# Controlling Alternans in Cardiac Cells

M Li*, RF Gilmour**, ML Riccio**, NF Otani*

*Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA
**Department of Biomedical Science, Cornell University, Ithaca, NY, USA

## Abstract

*We demonstrate that alternans, potentially dangerous alternations in action potential morphology, can be controlled in individual cardiac cells using stimuli that modify the underlying ion channel dynamics. The best time to apply the control current is during the early plateau phase of the action potential. Elimination of alternans has important clinical implications, since alternans is linked to dangerous cardiac rhythm disorders.*

## 1. Introduction

Sudden cardiac death secondary to ventricular fibrillation remains a leading cause of death in the United States[1]. Previous research has established the connection between alternans, the presence of action potentials of alternating morphology in cardiac cells, and ventricular fibrillation[2-6]. Since action potential alternans at the cellular level may be the basis for arrhythmia and fibrillation, controlling or eliminating alternans in a single cell or small patch of cells may prove critical for the development of effective methods for treating dangerous cardiac rhythm disorders.

Controlling alternans or more complex action potential patterns has been attempted in drug-induced arrhythmias in an isolated rabbit ventricular preparations[7], in simulations of canine ventricular cells[8] and in small preparations of bullfrog myocardium[9]. These control schemes all worked by adjusting the pacing interval, with different algorithms used to determine the interval in each case. In this paper, we present a new strategy for applying the control stimulus, based on modifying the ion channel dynamics rather than changing the pacing interval. The method is grounded in eigenmode theory[10], which is used to characterize the ion channel dynamics of the cell.

The theory considers alternans to be a period 2 orbit (a 2:2 pattern), existing as an eigenmode perturbation to an unstable period 1 orbit (1:1 pattern). The idea of our control algorithm is to apply a control current in the form of a short-duration pulse, which will force the system to move away from the period 2 orbit back to the unstable period 1 orbit, thus eliminating alternans. A major advantage in using eigenmode theory is that it allows us to determine the most energy-efficient time to apply stimulus. This optimal time turns out to occur during the early plateau phase of the action potential.

In our study, we used the Canine Ventricular Myocyte (CVM) model[11] as our model for the ion channel dynamics. A simulated cell employing these dynamics was subjected to external electrical pacing with a constant time interval. Action potential alternans appeared when the basic cycle length of the pacing was lowered below a critical value. We then applied the new control algorithm and successfully eliminated alternans at these short cycle lengths. Early experimental results support the validity of our new control algorithm.

## 2. Alternans can be cancelled out by applying an external control current

From an eigenmode theoretic viewpoint, we consider alternans to be an eigenmode perturbation superimposed on an unstable period 1 orbit. From eigenmode theory, we also know that new perturbations introduced by perturbing the membrane potential, gating variables and/or ionic concentrations can be represented as a sum of eigenmodes, which includes the alternans eigenmode. If the alternans eigenmode associated with the introduced perturbation is of the same amplitude but of opposite sign from the existing alternans eigenmode, the existing alternans mode will be totally cancelled out. The membrane potential, in turn, can easily be perturbed by applying a short current pulse to produce the situation.

Mathematically, we can express this idea as the follows. Any existing perturbation $\vec{p}$ can be decomposed into right eigenvectors ( $\vec{v}_i$ ) of different eigenmodes:

$$\vec{p} = \sum_{i=1}^{n} a_i \vec{v}_i \qquad (1)$$

A short square pulse current of amplitude $I$ and duration $\Delta t$ will produce a change in the membrane potential $\Delta V$ according to,

$$C\Delta V = I\Delta t \qquad (2)$$

where $C$ is the capacitance of the cell membrane. This perturbation of the membrane potential can be

decomposed into the right eigenvectors of the various eigenmodes:

$$\left[\Delta V \quad 0 \quad \cdots \quad 0\right]^T = \sum_{i=1}^{n} b_i \vec{v}_i \qquad (3)$$

