Suppression of cardiac alternans by alternating-period-feedback stimulations

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Alternans response, comprising a sequence of alternating long and short action potential durations in heart tissue, seen during rapid periodic pacing can lead to conduction block resulting in potentially fatal cardiac failure. A method of pacing with feedback control is proposed to reduce the alternans and therefore the probability of subsequent cardiac failure. The reduction is achieved by feedback control using small perturbations of constant magnitude to the original, alternans-generating pacing period T, viz., using sequences of two alternating periods of $T + \Delta T$ and $T - \Delta T$, with $\Delta T \ll T$. Such a control scheme for alternans suppression is demonstrated experimentally in isolated whole heart experiments. This alternans suppression scheme is further confirmed and investigated in detail by simulations of ion-channel-based cardiac models both for a single cell and in one-dimensional spatially extended systems. The mechanism of the success of our method can be understood in terms of dynamics in phase space, viz., as the state of activity of the cell being confined within a narrow volume of phase space for the duration of control, resulting in extremely diminished variation in successive action potential durations. Our method is much more robust to noise than previous alternans reduction techniques based on fixed point stabilization and should thus be more efficient in terms of experimental implementation, which has implications for clinical treatment for arrhythmia.

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I. INTRODUCTION

Rapid stimulation (pacing) of cardiac tissues is a commonly used technique [1] to generate wave trains for removing sources of irregular activity responsible for arrhythmias, potentially life-threatening disruptions in the normal rhythmic activity of the heart [2]. However, although using higher-frequency stimulation should increase the probability of suppressing the abnormal activity [3], extremely rapid pacing can generate a time-varying response of the cardiac tissue (referred to as alternans) [4] to the applied stimuli because of the nonlinear recovery properties of excitable cells [5]. Such alternans, producing beat-to-beat variation in the duration of cellular activity (action potentials), successively elicited by the applied stimuli can themselves produce further sources of arrhythmia, thereby defeating the very purpose of pacing.

Cardiac beating can be characterized by the cycle length (CL), which consists of an action potential duration (APD), followed by a recovery period or diastolic interval (DI) before the next beat starts (see Fig. 1). The CL can be controlled by external pacing and if the CL is too short, the cardiac system can develop alternating long and short APDs. The dynamical origin of the emergence of alternans can be best understood in terms of the cardiac restitution curve. For a cardiac system subjected to stimulation with an interval T_n between the generation of the nth and $(n+1)$th action potentials, the duration of the latter depends on the former according to

$$a_{n+1} = f(d_n) = f(T_n - a_n), \tag{1}$$

where a_n and d_n are the APD and the DI of the nth beat, respectively. The return map f relating successive APDs is the restitution function for the duration of an action potential that depends on the preceding DI, i.e., the period between the end of the earlier action potential and the beginning of the current one. For a constant slow pacing period T (i.e., fixed $T_n = T$), the APDs are constant, corresponding to a stable fixed point of the restitution return map: a^* [$= f(T - a^*)$]. However, for fast enough pacing (i.e., small T), this fixed point becomes unstable, giving rise to a period-2 attractor leading to a steady sequence of alternating long and short APDs.

Earlier methods for reducing alternans have been based on feedback control techniques to stabilize the dynamical fixed point by changing the pacing period with a proportional gain method [6–9]. In this proportional gain method, the pacing period T_n of the nth step is controlled as

$$T_n = T + \frac{\gamma}{2}(a_n - a_{n-1}), \tag{2}$$

where γ is a tunable parameter that defines that feedback gain. It can be easily shown [8] that the originally unstable trivial fixed point can be made stable if γ is tuned to lie in the range $1 - 1/f' < \gamma < 2/f'$, where $f' \equiv f'(T - a^*)$. Notice that the stable range of γ becomes small if f' is steep (the range vanishes as $f' = 3$). Furthermore, the pacing period of the proportional feedback method varies over many different values depending upon the difference between the last two APDs recorded. The range of variation can be quite large, especially at the initial stages after switching on the control, and is a possible source of additional complications in potential clinical applications. Furthermore, the proportional feedback gain method has had only limited success in controlling alternans in spatially extended systems [9].

In this paper we propose a method based on alternating period stimulation on an excitable cardiac system that reduces alternans significantly. The applied pacing period is made to alternate between two values $T \pm \Delta T$ ($\Delta T \ll T$ being a predetermined control parameter) that are just above and below the period T that is to be controlled. This makes our proposed algorithm more akin to open loop control, whereas the proportional feedback method is a closed loop scheme. As

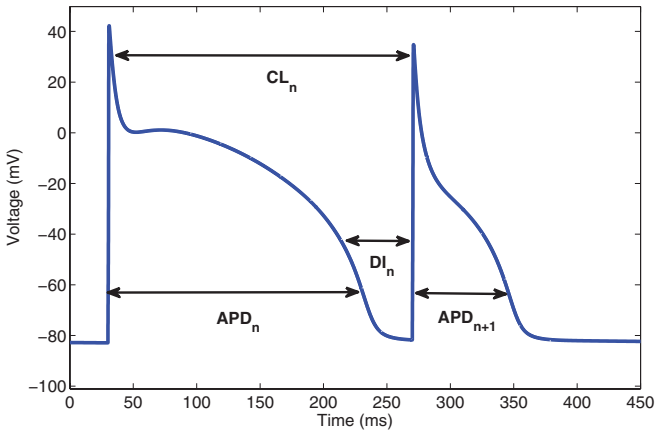

FIG. 1. (Color online) The time series of the transmembrane potential V for a cell subjected to rapid periodic stimulation of period T demonstrates alternans of the action potential duration (APD). The nth action potential is shown to have a relatively long duration compared to the period between successive stimulations (denoted as the cycle length CL_n). As the diastolic interval (recovery period) of the cell (denoted as DI_n) is short before the onset of the next excitation, the resulting $(n+1)$th action potential is shorter. Notice that CL_n, APD_n, and DI_n are the same as T_n, a_n, and d_n, respectively, in the text.

open loop control is easier to implement in general, this should be an appealing feature in practical applications. We further test our method experimentally in an isolated whole heart system and verify that alternans can indeed be significantly reduced.

