THE REPOLARIZATION PHASE OF THE CARDIAC VENTRICULAR ACTION POTENTIAL: A TIME-DEPENDENT SYSTEM OF MEMBRANE CONDUCTANCES

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ABSTRACT. A system for the generation of the repolarization phase of the ventricular action potential is described. The system is based on time-dependent changes in membrane conductance to sodium and potassium ions. However, the changes in conductance during an action potential retain a degree of voltage dependence through the initial conditions which depend on previous depolarizations of the membrane. The equations describing the system were solved with an analog computer and various action potential forms are reproduced. The effects of hyperpolarizing and depolarizing current applied during an action potential are investigated. The changes in shape of an action potential after a change in the rate of stimulation show partial agreement with previous experimental findings. The applicability of time-dependent and voltage-dependent systems for the generation of the repolarization phase of the ventricular action potential is discussed.

INTRODUCTION

The success of the Hodgkin and Huxley equations (HH,[1] 1952) in describing the generation of the action potential in squid giant axon has led to attempts to use these equations in a more or less modified form for a description of the generation of the cardiac action potential. The experimental evidence of Draper and Weidmann (1951) and Weidmann (1955, 1956) indicated that the generation of the initial depolarization phase of the action potential of cardiac muscle resembles closely that in the squid axon as described by HH. Weidmann (1951) was the first to report that during the repolarization phase of the cardiac action potential the membrane conductance was lower than in the resting state. Such a drop in membrane con-

[1] Hodgkin and Huxley will be referred to by HH in this paper.

ductance on depolarization is not predicted by the HH equations and the problem thus arose of assessing the importance during the repolarization phase of a system of the kind described by the HH equations. Two types of hypotheses have been put forward. In the first, exemplified by the model of the cardiac action potential put forward by Noble (1960, 1962), the conductances are at all times functions of the membrane potential and the HH equations (with some modifications) play an important part throughout the whole of the action potential. In the second hypothesis (Woodbury, 1960; Johnson and Tille, 1960; and George and Johnson, 1963), voltage-dependent conductance changes are important only during the first few milliseconds of the action potential. Thereafter, throughout the long phase of repolarization, the membrane conductance is a function of time and is independent of the membrane potential.

Although it would be difficult to reconcile a system of the kind described by Noble with the observed changes in shape of the cardiac action potential resulting from different patterns of stimulation (Gibbs, Johnson, and Tille, 1963, 1964), the available experimental evidence is, in our opinion, insufficient to allow a final choice in favour of one or the other of the two kinds of hypotheses. The possibility that the repolarization phase of the cardiac action potential is generated partly by voltage-dependent and partly by time-dependent processes should also be considered.

In the present paper we describe a simple system for the generation of the repolarization phase of the cardiac action potential based on time-dependent changes in sodium and potassium conductances. However both the sodium and potassium conductances retain a degree of voltage dependence through their initial values which depend on previous depolarizations of the membrane. This system is capable of reproducing various action potential shapes recorded in ventricular fibres and also some of the changes in shape of the action potential that occur when the rate of stimulation is altered.

RESULTS

The Action Potential Waveform. The model of the repolarization phase of the ventricular action potential which is described here is based on the concept of time-dependent membrane conductances. As a guide, we used the time courses of potassium and sodium conductances which were derived on the basis of certain assumptions in an earlier paper (Johnson, Tille, and Wilson, 1961) and also the observed fact that the fast terminal phase of repolarization is identical in action potentials of different durations. This superimposability of the fast terminal phase of repolarization has been observed in frog (Brady and Woodbury, 1960), and in the dog (Hoffman and Suckling, 1954). In rabbit ventricular fibres the terminal phases are superimposable only in action potentials initiated at the same rate of

stimulation (*e.g.* when the fibre is recovering after a high rate of stimulation). We have not attempted to account for the fast changes in the shape of the ventricular action potential in the rabbit which occur when the preparation is stimulated at irregular rates (Gibbs and Johnson, 1961; Gibbs, Johnson, and Tille, 1963).

