6.1 Introduction by Robert E. Burke

Rall, W. (1967). Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input. *J. Neurophysiol.* 30:1139–1169.

The paper reprinted in the next chapter, "Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input," is a landmark paper for several reasons. In many respects, it represented the culmination of Wil Rall's work over the previous decade (much of it included in this volume), in which he developed a mathematical framework for understanding the electrical properties of dendritic neurons and the synapses that contact them. Many of the applications of this elegant cable theory were implicit in rigorous mathematical formulas, where they were protected from the mathematically unwashed, such as myself. In this paper, however, Wil took explicit examples from experimental data and showed how those results were not only explicable but in fact predictable from an understanding of cable theory as applied to dendritic neurons. His exposition was deliberately nonmathematical, using examples of limiting cases that were clearly understandable to nonmathematicians. Even people like myself, whose eyes glaze over when confronted with a differential equation, could see the "why" of our experimental results. Although Wil's earlier work had influenced many people in biophysics, I believe that this 1967 paper revealed the power of applied mathematics for many neurophysiologists.

This is not to say that the paper was purely a didactic explication of things already published. In fact, there is much that was new. For example, Wil introduced the quantitation of postsynaptic potential (PSP) shapes using the notion of "shape indices" and showed how these depended not only on spatial location of the input but also on dendritic electrotonic length and the time course of conductance input (see his "Comment on nonuniqueness" in chapter 6.2). The last fact in particular has often been neglected in later papers by others who took shape index data as generally indicative of electrotonic location, without attention to the important underlying assumptions. In a final sentence, Wil provided the following summation: "A theme common to all of these computations and interpretations is that results, which may appear paradoxical when examined only at the soma, can be understood quite simply when attention is directed to the synaptic input location with special attention to the effective driving potential there."

This paper was the fourth in a series of five that were published in 1967 (Smith et al. 1967; Nelson and Frank 1967; Burke 1967, Rall 1967; Rall et al. 1967). The first three papers reported experimental observations on cat

α-motoneurons and the group Ia EPSPs generated in them. They were written by colleagues who had come to NIH in the 1950s and 1960s to work with the late Karl Frank, who was a major pioneer in using intracellular micropipettes to study cellular and synaptic processes. I was one of these people and can give a personal perspective on the genesis of this series, which is still referred to by some of our friends as "the '67 Book." My participation in this effort indelibly influenced my entire scientific career, and I hope that this brief reminiscence will give some idea of the excitement that comes to a young scientist who is lucky enough to work with great mentors.

I came to the NIH in 1964 to learn intracellular recording with Kay Frank (as he was universally known). He suggested that I could start by applying the method to cat motoneurons, in order to see whether or not group Ia EPSPs in motoneurons summated linearly. This question was of interest because Ia EPSPs did not always behave as expected for synaptic potentials that were generated by an increased postsynaptic conductance change. Working in Kay's lab, Tom Smith and Ray Wuerker had earlier found that Ia EPSPs were difficult, and frequently impossible, to invert by applying depolarizing current to the motoneuron soma, despite claims to the contrary (e.g., Eccles 1957). They also found that it was usually impossible to detect postsynaptic conductance changes during Ia EPSPs, even when using a sensitive AC analysis method (Smith et al. 1967). Phil Nelson and Kay had also observed that Ia EPSPs showed great variability in their response to currents injected at the motoneuron soma, which was only partially explainable by the nonlinear rectification behavior of the motoneuron membrane (Nelson and Frank 1967). Nonlinear potential summation would fit with the behavior expected for "chemical" synapses, while exclusively linear summation could have two interpretations: (1) Ia EPSPs are generated in part by electrical transmission (which we felt unlikely); or (2) Ia EPSPs are produced by purely chemical synapses that are widely distributed over the dendritic tree, in relative electrotonic isolation from one another. The latter notion seemed unlikely to me, probably because my earliest inspiration toward neurophysiology had come from John Eccles's classic monograph *The Physiology of Nerve Cells*, in which Eccles took the position that "the dendrites are so long, relative to their diameter, that changes in the membrane potential of more distal regions would make a negligible contribution to potentials recorded by a microelectrode implanted in the soma" (Eccles 1957, p. 6).

After starting experiments with electrically evoked composite Ia EPSPs, I also literally began playing around with the "synaptic noise" produced in motoneurons when their parent muscle was stretched (Granit et al.

1964). Much to my surprise, I found that it was often possible to recognize large-amplitude, rhythmically occurring EPSPs, ticking along within the background synaptic signals at frequencies that varied with levels of stretch, as would be expected for PSPs produced by an individual group Ia afferent (Burke and Nelson 1966). When I showed such records to Kay, he became quite excited and exclaimed, "You've got to stretch these signals out and look at their shapes!" He pointed me to Wil's 1964 paper describing the shape differences to be expected for EPSPs generated at different electrotonic locations. Luckily, my data had been recorded on FM tape, and reanalysis showed that, indeed, the shapes for any given single-fiber EPSP were quite consistent, but those produced by different fibers had very different shapes (Burke 1967). It was immediately obvious to us that we had an experimental validation of Wil's theoretical predictions. The single-fiber EPSP shape differences and the fact that composite Ia EPSPs often exhibited linear summation (Burke 1967) both fit very well with the idea that group Ia synapses were widely, and variably, distributed over the motoneuron surface. Furthermore, the fact that some Ia fibers produced somatic EPSPs with quite prolonged shape indices strongly suggested that synapses located on distal regions of the motoneuron dendrites could indeed produce significant voltages at the motoneuron soma. Needless to say, all this was very satisfying to both Wil and Kay, because it provided direct experimental support for Wil's view of dendritic function as critical to our understanding of neuronal input-output relations. For me, it was a revelation of what science was about!

