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Cardiac Alternans Annihilation by Distributed Mechano-Electric Feedback (MEF)

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Abstract— **The presence of the electrical alternans induces, through the mechanism of the excitation-contraction coupling, an alternation in the heart muscle contractile activity. In this work, we demonstrate the cardiac alternans annihilation by applied mechanical perturbation. In particular, we address annihilation of alternans in realistic heart size tissue by considering ionic currents suggested by Luo-Rudy-1 (LR1) model, in which the control algorithm involves a combined electrical boundary pacing control and a spatially distributed calcium based control which perturbs the calcium in the cells. Complimentary to this, we also address a novel mechanism of alternans annihilation which uses a Nash Panfilov model coupled with the stress equilibrium equations. The coupled model includes an additional variable to represent the active stress which defines the mechanical properties of the tissue.**

I. INTRODUCTION

Ventricular fibrillation (VF) is a certain type of arrhythmia that leads to sudden cardiac death (SCD) [1]. Experimental studies [2] have shown that cardiac alternans are precursors to the onset of much complex arrhythmias like the ventricular tachycardia (VT) and VF. Alternans is a phenomenon observed in cardiac cells, in which the cells exhibit beat to beat alteration in the action potential duration (APD) when paced at short pacing intervals. The cardiac cells exhibit alterations as long(L)-short(S)-long(L)-short(S) pattern in APD (see Fig.1, for L-S-L-S pattern in a cardiac tissue). The action potential in cardiac tissue is associated with the contractile properties of the tissue so physically alternans are manifested as alteration in ability of the cardiac tissue to produce complete contraction. Since alternans has been associated with the onset of VF, it is important to explore whether spatiotemporal alternans in cardiac tissue can be annihilated in principle as the annihilation can represent an effective strategy to annihilate heart arrhythmias in order to prevent SCD.

Studies have shown that electrical pacing control can successfully annihilate alternans in a single cell [1], [3], [4]. However, recent theoretical and experimental studies [1], [3], [4], [5], suggest that such electrical pacing control applied at the boundary of a cardiac tissue has finite controllability ($\approx 1cm$), and real time alternans control realizations [6], [7] cannot stabilize alternans in cardiac tissue exceeding $\approx 1cm$ in length. Boundary pacing based control algorithms, are realized by pacing at the boundary of the cardiac tissue which is realized as modulating the pacing interval based on the consecutive *APDs* at the pacing site [4]. This control algorithm's failure to annihilate alternans completely in tissue exceeding $\approx 1cm$ length is due to the lack of information of the evolution of alternans away from the pacing site. This limitation with electrical boundary pacing based controllers emphasize the need to look for electrical stimulus-independent techniques to annihilate alternans in medically relevant cardiac size tissue. Mechanical stimuli is one of the types of electrical stimulus-independent method.

Mechanical stimulus is usually applied to a cardiac cell in form of prod or a stretch. Through the mehano-electric coupling this stimuli influences the electrical activity in the cell which in turn affects the APD, see [8], [9]. In mechano-electric feedback system calcium is the most important ionic species that modulates the coupling in the cardiac cells [10], so that beat-to-beat variations in electric wave are linked to the alteration in the transient calcium concentration in cell [11]. Muscle stretch or shortening affects the myocardium which influences the shape and amplitude of the intracellular Ca^{2+} transient [12].

This work considers a control protocol involving mixed electrical boundary pacing control and a spatially distributed calcium based controller for stabilization of alternans in a 1D cardiac tissue. We demonstrate alternans suppression via mechano-electric feedback in both the 1D cardiac cell ionic model and a 1D three variable Nash and Panfilov [13]. We suggest a control method that employs a spatial distributed calcium controller along with a electrical boundary pacing controller to address alternans annihilation in a medically relevant sized cardiac tissue. In the three variable electromechanical model suggested by Nash Panfilov, we apply a distributed mechanical control to show the effect of mechanical feedback on stabilization of alternans.

