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Excitation and Conduction in Nerve: Quantitative Analysis

A. F. Huxley

Professor Hodgkin has told you how he was influenced as an undergraduate by the writings of four fellows of Trinity College, Cambridge. I too was an undergraduate at Trinity, but by the time I was taking physiology seriously, in my final year in 1938–39, there was yet another fellow of the College who influenced me even more directly than the ones mentioned by Hodgkin, and that was Hodgkin himself. He was one of my teachers during that year, and my first introduction to research was the short period that we spent together at the Marine Biological Laboratory at Plymouth in the summer of 1939, when we succeeded in recording the resting and action potentials of the giant nerve fiber of the squid with an internal microelectrode. This work was brought to a stop by the war, but we joined up again at Cambridge early in 1946, and almost the whole of my share in the work for which the prize was given was done jointly with him during the succeeding 5 or 6 years.

The "Voltage-Clamp" Method

Hodgkin has spoken about the ionic theory of the nerve impulse from a broad point of view, and I propose to go into greater detail on the quantitative aspects of the theory that we developed (*1*). The measurements on which this was based were made by a feedback method which has become known as the "voltage clamp." In this, a pair of wires is introduced along the axis of the giant nerve fiber, as shown diagrammatically in Fig. 1. The potential difference across the membrane is measured between one of these wires and an electrode in the sea water just outside the fiber, while the other wire is used for passing current through the membrane to another external electrode. The voltage wire is connected to the input of an amplifier whose output goes to the current wire, the direction of the connections being such that any accidental change of membrane potential is almost completely annulled by the current that the amplifier sends through the membrane. Rectangular pulses can also be fed into the amplifier through a second input. When this is done, the amplifier automatically sends through the current wire whatever current may be needed to make the membrane potential undergo stepwise changes proportional to those which are applied through the second input. This current is then displayed on a cathode-ray oscilloscope and photographed.

The net result is the same as would be obtained if a single ideal electrode was placed inside the fiber and connected to a low-impedance source of voltage steps, and the current was recorded. A method of this kind was indeed tried by Cole and Marmont in 1947 (*2*), and gave useful results, but it is not suitable for quantitative work because the current density that the electrode has to pass is really quite large and no one has yet made an electrode that is sufficiently free from polarization troubles.

Analysis of the Currents through the Nerve Membrane

In order to create a nearly instantaneous change in the potential difference across the membrane, the membrane capacity has to be charged or discharged by the passage of a substantial quantity of electricity in a very short time. This pulse of capacity current can be recorded by the voltage-clamp method, but in the figures reproduced here most of it cannot be seen because of its rapid rise and fall, and its very short total duration, which is only a few microseconds. Analysis of these pulses has confirmed the existence of the capacity in the membrane of about 1 microfarad per square centimeter which had been demonstrated many years earlier with alternating-current methods by Curtis and Cole (*3*). Our present concern is, however, with the currents which flow in the first few milliseconds after the completion of this capacity current, while the membrane potential is held constant by the feedback system.

The general features of these components of the current are illustrated in Fig. 2. The right-hand side of the figure shows that when the normal potential difference across the membrane is increased by 40 millivolts (the inside of the fiber thus being made more negative), the currents are very small. They are barely visible at the amplification used in these records, but with

The author is head of the department of physiology, University College of London. This is the lecture which he delivered in Stockholm, Sweden, 11 December 1963, when he received the Nobel prize in physiology and medicine, a prize which he shared with A. L. Hodgkin and Sir John Eccles. It is published with the permission of the Nobel Foundation. It will also be included in the complete volumes of Nobel lectures in English, published by the Elsevier Publishing Company, Amsterdam and New York.

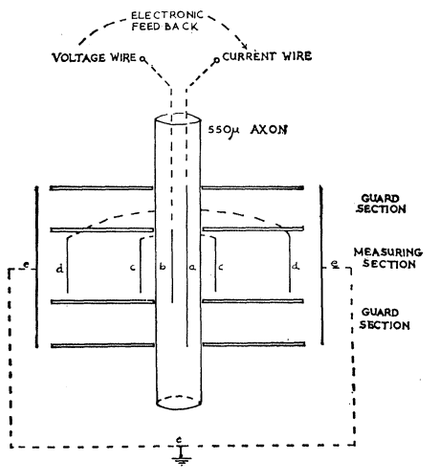


Fig. 1. Schematic diagram of voltage-clamp apparatus. The axon is immersed in sea water, and the horizontal lines represent partitions in a box made of insulating material which guided the current flow. Potential difference across membrane was measured between wires *b* and *c*; current passed from wire *a* to electrode *e*. Current through the middle section of the nerve was measured as potential drop in sea water between wires *c* and *d*. [From Hodgkin, Huxley, Katz (*1*)]

