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INFORMATION PROCESSING IN DENDRITIC SPINES

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ABSTRACT: Dendritic spines are small twigs on the dendrites of a very large class of neurons in the central nervous system. There are between 10^3 and 10^5 spines per neuron, each one including at least one synapse, i.e. a connection with other neurons. Thus, spines are usually associated with an important feature of neurons - their high degree of connectivity - one of the most obvious differences between present computers and brains. We have analysed the electrical properties of a cortical (spiny) pyramidal cell on the basis of passive cable theory, from measurements made on histological material, using the solution of the cable equation for an arbitrary branched dendritic tree. As postulated by Rall, we found that the somatic potential induced by a firing synapse on a spine is a very sensitive function of the dimension of the spine. This observation leads to several hypotheses concerning the electrical functions of spines, especially with respect to their role in memory.

This report describes research done at the Artificial Intelligence Laboratory of the Massachusetts Institute of Technology and the Max-Planck-Institut für biologische Kybernetik, Tübingen, Federal Republic of Germany.

The Problem

Since the discovery of dendritic spines by Ramon y Cajal[3], their functional role has remained a matter of speculation. The early hypotheses all consider the establishment of physical contacts with presynaptic terminals as the main function of spines. In a similar spirit, Swindale[23] has proposed that spines are primarily a morphological device for connecting axons and dendrites. Ideas of this type, as Swindale points out, do not preclude other functions of spines, nor do they explain why spines should be as plastic as a number of recent studies suggest[8,9,10,22].

Several other authors have indeed suggested that the functional significance of spines is strictly related to their electrical and biophysical properties. Chang[4] first proposed that the electrical resistance of the spine neck could control the weight of a synapse on the spine. Rall[20] and Rinzel later showed on the basis of a simple model that variations in the spine's neck could effectively change the amplitude of the somatic depolarization due to a synapse on the spine. For this reason, they suggested that memory might be stored in the diameter of the spine's neck. The general idea of spines as a site of neuronal plasticity is the underlying theme of many recent papers, in particular Crick's[6] novel hypothesis of 'twitching spines' and Boycott's[2] account of the effect of hybernation on cerebellar spines.

Crucial for these and other suggestions are the electrical properties of spines. Since it is impossible to study directly with electrophysiological techniques the effect of spine parameters (like the size of the spine neck) on somatic potential, a theoretical analysis is called for. The purpose of this paper is to review the main results of a computational study of the electrical properties of dendritic spines following and extending Rall's analysis ([19-21]; see also [11]) and then to discuss some implications for the functional roles of spines. We will, in particular, refer to our computer simulations of the 'spiny' pyramidal cell shown in Figure 1 ([13], [14]).

Theoretical framework

The theoretical framework on which Rall's and our analysis is based is one-dimensional cable theory, as developed by Lord Kelvin for undersea cables and applied to neuronal structure by Hodgkin, Katz and others (see Chapter 7 in the textbook by Kuffler and Nicholls[15]). The main tool that we have used is a program that computes the electrical properties of any given passive dendritic tree[13,14]. The branching structure as well as the lengths and the diameters of the individual branches have been measured from cells like those of Figure 1. Our algorithm approximates each dendrite in terms of several cylinders, each one with constant diameter. The spines are modeled by a thin and narrow cylindrical spine neck (of length l and diameter d) and a thick and short spine head, as shown in the inset of Figure 1.

The program computes the transfer resistances K_{ij} between two locations i and j. When the two locations coincide, K_{ii} is the familiar input resistance at location i. Although the calculations were performed for transient inputs, for simplicity we restrict here our explanation to the case of steady state, DC inputs. The more general case can be treated in a similar way but involves more complex equations. Knowledge of the transfer resistance makes it possible to predict–via Ohm's law–the change of potential V_i at any point i for a given current injected at location j:

$$V_i = K_{ij} I_j$$

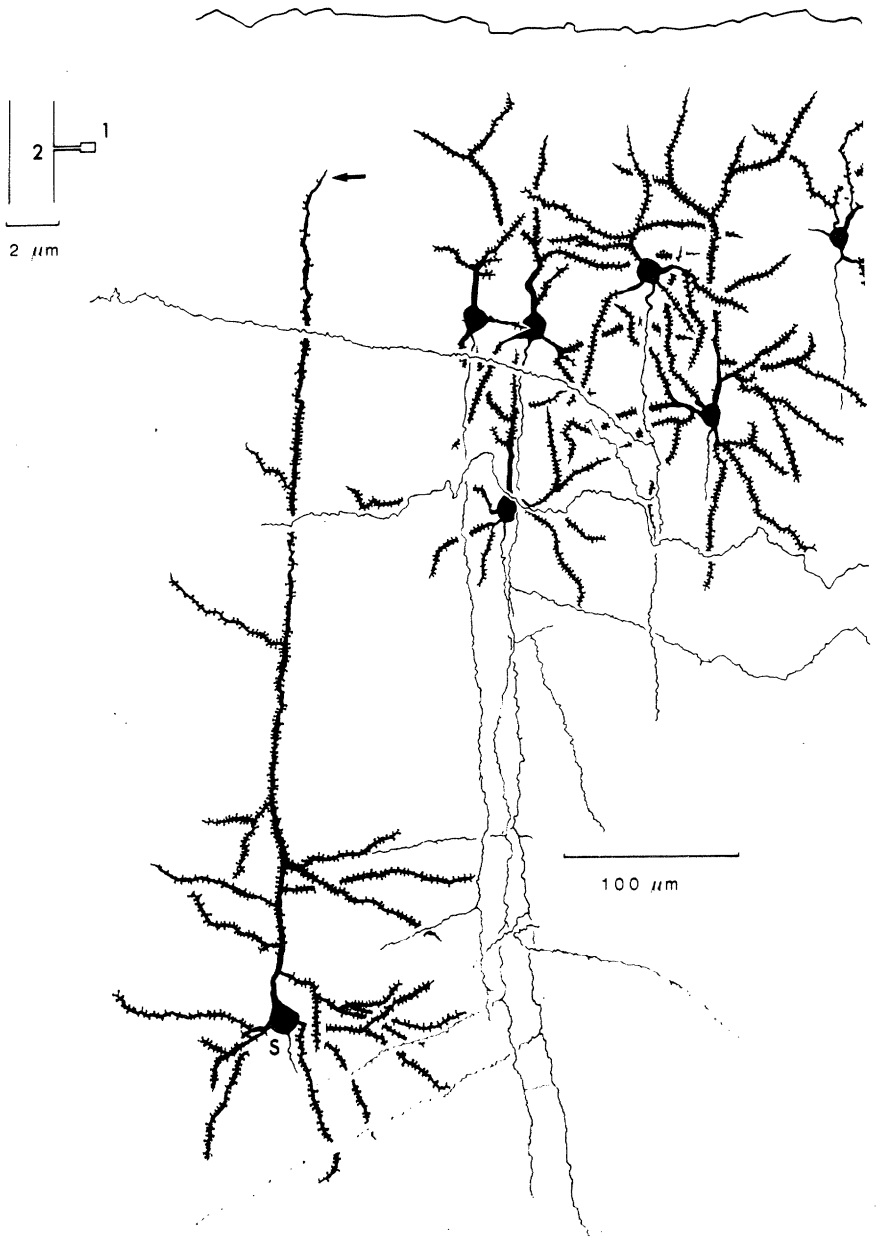

Figure 1 The pyramidal cell from the sensorimotor cortex of an adult mouse (on the left) used for our computer simulations. Golgi preparation (kindly provided by Prof. V. Braitenberg). The arrow shows the distal spine whose properties are computed in Figure 2 and 3. With our parameters ($R_m = 4000\Omega cm^2$, $R_i = 70\Omega cm$; see [13] and [14]) the electrotonic distance of this spine to the soma is 1.19 space constants. The inset shows our model of the spine.

The main assumption in this and Rall's analysis is that the membrane is passive.