II. IONIC MODEL

In this section, we study the control of alternans in a 1D tissue of length $L = 6.25$ cm. The ventricular action

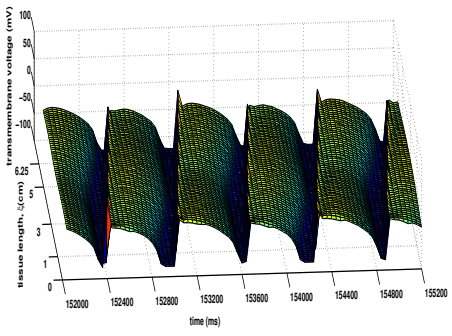

Fig. 1. Time evolution of transmembrane voltage showing discordant alternans

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potential is numerically reconstructed using the Luo-Rudy-1 (LR1) [14] ionic model. LR1 is a mammalian ventricular cell based model which incorporates interaction between depolarization and repolarization and is a updated version of the Beeler-Reuter model [15] which also accounts for the calcium dynamics in cardiac myocyte. The 1D model of cardiac cell tissue is given by the following nonlinear parabolic PDE as:

$$C_m \frac{\partial V(\xi,t)}{\partial t} = D\frac{\partial^2 V(\xi,t)}{\partial t^2} - I_{ion}(\xi,t) + I_{st} \quad (1)$$

Subject to boundary conditions,

$$\frac{\partial V(0,t)}{\partial \xi} = 0, \qquad \frac{\partial V(L,t)}{\partial \xi} = 0 \quad (2)$$

where, I_{st} refers to the electrical stimulus applied within [0, 0.025] cm i.e the first cell of the tissue, V is the transmembrane voltage and I_{ion} are ionic currents as suggested by LR1 model. The constants, diffusion rate $D = 10^{-3}\ cm^2/ms$ and membrane capacitance $C_m = 1\ \mu F/cm^2$. The voltage evolution in the Eq.1 is calculated using finite difference approximation with mesh size $\Delta\xi = 0.025$. Standard explicit Euler integration scheme with step size $\Delta t = 0.05$ ms is applied. The electrical stimulus (I_{st}) applied to cardiac myocytes, activates it and causes it to undergo a fast depolarization upstroke followed by a slow repolarziation that returns the cells to their resting potential, in complete called as the action potential duration (APD), (see Fig.1) The end of this action potential is followed by a finite time interval before the next action potential called as the diastolic interval (DI), which is required by the ventricles to fill with blood (diastolic filling) after a contraction, before the next activation. In case of a short DI, the cells lack sufficient time to fully recover their electrical properties which produces a short APD following a short DI. Hence, the APD has a increasing dependence in DI at lower DI values and is constant at higher pacing periods which is governed by the restitution relations. The S1S2 protocol can be used to develop the restitution curve describing the APD and DI map is given as:

$$APD_{n+1} = f(DI_n) \quad (3)$$

Due to the diffusive coupling term in Eq.1 this action potential propagates along length of tissue away from the pacing site. In the simulations, APD is calculated between the voltage values $-50mV$. It is well known fact that the cardiac tissue will manifest electrical alternans when the slope of the restitution curve is greater than unity at the critical pacing cycle length (PCL). This indicates that at lower DI, i.e at sufficiently short PCL the cardiac system shall undergo alternans, which are manifested by an alternating pattern of long and short APDs. The amplitude of alternans, $a_n(\xi)$, is defined as:

$$a_n(\xi) = APD_n(\xi) - APD_{n-1}(\xi) \quad (4)$$

where, n =beat number $= t/\tau$ Stabilization of such alternans in a long tissue can be achieved by coupling traditional electrical (at boundary) and spatially-distributed calcium feedback control. The boundary applied electrical feedback controller can be characterized as difference in APD values feedback at the pacing site.

$$T_{n(\xi=0)} = \tau + \gamma(APD_{n-1(\xi=0)} - APD_{n-2(\xi=0)}) \quad (5)$$

where, τ is the basic pacing cycle period that is capable of causing alternans in the tissue and γ is the adjustable feedback gain for APD alternation at the pacing site. τ = 311 ms and $\gamma = -0.21$.

