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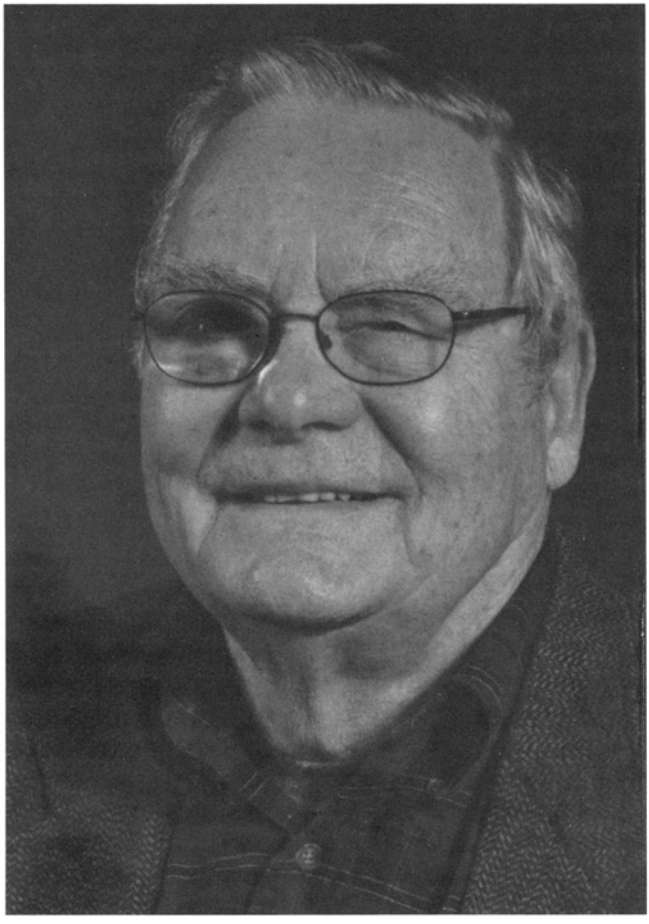

Wilfrid Rall

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Yale University, B.S. (Physics, 1943)
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Wilfrid Rall pioneered biophysical modeling and computation for dendritic neurons, with a focus on functional insights, testable predictions, and reinterpretation of experiments. With research collaborators, he demonstrated the functional importance of synapses on dendrites, predicted the discovery of dendrodendritic synapses, and identified the dendritic spine as a possible locus for plasticity.

Wilfrid Rall

On several occasions, younger scientists have asked me variations of the following question: Is it really true that you have had the exciting experience of seeing your theoretical modeling predictions confirmed by neurophysiological experiments? The answer is yes, more than once, and each time was an exciting experience. Several examples are described later.

The interplay between theoretical modeling and neurophysiological experiments has led to valuable functional insights; these insights provide a basis for improved models and improved experiments. Also, such modeling sometimes corrects previous misinterpretations of experimental results. Examples will be found later.

I welcome the invitation to contribute a chapter for this volume. At age 83 (in 2005), I can offer some perspective, as a Scientist Emeritus of the National Institutes of Health (in 1994), and as one of the Founders of the Society for Neuroscience (in 1970). Also, I have recently gained an almost Olympian perspective, living in the Virginia Blue Ridge at elevation 3400 feet, about 40 miles west of Thomas Jefferson's Monticello.

Background

In retrospect, I was fortunate in my choice of parents: They had mostly good genes, and they had nurturing instincts as teachers and idealists with a love of literature, of nature, and of creative activity, such as art, music, and poetry. Both were born in Europe: my father, Udo Rall, 1894 in Heilbronn, Germany; my mother, Doris, 1896 in Zug, Switzerland. They met in California, on a mountain-top, in 1920. I was born in Los Angeles, on August 29, 1922; my brother, Waldo, was born on March 20, 1924.

My brother and I grew up feeling different from our contemporaries: We spoke German at home before we started school; instead of church on Sunday, we went hiking in celebration of nature. My parents became pacifists, in reaction to the carnage of World War I (note that "Wilfrid" is a contraction of *will frieden,* "wish for peace"). We read books together: for example, the original German (pre-Disney) Bambi, and also poetry and mythology. It was assumed that my brother and I would do well in school, and we did.

We attended the UCLA teacher training school for 3 years, and then public elementary school in Los Angeles. Our public secondary schooling was in Washington, DC. Our move from California was due to the Depression: My father's small business could no longer support three partners. Fortunately, a good friend provided entrée to Franklin D. Roosevelt's (FDR's) "New Deal" (in 1933); my father became an expert in facilitating self-help cooperatives for the Federal Emergency Relief Administration (FERA) and for the Works Progress Administration (WPA). Later, he was invited to write a proposal for rural electric cooperatives; this contributed to the creation of the Rural Electrification Administration (REA). He served several years as a coop-education specialist in the REA. He was also active in consumer cooperatives in the DC area. At this time, my mother served for awhile on the National Board of the Women's International League for Peace and Freedom. In his retirement, my father enjoyed artistic pursuits: poetry, painting, sculpting, and experimenting with unusual enameled-copper compositions.

High School and College (1937–1943)

Western High School (located next to Georgetown University in Washington, DC) was academically oriented and encouraged students to apply for university scholarships. I kept busy with math and science courses, debating team, yearbook, and orchestra. Although a scholarship to George Washington University had already been awarded to me for being part of a champion high school debating team (in 1939, the DC-Baltimore area), it was my good fortune to win a Yale University Regional Scholarship (in 1940, SE region). This provided me with an outstanding educational opportunity.

My Yale class was 1944, but I graduated in October 1943, with highest honors in physics. Because of World War II, Yale held classes during the summers of 1942 and 1943. Many classmates were drafted or volunteered for military service, but science majors were deferred by their draft boards to continue their studies and become part of the scientific manpower pool. Within a week of graduation, I traveled to Chicago to join the Physics Division of the World War II Manhattan Project at the University of Chicago. My courses at Yale were mostly in math and science, but I did also enjoy courses in history and philosophy. I even joined the Yale Political Union (debating society), and became leader of the Labor Party. The leader of the Conservative Party was Lloyd Taft; Seth Taft was President of the Political Union (the classmates were the son and nephew, respectively, of Senator Robert Taft).

During my final two semesters at Yale, I was one of three undergraduate students admitted to the core physics course for graduate students. This course met for 90 minutes, 5 days a week, and required solving

all of the problems provided by our thick textbook, *Introduction to Theoretical Physics*, by Professor Leigh Page (who taught the course). I now appreciate that working through all those physics problems, as well as assisting in the advanced physics lab course, provided me with an unusual opportunity to develop my physical intuition and my approach to problem solving. These helped me later when confronting problems in biophysics and neurophysiology.

Manhattan Project during World War II (1943–1946)

The Manhattan Project operated at many sites, all given deceptive names. At the University of Chicago, it was the Metallurgical Laboratory. The director was Professor Arthur H. Compton, Nobel Laureate in Physics. The Head of the Physics Division was Professor A.J. Dempster, the founder of mass spectrography and the discoverer of the U-235 isotope of uranium. Upon my arrival (October 1943), I was assigned to Professor Dempster, along with two other recently arrived young physicists.

My first task in Chicago was to assist Dr. A.E. Shaw in the design and construction of an updated mass spectrograph, based on Dempster's suggested improvements of his original design. I actually produced the engineering drawings, with Shaw looking over my shoulder. Armed with a top priority at the physics machine-shop, as well as the electronics and glass-blower shops, we proceeded to assemble and test this new equipment, which had much in common with a cyclotron; it included a high-frequency spark source (that could ionize heavy metals inside a high vacuum), together with a high-voltage accelerator, a strong electromagnet, and a photographic collection system. A detailed description was later declassified for publication in the *Review of Scientific Instruments* (Shaw and Rall, 1947).

This equipment was needed in Hanford, Washington, where the Manhattan Project had sited its plutonium production facility, on a bend of the Columbia River (for supply of water cooling). Our equipment was disassembled and carefully packed aboard a U.S. Army truck. Four military policemen were assigned to drive this truck to Hanford. At the last minute, I was assigned to accompany this shipment. The trip was an adventure that took about a week. Upon our arrival at a vast conglomeration of temporary buildings, my presence became critical, because I insisted that the truck be taken, not to the general receiving dock, but directly to the building in which the equipment was to be reassembled.

It is relevant to note that uranium (a heavy metal element with atomic number 92) consists predominantly of atoms having atomic mass 238; only a small percentage of natural uranium is the isotope with atomic mass 235. A very special property of U-235 atoms is the following: If a neutron is captured by its atomic nucleus, this nucleus becomes unstable

and it undergoes fission; that is, it splits into two smaller atoms, whose combined mass is less than the parent mass, and the missing mass appears as a tremendous release of energy (as predicted by Einstein's equation). Also released are two neutrons; these neutrons can trigger more fission of U-235, and synchronous fission of many U-235 atoms is the key to an atomic bomb.

But that is not all. The common uranium isotope, U-238, has a different special property; when it captures a slow neutron, it can become a new element with mass number 239, and atomic number 94; this is known as plutonium, P-239. And remarkably, plutonium has the same special property noted previously for U-235; it is an alternative ingredient of an atomic bomb. But plutonium does not occur in nature; it must be manufactured in a specially constructed "pile" that consists of a three-dimensional lattice of uranium cylinders supported in a graphite structure (graphite slows the neutrons, favoring capture), together with special water-cooling. When conditions are perfect, the chain reaction of fission, neutron production, and neutron capture, can be controlled to produce significant quantities of plutonium. However, a possible complication was anticipated, because some fission product isotopes have a large capacity to capture neutrons. If too many neutrons are captured by these isotopes, this can quench the chain reaction and prevent the production of plutonium. Thus, it is important to monitor the fission product isotopes that result from pile activity; hence the need for our mass spectrograph. An interesting description of the quenching problem encountered at the Hanford plutonium production piles is provided in an excellent book by Richard Rhodes (1986).

Although the U.S. Army policy was to keep young scientists ignorant of activity at different Manhattan Project sites, we knew quite a lot via the insider-grapevine; however, we were very careful not to breach security to the outside. Two Yale classmates and two high school classmates also served on the Manhattan Project. My brother worked at four different sites: St. Louis, Chicago, Oak Ridge (Tennessee), and Los Alamos (New Mexico). His draft board drafted him while he was at Los Alamos; after completing basic training, he was assigned to a special engineering detachment (SED) and returned to Los Alamos. Before Shaw and I left Hanford, physicist friends of Shaw's took time to show us around the production facilities. They also mentioned that security policy provided code names for several distinguished European physicists who consulted at this site: Enrico Fermi was Mr. Farmer, Eugene Wigner was Mr. Wagner, and Neils Bohr was Mr. Baker.

After the scientists from Los Alamos completed their successful test at Almagordo, New Mexico (July 1945) we knew that the atomic bomb was proven possible. Dr. Leo Szilard felt a heavy burden of responsibility; it was he who had persuaded Einstein to write the letter to FDR that led to the Manhattan Project; also, although few knew this, it was Szilard

who held a top-secret British patent that described the design of a pile for plutonium production. The reason he and other European scientists dedicated their efforts to the Manhattan Project was their very real fear that the Nazis might succeed first in making an atomic bomb. Once Germany was defeated, Szilard felt strongly that the A-bomb should not be used on a populated Japanese city. He prepared a petition, addressed to FDR, urging that the Japanese be invited to observe a test-demonstration, on an uninhabited island, and then be given an opportunity to surrender. I signed that petition. It never reached FDR, but it did reach Secretary Stimson. Both Stimson and President Truman decided that first use of the atomic bomb was justified; many lives were saved (on both sides) by removing the need for an invasion of Japan.

Many years later, I had an opportunity to converse several times with a Japanese military historian. After I felt comfortable in talking with him, I told him that I had signed that petition, and I asked whether he thought the proposed test-demonstration might have succeeded. He said that he feared not; he said that his mother was a young schoolgirl at that time and said that she, and all of her friends, had sharpened sticks with which to defend their homeland from invasion.

Leo Szilard founded the "Council for a Livable World" because of his concern that unwise militarists might regard nuclear weapons as routine tools. He wanted to ensure that there are enough level heads in the U.S. Senate to curb unwise nuclear policy. His idea was to provide expert nuclear physics advice to all Senators and also to generate financial support to help elect enlightened Senators. This task has prospered, but much remains to be done. Szilard's legacy has recently been augmented by the establishment of a "Center for Arms Control and Non-Proliferation" in a newly renovated building on Capitol Hill, near the Senate Office Buildings. A dedicatory bronze plaque, at the entrance to this center, identifies many contributors; this list includes me, in memory of my parents.

Basic Physics Research (1946)

Before leaving the Manhattan Project, I had the opportunity to carry out some basic research, using Dempster's mass spectrograph. As fission products, the elements palladium and iridium each have two radioactive isotopes; the problem was to determine which isotope (atomic mass) belongs with which radioactive half-life. In each case, it was possible, by running a longer than usual experiment, to collect a sufficient amount of material in the spread-out mass spectrum so that these isotopes could be distinguished by radioautography: A brief photographic exposure to the mass spectrum identified the isotope with the short half-life, while a longer exposure identified also the isotope with the longer half-life.

These results were declassified as an abstract (Rall, 1946). In a different experiment, I provided careful measurement of nonuniform spacing in the mass-spectrum of zirconium isotopes (Rall, 1948); this measurement was of great interest to Dr Maria Goeppert-Mayer (1963 Nobel Laureate in Physics), because it confirmed a prediction of her theoretical model of nuclear structure. Although I could have continued with Professor Dempster, to complete a Ph.D. under his supervision, I decided to switch from nuclear physics to biophysics.

Biophysics at Woods Hole and Chicago (1946–1948)

Professor K.S. Cole had been with the Manhattan Project in Chicago. In 1946, he participated in founding an Institute of Radiobiology and Biophysics and also a Biophysics Ph.D. program at the University of Chicago. My friend, A.E. Shaw, introduced me to George Marmont, who was preparing to go to Woods Hole that summer (with Cole) for research on squid giant axons. I was offered an opportunity to participate in this research. I became a Biophysics Fellow of the new institute, both for summer research at Woods Hole and for predoctoral studies at the University of Chicago.

Thus, my switch from physics to biophysics began in Woods Hole, during two summers (1946 and 1947). I learned to dissect squid giant axons, to assist with special electrode manufacture, and to assist in the earliest experiments using "current clamp" and "voltage clamp" on a "space-clamped" giant axon. Marmont had designed a sea-water chamber that provided uniform extracellular voltage along a length of the squid axon (by use of two guard rings, flanking a longer central region of the chamber); he had also designed electronics that used negative feedback to maintain a constant current across the axonal membrane, from the extracellular bath to an axial intracellular electrode (Marmont, 1949). Thus, he expected to control a uniform membrane current density, and observe membrane voltage transients. It was Cole who argued the advantages of voltage clamping; it avoids the complication of capacitative current and puts the focus on the ionic current across the membrane. We did both experiments.

