Period-Doubling Instability and Memory in Cardiac Tissue

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Theoretical studies have indicated that alternans (period-doubling instability) of action potential duration is associated with a restitution relation with a slope ≥ 1. However, recent experimental findings suggest that the slope of the restitution relation is not necessarily predictive of alternans. Here, we compared a return map memory model to action potential data from an ionic model and found that the memory model reproduced dynamics that could not be explained by a unidimensional restitution relation. Using linear stability analysis, we determined the onset of the alternans in the memory model and confirmed that the slope of the restitution curve was not predictive.

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Several lines of evidence suggest that alternans, a beat-to-beat long-short alternation in the duration of the cardiac action potential, may play an important role in lethal heart rhythm disorders such as ventricular fibrillation [1–4]. Previous researchers have hypothesized that alternans can be accounted for by a simple unidimensional return map called the action potential duration restitution function [5–8]. This hypothesis assumes the duration D of an action potential depends only on its preceding rest interval I through some function $f(I)$ that is measured experimentally. All other degrees of freedom are presumed to be highly dissipative and are therefore ignored. If the restitution function has a slope ≥ 1, then a period-doubling bifurcation occurs for some value of the stimulus period.

According to this hypothesis, the slope of the steady-state restitution function should be predictive of alternans. However, recent experiments by Hall *et al.* [9] and Gray and Banville [10] show that the slope of the steady-state restitution function is not predictive in some cases. Hall *et al.* found that frog cardiac tissue can have restitution slopes of larger than 1 without alternans. Gray and Banville found similar behavior in pig heart tissue. These findings suggest that more degrees of freedom are necessary to accurately describe alternans behavior of cardiac tissue. In this regard, Hall *et al.* have suggested that D depends not only on I but also on a quantity called memory [9]. Memory has been invoked in several previous studies to explain more complex cardiac dynamics [11–15].

In this Letter, we used linear stability analysis to show why in excitable systems, such as heart tissue, the steady-state restitution function is not predictive of the dynamics. We used a return map memory model to demonstrate that period 1 behavior can occur even with a steep restitution function, provided that one of the eigenvalues falls below the stability boundary. We then compared the dynamics of the return map memory model to that of an ionic model that produces a more detailed representation of cardiac action potentials [16]. The dynamics produced by both models were similar. These results have important implications for understanding rhythm disorders such as ventricular fibrillation and for developing control algorithms to eliminate these arrhythmias.

In return map memory models, the memory variable M is assumed to accumulate during the duration D of the action potential and dissipate during the rest interval I (Fig. 1). Thus, M_{n+1} is a function of the previous M_n and the intervening D_n and I_n. D_{n+1} is now a function of M_{n+1} as well as I_n. As memory accumulates, D becomes shorter.

The form of the memory model equations that we studied is similar to those found in [9]. The model was given by

$$M_{n+1} = g(M_n, I_n, D_n) = e^{-I_n/\tau}[1 + (M_n - 1)e^{-D_n/\tau}]$$

$$D_{n+1} = f(M_{n+1}, I_n) = (1 - \alpha M_{n+1})\left(A + \frac{B}{1 + e^{-(I_n - C)/D}}\right)$$

$$I_{n+1} = T - D_{n+1}$$

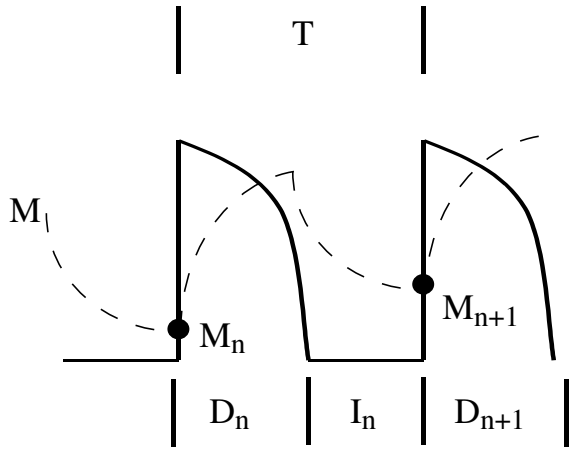

FIG. 1. Memory accumulation and dissipation. In the return map memory model, the memory variable M accumulates during the duration D of the action potential and dissipates during the rest interval I. M_{n+1} therefore depends on M_n, I_n, and D_n. D_{n+1} depends on M_{n+1} and I_n. T is the stimulus period.

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T was the stimulus period and τ was the time constant of accumulation and dissipation of memory (both constants were chosen to be the same). $A = 88$ msec, $B = 122$ msec, $C = 40$ msec, and $D = 28$ msec, as well as $\tau = 180$ msec, were chosen to produce good qualitative agreement with data generated by an ionic model simulation [16]. α determined the influence of memory on D and varied from 0 (no memory) to 1.

