

The branching structures called dendrites are among the most striking and characteristic features of nerve cells, and understanding their contributions to nerve function has been a supreme challenge to neuroscience. More than thirty years have passed since the three key papers of Wilfrid Rall on the biophysical properties of branching dendritic trees appeared (Rall 1957, 1959, 1960). These papers were revolutionary in several ways. They showed first that dendrites could be analyzed by a rigorous mathematical and biophysical approach, so that studies of the functional properties underlying impulse generation and synaptic responses could be carried out on a par with studies of similar properties in cell bodies and axons. They introduced a new theoretical framework for modeling these complex structures so that their integrative properties could be studied and, through this, their contributions to signal processing in the nervous system. Finally, these studies challenged the dominant hypothesis of contemporary neurobiologists and modelers that neurons are essentially *isopotential* units.

For neural modelers, the assumption of isopotentiality of neurons was very convenient because it allowed them to neglect the daunting spatial properties of dendrites and focus only on temporal aspects of the input-output properties at the cell body (an assumption that continues to this day in most neural network models). This had been the basic premise underlying all theoretical models since the pioneering study of McCulloch and Pitts (1943), in which the neuron was represented as a “point unit” that implements simple binary (“on-off”) computation. However, Rall showed that the interrelations between the unique morphology and the specific electrical properties of neurons can be critical for their input-output functions, and that by combining the different kinds of “neuron-ware” (dendrites, spines, axon, membrane channels, synapses) into complex structures, the neuron can be a computationally powerful unit.

In retrospect it is difficult to understand why dendrites were ignored, functionally, until Rall's pioneering work. They had been the focus of intense anatomical studies for many years since the classical studies of Ramón y Cajal and his contemporaries in the 1890s, and their extended and complex morphology was well appreciated (reviewed in Shepherd 1991). A glance at the drawings of Ramón y Cajal makes it clear that the majority of the surface area of most neurons is in the dendrites and that, most significantly, abundant inputs seem to converge onto the dendritic

trees. The electrically distributed nature of dendrites was actually known for many years, simply from the fact that extracellular electrical field potentials, such as the electroencephalogram, can be recorded in the brain; a tissue composed of isopotential units would not give detectable summed extracellular currents. Studies of field potentials in the cortex had further suggested that “decrementing conduction” occurs in dendrites. But these considerations were overridden by the need for simplifying assumptions in facing the complexity of the nervous system, and once they were established, it was difficult to abandon them in favor of new ones.

Reflecting Rall’s methodical approach and modest personality, his theory for dendrites penetrated the scientific community slowly and then deeply. It spread among cellular neuroanatomists and neurophysiologists, and, with time, the functional consequences of dendrites began to attract serious attention. Old experimental results were reinterpreted, and new experimental and theoretical studies were designed to explore the input-output function of dendrites (e.g., Rall et al. 1967; Rall 1967; see reviews in Jack et al. 1975; Rall 1977, Rall et al. 1992, and Mel 1994). We know now that most of the synaptic information transmitted between nerve cells is indeed processed in the dendrites, and that it is there that many of the plastic changes underlying learning and memory take place. It is now generally agreed that the specific aspects of dendritic morphology characteristic of different types of nerve cells must be considered when the computational and plastic functions of the brain are to be understood. Thus, we speak naturally today about “dendritic integration,” “spatiotemporal summation of synaptic inputs,” “dendritic nonlinearities,” “dendritic plasticity,” “chemical compartmentalization,” and ion diffusion along dendritic segments. Much of this new vocabulary has emerged from the work of Wilfrid Rall.

In pursuing these early studies, Rall was one of the first to realize the potential of digital computers for biology (Rall 1964). He was a pioneer not only in constructing the first computer-based models of the neuron complete with its dendrites but also in drawing attention to the dendrites as the main computational substrate for signal integration in the nervous system. Most neurobiologists entering the field now are unaware of Rall’s seminal 1964 paper on compartmental modeling and the foundations he laid in it and his subsequent papers for the present methods and concepts that are now taken for granted in the computer modeling of neurons. Through this work Rall may, in fact, be regarded as a founding father of computational neuroscience.

This book is a manifestation of the bulk of Rall’s theoretical thinking applied to the nervous system. It brings together his major articles that established many of our present concepts and insights regarding the infor-

mation-processing functions of nerve cells. Each article is accompanied by an introduction that highlights the main insights gained from the paper and puts the work in the appropriate historical perspective. These introductions are written by co-workers who collaborated with Rall in these studies or were his colleagues in the field. They have tried to convey a sense of the context within which the studies were carried out, and of their unique perspective from working with Rall on these problems and being inspired by him. The introductions also point toward the impact of specific papers on the present state of the art of single neuron modeling. Appropriate commentaries are also provided for several important papers that could not be included because of space limitations.

