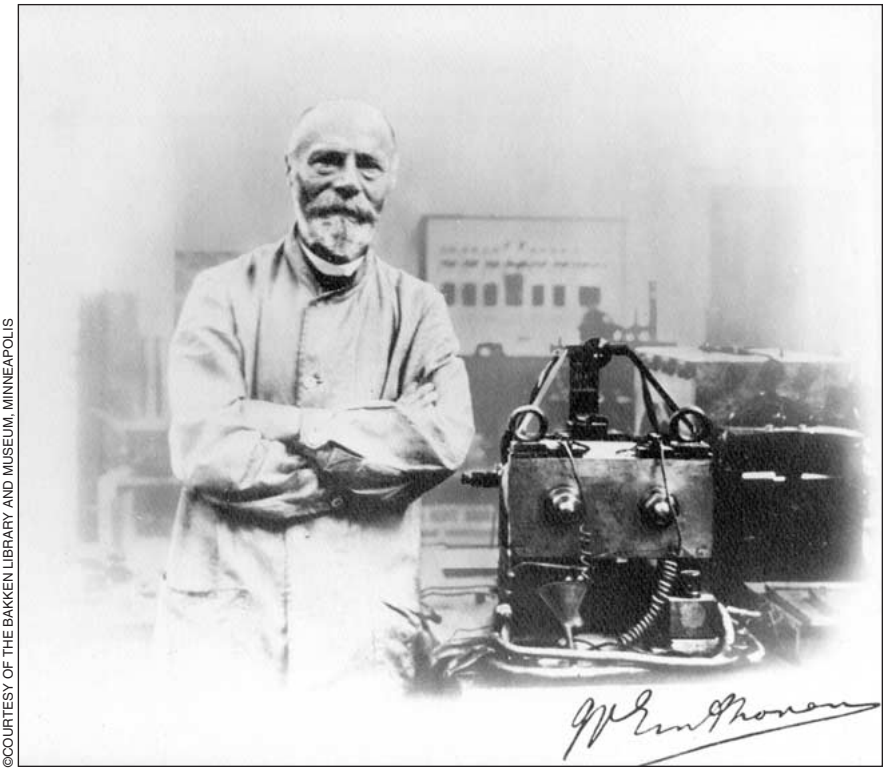
Robert L. Schoenfeld, The Rockefeller University

# From Einthoven's Galvanometer to Single-Channel Recording

## *With Electronics, Neuroscientists Get Inside the Membrane*



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The 20th century was the scene of the growth of electronic technology based on and contributing to the growth of the physical sciences. In 1921, Herbert Gasser was able to make use of a primitive three-stage triode amplifier coupled in 1923 to a rudimentary cathode ray oscilloscope to observe and work out the structure and functions of the individual nerve fibers in the frog's compound sciatic nerve. Gasser was one of the first to use the electron microscope to disclose the structure and function of the olfactory nerves. Detlev Bronk built an electrode within a hypodermic needle and dissected the phrenic nerve to a single axon, proving Adrian's "all or nothing" origin of the spike. Alan Hodgkin and Andrew Huxley used the voltage clamp technique to measure the changes in permeability of the nerve cell membrane to sodium, potassium, and chloride ions during a nerve impulse, leading to the formulation of a mathematical model for the cellular dynamics of the nerve impulse. John Eccles and Bernard Katz used the voltage clamp

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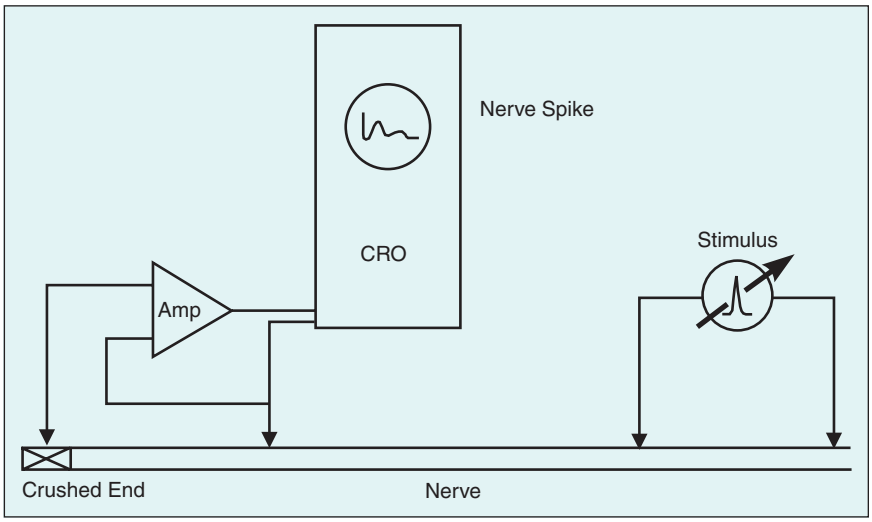
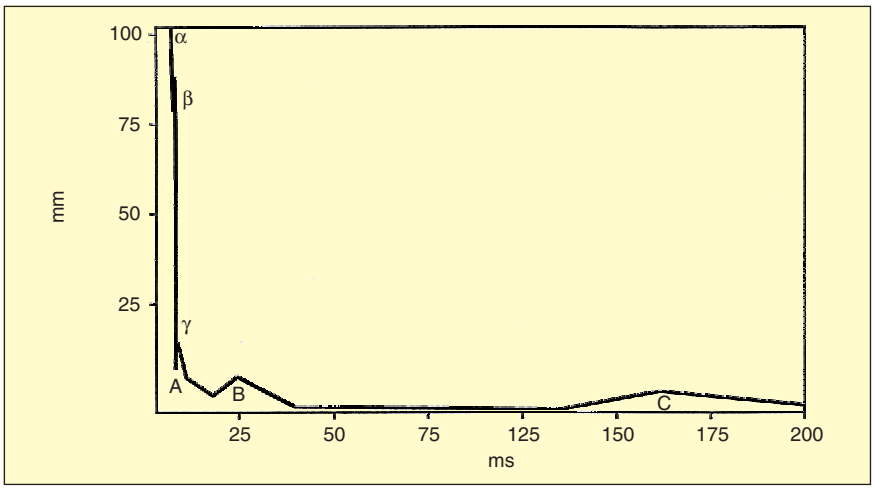