more gain it is found that the current is always inward—that is, in the direction it would take if the membrane obeyed Ohm's law. But where the inside of the fiber is made more positive by an equal amount (left-hand column), the currents are of a larger order of magnitude; further, if the fiber is in sea water (as in record *C*), there

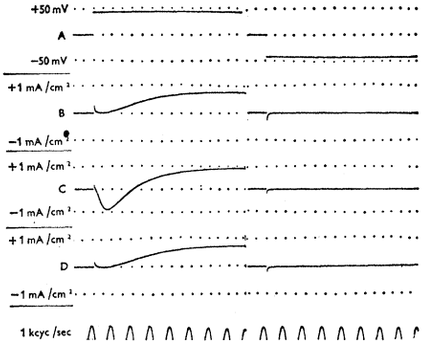


Fig. 2. Currents recorded during operation of the voltage clamp—(right) when potential difference across the membrane is increased from the resting value; (left) when it is decreased. *A*, Internal potential, measured from its resting level; *B*, currents with axon immersed in sea water with 90 percent of its sodium chloride replaced by choline chloride; *C*, axon in sea water; *D*, again in same solution as *B*. Temperature, 8.5°C. Outward current is plotted upward.

is a conspicuous early phase in which the direction of the current is against the change of membrane potential. If it were not for the feedback, this current would drive the inside of the fiber still more positive—that is to say, it would produce the rising phase of an action potential; similarly, the late phase of outward current is clearly a manifestation of the process responsible for the falling phase. The evidence derived from quite different experiments that Professor Hodgkin has already presented thus suggested that the inward phase of current was carried predominantly by sodium ions, moving under the influence of concentration differences and the potential difference across the membrane. If so, it should disappear when the external sodium concentration is lowered by an appropriate amount. Records *B* and *D* show that this is the case.

On this interpretation, the early phase of current should actually be reversed if the external sodium concentration is made low enough or if the internal potential is made high enough. This does actually occur, as is shown in Fig. 3. The curve which separates currents with an early inward phase from those with an early outward phase evidently has zero sodium current; it defines the "sodium potential" at which the effect of the electrical potential difference across the membrane just balances the tendency of the sodium ions to diffuse from the higher concentration outside to the lower concentration inside. This potential was found to vary with the sodium concentration in the external fluid, and indeed in exactly the way required by Nernst's equation. This result is perhaps the strongest evidence for the sodium theory, and it justified us in separating the current into two components the earlier of which is carried predominantly by sodium ions. This was done by comparing records obtained with the fiber in solutions with different sodium concentrations; the procedure is illustrated in Fig. 4. There is evidence of several kinds that the late outward current is carried by potassium ions. Perhaps the most convincing is the equivalence that we found between the potassium efflux, measured with radioactive potassium, and the outward current (*4*). This is illustrated in Fig. 5.

Each of the voltage-clamp records shown so far was taken with the membrane potential held constant after the

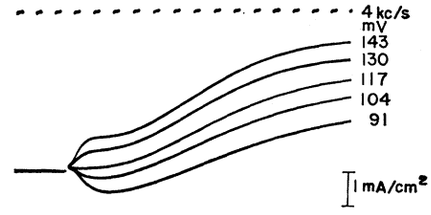


Fig. 3. Membrane currents when the internal potential is raised to values comparable to the peak of an action potential. Axon in sea water; temperature 3.5°C; outward current upward. The records for 91- and 104-millivolt displacement of membrane potential show a phase of inward current, while those for 130 and 143 millivolts show an early hump in the outward current. The record at 117 millivolts shows neither, and it is therefore taken to be very close to the sodium equilibrium potential, at which the current carried by sodium is zero. [From Hodgkin, Huxley, Katz (*1*)]

