

BEHAVIOR OF SOLUTIONS OF THE HODGKIN-HUXLEY EQUATIONS AND ITS RELATION TO PROPERTIES OF MECHANORECEPTORS

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ABSTRACT The membrane current in the Hodgkin-Huxley equations is considered to be a stimulus to the membrane and the responses to the stimulus are numerically calculated. Responses of the Hodgkin-Huxley model to an alternating current superimposed upon a constant bias current show qualitative analogy to responses of biological mechanoreceptors. The intensity of the bias current seems to correspond to the degree of adaptation of actual receptors.

INTRODUCTION

It was in 1952 that Hodgkin and Huxley constructed a model of excitable nerve membrane on the basis of a series of experiments on a squid giant axon (Hodgkin and Huxley, 1952). Although several questions have been put forward about the sodium theory, the role of the Hodgkin-Huxley equations (abbreviated as the H-H equations below) as an equivalent circuit model is still significant.

The H-H equations were originally formulated under the voltage-clamp condition. However, numerical solutions for the equations under other conditions have been reported. Hodgkin and Huxley (1952) calculated the response of the equations to a sudden displacement of the membrane potential. Cole, et al. (1955) computed the membrane potential to step current stimuli under the space-clamp condition. Propagation of nerve impulse under a non-space-clamp condition was also obtained (Fitz-Hugh, 1962; Cooley et al., 1965).

Furthermore, the mathematical structure of the H-H equations has been investigated by various authors. FitzHugh (1960, 1969) examined the excitation process of the equations to a sudden displacement of membrane potential using the phase-plane analysis. Cooley et al., (1965) studied the stability of the equations under a constant membrane current.

On the other hand, the H-H equations may be regarded not only as a model of the axon membrane but also as a more general model of excitable membranes. For

example, Agin (1964) explained "impulse frequency vs. stimulus intensity" relationship of biological receptors assuming that the impulse-initiation process of receptors does not differ essentially from the excitation process of axon membrane, and that the intensity of membrane current of the H-H equations corresponds to the intensity of external stimuli imposed upon receptors.

In spite of all these investigations, the H-H equations have not been examined under a dynamically changing membrane current. Indeed, step current stimuli treated by Cole et al. (1955) may be considered dynamic in one sense. In this case, however, once the membrane current changes from zero to a certain value, it remains constant and the whole equations form an autonomic system. In contrast to this case, there may be situations in which the total current flow of excitable membrane continues to change dynamically. One such instance may be an excitable membrane of mechanoreceptors which are subjected to repetitive external stimuli.

The purpose of this paper is to investigate the responses of the H-H equations to a dynamically changing membrane current. A sinusoidal current with a bias is used as input to the equations and the responses of the equations are computed for various amplitudes and frequencies of the sinusoidal current superimposed upon the bias current of low and high intensities. The results thus obtained are compared with the experimental results on mechanoreceptors of two different types.

THE HODGKIN-HUXLEY EQUATIONS

The H-H equations are nonlinear ordinary differential equations described in Eqs. 1-4.

$$I = C_M \cdot dV/dt + \bar{g}_K \cdot n^4(V - V_K) + \bar{g}_{Na} \cdot m^3 \cdot h(V - V_{Na}) + \bar{g}_L(V - V_L), \quad (1)$$

$$dm/dt = \alpha_m(V) \cdot (1 - m) - \beta_m(V) \cdot m, \quad (2)$$

$$dh/dt = \alpha_h(V) \cdot (1 - h) - \beta_h(V) \cdot h, \quad (3)$$

$$dn/dt = \alpha_n(V) \cdot (1 - n) - \beta_n(V) \cdot n, \quad (4)$$

where V is membrane potential (depolarization positive) (mV), I is membrane current density (outward positive) ($\mu\text{A}/\text{cm}^2$), m is sodium activation, h is sodium inactivation, n is potassium activation, and t is time (ms).

The sign convention of V and I is opposite to that originally used by Hodgkin and Huxley. Numerical solutions of the H-H equations to various waveforms of membrane current $I(t)$ are computed by the Runge-Kutta method with parameter values at 6.3°C.

PROPERTIES OF MECHANORECEPTORS

In this section, some of the properties of mechanoreceptors are briefly discussed in order to clarify the correspondence between the H-H equations and biological receptors.