**1. The nerve is crushed at one end. The input lead of the amplifier is connected to the crushed end. The ground lead is upstream toward the stimulating leads. This arrangement allows the negative traveling wave, approaching the amplifier, to be recorded as an upward deflection on the CRT. The horizontal deflection is a saw-tooth waveform, proportional to time logarithmically. (Adapted from Johnson Foundation Lecture Figure 1, page 5, with the permission of the University of Pennsylvania Press, copyright 1937 and 1968 [6].)**




**2. A composite sketch of the main components of the frog sciatic compound potential in linear coordinates—fiber type A, B, C, alpha, beta, gamma, and delta elevations in their correct temporal positions. Abscissa: time in milliseconds. Ordinates: amplitude in millimeters. (Adapted from Johnson Foundation Lecture Figure 6, page 9, with the permission of the University of Pennsylvania Press, copyright 1937 and 1968 [6].)**

with the Ling-Gerard micropipette to study chemical transmission in the neuromuscular junction and central nervous system synapses. Haldan Keffer Hartline used a digital computer as a recorder of impulse timing to determine the dynamic roles of inhibition and excitation in the compound eye of Limulus. Bert Sakmann and Erwin Neher developed the patch clamp technique. Later Neher discovered how to create a gigaseal ($\geq 10^{10}$ to $10^{12}\,\Omega$) at the tip of a micropipette. This article discusses these innovations, which made it possible to do single-channel recording and to study the release of chemical ions from a single channel in the cell membrane.

## Herbert Gasser's Use of Electronics

Gasser, who was the son of an immigrant, became a country doctor and reached the peak of accomplishment as the second Professor of Physiology at Cornell Medical School, second Director of Laboratories at Rockefeller Institute, and the first American neuroscientist with Erlanger to share the Nobel Prize in Medicine or Physiology.

Gasser's lifelong objective was to determine the structure and details of the functioning of the almost 1,000 single nerve fibers that make up many of the compound peripheral nerves of animals and man. Gasser was one of a group of scientists, the axonologists, who believed that the study of the peripheral nerves' structure and function would aid in understanding the role of the brain and central nervous system, similar in cellular structure but much more densely packed and intricately connected. It was not possible in the 1930s to study the brain directly. It remains difficult today.

Gasser was aware that following Michael Faraday's experiments in the early 19th century, a host of different kinds of voltage- and current-detecting devices, galvanometers, and stimulators based on coiled wires moving in a magnetic field had been used in neuroscience research. Helmholtz had used a myographic pendulum to measure nerve-muscle conduction velocity. Bernstein had invented a rheotome, a motor-driven device to deliver a periodic stimulus to a nerve, with a movable brush that could be connected to a galvanometer at various points in the cycle to sum up time-dependent portions of the nerve response. But even Einthoven's delicate string galvanometer was not sensitive enough or fast enough to go much beyond the sensitivity of several millivolts or the 100 Hz bandwidth of the electrocardiogram. It turned out that amplification from a fraction of a millivolt to tens of volts and frequency bandwidths up to 50 kHz or more were required to record the full contribution of individual axon spikes to the compound potential. A schematic diagram of Gasser's experimental set up is shown in Fig. 1 [6]. The compound action potential recorded from the Frog's sciatic nerve, with the apparatus sketched in Fig. 1, is shown in Fig. 2.

