

IMPULSE RESPONSES OF AUTOMATICITY IN THE PURKINJE FIBER

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ABSTRACT We examined the effects of brief current pulses on the pacemaker oscillations of the Purkinje fiber using the model of McAllister, Noble, and Tsien (1975. *J. Physiol. [Lond.]* 251:1–57). This model was used to construct phase-response curves for brief electric stimuli to find “black holes,” where rhythmic activity of the Purkinje fiber ceases. In our computer simulation, a brief current stimulus of the right magnitude and timing annihilated oscillations in membrane potential. The model also revealed a sequence of alternating periodic and chaotic regimes as the strength of a steady bias current is varied. We compared the results of our computer simulations with experimental work on Purkinje fibers and pointed out the importance of modeling results of this kind for understanding cardiac arrhythmias.

INTRODUCTION

Some biological oscillators, such as circadian oscillators and neuronal pacemakers, have been shown to be susceptible to phase resetting, and some even lose their regular rhythm when a stimulus of critical magnitude, timing, and duration is applied (1–3). Jalife and Antzelevitch have found that the spontaneous firing can be terminated in cat sinus nodes and in isolated dog Purkinje fibers (having maximum diastolic potentials of about -60 mV) by giving a brief current stimulus at the right moment. The same phenomenon has also been observed experimentally in membrane oscillators, including repetitive firing in space clamped axons maintained in low Ca^{2+} artificial sea water (6), as well as in normal sea water (3).

In the past, computational investigations (7–9) to study the abolition of a rhythmic action-potential train by depolarizing or hyperpolarizing short shocks were carried out, using the Hodgkin and Huxley equations (10) which represent quantitative expressions for the squid axon membrane. Analysis of these equations has identified the regions where values of kinetic parameters produce limit-cycle behavior and a “black hole” where oscillations in membrane potential cease (7–9).

The experimental demonstration of similar oscillatory responses in squid axon, sinoatrial node, and Purkinje fiber suggested to us the possibility that a similar analysis could be applied to a system of equations describing a cardiac pacemaker. Identifying regions where oscillations are annihilated has obvious clinical application in regard to sudden death by cardiac arrest (11).

For our modeling, we have used the quantitative description of electrical activity of the Purkinje fiber formulated by McAllister et al. (12). This model consists of a system of

10 first-order, simultaneous, nonlinear differential equations that include a Hodgkin-Huxley type sodium conductance, three time-dependent outward potassium currents, a transient outward chloride current, a secondary inward current carried by calcium and sodium ions, and a leak current. Using this model, we demonstrate the existence of a black hole, that is annihilation of rhythmic activity in a numerical solution of the system of equations. The close agreement between theory and experiment suggests that this model provides a sound basis for understanding the phase-resetting dynamics of the heart.

METHOD AND RESULTS

The dynamic behavior shown in Figs. 1–6 is the result of numerically solving a system of first-order, simultaneous, nonlinear, differential equations (12). The calculations were performed in double precision on a DEC 10 computer (Digital Equipment Corp., Maynard, MA) using a Gear algorithm (13), with the absolute and relative error tolerances set at 10^{-12} . McAllister et al. (12) gave two expressions for the transient chloride current. Our results shown here, except those of Fig. 6, are based on Eqs. 25 and 26 (i.e., the equations for α_r and β_r) of their paper. The values of the parameters used in the computation are given in their Tables 1A and 1B, except 0.000253 was used for α_r , which is the value given by Eq. 16 of the same reference. (We believe that the α_r value given in Table 1A is in error by a factor of 10.)

Fig. 1–4 show phase-resetting behavior of a Purkinje-fiber pacemaker with brief current pulses, where the maximum diastolic potential (i.e., the absolute minimum value) of the fiber was reduced to about -82 mV with the application of a bias depolarizing current of $+1.625$

$\mu\text{A}/\text{cm}^2$. Figs. 5 and 6 show the dynamic behavior of the fiber when a bias current of long duration was applied at different phases of the "original" cycle (i.e., the Purkinje fiber in the absence of a bias current).

As shown in Fig. 1 *a*, a small brief depolarizing current perturbation of $+0.1 \mu\text{A}/\text{cm}^2$ with a duration of 200 ms given to the cell at a certain point along its oscillation cycle (indicated in the figure by an arrow at -17.1 mV of the repolarizing phase) delayed the subsequent oscillations by 7.6% of a cycle. A larger current perturbation, $+0.4 \mu\text{A}/\text{cm}^2$, of the same duration, applied at the same point in the oscillation cycle, resulted in a sharp decrease in the oscillatory amplitude (slow approach to a steady state), as shown in Fig. 1 *b*. A still larger perturbation, $+2 \mu\text{A}/\text{cm}^2$, merely advanced the subsequent oscillations by 4% of a cycle (Fig. 1 *c*). Pacemaker activity in our simulation was restored from an almost inactive Purkinje fiber (Fig. 1 *b*) by applying a brief hyperpolarizing pulse of

sufficiently large magnitude (i.e., $-2 \mu\text{A}/\text{cm}^2$). See Fig. 1 *d*. Here, the initial condition was set at the point indicated by the arrow shown in Fig. 1 *b*. The trend shown in Fig. 1 agrees quite well with the experimental findings of Jalife and Antzelevitch (5).