We assume that the rising phase of the action potential is generated by a voltage-dependent, transient HH-like increase in the sodium conductance, g_{Na},[2] (see HH, 1952) which, however, is more strongly inactivated than in the squid axon and becomes unimportant within a few milliseconds after the upstroke of the action potential. Thereafter g_{Na} is assumed to follow a time-dependent course. The inactivation of the voltage-dependent part of g_{Na} can be accomplished, for example, by changing the HH equation for g_{Na} from $g_{Na} = \bar{g}_{Na}\, m^3 h$ to $g_{Na} = \bar{g}_{Na}\, m^3 h^2$ (George and Johnson, 1963). Our analog computer facilities were not sufficient to solve the HH equations for g_{Na}, so to obtain a realistic starting point for the computations (*i.e.* one with a very high value of g_{Na}) the decay of the HH increase in g_{Na} was approximated by the function $c_0 e^{-\gamma t}$ and computation was thus begun at the peak value of g_{Na}.

From the fact that the fast terminal portions of the repolarization phases are superimposable, one can deduce that the time courses of g_K must at that time be the same in all action potentials; the same applies to g_{Na}. It would seem therefore, that the different durations are caused mainly by a variable delay which precedes the fast part of the repolarization phase. The time courses of changes in g_K during an action potential derived by Johnson, Tille, and Wilson (1961) and by Johnson and Wilson (1962) consist of a fast drop in g_K followed by a slow and then fast rise back to the resting level. The initial drop in g_K from its high resting value is represented here by the function $a_0 e^{-\alpha t}$. To reproduce the rise in g_K a function is required which increases slowly at first and then, after a variable delay, increases rapidly to a final steady value; the time course of this terminal fast rise being the same in all cases. A function satisfying these requirements is the solution of the differential equation

$$\frac{db}{dt} = \beta b^2 (B - b), \qquad 0 < b < B \tag{1}$$

where β and B are positive constants. The solutions of this equation are superimposable (for any one set of values of β and B) and the duration of the slow initial portion depends on the initial value of b. Thus, finally, the total potassium conductance during the action potential was made the sum of three quantities:

$$g_K = a + b + g_{K0} \tag{2}$$

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[2] All conductances referred to in this paper are chord conductances unless specified as slope conductances.

in which g_{K_0} is a positive constant, b is the solution of equation (1), and a is the solution of the equation

$$\frac{da}{dt} = -\alpha a, \tag{3}$$

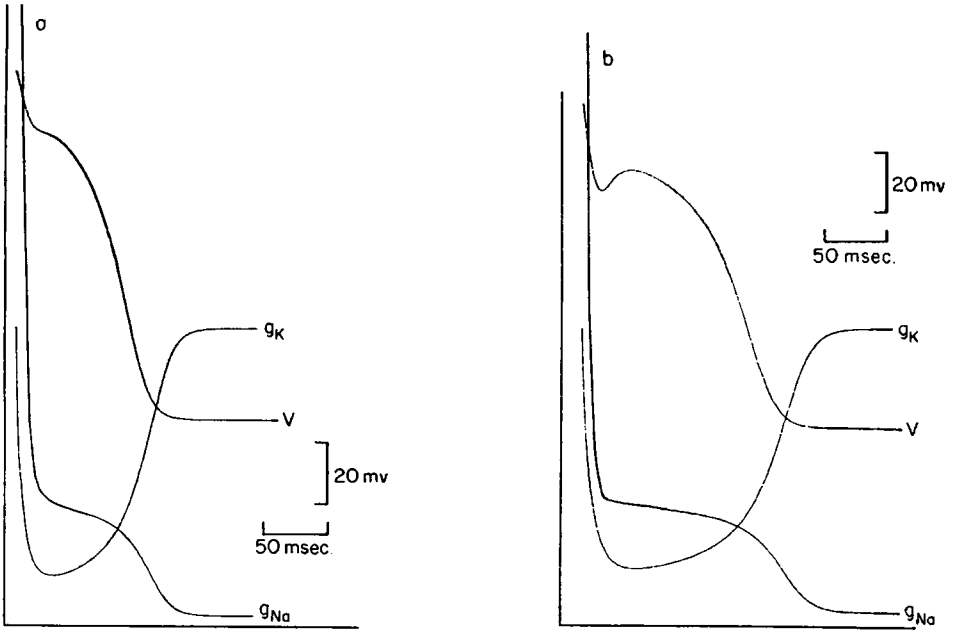
in which α is a positive constant. To make g_K the same before and after an action potential, the sum of a_0 and b_0 (which are the initial values of a in equation (3) and b in equation (1) respectively) was made equal to B in equation (1). The resultant time courses of g_K can be seen in Fig. 1.

