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Ionic characteristics in cardiac alternans suppression using $T \pm \epsilon$ feedback control

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Abstract – Using the Luo-Rudy I model, the recently proposed $T \pm \epsilon$ feedback control for suppressing cardiac alternans is investigated. It is shown that cardiac alternans, induced by fast pacing (of period T), can be dramatically reduced by small changes of fixed magnitude (ϵ) under feedback control when ϵ exceeds a critical threshold. Detail information on various ionic currents and cytosolic calcium concentration ($[\text{Ca}]_i$) are examined when the cardiac cell is under control. In particular, the alternans in ionic currents and $[\text{Ca}]_i$ are also reduced under the control. Furthermore, when ϵ exceeds the threshold value, the average $[\text{Ca}]_i$ level is significantly higher when the alternans is under control, suggesting a possible physiological improvement of cardiac contractions.

Introduction. – Cardiac alternans [1–4] are alternating long and short action potential durations (APD) in heart beats, which are precursors of fatal ventricular fibrillations. Such an alternate long and short APD variation is accompanied by alternans of high and low intracellular calcium concentration ($[\text{Ca}]_i$). If the external periodic pacing period T is sufficiently small, then the periodic beating of the heart will lose its stability and give way to period-2 oscillations resulting in the alternation of long and short APDs and hence in strong and weak alternate contractions of the heart. Alternans response in cardiac tissue during fast pacing can lead to conduction block, causing fatal cardiac failure. Previous attempts [5–8] have been made to control alternans by using proportional control on the APDs that renders the unstable period-1 oscillation to become stable again. Another novel method that exploits a different mechanism of pacing with feedback control is recently proposed [9] to suppress the alternans and therefore the conduction block and thus reduce the subsequent risk of cardiac fibrillations. This new control

scheme of alternans reduction is achieved by slight perturbation (with magnitude ϵ) of the original alternans generating pacing period T by two pacing periods of $T + \epsilon$ and $T - \epsilon$, with $\epsilon/T \ll 1$. That is: a very small perturbation to the pacing period can dramatically suppress the magnitude of the alternans. In this $T \pm \epsilon$ feedback control scheme, which has been demonstrated experimentally in whole heart preparations [9], APD alternans can be significantly reduced to more than 90% if ϵ exceeds some critical value.

Here, we study the reduction of alternans by applying the similar feedback control proposed in [9] using the Luo-Rudy model for a single cell to examine in detail the ionic characteristics of the cardiac system during alternans and when it is under the $T \pm \epsilon$ control, which has not been examined in detail before. But instead of using the APD as the detection variable for the feedback as in the theoretical studies in [9], the maximum cytosolic calcium concentration signal ($[\text{Ca}]_i^{\text{peak}}$) is employed for the $T \pm \epsilon$ control. There are two reasons for such a choice. First, as APD is not a direct dynamical variable in the governing equations of the ionic-current–based models of cardiac

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dynamics including the Luo-Rudy model, it would be more appropriate, in a dynamical sense, to implement the feedback control by detecting a direct dynamical variable in the model. Second, in the whole heart experiments described in [9], it is the left-ventricle contraction pressure that is being detected for feedback control. Since cardiac contraction is directly related to the $[Ca]_i$ [10], feedback control on $[Ca]_i$ would be closer to the experimental conditions used for contraction pressure feedback signals. In this paper, different channel conductance strengths are also studied to reveal how the alternans and the feedback control will be affected.

Luo-Rudy I model and the $T \pm \epsilon$ feedback control scheme. – As a first step to investigate the ion channel effects due to the $T \pm \epsilon$ control, we simulate a single cardiac cell by using the Luo-Rudy I model (LR1) [11], which is a mathematical model of the mammalian (guinea pig) ventricular action potential. Using a single-cell model is also justified by the fact that, in the experiments in [9], the pacing stimulations cause the whole heart to beat more or less synchronously. Briefly, LR1 is an ion-channel–based model for a single excitable cardiac cell which can be described generically by the following equation:

