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Applications of Control Theory to the Dynamics and Propagation of Cardiac Action Potentials

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Abstract

Sudden cardiac arrest is a widespread cause of death in the industrialized world. Most cases of sudden cardiac arrest are due to ventricular fibrillation (VF), a lethal cardiac arrhythmia. Electrophysiological abnormalities such as alternans (a beat-to-beat alternation in action potential duration) and conduction block have been suspected to contribute to the onset of VF. This study focuses on the use of control-systems techniques to analyze and design methods for suppressing these precursor factors. Control-systems tools, specifically controllability analysis and Lyapunov stability methods, were applied to a two-variable Karma model of the action-potential (AP) dynamics of a single cell, to analyze the effectiveness of strategies for suppressing AP abnormalities. State-feedback-integral (SFI) control was then applied to a Purkinje fiber simulated with the Karma model, where only one stimulating electrode was used to affect the system. SFI control converted both discordant alternans and 2:1 conduction block back toward more normal patterns, over a wider range of fiber lengths and pacing intervals compared with a Pyragas-type chaos controller. The advantages conferred by using feedback from multiple locations in the fiber, and using integral (i.e., memory) terms in the controller, are discussed.

Keywords

Alternans; Conduction block; Purkinje fiber; Controllability; Stability; Lyapunov methods; State feedback; Proportional integral control

INTRODUCTION

Ventricular fibrillation (VF), a particular type of uncoordinated heart rhythm, is known to be a major factor in the onset of sudden cardiac arrest,²² which is responsible for hundreds of thousands of deaths in the USA annually.^{1,23} Certain abnormal action-potential (AP) patterns, including action-potential-duration (APD) alternans (a beat-to-beat alternation in APD) and conduction block, are thought to be precursors to more complex arrhythmias such as VF.⁸ Alternans may emerge within a single, periodically stimulated cardiac cell when the basic cycle length (BCL) is made sufficiently short. Alternans may also appear in Purkinje

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ELECTRONIC SUPPLEMENTARY MATERIAL

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fibers when they are extracted from the heart and stimulated from one end. In this case, stimulation with successively shorter BCLs leads to spatially concordant alternans of AP waves (in which APDs in all parts of the fiber alternate in phase), then to spatially discordant alternans (in which different regions alternate out of phase), and then to 2:1 (2 stimuli for every AP) conduction block.⁸ This study is motivated by the search for new approaches for treating these precursors, since such techniques may be useful for preventing VF in its early stages.

To design methods for suppressing these dangerous abnormal AP patterns, researchers have applied control-theoretical and other concepts to mathematical models of cardiac dynamics, or to real cardiac tissue.^{2-7,9-12,19} In most of these studies, alternans was suppressed using appropriately timed electrical stimuli, delivered through electrodes embedded in simulated or real tissue. Other researchers have suggested using alternate methods, such as the application of mechanical stimuli¹⁶ or drug delivery,¹⁷ for reversing unwanted AP patterns. A feature of previous studies is that the ones that made liberal use of control-systems concepts (beyond stability analysis and chaos control) only focused on converting one type of VF-precursor pattern, alternans, back to a more normal rhythm,^{5,9} while those that considered a wider variety of precursors, such as spiral-wave breakup, did not extensively utilize ideas from modern control theory.^{10,18,19}

To help bridge this gap, control-systems tools were used in this study to analyze and design control schemes for suppressing a variety of VF-precursor patterns. Controllability tests were investigated first, since they served as a basic check on whether control methods could successfully affect a mathematical model of a single cardiac cell. Lyapunov stability analysis was then applied to assess the ability of state feedback (SF), a well-known type of control algorithm, to eliminate a wide-ranging set of abnormal AP patterns within a single-cell model. Finally, state-feedback-integral (SFI) control was tested in a simulation study to evaluate its effectiveness in suppressing two precursor factors, alternans and 2:1 conduction block, within simulated Purkinje fibers.

METHODOLOGY

Mathematical Model

In this study, a mathematical model of the *in vitro* Purkinje fiber experimental setup shown in Fig. 1 was examined. A stimulating electrode was situated at one end of the fiber, and sensor electrodes that measure membrane potential were assumed to be located at different points along the fiber. A version of the two-variable Karma model^{13,14} that employs physiologically realistic units¹⁹ was chosen as the mathematical model, due to its simplicity and ability to produce abnormal AP patterns such as alternans and conduction block. The equations were

$$\begin{aligned} V_t &= \gamma V_{xx} + \frac{1}{\tau_V} f(V, n) - c - i \\ n_t &= \frac{1}{\tau_n} g(V, n) - u_n, \end{aligned} \quad (1)$$

where $V(x, t)$ is the membrane potential (in mV) at location x at time t , $n(x, t)$ is the slow-potassium-channel gating variable (dimensionless), and $i(x, t)$ is the stimulus current (in $\mu\text{A cm}^{-2}$). $i(x, t)$ is only non-zero in a small region corresponding to the electrode location, and $u_n(x, t)$ (ms^{-1}) is an optional perturbation term applied to $n(x, t)$. Subscripts t and x indicate partial derivatives, e.g., $V_{xx} = \partial^2 V / \partial x^2$. Here, f and g are defined as

$$f(V, n) = -V - V_b + \left(V^* - \left(\frac{n}{n_B} \right)^M \right) h(V),$$

$$h(V) = \sum_{j=0}^3 c_j V^j$$

$$g(V, n) = \frac{1}{b} \theta(V - V_n) - n,$$

where $\theta(\cdot)$ is the Heaviside function. No-flux boundary conditions were assumed: $V_x(0, t) = V_x(L, t) = 0$. Default parameter values are $\gamma = 0.001 \text{ cm}^2 \text{ ms}^{-1}$, $\tau_V = 5 \text{ ms}$, $c = 1 \text{ cm}^2 \mu\text{F}^{-1}$, $\tau_n = 250 \text{ ms}$, $V_b = 85 \text{ mV}$, $V^* = 1.88$, $n_B = 1$, $M = 10$, $b = 0.7059$, $V_n = -60 \text{ mV}$, $c_0 = 72.83 \text{ mV}$, $c_1 = -0.83$, $c_2 = -0.04976 \text{ mV}^{-1}$, and $c_3 = -0.000352 \text{ mV}^{-2}$. A single-cell version of the equations was obtained by eliminating the dependence on x .