One may wonder why this book is assembled now. There are several reasons. First, in this "Decade of the Brain," when the field of computational neuroscience is becoming so active, it seems timely to group together the work of a major creator of the field. Second, a source book such as this, with appropriate perspectives, should help the newcomer to appreciate where things started and where they may lead. Third, some of Rall's papers are not easily accessible. Fourth, with the passage of time, many fundamental contributions of Rall have been forgotten or have been misinterpreted. For example, many erroneously believe that Rall considered only passive membrane properties, thereby neglecting the functional consequences of synaptic- and voltage-gated nonlinearities in dendritic trees. Nothing could be further from the truth, and this book provides the evidence in his papers and the commentaries. Finally, in keeping with his modest personality, Rall has never received the recognition one would expect of a major creator of modern neuroscience. As he enters retirement and devotes more time to his artistic pursuits, this book serves as an appreciation from all of us who have been influenced by his scientific thinking and personality.

In the remainder of this introduction we highlight for the general reader the major insights that were gained from the main studies of Rall and his collaborators and followers. We do so by emphasizing the leading questions that he posed along the path of his scientific career, and their answers. A fascinating account of the development of his ideas can be found in his recent brief memoir (Rall 1992). More on the general background for the development of his ideas can be found in Rall 1977, Shepherd 1992, and Segev 1992. This background is amplified in the various introductions and commentaries in this book, together with more personal comments by colleagues and co-workers that are not available elsewhere. Theoretical elaboration and extension of Rall's theory can be found in Jack et al. 1975, Butz and Cowan 1974, Horwitz 1981, Poggio and Torre 1978, Koch et al. 1982, Holmes 1986, Abbott et al. 1991, and

Major et al. 1993. The impact of Rall's ideas on computational neuroscience can be found in Sejnowski et al. 1988. The epilogue of this introduction discusses possible future directions for the theoretical and experimental studies on the computational functions of single neurons.

Early Training: From Physics to Neurophysiology

Wilfrid Rall received his early training in physics, graduating from Yale University with highest honors in 1943. The Second World War was in progress, and, like many other young physicists, he became part of the Manhattan Project. A glimpse of his role in that effort as a mass spectrographer at the University of Chicago can be gained from his memoir in Rall 1992. At the end of the war he became interested in applying physics to biology. As it happened, the first graduate program in biophysics was being formed at Chicago by K. S. Cole, and Rall enrolled as one of the first students in 1946. Over the next two years, his summers were spent at the Marine Biological Laboratory in Woods Hole as a research assistant to Cole and George Marmont, helping to develop and introduce the new space clamp and voltage clamp methods for the squid axon. At Chicago, in addition to courses in experimental biology, he took courses taught by Rashevsky, Carnap, Fermi, and Sewall Wright. All in all, not a bad way to start a career in biophysics!

While completing requirements for a master's degree in 1948, Rall had corresponded with John C. Eccles at the University of Otago Medical School in New Zealand about Eccles's new theory of synaptic inhibition. This resulted in an offer to come to Dunedin to carry out his doctoral work. There he was immediately plunged into the intensive studies of the neural basis of spinal reflexes that soon led to the pioneering intracellular studies of motoneurons by Brock, Coombs, and Eccles in 1951–1952. At that point Rall turned to a more independent project for his dissertation, a study of the monosynaptic activation of a motoneuron pool and the construction of a probabilistic model for the input-output relations. In this work Rall gained much from the wise counsel of A. K. (Archie) McIntyre, who became Professor when Eccles left for Australia in 1952. Among the students at Dunedin was Julian Jack, one of the contributors to this volume.

One should not think that this life in New Zealand was lived far off the beaten path, certainly not in neurophysiology. Eccles was always on the move. His intracellular studies made Dunedin the center of the world in the 1950s for the new neurophysiology of the central nervous system. McIntyre himself had recently studied at Cambridge, London, and the

Rockefeller Institute; in fact, the new instrumentation he brought back to Dunedin played a critical role in the pioneering intracellular studies. Rall was therefore ideally placed to experience the best in experimental neurophysiology and to be stimulated by the dynamic Eccles and the reflective McIntyre into constructing models that could give insight into experimental findings. Few have brought such a deep understanding of experimental biology, gained from first-hand experience, to the task of theoretical modeling.

After receiving the Ph.D. in 1953, Rall obtained a Rockefeller Foundation postdoctoral fellowship, which enabled him to gain further experience with the leading neurophysiologists of the time. In London in early 1954 he studied in the laboratory of Bernard Katz; during this period Katz and his students were laying the foundations of our modern concepts of the synapse by their work on the physiology of the neuromuscular junction. Rall also had the opportunity to discuss his approach to modeling the membrane properties of the nerve cell body (soma) with Alan Hodgkin in Cambridge, who provided him valuable encouragement (Rall 1992). In New York he worked at the Rockefeller Institute (now Rockefeller University) in the laboratory of David Lloyd, who was responsible for many of the classic experiments in spinal cord reflex physiology. He collaborated mainly with Carlton Hunt, who, with Stephen Kuffler, had established much of the basic physiology of muscle spindles and their contributions to spinal reflexes.

