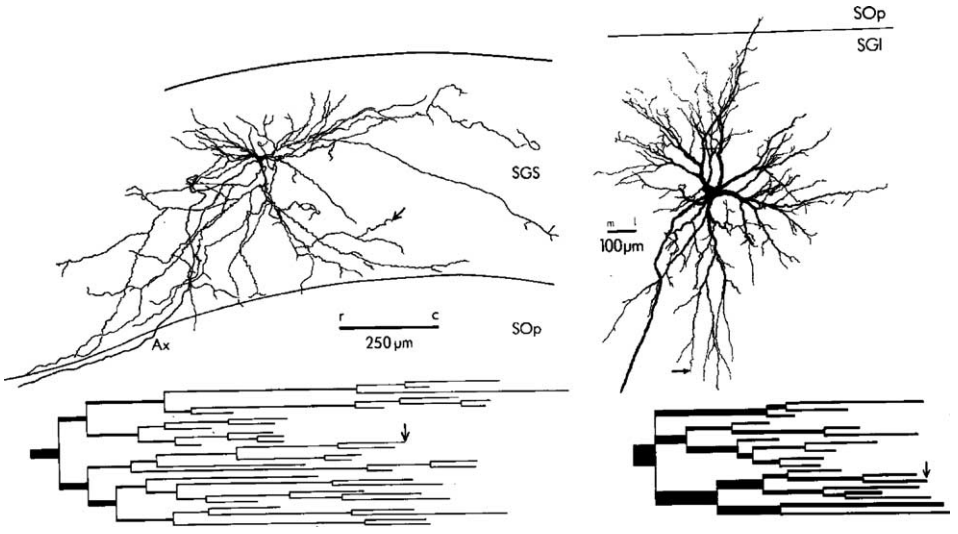

Fig. 1. Projected image of two SC neurons. Left: SLN, right: DLN, each with dendrogram of one dendrite indicated by arrow (below).

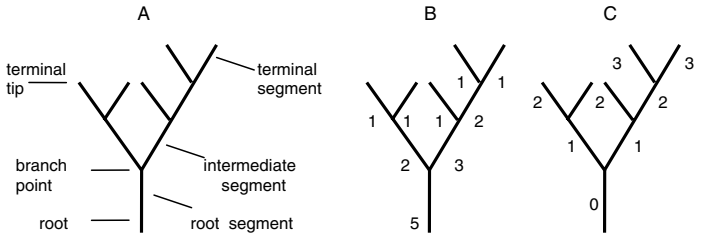

Fig. 2. Topological representation of a dendrite. (A) The tree is depicted by a set of connected segments which are labeled by (B) the degree of their subtrees and (C) their centrifugal order.

Order (γ). This represents the topological distance from the soma. Its value is an integer incremented at every bifurcation ('centrifugal order'). A value of $\gamma = 0$ is assigned to the primary segments, i.e. those emerging directly from the soma.

Degree (n). This represents the number of tips of a subtree (or partition) stemming from a segment. In a binary tree, it is related to m, the number of segments of the partition, by $m = 2n - 1$.

Asymmetry index (A). It is defined as the mean value of the asymmetry of its partitions (subtrees)

$$A = \frac{1}{n-1} \sum A_{\mathrm{p}}(r_i, s_i). \tag{1}$$

The summation runs over all $n - 1$ branch points of the tree with degree n while the partition (r_i, s_i) denotes the degrees of both subtrees at branch point i, and A_{p} denotes the partition asymmetry

$$A_{\mathrm{p}} = \frac{|r - s|}{r + s - 2} \quad \text{for} \quad r + s > 2 \quad \text{and} \quad A_{\mathrm{p}}(1,1) = 0. \tag{2}$$

The values of tree asymmetry range from zero for perfectly symmetrical trees to approaching one for most asymmetrical trees [7].

3. Growth model

The dendritic growth model has recently been presented in [8,9]. The full model is a metrical growth model as dendritic growth is modeled by a stochastic, non-stationary process of segment branching and elongation. In the following, only the modeling of topological aspects is considered. Dendritic growth is assumed to proceed by a sequence of branching events. At each branching event a new (terminal) segment is attached to one of the already available tree segments, thus creating a new bifurcation point. Randomness is assumed with respect to (i) the selection of the branching segment out of the tree segments and (ii) the occurrence of the branching event in time.