Desired Trajectories, Error Dynamics, and Alternate Forms of Equations

While $V(x, t)$ and $n(x, t)$ represented the actual AP behavior in the fiber, the targeted, presumably more normal behavior was represented by desired profiles $V^d(x, t)$ and $n^d(x, t)$. It was typically assumed that these profiles satisfy the two-variable Karma model:

$$\begin{aligned} V_t^d &= \gamma V_{xx}^d + \frac{1}{\tau_V} f(V^d, n^d) - c - i^d \\ n_t^d &= \frac{1}{\tau_n} g(V^d, n^d), \end{aligned} \quad (2)$$

and the no-flux boundary conditions, and that $u_n^d(x, t)$ was identically zero. The desired current profile $i^d(x, t)$ was, by default, defined to be a periodic train of rectangular pulses with a stimulus value of $-32 \mu\text{A cm}^{-2}$, and a stimulus duration of 2.5 ms for single-cell systems and 7 ms for fibers.

Except where indicated, the desired trajectories V^d and n^d were constructed using an approximate method for determining periodic 1:1 solutions of Eq. (2). When numerical simulations of Eq. (2) exhibited alternans at the targeted BCL, a desired APD was first calculated by time-averaging the APDs of equal numbers of long and short beats. For BCL values that caused simulations to start in 2:1 block, the desired APD was defined to be the steady-state APD that resulted from applying Pyragas control to a short fiber. In both cases, an AP with the desired APD was created by shortening or lengthening the beginning of the plateau of a selected simulated AP. A periodic AP time-series was then constructed by repeating the adjusted AP once per BCL.

Once the desired trajectories had been specified, “error” variables were defined by subtracting actual quantities from desired ones, e.g., $\tilde{V}(x, t) = V^d(x, t) - V(x, t)$, with analogous definitions for $\tilde{n}$, $\tilde{i}$, and $\tilde{u}_n$. Subtracting Eq. (1) from Eq. (2) yielded the “error” dynamics:

$$\begin{aligned} \tilde{V}_t &= \gamma \tilde{V}_{xx} + \frac{1}{\tau_V} f(V^d, n^d) - \frac{1}{\tau_V} f(V, n) - c - \tilde{i} \\ \tilde{n}_t &= \frac{1}{\tau_n} g(V^d, n^d) - \frac{1}{\tau_n} g(V, n) - \tilde{u}_n. \end{aligned} \quad (3)$$

Equation (3) was used as a general framework for designing and evaluating control strategies for suppressing VF-precursor patterns. It was used for testing whether controllers, $\tilde{i}(x, t)$ or $\tilde{u}_n(x, t)$, could drive $\tilde{V}(x, t)$ and $\tilde{n}(x, t)$ to zero, which would signify the conversion of abnormal AP patterns back toward normal patterns.

Certain simplified forms of the dynamic equations were useful for analyzing the system. A linearized version of Eq. (3) was obtained from expanding the terms about V^d and n^d , after approximating the Heaviside function $\theta(V - V_n)$ with $0.5(1 + \tanh(c_a(V - V_n)))$, where c_a is an adjustable parameter with default value 1 mV^{-1} .

The linear equations were discretized using a forward-Euler scheme, with the approximation $F_{xx}(x, \cdot) \approx (F(x + \Delta x, \cdot) - 2F(x, \cdot) + F(x - \Delta x, \cdot))/(\Delta x)^2$. The linearized, discretized equations could then be written as

$$\mathbf{s}(k+1) = \mathbf{A}(k) \mathbf{s}(k) + \mathbf{B}(k) \mathbf{u}(k), \quad (4)$$

with discrete time index $k \in \{0, 1, 2, \dots\}$. For an N -cell fiber, the state vector is

$$\mathbf{s}(k) = [\tilde{V}_1(k) \dots \tilde{V}_N(k) \tilde{n}_1(k) \dots \tilde{n}_N(k)]^T$$

with control input of the form $\mathbf{u}(k) = [\tilde{i}(k) \tilde{u}_n(k)]^T$. To approximate a point stimulus in the discretized system, it was assumed that both i and i^d were identically zero outside of cell 1.

To avoid “apples-and-oranges” comparisons in controllability computations, a non-dimensionalizing transformation was applied to the single-cell form of Eq. (4):

$\mathbf{s}'(k) = [\tilde{V}'(k) \tilde{n}'(k)]^T \equiv S \mathbf{s}(k)$ yielded $\mathbf{s}'(k+1) = S \mathbf{A}(k) S^{-1} \mathbf{s}'(k) + S \mathbf{B}_p(k) u_{p,\max} u'_p(k) = \mathbf{A}'(k) \mathbf{s}'(k) + \mathbf{B}_p'(k) u'_p(k)$. Here, $p \in \{1, 2\}$, $u_1(k) = \tilde{i}(k)$, $u_2(k) = \tilde{u}_n(k)$, $\mathbf{B}_1(k) = [b_1 \ 0]^T$, $\mathbf{B}_2(k) = [0 \ b_2]^T$, $u'_p = u_p / u_{p,\max}$, and S is a diagonal matrix with $s_{11} = 0.0102 \text{ mV}^{-1}$ and $s_{22} = 0.9683$ (no units), which are the approximate inverses of the maximum magnitudes attained by $\tilde{V}$ and $\tilde{n}$ in simulations of the non-linear system. The values $u_{1,\max} = 4 \mu\text{A cm}^{-2}$ and $u_{2,\max} = 0.0018$ (no units) are the approximations of maximum magnitudes attained by u_1 and u_2 .

Simulation Model and Performance Measure

A simulation model of the forward-Euler discretized version of Eq. (1) was set up in Matlab, with default step sizes $\Delta x = 0.0262 \text{ cm}$ and $\Delta t = 0.05 \text{ ms}$. The simulation program was capable of representing both single-cell geometries and multi-cell fibers.

A performance measure, the mean absolute APD error (MAE) over all cells, was chosen to quantify the long-term behavior of simulated cardiac fibers under the action of different control laws. The measure was defined as

$$\text{MAE} = \frac{1}{N} \sum_{m=1}^N \frac{1}{J} \sum_{j=1}^J |\text{APD}_{m,j} - \text{APD}^d|, \quad (5)$$

where the outer and inner summations are over the cell index m and the AP index j , N is the number of cells, J is number of APs in the range 10000–15000 ms, and APD^d is the desired APD that was used to construct the V^d trajectories. APD was defined as the time elapsed between the crossings of the depolarization and repolarization edges of an AP with the line $V = -40 \text{ mV}$.

