

Coordinate Systems for Dendritic Spines: A Somatocentric Approach

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Of fundamental importance in describing a neuron's activity and constructing biologically plausible neural networks is the unambiguous description of its smallest element of input in the integration process. Among neuronal input units are the synaptic spines: highly regulated and coordinated elements on the dendrites, exchanging both electrical signals and molecules with the soma along the dendritic branches. Mapping the physiological parameters of dendritic branches and their spines in anatomically compatible coordinates is important because of the interactions between "close" spines and between spines and the soma. We present a simple method for quantitatively locating dendritic spines by separating their coordinates into two components. The first takes into account the position of the dendritic branch on which the spine lies. In this component, the distance between a branch and the soma is given by the number of bifurcations along the dendrite ("level"). We have formulaically described the difference in this parameter between any two spines ("distance") in terms of the level of the common bifurcation farthest from the soma ("generator"). The second component of a spine's location is its position on the dendritic branch. Our system is fully analytical and easily implementable. It also defines a biologically plausible distance between any two spines, and between a spine and the soma. Based on this labeling method, we present a coordinate system in which a spine is described by a matrix encoding physiological parameters of the generating branches. A second set of coordinates is introduced to describe a neural state with a matrix of spine parameters. Finally, a third matrix notation is proposed to take into account interactions between spines. This treatment leads to some interesting speculations, such as the possibility of describing input dynamics of a neuron in terms of operators on vector spaces. © 1997 John Wiley & Sons, Inc.

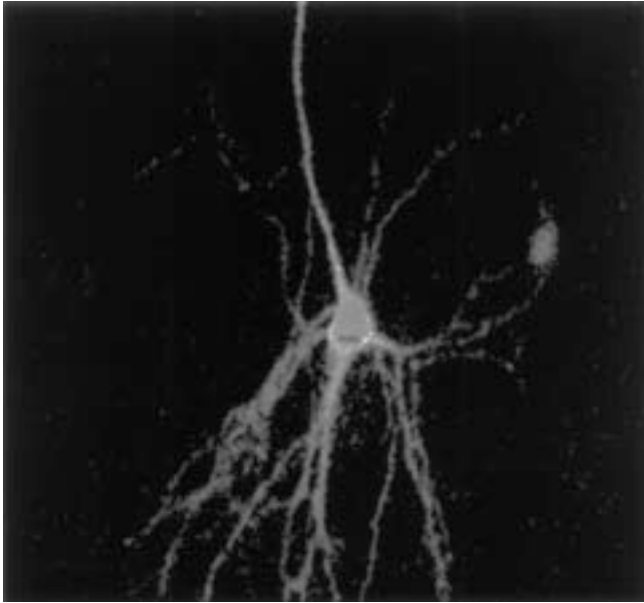
Key Words: spines, dendrites, neural modeling, coordinate system

1. INTRODUCTION

It is widely accepted that the neuron is not a simple switch or unit of transmission, but rather a complex system able to handle a large amount of data [1]. The integration of a large set of inputs by a single neuron constitutes a process of complex computation, ultimately responsible for many, if not all, macroscopic abilities of nervous systems. It has been pro-

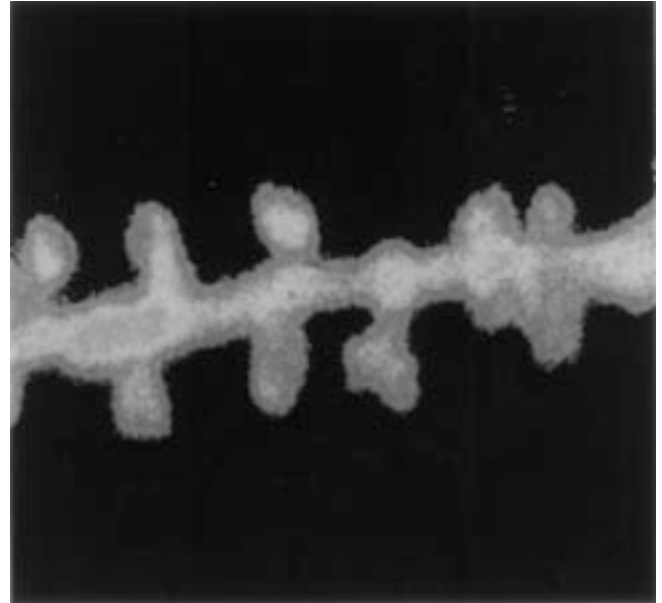
posed that even higher cognitive functions in mammals, such as learning and memory, find their molecular correlates not only in cellular interaction among neurons, but also in intraneuronal events involving subcellular organelles, the dendritic spines [2] (Figure 1a-c). Spines, small protuberances, about 20,000 to a cortical pyramidal cell, are one type of synaptic loci for the input in the neuron-to-neuron interactions,

