

Rall, W., and Rinzel, J. (1973). Branch input resistance and steady attenuation for input to one branch of a dendritic neuron model. *Biophys. J.* 13:648–688.

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Although it may not have been immediately obvious to everyone in 1959 and 1960 that synapses located out on the distal portions of the dendritic tree were important in neuronal function, it certainly was in 1973. By that time the issue of whether or not dendrites were important was considered settled, at least by students and other open-minded people (I was a student then). The emphasis of the discussion had shifted to making concrete predictions based on a knowledge of synaptic distributions on dendrites. The early 1970s was a period of great progress in neuroanatomy, riding on several revolutionary technical advances and spearheaded by the application of the electron microscope. The landmark book *The Fine Structure of the Nervous System* by Peters, Palay, and Webster, first published in 1970 (current edition, 1991), was having an impact that cannot easily be appreciated today. Investigators studying neurons in every part of the brain were discovering highly structured synaptic arrangements revealing the remarkable specificity of synaptic connections. The Golgi method (100 years old in 1973) was enjoying a renaissance; students were reading the work of Cajal and Lorente de Nó as enthusiastically as that of more contemporary authors. The spatial organization of inputs on a neuron was clearly shown to be one of the defining characteristics of a cell type and seemed certain to determine a large part of the functional properties of cells and circuits in the brain. Neuroanatomists looking for support for this notion were elated to find that there was an emerging theory of neuronal function based specifically on this concept. During the same period, many neurophysiologists abandoned the central nervous system of mammals, looking for more secure recording conditions, better characterized neuronal circuitry, and geometric simplicity in the somata of giant neurons of invertebrates. Because it is so difficult to record from more than one part of a neuron at a time, the announcement that the neuron is not isopotential is not always taken as good news by the neurophysiologist.

There's no question that these are difficult papers for the neuroscientist to read. They were written for the small audience of mathematical neuroscientists and published in the *Biophysical Journal*, an excellent journal but certainly not read by everyone at the time. Unlike the widely read experimental work, these papers could not be read in one sitting but required (for most of us at least) many hours of careful study. Still, because of the multidisciplinary mood in neuroscience at the time, and the enormous interest of the topic to so many neuroscientists, these papers were

widely discussed, and many brave attempts were made to understand them by scientists and students who would not normally have read mathematical work. Folklore about the implications of dendrites and synaptic integration in dendritic neurons was more plentiful than understanding of what Rall and others had actually accomplished up to that time, however, and this remained so for some time. Despite the obvious successes of theoretical work before 1973, there was really no general mathematical theory of synaptic integration in dendritic neurons prior to the Rall and Rinzel (1973) paper. The equivalent cylinder model, which had come to represent electrotonic theory in the minds of most people, was a spatially lumped model, not a model of distributed synaptic interactions. It was ideally suited for the analysis of the available neurophysiological data, in which the vicinity of the soma and the signals recorded there required exact representation but accuracy in the details of distal dendritic events was less important. The compartmental model, while computationally able to handle any problem, offered little in the way of insight. Its utility for simulating spatially complex situations had been demonstrated (Rall 1964), but it did not offer an analytical solution, whose special cases and asymptotic behavior could be enumerated and used to create a mental picture of the entire range of behavior of the system. An analytical solution, suitable for developing such a thorough understanding for the steady state, was provided by the Rall and Rinzel paper, and the later Rinzel and Rall article (1974) completed the analysis for time-varying signals.