Gasser worked at a time in 1921 when triode amplifiers required tender loving care to minimize noise and interference and often had to be returned to their manufacturer for improvement. Cathode-ray tubes were brutally primitive and required film mounted inside their phosphorescent recording surfaces, to sum periodically repeated impulses in a darkened room to make it possible to obtain photographs of waveshapes. It was not until Jan Toennies, a skillful engineer, out of a job in Hitler's Ger-

many, was hired in the mid 1930s that the new equipment that Toennies designed and built began to acquire the stability and linearity close to that of their present-day counterparts Within a few years, Gasser's innovations became the standard tools of the researchers. Alan Hodgkin spent a year during 1937-1938 in Gasser's Laboratory before returning home with a relay rack full of electronic equipment, paid for by a Rockefeller Foundation grant. This gear included Toennies' cathode followers and differential amplifiers. (Toennies was one of the first bioengineers to design and build cathode followers and differential amplifiers, later used during World War II in radar systems.) Hodgkin was able to improve not only his own laboratory at Plymouth but to set up a fully equipped student laboratory at Cambridge University. Harry Grundfest adapted similar equipment, originally developed by Toennies, at Fort Monmouth during World War II for use in clinical neurology and later for his own research and teaching at Columbia University.

As shown in Fig. 3, Gasser and Grundfest had related the frog's sciatic compound nerve action potential to the potentials of the numerous component single-cell axons that comprised the sciatic nerve [6]. They made histological measurements of the numbers and diameters of the component axons. They then related the amplitudes of potential in the composite to the product of numbers and diameters of all single cells in a 0.5-μm range. The delay from the largest and fastest cells as well as the width of the composite contribution was made inversely proportional to the velocity. The velocity was also assumed proportional to number times diameter. As seen from the figure, the calculated curve was a reasonably good fit to the experimentally measured one.

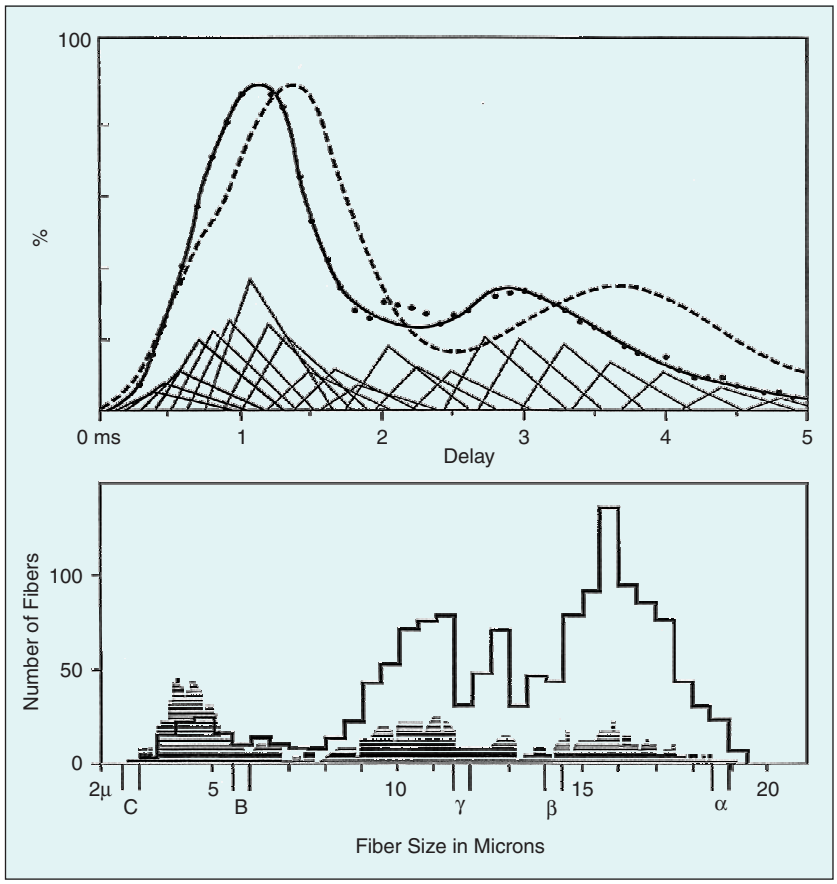
Subsequent experiments determined which fiber groups were sensory, motor, or pain fibers as well as their origins or terminations in the spinal cord.

Shortly before Gasser's retirement, Keith Porter and George Palade, founders of the Laboratory of Cell Biology at Rockefeller, appealed to Gasser as the director of laboratories to purchase one of the newly manufactured electron microscopes. At first, Gasser was reluctant to spend the large sum of money that was required for the purchase. He was persuaded after much discussion. After the microscope was set up, he asked Porter and Palade to teach him how to use it.

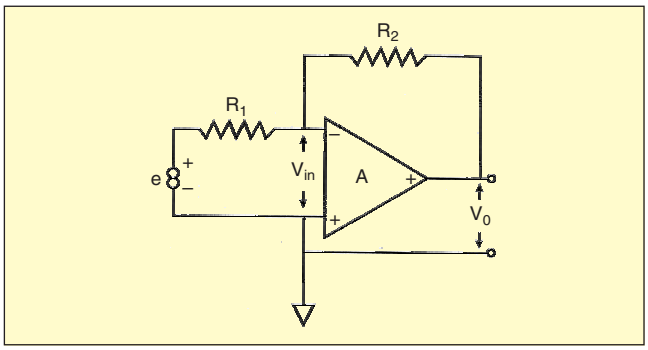
He applied this knowledge to study the histology of the olfactory compound nerve. Both Gasser and his friend Lord Adrian had been perplexed by the action potentials measured from this nerve [1]. With an optical microscope, it appeared that this nerve was a single, large myelinated fiber. However, the potentials measured were too low in amplitude and too slow in conduction velocity to support this conclusion. The electron microscope picture showed that the nerve consisted of many small fibers all surrounded by a large diameter sheath. This picture was consistent with the observed electrical behavior of the olfactory nerve. The new microscopy helped both Adrian and Gasser to improve their understanding of the behavior of axons of the peripheral nerves.