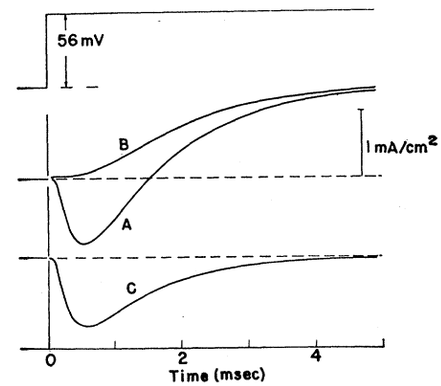


Fig. 4. Separation of ionic current into components carried by sodium and potassium ions. Curve *C*, representing the sodium current, is the difference between *A* (total ionic current) and *B* (sodium current brought to zero by lowering external sodium concentration). Temperature, 8.5°C. [From Hodgkin (*15*)]

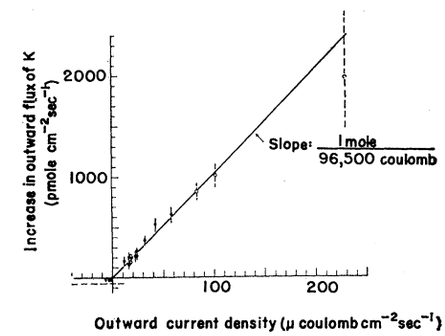


Fig. 5. Relation between potassium efflux and membrane current density when outward current is drawn from a *Sepia* axon. Vertical bars show ± 2 × standard error of means. [From Hodgkin and Huxley (*4*)]

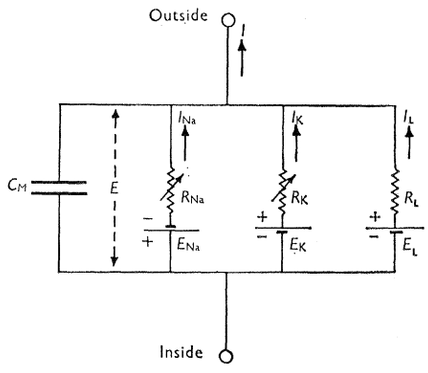


Fig. 6. Equivalent circuit of a small area of membrane of the giant axon. R_{Na} and R_K obey Ohm's law for rapid changes in the potential difference across the membrane, but change their values in times of the order of a millisecond if the membrane potential is held at a new value. R_L is constant.

initial step. The next stage in the analysis was to find how the two components changed if the membrane potential was suddenly altered. The result was unexpectedly simple: each component altered instantaneously to a value which depended in a linear manner on the new value of the membrane potential, and passed through zero at the "sodium potential" or the "potassium potential," respectively. This kind of behavior is what would be given by the circuit shown in Fig. 6: the resistances obey Ohm's law as far as concerns the effect of sudden changes in potential, but in addition the values of the resistances alter smoothly, in times of the order of a millisecond, to give the time courses of current that are shown, for example, in Figs. 2 to 4.

We can thus speak of a sodium conductance and a potassium conductance, both in parallel with the membrane capacity, so that the total current observed is the sum of the currents through these channels. There was also a small component of current which obeyed Ohm's law (with a constant resistance) and was not noticeably affected by changes in the composition of the external fluid. This is represented by the "leak resistance" in Fig. 6.

The final stage of the analysis was to define the time course with which the sodium conductance and the potassium conductance changed after the membrane potential had been brought to a new value. The main features to be incorporated are shown in Fig. 7. A striking point which for some time we found difficult to formulate is the fact that each of the conductances rises with an S-shaped time course at the start, but falls along something very like a simple exponential curve if the membrane potential is restored to its resting value. The manner in which we did in the end represent it is most simply illustrated in connection with the potassium system. We defined a quantity n which varied with ordinary first-order kinetics; that is to say, for each value of membrane potential there was a corresponding equilibrium value of n, and this equilibrium value was approached exponentially with a time constant which was also a function of membrane potential, and there was no discontinuity in the value of n if membrane potential was changed suddenly. Then the fourth power of n varies in much the same way as the potassium conductance does. In the same way, the time course of the sodium conductance behaves like the product m^3h, where m varies rather like n but an order of magnitude more rapidly, and h also obeys first-order kinetics but changes in the opposite direction—that is, its equilibrium value becomes smaller as the inside of the fiber is made more positive. The equilibrium values and time constants for n, m, and h were estimated from the curves of conductance change and converted into the equivalent pairs of first-order rate constants. Each rate constant varied according to the membrane potential during the step applied by the voltage clamp, and this dependence was fitted by an empirical equation.

