THE ADVANCE OF ELECTRICAL MODELS FOR CELLS AND AXONS

"Arma virumque cano"

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During the past few centuries physics and chemistry have grown by the development of powerful, exact concepts and definitions and mathematics has progressed to serve increasingly as the universal language of physical science. In contrast, probably one of the outstanding characteristics of biology is the tremendous amount of observation and speculation that has been accumulated over many centuries. But by comparison there has been singularly little of either the experiment or theory that has been quantitative. And of these only small fractions again have been reduced to analytical form and singularly few fundamental constants or laws have been found in them, (Delbrück (1949)).

Thus we have no long history of mathematical models for the many important biological structures and functions. So I count myself particularly fortunate to have had a part in one of the certainly older and more successful of these developments and I am especially honored to be asked to recall some of this advance of electrical models for cells and axons at this first International Biophysics Congress.

The advance does have a recognizable beginning even before Galvani but I will not trace it from him or through the ninteenth century. The history, such as it is, has been covered many times, (q.v. Gildemeister (1928) Cole (1933a) Katz (1939) Taylor (1962)), and although it included much of what was to become important, I do not believe that it produced a satisfactory model.

Clearly a mathematical model may be only an expression of experimental results or only a formulation of concepts. When, as often happens, these fail to agree, it can be interesting. For example the experimental physicist, F. K. Richtmyer, said "When experiment and theory don't agree you must look at the theory because experiments are facts." But then a few weeks later E. H. Kennard argued for the theorist that he is: "You must examine the experiment carefully. It must contain a mistake because you know what is in the theory." Out of respect and affection for these two teachers of mine I cannot do less than start with the first electrical model of a cell for which there was both adequate theory and adequate experiment—both of them produced by the same man.

CELL AND AXON STRUCTURE

The electrical structure of the red cell was published in 1925 by Hugo Fricke. With potential theory and alternating current bridge measurements, Figs. 1 and 2, he confirmed Bernstein's (1902) shrewd hypothesis that the cell was the electrolyte covered by a poorly permeable membrane which Höber (1910, 1912) had done much to establish. But far more importantly he also measured the electrical capacity of the membrane as almost a microfarad per square centimeter with a negligible conductance. With a nominal value of 3 for the dielectric constant, he estimated a thickness of 33 A which was a first indication of the molecular dimensions for a living membrane and still remains one of the best after a third of a century of various other and increasingly powerful efforts.

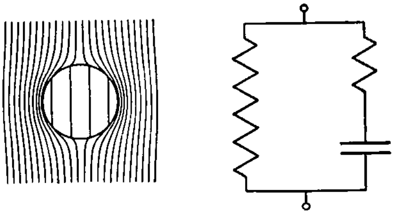


FIGURE 1 *a* (left) Potential theory calculations of the alternating current flow around and through a spherical cell model (Cole & Curtis, 1950). *b* (right) An equivalent circuit for the cell model (Fricke, 1925, Cole, 1928).

It is particularly happy and appropriate to pay a deserved tribute here in Scandanavia to Fricke who was born in Copenhagen and earned his doctorate in physics at Lund. I am also very pleased to remember that I met him and read his manuscripts before they were published and to acknowledge that the beauty of this work was the first and probably the most important factor that led me soon to devote myself to biology.

The roots of this work were certainly widespread and deep but one line of ascent is rather clear. The work of Kohlrausch on electrolytes made it possible to measure the electrical conductance of blood and tissues. Of the many investigations those of Osterhout (1922) on *Laminaria* were certainly the most extensive and penetrating. It was these that led Crile and his associates into similar work on mammalian tissues and it was to further this that Fricke was brought to Cleveland with such a spectacular result.

This achievement is not without its ironies. With potential theory a reasonable approximation to the red cell membrane capacity can be obtained from Höber's measurements. McClendon (1926) deduced both a membrane capacity and conductance from his excellent measurements of packed cells, and had he but had better intuition or the guidance of theory he too would have obtained the correct result. These are of course but examples of Helmholtz's conclusion (1853) that measurements at the surface of a "black box" permitted as many interpretations of internal properties as one made conjectures of the internal structure.

But a more surprising facet of this appeared a little later when I found that I could obtain the impedance of a suspension of spherical cells and the membrane capacity, (Cole, 1928), from a beautifully elementary theory given by Maxwell in his Electricity and Magnetism (1873) and furthermore that this included Fricke's result as a first approximation for a low cell volume concentration. Much the same thing happened to me when I worked out the impedance perpendicular the axes of parallel cylindrical cells, (Bozler and Cole, (1935), Cole and Curtis, (1936)) only to find that Rayleigh (1892) had done it too!

$$Z = r_1 \frac{(1 - \phi)r_1 + (f + \phi)(r_2 + Z_m/a)}{(1 + f\phi)r_1 + f(1 - \phi)(r_2 + Z_m/a)}$$

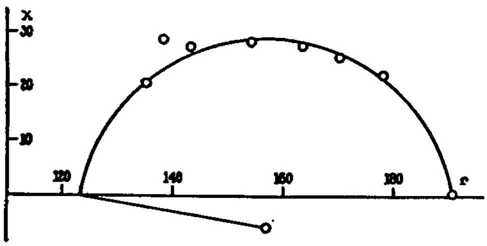


FIGURE 2 *a* (above) General equation for the impedance, Z, of a suspension of cells of radius a. r_1, r_2, Z_m are the medium, and cytoplasm resistivities and the membrane impedance. ϕ is the volume concentration and f a shape factor. 2. *b* (below) Complex impedance, resistance vs. reactance, of red cell suspension (Fricke, 1925, Cole, 1932).

In the decade and a half before World War II, the theory was variously extended and many different cells were measured by Fricke, Curtis, me and others and further extensions have been made since the war, principally by Schwan, as I somewhat summarized at our First Biophysics Conference in USA, (Cole, 1959). These permit the amazing generalization that not only all cells, including muscle and nerve, but also even yeast, bacteria and the intracellular mitochondria have impedance characteristics that can be interpreted by a surface membrane with a capacity of about this same one microfarad per square centimeter and an internal resistivity of about 100 ohm centimeters. Thus this simple electrical cell model has been powerfully quantitatively established.

The model is however not quite perfect. The concept of the capacity of a thin layer of dielectric was long and firmly established. Then Debye (1929) showed how the dielectric constant was far from constant as dipoles were free to rotate. But even this was not adequate for some cell membranes which followed rather the still unexplained pattern of a constant phase angle less than 90°, Fig. 3, similar to that found for most common solid insulators, Cole and Cole, (1941, 1942). It has however become increasingly attractive to compare the behavior of the cell membranes with that of long chain, strongly cross linked, solid polymers.

