Modeling the natural variability in the shape of dendritic trees: Application to basal dendrites of small rat cortical layer 5 pyramidal neurons[☆]

Jaap van Pelt*, Harry B.M. Uylings

Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam, Netherlands

Abstract

The emergence of dendritic complexity is studied by means of a mathematical model, based on randomly branching and randomly propagating growth cones. Branching probabilities, which depend on the position and decrease with the number of growth cones in the growing tree, are sufficient to account for the observed variation in the number and connectivity pattern of dendritic segments. Segment length distributions of small rat cortical layer 5 pyramidal cell basal dendrites are now accurately reproduced by also assuming randomness in the rate of growth cone propagation. Different mean propagation rates are predicted for two distinct phases of dendritic development. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Dendrites; Development; Growth cones; Morphology; Pyramidal cells

1. Introduction

Dendritic branching patterns are complex and show a large degree of variation with respect to shape, within as well as between different cell types and species. This variation is found in typical shape parameters, such as the number, length and connectivity pattern (topological structure) of the segments comprising the dendritic tree, the curved nature of these segments and the embedding of the dendrite

in three-dimensional (3D) space. Dendritic complexity emerges during neurite outgrowth from the dynamic behavior of growth cones, which are involved in branching and lengthening of dendritic segments. The best way to get insight into dendritic complexity is therefore to study how the dynamic behavior of growth cones ultimately result in the characteristics of dendritic shapes. In our ongoing studies, a mathematical modeling approach is used in which the actions of growth cones are assumed to be outcomes of a stochastic process. Previous studies [1,5,6] already showed that the observed variations in the number and connectivity pattern of segments in dendritic trees from many different neuronal cell types and species can accurately be reproduced by assuming that branching events occur randomly in time and at randomly selected growth cones. The time-dependent branching probabilities turn out to decrease with the number of segments in the growing tree, and also may depend on the position of the growth cones in the tree. Segment lengths are determined by both the propagation and the branching behavior of growth cones. The *propagation* of growth cones was recently included in the model in a study of segment lengths in large rat cortical layer 5 pyramidal cell basal dendrites [7]. It was shown that the mean and standard deviation of segment length and path length distributions could accurately be reproduced by assuming randomness in growth cone propagation, as well as different propagation rates during two distinct phases of pyramidal dendritic development. When applied to different cell classes, the optimized growth parameters may reflect characteristic differences in growth patterns between these cell classes. In this ongoing research we will now report on the analysis of basal dendritic trees of small rat cortical layer 5 pyramidal neurons. These small neurons distinguish themselves from large pyramidal neurons in layer 5 by smaller somata and the absence of an apical arborization in the upper cortical layer.

2. Description of the growth model

2.1. Branching process

The total developmental period T is divided into a series of N time bins, initially without defining the durations of the time bins. At each time bin i, any growth cone in the tree (located at the tip of each terminal segment) may branch (split into two daughter growth cones) with a probability p_i given by

$$p_i = \frac{B}{N} n^{-E} 2^{-S\gamma_i} / C, \tag{1}$$

with n denoting the number of growth cones in the tree (degree), γ the centrifugal order of a growth cone, N the total number of time bins in the developmental period T, and B the expected number of branching events in that period for a single growth cone. Exponent E determines the dependency on degree n, exponent S determines the dependency on order γ, and C equals a normalization factor, $1/n \sum_{i=1}^{n} 2^{-S\gamma_i}$. The number N is chosen arbitrarily but such that the branching probability per time bin
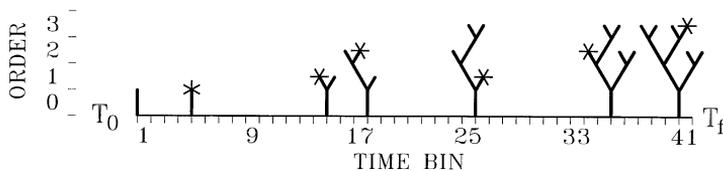
Fig. 1. Illustration of a branching sequence, starting at time T_0 and ending at time T_f. The stars indicate the occurrence of actual branching events at that time step, resulting in a branch point and two daughter growth cones. Note that the number of $N = 41$ time bins is taken unrealistically small for reason of illustration.

remains much smaller than one. An example of a sequence of branching events is given in Fig. 1.

2.2. Elongation process

Segment length has been modeled by including growth cone propagation (i.e., segment elongation) into the branching model. To this end, growth cones are assigned a propagation rate at the time of their birth (i.e., after a branching event), by randomly sampling a gamma-shaped distribution, characterized by its mean and standard deviation. In the present study we assume equal durations for all time bins, determined by the total period of development T, divided by the total number of time bins N.

