Cardiac Alternans Arising from an Unfolded Border-Collision Bifurcation

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Abstract

Following an electrical stimulus, the transmembrane voltage of cardiac tissue rises rapidly and remains at a constant value before returning to the resting value, a phenomenon known as an action potential. When the pacing rate of a periodic train of stimuli is increased above a critical value, the action potential undergoes a period-doubling bifurcation, where the resulting alternation of the action potential duration is known as alternans in the medical literature. Existing cardiac models treat alternans either as a smooth or as a border-collision bifurcation. However, recent experiments in paced cardiac tissue reveal that the bifurcation to alternans exhibits hybrid smooth/nonsmooth behaviors, which can be qualitatively described by a model of so-called unfolded border-collision bifurcation. In this paper, we obtain analytical solutions of the unfolded border-collision model and use it to explore the crossover between smooth and nonsmooth behaviors. Our analysis shows that the hybrid smooth/nonsmooth behavior is due to large variations in the system’s properties over a small interval of the bifurcation parameter, providing guidance for the development of future models.

1 Introduction

1.1 Background

Cardiovascular disease is the number one cause of death in the United States [1]. Over half of the mortality is due to sudden cardiac arrest that is often initiated by ventricular fibrillation, a fatal heart rhythm disorder. The induction and maintenance of ventricular fibrillation has been connected to the dynamics of local cardiac electrical properties [2, 3]. Therefore,

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studying cardiac dynamics is important for understanding life-threatening arrhythmias and developing therapies for preventing sudden cardiac death.

To develop an understanding of cardiac rhythm instability, we briefly review the electrophysiology of the heart. Cardiac cells respond to an electrical stimulus by eliciting an action potential \[4\], which consists of a rapid depolarization of the transmembrane voltage followed by a much slower repolarization process before returning to the resting value (Fig. 1). The time interval during which the voltage is elevated is called the action potential duration (APD). As shown in Fig. 1, the time between the end of an action potential to the beginning of the next one is called the diastolic interval (DI). The time interval between two consecutive stimuli is called the basic cycle length (BCL).

Figure 1: Schematic action potential showing the response of the transmembrane voltage to periodic electrical stimuli.

Under a periodic train of electrical stimuli, the steady-state response consists of phase-locked action potentials, where each stimulus gives rise to an identical action potential (1:1 pattern) when the pacing rate is slow. When the pacing rate becomes sufficiently fast, the 1:1 pattern may be replaced by a 2:2 pattern, so-called electrical alternans \[5, 6, 7\], where the APD alternates between short and long values. Using theory and experiments, a causal connection between alternans and the vulnerability to fatal cardiac arrhythmias such as ventricular fibrillation has been established by various authors \[2, 3, 5-13\]. Therefore, understanding mechanism of alternans is a crucial step in detection and prevention of fatal arrhythmias.

It has long been hypothesized \[8, 9, 10, 11, 12, 13\] that alternans is mediated by a classical period-doubling bifurcation, which can be described using a smooth iterated map, and which occurs when one eigenvalue of the Jacobian crosses the unit circle through \(-1\) \[14, 15\]. We restrict our attention to supercritical rather than subcritical bifurcations because the former are observed in most experiments and theoretical models exhibiting electrical alternans. Based on this hypothesis, various authors attempted to develop criteria for the onset of alternans \[8, 11, 10\] as well as algorithms to control alternans \[11, 12, 13\]. Recently, a few authors \[16, 17, 18, 19, 20\] proposed a different hypothesis: alternans may be mediated through a border-collision period-doubling bifurcation. Border-collision bifurcations occur in piecewise smooth maps \[21, 22\]. In contrast to classical period-doubling bifurcations, eigenvalues are not indicative of the onset of a border-collision period-doubling bifurcation.
Instead, a border-collision bifurcation occurs when a branch of fixed points collides with a border, i.e., a discontinuity surface in state space. Knowing the mechanism of alternans may help researchers to choose the proper types of functions to model this instability. More importantly, to develop model-based control methods requires knowledge of the underlying dynamics [17].