Previous works [6], [7], [5], have shown that simple feedback gain at the pacing site can effectively stabilize alternans only upto $\approx$ 1cm of length. This limitation reduces the practical value of a controller based solely on gain based modulation of pacing interval. To overcome this limitation, several such gain based pacing interval modulators can be placed multiple pacing sites but such a control in a real heart adversely disrupts the normal voltage wave propagation across the tissue. Instead, modulation of intracellular calcium levels over a short length of tissue is used for the gain based spatially distributed control of alternans described by Eq 1. The calcium based spatially-distributed actuator is motivated by recent studies [10], [11], [8], [12], which demonstrate that stretching of the cardiac myocyte modulates the internal calcium dynamics of the cell. The calcium dynamics has an effect on the APD, and hence manipulation of this calcium by an external source (viz stretch) [12] or from internal cell storages to have a desirable effect on the length of APD so as to annihilate the alternans. The spatially distributed [Ca^{2+}]-controller acts after the electrical boundary feedback controller stabilizes a finite part of the tissue ($\approx 1cm$). The spatially distributed [Ca^{2+}]-controller utilizes the difference between a stabilized delayed [Ca^{2+}] at the pacing site and [Ca^{2+}]$_i$ over the length of area under spatially-distributed control. The difference is used as input feedback correction term [Ca^{2+}]$_{err}(t)$ = [Ca^{2+}]$_{pacer}(t-\tau_d)$ - [Ca^{2+}]$_{i,control}$ augmented with the cell calcium dynamics in the LR1 model given as:

$$[Ca^{2+}]_i(t) = -10^{-4} I_{si} + 0.07(10^{-4} - [Ca^{2+}]_i) + \gamma[Ca^{2+}]_{err} \quad (6)$$

where, [Ca^{2+}]$_{pacer}$ and [Ca^{2+}]$_{i,control}$ are the intracellular calcium concentrations measured at the pacing site and sites under spatially-distributed control respectively. τ_d is the time delay factor to account for the electrical wave propagation resistance along the tissue length, i.e the measured [Ca^{2+}]$_{pacer}$ is compared with the [Ca^{2+}]$_{i,control}$ taking into consideration the time delay for the excitation of the i'th cell as compared to the excitation at the pacing site. The calcium dynamics demonstrates a lower peak [Ca^{2+}] concentration in case of a short *APD* in electrical alternans and a normal peak [Ca^{2+}] in case of a long. A spatially-distributed stabilizing [Ca^{2+}]-controller like this increases the height of the lower [Ca^{2+}], prolonging the APD for a short beat.

A. Numerical simulation experiments

In the numerical study of the model described by Eq.1 and ionic currents from the LR1 model, we use the control protocol that couples electrical boundary control and spatially distributed [Ca^{2+}]-control to stabilize a tissue of length over 1 cm without inducing conduction block. A medically relevant size cardiac tissue of length L= 6.25 cm ($>$ 1 cm so that electrical pacing controller does not stabilize alternans spatially in the entire tissue) was considered and electrical

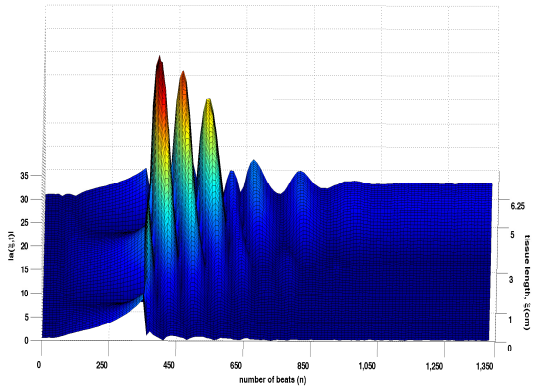

Fig. 2. Time evolution of amplitude of alternans showing annihilation of alternans using a calcium based controller