It can be inferred from Figs. 2 and 3 of Johnson, Tille, and Wilson (1961) that the time courses of g_K and g_{Na} during the action potential are coupled or synchronized in some way. For example, both the total duration of the changes in g_{Na} and the time of occurrence of the fast terminal change are the same as in the case of g_K. This synchronization was achieved by making the time-dependent part of g_{Na} proportional to $(B - b)$. Thus

$$g_{Na} = c + k(B - b) + g_{Na0}$$

in which g_{Na0} is the resting state sodium conductance. For convenience of computation this was rewritten as

$$g_{Na} = c + d \tag{4}$$



in which c is the solution of

$$\frac{dc}{dt} = -\gamma c, \qquad c_0 > 0 \tag{5}$$

and

$$d = \delta(1 - \epsilon b) \tag{6}$$

in which γ, δ, and ϵ are positive constants such that $\delta = kB + g_{Nao}$, $\epsilon = k/(kB + g_{Nao})$, and c_0 is the initial value of c. The resultant time courses for g_{Na} can be seen in Fig. 1.

Action potential waveforms were then obtained by solving on an analog computer the differential equations (1), (3), and (5) together with

$$\frac{dV}{dt} = -\frac{1}{C}(i_K + i_{Na}) \tag{7}$$

with

$$i_K = g_K(V - V_K) \tag{8}$$

$$i_{Na} = g_{Na}(V - V_{Na}) \tag{9}$$

in which V is the membrane potential at any time, and C is proportional to the membrane capacitance, and g_K and g_{Na} are given by equations (2) and (4) respectively. V_{Na} and V_K represent the sodium and potassium equilibrium potentials;

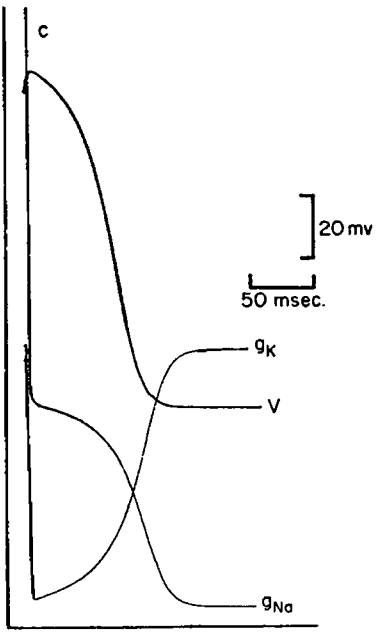


FIGURE 1*a* to *c* Computed action potential waveforms together with concurrent changes in membrane conductances. In each figure the trace marked V is the action potential and the traces marked g_K and g_{Na} are the time courses of the potassium and sodium conductances. All three traces in each figure are plotted on the same time scale. The conductances are plotted in arbitrary units; the abscissa corresponds to zero conductance. Values of constants used in the computation are given in the Appendix.

for ease of computation the voltage scale was shifted so that V_{Na} was set always at +200 mv while V_K could be varied and was usually kept at +60 mv. Three action potential forms commonly found in the rabbit ventricle are reproduced in Fig. 1 together with plots of the corresponding changes in g_K and g_{Na}.