We still look forward to the time that membrane chemistry, the theory of solids and interfaces and electron microscopy can join with us to advance the model to another stage of yet more intimate detail.

There are also distinct deviations to be found in measurements at both very high and rather low frequencies (Schwan and Cole, 1960). At high megacycle frequencies, where the membrane becomes an open window, we see that the cytoplasm is more than a simple electrolyte just as all microscopists have long insisted. The effects that become increasingly prominent at frequencies below one kilocycle may be of two kinds. One is certainly that of ions crossing the membrane (cf. p. 109) but the analogy for some cells with gelatine and suspensions of nonconducting particles may well have a tangential or surface conductance explanation in common.

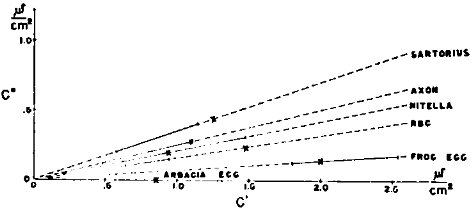
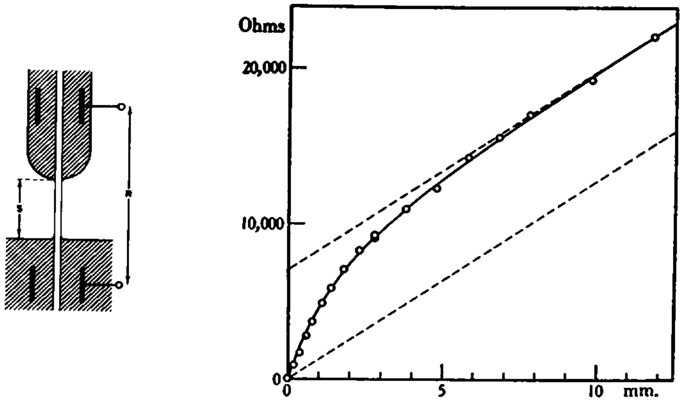


Figure 3 Complex capacity of cell membranes for the frequency ranges measured, solid lines, and the values at 1 kilocycle, crosses (Cole, 1947, 1949b).

These physical problems were reasonably straightforward and at least some of the answers seem satisfactory, but at no place did any of these answers give a certain indication of a conductance across the membrane. The biologists have long expected a movement of ions between the inside and outside of a functioning cell but different, more sensitive approaches were needed to detect it. The first estimate, from Blinks, (1930), was 5,000 ohm cm^2 for the resistance of the *Valonia* membrane and then Hodgkin and I (Cole and Hodgkin, 1939) were able to apply to the squid giant axon the approach developed by Kelvin (1856) for the submarine cable (Fig. 4). Here we obtained the value of 1000 ohm cm^2 that not only seemed to complete the list of passive parameters for this axon but quite surprisingly also was to become another almost standard value for animal membranes as determined in numerous cells and other axons and by several different methods, Hodgkin and Rushton (1946), Tyler *et al.*, (1956).

EXCITATION AND PROPAGATION IN NERVE

The nature of nerve function has had a deservedly wide and almost continual attention since the time of Galvani. But as we have seen, it had to evolve almost without physical help. The concept of excitation emerged very early and, except for the ionic mechanisms proposed by Nernst (1899, 1908) and Hill (1910), developed almost



$$R = \frac{r_1 r_2}{r_1 + r_2}\, s + \frac{2 r_1^2 \lambda}{(r_1 + r_2)(\kappa + \coth s/2\lambda)}$$

FIGURE 4 *a* (left) Measurement of the resistance of a squid axon between upper and lower sea water electrodes. *b* (right) Resistance vs. length measurements to determine the squid axon membrane resistance. *c* (lower) Cable analysis of experiment where λ is the characteristic length depending upon the membrane resistance and κ depends on electrode geometry.

entirely along electrical and descriptive lines. The excitation data became increasingly coherent until I was able to show that several of the phenomena were to be related in a quite impressive way by use of just the time honored principle of superposition, (Cole, 1933b). These efforts culminated in the essentially identical two factor theories of Rashevsky (1933), Monnier (1934), and Hill (1936) in which a rapid excitatory process is coupled with a slower opposing inhibition or accommodation. These two factors are not identified physically but are described by two first order linear differential equations, (Fig. 5, Young (1937)) as has been summarized

$$\frac{dU}{dt} = k_{11} U + k_{12} V + a_1 I$$

$$\frac{dV}{dt} = k_{21} U + k_{22} V + a_2 I,$$

FIGURE 5 Generalized two factor theory of excitation where U and V are excitatory and inhibitory factors and I is the stimulating current.

by Katz (1939). This formulation expresses quite adequately most of the facts of nerve excitation as they have emerged over a century and a half and, on the basis of passive electrical measurements, I was able to extend its application somewhat (Cole, 1941). Furthermore, I think that the future progress of physiology may depend to a large extent upon such phenomenological generalizations as this in which sordid details of mechanism can be ignored without loss of operational utility.

A long series of investigations by many investigators made it increasingly certain that the propagation of a nerve impulse was a propagation of excitation. It was, however, several decades before it was realized that the basic physical mechanism of this propagation might be electrical and that Kelvin (1856) had stated the electrical problem and worked it out in considerable detail for the submarine cable, (Taylor, 1962). Thus a theory of propagation followed almost automatically from any model of electric excitation and Rashevsky (1935) and Weinberg (1940) have given us good examples. Another interesting and useful approach is the comparative one by Hodgkin (1947) which shows the effects of physical factors upon the velocity with a constant membrane characteristic. On the other hand impressive investigations of the initiation and propagation of an impulse were made on the physical assumptions of a threshold loss of membrane electromotive force by Rushton (1937) and of a threshold increase of membrane capacity by Schmitt-(1937).

However, at the time I first heard about nerve the problems seemed rather more formidable. A friendly biologist had suggested that they should be interesting to a physicist because of the cable analogy but the fact that none of the elementary cable parameters was then known for any nerve was not at all encouraging. The first efforts, both unpublished and published (Cole and Curtis, 1936), made only a little progress in either theory or experiment. 'And although I had known the family of L. W. Williams and of his work on the anatomy of the squid (1909), it was not until Young (1936) showed us the half millimeter squid giant axon, Fig. 6, that we and others—most unsuspectingly—entered into a new area.