The aforementioned intrinsic differences between the two bifurcation types lead to differences in their bifurcation diagrams, as depicted in Fig. 2. Here, the two bifurcated branches of a smooth period-doubling bifurcation become tangent to each other at the bifurcation point, while the bifurcated branches of a border-collision bifurcation open at an angle. Thus, in principle the bifurcation diagrams should distinguish between the two bifurcation types. However, in practice, experiments can provide only a limited number of measurements (especially in biological systems), so the resulting bifurcation diagrams do not have sufficient resolution. This is illustrated in Fig. 2, where the discrete points representing experimental data along a bifurcation diagram do not readily reveal the true type of bifurcation. Therefore, there is a need for a more sensitive technique to differentiate between the two bifurcations.

Figure 2: Schematic bifurcation diagrams of period-doubling bifurcation: (a) a smooth type and (b) a border-collision type. Here, $B$ represents a bifurcation parameter and $A$ represents fixed-point solutions.

### 1.2 Prebifurcation Amplification

Based on prebifurcation amplification, our group has developed a robust technique to distinguish between smooth and border-collision bifurcations [27-30]. Here, we briefly review the results. It has been shown theoretically and experimentally that, near the onset of a smooth period-doubling bifurcation, subharmonic perturbations in a bifurcation parameter result in amplified disturbances in the response, a phenomenon known as prebifurcation amplification [23, 24, 25, 26]. In the following, we will show that, under variations in system parameters, prebifurcation amplification exhibits qualitatively different scaling laws in border-collision period-doubling and smooth period-doubling bifurcations. Thus, prebifurcation amplification is a useful technique to distinguish between the two possible types of period-doubling bifurcations.

To illustrate the concept of prebifurcation amplification, we consider a dynamical system described by the following map

$$x_{n+1} = f(x_n; B),$$

(1)
where $B$ represents a bifurcation parameter, e.g., the BCL in cardiac models. Both the function $f$ and state variable $x$ may be one- or multi-dimensional. Let us assume that, at a critical value $B = B_{\text{bif}}$, the system undergoes a period-doubling bifurcation that is either a smooth type for smooth $f$ \cite{14, 15} or a border-collision type for piecewise smooth $f$ \cite{21, 22}. We further assume that the stable period-one solution lies on the side $B > B_{\text{bif}}$, as indicated in Fig. 2.

When a subharmonic perturbation is applied to $B$ under conditions when $B > B_{\text{bif}}$, it renders map (1) as

$$x_{n+1} = f(x_n; B + (-1)^n \delta) \quad (2)$$

where $\delta$ is the amplitude of the perturbation. The perturbation may also be imposed in the form of $B - (-1)^n \delta$, which leads to a solution only different in phase from that of Eqn. (2). Since $B$ represents the pacing interval in cardiac models, such a variation in $B$ is referred to as alternate pacing. For $B$ greater than but close to $B_{\text{bif}}$ and small $\delta$, the steady-state response of Eqn. (2) consists of alternating recurrent states of $x_{\text{even}}$ and $x_{\text{odd}}$, which satisfy the following conditions

$$x_{\text{even}} = f(x_{\text{odd}}; B - \delta) \quad (3)$$

$$x_{\text{odd}} = f(x_{\text{even}}; B + \delta). \quad (4)$$

In cardiac models, one component of the vector $x$ is the APD, henceforth denoted by $A$. Alternate pacing of these models results in a long-short beat-to-beat variation in pacing intervals, which in turns cause alternation in $A$ even when $B > B_{\text{bif}}$. Since a period-doubling bifurcation is sensitive to subharmonic perturbations, perturbations in $B$ result in amplified disturbances in $A$. The effect of prebifurcation amplification can then be characterized by a gain defined as follows

$$\Gamma \equiv \frac{|A_{\text{even}} - A_{\text{odd}}|}{2\delta}. \quad (5)$$

### 1.2.1 Gain of Smooth Bifurcations

Several authors \cite{27, 23, 25, 26} have investigated the influence of parameters on prebifurcation amplification in smooth period-doubling bifurcations. In a previous paper \cite{28}, we explored the scaling laws between the amplification gain $\Gamma$ and the parameters $B$ and $\delta$, using a mapping model of arbitrary dimension. It was shown there that the gain of a smooth bifurcation satisfies the following relation,

$$c \delta^2 \Gamma^3 + (B - B_{\text{bif}}) \Gamma - |k| = 0, \quad (6)$$

where $c$ and $k$ are constants determined by the system’s properties at the bifurcation point. It was established that the gain is infinite if and only if $B = B_{\text{bif}}$ and $\delta = 0$. The rate of divergence as the parameters tend to $(B_{\text{bif}}, 0)$ depends on the path taken. For example, when $\delta$ is extremely small, the gain tends to infinity as $(B - B_{\text{bif}})^{-1}$; on the other hand, when $B = B_{\text{bif}}$, the gain tends to infinity as $\delta^{-2/3}$. 