where $T$ designates the transpose. If $\vec{v}_1$ stands for the right eigenvector of the alternans eigenmode, then to eliminate the alternans component of $\vec{p}$, we need to choose $\Delta V$ so that, $a_1 + b_1 = 0$. Let $\vec{w}_1$ stand for the *left* eigenvector of the alternans eigenmode. Multiplying Eqs. (1) and (3) from the left by $\vec{w}_1$, we obtain

$$\vec{w}_1 \cdot \vec{p} = a_1 \vec{w}_1 \cdot \vec{v}_1 \qquad (4)$$

$$\vec{w}_1 \cdot \left[\Delta V \quad 0 \quad \cdots \quad 0\right]^T = b_1 \vec{w}_1 \cdot \vec{v}_1 \qquad (5)$$

since $\vec{w}_1 \cdot \vec{v}_i = 0 \ \ (i = 2, \cdots, n)$. Multiplying the equation $a_1 + b_1 = 0$ by $\vec{w}_1 \cdot \vec{v}_1$ and substituting Eqs. (4) and (5), we obtain

$$\Delta V = -\vec{w}_1 \cdot \vec{p} / w_{1,1} \qquad (6)$$

where $w_{1,1}$ is the first element of $\vec{w}_1$. Now substituting Eq. (6) into Eq. (2) produces

$$I\Delta t = -C \cdot \vec{w}_1 \cdot \vec{p} / w_{1,1} \qquad (7)$$

Eq. (7) tells us the charge (that is, the amplitude I and duration $\Delta t$ of the pulse) required to kill the alternans mode, given the alternans left eigenvector and the pre-existing perturbation.

Note that, at the same time the alternans eigenmode is being canceled by the control current, other eigenmodes are, in general, being introduced, as shown in Eq. (3). However, those modes do not generally exhibit an alternating pattern, and usually decay with time. Their introduction into the system therefore generally does not interfere with the effort to control alternans.

## 3. Different amounts of charge are required during different phases of the action potential

In Eq. (7), $\vec{w}_1$, $\vec{p}$ and $w_{1,1}$ are all functions of time. Thus, at different stages during the action potential, different amounts of charge must be injected to eliminate an alternans eigenmode of a given amplitude. We conducted computer simulations using the CVM model, and calculated $\vec{w}_1$ and $\vec{p}$ at various times during the action potential. We then used Eq. (7) to determine the charge ($Q = I \cdot \Delta t$) required to kill an existing alternans mode at each time. As shown in Fig. 1, amount of charge needed is smallest when the control current is applied during early plateau phase, and is largest (by two orders of magnitude!) in the late repolarization phase of the action potential. Thus, from the point of view of energy efficiency, the control current should always be applied during the early plateau phase of action potential.

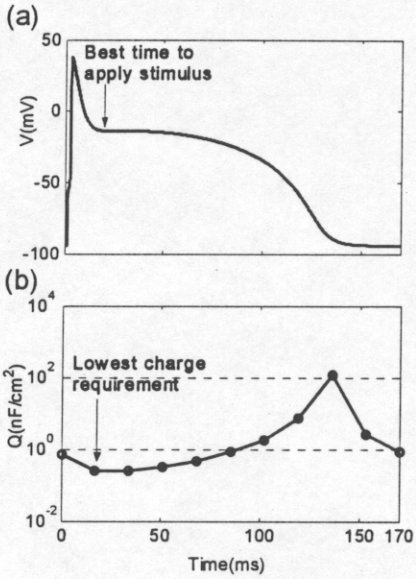


Figure 1. Charge required to eliminate alternans of a given amplitude at different times in the action potential in the CVM model. Basic cycle length is 170ms.