A brief current of $+0.4 \mu\text{A}/\text{cm}^2$, applied a little later in the phase than that of Fig. 1, resulted in a permanent cessation of periodic rhythm, with membrane voltage rapidly (compared with Fig. 1 *b*) approaching the steady state value. This is shown in Fig. 2 *a*, where a brief electric stimulus of $+0.4 \mu\text{A}/\text{cm}^2$ was applied at -32.6 mV of the repolarizing phase. Fig. 2 *b* shows the total ionic current vs. membrane potential, showing the path leading to the attractor basin of the steady state, when spontaneous firing of the cell was kicked off its stable cycle by a brief electric stimulus. A brief current of $-2 \mu\text{A}/\text{cm}^2$ (applied at the 30 s in Fig. 2 *a*) restored the rhythmic activity of a resting Purkinje fiber (as in Fig. 1 *d*). Note from both Figs. 2 *a*

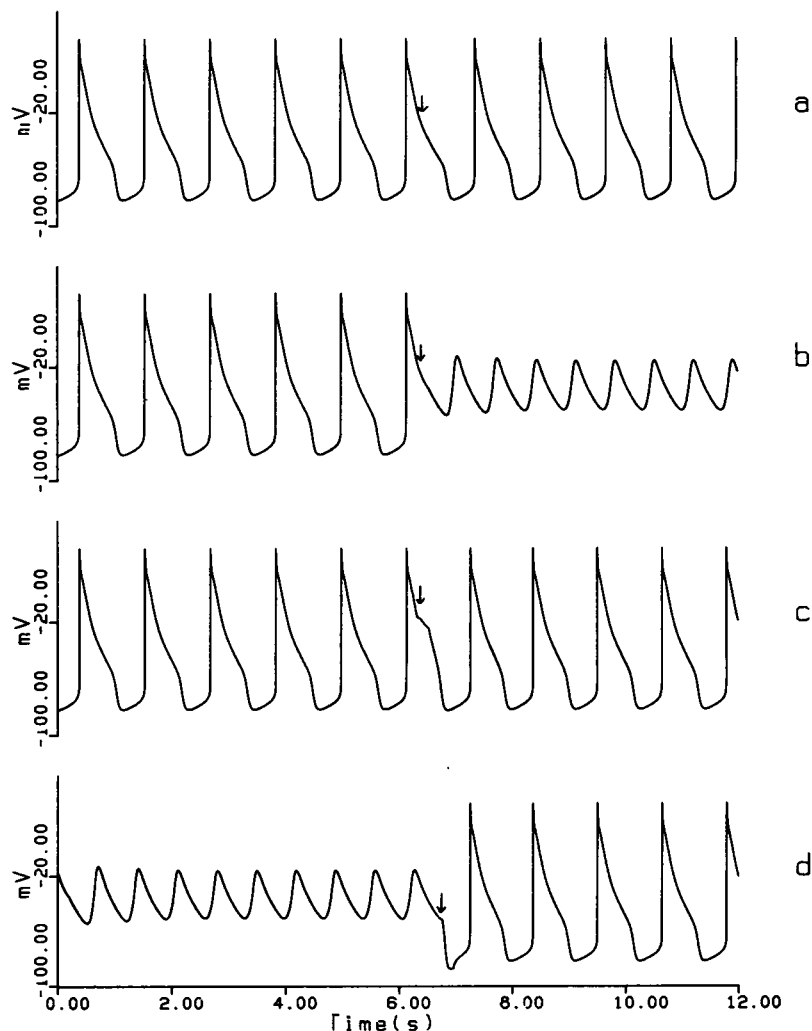


FIGURE 1 Membrane potential (in millivolts) vs. (in seconds), showing phase-resetting behavior of a Purkinje fiber pacemaker, using current pulses of the same duration (200 ms) but different magnitudes (from top to bottom: 0.1, 0.4, 2, and $-2 \mu\text{A}/\text{cm}^2$). Perturbing pulses are delivered at -17.1 mV of the repolarizing phase as shown by arrows in the figure. The maximum diastolic potential was reduced to about -82 mV by the application of a bias depolarizing current of $+1.625 \mu\text{A}/\text{cm}^2$, held constant for the entire duration.