Although Wil had illustrated the effects on dendritic location of synaptic potential shape in 1964, that paper (Rall 1964) was in a monograph that was not widely available. It seems fair to say that the 1967 paper under discussion here contained the first thorough theoretical exploration of the behavior of dendritic PSPs in the general neurophysiological literature. In it, Wil used compartmental equivalent cylinder models to explore examples of the interactive effects of conductance duration, amplitude, and spatial location on peak depolarization, illustrating important sources of nonlinear dependence between local voltage perturbation and fixed driving potentials at various points in the cylinder. He also looked at interactions between EPSPs and hyperpolarizations produced by injected currents at the soma and by simulated inhibitory conductances in different spatial locations. All of these simulations had immediate relevance for understanding our experimental findings.

A large fraction of this paper was devoted to an analysis of the detectability of dendritically located conductance changes underlying EPSPs when currents are injected into the soma. This section arose

directly from Wil's consideration of the largely unsuccessful attempts by Tom Smith and colleagues (Smith et al. 1967) to use AC currents and sensitive phase-detection methods to define the Ia EPSP conductance. Wil recognized that the problem was primarily one of signal-to-noise ratios. The key insight was that, if a major fraction of the Ia conductance were delivered to the dendrites (a view not generally accepted at the time), the electrotonic cable intervening between the soma (the source of current and the site of measurement) and the distant sites of conductance change produces an inevitable decrement to both the local perturbing voltage changes at the synaptic sites and the results of that perturbation as reflected at the soma. Any such detection system thus faces an electrotonic decoupling that is larger than the electrotonic distance involved. Given the relatively small perturbations of local EPSP driving force that were experimentally feasible, Wil concluded that the expected magnitude of signal distortion at the soma, though theoretically present, would be below detection threshold at remarkably short electrotonic distances. Furthermore, the time course of the distorted signal did not match that of the conductance change itself, even when detectable. To all of us involved in this series of papers, these insights came as major surprises. These inconvenient properties of dendrites continue to plague everyone who tries to voltage clamp dendritic neurons (see Rall and Segev 1985; Spruston et al. 1993).

My own favorite aspect of this paper is Wil's remarkable "computational dissection" of the synaptic and redistribution (or "loss") currents that are inherent as synaptic potentials are generated in dendrites (section 2 and figure 4). This brief section presents concise and wonderfully lucid insights into why synaptic potential shapes and amplitudes change in an electrotonic cable. It bears careful and repeated study by anyone interested in how dendritic neurons process synaptic information.

Wil was the senior author on the last paper in the series of five papers of 1967 entitled "Dendritic location of synapses and possible mechanisms for the monosynaptic EPSP in motoneurons" (Rall et al. 1967). This paper was a concerted attempt to discuss the implications of the experimental observations in the first three papers in the light of Wil's theoretical results (paper four of the series). For reasons of economy, the paper has not been reprinted in this volume, but there are several aspects of it that are worth attention. It was in this paper that the first graphs of EPSP shape indices appeared in the form that later became widely used. Figure 1 here (reproduced from figure 5 in the original) encapsulates the central theme of this paper—the comparison of experimental data with modeling results. At the time, this was a rather startling thing to do with respect to neuronal electrophysiology.