It is well-known that a mechanoreceptor responds synchronously to periodic stimuli. Impulse discharges in a rapidly adapting cutaneous receptor of the glabrous skin of a monkey and in a Pacinian corpuscle are shown in Fig. 1 *a-d*. Stimuli and responses are drawn together in a set of recordings. The stimulus consists of a stepwise indentation and a sinusoidal oscillation. As is shown by the figures, these receptors do not respond to the steadily maintained indentation and the response becomes synchronized gradually as the sinusoidal component of the stimulus increases. The relationship between the amplitude of the sine wave and the number of impulses initiated in one cycle of the sine wave is given in *e* and *f*.

The response of the rapidly adapting cutaneous receptor is synchronized (i.e. one impulse for each cycle of the sine wave) to the stimuli most easily at 40 Hz, which then may be called the optimum frequency. Fig. 1 *e* shows the experimental result for

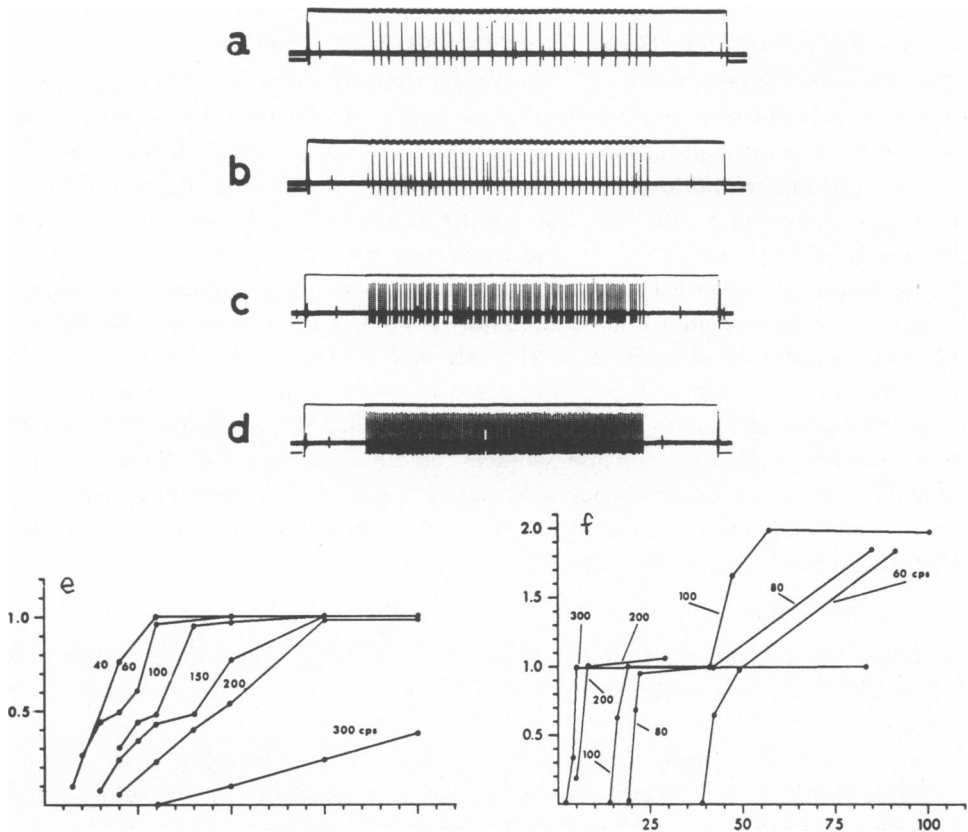


FIGURE 1 Impulse discharges (*a-d*) and intensity-response curves (*e* and *f*) of a rapidly adapting cutaneous receptor and a Pacinian corpuscle, responding to vibration superimposed upon indentation of 550 μm applied to the skin. *a*, *b*, and *e* are of the rapidly adapting cutaneous receptor, and *c*, *d*, and *f* are of the Pacinian corpuscle. The frequencies and amplitudes of the vibration shown in *a-d* are: (*a*) 40 Hz, 14 μm, (*b*) 40 Hz, 18 μm; (*c*) 150 Hz, 16 μm; (*d*) 150 Hz, 19 μm. See Talbot et al. (1968) for experimental details.

the stimulus frequencies 40 Hz and above. On the other hand, Fig. 1*f* shows the responses of the Pacinian corpuscle for frequencies 300 Hz and below. The optimum frequency for the Pacinian corpuscle is apparently 300 Hz. Note that each of the two experiments employed a half of what seems to be the desired frequency range, i.e. a range containing the optimum frequency in its center.