FIGURE 1



a 20 μm

Confocal microscopy of a pyramidal cell from the CA1 region of rat hippocampus. Scale bar: 20 μm . Slice/cultured neurons were stained with lucifer yellow and scanned with an argon-ion laser. The soma is visible in the middle, several dendritic trees on the bottom, and the axon on the top of the picture (Courtesy of C. Collin and M. Segal, Lab. Adaptive Systems, NINDS, NIH, Bethesda, Md).



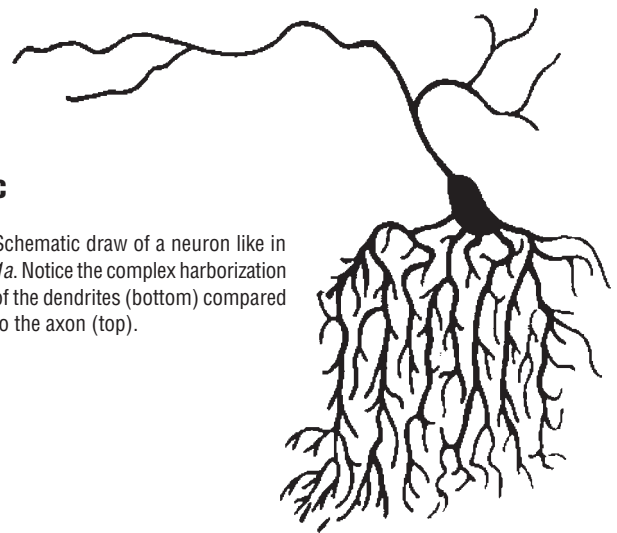
b

100X enlargement of a dendritic branch from 1a, several spines are evident (Courtesy of C. Collin and M. Segal, Lab. Adaptive Systems, NINDS, NIH, Bethesda, Md).

representing therefore a unit of integration. The neuron can also receive stimuli through direct synaptic contacts on the soma, although dendritic connections seem to play a pivotal role in the determination and regulation of fine-tuned processes of the neuron, such as association [3]. In addition, not all the synapses on the dendritic branches involve spines and, in general, the precise functional role of dendritic spines is still under debate [4, 5].

It has been postulated that, in principle, a complete map of synaptic activities would determine the state of the neuron entirely [6], and it appears evident that while the contribution of direct connections on the soma is more easily computable, dendritic inputs are both crucial and difficult to model. Even though the physiology and the biochemistry of dendritic spines are far from well known, a biologically meaningful way of describing spine location with respect to the soma or to other spines is clearly needed.

Furthermore, in classical neural network models, any intracellular cytoarchitecture and compartmentalization are ignored, and the system is completely specified when the connection weight between any two neurons is known [7]. Based on the neurobiological research, this approach seems to be too crude and simple to achieve the computational power of natural nervous systems, and indeed several models have been proposed in which the neuron is itself a neural network [8]. Therefore, of fundamental importance for those neural network researchers who wish to design biologically plausible



c

Schematic draw of a neuron like in 1a. Notice the complex harborization of the dendrites (bottom) compared to the axon (top).

models, is a system which numerically labels dendritic spines in a manner suitable to take physiological parameters into account. Moreover, there is no need to topologically distinguish dendritic spines from other dendritic synapses, thereafter a coordinate system for spines or dendritic branches furnishes a general mathematical tool to model highly modulatory neuronal inputs.

In order to match these needs, suitable coordinates for dendritic spines should fulfill the following characteristics, which we discuss below:

- 1) The position of a spine in these coordinates must encode (or be incorporated in) a simple definition of a distance between the spine itself and the soma of the neuron.
- 2) A distance between spines along the dendrites must be defined based on their positions relative to the soma.
- 3) The mathematics developed with the definition(s) of distance(s) must be easily implementable.