After a final year in Dunedin, Rall returned to the United States to head the laboratory of biophysics at the Naval Medical Research Institute in Bethesda, Maryland, under K. S. Cole. Cole soon left for the National Institutes of Health, along with several others, including J. Z. Hearon, who was asked to set up a new Office of Mathematical Research (OMR). Rall joined that group in 1957, and spent the rest of his career there. The congenial atmosphere established by Hearon, the institutional home for the OMR provided by DeWitt Stetten in the National Institute of Arthritis and Metabolic Diseases, and the overall support provided by the National Institutes of Health for the OMR deserve special mention and recognition. Mention should also be made of the Laboratory of Neurophysiology (LNP), with Wade Marshall, Kay Frank, Mike Fuortes, Phil Nelson, Tom Smith, and Bob Burke, where Rall established close friendships and collaborations with experimenters on the forefront of work on the motoneuron and spinal reflexes. In retrospect it may be seen that here OMR and LNP established one of the first working groups combining experimental and theoretical neuroscience. With this support and in this environment, Rall could concentrate his unique gifts on long-term projects uniting experimental data with theoretical models.

Insights Gained from Models of Motoneuron Populations

Rall's first study, for his doctoral thesis, involved an analysis of the input-output relations of motoneuron populations. This study linked the concept of the motoneuron pool of Sherrington, with whom Eccles had studied in the 1920s, with the modern analysis of activation of the pool by different intensities of afferent nerve stimulation, by Lloyd. Rall was interested in characterizing in a quantitative fashion the fractional activation of a pool at different levels of motoneuron excitability. He constructed a model based on several assumptions: each motoneuron has the same number of synaptic sites (e.g., 5,000); each site has the same probability of being occupied by a monosynaptic connection; each motoneuron fires an impulse when the number of activated monosynaptic connections exceeds a threshold value, which has an inherent variability. A model based on these assumptions gave a close fit to the experimental data (see Rall 1955a,b). Fuller discussion of these papers is to be found in the appendix to this volume, where Julian Jack notes that "this work has yet to be emulated for any other neuronal population" and remains a valuable example for those who may wish to construct models of neurons with a distribution of properties and models of populations of those neurons that perform a range of functions.

Although not directly involved with dendrites, which is the main theme of the present book, this early study was significant for Rall's later work in several ways. First, he brought to it a perspective on the function of a neuronal population in mediating a particular behavior, in this case a spinal reflex; similarly, in his later studies his interpretations went beyond the immediate biophysical properties to *implications for system functions and behavior*. Second, it focused on properties of individual neurons (numbers of synaptic sites; threshold for impulse generation) as being critical for the function of the neuron population; that is, *systems behavior arises out of the properties of realistic neuron models*. And third, it raised for him the question of how the *biophysical properties of the neuronal membrane contribute to the integrative actions of the neuron*, which came to lie at the core of his thinking.

Do Only Adjacent Somatic Synaptic Inputs Sum Successfully?

In thinking about the biophysical properties underlying neuronal integration, Rall became aware of a widely accepted assertion by Lorente de Nó (1938) that spatial summation between several synaptic inputs on the soma membrane is very local, and that successful summation occurs only

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when activated synapses are close to each other. This was in conflict with Rall's physical intuition, and in 1953 he addressed this question in a short abstract entitled "Electrotonic theory for spherical soma." Modifying the well-established passive cable equations (Hodgkin and Rushton 1946) to the case of a spherical membrane surface, he showed theoretically that the transient voltage in the soma membrane following focal depolarization equalizes very rapidly over the spherical surface. The implication is that, contrary to Lorente de Nó's assertion, synaptic potentials will sum effectively, independently of where they are located on the soma surface. In other words, Rall demonstrated that, functionally, *the soma can be treated as an isopotential unit.*

Can One Neglect the Cable Properties of Dendrites When the Input Is Applied to the Soma?

The next step was to examine the electrical consequences of the dendrites when the input is applied to the soma. By that time, Eccles and his collaborators in Dunedin had obtained their first pioneering results in recording and stimulating cat spinal motoneurons with an intracellular electrode in the soma. In interpreting the voltage transients recorded from the soma, they assumed that the current was confined mostly to the soma. Rall questioned whether it is valid to neglect the cable properties of the dendrites. In a letter to *Science*, Rall (1957) showed that when dendrites are coupled to the soma, a significant portion of the current spreads electrotonically from the soma to the dendrites. Thus, dendrites affect the charging (and discharging) rate of the soma membrane following an input to the soma. Indeed, the resultant voltage transients will build up (and decay) *faster* when dendrites are present compared to the case of a soma without dendrites (i.e., faster when the transient is normalized relative to the steady-state amplitude). In the limiting hypothetical case of a soma without dendrites, one has the case of an isopotential unit consisting of the membrane resistance and capacitance in parallel, and the voltage rise time (and its decay) in response to a step current input is governed by a single exponent having the membrane time constant, τ_m . When dendrites are present, the decay is faster than τ_m ; thus, fitting a single exponent to the experimental voltage transient recorded at the motoneuron soma underestimates the actual τ_m (by a factor of about 2 in the case considered by Rall). Rall showed that when the somatic transients were analyzed using the correct value of τ_m , there was no need to invoke a "residual synaptic current" in shaping the decay of the somatic EPSPs, as was assumed by Eccles and his co-workers. Thus, Rall provided the theoretical basis for recognizing that *dendritic neurons are not isopotential units.*

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What Is the Effect of Dendritic Inputs on the Soma Depolarization?