In cardiac experiments, it is very difficult to accurately locate the bifurcation point. Moreover, the existence of noise and the limitation on the number of measurements restrict one from using very small perturbations. Instead, one can investigate the gains under two protocols: i) let $B$ approach $B_{\text{bif}}$ while retaining a finite and constant $\delta$; and ii) let $\delta$ approach zero while retaining a constant $B > B_{\text{bif}}$. As has been established in [28] that, under constant $\delta$, $\Gamma$ scales according to $(B - B_{\text{bif}})^{-1}$ except when $B - B_{\text{bif}}$ is sufficiently small, where the gain becomes saturated. Alternatively, under constant $B > B_{\text{bif}}$, $\Gamma$ scales to $\delta^{-2/3}$ except when $\delta$ is sufficiently small, where the gain becomes saturated. Figure 3 (a) and (b) schematically show the behaviors of $\Gamma$ vs. $B$ and $\Gamma$ vs. $\delta$, respectively.

1.2.2 Gain of Border-Collision Bifurcations

The system (1) possesses a border-collision bifurcation if the function $f$ is piecewise smooth as follows

$$f(x; B) = \begin{cases} f_1(x; B), & \text{if } h(x) < 0 \\ f_2(x; B), & \text{if } h(x) > 0 \end{cases},$$

where $h$ is a smooth scalar function and $h(x) = 0$ indicates a “border” in the state space, on which $f_1(x; B) = f_2(x; B)$. An approximate expression for the gain is derived in the Appendix using a one-dimensional map; results for general maps can be found in [29]. To lowest order, the gain is piecewise smooth as follows

$$\Gamma = \begin{cases} \Gamma_{\text{const}}, & \text{if } (B - B_{\text{bif}})/\delta > \rho_{\text{crit}} \\ \Gamma_{\text{const}} - \gamma \left(\frac{B - B_{\text{bif}}}{\delta} - \rho_{\text{crit}}\right), & \text{if } (B - B_{\text{bif}})/\delta < \rho_{\text{crit}} \end{cases},$$

where $\Gamma_{\text{const}}$, $\gamma$, and $\rho_{\text{crit}}$ are positive constants determined by system properties. Therefore, the gain is a constant along any straight line $(B - B_{\text{bif}})/\delta = \text{const}$. Since all these lines intersect at $(B_{\text{bif}}, 0)$, the gain at this point is not defined.

Again, we apply the two protocols described in the previous subsection. When $\delta$ is constant, the gain is constant when $B > B_{\text{crit}} = B_{\text{bif}} + \rho_{\text{crit}} \delta$ and varies linearly as $B$ when $B < B_{\text{crit}}$. Alternatively, when $B$ is constant, the gain is constant when $\delta < \delta_{\text{crit}} = (B - B_{\text{bif}})/\rho_{\text{crit}}$ and varies as $\delta^{-1}$ when $\delta > \delta_{\text{crit}}$. Schematic diagrams of these behaviors are shown in Figs. 3 (c) and (d).

It is evident from Fig. 3 that behaviors of the gain are qualitatively different for a smooth bifurcation and for a border-collision bifurcation. However, the differences between Figs. 3 (a) and (c) may be difficult to detect for discrete data or for data disturbed by noise. Conversely, differences in Figs. 3 (b) and (d) are apparent even for discrete data and in the presence of noise. Therefore, investigating the $\Gamma$ vs. $\delta$ under alternate pacing provides an unambiguous way to distinguish between the two bifurcations. Moreover, since this technique relies on the trend of the gain rather than the magnitude, it allows one to distinguish between smooth and nonsmooth behaviors in experiments without the need to accurately locate the bifurcation point [31].
Figure 3: Prebifurcation gain $\Gamma$ of a classical period-doubling bifurcation (a,b) and of a border-collision period-doubling bifurcation (c,d). In panels (a) and (c), $\delta$ stays constant; in panels (b) and (d), $B_{\text{bif}} < B$ stays constant. Comparison between panels (b) and (d) provides the most revealing difference between the two bifurcations.

