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Using chaos control and tracking to suppress a pathological nonchaotic rhythm in a cardiac model

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Atrioventricular (AV) nodal alternans is a pathological cardiac condition characterized by a beat-to-beat alternation (period-2 rhythm) in AV nodal conduction time. Here we implement an AV nodal conduction model which undergoes a period-doubling bifurcation into alternans. We show that additive noise can be used to locate the unstable period-1 fixed point which underlies the alternans rhythm. We then use chaos control to suppress alternans by stabilizing the model about its unstable period-1 fixed point. We also show that the period-doubling bifurcation into alternans can be prevented by tracking the period-1 rhythm into its unstable regime. We demonstrate that these techniques are robust to imprecise measurements and experimental noise. Importantly, these methods require no knowledge of the underlying system equations. These findings suggest that chaos control and tracking may be useful for suppressing alternans in a clinical environment.

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Chaos control techniques have been applied to a wide range of experimental systems [1,2], including biological preparations [3]. The application of chaos control to biological systems has led to speculations that these methods may be clinically useful [3,4]. Recently, the principles of chaos control have been utilized to stabilize underlying unstable periodic orbits in nonchaotic systems [5,6]. From a clinical standpoint, these developments may be significant given that many pathological conditions are not chaotic in nature. Here we show that chaos control techniques can be used to suppress a nonchaotic, pathological rhythm in a cardiac model. Specifically, we demonstrate that chaos control and tracking can be used to suppress atrioventricular (AV) nodal alternans, which is a beat-to-beat alternation (period-2 rhythm) in AV nodal conduction time.

The intrinsic rhythm of the mammalian heart is controlled by electrical impulses which originate from a specialized region of cells within the right atrium known as the sinoatrial (SA) node. After leaving the SA node, a cardiac impulse propagates through the atrial tissue to the AV node, which is the electrical connection between the atria and the ventricles. The impulse then passes through the AV node and enters the bundle of His, from where it is distributed throughout the ventricular tissue. The AV node is an essential component of cardiac function because it generates a propagation delay which allows ventricular filling and thus facilitates the efficient pumping of blood.

With AV nodal alternans, the time required for a cardiac impulse to pass through the AV node alternates on a beat-to-beat basis. This conduction time is approximated by the atrial-His (A) interval, which is the time between cardiac impulse excitation of the atria (specifically, the low interatrial septum) and the bundle of His. Several experimental studies have shown that the A interval is a function of the nodal recovery time, which is the interval between bundle of His activation and the next atrial activation. This time interval is referred to as the H interval. Recently, Sun *et al.* [7] developed a model for AV nodal conduction time which accurately reproduced important features (including alternans) of AV nodal rhythms measured experimentally in rabbit hearts. In the model, A_n (the conduction time of the nth beat) is a function of H_{n-1} (the recovery time following the preceding beat), as given by the following discrete-time difference equation:

$$A_n = A_{min} + S_n + \beta \exp(-H_{n-1}/\tau_{rec}), \tag{1}$$

where

$$S_1 = \gamma \exp(-H_0/\tau_{fat}), \tag{2}$$

$$S_n = S_{n-1}\exp[-(A_{n-1}+H_{n-1})/\tau_{fat}] + \gamma \exp(-H_{n-1}/\tau_{fat}), \tag{3}$$

$$\beta = \begin{cases} 201 \text{ ms} - 0.7A_{n-1} & \text{for } A_{n-1} < 130 \text{ ms} \\ 500 \text{ ms} - 3A_{n-1} & \text{for } A_{n-1} \geq 130 \text{ ms}, \end{cases} \tag{4}$$

where H_0 is the initial H interval, $A_{min} = 33$ ms, $\tau_{rec} = 70$ ms, $\gamma = 0.3$ ms, and $\tau_{fat} = 30$ s.

In Ref. [7], isolated rabbit hearts were electrically stimulated near the SA node at a fixed time interval following bundle of His activation, i.e., the H interval was held constant ($H_n = \bar{H}$). Alternans rhythms were produced when $\bar{H}$ was reduced below a critical value. In the same study, the cardiac model Eqs. (1)–(4) reproduced the *in vitro* alternans rhythms if $\bar{H} < 57$ ms. This stimulation protocol was used as a simple experimental model of reentrant tachycardia. Reentrant tachycardia is a pathological condition characterized by a cardiac impulse which passes from the atria to the ventricles via the AV node and then rebounds back into the atria stimulating another beat. In the above protocol, the shortened H interval was analogous to the shortening caused by a reentrant impulse.