Linear properties

The input resistance of a spine K_{11} as seen by an imaginary electrode in the spine head, turns out to be well approximated by the sum of the input resistance of the dendritic shaft K_{22} and the resistance of the spine neck R_N ([13]). R_N is the resistance of a cylinder with constant diameter d: it increases linearly with the length l and the intracellular resistance R_i while it is inversely proportional to the square of the diameter d. The reason for the accuracy of this approximation is that essentially no current flows out of the spine membrane because of its very small surface. Figure 2a shows the input resistance of a spine as a function of the spine dimensions for the parameter values given in the legend. The neck is changed in such a way (as always in this paper) that the total membrane area remains constant: thus an increase in length $l$implies a decrease in diameter d. As one can see, input resistance values can be much higher than the input resistances on the dendrites for small enough spine neck dimensions. Thus a small current injected into the spine will produce a much larger depolarization than if injected in the dendritic shaft. But what about the effect on the soma?

It turns out that the transfer resistance to the soma is essentially the same, irrespective of whether the electrode injects current into the spine or directly in the dendritic shaft (since $K_{1s} \simeq K_{2s}$). The reason for this is again that practically all of the current injected into the spine reaches the dendritic shaft, and therefore it is irrelevant, from the point of view of the soma, whether the current input is in the spine or in the dendrite. Thus for soma depolarization, spines cannot play any role for *current* inputs.

Spines, however, make some interesting difference for transient inputs. In this case, the resistance of the spine neck R_N and K_{22} behave in a different way: the effective resistance seen at location 2 (i.e., K_{22}) decreases rapidly with more and more transient inputs, whereas the neck resistance R_N remains constant up to very fast inputs (in technical terms the impedance K_{22} is much more lowpass than R_N, with a time constant of a few msec. compared with the spine time constant in the microsecond range). We will discuss later the implication of this property.

Synaptic inputs are conductance changes

Synaptic inputs, however, consist of transient conductance changes $g(t)$ to specific ions and the resulting current is not proportional to the conductance change. Synaptic inputs effectively open "holes" in the membrane for ions with a reversal potential E. Since spines can have a very high input resistance, even a small flux of positive ions may immediately drive the potential in the spine towards the equilibrium potential, thereby limiting the amount of inflowing current during synaptic activation and therefore the depolarization, for instance at the soma. The neck resistance effectively "chokes back" the flow of ions resulting from a synaptic conductance change. This nonlinear saturation effect depends directly on the neck's resistance, which in turn depends on the neck diameter and length. The size of the effect depends on the relative size of the input resistance and conductance change and, to a lesser degree, on the electrical properties of the whole dendritic tree. The depolarization in the soma can be described exactly by:

$$V_S = \frac{gK_{1s}E}{1+gK_{11}} \simeq \frac{gK_{2s}E}{1+g(K_{22}+R_N)}.$$

If the synaptic input change g is 'small' (i.e., $gK_{11} << 1$), then $V_s/simeqgK_{2s}E$ does not depend on the spine. (E is the equilibrium potential of the excitatory input.) In this linear range ('small' synaptic inputs, i.e., 'large' neck diameters), spines do not have any special electric effect. In the opposite case of 'large' inputs ($gK_{11} >> 1$), the potential inside the spine saturates to the ion's reversal potential and the potential in the soma:

$$V \simeq EK_{1s}/K_{11} \simeq EK_{2s}/K_{11}$$

is now independent of synaptic strength g and depends mainly on the spine neck and dendritic shaft resistance. In the intermediate range of $gK_{11} = 1$, the somatic potential depends both on the attenuation and on the amount of saturation in the spine, which represents a gain control mechanism on g, set by the neck's diameter.

The question at this point is what actually happens in a realistic dendritic tree with physiological values of neuronal parameters. Figure 2b shows the effect of a synapse on a distal spine of our pyramidal cell on the somatic potential as a function of the neck's diameter or length for small, medium and large conductance changes. The actual size of the conductance change at a synapse on a cortical dendritic spine is an open question, though a value between 10^{-8} and $10^{-7}S$ is not unreasonable. For the sake of comparison, recall that a single Acetylcholine quantum at the neuromuscular junction induces a conductance change around $6 \times 10^{-8}S$ (with a total duration of about 1 msec). Fig. 2b shows that for conductance values of this size relatively small changes of the spine dimensions in the cell of Fig. 1 can significantly change the effectiveness of a synapse. Because of the large number of spines on most spiny cells, the overall effect of these small changes in the spine shape could easily be quite significant.