Fig. 2 shows the impulse discharges in a slowly adapting cutaneous receptor, which adapts slowly to a steadily maintained indentation. Its impulses are modulated by the sine wave superimposed upon the indentation.

In summary, there are two kinds of receptors of cutaneous sense, and they show synchronization and modulation in responses to vibratory stimuli (see Talbot et al., 1968).

A MODEL OF RECEPTOR BY THE H-H EQUATIONS

The Relationship Between Membrane Current and Stimulus

The membrane current $I(t)$ in Eq. 1 is assumed to be proportional to the mechanical stimulus. It is generally believed that the receptor potential evoked by stimuli causes the current flow through the adjoining part of the membrane which then fires an impulse. In this paper, however, the receptor potential is not taken into consideration as the cause of impulse initiation. Instead, the stimuli and the current are assumed to be directly related to each other. The reason is described briefly below.

The relationship between the receptor potential and the impulses in a Pacinian corpuscle has been examined in detail (Sato, 1961). If a Pacinian corpuscle is stimulated by a sinusoidal vibration of a relatively high frequency, the receptor potential also changes sinusoidally. In addition, it has a tonic component which seems to be formed by some summation effect caused possibly by the accumulation of ions. As the frequency of the vibration increases, so does the tonic component of the receptor potential, while the impulse frequency decreases. This can be explained by the hypothesis that the impulses are produced by the membrane current which does not have any summation effect, and not by the receptor potential.

DC Bias

In examining the responses of the H-H equations to an alternating current, the sinusoidal current is superimposed upon a DC bias current. The reasons are given below.

(a) If membrane current $I(t)$ does not have the DC component, it is naturally negative during a half of a cycle of the sine wave. It means that the stimulus current flows inward from outside of the membrane, which is at variance with the general concept of a receptor.

(b) In examining the responses of a mechanoreceptor, the stimulator is applied closely to the receptor or to the skin with a constant pressure.

(c) For cutaneous receptors no experiments have been reported employing vibration without constant pressure, but such experiments have been carried out by many physi-

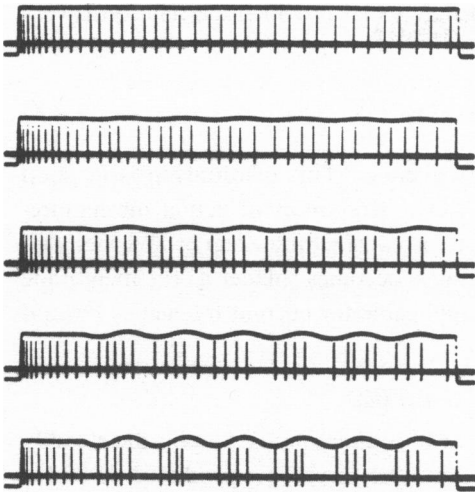


FIGURE 2

FIGURE 2 Impulse discharges of a slowly adapting cutaneous receptor to a steadily maintained skin indentation of $550\ \mu\text{m}$ (upper set of records), and when a 5 Hz sinusoidal stimulus is superimposed on that step, at sine wave amplitudes of $23\ \mu\text{m}$, $46\ \mu\text{m}$, $72\ \mu\text{m}$, and $114\ \mu\text{m}$, for the second, third, fourth, and fifth sets of records respectively. See Talbot et al. (1968) for experimental details.