1.3 Hybrid Behavior of the Prebifurcation Gain

To identify the bifurcation mechanism mediating cardiac alternans, we implemented the aforementioned technique in paced \textit{in vitro} bullfrog heart [30, 31], where the experiments reveal a novel phenomenon that cannot be explained by the above simple dichotomy of smooth/nonsmooth bifurcations. Specifically, our experiments show that very close to the bifurcation point, $\Gamma$ decreases with $\delta$, which agrees with the smooth bifurcation (Fig. 3b), whereas further away $\Gamma$ increases with $\delta$, which agrees with the border-collision bifurcation (Fig. 3d). A bifurcation that exhibits such a crossover between smooth and border-collision behaviors is named a hybrid period-doubling bifurcation [30, 31]. We further found that the essence of this hybrid behavior can be reproduced by a model of a so-called unfolded border-collision bifurcation. In the remainder of this paper, we will carry out a detailed analysis of the unfolded border-collision model. This analysis will help to understand the mathematical mechanism underlying the crossover between smooth and nonsmooth behaviors, providing guidance for the development of future models.

2 A Model of an Unfolded Border-Collision Bifurcation

We explore the mechanism of the aforementioned hybrid behavior using the unfolded border-collision model presented in [30, 31]. For illustration purpose, we first consider a piecewise smooth map

$$A_{n+1} = A_c + \alpha (D_n - D_{th}) + \beta |D_n - D_{th}|,$$

where $A_n$ and $D_n$ denote the $n$th action potential duration and diastolic interval, respectively. Note that $D_n = B - A_n$ as can be seen from Fig. [1]. Under the following conditions (cf.
\[ -1 < \alpha + \beta < 1 < \alpha - \beta \text{ and } -1 < \alpha^2 - \beta^2 < 1, \tag{10} \]

map (9) possesses a border-collision period-doubling bifurcation at
\[ B_c = A_c + D_{th}. \tag{11} \]

To remove the nonsmoothness of map (9), we “unfold” the singular term \( \beta |D_n - D_{th}| \) as follows
\[ A_{n+1} = A_c + \alpha (D_n - D_{th}) + \beta \sqrt{(D_n - D_{th})^2 + D_s^2}. \tag{12} \]

Map (12) represents a one-parameter family of maps that reduces to map (9) when \( D_s = 0 \). For any \( D_s \neq 0 \), the unfolded map (12) is smooth and exhibits what is technically a smooth period-doubling bifurcation. Nevertheless, the dynamics of map (9) and map (12) exhibit no significant differences except when \( B - B_c \) is less than or on the order of \( D_s \). It is worth noting that there are other ways to unfold the border-collision map (9). Here, we choose map (12) because of its simplicity and ease of analysis.

In the following, we show that map (12) has a smooth period-doubling bifurcation if \( D_s \neq 0 \). To this end, we denote the bifurcation point by \( A = A_{bif} = B_{bif} - D_{bif} \) and let the Jacobian of map (12) equal to \(-1\) at the bifurcation point; in symbols
\[ -\alpha - \frac{\beta (D_{bif} - D_{th})}{\sqrt{(D_{bif} - D_{th})^2 + D_s^2}} = -1. \tag{13} \]

It follows from Eqn. (13) that
\[ \beta (D_{bif} - D_{th}) = (1 - \alpha) \sqrt{(D_{bif} - D_{th})^2 + D_s^2}. \tag{14} \]

Since \( \beta < 0 \) as can be shown from the conditions in Eqn. (10), the term \( D_{bif} - D_{th} \) has an opposite sign as the term \( 1 - \alpha \); in symbols
\[ (D_{bif} - D_{th}) (1 - \alpha) < 0. \tag{15} \]

Evaluating \( D_{bif} \) from Eqn. (14) and considering the conditions (10) and (15) yields
\[ D_{bif} = D_{th} - \frac{(1 - \alpha) D_s}{\sqrt{\beta^2 - (1 - \alpha)^2}}. \tag{16} \]

