10.1 Introduction by Gordon M. Shepherd with Supplemental Comments by John Miller

Rall, W. (1974). Dendritic spines, synaptic potency and neuronal plasticity. In *Cellular Mechanisms Subserving Changes in Neuronal Activity*, ed. C. D. Woody, K. A. Brown, T. J. Crow, and J. D. Knispel. Brain Information Service Research Report #3. Los Angeles: University of California.

Miller, J. P., Rall, W., and Rinzel, J. (1985). Synaptic amplification by active membrane in dendritic spines. *Brain Res.* 325:325–330.

Wil Rall has had a long love affair with dendritic spines. Few realize the extent of his contributions to this area. Although a full account of the development of concepts of spine function goes beyond the scope of the present volume, it may be of interest to provide an orientation to the specific areas in which Wil's contributions have been ground breaking.

Presynaptic and Postsynaptic Functions of Dendritic Spines

Rall's first contribution to the subject of dendritic spines was made in the papers by Rall et al. (1966) and Rall and Shepherd (1968) (reprinted in this volume). The idea that the granule cell might send its inhibitory synaptic outputs through its dendritic spines onto the mitral cell dendrites arose out of the previous work with Phillips and Powell (Shepherd 1963), in which we envisaged the spines as functioning essentially like axon terminals for the axonless granule cell. The studies with Wil Rall supported this output function for the granule cell spines, but Reese and Brightman's work established that the granule cell processes are in fact dendritic in their fine structure, and the spines are therefore dendritic despite having presynaptic and postsynaptic relations. This effectively dissociated the identification of a terminal as pre- or postsynaptic from the criteria for identification of a terminal as axonal or dendritic, a lesson which is still not understood by many. Parenthetically it may be noted that the term gemmule was introduced to refer to these structures partly in order to avoid confusion with spines that occupy only postsynaptic positions.

Although our biophysical models did not explicitly include the spines, it was clear to us that the spines play a key role in the synaptic mechanisms. The new ideas with regard to the spines were (1) the locally generated EPSP in a spine activates the output inhibitory synapse from the same spine to provide for recurrent inhibition of the mitral cell, and (2) spread of the EPSP out of a spine and through the dendritic branch into neighboring spines provides for lateral inhibition of neighboring mitral cells. We discussed this in the text and illustrated it with a diagram (figure 15, Rall and Shepherd 1968) that shows the reciprocal and lateral actions mediated by the spines. We noted that spread between spines would be limited for spine stems that were unusually long or thin. This was the first published observation by Wil or myself about the control of the spread of

activity between a spine head and its parent branch. It was essentially a restatement of Chang's (1952) inference concerning spines on cortical dendrites.

Over the subsequent quarter of a century there have been many speculations about the general properties of dendritic spines. An often-repeated claim is that spines have no interesting properties and serve "only to connect." The granule cell spines still stand as an often-ignored example of spines to which can be attributed specific functional operations of generally acknowledged significance for information processing.

Dendritic Spines and Learning

As with most of his work, Wil's interest in the possible role of dendritic spines in learning had deep roots. His first publication on this topic was in a "Comment on dendritic spines" at the end of his paper on "Cable properties of dendrites and effects of synaptic location," delivered at a meeting on "Excitatory Synaptic Mechanisms" held in Oslo in September of 1969 (Rall 1970). His comment was stimulated by a hypothesis that was brought forward at the meeting by Diamond, Gray, and Yasargil (1970), and which attracted wide attention at the time. They speculated that an intermediary "unit" in a reflex circuit under investigation was a spine whose activity was relatively isolated from other synaptic activity in the neuron by virtue of a high spine stem resistance. They speculated that the function of this isolation might be to reduce the noise level at the synapse; others speculated that it might linearize the summation of responses in neighboring spines. Wil comments in his paper from this meeting that his own preference is that "spine stem resistance might be used physiologically to change the relative weights of synaptic inputs from different afferent sources; this could provide a basic mechanism for learning in the nervous system." He notes that this is only a "slight extension" of his earlier suggestion in Rall 1962b that the relative weight contributed by dendritic synapses to summation at the soma "could be changed by changing the caliber (and hence the electrotonic decrement) of a dendritic subsystem," and that "this would be useful for learning."