Controllability

Controllability analysis was used to determine which of the input variables, $\tilde{i}$ or $\tilde{u}_n$, is a better choice for suppressing unwanted AP patterns. The controllability Grammian, W_{cg} , was computed for selected trajectories of the primed system. To evaluate the coefficients of $\mathbf{A}'(k)$ based on the exact system dynamics, $V^d(k)$ and $n^d(k)$ were obtained by simulating the

non-linear, discretized, single-cell version of Eq. (1) with the default parameters and smooth approximation of $\theta(\cdot)$ listed previously. $i(k)$ was a periodic rectangular pulse train (i.e., no feedback control was used), with BCL = 225 ms. For the chosen parameters, $b_1 = -0.05 \text{ cm}^2 \text{ ms } \mu\text{F}^{-1}$ and $b_2 = -0.05 \text{ ms}$.

A typical definition for the controllability Grammian,

$W_{\text{cg}}(k_0, k_1) = \sum_{k=k_0}^{k_1} \Phi(k_1, k) \begin{bmatrix} B'_p(k) & B'_p(k)^T \end{bmatrix} \Phi(k_1, k)^T$ where $\Phi(k_1, k_0) = \prod_{k=k_0}^{k_1-1} A'(k)$, was used. The minimum singular value of the Grammian was calculated at a series of points in time for both the $p = 1$ and $p = 2$ cases. The two cases were compared using the criterion that the Grammian minimum singular value of a controllable system should be as large as possible, in order to minimize the control-input energy required to transfer the system from an initial state to a final state.

SF and Chaos Controllers

SF techniques were investigated as a means of suppressing abnormal AP patterns in the non-linear two-variable Karma model. For an N -cell fiber in the discretized dynamics of Eq. (1), reduced SF control laws of the form

$$\tilde{i}(k) = -[K_{p1} \dots K_{pN}] [\tilde{V}_1(k) \dots \tilde{V}_N(k)]^T = -\mathbf{K}_p \tilde{\mathbf{V}}(k), \quad (6)$$

where $\mathbf{K}_p$ is a row vector of proportional gains, and the current applied to the system is $i = i^d - \tilde{i}$, were tested in simulations in which it was assumed that the $n_m(k)$ variables could be neither measured nor manipulated. A standard extension to this method, SFI control, was also tested, using the following anti-windup version of SFI to keep the integral term from becoming overly large:

$$\tilde{i}(k) = \alpha \tilde{i}(k-1) - [\mathbf{K}_p \quad \mathbf{K}_I] \begin{bmatrix} \tilde{\mathbf{V}}(k) - \alpha \tilde{\mathbf{V}}(k-1) \\ \tilde{\mathbf{V}}(k) \end{bmatrix}. \quad (7)$$

Here, $\mathbf{K}_I = [K_{I1} \dots K_{IN}]$ is a row vector of integral gains, and α is a parameter chosen in the range (0, 1). For all SF and SFI tests, constraints were imposed on i at $\pm 32 \mu\text{A cm}^{-2}$, i was applied only to cell 1, and the controllers were turned on at $t = 2800 \text{ ms}$.

The SFI control method was compared with a Pyragas-type chaos controller that was studied in previous works.^{3,7,12} The formula for the Pyragas controller was

$$T_j = \text{BCL} + K_{\text{ch}} (\text{APD}_{1,j} - \text{APD}_{1,j-1}),$$

where T_j is the interval between the j th and $(j+1)$ th stimuli, and K_{ch} is an adjustable gain. For either single cells or fibers, a rectangular-pulse stimulus with the same parameters as i^d was applied to cell 1, and APD was measured in cell 1. For this study, a modification was made to help improve performance of the controller in cases of 2:1 block; when the difference between the repolarization times of APD_j and APD_{j-1} met or exceeded $1.8 \times \text{BCL}$ (the interval between APs during 2:1 block should be approximately $2 \times \text{BCL}$), $\text{APD}_j - \text{APD}_{j-1}$ was replaced with $\text{APD}_j - 0$.

Stability

An important aspect of performance is stability: will the control law cause the errors $\tilde{\mathbf{V}}$ and $\tilde{n}$ to remain bounded, and to eventually converge to zero? Lyapunov analysis, described in Khalil¹⁵ and elsewhere, was used to answer this question for the single-cell version of Eq.

(3). A Lyapunov candidate that was positive definite (PD) with respect to state, $\mathbf{s} = [\tilde{V} \tilde{n}]^T$, was defined as $W(\mathbf{s}) = \frac{1}{2} \tilde{V}^2 + \frac{1}{2} \tilde{n}^2$, and it was determined whether the control law could be selected to make dW/dt negative definite (ND).

RESULTS

Single-Cell Geometry

Controllability and stability tests were applied to the single-cell Karma model to gain insight in two areas: (1) the potential effectiveness of different control configurations, and (2) the stability properties of a SF-controlled system.

Controllability—Controllability Grammians were computed for two cases of the of the linearized, discretized, single-cell error dynamics.

Case 1: The control input takes the form of an electrical current. That is, in the single-cell version of Eq. (4), $\tilde{i}(k)$ is nontrivial, $\tilde{u}_n \equiv 0$, $u = \tilde{i}$, and the B matrix was simplified to $\mathbf{B}(k) = [b_1 \ 0]^T$.

Case 2: The control input consists of direct alterations to the gating variable, n . That is, in the single-cell version of Eq. (4), $\tilde{i}(k) \equiv 0$ while i^d remains a regular pulse train, $\tilde{u}_n(k)$ is non-trivial, $u = \tilde{u}_n$, and $\mathbf{B}(k) = [0 \ b_2]^T$.

For both cases, the maximum singular values of W_{cg} , as functions of time, were found to be non-zero. The minimum singular values of W_{cg} are plotted in Fig. 2. The Grammian window refers to the time duration, $k_1 - k_0$, used by a controller to drive the state vector to any point in the state space. For a shorter window length (1/10 of a BCL), as shown in Fig. 2a, the minimum singular value of Case 1 is lower than that of Case 2, except at times near the repolarization and depolarization edges. For a longer window (1 BCL), shown in Fig. 2b, the minimum singular value of Case 1 is usually greater than that of Case 2. Note that there is some arbitrariness in the singular values, since they depend on the particular choice of scaling factors, S and $u_{p, \max}$. It is clear, however, that both Cases 1 and 2 are technically controllable at the tested k_0 values, because in each case, there exists a final time k_1 for which the corresponding Grammians are non-singular. The required k_1 value is larger for Case 1 than Case 2.

Stability—The remaining portions of the study were restricted to the more practical scenario where $\tilde{u}_n \equiv 0$ that is, it was assumed that the n variables could neither be measured nor manipulated directly.

