

Rall, W. (1969). Time constants and electrotonic length of membrane cylinders and neurons. *Biophys. J.* 9:1483–1508.

Rall's paper "Time constants and electrotonic length of membrane cylinders and neurons" (1969) provides a classic example of how theory and experiment can be combined to allow insight into a major neurophysiological issue. Although the efficacy of distal synapses depended on how far they were electrotonically from the soma, the electrotonic length of various types of cells was not known. Several years earlier Wil had done some calculations based on anatomical measurements of a motoneuron and had concluded that the electrotonic length of that cell was between one and two space constants. However, these calculations were laborious. What was needed was a quick and simple procedure that could be used to estimate the electrotonic length of any cell. Such a procedure was presented in this paper.

Wil bent the rules of journal format somewhat when, immediately after the introduction, he included a three-page section titled "General Statement for Users." Perhaps he was influenced to do this by colleagues such as Bob Burke who had a "mental block activated by any differential equation" (as Bob expresses it in section 6.1). Whatever the reason, the strategy was extremely successful. This statement for users was easy to understand, and it clearly stated what had to be done to estimate electrotonic length.

With a minimum of mathematical detail, Wil showed that for cells that can be approximated as a cylinder with sealed ends, the electrotonic length,  $L$ , can be obtained from the simple formula  $L = \pi[\tau_0/\tau_1 - 1]^{-1/2}$ , where  $\tau_0$  and  $\tau_1$  are the first two time constants of a voltage decay transient following current input. The chief problem for the experimentalist was to get estimates for  $\tau_0$  and  $\tau_1$ . Although we now have many methods to estimate time constants from transients, the most popular method in 1969 was exponential peeling because it could be done with pencil and ruler. Wil described this method in detail for the experimentalist because it was "sometimes misunderstood and done incorrectly." At the end Wil recommended estimating time constants with "a well tested computer program," although, at the time, computer programs were keypunched on cards and, assuming a computer was even available, one was lucky to get one run a day.

For most neuroscientists, the paper began and ended with this three-page section, but that was all right, because in the next two decades this

simple procedure for estimating electrotonic length was followed in countless experimental studies. The term *electrotonic length* became part of the common vocabulary. Estimates of  $L$  were reported right along with resting potential and input resistance as basic properties of a neuron. In most cases reported  $L$  values were between 0.6 and 1.5, and this indicated that most synapses were close to the soma electrotonically. Thus, distal inputs could play a significant role in bringing a cell to its firing threshold.

Although investigators usually focus on the three-page statement for users, the remaining 22 pages of the paper provide a virtual treasure chest of results and insights that are still being rediscovered. To provide insight into why the electrotonic length formula worked, Wil remarked that after  $\tau_0$  the time constants of a voltage decay transient could be thought of as “equalizing” time constants governing the equalization of membrane potential over the length of the cylinder. The electrotonic length formula merely expressed a relationship between the time constants and electrotonic length obtained from the boundary conditions of the differential equation. The interpretation of the time constants as equalizing time constants became very important in future studies.

The theoretical work in this paper was not restricted to the derivation of the electrotonic length formula, and this fact is often overlooked. Wil had provided the experimentalists with a tool based on the assumption that the cell could be approximated as a cylinder with sealed ends, but he realized that, eventually, investigators would not be satisfied with this assumption. Therefore, he presented results in which he explored theoretically the effect on  $L$  estimates of various kinds of violations of the cylinder assumption. What is especially helpful is Wil’s use of illustrative examples. To some, these might seem tedious, but they do provide insight, particularly for the less mathematically sophisticated reader.

Wil’s theoretical treatment of a cylinder coupled to a lumped soma laid the basis for theoretical work on soma shunt models done by Durand (1984), Kawato (1984), Evans et al. (1992), and Major et al. (1993) and the formulas given in Holmes and Rall 1992a. Experimentalists found that the electrotonic length formula did not give results that were consistent with other data unless a soma with a soma shunt conductance (possibly due to electrode penetration) was included in the model. Although Wil’s theoretical treatment did not explicitly mention a shunt conductance, this was implicitly included in the expression for soma conductance. Adding an isopotential patch of membrane (the soma) adds an artificial value to the  $L$  calculated with the simple formula because of its effect on  $\tau_1$ . Wil gave expressions for the time constants in this case and noted that coefficients have to be determined with “special attention” (a modified orthogonality). Wil also introduced an approximate correction that one could apply to

the original-formula  $L$  estimate to account for the soma conductance (equation 23).

Wil also considered theoretically the case of several dendrites coupled to a soma. Each dendrite was represented as a cylinder, but because the cylinders could have different lengths and diameters, they could not be lumped together as a single cylinder. This work laid the theoretical basis for subsequent work by Segev and Rall (1983), Evans et al. (1992), Holmes and Rall (1992a), Holmes et al. (1992), and Major et al. (1993). What was interesting here was that the interpretation of the time constants changed as one went from the single-cylinder case to the multicylinder case. The time constants after  $\tau_0$  were still equalizing time constants, but for many time constants, the equalization was along particular tip-to-tip paths in the neuron instead of from the soma to the dendritic tips. In Wil's two-cylinder example, the  $L$  estimate was equal to the sum of the  $L$  values of the two cylinders when the  $\rho$  values of the cylinders were large and approximately equal; this happened because  $\tau_1$  represented equalization between the tips of the two cylinders. In subsequent work Wil and I found that we could interpret the time constants in complex branching structures (cf. figure 7 of Holmes et al. 1992) in the same way as equalizing time constants over particular paths in the neuron. The interpretation of time constants is important because it explains how and why electrotonic length estimates can be in error when the neuron cannot be approximated as a cylinder with sealed ends.

In the last section Wil derives expressions for the time constants for current transients under voltage clamp. Two additional formulas for electrotonic length are given that use these voltage clamp time constants. What is particularly appealing about the voltage clamp time constants is that they are independent of the soma conductance and, in particular, independent of any soma shunt that might exist. Intuitively, what happens is that the voltage clamp isolates the soma from the dendrites and effectively decouples the dendrites from each other. I discovered this result with the compartmental models I was using during my postdoctoral days in Wil's lab, and I showed the result to Wil. He thought about it for a moment, his legendary intuition told him the result was correct, and he remarked that this was an insight that seemed familiar to him. I later found this result in this paper, but fortunately for me, I found it before Wil remembered it was there.

Today, it is less popular to compute  $L$  with Wil's original formula because it is now known that many cells cannot be represented as a cylinder and this causes difficulties with obtaining meaningful estimates of  $\tau_1$ . What is astonishing is not that the formula is less highly regarded today but that it took two decades for the sophistication of experimental data to catch up to that of this simple theoretical expression. With more and

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better morphological and electrophysiological data available now, techniques for estimating electrotonic parameters of a cell have become more complex. Present methods include fitting parameters to transients (e.g., Clements and Redman 1989; Stratford et al. 1989) or finding parameter values via an inverse procedure (Holmes and Rall 1992b); see also Ali-Hassan et al. 1992. Estimating parameter values for voltage-dependent conductances has also become important as the sophistication of neuronal models has increased. Stochastic search, genetic algorithm, and simulated annealing methods are being developed to provide these estimates.

The complexity of these new techniques makes it more difficult to develop the intuitive insights that played such a large role in Wil's work. With the computer power available today, the temptation is to ignore theory and intuition until the mass of computed results reaches a point where this is no longer possible. What we can learn from this paper is that such an approach would be a mistake. Theory and intuition should be developed hand in hand with computed and experimental results to maximize insight into the issue being studied.

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