Very fast transient inputs show nonlinear saturation

It may be argued that this picture may change dramatically when transient inputs are considered. After all, the release of a single quantum of transmitter usually induces a fast change of conductance. Spines, however, have very little impedance attenuation at high frequencies, since their total membrane capacitance is very small. Their structure may indeed optimize the conflicting needs of a high input impedance for transients with a correspondingly small current loss. Thus a significant saturation effect would take place even for short transient inputs. In the cell of Figure 1, for instance, conductance changes much shorter than the membrane time constant show a voltage attenuation from the spine to the soma, which is much larger than in the DC case, since much more current leaks through the membrane capacitance of the dendrites. Saturation and choking effects in the spine itself remain, however, very high because the total capacity of the spine is exceedingly small. For instance, a transient conductance change at a distal spine with a rise-time of 0.25 msec, a total duration of 0.9 msec and a peak conductance change g yields for the spine depolarization the solid curve of Figure 3, which has the same form as the DC case except that the depolarization is scaled down somewhat. The corresponding dendritic depolarization for the same conductance input on the dendritic shaft, directly below the spine, shows practically no saturation (dotted curve). In summary, the spine geometry and dimensions are remarkably designed to provide a strong saturation effect even for very brief transient input. The dendritic shaft itself would provide a much smaller saturation or choking effect: the difference increases with transiency of the input.

