Oscillation and Repetitive Firing in Squid Axons

Comparison of experiments with computations

RITA GUTTMAN and ROBERT BARNHILL

From the Department of Biology, Brooklyn College, New York 11210, and the Marine Biological Laboratory, Woods Hole, Massachusetts 02543

ABSTRACT Space-clamped squid axons treated with low calcium and computed Hodgkin-Huxley (HH) axons were stimulated by steps of superthreshold current from 101 to 400% of the rheobasic value over a temperature range of 5–27°C. The natural frequency of sustained repetitive firing of real and computed axons depended weakly upon stimulus intensity and strongly upon temperature, with a Q_{10} of 2.7 (experimental) and 2.6 (computed). For real axons, but not the computed axon, the intervals between the first two spikes were shorter than between subsequent spikes. Constant spike frequencies from 75 Hz at low intensities and temperatures to 330 Hz at high intensities and temperatures were soon achieved. Subthreshold and superthreshold responses were sometimes intermixed in a train of responses from a real axon responding to a constant step of current, but not predicted by HH. The time interval following a spike was always longer than that following a subthreshold oscillation in slightly decalcified real axons, as Huxley and FitzHugh also found for computed axons. There was a bias toward spikes at the beginning of the train and toward subthreshold responses later on. Some repeated patterns were found, every second, third, or fourth response being a spike. Neither the HH equations nor the computed or experimental threshold behaviors show a critical temperature to support a membrane phase transition.

INTRODUCTION

In previous work (Guttman, 1962, 1966, 1968a, b, 1969) the effect of temperature upon a number of aspects of excitation, accommodation, and subthreshold oscillation was studied in space-clamped squid axons, using the double glucose gap. Various other interesting aspects of the effect of temperature upon subthreshold oscillation and repetitive firing (trains of spikes), however, had to be postponed until some refinements of technique were achieved. Better

control of solution flow rates gave better definition of experimental area. The other aspects also permitted higher amplification of the response, because a decrease in "noise" and, at such amplification, a stabilization of the base line trace on the oscilloscope permitted higher amplification of the response, so that slight variations in resting potential did not cause the response to wander off the screen. These technical modifications have permitted a comparison of frequency of subthreshold and superthreshold responses obtained in the same train of responses and a comparison of initial and final frequencies in trains of spikes, all evoked by steps of current over a temperature range of 5–27°C.

The results on real axons are compared with the computed results upon the standard theoretical (HH) axon of Hodgkin and Huxley (1952). In these experiments we reduced the external calcium to enhance the tendency toward repetitive firing. Frankenhaeuser and Hodgkin (1957) have shown that the major effect of modifying the calcium ion concentration is to shift the voltage dependence of the ionic conductances, and Huxley (1959) has used the result to compute several effects of the calcium ion concentration on excitability.

Wherever calculated values are presented in the figures or discussed in the text, unless otherwise noted, they were computed by James W. Cooley and Frederick A. Dodge, Jr., at our request.

A detailed review of the literature with regard to oscillations and repetitive firing was presented in a previous paper (Guttman, 1969).

The work reported here was carried out at the Marine Biological Laboratory, Woods Hole, Mass., during the summer of 1968.

MATERIAL AND METHODS

Dissection and Axon Chamber The giant nerve fiber of the hindmost stellar nerve of the squid, *Loligo pealei*, was used in this series of experiments. It was dissected out under running seawater and separated from neighboring smaller fibers under a binocular dissecting microscope. It was necessary to clean the axon of smaller fibers and connective tissue very carefully, if steady, clean seawater-glucose shear lines (described below) were to be obtained. It was then dipped in isosmotic glucose, blotted on tissue, and mounted in a Lucite chamber.

The axon chamber used (Fig. 1) was an improved version of the one used in previous work (Guttman, 1966). A double glucose gap (compartments *B* and *D*) isolated the experimental portion of the axon in compartment *C*. The Vaseline seals used previously were not needed between these compartments, because the chamber design created smooth interfaces between the laminarly flowing isosmotic glucose and experimental solutions. Compartments *A* and *E* contained noncirculating pools of 200 mM KCl solution, which provided zero potential in these compartments; Vaseline seals were interposed between these and compartments *B* and *D*.

After the partitions *AB* and *DE* had been coated with Vaseline, and with the glucose and experimental solutions flowing, the isolated axon was laid in place and the ligatures at its ends were secured between double vertical stainless steel posts in the floor of compartments *A* and *E*. The two Vaseline seals were completed with addi-

tional Vaseline, and the KCl pools were filled. Small glass pipettes containing Ag/AgCl electrodes made up in seawater-agar for recording were mounted with their tips dipping into compartments *C* and *E*. Two platinized platinum electrodes for stimulation were permanently mounted in compartments *A* and *C*.