## 4. Computer simulation results

According to Eq. (7), a single control stimulus is enough to totally kill small alternans perturbations if we know the perturbation and the left eigenvector at the time we apply the control current. To verify this, a small perturbation of the alternans eigenmode was added to the unstable period one orbit at the beginning of the simulation. The perturbation was measured 16ms after the pacing stimulus (that is, in the early plateau phase of the action potential) and then a square control pulse current of $\pm$ 10uA was applied to the cell. The polarization of the current was chosen to be consistent with the sign on the right side of Eq. (7). The results are shown in Fig. 2. Without control, the perturbation in alternans eigenmode grows from the first cycle to the second as shown by the black dashed curves in panel (b)–(d). With control, the alternans perturbation totally disappears in the cycle following the one in which the control stimulus was applied, as depicted by the solid gray curves in panel (b)–(d).

As pointed out previously, perturbations in the other eigenmodes are generally introduced when the control stimulus designed to eliminate alternans is applied. The presence of these modes is most clearly seen in panel (d) of Fig. 2, although they are present in all the perturbation

variables. These non-alternans modes are easily recognized because they do not change sign from one pacing cycle to the next the way the alternans mode does.

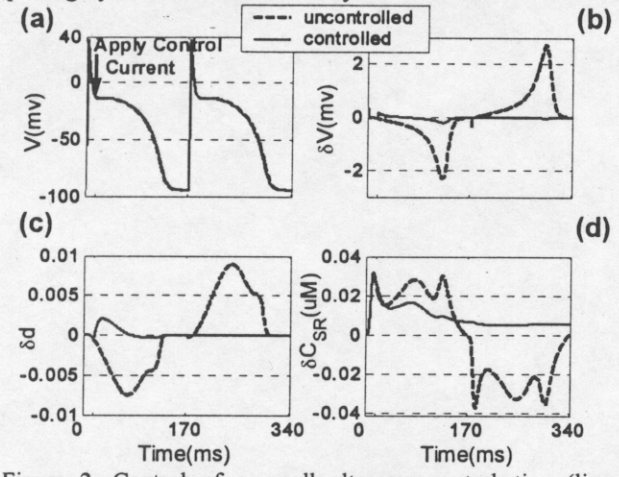


Figure 2. Control of a small alternans perturbation (linear regime) using the eigenmode method in CVM model. (a) membrane potential, shown for reference. (b),(c) and (d): perturbations of membrane potential, d gating variable, and sarcoplasmic reticulum calcium concentration, respectively. The pacing cycle length was 170ms.

One surprising feature of our control method is that the effect of the stimulus on the membrane potential is actually quite modest immediately following its application at t=17ms, as shown in Fig 2(b). Nevertheless, this small change to the membrane potential impacts many of the other variables, particularly the gating variables, quite substantially. The change in the d-gate perturbation variable, for example, is very dramatic immediately following the stimulus, as shown in Fig. 2(c). These modifications to the perturbation gating variables in turn lead to changes in the ionic currents, especially the potassium currents. Modifications to these currents then feed back positively into the membrane potential, creating a large departure from the uncontrolled case towards the end of the pacing interval (i.e., in the late repolarization phase) seen in Fig. 2(b).

We also wanted to see whether this control strategy could work with large amplitude, stable alternans. These alternans lie outside the linear regime; thus their dynamics are technically not governed by our linear eigenmode theory. Nevertheless, we found that we could still successfully control these nonlinear alternans through repeated use of stimuli defined by Eq. (7), applied on consecutive action potentials.

Finally, we wanted to develop a control protocol that can be used in both computer simulation and experiments. Eq. (7) requires knowledge of both the amplitude of the alternans eigenmode underlying the observed 2:2 pattern and the left eigenvector, neither of which can be measured in experiments. Assuming that the basic principle still applies, however, we were able to design a control scheme that only uses membrane potential as the control input. The assumption is that the unstable 1:1 pattern lies "between" the alternating states of two successive action potentials of the 2:2 pattern. The control scheme is shown in Fig. 3. The membrane potential is measured during the repolarization phase of two successive action potentials ($V_1$ and $V_2$ in Fig. 3). The amplitude of the alternans mode is then assumed to be proportional to the difference between the two measurements. These measurements were conducted during the repolarization phase of each action potential, because this is where the membrane potential differs the most from one beat to the next when alternans is present. The control current is then applied during the early plateau phase of the action potential immediately following the second of these two measurements. The amplitude of the control current is fixed at 10uA. The duration of the current is chosen to be a positive constant $\mu$ times $V_2$-$V_1$. The polarity of the current is chosen with the same sign as $V_1$-$V_2$.