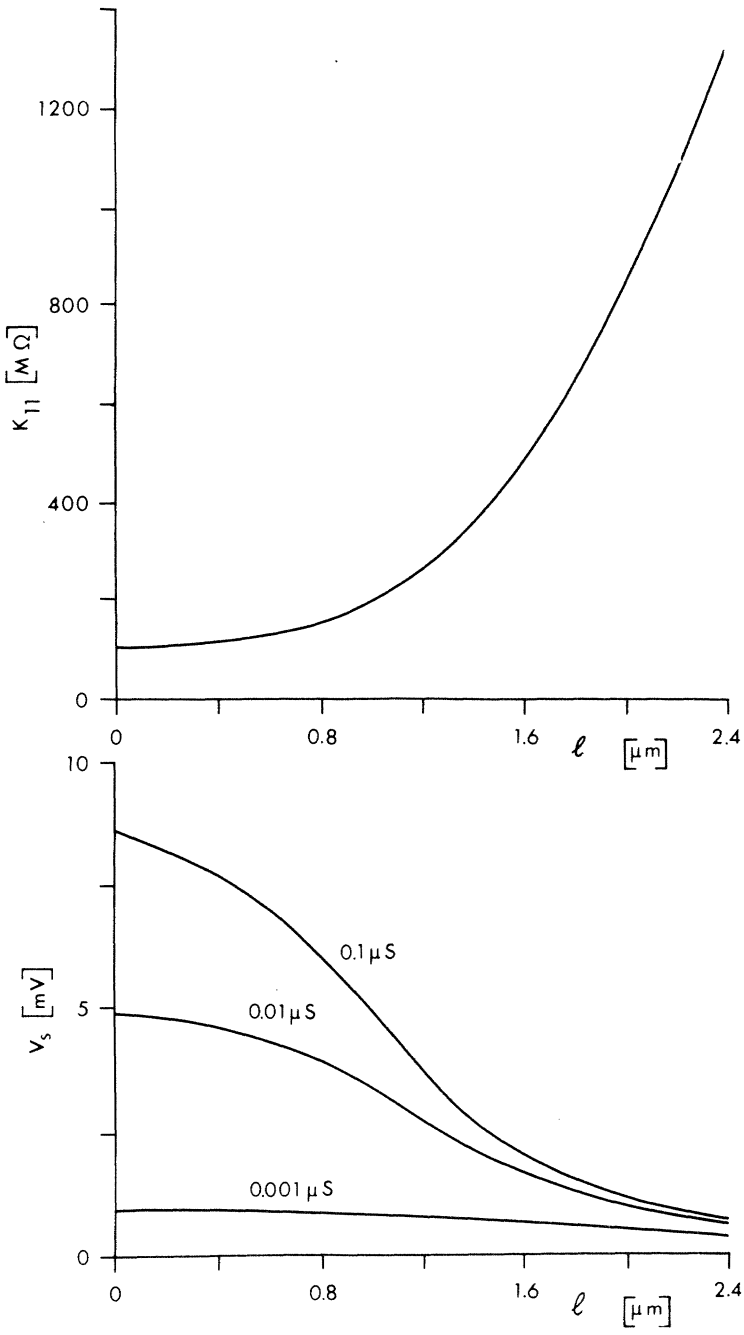

Figure 2(a) The spine input resistance K_{11} for the distal spine of Figure 1 as a function of the spine neck and diameter. The spine neck dimensions were changed in such a way as to leave the total neck surface area constant and equal to $0.1\mu m^2$. $R_m = 4000\Omega cm^2$; $R_i = 70\Omega cm$. The dendritic input resistance $K_{22} = 109M\Omega$. (b) The somatic voltage corresponding to different neck dimensions for small, medium and large DC conductance inputs. Transient inputs (time to peak 0.25 msec and total duration 0.9 msec) yield very similar curves for peak conductance values equal to the DC values shown here, except that they are scaled down by about a factor of 10. The assumed reversal potential is 80 mV. Optimal plasticity (for $g = 10^{-7}S$) implies a proximal spine neck length of about $0.59\mu m$ (neck diameter $0.17\mu m$) while distal spines should be about 50% longer. Plausible changes in neck length (from 1.0 to $1.6\mu m$) could alter the "weight" of the synapses by a factor 2.

What is the optimal neck's diameter?

A glance at Figure 2b shows that there is an optimal value around which small changes in the neck's diameter have maximum effect on the somatic depolarization. This value depends on K_{22} and therefore on the spine location. Rall has pointed out (for the case of maximum saturation) that this kind of impedance matching between the spine neck (R_N) and the dendritic shaft to which the spine is attached (K_{22}) implies that spines with long narrow necks should be found on the distal parts of the dendritic tree whereas proximal spines should be shorted and stubbier. (For the exact equation, see [13].) For the cell of Figure 1, optimal plasticity (for $g = 10^{-7}S$) implies a proximal spine neck length of around $0.59\mu m$ (neck diameter $0.17\mu m$) while distal spines should be about 50% longer, a systematic variation which seems consistent with experimental evidence[5,20]. Plausible changes in neck diameter (from 1.0 to 1.6 μm) could alter the "weight" of the synapse by a factor of 2. The somatic depolarization for fast inputs with a peak conductance change of about $10^{-7}S$ drops from 0.26 mV to 0.08 mV (—69%), while shortening the neck to 0.6 μm and correspondingly enlarging the diameter would increase the depolarization in the soma from 0.26 mV to 0.54 mV (+108%). Thus the effect may be quite appreciable for changes in spine neck length (and diameter) which are still smaller than the observed differences of spine dimensions within one cell[17].

Should spines have inhibitory input?

The previous discussion is restricted to single excitatory inputs on a spine, by far the most frequent case. Isolated inhibitory inputs are not expected on a spine (if inhibition has an equilibrium potential close to the resting potential, a possibly common situation in the cortex), since it can be proved[14] that for maximum effectiveness, shunting inhibition must be located on the direct path between excitation and soma. An off-path location, for instance on a spine, is almost ineffective. For inhibition to effectively veto excitation, the best design would be to locate excitatory inputs distally, possibly on spines, and inhibitory inputs proximal to the soma directly on the dendritic shaft[18]. This arrangement is indeed common in the cortex.