Lyapunov methods were used to assess the stability of a particular type of Case 1 control, where $u = \tilde{i} = -K \tilde{V}$ was applied as a feedback current to the non-linear dynamic equation for V , for the single-cell geometry. For the candidate Lyapunov function defined as $W(\mathbf{s}) = \frac{1}{2} \tilde{V}^2 + \frac{1}{2} \tilde{n}^2$, it was found that dW/dt can be made ND, in a particular way that implies local exponential stability of $\mathbf{s} = 0$, if K is chosen below a certain threshold (i.e., if K is set to a constant value that is sufficiently large and negative). Details of the proof appear in the Appendix. This result is consistent with simulation tests of the non-linear, discretized single-cell model, where $i^d(k)$ was a periodic pulse train with BCL = 225 ms (plots are not shown for brevity). In these tests, $K_1 = -0.03$ was found to reduce the alternans amplitude over time, while $K_1 = -0.01$ was not effective.

1D Fiber Geometry

The controllability results confirmed that the single-cell system is at least controllable through $\tilde{i}$ and the stability result verified that an SF law $\tilde{i} = -K\tilde{V}$ can stabilize the dynamics of a single cell about a desired behavior. These results motivated testing SF in spatially extended systems.

Simulation Tests for BCL 225 ms, Fiber Length 2.62 cm—A first set of simulations was performed to test the effects of SF and related methods on discordant alternans within a Purkinje fiber. Simulations were carried out using the discretized, non-linear two-variable Karma model. Current, APD, and space–time membrane potential plots from an open-loop simulation are shown in Figs. 3a, 3c, and 3e. BCL was set to 225 ms, with a fiber length of 2.62 cm (100 cells for the chosen Δx). These simulation conditions led to the development of discordant alternans. The resulting MAE was 24.05 ms, as indicated in the first row of Table 1. Next, a series of closed-loop strategies were tested in simulation, in an effort to suppress the discordant alternans shown in Figs. 3c and 3e. The Lyapunov stability analysis suggested using negative gains for SF; hence, the components of $\mathbf{K_P}$ in Eq. (6) were set to negative values in initial tests.

First, a feedback scheme that only employed membrane-potential measurements from cell 1 was tested by setting $K_{P1} = -7$ (all other gains zero). The resulting MAE of 14.86 ms is listed in the second row of Table 1. This feedback strategy was able to reduce but not eliminate the alternans amplitude. Larger-magnitude values of K_{P1} tended to induce large, sustained oscillations in i without providing any significant reduction in alternans amplitude. Moving the single measurement location away from the proximal end (e.g., setting $K_{P20} = -7$ as the only non-zero entry instead of $K_{P1} = -7$) did not appear to help. However, single-measurement-site feedback was not tested exhaustively in this configuration.

Further reductions in alternans amplitude were achieved in two additional simulation tests, one using SF (Eq. 6), and the other using SFI control (Eq. 7). MAE values and gains for these cases are given in the third and fourth rows of Table 1. It can be seen that the SFI approach yielded a lower MAE than SF by itself. The SF test used membrane-potential information from the first 40 cells, with $K_{Pm} = -0.02$, $m \in \{1, 2, \dots, 40\}$, and $K_{Pm} = 0$, $m > 40$. SFI control was implemented with the same K_{Pm} gains as the SF case, with the addition of $K_{I40} = -0.0004$, $K_{Im} = 0$, $m \neq 40$, and $\alpha = 0.999$. The current, APD, and membrane potential plots resulting from the SFI test are shown in Figs. 3b, 3d, and 3f. From Figs. 3d and 3f, it can be seen that the SFI controller significantly reduced the APD alternations compared with the open-loop case of Figs. 3c and 3e. Note that the current, i , delivered to the fiber in the SFI case in Fig. 3b was larger than that of the open-loop case in Fig. 3a. The fact that i did not converge to i^d in Fig. 3b as the APD oscillation amplitude decreased is most likely due to inaccuracies in the constructed V^d trajectories.

It is not realistic to have electrode-based measurements of V for each cell. A simulation test was therefore performed in which the gains were $K_P = -0.25$ at cells 1, 20, and 40 and $K_{I40} = -0.0004$, with all other gains zero, corresponding to an output-feedback-integral strategy with sensing electrodes at $x = 0.0262$, 0.524 , and 1.048 cm. To approximate sensor noise, the errors $\tilde{V}_m(k)$ were replaced with $\tilde{V}_m(k) + v_m(k)$ ($m = 1, 20, 40$) in the feedback law, where the $v_m(k)$ were independent, normally distributed pseudo-random number sequences with zero mean and unit variance. The resulting MAE, listed in the fifth row of Table 1, was somewhat worse than that of the SFI case, and the current amplitude converged more slowly. Excluding or including the noise did not appear to have a significant impact on the MAE.

Comparison with a Chaos Controller—The SFI and Pyragas controllers were tested for their ability to suppress abnormal AP patterns in simulated fibers. For both controllers, the feedback laws were turned on at 2800 ms. A comparison of MAEs is given in Fig. 4, over a range of BCLs from 165 to 240 ms, and fiber lengths from 0.52 to 4.19 cm. In an attempt to achieve the best performance for the Pyragas controller, for each length and BCL combination, a search was performed on K_{ch} values over the range of 0.05 to 1.00, in increments of 0.05. The reported MAEs in Fig. 4b correspond to those values of K_{ch} that minimized the MAE. A plot of minimizing gains is given in Supplementary Fig. S1. The overall mean of the minimizing gains was 0.55, with a standard deviation of 0.13 in the average minimizing gains for each BCL. For some conditions, the gains showed rough trends toward higher values for longer lengths or shorter BCLs, but the trends were not very consistent, perhaps due to “flat” behavior of the MAE near the minimizing gain, which is sometimes evident in MAE vs. K_{ch} plots. For the SFI gains, preliminary simulation tests revealed that an *ad hoc* structure, with $\alpha = 0.999$, $K_{Pm} = \zeta$, $m \in \{1, 2, \dots, m_{p, \max}\}$, and $K_{Im} = \zeta$, $m \in \{m_{l, \min}, m_{l, \min} + 1, \dots, m_{l, \max}\}$, where ζ and ζ were negative constants and K_{Pm} and K_{Im} were otherwise zero, was often sufficient to convert alternans to a 1:1 pattern. K_{Pm} , K_{Im} , and α were generally initialized to the values in the 0.52 cm, BCL = 165 ms entry of Supplementary Table S1 for fibers 60 cells or shorter, and to the values in the 2.10 cm, BCL = 225 ms entry for longer fibers. For each length and BCL combination in Fig. 4c, gains were tuned further by making ζ and ζ more positive if the default values yielded overly aggressive control currents. If a 1:1 pattern was not restored with the default values, adjustments consisted of making ζ and ζ more negative, increasing α or $m_{p, \max}$, or increasing the separation between $m_{l, \min}$ and $m_{l, \max}$. The space of K_{Pm} , K_{Im} , and α values was not completely explored, hence the tuning process almost certainly has not identified gains that are optimal in any practical sense. The tuned gains corresponding to Fig. 4c, which were in the range $-0.2 \leq K_{Pm} \leq 0$, $-0.002 \leq K_{Im} \leq 0$, with $0.9990 \leq \alpha \leq 0.9999$, are given in Supplementary Table S1.