What was attempted in these papers was not a model of the motoneuron or any other actual cell. The solution was for an idealized, simplified neuron. It included input to (the very end of) a single branch of a dendritic tree of a neuron consisting of several equivalent dendritic trees. The neuron had no soma other than that formed by the junction of the dendritic trees. There was no axon, and no action potentials. It was clear that this was not intended to be a realistic model of any particular neuron, and perhaps some very practical readers discounted the papers on this basis. The value of this model was actually as an abstraction applicable to all neurons. Anyone who has tried to make a model of a biological system knows that the art is not in deciding what details should be included in the model but in deciding what details should be excluded. In these papers, the things excluded were those which distinguished one neuron from another. The model was based on a set of carefully chosen symmetries that simultaneously (almost miraculously) abstracted the neuron and simplified the mathematics. Of course the most important (and widely discussed) simplification was the assumption of electrotonic continuity at dendritic branch points (the famous $3/2$ power rule). Discussions of which, if any, real neurons obey this constraint have continued unchecked since it was intro-

duced in earlier papers. There are only two possible approaches to the issue. One is to select a particular geometry to use as a template for an abstracted neuron, and the other is to obtain a solution that explicitly includes the geometry of the cell, and so will serve for all neuron shapes. Rall and Rinzel took the first approach. Since the publication of their papers, several approaches for the solution for passive neurons of arbitrary geometry have been offered, and they continue to be presented (Butz and Cowan 1974; Holmes 1986; Horowitz 1981; Koch and Poggio 1985; Cao and Abbott 1993; Majors et al. 1993). These important contributions, inspired by the work of Rall and Rinzel, continue to enrich neuron theory. But, to obtain the solution for an arbitrary geometry, these authors have been forced to abandon the search for a closed solution and have pursued recursive methods whose utility is comparable to that of the compartmental model.

The closed solution, with its potential for generating understanding and insight (not simply the correct answer) is still available only for one branching pattern, the one chosen by Rall and Rinzel. Time has proved the wisdom of their approach. The fundamental principles that have emerged from theoretical studies of such abstracted dendrites apply rather well to neurons of all geometry. The selection of one simple abstract neuron whose solution can be understood revealed the principles that govern synaptic interactions in linear neurons. To this day, if one wishes to analyze the implications of dendritic branching on synaptic inputs, rather than the effects of any particular branching pattern, the assumptions of the Rall and Rinzel paper should be adopted. For analysis of any specific neuron, a comparison should probably be made with results obtained using the generic branching pattern. Otherwise, one is not sure if the result of interest is due to the specific characteristics of the neuron type or is expected for any branching neuron. Thus, although not a numerically accurate model of any cell, this model gave, for the first time, the general form for the input impedance and for the propagation of synaptic potentials for all dendritic neurons.

The most obvious accomplishments of the analysis should be enumerated. These papers offer the first and best description of branch attenuation, which continues to be an important issue in studies of synaptic interaction. They also point out the surprisingly large effect of branching on the propagation of synaptic potentials. One still often hears the argument that because the total electrotonic length between an input and a recording site is small, the attenuation of the signal recorded should likewise be small. The fallacy in this argument is that it is based on the equivalent cylinder model. While very useful for some purposes, the equivalent cylinder model was not Rall's model of synaptic potential propagation in a

branched neuron. In these papers, the crucial effect of impedance loading at branch points is very clearly and beautifully explained. A related result, the fact that voltage attenuation within branching dendrites depends greatly upon the direction of signal propagation, proved critical for theoretical studies of the functional effects of dendritic spines and was very clearly presented in these papers. The finding that the time course of the somatic response to transient current injection in the dendrites is independent of how the current is distributed among the various branches, but depends only upon distance from the soma, proved important for neurophysiological studies of EPSP shapes. In the second paper, the relationship between transient and steady-state solutions was clarified in a section on the time integral of voltage and the distribution of charge dissipation in the dendrites. The approach was to use a single characteristic of the transient response at any location on the dendrites and solve for it in a manner similar to the steady-state solution for voltage. This is an excellent source of insight into the behavior of the model that cannot be duplicated in strictly numerical simulations of neurons. A similar approach, used recently by Agmon-Snir and Segev (1993) for analysis of the time course of synaptic potentials propagating throughout a neuron, was undoubtedly inspired by the Rinzel and Rall treatment. For those of us pursuing computer simulations to deal with the complexity of nonideal, nonlinear neurons, these relationships serve as an essential template for the interpretation of our results.