control was applied at the first cell. After stabilization of alternans in approximately 1 cm of the tissue the spatially distributed [Ca^2+]-control was applied over the region [3 3.5] cm. The tissue is initially paced at a sufficiently large pacing interval for approximately $10-15$ beats and then suddenly dropped to a lower pacing interval such that there is no conduction block. The pacing interval for every beat is reduced by 1 ms untill finally it drops to the basic pacing period (BCL) τ = 311 ms, after that the pacing interval is kept constant. Sustained cardiac alternans, an alternating long and short APD sequence can be seen which if not controlled leads to a conduction block (see Fig.1). For a longer lengths of tissue like in this case, one can observe that spatially there are two nodes where the phase of alternans changes (as in Fig.2 between beat number 50 and 300). If no control is applied the amplitude of alternans increases finally to develop a conduction block from non pacing end of the tissue. In orders to suppress these alternans the previously discussed control strategy is employed to annihilate such alternans. First electrical boundary pacing controller which is based on the difference in amplitude of two consecutive APDs is applied around beat number (n)≈370. Applying such a control stabilizes the alternans along a finite length of the tissue ($\approx$ 1 cm) and the rest of the tissue manifests an increasing amplitude of concordant alternans. The spatially distributed Ca based controller is applied at n $\approx$ 450, the actuator compares the calcium concentration at the boundary ($[Ca^{2+}]_{pacer}$) with the calcium concentration of the cell to be controlled ($[Ca^{2+}]_{i,control}$) and generates a control signal to compensate for the error. The [Ca^{2+}] based controller successfully suppresses the alternans to up to $\approx$ 3 cm of the tissue with a small constant amplitude of alternans towards the non pacing side of the tissue. Such a combined electrical boundary pacing based and spatially distributed [Ca^{2+}] based controller could successfully attenuate the amplitude of alternans and avoid a conduction block coming from the non pacing end of the tissue.

Direct measurements of intracellular [Ca^{2+}] concentrations is difficult. Hence implementation of the spatially distributed controller can be carried out in two ways 1. using the existing cardiac cell models to calculate the [Ca^{2+}] from local voltage (V) measurements or 2. the controller can be based on a measurable quantity like mechanical

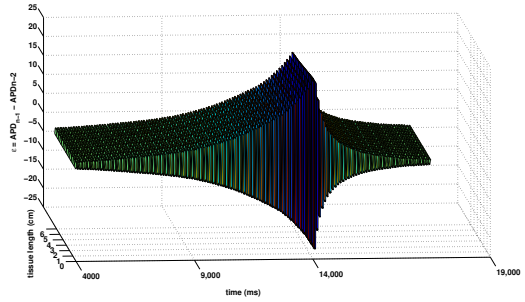

Fig. 3. Stabilization of alternans in model described by Eqs.(7)-(14) by a spatially distributed control signal based on the error ε_1 defined in Eq.15, for $\beta = 0.002$, $D = 1$, $a = 0.05$, $k = 8$, $k_{T_a} = 47.9kPa$, $\bar{c} = 16kPa$, $\mu_1 = 0.1205$, $\mu_2 = 0.3$, $\varepsilon = 0.01$, $\varepsilon(V) = 1$ for $V < a$ and $\varepsilon(V) = 0.1$ for $V > a$

deformations (stress) in the tissue. Therefore, in the next section a numerical study showing the effect of mechanical perturbations on cardiac alternans in a simple three variable Nash-Panfilov model is discussed.

III. THREE VARIABLE NASH-PANFILOV MODEL

Its known that electrophysiological changes in a cardiac tissue affects the mechanical contraction through the mechno-electric feedback. Also, it has been shown that the electrical properties of the tissue can be altered by mechanical perturbations [16]. Simulating mechanical stress-stain and electrophysiological models is computationally expensive and complex. To reduce this complexity, simple two variable models can be used to simulate a cardiac tissue. Although such models do not incorporate a detail description of the shape of the action potential, they are capable of reproducing the basic macroscopic characteristics of a cardiac tissue. In this section, we are interested in annihilation of cardiac alternans by using mechanical perturbation. Since this is concentrated on arrhythmias in a 1D cardiac tissue a simple two variable Nash-Panfilov model is relevant as detailed description of action potential shape is not necessary.

A. Electromechanical model for cardiac tissue

In this section, we consider a two variable Aliev-Panfilov model derived from FHN-model which is further coupled with mechanical stress and strain as proposed by Nash and Panfilov [17]. For the mechanical coupling, a simple global mechanoelectric feedback coupling is considered for small cardiac cell deformations as suggested by Alvarez-Lacalle et al. [18]:

$$C_m \partial_t V = D \partial_{X_i}(\sqrt{C} C^{MN} \partial_{X_i} V) - f(V) \tag{7}$$

$$\partial_t r = (\varepsilon + \frac{\mu_1}{\mu_2 + V})(-r - kV(V - a - 1)) \tag{8}$$

$$\partial_t T_a = \varepsilon(V)(k_{Ta} V - T_a) \tag{9}$$

$$\partial_X (S^{MN}) = 0 \tag{10}$$

where $f(V) = kV(V-1)(V-a) - rV - I_g$, V is dimensionless transmembrane potential, r is the recovery variable, T_a is the active stress, D is the diffusion constant, X_i are the fixed reference or undeformed coordinates and S^{MN} is the first Piola-Kirchoff stress tensor.