$$C_m \frac{dV}{dt} = -I_{ion}(V, g_{ion}) + I_{stim}(t), \tag{1}$$

where V is the cell membrane potential, C_m is the transmembrane capacitance, I_{stim} is the stimulus current, I_{ion} is the total current density through various ion channels on the cellular membrane, and g_{ion} describe the dynamics of gating conductances of different ion channels. LR1 is one of the simplest ion-channel model for cardiac cell that takes into account the basic currents for a cardiac cell to generate an action potential, where the total current density is composed of six essential currents,

$$I_{ion} = I_{Na} + I_K + I_{Ca} + I_{Kp} + I_{K1} + I_b. \tag{2}$$

These ionic currents include: a fast inward sodium current I_{Na}, which is responsible for the action potential rapid upstroke [12]; a slow inward current I_{Ca}, which is a calcium current and plays an important role in maintaining the action potential plateau [12]; a time-dependent potassium current I_K, which repolarizes the membrane to its resting state [13]; a time-independent inward-rectifying potassium current I_{K1}, which is responsible for the setting of the resting membrane potential [14]; a plateau potassium current I_{Kp}, which contributes only at high potential [11]; and a background potassium current I_b that exists at negative potentials [11]. The LR1 model did not consider the dynamic changes of ionic concentrations except for $[Ca]_i$ [11], which triggers the cardiac contraction.

The $T \pm \epsilon$ feedback control scheme has been applied to LR1 model in [9] to suppress alternans, albeit with an abnormally high K^+ conductance. As mentioned before, in isolated whole heart experiments [9], it is more convenient to perform the control on the ventricle pressure of

the heart. In fact, it is the contraction strength or ventricle pressure that has the direct physiological effects on the patient. Thus in this work, instead of detecting the APD for feedback, the peak intracellular Ca^{2+} concentration is used as the control signal. The $T \pm \epsilon$ scheme is carried out as follows: the pacing period at the n-th time step (T_n), depends on the previous intracellular calcium concentrations as

$$T_n = T + \epsilon, \qquad \text{if} \quad [Ca]_n^{peak} > [Ca]_{n-1}^{peak},$$
$$= T - \epsilon, \qquad \text{if} \quad [Ca]_n^{peak} < [Ca]_{n-1}^{peak}, \tag{3}$$

where $[Ca]_n^{peak}$ is the maximum of $[Ca]_i$ at the n-th time step and T is the basic pacing period. ϵ is a small perturbation of fixed magnitude to the pacing period in the feedback control and is the key quantity for successful alternans suppression.

The parameter settings we used here are the same as in the original LR1 model [11], except for one more value of the maximum conductance of I_K channel, g_K. Two values of g_K are used in our simulations: (1) $0.282 \, mS/cm^2$, as in the original LR1 model, and (2) $0.705 \, mS/cm^2$, to shorten APD [15] so as to allow direct feedback control on the APD using $T \pm \epsilon$ as in [9]. The Na^+-channel conductance (g_{Na}) is also varied to probe its effects on alternans. For all simulations, the model is stimulated with a square wave pulse of magnitude $80 \, \mu A/cm^2$ for a duration of $0.5 \, ms$. The MATLAB subroutine ode15s [16,17], which is a variable order solver based on the numerical differentiation formulae, is used for the numerical integration of the differential equations in the model.

For each beat, the areas under the curves (for all ionic currents and $[Ca]_i$) are calculated by using the trapezoidal rule to obtain the corresponding charges in one beat or the mean value over one beat. In the absence of control ($\epsilon = 0$), when there is no alternation of $[Ca]_i$ (for slow pacing), after the value of maximal $[Ca]_i$ becomes consistent for at least 100 beats, the areas for the first 100 beats are recorded; when the alternans of peak $[Ca]_i$ occur, after the alternans have repeated for at least 100 times, the areas for the first 200 beats are recorded. Consistent with the findings in [9], there exists a critical ϵ (ϵ_c) below which the alternans suppression is unsuccessful with alternans persisting, although with a slightly reduced magnitude. Alternans suppression can be achieved successfully for $\epsilon > \epsilon_c$, and for such a case, the areas for the next 1000 beats are recorded after the alternans are being steadily suppressed.

