

## Wilfrid Rall (1922–2018)

Wilfrid (Wil) Rall was an outstanding scientist and a unique person—warm and modest, despite being a scientific renaissance man. He is the founding father of the field of dendritic modeling and the developer of both cable theory and the compartmental modeling approach for studying dendrites and synaptic integration. He was the first to draw attention to the computational role of dendrites, to dendritic nonlinearities, and to plastic processes in dendritic spines. It is thanks to Rall's 40 years of pioneering theoretical studies, dendrites have become the focus of worldwide research interest, culminating in the recent evidence that local dendritic processing may play a key role in behavior. Rall is among a very few neuroscientists that, almost single-handedly, have changed our understanding of our own brain and of the operation of its sophisticated processors: the individual neurons. His passing is a great loss to science and to the many who knew and loved him; it signals the end of an era.

The beauty and structural diversity of dendrites was appreciated already at the end of the 19<sup>th</sup> century following the inspiring work of Camillo Golgi and Santiago Ramón y Cajal, whose artistic rendering of the structure of dendrites revealed their full glory. Cajal even nicknamed neurons “the butterfly of the soul” (could scientists use such romantic terms today?). Wil Rall had the soul of an artist (and indeed was a sculptor) and appreciated the beauty of dendrites early on. He was trained as a physicist (BS 1943, Yale University), participating in the Manhattan project, and then studied biophysics with Kacy Cole at the University of Chicago and earned an MS degree in 1948. His growing interest in neuronal biophysics and synaptic integration, and a recommendation from Cole, led Rall to study physiology in the labs of John Eccles and then Archibald McIntyre in Dunedin (PhD 1953, University of Otago). After early-career appointments, teaching, and research, Rall joined and spent the rest of his career at the National Institutes of Health in the Mathematical Research Branch (MRB, NIDDK) in Bethesda, MD.

The Rall revolution began with a brief paper in *Science* in 1957 with the demonstration that electric current flow in neurons is dominated not by the cell body, as previously thought, but by the extensive dendritic tree. He thus yearned to understand whether, and if so in what way, the branching structure and biophysical properties of dendrites could have functional implications. For a theorist, the message is clear: when estimating parameters like the specific membrane resistivity ( $R_m$ ) in a spatially distributed system, one should use the appropriate theoretical treatment/formulation. In this case Rall applied cable theory, challenging the “point-neuron model” proposed by Eccles, which overestimated the leakiness (i.e., underestimated the value of  $R_m$ ) of the dendrites. Initially, Rall's demonstration was strongly opposed by leading electrophysiologists (and especially by John Eccles) that were committed to a soma-centric view of neuron activity, resulting in rejection of his first full paper on dendrites and eventual publication of this work (1959) in a new journal (*Experimental Neurology*, reproduced in [Segev et al., 1995](#)). This opposition delayed the recognition of the importance of Rall's new methods and interpretations by mainstream neuro-



Wilfrid Rall

science. But good work prevails, and indeed Rall's fundamental and deep insights regarding the implications of cable properties of dendrites gradually penetrated deeply into the scientific community interested in understanding signal flow and synaptic integration in dendrites. The basis of this work was the cable equation (first introduced by Lord Kelvin), which was solved by Rall to describe current flow in dendrites as branching cylindrical structures. This meant solving analytically the cable equation with boundary conditions that represent repeatedly branched cables, each branch having a particular diameter, specific membrane resistivity ( $R_m$ ), capacitance ( $C_m$ ), and cytoplasmic resistivity ( $R_i$ ). Rall's recursive solution method enabled the calculation of the impact of a dendritic synapse, both in terms of the dendritic voltage response at the site of the synapse as well as on the resultant voltage change at other locations, including the soma and axon region. It enabled, for the first time, the rigorous understanding of “synaptic integration” in dendrites. In his seminal 1959 work, Rall not only solved the cable equation for arbitrarily branched passive dendrites, but he also sought ways to simplify this solution. Indeed, he found a set of dendritic trees that are, mathematically, equivalent to a single finite cylinder. His “equivalent cylinder” theory defined the set of key parameters that determine signal flow in dendrites: namely, the electrotonic (cable) length of the dendritic tree ( $L$ ), the membrane time constant ( $\tau_m$ ), and the branching structure/dimensions of the dendritic tree.