These papers also explored the fundamental relationship between input resistance, local synaptic potential, and synaptic effectiveness. Although it may seem obvious now, the high input resistance of distal dendritic sites was not well appreciated at the time and had been dealt with only briefly in theoretical work (e.g., MacGregor 1968). The dramatic potential for saturation of synaptic current due to giant local synaptic potentials (which do not seem giant when seen from the soma) was not well appreciated until clearly explained in the Rall and Rinzel papers. The importance of the duration of synaptic conductances, both in the local saturation effects and in propagation within the dendrites, was also explained there for the first time. The possibility that synaptic current might be limited by factors dependent upon the shape of the postsynaptic neuron, of course, laid the groundwork for all subsequent work on changes in cell shape as mediators of synaptic plasticity. This issue later acquired great importance for students of dendritic spines, and it is obvious that Rall and Rinzel saw the application of their approach to the dendritic spine problem at the time these papers were written. Of course, they also successfully applied the approach explicitly to the issue of dendritic spines.

Most important, the papers laid out the symmetry rules that became the basis for our intuitive understanding of signal propagation in branching dendritic trees. This intuition is still valuable, and those wishing to develop it within themselves can do no better than to consult these two papers. Because much of what is explained there continues to be discussed, rediscovered, and misunderstood today, these papers continue to be on the list of required reading for those who would understand synaptic interactions or interpret synaptic potentials in dendritic neurons.

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Supplemental Comments by John Rinzel

In 1968, I came to the NIH with no post-high-school biology background (I had a B.S. in engineering and an M.S. in applied mathematics) to serve in the U.S. Public Health Service. My alert supervisor in the computer division directed me to some of Wil's papers and then introduced us. Coming from outside the field, I had little appreciation of Wil's scientific stature. I did not realize that he was heading a revolution in neurophysiology and drastically affecting the way many neuroscientists thought

about dendritic function. His pleasant, soft-spoken, gentle presentation did not fit any stereotype I had of a revolutionary. He did not direct a large working group; in fact, he usually worked with one, sometimes two, young scientists. Fortunately, Wil took me on as a collaborator. We were going to consider questions related to dendritic spines, and I was to carry out the computations (at which I was well experienced for physics problems). It soon became clear that this man was superextraordinary. His time and availability seemed limitless, and his patience with my ignorance of biophysics, impressive. He was fostering me, and I was learning so many new things.

For our initial computations, I was conservative, concerned about numerical accuracy, and I used a rather fine spatial discretization for solving the cable equation with a single spine in an explicitly branched dendritic architecture. This became a costly task on the NIH computers, in spite of my numerical and programming tricks. This constraint was a factor in our search for an alternative strategy, an analytical one. In addition, Wil knew, of course, that the input resistance at the spine site was an important quantity for us to determine. Earlier (Rall 1959), he had developed a recursive formula for dendritic input resistance, but the solution was not in closed form. Formulating a solvable, idealized model problem became the next challenge, at which point I saw Wil's creative mastery begin to strike.

As a young mathematical scientist, I was excited to see Wil put mathematical physics to work on a biological problem. His keen physical intuition played a key role. First, he used the principle of superposition to simultaneously formulate and solve this problem, physically. Then we expressed the solution mathematically, computed some examples, and, again with Wil leading, we developed the physiological implications of our theoretical results. All of the essential results for these two papers, as well as those from our modeling of passive dendritic spines, were obtained before I returned to graduate school in 1970. (The writing came significantly later, due partly to Wil's worsening vision problems and partly to his high standards and dedicated effort to communicate theoretical results clearly.)

Without question, Wil's mentoring was inspirational and career determining for me. We bonded, beyond the level of scientific colleagues, and his outlook on life has been a guide for 25 years.

Supplemental Reference

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