Alternans reduction by $T \pm \epsilon$ control. – The time-series data for $V(t)$ in which alternans has been developed and $T \pm \epsilon$ control is applied are shown in fig. 1. As shown in fig. 1(a) for the normal conductance employed in the original LR1 model for guinea pig, alternating long and short APDs developed at sufficiently rapid pacing. Usually, the APD is defined as the time for the membrane potential V to fall to a fixed fraction (say 10%) of its peak amplitude. However, for fast pacing, the voltage cannot fall to a low
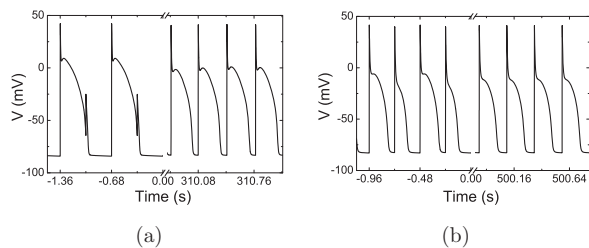
(a)

(b)

Fig. 1: Time series of the membrane potential when $T \pm \epsilon$ feedback control is applied on a Luo-Rudy cell under steady alternans state. Control is applied at time = 0. The action potential alternans before (first four beats on the left showing steady alternans state) and after (last four beats on the right showing alternans are under steady control) $T \pm \epsilon$ control are shown. (a) $g_K = 0.282 \, \text{mS/cm}^2$ and the cell is under a base pacing period of $T = 340 \, \text{ms}$ and $\epsilon = 9.029 \, \text{ms}$. (b) $g_K = 0.705 \, \text{mS/cm}^2$ and the cell is under a base pacing period of $T = 240 \, \text{ms}$ and $\epsilon = 0.892 \, \text{ms}$.

enough value for APD to be properly measured, as shown in fig. 1(a) for the time-series data before the control is applied. Thus if one wants to measure APD and use it as the feedback control variable, it would not be feasible in some situations unless some parameters in the model are varied to ensure a well-defined APD can be measured in the regimes of interests. This can be achieved by using a large g_K to increase the potassium current so that the membrane voltage will drop rapidly enough as shown in fig. 1(b) for $g_K = 0.705 \, \text{mS/cm}^2$. Thus using APD as the feedback control variable only works for the LR1 model in some situations such as those with an unusual large g_K [9]. On the other hand, feedback control using the peak $[\text{Ca}]_i$, as proposed in this work, can generally carry out the feedback control successfully. As shown in fig. 1 for both values of g_K, when $T \pm \epsilon$ is applied to feedback control on the peak $[\text{Ca}]_i$ for steady developed alternans, the magnitude of the APD alternans is reduced dramatically to a level that is not noticeable in the time-series of V in fig. 1.

We now turn to the microscopic ionic details when the cardiac cell is in the alternans states and under the $T \pm \epsilon$ feedback control as revealed by the LR1 model. Figure 2 shows the time traces of $[\text{Ca}]_i$ for well-developed alternans and when the alternans is under $T \pm \epsilon$ feedback control. For $g_K = 0.282 \, \text{mS/cm}^2$, the magnitude of Ca^{2+} alternans is large with the small $[\text{Ca}]_i$ profile being much smaller than the large $[\text{Ca}]_i$ counterpart and can barely be seen (fig. 2(b)); whereas for high $g_K = 0.705 \, \text{mS/cm}^2$, the large and small $[\text{Ca}]_i$ alternans are much clearer (fig. 2(c)). Moreover, for some cases as in fig. 2(a), the large $[\text{Ca}]_i$ profile recovers slowly such that it does not have time to return to baseline before the next stimulation. However, upon $T \pm \epsilon$ feedback control, the $[\text{Ca}]_i$ alternans are hardly noticeable in their time series and the $[\text{Ca}]_i$, as well as the membrane potential V in fig. 1, returns to its baseline level between stimuli. The latter implies that the contractile force relaxes to baseline at the end of each beat. The cardiac Ca^{2+} transport, to some extend, can be reflected
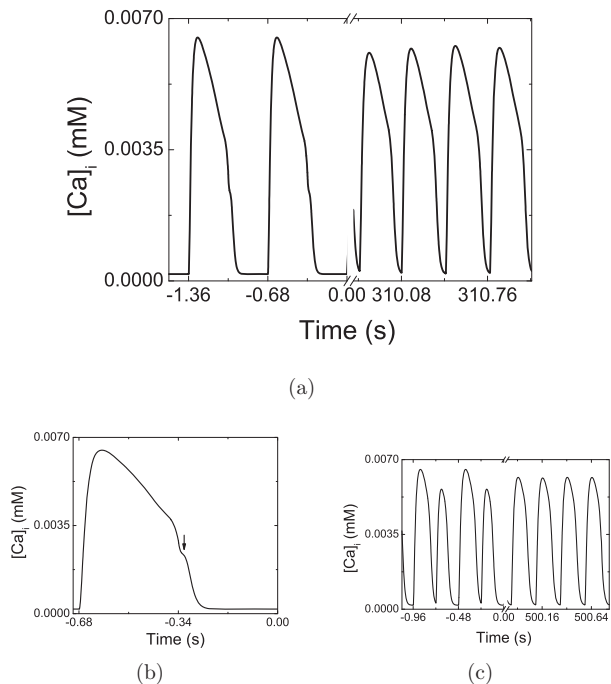