In his comment, Wil notes that he has begun a theoretical exploration of this problem with his colleague John Rinzel. Anatomists were just beginning to make accurate measurements of spine dimensions, and Rall and Rinzel drew their data from the studies of Laatsch and Cowan (1966), Jones and Powell (1969), and Peters and Kaiserman-Abramof (1970) on dendritic spines of cortical pyramidal cells. These spines are exclusively postsynaptic in position and could be categorized into different types de-

pending on their outward morphology. Jones and Powell had noted that spines with thin stems frequently arise from thin distal dendrites and spines with stubby stems from thick proximal dendrites. The key insight of Rall and Rinzel was that this anatomical correlation would have critical implications for the electrotonic relations between spines and dendrites, which in turn could have profound functional importance.

Their results were first contained in two abstracts (Rall and Rinzel 1971a,b), one presented to the IUPS Congress in the summer of 1971 and the other presented at the first meeting of the new Society for Neuroscience, held in Washington, D.C., in the fall of 1971. In these, Rall and Rinzel point out for the first time that the amount of spread of a synaptic potential from a spine to its parent branch is governed not just by the spine stem resistance alone but rather by the ratio of the spine stem resistance to the input resistance of the branch; in other words, one is dealing with an impedance matching problem. When this ratio is either very large or very small, changes in spine stem diameter (hence, spine stem resistance) have little effect on synaptic potential spread to the branch. In the middle range, however, where the ratio is near unity, a small change in spine stem resistance has a relatively large effect on the amount of spread. "Over this favorable range ... fine adjustments of the stem resistances of many spines, as well as changes in dendritic caliber ... could provide an organism with a way to adjust the relative weights of the many synaptic inputs received by such neurons; this could contribute to plasticity and learning of a nervous system" (Rall and Rinzel 1971b).

The reason that these abstracts are quoted here is that they were the only generally accessible publication of the hypothesis. The details of the study were published in the privately printed UCLA research report reproduced here (Rall 1974), and repeated and extended in an article in a festschrift volume for Archie McIntyre (Rall 1978). The hypothesis was first presented to a general readership in a book on synaptic organization (Shepherd 1974) in much the summary form given here, together with an extension to the concept of a microcompartment created within the spine head. As to why Wil did not publish this seminal work more fully, the answer is mainly to be found in his battle throughout the 1970s with cataracts and the consequences of cataract surgery. The fact that the study was well known among those working on the cellular basis of memory during that time was a further disincentive to more complete publication. Finally, there has always been enough of the mathematician in Wil for him to feel that "what is known is trivial," and that publishing a study once, however succinctly, should suffice for those who are interested. It is a luxury that few scientists nowadays can afford!

In the 1974 paper reprinted here, Wil shows how the anatomical dimensions of the different types of spines translate into simplified equations for impedance matching of the spine stem resistance to the branch input resistance. He explains that this approach builds on the theoretical method for estimation of branch input resistance presented fully in the study of Rall and Rinzel (1973); this paper is included in the present volume. He notes further that these results based on the assumption of steady-state electrotonic spread can be extended to the case of transient synaptic potentials with only qualitative differences.

From this study came several important concepts. First was the idea of an "optimal operating range" for the relation between a spine and its parent dendrite. Second was the idea of "synaptic potency." As is typical of Wil, he did not confine himself to spine stem length and diameter as the only possible mechanisms regulating synaptic potency. Among other candidates he mentions are synaptic contact area, amount of released chemical transmitter, duration of synaptic action, and changes in internal spine stem resistance. The possibility of changes in spine stem dimensions was soon examined in the experiments of Fifkova and van Harreveld (1977). Others of these suggestions were remarkably prescient. Later Bailey and Chen (1983) indeed found evidence in Aplysia for changes in synaptic contact area associated with activity. The prolonged duration of NMDA receptor actions in spine synapses and their possible relevance for learning mechanisms is another current example.