Having shown that signals at the soma are affected by the presence of dendrites, Rall turned his attention to the question of how inputs to the dendrites are integrated at the soma. This question inspired the majority of Rall's studies. The working hypothesis during the 1950s was that synapses on the dendrites, in particular on distal branches, are essentially ineffective, and that only the synapses at the soma and the proximal dendrites contribute to a neuron's output. The complex patterns of dendritic branching made this problem seem intractable to most approaches. In order to deal with it, Rall developed first an analytical cable theory for dendrites (Rall 1959, 1960), followed by a numerical approach utilizing compartmental models (Rall 1964); these form the theoretical foundation for exploring the input-output functions of dendrites.

In order to make his methods as accessible as possible to experimentalists, Rall drew attention to certain simplifying approaches among the broader theoretical framework he constructed. Although this had the virtue of facilitating use of the methods, it meant that many workers have been unaware of the full power of the comprehensive theory. For example, there is a misunderstanding that Rall's cable theory for dendrites can treat only passive trees with uniform membrane resistance, unvarying branch diameters, and a rigid branching pattern. In fact, the methods specifically embrace *arbitrary branching geometries* and *branching patterns* and in which the branches may have *nonuniform membrane properties* (for example, simulating steady background synaptic conductance input to the tree: see Rall 1959, 1962a). For simplicity Rall first applied his analytical theory assuming that the dendritic tree belongs to a class of trees that are electrically *equivalent to a single cylinder*.

It is difficult for a person coming into the field today to appreciate how this simple "equivalent cylinder" model provided for a new world of understanding of dendritic functions. The major insights regarding voltage spread in passive trees came from the analysis of such trees (Rall and Rinzel 1973; Rinzel and Rall 1974). Here we briefly summarize these insights.

1. The degree of branching and the extremely thin diameters of dendritic branches at distal locations, together with the small dimensions of dendritic spines, imply large input resistances (and input impedances) at these locations (on the order of a few hundred megohms and more). Thus, a small excitatory synaptic conductance change (of less than 1 nS) is sufficient to produce a large local dendritic depolarization of a few tens of mV

(Rall and Rinzel 1973; Rinzel and Rall 1974; Rall 1977). In brief, small processes generate large local responses.

2. The local dendritic depolarization is expected to attenuate severely in the central (dendrites-to-soma) direction. Steady voltage is expected to attenuate about 10-fold whereas fast transients may attenuate 100-fold or more when spreading from distal dendritic tips to the soma. The attenuation within the tree is asymmetrical; a much less severe attenuation is expected in the peripheral (soma-to-dendrites) direction. This asymmetry in peripheral versus central directions implies that from the *soma viewpoint*, dendrites are electrically rather compact (average electrotonic length of 0.3–2), whereas from the *dendrites (synaptic) viewpoint* the tree is electrically far from being compact (Rall and Rinzel 1973; Rinzel and Rall 1974).

3. The large voltage attenuation from dendrites to soma for transient synaptic inputs implies that many (several tens) excitatory inputs should be activated within the integration time window, τ_m , in order to sum and produce sufficient (10–20 mV) somatic depolarization that can reach threshold for impulse initiation at the axon hillock.

4. Although severely attenuated in *peak* values, the degree of attenuation of the *area* of transient potentials is relatively small because of the more prolonged time course of the response. Thus, the “cost” (in term of voltage area as well as the charge) of placing the synapse at the dendrites rather than at the soma is quite small. Hence, even in completely passive trees, distal dendritic synapses contribute to the somatic depolarization and can modify the output discharge of the neuron (Rall 1964).

5. Synaptic potentials are delayed, and they become significantly broader, as they spread away from the input site (Rall 1964; Rall 1967; Rall et al. 1967; Rinzel and Rall 1974). The input response at a distal branch (see figure 2 of Rinzel and Rall 1974) implies that, locally, synaptic potentials are very brief. At the soma level the time course of the synaptic potentials is primarily governed by τ_m . This range in width (duration) of the synaptic potential implies multiple time windows for synaptic integration in the tree (Agmon-Snir and Segev 1993, and see also Stratford et al. 1989).

