COMPUTED ACTION POTENTIALS FOR PURKINJE FIBER MEMBRANES WITH RESISTANCE AND CAPACITANCE IN SERIES

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ABSTRACT The Hodgkin-Huxley equations, as modified by Noble for computation of Purkinje fiber action potentials, have been solved numerically for a membrane whose equivalent circuit contains a constant resistance in series with part of the capacitance. The rates of depolarization and repolarization of the computed action potential have thereby been brought into agreement with measured values. Possible explanations of the frequently observed pre-plateau notch and of fibrillatory activity arise. The effects of a time-dependent K conductance dependent on the second power of the parameter n, instead of the fourth, have also been considered.

INTRODUCTION

In 1962, Noble published a modified version of the Hodgkin and Huxley (1952) equations which produced action potentials similar to those recorded from cardiac Purkinje fibers, and which could account for many of the changes in action potential shape found when stimulation rates or ionic concentrations were altered. He assumed an equivalent circuit for the membrane similar to the one employed by Hodgkin and Huxley (a pure capacitance in parallel with one emf + conductance path for each ion species contributing to the electrical behavior), except that the potassium ion conductance was divided into two parts (a time- and voltage-dependent outward rectifier, and an instantaneously voltage-dependent inward rectifier). Since then, experimental evidence has been obtained both for skeletal muscle (Falk and Fatt, 1964) and for cardiac muscle (Fozzard, 1966) which indicates that a considerable fraction of the membrane capacitance is not "pure," but has a significant resistance in series with it. Fozzard found that of a total Purkinje fiber capacitance of 9.4 $\mu F/cm^2$, 7 $\mu F/cm^2$ was in series with a resistance of 300 Ω cm^2. Apparently, then, the electrical equivalent circuit of the membrane must be modified; effects of this modification on the form of the computed action potential will be discussed in this paper.

THE EQUIVALENT CIRCUIT

Many different circuits which could account for the experimental measurements can be devised, and selection of a suitable one depends upon both morphological and practical considerations. Fig. 1 *A* illustrates the simplest acceptable one, which has already been used in the analysis of membrane impedance data (Falk and Fatt, 1964; Fozzard, 1966), and which is used for the computations of this study. It has been suggested that C_s arises in the walls of the tubules forming the sarcoplasmic reticulum, R_s being the resistance of the current path via the tubules to the cell surface. In reality, if C_s is the capacitance of a membrane, there will also be some "leakage" resistance R_p in parallel with C_s; in this case, when experimental data is analyzed in terms of the circuit of Fig. 1 *A*, then R_m, R_s, and C_s will be in error by an amount dependent on R_p. (This can be verified by equating the Laplace transform expressions for the impedances of the two circuits. Note that R_m is itself

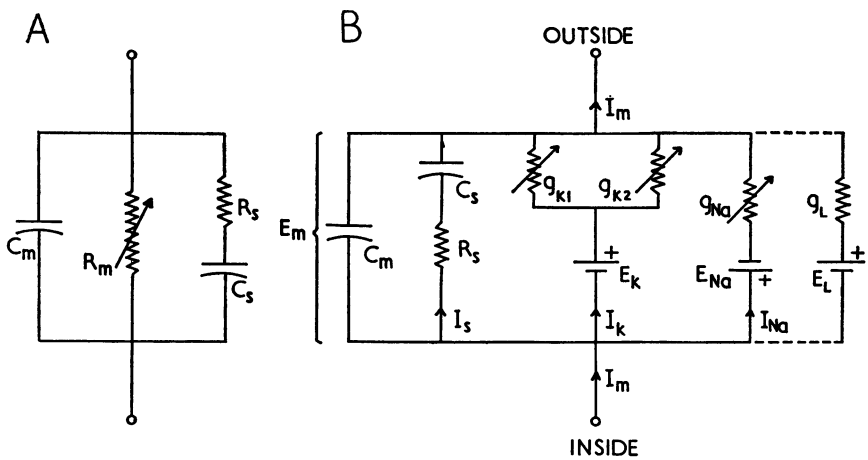

FIGURE 1 *A*. Simplified equivalent membrane circuit. *B*. Equivalent electrical circuit representing the cardiac muscle membrane. "Leakage" currents would flow through the branch on the right; other elements of the circuit are described in the text.

an equivalent, replacing all the ionic conductances of Fig. 1 *B*.) If R_p is very large, it has little effect on the size of the components of Fig. 1 *A*, and may be completely ignored. If R_p is not large but constant, then R_s and C_s will be constant but R_s will appear larger and C_s smaller than their true values. Finally, if R_p is neither large nor constant, then R_m, C_s, and R_s will all fluctuate together with R_p.

Theoretical considerations concerning the properties of cell membranes suggest an upper limit for the capacitance of 1–2 $\mu F/cm^2$ (e.g. Fozzard, 1966); the higher values reported for muscle are therefore presumed to arise from additional membranes, usually of the sarcoplasmic reticulum, which may have a total area several times greater than the surface of the cell. If R_p is not large, the necessary ratio of

additional membrane area to surface membrane area becomes even larger; if there is an upper limit to this ratio, there must also be a lower limit to R_p.

