SQUID AXON MEMBRANE: Impedance Decrease to Voltage Clamp

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Introduction

Galvani started the serious investigations of electrical nerve excitability with his frog leg experiment and, in his controversy with Volta, helped the start of electrochemistry. Both fields progressed with the newest apparatus and best concepts—I've heard that for a while a nerve-muscle preparation was considerably the most sensitive electrical measurer. Among the 20 good experimenters and theorists, Nernst led the way with applications of his thermodynamic concepts of excitability. Following him was Bernstein, who produced a most durable and reasonable theory of nerve structure and function.

My first efforts on nerve followed the St. Louis School—Erlanger, Blair, and Bishop—in which excitability was measured in terms of itself. In this I found that a number of phenomena could be related by the principle of superposition and I published this in the first 1933 Cold Spring Harbor Symposium on Quantitative Biology (Cole 1933) to help replace drop-outs who didn't think our symposium would fly. I was barely ahead of Rashevsky, Monnier, and A. V. Hill with their two-factor, excitation and accommodation, formulations. This era was nicely wrapped up by Katz with his book, “Electric Excitation of Nerve,” in which he was just able to include our squid axon membrane impedance change as I was about to give it at the Physiological Congress in 1938.

I'd heard of L. W. Williams’s 1912 squid monograph in 1927, but it meant nothing until John Zed Young rediscovered the giant axons that he told us about in 1936 at Cold Spring Harbor. This was a most dramatic passing on of the baton, from an anatomist to biophysicists. Young was clearly the pivotal character who turned axon research from the poorly...
specified multifiber terms to the clearly defined physical and electrical axon properties—such as \( \mu F \text{ cm}^{-2} \), phase angle, \( \Omega \text{ cm} \), and cycles sec\(^{-1} \)—that have dominated my career.

**Early Years**

Some fifty years ago, I first heard of the selenium photovoltaic “Photronic Cell” from Weston Instruments. The published data of output current as a function of illumination (Figure 1) showed that the lower external resistances not only gave larger currents, but they became linear in light intensity when extrapolated to a zero external resistance (Romain 1933). The Poggendorff potentiometer was a favorite in those days, measuring potentials without current flow, but how was a current flowing without an external potential difference to be measured? I designed, but didn’t build, a circuit similar to that published by Wood (1936). It was also about the same as the one Ussing & Zehran (1951) used to prove that frog skin was a sodium pumper. In retrospect, this was my first encounter with a voltage clamp, and the power of interchanging currents and potentials made a deep impression on me.

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Figure 1  Photronic cell characteristics. Illumination vs current for external resistances as marked. After (Romain 1933).
During graduate work in physics at Cornell, I picked up some bits of information that were to come in handy. I remember being impressed by the nonlinear work of the engineer, van der Pol, on relaxation oscillators (1926) as well as Barkhausen's negative resistances (1926). I heard later about van der Pol's (1934) oscillation theory, Thévenin's theorem (Guillemin 1935) (which was to reinforce my Photronic experience), and the complex biquadratic equation treating a second reactance. Somewhere
along the line, perhaps from Steimel (1930), I learned about stability conditions—as apparently every physicist does.

My introduction to biology, as I've told so often (Cole 1979), had been in 1923 in Fricke's laboratory where I checked the calibrations of his fabulously complicated Wheatstone bridge for measuring impedances. I managed to avoid a similar arrangement until 1935, when I finally had to spend the year designing and building the beautiful instrument that is still operating at Woods Hole. In it (Cole & Curtis 1937) we balanced the unknown against a similar arrangement on the opposite side and then, for high accuracy, replaced the unknown by a carefully calibrated variable electrolytic cell and capacitors. (An example of its performance is Figure 3.) Then H. J. Curtis joined me and we rushed to get data for a paper at the 1936 Cold Spring Harbor Symposium.