## Detlev Wulf Bronk, Scientist and Supporter of Science

A year after getting his doctorate in physiology, after spending most of his graduate years doing research in physics and engineering, Bronk arranged a fellowship with E.D. Adrian and A.V. Hill in Oxford and London for 1927-1928, where his background in physics and electrical engineering came to the fore. In his memorial address for Bronk, Adrian cites Bronk's invention of the hypodermic electrode for two important reasons [2]. The first was that, because the grounded shell surrounded the active inner electrode, the need for an external shield to eliminate interference was unnecessary. Laboratory work was simplified and made suitable for lecture demonstrations, a forte of Adrian's.




**3. Compound action potential including only alpha, beta and gamma elevations. Lower graph: numbers of fibers, ordinate, against abscissa, a given diameter size in microns with a summation block diagram grouped in increments of 0.5 microns. Upper graph: The broken curve shows a plot of the recorded action potential amplitude, relative to the peak value, at 100%, versus time in milliseconds. The solid curve is a synthesis of assumed waveforms and delays of the grouped date from the lower curves. Thus, the potentials of the largest fibers at the right in the lower graph appear at the origin of the upper curve. Smaller fiber potentials are appropriately delayed and stretched inversely according to their assumed conduction velocity. (Adapted from Johnson Foundation Lecture Figure 11, page 20, with the permission of the University of Pennsylvania Press, copyright 1937 and 1968 [6].)**




**4. Operational amplifier.**
**Analysis:**
**(1) $V_{in} = (V_0 \quad e) * R_1/(R_1 + R_2) + e$. $V_{in} = V_0 * R_1/(R_1 + R_2) - e * R_1/(R_1 + R_2) + e$. $V_0 = \quad A * V_{in}$. Combining terms in e yields:**
**(2) $V_{in} = \quad A * V_{in} * R_1/(R_1 + R_2) + e * R_2/(R_1 + R_2)$. Yields:**
**(3) $V_{in} = e * R_2/(R_1 + R_2) / (1 + A * R_1/(R_1 + R_2))$.**
**(4) $V_0 = \quad A * e * R_2/(R_1 + R_2)/(1 + A * R_1/(R_1 + R_2))$.**
**(5) As A >= 105 to 106.**
**(6) $V_0 \sim= \quad R_2/R_1 * e$. If $R_1 = 0$, $V_0 = \quad A * e$, $I = V_0/R_2$.**
**Equation (1) is based on the assumption that the input impedance to the amplifier is infinite and no current flows into its input. It also assumes that the output of the amplifier is simply a voltage source with zero series resistance. With these assumptions Eq. (1) states that $V_{in}$ is equal to the sum of the voltage e plus the voltage drop produced by the current through $R_1$ and $V_0 = \quad A * V_{in}$. Equation (2) follows by substitution for $V_0$. Solving for $V_{in}$ and then $V_0$ we obtain Eq. (4), and with A large, Eq. (6) follows.**

Secondly, the hypodermic electrode made possible both research and clinical neurological diagnosis with minimal discomfort and no harm to human subjects. This technique is still widely used in the diagnosis of neuromuscular diseases involving the spinal cord and the peripheral nervous system.

Bronk played a key role in collaboration with Adrian in dissecting the phrenic nerve so that only a single fiber remained. By so doing he pioneered the study of the behavior of a single motor nerve cell. This technique was widely followed by Erlanger and Gasser and others.

With A.V. Hill, Bronk was responsible for improving the methodology for measuring heat production and energy loss in muscle. With Stella, he was able to work out the way heart rate and blood pressure were controlled through feedback from receptors in the carotid sinus. This was a biological application of engineering methodology for studying the performance of electronic control systems.

As a supporter of science, Bronk's role as director of the Johnson Foundation, head of the National Research Council, the National Academy of Science, Rockefeller University, and advisor to Presidents is responsible, in large part, for the whole present-day structure of American governmental support of science. Bronk played a leading role in establishing the National Science Foundation [3]. He was also influential in establishing the legal requirement that priority in awarding government scientific research grants be dependent on peer review. As the head of the Johnson Foundation and President of both Johns Hopkins and Rockefeller universities, he supported with institutional funds engineering, instrument-making professionals, and fabricating shops. In addition to biologists, he hired physicists, chemists, and engineers and helped found the science of biophysics and bioengineering.