Figure 2 shows that the return map memory model with $\alpha = 0.2$ agreed well with the ionic model data generated under control conditions; it produced alternans of the same magnitude and over the same range of stimulus period [Fig. 2(a)], and the steady-state restitution curves were also similar [Fig. 2(b)].

The ionic model allowed us to study the effect of changing ionic current conductances on alternans in a systematic and precise way. For example, increasing the conductance of I_{K1}, I_{Kr}, or I_{Ks}, or decreasing the conductance of I_{Ca} eliminated alternans [16]. For some values of these conductances, no alternans occurred despite a restitution slope ≥ 1. We therefore attempted to fit the memory model to an ionic simulation that had a steady-state slope ≥ 1 but did not exhibit alternans. To do this, we increased the maximum conductance of I_{Kr}, one of the plateau currents in the canine ionic model, by a factor of 2. This eliminated alternans while maintaining a slope ≥ 1 (Fig. 3), suggesting that I_{Kr} may play a role in the ionic basis for memory. Increasing α to 0.58 in the return map model produced good agreement with the ionic model data; alternans was eliminated, while the restitution slope remained ≥ 1.

After verifying agreement between the return map and ionic models, we used linear stability analysis to find the instability to alternans analytically in the return map model. We linearized about the period 1 solution, (M^*, I^*).

$$M_{n+1} = g(M_n, I_n, D_n) = M^* + \delta M_{n+1},$$
$$I_{n+1} = T - f(M_{n+1}, I_n) = I^* + \delta I_{n+1},$$

and found the eigenvalues λ of the resulting matrix equation. Because perturbations grow as $\delta_n = \delta_0 \lambda^n$, the period 1 fixed point goes unstable when $|\lambda| \geq 1$. In particular, a period-doubling (or flip) bifurcation occurs when one of the eigenvalues falls below -1. We also calculated the steady-state restitution slope. It can be shown that the steady-state slope is not related to the eigenvalues in any simple way.

To check the linear stability calculation, we plotted the eigenvalue as a function of stimulus period T, as well as the instability boundary -1 for $\alpha = 0.2$. Figure 4 illustrates that the eigenvalue was indeed predictive of the dynamics: alternans occurred when $\lambda \leq -1$. Finally, we plotted the eigenvalue as a function of T for $\alpha = 0.58$ (Fig. 5). As expected, the eigenvalue never fell below -1, so no alternans occurred. We note that the slope of the steady-state restitution curve was not predictive. In Fig. 5, we plotted the negative of the slope (so that it fell on the same side of zero as the other quantities). Even though there was a region of T over which the slope is ≥ 1, no alternans occurred.

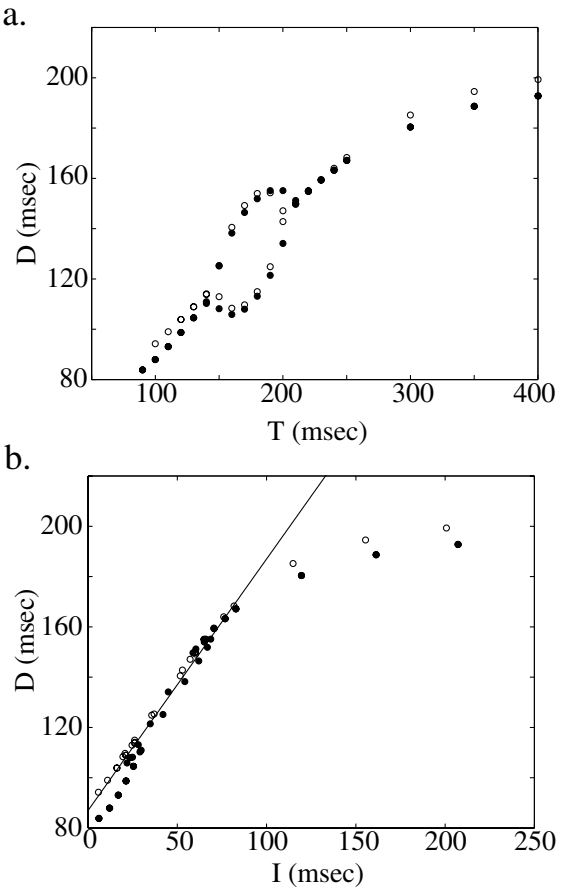

FIG. 2. Steady-state dynamics in the wild-type ionic (filled circle) and return map (unfilled circle) models. $\alpha = 0.2$ in the return map model. (a) Steady-state duration plotted versus stimulus period. Alternans of similar magnitude appeared in both models over similar ranges of stimulus period. (b) Steady-state restitution. As expected, both models had regions where the restitution slope was ≥ 1. (Solid line is a reference of slope 1.)