The Effects of Applied Current. To simulate the passage of current from an intracellular electrode through the fibre membrane equation (7) was modified to

$$\frac{dV}{dt} = -\frac{1}{C}(i_K + i_{Na} + i) \tag{10}$$

in which i could be preset to any constant value and turned on or off at any time. Fig. 2 shows action potential forms modified by the application of various amounts of hyperpolarizing current (cf. Fig. 1, Johnson and Tille, 1960).

Fig. 3 illustrates the effects of short pulses of hyperpolarizing and depolarizing current of the same magnitude passed during approximately the same time interval in the repolarization phase. The effects of current pulses of the same magnitude during the resting state are shown for comparison. It can be seen that although the

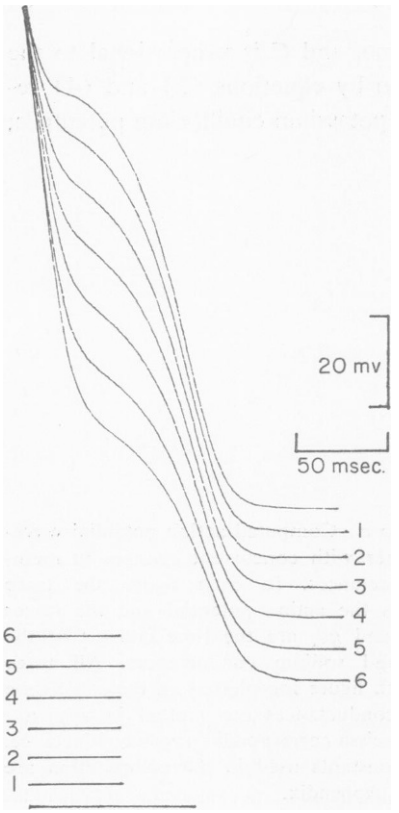


FIGURE 2 Modification of an action potential waveform (the same as that shown in Fig. 1*a*) by applied current. The uppermost trace shows the computed action potential. Traces marked 1 to 6 show the action potential waveform modified by constant hyperpolarizing currents of magnitudes given by the correspondingly numbered bars in the left-hand corner of the figure. The value of current in each case is proportional to the vertical displacement of each bar from the lowermost (unmarked) bar. The polarizing currents were turned on at the crest of the action potential and terminated at long times afterwards. (The termination of the current is not shown in the figure.)

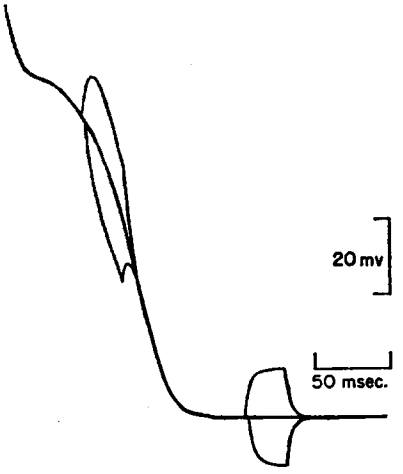


FIGURE 3 The effect of hyperpolarizing and depolarizing current of the same magnitude passed during approximately the same time interval in the repolarization phase of an action potential. The effect of current of the same magnitude and duration during the resting state is shown for comparison. The action potential is the same as that in Fig. 1*a*.

membrane conductances are voltage-independent, the changes in membrane potential caused by current pulses during the repolarization phase appear to be nonlinear.