The first characteristic is justified by the need to describe the complex interactions between the spines and the soma. For instance, spines send electrical signals to the soma, and as a first approximation one may consider spines farther away to have a smaller weight in the final integration of the neuron [9]. On the other hand, small molecules and biopolymers travel along the dendrites in both directions, and both active transportation and passive diffusion seem to play a role in this process [10]. An important example is given by calcium ion, a second messenger that also plays a role in dendritic action potential [11]. In the case of the soma delivering molecules to the spines, it is likely that a smaller amount of substance will be available for spines farther from the soma [12]. A particular example of this process will be discussed in another section of this paper. It is interesting to note that in order to describe the two above-mentioned examples (electric signaling and molecular transportation) different information content (length and size of the branches, number of bifurcations, and so on) may in principle be useful in the definition of distance of the spine from the soma. In general, it is convenient to develop a flexible coordinate system that allows the definition of several distances, or of one distance with several possible biological applications.

The second characteristic is necessary in order to describe interactions between spines: evidence suggests that adjacent spines undergo mechanisms of cooperativity or mutual inhibition as a subcellular basis of associative learning and memory [13, 14]. Models have been proposed in which the association between two distinct neural pathways, as in the case of classical (Pavlovian) conditioning, is explainable in terms of association between spines in single neurons shared by the two pathways [15]. In this model, close spines are simply likely to interact more efficiently. A more elaborate model holds that each cluster of spines (on a branch or even a group of branches) can also interact with other close clusters, thus forming the second of several levels of association, eventually integrated by the neuron [16]. In these models, the definition of a distance between spines would allow the description of a "sphere" of interaction around a spine.

These two characteristics imply that the anatomy (topology) of the neuron should be conserved (or taken into account) in the coordinate system: for example, locating spines in standard Cartesian coordinates is a very inefficient system to describe processes along the dendrites, and any correction factors make the system inconveniently com-

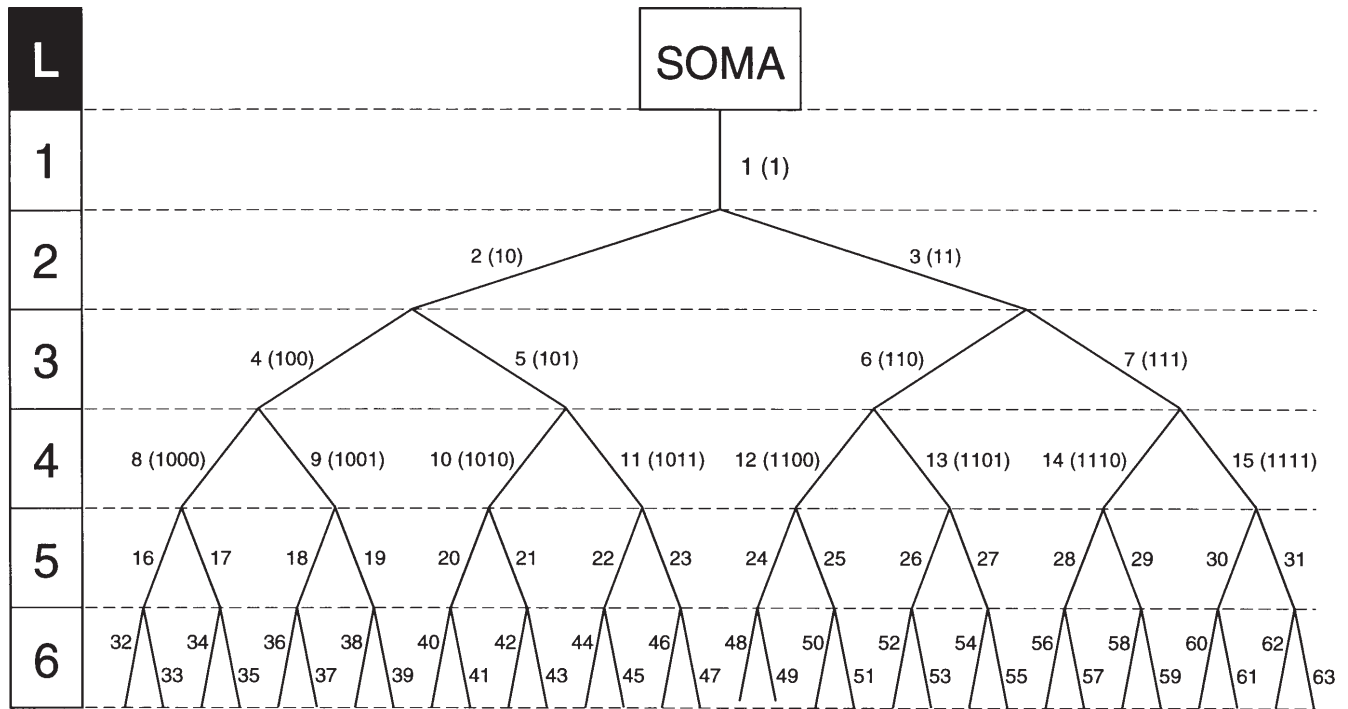
plicated. Nonetheless, some neural phenomena are actually well described in simple Cartesian coordinates, such as the possibility for spatially close spines to receive synaptic contacts from the same axon [17], or the influence of the concentration of specific extracellular substances on intracellular activities. The final description of the neural state will have to consider both the Cartesian and the non-Cartesian coordinate contribution, although only the second component is the domain of this paper.