(a)

(b)

(c)

Fig. 2: Time series of the corresponding cytosolic calcium concentration $[\text{Ca}]_i$ for $T \pm \epsilon$ feedback control corresponding to the situations in fig. 1. (a) $g_K = 0.282 \, \text{mS/cm}^2$, (b) magnification of an alternans before control in (a) where the peak of the small $[\text{Ca}]_i$ profile is indicated by an arrow, and (c) $g_K = 0.705 \, \text{mS/cm}^2$.
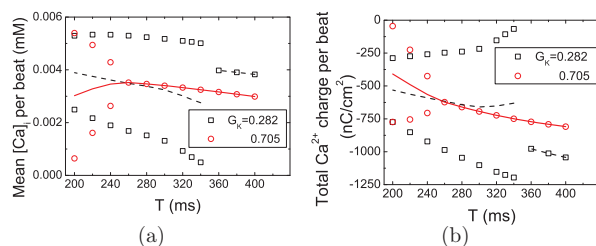

(a)

(b)

Fig. 3: (Colour online) (a) Mean $[\text{Ca}]_i$ per beat and (b) total Ca^{2+} charge per beat for $g_K = 0.282 \, \text{mS/cm}^2$ and $0.705 \, \text{mS/cm}^2$ at different base pacing period T when there is no control. Negative value of Ca^{2+} charge indicates inward current. Solid and dashed curves represent the time averages.

by the mean $[\text{Ca}]_i$ per beat which is defined as the area of a $[\text{Ca}]_i$ bump under the time series curve divided by T_n. When there is no control ($\epsilon = 0$), fig. 3(a) shows that when the base pacing becomes faster, Ca^{2+} alternans develops as reflected by the alternating large and small mean $[\text{Ca}]_i$ per beat. For nominal value of $g_K = 0.282 \, \text{mS/cm}^2$, alternans occurs discontinuously as the base pacing is faster than some threshold. Furthermore, the time average of the mean $[\text{Ca}]_i$ per beat (the average of large and small mean $[\text{Ca}]_i$ in the case of alternans) during the presence of alternans are smaller compared to that of the case when there is no alternans, as shown by the dashed curves in fig. 3(a). This implies that the average strength of the
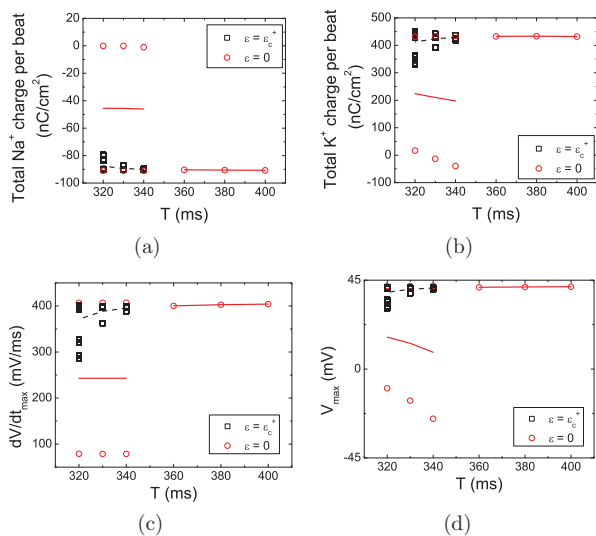
Fig. 4: (Colour online) Comparison of total charges per beat for (a) Na^+ and (b) K^+ (of I_K channel) with no control ($\circ$) and when $T \pm \epsilon$ control is turned on with $\epsilon = \epsilon_c^+$ (just above the critical value, $\square$) at different base pacing period T for $g_K = 0.282 \, \mathrm{mS/cm^2}$. The corresponding (c) dV/dt_{max} and (d) maximum V are also compared. Solid and dashed curves represent the corresponding time averages.