**Squid Axon Impedance**

After Young (1936) sold us on the squid giant axon at the Cold Spring Harbor Symposium, Curtis and I used *Nitella* (1937) during the winter and went to Woods Hole for squid (1938) to do our first external electrode work on single cells. The transverse impedances both gave about 1 \( \mu F \ \text{cm}^{-2} \) membrane capacities, with dielectric loss. However, in 1938, with better equipment, and with *Nitella* again leading the way, we got impedance decreases of usually a few percent during the passage of an impulse (Figure 2) (Cole & Curtis 1939). Alan Hodgkin paid us a surprise visit when we had the squid axon impedance change on the oscilloscope—he literally jumped up and down. Ralph Gerard was the first to reproduce this figure, which became a classic in his "Unresting Cells." Then, with an assist from Sten Knudsen, it appeared 15 years later in the Danish "La Femme" as a wall decoration in a newlywed's apartment, to be "most modern art greatly admired by all." When I showed the slide in Seattle, Walt Woodbury said they were furnishing their house in Danish modern—wouldn't I send him a print? Yes, but only if he'd give me a picture, which he did in 1965. We also replaced the time axis by the impedance change on the scope. This I called an owl, which Bill Adelman painted for my birthday two summers ago.

The impedance decrease did not begin until the inflection in the action potential occurred and, in squid, went to about 30 \( \times \) the resting conductance of 1 mmho cm\(^{-2}\) that Hodgkin and I found later (Cole & Hodgkin 1939). A neat analysis (Figure 3) showed the membrane as an almost fixed 1 \( \mu F \ \text{cm}^{-2} \) capacitor, shunted only by a resistor decreasing with activity. These measurements showed for the first time that this action potential involved only an increased conductance to ions. They further made it evident that there could be no more than a slight
change of membrane structure, either general or localized. This work has been described as "the beginning of a new era of axonology."

Baker and I did the same sort of a high frequency experiment (Cole & Baker 1941a), with a similar result for applied currents—a steady state increased conductance, independent of frequency above 5 kHz. We then knew how many ions got through the membrane and when during an action potential, but I had no idea how the two were related. Baker and I found the inductive reactance, which Hodgkin and I had found at low frequency, to be in the membrane at about 0.1 henry cm\(^{-2}\) (Cole & Baker 1941b) and it was subsequently explained by potassium ion nonlinearity or "delayed rectification." This and a similar anomalous capacity could be explained with a potassium permeable membrane between high and low potassium concentrations. A sudden change from a steady state field would give, first, an ohmic or linear change of current. Then as the ions began to move, the conductance would increase or decrease respectively, as the number of ions in the membrane was increased or decreased (Cole 1968, Figures 2:38 and 2:50).

We then (Cole & Curtis 1941) turned to early oscilloscope records of internal potential changes for currents applied externally and—ignoring the initial oscillations and impulses—we had perfectly smooth \(V,I\) curves. I could convert these into uniform membrane potentials and current densities, by what Hodgkin called Cole's theorem, with a high rectification ratio of about 100 to 1.
So we had confusing membrane properties: high frequency conductance increases, independent of frequency for a passing impulse and for current flow; an inductive reactance; and highly nonlinear V,I steady state curves, showing almost no trace of the impulse threshold. Although I didn’t think that clearly at the time, around 1940, all of the excitation and propagation effects must have been happening between about 5 kHz and direct current.

It had long been known that the foot of an action potential was usually an exponential function of time as the impulse bore down on the recording point. Before the start of the conductance increase, the Kelvin cable equation (Figure 4) could be juggled (Cole 1968, p. 142) to give the conductance current V,I within the impulse (Figure 5). The negative resistance of \(-45 \, \Omega \, \text{cm}^2\) in the rising potential portion had to be considered very seriously as the driving force for the impulse. But what kind of a negative resistance was it? We have usually made a potential difference the independent variable and the current flow dependent so a V,I plot corresponds to the usual x,y plot. Then the usual resistances or conductances go northeast and southwest. But if a device has a northwest and southeast region, such as AB of Figure 6, we consider that region as a negative resistance or conductance segment, which produces energy instead of consuming it. And it is simple to specify the two types of devices shown as N or S according to the Roman capital letter they resemble on Figure 6. Bell Laboratories had shown me their thermistor about 1940—a uranium bead between two platinum wires—which gave a steady state S characteristic as shown on a V,I diagram, along with many other systems. But there were also N characteristics, and
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Figure 4 Kelvin cable schematic, above; equation, below; $C$, membrane capacity; $r_2$, $r_1$ internal, external resistance; $i_m$, membrane current; $i_i$, conduction current (Cole 1968, Figure 2:21).

how could we choose between them when we'd seen only the region AB in an impulse?