2. METHOD

The numerical system we present assigns a unique pair of numbers to each spine, designating its position on the dendritic tree. The first number indicates on which branch of the dendrite the spine is located. The second measures how far along this dendritic branch the spine lies (the spatial distance from the last bifurcation of the dendrite). We define a *topological distance* between any spine and the soma by the number of branch bifurcations between the branch on which the spine is located and the soma itself, *and* by how physically close the spine is to the bifurcation which defines the branch. This easily generalizes to a distance between any two spines. The first number in the pair is useful to describe those interactions between the soma and a specific spine, or between two spines, which depend more acutely on the number of bifurcations along the dendritic branches than they depend on the actual measured distance of the spine from the soma. The use of the second number, however, targets a specific spine after finding the branch on which it lies, like a house number on a named street.

Of primary importance, then, is finding a simple system to number the dendritic branches themselves. Directions from the soma to a specific dendritic branch may be specified by a series of choices, either "right" or "left" at each bifurcation of the branch. Right and left are arbitrarily defined in three-dimensional space using a choice of orientation at each bifurcation. It is opportune to standardize this choice by identifying, univocally, a given branch by its label. An example of such a standardization is briefly described here: first orient the neuron in three-dimensional space with a choice of orthogonal axes (labeled x , y , and z .) centered at the soma. This choice of Euclidean coordinates is the only part of the orientation that is arbitrarily assigned. At each bifurcation, the two protruding branches are distinguished from one another by any plane that separates them in three-space. Translate the coordinate axes to the point of bifurcation. If the two branches span a plane that is not perpendicular to the xy -plane, they can be separated by a plane through the z -axis as follows. If the yz -plane separates the two branches, call "right" the branch in the positive x -hemisphere and "left" the branch in the negative x -hemisphere. If the plane does not separate them, simply rotate the coordinate system about the z -axis counterclockwise until it does; label "right" and "left" as prescribed. If the two branches lie in a plane that is perpendicular to the

FIGURE 2



Schematization of the numbering system for a dendritic tree. The branches are labeled in decimal notation, with the corresponding binary number in parentheses. The level (on the left) is the number of bifurcations between the branches and the soma.

xy -plane, separate them by the xy -plane after a counterclockwise rotation of the coordinate system around the x axis. Label the branch in the positive z -axis right, and the branch in the negative z -axis left.

It should be noted that theoretically there are no circumstances in which there is a three-way (or more) bifurcation. One may consider such occurrences as single bifurcations followed closely by secondary bifurcations. Since there is only one path from the soma to any branch within a specific dendritic tree, the address of the branch is uniquely specified by a sequence of left's and right's, indicating directions from the soma to the branch. We replace this awkward language with binary code; each dendritic branch is labeled by a unique binary number, where 1 stands for left and 0 stands for right. We convert it to the decimal system to obtain a unique positive integer assigned to each branch. The branch protruding from the soma which defines the dendritic tree is labeled 1.

With this numbering system in place, one can easily calculate the "branch-distance" of the spine to the soma, defined as the number of bifurcations there are in between the soma and the branch. This distance will be called the *level* of the branch (Figure 2). If we refer to the binary number associated with this branch, it is simply the number of 0's or 1's in the number; each 0 or 1 indicates one bifurcation. The equivalent description in decimal notation is to define the level l of a branch x to be

$$l(x) = 1 + \text{Int}(\log_2 x).$$

where $\text{Int}()$ is the integer of $()$. The topological distance between a spine and the soma is then defined by a pair of numbers; the first is the level of the branch, and the second is the measured distance between the spine and the bifurcation generating the branch. The ordering amongst the spines is the following: any spine with a lower level is closer to the soma than any spine with a higher level. Amongst spines which are at an equal level, those which have a smaller second number in their addresses are closer to the soma than those with a larger one.