Temperature Control The temperature of the seawater or experimental solution flowing into compartment *C* was measured with a glass probe thermistor (Veco 32A129), located close to the axon, and a calibrated bridge circuit (Cole, 1957). Temperature was controlled by first cooling the solution to about 2°C by passing it

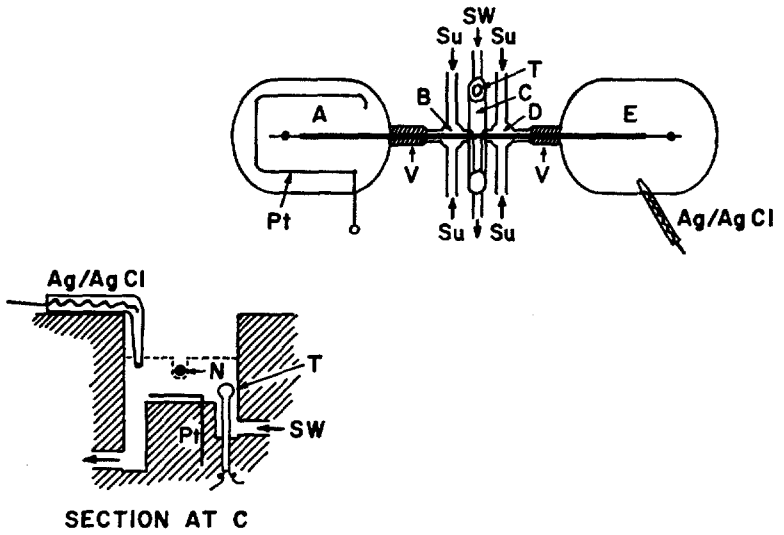

FIGURE 1. Experimental chamber for studying subthreshold oscillations and repetitive firing in space-clamped squid axons. The chamber is internally divided into five compartments—*A*, *B*, *C*, *D*, and *E*—by partitions provided with aligned clefts in which the axon, *N*, rests. *Pt* are platinized platinum electrodes for application of current. The Ag/AgCl electrodes are used for potential measurement. *T* represents a thermistor. *Su* represents flowing sucrose; *Sw*, flowing seawater; and *V* is vaseline seal. For further details, see the text.

through a stainless steel tube in direct thermal contact with the cold side of a thermoelectric heat pump. The solution was then heated to the desired temperature by a small heating coil as it passed into the axon chamber. The heating power was controlled by the error signal from the thermistor bridge. This arrangement provided for fast (less than 30 sec) temperature changes with reasonable accuracy of automatic control (within ±0.5°C up to 20°C, and within ±1°C at 30°C).

Experimental Membrane Area The portion of axon in the experimental solution was between 0.5 and 1.0 mm long in various experiments. This short gap length contributed to the difficulties of measurement. Nevertheless, measurements made through

the microscope and those based on the electrical capacity (see Guttman, 1962), made after the apparatus was calibrated with known components, agreed within the experimental accuracy of a few per cent. The "visual" area measurement was used throughout.

However, with so short a gap length, less than 3 times an axon diameter, simple cable theory may not be adequate (Taylor, 1963). The approximation should not be serious between rest and rheobase, where the characteristic length is between 3 and 6 mm, and the membrane current density should be nearly uniform.

Fibers of larger diameter were preferable for these experiments, since the small residual amount of fluctuation of shear lines remaining with the new method of flow control caused a smaller percentage variation in the large fibers as compared to the smaller ones. Also, since an increase in experimental membrane area was involved in the case of large fibers, threshold values were larger and accuracy of measurement was higher.

Instrumentation Long square wave pulses (up to 80 msec) were provided by a Tektronix 161 pulse generator at the rate of 1 pulse/sec and applied through a 470 kilohm isolating resistance to the platinum electrode in compartment *A* of the chamber. These pulses were considered steps of current, because all observations were completed before they were turned off. Stimulating current to the platinum electrode in compartment *C* was measured with an operational amplifier and a 10 kilohm resistor serving as a current-to-voltage transresistor. This derived potential was applied to the upper trace of a Tektronix 502 oscilloscope.

Differential recording was made between the two Ag/AgCl electrodes. The potential developed by each was buffered by an operational amplifier used as a unity gain follower, and the difference was taken by another operational amplifier acting as a subtractor with a gain of 10. This signal was monitored with a Keithley 610BR electrometer to give the resting potential and was also supplied to a base line stabilization circuit. This circuit consisted of synchronization and track-and-hold memory circuits, and an adder. The track-and-hold memory circuit was synchronized with the stimulus in such a way that the base line was sampled for 133 msec, ending about 16 msec prior to each stimulation. The negative of this potential was held for the remainder of the 1 sec repetition period and was added to the unaltered response signal. The sum produced the lower trace on the oscilloscope. The effect of this circuit was to set the oscilloscope base line to zero immediately before each stimulation, thus virtually eliminating the effect of changes in resting potential while introducing no distortion to the active response. In this way, large amplifications (up to 1 mv/cm) of interesting portions of the response became practical.