In the particular case of cardiac Purkinje fibers, the sarcoplasmic reticulum is poorly developed (Muir, 1957; Sommer and Johnson, 1968); therefore the series resistance and capacitance observed by Fozzard is apparently a product of surface membranes. Two possible sources of this are (*a*) the cell membranes bounding the intercellular spaces within the fiber (intrafiber surface membranes), and (*b*) the intercalated disc.

Estimates of the width of the intercellular space vary from 13 mμ (Muir, 1965) to 20–30 mμ (Sommer and Johnson, 1968); the resistance of a path via this space to the surface of the fiber would correspond to R_s. There are 1–6 chains of roughly cylindrical cells in a sheep Purkinje fiber (Muir, 1957), and, assuming a very large resistance for intrafiber surface membranes, it is conceivable that the ratio of intrafiber to exterior surface membrane areas accounts for the observed C_s/C_m ratio. However, there is no reason to suppose a different construction for this intrafiber part of the sarcolemma; and if the resistance R_p is of the same order of magnitude as in the normal sarcolemma, the required membrane area ratio increases considerably. Also, the leakage of K ions via any low-resistance path would probably cause some accumulation in the intercellular space and further diminish the membrane resistance; such accumulation effects have already been seen affecting the whole fiber (McAllister and Noble, 1966). (It is possible that the normal intercellular K concentration is high enough to remove any excitability of the adjacent membranes but keep them highly conductive to action currents, thus contributing to the syncytial nature of Purkinje fibers.) Therefore, this source seems rather unlikely, though it cannot as yet be excluded.

There are some grounds for belief that the intercalated disc membranes differ from the normal sarcolemma both histologically (and therefore possibly in capacitance: Caesar, Edwards, and Ruska, 1958) and physiologically. The well-known phenomenon of "healing-over" appears to occur here in the presence of calcium ions from the extracellular medium (Délèze, 1965; see also Weidmann, 1967), membrane resistance thus being sharply increased. Such healing-over would give rise to a high R_p; Ca ions may exist in the spaces between intercalated disc membranes of adjacent cells (except where the membrane fuse or form desmosomes, when they appear to acquire high conductivity to action currents: Barr, Dewey, and Berger, 1965), and the resistance of these spaces would correspond to R_s. In this case (i.e. with high R_p), the C_s and R_s values of Fozzard would not require correction. Otherwise, it is possible that the disc membrane is *normally* a high-resistance one, except at specialized junctions, and that the healing-over effect is not involved. Once again, definite information on membrane areas is lacking; however, the disc membrane appears to follow a step-wise course across the cell, so that its area is certainly considerably larger than that of a simple cross-section of the cell.

The computations of this paper are based on the circuit of Fig. 1 *B*, assuming constant values for R_s and C_s. Any resistance in parallel with C_s is assumed to be very large at all times, and has therefore been neglected. Providing it is not time dependent, however, a low R_p would affect only the conversion factor between experimental R_s and C_s measurements and actual values, and the results presented here would still be relevant.

METHODS

The equations used were essentially those of Noble (1962). The time-dependent potassium and sodium conductances are generated by parameters obeying the same first-order differential equation that describes a very simple chemical reaction:

$$\frac{dx}{dt} = \alpha_x(1 - x) - \beta_x x. \tag{1}$$

The rate constants α_x and β_x are empirical, voltage-dependent functions; three different pairs generate solutions of equation 1 for the three conductance parameters n, m, and h.[1] The conductances are then given by

$$g_{K2} = An^\gamma \quad \text{and} \quad g_{Na} = 400\, m^3h + 0.14. \tag{2}$$

The other (instantaneous) component of the potassium conductance, g_{K1}, is given by an empirical function of the driving force for K ions. The electrical behavior of the membrane circuit is then described by

$$I_m = C_m \frac{dE_m}{dt} + (g_{K1} + g_{K2})(E_m - E_K) + g_{Na}(E_m - E_{Na}), \tag{3}$$

where I_m is the total current flowing across the membrane, E_m is membrane potential, and E_K and E_{Na} are the potassium and sodium equilibrium potentials, respectively. Other ionic ("leakage") currents have been neglected, although their effects were investigated in Noble's analysis. In the case to be considered here, the membrane is assumed to be uniformly polarized and therefore I_m is zero; this situation is a valid approximation for short cardiac Purkinje fibers (Deck, Kern, and Trautwein, 1964).

The equation to be solved for the circuit of Fig. 1 *B* is similar to equation 3, except that there are additional terms on the right side describing the current through the series resistance-capacitance (series-*RC*) branch. It is assumed that during each small time interval, the membrane potential changes at a constant rate; in practice the time steps are chosen small enough to validate this approximation. Then, if R_s and C_s are the resistance and capacitance in series and I_s is the current through R_s at the beginning of the step, equation 3 leads to

$$I_m = [C_m + C_s(1 - \exp(-t/R_sC_s))]\frac{dE_m}{dt} + (g_{K1} + g_{K2})(E_m - E_K) + g_{Na}(E_m - E_{Na}) + I_s \exp(-t/R_sC_s). \tag{4}$$

[1] These expressions are based on the original Hodgkin-Huxley ones, but it must be mentioned that they are as yet not so well-founded. Noble made certain assumptions regarding the time constants of g_{K2}, and after accepting Weidmann's data on h, he adjusted m so as to provide repetitive action potentials (hence the empirical constants in the expression for g_{Na}); his justification was the similarity between the computed results and experimental ones, under many different conditions.