This framework suggests a notion of distance between two spines as well. Such a distance must be faithful to the anatomical path taken in traveling from one spine to another. The shortest path from one spine to another is the (unique) route which goes from the first spine "up" the dendritic tree to the first branch it has in common with the other spine, then "down" different branches until it reaches the second spine. It is, therefore, useful to define the *generator* of two spines, or the branch farthest from the soma which is in the path from the soma to *both* spines (Figure 2). We define a *parent* of a spine to be any branch in the path from the soma to the spine. The generator of two spines is thus the common parent which is farthest from the soma. The topological distance between two spines has two components, defined as follows: the first is the sum of the differences in levels between each spine and the generator. The second component is the sum of the sec-

ond numbers of the addresses of the spines. Two spines are closer to each other than two other spines if either the first component of the distance between them is smaller than that of the other pair of spines, or if the first component is the same and the second is smaller. To calculate the first component of the distance between two spines, we need only know on which branches they lie. Let x and y be the positions of two branches. Then the distance between the branches (which is also the first component in the pair that defines the topological distance between two spines) is described by:

$$d(x,y) = l(x) + l(y) - 2l(g(x,y)) \quad (*)$$

where $g(x,y)$ is the position of the generator of x and y . Notice that the generator of two spines depends only on the branches on which the spines lie.

It must be feasible to calculate the level of the generator of two spines on branches labeled x and y . Assume for the moment that the two spines in question have the same level. If x and y were the same number, the level of the generator would be simply that of x (or y). If they are not the same number, we want to find the unique parent branch one level lower ("higher" on the dendritic tree) than each spine and compare these two. If they are the same, we have found the generator, and if not, we continue this process. The corresponding mathematics to specifying the level of the parent of the branch x one level lower is dividing by 2 (using decimal notation), and taking the integer of $x/2$. This is an iterative process: at each step, we evaluate $Int(2^{-n}x)$ and $Int(2^{-n}y)$ and compare them, where n is the number of times we have already iterated (n begins at 0, which compares the numbers x and y themselves). The level of the generator will be the level of the number $Int(2^{-n}x)$ when it first coincides with $Int(2^{-n}y)$, i.e., for minimal n .

To formalize this process mathematically, we would like to find an expression which is 1 when we have a common parent, and 0 otherwise. The level of the generator is then a sum of these numbers, for there are precisely $l(g(x,y))$ common parent branches of x and y . It is sufficient to find such an expression which is between 0 and 1 for each n , and strictly less than 1 if and only if the n th iteration of moving up along the tree (decreasing the level by one) does not yield a common parent; applying the $Int()$ function makes the expression equal to 1 when we have a common parent, and 0 otherwise, as desired. The expression

$$[Int(2^{-n}x)]^{-1} - [Int(2^{-n}y)]^{-1}$$

has these properties, except it equals 0 if and only if the two numbers are equal. The expression:

$$\cos\{(\pi/2)[Int(2^{-n}x)]^{-1} - [Int(2^{-n}y)]^{-1}\}$$

equals 1 exactly when we have a common parent, and is otherwise strictly less than 1. Apply $Int()$, and we have a new ex-

pression which is 1 when we have found common parents of x and y , and 0 otherwise. Summing over n , we obtain the level of the generator:

$$l(g(x,y)) = \sum Int(\cos\{(\pi/2)[Int(2^{-n}x)]^{-1} - [Int(2^{-n}y)]^{-1}\})$$

where the sum is from $n = 0$ to $n = l(x)$.

Now for the more general case. Without loss of generality, assume that $l(x) \leq l(y)$. We find the unique parent of y which is on the same level of x , and then apply the method above. Call this parent y' . We have:

$$y' = Int(2^{-(l(y)-l(x))}y).$$

Any easy check shows that $l(y')=l(x)$. The formula given in (*) is now calculable.

This method of numbering branches and spines establishes two closely related notions of somatocentric coordinates. The first ("branch coordinates") describes a particular spine, where the i th coordinate corresponds to the i th branch in the path from the soma to the spine. Alternatively, the "spine coordinates" describe a dendritic tree, where the i th coordinate corresponds to the i th spine in the tree.

3. APPLICATIONS

There are several applications of Section 2, three of which we briefly attempt to explore here. The first is to model a single spine, describing several physiological features which can be represented through the coordinate system we have developed. The second is a model for the entire neural input map, described in terms of dendritic spine parameters. The third application is to model the interactions between any two spines of the neuron, such as association, cooperativity or mutual inhibition.