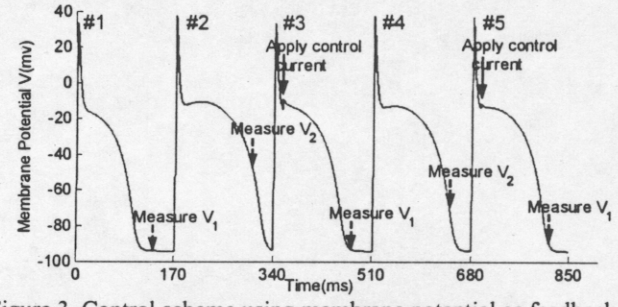


Figure 3. Control scheme using membrane potential as feedback input.

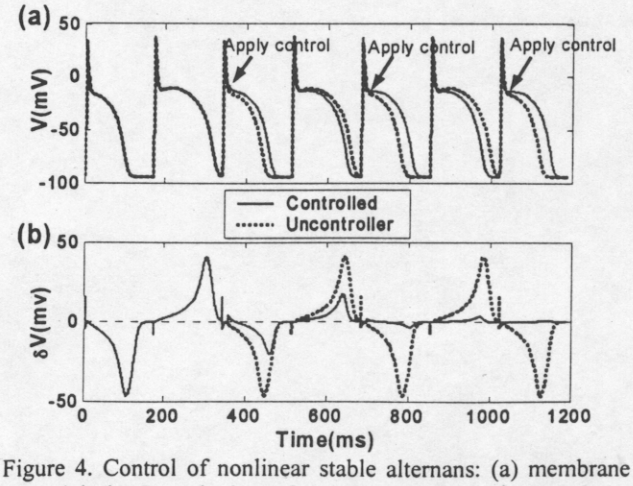


Figure 4. Control of nonlinear stable alternans: (a) membrane potential (b) Perturbation of membrane potential around the unstable 1:1 pattern.

Simulation results using the membrane potential feedback control scheme are shown in Fig. 4. The pacing cycle length is 170ms. The membrane potential was measured 135ms after the pacing stimulus of each cycle. The control current was applied 17ms after every other

pacing stimulus. Control currents of amplitude 10uA were applied during the 3rd, the 5th and 7th action potentials with the calculated durations of 0.565ms, 0.232ms and 0.042ms respectively (corresponding to $\mu$=0.12). As shown in Fig. 4, alternans was quickly eliminated using this protocol. Very small amounts of current (lasting from 1 to 3$\mu$s) were then occasionally needed to prevent the redevelopment of alternans.

## 5. Experimental results

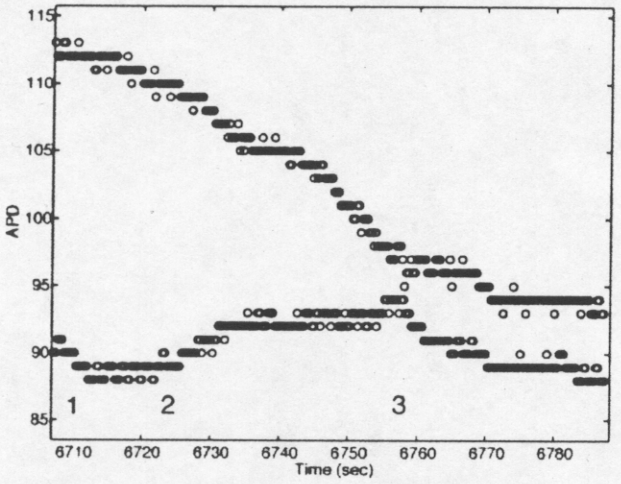


Figure 5. Effect of control stimuli on alternans of action potential duration (APD) in canine ventricular muscle. APD is plotted as a function of time during pacing at a cycle length (CL) of 150 msec. In the absence of a control stimulus, APD alternans occurred at this CL (beginning of record). At **1**, a hyperpolarizing control stimulus was delivered to the short duration action potential of the short-long pairs. At **2**, the control stimulus was switched to the long duration action potential. The control stimulus was turned off at **3**.