The results of this study illustrate that the dynamics of cardiac tissue may not be described by a simple unidimensional mapping. This idea is neither new [8,9,12] nor surprising, given that the dynamics of a heart cell is determined by the interaction of many degrees of freedom. For example, the ionic model studied here, which already ignores several degrees of freedom, consists of 13 coupled differential equations describing the interaction of membrane voltage and 13 ionic currents [16]. Still, simplified descriptions of heart dynamics seem possible, in that the results generated by the return map memory model agree well with those obtained from the ionic model. Further, the stability analysis in this Letter provides a simple explanation for the ionic model results and

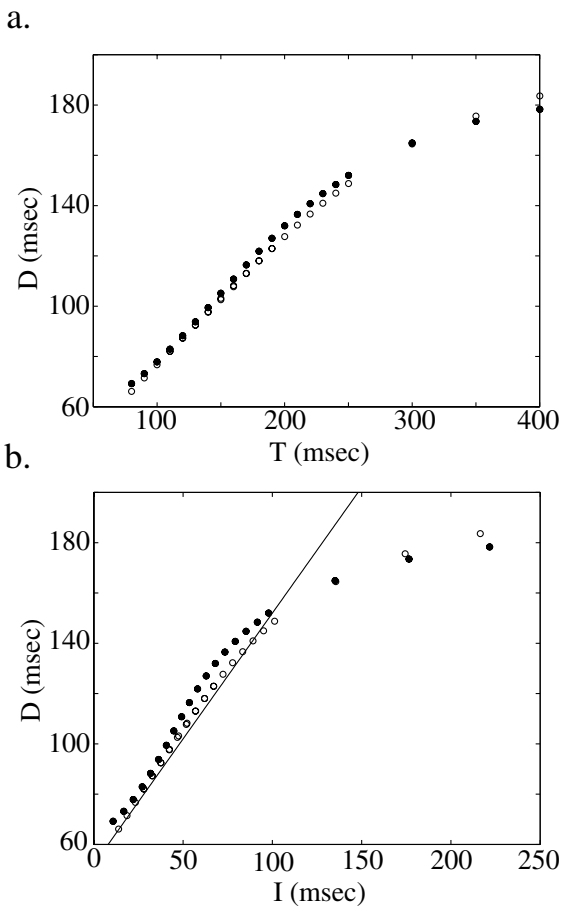

FIG. 3. Steady-state dynamics in the ionic (filled circle) and return map (unfilled circle) models. I_{Kr} was doubled in the ionic model. $\alpha = 0.58$ in the return map model. (a) Steady-state duration plotted versus stimulus period. In both the ionic model and return map model, no alternans occurred. (b) Steady-state restitution. Both models had regions of the restitution relationship with slope larger than 1. (Solid line is a reference of slope 1.)

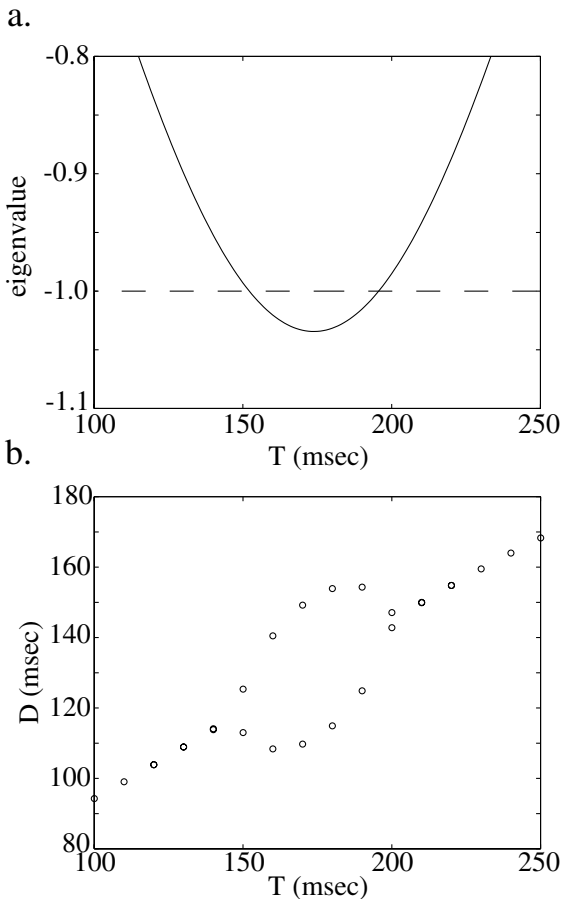

FIG. 4. Period-doubling bifurcation in the return map memory model. $\alpha = 0.2$ to reproduce the dynamics of the wild-type ionic model. (a) Linear stability in the return map model. The solid line is the eigenvalue calculated from linear stability analysis plotted as a function of the stimulus period T. The dashed line is the stability boundary. If the eigenvalue fell below -1 a period-doubling bifurcation was predicted to occur. (b) Numerical iteration of the return map memory model. The duration D is plotted versus T. The return map generated alternans over the same range of T as predicted by the linear stability analysis.

the experimental findings by Hall *et al.*: in systems with memory, the restitution function is not predictive of dynamical instabilities such as alternans. Instead, the eigenvalues of the system must be calculated to find the bifurcations.