II. ALTERNATING PERIOD STIMULATION SCHEME FOR CARDIAC ALTERNANS SUPPRESSION

We now describe our proposed alternating period pacing algorithm that markedly reduces the variation between successive action potentials even when the system is driven by rapid periodic stimulation that would, in the absence of control, lead to significant APD alternans. As implied by the name "alternating period," the method relies on switching continually between two different periods of successive stimulation of the system, measured by the cycle length T_n for the period between the nth and $(n+1)$th action potentials (Fig. 1). As alternans involves variation in the APDs, our proposed method has to ensure that the APDs resulting from successive stimuli remain almost the same. To ensure this, the algorithm decides the time of next stimulation between two possible values $T_+ \equiv T + \Delta T$ and $T_- \equiv T - \Delta T$, where ΔT is a free parameter chosen at the beginning of the simulation. Based on the difference between the current and previous APDs, one chooses T_n as follows:

$$\text{If } a_n > a_{n-1}, \text{ then } T_n = T_+; \text{ otherwise } T_n = T_-. \qquad (3)$$

This ensures that if APD_n is short, the following APD will also be short (as the cycle length is short); in contrast, if APD_n is long, the use of a longer cycle length will ensure that the next APD will also be long. For most of the period during which the alternating period pacing is applied, the cycle lengths follow either the sequence $T_+T_-T_+T_-\ldots$ or the (effectively equivalent) sequence $T_-T_+T_-T_+\ldots$, switching from one to the other whenever an APD is shorter (or longer) than both its preceding and following APDs. The choice of $T_\pm$ ensures that the mean value for the cycle length is T, the period of rapid stimulation for which we seek a steady response of the system. For the results reported here, the value of T has been chosen such that while for $\Delta T = 0$ we observe large alternans, the magnitude of the period-2 response is significantly reduced for a suitable choice of $0 < \Delta T \ll T$.

III. EXPERIMENTAL RESULTS

The control scheme for the suppression of alternans proposed above has been tested in isolated heart experiments in a Langendorff system. Briefly, the Langendorff system is used to maintain the physiological condition of an isolated heart and keeping it functional by providing perfusion with nutrient-rich oxygenated solution at a constant temperature. In our experiments the hearts are extracted from Wistar rats (weight between 250 and 300 g, both males and females). Usually, the preparation can last for 3–4 h. In the experiment, pseudo electrocardiograms (ECGs) of the hearts at various locations are monitored by inserting the electrodes in the heart tissues. A pacing electrode placed on the septum between two ventricles is used to provide controlled stimulation to the isolated heart. The contraction pressure of the left ventricle (LVP) is monitored by a water-filled balloon (1 cm long, made of latex) inserted inside the left ventricle through a pressure transducer. Detailed descriptions of our setup and experimental conditions can be found in Ref. [10]. The protocols of the present study was approved by the Board of Ethics of Academia Sinica and conducted according to National Institutes of Health Guidelines for the Use and Care of Laboratory Animals [11].

Implementation of the T_+T_- control scheme (3) is through a PC equipped with a data acquisition system NI-6221 (National Instruments, USA). A customized program written in IDL (Research System Inc., USA) is used to monitor the pressure LPV of the nth beat and send out a stimulation to the heart with correct pacing interval (precision with 0.1 ms) for the $(n+1)$th beat. The electric stimulation to the heart is delivered through an isolated stimulator (Model 2100, A-M Systems, Carlsborg, WA, USA). The form of a single electrical stimulation is a rectangular monophasic current pulse with a duration of 1 ms and the amplitude is twice the diastolic threshold current. Notice that, instead of using the a_n in the isolated heart for control, we have used the p_n in our control scheme, where p_n is the peak value of the LVP of the nth beat. Since it is known that [12] a longer APD will lead to a stronger cardiac contraction, there is a one-to-one correspondence between a_n and p_n. In fact, the first documented phenomenon of alternans was based on the pulse pressure [2]. Therefore, we simply replace the a_n with p_n, with n being the beat number. Signals from ECGs and the pressure transducer (LVP) are recorded by another NI-6221, which is controlled by POWERGRAPH PROFESSIONAL software (version 3.3.7, Russia) with a 4-kHz sampling rate. The experiments reported below were all carried out at 20 °C because it is much easier to generate alternans at lower temperature with slow pacing [13]. We have checked that experiments carried out at 37 °C produce qualitatively similar results.

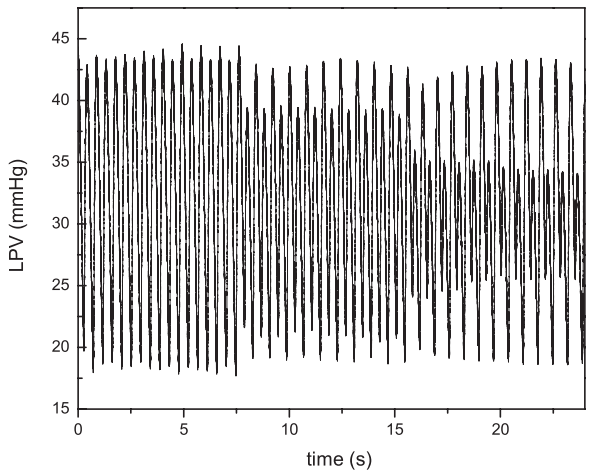

FIG. 2. Time course of the LVP during the generation of alternans. The pacing period is decreased from 450 to 400 ms and then to $T_0 =$ 350 ms. It can be seen that there is a transition from a single-period to a period-doubling response of the heart. Notice that if the rate of decrease of the pacing period is too fast or T_0 is too small, there might be inductions of tachycardia or fibrillations.