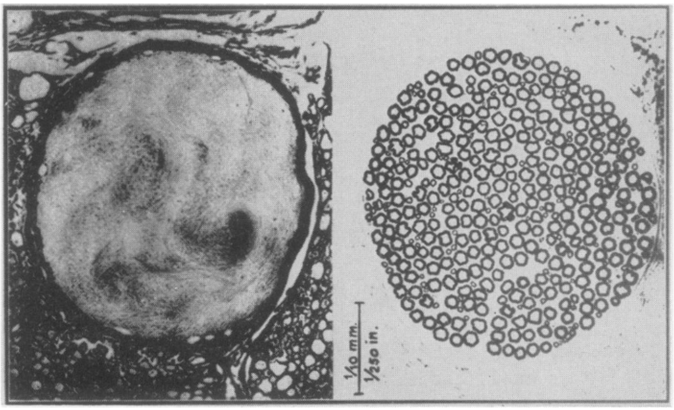


FIGURE 6. Comparison of a squid giant axon, left, and a mammalian nerve, right. (Young, 1951)

THE SQUID ERA

We first got some of the passive cable characteristics of the squid axon, as I have mentioned, and these were the starting point for excitation and propagation. First we used Nitella as a model (Cole and Curtis (1938)) and found a decrease of membrane impedance during the passage of an impulse, Fig. 7*a*. After having worried about the fact that the resting squid axon had shown no certain impedance change until long after it failed to conduct it was rather simple and highly satisfying to show that the data could be explained just by an increase of a conductance in shunt with the membrane capacity, Fig. 7*b*. Once over this hurdle, the squid experiments were something of an anti-climax although they did produce much more photogenic results, Fig. 8, (Cole and Curtis, 1939). In an extreme case the membrane capacity decreased by as much as 15 per cent as its conductance increased forty-fold during the passage of an impulse but much less—if any—change of capacity was more usual as in Fig. 9. This unique allocation, by experiment and analysis, of function to a membrane conductance has turned out to be yet another rather general and durable addition to the models of both cells and axons.

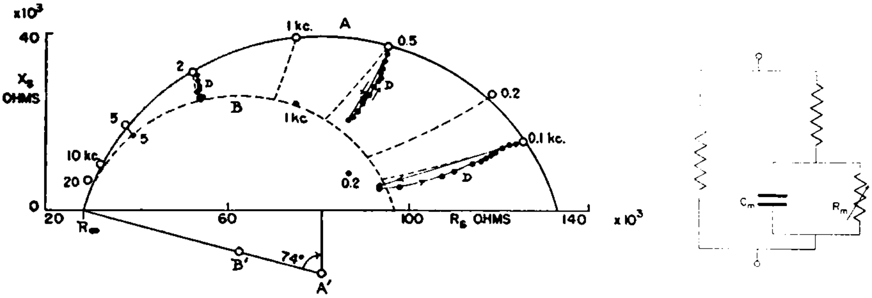


FIGURE 7 *a* (left) Paths of impedance changes in *Nitella* at several frequencies during the passage of an impulse. *b* (right) Equivalent circuit for *Nitella* in which a decrease of the membrane resistance gives the dotted arcs shown in (*a*).

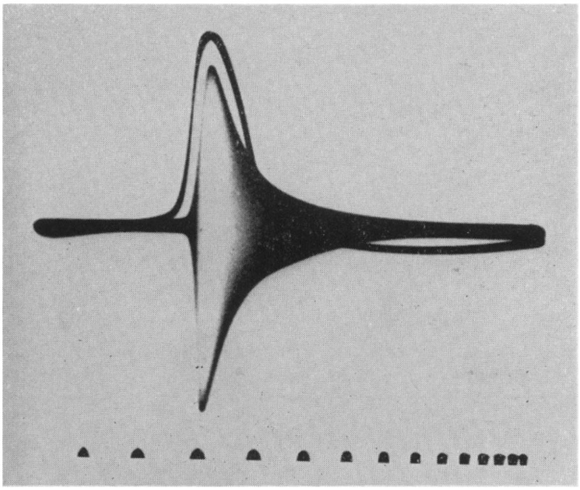


FIGURE 8 Action potential, line, and membrane conductance, band, during passage of an impulse in squid giant axon.

At this stage, Offner, Weinberg, and Young (1940) set up a model for propagation with a membrane conductance increase upon excitation. It is interesting to note that although a decade and a half later the equivalent membrane conductance and e.m.f. and even a capacity were all to change, this development was neither obvious nor easy.

It now seemed important to get some idea of the extent to which this conductance depended upon current flow and we found that we were in the new, vast, and confusing field of non-linearity. Steady state measurements of the high frequency impedance, Fig. 10*a*, (Cole and Baker, (1941a)) and the membrane potential, Fig. 10*b*, (Cole and Curtis, (1941)) gave what later became "chord" and "slope" resistances. As we groped about, the relationship between them and the thoroughly

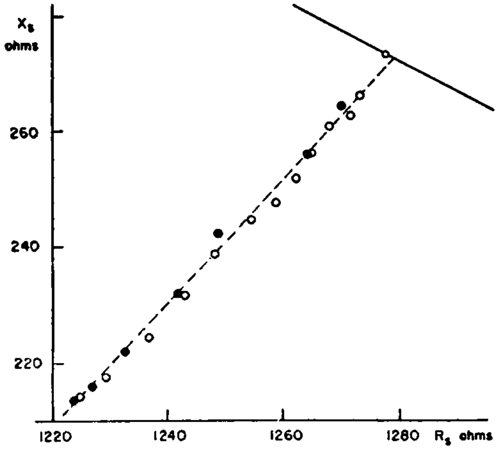


FIGURE 9 Impedance change in squid axon during rising (solid circle) and falling (open circle) phases of squid axon action potential. Dotted arc is theoretical path for increase of membrane conductance without change of capacity.