Solutions The isosmotic glucose solutions (0.83 M) were made up in glass-distilled water and passed slowly through ion-exchange resin (Barnstead Red Cap) while warm. The conductivity of the glucose solution was continuously monitored with a meter in the flowing system and was 1 μmho/cm or less.

The artificial seawater solutions with varying amounts of $CaCl_2$ were made up according to the method of Frankenhaeuser and Hodgkin (1957). Calcium was varied in a magnesium-free solution by mixing various proportions of 0 mM $CaCl_2$

solution and 50 mM $CaCl_2$ solution, made up as follows:

0 mM $CaCl_2$ solution	50 mM $CaCl_2$ solution
560 mM NaCl	50 mM $CaCl_2$
10 mM KCl	485 mM NaCl
5 mM Tris	10 mM KCl
	5 mM Tris

These solutions followed the formula, Na + 3/2 Ca = 560 mM, used by Frankenhaeuser and Hodgkin (1957). The pH of each solution was adjusted between 7.3 and 7.5 with HCl. The fiber was first bathed in a "holding" solution of 35 mM $CaCl_2$ (considered equivalent to Woods Hole seawater), followed by artificial seawater solutions containing various smaller amounts of $CaCl_2$. These solutions were obtained by automatic continuous mixing of 0 mM and 50 mM solutions in a dual metering pump system. (The calcium solutions used ranged from 7.5 to 35 mM.) The pumps were Sage model 220 unlimited-volume syringe pumps, modified and calibrated to pump at rates determined by external control signals. The control signals were generated by operational amplifier circuits providing for independent control of the total (sum) rate and the ratio of the individual rates. A third pump, also remotely controlled, pumped glucose solution. This control of the solution flow rates provided much steadier shear lines between glucose and seawater in compartment *C* than was possible with previous gravity-feed systems.

Experimental Design and Axon Deterioration The procedure was to search for calcium concentrations which gave either subthreshold oscillations after an initial spike, or trains of spikes. A variety of experimental designs were used, depending upon which of these two classes of responses occurred. Temperature and stimulus intensity were varied to investigate (*a*) the difference in intervals between subthreshold responses and spikes appearing in the same train of responses and (*b*) the difference between the initial and the ultimate frequency in trains of spikes. After as much information as possible had been obtained, a second low calcium concentration was used and an attempt was made to repeat the procedure, but by this time deterioration of the fiber usually set in and the experiment had to be abandoned.

As mentioned earlier (Guttman, 1969), oscillation and repetitive firing during treatment with low calcium usually appeared only if the fiber was in excellent condition. Often fibers with high resting potentials and excellent spikes were obtained, and yet oscillations or repetitive firing was not produced by treatment with low calcium. The presence or absence of repetitive responses seemed to depend more upon the condition of the animal when killed than upon mishandling during dissection, because paired axons from the same animal usually showed similar responses after dissection.

As fibers deteriorated during prolonged treatment with low calcium solutions, the following usually occurred. The resting potential declined from about 90 mv to 40–50 mv and its variability increased. After prolonged treatment with very low calcium concentrations, e.g. 10 mM or less, specifically after stimulation, the membrane potential decreased, lingered at a low value for a period of up to several seconds, and

then suddenly returned to the resting value. In a few instances after prolonged treatment with low calcium, spontaneous trains of spikes appeared immediately after cessation of stimulation. Associated with deterioration during an experiment, the hyperpolarization caused by the glucose gaps decreased and the threshold was lowered. Also the "plateau" (membrane potential displacement during stimulation but after or between active responses) decreased markedly in amplitude.

In some (usually dying) fibers the response to a stimulus of threshold intensity (i.e. such that a slightly lower value resulted only in a local response) was quite variable in that it could evoke successively one spike, two spikes separated by various time intervals, three spikes, or even a train. Whether this was caused by a variation in the noise level of the membrane or by some other factor was not known, but it did not seem to be well correlated with temperature cycling or variation of instrumentation noise with time.

DISCUSSION OF RESULTS

Throughout, an attempt was made to compare experimental results on real axons with computations. The computations involved a calcium shift of 8 mv in the manner of Huxley (1959). This figure was chosen since it is nearly the maximum possible at which the membrane is stable at the resting potential, and, in agreement with experiment, the subthreshold oscillation has a slightly shorter period than the interspike period of the superthreshold response.

Repetitive Firing

When trains of spikes elicited by superthreshold steps of current were examined, it was apparent that while the frequency of spikes soon became uniform in experimental axons, the interval between the first two spikes was somewhat shorter than those appearing between spikes later on in the train. Under some conditions, later interspike intervals might be as much as 25% longer than the first. Nonetheless, we used the interval between the first two spikes to measure frequency values in the experimental work as a matter of expediency, since at low temperatures, where the frequency is low, often only two spikes appeared on the screen. In the computed axon, no significant difference between initial and steady-state frequency appeared in the stimulus intensity range used in the experiments: 101–400% of rheobasic intensity. This suggests that some slow processes in the real axon are not represented in the equations.