This result may have important implications for identifying the mechanisms for lethal heart rhythm disorders. The restitution hypothesis argues that arrhythmias such as ventricular fibrillation are caused by dynamical spatial heterogeneity in association with alternans and a restitution slope ≥ 1 [1–4]. The present study analytically identifies the role that memory plays in determining alternans, thereby illustrating that analyses of restitution alone may not be adequate for accurately predicting heart disorders.

Because of the association between arrhythmias such as ventricular fibrillation and alternans, several groups have attempted to develop algorithms to control the alternans instability, as well as other more complex dynamical instabilities [17–20]. The fact that the restitution function is in some cases not predictive of alternans may impact on these attempts to control instabilities. For example, it may be necessary to incorporate memory into algorithms such as the one used in [19] if they are to be effective *in vivo*.

Control of alternans also might be achieved pharmacologically, provided the ionic basis for memory is known. At present, however, the ionic mechanism for memory remains to be determined. Hund and Rudy found that memory in an ionic model was related to slow changes in intercellular ion concentrations [21] over a time scale of minutes. On an even shorter time scale, it

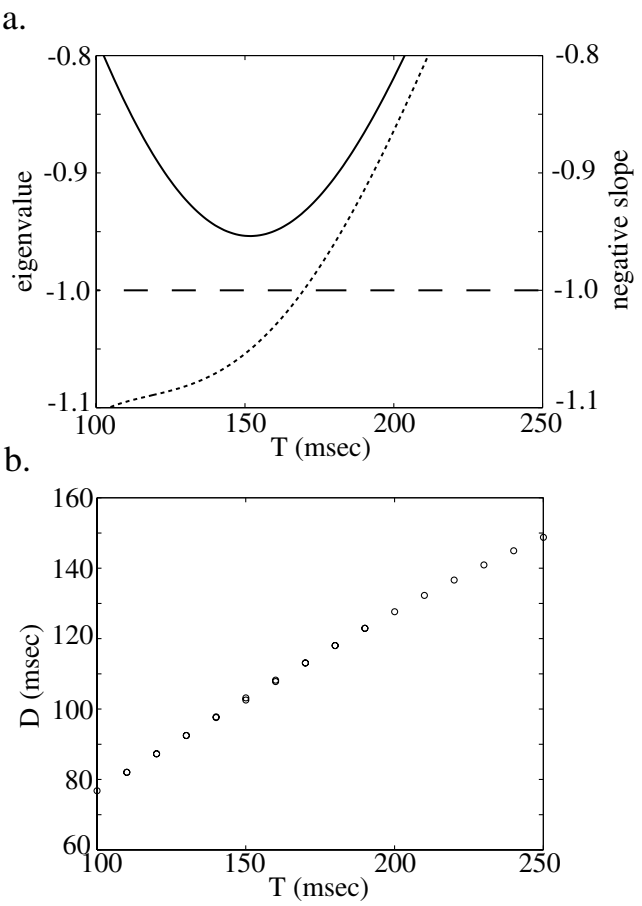

FIG. 5. Linear stability in the return map model with $\alpha = 0.58$ to reproduce the dynamics of the ionic model with I_{Kr} increased by a factor of 2. (a) The solid line is the eigenvalue calculated from linear stability analysis plotted as a function of the stimulus period T. The dashed line is the stability boundary. The dotted line is the negative of the steady-state restitution slope (so that it is on the same side of zero as the other quantities). Since the eigenvalue never fell below -1, no period-doubling bifurcation was predicted. (b) Numerical iteration of the return map memory model. The duration D is plotted versus T. The return map did not produce alternans even though the slope of the steady-state restitution function was larger than 1 over a wide range of T.

seems likely that the dynamics of ion channels themselves may contribute to memory. In the ionic model we studied, I_{Kr} appeared to play a role in memory, based on the fact that doubling the conductance of I_{Kr} eliminated alternans while maintaining a restitution slope ≥ 1. Further studies are needed to identify other time dependent currents and processes, such as release of calcium from intracellular stores, that may contribute to memory.

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