B. Cardiac tissue mechanics

Due to the electrical activity in cardiac tissue the cells deform to a new position x_i from a undeformed or reference configuration X_i. The deformation gradient tensor, **F**, that

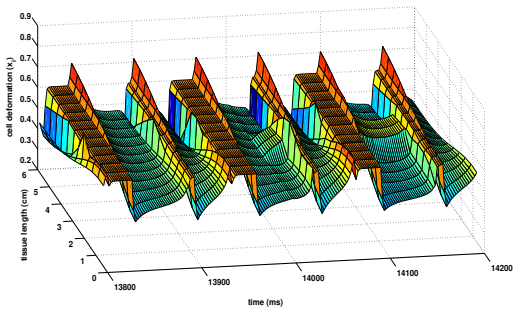

Fig. 4. Shows the time evolution of the deformation variable x_i. The change in the shape of the curve after 14000 ms is attributed to the action of controller. The sudden expansion at the point of excitation is due to the linear approximation of deformation gradient, F(X).

transforms the undeformed cell length to a deformed length in 1D is defined as:

$$\mathbf{F} = \frac{\partial x}{\partial X} = F(X). \tag{11}$$

The Caushy-Green deformation tensor C_{MN} is defined as:

$$C_{MN} = \mathbf{F}^{\mathbf{T}}\mathbf{F} = F(X)^2. \tag{12}$$

For small deformations, the equilibrium conditions defined in Eq.9 can be simplified to obtain a global feedback term F(X) where the average values of active tension $\bar{T_a}$ affect the evolution of voltage given by:

$$F(X) = 1 + [\bar{T}a - Ta(X)]/\bar{c}, \tag{13}$$

$$\bar{T}a = \frac{1}{L}\int_0^L T(X)dX, \tag{14}$$

at any particular position when $\bar{T_a} > T_a$, then the tissue undergoes elongation or stretch. Current I_g described in Eq (7) is active only when the cell stretches locally and it is given as, $I_g = (g/\bar{c})(V-1)(\bar{T_a} - T_a)^2$.

The Nash Panfilov model in 1D with small deformation approximation is defined by Eqs.(7)-(13). Eqs.(7)-(8) are evaluated numerically by semi implicit finite difference method as time integration scheme with Δt = 0.02 and $\Delta X = 0.1$. For the mechanical model i.e Eqs.(13)-(14) a space step $\Delta X = 0.6$ is used. A cardiac tissue of length L = 7 cm was considered. The tissue is paced in such a way that beat to beat alternations in the voltage APD are developed as seen in Fig.3. Basic full state feedback algorithm which takes error ε_1 (see Eq.15) generated between two consequent APDs provides a control signal which is applied over the region 3-4.5 cm. The control signal is active only when $\varepsilon_1 < 0$ due to which the controller only acts on the long-APD (see Fig.3 after 14000 ms, when the controller is actived) . Thus, Eq(9) is modified to incorporate the spatially distributed controller yields the following error based control.

$$\varepsilon_1 = (APD_{n-1} - APD_{n-2}) \tag{15}$$

$$\partial_t T_a = \varepsilon(V)(k_{Ta}V - T_a) + \beta\varepsilon_1 \tag{16}$$

From Fig.3 we see that the alternans developed in the cardiac tissue can be annihilated by using a spatially distributed mechanical stress-strain based controller which was activated at 14000 ms. Finally, Fig.4 shows the action of controller over the region [3, 4.5] cm.

IV. CONCLUSIONS

The control algorithm suggested in this paper includes a boundary pacing control with a spatially distributed non electrical based controller. This spatially distributed controller collects the information of alternans evolution in a cardiac tissue away form the pacing site to generate the necessary control signal. This method can successfully annihilate alternans in a cardiac tissue exceeding 1cm length. Numerical results showing the performance of the proposed method was presented using a calcium based controller for LR1 ionic model and also mechanical stress-strain based controller using Nash-Panfilov model. The Nash-Panfilov model can be further extended to a two dimensional problem based on the numerical analysis provided by Whitely et al. [19].

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