3. Basal dendrites of small layer 5 rat cortical pyramidal neurons

The basal dendrites of these neurons start growing by branching and elongation one day before birth (H.B.M. Uylings, unpublished observation) up to day 10 postnatally, after which the branching process terminates, while the elongation of segments continues up to day 18 [4]. Geometrical properties are further summarized in Table 2.

4. Results

Previous studies showed that the branching model was able to give an accurate account of the topological variation [1,5], as well as of the shape of the distribution of the number of dendritic segments in many cell types [6]. For small rat cortical layer 5 pyramidal basal dendrites this correspondence was obtained for parameter values for B, E and S, as given in Table 1.

The mean growth cone propagation rate of 0.406 μm/h for the whole period was first estimated from the mean pathlength (185 μm) in the dendrites and the total period of elongation (456 h, 19 days). With these model parameters for branching and

Table 1
Optimized parameter values for basal dendrites of small layer 5 rat cortical pyramidal neurons

Parameter	Use	Optimization on	Ref.
$B = 3.35$	Free	*Degree* mean, SD	[6]
$E = 0.63$	Free	*Degree* mean, SD	[6]
$S = 0.87$	Free	Mean asymmetry	[5]
$V_{el} = 0.64\,\mu m/h$	Free	Mean terminal segment length	
$cv_V = 0.4$	Free	SD in pathlength	
$V_{br} = 0.24\,\mu m/h$	Calculated	a	

[a]The mean propagation rate V_{br} during the branching phase is calculated from the distance L_{br}, traversed in the branching phase and the duration $T_{br} = 264$ h. The distance L_{br} is obtained via $L_{br} = L_p - L_{el}$, with a total mean pathlength $L_p = 185\,\mu m$ and the distance L_{el}, traversed in the elongation phase, estimated via $L_{el} = V_{el}T_{el}$, with $T_{el} = 192$ h.
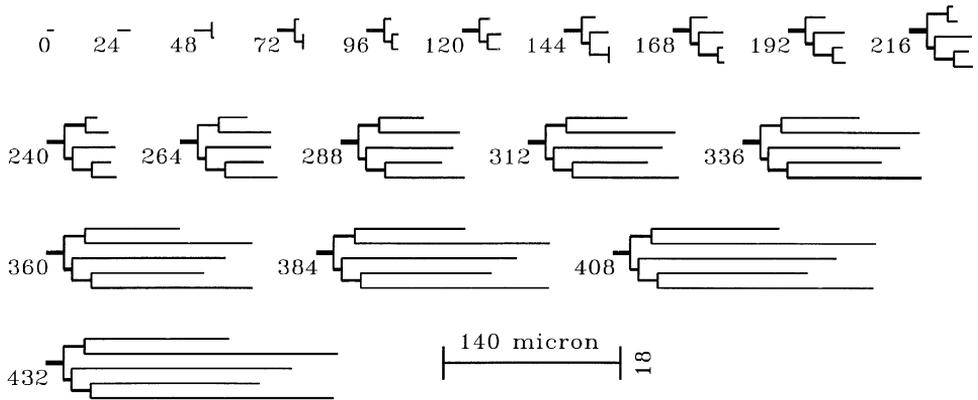

Fig. 2. Plot of a model dendritic tree at successive days of its development. The age (in hours) is indicated by the number at the root of the tree. The growth parameters used were optimized for basal dendrites of small layer 5 rat cortical pyramidal neurons and are given in Table 1. A period of branching and elongation from one day before birth up to 10 days postnatally is followed by a period of elongation only up to day 18. Note the different elongation rates in both periods. For reason of visualization, the segments have been given a diameter, which has been calculated by means of a branch power rule.

propagation and including different stop times for branching and elongation, dendrites were produced with a median length of 20.5 μm for intermediate segments and a mean length of 114.2 μm for terminal segments. These values appeared to be longer, respectively, shorter than the observed values of 11 μm (median) and 143 μm. Thus, the assumption of a constant mean growth cone propagation rate led to incorrect results. The observed mean segment lengths could be accurately reproduced, however, if different mean propagation rates were assumed of 0.24 μm/h during the branching phase and of 0.64 μm/h during the elongation phase. Stochasticity in the propagation rate was included by assuming a coefficient of variation of $cv_V = 0.4$. With this value

Table 2
Shape properties of model dendrites compared with empirical data. In the last column is indicated which shape variables were matched to the observed values by optimizing the model parameters (see Table 1) and which shape variables are new outcomes of the growth model