Cole and Marmont argued the pros and cons with Alan Hodgkin, when he visited the University of Chicago in 1948 (see pp. 281–283 of Hodgkin, 1992). Hodgkin understood Cole's interest in the diphasic current transient observed under voltage clamp, and together with Katz and Huxley, he succeeded in distinguishing the initial inward sodium ion current from the slower outward potassium ion current (Hodgkin, Huxley, and Katz, 1949; see also pp. 288–303 of Hodgkin, 1992). This was a major breakthrough; it depended not only upon excellent biophysical experiments and mathematical modeling but also upon awareness of sodium and potassium ionic concentration differences and the importance of rapid changes in

membrane permeability to sodium versus potassium ions in the generation of an action potential. This research fully deserved the Nobel Prize that it won.

The University of Chicago provided excellent interdepartmental courses to facilitate a switch from physics to biophysics and physiology. In 1946, the university had an influx of advanced students (from the GI Bill, and from World War II research labs); new courses were organized, including a 200-level survey of biology, given by senior faculty of many departments. Richard Podolsky and I both enjoyed this course as a part of Cole's biophysics predoctoral program. An advanced course in general physiology was organized by Manuel Morales, Herbert Landahl, John Hearon, and others of several departments. It is remarkable that later, Cole, Morales, Hearon, and Podolsky were all at the Naval Medical Research Institute (NMRI) when I visited there in 1954; it was Morales who had facilitated biophysics at NMRI. I audited a course in mathematical biophysics by Nicholas Rashevsky, a nuclear physics course by Enrico Fermi, and a symbolic logic course by Rudolph Carnap. I also took a genetic-statistics-probability course with Sewall Wright; this provided me with a grasp of probability theory that helped me in later modeling of motoneuron populations (Rall, 1955a; Rall and Hunt, 1956).

During my time at the University of Chicago, I put some effort into uniting several student housing co-ops. Also, I married Ava Lou Freed (in 1946); she was a co-op member and a graduate student with the interdepartmental Committee on Human Development. She completed her M.A. degree in 1948. She deserves credit for being supportive of my preference for basic biophysical research, when her father was urging me to pursue an M.D. degree.

The university provided a stimulating environment, but my wife and I began to think about a change from the Chicago climate. I had not yet chosen a Ph.D. thesis problem and had found that Cole and Marmont did not provide a harmonious research environment. I became interested in a theory of synaptic inhibition proposed by J.C. Eccles, in New Zealand. Eccles responded positively to my exploratory letter, and I decided to accept his offer of a lectureship in his physiology department. Because I had more than enough course credits for an M.S. degree at the University of Chicago, I only needed to write a suitable essay to complete the requirements. I chose to discuss "The Field of Biophysics."

Although I explored Professor Cole's suggestion of a two-dimensional array that would focus on the intersections of subdivisions of physics in one dimension, with subdivisions of biology in the other, I found that I preferred a different approach. This was a hierarchy of systems, from subatomic systems, with integration into atomic systems, then molecular systems, then self-reproducing systems and simple unicellular organisms, then multicellular organisms, and onward to large ecological systems.

Biophysics is key to many of these systems and to the integration from one level to the next. My essay explored biophysics from this point of view (Rall, 1948).

Spinal Cord Physiology in Dunedin, New Zealand (1949–1956)

Professor J.C. Eccles headed the physiology department of the Medical School at the University of Otago, in Dunedin, New Zealand. The Province of Otago was settled by Scotsmen who named Dunedin after Edinburgh; a statue of Robert Burns stands in the central octagon. The local citizens established the first university and the first medical school in New Zealand. Although now part of the University of New Zealand, they proudly retain the original name, the University of Otago.

My wife and I made a 3-week trip by sea, from Vancouver, B.C., via Hawaii and Fiji, to arrive in Auckland, New Zealand in January 1949. At Eccles' suggestion, we brought our car on the same ship, and we drove from Auckland to Wellington, where we visited friends. A ferry took us to Christchurch, in the South Island, and we drove southward to Dunedin. Americans were scarce in Dunedin, and we received a warm welcome from the Eccles family, as well as others in the department and in the community.

The physiology department had a very busy schedule, which included lectures and labs for 2 years of medical school, plus a general physiology course, as well as special courses for dental, nursing, and home science students. Nevertheless, Eccles aimed to keep up his basic research momentum with at least one experiment a week; this involved an all-day/night experiment on cat spinal cord. I gave lectures in general physiology and helped run the student lab courses, but my major responsibility was to be fully involved in the research. This included dissections, assembling the set-up, and sharing with Eccles the planning and conduct of the experiments and the subsequent analysis of the data (recorded on glass photographic plates). When the experiment went well, it continued far into the night. Fortunately, I had the needed stamina and interest to keep up with Eccles during this rigorous routine.

Both A.K. Mcintyre and L.G. Brock, who joined the department around the same time, became friends who coached me in the fine points of dissecting the spinal cord, dorsal and ventral roots, and also the muscle nerves of the cat hind limb. Two busy years of effort produced the following research papers (Brock, Eccles, and Rall, 1951; Eccles and Rall, 1950, 1951a, 1951b). We studied post-tetanic potentiation in motoneurons and the effects of graded strengths of stimulation to a number of muscle nerves in the cat hind limb. Much of this research was related to that of D.P.C.

Lloyd, the author of the neurophysiology chapter in Fulton's *Textbook of Physiology*. I believe that Lloyd had done his degree at Oxford, with Eccles as supervisor; also Mcintyre had visited Lloyd shortly before coming to Dunedin.

At that time, most of our recording was from ventral roots; some was also done with steel electrodes inserted into the spinal cord. This was 2 years before the beginning of micropipette recording from individual motoneurons. In Dunedin, we first learned about micropipette recording from Dexter Easton, who came as a Fulbright Fellow from the University of Washington (in 1950); he was aware of the early experiments by Woodbury and Patton. Woodbury, and also Karl Frank, had learned the micropipette technique at the University of Chicago, from Gilbert Ling, who had pioneered this technique on single muscle fibers. Also, Hodgkin (1994, p. 283) acknowledges learning this technique from Ling in 1948; this technique was rapidly adopted by many, including Nastuk and Hodgkin, Fatt and Katz, and others noted by Hodgkin (1994, p. 287). Incidentally, I got to know Gilbert Ling in 1947, when he taught the physiology lab course that I took. He was very bright and very helpful. When I met him again, many years later, he seemed to have become lost on a side track.

Eccles decided promptly that he must not fall behind in the application of micropipettes to motoneurons of cat spinal cord. Brock was asked to focus on learning to make micropipettes, and Coombs was recruited from the physics department to take charge of modernizing stimulating and recording electronics. They produced early results in time for the Cold Spring Harbor Symposium on Quantitative Biology held in June 1952. Although I could have been part of this effort, I had already begun work on independent Ph.D. thesis research, described later.

Here, I note that Eccles (an Australian) moved from Dunedin to Canberra, to be the first Professor of Physiology at the Australian National University (in 1952). Archie Mcintyre (also Australian, born in Tasmania) succeeded Eccles as Professor in Dunedin; also, I became Senior Lecturer in Physiology. Several years later, Mcintyre became the first Professor of Physiology at Monash University, in Melbourne.

Monosynaptic Input-Output: Theory and Experiment (1951–1953)

Archie Mcintyre had drawn my attention to the monosynaptic input-output relation that had been demonstrated by Lloyd (1943, 1945) at the spinal segmental level. The magnitude of the almost synchronous output voltage transient (recorded in the ventral root) was plotted against the magnitude of the almost synchronous input voltage transient (recorded in the dorsal root). The resulting input-output curve rises almost linearly from zero over the first half of increasing input, but then it bends over into a level plateau,

for larger values of the input measurement. A correct understanding of this plateau proved to be of critical importance.

I had become interested in developing and testing a theoretical model of this input-output relation, based on the concept of a population of motonuerons upon which the relevant synapses were randomly distributed. This leads to a probabilistic model of the population response; as the number of active synapses is increased, those motoneurons which happen to receive more of this monosynaptic input will reach threshold for discharge of an action potential. The simplest assumption to try first is that the motoneuron population fits a normal probability distribution, with respect to synaptic numbers and discharge threshold. The input-output relation implied by such a statistical model was formulated and computed (Rall, 1953b, 1955a).

We knew that only the largest afferent fibers (group Ia) in the muscle nerve make direct synapses with the motoneuron population of that nerve in the spinal cord. These afferent fibers differ from smaller diameter afferent fibers in having the lowest threshold to electrical stimulation and the highest conduction velocity. Thus, a brief shock to a muscle nerve (in the cat hind limb) produces an almost synchronous impulse volley in these (group Ia) afferents; this volley reaches the direct (monosynaptic) synapses on the motoneuron population long before slower impulses in smaller afferent fibers reach other targets, some of which can provide later, polysynaptic input to this motoneuron population. This knowledge ensures that the almost synchronous output volley, recorded in the ventral root, is truly a monosynaptic output from this motoneuron population, caused by the group Ia input volley.

However, it was important to understand that the magnitude of the input volley (recorded from the intact dorsal root) can include contributions from impulses in group Ib and perhaps some group II afferent fibers, especially with a large stimulus shock. This portion of the input record does not contribute to the monosynaptic input. It was necessary to correct for this by determining the relation between "effective monosynaptic input" and the "recorded input volley magnitude."

This insight explains the error of previous interpretations of the input-output relation: The plateau of maximum output for input magnitudes greater than 60% had been misinterpreted as "output saturation," implying that all of the motoneurons in that population had fired an impulse into the ventral root. My experiments demonstrated the error of this misinterpretation in two different ways: (a) they showed that the last 40% of the input measurement does not represent "effective monosynaptic input"; (b) they also showed that the observed maximum output did not represent the total discharge of the motoneuron pool (see next).

Point b was demonstrated by performing the input-output experiment at four different levels of reflex excitability, in the same preparation: (1) the

maximum output at the first level was estimated as 72% of total pool discharge; then (2) the reflex output was enhanced by using brief post-tetanic potentiation, yielding a shifted input-output relation whose maximum output was estimated as 84%; then (3) added anesthetic was used to reduce reflex excitability, yielding a shifted input-output relation whose maximum output was estimated as 37% of total pool discharge; then (4) brief post-tetanic potentiation was used to produce another shifted input-output relation whose maximum output was estimated as 60% of total pool discharge (Rall, 1951, 1953b, 1955b).

Note that without the correction for ineffective input, each of these four experimental input-output relations showed a plateau. These four different levels of output plateau clearly could not all represent output saturation (total pool discharge). This further supported the importance of finding the relation between the "effective monosynaptic input" and the experimentally recorded input volley magnitude. It was very satisfying that, with this correction, these four experimental input-output relations could be fitted with a simple probabilistic model, by adjusting the value of only one model parameter, namely the one that corresponds to reflex threshold (Rall, 1953b, 1955a,b). This agreement provides a good example of where predictions of a simple theoretical model were confirmed by experiment, (especially when the experiment was sufficiently comprehensive).

I note further, that two probabilistic models (differing in the definition of the threshold condition) were tested. The simplest assumed that a motoneuron discharges when the number of simultaneously activated synapses on this motoneuron reaches or exceeds a specified threshold number; the other model assumed that a smaller number of activated synapses could succeed, provided that they were concentrated in a subregion (zone) of the motoneuron's receptive surface. I found that the experimental data could be fitted by both models. Thus, this test did not settle the question about whether the threshold region is zonal. However, it did show that the local, zonal concept of Lorente de Nó (1938) is not necessary to explain the input-output relation, as others had thought. My Ph.D. thesis was completed in 1953; my sabbatical leave began in 1954.

More complete description and discussion of this research can be found in several places: There are the original papers (Rall, 1955a, 1955b); a useful summary appeared later in a book chapter (Rall, 1990), and also as Appendix A.2 in another book (Segev, Rinzel, and Shepherd, 1995), in which Appendix A.1, by Julian Jack, is also relevant.

Isopotential Soma (1953)

In my input-output study, I gave no explicit consideration to the dendrites of the motoneurons. Lorente de Nó had put his focus on the soma and on subzones of the soma surface; in fact, he asserted that

the effects of activated synapses would be cumulative only for synapses located close together, and not for synapses located far apart (Lorente de Nó 1938). Thus, I was interested in exploring questions about the rate of spread of localized membrane depolarization on the motoneuron soma surface.

I considered the mathematical physics of passive membrane depolarization on a spherical soma (Rall, 1953a, 1953b). What I discovered is that passive (electrotonic) spread of local membrane depolarization is very much more rapid over a spherical soma surface than it is along cylinders of axonal and dendritic dimensions. The mathematical solutions contain time constants for equalization of passive membrane potential over a spherical soma. By using reasonable values for resistance and capacitance, these time constants are found to be about a thousand times smaller than the (RC) time constant of the passive membrane; i.e., microseconds compared to milliseconds. Thus, I was able to conclude that "the passive electrotonic response to a focal (synaptic) current loses its spatial decrement almost completely by the time the 'synaptic potential' reaches its maximum value" (Rall, 1953b, 1955a).

The physical-intuitive explanation of this mathematical result depends upon the relatively low electrical resistance between different regions of the sphere interior. It is this low resistance that is responsible for the small equalizing time constants that correspond to rapid equalization of soma membrane potential. This low resistance contrasts with the relatively high core resistance found along the interior of a thin cylinder, which is responsible for the length constant, lambda, and for equalizing time constants found for dendrites (Rall, 1969).

Once this is understood, it becomes clear that this biophysical result does not really depend on the precise spherical shape that was assumed for the mathematics; this result should hold true for any globular shape that is free of constricted cross-sections. This insight provides the basis for the simplifying assumption that the soma membrane may be regarded as isopotential, relative to nonuniform membrane potentials in dendritic trees (Rall, 1959b).

Sabbatical Leave in London and New York (1954–1955)

As beautiful as the mountains and coastline of New Zealand really are, academics do feel isolation from the rest of the world. Consequently, the university was inclined to approve sabbatical leave after 5 years of faculty service. The local salary scale was not sufficient for travel and subsistence elsewhere, but I was fortunate to be awarded a travel fellowship from the Rockefeller Foundation, for research visits with Bernhard Katz, at University College London, and with David Lloyd, at the Rockefeller

Institute for Medical Research (about to become Rockefeller University). Both Katz and Lloyd were friends of Archie Mcintyre, and both had read my Ph.D. thesis.