A notable quality of Wil's biophysical work has been his ability to generalize from biophysical property at the membrane or cellular level to the function of the system. We have already seen an example of this in the study of granule cell spines, where the reciprocal synapses were immediately seen to provide the mechanism for the system functions of recurrent and lateral inhibition underlying sensory processing. It is also seen in his 1974 paper in his inference, from adustable spine stems, of the larger functional view that "delicate adjustments of the relative weights (potency) of many different synapses" could be "responsible for changes in dynamic patterns of activity in assemblies of neurons organized with convergent and divergent connective overlaps." Thus, from these purely biophysical deductions, Wil essentially deduced the blueprint for neural networks consisting of nodes interconnected by synapses with adjustable weights. This general concept of course was not new; what was novel was directing attention to a critical site and suggesting some testable mechanisms.

This work had a large effect on investigators interested in the synaptic basis of learning and memory. During the 1970s and 1980s it provided one of the main organizing hypotheses for possible mechanisms of learning and memory. The fact that dramatic changes in spine size and shape were

reported to be associated with sensory deafferentation as well as with specific types of mental disorders gave further credence to the hypothesis. With the rediscovery of Hebb and his learning rules around 1980, and the wealth of new data on the activity dependence of different types of membrane channels in the 1980s, interest has broadened to include these and other mechanisms in the basis of learning and memory. These can be seen as additions to the mechanisms previously suggested by Rall. They add to the complexity of spine synapses and the functional links between spine synapses, reinforcing the notion that they are likely to be critical to the integrative actions underlying higher cortical functions.

Active Dendrites and Dendritic Spines

No topic illustrates more clearly the common misconceptions about Rall's work than the question of nonlinear properties of dendrites in general and the active properties of dendrites and spines in particular. In the popular mind, Rall's contributions are regarded as lying entirely within the domain of passive cable properties of oversimplified dendritic trees. As such, they seem mainly to be of historical interest, because it is currently believed that active properties are the critical agents in dendritic integration. But the facts speak otherwise. They show that Rall led the way in analyzing the nonlinear properties of synaptic interactions, in incorporating active membrane into computational models of dendritic trees, in pointing out the logical possibilities of local active membrane in dendritic trees, in incorporating active membrane into models of dendritic spines, and in exploring the functional implications of populations of active dendritic spines. Let us consider each of these contributions.

Nonlinear Properties of Synaptic Interactions

This topic was first introduced into the literature in the landmark paper of Rall 1964, reproduced in this volume. As already pointed out in the introduction to that paper, the compartmental model presented in that paper enabled Rall to put synapses at different distances from each other in a dendritic tree and explore their interactions. A cardinal result from that analysis was that, contrary to the then-popular belief that excitation and inhibition sum algebraically (i.e., linearly), such summation was true only for summation of responses to injected current, in which the system was unperturbed. For the case of synaptic interactions, their summation was in general nonlinear, because the synaptic conductances perturbed the system. The nonlinear nature of these interactions was dependent on several

key parameters. These included (1) the distance between two active synapses (i.e., the degree of shunting between them), (2) the relation of the membrane potential to the reversal potentials for the ions involved, and (3) the geometrical relations between the synapses within the branching structure of the dendritic tree (whether they were on different branches, on the same branch extending to the soma, and whether the excitatory or inhibitory synapse was proximal or distal in the on-line configuration).

At the time, these were recognized as new and fundamental insights into the nature of synaptic integration in dendrites. No longer could synapses be modeled by current injection, and no longer could dendrites with even purely passive membrane be regarded as linear systems. Unfortunately, there has been a tendency for people to forget this work and connect Rall with the exploration of only passive linear models of dendritic integration. The new generation of neural modelers has yet to rediscover the truths that Rall revealed some 30 years ago.

