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ESSAYS ON APS CLASSIC PAPERS

What do dendrites and their synapses tell the neuron?

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This essay looks at the historical significance of four APS classic papers that are freely available online:

Rall W. Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input. *J Neurophysiol* 30: 1138–1168, 1967 (http://jn.physiology.org/cgi/reprint/30/5/1138).

Rall W, Burke RE, Smith TG, Nelson PG, and Frank K. Dendritic location of synapses and possible mechanisms for the monosynaptic EPSP in motoneurons. *J Neurophysiol* 30: 1169–1193, 1967 (http://jn.physiology.org/cgi/reprint/30/5/1169).

Rall W and Shepherd GM. Theoretical reconstruction of field potentials and dendrodendritic synaptic interactions in olfactory bulb. *J Neurophysiol* 31: 884–915, 1968 (http://jn.physiology.org/cgi/reprint/31/6/884).

Segev I and Rall W. Computational study of an excitable dendritic spine. *J Neurophysiol* 60: 499–523, 1988 (http://jn.physiology.org/cgi/reprint/60/2/499).

"WE"—OUR BRAINS—ARE MOSTLY composed of dendrites, and it is through dendrites and their synapses that neurons communicate with each other and form large connected networks of neurons. It is therefore only natural for us to be curious about dendrites, about the thousands of synaptic inputs that dendrites of each neuron attract and about the way that these synaptic inputs are processed, and plastically change, before they are transformed into another electrical signal, the action potential, that typically serves as an output signal to other neurons in the network.

The aesthetics of dendrites was highly appreciated and beautifully sketched by Ramon Y. Cajal and Camillo Golgi, the great anatomists of the late 19th and early 20th centuries. On the basis of the proximity of axons of one neuron to dendrites of another, Ramon Y. Cajal hypothesized in his theory of "dynamic polarization of the neuron" that some sort of signal is transmitted from dendrites to the cell body (21). But the biophysical nature of dendrites and their role in signal processing became a focus of a direct experimental research only in the late 1960s, following Wilfrid Rall's (Fig. 1) groundbreaking theoretical framework for modeling electrical current flows in dendritic trees. His linear cable theory for branching dendrites handled the passive case analytically (3, 9, 13), and his compartmental modeling method could treat numerically the case of nonlinear (excitable) dendrites (10).

Until very recently, most intracellular electrical recordings from neurons were made at (their relatively large)

somata. The challenge of Rall was to develop a theory that would enable the experimentalists to "sit" with an electrode at the soma and say educated things about what happens at the dendritic sites, where most synapses contact the neuron (some at distal dendritic locations). This sounds like an impossible task; yet Rall showed that a good modeling approach could do it. Indeed, in two highly influential papers published in 1967 in the *Journal of Neurophysiology*, Rall and colleagues (11, 14) first analyzed theoretically how synaptic potentials (and currents) spread in the dendritic tree, and how they are expected to influence the voltage response at the neuron's soma and axon attached to it. He showed that, in contrast to the accepted notion at the time, distal excitatory synapses do contribute to the depolarizing charge that reaches the cell body and that, due to filtering of high frequencies by the distributed capacitance along the dendritic membrane, the time course of the somatic excitatory postsynaptic potential (EPSP) changes as a function of input location. The more distal the synapse is, the slower the EPSP rises and the broader it is at the soma (14, 18).

This result came as a surprise, since, at the time (when neurons were conceptualized and modeled as isopotential, spherical units), differences in shape of somatic EPSPs were interpreted to imply that their underlying mechanisms were different (that they activated different receptors). Rall showed that the exact same synaptic conductance change generates EPSPs with different time courses just because of the electrotonic distance, X (in units of the space constant, λ), of the synapse from the recording site (soma). This change in EPSP time course has served as a powerful tool for estimating, from somatic recording, where electrotonically synapses are located in the dendritic tree.

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FIG. 1. Wilfrid Rall. (Photograph reproduced with the kind permission of Springer Science and Business Media: F. E. Sampson, *The Neurosciences: Paths of Discovery II,* edited by G. Adelman. Boston, MA: Birkhauser, 1992, p. 214.)

An important principle elucidated by this early work was that a dendritic tree with only passive membrane does not sum synaptic potentials linearly (10). This is due to the fact that the synaptic input is inherently a conductance change which, when activated, perturbs (shunts) the dendritic membrane. The closer the synapses are to each other, the more they shunt each other and the more sublinear the resultant voltage is. When many synapses bombard the neuron, as is the case in vivo, the cable properties of the neuron may change dramatically (the input resistance and membrane time constant reduce significantly and the cable length, L, increases). Thus, models that simulate linear synaptic integration with current injection do not represent accurately what actually happens in the neuron. This insight formed the basis for later recognition of "shunting inhibition" and the importance of its positioning along the dendrite for synaptic integration.

In 1969, Rall used his cable theory to show that, when a passive isopotential soma compartment is coupled to an electrically extended passive dendritic tree, the transient voltage response, $V(t)$, following a step current pulse injected at the soma can be described by an infinite sum of decaying exponentials [in a passive isopotential soma, $V(t)$ is governed by a single exponent, $\exp(t/\tau_m)$, where τ_m is the membrane time constant]. In electrically distributed dendrites, the slowest (largest) time constant governing $V(t)$ is τ_m (or τ_0), whereas the progressively faster (smaller) time constants, τ_1, τ_2, etc., determine the rate at which voltage equalizes between various parts of the (nonisopotential) dendritic tree. Rall further showed that it is possible to "peel" the first few time constants (τ_0, τ_1 and sometimes also τ_2) from $V(t)$ and thus obtain a correct estimate of τ_m from the "tail" of $V(t)$. He further showed that the ratio τ_0/τ_1 could be used for estimating the electrotonic length L of the dendritic tree; the closer this ratio is to unity, the longer electrotonically the dendritic tree.