Our travel began with an ocean voyage from Wellington to Sydney, across the Tasman Sea; this was the roughest sea voyage in my experience; in fact, I was one of the few passengers who did not become fully seasick. We visited with friends in Sydney, and also with Coombs, Eccles, and Fatt in Canberra, before boarding an Italian ship that stopped in Sydney, Melbourne, Perth, Jakarta, Colombo, Aden, and the Suez Canal, on the way to Naples and Genoa. We got off in Naples, and then enjoyed our first visit to Italy, which included visits to Rome and Florence. Coming from New Zealand, we appreciated the ruins and the sense of history. The museums were cold (heated only by small charcoal burners in February 1954), but seeing the paintings and sculptures was a treat, anyway. Then, via rail, we made our way to Paris and to London.

It was a pleasure to meet Bernhard Katz and the active group of young investigators in his Biophysics Group, at University College London. This group included Jose del Castillo, who later came to the National Institutes of Health (NIH) and then to a chair in Puerto Rico; Liam Burke, who later moved to Australia and to a chair in Sydney; Bob Martin, who later moved to Yale and then to a chair in Salt Lake City; B.L. Ginsborg, who later moved to a chair in Glasgow; and Charles Edwards, who later was at Yale and at NIH. Paul Fatt was then in Canberra, where I had met him several weeks earlier.

I knew that Katz had originally come from Germany to London at the invitation of Professor A. V. Hill. In the preface to Katz's classic first book, *Electric Excitation of Nerve,* Oxford Press, in 1939, it was noted that this had originally been written as a review to be published in *Ergebnisse der Physiologie,* but due to Nazi policy at that time, the editors informed Katz that they could publish his review only if he would accept an Aryan coauthor. Fortunately, this persuaded Katz that it was time to leave Germany and accept Hill's offer to help him get his review published in England. Later, Katz served in the Australian Armed Forces; this included duty on a Pacific island as a spotter of Japanese aircraft. In the late 1940s, there was a research collaboration on the neuromuscular junction, by Eccles, Katz, and Kuffler, at a research institute in Sydney. Much later, when Katz held a Readership in London, Eccles offered Katz a new Chair in Biophysics at Canberra; it is my understanding that this offer prompted University College to offer him a Biophysics Chair in London.

At the time of my visit in 1954, Katz was doing experiments with Jose del Castillo on the neuromuscular junction; I played a small role by doing some theory and calculations related to their iontophoresis from micropipettes. I also had my first experience of presenting some of my

research results to a meeting of the Physiological Society. Before this meeting, several of us did practice runs for Katz and Professor G.L. Brown; we all received the important advice: if you try to cram too much into your slides and words, you actually communicate less. On several occasions since, I have passed this good advice on to others.

On the day that I was to go to Cambridge for a visit with Alan Hodgkin, Katz offered to drive us there; he had just acquired his first car, from A.V. Hill. Displaying the required "Learner" plates, he drove with Bob Martin as his driving mentor. Hodgkin and Katz were old friends, and we all enjoyed lunch together. During my research visit with Hodgkin, I discussed a number of my theoretical approximations and calculations (including iontophoresis, spherical electrotonus, and my input-output thesis). He was interested and offered me encouragement that was very important to me, coming, as I did, from voluntary exile in the Antipodes. I never actually published my work on iontophoresis, but it provided a valuable interaction with colleagues at that time. We also visited physiologist friends at Oxford, including L.G. Brock and Marianne Fillenz (both had only recently come there from Dunedin), and also Charles Phillips (who learned micropipette technique from Brock). Later, Phillips wrote me when he, with Powell and Shepherd, was writing up their experimental research on the olfactory bulb. He expressed their interest in a theoretical approach to their experimental results; this was followed up when Shepherd came to NIH to work with me.

While based in London, my wife and I did visit the continent, including brief visits to relatives in Switzerland and Paris. But then it was time to sail to the United States, to visit Dave Lloyd and Cuy Hunt in New York, as well as NIH and family in Bethesda, Maryland.

The Rockefeller Institute for Medical Research was impressive. I met many distinguished scientists, including Herbert Gasser, who was in close touch with Lloyd and Hunt. Gasser had recently retired from the directorship of the institute; he was succeeded by Detlev Bronk, who then oversaw the transition into Rockefeller University. I briefly met Rafael Lorente de Nó; his laboratory was near that of Lloyd, but there did not seem to be much scientific interaction, because his interest had shifted from electrophysiology to biochemical research. I sensed that he was of the old Herr Professor tradition (with dogmatic tendencies), and there seemed little point in trying to explain to him the insights about soma and dendritic electrotonus that I had gained.

Several years later, when Lorente de Nó presented a seminar at NIH, there was a very emotional incident. During questions and discussion, Tasaki went to the blackboard to explain a point; he erased a small area that happened to include some equations from Helmholtz. Lorente exploded, "You can't do that to Helmholtz." The audience was astonished and amused. At that time (perhaps 1960) both Lorente and Tasaki

did not accept the Hodgkin-Huxley theory of nerve membrane permeability changes causing the action potential. I felt a little sad; I had admired the pioneering neuroanatomy and electrophysiology that Lorente de Nó had accomplished in earlier years (in Spain and St. Louis); I had also read his two thick monographs on electrotonus, which included a valuable mathematical-physics section by Leveret Davis Jr, with whom Lorente had studied and collaborated at Cal Tech. But I could see that Lorente, even with his demonstrated versatility, had dogmatic tendencies that made it impossible for him to accept insights from others that did not fit his own insights and prejudices.

I did one or two experiments with Dave Lloyd, but then his time was preempted by his participation on the scientific committee that advised the National Polio Foundation on the Salk vaccine research; this was then in its final stages. Here I note that an excellent neurophysiologist Birdsey Renshaw (whom I had met briefly at Woods Hole in 1947) had recently died of polio, after nursing his family; this was a tragic loss to neurophysiology.

Cuy Hunt and I performed a number of experiments that followed earlier research by Hunt, Lloyd, and Mcintyre on "firing index" distributions in a motoneuron population. We succeeded in providing a theoretical model that could account for the data in terms of excitability fluctuations imposed on a neuron population having a normal probability distribution of firing thresholds (Rall and Hunt, 1956). This provides another example of theoretical model predictions that were confirmed by targeted experiments.

Also, while living in Manhattan, I discovered a small sculpture gallery that offered classes in a studio on the second floor. Attending one evening a week, I enjoyed learning to model in clay and produced four pieces (two heads, one torso, and an abstract swirl); these were kiln-fired, to become unglazed terra-cotta sculptures. My interest in making sculptures has continued for many years.

During brief trips to Bethesda, Maryland, I met people at NIH when I gave a seminar there. I also saw my biophysics friends from Chicago (Cole, Morales, Hearon, Podolsky, Blum, and Botts) who were then at the Naval Medical Research Institute (NMRI), located across the road from NIH; they were excellent in biophysics and biochemistry. Also in Bethesda, we visited my parents, who lived in Bannockburn, a community that my father had helped to organize as a cooperative housing development.

When we returned to New Zealand (by air this time), we found many friends pleased to see us back. Some expressed surprise that I had not taken a research position in England or the United States. We chose to return; we had built a house on the Otago Peninsula with a great view of the ocean. Also, I had accepted an obligation to return for at least 1 year after my sabbatical; this I did (during 1955–1956). However, I had overstayed my leave (for about 1 month, mainly in order to complete the manuscript

of my research with Cuy Hunt). Even though I had completed three publishable papers during my leave, the university administrators had decided that I should be penalized for tardiness. This induced me to communicate with my biophysics friends at NMRI. They responded with an offer of a position for me as Head of their Biophysics Division. Before leaving New Zealand, my wife and I adopted a newborn baby girl whom we named Sara Elisabeth. Almost 5 years later, another daughter, Madelyn, was born in December 1960.

Biophysics at NMRI (1956–1957)

Arriving in Bethesda in July 1956, I soon was involved in many informal scientific seminars, both at NMRI and at NIH; it was a very stimulating research community. It had been my intention to equip a laboratory for experimental neurophysiology research at NMRI; I wrote research proposals and devoted considerable effort in determining the best items of equipment and supplies to order. Then, out of the blue, the federal government (Eisenhower Administration) imposed the startling austerity measure of an absolute freeze on all government purchases and hiring. With my experimental plans frustrated, I turned again to theoretical research. I remember having a conversation with Dick Fitzhugh at that time; we agreed that, because we both already had considerable experimental research experience, and because there were numerous colleagues who were happy to do more experiments, it was OK for us to decide to focus our attention on theoretical research. We recognized the importance of good experiments, but we also believed in the importance of theory, based on biophysical-mathematical modeling.

The new executive officer at NMRI had tried to orient me with this advice: "Basic research is OK, as long as it is not too basic." This was my first hint that the new command at NMRI did not appreciate the strength in biophysics and biochemistry that Cole and Morales had assembled with the cooperation of the previous command. The rationale had been that excellence in basic research would provide NMRI with a valuable scientific resource, for any emergency. The new command did not accept this rationale and soon learned that top scientific talent moves elsewhere when given only lukewarm support. Cole had already moved to NIH before I arrived; Terrel Hill soon moved to the University of Oregon and later to the University of California; John Hearon was invited to form a mathematical research group at NIH. Early mainframe computers were already used by the NIH payroll office, and the director of NIH was advised by Cole and others that the NIH should have an Office of Mathematical Research, as a research resource for all of the institutes. This office was formed in 1956; I joined Hearon in December 1957.

Mathematical Research Group at NIH (1957–1994)

Dr. Hans Dewitt Stetten, the research director of the National Institute for Arthritis and Metabolic Diseases (NIAMD) offered to provide us with space and positions; thus our Office of Mathematical Research was originally attached to his office (OD) at NIAMD. There was also a very large biophysics lab in NIAMD, and Dr. Stetten invited me to consider becoming its lab chief, but I declined because by this time I knew that I much prefer to focus on my own research, with one or two colleagues, than to do administration for a large number of people. Some years later, we became the Mathematical Research Branch of NIAMD, and later, when arthritis research was split off into a new institute, we remained in what then became the National Institute for Diabetes, Digestive and Kidney Diseases (NIDDK). However, many of my research collaborations were with friends in the neurology institute (NINDB), later NINCDS. Also, when Dr. Stetten became Director of the General Medical Sciences Institute (NIGMS), J.E. (Ed) Rall succeeded him as research director of NIAMD, and later became the Intramural Research Director (Dean) of all the institutes. Here I note that brothers, Ed and Dave Rall, are distantly related to me (perhaps fifth cousins); we had not met before coming to NIH.

John Hearon provided me with complete research freedom. He was very sharp and had two Ph.D.s, one in biochemistry and another in mathematical biophysics (with Rashevsky at the University of Chicago). He was expert in the mathematical treatment of metabolic-kinetics and was helpful to me as a referee of my research manuscripts. The third person to join our group was Mones Berman, with a Ph.D. in electrical engineering; he could take charge of advanced lab equipment, but his real interest was in mathematical treatment of metabolic-kinetics and the application of computers to kinetic data. It was his early computer simulation program (SAAM, written in FORTRAN) that enabled me to do my first compartmental modeling. The fourth person to join our group was Jose Gonzales-Fernandez, who had both a medical degree from Argentina and a Ph.D. in applied mathematics from Northwestern University; he had many interests, including theory of microcirculation. Also attached to our group was John Stephenson, who had been a physicist on the Manhattan Project and then did an M.D. degree; he was supported by the Heart Institute but roomed with us. He was expert in the biophysics of kidney function. We all became friends and had many valuable interactions, in informal discussions, and in formal seminars that included other biophysicists and theoretical statisticians at NIH. Thus, we were a resource for others at NIH, as well as for each other.

Later several more people joined our group for different periods of time; these included John Rinzel, Gordon Shepherd, Steve Goldstein,

Maurice Klee, John Miller, Bob Miller, John Evans, Idan Segev, Bill Holmes, Wayne London, David Lipman, and Arthur Sherman. Also, Marge Weiss, Susie Atta, Ezra Shahn, and Jeanne Altman provided valuable assistance to one or more of us with our computations, especially in the early days. When Hearon retired, I sponsored John Rinzel as Branch Chief; later, when Rinzel left NIH for a professorship at New York University (NYU), Arthur Sherman became our Branch Chief.

Membrane Time Constant of Motoneurons (1956–1957)

In 1956 several research groups (in Australia, Japan, and at NIH) recorded surprisingly rapid voltage transients in cat spinal motoneurons. These were experiments using glass micropipettes to stimulate and record from individual cells deep in the spinal cord. The point of penetration was generally assumed to be the motoneuron soma, and these transients were interpreted as properties of the motoneuron soma membrane. First Frank and Fuortes, and then Eccles (with collaborators) concluded that the membrane time constant of these motoneurons must be significantly smaller (less than half, in some cases) than the earlier estimates that were based on synaptic potentials recorded in ventral roots. In an attempt to account for this discrepancy, Eccles introduced new hypotheses about prolonged synaptic activity.

After pondering this discrepancy, I came to realize that the new time constant estimates had resulted from misinterpretation of the voltage transient. The transient had been treated as a simple exponential. That assumption would have been valid only if the motoneuron were a soma without dendrites, or if it had been possible to apply the current uniformly across all of the soma and dendritic membrane. Because neither of these options held true, it became necessary to ask how the shape of the voltage transient must be modified by the fact that current, applied inside the soma, must flow not only across the soma membrane but must also flow into the dendrites for considerable distance before flowing out across dendritic membrane.

A note to *Science* (Rall, 1957) made this point by contrasting two limiting cases, "soma without dendrites," versus "dendrites without soma." The transient in the first case is a single exponential, but in the second case it is a significantly different mathematical function. If each dendritic tree is represented simply as a very long cylinder, this function is the same as that already known to axonal biophysics from earlier studies of electrotonus in nonmyelinated axons (Hodgkin and Rushton, 1946). An intermediate case was also computed, based on the best data then available; it was assumed that the steady current into the dendrites was five times the steady current across the soma membrane; this curve lies close to the curve for "dendrites without soma" and it was suggested that, for most motoneurons, the true

curve probably lies between these two. When such a transient is erroneously treated as a single exponential, an erroneously low membrane time constant is obtained. The bottom line is that when you assume an incorrect model (whether explicitly or implicitly) your interpretation of experimental data is likely to be erroneous.

Many years later, a young British physiologist told me that he remembered being in the physiology tea room at Cambridge when that issue of *Science* was first received. He said that there was an excited discussion (of my 1957 note) that went on for some time. I asked him how this ended. He said they concluded that my point was valid. Frank and Fuortes accepted my conclusion, as did Paul Fatt, but Eccles did not; he argued that the dendrites made only a small contribution. Regarding this issue, see a discussion by Jack and Redman in Segev, Rinzel, and Shepherd, 1995.