## Hodgkin and Huxley Probe Inside the Nerve

The first step to understanding membrane conductance was accomplished during the summer of 1939 by Curtis and Cole [4] and Hodgkin and Huxley [10]. Both teams were able to place an electrode within the large squid axon without seriously damaging it. Hodgkin and Huxley obtained the surprising result that during the crest of the nerve impulse the potential across the membrane, measured from inside out, did not swing from –60 millivolts to zero, as previously observed, but went positive by as much as +40 millivolts. World War II intervened before this important finding could be investigated more thoroughly.

During the war both Hodgkin and Huxley were involved with radar and military electronics, as were most of the young American physiologists. They became familiar with the use of operational amplifiers, as shown in Fig. 4. This circuit is a form of feedback amplifier, which was the basic circuit for analog computers that modeled the dynamics and became the electronic control for guided missiles, or more generally could be used to determine the solution of differential equations for particular parameters and initial conditions. After the war, Hodgkin and Huxley were one of the first teams of physiologists to use a variant of these circuits, voltage-clamping amplifiers, in neuro-research, as shown in Fig. 5. Such systems became the main tool for setting the membrane potential to a prearranged value while measuring the forcing current. This arrangement permitted an exact study of the dynamics of membrane conductance, prior to and during a nerve impulse. Hodgkin and Huxley returned to the project of studying the membrane inside and out, after their release from active duty.

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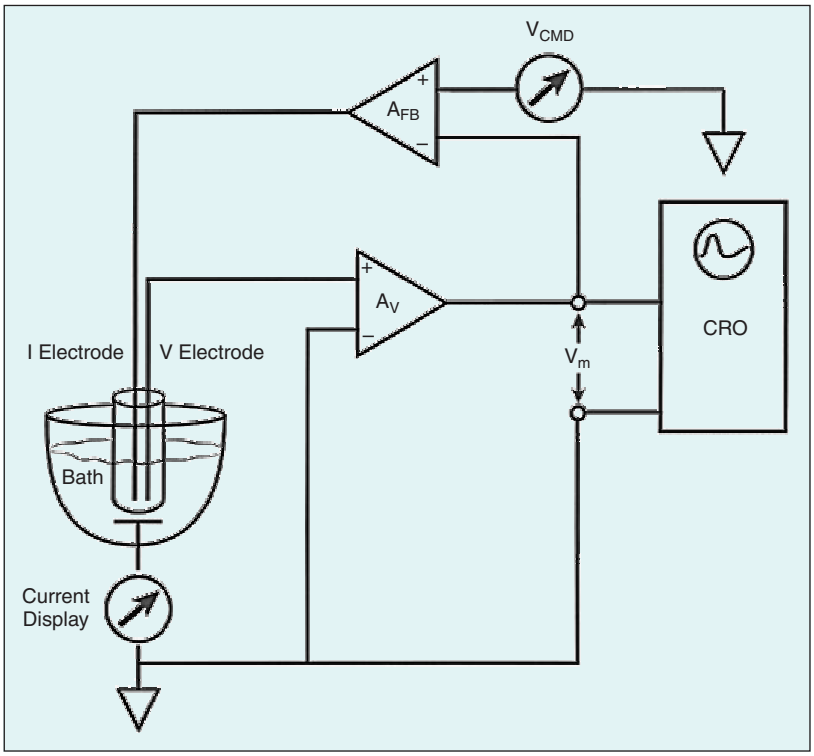
Hodgkin, on a visit to Gerard's laboratory in Chicago in April 1948, was shown how to make the Ling-Gerard micropipette electrode, initially a capillary glass tube filled with a 3 molar KCL solution and a silver-silver-chloride inner electrode, drawn to about a 1 μm tip. With this new device Hodgkin and Huxley were able to study frog nerve membranes as well as that of the giant squid axon.

With these new tools, Hodgkin and Huxley, by changing the ionic composition of the bathing solutions, were able to measure the dynamic and individual ionic values of the sodium, potassium, and chloride permeability and conductance during the action potential [11]. It was Huxley who first hypothesized that the initial inflow of sodium was responsible for the fast rise of the spike. Hodgkin, who had trained himself to apply Maxwell's electrical theory, formulated a trio of first-order linear differential equations to account for the general form of the three different ionic conductance curves with time, for sodium, potassium, and chloride ions. He then expressed the conductance values to

the fourth power in nonlinear current-voltage differential equations that described the dynamics of the current-voltage in time and space along the axon. Hodgkin and Huxley planned to use the one and only Cambridge computer to test their model against the experimental measurements. However, the computer was undergoing a six-month overhaul and Huxley had to spend weeks solving the equations on a hand-operated calculating machine. The Hodgkin-Huxley equations have stood the test of time, with extensions and some modifications, to the present day. Shortly after these researches were completed, Richard Keynes [12] was able to use the Cambridge cyclotron to prepare radioactive isotopes of sodium and potassium. These could be injected into the membrane through a micropipette, and their quantity could be measured with a Geiger Counter. Hodgkin's and Keynes' results verified Hodgkin and Huxley's purely electrical measurements of the changes in the concentration of these ions within the membrane.