Using this theoretical relationship, Burke and ten Bruggencate (2) estimated L to be around 1.5 in dendrites of α-motoneurons (namely, the average electrotonic distance from the soma to the dendritic tips is $\sim 1.5\lambda$). Since then, Rall's "peeling" method has become very popular and has been used in hundreds of studies for estimating L of many neuron types (from cortical pyramidal cells to cerebellar Purkinje cells to hippocampal neurons, etc.). It became clear that, indeed, dendrites are not isopotential units, and this led to the intriguing possibility that different parts of the dendritic tree may behave electrically (and chemically) differently from each other. Should then dendrites be considered as composed of numerous functional subunits (subtrees or compartments), each processing synaptic information almost independently and, consequently, expanding enormously the computational power of each neuron (see Refs. 4–7, 22).

But probably the tour de force of Rall's works (and perhaps of computational neuroscience in general) is the 1968 paper of Rall and Shepherd in the *Journal of Neurophysiology* (16). Unlike most other Rall studies that provided a conceptual framework, this one is different because it really dived into the guts of a specific system, the olfactory bulb. This work of art led to a new (and, at the time, revolutionary) prediction that mitral and granule cells interact with each other via dendrodendritic synapses. The process of developing this powerful prediction relied on the following steps: *1*) formulating the model by looking very, very closely at experimental data, specifically identifying the three dynamic phases in the recorded field potential; *2*) taking into account the known anatomy, including the layering of the cell populations involved; *3*) modeling these cells using (for the first time) a conductance-based spiking network model, composed of neurons with cable properties (rather than of "point neurons"); *4*) keeping the cell biophysics at a proper level of idealization, namely unbranched dendrites with a phenomenological (type I) action potential; *5*) mapping inputs onto specific areas of the dendrites; *6*) introducing the concept of potential divider to properly set a reference for the extracellular potentials; and *7*) considering the effects, again for the first time, of active dendrites. This work still stands as a rare example of a theoretical model that was used to predict a previously unknown anatomical connection and its physiological action. Even though the preliminary modeling results were reported in a joint publication with neuronanatomical evidence for dendro-dendritic synapses (17), this possibility was initially rejected by many neuroscientists who held to the preconception that dendrites are purely postsynaptic elements. This model has been tested many times and is fundamental for current concepts of processing in several neural systems, including the olfactory bulb, the retina, the olivary nucleus, etc.

The possibility that dendrites may be decorated by nonlinear (excitable) ion channels, which was raised by Rall and Shepherd (Ref. 16) (much before these channels were actually found in dendrites and became as popular as they are today), was further explored in a theoretical study (19) in which dendritic spine membrane was assumed to be excitable. This study showed how dendritic ion channels may boost the local EPSPs (and may even trigger a local dendritic Na or Ca spike) and how a "chain reaction" of EPSPs may spread actively in subtrees of dendrites and, consequently, how dendritic nonlinearity can significantly shape the input-output response of neurons (1). New optical and molecular technologies confirmed that, indeed, in many cases the membrane of dendritic spines possesses excitable channels.

Taken together, Rall's work can be considered to constitute "The Theoretical Foundation of Dendritic Function" (20). In the last 40 years, this foundation has inspired theoreticians to study dendrites with powerful mathematical and computational methods. Important questions were explored in these studies, including the effect of the strategic placement and activation time of synaptic inhibition on the input/output capabilities of dendrites, the possible computations that dendrites with their synapses may implement, and the degree of compartmentalization (both chemical and electrical) that might exist in various types of dendritic structures (reviewed in Refs. 5 and 6; see also Ref. 8). With new and fast computers for detailed simulation of the electrical behavior of dendrites receiving a realistic number of synaptic inputs, and with the development of fantastic new experimental technologies (e.g., the 2-photon microscope, excised patch technique, fast multisite uncaging system, ion-sensitive dyes and molecular probes such as green florescence protein), the secrets of dendrites are beginning to be exposed. It is now widely known that most synaptic inputs are made on dendrites and that it is there where important plastic changes (which probably underlie learning and memory processes in the brain) take place.

Wilfrid Rall is now 83, following another artistic pursuit, being a sculptor. He recently participated in a special workshop on dendrites entitled "School of Dendrites" (Institute for Advanced Studies, Hebrew Univ. of Jerusalem, April 10–14, 2004; lectures, including Rall's, can be found at **http://www. as.huji.ac.il/schools/ls13/media.shtml**) (after all, our learning capabilities in the school of life are due to dendrites and their synapses). Wilfrid Rall was the first speaker, and he presented his route for developing the foundation of dendritic modeling. Sitting there for 5 days from morning to evening, he himself was amazed to learn how much more we know today about dendrites, and with what a fast pace we have succeeded in the last decade to intimately probe into their intricacies and force them to start to surrender and give up their secrets. One of the major challenges that is still open is the type of computations being implemented by dendrites, as you now read this article or in Rall's own dendrites, when he developed the theoretical framework for modeling dendrites. Indeed, in our quest to understanding the computational function of dendrites, Rall's pioneering and inspirational work will always stand as a guiding torch.

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