These results demonstrated that the distributed structure of dendrites and their morphological complexity have the functional consequence that dendritic synaptic inputs should give large local responses that undergo marked attenuation within the tree. This implies that, in principle, the tree can be functionally fractionated into many *semi-independent functional subunits*, each of which can perform its computational task locally. The result of this local computation can have a global effect on the input-output

(dendrites-to-soma) function of the neuron under appropriate conditions of synchronous activation of critical numbers of inputs with critical spatial relations. There can also be very local effects controlling local input-output dendritic processing through dendrodendritic synapses. And there can be local activity-dependent plasticity, as in dendritic spines (see Rall et al. 1966; Rall 1974; see also Koch et al. 1982; Shepherd and Brayton 1987; Rall and Segev 1987; Rinzel 1982; Woolf et al. 1991; and a recent review by Mel [1994]).

What Can We Learn about the Dendrites from Intracellular Recording at the Soma?

Being both theoretician and experimentalist, Rall felt it was important that his theoretical models would help experimentalists to learn more about the electrical properties of neurons. Indeed, Rall's theory is based on biophysical parameters that, in principle, can be measured experimentally. Furthermore, in many of his studies Rall suggested critical experiments that allow one to extract these biophysical parameters (e.g., the "shape index" to characterize and compare synaptic potentials in Rall et al. 1967, and the "peeling method" for estimating the membrane time constant and the time constants for equalization of transient potentials in Rall 1969).

The challenge was to get these biophysical estimations from recordings made with an intracellular electrode at only one point, the soma. At first, it may seem quite impossible to gain information about a large treelike structure from a local (somatic) recording at its origin. Yet Rall showed that many of the important electrical properties of dendrites can be estimated rather faithfully from such recordings. He showed how one can estimate the cable length of the dendrites (L), the specific properties of the membrane (R_m , C_m) and of the cytoplasm (R_i), the time constant of the dendritic tree (τ_m), the dendrite-to-soma conductance ratio (ρ), and, surprisingly, the properties of the synaptic input (i.e., its electrical distance from the soma ($X = x/\lambda$), its time course ($\alpha = 1/T_{\text{peak}}$), and its amplitude).

From the application of Rall's experimental suggestions and from their extensions by Jack and his collaborators (Jack et al. 1975) we know that, depending on the neuron type and experimental condition, R_m ranges between 5,000 and 50,000 ohm cm^2 . Present-day researchers may be surprised to learn that the earliest suggestions for the specific membrane resistance, based on assumptions of current flow only across soma membrane, were less than 1,000 ohm cm^2 ; when Rall first suggested, based on his analysis of current flow into the dendrites in 1959, that it should be at least 2,000 ohm cm^2 and probably 4000, or even higher, his was a lone voice in the wilderness. The specific capacitance (C_m) is assumed to be

constant at $1-2 \mu\text{F}/\text{cm}^2$, and R_i is estimated to range between 70 and 250 ohm cm. The time constant of dendritic membrane is, thus, 5–50 msec. The cable length of dendrites (from the soma viewpoint) was estimated to be rather small ($0.3-2$) λ ; this implied that, for steady input to the soma, dendrites are electrically compact. The dendrite-to-soma conductance ratio (ρ) was estimated to be between 4 and 25 (and maybe more), and, this implied that most of the membrane conductance is in the dendrites.

Regarding the properties of the synaptic input, Rall showed that the variable time courses of EPSPs recorded at the soma are indicative of a wide distribution of the excitatory inputs over the dendritic surface. Thus, the electrotonic distance to the soma (X) may range from 0 (a somatic input) to 1.5 or 2 (distal dendritic inputs). The theory (Rall 1967) allowed estimations of X for individual synaptic inputs. Dramatic confirmation was obtained in the study of Redman and Walmsley (1983) who showed that the value for X that was estimated from Rall's theory agrees extremely well with the actual anatomical location of the synapse as found by labeling and reconstructing both the presynaptic (Ia) axon and the postsynaptic dendrites of the spinal alpha motoneuron.

Current experimental work on synaptic integration is concerned with discriminating between different subtypes of excitatory and inhibitory synapses. A summary of this work is beyond the scope of this introduction. Suffice it to say that synaptic inputs can be generally divided into at least two types of excitatory inputs, one with a fast (AMPA) time course (rise time of smaller than 1 msec) and the other with 10-fold slower kinetics (NMDA), and at least two types of inhibitory inputs, a fast one (GABA_A) and a slow one (GABA_B). Rall's theory of dendritic function will continue to be a critical tool in analyzing the contributions of each type of synaptic response to the integrative functions of the neuron.

What Can We Learn about Neuronal Organization from Extracellular Potentials?

Thus far we have considered analysis of the functional organization of the neuron based only on recordings of intracellular potentials. However, the extracellular potentials due to extracellular current also provide important information. At the time that Rall became interested in these potentials in relation to dendritic function, nearly a century of research had been carried out on the extracellular currents generated by the impulse in peripheral nerves. From this had emerged generally accepted concepts for interpreting the compound extracellular potentials recorded by two different methods: between a focal electrode and a distant ground when the nerve is placed in a volume conductor, and between two electrodes on the

nerve when it is surrounded by a nonconducting medium (i.e., mineral oil) (see Fulton 1955).