One of the consequences of being able to make measurements inside the membrane was to note that in myelinated nerve, the sheath was impervious to sodium and potassium ions so that inward currents occurred only at the nodes of Ranvier. Lorente de No, defending implications from his own previous measurements made many years earlier with electrodes outside the membrane, consistently refused to accept these new results, earning some disrespect from his peers.




**5. Voltage clamp amplifier. The voltage across the membrane, measured at $V_0$, is forced by the command voltage through the feedback amplifier to change from its resting potential to the command ($V_{cmd}$) value. The amplifier, which supplies the current electrode, is a differential amplifier, which amplifies only the difference between the command voltage and the membrane voltage until the latter is forced to become equal to $V_{cmd}$. The current that produces the voltage change across the membrane is measured as shown in the figure. (Adapted from Fig. 8-1B, page 106, with permission of McGraw Hill Companies Inc. (current publisher), from E.R. Kandal, J.H. Schwartz, and T.M. Jessell, *Principles of Neural Science*. 1991, Appleton & Lange, copyright 1991.)**

## Synaptic Chemical Transmission and Quantum Release

John C. Eccles previously had espoused electrical transmission across the synapse. With his return to neural research after World War II, Eccles made an about face and wholeheartedly embraced the new technology, leading to deepening support for chemical transmission across the synapse and earning respect for his change of heart. This work included noteworthy research on the neuromuscular junction and the synapses of the central nervous system of vertebrates. With the use of the electron microscope, micropipette electrodes measuring both voltage and current, and an elaborate vibration resistant stereo-tactic instrument to hold rigidly both the subject and the measuring equipment, it was possible to make extensive intracellular recordings [13].

The result was that Eccles discovered that a nerve impulse arriving at a synapse caused the presynaptic membrane to release large amounts of a chemical substance, specifically acetylcholine, at the neuromuscular junction. Other chemical transmitters played a similar role in the central nervous system synapses. These transmitters rapidly transverse the synaptic cleft and depolarize or hyperpolarize the postsynaptic nerve cell or muscle. Synapses exist in abundance particularly in the central nervous system and can be either excitatory or inhibitory. Eccles examined in detail how excitation and inhibition could be expressed by voltage clamping, or by changes in the biochemical environment, of the postsynaptic membrane.

The electron microscope was used to study tissues, both to show the detailed structure of synapses and to determine the location of the penetration of the microelectrode. In his Nobel lecture [5], Eccles focuses on inhibitory synapses and shows that the transmitter releases inhibitory postsynaptic pulses of amplitude that are frequency dependent on the number and rate of the presynaptic train of impulses, opposite in sign to those produced by excitatory synapses. He investigates the dependence of both excitatory and inhibitory postsynaptic impulses on membrane potential and the effects of the chemical environment on the synaptic cleft.

Fatt and Katz [7] were the first to observe that the amplitudes of excitatory and inhibitory postsynaptic potentials are dependent on the amount of the chemical transmitter released from the presynaptic terminal. They also observed that even in the absence of nerve impulses, there is a random release of the transmitter substance from the vesicles of the presynaptic cell. Katz was able to show that a Poisson process could accurately model the release of transmitters at the neuromuscular junction.

## Inhibition and Excitation in the Horseshoe Crab Eye

Haldan Keffer Hartline (1903-1983) was noted as an inventor, skilled in dissection, well trained in mathematics and physics, and as a creative neuroscientist focused on the study of

vision, for which he shared the Nobel Prize in Physiology or Medicine in 1967 with Ragnar Granit and George Wald. As he pointed out in his Nobel Prize lecture, the compound eye of the horseshoe crab, Limulus, was a fortuitous choice because both the structure of each eye, the ommatidium, the optic nerves, and the nerve network leading to the brain were relatively simple and of large size [9]. With his skilled hands and ingenuity, he was able to focus light beams on one or more ommatidia and place electrodes on the respective optic nerves leading from each of the ommatidia illuminated. To study excitation and inhibition he invented light switches, with opening and closure times of 0.5 ms, optical systems, galvanometer-based recording devices, dividing engines for measuring timing of nerve impulses, and finally mathematical models for the interaction among responses to carefully timed and spaced light flashes.

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His results showed that the Limulus compound eyes and their network of interconnected optic nerves were spatially organized so that when adjacent units were simultaneously illuminated they had an inhibitory effect on the responses of one another. Moreover, if three or more units were spaced along a linear distance, inhibition on adjacent eyes could release inhibition on a more distant unit. There was also self-inhibition and greater effects at the onset of illumination than during the steady state of illumination. The nerve network near the eyes and not at the brain mediated these effects.

The disadvantage in studying both the transient and steady-state responses to patterns of illumination was that with the equipment available from 1930 to 1950, it took many weeks to analyze the results of each experiment. Also, there was no opportunity to change the protocol in the midst of an experiment.