Theoretical Implications of Motoneuron Dendrites (1958–1960)

A detailed presentation of biophysical-mathematical theory and computations was submitted (in 1958) for publication in the *Journal of General Physiology*. A negative referee persuaded the editors to reject this manuscript. The fact that this referee was Eccles, was clear from many marginal notes on the returned manuscript (also confirmed by subsequent evidence). This manuscript did appear as a research report of the NMRI (Rall, 1959a). I confess that I felt rather depressed by the rejection. Fortunately, K. Frank and Bill Windle came to my rescue, by encouraging me to revise my manuscript into two papers for publication in their new journal, *Experimental Neurology*. One paper (Rall, 1959b) focused on steady-state current flow into dendritic trees, including implications for calculating membrane resistivity; the other (Rall, 1960) focused on transient solutions, including implications for estimating the membrane time constant.

The steady-state analysis yielded a computational algorithm for step-by-step calculation of the input resistance of a general dendritic tree having arbitrary branch lengths and diameters; this algorithm was later adopted by others in their computation packages. This paper also provided a detailed overview of the data then available and emphasized the importance of considering a reasonable range of values for the membrane resistivity and for the ratio of dendritic input conductance to soma conductance. A membrane resistivity range from 1000 to 9000 ohm(cm)squared, with a mean around 5000, was contrasted with a value of 400 to 600 estimated by Eccles and his collaborators. The dendritic/soma input conductance ratio was estimated to lie within an extreme range of 10 to 47, with a midrange from 21 to 35, to be contrasted with a value of 2.3 used by Eccles for his "standard motoneurone." Large values for this ratio provide a measure of dendritic dominance in the responses and the functions of motoneurons.

The transient analysis yielded a better method of estimating the membrane time constant from experimental transient data. It was shown that when the log of the product: (square root of t, times the slope, dV/dt) is plotted against t, the data can be expected to fit a straight line; also, when calculated with natural logarithms, the negative slope of this line equals the reciprocal of the membrane time constant. Examples and qualifications are discussed at length in the paper (Rall, 1960). The revised membrane time constant values obtained by Eccles and collaborators were found to be 30% below my new estimates, which were made from the same data.

This may seem to be a small discrepancy, but it was very relevant to Eccles' argument for the "residual synaptic current" that he had postulated in an attempt to account for the misunderstood discrepancy. Instead of acknowledging his error, Eccles continued to publish his calculated "residual synaptic current" in many papers and reviews; later, these calculated magnitudes were reduced, and finally they disappeared, without comment. See relevant discussion by Jack and Redman in Segev, Rinzel, and Shepherd, 1995.

Because Eccles asserted that I had exaggerated the dendrites, there was a latency period during which many neurophysiologists did not know whom to believe. I found that neuroanatomists, with their knowledge of dendrites, were more ready to believe that Eccles was mistaken. As late as 1964, Eccles asserted "that synapses on dendrites are virtually ineffective if situated on the more remote regions of dendrites that are about 1 mm in length" (p. 111 in Eccles, 1964).

By 1960, I had decided not to argue further about the value of the time constant, because it was more important to focus on theoretical modeling and computation of synaptic input to different dendritic locations and on computation of different spatiotemporal input patterns. Some of this is described in the next four sections. It may be noted here that this theoretical modeling, together with the experimental testing done by my friends in the Spinal Cord Section of the Neurophysiology Lab at NIH, led to a joint paper (Rall et al., 1967), which did persuade most neurophysiologists about the significance of synaptic input to the dendrites.

D3/2 and the Equivalent Cylinder Concept (1959–1962)

Already in the 1959 papers, theory and computation of the steady-state distribution of current in the branches of dendritic trees had revealed the important role of the 3/2 power of the diameter of each branch cylinder. The mathematical treatment made use of the kind of simplifying assumptions that physicists usually make; each branch is a cylinder, and, at least at first, all branches have the same uniform passive membrane properties. Because the input conductance of a membrane cylinder depends on the 3/2

power of its diameter, it is important to consider, at every branch point of a dendritic tree, the d3/2 ratio, which is composed of the sum of the d3/2 values of the two daughter branches divided by the d3/2 value of the parent branch. In an idealized case, where this ratio is 1.0 at every branch point, the entire dendritic tree can be mapped onto an equivalent cylinder (provided also that all terminal branches terminate at the same electrotonic distance from the soma; note that dimensionless electrotonic length is the actual length divided by lambda, the length constant, which depends on the square root of branch diameter). Such a tree need not be symmetrical. Also, it is important to point out that this equivalent cylinder is valid not only for steady states but also for transient solutions of the partial differential equation.

Although I did not expect natural dendritic trees to satisfy these constraints exactly, dendritic trees of motoneurons have been found to approximate these conditions. Thus, the equivalent cylinder provides a useful model with which to compare the effects of proximal input locations with those of distal locations, where the distal input is assumed to be delivered to all distal branches at the same electrotonic distance from the soma. It may be noted that some years later, John Rinzel and I published mathematical solutions for distal input delivered to a single distal branch (Rall and Rinzel, 1973) for steady states and (Rinzel and Rall, 1974) for transients.

In 1961, Nicholas Rashevsky organized a Mathematical Biology Symposium for the New York Academy of Science. There I presented the equivalent cylinder concept and used it to provide the first computed synaptic potentials, contrasting distal with proximal synaptic input locations. Here I made explicit the mathematical treatment of synaptic excitation and synaptic inhibition, in terms of a membrane conductance change associated with an appropriate battery (reversal potential), consistent with the ideas of Fatt and Katz, and of Hodgkin and Huxley. I also derived a partial differential equation that provided for more general branching, corresponding to a tapered, equivalent noncylinder (Rall, 1962a). That more general model was used some years later, when Steve Goldstein and I explored questions about impulse propagation (including block, delay, and possible reflection of an impulse) in axons with nonuniform geometry (Goldstein and Rall, 1974); see later.

Compartmental Model of Soma with Dendrites (1962–1964)

In 1962, a Neural Theory and Modeling Symposium was held at Ojai, California; the organizers included Richard Reiss and others associated with the defense contractory, General Precision; it was also supported

by the Air Force Office of Scientific Research. This may have been the earliest symposium to bring this many (about 25) neural modelers together; it was a stimulating occasion. The resulting book was published in 1964, by Stanford University Press. I presented my assumptions, for the mapping from tree to equivalent cylinder, and then introduced a compartmental model approximation to facilitate computations with different input locations and different spatiotemporal input patterns. Here I note that Mones Berman, my friend and colleague in our NIH mathematical research group, had created an early FORTRAN program for compartmental modeling of metabolic system kinetics (Berman et al., 1962). With his advice, and with logistic help from Marge Weiss (punch-card inputs were transported, by car, from Bethesda to the IBM-7090, at the old DC location of the National Bureau of Standards; there was a 24-hour turnaround to obtain printed paper output), I was enabled to do simulation computations for a soma with dendrites, approximating the equivalent cylinder model.

The particular model consisted of a chain of 10 equal compartments, where compartment #1 represented the motoneuron soma, and compartments #2 to #10 represented increasing electrotonic distance out into the dendritic trees. Computations demonstrated significant differences in the shape of the synaptic potential obtained at the soma (voltage transient in compartment #1) when the same brief synaptic input was applied at different dendritic compartments. For input located in proximal compartments (e.g., #2 and #3), the response at the soma showed a steep rise to an early peak followed by fairly rapid decay; in contrast, for input located in distal dendritic compartments (e.g., #6 and #7, or #8 and #9), the resulting synaptic potential (at the soma) showed a delayed onset, and a much slower rise to a later peak (more rounded and of much smaller amplitude), followed by slow decay. Such differences in shape can be understood in terms of electrotonic spread from the input compartment to adjacent compartments. In fact, the initial nonuniformity of membrane potential tends to equalize rapidly, such that the late decay (for times greater than twice the membrane time constant, tau) is essentially the same in all cases; this implies also that the late decay is essentially the same in all compartments, meaning at the soma and at all dendritic locations (assuming uniform membrane).

In these simulations, the synaptic conductance had a square time course; it was turned on and kept constant for 0.25 tau and then turned off. A few years later, I simulated more realistic transient synaptic conductances (Rall, 1967). Nevertheless, even the square synaptic conductance enabled me not only to demonstrate the effects of different input locations, and different spatiotemporal input patterns, but also to simulate nonlinear interactions between several synaptic input conductances, both excitatory and inhibitory.

The effects of steady synaptic inhibition at different locations upon a mid-dendritic (#5 and #6) synaptic excitatory input were compared. Distal inhibitory conductance (#9 and #10) was not effective in reducing the peak of the excitatory synaptic potential (EPSP) at the soma, but it did slightly reduce the falling phase of the EPSP. In contrast, both proximal (#1 and #2) and mid-dendritic (#5 and #6) inhibitory locations were effective in reducing the EPSP peak; the proximal location was the most effective. More complicated situations involving timing were also discussed (Rall, 1964). These results anticipated similar results that were obtained and discussed later by others.

A different compartmental model departed from the straight chain by providing branching that ended in four distal compartments. This permitted me to verify the conjecture that synaptic excitatory inputs sum linearly in the somatic EPSP when these inputs are segregated to different distal compartments; in contrast, synaptic excitatory conductance inputs combine nonlinearly when placed at a common input location (Rall, 1964).

Compartmental Models Can Be Much More General

Although these examples all assume passive membrane, it is important to note two powerful general advantages of compartmental models: (1) the simulations need not assume uniform passive membrane and (2) they are not limited to the constraints of the equivalent cylinder model. Each compartment can be different. Each can include any nonlinear membrane properties that we choose to specify. Also, each can incorporate any departure from equivalent cylinder constraints that we choose to specify.

Spatiotemporal Patterns of Synaptic Input (1962–1964)

One of the simulations, in the 1964 chapter, compared the effects of opposite spatiotemporal synaptic input patterns. The patterns made use of the four synaptic excitatory conductance input locations, A, B, C, and D used before; these are A (#2 and #3), B (#4 and #5), C (#6 and #7), and D (#8 and #9). The input sequence, A, then B, then C, then D (meaning first proximal, and then successively more distal), produced a synaptic potential at the soma whose rising phase and peak amplitude differed little from that for A alone, but the falling phase was much prolonged as a plateau with slow decay. This computed result can be understood because the effects of later distal inputs reached the soma too late to contribute to

the peak, but still in time to contribute to the plateau. In contrast, the opposite input sequence, D, then C, then B, then A (meaning first distal, and then successively more proximal), produced a delayed synaptic potential that rose more slowly to a peak whose amplitude is nearly twice that for ABCD (or for A alone); it decayed without a plateau. This computed result can be understood because the effects of the distal input reach the soma with significant delay, and thus they can build upon the delayed proximal input.

Both spatiotemporal input patterns can have functional value. If the impulse threshold at the soma were between these two amplitudes, this would provide a means of distinguishing between these two patterns: DCBA would fire an impulse, whereas ABCD would not. This could be used for movement detection or for some other discrimination. On the other hand, the prolonged plateau produced by ABCD could be used to bias the soma membrane potential just slightly below threshold, in readiness for a well-timed somatic input that could trigger an impulse.

This simulation may represent the first computed demonstration of such an effect of spatiotemporal input pattern for otherwise equal amounts of synaptic input.

EPSP Shapes; Shape Index Plots; Theory and Experiment (1964–1967)

The different computed EPSP shapes caught the eye of K. Frank, who knew that Bob Burke was recording unitary EPSPs from cat spinal motoneurons. Burke had mastered the experimental technique for eliciting synaptic input delivered by a single afferent fiber of a muscle nerve in the cat hind limb, and for recording the resulting unitary EPSP in a motoneuron (Burke, 1967). Thus, we had an opportunity to compare these experimental EPSP shapes with theoretical EPSP shapes computed for different locations in the compartmental model. To facilitate the comparison, we chose two shape indices: "time-to-peak" and "half-width"; then each shape can be represented as a point in a two-dimensional plot. Later, Jack, Redman, and colleagues preferred "rise-time" to replace "time-to-peak," because its slightly different definition made it more suited to coping with the variability of experimental EPSP shape measurements (Jack et al., 1971).

The theoretical EPSPs were made more realistic by introducing a transient time course for the synaptic conductance input. This one-parameter transient function (later named alpha-function, by Jack and Redman) rises to an early peak followed by brief decay; we used three versions: "fast," "medium," and "slow," whose peak times were 0.02, 0.04, and 0.092 of the membrane time constant, tau. Thus, for tau = 5 msec, these three peak times are 0.1, 0.2, and 0.46 msec, which proved to be a reasonable range

of values. Using these transient synaptic inputs, theoretical EPSP shapes (at the soma) were computed for each input location in the 10-compartment model (Rall, 1967).

A theoretical shape index locus was obtained by plotting the points defined by the paired shape index values for each theoretical EPSP, for each input location. Three loci were obtained, using the slow, medium, and fast inputs. A significantly different locus was obtained when the input was delivered uniformly to all compartments, and only the time course of the input was varied (Rall, 1967; Rall et al., 1967).

Given these shape index loci, the experimental EPSP shapes could be plotted and compared with the theoretical loci. The results were very encouraging; the range of experimental points agreed better with the loci for localized input. Although there was experimental scatter, much of this could be accounted for. The membrane time constant of each neuron had not been measured for the original set of experimental EPSPs; we had to assume a reasonable value (such as 5 or 7 msec). Later experiments by Jack et al. (1971), by Mendell and Henneman (1971), and by lansek and Redman (1973) included a time constant measurement and thus provided much closer fits with the theoretical loci. Also, some experimental EPSP shapes had larger half-widths than expected (for their time-to-peak); these could be understood as resulting from a single afferent fiber that must have delivered synapses to more than one location; such EPSP shapes were successfully simulated by computations with two or more input locations (Rall et al., 1967).

These results can be added to the list of theoretical modeling predictions that were confirmed by neurophysiological experiments. Our collaborative paper (Rall et al., 1967) also summarizes several other successful tests that we carried out at that time. Without going into further detail, I quote the final sentence of the summary to my 1967 paper: "A theme common to all of these computations and interpretations is that results, which may appear paradoxical when examined only at the soma, can be understood quite simply when attention is directed to the synaptic input location with special attention to the effective driving potential there."