In Fig. 2 a comparison of frequency of repetitive firing in real experimental axons (left) and computed axons (right) is presented. Here frequency is plotted against percentage of the threshold membrane current value. When results are expressed in terms of microamperes per square centimeter, it is difficult to discern a pattern because of the variability among axons, but when data are expressed in terms of their ratio to rheobasic currents, much higher consistency of results from one axon to another is seen.

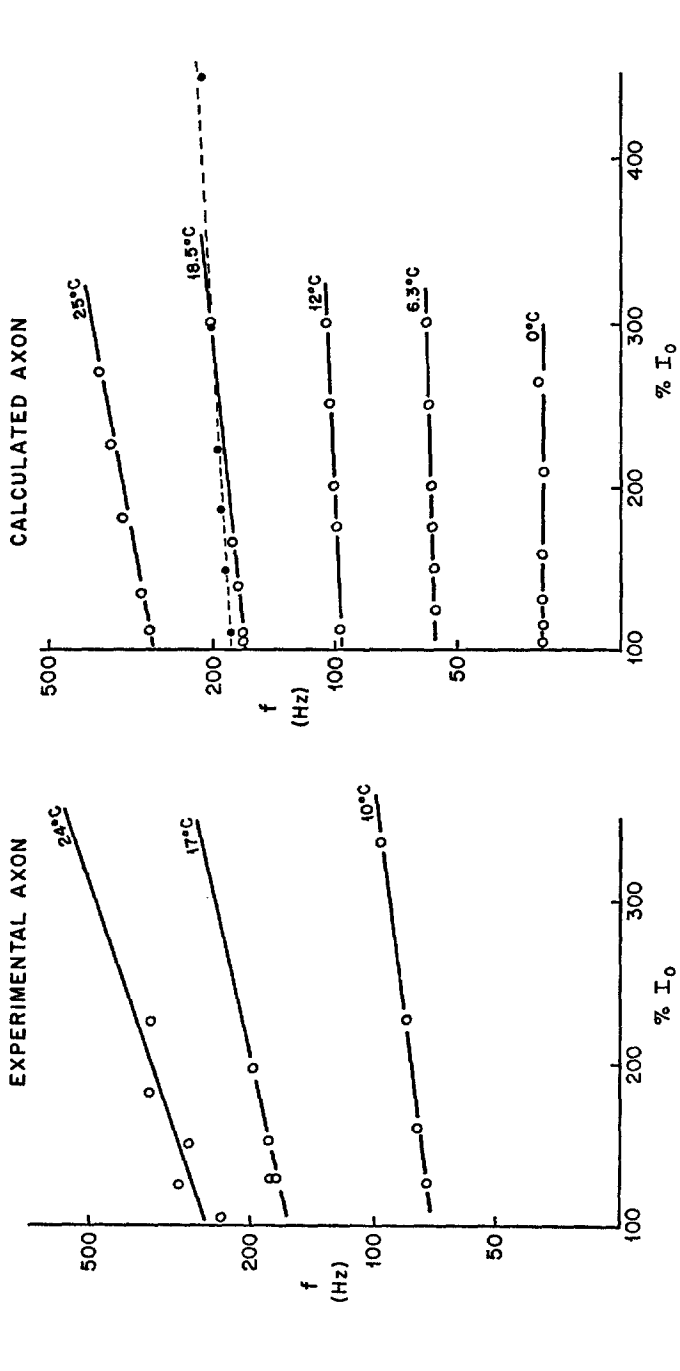

FIGURE 2. Effect of stimulus intensity, expressed as percentage of rheobasic value (% I_0), on frequency (Hertz) at various temperatures in an experimental axon (left) and computed axon (right) in low calcium. The broken line is the result when all conductances were increased by a factor of 1.5 to take into account the change of conductance with temperature. See the text for discussion.

In Fig. 2, left, frequency is plotted against the percentage of threshold at various superthreshold values of stimulating current at 10°C, 17°C and 24°C, and, in contrast to sensory systems, only slight dependence upon stimulus in-