Fig. 5: (Colour online) (a) Mean $[Ca]_i$ in a beat and (b) total Ca^{2+} charge per beat for no control ($\epsilon = 0$, $\circ$) and when the control is turned on with $\epsilon = \epsilon_c^+$ (just above the critical value, $\square$) at different base pacing period T. (c) Mean $[Ca]_i$ per beat with control is turned on as a function of ϵ. $g_K = 0.282 \, \mathrm{mS/cm^2}$. Solid and dashed curves represent the time averages.

cardiac contraction is weaker during the existence of alternans. The Ca^{2+} ionic charges influx in one beat in fig. 3(b) also indicates such an effect. On the other hand, for high $g_K = 0.705 \, \mathrm{mS/cm^2}$, alternans magnitudes increase continuously from zero, and there is no big drop in the mean $[Ca]_i$ per beat as alternans develop. Hereafter, we shall present results with nominal value of $g_K = 0.282 \, \mathrm{mS/cm^2}$.

As shown in fig. 4, similar improvement are also found in other ionic currents such as I_{Na} and I_K when alternans are being suppressed by the control. The voltage-gated Na^+ channels are responsible for the rapid upstroke and propagation of action potentials in cardiac myocytes, and therefore, the fast inward sodium current I_{Na} is a major determinant of the rate of depolarization and conduction velocity of the action potential [18–21]. When alternans exist, fig. 4(a) shows that the time average Na^+ influx in one beat is smaller and the corresponding maximal rate of depolarization (dV/dt_{max}, in fig. 4(c)), as well as the peak V (fig. 4(d)), per beat is lower, which suggest that the average excitability of the cardiac cell is reduced. The conduction velocity of action potential cannot be investigated in the present single-cell model, but can be studied in a spatially coupled model in future. Similarly, fig. 4(b) shows that the time average of K^+ influx (through the I_K channel) per beat decreases in all alternans cases, suggesting an abnormal ventricular repolarization which is commonly observed in the failing hearts [22–25]. The above ionic characteristics agree with the expectation that alternans is not a physiologically healthy state.

Next we examine the change in $[Ca]_i$ across ϵ_c. When the $T \pm \epsilon$ control scheme as described in eq. (3) is applied with ϵ just above the critical value ($\gtrsim \epsilon_c$) to suppress
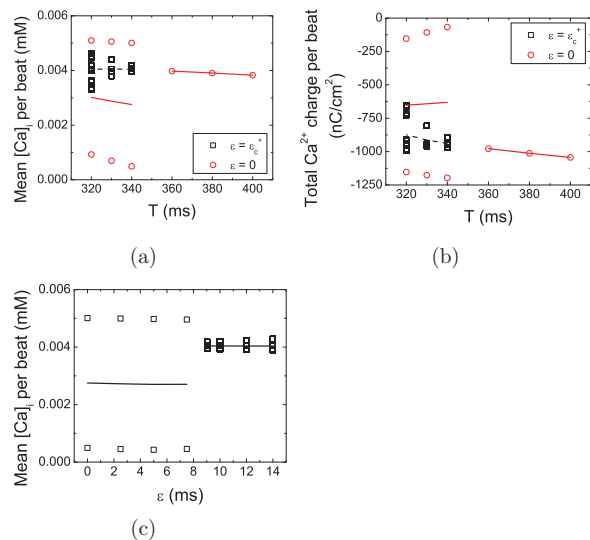
the alternans, the time average mean $[Ca]_i$ per beat are increased by 46.85%, 40.97% and 34.04%, respectively, for $T = 340 \, \mathrm{ms}$, $330 \, \mathrm{ms}$ and $320 \, \mathrm{ms}$ —see fig. 5(a). The total Ca^{2+} per beat also increases significantly when alternans are suppressed, as shown in fig. 5(b). These results suggest that the average strength of the cardiac contraction is improved when alternans are suppressed by $T \pm \epsilon$ with $\epsilon \gtrsim \epsilon_c$. Furthermore, the upstroke and repolarization of the action potential are improved since the time average influxes of I_{Na} and I_K both increase, as shown in fig. 4. Moreover, the $[Ca]_i$ alternans can be sharply reduced significantly if $\epsilon > \epsilon_c$. For example, in fig. 5(c), the $[Ca]_i$ alternans still exist when $\epsilon < 9.029 \, \mathrm{ms}$. However, when ϵ is above and still close to $9.029 \, \mathrm{ms}$, the $[Ca]_i$ alternans are reduced significantly. If ϵ continues to increase, the range of the $[Ca]_i$ peak will also increase. In addition, fig. 5(c) shows that as ϵ increases above ϵ_c, the time average of mean $[Ca]_i$ has a jump, and stays almost constant for $\epsilon > \epsilon_c$. This suggests that the average strength of cardiac contraction is improved if ϵ is above and close to ϵ_c.