Numerical integration of equation 4 was performed using the Runge-Kutta method, whereby four different approximations for the value of E_m are calculated for each step and a weighted mean is taken. Analytical solutions were used for equation 1; the value of x at the end of the step is found by assuming that α_x and β_x are constant over one step length. Thus,

$$x = x_\infty - (x_\infty - x_0) \exp(-t/\tau_x), \tag{5}$$

where $$\tau_x = (\alpha_x + \beta_x)^{-1} \quad \text{and} \quad x_\infty = \alpha_x \tau_x ,$$

and x_0 is the value of x at the beginning of the step. This method of computing the conductance parameters n, m, and h affords a considerable saving in computation time, and does not impair the accuracy of the solution. It has been tested by recomputing Noble's action potential; his numerical results were available, and did not differ to any significant degree from the new ones. At the beginning of a computation, an initial value of I_s is required. This was usually chosen by multiplying the rate of change of membrane potential in a slowly-changing part of the diastolic depolarization phase by the value of C_s ; i.e., by assuming I_s had reached its steady-state value for an applied slowly-changing ramp voltage. When the new value of E_m at the end of the step was found, the average dE_m/dt over this step was also calculated; the new value of I_s was found from the expression

$$I_s' = C_s \frac{dE_m}{dt} [1 - \exp(-dt/R_s C_s)] + I_s \exp(-dt/R_s C_s), \tag{6}$$

which gives the current at the end of a time step dt when dE_m/dt is constant during the step.

The stages in the computation were as follows:
(*a*) Initial values of E_m , t, conductances, and control variables supplied. (*b*) Parameters dependent only on E_m (those corresponding to α_x , β_x , τ_x , x_∞ , and also g_{K1}) calculated. (*c*) New values of n, m, h, g_{Na} , and g_{K2} calculated. (*d*) Using equation 4 with $I_m = 0$ and step length zero, first extrapolation to E_m performed. (*e*) Steps 2 and 4 repeated for this new value of E_m and step length $dt/2$, yielding a second approximation of E_m . (*f*) Steps 2 and 4 repeated for this second value of E_m and step length $dt/2$, yielding a third approximation of E_m . (*g*) Steps 2 and 4 repeated for this third value of E_m and step length dt, yielding a fourth approximation of E_m . (*h*) Weighted mean of the approximations of E_m taken, to obtain a final new value of E_m . (*i*) New value of I_s computed, from equation 6. (*j*) Time advanced one step and control returned to step 2. This cycle was repeated until the required time interval was covered. The length of the time step dt was automatically varied, according to the rates of change of the time-dependent variables; it typically ranged between 30 μsec and 1 msec.

Programs were written in Algol for the KDF-9 digital computer (manufactured by English Electric-Leo-Marconi Computers Ltd., Kidsgrove, Stoke-on-Trent, England) of the University Computing Laboratory, Oxford, which has a 6 μsec cycle time. One complete action potential could be computed in about 6 min, using a store not exceeding 6000 48-bit words.

RESULTS

The exponent of n in the first of equations 2 was usually chosen to be 4 in accordance with Noble (1962); in this case, A also had Noble's value of 1.2. However, results with $\gamma = 2$ will be described later.

Noble used as the value of the (assumed) pure membrane capacitance 12 μF/cm², which is about the value determined by Weidmann (1952) for Purkinje fibers.