This analysis was in fact carried out in the sequence I have presented, and the voltage clamp results led directly to the formulation that we gave. But we had thought up many of its features long before the voltage clamp was developed, and even before Hodgkin and Katz (*5*), in the summer of 1947, demonstrated the part played by sodium in the generation of the action potential. Hodgkin and I spent a good deal of time in the early part of 1947 thinking what kind of system might give rise to an action potential. For the rising phase, we postulated, in the membrane, a system of sodium carriers which had a large dipole moment. In the resting state, the dipoles were held in one position by the rest-

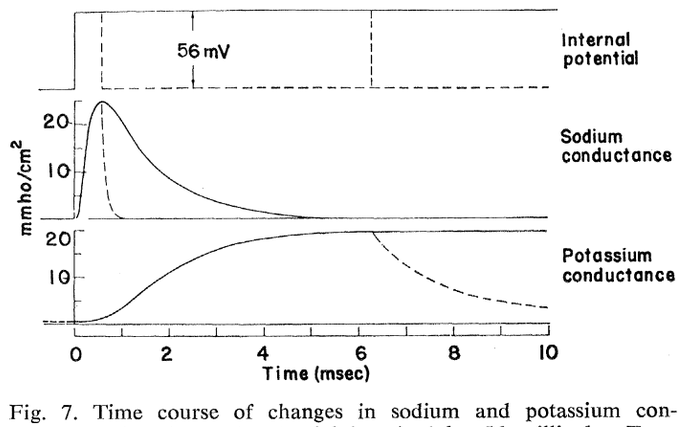


Fig. 7. Time course of changes in sodium and potassium conductance when internal potential is raised by 56 millivolts. Temperature, 8.5°C. The continuous curves are from the experiment of Fig. 4 and show the changes of conductance when the potential was maintained at the raised value; the broken curves show the effect of restoring the membrane potential to its resting value after 0.6 or 6.3 millisecond. [From Hodgkin (*15*)]

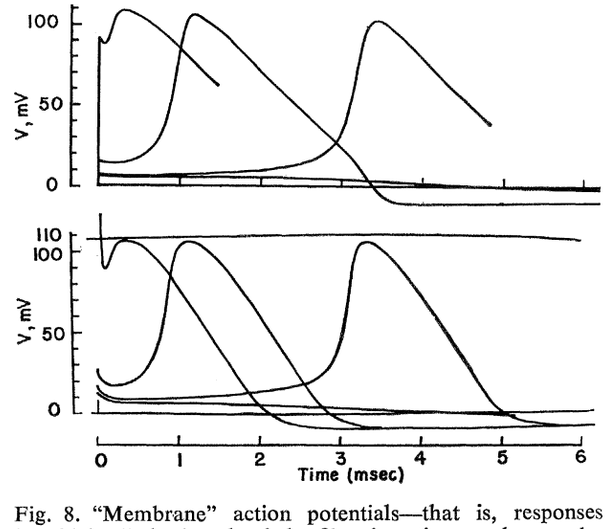


Fig. 8. "Membrane" action potentials—that is, responses in which all the length of the fiber is active synchronously. (Top) Computed; (bottom) observed. Temperature, 6.3°C. [From Hodgkin and Huxley (*7*)]