Iron Wire

James Bartlett, a theoretical physics graduate student I'd known at Harvard and Leipzig, came in 1940 to Cornell Medical School in New York for his sabbatical. He proposed to work on the Ostwald-Lillie passive iron wire nerve analogue of iron in concentrated nitric acid. In this, a bit of zinc can activate a region that will grow, propagate, and recover. A potential applied to a small region produces a current on the left-hand passive limb of Figure 7a until the dashed line is reached, which the current and potential follow

Figure 5 Membrane potential vs conduction current during impulse, after passive foot. Time in msec in parentheses (Cole 1968, Figure 2:23).
Figure 6  Schematics of negative resistances, potential vs current. Solid line for N characteristics, dashed line for S (Cole 1968, Figure 2:62).

to the right-hand solid, active, region. But recovery can only take place along the lower dashed line, as indicated. I was thoroughly puzzled by these absolutely straight parallel transient lines that he’d found, in old literature, for the hysteresis loop between the passive and active states. Finally, the light dawned: they were the load lines for the external equipment, and the iron-acid surface had an N characteristic. I insisted, and Jim agreed, that the only way to investigate the transition region was with as low resistance external circuitry as possible to give only one solution, B (Figure 7b), instead of three, as for a higher external resistance, A. Although he could use a small uniform surface, his results were far from simple (Bartlett 1945). Since the iron wire was so good an analogue for an axon and had an obvious N characteristic, my wavering was ended and I was committed to the N axon behavior used by van der Pol. With a capacitor, the inductor and three-segment N resistor, I was able to explain oscillations, threshold, and a spike by graphical integrations, as recounted—I’m afraid ad nauseum—in my book, Membranes, Ions, and Impulses (Cole 1968).

War

The battle of Britain was on and as our overseas colleagues fought it, George Marmont and I used longitudinal squid axon impedance measurements to investigate the effects of external K and Ca ions. I spent much of the year of Pearl Harbor on my only sabbatical at Fine Hall, beneath the joint physics and mathematics library at Princeton. I reveled in nonlinearity—mostly what I could glean from Russian and Japanese equations and illustrations, although I could not see how to use any of their techniques for a squid axon.
Marmont and I did war chores for four years but, near the end, I painfully slugged through a few membrane admittance (reciprocal impedance) loci, such as Figure 8 for 2 X K. The low frequency conductance and inductive limb were almost certainly potassium. The excursion into the left half plane was a negative conductance, but it and the higher frequency capacity limb were complete mysteries. I also started work on the first two parts of Minorsky’s *Introduction to Non-linear Mechanics* (1947), which had been leaked to me through an unclassified channel. I put most of my prewar work in order (Cole 1968, p. 218), and I found I could propagate an impulse graphically.

**Post War**

Marmont and I shifted our base to the University of Chicago just in time to return to Woods Hole for squid in 1946. It was a disastrous summer, as we tried to get effects of current flow on longitudinal impedance. Near the end of the summer, Jimmie Savage, a mathematician, showed up. He’d had a Rockefeller Fellowship foisted on him so he could work with me. He asked, why didn’t we just put an electrode in the axoplasm and measure across the membrane to an outside electrode? In spite of my objections that an unruly electrode polarization impedance would swamp any membrane effect, Marmont put Will Rall to work drawing 100 μm glass tubes while Marmont worked on a photographically developed silver chloride electrode.