On the other hand, the pairing on one spine of two inputs of different types offers the possibility of synthesizing local circuits performing different operations. For instance, the combination on one spine of an excitatory and a (shunting) inhibitory input would represent an almost ideal module for performing selected AND-NOT -like operations effectively decoupled from other such subunits. All the available data indicates that inhibitory inputs (Gray Type 2) on spines, when present, are never alone but always accompanied by an excitatory synapse (Gray type 1[18,12].) Spines with both excitatory and inhibitory inputs are not very common but still represent 5% to 20% of the total number of cortical spines.

What is especially remarkable is that the vetoing effect of inhibition is very sharply dependent on relative timing of inhibition and excitation. Whereas inhibition on the dendritic shaft can effectively veto more distal excitation within a temporal window of the order of the membrane time constant (5-10 msec), inhibition on a spine is stronger and more selective, being effective only in a window of $\pm 120\mu sec$ (for inputs with time-to-peak = 0.25 msec). Thus, an inhibitory and an excitatory input on a spine could implement a discrimination circuit of the AND-NOT type with a time resolution around the $100\mu sec$ range[7,13] .

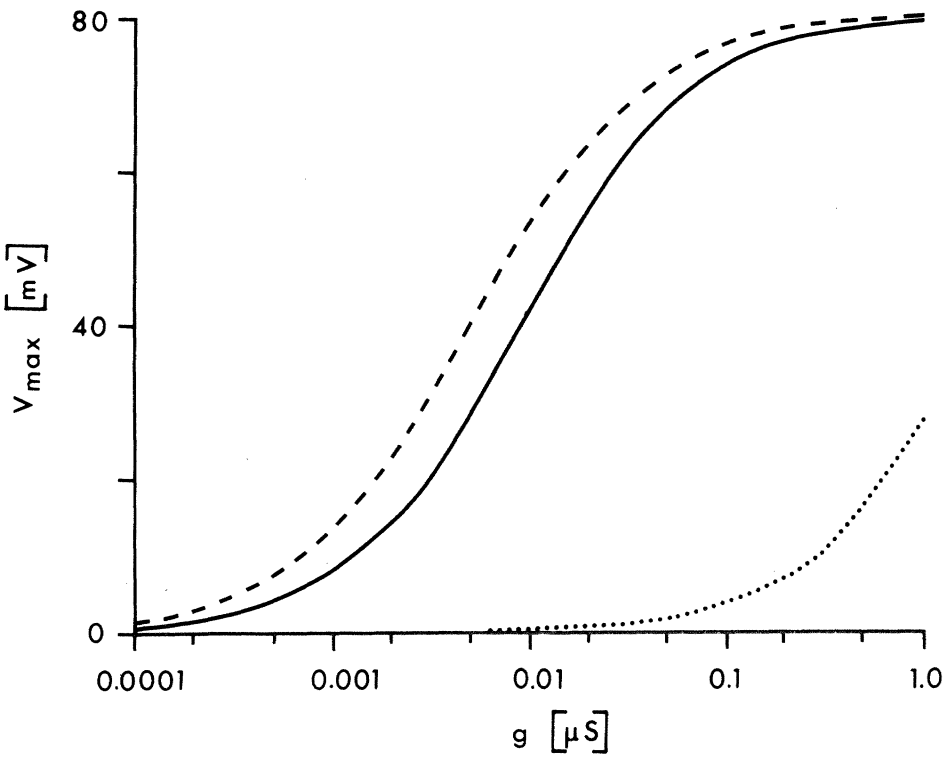

Figure 3 The maximum of the depolarization *at the synapse*, for a fast transient conductance input of peak amplitude g (time to peak = 0.25 msec and total duration 0.9 msec) at the distal spine of Figure 1 (solid line; at location 1 in inset) or at the dendritic shaft just below the spine (dotted line; at location 2). The dashed line shows that a DC conductance change yields essentially the same depolarization in the spine as the transient input; the membrane time constant is 8 msec.

The main properties of spines

In summary, the electrical properties most characteristic for spines are:

1. Depending on the size of the conductance inputs, a spine may have no special role at all (small g), perform a simple gain control mechanism on the inputs (medium g) or totally saturate to a level independent of the input (large g). In the middle range, the effect of the spine is to map a possible wide range of input amplitudes onto a restricted range of output depolarizations, that is to perform nonlinear range compression.