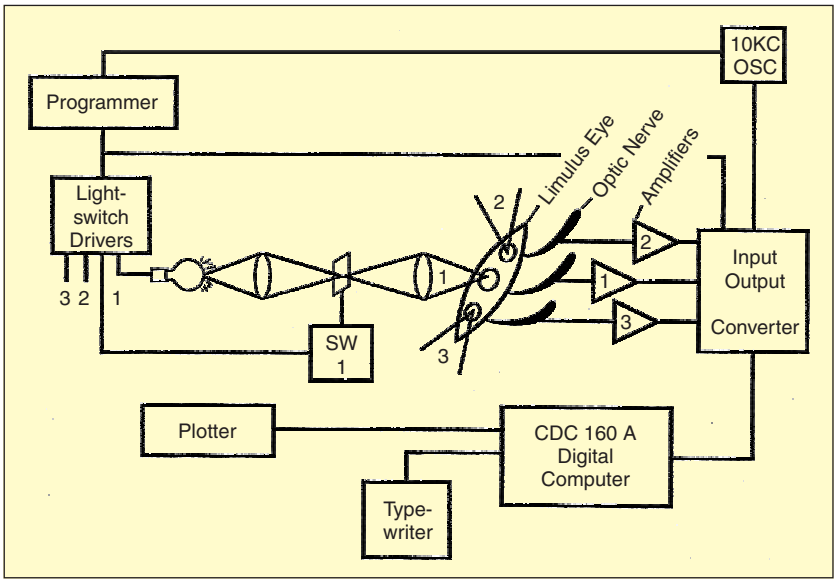
Hartline kept up to date in technology. Amplifiers and cathode-ray oscillographs with moving picture photographic equipment mounted on them replaced galvanometers and smoked-drum kymographs. An electronic device that read out the time in milliseconds between spikes was built and mounted on the oscilloscope. Its numerical output was superimposed on each impulse as it occurred, and both the traces and the timing could be photographed. A digital logic-programming device for controlling the light switches was used to establish the desired sequence of light flashes, which included sequences, designed to equalize accommodation in different ommatidia. Finally in 1962 a small digital computer, as shown in Fig. 6, previously used to navigate the first nuclear submarine, was used to automate the Limulus visual experiments, to plot impulse frequency results "on line," and to make possible the opportunity to try different protocols during an ongoing experiment [17].

It is fair to say that Hartline's Nobel Prize was won on work done long before the computerization of the experiment. However, Hartline's inventiveness and willingness to use more powerful technology led the way for the creative use of computers in the neuroscience laboratory for a whole new generation of researchers.

## Single-Channel Recording

Erwin Neher and Bert Sakmann were the principal architects of the patch clamp. Later Neher discovered that by careful cleaning and a small inward pressure, the micropipette seal could be increased to a gig-ohm (GΩ, $10^{10}$ to $10^{12}$ Ω). These technological improvements made single-channel recording possible, through which the behavior of a macromolecukar ion channel could be studied with the aid of a microelectrode patch clamp [15], [14].

This was a technique that isolated voltage and current measurements made on the channel from those of its surroundings. Early studies of the neuromuscular junction by this technique required a denervated muscle and the removal of the motor nerve terminal. Neher and Sakmann developed procedures that resulted in a single muscle fiber preparation with its end plate freely accessible. Through suction, the micropipette could be subject to a gigaseal, and with special cleaning and preparation of the 0.1 to 1 micron tip, the resistance of the pipette interior to the outside medium could be raised to 1 to 100 GΩ. The resulting Johnson noise of the current through the seal was thus re-




**6. Automated Hartline 3 fiber experiment on the horseshoe crab eye. A light beam is directed through an optical system to one of three facets of the Limulus compound eye. Each light beam is directed through a Hartline light switch controlled by the digital programmer. The nerve fibers associated with each receptor rest on wick electrodes connected to an amplifier. The times of occurrence of spikes from the respective ommatidia are measured by the input-output converter and stored separately in the computer memory. The results can be plotted or listed. (With permission of the N.Y. Academy of Sciences and Rockefeller University Archives [16].)**

duced to $10^{-12}$ amps or less and comparable elementary ion currents could be measured within the membrane with a suitable patch clamp amplifier. The result was that the elementary ion channels postulated by Hodgkin and Huxley, Katz, and Miledi were actually recorded for the first time. Neher and Sakmann were awarded the 1991 Nobel Prize in Physiology or Medicine for these discoveries.

Just as the microelectrode preparation represented a culmination of 20th century electrode development, the patch-clamp amplifier represented the culmination of the Gasser-Toennies invention of specialized biomedical electronics circuits. Since then vacuum tubes have given way to transistors and integrated circuits. Cathode-ray oscilloscopes have given way to data acquisition computers. Cathode followers have been replaced with gated field effect transistors (FETs) arranged in emitter-follower configurations with much higher input impedance. At the present time differential amplifiers are constructed from integrated solid-state amplifiers. The patch-clamp amplifier is a specialized voltage-clamping circuit designed for both voltage clamping and current measurements. Various circuits are used such as special feedback circuits to introduce negative capacitance in the input to reduce capacitance loading. A number of such special circuits are required to reduce noise and optimize performance in measuring pico-ampere currents.