**Space and Current Control**

After we returned to Chicago, Marmont presented me with a well-thought out experimental plan. He would line up 500 μm diameter holes in plastic discs spaced 3 mm apart and place a concentric spiral electrode in each of the three outside chambers (Figure 9). After pulling the axon through the holes, he would run a 100 μm glass tube, coated at the end for 12 mm with his treated silver electrode, down the center of the axon. The end outside electrodes served as guards to prevent things happening at the ends from...
reaching the center measuring electrode. All potentials were measured between the axial electrode and the center external electrode. The Kelvin cable equation (Figure 4) was a partial differential equation with distance and time as independent variables. But with inside and outside electrodes, $r_2$ and $r_1$ were negligible, spatial variations were eliminated, and the remaining terms were just an ordinary differential equation in time—the axon was "space clamped." Marmont would then control the center chamber current by electronic feedback of the difference between it and a command.

**Figure 8** Membrane ionic admittance locus; $A$, real, vs $B$, imaginary, parts as derived from longitudinal impedance data at $2 \times$ external K (Cole 1968, Figure 1:51).

**Figure 9** Sketch of space clamp for axon, with axial electrode inside, outside measuring electrode between guard electrodes and separated by insulating spacers (Cole 1968, Figure 3:2).
In this control system a signal proportional to the membrane current and the desired, command, current were fed into the inputs of a differential amplifier. The amplifier output was then applied to the axial electrode and the potential recorded. Marmont probably got the idea for this system from H. W. Bode of Bell Labs and used it in his war work. Thus, no matter how the membrane potential changed, the current density would be under control. As far as I know it was the first application of such an electronic control for a biological system. I added that, conversely, it would be possible to control the membrane potential and to measure the current necessary to hold it; Marmont agreed, but without any particular enthusiasm.

At Woods Hole in 1947, after we got the bugs out of the new equipment, we made quite a series of tests, many of them near and above the excitation threshold, and measured directly many numbers that we'd had to calculate or guess at before (Marmont 1949). I was more interested in linear behaviors near rest than in excitation thresholds, and the results for a short, small current step were useful (Figure 10). There were jumps of potential from the resistance in series with the membrane with a nearly linear rise between, as the 1 $\mu$F cm$^{-2}$ membrane capacity was charged. But the jumps were surprisingly large. For external sea water, the calculated axoplasm resistivity averaged about 100 $\Omega$ cm as compared with Hodgkin's and my less direct determination of 1.4 X sea water or about 30 $\Omega$ cm. I had suspected from the large and erratic internal resistivity calculations on other cells that there might be a series resistance directly associated with the membrane capacity. On this basis, the squid membrane had a resistivity of 5 to 3 $\Omega$ cm$^2$ depending on whether the axoplasm resistivity was once or twice that of sea water.

As I saw more of the space-current clamped action potentials after short stimuli, I realized that—with zero externally applied current—the membrane ion conduction current must be supplied by the membrane capacity charge—and similar to Figure 5, which had no propagating factor. I became

Figure 10  Current control: Time vs potential. Showing series resistance, membrane capacity, and conductance (Cole 1968, Figure 3:7).
convinced that the capacity had to be kept from functioning and the only way to do this was to keep a constant potential across it. Then we would have only the conduction current between the inner and outer electrodes. These currents could be measured as a function of time and there should be no threshold of current or potential for excitation if the membrane did indeed have the N characteristic that seemed almost obvious. Then everything fell into place.

**Potential Control**

We had to measure the membrane current through an external short circuit—as for the Photronic cell. But all of this was only bits and pieces of theory, approximations, and assumptions and, as I've said often, theories come at about a dime a dozen. Nonetheless, it could now be tried with a real, live axon. Further, a constant potential across a membrane had never been used before.

Marmont, however, was firmly opposed to wasting time and effort on any such silly and unphysiological work and he tried to divert me into intriguing threshold experiments. But he had a spare terminal block to connect the axon to the electronics and I wired it for potential control (Figure 11). Eventually, he gave me permission to use the equipment for my experiment and finally even agreed to run the electronics—making it completely clear that he would take no responsibility for the design of such an experiment or for whatever the results might be. With this cooperation, I managed to do only about four experiments. But for the only time in my long memory, even the first experiment worked and all agreed in general (Figure 12). I had made excitation stand still in space, if not in time.