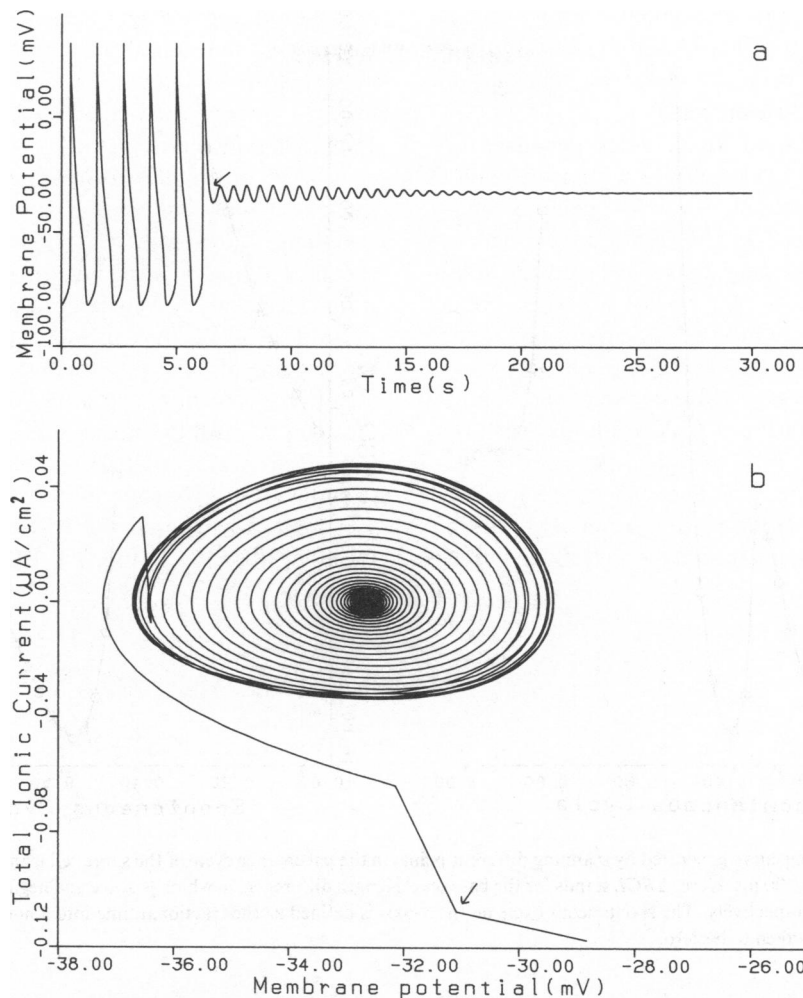


FIGURE 2 The path leading to the attractor basin of the steady state from the limit cycle, when $+0.4 \mu\text{A}/\text{cm}^2$ of a brief depolarizing current pulse was applied at the arrow (i.e., at -32.6 mV) to the same cell but a little later in the phase than that of Fig. 1 *b* show membrane potential vs. time and the spiral current-voltage trajectory, respectively. The second jump on the *top left* after the arrow in *b* is due to the termination of the brief stimulus.

and 2 *b* that, as a brief pulse was applied to the rhythmic fiber, the amplitude (of membrane potential in Fig. 2 *a* and of total ionic current in Fig. 2 *b*) instantaneously decreased and then increased slightly for the next few cycles, eventually approaching the steady state value. Note also that the steady state potential of annihilation (-32.63 mV) was not in the plateau range of membrane potential.

Fig. 3 shows the phase-resetting curve (PRC) of the same cell; the curve was generated by scanning the pacemaker cycle with a brief current pulse of $+0.1$ (Fig. 3 *a*) and $-0.5 \mu\text{A}/\text{cm}^2$ (Fig. 3 *b*), both with a duration of 200 ms. Here, the spontaneous cycle was defined as the fractional time into a normal cycle period, such that the phase at the maximum diastolic potential (MDP) was taken to be zero. The new cycle length (i.e., from the MDP just before the stimulus to the first MDP afterwards, where the MDP of this fiber is -82 mV) minus the basic cycle length (1,150 ms) divided by the basic cycle length gives ΔBCL .

When a brief depolarizing pulse was applied at a point

lying between 55 and 75% (see Fig. 3 *a*) of the spontaneous cycle, the amplitude of membrane potential instantaneously decreased and slowly went toward a steady state. When a brief hyperpolarizing current was applied at a point lying between 25 and 45% (see Fig. 3 *b*), the membrane potential behaved in the same manner. For other phases of the spontaneous cycle, a nonannihilating repetitive rhythmic activity resumed with unaltered frequency but with phase resetting. In other words, if a positive stimulus was applied soon after the MDP, the only effect was to advance the next beat slightly. If the stimulus was given just before the "vulnerable phase," the effect was to delay the next beat by a significant amount. If the stimulus was given during the vulnerable phase, the fiber stopped firing and did not resume its activity. If the stimulus was given after this phase, the next beat was also delayed slightly. Such a delay (after the vulnerable phase) is opposite to what is observed experimentally by Jalife and Antzelevitch (5). Also, our PRC for depolarizing pulses

