

Rall, W. (1957). Membrane time constant of motoneurons. *Science* 126:454.

Rall, W. (1959). Branching dendritic trees and motoneuron membrane resistivity. *Exptl. Neurol.* 1:491–527.

Rall, W. (1960). Membrane potential transients and membrane time constant of motoneurons. *Exptl. Neurol.* 2:503–532.

After Wil Rall arrived in Dunedin, New Zealand, in 1949, to study for his Ph.D. under the supervision of John Eccles, significant events in the history of neuroscience took place there. Eccles, with his colleagues Brock and Coombs, made his first intracellular recordings from motoneurons. EPSPs and IPSPs were recorded for the first time. The scientific disputes that subsequently arose between Rall and Eccles (after Rall had returned, in 1956, to the United States) over the correct interpretation of recordings from motoneurons can be traced to the lack of attention that Eccles paid to cable properties of motoneurons. These disputes were over the correct value of the specific membrane resistivity for the motoneurone membrane, the time course of excitatory and inhibitory synaptic currents, and the effectiveness of synapses on dendrites.

Rall began his analysis of the electrotonic characteristics of dendritic trees with very little quantitative morphological material available. One motoneurone had been reconstructed from serial sections by Haggard and Barr (1950). Chu (1954) had obtained motoneurons from human spinal cord by shaking fresh autopsy tissue in a jar containing glass beads. (This was probably the first preparation of dissociated neurones.) The cell bodies and their proximal dendrites remained intact. The branching patterns, dendritic lengths, and diameters obtained from these data formed the basis of Rall's 1959 paper, "Branching dendritic trees and motoneurone resistivity." His aim was to provide a method for reducing the geometrical complexity of a branching dendritic tree, while preserving its electrical properties. The scheme he used was a recursive calculation for the steady-state input conductance of a finite length of a cylindrical dendrite terminating with further branching. Each length of dendrite was terminated by a conductance that was the input conductance of the subsequent branchings. Repeated substitutions for the input conductance at each branch point led to a compact expression for the input conductance of a dendritic trunk. This procedure placed no restrictions on branching rules and did not require the specific resistivities of the membrane and cytoplasm to remain constant throughout the dendrites. Rall made the important observation that if  $k$  branches (of diameter  $d_{jk}$ ) originate at the  $j$ th branch in a tree and satisfy the relationship

$$d_{j-1}^{3/2} = \sum_k d_{jk}^{3/2}$$

then these  $k$  branches could be collapsed into a continuation of the

( $j - 1$ )th element (diameter  $d_{(j-1)}$ ) with no electrical discontinuity occurring at the  $j$ th branch point. If this branching rule (which became known as the 3/2 power law) applied throughout the entire dendrite, the dendritic tree could be collapsed to a continuous extension of the trunk dendrite. (In this treatment, the question of how to terminate the dendritic cylinder was not discussed, although it was implicit in the recursive procedure that the dendritic cylinder would terminate.) The limited morphological material available to Rall at the time suggested that the 3/2 power law might be approximately obeyed, at least at proximal branches. This simplification was enormously important for the subsequent mathematical treatment of transient potentials in dendrites.

Rall's reduction of a dendritic tree to an equivalent dendrite was sometimes criticized in the mistaken belief that it was only valid when the 3/2 power law could be applied at branch points. This misunderstanding may have arisen because much of the subsequent analytical treatment of the neurone model in the 1960s and 1970s assumed an equivalent dendrite of uniform diameter, which does require the 3/2 power law.

Input resistances of motoneurons were measured by Coombs, Eccles, and Fatt (1955); Coombs, Curtis, and Eccles (1959); and Frank and Fuortes (1956). Eccles and his collaborators described a "standard motoneurone," derived from the same morphological data that was available to Rall, as having five dendrites of 5  $\mu\text{m}$  diameter and infinite length attached to a 70  $\mu\text{m}$  diameter soma. Using this model, Coombs et al. (1955) calculated the membrane resistivity ( $R_m$ ) to be 500  $\Omega\text{cm}^2$ . Rall went to considerable effort to demonstrate that Eccles had seriously underestimated the size of the dendritic tree, and therefore  $R_m$ . Rall's calculations suggested a mean value of 4,000  $\Omega\text{cm}^2$ . The difference between these two estimates of  $R_m$  was to have a profound influence on the opposing positions Rall and Eccles subsequently took on the effectiveness of dendritic synapses. Eccles (1957, 1960) calculated that the dendrites would exceed three space constants in length, and that synapses located at such large electrotonic distances from the soma could not contribute to the somatic membrane potential. Thereafter Eccles attached little significance to synapses on dendrites. In contrast, Rall subsequently calculated that motoneurone dendrites extended to between one and two space constants and that dendritic synapses could make significant alterations to the somatic membrane potential.