The effects of varying the Na^+ channel conductance are also examined. It is known that Na^+ channel inhibition can alter action potential, especially on the repolarization phase. Hence lowering in Na^+ channel conductance could enhance alternans. In fact it has been reported that sodium channel blocker, flecainide, can induce alternans and reentrant arrhythmia on intact canine heart [26]. Here we examine such an effect on our control scheme by lowering the value of Na^+ channel conductance. A value of $g_{Na} = 8 \, \mathrm{mS/cm^2}$, which is considerably lower than the
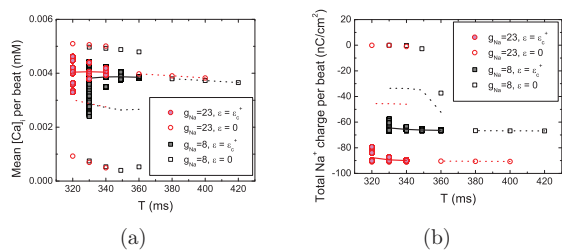
Fig. 6: (Colour online) (a) Mean $[Ca]_i$ per beat and (b) total Na^+ charge per beat for no control ($\epsilon = 0$, open symbol) and when the control is turned on with $\epsilon = \epsilon_c^+$ (just above the critical value, filled symbol), as a function of the pacing period for normal Na^+-channel conduction $g_{Na} = 23\,\mathrm{mS/cm^2}$ (red) and low conductance with $g_{Na} = 8\,\mathrm{mS/cm^2}$ (black). $g_K = 0.282\,\mathrm{mS/cm^2}$. Solid and dashed curves represent the corresponding time averages.

nominal value of $23\,\mathrm{mS/cm^2}$, is used to mimic the situation of Na^+-channel blocking. For lower g_{Na}, the cardiac cell is more susceptible to alternans, which can be observed from the $\epsilon = 0$ data in fig. 6(a) showing that the mean $[Ca]_i$ alternans already starts to occur for slower pacing as compared to the case of higher g_{Na}. Alternans suppression can be achieved for both nominal and low values of g_{Na}, but a higher ϵ_c is needed for the low conductance case. The time average of mean $[Ca]_i$ also shows a marked increase when the alternans are under control for low g_{Na} (see fig. 6(a)). Figure 6(b) shows the Na^+ ion influxes as a function of the base pacing for both values of g_{Na}. As expected, for low g_{Na} the magnitude of Na^+ influx is less. Upon control, the time average Na^+ influx resumed to a value similar to its uncontrolled value at slow pacing, for both high and low g_{Na}.