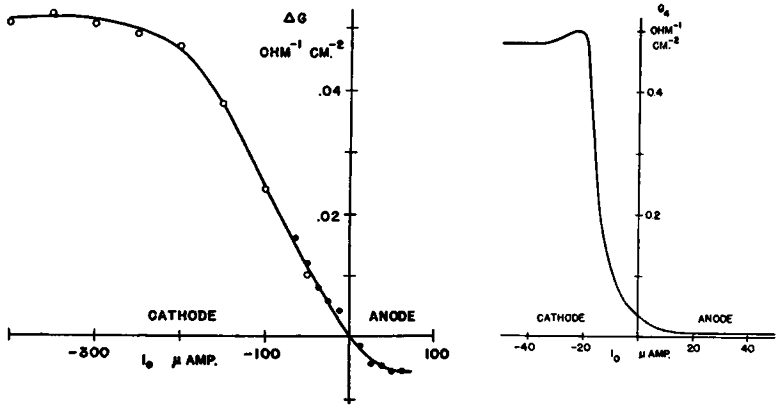


FIGURE 10 *a* (left) High frequency membrane conductance change as a function current applied to squid axon. *b* (right) Direct current membrane conductance as a function of current.

disconcerting inductive reactance, Fig. 11, (Cole and Baker, (1941b)) that Hodgkin and I had first seen, only became apparent as an example, now often called "delayed rectification," of my generalization that reactive phenomena are to be expected in non-linear systems (Cole, (1947, 1949b), Mauro (1961)). At low frequencies and long times, the non-linear process reaches its steady state to give the resistance r_0 as shown in Fig. 12. But at high frequencies and short times this process does not come into operation because of its rate constant, β, and the resistance becomes r_∞. At intermediate frequencies and times the reactive characteristics of the system appear and depend upon the relative values of r_0, r_∞ and β.

Today the situation is far better in that we have much more detailed experimental descriptions of the parameters. It is however, rather worse, practically, because there are now three such processes. But it remains fundamentally unchanged with no particularly probable mechanism having made its appearance between then and now.

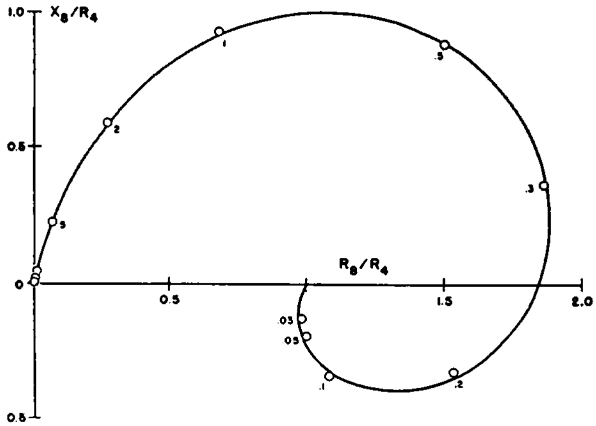
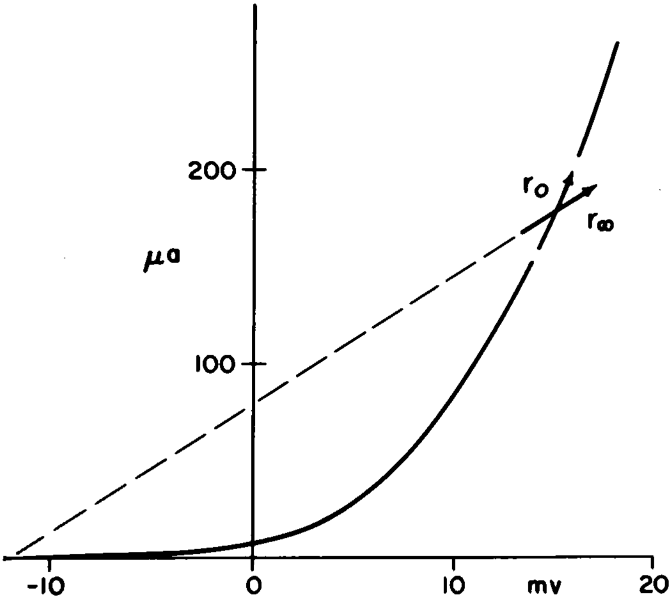


FIGURE 11 Relative impedance of squid axon membrane showing inductive reactance at low frequencies.

SODIUM THEORY

But the squid axon model also made amazing progress along other lines of experiment and interpretation. At about the same time and probably for the same reason —just to see what was there—Hodgkin and Huxley (1939, 1945) at Plymouth and we (Curtis and Cole, 1940, 1942) at Woods Hole had introduced long potential electrodes into the axoplasm from one end of the axon. We all agreed in finding that the potential during an impulse did not—as Bernstein had led us to expect—just go from its resting value to about zero but actually reversed by some tens of millivolts before turning back for recovery, Fig. 13. After the war Hodgkin and Katz (1949) did the crucial experiments and gave the explanation, Fig. 14,—too



$$\frac{de}{dt} = r_\infty \frac{di}{dt} - \beta(e - r_0 i).$$

FIGURE 12 *a* (upper) A non-linear steady state characteristic with resistance r_0 at low frequency and resistance r_∞ for high frequency at which the non-linear process is not effective. *b* (lower) A formal description of the current-potential relations for a non-linear process of rate constant β.

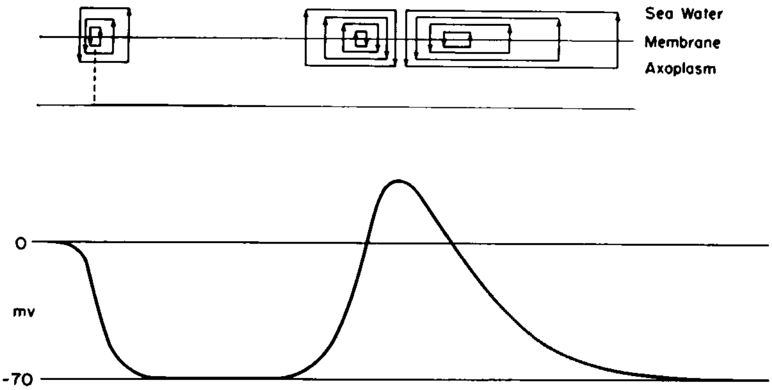


FIGURE 13 Current flow (above) and potential of the interior (below) along an axon with propagating impulse in which the peak of the action potential "overshoots" the resting potential (Curtis & Cole, 1950).

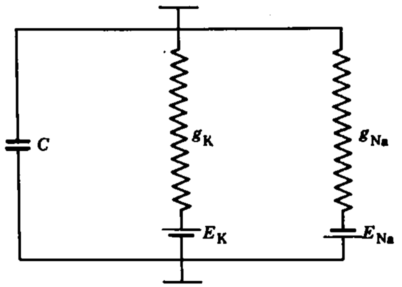


FIGURE 14 Membrane model in which sodium and potassium conductances, g_{Na} and g_K, depend upon potential and time.

good to be untrue—that the membrane became permeable, upon excitation, to sodium ions and, as this waned, an increase of potassium permeability returned the potential to the resting value. Both the "overshoot" and its explanation have long since come to be expected for excitable membranes but I well remember having told Curtis that I didn't think our original experiment would be worth the effort—that we'd only see an action potential upside down!