Apart from the issue of whether dendritic synapses were effective, a second debate developed about the time course of the synaptic current generating the EPSP in the motoneurone. Both Frank and Fuortes (1956) and Coombs, Curtis, and Eccles (1956) had concluded that the time constant of the motoneurone membrane was much shorter than the time

constant of decay of the EPSP; Coombs, Curtis, and Eccles took this further and suggested that the explanation for the difference was that there was a prolonged phase of transmitter action (i.e., a prolonged current injection) lasting throughout the time course of the synaptic potential. At that time, Fatt (1957) offered a different interpretation, suggesting that the slow decay was "passive and involves a spatial factor." Fatt had presented evidence from extracellular recording that he interpreted as indicating that a substantial part of the synaptic input came from the dendrites. Nevertheless, Fatt accepted the measure of the "somatic" membrane time constant provided by the other groups and concluded that there was a difference between somatic and dendritic membrane time constant.

The scene was set for Rall to provide the calculations arising from his soma-dendritic model of the cell. In his brief report in *Science* (1957), he set out the issue with stark clarity and concluded that all the data was compatible with the assumption of a uniform membrane time constant of higher value than the previous estimates. The "somatic" membrane time constant measured by passing a pulse of current through a microelectrode in the soma was underestimated if the time course was assumed to be a simple exponential, by a factor of about two. Thus, in both this debate as well as the one arising from consideration of the input resistance of motoneurons, the issue was the value of the membrane properties.

Eccles and his colleagues resisted this conclusion and in 1959 published two papers (Coombs, Curtis, and Eccles 1959; Curtis and Eccles 1959) reasserting that the membrane time constant was less than the decay time constant of the EPSP, although, as a result of partly acknowledging Rall's criticism, the difference between the two was now judged to be smaller. They insisted that there was clear evidence for a residual phase of synaptic excitatory current and adduced two further pieces of evidence in favor of such residual action: (i) the fact that an antidromic action potential did not abolish the EPSP when timed to coincide with its peak; (ii) the observation that hyperpolarization shortened the time constant of decay of the EPSP. Curtis and Eccles argued that this could not be accounted for other than by the hyperpolarization having a direct action on either the binding or clearance of the transmitter substance. A final, ingenious argument was offered by Curtis and Eccles. Having accepted that there would be some current spread from soma to dendrites, they suggested that it would be much less than Rall calculated, and hence maintained that the membrane time constant was less than the synaptic decay time constant. Using the assumption of a simple spherical model of the nerve cell, they derived the time course of the synaptic current anew and found that between the initial brief phase and a subsequent prolonged residual phase there was a brief reversal of the current. They offered the interpretation that the

preponderance of active synapses were on the soma and proximal dendrites and this brief current reversal was attributable to spread of the excitatory current into the distal dendrites, temporarily “hiding” the low residuum of synaptic excitatory current. The fact that they used an isopotential, non-distributed model to derive the time course of synaptic current and then assumed a nonisopotential distributed model to interpret it, seemed to have escaped them!

Rall’s response in his 1960 paper was magisterial. In the introduction he reviewed the past history and then started the analysis by introducing a simple procedure for the soma-dendritic model that would allow determination of the membrane time constant; this was to plot  $\sqrt{t}$  times  $dV/dt$  (for response to a current step) versus  $t$ , instead of the conventional  $dV/dt$  versus  $t$ , on a semilogarithmic scale. The negative slope of the resulting line gives the reciprocal of the membrane time constant, providing there is a “dendritic dominance” (i.e., more current spreads into the dendrites than passes across the soma membrane) of the order that he, and Eccles, calculated to be appropriate. He then showed that the experimental data from two cells reported by Coombs, Curtis, and Eccles (1959) gave an estimate of the membrane time constant greater than that deduced by them (of the order of 30 percent).