3.1. Modeling topological variation (QS-model)

Topological variability emerges by branching events occurring on different segments of the growing tree. In the *QS*-model the selection probability of a segment for branching is assumed to depend on the type of a segment and its order. The branching probability of a terminal segment at centrifugal order γ is given by

$$p_{\mathrm{TS}} = C \cdot 2^{-S\gamma}, \tag{3}$$

with parameter S modulating the dependence on centrifugal order. C is a normalization constant (see below). The selection probability of an intermediate segment for branching can be calculated from that of a terminal segment of the same order by

$$p_{\mathrm{IS}} = p_{\mathrm{TS}} \cdot Q/(1-Q). \tag{4}$$

The parameter Q ($0 \leqslant Q \leqslant 1$) determines the total branching probability of intermediate segments, with $Q = 0$ and 1 corresponding to no branching and exclusive branching of intermediate segments, respectively.

With the two parameters Q and S a great variety of growth modes can be described, including the well-known random terminal growth mode, $(Q,S) = (0,0)$, and the random segmental growth mode, $(Q,S) = (0.5,0)$, the latter allowing all segments to branch with equal probability. The topological variability of dendrites of several neuron types and species has been accurately described by the *S*-model, i.e. assuming branching to occur at terminal segments only ($Q = 0$), see [7,10]. Therefore, $Q = 0$ is assumed in the following.

3.2. Modeling degree variation (BE-model)

The degree of a dendrite is determined by the number of branching events during growth. In the *BE*-model branching events occur at random points in time. The developmental period T is divided into a number N of time bins. The branching probability of a terminal segment per time bin is given by $p_i = B/Nn_i^E$, with n_i the actual number of terminal segments in the tree at time bin i. Parameter B denotes the expected number of branching events at an isolated segment in the full period. Parameter E determines how strong the branching probability of a terminal segment depends on the actual number of segments. For $E = 0$ the branching probability is constant, independently of the present tree degree.

3.3. Modeling the variation of both the topological structure and the degree (BES-model)

In the *BE*-model all terminal segments have equal probability for branching, and the topological variation produced by the *BE*-model is similar to that produced by the random terminal growth mode ($Q = 0$, $S = 0$). An accurate account of the topological variability is given in the combined *BES*-model taking the branching probability p_i of a terminal segment per time bin also dependent on the centrifugal order of the segment as described in the *S*-model. Thus,

$$p_i = C \cdot 2^{-S\gamma} B/Nn_i^E, \tag{5}$$

while $C = n_i / \sum_1^{n_i} 2^{-S\gamma_i}$ is a normalization constant with summation running over all n_i terminal segments. The normalization ensures that the summed branching probability per time bin of all the terminal segments in the tree is independent of the value of S.

3.4. Simulation procedure

The simulation of the growth process for the general *BES*-growth model proceeds according to the following algorithm. For a given tree at a given time bin, the branching probabilities are calculated for all of the n terminal segments while, for $S \neq 0$, the centrifugal order γ is considered for each of them. Then, using a uniform random number between 0 and 1, it is decided for each terminal segment whether a branching event indeed occurred in the given time bin, i.e. if the random number is smaller than or equal to the branching probability for that segment. A branching event implies that a new terminal segment is attached to the branching segment. When no branching happened, the tree structure is unmodified transferred into the next time bin. The process starts at the first time bin with a single (root) segment and stops at the last time bin (the number of time bins is arbitrarily chosen but such that the branching probability per time bin is much smaller than unity).

3.5. Parameter optimization

The model parameters B, E, S need to be set in such a way as to minimize the differences between model-generated trees and a particular set of experimentally discovered branching patterns.