Active Membrane in Dendrites

The first experimental evidence that dendrites might contain sites of active membrane came from the studies of Eccles et al. (1958) on chromatolytic motoneurons and those of Spencer and Kandel (1961) on hot spots in pyramidal cell dendrites in the hippocampus. When in 1962 we began to construct our computational model of the mitral cell, it was clear to us that it would be essential to explore the functional consequences of active dendritic membrane. Our simulations therefore included either passive or active membrane in the mitral cell dendrites; the active properties could have either "hot" or "cold" kinetics. As reported in the initial abstract (Rall and Shepherd 1965) and the full papers (Rall et al. 1966; Rall and Shepherd 1968; see this volume), dendrites with active membrane facilitated antidromic invasion to the extent that we could rule out fast kinetics in large dendrites, because the near-simultaneous invasion would not produce sufficient longitudinal current flows to give the large amplitude extracellular field potentials that had been recorded experimentally. We concluded that the simulations were consistent with either antidromic invasion of thin dendrites by a relatively slowly propagating impulse, or passive invasion of relatively large dendrites (Rall and Shepherd 1968).

We also modeled active properties in the granule cell. For these we used only weakly active membrane, because active properties in the granule cell dendritic tree promoted rapid spread that, as in the mitral cell, reduced the field potential amplitudes unacceptably. A satisfactory result for the case of weakly active dendritic membrane could be obtained only if synaptic inhibition was applied to the deep granule cell processes at the same time as synaptic excitation was applied to the superficial processes. This was

probably the first computational neuronal model to contain all three basic functional properties: active membrane and both synaptic excitation and inhibition. Note that the model was heavily constrained in multiple ways: the anatomy of the granule cells; the intracellular and extracellular unit recordings; the time course of inhibitory synaptic output; the ratio of extracellular to intracellular current paths; and the time course, amplitude, and depths of the extracellular field potentials. We concluded that the brief repetitive impulse discharges that can be recorded from granule cells likely are localized to their cell bodies, and that the spread of activity within the granule cell dendritic tree and the activation of the output synapses from the granule cell spines probably do not involve a prominent role for active membrane. Subsequent studies of granule cell responses have been consistent with that interpretation, without, of course, ruling out that weak voltage-sensitive inward currents could contribute to inhibitory synaptic output, as originally suggested.

Given the explicit incorporation of active membrane properties in the models of both mitral and granule cells, it seems past time to recognize that Rall was a pioneer in analyzing active properties in compartmental models of neuronal dendrites.

Functional Implications of Active Dendrites

In the same paper in which he first mentioned the idea of changes in spine stem resistance underlying learning (Rall 1970), Rall also commented on the more general functional implications of active membrane in dendrites in relation to information processing:

> Active dendritic membrane could result in unusual logical properties that have interested a number of people (Lorente de Nó and Condouris, 1959; Richard FitzHugh, personal communication, also Arshavskii et al., 1965). The notion is that the excitation initiated in a dendritic branchlet will propagate centripetally beyond each point of bifurcation only if it is aided at the right moment by excitation from several sibling branches along the way, and provided also that it does not meet inhibition along the way. Such multiple possibilities of success or failure, at many different points of bifurcation, could lead to elaborate sets of contingent probabilities which would provide a single neuron (if it has suitable input patterns over the dendritic branches) with a very large logical capacity.

Rall then went on to define some of the rules for these types of interactions:

> Even for passive dendritic membrane, localized dendritic synaptic excitation has the property of being especially vulnerable to synaptic inhibitory conductance which is delivered to the same dendritic location: the larger the amplitude of the uninhibited local membrane depolarization, the larger is the reduction produced by a locally superimposed inhibitory conductance. This is very nonlinear in that

the EPSP amplitude is reduced by much more than the amplitude of a control IPSP (which may be negligible). In contrast, when the inhibitory input is delivered to a different dendritic tree, the effect at the soma is simply a linear summation of the separate EPSP and IPSP observable at the soma; see Rall et al. (1967, pp. 1184–1185) for examples of both kinds. Synaptic inhibition delivered to the soma is effective against all excitatory inputs, provided the timing is correct, while synaptic inhibition delivered to a dendritic branch is selectively effective against excitatory inputs to the same branch.