Before the start of an experiment, the excised heart was first maintained in the Langendorff system for at least 30 min to allow it to adapt to the Langendorff environment, beating with its own sinus rhythm period T_{SR}. Then external stimulations are used to produce alternans by slowly decreasing the pacing (beating) period from T_{SR} to T_0. Alternans can be seen as the occurrence of two values of measured LVP for a single pacing period. Figure 2 shows the time course of the generation of the alternans. The pacing period in Fig. 2 is decreased in three steps to the desired T_0. It can be seen from Fig. 2 that while the stimulation has a single period, the response of the LVP undergoes a period-doubling transition. The alternans can be seen as the LVP alternating between two different values. The stability of this period-2 behavior depends on the state of the heart and the magnitude of the alternans. In our experiments, we have always checked that the alternating state is stable for at least 10 min before we start our experiments. To start a T_+T_- control experiment, procedures similar to those used in Fig. 2 are used to first produce the alternans and then the T_+T_- control is started 15–30 s after T_0 has been reached.

Figure 3 shows the time course of the LVP in a typical T_+T_- control experiment. The suppression of alternans can be seen as the decrease in the magnitude of the difference between two successive LPVs. In Fig. 3(a), T_+T_- control is started at $t =$ 5 s and kept on up to $t = 20$ s. It can be seen that the response of the heart changes immediately after the control is switched on and the magnitude of the alternans (difference between alternating peaks) decreases monotonically. From the figure it can be observed that the alternans is suppressed around $t =$ 17 s or within 40 beats. Another remarkable feature seen in Fig. 3 is that the control itself has some systematic long-term effect on the alternans state. This effect can be seen in Fig. 3(b) once the control is switched off. From the figure it is clear that the alternans state reemerges at ($t = 25$ s) once control is switched off and the new state has a smaller alternans magnitude compared to that before the control was applied. It seems that the T_+T_- control has changed the alternans

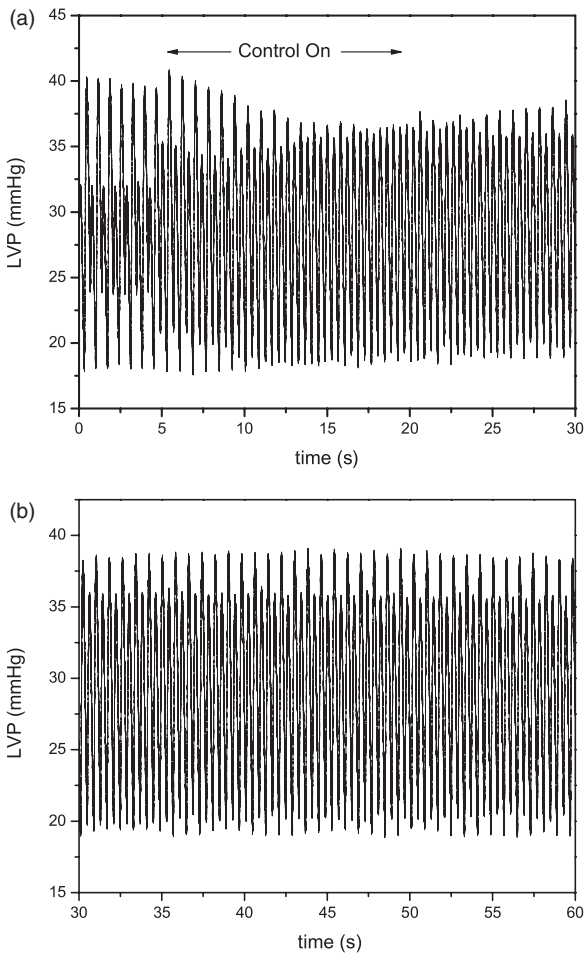

FIG. 3. Time course of the LVP under 15 s of T_+T_- control with $\Delta T = 10$ ms and $T_0 = 400$ ms. (a) Control started at $t = 5$ s and lasted until 20 s. (b) Continuation of (a) after control has stopped. Notice that the magnitude of alternans after control is smaller than that before control.

response of the heart. There are some hysteresis effects of T_+T_- on the heart.

The time for which the control is applied in Fig. 3 is kept short so as to demonstrate the efficacy of the scheme. To study the properties of the controlled state, we have also performed experiments with much longer control time as shown in Fig. 4. In this figure we show p_n (the peak values of the LVP at the nth beat) as a function of the beating number n. The initial alternans state is prepared between $n = 0$ and 1350 with $T_0 =$ 500 ms. The alternans state can be seen as the existence of two main values of the p_n. Their difference is the magnitude of the alternans. Similar to Fig. 3, it can be seen from Fig. 4 that the suppression of alternans is fast once the control is switched on. Now, with a control time of 600 s, it can be seen clearly that the p_n under control is not constant but takes on a range of values more or less randomly. It would be desirable to control the system to have a very short range of p_n by using a smaller ΔT. Figure 5 shows such an attempt with $\Delta T = 2$ ms. It can be seen that there is little suppression with this control. That is, ΔT cannot be too small and there seems to be an minimal value of ΔT for effective control.