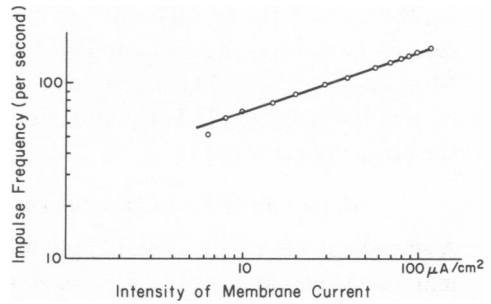


FIGURE 3

FIGURE 3 Relationship between the intensity of the membrane current and the impulse frequency. The open circles represent the points where the H-H equations are numerically solved and the impulses are counted.

ologists to examine such receptors as Johnston's organ or hair cells of the auditory organ which can be easily fixed firmly in position. For example, a sensory hair of the auditory organ of a bell-ring insect (*Homoegryllus japonicus*) moves synchronously to the sound wave, producing the receptor potential and impulses at its base. The receptor potential is perfectly synchronized to the sound wave of frequency below 300 Hz, and it has a wave form of a rectified sinusoidal wave. Similar receptor potentials can be observed for sensory hairs of insects, the vestibular organ, the cochlea, etc. Therefore, a similar result would be expected for a cutaneous receptor if it was stimulated by a vibration without a constant pressure.

In any case it seems proper to have DC bias with the sinusoidal current so that the current is assumed to be proportional to the stimulus.

Responses to DC Current

Fig. 3 shows the relationship between the intensity of the membrane current and the impulse frequency. Both abscissa and ordinate have logarithmic scales. Impulse frequency is defined as the reciprocal of the mean of 10 intervals between successive impulses. Impulses produced within 100 ms after the onset of the stimulus are discarded in order to exclude the transitional state. This relationship was first presented

by Agin (1964). Here it is rewritten in logarithmic scales in which the relation is very well approximated by a line given by

$$R - 50 = 10(I - 6.3)^{0.5}, \quad (8)$$

where R (per second) stands for the impulse frequency. This relationship is in good agreement with the so-called Steven's Power Law. Responses of actual mechanoreceptors have been shown to follow this law to a considerable degree (Werner and Mountcastle, 1965). The amplitude of the impulse becomes smaller as the membrane current increases; the H-H equations are not applicable for current intensities beyond the range indicated in Fig. 1.

Responses to Sinusoidal Current with a Small Bias

A sinusoidal wave with an initial phase angle of 0° is superimposed upon the steadily maintained bias at its onset. Fig. 4a shows the impulse discharges produced by 80 Hz sinusoidal current of various amplitudes superimposed upon $6.5 \mu\text{A}/\text{cm}^2$ DC bias.

It is interesting that a very weak AC current inhibits impulse initiation; e.g., impulses are generated at a rate lower than 25 impulses/s for $0.5 \mu\text{A}/\text{cm}^2$ AC current with $6.5 \mu\text{A}/\text{cm}^2$ bias (the uppermost trace of Fig. 4a), while 55 impulses are generated in 1 s for $6.5 \mu\text{A}/\text{cm}^2$ DC bias alone (Fig. 3). This inhibition of impulse initiation by weak AC current can be explained qualitatively by the structure of the H-H equations as follows. As Cooley et al. (1965) pointed out, the stable states of the H-H equations under a constant membrane current can be summarized as Fig. 5. With no AC current, the system state of the H-H equations is attracted to the stable limit cycle at the onset of $6.5 \mu\text{A}/\text{cm}^2$ bias and continues to trace the cycle with repetitive