Thus, APD at the bifurcation point can be written as
\[
\begin{align*}
A_{bif} &= A_c + \alpha (D_{bif} - D_{th}) + \beta \sqrt{(D_{bif} - D_{th})^2 + D_s^2}, \\
&= A_c + \alpha (D_{bif} - D_{th}) + \frac{\beta^2 (D_{bif} - D_{th})}{1 - \alpha}, \tag{17} \\
&= A_c - \frac{\alpha (1 - \alpha) + \beta^2}{\sqrt{\beta^2 - (1 - \alpha)^2}} D_s,
\end{align*}
\]
and the corresponding value of BCL is

$$B_{\text{bif}} \equiv A_{\text{bif}} + D_{\text{bif}} = A_c + D_{\text{th}} - \frac{(1 - \alpha^2 + \beta^2) D_s}{\sqrt{\beta^2 - (1 - \alpha)^2}}.$$  

(18)

Comparing $B_{\text{bif}}$ and $B_c$ reveals that the smooth period-doubling bifurcation in map (12) reduces to the border-collision period-doubling bifurcation in map (9) as $D_s \to 0$. Moreover, it can be shown from Eqn. (10) that $1 - \alpha^2 + \beta^2 > 0$ so that $B_{\text{bif}} < B_c$. Figure 4 demonstrates schematically the relation between a border-collision bifurcation and the unfolded bifurcation.

![Figure 4: Schematic diagram showing a border-collision bifurcation (solid) and the unfolded bifurcation (dashed).](image)

2.1 Analysis of the Response to Alternate Pacing

To study the prebifurcation amplification of map (12), we apply an alternating perturbation to the BCL's; in symbol, $B_n = B + (-1)^n \delta$, where $B$ is a baseline BCL and $\delta$ is a small but nonzero perturbation. Under this alternate pacing, it follows that $D_n = B + (-1)^n \delta - A_n$. Here, we require that $B > B_{\text{bif}}$ because prebifurcation dynamics is of interest. Denoting the steady-state APDs under alternate pacing by $A_{\text{even}}$ and $A_{\text{odd}}$, it follows from Eqn. (12) that

$$A_{\text{even}} = A_c + \alpha (D_{\text{odd}} - D_{\text{th}}) + \beta \sqrt{(D_{\text{odd}} - D_{\text{th}})^2 + D_s^2},$$  

(19)

$$A_{\text{odd}} = A_c + \alpha (D_{\text{even}} - D_{\text{th}}) + \beta \sqrt{(D_{\text{even}} - D_{\text{th}})^2 + D_s^2},$$  

(20)

where

$$D_{\text{odd}} = B - \delta - A_{\text{odd}},$$  

(21)