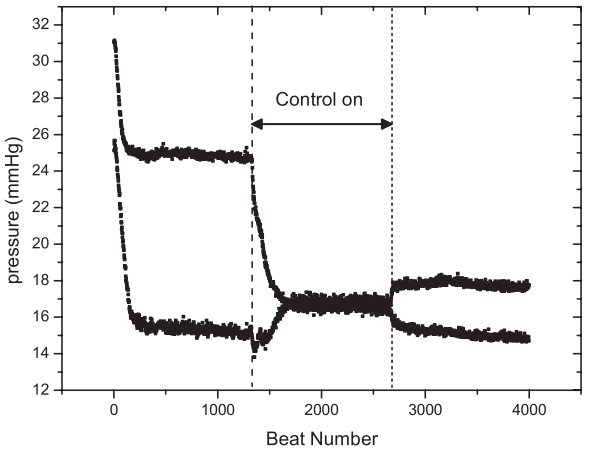

FIG. 4. Time course of the peak value of the LVP under 600 s of T_+T_- control with $\Delta T = 14$ ms and $T_0 = 500$ ms. Time is being shown as beat numbers. Control started at beat number 1350 and ended at 2650. It can be seen that the magnitude of alternans after control is smaller than that before control.

If we examine the reemerged alternans state after the control is stopped in the experiments discussed above, it can be seen that the reemerged state always has a smaller alternans magnitude. There seems to be a hysteresis effect on the heart when the control is applied. To check whether this observation is an artifact of the T_+T_- control scheme, we have also implemented the proportional control scheme of Eq. (2) in our experiment. In experiments with the proportional control scheme, we have also found similar effects (data not shown). However, this hysteresis is not a long-term effect due to a change in the physiology of the heart as we can always reproduce the initial alternans state by regenerating it from a nonalternans state with a much longer T_0 as depicted in Fig. 2. It seems that the control has put the heart in a different dynamical state even after the control has been stopped. Furthermore, to eliminate variabilities due to different samples, the above experiments have all been repeated for at least five different hearts and similar results were found.

IV. MODEL AND SIMULATION RESULTS

Our alternans suppression scheme can be investigated in more detail by simulations for the cases of a single cell and spatially extended systems of coupled excitable cells. The spatiotemporal dynamics of several biological excitable systems can be described by models having the generic form

$$\frac{\partial V_t}{\partial t} = \frac{-I_{\rm ion}(V,g_i) + I_{\rm noise}(x,t) + I_{\rm ext}(x,t)}{C_m} + D\nabla^2 V, \quad (4)$$

where V (mV) is the potential difference across a cellular membrane, C_m ($= 1\ \mu$F cm^{-2}) is the transmembrane capacitance, $I_{\rm ion}$ (μA cm^{-2}) is the total current density through ion channels on the cellular membrane, and g_i describes the dynamics of gating variables of different ion channels. The stochastic current density term $I_{\rm noise}$ represents an additive thermal or channel noise [14] that is randomly fluctuating in both time and space within a limited range (uniformly distributed between 0 and 0.5 μA cm^{-2} here). The space- and time-dependent pacing current density $I_{\rm ext}$ (μA cm^{-2}) represents the external stimuli

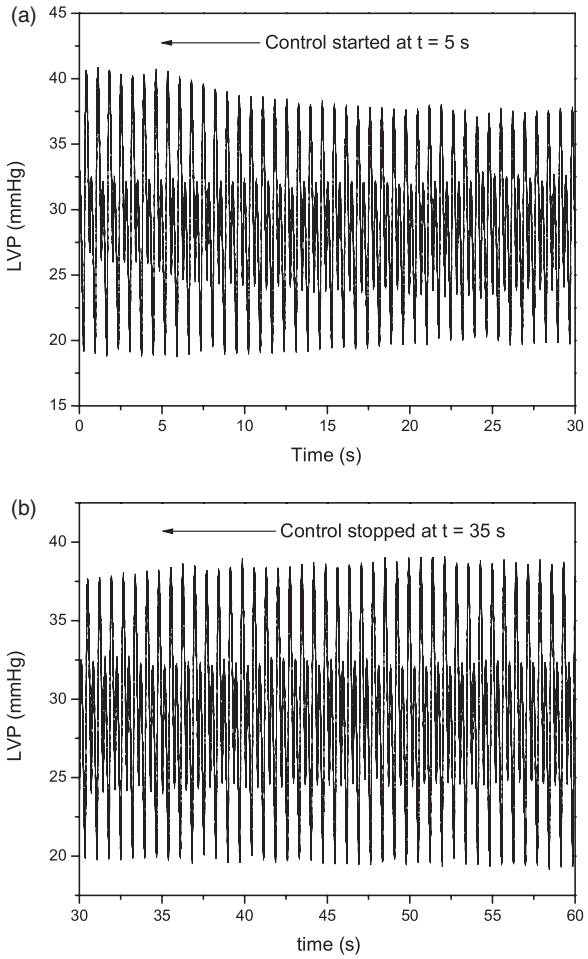

FIG. 5. Time course of the LVP under 30 s of T_+T_- control with $\Delta T = 2$ ms and $T_0 = 360$ ms. (a) Control started at $t = 5$ s. (b) Continuation of (a) and the control is stopped at $t = 35$ s. Notice that the magnitude of alternans after control is smaller than that before control.