There was still one significant loose end; we did not know the actual dendritic location of the synapses that produced the experimental EPSP shapes. A new histological technique, involving horseradish peroxidase injection, was used to "demonstrate that putative la-boutons are indeed widely distributed in the dendritic trees" (Burke et al., 1979). Then, a remarkable experiment by Redman and Walmsley (1983) succeeded in combining such histology with electrophysiology (in the same motoneuron) and found agreement between the actual synaptic input locations and the theoretical location implied by two different EPSP shapes—another example of experiment confirming theory.

Extracellular Potentials During Passive Electrotonic Spread into Dendrites (1960–1962)

In the summer of 1960, I also computed extracellular potentials, with the help of Ezra Shahn and Jeanne Altmann. This was early computing with an IBM-650, using punch-card inputs. In order to find equipotential contours, we had to interpolate by hand. The first case was a simplified neuron consisting of a soma with a single cylindrical dendrite (solved with Legendre polynomials). Next, we used superposition to compute the field for a spherical soma with seven cylindrical dendrites: one polar (at 0 degrees), three equally spaced (at 60 degrees), and three more (at 90 degrees); an illustration of this can be found in the references cited later. It was assumed that the soma membrane generated an action potential and that the dendritic membrane was passive, receiving passive electrotonic spread from the soma into the dendrites. We froze the system at the instant of peak action potential and then used the distribution of membrane current density (at that instant) to define the sources and sinks of current flow in the (homogeneous) extracellular volume. We found the extracellular potential field to be negative (relative to a distant reference electrode) everywhere near the soma and proximal dendrites and found only weakly positive sleeves around the distal dendrites. These results were presented at the First International Biophysics Congress that was held in Stockholm in 1961; the Congress proceedings were published in a special issue of the *Biophysical Journal* (Rall, 1962b). Illustrations of these results can be found there, and also in a handbook chapter (Rall, 1977); in Rall, 1992; or in Segev, Rinzel, and Shepherd, 1995.

Because we know that sodium ion current is inward across the spherical soma membrane at peak action potential, we also know that the intracellular current flows from the soma into the dendrites; this current then flows out across the dendritic membrane, and then all of this current must flow through the extracellular volume, back to the soma surface. Thus, it should not be surprising that we find (near the soma) negative equipotential surfaces that are essentially spherical and concentric with the soma. Indeed, if the current sources were at great distance, these surfaces would be exactly spherical, concentric, and with negative polarity relative to a distant reference electrode. Because the current sources are distributed along the seven dendritic lengths, at relatively low density, small positive potentials were found only near distal dendrites; at proximal locations, the strong somatic sink outweighed the weak dendritic source. (Note also, that if the seven long cylinders are replaced by branched dendritic trees, the source current density at a branch will be significantly smaller than for the cylinder.)

These results provided me with an important insight. I had been taught that extracellular positivity was always found next to a current source;

this is true for an axon in a volume conductor, but here we found it not to be true near the proximal dendrites of a multipolar neuron. Also, the concentric equipotential surfaces dominated by current to the soma bore a similarity to the "closed field" concept of Lorente de Nó (1947, 1953). Later, I learned that George Bishop had also discussed extracellular electric fields. It is noteworthy that Bishop and Lorente de Nó both worked in St. Louis at about the same time; I never met Bishop, and never learned if these two scientists had interacted at that time. Here I note that the concept of open and closed fields was relevant to my later computations of field potentials in the olfactory bulb (Rall and Shepherd, 1968), discussed in a later section.

Extracellular Diphasic Does Not Imply Impulse in Dendrites (1960–1962)

Also presented in the 1961 International Biophysics Congress were extracellular transient potentials computed for a complete action potential generated by the soma membrane, with the dendritic membrane assumed to be passive. This extracellular transient is diphasic (brief negative peak followed by a smaller positive peak) in the volume near the soma and proximal dendrites. This computed result had an important impact on the interpretations that several neurophysiologists were making with their diphasic experimental potentials, recorded near a motoneuron when it was activated (by an antidromic impulse). Some of them believed that such a diphasic $(-, +)$ transient could be taken to provide evidence of impulse propagation in the dendrites; but now, these computations demonstrated that such a diphasic also occurs with passive dendrites that do not propagate an action potential. My result did not prove that motoneuron dendrites are passive, but it did tip the scales in a careful discussion of the issues (Nelson and Frank, 1964). This involved a significant reinterpretation of experimental observations.

A valuable biophysical insight can explain my computed result. The key is the rapid repolarization of the soma membrane by the active potassium ion current during the falling phase of the action potential at the soma membrane; this causes reversal of the direction of extracellular current flow. The negative peak potential corresponds to active sodium ion current flow inward across the soma membrane (the extracellular current flows from dendrites, radially toward the soma). The positive peak potential corresponds to active potassium ion current flow outward across the soma membrane (the extracellular current flows from the rapidly repolarized soma membrane, radially outward toward depolarized dendrites) (Rall, 1962b). These results and insights persuaded several investigators to desist from claiming that they had evidence for impulse propagation in dendrites.

A sociological note seems relevant here. In the 1960s, before the Society for Neuroscience was founded (in 1970), there were informal neurophysiology meetings held in Atlantic City, a day or two before the large Federation of American Societies for Experimental Biology (FASEB) meetings that were held there every year (in April, I believe). One of the organizers of these meetings was K. Frank; I do not remember who the others were. I do remember that many of the insights, gained by my interactions with K. Frank's spinal cord research group, were presented to the wider neurophysiological community at these meetings. These meetings augmented the scientific grapevine by which new insights were disseminated.

Farm Family (1963–present)

In 1963, it happened that four NIH families together bought a 500-acre farm located about 60 miles west of NIH, in Washington County, Maryland. Two old farm houses had electricity, but no indoor plumbing and no telephone. Lack of telephone was important to having quiet weekends, away from NIH. It was mostly woodland and pasture; crops were corn and hay; repairing fences was a regular activity. We managed a small herd of cattle with the help of our neighbors, the Poffenberger family. Some skeptics thought that this cooperative effort could not last, but it has lasted for more than 40 years. Our farm family consisted of Jean and Barry Blumberg, Caroline and Ed Rall, Jean and Jacob Robbins, Ava Lou and me, all with children who enjoyed the farm. Today, my daughter Sara lives on the farm with her daughter, Megan, and with four dogs and four horses (she has a job in Hagerstown). Sara and Ed Rall (the younger) now do much of the managing.

International Brain Research Organization (IBRO), NAS-NRC Committees, Society for Neuroscience (1963–1972)

It must have been in the mid-1960s that I was invited to join the Biophysics Panel of IBRO. I attended a meeting in Munich, where one felt some East-West tensions; I remember speaking for international cooperation in scientific research. I was also a member of two NAS-NRC committees; one was for liaison with IBRO. The other was a Committee for Brain Sciences, which engaged in several projects, including founding a new society (originally to be named Society for Brain Sciences); when I voiced a preference for the word, "neuroscience," the other committee members agreed. We subsequently signed the Articles of Incorporation, becoming the Founders of the Society for Neuroscience. Some critics regarded this new society as superfluous. The first annual meeting had about 1000 participants; recently that number has swelled to around 30,000. I was elected

to the first National Board and also held office in the local (Potomac) chapter. Looking back, my role has been as an independent scientist; I did not find myself drawn to administration or committee work.

The Role of Mathematical Theory in the Neurosciences (November 1968)

In 1968, the Committee for Brain Sciences received a draft statement about the present and future complexion of brain sciences. Because this statement included no mention of mathematics, I felt the need to prepare the following statement (that I just rediscovered among the few files I preserved in my retirement):

> The development and future integration of the brain sciences must be viewed as a very long range project in which mathematics is bound to play a fundamentally important role. The role of mathematics in modern theoretical physics is unquestioned; yet the central nervous system is much more complex than the well-studied systems of physics.
>
> Although mathematical and biophysical theories are already well-established in some areas of basic neuroscience, many problems in the neurosciences are not yet ready for mathematical theory. Also, it seems likely that future theory will depend partly upon mathematical methods developed specifically for the neurosciences; we cannot expect to leap to this future level of sophistication overnight. In any case, there is much that can be done, and is being done now, with the mathematical tools already available.
>
> The present task is to explore and develop theoretical models in areas where they can be tested experimentally, and can provide new insights. The future development of basic theoretical neuroscience depends not only upon new data and new hypotheses; it depends upon careful exploration and evaluation of quantitative theoretical predictions coupled with carefully planned experiments. Sustained interaction between well conceived theory and experiment can be expected to lead to new syntheses of fundamental understanding.

The previous statement is on one page; it was followed by two pages that briefly describe seven examples "of theoretical neurophysiology in which mathematical formulation plays an important role." The best of these was the Hodgkin-Huxley achievement. Here, I do not burden you with the diverse other six, but note that two references were added, as sources for additional detail (Harmon and Lewis, 1966; MacKay, 1968).

Theoretical Reconstruction of Field Potentials in the Olfactory Bulb (1963–1964)

The field potentials recorded in the olfactory bulb of rabbit by Gordon Shepherd in his thesis research with Phillips and Powell, in Oxford, provided an unusual theoretical modeling challenge that required me to go beyond my earlier modeling efforts. Here, the experiment provided simultaneous action potentials in a large population of mitral cells.

These mitral cells happen to be arranged in an almost spherical cortical layer, known as the mitral body layer (MBL). Their apical dendrites extend more or less radially outward into a layer known as the external plexiform layer (EPL), and end in glomeruli where they receive synaptic input from the olfactory nerve; these glomeruli form an almost spherical outer layer, the glomerular layer (GL). Deeper (radially inward from the MBL) lies a volume containing the axons of the mitral cells, and the cell bodies of a very large population of granule cells; this is known as the granular layer (GRL). It should be added that the granule cells have dendrites (not axons) that extend throughout the GRL, and through the MBL into the EPL, where they intermingle with dendrites of the mitral cells.

To a first approximation, this cortical system can be idealized as having complete spherical symmetry, where the layers are spherical shells, and where the dendrites are oriented radially. Such symmetry allows us to reduce a three-dimensional field to one dimension, the radial dimension. Then we introduced the concept of punctured spherical symmetry, for two reasons: (1) the olfactory bulb is indeed punctured by the lateral olfactory tract, which contains the axons of the mitral cells, and (2) the experimental field potentials at the bulb surface were not zero (relative to a distant reference electrode), whereas zero is expected if there were a completely "closed field" (Lorente de Nó, 1947, 1953). Punctured symmetry provides an extracortical path for current to flow from the outer surface (GL) around (in the extrabulbar volume) to and through the puncture, and into the deep edge of the deep layer (GRL) of the cortical system. At some point, this path must be equipotential with the distant reference electrode; this provides the basis for a "potential divider" correction, which proved essential to the success of our simulations (Rall and Shepherd, 1968).

In the experiments of Philips, Powell, and Shepherd (1963), a sharp electric shock was applied to the lateral olfactory tract, such that a synchronous volley of antidromic impulses reached the mitral cell bodies and produced simultaneous action potentials in the mitral cell population. The field potentials generated by this activity were recorded by an extracellular electrode, placed at many depths along the electrode path into the olfactory bulb; these recordings were made relative to a distant reference electrode. Reproducible patterns of responses were recorded at specific depths, which they carefully correlated with the histological layers. Thus, our task was to

try to reconstruct (simulate) the voltage transients that they had recorded at depths corresponding to the layers, GL, EPL, MBL, and GRL, along the radial dimension of our cortical model.

Gordon Shepherd and I devoted a substantial part of 2 years (1963 and 1964) in testing and fine tuning our simulations on the Honeywell 800 computer then at the NIH (still using punch-card inputs). I programmed the computation in Honeywell Algebraic Compiler (HAC), which was essentially the same as IBM-FORTRAN. We used a compartmental model of a mitral cell, where a chain of three small axonal compartments was attached to a large compartment representing the soma; these four compartments were programmed with excitable membrane properties that could generate and propagate an action potential. The soma was also connected to a chain of 5 to 10 dendritic compartments; these were usually assumed to have passive membrane properties, but we also did a series of computations with excitable membrane properties in the dendrites. We did not use the Hodgkin-Huxley equations to model the excitability properties, for two reasons: (1) their original theoretical parameters had been determined for squid membrane, and the correct parameter values for mammalian neurons were unknown, and (2) their set of equations would have added a major computational load to an already complicated computation (on an early computer). Fortunately, I succeeded in devising a pair of nonlinear differential equations that captured the essence of the Hodgkin-Huxley model; it generated a brief excitable conductance transient (corresponding to Na ion permeability), and a slightly delayed quenching conductance transient (corresponding to K ion permeability). This model is described under methods in Rall and Shepherd, 1968; it is an understatement to note that much trial and error was required to find a good set of model parameter values.

With this model, we could simulate the following sequence of events: propagation of an action potential along the three axonal compartments, and the resulting action potential in the soma compartment, together with the passive electrotonic spread of current and of membrane depolarization into the dendritic compartments. This sequence was assumed to occur in all of the mitral cell population. Thus every mitral cell is assumed to provide the same radial distribution of current sources and sinks; these sources and sinks are the generators of extracellular current. For closed spherical symmetry, the extracellular current is constrained to flow along radii in the extracellular space between the dendrites; thus one can compute the extracellular potential (relative to the bulb surface) for all radial locations and at all times. For punctured spherical symmetry, the primary extracellular current is reduced by the amount of secondary extracellular current that flows outside the bulb and through the puncture; the computed values of extracellular potential in the bulb must be adjusted as described in the method section of Rall and Shepherd, 1968.

This computation succeeded in simulating both the large (−, +) diphasic potential recorded at the MBL level, and the smaller, simultaneous (+, −) diphasic potential recorded at the GL (outer surface). Here, as with the motoneuron computations, the (−, +) diphasic recorded near the soma occurs without impulse propagation in the dendrites. We also made computations with excitable dendrites and found that these were successful only if the excitability was set very low. The explanation, with passive dendrites, is essentially the same as given earlier for the motoneuron. We distinguish two time periods. In Period I, the soma membrane is rapidly depolarized (by inward Na ion current); in Period II, extracellular current is reversed because the soma membrane is rapidly repolarized (by outward K ion current), while the passive dendrites remain depolarized. Thus, antidromic activation of the mitral cell body population accounts for Periods I and II of the recorded field potentials. However, in the following time period, designated Period III, the distribution of potential cannot be generated by mitral cell activity; see next.

Period III Must be Generated by the Granule Cell Population (1964)

The recorded field potentials have a significantly different depth distribution during Period III. They exhibit a large positive potential, deep in the GRL, coupled with a negative potential in the EPL. This implies that significant extracellular current must flow from extensive current sources lying deep in the GRL, through the MBL, to current sinks in the EPL. The mitral cell population cannot generate significant current deep in the GRL, because there they have no dendrites, only axons whose large core resistance severely limits the current they produce. (We estimated, from anatomical measurements, that the combined axonal core resistance is at least 25 times the combined dendritic core resistance.) Anatomically, there is no candidate other than the large granule cell population, whose dendrites do extend the full distance, from deep GRL into outer EPL.