The first application of the somatocentric coordinates constructed in Section 2 is a matrix description of a single spine. Branch coordinates allow an efficient tabulation of the information about a spine, including as many or as few parameters as desired, in a matrix of real numbers or functions. For the purposes of this exposition, we consider a matrix as a collection of column vectors, each of which will represent some category of information. The coordinate system for the matrices is that described in Section 2; the i th entry in each vector corresponds to the i th branch in the path from the soma to the spine in question. Thus, if there are n branches in this path (including the branch on which the spine lies), there will be n entries in each vector.

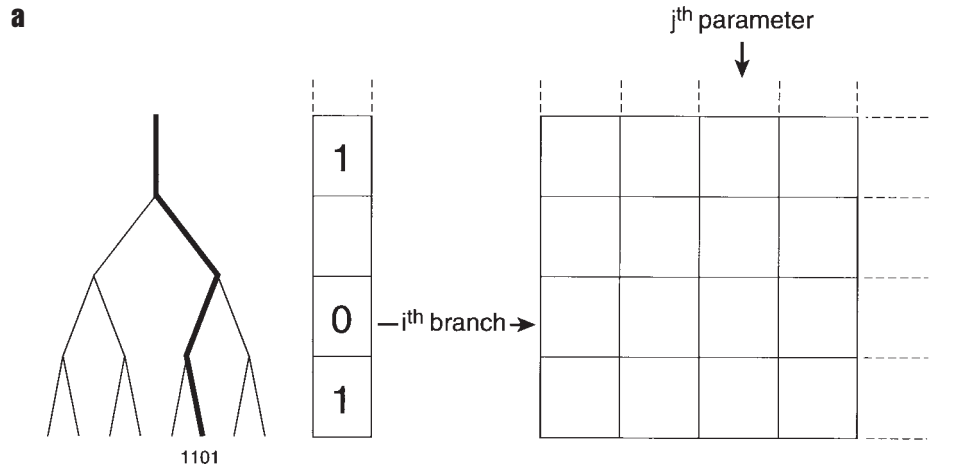
With this coordinate system in place, the first vector in the matrix associated to a specific spine is the *branch vector*, which consists of the sequence of 0's and 1's corresponding to the path from the soma to the spine. The branch vector is obviously motivation for the choice of coordinate system, but the coordinate system allows us to incorporate far more information in vectors of the same form (Fig-

FIGURE 3

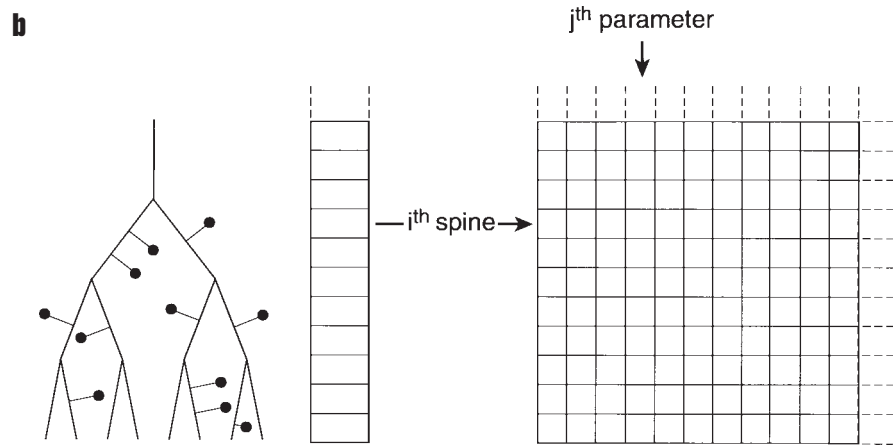
ure 3a). For example, we can define a vector of branch length, where the i th entry is the length of the i th branch; the last entry will be weighted in the sense that it will record the length of the last branch from the defining bifurcation to the spine, not the entire length of the branch.

Correspondingly, we can define the branch diameter vector; in this case, the last entry will not need to be weighted because of the position of the spine on the branch. In fact, one can define a column vector for any local physiological property, i.e., any property that does not depend on the state of the entire neuron, rather is well-defined for individual branches. In particular, information pertaining to the electrical properties of the branch, such as conductivity, permeability to several specific ions, presence of active pumps etc., can be neatly tabulated. Such information can be used to calculate the contribution of a spine's electrical activity to the soma potential. This method, in a simplified version, can also be applied to a description of nonspine mediated dendritic synapses.