applied in a local region in order to generate wave trains. The last term on the right corresponds to spatial coupling in a multicellular array, with an effective diffusion constant D ($=0.001$ cm^2 s^{-1} for the results reported in the paper). The specific functional form for $I_{\rm ion}$ varies for different biological systems. For the results reported here, we have used the Luo-Rudy I model that describes the ionic currents in a ventricular cell [15]. In this model, $I_{\rm ion}$ is considered to be composed of six different ionic current densities, viz., $I_{\rm ion} = I_{\rm Na} + I_{\rm K} + I_{\rm K1} + I_{\rm Kp} + I_{\rm Ca} + I_b$, where $I_{\rm Na}$ is the sodium ion channel current; $I_{\rm Ca}$ is the slow inward calcium channel current; $I_{\rm K}$, $I_{\rm K1}$, and $I_{\rm Kp}$ correspond to different potassium channel currents; and I_b is the background current. These currents are determined by several time-dependent ion-channel gating variables whose time evolution is governed by ordinary differential equations of the form

$$\frac{d\xi}{dt} = \frac{\xi_\infty - \xi}{\tau_\xi}. \quad (5)$$

Here $\xi_\infty = \frac{\alpha_\xi}{\alpha_\xi+\beta_\xi}$ is the steady state value of ξ and $\tau_\xi = \frac{1}{\alpha_\xi+\beta_\xi}$ is the corresponding time constant. The voltage-dependent rate

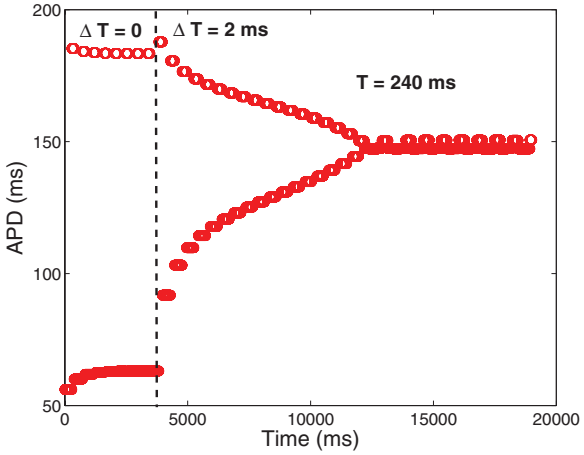

FIG. 6. (Color online) Suppression of APD alternans in a single cell subject to rapid alternating period pacing. The figure shows that when the cell is initially stimulated with constant period pacing ($T = 240$ ms), the APD shows a marked alternans behavior. After the alternating period pacing is switched on (indicated by the dashed line) where the stimulation period switches between $T_+ = T + \Delta T$ and $T_- = T - \Delta T$ with $\Delta T = 2$ ms, the APD variation becomes negligible within a period of 10 s.

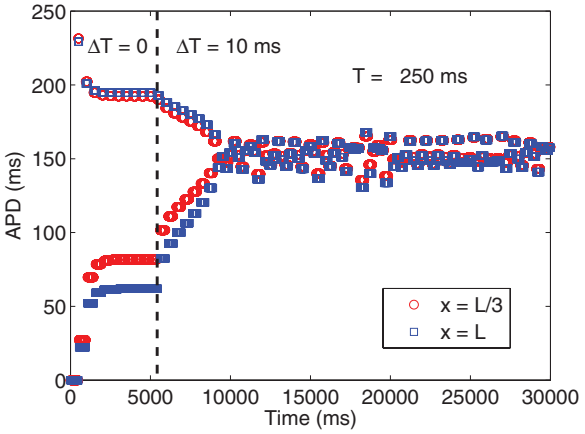

FIG. 7. (Color online) Reduction of APD alternans in a one-dimensional fiber of excitable cells by alternating period pacing. An array of excitable cells with $L = 30$ subjected to pacing at the $x = 0$ end shows variation in the duration of successive action potentials when it is subjected to a constant periodic stimulation ($T = 250$ ms), with the magnitude of alternans increasing as one moves further away from the pacing end along the fiber. Once the alternating period pacing is switched on (indicated by the dashed line) with the stimulation at the pacing end switching between $T_+ = T + \Delta T$ and $T_- = T - \Delta T$ with $\Delta T = 10$ ms, the APD variation is significantly reduced within 5 s. Notice that different points in the fiber show a similar degree of reduction in the magnitude of alternans.

constants α_ξ and β_ξ are complicated functions of V obtained by fitting experimental data.

For all our simulations, the maximum K^+ channel conductance G_K has been increased to 0.705 mS cm^{-2} to reduce the APD [16]. To generate alternans in a single cell under rapid pacing the maximum Ca^{2+} channel conductance has been taken to be $G_{si} = 0.09$ mS cm^{-2}. We have explicitly verified that our results are not sensitively dependent on small variations in the model parameters. It is also model independent as similar effects were observed in models for a single cell with other realistic channel-based descriptions of the ionic current, such as the ten Tusscher–Noble–Noble–Panfilov model [17].

We consider in turn the response of a single cell and a one-dimensional cable of excitable cells subjected to periodic stimulations. The equations are solved using a forward-Euler scheme with a time step $dt = 0.01$ ms. The spatially extended system is discretized on an array of size L with space step $dx = 0.0225$ cm and a standard three-point stencil for the Laplacian describing the spatial coupling between the units. For most results reported here L is between 30 and 40, although we have used L up to 60. No-flux boundary conditions are implemented at the edges. Pacing stimuli are implemented by applying an external current I_{ext} of magnitude 100 μA cm^{-2} for a duration of 1 ms. For a one-dimensional cable, it is applied from one end of the system ($x = 0$) over a region of finite width (0.225 cm). Action potential duration is measured as the period between the successive instants when V crossed -60 mV from below and from above.