For concordant alternans, which appeared in open-loop simulations of a 0.52-cm (20-cell) fiber at BCL values of 195, 210, 225, and 240 ms, the Pyragas and SFI controllers performed similarly to one another. The means and standard deviations of MAEs over the four cases were 3.06 and 2.72 ms for Pyragas control and 2.97 and 2.70 ms for SFI control. For the remaining lengths and BCLs below the black dash-dotted line in Fig. 4a, the simulated fibers predominately exhibited discordant alternans. At a BCL of 225 ms, fibers of lengths 3.14, 3.67, and 4.19 cm manifested both discordant alternans and 2:1 block during the MAE measurement period (10000–15000 ms), with 2:1 block becoming increasingly dominant at the longer lengths. The means and standard deviations of MAEs over the discordant alternans cases were 7.08 and 5.36 ms for Pyragas control and 4.47 and 1.03 ms for SFI control. For 2:1 block, the means and standard deviations of MAEs were 48.97 and 27.81 ms for Pyragas control, and 22.05 and 19.03 ms for SFI control. Comparing Figs. 4a–4c, it can be seen that the SFI controller was able to suppress more cases of open-loop discordant alternans (e.g., BCL of 225 ms at length 3.14 cm) and 2:1 block (e.g., BCL of 165 ms at length 1.57 cm) than the Pyragas controller.

Sensitivity Tests—The noise-free version of the output-feedback-integral simulation was tested under $\pm 5\%$ variations of the default Karma model parameters. One parameter was modified at a time, holding all other values constant. When one set of parameters, γ , τ_V , V_n , V^* , M , c , and τ_n were varied, the open-loop APD trajectories remained qualitatively similar to those of the unperturbed case, and the controller successfully stabilized the perturbed system. For another set of parameters, V_b , c_0 , c_1 , c_2 , and c_3 , the open-loop behavior of the model (alternans) was qualitatively altered (e.g., showing irregular APD sequences) for either one or both signs of the variation. In these cases, the controller was not helpful in restoring a 1:1 pattern. Perturbations to a third set, n_B and b , showed an intermediate type of

result, wherein the open-loop evolution still resembled alternans for all of the $\pm 5\%$ variations, but the controller was not successful at stabilizing either of the $+5\%$ perturbed systems. The performance of the output-feedback-integral controller did not appear to be very sensitive to gain perturbations. Altering the K_P and K_I gains, collectively and uniformly, by $\pm 5\%$, had no significant effect on qualitative controller performance (the resulting shifts in MAEs were both less than 2%).

DISCUSSION

In this study, control-systems tools, specifically controllability analysis, Lyapunov stability analysis, and SF design, were applied to a model of AP dynamics in order to investigate strategies for suppressing AP patterns that are suspected to be precursors to VF. The two-variable Karma model^{13,14} was chosen since it is able to produce alternans and conduction block while having a low number of dynamic variables, which facilitated the controllability and stability analyses. The main disadvantage of the model is that, due to its simplified dynamics, it lacks a high level of physiological detail.

For the single-cell version of a non-dimensionalized two-variable Karma model, two cases for the structure of the control input were considered. In the first case, an electrical current, which would directly affect the cellular membrane potential, was assumed to be applied to the cell. In the second case, it was assumed that the slow-potassium variable dynamics could be perturbed directly. For the first case, it was shown in Figs. 2a and 2b that the controllability Grammian was more reliably non-singular at the longer time scale (1 BCL) than at the shorter one (1/10 BCL). If this property holds for fibers, it provides a possible explanation for the ability, summarized in Fig. 4, of SFI controllers to outperform Pyragas controllers. A controller that is active continuously over longer time scales (e.g., an SFI controller) may be able to exploit the improved controllability shown in Fig. 2b, unlike a Pyragas controller, which only acts upon the system during intervals much shorter than any of the tested BCLs.

The controllability analysis further revealed that perturbing the slow-potassium variable dynamics (Case 2) typically yielded improved controllability, compared with perturbing the membrane potential (Case 1), over the shorter time scale. This result is significant because it indicates, in situations where the time available for suppressing VF precursors is relatively short, that direct alteration of dynamics of the refractory variable, n , would be a more effective method of control, when compared to the more widely known approach of applying electrical stimuli to a cell. Additional tests, not shown for brevity, indicate that similar controllability results are obtained for a wider range of AP patterns (e.g., 2:1 block at BCL = 210 ms) beyond the one shown in Fig. 2. That said, there are mathematical and practical limitations worth noting. First, due to the linearization step, the controllability results are limited in their predictive ability when applied to the non-linear system. Second, given present technological limitations, making time-varying adjustments to the dynamics of n is not possible.

The controllability results presented here appear to partly corroborate previous studies.^{10,17} Osipov and Collins¹⁷ tested various kinds of Case 2 control within a FitzHugh-Nagumo simulation model, which has a fast variable analogous to V , and a slow variable analogous to n . They showed that certain types of perturbations to the slow-variable dynamics could successfully suppress the propagation of traveling and spiral waveforms, and stated that they expected their slow-variable perturbations to be relatively weak, in contrast with the large fast-variable perturbations required for defibrillation-based suppression of such waveforms.¹⁷ In another project, Gray¹⁰ examined the effects of different Case 1 defibrillation schemes on a FitzHugh-Nagumo model, and found that longer-duration stimuli

were more effective at control, in the sense of requiring less overall energy than shorter-duration pulses. Here, a direct comparison is made between control applied to the fast vs. the slow variables, and it was demonstrated that Grammian methodology is a useful means for quantifying the relative advantages in control effectiveness that follow from perturbing different variables. Controllability tools have also been used to analyze physiological systems beyond the one considered in this study.²¹ For cardiac systems, Grammian tests could be applied to ion-channel models to determine the relative importance of each variable in controlling the system. Such results could provide better guidance in developing new control designs, which could be useful if future technologies emerge to allow direct, possibly short-term perturbations of ion-channel behavior.