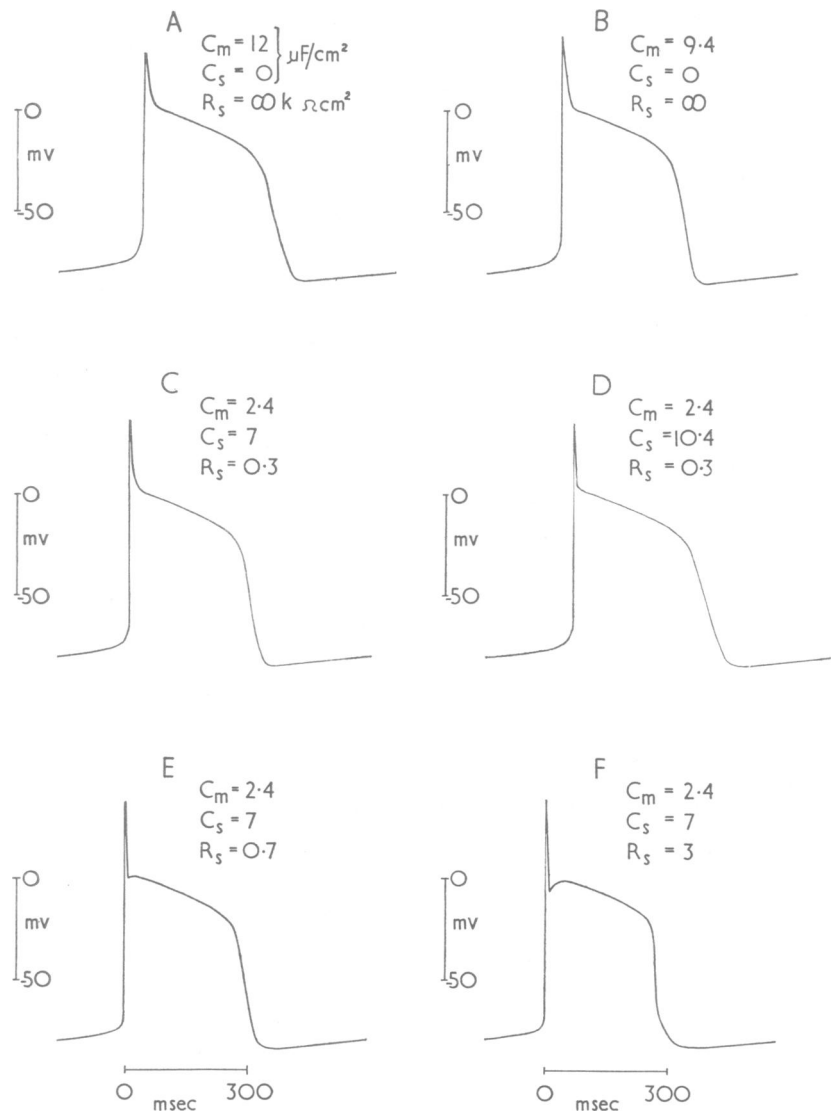

FIGURE 2 Computed cardiac action potentials, with $g_{K2} = 1.2n^4$ and a series-*RC* element in the membrane. Starting potential is −80 mv in every case. Pure capacitance (C_m), series capacitance (C_s), and a series resistance (R_s) are indicated above each AP, in $\mu F/cm^2$ and $k\Omega\ cm^2$.

A and *B* of Fig. 2 show the effect on the computed action potential (AP) of reducing C_m to 9.4 $\mu F/cm^2$, one of Fozzard's measured values. The maximum rate of depolarization during the spike increased, while the overshoot increased by 10 mv; AP frequency increased about 5%. However, the shape of the AP is very similar, and not unlike many which have been recorded in experiments. The rest of Fig. 2

shows the effects of placing part of the membrane capacitance in series with a resistance. In *C*, the values calculated by Fozzard from Purkinje fiber experiments have been used: 7 μF/cm^2 is in series with 300 Ω cm^2, and 2.4 μF/cm^2 has no series resistance. The shape of the AP is practically unchanged, except in one notable respect: the spike is sharper and of shorter duration, with a maximum rate of depolarization of 286 v/sec (compared with 97.3 v/sec for the pure-capacitance-only case). The AP frequency is increased about 1.5%. The time constant (R_sC_s) of the series-*RC* element is 2.1 msec, so that the potential on C_s can lag appreciably behind that on C_m if the latter potential is changing rapidly; in this case, when the peak overshoot potential is reached, C_s is charged only to -40 mv and is therefore drawing a considerable current. (The current drawn by C_s is given by the difference in potentials on C_m and C_s, divided by R_s.) This current load slows the rate of depolarization, since less current is available to charge C_m; but C_m is much smaller than the 9.4 μF/cm^2 of Fig. 2 *B*, so that despite the reduced current the capacitance is charged more quickly.

Depolarization is brought about by a rapid increase in g_{Na}, accountable almost entirely to an increase in the conductance parameter m which occurs with a time constant of 0.1–0.2 msec over the range -80 to $+35$ mv; by the time the peak overshoot is reached, m is within 1% of its steady-state value at that level. The potential would undergo a further slight increase as C_s is charged to the same potential and I_s disappears, except that the inward (Na) current is so reduced by the fall in electrochemical potential gradient that it cannot supply the required charging current; therefore current is drawn from C_m, and repolarization begins even before the net ionic current (the algebraic sum of those through g_{Na}, g_{K1}, and g_{K2}) reverses in sign. This cannot occur if none of the membrane capacitance is in series with a resistance. At the same time but at a slower rate, the parameter h is declining toward its very small steady-state value at the peak potential, so the inward current will decline with time nevertheless and cause repolarization; the time constant for changes in h varies from 8 msec at -80 mv to 1 msec at $+35$ mv. The two important points to note at this stage of the analysis are, then, (*a*) the rate of depolarization is increased when C_m or C_s is decreased or when R_s is increased; and (*b*) repolarization begins earlier when the charging current I_s is greater at the peak of the spike. Condition *b* will be satisfied when C_s is made larger for a given C_m and R_s: compare Figs. 2 *C* and 2 *D*, computed for capacitances of 7 and 10.4 μF/cm^2 in series with 300 Ω cm^2. It will also be satisfied when R_s is large enough to allow a fast rate of depolarization and slow rate of charging C_s, but also small enough to allow a substantial I_s to flow when potential on C_s lags behind E_m. Clearly, then, there will be an optimal value of R_s giving the earliest repolarization for given C_m and C_s; in Figs. 2 *C*, 2 *E*, and 2 *F*, all with the same capacitances, the widths of the spike at the $+20$ mv level are respectively, 4.67 msec ($R_s = 300$), 4.04 msec ($R_s = 700$), and 4.95 msec ($R_s = 3000$ Ω cm^2).

