

Rall, W. (1964). Theoretical significance of dendritic trees for neuronal input-output relations. In *Neural Theory and Modeling*, ed. R. F. Reiss. Palo Alto: Stanford University Press.

This paper (Rall 1964) is one of the most significant landmarks in the modern era of computational neurosciences. Here, Rall first introduced the compartmental modeling approach, which is now widely used for simulating electrical and chemical signaling both at the level of dendritic (and axonal) trees and at the level of networks of neurons. The paper is of special significance for me personally because the compartmental modeling technique has become the primary method in my theoretical studies.

In his previous work, Rall introduced the cable theory for dendritic neurons and solved analytically cases of idealized, passive trees. However, the electrical consequences of complex spatiotemporal patterns of synaptic input impinging on dendritic trees could not be explored analytically, so numerical techniques were necessary. Rall introduced the compartmental modeling method, which, in principle, allows computation of voltage and current spread in nonidealized, and hence biologically realistic, trees, with any specified voltage- and time-dependent membrane nonlinearities. Rall used digital computers to implement this approach, carefully choosing examples that focus on the nonlinear interactions between synaptic inputs in passive dendritic trees and on their effect on the resultant somatic potential. The principles that emerged from these simulations have shaped many of our current ideas about the computational capabilities of neurons. The implications of the method for experimental neurobiologists were also immense. By making possible comparison of experimental findings with model predictions, the method allowed Rall and his colleagues (Rall et al. 1967) to estimate important biophysical parameters for the modeled α motoneurons (see also Barrett and Crill 1974; Fleshman et al. 1989; Jack et al. 1975; Stratford et al. 1989; and a recent review by Rall et al. [1992]).

After presenting compartmental models formally, Rall solved the system of equations numerically and explored the nonlinearity produced by patterns of synaptic inputs distributed in a passive dendritic tree. Because synaptic inputs were modeled as transient conductance changes, the shunting effect inherent to the mechanism of synaptic inputs was explicitly considered in the models. Rall showed that for excitatory inputs, summation of excitatory postsynaptic potentials (EPSPs) may deviate markedly from linearity when the synapses are electrically adjacent, but that the effects of brief synapses that are located at electrically remote distal dendritic branches sum almost linearly. Hence, when the tree receives

spatially distributed excitatory synaptic activity, it tends to operate as a linear summing device, whereas when these inputs are spatially clustered, the tree operates in its nonlinear regime.

Another point Rall highlights in his simulations is the importance of the spatial (and temporal) organization of inhibitory and excitatory inputs for dendritic computation. He showed that, as a general rule, an excitatory input is most efficiently reduced by an inhibitory input when the latter is placed between the excitatory synapse and the target (output) site (e.g., the soma and axon hillock). The optimal location depends on several factors, such as the electrotonic structure of the tree, the time course and magnitude of the synaptic conductance involved, and the activation time of inhibition and excitation. The idea that strategic placement of inhibitory and excitatory inputs and temporal relation between these inputs can implement a wide repertoire of input-output operations was later explored more fully by Jack et al. (1975), Koch et al. (1983), and Segev and Parnas (1983). Although not explicitly discussed, perhaps Rall's most significant contribution in this paper was the demonstration that the single neuron can be computationally a very powerful unit. In a simple and elegant example he demonstrated that, by virtue of its distributed (nonisopotential) electrotonic structure, the neuron becomes sensitive to the temporal sequence of inputs and, as explored later by Erulkar et al. (1968) and by Torre and Poggio (1978), the neuron could act as a device that computes the direction of motion. This nontrivial computation was implemented by a neuron model consisting of a straight chain of 10 compartments, with compartments 2–9 each receiving a transient excitatory input. The depolarization at the model soma (compartment 1) was computed for two different temporal sequences of synaptic activation. One sequence starts at the distal compartment (9) and proceeds successively to activate more proximal synapses. The second sequence follows the reverse order in time (i.e., compartments 2 → 9). Rall showed that the distal-to-proximal sequence would produce a larger somatic depolarization compared to the depolarization resulting from the reverse sequence. The output of this neuron is, therefore, sensitive to the spatiotemporal direction of synaptic activation. It essentially becomes a directionally sensitive unit.

Finally, Rall showed that because of the electrotonic structure of neurons, excitatory potentials originating at the dendrites are expected to have multiple time courses when measured at the soma. Distal dendritic inputs result in broad (and more delayed) EPSPs as compared to the earlier, faster-rising, and narrower EPSPs due to proximal inputs. The functional significance of these differences was briefly discussed. In one mode of neuronal operation, the smooth, relatively “sluggish” EPSPs

from distal inputs might set the background (subthreshold) depolarization at the soma, while the proximal inputs, when precisely timed, would trigger the axonal spikes. In this way the neuron may operate as an integrator for distal inputs and as a coincidence detector for the proximal inputs. Rall also discussed another possible mode of behavior, in which background synaptic activity is sufficient to cause a rhythmic discharge at the axon. In this case, inhibition near the soma could block axon firing over specific periods, thereby “shaping” the temporal pattern of the neuron’s output.

In retrospect, in addition to specific contributions previously discussed, this paper marked three more general pioneering advances for neuronal modeling. First, Rall shows the potential power of digital computers in exploring and explaining physiological problems; in the mid-1960s digital computers were only rarely used in biology. Second, Rall brought his background from the inanimate world of physicists and engineers to bear on problems of physiological systems. Third, Rall showed great vision by suggesting computational approaches to modeling aspects of neurons that could not *yet* be measured, such as the detailed dimensions of dendrites. Unlike many physicists who are satisfied with simple cases that allow “pretty” analytical solutions, Rall sought to understand the rich, but complicated, possibilities that nonlinear systems typically introduce, and he developed sophisticated *numerical* methods to achieve this goal.

During this “decade of the brain,” computers have become an essential tool in neurobiology, and detailed compartmental models of diverse types of neurons are constantly under construction. Sophisticated software tools for implementing compartmental techniques (e.g., NEURON, GENESIS, NODUS, AXONTREE, MNEMOSIS) have been developed (see reviews by Segev et al. [1989] and De Schutter [1992]). This theoretical approach has been proven to be extremely useful for probing the computational role of dendrites and of dendritic spines (see reviews by Mel [1994] and Segev [1995]) and exploring their possible significance for plastic processes in dendrites (review by Koch and Zador [1993]).

Sometimes neuronal models become too complicated, and we do well to heed the message implicit in Rall’s approach to modeling. He started with the simplified, idealized case and used it as a reference. Then he added complexities to the model, one at a time. Following theoretical explorations of the models, he formulated the main principles that govern their behavior and then used these to build reduced models that retain the essential properties of the complex models. Rall’s work teaches that this path, from the simple to the complex to the reduced, can be a real route to understanding.

I conclude this introduction with a personal comment about Wil Rall. When I came to the NIH as a postdoctoral fellow in 1982, I was rather overwhelmed by my move to the United States. Feeling that I had little to offer the renowned Rall, I feared that he would be disappointed by my ignorance. Even though, from our previous written correspondence (which he always wrote by hand), I could sense his warmth and kindness, I was still extremely tense. When I finally met him I was amazed, and still am, at how modest and generous Wil is. He respects his colleagues whatever their status, and he considers their ideas, however naive. He listens! It was a most important lesson for me, and a crucial step toward independence, to see how Wil, with all his powerful physical insights and his mathematical tools, is self-confident enough to reexamine his thinking and reevaluate his conclusions again and again in light of our discussions. This is the ultimate expression of intellectual honesty. Few are fortunate to have such a mentor and a friend as Wil Rall.

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