$$D_{\text{even}} = B + \delta - A_{\text{even}}.$$  

(22)
For later convenience, we let
\[ B = B_c + \Delta B = A_c + D_{th} + \Delta B \] (23)
and we define \( \Delta_{\text{even}} \) and \( \Delta_{\text{odd}} \) by
\[ A_{\text{even}} = \Delta_{\text{even}} + A_c \quad \text{and} \quad A_{\text{odd}} = \Delta_{\text{odd}} + A_c. \] (24)
Substituting the above equations into Eqns. (19) and (20) yields
\[ \Delta_{\text{even}} + \alpha (\Delta_{\text{odd}} + \delta - \Delta B) = \beta \sqrt{(\Delta_{\text{odd}} + \delta - \Delta B)^2 + D_s^2}, \] (25)
\[ \Delta_{\text{odd}} + \alpha (\Delta_{\text{even}} - \delta - \Delta B) = \beta \sqrt{(\Delta_{\text{even}} - \delta - \Delta B)^2 + D_s^2}. \] (26)
One can then show that
\[(1 - \alpha) (\Delta_{\text{even}} - \Delta_{\text{odd}}) + 2 \alpha \delta \delta (\Delta_{\text{even}} - \Delta_{\text{odd}}) - 2 \alpha \Delta B)\]
\[= \beta^2 (\Delta_{\text{odd}} - \Delta_{\text{even}} + 2 \delta) (\Delta_{\text{odd}} + \Delta_{\text{even}} - 2 \Delta B) \] (27)
Let
\[ \gamma = \frac{\Delta_{\text{even}} - \Delta_{\text{odd}}}{2 \delta}; \] (28)
i.e., \( \gamma \) is a gain-like quantity that can be either positive or negative (cf. 5). Substituting the definition of \( \gamma \) into Eqn. (27) yields
\[ 2 \delta ((1 - \alpha) \gamma + \alpha) ((1 + \alpha) (\Delta_{\text{even}} - \Delta_{\text{odd}}) - 2 \alpha \Delta B)\]
\[= 2 \delta \beta^2 (1 - \gamma) (\Delta_{\text{odd}} + \Delta_{\text{even}} - 2 \Delta B). \] (29)
Because we consider nonzero \( \delta \), Eqn. (29) can be reduced to
\[ \gamma (c_1 \Delta B + d_1 (\Delta_{\text{even}} + \Delta_{\text{odd}})) = c_2 \Delta B + d_2 (\Delta_{\text{even}} + \Delta_{\text{odd}}), \] (30)
where
\[ c_1 = -2 \left( \beta^2 + \alpha (1 - \alpha) \right), \] (31)
\[ d_1 = 1 - \alpha^2 + \beta^2, \] (32)
\[ c_2 = 2 \left( \alpha^2 - \beta^2 \right), \] (33)
\[ d_2 = -\left( \alpha (1 + \alpha) - \beta^2 \right). \] (34)
It then follows that
\[ \gamma = \frac{c_2 \Delta B + d_2 (\Delta_{\text{even}} + \Delta_{\text{odd}})}{c_1 \Delta B + d_1 (\Delta_{\text{even}} + \Delta_{\text{odd}})}. \] (35)
Since \( \Delta_{\text{even}} \) and \( \Delta_{\text{odd}} \) depend on \( \Delta B \) and \( \delta \), \( \gamma \) is a function of \( \Delta B \) and \( \delta \).
Recalling definition (5), we find the prebifurcation amplification gain as

\[
\Gamma = \left| \frac{c_2 \Delta B + d_2 (\Delta_{\text{even}} + \Delta_{\text{odd}})}{c_1 \Delta B + d_1 (\Delta_{\text{even}} + \Delta_{\text{odd}})} \right|. \tag{36}
\]

Particularly, when \(\Delta B = 0\), i.e. \(B = B_c = A_c + D_{\text{th}}\), the gain is

\[
\Gamma = \left| \frac{d_2}{d_1} \right| = \frac{\alpha + (\alpha^2 - \beta^2)}{1 - (\alpha^2 - \beta^2)}. \tag{37}
\]

Therefore, when \(B = B_c\), \(\Gamma\) is same for all \(\delta\). With some manipulation, one can show that \(\partial \Gamma / \partial B \neq 0\) at \(B = B_c\). Moreover, when \(B\) is sufficiently close to \(B_{\text{bif}} < B_c\) and \(\delta\) is fixed, \(\Gamma\) decreases as \(B\) increases as described in previous section and proven in [28]. Thus, for a given \(\delta\), \(\Gamma\) is a monotonically decreasing function of \(B\) and \(\Gamma\) becomes constant at \(B = B_c\). Because \(\Gamma\) is a monotonically decreasing function of \(\delta\) when \(B \gtrsim B_{\text{bif}}\), as shown in the previous section (see also [28]), it follows by continuity that \(\Gamma\) will increase as \(\delta\) increases in the region of \(B > B_c\). In other words, the map (12) exhibits smooth like behavior when \(B\) is sufficiently close to \(B_{\text{bif}}\) and border-collision like behavior when \(B > B_c\) (see the relation between \(B_{\text{bif}}\) and \(B_c\) in Fig. 4).

### 2.2 Numerical Example

Before comparing the proposed model to experimental data, we review the class of models that are most commonly used in the cardiac research community. These models relate APD and DI through exponential functions. Typically, parameters of a model are obtained by fitting the model to the so-called dynamic restitution curve, which is a plot of the steady-state APD vs. DI. For example, in their pioneering work, Guevara et al. [32] proposed a model of cardiac dynamics as

\[
A_{n+1} = 201 - 98 e^{-D_n/43} - 35 e^{-D_n/653}, \tag{38}
\]

where all variables and parameters have the unit of millisecond. Parameters of map (38) were obtained by fitting the dynamic restitution curve measured in experiments performed on quiescent aggregates of ventricular cells from 7-day-old embryonic chick hearts [32]. Although the model of Guevara et al. fits the dynamic restitution curve reasonably well (Fig. 5, top panel), it does not accurately describe the response beyond the bifurcation to alternans, as is evident from the bifurcation diagram of steady-state APD vs. BCL (Fig. 5, bottom panel).