Figure 6 shows the result of applying the alternating period pacing method on a single cell to suppress APD alternans when stimulating at a mean period of $T = 240$ ms. As seen from the variation of the APD before the alternating method is switched on (i.e., the region to the left of the dashed line), stimulation at constant period T results in a significant degree of alternans, with successive action potentials having durations of 183 and 63 ms, respectively. However, when alternating period stimuli with $\Delta T = 2$ ms are applied, the alternans is suppressed within 10 s to a relatively negligible magnitude, with the action potentials at the steady state having durations ranging between 147 and 151 ms. This finding is consistent with our experimental observations that the alternans can be suppressed within 50 beats after the start of the control. Notice that the condition for switching between T_+ and T_- based on the difference between successive APDs [Eq. (3)] is crucial as a simple two-period pacing of the cell, i.e., using either the sequence $T_+T_-T_+T_- \ldots$ or $T_-T_+T_-T_+ \ldots$ exclusively without switching between them would result, after a short initial transient of converging APDs, in successively diverging APDs.

While the suppression of alternans in a single cell is encouraging, for the method to be applicable in practical situations the alternating period pacing should be successful in significantly reducing alternans in spatially extended systems. Figure 7 shows the results of applying the alternating period pacing method on a one-dimensional fiber of excitable cells with $L = 30$. When the system is stimulated (the pacing end is at $x = 0$) at a constant period $T = 250$ ms, different points on the fiber show alternans having magnitude that increases as one proceeds along the fiber away from the pacing end. For example, at $x = L/3$, the successive APDs alternate between 82 and 192 ms, respectively, while at the farthest end ($x = L$) APDs switch between 62 and 195 ms, respectively, for successive pacing stimuli (see the time series to the left of the dashed line in Fig. 7). Within a few seconds of switching on the alternating period pacing, the APD alternans is significantly reduced and in the steady state the APDs fluctuate over a relatively small range between approximately 141 and 166 ms that does not vary significantly with the location on the fiber.

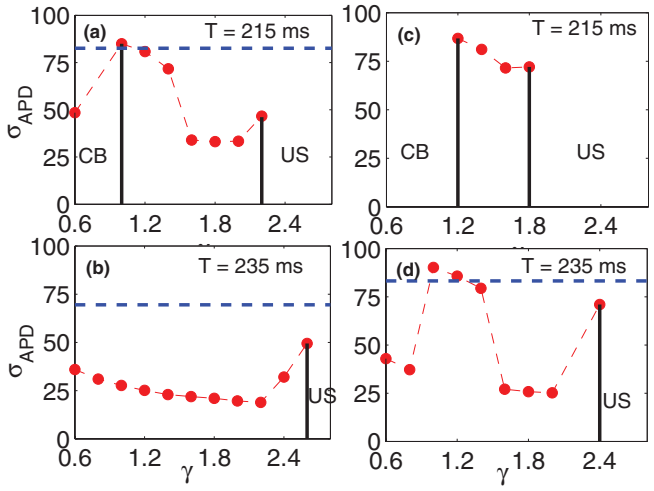

FIG. 8. (Color online) Performance of the proportional feedback control method in suppressing alternans in a one-dimensional fiber ($L = 40$) of excitable cells in the absence and presence of noise. The efficiency of the method is obtained from the standard deviation of the durations of a long sequence of action potentials measured at the center of the system ($x = L/2$) as a function of the feedback gain parameter γ. The system is subjected to two different imposed pacing periods (a) and (c) $T = 215$ ms and (b) and (d) 235 ms in the (a) and (b) absence and (c) and (d) presence of noise. The dashed blue line shows the standard deviation of the APD for constant pacing with period T in the absence of feedback control ($\gamma = 0$). Applying control can sometimes result in conduction block (CB) at a location downstream of the pacing site ($x = 0$). For certain cases, no response is elicited even at the pacing end; the control is said to be unstable (US) in such cases.

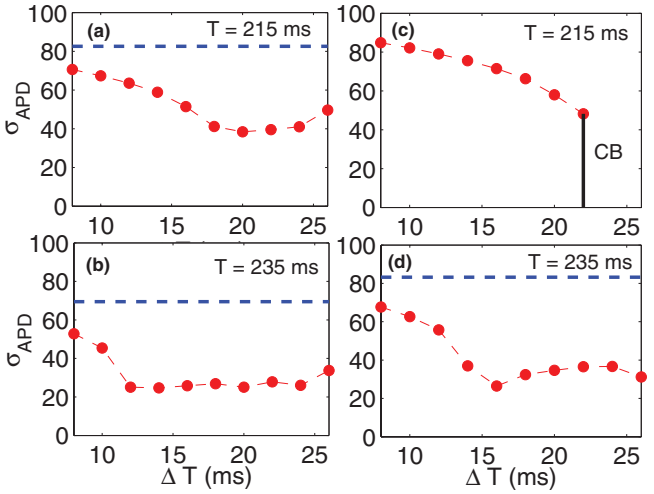

FIG. 9. (Color online) Performance of alternating period pacing in suppressing alternans in a one-dimensional fiber ($L = 40$) of excitable cells in the absence and presence of noise. As in Fig. 8, the efficiency in reducing alternans is obtained from the standard deviation of the durations of a long sequence of action potentials measured at the center of the system ($x = L/2$) as a function of the difference in the alternating periods ΔT. The system is subjected to two different pacing periods (a) and (c) $T = 215$ ms and (b) and (d) 235 ms in the (a) and (b) absence and (c) and (d) presence of noise. The dashed blue line shows the standard deviation of the APD for constant pacing with period T ($\Delta T = 0$). Alternating period pacing can occasionally result in conduction block at a location downstream of the pacing site ($x = 0$).