Changes in the Action Potential Shape on Changing the Frequency of Stimulation. It was mentioned above that the duration of the computed action potential depends on the initial value of b in equation (1). To simulate the slow, experimentally observed, decrease in the action potential duration caused by an increase in the rate of stimulation, the initial value of b, b_0, must be made to increase when the rate of stimulation is increased. We therefore define another variable, $\mathfrak{B}$ the value of which during the upstroke of an action potential acts as the initial value of b. The required dependence of b_0 on time and stimulation was obtained by making $\mathfrak{B}$ the solution of the equation

$$\frac{d\mathfrak{B}}{dt} = \beta_1(V - V_r) - \beta_2(\mathfrak{B} - \beta_3) \tag{11}$$

in which β_1, β_2, and β_3 are positive constants, V_r is the membrane resting potential, and V is the membrane potential at any time. Thus $\mathfrak{B}$ is increased during every action potential and declines at all times towards the value $\mathfrak{B} = \beta_3$. With the addition of equation (11) to the model described above, the action potential shape becomes dependent on the rate of stimulation. Fig. 4 shows the relationship between the steady-state action potential area (the action potential area is defined as $\int(V - V_r)dt$ over the duration of the action potential), the steady-state value of b_o, and the rate of stimulation. The stable action potential shapes at various rates of stimulation are shown in Fig. 5. Fig. 6 illustrates the changes in area after changes in the rate of stimulation. The time courses of the changes in action potential area shown in Fig. 6 are about three times faster than the experimentally observed

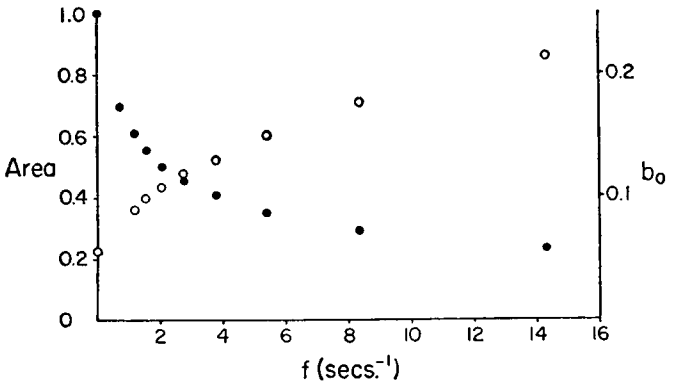


FIGURE 4 The steady-state values of the action potential area, (●), and of b_0, (○), plotted against the frequency of stimulation. The values of b_0 are given in computer units and should be divided by 10 to give the real values. Area = 1 corresponds to the maximum area; *i.e.*, the area of the first action potential after a long period of rest. Some of the action potentials are shown in Fig. 5.

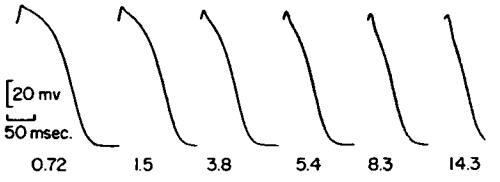


FIGURE 5 Computed steady-state action potential forms at various rates of stimulation. The rates (in beats/second) are given by the numbers below each action potential. Values of constants used in the computation are given in the Appendix.

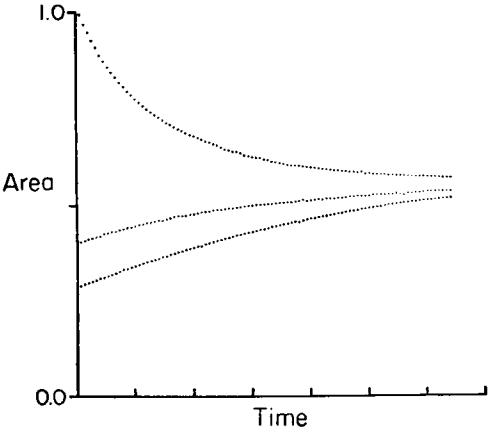


FIGURE 6 Changes in the action potential area after a change in the rate of stimulation to the rate 1.5 sec.$^{-1}$ The dots represent the areas of successive action potentials. The rates of stimulation prior to the change were: upper set of points, 0 sec.$^{-1}$ (a 2 minute period of rest); middle set of points, 3.8 sec.$^{-1}$; and lower set of points, 8.3 sec.$^{-1}$. Ordinate: area in arbitrary units. Abscissa: marked at 10 sec. intervals. The results were obtained from the same system as those in Figs. 4 and 5.

ones (*e.g.* Fig. 2 of Gibbs, Johnson, and Tille, 1963). These fast changes were adopted to save time on the computer; the required slowing can be achieved easily by reducing the rate constants β_1 and β_2 in equation (11).