While the controllability results gave confidence that Case 1 control could be used to manipulate a single-cell system, they did not guarantee that the long-term behavior of the controlled system would be favorable. Hence, Lyapunov stability analysis was applied to the non-linear single-cell two-variable Karma model, to determine whether an SF law, where the stimulus current depended on the membrane potential, could suppress VF-precursor patterns. SF control was investigated, since it is a well-known method that has been shown to be successful in a variety of applications involving non-linear dynamic systems. It was determined that feedback gains below a certain threshold would render the closed-loop system locally exponentially stable about the desired profile. The significance of this result is that, for initial values of V and n representing sufficiently small perturbations from the desired trajectories, the controller can cause the values to remain bounded and eventually converge to the V^d and n^d profiles. A very general class of initial AP patterns, namely any pattern that satisfies the single-cell version of Eq. (1) under the action of SF, was considered in the analysis. Hence, the analysis can, in principle, be valid for the suppression of other abnormal patterns in addition to alternans. However, a main limitation is that the stability result is only local to the point ($\tilde{V} = 0, \tilde{n} = 0$). Specifically, stability has not been proven for situations where the initial AP pattern represents a large deviation from the desired pattern, which is assumed to be chosen as a 1:1 periodic waveform. A useful extension to the stability analysis would be to derive ranges of stabilizing feedback gains for different control schemes. This could help explain the results of Fig. 4, which strongly indicate that for certain conditions (e.g., a 3.14-cm fiber paced at BCL = 225 ms), the range of stabilizing gains is larger for the SFI case compared to the Pyragas one. It is noted that the stability analysis presented here overlaps with that of Sinha *et al.*,²⁰ although Sinha *et al.* made use of analytical tools for time-periodic systems, and did not explicitly consider the suppression of VF precursors. While Lyapunov analysis was used here mainly for verification purposes, to show that SF can confer beneficial effects, related methods²⁰ may prove useful in the design of novel control laws for suppressing abnormal AP patterns in cardiac tissue.

The single-cell stability results motivated the extension of SF control to 1D Purkinje fibers modeled by the two-variable Karma model. Simulations were conducted to assess the ability of selected feedback methods to suppress abnormal AP patterns within such fibers. To reflect typical experimental limitations, the simulations were confined to using a single stimulating electrode at one end of the fiber, and the feedback signals depended only on the membrane-potential variables. The first round of tests was restricted to the control of discordant alternans within a 2.62-cm fiber, paced at BCL = 225 ms. The first important observation was that SF based on measurements from multiple locations was more effective in reducing the alternans amplitude than feedback based on one location in the vicinity of the stimulus site. This is consistent with a previous claim.⁶ The next major result was that the addition of an integral term (SFI control) yielded an improved MAE compared with SF by itself. SFI control was investigated since, for certain systems, adding an integral term is known to improve the convergence of the error variables toward zero, and the ability of the systems to resist the influence of external disturbances. An output-feedback-integral (OFI)

controller, which used feedback from only three sensors, was tested in simulations with approximate sensor noise, and was shown to perform similarly to the SFI controller. Hence, this more practical approach may be a viable alternative to the SFI controller, which would be more difficult to realize. The performance of the output-feedback strategy could potentially be improved further by constructing an observer or estimator to infer any unmeasured V_m and n_m from the available sensor data. Finally, SFI control was shown to convert both discordant alternans and 2:1 conduction block back to more normal patterns, over a greater range of BCL and fiber-length conditions, compared with the more widely studied^{3,7,12} Pyragas controller. In terms of MAE, the improved performance of SFI control compared to Pyragas control was not significant for concordant alternans, but was substantial for cases of discordant alternans and 2:1 conduction block. A limitation is that the control gains in the state- and output-feedback simulation studies were hand-tuned. Application of an automated gain selection method such as linear quadratic control may provide insight into which gain values and distributions are optimal for a given application. It is likely that the anti-windup design in Eq. (7) could also be improved. Since real cardiac tissue is characterized by significant spatial inhomogeneities and temporal variations, techniques such as optimal and robust control are worth investigating as a means of producing controllers that can function in the presence of large uncertainties.

The purpose of this study was to contribute to the body of knowledge about possible methods for the control of AP dynamics. Insights gained from analyzing the two-variable Karma model may carry over to more complex or realistic models, which may in turn lead to the development of improved control strategies. It is important to note that, since they only adjust the timing of stimuli and require APD measurements from only one location, chaos-control methods (such as Pyragas) can be applied in a clinical setting. In contrast, additional effort would be needed to bring the controller designs presented in this study in a closer agreement with real-world device limitations.

In conclusion, standard methods from control theory were applied to a model of AP dynamics for the purpose of evaluating and designing methods to suppress abnormal AP patterns, such as alternans and conduction block. The main original contributions are the use of Grammian-based controllability analysis to assess the advantages and disadvantages of alternative approaches for controlling the dynamics of a single cell, a Lyapunov stability proof confirming that SF control can stabilize the non-autonomous, non-linear dynamics of a single cell about a specified AP pattern, and a simulation study of Purkinje fibers demonstrating both the effectiveness of SFI control and its ability to outperform a chaos controller in the regulation of discordant alternans and 2:1 block. These contributions may lead to further work in the application of controls concepts to mathematical models of cardiac dynamics, which could eventually result in improved treatments for the prevention of VF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

Lyapunov analysis was used to assess the stability of Eq. (3), which is non-autonomous. A number of restrictions were imposed: $\theta(\cdot)$ was replaced by $\theta_c(V - V_n) = 0.5(1 + \tanh(c_a(V - V_n)))$ in Eqs. (1)-(3), and it was assumed that $i^d(t)$ is a continuous function of time, and that $\tilde{r}(t) = -K \tilde{V}(t)$. The single-cell case of the dynamic equations was used. Under all these assumptions, the right-hand sides of Eqs. (1) and (2) satisfy sufficient conditions for existence and uniqueness of solutions, local to a given initial time and set of initial conditions. However, a stronger assumption was made, that the desired trajectories, $V^d(t)$, and $n^d(t)$, are bounded (not necessarily periodic) for all times $t \geq t_0$. A shorthand version of the continuous-time error dynamics (Eq. 3), for the closed-loop single-cell case, was written as $\dot{\mathbf{s}} = \phi(\mathbf{s}, t)$. Here, the system state consists of the errors for the membrane potential and gating variable of the single cell, i.e., $\mathbf{s} = [\tilde{V} \tilde{n}]^T$. The point ($\tilde{V} = 0, \tilde{n} = 0$) is an equilibrium point of the system.

The following theorems are equivalent to statements found in Khalil.¹⁵ Specifically, Theorem 1 corresponds to Corollary 3.4 of Theorem 3.8, and Theorem 2 corresponds to Theorem 3.11.