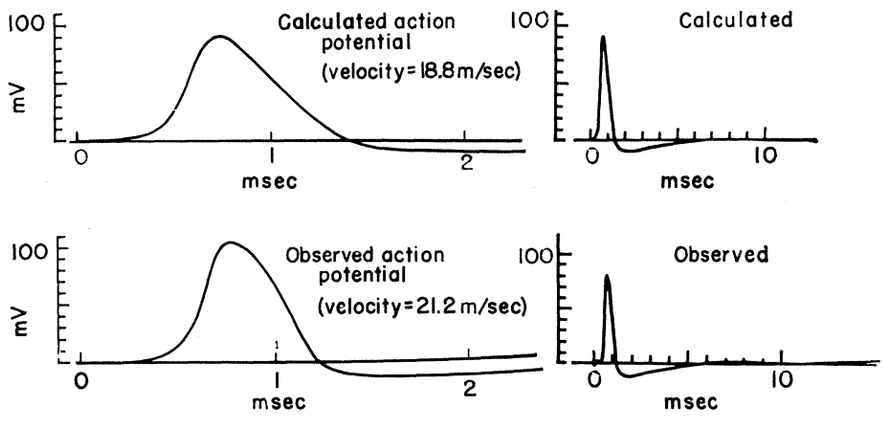
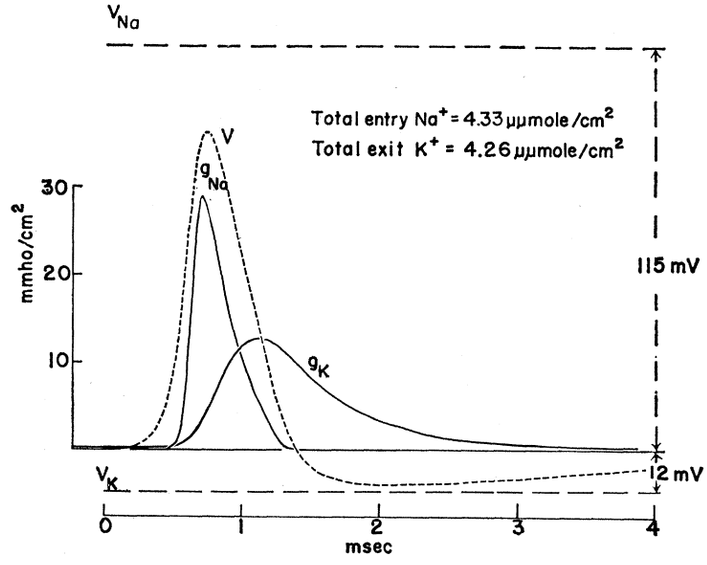


Fig. 9. Propagated action potentials. (Top) Computed; (bottom) observed. Temperature, 18.5°C. [From Hodgkin and Huxley (*7*)]

ing potential difference across the membrane. As the potential difference was reduced, the dipoles became free to turn and thus to ferry sodium ions across. These carriers were assumed to become subject to "inactivation" by reacting relatively slowly, but reversibly, with some substance in the axoplasm when they were in the position opposite to the one they took up in the resting state. The outward movement of charge in the falling phase was attributed to an increase in the potassium permeability of the membrane which took place with a delay when the membrane potential was reduced; this was suggested directly by Cole's observation (*6*) of this kind of rectification in the membrane, together with the "inductance" which he had found and had attributed to a lag in the establishment of the new resistance after the membrane potential had been changed. Using these assumptions we computed the time courses of membrane potential change that would be caused by the ion movements, and after a good deal of trial and error we found that plausible-looking action potentials resulted when appropriate numerical values were inserted. A propagated action potential computed in May 1947 incorporated the main features that emerged 2 or 3 years later from the voltage-clamp analysis: reduction of membrane potential caused (i) a rapid rise of sodium permeability, (ii) a slower decay of sodium permeability as the carrier became inactivated, and (iii) a delayed rectification due to a rise in potassium permeability. Features of the voltage-clamp results that we did not anticipate were the finite delay in the rise of sodium permeability and the S-shaped curve of potassium permeability increase; the form of the variations of permeability with membrane potential was of course also different from what we had assumed in 1947.

Application to Various Phenomena in Nerve

Returning to the voltage-clamp analysis, the procedure that I have described led to a set of equations which described the time course of current through the membrane when the potential difference across it was changed in a stepwise manner. It was clear that the formulation we had used was not the only one that might have fitted the voltage-clamp results adequately, and it was by no means a foregone conclusion that the same equations would describe the behavior of the membrane under its normal conditions of operation, where the ionic currents bring about changes of membrane potential instead of being drawn off by the feedback amplifier. We therefore calculated the responses of our mathematical representations of the nerve membrane to the equivalent of an electrical stimulus. Some of the computations of this kind that we made in 1951 are shown in Figs. 8–14. They included the "membrane action potential" (that is, an action potential in which all parts of the membrane are active synchronously); the propagated action potential; the impedance changes and the total movements of sodium and potassium into and out of the fiber in these action potentials; recovery during the relative refractory period; anode break excitation; and the oscillatory response