Once the repolarization has begun, its rate will be controlled by the interrelation between I_s and the net ionic current; it will cease when these are equal. Without a series-*RC* element, a balance between the inward Na current and the outward K current arises near the 0 mv level because of the changes in g_{Na} and the driving forces for K and Na ions, and a "plateau" begins. With a series-*RC* element, however, the repolarization ceases when a balance between the currents is reached such that $I^s + I^K + I^{Na} = 0$. Even during the briefest spikes, h declines to a level below its steady level at 0 mv. If the repolarization occurs slowly, it will remain near its steady-state value thereafter; however, if the repolarization is rapid, it may still be significantly below its steady-state value when the plateau level is reached. In such case, I_s decreases as C_s is charged nearer the plateau level, as usual; but in addition, I_{Na} increases with a time constant of about 1 msec as h rises towards its steady-state value. Thus there arises the possibility of a significant alteration in AP shape: the appearance of a "notch" between the spike and the plateau. The delayed increase in I_{Na} means a decrease in the net outward ionic current. Both this and the normal decrease of I_s will tend to slow the rate of repolarization, and if their sum is sufficiently great a secondary depolarization can occur.

As mentioned above, I_{Na} will increase with a time constant of about 1 msec. This must be much faster than the decrease in I_s, for if the series-*RC* element had such a short time constant C_s would be practically fully-charged by the time the repolarization to the plateau is complete, and I_s would be zero. Thus it is clear that the controlling factor in the generation of the notch is h; it certainly will not have a nonsteady value at the beginning of the plateau, however, unless the repolarization to that level is hastened by a series-*RC* element.

Figs. 2 *E*, 3 *A*, and 3 *B* show computed AP's with a notch which grows deeper as the series-*RC* time constant approaches 20 msec. Fig. 4 shows the changes in the sodium current during the notch of Fig. 3 *B*, on a much-increased time scale; the changes in I_s and I_K during this time are relatively slight. If R_s is increased somewhat further, the peak of the effect is reached, beyond which it begins to decline; I_s is reduced and the repolarization from the peak potential occurs more slowly, allowing h to approach its steady state more closely. The limit for large R_s is the case for which $I_s = 0$, i.e. when C_m is 2.4 μF/cm^2 but C_s and R_s are omitted; the highest possible rate of depolarization (393 v/sec) is attained, and only a slight trace of a notch remains (Fig. 3 *D*). With this low membrane capacitance, even the final repolarization to the resting level is very rapid, and the AP assumes a very rectangular appearance. The AP of Fig. 3 *C* is practically identical to that of Fig. 3 *D*; the product R_sC_s has been kept the same as for the AP with the greatest notch, Fig. 3 *B*, but C_s was reduced and R_s increased. This indicates the importance of a large I_s, prevented here by the large R_s, in causing the rapid repolarization and hence the notch.

If the capacitance C_s is increased from 7 to 10.4 μF/cm^2 and the other elements are as for Fig. 3 *B*, another interesting result is obtained (Fig. 3 *E*): a repetitive