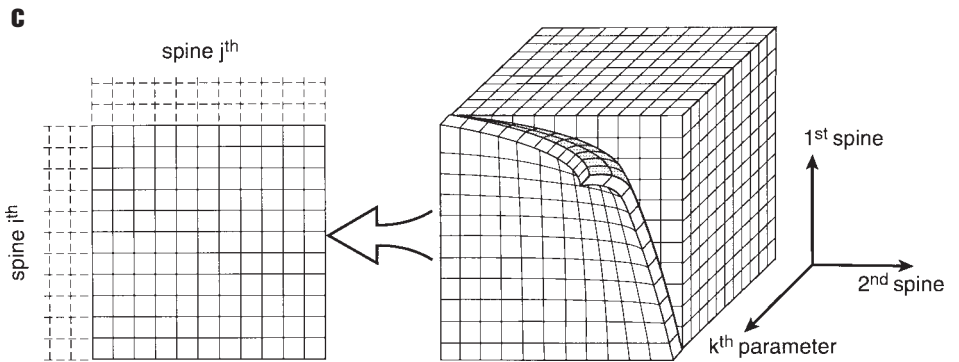
As an example of the utility of this description, we discuss below a problem concerning molecular transportation. When a specific dendritic spine drastically changes its activity, for instance following a sustained activation of the neural pathway in which it is involved, it undergoes functional and morphological changes that require the synthesis of new proteins and thereafter the activation of specific translational and/or transcriptional processes [18, 19]. An extremely intriguing open problem in neurobiology is: how can the soma



“Branch” coordinates for spines: the resulting matrix describes a single spine in terms of its branch parameters. The binary number of a spine describes its address as a “route” of bifurcations from the soma (1: left, 0: right). The number of 0’s and 1’s in such a binary address is the level of the spine.



“Spine” coordinates for dendritic trees: the resulting matrix describes an entire dendritic tree in terms of its spine parameters. Spines are numbered by their branch number and, within the same branch, by their distance from the previous bifurcation.



Three-dimensional association matrix, built to describe the parameters of interaction between any two spines on a dendritic tree. Typical parameters for this matrix are spine distances. A simple topological distance between two spines is defined in the text.

(where the genes are expressed) specifically target the activated spine (where the proteins carry out their function) with the delivery of a macromolecule? A model has recently been proposed in which a regulatory protein exists both within the nucleus, associated with plasticity-related genes, and in the dendrites [20], associated with the spine-localized polyribosomes [21]. Instead of binding upstream to the exon, such transcription factor would bind, when activated, within the c-strand of the exon itself in order to enhance or promote gene transcription.

The resulting mRNA would have the desirable effect of also being a "receptor" for such protein. The mRNA product would then be carried along the whole dendritic tree by means of the active transport machinery [22, 23], but would be selectively "captured" by those spines containing the activated promoter itself. How much of the macromolecule produced in the soma actually reaches the targeted spine? A simple estimate of the quantity of gene available for a specific spine is obtainable by its level as defined in the Method; at every bifurcation the amount of the macromolecule is roughly halved, so we might expect that $1/2^n$ of the material reaches a spine on the n th branch. A more accurate description is provided by considering other parameters such as the diameter of each branch (at each bifurcation, more material flows into larger branches) or the activity of the transportation machinery in each branch, and could be computed by means of the spine matrix in branch coordinates introduced above.

A more general application of our coordinate system might be used to handle information concerning the whole neuron, whose electrical input basically depends on the activity of its dendritic trees. The same idea used for a matrix associated to a single spine can be employed to describe an entire dendritic tree. This matrix is also written in somatocentric coordinates, but now we consider the spine coordinates instead of the branch coordinates; the i th entry of the tree matrix corresponds to the i th spine. As described for the matrix associated to a spine, the dendritic tree matrix may include any parameters which are well defined for individual spines (Figure 3b). Each column in the matrix will be a vector of a chosen parameter such as spine activity, and the i th entry of this vector will be the activity of the i th spine in the tree. Whereas a spine matrix records data associated to a particular spine and its relationship to the soma, the dendritic tree matrix tabulates information about every spine, such as each spine's weight, activity, etc., without specifying anything about the branches which lead from the soma. Interestingly, some of the information needed for the dendritic tree matrix, i.e., to model the neuron, might be obtained from the spine matrix.