In 1964 Rall published his next breakthrough, the compartmental modeling method for describing the spread of activity in dendrites. In this work Rall was one of the first to realize the potential of digital computers for biology and especially neurobiology. A colleague at the Mathematical Research Branch, Mones Berman, had been developing digital methods for simulating physiological dynamics, such as exchange of metabolites between major “compartments” in the body (e.g., lung, blood, etc.). Rall

adapted this approach for spread of activity in dendrites by discretizing the continuous cable equation to a set of interconnected small “compartments,” each representing a dendritic section or branch. Each compartment was assumed to be isopotential, with voltage changes along the dendrite due to the axial resistance (Ohm’s law) between adjacent compartments. Importantly, this enabled one to model both passive and active, nonlinear processes (e.g., voltage-dependent ion channels). With this approach Rall provided new and surprising results. The range of time courses (the shapes) of excitatory postsynaptic potentials (EPSPs) measured at the soma of  $\alpha$ -motoneurons could be explained simply by the dendritic location of the synapse. Distal synapses would be expected to generate significantly delayed and broader somatic EPSPs as compared to identical synapses activated more proximally. This result settled a major controversy: before this result, differences in the shape of somatic EPSPs were attributed to differences in the kinetics of the respective synapses. Rall showed that an identical synaptic conductance change generates EPSPs with different time courses solely because of the electrotonic distance (in units of the space constant,  $\lambda$ , another important parameter defined by Rall’s cable equation) of the synapse from the recording site (soma). Since Rall’s 1964 and 1967 studies (reproduced in [Segev et al., 1995](#)) using compartmental models for dendrites, the EPSP “shape index” has become a standard method for estimating the location of the dendritic synapses from experimentally measured somatic EPSPs.

Another fascinating result and important conceptual jump that emerged from Rall’s 1964 study was the demonstration that dendrites with spatially distributed excitatory synapses could perform specific computations. Rall showed that the somatic depolarization is both larger and more delayed when the synapses are activated sequentially in time, starting distally and progressing proximally, as compared to when the same synapses are activated in the reverse order in time. This difference in somatic voltage between these two spatio-temporal sequences of synaptic activation could serve as a biophysical mechanism for

computing the direction of motion (e.g., of a visual target moving from right to left versus from left to right). It was the first theoretical demonstration that the electrical extent of dendrites could allow specific computations to be performed. This opened the rich and presently highly active field of “dendritic computation” and, more generally, helped to found the field of computational neuroscience. For example, Rall’s work inspired the landmark book on cable theory, *Electric Current Flow in Excitable Cells* by [Jack, Noble, and Tsien \(1975\)](#); the theoretical studies of Koch, Poggio, and Torres on logical operations in dendrites; the work of Mel, Brannon, and Poirazi on dendrites as multi-layer networks, and the recent experimental work by Branco, Clark, and Häusser showing that dendrites can discriminate input sequences.

Since then, compartmental models of neurons have become the primary tool for simulating subcellular neuronal processes (e.g., flow of  $\text{Ca}^{2+}$  ions in dendritic spines, or of action potentials in branches and axons), for simulating 3D reconstructed and biophysically characterized neurons receiving thousands of synapses, and for simulating large-scale neuronal networks (e.g., the *Blue Brain Project* and the Allen Institute *MindScope* project). These projects use implementations of Rall’s compartmental modeling approach in powerful and user-friendly software packages (e.g., *NEURON* and *Genesis*). One of us (M. Häusser) was inspired by Rall’s compartmental modeling work to take advantage of the advent of dendritic patch-clamp recording to directly test some of the predictions of cable theory, such as the differential filtering of fast (action potential) and slow (steady-state) signals in the dendritic tree (see [Stuart et al., 2016](#)).

The first application of the compartmental modeling method to neurons in the brain was his 1968 paper (reproduced in [Segev et al., 1995](#)) with one of us (G. Shepherd) on the functional organization of the olfactory bulb. Using detailed compartmental models tightly linked to experimental results—including anatomically and physiologically detailed simulations of a spiking neuron (mitral cell) and an interneuron (granule cell), and, for the first time, also active dendrites—this work predicted that mitral and granule

cells interact with each other via dendrodendritic synapses. This comprehensive modeling study illustrates Rall’s extraordinary ability to work closely with an experimentalist to develop idealizations that capture the essential features of a neuronal system (here, for the first time, a specific neural circuit). The experimental and simulated field potential transients were tightly matched with dendrites treated as equivalent cylinders; the 3D distributed spatial architecture was reduced to a two-neuron 1D cable problem; and a *de novo* conductance-based active membrane model developed by Rall was painstakingly fitted to the experimental recordings. As one of the first neurophysiologists interested in applying computational methods to experiments, G. Shepherd was eager to work with Wil on this project; being involved in the creation of the field of computational neuroscience over 50 years ago was a privilege that has lasted a lifetime.

These modeling results were first reported in a joint publication (in [Segev et al., 1995](#)) with electron microscopical evidence for the dendrodendritic synapses between mitral cell dendrites and granule cell spines, which went against the idea enshrined in Ramón y Cajal’s neuron doctrine that dendrites are purely postsynaptic elements. Today we know that many systems (olfactory bulb, retina, thalamus, inferior olivary nucleus, and many invertebrate neurons) have these types of local synaptic interactions, often characterized as microcircuits, greatly enlarging the processing capacity of the individual neuron.