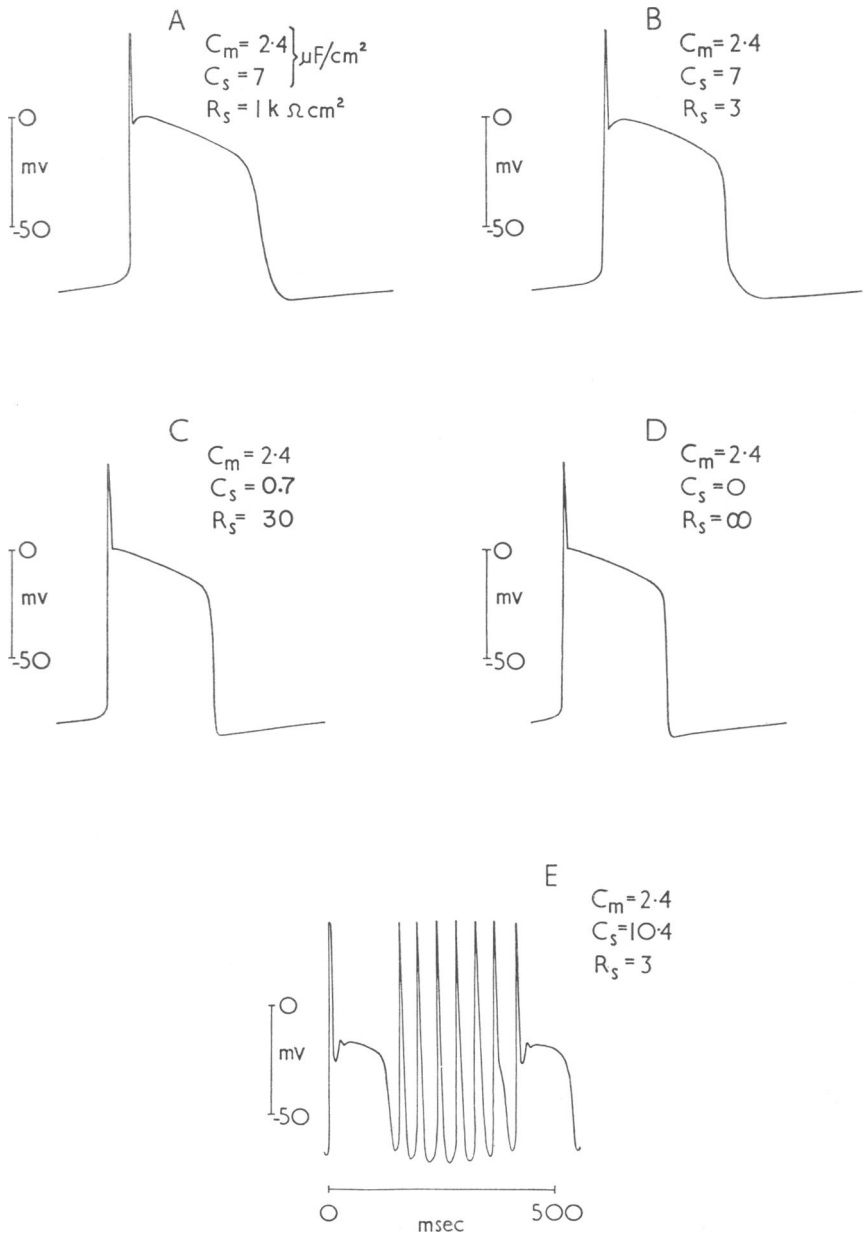

FIGURE 3 Computed cardiac action potentials. Starting potential is −80 mv in every case, but in *E* only the steady-state configuration is shown. The values above each AP give C_m, C_s, and R_s in μF/cm² and kΩ cm².

train of six spikes of varying amplitude and a seventh one followed by a short notched AP. The notch after each of the first six spikes is apparently deep enough to cause all-or-nothing repolarization (Hall and Noble, 1963). This configuration only occurs after g_{K2} has been increased, as during the plateau of a normal AP;

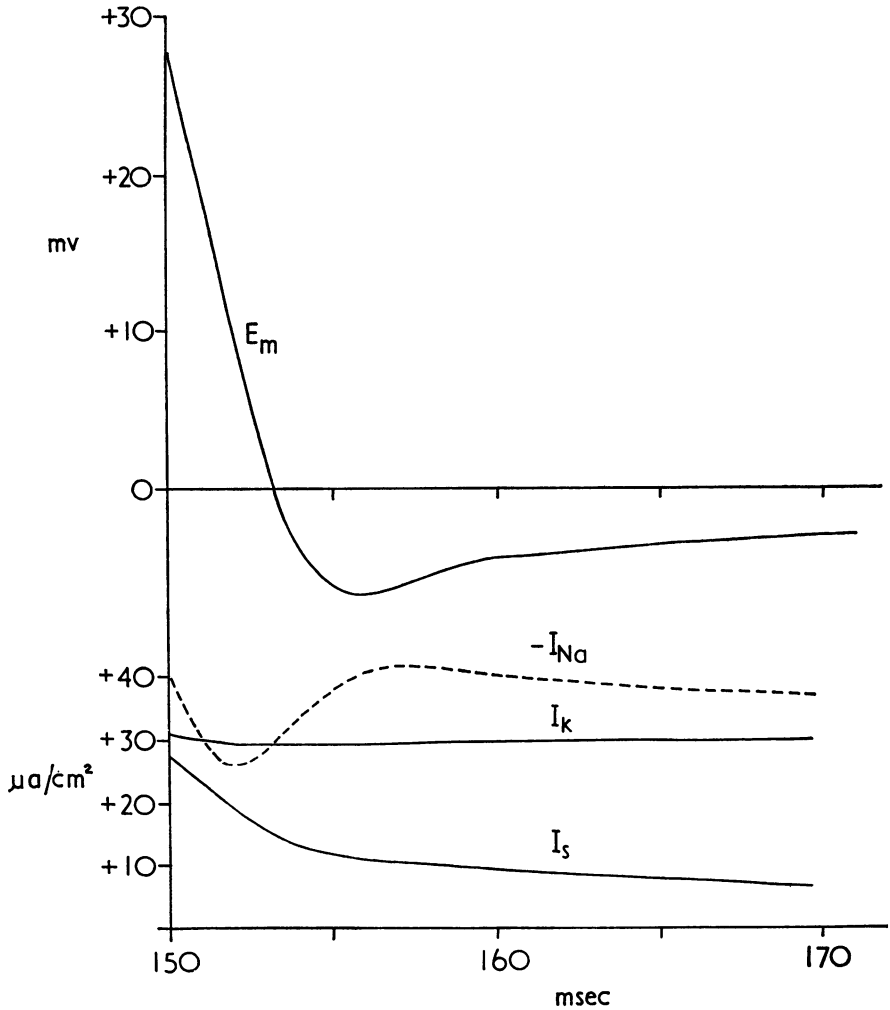

FIGURE 4 Events during the notch in the AP of Fig. 3 *B*. Upper solid curve is E_m. Lower curves: sodium and potassium currents, and current drawn by C_s. The time scale is greatly expanded. Only I_{Na} (of which the negative has been plotted) varies considerably during the notch, principally because of changes in *h*.