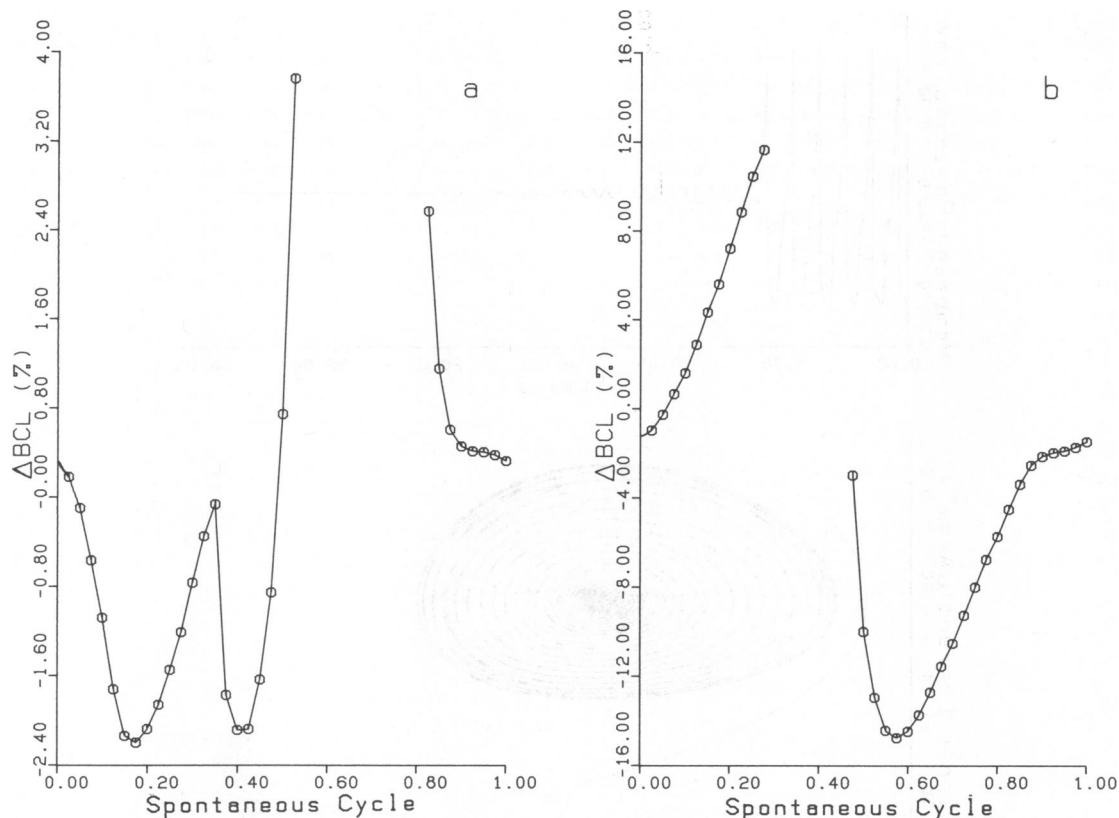


FIGURE 3 Phase resetting curve generated by scanning different points in the pacemaker cycle of the same cell using a current pulse of $+0.1$ (a) and $-0.5 \mu\text{A}/\text{cm}^2$ for 200 ms. Here, ΔBCL stands for the basic cycle length difference, in which positive and negative ΔBCL mean delayed and accelerated phases, respectively. The spontaneous cycle on the x-axis is defined as the fractional time into a normal cycle period, so that the phase at the MDP is taken to be zero.

was very different from that in the experimental observation (5). A possible explanation for the discrepancy is given in the next section.

For hyperpolarizing stimuli, there was an advance in phase resetting when the stimulus was given after the vulnerable phase (see Fig. 3 b). Our PRC for hyperpolarizing pulses was very similar to that observed in the experimental sinus node preparations (4); however, the position of the black hole was quite different. Unfortunately, no experiment using hyperpolarizing stimuli has been reported on the Purkinje fiber to verify Fig. 3 b.

Fig. 4 shows two black holes obtained by applying current pulses of various magnitude and of 200 ms duration to the same cell at intervals along the pacemaker cycle. Here, the numbers in both Figs. 4 a and 4 b refer to the percent ΔBCL , and the contour lines in Fig. 4 b represent isochrons, which connect points with the same ΔBCL . The stippled areas in Fig. 4 a include all the ΔBCL values $>100\%$. On the boundary of the black holes, a stimulus yielded instantaneous decrease in amplitude (as in Fig. 1 b), which either grew to the large amplitude oscillation after more than 30 s or decayed to the steady state within 20 s. As in studies using the Hodgkin-Huxley equations, the Purkinje fiber was sensitive to both excitatory and inhibitory stimuli. Unlike the Hodgkin-Huxley case, how-

ever, the response of the Purkinje fiber to negative perturbations was quite different from its response to positive ones. We found that the bottom boundary of the black hole was located at $-5 \mu\text{A}/\text{cm}^2$ of stimuli (not shown here). But, there was another black hole with the stimuli strength greater than $-30 \mu\text{A}/\text{cm}^2$. Between -5 to $-30 \mu\text{A}/\text{cm}^2$, a hyperpolarizing stimulus given during the vulnerable phase yielded the small amplitude oscillation of the type shown in Fig. 1 b, which lasted for a long period of time and finally grew into the large-amplitude oscillation.

As shown in Fig. 4, the McAllister et al. (12) model predicts the existence of bistability in the Purkinje fiber; a stable, continuous oscillation and a time-independent, stable steady state. Bistability can also be demonstrated by the application of a steady bias current at different phases of the "original" Purkinje fiber cycle. This is shown in Fig. 5, where the top trace was obtained by starting a bias current of $+1.625 \mu\text{A}/\text{cm}^2$ immediately after the MDP, i.e., at -87.16 mV. The second trace was obtained by starting the same current at $+9.15$ mV and the third one at -28.38 mV, both during the downstroke of the action potential. The middle trace (and also Fig. 1 b) should not be interpreted as evidence of a third stable response (the third stability being a stable, small-amplitude maintained oscillation, oscillating between -48 and -17 mV with a