An important feature characterizing spines is their relationship with each other. Spine interaction heavily influences neural activity, and models have been proposed in which the nonlinear summation of the electrical contribution of spe-

cific spines on a dendritic tree constitutes the subcellular basis of associative memory such as in classical conditioning [24]. The third example of applications of the coordinate system presented in this paper is then a way of tabulating the interaction between any two spines on a dendritic tree. For each pair of spines, we would like to describe parameters of interaction, such as cooperation, inhibition, topological or electrical distance between the two spines, etc. For each parameter, we construct a matrix of the interactions of the spines; the ij th entry of the matrix is the parameter applied to the spines i and j (such as the topological distance between spines i and j). Placing these matrices together in a three-dimensional matrix, we have constructed a table of interactions between spines (Figure 3c); the ijk th entry of the matrix is the k th parameter of spines i and j . Based on the information encoded in this matrix, correction factors might be introduced in both previous matrices (for spines and for the whole dendritic tree), for any parameter influenced by spine-to-spine interactions.

4. CONCLUSION

In the present paper we introduced a numerical algorithm useful for a mathematical description of dendritic branches, spines and their interactions with the soma and with each other. We consequently introduced two new coordinate systems, called *somatocentric*, in which the cellular anatomy of the neuron is conserved, in that only the space along the dendritic tree is considered. This numerical algorithm and these coordinate systems can, therefore, be adopted for every problem in which the structure of the dendrites is important. Although modern neurobiology suggests that this is indeed the vast majority of cases, it should be noted that other coordinates (Cartesian or polar for instance) may be used to describe phenomena that do not depend on the dendritic structure.

Very few attempts have been made in the past to label the dendritic space in a biologically plausible fashion. In one of the most successful examples, a model of a Purkinje cell was developed based on simplified channel kinetics [25]. The simulations were in excellent agreement with the experimental recordings in the soma and in the proximal and distal dendrites. The model used a Purkinje cell morphology reconstructed on the basis of 1089 branch compartments grouped and numbered in a purely anatomical (nontopological) way [26]. The above work allowed one to take into account as many as seven ionic conductances, and it seems possible to generalize the method for different branch parameters. While such a description successfully reconstructed a Purkinje cell of rat cerebellum, the coordinate systems proposed in the present paper allow a more general description of dendritic structures, and also easily tabulates the interactions among spines.

The proposed algorithm and coordinate systems are easily implementable and extremely flexible, as they can take into

account as many parameters as needed. Some of these parameters might be experimentally measured and others may be calculated, which allows these coordinates to be used not only for a univocal description of an observed cellular system, but also as a basis for the design of biologically plausible neural networks, in which the subcellular input units (dendritic branches and/or spines) are also modeled. The flexibility of this system is mostly due to the assignment of an ordered integer number to each branch of the dendrite, and thereof to the possibility of building vectors whose elements correspond to specific branches or specific spines. This naturally leads to the use of matrix notation for physiological parameters. In particular, we suggested some applications that can be developed in the future, such as the detailed description of the properties of a dendritic spine, in terms of the parameters of the branches generating it, or the overall description of the properties of an entire dendritic tree, in terms of the parameters of the spines on it. Many processes can be described in these coordinates, such as electrical flow (which takes into account e.g., ion channel and active pump distribution, myelination, dissipation, and path length), or molecular transportation (which depends on e.g., branch diameter, passive diffusion, active transportation and path length).

We have shown how these coordinates may be used to obtain the distribution of molecules passively diffused from the soma to the spines. This parameter, expressed in terms of the spine's level, is useful in the solution of problems related to gene activation and spine targeting [20, 21]. Naturally, more complex parameters must be incorporated to model active transportation or ionic conductances. A more complete description of the spine's parameters (which is beyond the scope of the present paper) is being developed in these coordinates based on the recently proposed model of Qualitative Reasoning Neuron (QRN) [27-29].

Given an opportune definition of distance, spines can also be grouped in spheres or clusters, "close" in regard with a particular physiological property. Furthermore, interaction between spines or spine clusters can be expressed to model properties such as cooperativity or inhibition, responsible for nonlinear behavior which is crucial for modeling associative memory.

Finally, the matrix notation adopted to describe physiological characteristics of spines and dendrites, introduces the possibility of using operators on vector spaces representing the dependence of considered parameters on time and neural activity. This structure suggests that the method presented in this paper offers extremely powerful computational tools.

These somatocentric coordinate systems need to be tested on experimental data analysis and on existing or new neural networks to fully prove a physiological consistency and a computational utility, nonetheless they represent one of the first attempts to describe mathematically the subcellular structure of neuronal inputs with a direct anatomical approach.

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