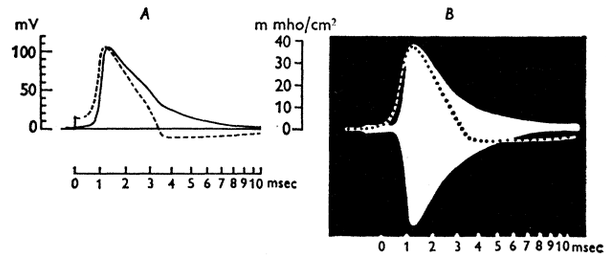


Fig. 10 (left). Changes of sodium and potassium conductances (solid lines and scale at left) during a propagated action potential (membrane potential change shown by dotted line; scale at right). Computed for temperature of 18.5°C. [From Hodgkin and Huxley (*7*)] Fig. 11 (above). Changes in total conductance of the membrane during an action potential. *A*, Computed: dashed line, membrane action potential, 6°C; solid line, total membrane conductance. *B*, Records of propagated action potential (dotted line) and conductance change. [From Hodgkin and Huxley (*7*), where it is reproduced from K. S. Cole and H. J. Curtis, *J. Gen. Physiol.* **22**, 649 (1939)]

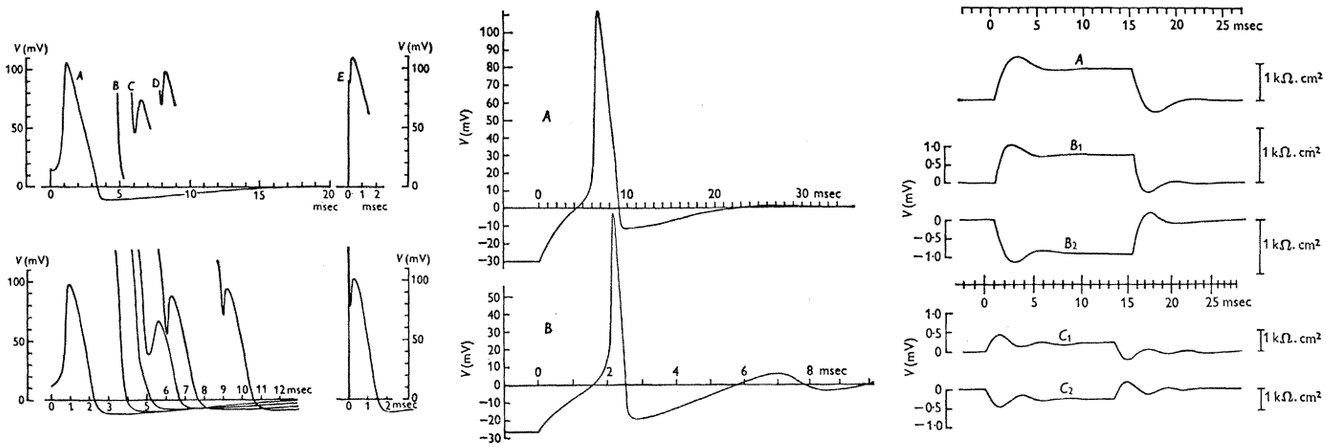


Fig. 12 (left). Recovery during the refractory period. Membrane responses: (top) computed for 6.3°C; (bottom) records from an actual nerve, 9°C. Time scales differ by a factor appropriate to the temperature difference. *A* and *E*, Responses in resting nerve to weak and strong stimuli, respectively; *B–D*, responses to stimulus of the same strength as that of *E* at various times after *A*. Fig. 13 (middle). Anode break responses. (Top) Computed, 6.3°C; (bottom) record from a real nerve, 18.5°C. Time scales differ by a factor appropriate to the temperature difference. In each case, a long-lasting steady current lowering the internal potential below its resting value is terminated at time zero. Fig. 14 (right). Responses of the membrane to a constant current, uniformly applied. *A*, computed; B_1 and B_2, observed, for currents of + 1.49 μA/cm² and − 1.49 μA/cm², respectively; 19°C. [Figs. 12–14 from Hodgkin and Huxley (*7*)]

of the membrane to a rectangular pulse of current. All these results were published in 1952 (*7*) and showed a surprisingly good agreement with the behavior of the real giant axon of the squid.