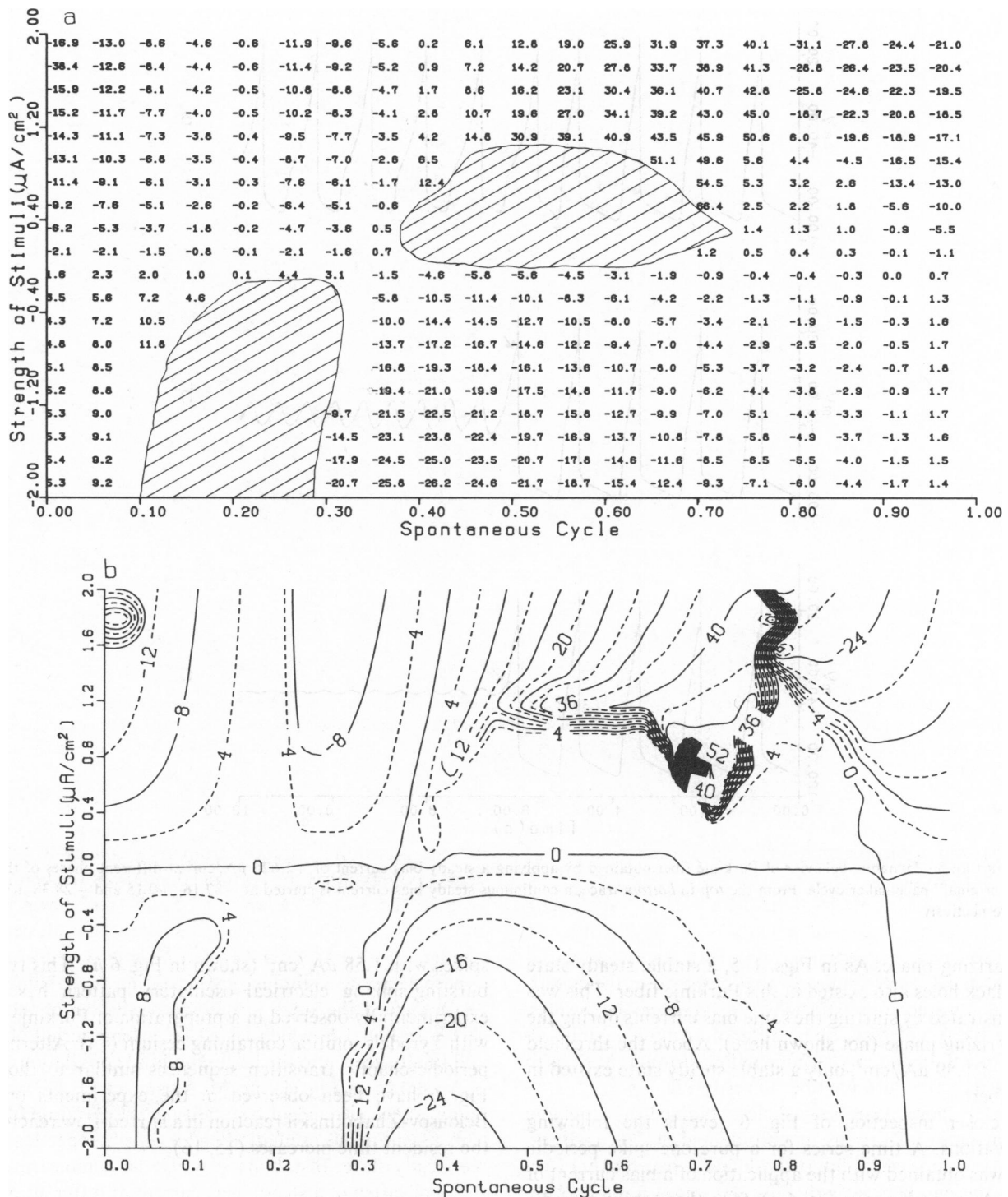


FIGURE 4 Stimuli vs. spontaneous cycle, obtained by giving both negative and positive brief current pulses. As in Fig. 1-3, the MDP of the fiber is reduced to -82 mV with a bias current of $+1.625 \mu\text{A}/\text{cm}^2$. The numbers shown in *a* and *b* refer to the percent ΔBCL at the point in the cycle given on the x-axis where a brief stimulus, whose magnitude is given on the y-axis was applied. The contour lines in *b* are isochrons representing lines of constant ΔBCL . The stippled areas are the regions where ΔBCL takes the value $>100\%$.

period of 670 ms). We found that this mode of oscillation either very slowly approached a steady state or grew to a higher amplitude oscillation, when a sufficient time was given to the computation.