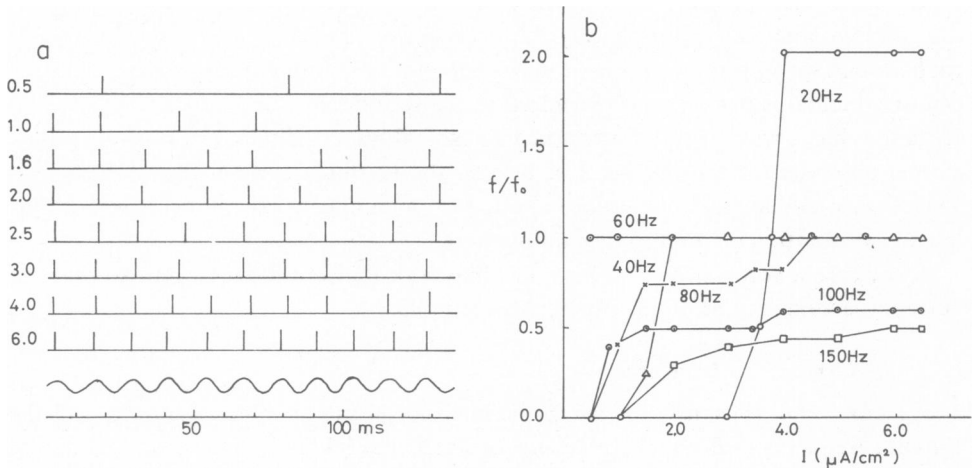


FIGURE 4 (a) Impulse discharges of the H-H model to a 80 Hz sinusoidal current of various amplitudes ($\mu\text{A}/\text{cm}^2$) superimposed on $6.5 \mu\text{A}/\text{cm}^2$ DC bias. (b) Intensity-response curves for the H-H model to a sinusoidal current of various frequencies superimposed on $6.5 \mu\text{A}/\text{cm}^2$ DC bias.

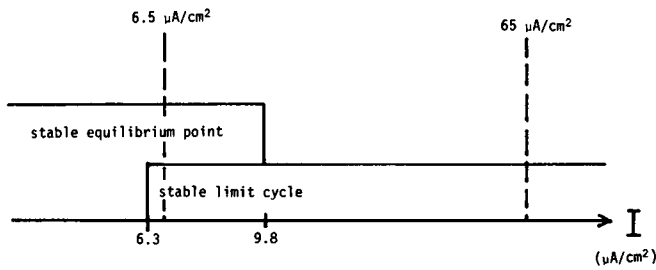


FIGURE 5 Stable states of the H-H eqs. Note that the stable equilibrium point and the stable limit cycle exist simultaneously for $6.3 < I < 9.8 \mu\text{A}/\text{cm}^2$. Broken lines show the intensities of small and large DC bias current employed in the calculations.

impulses. On the other hand, when a weak AC current is superimposed, the system state of the equations floats between the equilibrium point and the limit cycle, resulting in a rather slow discharge rate.

As the amplitude of the AC current increases, the impulse initiation becomes regular, and at $6.0 \mu\text{A}/\text{cm}^2$ it is perfectly synchronized to the AC component of the membrane current.

Fig. 4 *b* shows the processes of synchronization for various frequencies. The ratio of the impulse frequency f to the frequency of the AC component f_0 is plotted against the amplitude of the AC component. The time length for which the impulses are counted is arbitrarily determined so that the ratio f/f_0 may be a simple fraction. If the impulses are counted for a longer time length, the curve will become smoother. However, there is no point in taking a very long period considering that an actual physiological experiment ends in a certain short time. Furthermore, a longer period would make this curve only smoother and not change the essential qualitative property of it. In this figure responses to very weak AC current (too weak to cause the inhibitory effect mentioned above) are omitted, but they are naturally the same as those to DC current with no AC component superimposed; i.e. 55 impulses are generated in 1 s. At 60 Hz, the impulse initiation is apparently synchronized at any amplitude of the sine wave, but this is because the impulse frequency for DC current of amplitude $6.5 \mu\text{A}/\text{cm}^2$ is 55/s which is very close to the frequency of the sine wave. At higher frequencies the inhibition of impulse initiation is weak but at the same time synchronization of one to one response (one impulse for one cycle of the sinusoidal wave) is not easily obtained.

Fig. 4 *a* and Fig. 1 *a-d* bear a significant resemblance, except that the H-H model of a receptor continues to initiate impulses to DC current while a rapidly adapting receptor does not. This difference seems to result from the fact that the H-H equations represent the membrane characteristics and not the tissues surrounding the receptor which are estimated to affect the receptor's characteristics especially in its adaptation to a constant indentation.

Synchronization of impulse initiation of the model (Fig. 4 *b*) and that of an actual receptor (Fig. 1 *e* and *f*) look quite alike. As has been already mentioned, Fig. 1 *e*