In the present study, we implemented the cardiac model Eqs. (1)–(4). Figure 1 shows the output of the model for $\bar{H} = 45$ ms. In Fig. 1, it can be seen that near $n = 250$, the A interval bifurcated into an alternans rhythm. From

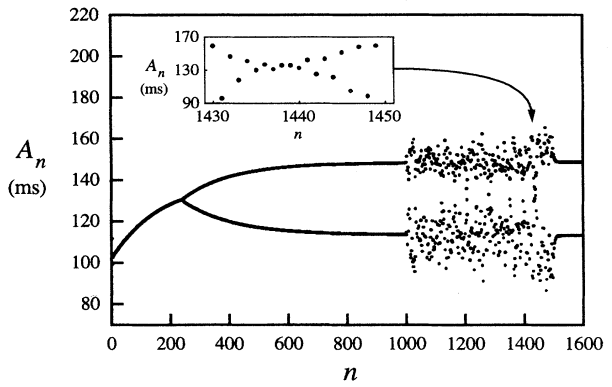

FIG. 1. (a) The output of the cardiac model Eqs. (1)–(4) for $\bar{H}=45$ ms. From $n=1000$–1500, Gaussian white noise ξ_n, with zero mean and standard deviation $\sigma_\xi=5$ ms, was added to each H interval ($H_n=\bar{H}+\xi_n$). A magnified plot of the A intervals ($n=1430$–1449) is shown in the inset.

$n=1000$–1500, Gaussian white noise ξ_n, with zero mean and standard deviation $\sigma_\xi=5$ ms, was added to each H interval ($H_n=\bar{H}+\xi_n$), causing the A interval to fluctuate. The inset in Fig. 1 shows that there is deterministic structure underlying these fluctuations, i.e., the A intervals ($n=1430$–1449) in the inset enter the neighborhood of an unstable period-1 fixed point and remain near that fixed point for several iterates (i.e., beats).

Recently, it has been shown that chaos control can be used to stabilize unstable periodic fixed points in a nonchaotic system [5,6]. Motivated by this finding, we explored the possibility of exploiting the dynamics depicted in Fig. 1 to suppress AV nodal alternans in the cardiac model Eqs. (1)–(4). We implemented a control scheme based on a one-dimensional map simplification [2,8] of the original model-independent chaos control algorithm of Ott, Grebogi, and Yorke [9]. This simplified method applies parameter perturbations which are directly proportional (according to a proportionality constant g) to the difference between the system's state point and the unstable period-1 fixed point. The parameter perturbed in this study was the H interval; importantly, this parameter is experimentally accessible. The proportionality constant g, also known as the fixed-point sensitivity, was estimated as the difference between the fixed point [10] for a given $\bar{H}_1$ and the fixed point for a nearby $\bar{H}_2$ divided by $(\bar{H}_1-\bar{H}_2)$.

Figure 2 shows the A and H intervals as functions of beat number n for a representative alternans control trial. The first 1000 points of Fig. 2(a) show an alternans bifurcation produced by $\bar{H}=50$ ms. At $n=1000$, chaos control was activated to eliminate the alternans rhythm. Chaos control activation typically requires the system's state point to wander into the neighborhood of the unstable periodic fixed point. As shown in Fig. 1, additive noise could be used to move A_n from the stable alternans rhythm into the neighborhood of the underlying unstable period-1 fixed point. However, this process sometimes took a relatively long time, e.g., in Fig. 1, 439 iterations (beats) were required before the system wandered near the fixed point. In certain clinical settings, such