DISCUSSION

Experimental results obtained from fibres in Purkinje bundles by Weidmann (1951); Chang and Schmidt (1960); Hutter and Noble (1960); Carmeliet (1961 *a* and *b*); Trautwein and Kassebaum (1961); and Hall, Hutter, and Noble (1963) represent strong evidence for voltage dependence of sodium and potassium conductances during the repolarization phases of action potentials in those fibres. In ventricular fibres there is evidence both for (Cranefield and Hoffman, 1958; Trautwein and Kassebaum, 1961) and against (Johnson and Tille, 1960, 1961; Johnson and Wilson, 1962) such voltage dependence.

The strongest argument in favour of time-dependent changes in membrane conductances, however, can be found in the changes of shape of the ventricular action potential, particularly in the rabbit, caused by changes in the pattern of stimulation. A quantitative description of these changes can be found in our paper (Gibbs, Johnson, and Tille, 1963). In this paper it has been shown that the electrical aspect of a ventricular fibre comprises a system capable of fast changes during an action potential but one in which the time course of these changes is determined in some way by quantities which change only slowly in time and one of which, in particular, can be made to stabilize at different values in the absence of stimulation.

It is clear that a successful theory of the generation of the ventricular action potential must account for the changes in shape of the action potential. At the present time at least three systems of changes in membrane conductances are consistent with the available experimental results: (*a*) a voltage-dependent system of the HH type, modified to reproduce the electrical properties of the cardiac action potential (*e.g.* Noble, 1962), but in which (unlike Noble, 1962) the voltage dependence of the various functions of membrane potential is not unique but changes with time and stimulation, (*b*) a system of time-dependent changes in conductance in which the "constants" in the differential equations governing the membrane conductance can be considered constant during an action potential but change slowly with time and stimulation, and (*c*) a system of time-dependent conductance changes in which the constants in the differential equations are truly constant and the different action potential shapes are determined by the initial values of the quantities concerned (an example of such a system is the model described in this paper). A combination of any of these three systems is also a possibility.

A fourth kind of system, examples of which are the HH equations for squid axon and Noble's model of the cardiac action potential, is one in which the membrane conductances are either time-independent functions of membrane potential or are given by the solutions of differential equations in which the rate constants

are time-independent functions of membrane potential. Such a system cannot reproduce the observed changes in the action potential shape together with a constant resting membrane potential and resting membrane resistance. In this kind of system all the variable quantities have a direct effect on the membrane conductances and hence slow changes in these quantities must result in concurrent changes in the membrane resting potential or the resting membrane resistance or both. In ventricular fibres, however, the membrane resting potential and resting membrane resistance are constant between action potentials. In these fibres the half-times of the changes in the variables would thus have to be shorter than the duration of the action potential, otherwise the fibre could not return to its resting potential and resting resistance. In this case there is no provision left for the slow changes in the resting fibre which must occur in order to determine the shape of the next action potential. The fact that a ventricular fibre can be conditioned (as far as the shape of the next action potential is concerned) prior to a pause in stimulation and that this conditioning persists for long times (Gibbs, Johnson, and Tille, 1964) constitutes yet more evidence that a system of this type cannot account for the ventricular action potential since at the same resting potential such a system would always tend towards the same condition after a long pause.

The changes in the action potential area caused by changes in the pattern of stimulation comprise a critical test for a model of the repolarization phase. The simple model presented in this paper does not account with any accuracy for the observed changes in area. However, there is no doubt that with the aid of various refinements the model could be made to reproduce the experimental results as accurately as desired. In this respect it is fundamentally different from Noble's model, which, even in principle, is incapable of reproducing the experimentally observed long term changes in the shape of the action potential.