1. There were the short initial capacity transients to be expected as the command potential was changed from rest to less negative constant potentials.
2. There was not even a slight indication of threshold response as the potential was changed and probably the N characteristic was quasistable.
3. For moderate depolarizing potentials, there was a transient inward "wrong way" current—which could account for excitation.
4. At high depolarizations, the early inward current did not appear.
5. All of the early currents eventually turned later to the outward current to be expected for potassium—except for the droop from the axial electrode polarization.

I wanted to see such behavior on the V,I plane but I didn’t know where to put the early current. Probably only because it was easy, I took the maxima as an approximation. This, however, brought me face to face with
the resistance in series with the capacity. I knew it reasonably well from current clamp experiments and I put it into the calculation to give Figure 13. The near horizontal dashed line has the slope of the resting membrane conductance and the voltage step aims through the capacity transient to one of the points shown by an X. About as it arrives there, the early inward current begins and the point goes down the series conductance line to a solid point for the inward maximum. Here it turns and goes back up the line for the open circle outward current maximum.

Here was a clear indication of the negative resistance—but I was horrified to see how close the series resistance line came to it and instability. If the series conductance had been only a little less and/or the membrane negative conductance only a little larger, the two lines would have had three intersections and would have been unstable between the two outer ones.

**Figure 11**  Potential control: Current, $I$, through membrane and center, guarded external electrode to give axial electrode potential command, $E$ (Cole 1968, Figure 3:15).

**Figure 12**  Potential control: Time vs membrane current after indicated depolarizations from rest potentials (Cole 1949; Cole 1968, Figure 3:16).
These curves I integrated graphically for a space-clamped response (Figure 14). Up to depolarizations of 18 mV there was a slight current outward from the axon. But between 18 mV and 27.5 mV the inflow became large enough to produce a net inflow and a threshold. This current then increased to its largest value of about 0.8 mA cm$^{-2}$, while charging the capacity at 800 V sec$^{-1}$, which was found at 40–50 mV or about half way up the action potential. The spike height was given by the potential at which the early current vanished—somewhere between 64 mV and 128 mV above the resting potential. It was harder to estimate whether or not such an action would propagate. Then at later times, as the clamp membrane current changed its direction, the action potential went down through its point of inflection and returned to rest potential, ready for another impulse.

I was ecstatic that my assumptions and approximations all along the line had not been so bad as to keep me from proving my major goals experimentally. The conductance increase and the threshold and all-or-none charac-
characteristics of the spike could be explained by the negative slope characteristic and capacity of the membrane as seen in Figures 5 and 14. But I persisted in trying to explain my data on the basis of a single independent variable—such as potassium. Hodgkin had written, near the end of the war when there were no new or major radar problems, that he had convinced himself the action potential overshoot could and must be caused by an increase of sodium permeability. However, I did not appreciate this—I was addicted to calcium, which had such dramatic effects (Cole 1968, Figure 1:49).

**Hodgkin's Visit**

As Hodgkin related in his Physiological Society Centennial address (Hodgkin 1976), I broke the news of what we'd been up to in the Fall of 1947. This he wanted to see and we made arrangements for him to visit Chicago—probably in early April, 1948. In order to take his Rockefeller money out of England for the trip, he had to have a foreign invitation, so I arranged that. But he was disgusted to find that I'd also arranged for him to give the annual Biology Division lecture. He had slides and gave his usual compelling and convincing dissertation to a full house on his postwar work with Katz. This essentially proved that external sodium ions, invoked for the first time since Overton did so in 1902, were the cause of the action potential overshoot beyond the resting potential (Hodgkin & Katz 1949).

I tried telling Hodgkin my story much as I have here, but he seemed more interested in my experiments rather than how I got there. I have no recollection of his commenting on my voltage clamp, my N characteristic or the
stability problems. We did agree that a second internal electrode was obviously needed, and I emphasized my trouble with the series resistance.