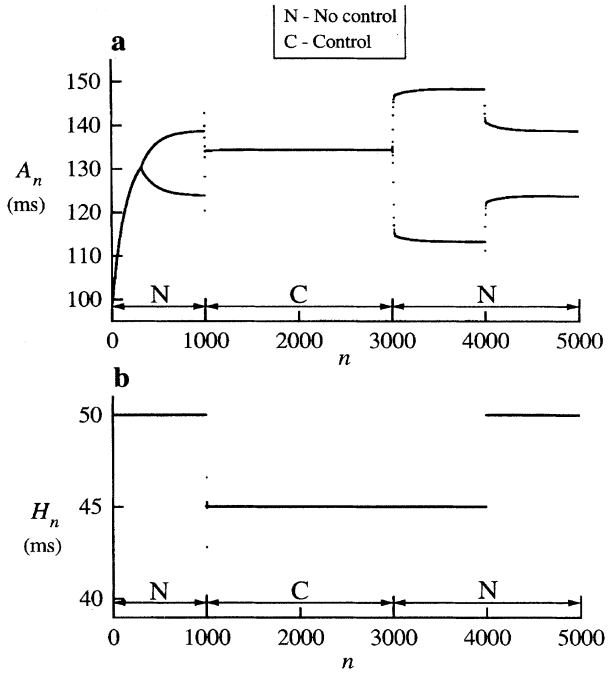

FIG. 2. (a) A and (b) H intervals as functions of beat number n for a representative alternans control trial. The respective control stages are annotated in (a) and (b).

long times may be infeasible (i.e., fatal) [11]. Thus, as shown in Fig. 2, we attempted to activate control directly from the alternans branches. The targeted fixed point was initially estimated as the midpoint of the two A branches. Following each H control perturbation, a new fixed point was adaptively estimated as the midpoint of the previous fixed point and the A interval resulting from the control intervention [12]. Importantly, the H control perturbations were made to $\bar{H}=45$ ms. Because this value was less than the "natural" interval of 50 ms, control stimulations were not preempted by natural impulses [13]. (This control scenario may be appropriate for suppressing an alternans rhythm arising from reentrant tachycardia, i.e., the control stimulations would not be preempted by reentrant impulses.) Figure 2(a) shows that stabilization of the unstable period-1 fixed point occurred within a few beats and was maintained until adaptive control was turned off at $n=3000$. From $n=3000$–4000, H was held constant at its final control value $H_f\approx 45$ ms [Fig. 2(b)]. Due to the unstable nature of the period-1 fixed point, the A interval quickly departed from the period-1 rhythm and settled into the stable alternans rhythm corresponding to H_f. At $n=4000$, $\bar{H}$ was returned to its natural value of 50 ms and the system quickly settled into its original alternans rhythm [14].

Figure 2 shows that chaos control can be used to suppress alternans in the cardiac model Eqs. (1)–(4). This simulation, however, did not take into account real-world experimental limitations. Two such limitations, imprecise measurements and experimental noise, are inevitable factors associated with biological experiments. Figure 3 shows the results of a control simulation for which each A iterate [computed using Eq. (1)] was "measured" (by the control algorithm) with a precision of 0.2 ms (the measurement precision reported in Ref. [7]) following the addition of measurement noise

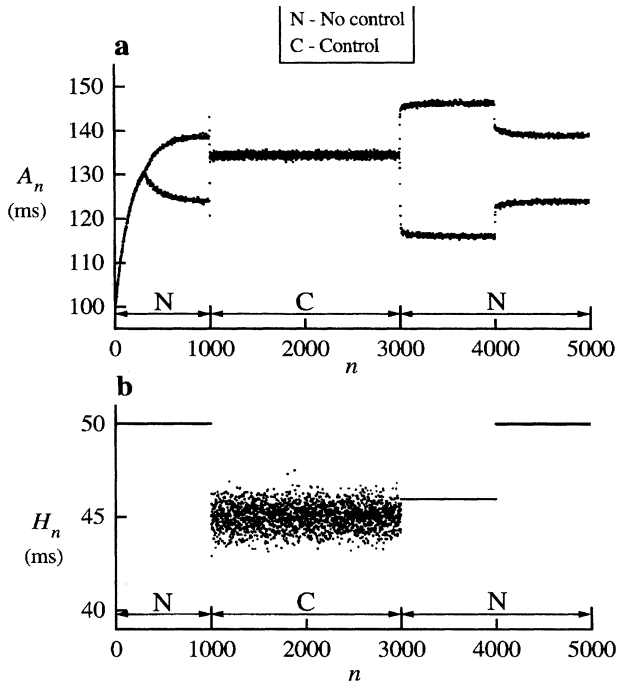

FIG. 3. (a) A and (b) H intervals as functions of beat number n for a representative alternans control trial. Each A iterate, computed using Eq. (1), was "measured" with a precision of 0.2 ms following the addition of measurement noise ($\sigma_\xi = 0.25$ ms). The respective control stages are annotated in (a) and (b).