Unitary Extracellular Potentials

When the first unitary extracellular potentials were recorded routinely from neurons in the 1950s, it was presumed that the volume conductor interpretation was applicable, and it was expected that the potentials, interpreted in this way, could be used to answer such critical questions as whether impulses spread actively or passively into the dendrites. The biphasic nature of the spikes recorded from near the soma seemed to support the idea of active impulse invasion into the dendrites; that is, the second phase of positivity of the soma recording was assumed to reflect active current sinks associated with the spike in the dendrites (see Fatt 1957). However, Rall's earliest studies of intracellular current indicated to him that the biphasic nature of the extracellular spikes was more likely due to a reversal of longitudinal current between an active soma and largely passive dendrites. Building on his analysis of intracellular currents, he carried out laborious and detailed calculations of the associated currents along the dendrites, and he showed that the second positive phase of the soma spike could be due to the rapid repolarization of the soma rather than to active impulse invasion of the dendrites (Rall 1962b).

Although the interpretation of extracellular unitary spikes now seems a somewhat arcane subject, it was a hotly debated topic at the time because of the possible insights it could give into the question of active dendrites. Excerpts from Rall's paper are published here, together with commentaries that explain the significance of this study for the interpretation of extracellular unit potentials recorded from motoneurons in the spinal cord (Nelson and Frank 1964). This work was of further importance as one of the foundations for the study that led to the identification of dendrodendritic synaptic interactions in the olfactory bulb.

Extracellular Field Potentials

In contrast to extracellular unitary potentials, extracellular field potentials are due to the summed activity of populations of synchronously active neurons. Building on his insight into the longitudinal currents in dendrites set up by impulses or synaptic potentials, Rall inferred that field potentials are due to summed extracellular currents outside dendrites arranged in parallel. This meant that the situation contains elements of recording both from peripheral nerves in oil and from a nerve in a volume conductor: within the active region the current paths are constrained in parallel, but outside the region the current returns within a volume conductor. This

gives rise to a “potential divider” effect of the recording electrodes along these current paths.

The utility of this concept was demonstrated in reconstructing evoked potentials in the olfactory bulb in the study of Rall and Shepherd (1968). The concept provided the key to understanding the way that different phases of the extracellular field potentials could be correlated with the sequence of intracellular potential changes associated with impulse generation. This was a break with a long tradition in electrophysiology (unfortunately still surviving) of assigning labels to different parts of an extracellular transient and assuming that each is a direct reflection of a propagating intracellular impulse or spreading synaptic potential. With the increased accuracy of the model, it was possible to use the field potentials to localize sites of synaptic interactions, which led to the prediction of dendrodendritic synapses between mitral and granule cells in the olfactory bulb. The generality of the potential divider model in reconstructing evoked potentials for different extents of activated neuronal populations in the cerebral cortex was subsequently demonstrated by Klee and Rall (1977).

Output Functions of Dendrites: Dendrodendritic Synaptic Interactions

The new approaches that Wilfrid Rall developed during the late 1950s and early 1960s came together during the 1960s in a study of the functional organization of neurons in the olfactory bulb. Up to that time Rall had worked mainly with the group of Kay Frank, Michael Fuortes, and their colleagues at NIH on the motoneuron model. His motivation for becoming interested in the olfactory bulb came first from the realization that the field potentials elicited in the bulb by antidromic activation of the output neurons come very close to meeting criteria of synchrony and symmetry, and that the bulb would therefore be an attractive model in which the “potential divider” approach could be used to analyze the relation between field potentials and underlying intracellular activity.

The study of mitral and granule cells in the olfactory bulb brought together most of the methods that Rall had developed in his classical work and added several new ones. Thus, the compartmental approach, developed initially for the motoneuron, was used to construct a model of the output neuron, the mitral cell, and the main interneuron, the granule cell, in the olfactory bulb. Excitatory and inhibitory synaptic potentials were simulated as in the motoneuron model. A new action-potential model, approximating the conductances of the Hodgkin-Huxley model, was developed specifically for this study. The extracellular currents were derived

from the intracellular potential distributions, and the extracellular potentials were calculated according to the “potential divider” model. It was the first study to combine all of these experimental and theoretical approaches.

The hypothesis tested in this work was that the Renshaw circuit for recurrent inhibition in the spinal cord, by means of axon collaterals through an inhibitory neuron, could be extended to the olfactory bulb in the form of a recurrent inhibitory circuit from mitral cell axon collaterals through the granule cells. The unexpected result from the study, however, was that this feedback is mediated primarily not by an axon collateral pathway but by a reciprocal synaptic interaction between the mitral dendrites and the granule cell dendrites. The morphological evidence subsequently supported this interpretation, and the combined electrophysiological, biophysical, computational, and morphological study was published in Rall et al. 1966 and Rall and Shepherd 1968.