Theorem 1

Let $\mathbf{s} = 0$ be an equilibrium point for $\dot{\mathbf{s}} = \phi_1(\mathbf{s}, t)$, where ϕ_1 is piecewise continuous in t and locally Lipschitz in a domain D that contains $\mathbf{s} = 0$. Let $W(\mathbf{s})$ be a continuously differentiable function such that W is PD and $\dot{W}(\mathbf{s})$ is ND for all $\mathbf{s} \in D$. Furthermore, suppose that $W(\mathbf{s}) = k_1 \|\mathbf{s}\|^q$ and $\dot{W}(\mathbf{s}) \leq -k_2 \|\mathbf{s}\|^q$, for some positive constants k_1, k_2 , and q . Then $\mathbf{s} = 0$ is exponentially stable.

Theorem 2

Let $\mathbf{s} = 0$ be an equilibrium point for the system $\dot{\mathbf{s}} = \phi(\mathbf{s}, t)$, where $\phi: [t_0, \infty) \times D \rightarrow \mathbb{R}^N$ is continuously differentiable, $D = \{\mathbf{s} \in \mathbb{R}^N \mid \|\mathbf{s}\|_2 < r\}$, $r > 0$; and the Jacobian $\frac{\partial \phi}{\partial \mathbf{s}}$ is bounded and Lipschitz on D , uniformly in t . Define $A(t) = \frac{\partial \phi}{\partial \mathbf{s}}(\mathbf{s}, t)|_{\mathbf{s}=0}$. Then, $\mathbf{s} = 0$ is an exponentially stable equilibrium point for the nonlinear system if it is an exponentially stable equilibrium point for $\dot{\mathbf{s}} = A(t) \mathbf{s}$.

The version of Theorem 1 in Khalil¹⁵ is more general in that it covers cases where W either has explicit time dependence or takes forms other than $k_1 \|\mathbf{s}\|^q$. In Theorem 2, note that the region over which stability holds may be smaller than r . See Khalil¹⁵ for proofs of the theorems.

Let D be a ball of finite radius that includes the origin. To apply the first theorem, let $\phi_1(\mathbf{s}, t) = A(t)\mathbf{s}$, where $A(t)$ is the Jacobian of $\phi(\mathbf{s}, t)$ (where ϕ is the right-hand side of the closed-loop single-cell error dynamics), evaluated at $\mathbf{s} = 0$. Specifically,

$$\begin{aligned} \dot{\mathbf{s}} &= \phi_1(\mathbf{s}, t) = A(t) \mathbf{s} \\ &= \frac{d}{dt} \begin{bmatrix} \tilde{V}_1 \\ \tilde{n}_1 \end{bmatrix} (t) = \begin{bmatrix} \alpha_{11}(t) + cK & \alpha_{12}(t) \\ \alpha_{21}(t) & \alpha_{22} \end{bmatrix} \begin{bmatrix} \tilde{V}_1 \\ \tilde{n}_1 \end{bmatrix} (t), \end{aligned}$$

where

$$\begin{aligned}\alpha_{11} &= \frac{1}{\tau_V} \left(-1 + \left(V^* - \left(\frac{n^d}{n_B} \right)^M \right) h' (V^d) \right), \\ \alpha_{12} &= \frac{1}{\tau_V} \left(-M \left(\frac{n^d}{n_B} \right)^{M-1} \left(\frac{1}{n_B} \right) h (V^d) \right) \\ \alpha_{21} &= \frac{1}{\tau_n} \left(\frac{1}{b} \theta'_c (V^d - V_n) \right), \quad \alpha_{22} = -\frac{1}{\tau_n}.\end{aligned}$$

$\phi_1(s, t)$ is at least piecewise continuous in t (in fact, it is fully continuous in t), since the elements of $A(t)$ are continuous functions of the continuous functions $V^d(t)$ and $n^d(t)$. Additionally, $\phi_1(s, t)$ is Lipschitz in D because all the elements of $A(t)$ are bounded for all $t \geq t_0$. Each matrix element is bounded for bounded values of V^d and n^d , which are bounded by assumption.

Consider the function

$$W(s) = \frac{1}{2} \|s\|_2^2 = \frac{1}{2} \tilde{V}^2 + \frac{1}{2} \tilde{n}^2. \quad (8)$$

W as defined in Eq. (8) is continuously differentiable and PD by inspection. Applying the chain rule and substituting in the linearized two-variable Karma equations for a single-cell,

$$\dot{W} = \tilde{V} \dot{\tilde{V}} + \tilde{n} \dot{\tilde{n}} = (\alpha_{11} + cK) \tilde{V}^2 + (\alpha_{12} + \alpha_{21}) \tilde{V} \tilde{n} + \alpha_{22} \tilde{n}^2$$

is obtained. To satisfy the remainder of Theorem 1, it would be sufficient to find $k_2 > 0$ for which

$$\dot{W} = (\alpha_{11} + cK) \tilde{V}^2 + (\alpha_{12} + \alpha_{21}) \tilde{V} \tilde{n} + \alpha_{22} \tilde{n}^2 \leq -k_2 \|s\|_2^2.$$

Moving all terms to the left side of the inequality, and completing the square (which involves adding a net zero quantity to both sides) yields

$$\begin{aligned}\dot{W} + k_2 \|s\|_2^2 &= \left(\bar{\alpha}_{11} + cK \right) \tilde{V}^2 + \bar{\alpha}_{22} \left(\frac{(\alpha_{12} + \alpha_{21})}{2\bar{\alpha}_{22}} \tilde{V} + \tilde{n} \right)^2 \\ &\quad - \frac{(\alpha_{12} + \alpha_{21})^2}{4\bar{\alpha}_{22}} \tilde{V}^2 \leq 0,\end{aligned}$$

where $\bar{\alpha}_{11} = \alpha_{11} + k_2$ and $\bar{\alpha}_{22} = \alpha_{22} + k_2$. Suppose that $0 < k_2 < \frac{1}{\tau_n}$ ($\tau_n = 250$ in the default units).