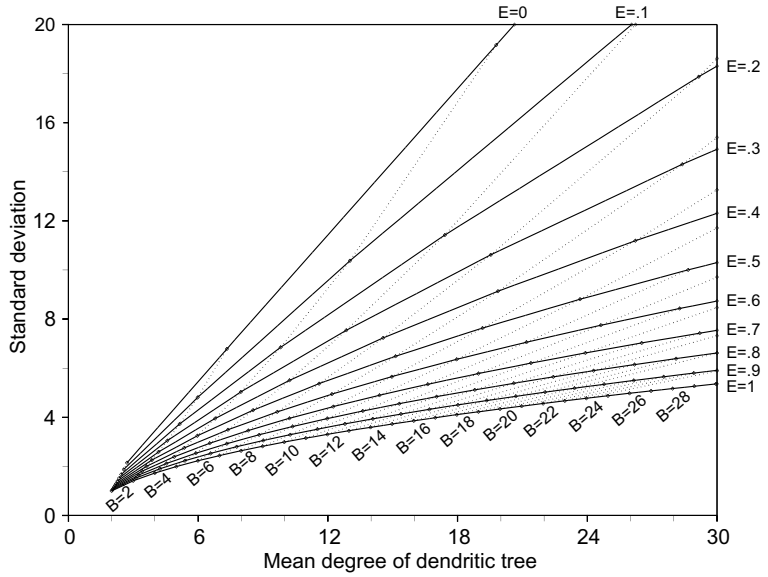

Fig. 3. Relationship between degree of dendritic tree and model parameters B and E. Displayed is the mapping of the (B, E) parameter grid onto the (mean, SD) plane. For many (B, E) pairs the corresponding values of mean and standard deviation of the degree distribution resulting from the model are plotted as data points in the (mean, SD) plane. Continuous and dotted lines connect points with equal E and B value, respectively. Adapted from [9].

Table 1
Shape properties of observed and modeled dendrites of SC neurons

Shape variables	Observations			Model outcomes	
	N_{obs}	Mean	SD	Mean	SD
DLNs					
Degree	26	12.58	7.46	12.49*	7.39*
Tree asymmetry	26	0.41	0.15	0.41*	0.14
Centrifugal order	628	3.58	1.74	3.53	1.70
SLNs					
Degree	12	28.3	18.1	28.6*	17.7*
Tree asymmetry	12	0.39	0.14	0.42*	0.1
Centrifugal order	659	5.03	2.06	4.92	2.04

Model outcomes are indicated by $*$ if the corresponding shape variables were fitted to the observed values by parameter optimization. Shape variables unmarked are model predictions. N_{obs} denotes the number of experimental findings of dendritic trees. Model outcomes result from 100 model-generated trees each.

In general, this is a multidimensional optimization task which can be done using various parameter search methods [11].

The structure of this model facilitates determining optimal parameter values in two steps [9]. Parameter S is estimated from the value of the topological asymmetry-index as follows. A set of trees of different degrees is generated as a function of S, and the expected value of the asymmetry-index of the set is calculated according to Eqs. (1) and (2).

The following method has been used for finding the optimal values for the parameters B and E for a given set of observed dendrites. The (mean, SD) values of the observed degree distribution are plotted as a data points in the parameter map (Fig. 3), and the corresponding (B, E) values are derived from the position of this point in the (B, E) parameter grid. The shape of the model degree distribution, calculated for these model parameters, is subsequently tested against the shape of the observed distribution by means of the χ^2 test.

4. Results

The observed frequency distributions of the shape parameters were used to optimize the parameters of the growth model. The parameters of SLNs ($B = 4.94$, $E = 0.20$, $S = 0.25$) clearly differ from those of DLNs ($B = 3.89$, $E = 0.29$, $S = 0.40$).

The shape properties of 100 model trees each generated with these parameter values are given by their mean and SD and compared to experimental values in Table 1. In the last two columns it is indicated whether the agreement is the result of parameter optimization or predictions derived from model simulations.

Observed (dashed histograms) and model generated (continuous lines) frequency distributions of shape properties are contrasted in Fig. 4. By the χ^2 test the model distributions were shown to be not significantly different from the observed ones.