and f show the responses of a rapidly adapting cutaneous receptor and of a Pacinian corpuscle, and the frequencies employed in these experiments range above the optimum frequency for the rapidly adapting cutaneous receptor and below the optimum for the Pacinian corpuscle. The responses of the H-H model shown in Fig. 4*b* have its optimum frequency around 60 Hz. Therefore, in this case the responses are shown for the frequencies ranging from the lower to the upper regions around the center optimum frequency. The characteristics of both of the two kinds of receptors shown in Fig. 1*e* and *f* are represented together in Fig. 4*b*. If the curves in Fig. 4*b* are divided into two groups so that one of them consists of traces for frequencies 60 Hz and below and the other consists of traces for 60 Hz and above, then these two separate groups will resemble the experimental results shown in Fig. 1*e* and *f*. In comparing the calculated responses of the model with the actual experimental results, the values of the optimum frequencies have no importance at all, for the optimum frequency of the model may be easily changed by choosing values for the parameters of the equations. In this paper they are given the values originally measured for the giant squid axon at 6.3°C. These parameter values were adopted just for convenience sake and some other values are equally acceptable as long as they are in reasonable ranges. Furthermore, we are interested only in qualitative aspects of the H-H equations.

It is not surprising that the solutions of the H-H equations should have properties such as shown in Fig. 4, as any system described by nonlinear differential equations may well have properties of synchronization. However, it is nonetheless of interest that synchronization found in actual receptors can be, at least qualitatively, simulated by the H-H equations.

Responses to Sinusoidal Current with a Large Bias

In this section the DC bias is set at 65 $\mu\text{A}/\text{cm}^2$. The amplitude of the impulses initiated for 6.5 $\mu\text{A}/\text{cm}^2$ DC current is about 100 mV, while for 65 $\mu\text{A}/\text{cm}^2$ DC current the impulses have amplitude of about 60 mV. Furthermore, the possible dynamic range of the amplitude of the sine wave is larger at a large bias. These are the two major points that differentiate the situation from that under a small bias.

Fig. 6*a* shows the impulses produced by a 20 Hz sinusoidal wave of various amplitudes. One to one response cannot be obtained at any amplitude of the sinusoidal wave probably due to the high impulse frequency under a strong DC current with no AC component. In this case, "pulse position modulation" is a more proper term than "synchronization." Note that up to the amplitude of 30 $\mu\text{A}/\text{cm}^2$, the ratio f/f_0 does not change with the amplitude's increase, while the interval lengths and the amplitudes of the impulses are modulated. At 40 $\mu\text{A}/\text{cm}^2$ impulses produced in one cycle of the sinusoidal wave line up in a decreasing order in their amplitudes.

Fig. 2 differs from Fig. 6*a* in that the impulses of an actual receptor are not obviously modulated in their amplitude. However, the impulses shown in Fig. 2 were recorded by an electrode applied to a cutaneous fiber, so that we may not observe the impulses within the receptor itself. Impulses recorded from a Pacinian corpuscle imply that the receptor of this fiber (Fig. 2) produce impulses that are also modulated

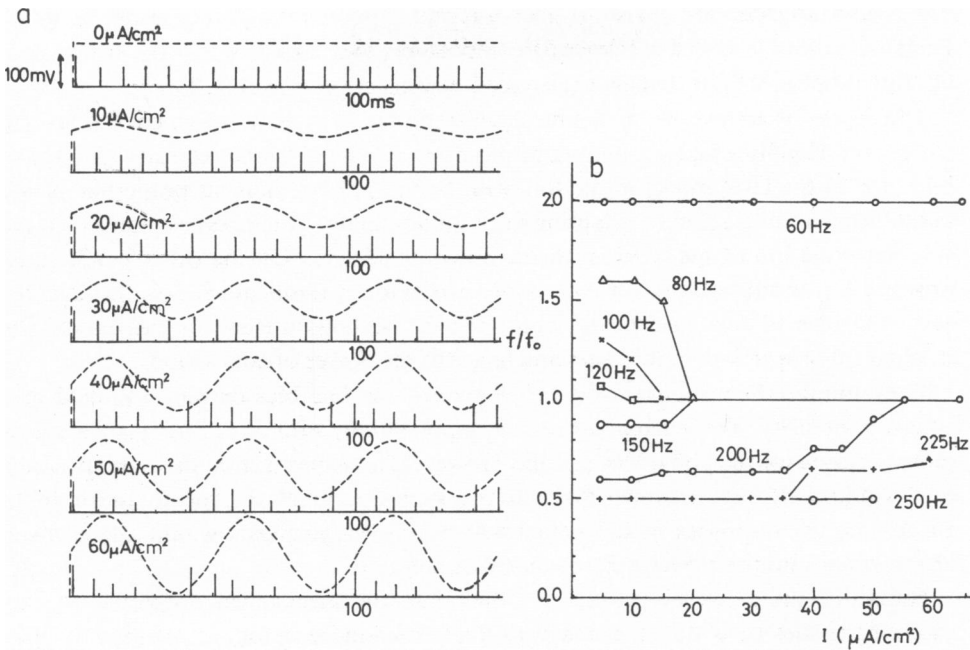


FIGURE 6 Impulse discharges and intensity-response curves of the H-H model. See the caption for Fig. 4. The DC bias in this case is $65 \mu\text{A}/\text{cm}^2$ and the frequency of the sinusoidal current in *a* is 20 Hz.