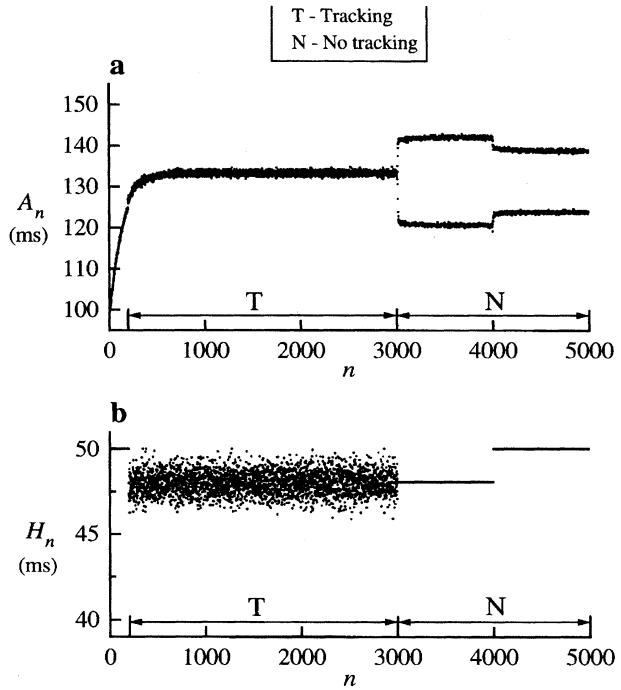

FIG. 4. (a) A and (b) H intervals as functions of beat number n for a representative A-interval tracking trial. Each A iterate, computed using Eq. (1), was "measured" with a precision of 0.2 ms following the addition of measurement noise ($\sigma_\xi = 0.25$ ms). The respective tracking stages are annotated in (a) and (b).

($\sigma_\xi = 0.25$ ms). Control was robust to the effects of these limitations, i.e., the A intervals were successfully constrained within the neighborhood of the unstable period-1 fixed point [Fig. 3(a)].

If chaos control is initiated prior to the period-doubling bifurcation, the method described above reduces to "tracking," which is a technique that can be used to follow a stable fixed point into its unstable regime [5]. Figure 4 shows a representative A-interval tracking trial with the same limitations that were used for Fig. 3. Tracking was activated at $n = 200$. The period-1 rhythm was effectively stabilized beyond the point ($n \approx 250$) at which the alternans bifurcation was expected. When tracking was turned off at $n = 3000$, the system quickly settled into an alternans rhythm, as in Figs. 2 and 3.

Tracking offers an appealing method for AV nodal alternans prevention if the period-doubling bifurcation into alternans is predictable. However, if it is not known when (or if) the bifurcation will occur, tracking may be impractical given that it may be clinically inappropriate to stimulate a patient's heart before intervention is required. Thus, for an unpredictable alternans bifurcation, a more appropriate approach may be to initiate chaos control immediately following the bifurcation, thus permitting only a brief period of uncontrolled alternans.

In this study, chaos control and tracking were used to suppress AV nodal alternans in a cardiac model by adaptively shortening the H interval to stabilize the underlying unstable period-1 A fixed point. The techniques were shown to be robust to imprecise measurements and experimental noise. Importantly, these methods require no knowledge of the underlying system equations. These findings suggest that chaos control and tracking may be useful for suppressing alternans in a clinical environment. This work thereby lends further support to the notion that the principles of chaos control may be clinically useful [3,4].

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[10] The unstable period-1 fixed point corresponding to each $\bar{H}$ was located by adding Gaussian white noise to each $\bar{H}$.

[11] Although it sometimes took a relatively long time, we were able to initiate chaos control by using additive noise to move the system's state point into the neighborhood of the unstable period-1 fixed point.

[12] Adaptive fixed-point estimation may be particularly appropriate for biological systems, which are inherently nonstationary.

[13] Although lengthening the H interval would be a simple way to eliminate AV nodal alternans, this approach is impractical because eliciting beats via electrical stimulation can only shorten the H interval.

[14] Sun *et al.* [7] also produced A alternans in rabbit hearts and in the cardiac model Eqs. (1)–(4) by stimulating the respective systems at a constant $(A+H)$-interval. Using chaos control, we were able to suppress such alternans in the cardiac model by making adaptive perturbations to the $(A+H)$-interval.