For our theoretical model, we lumped the granule cell dendrites into equivalent cylinders that extend radially over this full distance. Then we represented this as a 12-compartment model, where 6 compartments are assumed to be in the EPL, where they are assumed to receive synaptic excitation, while the other 6 compartments are assumed to be in the GRL, where they are assumed to receive no synaptic input.

Computations with this model succeeded in producing good agreement with the experimental field potentials during Period III, provided that an appropriate potential divider correction was included. It is important to note that excitatory input to the deep (GRL) compartments would not have fit the data; this ruled out an earlier idea that granule cells might receive

their input from axon collaterals in the GRL. Because axon collaterals are not present in the EPL, we needed to consider other sources of synaptic input in the EPL.

Dendrodendritic Synapses in the EPL (1964–1966)

Because the EPL consists mainly of large numbers of dendrites belonging to two cell populations, mitral cells and granule cells, we were forced to consider the possibility that the synaptic excitation of many granule cell dendrites during Period III must be provided by synaptic contacts from the secondary dendrites of mitral cells. Although such dendrodendritic synapses were unprecedented, we had two good reasons for entertaining this idea: (1) the mitral secondary dendrites were being depolarized (during Periods I and II) by electrotonic spread from the action potential at the mitral cell bodies and (2) then the granule cell dendrites in the EPL are depolarized by synaptic excitatory input in Period III, and there are no other cells in the EPL that could deliver this synaptic excitation (August 1964 lab notes).

Gordon Shepherd also knew that many mitral cells are inhibited at times corresponding to Period III, and it had been previously assumed that the granule cells might deliver inhibitory synaptic input to the mitral cells (in response to axon collaterals of mitral cells). But here we had depolarization of the granule cell dendrites, just at the time that synaptic inhibitory input was received by the mitral cells; we could not resist considering the possibility of dendrodendritic synaptic inhibition, delivered by dendrites of granule cells to dendrites of mitral cells. We even wondered if a dendrodendritic contact could be specialized to perform both functions: synaptic excitation, from mitral to granule, followed by synaptic inhibition, from granule to mitral (August 1964 lab notes).

The answer was provided by electron microscopy in March 1965. Tom Reese and Milton Brightman, working independently at NIH, had begun research on the olfactory bulb of rat. Gordon Shepherd, who was doing light microscopy measurements on the bulb, had asked them to let us know if they found unusual synaptic contacts in the EPL. Several months later, they did. They found dendrodendritic contacts of two kinds, which were sometimes seen side-by-side in a single tissue slice, but more often neighboring contacts were found in reconstructions from serial sections. What was most remarkable was that they found that the polarity of these contacts (judged by histological criteria) was always what we had needed for our model: the mitral-to-granule contacts were always excitatory, and the granule-to-mitral contacts were always inhibitory.

This was exciting news. Gordon Shepherd and I had entertained a rather heretical conjecture about dendrodendritic synapses (in both directions), based on a theory that combines electrophysiology, gross neural

anatomy, and biophysics, and now we found this conjecture confirmed by subsequent electron microscopy.

Then we learned that a few others had also seen such contacts in the EPL, but they did not know what to make of them. Someone commented that this looked like a short circuit. Our answer to that notion was to point out our functional interpretation: first synaptic excitation, from mitral to granule, then subsequent synaptic inhibition, from granule to mitral. Theory and experiment fitted so well that we agreed to write a joint (four author) paper, which we submitted as a note to *Science* in 1965. It was rejected because the referee found it "not of general interest." William Windle did appreciate our joint manuscript; it appeared in *Experimental Neurology* a year later (Rall, Shepherd, Reese, and Brightman, 1966).

Reese and Brightman presented their electron microscopy results, together with our interpretation of their function, to an anatomy meeting in Miami, in April 1965. At first, some anatomists protested that these were not dendrites, because there had been a dogma that dendrites only receive synaptic inputs; if a process sends, they argued, it cannot be a dendrite. But, with time, such protests subsided. Our case was strong; furthermore, dendrodendritic synapses were also being found in other parts of the nervous system.

In our case, we had demonstrated a new pathway for recurrent inhibition, and for lateral inhibition. Also, this had important implications for neuronal interactions. Previously, neural circuits depended entirely upon axons delivering all-or-none action potentials to their synaptic contacts with the soma or the dendrites of other neurons. Now, with dendrodendritic synapses, we can have graded interactions that are not mediated by axons or by action potentials. The implications for functional interactions, and for neural circuit modeling, are immense.

Here is a note about the neuroscience grapevine. In 1965, I attended the International Physiological Congress in Tokyo. When I visited Osaka, my friends told me that I must visit Professor Hama. When I did so, Hama promptly handed me a large photographic print. As I looked at it, I could see that it was a section in the EPL that was simply loaded with very clear dendrodendritic synapses. There was a large grin on his face. I had not presented the dendrodendritic story at the congress, and our publication did not appear until 1966, but he obviously had heard about our research, presumably from reports about the presentation Reese and Brightman made in Miami, April 1965.

International Symposia (1969)

Two excellent symposia were held in 1969. The Neurosciences: Second Study Program, organized by F.O. Schmitt, was held in Boulder, Colorado.

It included many interesting lectures and discussions, and included our olfactory bulb story in two lectures (Shepherd, 1970; Rall, 1970a). A symposium on Excitatory Synaptic Mechanisms, organized by Andersen and Jansen, was held at Sandefjord, near Oslo, Norway. My paper reviewed the equivalent cylinder concept, the compartmental model, and the EPSP shape theory and experiment (Rall, 1970b). Another paper (Lux et al., 1970) included anatomical measurements that supported the equivalent cylinder concept; this paper also presented a table that summarized careful estimates of membrane resistivity and electrotonic length (L) using both anatomy and electrophysiology. Their results confirmed the relative constancy of electrotonic characteristics despite variation in cell sizes, making reference to Burke, 1969 and Nelson and Lux, 1970. A paper by Jack, Miller, Porter, and Redman (1970) summarized their study of 252 EPSPs in 169 motoneurons, in which they estimated the locations of the synaptic inputs on the dendrites, making comparisons for afferent fibers of different velocity and also for homonymous versus heteronymous fibers.

Equalizing Time Constants and Electrotonic Length, L (1962–1969)

Although the essential results were already contained in the transient solutions presented in Rall, 1962a, my involvement in several different collaborations, during the 1960s, resulted in publication delays. Completing the EPSP shape story (published in 1967), delayed the completion of the Olfactory Bulb Theory (published in 1968), and both of these delayed completion of my demonstration that equalizing time constants could be used to estimate the electrotonic length, L, of an equivalent cylinder (Rall, 1969a).

Transient solutions of the partial differential equation (cable equation), for a finite length of the equivalent cylinder, can be obtained by the method pioneered by Fourier, which is now common in physics and applied mathematics. If the initial condition is a uniform membrane potential over the full length, then this potential decays uniformly, with an exponential decay governed by the passive membrane time constant, tau-m, which is also designated tau-O to distinguish it from several smaller equalizing time constants, tau-N, where N can be 1, 2, 3, etc. When a local current injection, or synaptic input, produces a nonuniform distribution of membrane potential along the cylinder, the nonuniformity decays more rapidly than the final uniform decay. This is due to rapid spread from the more depolarized regions to the less depolarized regions. This equalizing spread is governed by the equalizing time constants, whose values depend upon the electrotonic length, L, of the cylinder. L is a dimensionless length defined by the actual length (e.g., in mm) divided by the length constant, lambda. The mathematical theory provides exact expressions for the equalizing

time constants, such that the ratio of tau-O to any measured tau-N can be used to calculate the value of L (Rall, 1969a).

This method was used successfully by numerous neurophysiologists (e.g., Nelson and Lux, 1970; Lux, Schubert and Kreutzberg, 1970; Burke and ten Bruggencate, 1971). For many motoneurons, L values in the range from 0.6 to 1.5 were reported. Such values were in agreement with my earlier attempts to estimate L from anatomical data, using my estimate of reasonable values for membrane resistivity (Rall, 1959b). (Note that the much larger L values, inferred by Eccles, were due to his membrane resistivity values that were 10 times too small.) Although the anatomical approach is basic, this electrophysiological method proved to be much simpler and became widely used.

This theoretical paper also presented mathematical solutions for the case where a lumped soma is attached to one end of the cylinder, and then for several cylinders attached to a common lumped soma. A different set of solutions was presented for the case of a voltage clamp applied to the neuron soma. These have the advantage of avoiding complications that may result from electric shunting of the soma membrane at the site of micropipette penetration. Numerous numerical examples, throughout this paper, serve to clarify the issues (Rall, 1969a).

A companion paper, appearing in the same issue of the *Biophysical Journal*, provided solutions for the three-dimensional problem of a membrane cylinder placed in a large extracellular volume. It was a response to a physicist friend (John Blair, a Yale classmate, and Manhattan Project alumnus) who had commented that this problem could be solved by means of Bessel functions. Very briefly, this solution contains additional time constants for equalization around the circumference of the cylinder. Such equalization was found to be extremely rapid (in microseconds). The conclusion was that the one-dimensional solutions, with their theoretical time constants (depending on L), are all we need for most electrophysiological purposes (Rall, 1969b).

Theory for Input to a Single Branch of a Dendritic Neuron Model (1969–1974)

Because dendritic branches had been collapsed to an equivalent cylinder in my earlier theoretical studies (Rall 1962, 1964, 1967, 1969), it became important to me to undo this collapse and consider what happens in the individual branches when an input is delivered to a single branch. Then we could address questions about how much the input resistance is increased by this segregation, and how the resulting voltage becomes increased locally and then attenuates from the input site to the soma; voltage attenuation also occurs in the other branches of the input tree, as well as in the other trees of the neuron model. Although John Rinzel and I obtained most of

these results in 1969, we did not finish getting them ready for publication right away. (The delay was partly due to the fact that Rinzel returned to NYU in 1970, to complete his Ph.D. in applied math.) Our steady-state analysis was published first (Rall and Rinzel, 1973) and the transient analysis was published a year later (Rinzel and Rall, 1974).

The key to making the mathematics tractable was to preserve the equivalent cylinder constraints on branching and also to assume symmetry of branching. This idealized model permitted us to obtain analytical solutions, both steady state and transient. Because we had analytical solutions, we did not need compartmental models for this idealized case.

Our idealized neuron model was composed of several equivalent dendritic trees (N in number); the input tree had several orders of symmetric branching (M in number). An explicit example, with $N = 6$ and $M = 2$, is illustrated in Figures 1, 2, and 3 of Rall and Rinzel, 1973. It is explained, with the help of those figures, how we made repeated use of the principle of superposition to (piecewise) construct a solution for input to a single branch. This set of superpositions was conceived intuitively, but then we actually carried it out, first for the steady-state solution and later for the transient solution.

Steady-State Solutions for Input to a Single Branch (1969–1973)

A dramatic aspect of the steady voltage attenuation calculations was found when comparing the input branch with its sister branch (which received no input). Although these two branches have exactly the same length and diameter, the calculated voltage attenuation is extremely different. This provides a warning to anyone who thought that voltage attenuation along a branch would depend only on its length and diameter (given equal membrane properties).

The input branch shows a very steep voltage gradient, because all of the applied current flows through its core resistance and onward. The sister branch (which is terminated by a sealed end) has very little current flowing through its core resistance; no current flows out of the sealed end, and very little current flows across its membrane. This difference is due to the boundary conditions: The input branch current finds ample input conductance at its output end (the branch point), while the sister branch finds zero input conductance at its output end (the sealed terminal). Similar results are seen also for the first-cousin and second-cousin branches. Understanding this result is important because it holds also for dendritic spines; there can be large voltage attenuation in the spine-stem of a spine that receives input and very little voltage attenuation in the spine-stem of a spine that receives no input. The theory provides expressions for the ratio of input resistance at a terminal branch to the input resistance at

the soma, and for steady-state voltage attenuation of voltage from the input site to the soma. These expressions have been used to calculate a table of these values for different sets of the parameters, L, M, and N. The input resistance ratio is always smaller than the attenuation factor. This means that if we compare the steady voltage (e.g., 1 mv) at the soma (produced by injection of a steady current at the soma) with the steady voltage (e.g., 15.5 mv) at a branch terminal (due to injection of equal steady current to that branch terminal), the attenuation factor (e.g., 23.9) means that this branch input alone would produce a steady voltage at the soma of 15.5/23.9, which is about 2/3 of the reference value for direct input to the soma (e.g., for $L = 1$, $M = 3$, $N = 6$). Thus, the distal input does deliver less to the soma than an equal soma input, but 2/3 for the steady state is not negligibly small; many such contributions could sum effectively at the soma. Note that, for brief transients, the attenuation is more severe (Rinzel and Rall, 1974).

For the steady-state results, who could have guessed that, when L is doubled from 1.0 to 2.0, the attenuation factor increases roughly fivefold, while the input resistance ratio is roughly doubled. When the number of trees, N, is increased from 6 to 10, both quantities increase roughly by the factor, 10/6. When the orders of branching, M, are increased from 3 to 7, both quantities are increased nine- or tenfold, which can be attributed mainly to the smaller diameters of the higher order branches.

The terminal branch input resistance values are estimated to lie in the range from 40 to 750 megohms, depending on the size of the motoneuron. Generalization of the theory to include mid-dendritic input sites and unequal branching are solved in the Appendix of Rall and Rinzel, 1973.

An important functional consequence of the large local depolarization produced by synaptic excitation at a distal branch is that nonlinearity of local summation is increased (because the local depolarization reduces the effective synaptic driving potential). Numerical examples are provided. As was already pointed out in Rall et al., 1967, nonlinearity of EPSP summation seen at the soma can be understood as originating between neighboring distal synaptic inputs; it thus provides evidence of synaptic activity at neighboring distal dendritic locations. However, when synaptic inputs are on widely separated branches, their effects do sum linearly at the soma, as noted previously, from compartmental computations (Rall, 1964).

The application of these results to cat spinal motoneurons is discussed in relation to new experimental evidence that the equivalent cylinder constraints are approximately satisfied and that L-values range between 1 and 2, with a mean around 1.5; (Nelson and Lux, 1970; Burke and ten Bruggencate, 1971; Jack et al., 1970, 1971; Lux et al., 1970; Barrett and Crill, 1971).