Olfactory bulb granule cells interact through numerous dendritic spines—small,  $\sim 1\text{-}\mu\text{m}$ -long branches, each consisting of a thin neck and bulbous head—which stimulated Rall’s further theoretical studies of dendritic spines. He was aware of the anatomical studies showing that dendrites of several neuron types, most notably the cerebellar Purkinje cells and cortical and hippocampal pyramidal cells, are decorated with thousands of dendritic spines. Interestingly, Cajal drew dendritic spines in a notebook on his deathbed, exemplifying his obsession with these small but crucially important dendritic protrusions. With the development of the electron microscope in the 1950s, it became clear that dendritic

spines are the post-synaptic locus for excitatory synapses (and sometimes also of inhibitory synapses). What could be the functional implications of dendritic spines with their synapses?

In 1969, Rall embarked on a series of projects to model spine function. In a fundamental step, together with John Rinzel (at the time a New York University applied mathematics PhD student, working at the NIH for 2 years during the Vietnam war), he obtained in closed form the steady-state and impulse response functions and transfer functions for input to a single dendritic location. These provided easily computable, explicit estimates of input resistance at dendritic locations. They were used in showing that if the spine neck resistance ( $R_{neck}$ ) matches the input resistance at the spine base  $R_{base}$ , then small changes in  $R_{neck}$  will have a dramatic effect of the somatic EPSP originating from the spine synapse. Rall thus suggested that modulation of the diameter of the spine neck could serve as a mechanism for synaptic plasticity. The modeling results were presented at the first Society for Neuroscience meeting (1972, Washington, D.C.). Rinzel notes that working with Rall shaped his career choice of computational neuroscience, including the incredibly positive experiences with Rall later as colleagues in the MRB (1975–1997). Two subsequent accounts about modeling of dendritic spines by Rall inspired one of us, Idan Segev, to choose dendritic modeling as his research field. Rall's modeling results, and the anatomical discovery of the spine apparatus in the cytoplasm of the spine neck, and the possibility of spines containing actin microfilaments, inspired Francis Crick in 1982 to write a short TINS paper asking "Do dendritic spines twitch?" (as muscles do). Since that time, many experimental studies have attempted to estimate  $R_{neck}$ ; the actual value (ranging between 50 M $\Omega$  and 1 G $\Omega$ ) is still under debate. Rall's models of spines also inspired recent sophisticated studies, using advanced optical and genetic methods, to directly measure spine motility and functional signals in the spine head in order to explore the role of dendritic spines in synaptic plasticity.

The theoretical possibility that dendritic spines may possess nonlinear (excitable) ion channels was further explored by Rall and his colleagues (see review by Segev

and Rall, 1998). These studies showed how dendritic voltage-gated channels may boost local EPSPs and can even trigger  $Na^+$  or  $Ca^{2+}$  spikes in the spine head. Further, this study showed how a "chain reaction" among excitable spines may spread actively in dendritic subtrees and, consequently, how dendritic nonlinearities can significantly shape the input-output response of neurons. Today, "hot dendrites" is a hot research topic; active dendritic and spine properties have been demonstrated using sophisticated optical, electrophysiological, and molecular techniques (Stuart et al., 2016). Moreover, recent *in vivo* imaging and recording from dendrites of behaving mice have revealed that nonlinear dendritic events enhance feature selectivity in sensory cortex and drive grid cell firing in the entorhinal cortex, and are correlated with formation of place cells in the hippocampus and perceptual detection during behavioral tasks. What a wonderful story, which can be traced back to Rall's original vision and to his exploration of excitable dendrites.

Wil Rall embodied a rare and contrasting combination of human qualities: the purity and curiosity of youth in a tall and strong mature personality. He was a scholar in many fields ("a man of all times"), a lover of both art and science, and a great lover of nature (birds, in particular). For his friends and colleagues, he was a sensitive and caring person, wonderfully thoughtful and deep. Those who worked with him feel very lucky to have had the privilege to interact with and learn from him. He is survived by his beloved wife, Mary Ellen Condon-Rall; two daughters, Sara Rall and Madelyn Rall Badger; four grandchildren, Megan Kaetzel, Andrew Badger, Stuart Badger, and Charlotte Badger; and two great-grandchildren, Weston and Camille Kaetzel. In addition to his parents, he was preceded in death by his first wife, Ava Lou Rall, and his brother, Waldo Rall.

Rall was extremely modest, never promoting his many accomplishments. Toward the end of his long career he finally received recognition as the first winner of the Swartz Prize for Computational Neuroscience and by election to the American Academy of Arts and Sciences. But perhaps the greatest tribute to his genius is the flourishing of computer models of neurons and microcircuits

throughout the nervous system (many of them accessible at <https://senselab.med.yale.edu/ModelDB/>). The three lectures on the development of cable theory for dendrites that he gave in Jerusalem in 1993 are now available online (<https://youtu.be/ZBumiZuUMGs2>; <https://youtu.be/QNhK3BoOCPk>; <https://youtu.be/nI-0HvGvqBA>), in addition to a digital version of the book *The Theoretical Foundation of Dendritic Function*, generously provided by MIT for this obituary (<http://mitpress.mit.edu/books/theoretical-foundation-dendritic-function>). His death is a huge loss, but his memory will remain in the brains (and dendrites!) of the many who knew him and of those who now know him better through this obituary. Wil Rall's legacy as a person and as a scientist stays with us.

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