We may obtain much more complex phase resetting by

using Eqs. 27 and 28 of reference 12 with the application of a steady, depolarizing bias current. This is shown by Fig. 6, where an alternating periodic-chaotic transition sequence was achieved as the bias current was increased from 1.40 to $1.58 \mu\text{A}/\text{cm}^2$, all of them starting at -87.045 mV of the

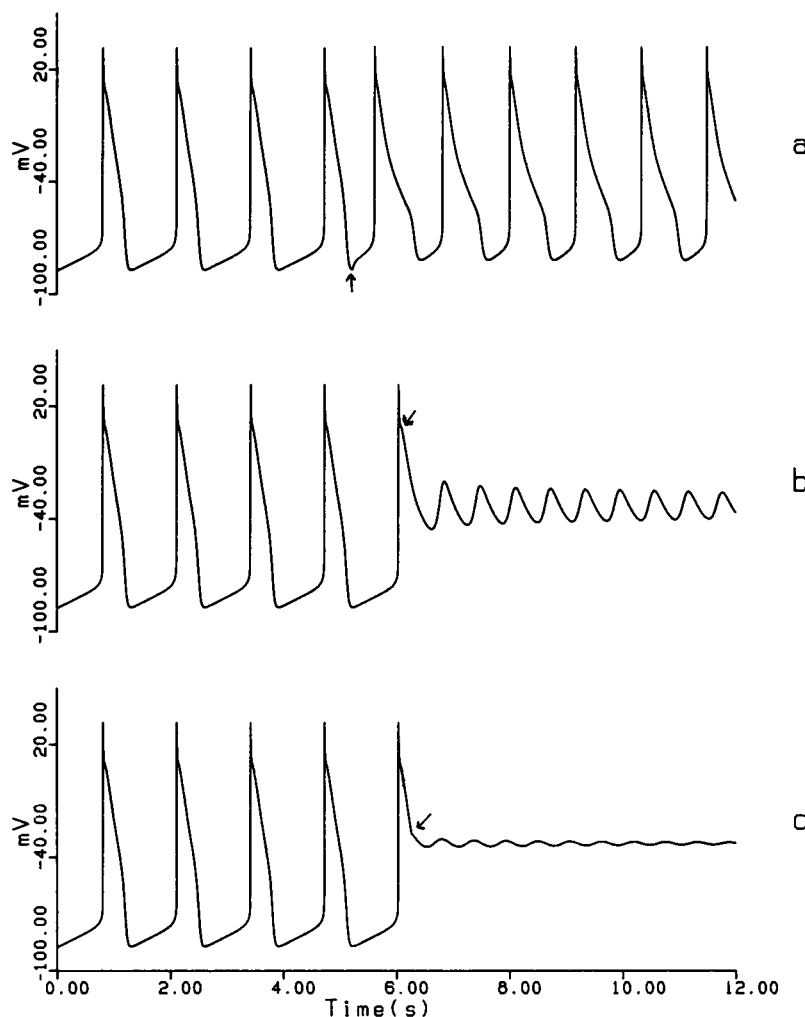


FIGURE 5 Dynamic behavior of Purkinje fiber obtained by applying a steady bias current of $+1.625 \mu\text{A}/\text{cm}^2$ at different phases of the "original" pacemaker cycle. From the top to bottom trace, a continuous steady bias current is started at -87.16 , $+9.15$ and -28.38 mV, respectively.

depolarizing phase. As in Figs. 1–5, a stable, steady state and black holes also existed in this Purkinje fiber. This was demonstrated by starting the same bias currents during the repolarizing phase (not shown here). Above the threshold value of $1.59 \mu\text{A}/\text{cm}^2$, only a stable steady state existed in this fiber.

A closer inspection of Fig. 6 reveals the following observations. A time series for a pure one-spike periodic state was obtained with the application of a bias current of $1.40 \mu\text{A}/\text{cm}^2$ (shown in Fig. 6 *a*), for a three-spike periodic state with $1.52 \mu\text{A}/\text{cm}^2$ (shown in Fig. 6 *c*), for a four-spike periodic state with $1.545 \mu\text{A}/\text{cm}^2$, (shown in Fig. 6 *e*), and for a seven-spike periodic state with $1.57 \mu\text{A}/\text{cm}^2$ (shown in Fig. 6 *g*). The time series for the chaotic states that occurred between these pure periodic states is also shown in every other trace: A random appearance of one and 2 spikes was achieved with the application of a bias current of $1.45 \mu\text{A}/\text{cm}^2$ (shown in Fig. 6 *b*), three and four spikes with $1.53 \mu\text{A}/\text{cm}^2$ (shown in Fig. 6 *d*), four and five spikes with $1.55 \mu\text{A}/\text{cm}^2$ (shown in Fig. 6 *f*), and 9, 10, and 11

spikes with $1.58 \mu\text{A}/\text{cm}^2$ (shown in Fig. 6 *h*). This type of bursting-spiking electrical oscillatory pattern has been experimentally observed in a preparation of Purkinje fiber with Tyrode's solution containing cesium (14). Alternating periodic-chaotic transition sequences similar to those in Fig. 6 have been observed in the experiments on the Belousov-Zhabotinskii reaction in a stirred-flow reactor, as the resident time increases (15, 16).