In this same period, Marmont (1949) proposed to eliminate propagation and reduce the Kelvin partial differential equation, Fig. 15*a*, to an ordinary differential equation in time by a long internal current carrying electrode and an external guarded electrode, Fig. 15*b*. Our potential measurements, mostly unpublished, with

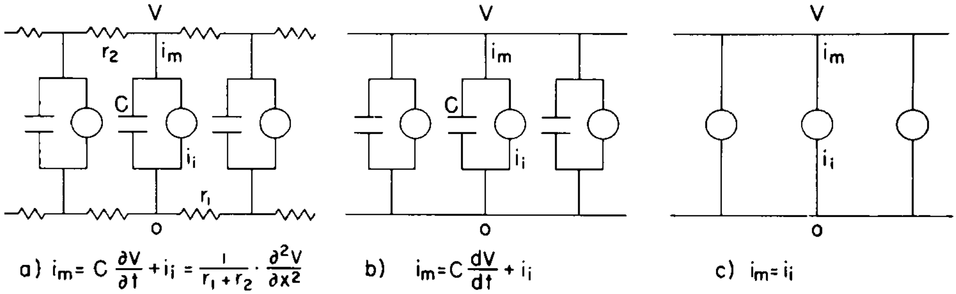


FIGURE 15 *a* General cable model of axon. *b* Cable model of axon with long internal and external electrodes. *c* Cable model of axon for a constant difference of potential across the membrane.

a controlled membrane current gave new, direct, measurements of the membrane capacity and resting resistance along with threshold characteristics that were otherwise almost unobtainable, but the axon was still excitable and many data were disappointingly comparable to those available in a propagating impulse, Cole (1955). They did, however, emphasize that in the absence of external current flow, the membrane capacity must be discharging into a negative conductance.

So it seemed that by an abrupt, but controlled, increase of the membrane potential the capacity current would be eliminated after an initial transient and that the negative conductance might be stable, Figs. 15*c* and 17*a*. My preliminary results in 1947, Fig. 16, (Cole, 1949a) showed this to be true in that the membrane current was entirely continuous both in time and potential. But only after both propagation and excitation had been denied the axon as it put up the battle of a worthy, dedicated, adversary. The vaguely expected initial "reverse" or inward current was qualitatively adequate to explain the threshold and amplitude of the action potential as was the later steady outward current to explain recovery.

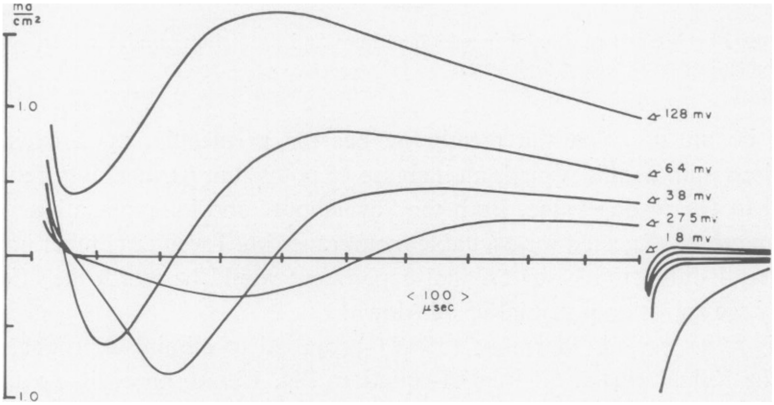


Figure 16 Ionic currents after changes of the membrane potential.

On the basis of these results, Hodgkin, Huxley and Katz (1952) adopted the potential control concept—christening it the "voltage clamp"—improved the technique, Fig. 17*b*, and confirmed the earlier work. Hodgkin and Huxley (1952a, b, c) then separated the ionic currents into a sodium and a potassium component, Figs. 14 and 18. After a step depolarization the sodium conductance increased rapidly and then decreased as the potassium conductance rose to a steady state value. Then in the final paper of this monumental series (Hodgkin and Huxley, (1952d)) they put these results into analytical form, Fig. 19, and showed that this description was an adequate explanation for most of the classical electrophysiology as it had developed over the century and a half of its active growth. Subsequent calculations (Cole, Antosiewicz and Rabinowitz (1955, 1958), FitzHugh and Antosiewicz (1959), Huxley (1959), FitzHugh (1960)) have very considerably extended the range of application of these empirical equations without uncovering any serious or fundamental defects.

This concept of membrane potential control was, both intellectually and technically, a novel approach to membrane phenomena. In its novelty it was fundamen-

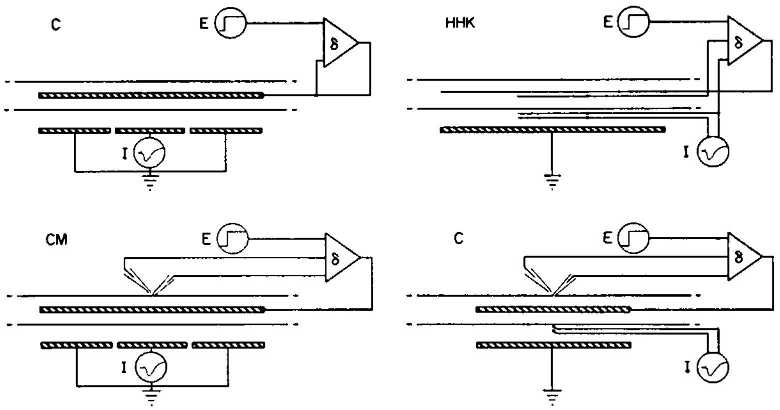


FIGURE 17 Potential control techniques (Cole, 1961b). *a* (upper left) Common potential and current electrodes. *b* (upper right) Separate, extended potential and current electrodes. *c* (lower left) "Point control" with reversible internal and external potential electrodes. *d* (lower right) Localized current density measurement with differential current electrodes.

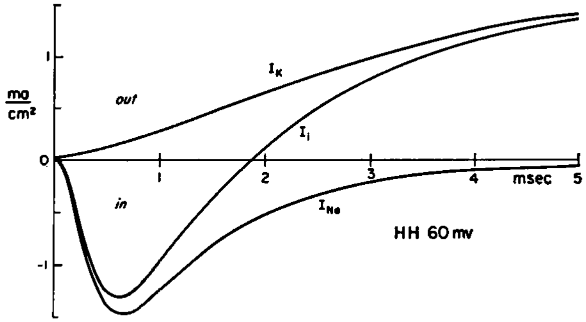


FIGURE 18 Resolution of an ionic current, I_i, after a change of membrane potential into the inward sodium, I_{Na}, and outward potassium, I_K, components.

tally no different from many other bright ideas. In that it has been a means to support and expand the revolutionary sodium theory, it is of course highly suspect. When it can so reduce and consolidate areas of confusion and ignorance it presents a stimulating challenge with which a qualitative mysticism cannot effectively compete. But the undoubted fact that it was also a good idea is perhaps but an example of a motto of mine that "One can't be unlucky all the time."