Conclusion and outlook. – From the discussions above, it is clear that the $T \pm \epsilon$ control can suppress the $[Ca]_i$ alternans significantly and is capable of improving the physiological conditions. After the alternans have been reduced, the time average mean $[Ca]_i$ per beat increases, and thus the average strength of the cardiac contraction is improved. Furthermore, the average upstroke and repolarization of the action potential are improved due to the increment in the averages of the influxes of I_{Na} and I_K per beat, respectively. Many experimental studies [27–32] have observed the alternation of $[Ca]_i$ during mechanical alternans (pulsus alternans), which is a condition associated with severe heart disease and/or heart failure [33–36], suggesting that $[Ca]_i$ alternans is responsible for mechanical alternans. Moreover, electrocardiographic T-wave alternans, which arises from the ventricular repolarization alternans (APD alternans) [37–40], has been reported in patients with long-QT syndrome [41,42] and *torsade de pointes* ventricular tachycardia [43], and is associated with sudden cardiac death [37,44]. Experimental evidence [28,45–47] supported that the cycling of $[Ca]_i$ plays an important role in the mechanism of APD alternans, and therefore, the mechanism of T-wave

alternans. The control algorithm in this present study might provide an alternative way to suppress both mechanical and T-wave alternans, as well as improve the conditions such as reduced cardiac excitability and conduction caused by reduced availability of sodium current during ischemia [48,49], and abnormal repolarization due to reduced outward potassium current during heart failure [22–25].

For nominal parameter values of LR1 model for guinea pig, when alternans is under $T \pm \epsilon$ control, not only is the alternans dramatically reduced, there is also significant physiological improvement in terms of cardiac contraction. It is worth to examine such an effect in even more realistic ionic models, such as the Luo-Rudy II model [13], and in other animal models to see how animal dependent it is. Effects of some changes of the ionic conductances on the control is also studied, indicating that alternans suppression control can still be achieved. Such information would be useful if the control is applied in combination with drugs that can affect specific ionic conductances. Hopefully, these studies can reveal the physiological advantages or side-effects of our control scheme in detail, which are essential for possible medical applications. Finally, it is interesting to find out in the future if our control algorithm can be extended to control even more complex cardiac dynamics, such as the rhythms described by a model with neuroautonomic regulation [50] and the abnormal heartbeats generated by the models proposed in [51,52]. This may lead to the understanding of whether $T \pm \epsilon$ control can be generalized, for example, similar to the method in [53–55], to control spiral waves, which are associated with ventricular fibrillation [2,3] and sudden cardiac death [56,57].

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REFERENCES

[1] FISHER J. D. *et al.*, *Am. J. Card.*, **41** (1978) 94.
[2] CAO J. M. *et al.*, *Circ. Res.*, **84** (1999) 1318.
[3] KARMA A. and GILMOUR R. F., *Phys. Today*, **60**, issue No. 3 (2007) 51.
[4] LIVSHITZ L. M. and RUDY Y., *Am. J. Physiol. Heart Circ. Physiol.*, **292** (2007) H2854.
[5] HALL K. *et al.*, *Phys. Rev. Lett.*, **78** (1997) 4518.
[6] HALL G. M. and GAUTHIER D. J., *Phys. Rev. Lett.*, **88** (2002) 198102.
[7] ECHEBARRIA B. and KARMA A., *Phys. Rev. Lett.*, **88** (2002) 208101; *Chaos*, **12** (2002) 923.
[8] CHRISTINI D. J. *et al.*, *Phys. Rev. Lett.*, **96** (2006) 104101.
[9] SRIDHAR S., LE D. M., MI Y. C., SINHA S., LAI P. Y. and CHAN C. K., *Phys. Rev. E*, **87** (2013) 042712.
[10] BERS D. M., *Circ. Res.*, **87** (2000) 275.
[11] LUO C. H. and RUDY Y., *Circ. Res.*, **68** (1991) 1501.

[12] Beeler G. W. and Reuter H. J., *Physiology*, **268** (1977) 177.

[13] Luo C. H. and Rudy Y., *Circ. Res.*, **74** (1994) 1071.

[14] Sakmann B. and Trube G. J., *Physiology*, **347** (1984) 641; 659.

[15] Ten Tusscher K. H. W. J. and Panfilov A. V., *Am. J. Physiol. Heart Circ. Physiol.*, **284** (2003) H542.

[16] Shampine L. F. and Reichelt M. W., *SIAM J. Sci. Comput.*, **18** (1997) 1.

[17] Shampine L. F., Reichelt M. W. and Kierzenka J. A., *SIAM Rev.*, **41** (1999) 538.

[18] Tse G. and Yeo J. M., *IJC Heart Vasc.*, **9** (2015) 75.