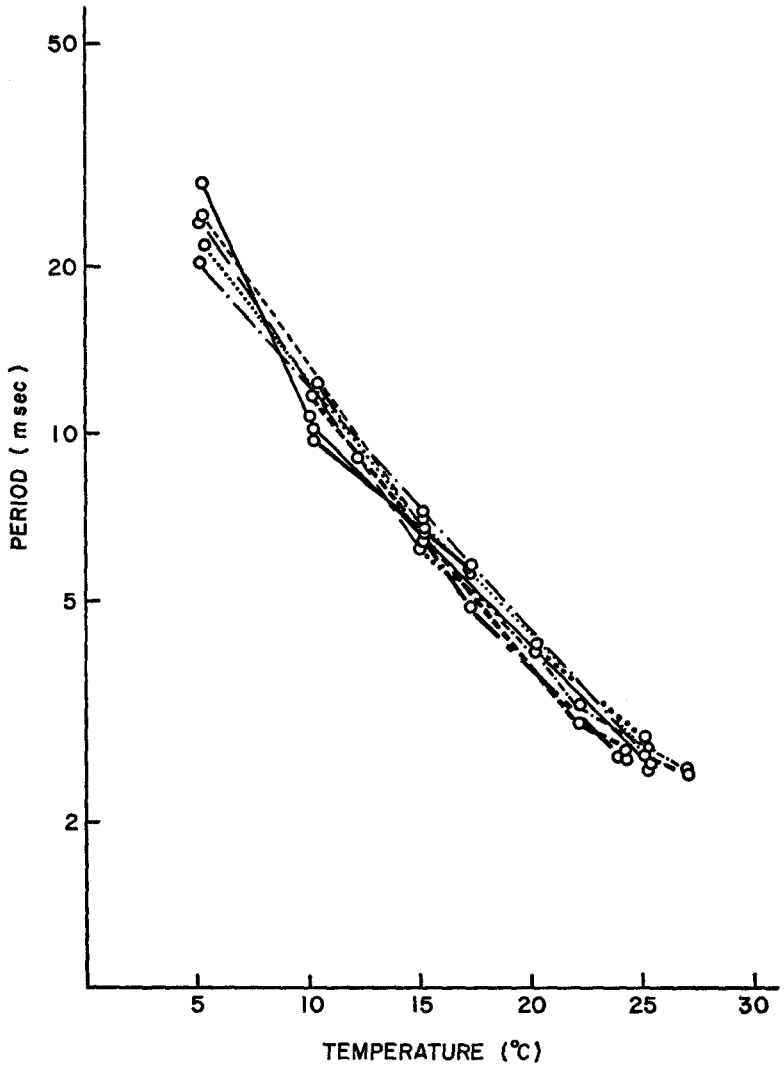

FIGURE 3. Effect of temperature upon period in repetitive firing of experimental axons. Composite of data taken in 14 runs on 10 fibers, displaced up or down by an average of 13.6% of the mean value for best fit.

tensity is found. Both (*a*) the slight dependence of frequency upon stimulus intensity and also (*b*) the increase in slope with increase in temperature, which we found for the experimental axon, are present also in the calculated axon (Fig. 2, right).

In Fig. 3, the effect of temperature variation upon the period in repetitive firing of experimental axons is shown. This figure represents a composite of data taken in 14 runs on 10 fibers and displaced by an average of 13.6% of the mean value for best fit. A strong dependence of period upon temperature is apparent.

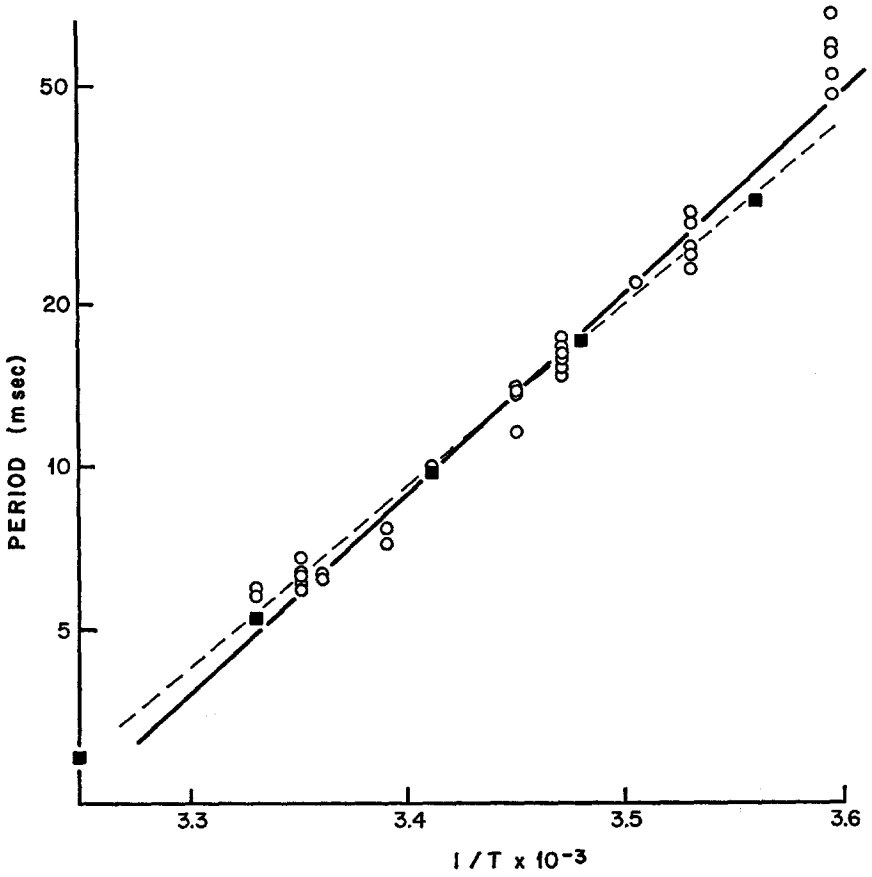

FIGURE 4. Period of repetitive firing vs. reciprocal of absolute temperature (T) $\times 10^{-3}$. Experimental data from Fig. 4 (○——○) and computed data (■- - -■). The ordinate pertains only to the computed axon, since experimental runs have been displaced vertically for best fit.