in their amplitude. If a threshold level is set to equalize amplitudes greater than the level and to erase impulses below it, then the response shown in Fig. 6 *a* will be converted to one such as shown in Fig. 2.

Fig. 6 *b* shows how this model with a high bias current synchronizes to the stimuli. As seen in the figure, a sinusoidal wave of a small amplitude does not inhibit impulse initiation. This is obviously because the equilibrium point of the H-H equations is unstable and the limit cycle is the only stable state for the equations under high bias current (see Fig. 5). Furthermore, there is no obvious jump from nonsynchronized state to synchronization. As has been already mentioned, the term "modulation" is better fit for the behavior than "synchronization."

Adaptation and Bias

In examining the responses of the model to sinusoidal current, DC bias current has been added to AC current in order to achieve a good similarity to actual responses. Responses of a rapidly adapting receptor which does not respond to a steadily maintained indentation can be simulated well by the model under a small bias. The model under a large bias behaves like a slowly adapting receptor. This result corresponds with the view that at least part of adaptation is due to the properties of surrounding tissues. Ozeki and Sato (1965) investigated the receptor potentials of the non-myelinated nerve terminal in Pacinian corpuscles of which the lamellae were removed.

The results indicated that the short-lasting receptor potential obtained from the intact Pacinian corpuscle under a sustained compression was attributed to the mechanical filtering properties of the lamellae (also see Loewenstein and Skalak, 1966).

The degree of adaptation of the mechanoreceptors such as Pacinian corpuscles and slowly and rapidly adapting cutaneous receptors is related to the intensity of the DC bias used in the H-H model in the following way. The mechanical properties of the tissues surrounding a rapidly adapting receptor attenuate static pressure applied to the skin, resulting in low bias current through the membrane. On the other hand, static pressure is transmitted to a slowly adapting receptor without much loss through tissues, the bias in this case being large. Thus the bias intensity is related to the mechanical properties of the tissues and hence to the degree of adaptation.

In examining the responses of the H-H model, the DC bias current was held at a constant intensity. Bias current decreasing exponentially with time, for instance, seems more accurate for the above discussion. However, no experimental data are available that would verify the assumed form of the time course of the membrane current. Examining the responses of the model with a time-varying bias would admit much arbitrariness into the model and was therefore abandoned.

Naturally, there are several factors other than the mechanical properties of surrounding tissues to which the adaptation of mechanoreceptors is attributed. For instance, the work of Nakajima and Onodera (1969) indicates that adaptation of the stretch receptor in the crayfish is mainly due to the action of an electrogenic sodium-pump of the impulse-generating membrane. The H-H equations do not provide any explanation for this sort of adaptation attributed to the properties of the membrane itself. However, the relationship between the degree of adaptation and the bias intensity shown in this paper is related to the filtering property of the surrounding tissues without serious contradictions, and the mechanical property contributes to the adaptation at least partly. Thus, relating the degree of adaptation to the bias intensity, however simple it may be, helps to simulate some aspects of the mechanoreceptors qualitatively.

CONCLUSION

Responses and characteristics of the H-H equations to membrane current regarded as a stimulus have been investigated in connection with the properties of mechanoreceptors.

Responses of the H-H equations to membrane current with AC component show the characteristics of synchronization and modulation which indicate the validity of the H-H equations as a model of mechanoreceptor such as cutaneous receptors and Pacinian corpuscles.

Membrane current with a low bias has been shown to produce responses similar to those of a rapidly adapting receptor, and a slowly adapting receptor has been well simulated by the model under a large bias. This may be ascribed to the difference of surrounding tissues which attenuate the static pressure applied to the skin.

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