DISCUSSION

Jalife and Antzelevitch (5) observed that a spontaneously beating dog Purkinje fiber, mounted in a sucrose-gap chamber, fires with an average BCL of 1,600 ms and MDP of -82 mV. When a sufficiently brief current is applied at various phase points of the rhythmic cycle, the ΔBCL decreases smoothly over one natural period as the spontaneous cycle is increased, thus showing a weak rescheduling (1, 2). Our computation, on the other hand, shows that the theoretical Purkinje fiber had a cycle length of 1,300 ms

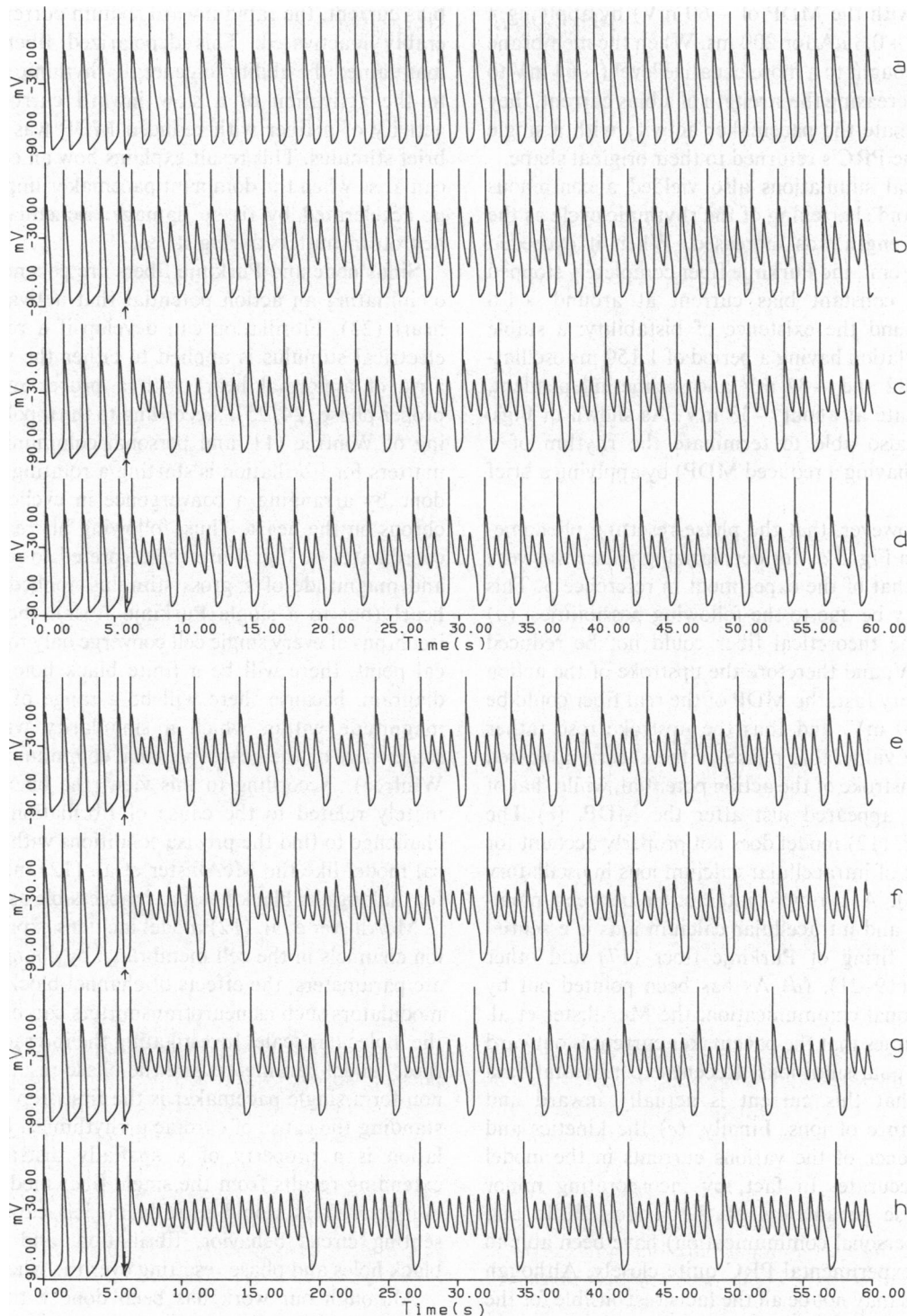


FIGURE 6 Alternating period-chaotic sequences achieved by the application of a steady bias current of increasing magnitude, started at -87.05 mV of the original cycle, using Eqs. 27 and 28 of reference 12. From the *top* and *bottom* trace, the magnitudes of bias current used for this computation are 1.40 , 1.45 , 1.52 , 1.53 , 1.545 , 1.55 , 1.57 , and 1.58 $\mu\text{A}/\text{cm}^2$, respectively.

and MDP of -87.2 mV. The theory also yielded a weak rescheduling, in agreement with the experiment, as a brief current was applied at various phase points of the natural period (not shown here).

When the membrane potential of the pacemaker was

continuously depolarized with a steady bias current, Jalife and Antzelevitch observed that the MDP decreased to -60 mV and that the pacemaker was beating at an average BLC of $1,450$ ms at steady state. They were able to terminate the rhythmic cycle of this preparation (i.e., the

Purkinje fiber with the MDP of -60 mV) by applying a brief current of $+0.8$ μ A for 200 ms. When the membrane potential was brought to a more negative level (-64 mV to -91 mV) by decreasing the strength of a bias current, they could not terminate the pacemaker activity with a single stimulus, and the PRC's returned to their original shape.