Using twice the rheobasic values of the calculated axons from Fig. 2, we then plotted $1/T$ (absolute temperature) vs. period (broken line, Fig. 4). We did the same for our experimental data obtained on real axons (same figure, continuous line). The slopes of calculated and experimental values are very similar, indicating that our experimental results agree well with the HH equations in this respect. The Q_{10} is 2.7 for the experimental axon and 2.6 for the computed axon.

If a possible conductance change with temperature is taken into account (broken line, Fig. 2, right), where all conductances have been increased by a factor of 1.5, representing a conductance change of 4%/degree (see Hodgkin, Huxley, and Katz, 1952; Moore, 1958), the frequency of firing of the theoretical axon is even less sensitive to changes in stimulus intensity.

To summarize, the frequency of repetitive firing of the theoretical axon does not depend strongly upon stimulus intensity. It does depend very strongly upon temperature variation. The degree of dependence of the frequency of experimental axons upon stimulus intensity is somewhat variable, but the frequencies of the experimental and the theoretical axons are invariably strongly dependent upon temperature. It may be emphasized that in the HH equations the various parameters are rather gradual, smooth functions of temperature, without any indication of a sharp transition in any temperature range. Similarly, in this work, as in the previous experimental tests of the equations near threshold and over considerable temperature ranges (Guttman, 1962, 1966, 1968a, b, 1969), the data have not given any evidence of a critical temperature or of significant differences between two distinct ranges of temperature. Thus, although it has been suggested (Tasaki, 1968; Changeux et al., 1966; Adam, 1968) that first-order phase transitions in the membrane may be responsible for excitation, neither the HH equations nor our observations give any evidence in support of such a process.

"*Skip Runs*"

In some trains of responses elicited by a step of constant current, subthreshold responses were intermixed with spikes (Fig. 5). We have called these "skip runs." In these there is a bias toward spikes at the beginning of the train of responses, and a bias toward subthreshold responses is apparent later on. Sometimes, however, a rhythmicity appears (Figs. 5 and 6), with every second, third, or four maximum being a spike.

The time intervals between the peaks of (*a*) spike and spike, (*b*) spike and subthreshold response, (*c*) subthreshold and subthreshold response, and (*d*) subthreshold response and spike, respectively were carefully measured, and the results are presented in Fig. 6. where response number, indicating the position of the response in the train, is plotted against interval in milliseconds. If spike-spike and spike-subthreshold responses are considered together, their intervals are significantly larger than those of subthreshold-spike and subthreshold-subthreshold responses lumped together. In other words, the interval following a spike was invariably larger than that following a subthreshold response.

This was true without exception in 10 skip runs observed in eight partially decalcified axons bathed in 7.5, 10, or 15 mM $CaCl_2$ solution. The ratio of the interval following a subthreshold response to the interval following a spike

showed an excellent correlation with temperature, increasing 2.8%/degree as the temperature was raised (Fig. 7).

That the interval following a spike should be longer than that following a subthreshold response might be expected, since there is a more extensive undershoot following a spike and more time must elapse to regain the base line when the undershoot is more extensive.

In their study of the behavior of the computed axon, Cooley, Dodge, and Cohen (1965) demonstrated an unstable limit cycle for the theoretical axon

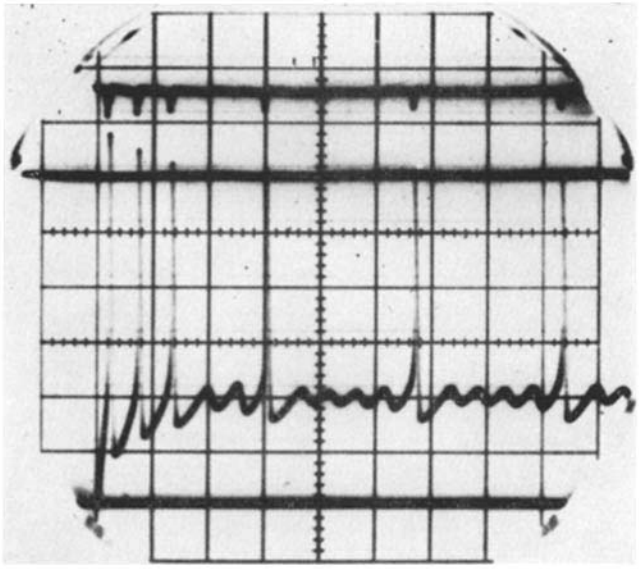

FIGURE 5. Photographic record of response trace (below) and stimulus trace (above) for an axon, stimulated by a uniform step of current, responding by a train of spikes and subthreshold oscillations intermixed. The interval after the spike is longer than after the subthreshold response. There is bias toward spikes at the beginning of the train and toward subthreshold oscillation later on. Calibration: 1 μamp, 20 mv, 5 msec. Temperature, 25°C. Typical record.