PRESENT STATUS

Moore and I then resumed the development for the squid axon with reversible potential electrodes close to the inside and outside of the membrane and with considerable modifications of the electronic measurement and control system, Fig. 17*c*,

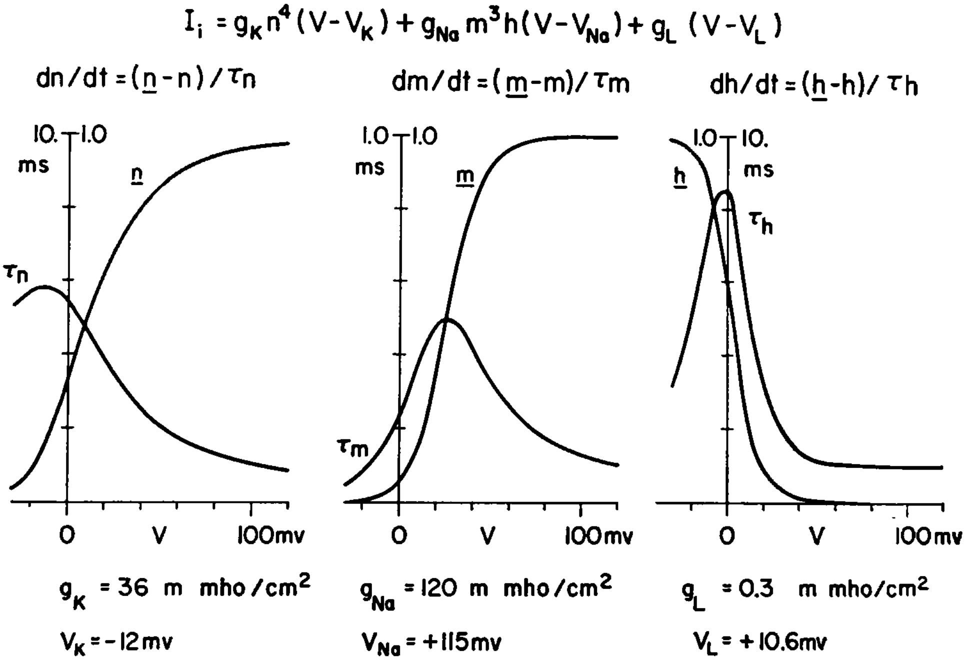


FIGURE 19 The Hodgkin-Huxley squid axon model. The ionic current is given by the top equation in terms of the parameters n, m, h describing the "potassium on," "sodium on" and "sodium off" processes. The time dependence of these parameters are above the graphical representation of their steady state values and time constants as functions of membrane depolarization, V. The values of the constants are given at the bottom.

(Cole and Moore (1960), Moore and Cole (1962)). Dodge and Frankenhaeuser (1958, 1959) applied the potential control concept without the use of internal electrodes to characterize a single node of medullated axons, rather similarly Julian and Goldman (1960) applied it to the somewhat giant lobster axon while Hagiwara *et al.*, (1959a, b, c) have applied it directly with internal current and potential electrodes to central cell bodies. In each of these cases the membrane current densities were generally of much the same form as appeared in the earlier squid work but often larger, Fig. 20, (Cole and Moore (1960)).

The occasional anomalous current patterns, somewhat similar to those encountered by Frankenhaeuser and Hodgkin (1957), Tasaki and Spyropoulos (1958) and others, were attributed to an inadequate control of the potential over the current measuring area of the membrane and did not appear with adequate control in the negative conductance region, Fig. 20*b*, (Taylor, Moore and Cole (1960), Dodge and Frankenhaeuser (1958), Julian, Moore and Goldman (1961)). Such control can be more difficult for powerful axons than it was in the first experiments. The current measuring area may have to be restricted for the squid, Fig. 17*d*, (Cole

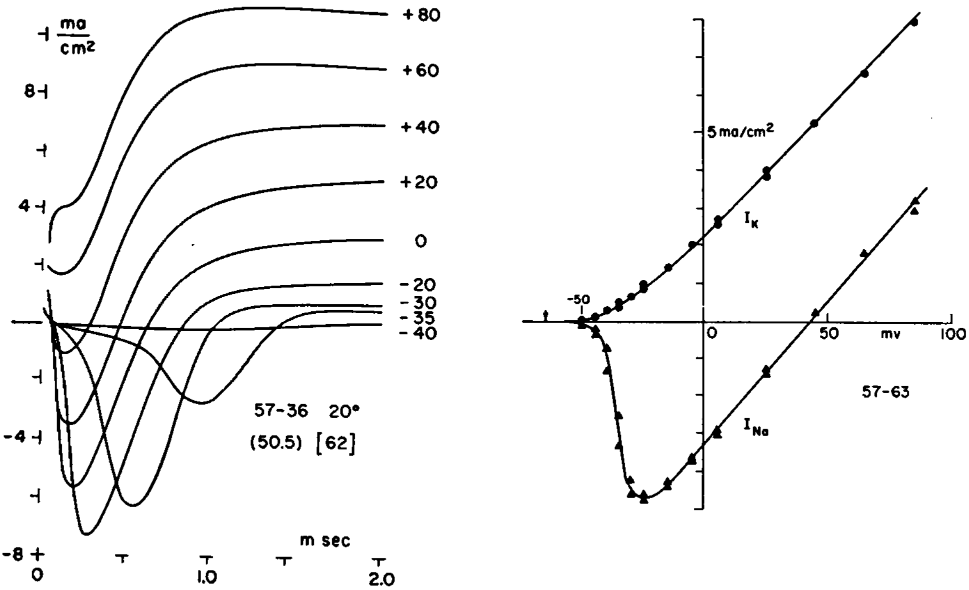


FIGURE 20 *a* (left) Ionic membrane currents after increases of the squid axon membrane potential from —62 mv. *b* (right) Outward steady state potassium current and early peak sodium current in a squid axon membrane.

(1961a)) and lobster while amplification and shielding are found important for the nodes.