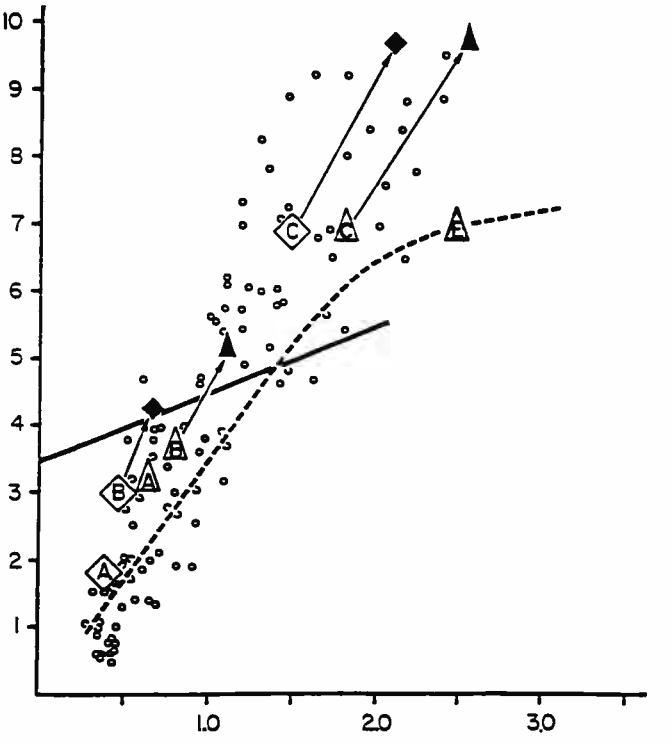

Figure 1
Shape index plot of EPSP half-width (ordinate) versus time to peak (abscissa), with scales in ms (from Rall et al. 1967). Small open circles denote experimentally observed single-fiber EPSPs. Large open symbols show shape indices for simulated EPSPs with "fast" (diamonds; alpha function with peak time of 0.1 ms) and "medium" (triangles; peak time of 0.2 ms) synaptic conductance time courses, recorded in compartment 1 of a 10-compartment cylinder (time constant = 5 ms; $L = 1.8$). Compartmental location of active conductances: $A = 1, 2, 9, 10$; $B = 1, 2, 3, 4, 9, 10$; $C = 3, 4, 9, 10$; $E =$ all 10, weighted to produce equal somatic amplitudes. Arrows and solid symbols show the effects of increasing time constant to 7 ms. The dashed line indicates the locus of shape indices for somatic EPSPs produced by conductances in individual compartments. The solid line shows the locus of shape indices of composite EPSPs produced by conductance changes of different durations applied at equal strength in all 10 compartments. Reproduced from Rall et al. 1967.

Figure 1 illustrates the time to peak and half-width of experimental single-fiber EPSPs from paper three (Burke 1967), with overlays derived from idealized cable models with ten compartments. The membrane time constant and electrotonic length (5 ms and 1.8, respectively) chosen for the model were thought to be representative of cat motoneurons. Subsequent experiments showed that these guesses were quite reasonable. The small open circles denote shape indices of individual EPSPs produced by 11 group Ia afferents in seven cat motoneurons. The dashed line shows the locus of shape indices for EPSPs generated in individual compartments of the model and recorded in the "soma" compartment. The large open symbols denote the shapes of composite EPSPs generated by conductances with "fast" or "medium" time courses, activated simultaneously in multiple compartments. The large filled symbols and arrows indicate changes that were produced when the model time constant was increased from 5 to 7 ms. The point of the figure was to show that a model system with a realistic range of parameters could generate synaptic potentials that fit reasonably well with experimental results. Although the simple compartmental model used for this figure is unrefined by today's standards, it represented a significant step in the evolution of thinking about dendritic function and the importance of synapses that are found on dendrites, because it brought together theoretical and experimental results in a way that was new and compelling.

An important deficiency in the 1967 comparison was the lack of time-constant estimates for the motoneurons; I had not looked at them because I did not anticipate their eventual importance. It was clear that variations in motoneuron time constant could not explain all of the observed shape differences because one notable example showed that two Ia fibers that ended on the same motoneuron generated EPSPs with markedly different shapes (Burke 1967, figure 10). However, figure 1 clearly shows that even a modest variation in time constant can account for a considerable range of shapes. Subsequent work by Jack et al. (1971) addressed this problem by plotting Ia EPSP shape indices that were normalized by motoneuron time constant. In addition, these authors plotted regions on the shape index plot that would account for likely variations in the values of dendritic electrotonic length, dendritic to somatic conductance ratios, and normalized synaptic-current time course. Their results, for a large sample of single-fiber EPSPs, allowed Jack and co-workers to conclude that Ia EPSPs arose from all regions of the dendritic membrane. Other studies soon confirmed and extended these observations (Mendell and Henneman 1971; Iansek and Redman 1973). Later, it became possible to inject horseradish peroxidase into individual group Ia afferents and motoneurons

postsynaptic to them, to demonstrate that putative Ia boutons are indeed widely distributed in the dendritic trees (Burke et al. 1979; Brown and Fyffe 1981). In a remarkable experiment, Redman and Walmsley (1983) then combined such histological reconstructions with electrophysiology to show that the two methods produced the same estimates of electrotonic location. More recently, anatomical data on motoneurons and Ia bouton locations have been combined with estimates of motoneuron membrane properties to model the range in size and amplitude of composite group Ia EPSPs that arise from spatially dispersed boutons (Segev et al. 1990). The steady accumulation of evidence that group Ia EPSPs are generated largely in the motoneuron dendrites has been a source of much satisfaction for Wil and for all of us involved in this work.

In 1967, most of us felt that Ia EPSPs were generated by "chemical" synapses despite the existence of some experimental data that seemed incompatible. The wide spatial distribution of group Ia synapses proved to be the factor that brought all of the evidence back into line. It will be obvious to readers of this paper that the linchpin in this effort was Wil Rall. His insights and model results were essential to generating a cohesive and rigorous summation of the experimental results then available. It may be difficult for readers today to imagine that, only 25 years ago, the function of neuronal dendrites was poorly understood, frequently neglected, and even explicitly denied. The fact that dendrites now enter into everyone's thinking about neuronal function is a tribute to the clarity and force of Wil Rall's pioneering contributions to neuroscience.

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