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Neher and Sakmann and their many colleagues have done more than apply electronic technology, they have made unique applications of technology to reach new and far-reaching innovations in both physical and physiological insight in the continuing search for the fundamental cellular basis of neuroscience, so much so that the applications of patch clamping and single-cell recording have opened new vistas in understanding synapses, secretion, and cell development. These diverse new applications include:

- Using capacitance measurements to detect single fusion events of secretory vesicles.
- Whole cell recording from neurons obtained from brain slices in combination with imaging techniques.
- The use of fluorescence photomicrography to verify the locations of dendritic and axonal recording [15].

There is an interesting sociological aspect to the work of Neher and Sakmann. Erwin Neher spent a year working with Charles Stevens, who was one of the early Rockefeller graduates who worked in the laboratories of Frank Brink and Haldan Keffer Hartline. As a student, Charles Stevens used to joke that after acquiring a Yale MD, he had come to Rockefeller to study math and physics. On the other hand, Bert Sakmann spent several proud years in England mentored by Katz, a 1934 German Jewish refuge from Hitler's regime. Sakmann was proud that he was the first German scientist to win the Magnes Award of Hebrew University (1982) and the Harvey Prize of the Technion (1991).

*Robert L. Schoenfeld* received a premed B.A. from New York University in 1942 followed by a B.S. in electrical engineering from Columbia University in 1944. After service in the U.S. Signal Corps during World War II, he received an M.E.E. and D.E.E. from Polytechnic University in 1949 and 1956, respectively. Following a stint in industry, he worked in biomedical engineering at Columbia Neurological Institute and Sloan Kettering Institute. He taught at Polytechnic Institute from 1949 to 1983. From 1957 until his retirement in 1990, when he became emeritus, he was a Rockefeller University faculty member and head of the laboratory of electronics. He is a Life Fellow of the IEEE, an IEEE Centennial medalist, and a fellow of the AIMBE.

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## References

[1] E.D. Adrian, letter to Gasser dated 07/10/54, Rockefeller University Archives 302, Box 1, Folder 1, 1954.

[2] E.D. Adrian, "Detluf Wulf Bronk 13 August 1897-17 November 1975," in *Biographical Memoirs of the Royal Society*. London, U.K.: The Royal Society, 1976, pp. 1-6.

[3] D.W. Bronk, "National Science Foundation: Origins, hopes and aspirations," *Proc. Nat. Acad. Sci.,* vol. 73, no. 8, pp. 2839-2842, 1975.

[4] H.J. Curtis and K.S. Cole, "Membrane action—Potentials from the squid axon," *J. Cell. Comp. Physiol.,* vol. 19, pp. 135-147, 1940.

[5] J.C. Eccles, "The ionic mechanism of postsynaptic inhibition" (Nobel Lecture, 11 Dec. 1963), in *Le Prix Nobel*. Stockholm, Sweden: Imprimerie Royal F.A. Norstedt & Sons, 1963, pp. 261-283.

[6] J. Erlanger and H.S. Gasser, *Electrical Signs of Nervous Activity,* 2nd ed. Philadelphia, PA: Univ. of Pennsylvania Press, 1968.

[7] P. Fatt and B. Katz, "Spontaneous subthreshold activity at motor nerve endings," *J. Physiol.,* vol. 115, pp. 109-128, 1952.

[8] H.S. Gasser and J. Erlanger, "A study of the active currents of nerve cells with the cathode ray oscilloscope," *Amer. J. Physiol.,* vol. 62, pp. 406-524, 1922.

[9] H.K. Hartline, "Visual receptors and retinal interaction" (1967 Nobel Lecture), in *Le Prix Nobel*. Stockholm, Sweden: Imprimerie Royal F.A. Norstedt & Noble, 1968, pp. 242-249.

[10] A.L. Hodgkin and A.F. Huxley, "Action potentials recorded from inside a nerve fiber," *Nature,* vol. 144, pp. 710-711, 1939.

[11] A.L. Hodgkin and A.F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *J. Physiol.,* vol. 117, pp. 500-544, 1952.

[12] A.L. Hodgkin and R.D. Keynes, "Experiments on the injection of substances into the squid giant axon by means of a micro-syringe," *J. Physiol.,* vol. 131, pp. 592-616, 1955.

[13] B. Katz, *Nerve, Muscle, and Synapse*. New York: McGraw-Hill, 1966.

[14] E. Neher, "Ion channels for communication between and within cells" (Nobel Lecture, 9 Dec. 1991), in *Le Prix Nobel*. Stockholm, Sweden: Imprimerie Royal F.A. Norstedt & Noble, 1992, pp. 117-135.

[15] B. Sakmann, "Elementary steps in synaptic transmission revealed by currents through single ion channels" (Nobel Lecture, 9 Dec. 1991), in *Le Prix Nobel*. Stockholm, Sweden: Imprimerie Royal F.A. Norstedt & Noble, 1992, pp. 137-168.

[16] R.L. Schoenfeld, "The role of a digital computer as a biological instrument," *Ann. New York Acad. Sci.,* vol. 125, no. 2, pp. 915-942, 1964.

[17] R.L. Schoenfeld, "How we know what the eye and the mind's eye sees," *IEEE Eng. Med. Biol. Mag.,* vol. 11, pp. 47-71, Sept. 1992.