once g_{K2} is sufficiently high, spike-like action potentials as computed by Noble (1962; see his Fig. 13, curve *a*) for a membrane with high g_K occur. In the present case, after the plateau of the short notched AP, g_{K2} declines during the next six spikes because the positive excursions are of too little duration to cause a net increase. At the same time, however, C_s is discharging from its high potential of −19 mv reached during the plateau; as it does so it provides progressively less depolarizing current, and the maximum diastolic potential rises after each of the first three spikes. Then, the continued decline in g_{K2} takes precedence and maximum

diastolic potential falls again, until g_{K2} becomes so low that there is insufficient repolarizing current after a spike to turn the notch into a complete repolarization, and another plateau occurs. The cycle then repeats, and in this way Noble's spike-like AP's become repetitive. (Damped oscillations of h about its steady-state level occur early in the plateaux of this figure, because the rise in h towards its plateau level carries the membrane potential far enough to establish a new and lower steady-state level, etc.) If C_m is made smaller, the same process appears to occur, but at a much higher frequency because of the slight current needed to change the potential

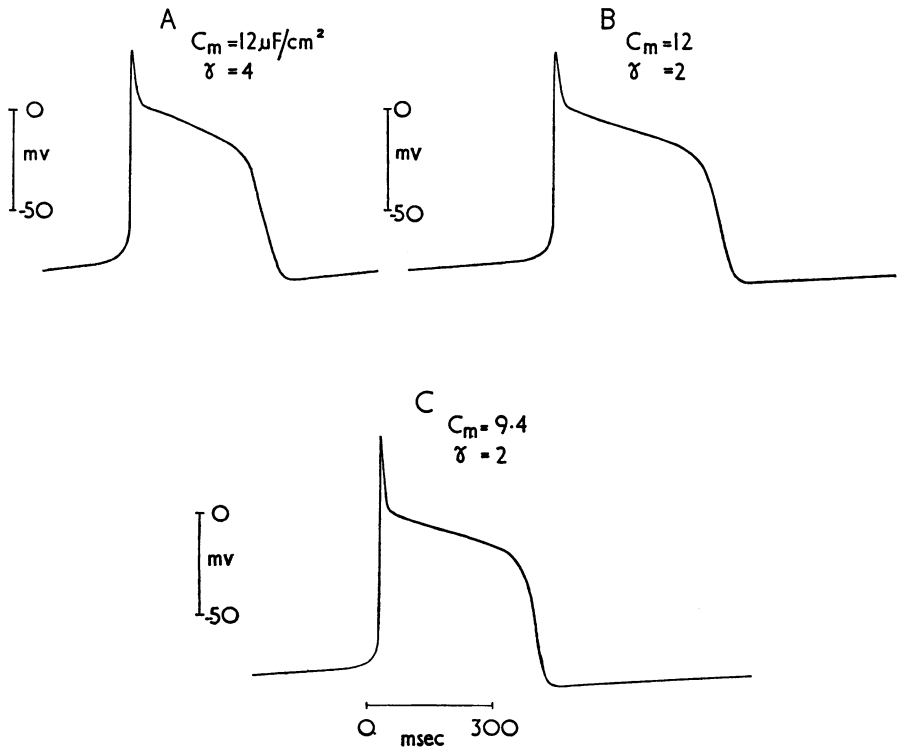

FIGURE 5 Computed cardiac action potentials. *A*. $g_{K2} = 1.2\ n^4$ and $C_m = 12\ \mu F/cm^2$. *B*. $g_{K2} = 0.6\ n^2$ and $C_m = 12\ \mu F/cm^2$. *C*. $g_{K2} = 0.6\ n^2$ and $C_m = 9.4\ \mu F/cm^2$. The starting potential is −80 mv in each case.

on C_m. Sixteen spikes have been computed in 200 msec this way when C_m is only 0.1 $\mu F/cm^2$, their envelope appearing much like that of the first three spikes in Fig. 3 *E*; however, step lengths of integration as low as 5 μsec were needed, and too much computer time was required for this computation to be extended to cover the whole steady-state configuration. Obviously, though, at least some of the membrane capacitance must *not* have a resistance in series with it, if the Hodgkin-Huxley model is valid.