To determine the whether introduction of current pulses during the early plateau phase of the action potential suppresses electrical alternans, we have conducted preliminary experiments (n = 4) in small preparations of canine endocardial muscle and Purkinje fibers. Short segments of the fibers (2-3 mm long x 1-2 mm wide x 1 mm thick) were used to permit simultaneous delivery of current to the entire preparation. Action potentials were recorded from the tissue during constant pacing at a cycle length that produced electrical alternans and during the delivery of control stimuli. Both pacing and control stimuli were delivered using a bipolar electrode having an interelectrode spacing of 3 mm (i.e., the poles of the pacing electrode spanned the entire preparation). In the example shown in Fig. 5, 1.0 msec duration hyperpolarizing constant-current pulses of 100 $\mu$A intensity were delivered 15 msec after the upstroke of every other action potential during alternans. Delivery of the current pulse during the short duration action potential tended to increase alternans magnitude, whereas delivery of the current pulse during the long duration action potential markedly reduced alternans magnitude. Alternans was totally eliminated after some time. When the control stimulus was turned off, alternans was restored, although the magnitude of the alternans was smaller than before delivery of the control stimulus.

## 6. Conclusions

Previous studies have modified the pacing interval to control alternans in cardiac tissue. The current study shows that alternans in cardiac cells can also be controlled by modifying the ion channel dynamics. This opens a whole new line of investigation in the development of algorithms intended to control dangerous rhythm disorders in the heart.

## References


[1] Zipes DP, Wellens HJJ. Sudden cardiac death. Circulation. 1998;98:2334-2351.

[2] Courtemanche M. Complex spiral wave dynamics in a spatially distributed ionic model of cardiac electrical activity. Chaos 1996;6:579-600.

[3] Karma A. Spiral breakup in model equations of action potential propagation in cardiac tissue. Phys. Rev. Lett. 1993;71:1103-1106.

[4] Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. Circulation 1999;99: 1385-1394.

[5] Qu Z, Weiss J, Garfinkel A. Cardiac electrical restitution properties and stability of reentrant spiral waves: a simulation study. Am. J. Physiol. 1999;276: H269-H283.

[6] Weiss, JN, Garfinkel A, Karagueuzian HS, Qu Z, Chen PS. Chaos and the transition to ventricular fibrillation: A new approach to antiarrhythmic drug evaluation. Circulation 1999;99:2819-2826.

[7] Garfinkel A, Spano ML, Ditto WL, Weiss JN. Controlling cardiac chaos, Science 1992;257:1230-1235.

[8] Watanabe M, Gilmour RF. Strategy for control of complex low-dimensional dynamics in cardiac tissue, J. Math. Biol. 1996;35:73-87.

[9] Hall MG, Gauthier DJ, Experimental control of cardiac muscle alternans. Phys. Rev. Lett. 2002;88(19), art. no.-198102.

[10] Li M and Otani NF, Ion channel basis for alternans and memory in cardiac myocytes. ABME, in press.

[11] Fox JJ, McHarg JL, Gilmour RF. Ionic mechanism of electrical alternans. Am. J. Physiol. 2002;282: H516-H530.



Address for correspondence.

Niels F. Otani, Ph.D.
Department of Biomedical Engineering
Case Western Reserve University
10900 Euclid Ave.
Cleveland, OH 44106
USA
Email: nfo@po.cwru.edu