with normal parameters. They investigated the response of a space-clamped axon to two brief depolarizing pulses superimposed at the beginning of a step of constant current of subthreshold intensity (Fig. 8). The first pulse resulted in subthreshold oscillation. The second pulse caused the subthreshold oscillation to break into repetitive firing. Measuring intervals in their figure, we find that the interval between subthreshold responses is shorter than the interval between spikes, which corroborates our finding for the real axon.

An oscillating parameter with a period of about 15 msec at 25°C and 20 msec at 15°C could account for most of the skip runs. The period of this oscillatory parameter is several times longer than the longest time constant of the HH equations. Thus some parameter would obviously have to be added to the

HH equations to account for the skip run phenomenon. (However, a more complicated repetition pattern, such as a spike, two subthreshold responses, spike, and subthreshold response, did occur.)

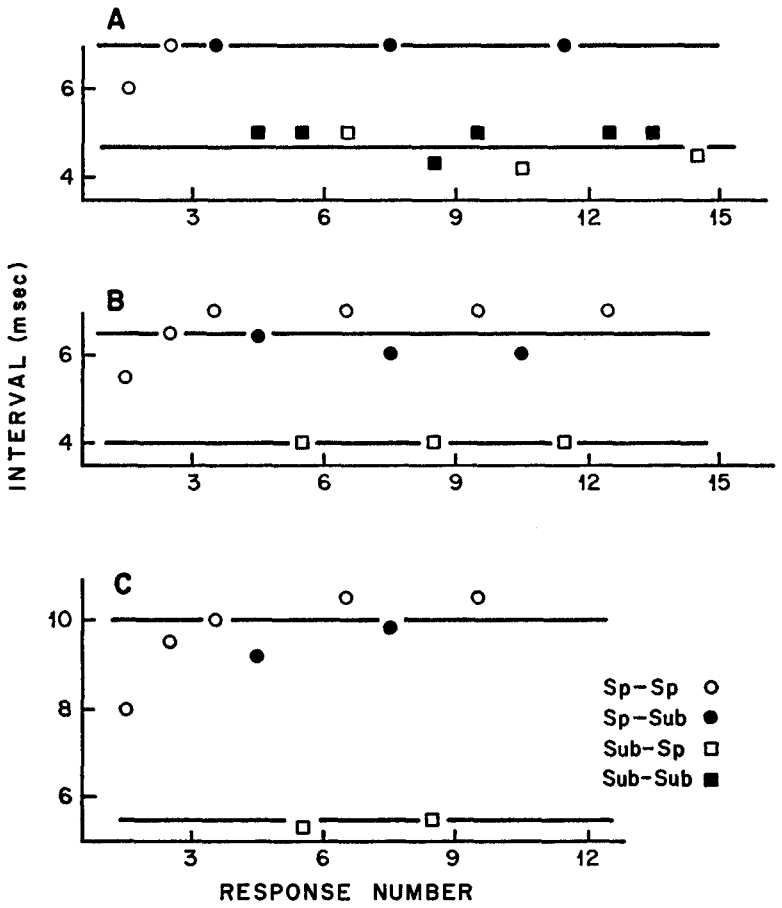

FIGURE 6. Three trains of responses, consisting of spikes and subthreshold oscillation intermixed, all obtained on the same axon bathed in 15 mM $CaCl_2$ at 15°C. Intervals in milliseconds are plotted against position of response in train (response number). At *A*, the stimulus is 318% I_0; at *B*, 218% I_0; and at *C*, 169% I_0. Note that in every case the interval following a spike is longer than that following a subthreshold response. At *A*, a repeated pattern of three subthreshold oscillations and a spike is apparent. At *B* and *C*, the repeated pattern is two spikes followed by a subthreshold oscillation.

At least two alternative hypotheses may be offered to account for the rhythmicity. An accommodation may follow a spike, allowing only subthreshold responses to appear until it wears off. Another hypothesis suggests that a spike frequency and a subthreshold frequency coexist and, depending upon the relative phases, one rhythm or another will be established.