The results of recent voltage-clamp experiments on short Purkinje fibers (McAllis-

ter and Noble, 1966 *a*, *b*) have suggested that the exponent of n in equation 2 is at least as low as 2. Using this value, some of the computations above have been repeated. A value of 0.6 was required for A, in order to keep g_{K2} to a satisfactory amplitude; lower values than this prevented repolarization from the plateau, and higher values decreased the AP frequency and shortened the AP duration. Fig. 5 compares the effects of 4th and 2nd powers of n, and also in the latter case of decreasing the membrane capacitance from Weidmann's (1952) value of 12 μF/cm^2 to 9.4 μF/cm^2, a total value measured by Fozzard (1966). The lowest value of A which would permit repolarization after the plateau also caused the highest firing frequency, and this was increased further when C_m was decreased. However, it is apparent that when the exponent of n is changed, the same frequency of firing cannot be reproduced without altering some other conductance parameter. Altering the magnitude of g_{K1} would probably be the simplest solution, until more voltage-clamp data is available to suggest a better one. The difference in frequency apart, there seems little reason for preferring a 4th power of n relation, if a 2nd power relation is indicated by experimental data. Also, the slower rate of firing connected with an n^2 relation is by no means an unphysiological one.

DISCUSSION

The finding that the rate of depolarization during the spike is increased when part of the membrane capacitance is in series with a resistance—and in particular that, when the configuration is as measured by Fozzard, the maximum rate of depolarization is near the range found by Weidmann—eliminates the main discrepancy between Noble's computed AP and that found in experiments. Noble (1962) suggested that such a membrane circuit could overcome the difficulty, but had only the measurements from skeletal muscle with which to speculate. Another difference between his computed AP and the recorded ones was in the rate of repolarization after the peak overshoot; the reduced pure capacitance in the membrane could account for this, as could a delayed fall in g_{K1} which he postulated might also account for the notch sometimes seen before the plateau. It has now been shown that the notch is a logical result of the equations when a series-RC circuit is considered, even when changes in g_{K1} are (as usual) considered instantaneous.

The notch or hump early in the plateau has been recorded by almost every investigator of Purkinje fiber electrophysiology at some time. (Records of notched AP's are reproduced in: Draper and Weidmann, 1951; Trautwein, Gottstein, and Dudel, 1954; Hoffman and Cranefield, 1960; Carmeliet, 1961; Johnson and Tille, 1961; Deck and Trautwein, 1964; Moore, Preston, and Moe, 1965; Vassalle, 1966; Temte and Davis, 1967.) Fozzard (1966), however, did not show such a notch or mention recording it; possibly, therefore, the series resistance and capacitance measured in his experiments were not the same as would be found for fibers showing a notched AP. If the resistance R_s were only twice the value found by him, a notch

might occur; higher values of R_s would make a notch even more likely, and would not seem to be "unphysiological" in view of the resting membrane resistance of 1900 Ω cm² found by Weidmann (1952).

The basic requirements for a notch are an overshoot of membrane potential lasting long enough for h to decline to near its steady-state value, and a repolarization at the end of this time too fast for h to follow. With the equations as used, this can only occur for normal values of membrane capacitance when there is a resistance in series with some of the capacitance. The equations for h adopted by Noble were related to Weidmann's experimental values, and so should not be far in error; R_m, R_s, and C_s have all been measured in experiments, so that all the factors directly involved in creating a notch are known quantitatively. If some other mechanism or agent were to assist in the repolarization, it could add to this effect (although the series-RC would probably still be necessary in order to achieve a sufficiently fast depolarization); a possibility here is some other ion whose equilibrium potential is at or below the plateau potential, such as the passive anion current considered by Noble, or the active chloride current suggested by Dudel, Peper, Rüdel, and Trautwein (1967) on the basis of their observations.

It is tempting when considering the result shown in Fig. 3 E to suppose a role for the series-RC, together with an increased g_{K2}, in cardiac fibrillation. Cooling is known to increase the tendency to fibrillation, and might also be expected to slow changes in h and thus cause a larger pre-plateau notch. Decreasing the magnitude of h with drugs and depolarizing with high external K concentration are both known to stop fibrillation; so is a large electric shock, which might have the effect of reducing g_{K2}. It would presumably be possible to reconstruct Fig. 3 E by other means than increasing C_s, if C_m and R_s were suitably varied, and possibly to reduce the frequency of occurrence of plateaux (but not eliminate them, if the train of spikes is to continue for long). This has not yet been attempted, and further such speculation on fibrillar mechanism may be premature. In any case, it is not yet certain exactly what membrane potential changes occur during fibrillation. It is interesting, however, that Pillat (1967) has obtained spike-like responses from sheep ventricular fibers in the extended post-AP relative refractory period caused by quinidine-like drugs. He has suggested that the drugs may cause a blocking of g_{K2} in the fully-activated state, since stimulation-rate effects on AP duration are also abolished. Toward the end of the relative refractory period, the spike potentials changed to normal action potentials with a very deep notch.

Many AP's are recorded in a cable-like preparation, yet still show a notch; the present calculations have been for an AP occurring uniformly over the entire fiber. In the cable, some current is diverted along the axis of the fiber and so is not available for charging the capacitance. This will slow the rates of depolarization, but not so greatly that a notch need not occur by the mechanism described here; for with a conduction velocity of 1–2 m/sec along the fiber, even during the fastest

conductance changes several millimeters of fiber will have practically the same membrane conductance (except when m is changing rapidly during the upstroke, and this does not directly concern the notch). On the other hand, a series-RC element in the cell membrane would be advantageous to the organism by increasing the AP conduction velocity and safety factor.

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