The method is effective for even longer fibers; however, the efficacy rapidly diminishes with system size, the decrease in APD alternans as a result of alternating period pacing becoming less marked for larger values of L.

It is instructive to compare the alternating period pacing method with previously proposed algorithms for reducing alternans [8]. These feedback control methods seek to stabilize the unstable fixed point of the effective periodically perturbed dynamical system by adopting the cycle length according to the proportional control scheme given by Eq. (2). If the duration of the nth action potential is larger than the $(n-1)$th one, Eq. (2) ensures that the next action potential has a longer duration than would have been the case without control, thereby suppressing alternans behavior. Figures 8(a) and 8(b) show the performance of the proportional gain method on a fiber with $L = 40$ for two different values of T, where the success of alternans reduction is measured in terms of standard deviation for the sequence of APDs. The dashed line shows the APD standard deviation in the absence of control ($\gamma = 0$) and a comparison with the corresponding values in the presence of control for different values of the gain parameter shows that while this feedback control can reduce alternans, it also sometimes results in conduction block of the stimulation away from the pacing site. Moreover, for higher values of the gain parameter, even the pacing site may be incapable of being activated, a situation we have referred to as the control being unstable.

As in any experimental implementation of the control, one will always have to encounter the effect of noise. We have also examined the efficacy of the method by switching on the stochastic fluctuation term I_{noise} in Eq. (4). As seen from Figs. 8(c) and 8(d), the region of parameter space over which the method is successful in reducing alternans is markedly reduced in the presence of noise, with conduction block becoming prominent at lower values of γ, while at higher values of γ, the control tends to become unstable. When we compare the performance of the alternating period pacing method with that of the proportional gain method, we find that the former performs favorably in terms of a reduced number of instances where conduction block and instabilities of control occur, while the degree of reduction of alternans is of a similar magnitude (Fig. 9). This can be observed particularly in the presence of noise [Figs. 9(c) and 9(d)], where the alternating pacing period scheme can consistently perform well compared to the proportional feedback control method.

To understand the better performance of the alternating period pacing scheme in reducing alternans in the presence of noise, we note that unlike the proportional feedback control method, our control does not seek to alter the stability of the fixed point. Instead it tries to confine the state of the system in a small volume of phase space such that all variations in the duration of action potential occur within a narrow interval. The function f of Eq. (1) can be obtained by stimulating the cell at different DIs and measuring the corresponding APDs [18]. For long interstimuli interval T, the action potentials have an almost constant duration and the corresponding system

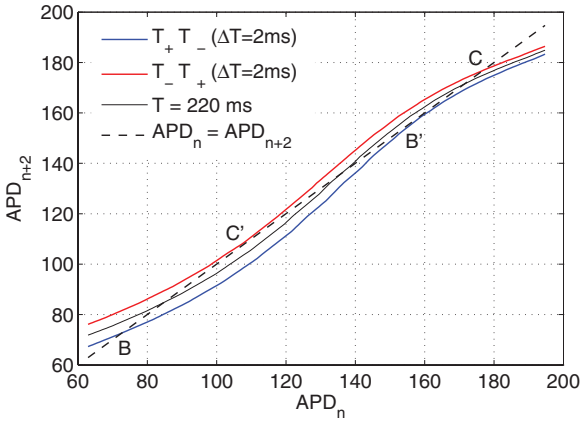

FIG. 10. (Color online) The alternating period pacing scheme reduces alternans by confining the system state in a small region in phase space. The curves correspond to the composite return map $f \circ f$(APD) obtained from the restitution function Eq. (1) numerically computed from a single cell. The middle curve corresponds to the situation where the cell is subjected to a constant period stimulation with $T = 220$ ms. The two other curves correspond to alternating period stimulation following the sequence S: $T_+T_-T_+T_- \ldots$ or S': $T_-T_+T_-T_+ \ldots$ with $T_\pm = T \pm \Delta T$ (here $\Delta T = 2$ ms). The intersection of the curves with the diagonal line $\mathrm{APD}_{n+2} = \mathrm{APD}_n$ shows the fixed points of the system dynamics. For alternating period pacing the system has a stable fixed point (B and C for S and S', respectively) and a constriction point (B' and C' for S and S', respectively) where the system dynamics slows down considerably while it is transiting through this region of phase space. By switching appropriately between the sequences S and S' the system state can be maintained indefinitely within the interval $(\mathrm{APD}_{B'}, \mathrm{APD}_{C'})$ around the unstable fixed point of f, which reduces the magnitude of alternans (for constant T the system switches between APD_B and APD_C).

dynamics has a stable fixed point at a^* [$= f(T - a^*)$]. When T is reduced, this fixed point becomes unstable and a period-2 attractor is generated where a long APD is followed by a short APD and vice versa. It is easy to see that such stable alternans will correspond to three fixed points in the composite return map $f \circ f$ as shown in Fig. 10. In the figure, the middle fixed point is unstable while the other two are stable. When the alternating period pacing scheme is applied, the system follows one of two possible maps depending on the exact sequence of the two pacing periods $T_\pm = T \pm \Delta T$ being used, viz., $S : T_+T_-T_+T_- \ldots$ or $S' : T_-T_+T_-T_+ \ldots$. Both of these maps are characterized by the existence of a stable fixed point (close to one of the two APDs seen during alternans induced by constant period pacing) and a constriction point near the unstable fixed point of the map where the curve comes very close to the diagonal line $a_{n+2} = a_n$. In a situation analogous to that observed during intermittency in deterministic systems [19], the system dynamics slows down significantly as it negotiates this region of phase space and thus can act as a trapping region. By switching between the sequences according to Eq. (3), the system is maintained indefinitely in the narrow region whose limits are defined by the constriction points of the two maps S and S' (Fig. 10). We can observe this by comparing the system trajectory on the first return maps [Eq. (1)] corresponding to the uncontrolled and controlled cases shown in Fig. 11. Figure 11(a) shows the evolution from an initial APD equal to 100 ms to a stable period-2 behavior having a large alternans amplitude when only a single pacing period T is used. Figure 11(b) shows the result of using the alternate pacing period scheme, where instead of pacing at a constant T, we apply T_- and T_+ alternately. As shown in the figure, starting from the same initial APD as in the uncontrolled case, the magnitude of