The computations so far described were done by hand. This was a laborious business: a membrane action potential took a matter of days to compute, and a propagated action potential took a matter of weeks. But it was often quite exciting. For example, when calculating the effect of a stimulus close to the threshold value, one would see the forces of accommodation—inactivation of the sodium channel, and the delayed rise of potassium permeability—creeping up and reducing the excitatory effect of the rapid rise of sodium permeability. Would the membrane potential get away into a spike, or die in a subthreshold oscillation? Very often my expectations turned out to be wrong, and an important lesson I learned from these manual computations was the complete

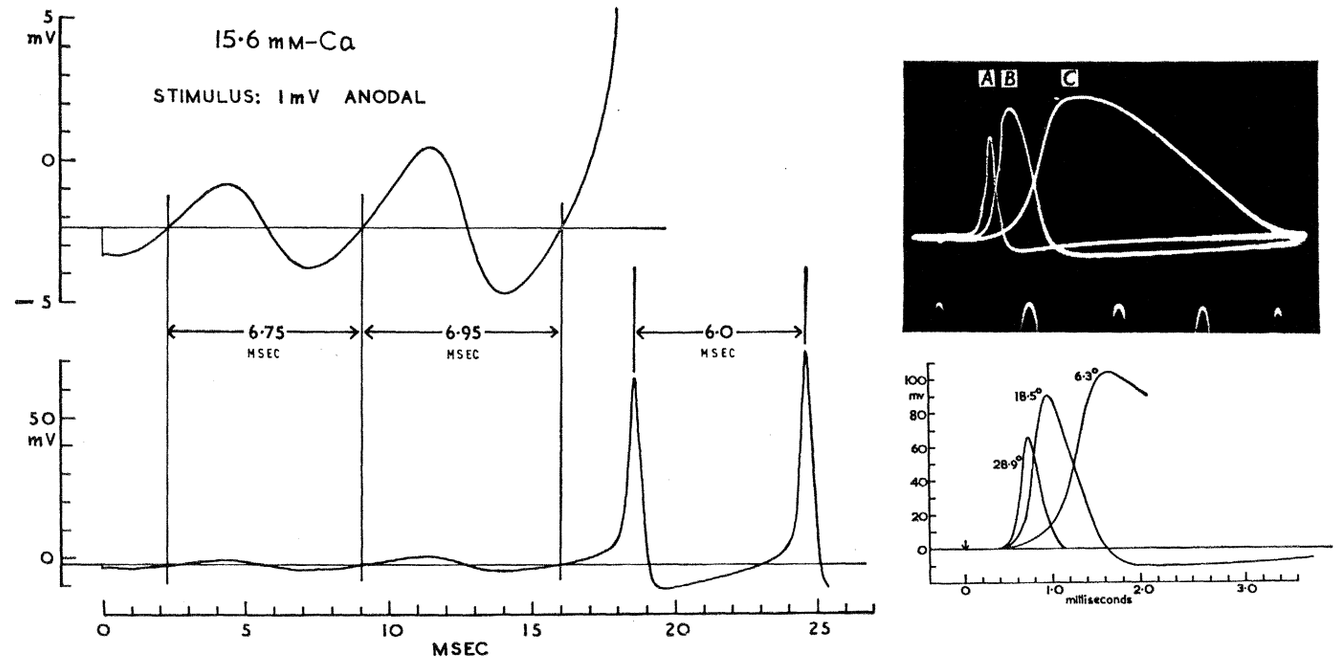


Fig. 15 (left). Computed response of the membrane of an axon in a solution with 0.35 times the normal calcium concentration. A small anodal stimulus gives rise to increasing oscillations which build up into a series of spikes which is continued indefinitely. The ordinate scale in the top record is ten times that in the bottom record. Fig. 16 (right). Effect of temperature on the propagated action potential. (Top) Records by Hodgkin and Katz (*11*) from a real axon; *A*, 32.5°C; *B*, 18.5°C; *C*, 5°C. (Bottom) Computed. In both the real and the computed case, conduction failed at a temperature slightly above the highest shown temperature.

inadequacy of one's intuition in trying to deal with a system of this degree of complexity.

Later on, we extended the range of our calculated responses by using the electronic computers EDSAC I and EDSAC II in the Mathematical Laboratory of Cambridge University. The first case we dealt with in this way (*8*) was the effect of lowered calcium concentration. Frankenhaeuser and Hodgkin (*9*) in 1957 had shown with the voltage clamp that the main effect of changing the calcium concentration was to shift along the membrane potential axis all the functions which govern the permeability changes. Incorporating this change alone into the equations made the computer deliver a variety of oscillatory responses that were closely similar to the responses of real nerve fibers in low-calcium solutions. An example is shown in Fig. 15, where a single anodal shock starts off a series of increasing oscillations which build up into repetitive action potentials.