Our numerical simulations also yielded a continuous depolarization and shortening of the rhythmic cycle as the bias current strength was increased. When it exceeded about $+1.7$ μ A/cm², the Purkinje fiber completely stopped firing. With a constant bias current at around $+1.6$ μ A/cm², we found the existence of bistability: a stable continuous oscillation having a period of 1,150 ms oscillating between -82 and $+32$ mV and a time-independent, stable steady state at about -33 mV. As shown in Figs. 1–4, we were also able to terminate the rhythm of a Purkinje fiber (having a reduced MDP) by applying a brief current pulse.

We found, however, that the phase-resetting phenomenon, as shown in Fig. 3 *a*, for depolarizing pulses was very different from that of the experiment in reference 5. This discrepancy may be due to the following possibilities: (*a*) the MDP of the theoretical fiber could not be reduced beyond -82 mV, and therefore the upstroke of the action potential rose very fast; the MDP of the real fiber could be reduced to -60 mV, and thus the upstroke rose rather slowly. (*b*) The vulnerable phase of the theory appeared during the downstroke of the action potential, while that of the experiment appeared just after the MDP. (*c*) The McAllister et al. (12) model does not properly account for the involvement of intracellular calcium ions in oscillatory current (17, 18). A two-way interaction between membrane potential and intracellular calcium ions is essential to spontaneous firing of Purkinje fiber (17) and other excitable cells (19–21). (*d*) As has been pointed out by Jalife in a personal communication, the McAllister et al. (12) model assumes that the pacemaker current is outward and carried by potassium ions. Recent experimental data (22) suggest that this current is actually inward and carried by mixture of ions. Finally, (*e*) the kinetics and voltage dependence of the various currents in the model may not be accurate. In fact, by incorporating minor changes in these parameters of the model, Jalife and Antzelevitch (personal communication) have been able to reproduce the experimental PRC quite closely. Although the above points may not be all the facts responsible for the discrepancy, we believe that these are the most important sources.

For hyperpolarizing stimuli, the theoretical vulnerable phase appeared just after the MDP, and there was an accelerated phase resetting following this phase. Thus, our PRC looks very similar to that of the experimental sinus node (5).

It appears that a reduction of the MDP is necessary for the existence of a black hole in phase resetting. When the Purkinje fiber was depolarized with the application of a

bias current, the rapid inward sodium current was considerably inactivated. This depolarized fiber might have maintained the ability to generate rhythmic activity owing to the activation of a slow inward current. Rhythmic activity of a fiber with reduced MDP was sensitive to a brief stimulus. This result explains how an ectopic rhythm can arise when the dominant pacemaker impulse is slowed or accelerated by tissue damage, ischemia, or effect of neurotransmitters during stress.

Sinus node and Purkinje fibers are pacemakers capable of initiating an action potential that activates the whole heart (23). Fibrillation can develop if a relatively small electrical stimulus is applied to either the ventricle or to atria of a normal heart with a proper magnitude and proper phase (24, 25). According to the topological reasoning of Winfree (11, and personal communication), what matters for fibrillation is starting a rotating wave. That is done by arranging a convergence in cyclic order of isochrons on the heart. Thus, following his reasoning, if the coordinates of Fig. 4 are reinterpreted to indicate timing and magnitude of a gross stimulus applied to the whole heart (not to a single Purkinje fiber), then even if the isochrons of every single cell converge only to a mathematical point, there will be a finite black hole on that gross diagram, because there will be a range of timing and a magnitude within which a singularity will be created somewhere on the heart (personal communication with Dr. Winfree). According to this view, the black hole is ultimately related to the cause of fibrillation; thus, it is a challenge to find the precise conditions with a mathematical model like the McAllister et al. (12) model necessary for making the black holes as inaccessible as possible.

McAllister et al. (12) model includes expressions for the ion channels in the cell membrane; by changing appropriate parameters, the effects of channel-blocking drugs and modulators such as neurotransmitters can be examined on the molecular scale. Investigating the interactions between these model parameters and the phase-resetting phenomenon for a single pacemaker is the first step toward understanding the cause of cardiac arrhythmias. Because fibrillation is a property of a spatially distributed system, extending results from the single-fiber model to networks of pacemakers would provide models capable of representing circus behavior, fibrillation, and generation of black holes and phase resetting over the whole heart (27).

Although our work has been done with the Purkinje fiber, it demonstrates the resetting character to be expected from the oscillatory system of any pacemaker cell. As in the work of Best (7), a phase-stimulus plot like Fig. 4 provides a way of understanding the dynamic characteristics of a rhythmic system. Fig. 6 opens up a way to search for the mechanism of chaos, which apparently exists in the rhythmic activity of the Purkinje fibers. To our knowledge, this is the first example that displays a sequence of alternating periodic and chaotic regimes in deterministic nonlinear equations.

Our simulations indicate that, given the appropriate conditions, triggering the initiation and termination of rhythmic activity of pacemaker cells may be a basic characteristic of all automatic systems. Our demonstration that the phase shifting and the annihilation of Purkinje fiber rhythms can be modeled is a proper step toward understanding the cause of arrhythmias on a molecular scale. We thus expect that our simulation work can be used to predict the initiation of reentrant waves and help us understand the relationship between the reentrant and pacemaker mechanisms of cardiac arrhythmias.

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