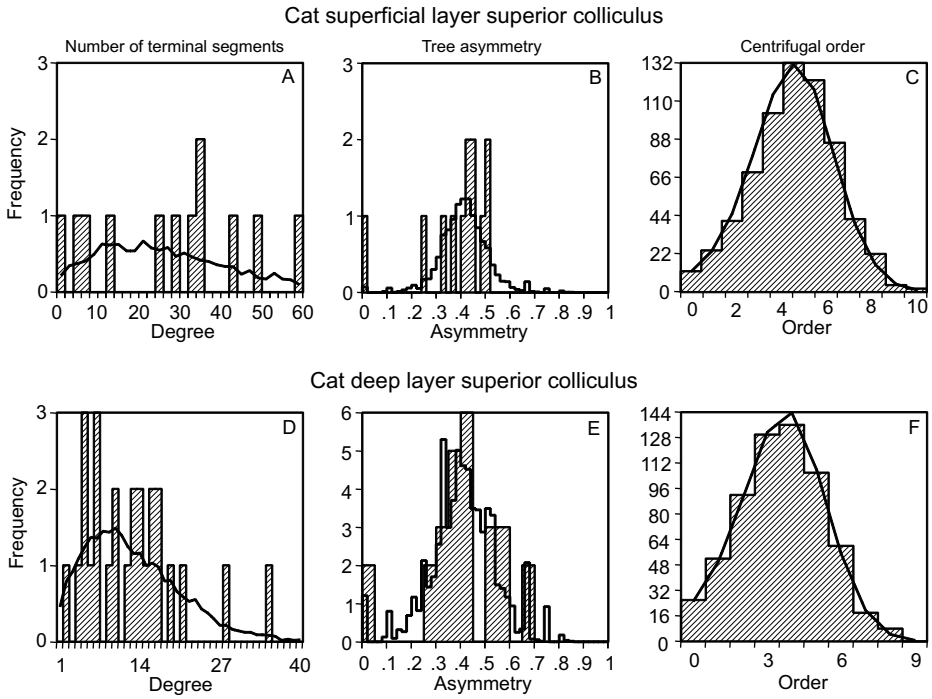

Fig. 4. Frequency distributions of shape parameters of SC neurons (dashed histograms) and model-generated trees (continuous lines) using the optimized parameter values.

In Fig. 5, the (B, E) values calculated for the two classes of SC neurons are compared with those of various neuron types from several species analyzed previously [11]. With respect to topological shape, SC neurons (h) are close to motoneurons (f and g) and interneurons (e), respectively. In contrast, cortical pyramidal and non-pyramidal neurons (a, b) significantly differ from SC neurons.

5. Discussion

The growth model describes dendritic growth as a stochastic branching process. The model is simple in structure, based only on order and size dependent branching probabilities. The correspondence between frequency distributions of shape parameters derived from reconstructed SC neuron dendrites and model-generated trees indicates, however, that the stochasticity assumptions employed in building the dendritic growth model are successful in explaining the variability of neuronal dendrites. It is important to note that agreement between model outcomes and empirical data was obtained also for parameters which were not used for optimization (see Table 1). Thus, the dendritic trees of each of the two classes of SC neurons have been effectively represented by a specific set of the model parameters B, E and S, as it has been achieved in previous studies on other neuron types, too [11,12]. In this way, a considerable compression of the morphological data has been obtained, and the analysis and comparison of the dendritic shapes of neuron classes during development, maturity and disease become feasible.

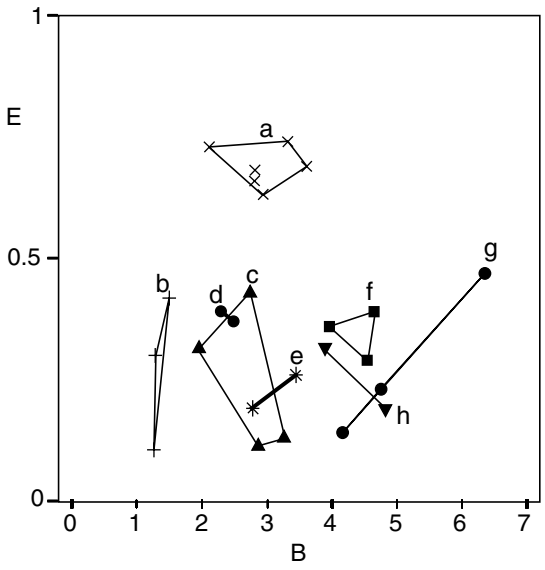

Fig. 5. Scatterplot of the growth model parameters B, E optimized for (a) – rat cortical pyramidal basal dendrites, (b) – rat cortical multipolar non-pyramidal neurons, (c) – rat motoneurons, (d) – human dentate granule cells, (e) – cultured cholinergic interneurons, (f) – cat motoneurons, (g) – frog motoneurons and (h) – cat SC neurons. Data corresponding to (a)–(g) were taken from Ref. [11].

Three aspects have been considered in modeling dendritic growth, viz. (1) the basic process of branching of an isolated segment, defined by the expected number B of branching events during the developmental period, (2) the increase of the segment number in the growing tree, and (3) the adjustment of the basic branching probability by the increasing degree of the tree (determined by parameter E) and the position of the segment in the tree (determined by parameter S).

In a previous study based on data from several neuron types [11], parameters B and E were shown to be uncorrelated in the analyzed data sets. This suggests that aspects (1) and (3) reflect different mechanisms in dendritic branching while all aspects together finally determine the shape of tree degree distribution.

The optimized (B, E) values tend to show clustering (see Fig. 5). Parameter E evidently discriminates between rat cortical pyramidal dendrites and other neuron classes, including SC neurons. The larger E value of pyramidal cells indicates that during growth of their dendrites the branching probabilities decrease stronger with increasing tree degree than in the other neuron types. On the other hand, the clustering also suggests a differentiation in B values between the other neuron groups. Although the statistics need to be improved, it seems reasonable to deduce from these results that the parameters B and E may both represent basic cell-type specific mechanisms of dendritic growth.