Thus for at least these forms something rather like the Hodgkin-Huxley equations, Fig. 19, can be expected to be an adequate electrical model. Although other nervous elements may also conform to this pattern, there are certainly indications that heart and other muscle membranes may be found to have considerably different characteristics when they too are successfully "clamped."

THE FUTURE

It is indeed a tremendous progress for the electrical model of cells and axons to have advanced so far in only a third of a century. But we must admit that, again at the present time, the experimental model is far ahead of the theoretical. True the Hodgkin-Huxley separation of the clamp current into the sodium and potassium components, Fig. 18, is of outstanding significance, their successful calculation of the tracer ion exchange across the membrane during the passage of an impulse is independent evidence of the validity of the analysis that is hard to deny, and the preliminary isotopic evidence (Mullins, Adelman, and Sjodin (1961)) that the early transient clamp current is indeed sodium and the later steady current, potassium, is at least in the direction of a final proof even for those who wish not to believe it.

For me three characteristics of the ion conductances are most impressive challenges for the advance to come.

The first is that both the amplitudes and time rates of change of the conductances can be uniquely expressed in terms of the potential difference across the membrane. This seems certainly to be a worthy and necessary goal for theory.

The second is that the steady state conductances practically vanish as the inside of membrane is made 80–100 millivolts negative. This has been a most obvious and important property of the sodium conductance as seen in the peak sodium current, Fig. 20*b*, but I didn't really believe the Hodgkin-Huxley statement of the same characteristic for potassium until the direct demonstration of it for squid, Fig. 21, (Moore (1959)), a node (Frankenhaeuser (1960)) and a cell body (Hagiwara *et al.* (1961)). Consequently I fully expect that the key theoretical model will be one built to explain this characteristic—so similar to that of the new tunnel diode!

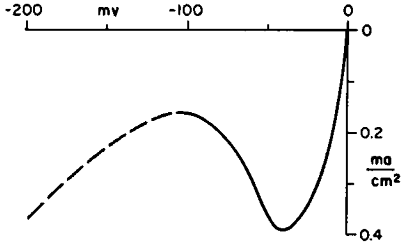


FIGURE 21 Approximately steady state voltage clamp characteristic for squid axon in iso-osmotic potassium chloride.

A third characteristic is that the conductances seem to depend so little upon the external or internal potassium and sodium concentrations while external calcium affects the cut-off potentials without appreciable changes in the maximum values (Frankenhaeuser and Hodgkin (1957)). These observations should again be highly significant landmarks for theory.

It now appears certain that the next important advance will have to be made at the molecular level—molecular biophysics, if you please. There are many possibilities to be considered—no one of which can yet be given a marked preference or eliminated.

The classical liquid junction with its several improvements does not now seem possible without some additional factor—for which electro-osmosis and hydraulic flow have been proposed (Teorell (1959)). It is not certain whether every membrane molecular interface is a possible ion path, or if larger pores may be fixed in position, or perhaps areas approaching microscopic dimensions have uniform and active properties. Beyond this there is the possibility that ions may block each other in a narrow pore, that they may ride "piggy-back" on carriers through a lipid layer, that a denatured protein or an adsorbed calcium may block them, that a strong electric field distorts pores or adsorption sites, or that an enzyme activates a "stepping stone."

The future belongs to theory but clearly it must develop an approach with a power comparable to that of the "voltage clamp" if we are to have a membrane model that is highly satisfactory as to both theory and experiment. But I hope and believe that this will come in considerably less than another third of a century!

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REFERENCES

Bernstein, J., 1902, Arch. ges. Physiol., **92,** 521.
Blinks, L. R., 1930, J. Gen. Physiol., **13,** 361.
Bozler, E., and Cole, K. S., 1935, J. Cell. and Comp. Physiol., **6,** 229.
Cole, K. S., 1928, J. Gen. Physiol., **12,** 29.
Cole, K. S., 1932, J. Gen. Physiol., **15,** 641.
Cole, K. S., 1933a, Cold Spring Harbor Symposia on Quantitative Biology, **1,** 107.
Cole, K. S., 1933b, Cold Spring Harbor Symposia on Quantitative Biology, **1,** 131.
Cole, K. S., 1941, J. Gen. Physiol., **25,** 29
Cole, K. S., 1947, Four Lectures on Biophysics, Institute of Biophysics, Univ. of Brazil.
Cole, K. S., 1949a, Arch. d. Sci. Physiol., **3,** 253.
Cole, K. S., 1949b, Proc. Nat. Acad. Sci., **35,** 558.
Cole, K. S., 1955, in Electrochemistry in Biology and Medicine (T. Shedlovsky, editor), John Wiley & Sons, New York, 121.
Cole, K. S., 1959, in Proc. First Nat'l Biophysics Conf., (H. Quastler and H. J. Morowitz, editors) Yale Univ. Press, New Haven, Conn., 332.
Cole, K. S., 1961a, Biophys. J., **1,** 401.
Cole, K. S., 1961b, Actualites Neurophysiologiques, **3,** xxx.
Cole, K. S., Antosiewicz, H. A., and Rabinowitz, P., 1955, J. Soc. Indust. Appl. Math., **3,** 153.
Cole, K. S., Antosiewicz, H. A., and Rabinowitz, P., 1958, J. Soc. Indust. Appl. Math., **6,** 196.
Cole, K. S., and Baker, R. F., 1941a, J. Gen. Physiol., **24,** 535.
Cole, K. S., and Baker, R. F., 1941b, J. Gen. Physiol., **24,** 771.
Cole, K. S., and Cole, R. H., 1941, J. Chem. Physics, **9,** 341.
Cole, K. S., and Cole, R. H., 1942, J. Chem. Physics, **10,** 98.
Cole, K. S., and Curtis, H. J., 1936, Cold Spring Harbor Symposia on Quantitative Biology, **4,** 73.
Cole, K. S., and Curtis, H. J., 1938, J. Gen. Physiol., **22,** 37.
Cole, K. S., and Curtis, H. J., 1939, J. Gen. Physiol., **22,** 649.
Cole, K. S., and Curtis, H. J., 1941, J. Gen. Physiol., **24,** 551.
Cole, K. S., and Curtis, H. J., 1950, in Medical Physics, (O. Glasser, editor) Year Book Publishers, Inc., Chicago, **2,** 82.
Cole, K. S., and Hodgkin, A. L., 1939, J. Gen. Physiol., **22,** 671.
Cole, K. S., and Moore, J. W., 1960, J. Gen. Physiol., **44,** 123.
Curtis, H. J., and Cole, K. S., 1940, J. Cell. Comp. Physiol., **15,** 147.
Curtis, H. J., and Cole, K. S., 1942, J. Cell. Comp. Physiol., **19,** 135.
Curtis, H. J., and Cole, K. S., 1950, in Medical Physics, (O. Glasser, editor) Year Book Publishers, Inc., Chicago, **2,** 584.
Debye, P., 1929, Polar Molecules, Chemical Catalog Co., New York.