Later, we calculated the propagated action potentials corresponding to various temperatures. It was assumed that the only effect of altered temperature was to change the rates of the permeability factors with a Q_{10} of 3; it is now known that there are also appreciable changes in the absolute values of the ionic currents (*10*), but Fig. 16 shows that the single assumption led to results that were strikingly similar to the experimental records that Hodgkin and Katz (*11*) had obtained in 1947 from real squid fibers.

Another case we computed was the effect of an anodal pulse during the action potential itself. Various authors had shown that such a pulse, if of sufficient strength, could cause an all-or-none return of the membrane potential to approximately its resting level. Figure 17 shows that the computed action potential can be abolished in the same way.

The other situation we have explored to some extent with EDSAC II is the response in a continuous nerve to stimuli of just threshold value applied at one point. Some of these computations have required that the mathematical representation be set up as a partial differential equation, with the membrane properties represented separately for each of a number of points along the length of the nerve. Several intriguing results have emerged, but it is not worth laying much emphasis on them since the equivalent experiments

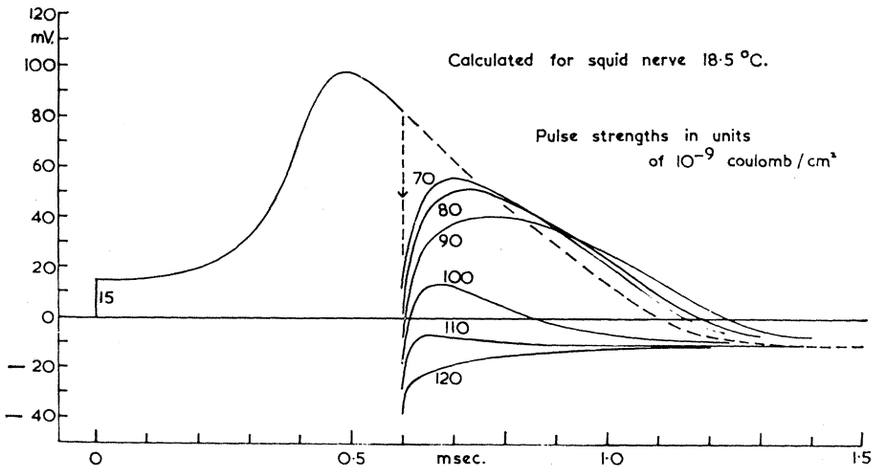


Fig. 17. Abolition of an action potential by anodal pulses, computed for membrane response of squid nerve at 18.5°C. Pulses of 90 × 10^{-9} coulomb or less per square centimeter cause only a temporary drop from the time course of the spike; pulses of 100 × 10^{-9} or more per square centimeter cause the internal potential to fall to a level close to that reached in the "positive phase" of the normal spike. [From Huxley (*8*)]

on the real nerve have not been performed, and the situations in question are so unstable that it may well be impossible to realize them in practice even if they are possible in principle. For example, the equations lead to solutions representing a wave, or even a series of waves, of just threshold amplitude, travelling along the fiber at much lower velocity than the normal spike (*12*). Also, when a just-threshold pulse is applied at one point, action potentials may propagate away in both directions although the membrane potential change at the stimulated point only reaches about 20 millivolts.

Conclusion

The agreement between these computed responses and the potential changes that can be recorded from real nerve fibers is certainly encouraging, but I would not like to leave you with the impression that the particular equations we produced in 1952 are definitive. First, it has been clear all along that these equations only cover the rapid events in and immediately after the action potential, and that they are inadequate for dealing with questions like the maintenance of the resting potential. Second, Cole and Moore (*13*) have shown that the rise of potassium conductance can in some conditions be much more delayed than is accounted for by our fourth-power formulation. Thirdly, a recent paper by Rosalie Hoyt (*14*) shows that the sodium conductance change may satisfactorily be represented by a single variable governed by a second-order differential equation, while in our formulation it was represented by a product of two variables each governed by a first-order equation. Fourth, Bernhard Frankenhaeuser of the Nobel Institute has achieved the remarkable feat of making voltage clamp measurements on single nodes of Ranvier in myelinated nerve fibers and has found that there are substantial differences in behavior from the squid giant axon, although the main outlines are the same. Both Hodgkin and I feel that these equations should be regarded as a first approximation which needs to be refined and extended in many ways in the search for the actual mechanism of the permeability changes on the molecular scale.

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