These two comments taken together essentially set forth an agenda for specifying the rules of synaptic interaction in dendrites and relating them to the kinds of logical operations that they would support with the aid of active dendritic membrane properties. Much of this agenda was to be realized in the work of Christof Koch and Tomaso Poggio and their colleagues in the following decade, through detailed delineation of on-line excitatory and inhibitory synaptic actions, characterization of shunting versus summating synaptic inhibition (which constitute two extremes along the continuum of interactions Rall had explored), and modeling of explicit logic operations arising from excitatory and inhibitory synaptic interactions within a dendritic tree (Koch et al., 1982; see also Segev and Parnas 1983). The relevance of these properties for network models of cortical circuits underlying cognitive functions was addressed by Sejnowski, Koch, and Churchland (1988).

Active Dendritic Spines

The opportunity to explore more fully the question of the membrane properties of dendritic membrane came with the use of more powerful and flexible computational modeling programs. I had intended to pursue this question with Wil, but the problem with his cataracts made this impossible. I therefore began the collaboration with Robert Brayton that resulted in the more detailed simulation of the reciprocal dendrodendritic synaptic circuit (Shepherd and Brayton 1979). This simulation placed the Hodgkin-Huxley model in a proximal dendritic compartment of the mitral cell; the rest of the membrane in the mitral and granule cell dendritic models was passive.

By 1980 we had begun to explore the functional consequences of placement of active membrane at other dendritic sites in this model, including the granule cell spines. We also began to adapt our model to the case of the exclusively postsynaptic spines of cortical pyramidal cells, to deal with the question of whether active membrane would help to boost the responses of dendrites and spines in the most distal parts of the tree. We were especially interested in the case of pyramidal neurons in the olfactory cortex, where it is clear that the specific sensory information is conveyed

from the input fibers (of the lateral olfactory tract) onto spines on the most distal dendrites. This placement is of course counterintuitive and against the common belief, still widely held, that synaptic inputs must be directed to the cell body of a neuron in order to transmit specific information in a rapid manner, distal synaptic inputs being believed to convey only slow background modulation. It should be clear from the previous discussion that we never believed that this could be a valid rule.

About this time John Miller joined Wil's laboratory to further the studies of dendritic integration. John and I met at a Winter Brain Conference, and I told him about the advantages of ASTAP for neural modeling. However, I soon learned, to my chagrin, that ASTAP was a proprietary IBM product that was not available for general use. This was a distinct disappointment, because I had become convinced that the use of large general-purpose circuit simulators, such as ASTAP, was the most effective way to make neural modeling more accessible for incorporation into experimental laboratories for parallel exploration of neuronal properties, in the same way that Wil had begun to develop the compartmental approach by adapting the general model of his colleague Mones Berman. However, in our 1979 paper Brayton had suggested that other more generally available circuit simulation programs such as SPICE could also be adapted for this purpose, so we recommended that John and Wil look into that. Doron Lancet was with me at the time, and he had several interactions with John in setting this up. Also, Wil and John came to IBM so that Brayton and I could demonstrate how ASTAP worked. We pointed out the advantage of being able to adjust the Hodkin-Huxley parameters from trial to trial, which was especially useful for exploring the values appropriate for active properties of thin dendritic branchlets and spines.

By 1984 John and Wil had successfully adapted SPICE for carrying out simulations of active properties of a single dendritic spine and the possible contribution to boosting the response of the spine to an excitatory synaptic input. A number of different lines of work then came to a head. Don Perkel and his son David had independently become interested in the same problem, using the neural modeling program MANUEL that Don had developed. The two groups were in touch with each other and agreed to submit companion papers to *Science*, consisting of Perkel and Perkel 1985 and the paper reproduced here (Miller et al. 1985). They were rejected as being of insufficient interest to a general audience, and were subsequently published in *Brain Research*. Brayton and I meanwhile had gotten our model of active dendritic spines going. We wanted especially to disprove the received wisdom that distal spines could mediate only slow background modulation, and chose first to show that interactions between active spines could provide for a kind of saltatory conduction that would

convey distal active responses toward the soma. We kept in close touch with Wil and his team at NIH, which by then included not only John Miller but also John Rinzel and Idan Segev. We decided to submit a joint paper on our initial finding on the active boosting model; it was first rejected by *Nature* as being of insufficient interest but subsequently was sponsored by Ed Evarts in the *Proceedings of the National Academy* and accepted (Shepherd et al. 1985).