Shape variables		Observations		Model outcomes	
Degree (no. of tips/dendrite)	mn	5.9	[2]	5.8	Optimized
	SD	2.9	[2]	2.9	Optimized
Asymmetry	mn	0.38	[5]	0.37	Optimized
	SD	0.22	[5]	0.20	*Prediction*
Centrifugal order	mn			2.3	*Prediction*
	SD			1.3	*Prediction*
Total dendritic length	mn	923 µm	[a]	912	*Prediction*
	SD			462	*Prediction*
Terminal segment length	mn	143 µm	[2]	144.1	Optimized
	SD	48	[2]	52	*Prediction*
Intermediate segment length	mn			16.3	*Prediction*
	SD			15.9	*Prediction*
	Median	11 µm	[2]	11.3	*Prediction*
Pathlength to tips	mn	185 µm	[2]	186	Estimated
	SD	53	[2]	51	Optimized

[a]The mean total length per dendritic tree of 923 µm is estimated from the total basal dendritic length per small layer 5 pyramidal neuron of 4.06 mm (SD = 1.19) [3], and the mean number of basal dendrites per small layer 5 pyramidal neuron of 4.4 (SD = 0.7) [2].

the model predicted a pathlength variation that optimally matched the observed one. The parameter values used are summarized in Table 1. A typical example of a growing dendrite is given in Fig. 2. Note, that after day 10 (240 h) no branching events occur anymore. The mean and standard deviations of the distributions of the different dendritic shape parameters are calculated from a sample of 2000 model trees, and are summarized in Table 2. The theoretical results are in good agreement with the available empirical data.

5. Discussion

The present model, based on randomness in branching as well as propagation of growth cones, has shown to give an accurate description of all the presented dendritic shape properties, both in their mean and in their variation. This agreement is obtained by optimizing only five free parameters (i.e., B, E, S, V_{el}, and cv_V), supporting the explanatory power of the model. Further experimental data is needed to assess the correctness of the predicted values as well as the shape of the distributions. Agreement in shape has already been demonstrated for the distribution of the number of terminal segments in basal dendritic trees of small rat cortical layer 5 pyramidal neurons [6]. An additional property of the growth model approach is that possible dependencies among dendritic shape parameters, arising during development, are implicitly

accounted for. The optimal growth parameters between large and small layer 5 pyramidal cell basal dendrites do not show large differences, with values of (B, E, S, V_{el} and cv_V) of $(3.85, 0.74, 0.87, 0.51, 0.28)$ for the large pyramidal cells [6,7] and $(3.35, 0.63, 0.87, 0.64, 0.4)$ for the small pyramidal cells. Information about the underlying variances, both within and between celltypes, is, however, needed to give a meaningful interpretation of these differences. Our ongoing research is aimed at applying the model-based analysis to different cell types, which will provide the basis of such comparisons. Additionally, the ability of generating random dendrites with realistic variation in their shape contributes to studies of the impact of this variation on the integration of electrical signals in dendritic trees. In conclusion, mathematical modeling of dendritic growth on the basis of random behavior of growth cones has brought many dendritic shape parameters and their variations into a coherent framework.

References

[1] 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) 505–516.

[2] A.U. Larkman, Dendritic morphology of pyramidal neurones of the visual cortex of the rat: I. Branching patterns, J. Comp. Neurol. 306 (1991) 307–319.

[3] A. Larkman, A. Mason, Correlations between morphology and electrophysiology of pyramidal neurons in slices of rat visual cortex. I. Establishment of cell classes, J. Neurosci. 10 (1990) 1407–1414.

[4] H.B.M. Uylings, J. van Pelt, J.G. Parnavelas, A. Ruiz-Marcos, Geometrical and topological characteristics in the dendritic development of cortical pyramidal and non-pyramidal neurons, in: J. van Pelt, M.A. Corner, H.B.M. Uylings, F.H. Lopes da Silva (Eds.), Progress in Brain Research, vol. 102, The Self-Organizing Brain: From Growth Cones to Functional Networks, Elsevier, Amsterdam, 1994, pp. 109–123.

[5] 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) 759–784.

[6] 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) 325–340.

[7] 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 Publishers, Amsterdam, 1999, 79–108.

Jaap van Pelt received his PhD in Physics in 1978 at the Free University in Amsterdam, The Netherlands. His research group Neurons and Networks at the NIBR works both experimentally and theoretically on neuronal morphology and activity-dependent mechanisms in neurite outgrowth and neural network formation.

Harry B.M. Uylings received his PhD in Neurobiology in 1977 at the University of Amsterdam, The Netherlands. His research group at the NIBR works on the functional and structural organization of the prefrontal cortex, both in animals and in humans.