

Goldstein, S., and Rall, W. (1974). Change of action potential shape and velocity for changing core conductor geometry. *Biophys. J.* 14:731–757.

Nearly all neuroscientists are aware that Wil Rall's theorizing was fundamental to our current understanding of the functional significance of dendritic trees. Most of his work exploited the simplifying assumption that membrane potential remained below threshold level for activating voltage-dependent currents, that is, that the membrane was passive. Few may be aware that Wil had also studied action-potential propagation in branching geometries for active membrane cables, one of the subject areas of Goldstein and Rall 1974. More broadly, this work considers active propagation in regions of changing diameter and propagation toward cable (axon) termination.

As is typical of Wil's work, the problems are cast in a general framework. The model is formulated in an idealized way, retaining the barest essentials, thereby enabling conclusions with wide application. Both the active membrane model and the core conductor geometry are formulated with minimal detail.

The model of membrane excitability is qualitative, rather than quantitative; it originated with the Rall and Shepherd 1968 work (see that paper and Shepherd's commentary in section 5.1). It served adequately for the questions being addressed by Goldstein and Rall, for which particular gating properties of the conductance variables were thought unimportant. Additional motivation for this model included computational efficiency. Its nonlinearities are polynomial, rather than exponential, and so it can be integrated numerically more quickly than the Hodgkin and Huxley (1952) model. Moreover, the HH model had only been quantitatively determined for squid axon membrane, so its generality was limited.

Earlier, when Wil was developing a generalized definition of electrotonic length, he formulated a general cable equation that allowed for arbitrarily changing diameter with distance (Rall 1962a). A special case, the exponential taper, led to a particularly simple, modified cable equation. The only change was a convective term,  $K dV/dZ$ , added to the equation; here,  $Z$  is electrotonic distance, and  $K$ , the taper rate. As a consequence the velocity of a steadily propagating impulse was increased by an amount  $K$  in the direction of outward flare, or decreased by  $K$  in the opposite direction.

For one of us (John Rinzel), the mathematics in Rall's 1962 paper was magnetic, highly attractive. Here, a physiologist was carrying out mathematics similar to what I was seeing in my early graduate study in applied

mathematics. I read this paper many times; my copy has numerous marginal notes and so many underlines that I probably should have underlined that which I wanted to skip over rather than read again. The work showed a unique combination of abstract formulation and mathematical analytic skill being brought to bear on identifiable physiology.

The Goldstein-Rall paper also reiterated Wil's general observation of 1962 that, if membrane and cytoplasmic properties are uniform in a branching tree, the treatment of propagation through branch points with impedance mismatch is equivalent to allowing a sudden change in diameter in an unbranched cable (assuming that effects of boundary conditions at terminals, or subsequent branching, could be ignored). As Wil had been pointing out for some time, impedances are matched if the parent diameter raised to the  $3/2$  power equals the summed daughter diameters each raised to the  $3/2$  power. A new corollary presented here was that if an action potential successfully propagated into one daughter branch, then it did so in every daughter. This meant under the stated assumptions that branching *per se* could not mediate selective filtering of action potentials, that is, routing of some impulses to, say, smaller or larger branches and not to others. Goldstein and Rall argued that branch points (and step change in axon diameter) can filter repetitive spikes but that this filtering would be the same for all postchange branches.

Experimentally it was, however, shown that differential filtering effects do occur at some branching axons (Grossman et al. 1979). The theoretical result of Goldstein and Rall thus forced many researchers to seek alternative explanations for this experimental observation. For example, differential channeling of action potentials into branches of the same axon could be explained when differences in membrane excitability or in the extracellular space (Parnas and Segev 1979) or in the axial resistivity of the daughter branches (Stockbridge 1989) were assumed (see reviews by Khodorov and Timin [1975]; Parnas [1979]; Swadlow et al. [1980]; and Waxman [1985]). A recent computational study (Manor et al. 1991a,b) on active propagation in axonal trees contains many references to related theoretical work on information channeling in geometrically nonuniform axons.

The equivalence of these two cases, the branching and the step change in diameter, meant that it was sufficient to study propagation in an unbranched cable in which the diameter jumped from one value to another at a location  $Z'$ . The quantity GR (geometrical ratio) was introduced to quantify the different cases of interest. GR equals the ratio of the two diameters raised to the  $3/2$  power (for a given direction of propagation, the diameter beyond the branch point appears in the numerator or, for

branching, the sum of the daughter diameters each raised to the  $3/2$  power forms the numerator). Numerical solutions of the cable equations showed here that propagation fails if  $GR$  is much greater than one and succeeds when  $GR$  is less than a critical value, which exceeds one. (The case of failure was characterized analytically for an idealized problem by Pauwelussen [1982]). The reciprocal of  $GR$  (relative to its critical value) can be thought of as the physiologist's safety factor for this problem. From dimensional analysis, the asymptotic speed beyond the branch point must be either less or greater than the approach speed depending on whether  $GR < 1$  or  $GR > 1$ , respectively. Goldstein and Rall showed, however, that impulse speed changed transiently near  $Z'$ ; say for  $GR > 1$ , decelerating before and accelerating after encountering  $Z'$ . Overall, the action potential is delayed in this case as compared to the case with  $GR = 1$ .

The deceleration on approach to  $Z'$  for  $GR > 1$  leads to an intermediate case for  $GR$  just less than the critical value. This paper showed that if the delay associated with this deceleration was substantial enough, the membrane behind  $Z'$  would recover from refractoriness. Then it could become reexcited by current spreading from the depolarization associated with the (delayed) impulse traveling successfully away from  $Z'$  in the forward direction. As a consequence, a second impulse was initiated that traveled in the backward direction, an echo or reflected wave. This phenomenon has been seen in some other models, although not very robustly for the HH model (Ramon et al. 1975). Some progress is being made to reveal for models such as Wil's the mathematical structure that underlies reflection (Rinzel 1990). Experimentally, the delay at axonal sites with low safety factor for propagation is reflected by a depolarizing hump on the falling phase of the action potential just before these sites. Typically this hump attenuates in the backward direction and does not succeed to elicit a second, full-blown, action potential (e.g., Khodorov and Timin 1975; Parnas and Segev 1979).

Goldstein and Rall also explored the case of an action potential traveling toward an axon termination where the sealed-end boundary condition was assumed. An interesting insight gained from this work is that this boundary condition is also satisfied, by even symmetry, at the point where two action potentials traveling towards each other along a uniform axon collide. As in the case of other nonuniformities, the action potential's velocity and shape are expected to change near the region of nonuniform properties. In the case of a sealed-end boundary (which is the limiting case for a sudden narrowing of the axon) the velocity and amplitude of the action potential increase.

This work was thought provoking for both experimentalists and theoreticians. It touches upon an important controversy (still unsettled) about

axons. Does the axon function as a faithful transmission line, or should axons be treated as rather complicated processing devices where, under some conditions, spikes may differentially travel into one subtree and not to another? In this context, it has been speculated that branch-point failure may affect synaptic reliability and probability of release (Henneman et al. 1984). Goldstein and Rall's study shed some light on these issues and directed the experimentalists and theoreticians to further explore this topic. Theoretically, this work can also be viewed as part of the attempt, initiated by R. FitzHugh (1961), to develop reduced models of membrane excitability that can be explored analytically, using phase-plane techniques. Such reduced models of excitable membrane give important insights into the role of the various neuronal parameters in determining the repertoire of electrical activity of neurons (see Rinzel and Ermentrout 1989 for a review).

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