I remember him telling me that he and Huxley had talked of a string of micropipettes along an axon for a space clamp. I had the impression that neither he nor Huxley had any idea of potential control until I mentioned it in my letter. But he seemed to accept the concept without question and was already thinking ahead about using it to test his and Huxley's carrier theory (Hodgkin 1976) that they had been working on—especially when frozen out of the lab by lack of heat in 1947. This required a near instantaneous maximum inward current for small and moderate depolarizing voltage clamps. Consequently, he argued, my records, such as Figure 12, would be wrong and their relatively slow rise of inward current must be a fault of the equipment. Although he had no specific objections, he could only say that anything could happen in a negative resistance feedback system such as ours. I had only a weak theory to defend and no analogue to test, but Hodgkin granted that, if my measurements were valid, they "shot down" the carrier theory and we left it at that. Hodgkin and Huxley borrowed all of the various pieces of apparatus to repeat my experiments and, by late 1948, Hodgkin wrote that they had confirmed my results!

Paris Symposium

I moved to the Naval Medical Research Institute in early 1949 and went to the Paris Symposium on "Electrophysiologie des Transmissions et Facteurs Ioniques" in honor of Louis Lapicque in April. I gave only a short introductory paper, telling of my earlier work and Marmont's current clamp development, and closed with my Figure 12 and a short paragraph on my voltage clamp results (Cole 1949). But I was surprised the next day when Hodgkin gave the paper with Huxley and Katz (1949), using both the terms "potential control" and "voltage clamp," confirming most of our results with details of their modification of my circuit, the effects of changing external sodium, and giving the Hodgkin and Huxley carrier model. It seemed obvious to me that he had thought, at Chicago, of my early inward currents as sodium, although I remember no mention of it. I'm still curious as to when he thought of feedback compensation for the resistance in series with the membrane capacity—particularly after I. I. Rabi's glowing report to the Radiation Laboratory of Hodgkin's—a physiologist's—war achievements in the Royal Air Force radar work.

In the summer of 1949, they had given up the carrier model, added external guard electrodes and, going to low temperatures, got most of the data for their 1952 series (Hodgkin 1976).
1952 Series

In the late Spring of 1952, Hodgkin sent me the manuscripts of their five papers to appear in the Journal of Physiology and at about the same time I was invited to attend the upcoming Cold Spring Harbor Symposium. I was profoundly impressed by the magnitude of the difficulties they had overcome and by the breadth and depth of detail of the work. As a whole, the 91 pages (Hodgkin et al 1952, Hodgkin & Huxley, 1952a–d) were a truly magnificent advance in axonology. Hodgkin gave an excellent summary at Cold Spring Harbor (Hodgkin & Huxley 1952e) of the entire work and, as he said in discussion, they had confirmed my 1947 results. Most remarkable of all, however, was that the entire achievement was based on a measurement concept that had been recognized and proven only five years before.

In spite of my uncompensated series resistance and polarizing axial electrode, they had proven that my early inward currents were indeed sodium while the late outward currents were potassium as I’d suspected. There was, however, one startling difference. My time scales were roughly 10 X faster and so the capacity transients appeared much longer. But these they could have explained by their finding (Hodgkin et al 1952) of the high temperature coefficient for the ion conduction processes. At Woods Hole we had no air conditioning, a lot of electronics, and no local cooling, so our axon temperatures were 25°C to 30°C—corresponding to their Q10 of 3!

They might also have pointed out that their first clamp currents (Figures 11 and 12, Hodgkin et al 1952) and their final experimental patterns, shown to test their analytical analyses (Figure 11, Hodgkin & Huxley 1952d), were very similar to those Hodgkin had seen in Chicago in 1948 (Figure 14).

Conclusion

A long, torturous path, leading to a test of the voltage clamp concept in 1947, established it as the valid basis for the Hodgkin and Huxley contribution in 1952. Following their spectacular success, similar approaches have been used in so many and such diverse fields as to justify the statement, “The voltage clamp revolutionized electrophysiology.” It is difficult to fault those who attribute the voltage clamp to Hodgkin and Huxley. I finally realized that I was probably the only one who could reorganize and present the pertinent material—mostly from my book (Cole 1968), and my memory—as I have now done.
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