Delbrück, M., 1949, Trans. Conn. Acad. Arts and Sci., **38,** 173.
Dodge, F., and Frankenhaeuser, B., 1958, J. Physiol., **143,** 76.
Dodge, F., and Frankenhaeuser, B., 1959, J. Physiol., **148,** 188.
FitzHugh, R., and Antosiewicz, H. A., 1959, J. Soc. Indust. Appl. Math., **7,** 447.
FitzHugh, R., 1960, J. Gen. Physiol., **43,** 867.
Frankenhaeuser, B., 1960, Personal communication.
Frankenhaeuser, B., and Hodgkin, A. L., 1957, J. Physiol., **137,** 217.
Fricke, H., 1925, J. Gen. Physiol., **9,** 137
Fricke, H., and Morse, S., 1925, J. Gen. Physiol., **9,** 153.
Gildemeister, M., 1928, Bethes Handbuch d. Physiol. VIII, 12, p. 657.
Hagiwara, S., Kusano, K., and Saito, N., 1961, J. Physiol., **155,** 470.
Hagiwara, S., and Saito, N., 1959a, J. Neurophysiol., **22,** 204.
Hagiwara, S., and Saito, N., 1959b, J. Physiol., **148,** 161.
Hagiwara, S., Watanabe, A., and Saito, N., 1959c, J. Neurophysiol., **22,** 554.
Helmholtz, H., 1853, Ann. Physik u. Chem., **89,** 211.
Hill, A. V., 1910, J. Physiol., **40,** 190.
Hill, A. V., 1936, Proc. Roy. Soc., **B119,** 305.
Höber, R., 1910, Arch. ges. Physiol., **133,** 237.
Höber, R., 1912, Arch. ges. Physiol., **148,** 189.
Hodgkin, A. L., 1947, J. Physiol., **106,** 305.
Hodgkin, A. L., and Huxley, A. F., 1939, Nature, **144,** 710.
Hodgkin, A. L., and Huxley, A. F., 1945, J. Physiol., **104,** 176.
Hodgkin, A. L., and Huxley, A. F., 1952a, J. Physiol., **116,** 449.
Hodgkin, A. L., and Huxley, A. F., 1952b, J. Physiol., **116,** 473.
Hodgkin, A. L., and Huxley, A. F., 1952c, J. Physiol., **116,** 497.
Hodgkin, A. L., and Huxley, A. F., 1952d, J. Physiol., **117,** 500.
Hodgkin, A. L., Huxley, A. F., and Katz, B., 1952, J. Physiol., **116,** 424.
Hodgkin, A. L., and Katz, B., 1949, J. Physiol., **108,** 37
Hodgkin, A. L., and Rushton, W. A. H., 1946, Proc. Roy. Soc. B, **133,** 444.
Huxley, A. F., 1959, Ann. N. Y. Acad. Sci., **81,** 221.
Julian, F. J., and Goldman, D. E., 1960, Biophysical Soc. Abstracts, E3, Philadelphia.
Julian, F. J., Moore, J. W., and Goldman, D. E., 1961, Fed. Proc., **20,** 338.
Katz, B., 1939, Electric Excitation of Nerve, Oxford Univ. Press, London.
Kelvin, Lord (William Thomson), 1856, Phil. Mag., **11** (4), 146.
Marmont, G., 1949, J. Cell. Comp. Physiol., **34,** 351.
Mauro, A., 1961, Biophys. J., **1,** 353.
Maxwell, J. C., 1873, Treatise on Electricity and Magnetism, Clarendon Press, Oxford, Sec. 313.
McClendon, J. F., 1926, J. Biol. Chem., **69,** 733.
Monnier, A. M., 1934, L'Excitation Electrique des Tissus, Hermann, Paris.
Moore, J. W., 1959, Nature, **183,** 265.
Moore, J. W., and Cole, K. S., 1962, Voltage Clamp Techniques, Physical Techniques in Bio. Research Vol. VI, (W. L. Nastuk, editor), Academic Press, New York. (in press)
Mullins, L. J., Adelman, W. J., Jr., and Sjodin, R. A., 1961, Biophys. Soc. Abstract, FC6, St. Louis, Mo.
Nernst, W., 1899, Gött. Nachr., Math., Physik, Kl., **1899,** 104.
Offner, F., Weinberg, A., and Young, G., 1940, Bull. Math. Biophysics, **2,** 89.
Osterhout, W. J. V., 1922, Injury, Recovery and Death in Relation to Conductivity and Permeability, J. B. Lippincott Company, Philadelphia.
Rashevsky, N., 1933, Protoplasma, **20,** 42.
Rashevsky, N., 1935, Physics. **6,** 308.
Rayleigh, Lord (Strutt, J. W.), 1892, Phil. Mag., **34,** 481.
Rushton, W. A. H., 1937, Proc. Roy. Soc. B., **124,** 201.

SCHMITT, O. H., 1937, Am. J. Physiol., **119**, 399.
SCHWAN, H. P., and COLE, K. S., 1960, Medical Physics., **3**, 52, (O. Glasser, editor) Year Book Publ., Chicago.
TASAKI, I., and SPYROPOULOS, C. S., 1958, Am. J. Physiol., **193**, 309.
TAYLOR, R. E., 1962, Cable Theory, Physical Techniques in Biological Research, Vol. 6, (W. L. Nastuk, editor) Academic Press, New York (In press).
TAYLOR, R. E., MOORE, J. W., and COLE, K. S., 1960, Biophys. J., **1**, 161.
TEORELL, T., 1959, J. Gen. Physiol., **42**, 847.
TYLER, A., MONROY, A., KAO, C. Y., and GRUNDFEST, H., 1956, Biol. Bull., **111**, 153.
WEINBERG, A. M., 1940, Bull. Math. Biophys. **2**, 127.
WILLIAMS, L. W., 1909, The Anatomy of the Common Squid, *Loligo pealii* (Leseur), Leiden.
YOUNG, G., 1937, Psychometrika, **2**, 103.
YOUNG, J. Z., 1936, Cold Spring Harbor Symposia on Quantitative Biology, **4**, 1.
YOUNG, J. Z., 1951, Doubt and Certainty in Science, Clarendon Press, Oxford.