2. The saturation property is valid not only for slow, but also for very fast conductance changes. The local voltage increase is much higher than for the same input on the dendritic shaft (see Fig. 3).

3. Except for very small conductances changes, the effectiveness of a synaptic input on a spine in terms of somatic depolarization depends on the diameter of the spine's neck more than on any other parameter.

4. There is an optimal neck's diameter for which relatively small variations of the neck are most effective in controlling the weight of the excitatory spine synapse

(see Fig. 2b). For reasonable parameter values, this optimal value is consistent with anatomical data[13,17].

5. Isolated inhibitory synapses on a spine cannot have any interesting electrical properties and are not expected to occur (they do not). Conjunction of shunting inhibition with excitation on a spine can implement a veto operation which is very specific, both in space and time.

Do these results depend on parameter values?

All these properties depend on the assumed parameter values, most critically on the size of the synaptic conductance change at the spine. Although our calculations rest on standard values, the reasonable physiological range is rather wide. Different values of the membrane time constant τ_m and the membrane resistance R_m are however unlikely to affect our results. Different values of R_m affect only slightly the input resistance of the spine K_{11} (since the neck resistance R_N is independent of R_m). Our results are quite sensitive to drastic changes in the cytoplasmatic resistivity R_i, since the neck's resistance depends linearly on it. If R_i differs from our assumed value, it would probably be larger and therefore increase even more our estimates of the input resistance.

Precise data about conductance changes at a spine and their time course seem much more difficult to obtain. If the peak value of the conductance change were much smaller than $10^{-8}S$, a spine would behave almost linearly, other parameters being equal, and would have no useful electrical function.

All our conclusions rest on the assumption of passive or non-regenerative membrane properties. The situation could change if the dendrites or even the spine itself would be capable of producing spikes. Although we did not perform the required simulations, it is likely that even in this case, the neck's dimension could control the effectiveness of the synaptic input.

Functional role of spines

Assuming that spines have the non-linear saturation properties outline above, we now ask what their function could be (in the case of isolated excitatory synapses). At least six somewhat different possibilities can be envisaged, none excluding the others. (1) Spines may effectively compress the range of each single synapse, showing a high sensitivity to small conductance inputs and keeping the maximum depolarization which could be achieved by a single synapse below a certain predetermined value. (2) This maximum value may be always attained: the synapse would always work in the saturation range and the spine would effectively " binarize" the synaptic input. (3) It is possible that–because of nonlinear range compression–inputs on different spines are kept more isolated than they might otherwise be, simply because the spine would reduce their effectiveness. (4) As suggested by Perkel (personal communication), the strong depolarization within the spine may have a number of local effects, such as triggering local action potentials in excitable membranes or opening calcium channels. (5) Fine control of synapse effectiveness via the spine neck diameter (and length) may be used during development to fine-tune the relative importance of the various inputs. (6) In a similar vein, as Rall first suggested, this may also represent a basic mechanism for learning in the nervous system. Several authors have followed this suggestion[6,8–10,22] and presented experimental

evidence that spines can indeed change their shape (for instance following massive stimulation). Crick[6] has recently proposed that the spine's neck diameter may be controlled on a very short time scale by a contractile protein in the spine's cytoplasm.

An obvious area of the brain where this hypothesis could be tested is the cerebellum. As proposed by Marr[16], later modified[1], the conjunction of an active parallel fibre and an active climbing fibre may change the weight of the parallel fibre–Purkinje cell synapse, which is always on a spine. If spines have a role in memory, we would clearly expect that this change in synaptic efficiency (probably a depression) is correlated with a decrease in the spine's neck diameter.

In conclusion, Rall's and our calculations suggest that learning may result in the change of the shape of a class of spines. The hypothesis does not specify the variables on which this change may depend, though the local intracellular potential seems well-suited as the "intracellular messenger". It should, however, be clear that this is little more than an attractive possibility. Given the present uncertainty about appropriate parameters, it is possible that conductance changes at a spine are small: in this case spines would not have any specific electrical properties that could play a role in learning.

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