Rall then went on to draw attention to a technique using sinusoidal applied current, which might have been useful in judging the dendritic dominance. He thus provided a safeguard in terms of the techniques available, so that both dendritic dominance and the membrane time constant could be estimated, with the method for their joint estimation achieved by successive approximation if dendritic dominance was not large.

The final part of the paper (other than the mathematical appendix, presenting the detailed derivation of the equations on which the reasoning in the paper is based) then gave a clear and decisive review of the hypotheses advanced both by Fatt and by Eccles and his colleagues. Rall pointed out that Fatt’s suggestion was not in conflict with his conclusion, but that there was no necessity to adopt this more complicated model (different time constants for soma and dendrites). The discussion (pages 519–523) then systematically treated the arguments that Eccles and his colleagues had advanced and showed that there was an alternative explanation for each.

Eccles (1961) subsequently stoutly defended his view that there was a prolonged phase of synaptic current, using new data on the structure of motoneurons provided by Aitken and Bridger (1961) and further electrophysiological measures. It would be inappropriate to give a detailed critique of his arguments, but it was hardly a compelling defense. As Eccles himself pointed out in 1964, the analysis remained unsatisfactory unless

the structure were known of the particular neurone from which the experimental results were obtained.

It may seem strange to introduce Rall's classic early papers on nerve cell modeling by describing a controversy. But the controversy, which rumbled on for about a decade, was a decisive influence in shaping the way Rall presented his initial work. Until recently, when specialist journals have become available, it was always a struggle to persuade the editorial boards of physiological journals to accept papers of a purely theoretical nature. Rall was the pioneer of nerve cell modeling—for structures more complicated than the axon—and remained virtually the sole worker in the field for nearly two decades (his first publication, studying the isopotentiality properties of spherical nerve cells, was published in 1953). In that time, he not only laid a complete foundation for the more sophisticated models of today but did so in a period where his work was commonly greeted with indifference or, as in the case of the aforementioned controversy, strong opposition. It may not have escaped the reader's attention that a substantial period elapsed between the preliminary report in *Science* and the subsequent publications two and three years later in the new and then rather obscure journal *Experimental Neurology*. To those of us who developed an interest in the field at this time, it was with a sense of justice finally done that we saw Rall's subsequent work being published in prestigious journals such as *Biophysical Journal* and the *Journal of Neurophysiology*.

We would like to add some even more personal aspects to our commentary. One of us (Julian Jack) was a young premedical student in Dunedin, in the period after Eccles had gone to Canberra but before Wil returned to the United States. Wil presented two seminars to interested students on his cable theory. This work was of such novelty and interest that it inspired J. Jack to attend undergraduate mathematics lectures in his spare time and subsequently (in 1959, long after Rall had left) to persuade his research supervisor, Archie McIntyre, to allow him to take a break from spinal cord reflex studies and make a few intracellular recordings from cat motoneurons. The explicit objective of these experiments was to see whether, with very restricted stimulation of the group Ia fiber excitatory input, it might be possible to detect EPSPs with different rise times; the hope was that individual fiber inputs might be located either near to the soma or further out on the dendrites and thus show different time courses, since this was the possibility that Rall had implied in his seminar. The experiments did indeed confirm Rall's prediction, but they were not pursued further until after J. Jack had completed his medical studies in

England and subsequently linked up with Bob Porter, Simon Miller (Jack, Miller, and Porter 1967), and, finally, S. J. Redman (see Jack, Miller, Porter, and Redman 1971). The long incubation on this occasion was not because of any external opposition but because in order to make as satisfactory as possible a quantitative treatment of the data, we had to develop the theory and make matching computations. By then the similar work from NIH was published (see Rall 1967; Rall et al. 1967). Both of us have the most pleasant memories of first meeting Wil and then visiting him at NIH together. He was extremely encouraging to us and subsequently very generous in his referencing of our work, even before it was published (see Rall 1969a, footnotes 10, 18, 19). He subsequently made very helpful suggestions on drafts of our papers. Since those days, he has remained a good friend and a supportive colleague. We have admired the high standards he has maintained in his publications, and his scholarly attitude and integrity has been an inspiration for us.

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