I have summarized this series of events to indicate that Wil not only pointed to the new era of investigation of active properties of dendrites with his earlier speculations, but he was also a driving force behind developing the first computational models that demonstrated these properties.

During this time Barry Bunow at NIH was working on adapting SPICE for more effective modeling of the nonlinear properties of the Hodgkin-Huxley equations. The problem was that the equations had to be simulated by a polynomial expansion, which made it cumbersome to manipulate the parameters. A great deal of effort went into this study (Bunow et al. 1985), and SPICE in this version played an important role during the latter part of the decade in providing a means for modeling complex dendritic systems. The studies of Robert Burke, involving detailed reconstructions of motoneuron dendritic trees, were among the best known (Fleshman et al. 1988). During this period Peter Guthrie wrote a version of SPICE specifically adapted for neuronal simulation, called NEUROS. At about this time Michael Hines was developing the program that became NEURON (Hines 1984, 1989), and shortly thereafter Matt Wilson and Jim Bower developed GENESIS (1989).

After developing the single active spine model, Wil teamed with Idan Segev to explore the functional implications of groups of active spines. This was again a natural step in going from the level of a single functional unit to the level of multiple units. They analyzed the rules governing the coincident activation of different subpopulations of active spines located on different dendritic branches (Rall and Segev 1987). These rules will likely govern the ways that subpopulations of spines control both the immediate responses of a neuron to synaptic inputs as well as the activity-dependent responses under conditions of long-term potentiation or depression. Rall has conceived of the properties governing spine potency very broadly; thus, the nonlinearities of spine responses may be due to active conductances in the spine heads, spine necks, or spine bases, as modeled in these studies; to changes in Ca++ concentration; to metabolic changes as might be mediated by protein kinases; and to effects mediated through the genome such as by immediate early genes. The importance of Rall's studies lies not only in the exploration of specifically

electrical changes contributing to spine functions but also in the provision of a broader focus on nonlinear changes in synaptic potency by any or all of these mechanisms that endow the neuron with increased computational capacity, as indicated in the passages cited earlier. When these mechanisms can be correlated with specific logical or computational operations, we will have begun to solve one of the deepest and most perplexing problems in neuroscience: the specific contributions that neuronal dendrites make to brain functions.

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Supplemental Comments by John Miller

The paper on synaptic amplification by active membrane in dendritic spines that I authored with Wil and John Rinzel was cathartic, in several senses. From a scientific standpoint, it finally got down on paper some speculative ideas that Wil and John had been thinking about for a long

time: that is, that spines might act as "current augmentation devices" to boost synaptic efficacy, if there were voltage-dependent conductance channels in the spine heads and the biophysical parameters of the spines were within appropriate ranges.

From a personal standpoint, the whole project represented a culmination of my education about neuronal integration that had begun in my first year of grad school. When asked by my advisor (Al Selverston) what I wanted to do with myself for the next few years, I replied that I wanted to "learn how nerve cells worked." His response was, "In that case, you'd better go read everything Rall has ever written." Having already glanced through the pile of abstruse-looking reprints by Rall that he was collecting, it was as if he had just whacked me upside the head with a giant integral sign ... one of those French ones with the big knobs on each end. Then he added, "You may as well read all of Rinzel's, too." Whack! Double integral. As it turned out, it was excellent advice, and I (and numerous others, I imagine) have repeated it many times over.