Agreement between the Model and Experimental Results. It is by no means remarkable that the present model reproduces many of the experimentally observed action potential shapes since these shapes were built into the model in terms of the conductance time courses. The differential equations governing the conductances were selected to reproduce as closely as possible the conductance time courses determined from experimental results with the assumption that during the repolarization phase the chord and slope conductances are equal for both sodium and potassium ions. However, in some action potentials the magnitude of the negative curvature of the action potential waveform near the end of the plateau is very much smaller than the positive curvature during the last 10 or 20 msec. of the action potential. For this reason it is possible that the equation

$$\frac{db}{dt} = \beta b^3(B - b) \tag{12}$$

would provide an even better representation of the results than equation (1).

The variable M which is related to the action potential duration was found to obey a second order differential equation (Gibbs, Johnson, and Tille, 1963). In the present model, b_0, which controls the duration of the action potential, is given by a first order differential equation (equation 11) and hence the model in its present form cannot reproduce the result, described in the above paper, that at the same rate of stimulation the rate of recovery of the action potential area at any time is not uniquely related to the value of the area at that time. Thus, a second order differential equation would be required instead of equation (11) to provide a more accurate description of this aspect of the results. On the other hand, the slowness of the recovery of the area after a high rate of stimulation as compared with the rapidity of the decrease after a pause follows naturally from the relationship between b_0 and area, and does not have to be introduced artificially as is the case in the equation given by Gibbs, Johnson, and Tille (1963).

The dependence of b_0 on membrane potential given by equation (11), is hypothetical and is not a necessary consequence of the experimental results. It has not yet been determined by what mechanism does an action potential affect the shapes of subsequent action potentials. In the present model it is assumed that the shape of an action potential depends on previous depolarizations of the membrane. With this assumption the behaviour of b_0 given by equation (11) is consistent with the available experimental results; *viz.*, that the duration of an action potential depends in a certain way on the number and spacing of action potentials preceding that action potential and that the membrane resting potential and the resting membrane resistance are independent of the preceding action potentials.

With a suitable second order differential equation governing b_0 the model should give a good representation of the changes in area of the ventricular action potential in animals such as the guinea pig in which irregular rates of stimulation have little effect on the shape of the action potential. In the rabbit, where irregular stimulation has a pronounced effect on the action potential area, the conductances must depend in some way on yet another variable also obeying a second order differential equation.

APPENDIX

VALUES OF CONSTANTS EMPLOYED IN COMPUTING ACTION POTENTIAL WAVEFORMS SHOWN IN THE FIGURES

Constant	Equation	Figures			
		1*a*, 2, 3	1*b*	1*c*	4, 5, 6
b_0	1	0.00693	0.00616	0.00902	–
β (msec.$^{-1}$)	1	18.5	14.6	17.4	32.68
B	1	0.090	0.0892	0.090	0.090
g_{K0}	2	0.00484	0.00704	0.001	0.00594
α (msec.$^{-1}$)	3	0.160	0.116	1.372	1.292
a_0	3	0.083	0.083	0.081	0.083
γ (msec.$^{-1}$)	5	0.240	0.268	1.24	1.136
C_0	5	0.520	0.520	0.285	0.298
δ	6	0.0419	0.0419	0.0793	0.0830
ϵ	6	10.21	10.20	10.2	10.21
V_K (+mv)	8	62	64	64	58
V_{Na} (+mv)	9	200	200	200	200
V_r (+mv)	11	67	67	71.5	68
β_1 (sec.$^{-1}$)	11	–	–	–	0.06
β_2	11	–	–	–	0.0057
β_3 (sec.$^{-1}$mv^{-1})	11	–	–	–	2.14×10^{-6}
C (see τ)	7, 10				
*τ (msec.)		3.3	3.2	2.1	1.76

*The membrane conductances and membrane capacitance (C) are in arbitrary units. The desired membrane time constant was obtained by adjusting the value of C.

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