Transient Solutions for Input to a Single Branch (1969–1974)

By using the same idealized assumptions, and the same system of superpositions of component solutions (as for the steady-state problem), we obtained mathematical expressions for the "response function," which defines the transient membrane potential at every location in the model neuron, in response to injection of an instantaneous point charge at the terminal of a single branch. For our computations, we used two different mathematical expressions: one infinite series converges best for large values of T, while the other converges best for small values of T; (they agree for midvalues of T). The computations, although formidable, were easy for John Rinzel.

In order to compute the response for any specified input function (time course), one must compute the mathematical convolution of this function with the "response function." This we did to provide several numerical examples and illustrative figures. For example, Figure 3 of Rinzel and Rall, 1974 illustrates an input current function that peaks at $T = 0.02$ (applied at a branch terminal of a model neuron with $N = 6$, $M = 3$, $L = 1$); the voltage transient at this branch terminal peaked at $T = 0.04$, while the much attenuated voltage transient at the soma peaked at $T = 0.35$; the attenuation factor for peak voltage was 235, which is nearly 10 times greater than the 23.9 value found for the steady state. Peak values and attenuation factors at several other locations can be found in Table 1 of Rinzel and Rall, 1974. A peak time, $T = 0.12$, in the sister branch implies rapid voltage equalization between the sister and input branches.

Also, although there is severe attenuation of voltage transients from branch input sites to the soma, the fraction of total input charge actually delivered to the soma (plus other trees) is about one half. Details of charge dissipation are presented for all branches and trees. Details are also presented to illustrate the nonlinearities found when synaptic input is treated as a conductance transient; the key is that the effective synaptic driving potential is reduced by local depolarization.

It is important to note that many of the issues discussed in this paper were also discussed by Redman (1973), Iansek and Redman (1973), and Barrett and Crill (1974) showing that several investigators were almost simultaneously tuned to these issues.

Chapter in *Handbook of Physiology* (1974–1977)

It must have been in 1973 or 1974 that Eric Kandel invited me to contribute a chapter, "Core Conductor Theory and Cable Properties of Neurons" for *The Nervous System, Vol. 1, Cellular Biology of Neurons* that he was editing for a new edition of the multivolume *Handbook of Physiology*, edited by

Brookhart and Mountcastle for the American Physiological Society. This volume was published in 1977. Kandel had previously been at NIH; he had attended some of my seminars there, and we had discussed the relation between theory and experiment on several occasions.

I put much effort into writing a comprehensive chapter (58 large pages) that included historical background, careful definitions and derivation of the cable equation, with tables of cable parameters for invertebrate axons, for frog myelinated axons, and for cat spinal motoneurons. It also presented the assumptions and results of several of my modeling efforts of the 1960s and early 1970s: the equivalent cylinder model, compartmental models, the effects of different dendritic input locations, and different spatiotemporal input patterns, as well as the comparison of experimental, unitary EPSP shapes with theoretical EPSP shape loci, with discussion of implications. The computed extracellular $(-, +)$ diphasic was presented and discussed (in relation to passive dendrites), as were the computed extracellular fields for a single multipolar neuron and for populations of mitral cells and granule cells in an idealized olfactory bulb. Dendrodendritic synapses were discussed. Mathematical solutions for transients in cylinders of finite length-L were presented and used to explain the relation between L and the equalizing time constants. Results for voltage clamp at the soma and also the results for input to a single branch of a multibranched neuron were included. Finally, there was an updated discussion of the interrelations between neuron model parameters. This chapter tried to be useful to those who wished to understand the biophysical approach to neurons (Rall, 1977).

Action Potential Shape and Velocity, Changed by Nonuniform Geometry (1973–1974)

Steve Goldstein had a degree in electrical engineering before he did his M.D. at the University of Chicago; he visited our group during a quarter off, and then came as a research fellow for 2 years. We decided to study the propagation of action potentials in axons in the vicinity of axonal branch points, and also for both abrupt and tapering changes in diameter. We used the action potential model that I had invented for the earlier olfactory bulb simulations; one nonlinear differential equation simulates the brief Na ion conductance transient of the Hodgkin-Huxley model; the other simulates the slightly delayed K ion conductance transient of the H-H model. These nonlinearities have the advantage of being polynomial, rather than exponential, which contributes to computational efficiency.

Our first example was to compute the changes in action potential shape and velocity with approach to a sealed end of a long uniform cylinder. Note that the slope, dV/dx, is zero at a sealed end; note also, that a zero

slope occurs at the point of collision of two action potentials traveling in opposite directions, in a long uniform cylinder. We found that the action potential increases its peak height and its velocity as it approaches (within a distance, ½ lambda) the sealed terminal, or point of collision; the half-width is decreased. These computed results can be explained in terms of physical intuition, as follows. The propagation of an action potential involves core current that extends ahead for some distance; this current crosses the extensive membrane ahead at relatively low current density, causing passive membrane depolarization, that finally reaches excitation threshold (which ensures onward propagation). Such leading core current cannot flow beyond the sealed end; it must flow out across the near membrane at high current density; thus, the near membrane reaches threshold sooner, and the peak is higher, than when far from a sealed end.

Similar physical intuition applies when an action potential propagates toward a point of step decrease in cylinder diameter, where the core resistance increases step-wise. The computed results showed the expected increase in peak and velocity as the impulse approaches the step; however, beyond the step, we found reduced action potential velocity in the thinner cylinder, with its larger core resistance (and smaller lambda). It is interesting that (when well beyond the step) this action potential has the same time course as before. Its shape is the same in the time domain, but it is significantly changed when computed in the length domain (its shape is more narrow). These effects were computed for three different diameter ratios (Goldstein and Rall, 1974).

For a step-wise increase in cylinder diameter, computations showed a decrease in velocity with approach to the step. Propagation onward was blocked if the diameter increase was too large (a diameter ratio of 3.5, for these action potential kinetics). Also, propagation onward at increased velocity was found for smaller diameter increase. We computed illustrations of the shape changes in both time and length domains.

Most fascinating was an intermediate case (a diameter ratio of 2.5), which showed delay (instead of block) followed by both forward and reverse propagation. The computed results are clear and were illustrated. The physical intuitive explanation hinges on the delicate fact that the delay was sufficient for the upstream membrane to recover from its refractory period (which always follows immediately after generating an action potential). This meant that when the membrane downstream, beyond the step, fired its delayed action potential, this produced sufficient current to bring the recovering membrane (upstream) to threshold, such that two action potentials were able to propagate, one forward and one backward. This was of great interest to many neurophysiologists. Actually, Shepherd and I had seen something similar in our computed antidromic activation of mitral cells; a delay in impulse invasion of the soma resulted in back propagation. Also Zeevi (personal communication) had an example of

"decremental reverse conduction" in his Ph.D. thesis (Zeevi, 1972), and something similar was reported by Khodorov et al. (1969).

We also did computations for taper, and for branching, and provided discussion of various functional implications. In particular, there is a discussion of filtering and of issues involved in preferential propagation into different branches (Goldstein and Rall, 1974). Steve Goldstein subsequently did a neurology residency at Johns Hopkins and then entered private practice in neurology.

Computed Extracellular Potentials for Open Cortex (1974–1977)

Because Maurice Klee had done his Ph.D. thesis in an electrical engineering department (advised by Plonsey), doing theory and computations of extracellular fields, we found it strategic to revisit the subject of punctured spherical cortical symmetry. Thus we could test the validity of the "potential divider" approximation that was used earlier for the olfactory bulb simulations (Rall and Shepherd, 1968).

We started by defining, computing, and illustrating the problem for a hemispherical cortex. We also solved two other cases: a more nearly completely spherical cortex (radius from 0 to 135 degrees), and a less complete cortex (radius from 0 to 45 degrees). We illustrated these fields as equipotential contours. We also found the "potential divider" ratio that fits each of these three cases and discussed the validity of the approximations made earlier for the olfactory bulb. Although we expected agreement, it was satisfying to have physical intuition confirmed by a rigorous computation. This research was done mostly in 1974, but publication appeared in 1977 (Klee and Rall, 1977). Here I note that theory and computation of extracellular fields generated by neurons were presented by a few others around this time (e.g., Plonsey, 1964, 1969; Pickard, 1971; Rosenfalck, 1969, Ph.D. thesis).

Trauma Caused by Cataracts and Disastrous Surgery (1977–1978)

In retrospect, it is clear that my research momentum took a big hit, when routine cataract surgery (March 1977) resulted in the complete loss of vision in my left eye. The vitreous had became infected; a vitrectomy resulted in retinal detachment; surgery to reattach the retina was only briefly successful; after 2 months of effort, this eye was pronounced phthisic (i.e., shot). My right eye also had a cataract; it was axial and it multiplied images of the moon, when I looked at it. Surgery was needed in 1978; fortunately, Professor A.E. Maumenee, head of the Wilmer Eye Institute

at Johns Hopkins, performed successful surgery. I do treasure my aphakic right eye. Because my cataracts were so early (in my 50s, whereas my father had his in his 70s), I suspect that this may have resulted from exposure of my eyes to soft x-rays, during long-duration experiments performed for the Manhattan Project (Rall, 1946). The overall trauma was more than my wife's anxieties could handle, resulting in the end of our marriage.

I was not ready for marriage again until 1983, when I married Mary Ellen Condon. She is a historian who did her Ph.D. in London. We share interests in music and theatre, in academic writing, and in art and nature. This summer (2005) we are both under pressure to meet writing deadlines before departure on a trip to Australia, to participate in Steve Redman's retirement symposium on Heron Island; also, a side trip to New Zealand gives me a chance to revisit the Otago Peninsula and, also, the Fiordland National Park.

Symposium on Neurons Without Impulses (1979–1981)

Invitation to participate in a symposium, held at the University of York in April 1979, stimulated me to review my research and prepare my contribution. Gordon Shepherd also made an important contribution in his review chapter. Most of the meeting was devoted to invertebrate examples. The resulting book was published in 1981; in the preface, the editors remarked "It was in the vertebrate olfactory bulb that extensive evidence of graded interactions between neuron dendrites was first found in the mammalian brain." My chapter also included some modeling results for a nonspiking interneuron of locust, which had been carefully studied by Burrows and Siegler, at Cambridge, as well as other modeling results, done with Rinzel and Bob Miller, for a photoreceptor studied by Dan Alkon at Woods Hole in a nudibranch mollusc. These were presented as examples of how our neural modeling methods could be applied to different neurons (Rall, 1981).

Comment on Symposia

It happened that some of my major results were first published as chapters of volumes that resulted from symposia. If an invitation to a symposium came just as I was getting a new result, this would often be presented there. This helped keep up the research momentum, but then a full presentation of the results did not get published in a regular scientific journal, especially because the journal did not choose to publish research that had been previously published. This was one reason that my friends took the trouble to include some of these chapters in Segev, Rinzel, and Shepherd, 1995.

I also attended several Gordon Conferences (summer in New England) and also several Winter Conferences on Brain Research (in Colorado),

and Neuroscience Workshops (in Boston). These had two special advantages: (1) they did not require a chapter for a book and (2) they did offer opportunity for investigators from different parts of the country to interact informally.

Dendritic Spines Re Plasticity and Learning (1969–1978)

Although the granule cells of olfactory bulbs have spines (or gemmules) that participate in the dendrodendritic synaptic interactions, we did not do detailed spine computations at that time. It was during a workshop organized by the Scheibels in 1968 that I was urged by Arnie Scheibel and Dom Purpura to apply my theoretical approach to dendritic spines. It was probably in 1969 that John Rinzel and I started to look at this problem, along with input to a single dendritic branch. The biophysics and implications of this research were presented briefly at two major meetings: an International Physiological Congress, and the first annual meeting of the Society for Neuroscience; both abstracts are dated 1971. More detail appeared later in two rather obscure publications: one is a Brain Information Research Report of a symposium organized by Chuck Woody at UCLA (Rall, 1974), and the other is a *festschrift* for Archie McIntyre, edited by Bob Porter and published by Cambridge University Press (Rall, 1978). The 1974 report has been reproduced in Segev, Rinzel, and Shepherd, 1995.

Many spines have long, thin spine stems whose large core resistance can be expected to produce significant voltage attenuation, from the spine head to the point where the spine stem is attached to the neuron (Chang, 1952). Our steady-state analysis (for passive spines) brought our focus upon the ratio of the spine stem resistance to the input resistance at the branch to which it is attached. When this resistance ratio is 0.01 or less, steady voltage at the spine head is delivered to the branch without significant attenuation; then a synapse on the spine head is equal to a synapse directly on the branch. However, when this resistance ratio is 100 or more, the voltage attenuation is so severe that negligible voltage is delivered to the branch; then a synapse on the spine head is ineffective.

Thus, we were able to identify an intermediate range, especially from 0.1 to 10, for this resistance ratio, where the attenuation ranges approximately between 10% and 90%. We labeled this as a possible "operating range" for plasticity and learning. The concept was that if spine stem resistance can be adjusted, this can change the weight of a synapse. If the relative weights of many synapses can be adjusted, this could be part of a means to accomplish plasticity and learning.

It was interesting that, at least in some neurons, long, thin spine stems were more common on distal dendritic branches (with large

input resistance), whereas less long ones were located at more intermediate branches (with smaller input resistance). This suggested that possibly both of these could be in their "operating range." This was encouraging at that time, but I have been told that some other data do not support this particular idea.

In this research report, we also included computations for transient potentials and found that a similar "operating range" holds also for the much larger attentions that occur with transient potentials. Here I note that my colleagues, Holmes and Levy (1990), shifted their theoretical focus from electric resistance to diffusional resistance in the spine stem (effect on calcium ion concentrations; see also Holmes, 1990).

Excitable Dendritic Spines, Synaptic Amplification (1974–1985)

Although we and others had speculated about possible effects of placing excitable membrane properties in a spine head, and Julian Jack had included some astute steady-state considerations in Jack, Noble, and Tsien, 1975, as far as we know, no one had done detailed transient computations with excitable spine heads until around 1983; see discussion by Shepherd on pages 404–406 of the book Segev, Rinzel, and Shepherd, 1995. Computations by Brayton and Shepherd used an IBM modeling program, ASTAP; Don Perkel and his son, David, used their modeling program, MANUEL, whereas John Miller (with Rinzel and me), used an electrical engineering modeling program, SPICE (with some adaptation by Barry Bunow). Related computations were done by Wilson (1984) and by Koch and Poggio (1983). At a neuroscience meeting held in 1984, two presentations were so similar that we agreed to publish our papers together; they appeared in *Brain Research* (Perkel and Perkel, 1985; Miller, Rall, and Rinzel, 1985).