Then, $\bar{\alpha}_{22} = -\frac{1}{\tau_n} + k_2 < 0$, which renders the second term, $\bar{\alpha}_{22} \left(\frac{(\alpha_{12} + \alpha_{21})}{2\bar{\alpha}_{22}} \tilde{V} + \tilde{n} \right)^2$, on the left side of the inequality nonpositive; hence,

$$\dot{W} + k_2 \|s\|_2^2 \leq \left(\bar{\alpha}_{11} + cK \right) \tilde{V}^2 - \frac{(\alpha_{12} + \alpha_{21})^2}{4\bar{\alpha}_{22}} \tilde{V}^2.$$

The quantity on the right side of the inequality is non-positive as long as

$$K \leq -\frac{1}{c} \left(\bar{\alpha}_{11}(t) - \frac{(\alpha_{12}(t) + \alpha_{21}(t))^2}{4\bar{\alpha}_{22}} \right),$$

for all $t \geq t_0$. The expression on the right side of the inequality is bounded, since the elements of $A(t)$ are bounded, and $\bar{\alpha}_{22} \neq 0$. For values of K sufficiently far to the left

(possibly negative) on the real axis, the conditions of Theorem 1 are satisfied for $k_1 = \frac{1}{2}$, $0 < k_2 < \frac{1}{\tau_n}$, and $q = 2$. Thus, the origin is exponentially stable for $\dot{\mathbf{s}} = \phi_1(\mathbf{s}, t) = A(t)\mathbf{s}$.

The first condition of Theorem 2 concerns the non-linear system $\dot{\mathbf{s}} = \phi(\mathbf{s}, t)$. Note that $\phi(\mathbf{s}, t)$ exists and is continuous, since V^d and n^d are continuous by assumption. Writing out the

Jacobian matrix, $J(\mathbf{s}, t) = \frac{\partial \phi}{\partial \mathbf{s}}$, reveals that its elements are continuous functions of $V^d - \tilde{V}$ and $n^d - \tilde{n}$. Hence, $\phi(\mathbf{s}, t)$ is continuously differentiable. The Jacobian is bounded for all $t \geq t_0$, since its elements are functions that are bounded for all bounded values of $V^d - \tilde{V}$ and $n^d - \tilde{n}$. V^d and n^d are bounded, for all time, by assumption, and $\tilde{V}$ and $\tilde{n}$ are bounded because $\mathbf{s} \in D$. For the product of the Jacobian and the state, $\zeta(\mathbf{s}, t) = J(\mathbf{s}, t)\mathbf{s}$, to be Lipschitz in D , with the same Lipschitz bound for all $t \geq t_0$, it is sufficient to establish that (1) ζ is continuous in

its arguments, (2) $\frac{\partial \zeta}{\partial \mathbf{s}}$ exists and is continuous, and (3) $\frac{\partial \zeta}{\partial \mathbf{s}}$ is bounded, for all $t \geq t_0$ and points in D . $\zeta(\mathbf{s}, t)$ is continuous since $J(\mathbf{s}, t)$ is continuous in its arguments. Assuming $M \geq 2$, and noting that the elements of the Jacobian are continuously differentiable functions of $V^d - \tilde{V}$

and $n^d - \tilde{n}$, the elements of $\frac{\partial \zeta}{\partial \mathbf{s}}$ exist and are continuous functions of $\mathbf{s}$ and t , defined for all

bounded values of $\mathbf{s}$ and all $t \geq t_0$. Finally, $\frac{\partial \zeta}{\partial \mathbf{s}}$ is bounded for all $t \geq t_0$, since its elements are functions that are bounded for all bounded values of $V^d - \tilde{V}$ and $n^d - \tilde{n}$. Therefore, the conditions of Theorem 2 are satisfied, which means that $\mathbf{s} = 0$ is an exponentially stable equilibrium point for the non-linear system $\dot{\mathbf{s}} = \phi(\mathbf{s}, t)$, because it is an exponentially stable equilibrium point for $\dot{\mathbf{s}} = A(t)\mathbf{s}$.

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FIGURE 1.

Sketch of an experimental configuration for a Purkinje fiber. A stimulating electrode is situated at the left end of the fiber ($x = 0$), and both pacing and control stimuli are assumed to be applied at this location. A number of sensing electrodes, which provide measurements of membrane potential, are embedded along the fiber. A typical fiber length is $L = 2$ cm.

FIGURE 2.

Minimum singular values of controllability Grammian (Case 1, crosses; Case 2, squares), for (a) a Grammian window = 22.5 ms, and (b) a Grammian window = 225 ms. Scaled versions of the selected V^d (dashed) and n^d (dash-dotted) curves are included for reference. The selected AP train, with BCL = 225 ms, exhibits alternans. Since there exists a window size for which the Grammian is non-singular for both Cases 1 and 2, the single-cell system is controllable for both cases.

FIGURE 3.

Current, APDs, and membrane potentials for open-loop (a, c, e) and SFI-controlled (b, d, f) cases of a 2.62-cm fiber paced at BCL = 225 ms. (a, b) currents i and i^d vs. time; (c, d) APDs of the first and last cells (1 and 100) vs. time; (e, f) membrane potential vs. distance and time. The dashed line in (c) and (d) is the desired APD. Spatially discordant alternans is evident in the open-loop responses (c and e). SFI control was able to reduce the alternans amplitude throughout the fiber in (d) and (f).

FIGURE 4.

MAEs for open-loop and closed-loop cases: (a) open-loop; (b) Pyragas control; (c) SFI control. The white dashed lines in (b) and (c) are a qualitative assessment of the conditions over which each controller was judged successful. Below these lines the controllers were able to suppress abnormal AP patterns over the entire length of the fiber, instead of just the proximal region. Above the black dash-dotted lines in (a) and (b), the fibers were considered to be predominately in 2:1 block. The majority of the region above the white dashed line in (c) is characterized by intermediate blocking patterns, with ratios between 2:1 and 1:1. The SFI controller was successful over a wider range of fiber length and BCL conditions, compared with the Pyragas controller.

TABLE 1
MAE, as defined in Eq. (5), for simulation tests of a 2.62-cm (100 cell) fiber, paced at BCL 5 225 ms

Strategy	List of non-zero gains	MAE (ms)
Open-Loop	None	24.05
Single-Sensor Feedback, 1 cell	$K_{p1} = -7$	14.86
SF, 40 cells	$K_{pm} = -0.02, m \in \{1, 2, \dots, 40\}$	11.71
SFI, 40 cells	$K_{pm} = -0.02, m \in \{1, 2, \dots, 40\}$, and $K_{i40} = -0.0004$	4.71
Output Feedback Integral, 3 cells	$K_{pm} = -0.25, m \in \{1, 20, 40\}$ and $K_{i40} = -0.0004$	4.98

The first column gives the name of the strategy and the number of cells from which feedback measurements were derived. The second column lists any non-zero proportional (K_p) and integral (K_i) gains, along with the cell indices (m values) associated with these gains. For the tests of the last two rows, there was an additional parameter, α , which was set to 0.999. In terms of MAE, all feedback strategies yielded an improvement upon the open-loop case. SFI control produced the lowest MAE of the tested strategies.