If Rall’s previous studies had given a new picture of the functions of dendrites in receiving and integrating synaptic *inputs*, the olfactory bulb study opened up new ideas concerning the *output* functions of neurons in general and the dendrites in particular. The classical idea, dating back to the doctrine of the “dynamic polarization of the neuron” of Cajal and van Gehuchten (see Ramón y Cajal 1989), was of the dendrites as exclusively receptive parts of the neuron and the axon as the exclusively output part. The olfactory bulb study showed that this classical idea needed to be replaced by an enlarged view, in which dendrites are also potential output sites. The fact that outputs from granule cell spines can be activated by the mitral cell dendritic inputs indicated that neuronal outputs can be activated locally, so that parts of a neuron can mediate semi-independent input-output functions. The computational complexity of a neuron and its interactions was thus greatly increased over the classical model.

This was the first evidence for the possible output functions of dendrites, which subsequently has become a rich field of study, embracing not only synaptic outputs from many kinds of dendrites but also nonsynaptic transmitter release from dendrites (cf. Glowinski et al. 1984), and currently the implication of gaseous messengers such as NO and CO in feedback from dendritic spines onto axon terminals (Garthwaite 1991) and onto other dendrites (Breer and Shepherd 1993). The dendrodendritic circuit was subsequently modeled as a functional unit mediating reciprocal and lateral inhibition of mitral cells (Shepherd and Brayton 1979), an early example of a specific “microcircuit” in the nervous system (Shepherd 1978).

What Are the Consequences of Synaptic Nonlinearities in Dendrites?

In his early analytical studies Rall assumed that as a first approximation the synaptic input can be modeled as a transient current input. This allowed analytical solutions for passive trees. Rall was the first to point out that synaptic responses and their interactions are inherently nonlinear—that they characteristically involve a transient conductance change in the membrane that perturbs the electrical properties of the entire tree considered as an interconnected system. One of the great utilities of the compartmental approach introduced by Rall in his classical paper of 1964 was the ability not only to model arbitrarily complex branching geometries but also to incorporate and explore the consequences of dendritic nonlinearities, either synaptic (time-dependent) or excitable (time- and voltage-dependent) membrane channels.

In the 1964 paper Rall started to explore how *synaptic nonlinearities* influence the input-output properties of dendrites. The main results are summarized:

1. Because of the inherent conductance change associated with synaptic inputs, it is a general rule that synaptic potentials summate nonlinearly (less than linearly) with each other. This effect decreases with increasing separation between the synapses. Consequently, in passive trees, spatially distributed excitatory inputs summate more linearly (produce more charge) than do spatially clustered synapses.
2. Inhibitory synapses located on the path between the excitatory input and the “target” point (e.g., soma) can reduce the excitation more effectively than when placed distal to the excitatory input. This basic property has been studied and emphasized in subsequent work (see Jack et al. 1975; Koch et al. 1982). Thus, the strategic placement of inhibition relative to excitation is critical for dendritic integration. Another important rule of dendritic integration is that inhibition near the soma will have a global veto effect whereas inhibition on dendrites will have more localized veto effects on the responses and integration in local subunits.
3. The somatic depolarization, resulting from activation of excitatory inputs at the dendrites, is very sensitive to the temporal sequence of the synaptic activation. It is largest (but most transient) when the excitatory synaptic activation starts at distal dendritic sites and progresses proximally. Activation of the same synapses in the reverse order in time (proceeding from soma to distal dendrites) will produce smaller (but more sustained) somatic depolarization. Thus, the output of neurons with dendrites is inherently *directional selective* (see also Torre and Poggio 1978).

4. Background synaptic inputs effectively alter the cable properties (electrotonic length, input resistance, time constant, etc.) of the postsynaptic cell. Hence, this activity dynamically changes the computational (input-output) capabilities of the neuron (Rall 1962a; Holmes and Woody 1989; Bernander et al. 1991; Rapp et al. 1992).

Finally, at an early stage, Rall pointed out that, in principle, nonlinear dendrites are computationally richer than passive dendrites (see Rall 1970). The electroanatomical properties of the dendritic tree, the functional architecture of synaptic inhibition and excitation on the tree and their precise timing, and the context (background activity) upon which the input acts, combine to determine the integrative capability of the tree. The repertoire of operations within a tree is greatly extended by excitable channels in dendrites (cf. Llinas 1988).

What Are the Functional Properties of Dendritic Spines?

Dendritic spines are very thin and short appendages that terminate with a bulbous head. In spiny neurons, they come in large numbers and cover much of the dendritic surface, and are the major target for excitatory synaptic inputs. But what is their function? To paraphrase the old saying, if dendrites have been a puzzle, their spines have been an enigma wrapped in that puzzle. Rall was led to this enigma by several routes, including the work on the cable properties of thin dendritic branches, the analysis of current spread between granule cell spines in the olfactory bulb, and exposure to new data on the dimensions of dendritic spines in cortical pyramidal neurons.