If the full growth model is employed, the metrical properties of dendritic trees (length and diameters of segments showing great variability) are included. Meanwhile it has been shown in several studies that both the topological and metrical properties of the empirically observed dendritic trees can be accurately reproduced by the full model using optimized parameters for the particular neuron types (for review see [8,9]).

The full growth model also provides a tool for generating sets of random dendritic trees which can be used to explore the functional implications of morphological variations. The method of choice then is to employ one of the powerful neuron function simulators, e.g. NEURON (http://neuron.duke.edu) or GENESIS (http://www.genesis-sim.org/GENESIS). A question of topical interest in this realm has been to what extent neurons can be treated as integrators summing up a number of small synaptic inputs over some characteristic period, or as coincidence detectors which fire when a few synaptic inputs arrive at the trigger zone within that period. Simulations with NEURON showed that the geometry of dendritic branching pattern indeed influences SC neuron function. While the functional parameters (signal attenuation, delay and time window) derived on SLNs are compatible with time-critical functions, DLNs in contrast show integrator traits [13]. NEURON simulations with a set of dendritic trees generated by the growth model have demonstrated that dendritic morphology also might influence firing patterns [14].

References

[1] A. Schierwagen, Scale-invariant diffusive growth: a dissipative principle relating neuronal form to function, in: J. Maynard-Smith, G. Vida (Eds.), Organizational Constraints on the Dynamics of Evolution, Manchester University, Manchester, 1990, p. 167.
[2] R.W.H. Verwer, J. Van Pelt, H.B.M. Uylings, An introduction to topological analysis of neurons, in: M.G. Stewart (Ed.), Quantitative Methods in Neuroanatomy, Wiley, New York, 1992, p. 295.
[3] R. Grantyn, R. Ludwig, W. Eberhardt, Neurons of the superficial tectal gray. An intracellular HRP-study on the kitten superior colliculus in vitro, Exp. Brain Res. 55 (1984) 172.
[4] A. Schierwagen, R. Grantyn, Quantitative morphological analysis of deep superior colliculus neurons stained intracellularly with HRP in the cat, J. Hirnforsch. 27 (1986) 611.
[5] A. Schierwagen, Comparative analysis of dendritic geometry and electroanatomy of superior colliculus neurons in the cat, Verh. Anat. Ges. (Anat. Anz. Suppl. 164) 82 (1988) 887.
[6] A. Schierwagen, The collicular motor map as modelled by a two-dimensional mapped neural field, in: W.H. Zangemeister, H.S. Stiehl, C. Freska (Eds.), Visual Attention and Cognition, Elsevier, Amsterdam, 1996, p. 45.
[7] J. Van Pelt, H.B.M. Uylings, R.W.H. Verwer, R.J. Pentney, M.J. Woldenberg, Tree asymmetry – a sensitive and practical measure for binary topological trees, Bull. Math. Biol. 54 (1992) 759.
[8] J. Van Pelt, H.B.M. Uylings, Natural variability in the geometry of dendritic branching patterns, in: R.R. Poznanski (Ed.), Modeling in the Neurosciences – From Ionic Channels to Neural Networks, Harwood Academic, Amsterdam, 1999, p. 79.
[9] J. Van Pelt, A. Van Ooyen, H.B.M. Uylings, Modeling dendritic geometry and the development of nerve connections, in: E. De Schutter, R.C. Cannon (Eds.), Computational Neuroscience: Realistic Modeling for Experimentalists, CRC, Boca Raton, FL, 2000, p. 179.
[10] A.E. Dityatev, N.M. Chmykhova, L. Studer, O.A. Karamian, V.M. Kozhanov, H.P. Clamann, Comparison of the topology and growth rules of motoneuronal dendrites, J. Comp. Neurol. 363 (1995) 503.
[11] J. Van Pelt, A.E. Dityatev, H.B.M. Uylings, Natural variability in the number of dendritic segments: Model-based inferences about branching during neurite outgrowth, J. Comp. Neurol. 387 (1997) 325.
[12] J. Van Pelt, A. Schierwagen, H.B.M. Uylings, Modeling dendritic morphological complexity of deep layer superior colliculus neurons, Neurocomputing 38–40 (2001) 403.
[13] A. Schierwagen, C. Claus, Dendritic morphology and signal delay in superior colliculus neurons, Neurocomputing 38–40 (2001) 343.
[14] A. Van Ooyen, J. Duijnhouwer, M.W.H. Remme, J. Van Pelt, The effect of dendritic topology on firing patterns in model neurons, Network: Computat. Neural Systems 13 (2002) 311.