For carefully chosen sets of theoretical parameters, we all found that, with excitable membrane at the spine head, a synaptic excitatory input can result in an action potential at the spine head and that this delivers a significantly amplified depolarization to the spine base. In our published example, the EPSP peak (at the spine base) was 6.5 times that for a passive spine head; together with the increased duration of this EPSP, this meant a 10-fold amplification, in terms of the charge delivered to the spine base (Miller, Rall, and Rinzel, 1985).

We also discussed the dependence on spine stem resistance; if this is too small, the depolarization at the spine head may not reach the threshold for an action potential; if it is too large, the increase of voltage in the spine head is limited (by the synaptic reversal potential), and also, the voltage attenuation by the spine stem is large. Over an intermediate range of

parameter values, the spine stem could be a locus for plasticity (as previously noted for passive spines).

Local Interactions in Clusters of Excitable Spines (1985–1987)

Further insights were gained when Idan Segev and I explored interactions between spines (both passive and active) within the clusters of spines located on distal dendritic branches. One insight had to do with the economics of Na channels in dendrites. Because the spine stem resistance semi-isolates the spine head membrane from the dendritic branch membrane, this changes the efficacy of Na channels on the spine head. The number of channels sufficient to generate an action potential at the spine head is much too small to generate an action potential on the branch because of the large membrane surface that provides a large conductance load. Also, doubling this number of channels on one spine head does not double the result, whereas giving these extra channels to a neighboring spine head does double the result delivered to the branch (assuming that both spines receive equal synaptic input). This means that, if you have a limited number of Na channels (for the dendrites), the optimal design would allocate them entirely to the spine heads, with a threshold number of Na channels in as many spine heads as possible.

Another insight had to do with the input resistance at distal branches. A large input resistance increases the amount of local depolarization of the branch membrane. Because of negligible attenuation of voltage from this local depolarization into neighboring spine heads, it can happen that the local depolarization produced by two or three synaptically excited spine head action potentials can cause a threshold amount of depolarization to spread into neighboring spine heads (which did not receive synaptic input). Those spine heads (which are excitable) will then produce their action potentials (with a slight delay). These additional action potentials provide further amplification of the original synaptic input (Rall and Segev, 1987).

We provided examples in which a threshold depolarization spreads into a distal sister branch, thus firing the excitable spines in this branch and providing significant amplification at the point where these two branches meet. Such action potential spread would occur only (centrifugally) into distal branches; it would not occur (centripetally) toward the soma, because of the asymmetry of attenuation in branched trees noted earlier (Rall and Rinzel, 1973). Synaptic input to passive spine heads in the sister branch can, in some cases, facilitate reaching threshold in the active spine heads; conversely, well-timed synaptic inhibition can prevent this. Such considerations support a concept of possible logical processing in the distal dendrites of a neuron.

Many of these results were presented at a symposium on Synaptic Function, sponsored by the Neurosciences Research Foundation (in 1986); the book appeared in 1987, edited by Edelman, Gall, and Cowan. Our chapter provided detailed illustrations and discussion of the results and insights summarized previously (Rall and Segev, 1987).

Space-Clamp Problems with Voltage Clamp Applied to Neurons (1984–1985)

A 1984 symposium on voltage and patch clamping stimulated me, together with Idan Segev, to explore the mathematics and compute examples of what to expect when a voltage clamp is applied to the soma of a dendritic neuron. Early solutions and time constants had already been included in Rall, 1969. We knew that a clamp at the soma cannot clamp the dendrites, but asked what does it do. We found that for very short dendritic trees ($L < 0.2$), both direct current (DC) steady states and low-frequency alternating current (AC) steady states are nearly space-clamped (within 2% error) but that much larger error occurs for larger L and for higher frequencies. The DC steady-state solution provides the basis for estimating the dendritic synaptic equilibrium potential from the reversal potential observed at the soma. The AC steady-state solution provides expressions for the decrement of amplitude (and increasing phase lag) with distance, at different frequencies. The transient response, at all dendritic locations, for a voltage clamp step at the soma, defines how the distal dendrites charge less rapidly than the proximal dendrites. Theoretical transfer functions permit one to compute the time course of synaptic current (at a specified dendritic location) from the current detected at the soma, by the voltage clamp (Rall and Segev, 1985).

Two Book Chapters to Be Noted (1989, 1991)

In 1989, the first edition of *Methods in Neuronal Modeling*, edited by Koch and Segev, included my 51-page chapter entitled "Cable Theory for Dendritic Neurons," which provided a fairly comprehensive presentation of the equations, results, and insights gained from my dendritic modeling efforts (Rall, 1989). The following chapter (Segev, Fleshman, and Burke, 1989) provided details of compartmental modeling methods. Later, in the second edition of this book, my chapter included some additions and revisions carried out with a coauthor (Rall and Agmon-Snir, 1998).

In 1991, an autobiographical chapter, "Path to Biophysical Insights about Dendrites and Synaptic Function" was published in *The Neurosciences*: Paths of Discovery, II, edited by Samson and Adelman (Rall, 1991). This aimed to give my personal perspective on my research path.

Although that was written 15 years ago, it obviously must have much in common with the present essay. These chapters do include key illustrations.

Equalizing Time Constants and Electrotonic Length in Branched Neurons (1987–1992)

The earlier relation between L and the equalizing time constants was strictly valid only for a single cylinder of finite length. We knew that a multipolar neuron with extensive branching must have many additional time constants. Most of these would have zero coefficients in transients initiated at the soma; however, some of these coefficients will not be zero, especially in transients produced by input delivered to individual branches.

The mathematical details are presented, illustrated, and discussed in Holmes, Segev, and Rall, 1992. Many of these computations made use of a supercomputer located at the Frederick Cancer Research Facility. This computing power was needed, for example, to simulate one motoneuron (with detailed morphology) represented by 732 compartments. A different branched model involved 169 compartments; this model confirmed the insight that many of the time constants, produced by the mathematical solutions, can be interpreted as corresponding to voltage equalization from the tip of a distal branch (of one dendritic tree) to the soma, and all the way out to the tip of a distal branch of a different dendritic tree; each pair of such branches contributes an equalizing time constant, but their coefficients tend to be small in most transients.

In a closely related paper (Holmes and Rall, 1992b) we present a "constrained inverse computation" for compartmental models. To solve for N unknown electrotonic parameters, we must have at least N independent experimental quantities We showed that the solution is nonunique if the data are only electrophysiological; uniqueness requires that morphological data be included. Many examples are presented and discussed.

In another related paper (Holmes and Rall, 1992a) we deal with the effect on electrotonic length estimates of such complications as dendritic taper or somatic shunt. Many examples are presented and discussed. It is concluded that the standard formula for computing L underestimates L when dendrites taper, and overestimates L when a soma shunt is present. Methods to deal with these problems are provided.

Workshop and Resulting Physiological Review (1987–1992)

An intensive workshop, limited to six participants, was held in New York in 1987; it was sponsored by the Neurosciences Research Foundation (Edelman and Gall) at Rockefeller University. The participants were Bob Burke, Bill Holmes, Julian Jack, Steve Redman, Idan Segev, and myself.

All of us were working on related problems, and it seemed a good time to exchange ideas and assess where our research stood at that time. I believe that we all enjoyed this occasion very much. A joint writing effort produced a draft manuscript that was distributed among the authors and some friends (in May 1988), but final revisions were delayed. Later, an invitation to contribute to a special issue of *Physiological Reviews,* commemorating the pioneering research contributions of Hodgkin, Huxley, and Katz, was accepted with the understanding that our draft manuscript was to be updated and completed. We all added illustrations and discussion; part of my effort was shared with Steve Redman during a 3-month visit to Canberra; Bob Burke helped me with the final wrap-up.

This was published in 1992. The title and focus of our review was "Matching Dendritic Neuron Models to Experimental Data." In this review (26 large pages), we provide some history and discuss early simplifying assumptions, together with new evidence for nonlinearities and voltage dependent membrane conductances. We present an example (provided by Burke and his colleagues) of the branching details of a cat alpha-motoneuron, together with a corresponding model consisting of a soma with 777 cylindrical branch elements, and discuss the steady-state solution, plus our best estimates of membrane resistivity, core resistances, lambda values, and how to calculate the input conductance of such neurons and models. A table summarizes parameter estimates and experimental data for six alpha-motoneurons of three different types. We discuss complications and methods for dealing with them. We discuss several robust parameter ratios for different neuron types. We also present and discuss a pyramidal cell model (provided by Jack and his collaborators). We review several of the uncertainties that complicate the estimation of neuron parameters. We touch on the nonuniqueness of solutions, and discuss the "constrained inverse" problem, noted previously and discussed further later.

One point that we all agreed to was the following: It is essential to have a firm grasp of the consequences of neuron morphology on electrotonic properties, using passive membrane assumptions, before adding the next layer of problems posed by nonlinear membranes. Given this foundation, modern computational techniques should make it possible to build realistic, nonlinear neuron models, as experimental research provides us with constraints about the properties and local densities of these channels for different neuron types (Rall et al., 1992).

Nonuniqueness and "Constrained Inverse" Computation (1962–1994)

In the 1960s, Mones Berman and I (together with others in our group) had a number of discussions about the issue of nonuniqueness of solutions obtained by modeling and computation. At our 1987 workshop,

Jack presented particular examples of nonuniquenss that had been explored by one of his students; for example, the ratio between two parameters could be determined but not the separate parameter values. At the same time, other examples of this became apparent as Holmes, Segev, and I explored the "constrained inverse" computation, for models with very large numbers of compartments.

There is first the issue of how well an idealized model corresponds to the biological object of study. By our choice of simplifying assumptions, we reduce the number of unknowns to be determined by fitting the data. The hope is to evolve a model which fits data from a variety of experiments (using the same object or system).

A model that specifies a soma with different membrane properties, and shunted (by leakage around the microelectrode), requires more model parameters (and hence more unknowns) than does a uniform cylinder, or chain of equal compartments. A forward computation uses estimated values for all of these parameters (to compute voltage transients and input resistance). An inverse computation attempts to work backward, from experimental data, to the best set of parameter values (that fit the data); this can be done by trial and error, which can be computed systematically. This we call the "constrained inverse" computation, which Holmes programmed for a supercomputer; see previous references, and a useful description in Holmes and Rall, 1992c.

Solutions for Transients in Arbitrarily Branching Cables (1992–1994)

A remarkable mathematical success was achieved by Julian Jack's group in Oxford. Two papers by Major, Evans, and Jack (1993a, 1993b), together with two more (Major, 1993; Major and Evans, 1994) presented analytical solutions for the general problem of arbitrary branching. John Rinzel and I had solved a simpler problem, which did include branching details but took advantage of symmetric branching, assumed to satisfy the d3/2 constraint for an equivalent cylinder. Here, Major et al. had solved a much more difficult problem and applied this to pyramidal neurons (Major, 1992; Major, Larkman, Jonas, Sakmann, and Jack, 1994). The editors of the Biophysical Journal invited me to provide an appreciative commentary on the two 1993 papers (Rall, 1993).

These transient solutions consist of infinite series of terms having different time constants, as is true also for the arbitrary compartmental model solutions of Holmes, Segev, and Rall (1992). It would be interesting to compare solutions obtained by both methods for equivalent arbitrary branching. One limitation does apply to both of these analytical solutions; they both assume uniform passive membrane. If one needs to include nonlinear membrane properties, one cannot use these analytical solutions,

but one can perform computations with a compartmental model that specifies these complications.

Perspective on Neuron Model Complexity (1995)

Michael Arbib invited me to write a short essay for his *Handbook of Brain Theory and Neural Networks* (1st edition, 1995; 2nd edition, 2002). I chose to discuss model complexity. With improved anatomical methods, and with increased computing power, there is a temptation to create neuron models consisting of hundreds of compartments. Such a model can have far too many degrees of freedom. One can reduce this number by means of simplifying assumptions: specify many compartments to have the same passive membrane properties, reduce the number of compartments, or both.

My preference is to use the fewest compartments that represent the most essential morphological aspects of the neuron and also represent what is known about different membrane properties, or synaptic input distributions, for different areas of the neuron. With fewer degrees of freedom, there is more chance of gaining functional insights.

Nerve-net modelers often represent a neuron as a binary unit; this ignores the richness of biological neurons. I believe it is important to work with neuron models that can receive synaptic inputs on different dendrites, and perhaps on dendritic spines (both passive and excitable), and perhaps also with dendrodendritic synapses. Then, when one has succeeded in modeling an interesting behavior for one neuron, or for a network of such neurons, ask what happens to the simulation when all dendritic compartments are lumped together with the soma. I expect that the interesting behavior will disappear. The more good demonstrations we can provide, the more we establish the need for models that are not too reduced.

This essay provides several examples that can meet that test. The computation of spatiotemporal patterns of synaptic input to dendrites (Rall, 1964) and of dendrodendritic synaptic interactions in olfactory bulb (Rall and Shepherd, 1968) are discussed. A 19-compartment model of rhythmogenesis (Traub et al., 1991) is compared with a 2-compartment model by Pinsky and Rinzel, 1994; this example demonstrates that at least two compartments are required to separate the synapses and membrane properties of soma versus dendrites in order to get the rhythmic behavior.

I prefer intermediate models with few compartments, for two important reasons: (1) it helps sharpen our intuitive understanding about what is essential to obtaining the behavior of interest and (2) it can greatly facilitate computations with networks composed of such neuron models. This essay closed with remarks about having enjoyed the creative activity inherent in pioneering dendritic neuron modeling. This essay remained unchanged in the second edition of Arbib's handbook (Rall, 2002).

Late Comments

In 1994, I felt very touched when the six editors of the *Journal of Computational Neuroscience* dedicated their first issue to me. Also, in 2004, Gordon Shepherd kindly dedicated the fifth edition of his *The Synaptic Organization of the Brain* to me.

In April, 2005, I had the pleasure of participating in a "School of Dendrites," held in Jerusalem by the Israeli Institute for Advanced Studies, organized by Sakmann and Segev. We had 120 graduate students, 80 from Israel, and 40 from Europe and the United States. I enjoyed hearing about much remarkable recent research and was awed by how much this field of research has grown in my lifetime.

Retirement (1994–present)

I retired from NIH in 1994, at age 72. Although there were some loose ends, such as revisions of earlier chapters, I was happy to have more time for my sculptures. There were several pieces that needed some additional work; this was done in time for a show of 14 pieces, displayed for about 75 friends and family (at our home in Maryland, September 1998). We moved from Maryland to Charlottesville, Virginia (in August 2000), in order to supervise the construction of a home at Wintergreen Mountain Village, in the Blue Ridge (completed August 2001). We have a great view (of several mountains, with granite boulders and oak trees in the foreground); we feed lots of birds and squirrels. We occasionally drive to D.C. and Maryland, for the Washington National Opera and for visits with relatives and friends.

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