Although skip runs cannot be expected for the digital-computed axon, the interval following a spike is longer than that following a subthreshold response in the computed axons of FitzHugh (cf. Fig. 4 of Guttman, 1969) and, under certain circumstances, of Huxley (1959). Huxley (Table I, 1959) lists intervals between spikes and intervals between subthreshold responses, respectively, for a number of different ΔV values, representing calcium concentrations from 44

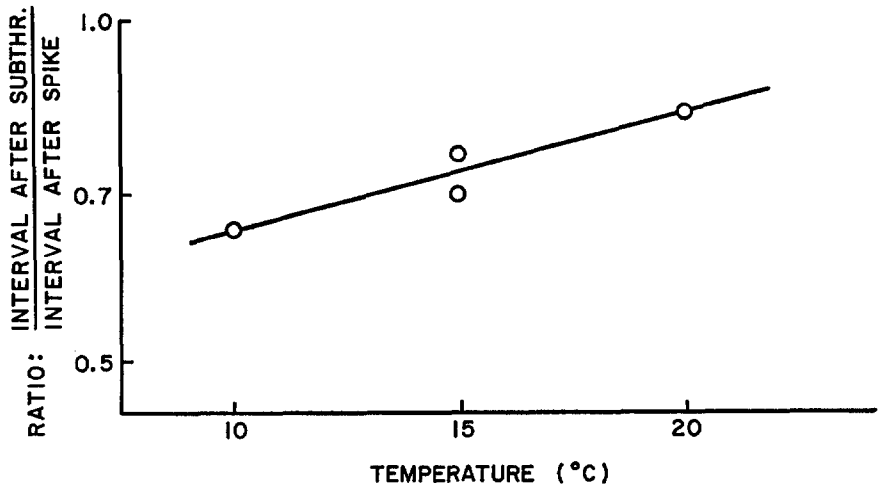

FIGURE 7. Effect of temperature upon the ratio of interval after subthreshold response to interval after spike. Temperature on a linear scale is plotted against ratio on a logarithmic scale. The ratio increases by 2.8% per degree.

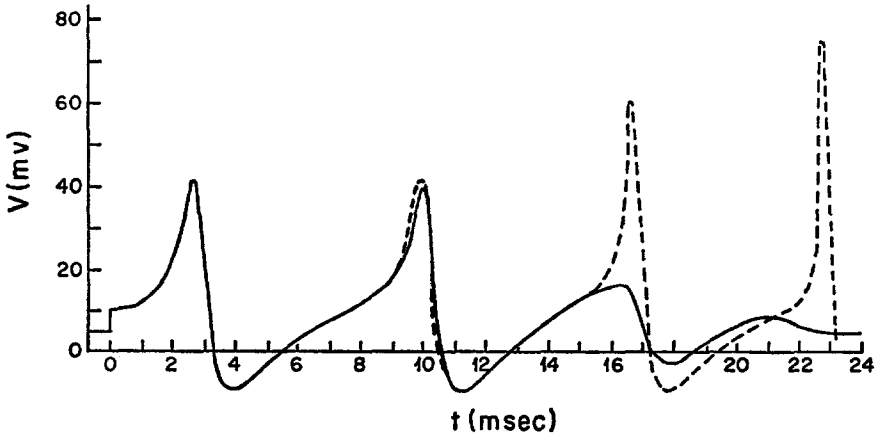

FIGURE 8. Response of the space-clamped calculated axon to brief depolarizing pulses, superimposed upon a constant current of 8.75 μamp/cm^2. This predicted behavior approximates that of a system demonstrating an unstable limit cycle. Temperature, 18.5°C. *Redrawn from Cooley, Dodge, and Cohen (1965).*

mM $CaCl_2$ (normal) to 4.4 mM $CaCl_2$ (extremely decalcified). In partially decalcified computed axons with an intermediate calcium concentration (e.g. 18 or 19 mM $CaCl_2$), the interval between spikes exceeds the interval between subthreshold responses. This approximates the conditions prevailing for most of our experimental axons and confirms our results. At lower calcium concentrations (e.g. 11 mM $CaCl_2$), intervals between subthreshold responses exceed intervals between spikes for the calculated axon. Whether a cross-over point also exists for the real axon is not known. All that can be said is that at our lowest $CaCl_2$ concentration, 7.5 mM, a cross-over point was not found in the real axon.

In conclusion, an explanation for the existence of skip runs is somewhat difficult. They may possibly be caused by variation in membrane area with fluid flow rate fluctuations in the glucose gap. Or they may possibly reflect random variation in threshold caused by fluctuation of voltage across the resting membrane (cf. Verveen and Derksen, 1968; Lecar and Nossal, 1968).

It is not probable that the intermittent spike phenomenon is caused by membrane area fluctuations, since both the frequency of all events (super and subthreshold) in the train and the proportion of spikes in the train are functions of temperature and of stimulus intensity. Membrane area does not depend directly upon these factors. It is therefore a distinct possibility that the intermittent spike phenomenon may reflect a systematic variation in some parameter closely related to threshold.

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