[19] Berecki G. *et al.*, *PLoS ONE*, **5** (2010) e15772.

[20] Kleber A. G. and Rudy Y., *Physiol. Rev.*, **84** (2004) 431.

[21] Bezzina C. R., Rook M. B. and Wilde A. A. M., *Cardiovasc. Res.*, **49** (2001) 257.

[22] Li G. R. *et al.*, *Am. J. Physiol. Heart Circ. Physiol.*, **283** (2002) H1031.

[23] Aiba T. and Tomaselli G. F., *Curr. Opin. Cardiol.*, **25** (2010) 29.

[24] Tsuji Y. *et al.*, *Circulation*, **113** (2006) 345.

[25] Lau E. *et al.*, *PLoS One*, **10** (2015) e0122754.

[26] Tachibana H. *et al.*, *Circulation*, **99** (1999) 1637.

[27] Lab M. J. and Lee J. A., *Circ. Res.*, **66** (1990) 585.

[28] Orchard C. H. *et al.*, *Circ. Res.*, **68** (1991) 69.

[29] Kotsanas G. *et al.*, *Am. J. Physiol.*, **271** (1996) H2490.

[30] Brooks W. W. *et al.*, *Hypertension*, **24** (1994) 347.

[31] Kihara Y. and Morgan J. P., *Am. J. Physiol.*, **261** (1991) H1746.

[32] Lee H. C. *et al.*, *Circulation*, **78** (1988) 1047.

[33] Nguyen T. *et al.*, *World J. Clin. Cases*, **1** (2013) 162.

[34] Michaels A. D. *et al.*, *Catheter Cardiovasc. Interv.*, **51** (2000) 335.

[35] Vidwan P. and Stouffer G. A., *Cardiol. Res. Pract.*, **2009** (2009) 703793.

[36] Gagnon R. M. and Doyle D., *Cardiology*, **4** (1988) 217.

[37] Walker M. L. and Rosenbaum D. S., *Cardiovasc Res.*, **57** (2003) 599.

[38] Surawicz B. and Fisch C., *J. Am. Coll. Cardiol.*, **20** (1992) 483.

[39] Narayan S. M., *J. Am. Coll. Cardiol.*, **47** (2006) 269.

[40] Weiss J. N. *et al.*, *Circ. Res.*, **108** (2011) 98.

[41] Schwartz P. J. and Malliani A., *Am. Heart J.*, **1975** (89) 45.

[42] Roden D. M. *et al.*, *Circulation*, **94** (1996) 1996.

[43] Armoundas A. A., Nanke T. and Cohen R. J., *Circulation*, **101** (2000) 2550.

[44] Ikeda T. *et al.*, *Am. J. Cardiol.*, **89** (2002) 79.

[45] Shimizu W. and Antzelevitch C., *Circulation*, **99** (1999) 1499.

[46] Chudin E. *et al.*, *Biophys. J.*, **77** (1999) 2930.

[47] Diaz M. E., Oneill S. C. and Eisner D. A., *Circ. Res.*, **94** (2004) 650.

[48] Janse M. J. and Wit A. L., *Physiol Rev.*, **69** (1989) 1049.

[49] Fozzard H. A. and Makielski J. C., *Annu. Rev. Med.*, **36** (1985) 275.

[50] Ivanov P. Ch. *et al.*, *Europhys. Lett.*, **43** (1998) 363.

[51] Schulte-Frohlinde V. *et al.*, *Phys. Rev. Lett.*, **87** (2001) 068104.

[52] Schulte-Frohlinde V. *et al.*, *Phys. Rev. E*, **66** (2002) 031901.

[53] de la Casa M. A., de la Rubia F. J. and Ivanov P. Ch., *Phys. Rev. E*, **75** (2007) 051923.

[54] de la Casa M. A., de la Rubia F. J. and Ivanov P. Ch., *Chaos*, **17** (2007) 015109.

[55] de la Casa M. A., de la Rubia F. J. and Ivanov P. Ch., *EPL*, **86** (2009) 18005.

[56] Gray R. A. *et al.*, *Science*, **270** (1995) 1222.

[57] Witkowski F. X. *et al.*, *Nature*, **392** (1998) 78.