The Role of Dendritic Spines in Synaptic Plasticity

Rall was particularly intrigued by the finding that, in the apical dendrites of cortical pyramidal neurons, distal dendritic spines tend to have longer and thinner stems than do more proximal spines. This seemed counter-intuitive (always a useful starting point for a theoretical study) because it would appear to add a further disadvantage to the distal location. In the late 1960s and early 1970s, Rall and Rinzel constructed an electrical model of the dendritic spine and explored the consequence of the partial electrical decoupling of the spine head (the synaptic input) from the dendrite (and soma) provided by the thin spine stem (large resistance).

Rall and Rinzel (1971a,b) and Rall (1974) showed that, although the efficacy of spiny synaptic inputs is reduced because of the spine stem resistance, this resistance could be a locus for neural plasticity because changes in the stem (e.g., increased diameter) could change (e.g., increase) the effi-

cacy of spiny synapse in a very specific manner. They showed that small changes in spine neck resistance would have a significant effect on the synaptic efficacy only if the spine stem resistance is matched with the input resistance at the spine base, and that this could explain the observation that distal spines tend to have thinner (larger resistance) stems.

Excitable Spines

These theoretical results led to further exploration of the possible consequences of excitable channels in dendrites as found recently in many neuron types (e.g., Stuart and Sakmann 1994). These studies have demonstrated that excitable channels in dendrites, in particular on dendritic spines, can amplify synaptic efficacy. Furthermore, compared to the case of spines with passive membrane, spines with voltage-gated or voltage-sensitive membrane properties can produce a sharper "operating range" for changes of synaptic efficacy. These changes can be brought about by changes in the spine stem dimensions, or by other modifications (such as changes in internal cytoplasm resistivity or movement of organelles). A "chain reaction" of firing of excitable spines following excitatory synapses to a few spines was conjectured, and the great sensitivity of the spread of this chain reaction on the location and timing of inhibition was theoretically explored (Segev and Rall 1988). The consequences of such chain reactions for synaptic amplification and for the repertoire of possible logical operations in dendrites have been discussed (e.g., Miller et al. 1985; Shepherd et al. 1985; Rall and Segev 1987; Shepherd and Brayton 1987; Baer and Rinzel 1991). A recent review on the electrical and chemical properties of dendritic spines can be found in Koch and Zador 1993.

Epilogue: The Future

Currently there is great excitement in the neurobiological community in the finding of the richness of ion channels in the soma-dendritic membrane, in particular voltage-dependent channels (see Llinas 1988). One challenge for the experimental research on dendrites is to characterize these channels in terms of types, kinetics, and distribution over the dendritic surface. Theoretical explorations of the consequences of these channels (e.g., the NMDA channel) for the computational functions of single neurons as well as for their plastic functions are already underway (e.g., Mel 1993; De Schutter and Bower 1994). Thus it is apparent that, for molecular biologists, the methods of Rall have special relevance. It is well recognized that the cloning of a gene is only the start in understanding its role in nervous function. A critical step is to understand the cellular

function of a gene product, such as a synaptic- or voltage-gated membrane channel. Because in a neuron that channel will be expressed in a specific location, the methods of Rall will be necessary for understanding the contribution of that gene product to the overall functioning of the neuron. Research on the consequences of nonlinear channels for the dynamics of neural networks has also started and is expected to flourish in coming years (cf. Traub and Miles 1991).

Novel technologies are proving useful for probing, physically emulating, and finely altering local sites of active neurons within the nervous system. Among these are voltage-dependent dyes that enable one to view, in real time, the electrical activity of neurons when the system carries out specific computations. VLSI technology potentially makes it possible to emulate the electrical (and chemical) activity of synapses, dendrites, and axons and to construct realistic neural networks in chips that operate in real time. These, and molecular biological methods including antibodies against specific ion channels, combined with high-resolution optical probes, may serve as the essential link between the single-neuron level and the system levels. Again, the theoretical basis for this link between single-neuron computations and systems computations will continue to draw on the methods of Rall.

We are presently in an era when the new methods are revealing the complexity of dendritic branching systems in all their glory. An important theoretical endeavor that is likely to develop in the next few years is the search for systematic methods to reduce this complexity in single-neuron models while retaining the essential input-output functions of the full models. Rall has argued eloquently for focusing on such reduced and tightly constrained models as the means to obtain the best insights into principles, rather than building models incorporating more and more complexity without adequate constraints (see Rall 1992). These “canonical” models will not only elucidate the principles that govern the operation of neurons, but they will also be the building blocks of models of large neuronal networks (see Stratford et al. 1989; Shepherd 1992; and Segev 1992).

We are at the dawn of interesting times, when experimental and theoretical tools are developing very rapidly. Many of the mysteries of neurons and dendrites may soon be solved. At the core of these mysteries is the contribution of individual neurons and their dendritic trees to the processing of information in neural systems, as the basis for behavior and cognitive functions. The contributions of Wilfrid Rall gathered in this volume will likely serve as key tools in unlocking the doors to those mysteries.

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