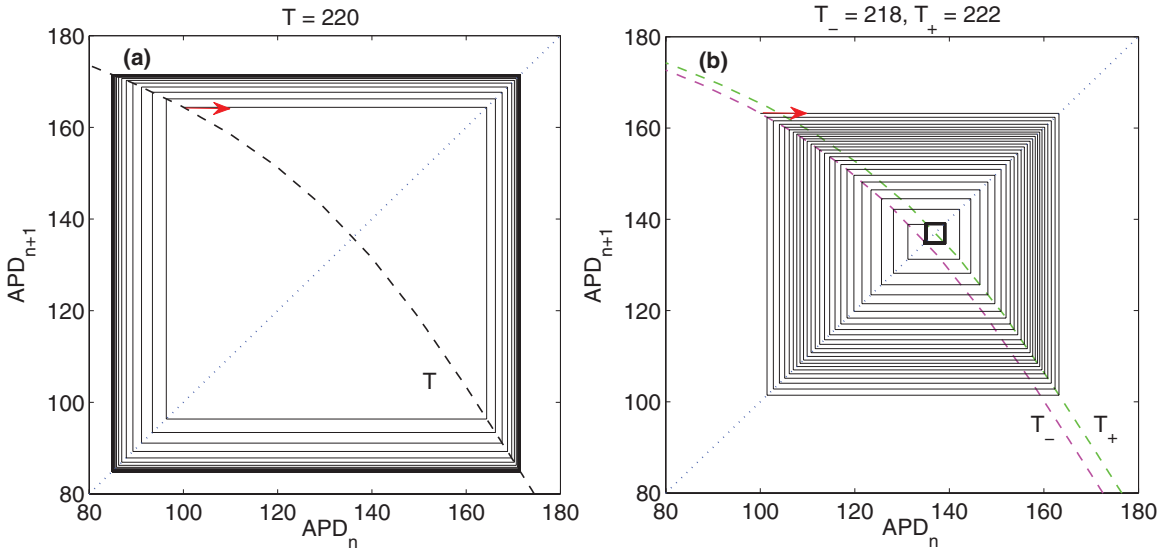

FIG. 11. (Color online) Trajectory of the system on the first return map Eq. (1) in the (a) uncontrolled and (b) controlled cases. (a) The cobweb diagram on the return map (dashed curve) for constant periodic pacing with $T = 220$ shows that the system converges to stable, large-magnitude period-2 alternans. (b) The magnitude of the alternans reduces drastically when the pacing is alternated between the periods $T_- = 218$ and $T_+ = 222$ according to the proposed control scheme. The return maps corresponding to the two periods are shown as dashed curves and are indicated by T_- and T_+, respectively. The dynamical evolution of the return map in both cases begins from APD = 100 (the initial trajectory is indicated by an arrow). The dotted line corresponds to the $\mathrm{APD}_n = \mathrm{APD}_{n+1}$ line.

the alternans reduces remarkably [Fig. 11(b)]. The final state in the presence of control corresponds to very-low-amplitude oscillations around the $a_n = a_{n+1}$ state.

Our analysis of the control mechanism implies that there is an optimal range of values of ΔT for which the pacing scheme will be most effective: Increasing ΔT increases the space between the curves and the diagonal line at the constriction points, thereby reducing the efficacy of the method; in contrast, reducing ΔT can decrease the robustness of the scheme as fluctuations can easily eject the system state from the very small trapping region between the constriction points. In practice, the optimal values of ΔT can be easily obtained through trial and error.

V. CONCLUSION AND OUTLOOK

From the discussions above, it is clear that the T_+T_- control is capable of reducing the alternans in both simulation models and experiments. Similar to the proportional scheme, the T_+T_- control is also not stable in spatially extended system if there is only one control point. It would be desirable to have a scheme that can have global stability even when there is only a single control point. In contrast, simulation results indicate that T_+T_- control has a smaller number of conduction blocks and control instabilities; especially in the presence of noise. It would be important to understand the physical mechanism of the T_+T_- control scheme; presumably investigations on the phase space dynamics of the control can provide deeper insights both theoretically and experimentally. Similar to the situation that alternans will occur only for fast enough pacing (less than a critical value of T), we anticipate that our T_+T_- control scheme will be able to suppress alternans magnitude for ΔT larger than some critical value.

For the whole heart experiments, it is still a puzzle why the alternans response of the heart would be different after alternans suppression control. Since the magnitude of the alternans response is governed by the restitution curve, a different response after the feedback control suggests that the restitution properties of the cardiac cells have been altered by the control. Experimentally, it is found that for both the proportional feedback and T_+T_- controls, the pacing interval changes from a constant value to an almost constant value plus a small random fluctuating part when compared to that of without control. This small fluctuating part is always only a few percent or less of the original constant value. Its large systematic effect on the alternans is not expected. It is interesting to find out why such a small random change in the pacing interval can have a large systematic effect on the restitution on the cardiac cells.

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