In reading through Wil's work and other related papers, many of which have been mentioned in the other notes in this volume, I became particularly intrigued by the few published passages about spines. The papers in *Excitatory Synaptic Mechanisms* by Diamond, Gray, and Yasargil and by Wil, noted in Gordon's preceding comments, attracted considerable attention, and I remember discussing spines at great length in one of our journal clubs. I was working in a lab that focused on the generation of motor patterns by neurons known to have voltage-dependent conductances out in the dendritic membrane, and I was drawn to speculations about how the functional characteristics of spines might change if they, too, had active membrane on their heads. (I also remember Selverston's astute tounge-in-cheek hypothesis: "Yeah, spines probably evolved to keep the neurons stuck together better so they wouldn't fall out of the cortex ... sort of like neuro-velcro.") Wil and John Rinzel visited Al's lab sometime later (1976) and I remember asking them about any thoughts they may have had about active membrane on spines. As I remember, Wil then and there anticipated the "gestalt" of most results we were later to obtain through our simulations, by either reconstructing his previous thoughts or realizing them on the spot.

Since I still had not quite figured out how nerve cells worked by the completion of my thesis work, Selverston thought it would be a good idea for me to do a postdoc in Rall and Rinzel's group. Many experimentalists at the time were realizing the necessity of transforming our qualitative hypotheses concerning synaptic integration into a more quantitative format and were inspired by the spectacular advances Pete Getting had made toward understanding one particular central pattern generator network

using the compartmental modeling software developed by Don Perkel and colleagues. I had always been impressed by Wil's use of practical, well-thought-out simulations in his studies of complex neurons and subsystems to complement his analytical derivations in the "simpler" cases, and I thought that doing a postdoc with Wil would offer a unique opportunity to learn more about both analytical and compartmental modeling approaches.

Our interest in spines was actually very far from our minds for most of my stay at NIH but was brought to the surface again by several excellent papers on spine morphology, including one by Fifkova and Anderson (1981) and one by Charlie Wilson and colleagues (1983). Considering a slew of speculative papers that were appearing in the popular press about the possible involvement of "twitching" (but electrically passive) spines in synaptic plasticity, the time seemed ripe for a careful consideration of the functional implications of active spines. The basic idea of the "active spine" study was very simple, and our demonstration of the possibility of synaptic amplification should have come as no surprise.

There were really only two outcomes of the simulations that surprised us, at least, at the time. The first was the large magnitude of the augmentation effect that could be acheived within what we thought at the time to be the most reasonable estimates for spine dimensions: the net charge delivered to the dendrite at the base of an active spine could be as much as an order of magnitude greater than the charge delivered from a passive spine of the same dimensions. The second surprise was the extreme sensitivity of the augmentation effect to small variations in biophysical parameters of the spines: for any particular configuration of parameters determining the dendrite input resistance, spine head input resistance, and voltage-dependent conductance kinetics, there existed an extremely narrow "operating range" of spine stem resistance within which the synaptic augmentation could result. Thus, the degree of augmentation could be substantial, and could possibly be modulated dynamically over a wide range by fine "adjustments" of (for example) spine neck diameter.

Several other people including (at least) Gordon Shepherd, Idan Segev, Don Perkel, and Dave Perkel had been thinking along identical lines and had all arrived at essentially identical conclusions by the time we had completed our illustrative simulations. Wil, John, and I were aware of Gordon's thoughts; in fact, he had been extremely generous and encouraging to our pursuit of these simulations, and we discussed the ongoing work regularly. Indeed, the studies really grew out of the work on spines that Gordon had already done with Robert Brayton. As well as getting us on the right track conceptually, Gordon also steered us toward the use of large general-purpose network simulation programs such as SPICE.

When we were well into our own simulations, Wil, John, and I discovered that Idan had begun simulations very similar to ours. Idan and Wil went on to explore the functional significance of active spines in much greater detail, and they continue to pursue the functional possibilities.

After our studies were completed, we also discovered that Don and David Perkel had carried out essentially identical simulation studies. We did not find this out until the accidental scheduling of back-to-back presentations at a Neuroscience meeting symposium. It was this surprise and realization of mutual interest that led us to publish the two papers back-to-back (Perkel and Perkel 1985). This has always been an essential aspect of Wil's character: he is an innate "collaborator," not a "competitor." In this respect, the lessons he teaches us go far beyond dendritic electrotonus.

Supplemental References

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