A careful examination reveals that the dynamic restitution curve is well approximated by two distinct parts with significantly different slopes. The transition between the two slopes occurs with a small interval near \(D_1 \approx 60\) ms, which is also approximately where the transition to alternans occurs. Now, we recall that the unfolded border-collision model (12), with properly chosen parameters, describes such rapid changes between two distinct slopes. Fitting map (12) to the experimental dynamic restitution data, we obtain a set of parameters

\[
\alpha = 0.69, \quad \beta = -0.64, \quad A_c = 161\, \text{ms}, \quad D_{\text{th}} = 62\, \text{ms}, \quad \text{and} \quad D_s = 15\, \text{ms}. \tag{39}
\]
As shown in Fig. 5, the unfolded border-collision map (12) with these parameters faithfully reproduces the bifurcation diagram, including the alternans branches. As demonstrated in Fig. 4, the bifurcation diagram of a border-collision map is close to that of its unfolded counterpart except near the bifurcation point. Thus, one expects a reasonable fit to the experimental data in Fig. 5 using a pure border-collision map, i.e., letting \( D_s = 0 \). However, as has been established in the previous section, the nonsmooth map can not capture hybrid behaviors in the prebifurcation gain. Here, for clarity, the bifurcation diagram of the corresponding border-collision model is not shown in Fig. 5.

Figure 5: Comparison between the model of Guevara et al. (solid) and the unfolded border-collision model (dashed) in fitting the experimental data in [32] (points). Although both models fit the dynamic restitution curve well (top panel), the unfolded border-collision model fits alternans data much better (bottom panel).

We then simulate map (12) with alternate pacing. Figure 6 shows \( \Gamma \) vs. \( B \) for different values of \( \delta \). These curves cross one another at \( B = B_c = 223 \) ms. Note that a period-doubling bifurcation occurs at \( B = 198 \) ms. It is clear that \( \Gamma \) vs. \( \delta \) displays a trend consistent with a smooth bifurcation (cf. Fig. 3 (b)) when \( B < B_c \) and, on the other hand, \( \Gamma \) vs. \( \delta \) shows a trend consistent with a border-collision bifurcation when \( B > B_c \) (cf. Fig. 3 (d)). Since Guevara et al. did not perform alternate pacing experiments, no data are available for comparison. However, we note that the simulation here is in qualitative agreement with our previous experiments on bullfrog ventricles [30, 31].
3 Discussion and Conclusion

Theoretical analysis of the prebifurcation amplification reveals that different scaling laws are associated with smooth and border-collision period-doubling bifurcations. The differences appear in the following three aspects. First, the gain of a smooth bifurcation tends to infinity as \((B, \delta)\) approaches \((B_{bif}, 0)\); conversely, the gain of a border-collision bifurcation is finite everywhere but not defined at \((B_{bif}, 0)\). Second, the gain of a smooth bifurcation varies smoothly under changes in system parameters while that of a border-collision bifurcation undergoes a nonsmooth variation as parameters cross a boundary in the parameter space (see Figs. 3 (a,b) and 3 (c,d)). Third, under constant \(B\) and increasing \(\delta\), the gain of a smooth bifurcation decreases while that of a border-collision bifurcation increases. Thus, the gain versus perturbation size relation provides a more sensitive criterion to differentiate between the two bifurcation types. As can be seen from Fig. 3 (b) and (d), even with few data points, the \(\Gamma\) vs. \(\delta\) relation clearly reveals the underlying bifurcation mechanism. On the other hand, the bifurcation diagram does not allow one to distinguish between the two bifurcations with only a few data points nor does the \(\Gamma\) vs. \(B\) relation.

Although the technique described here was developed with a goal of identifying the type of bifurcation mediating alternans, the analysis is based on general iterated maps. Thus, the results are independent of any physical details of cardiac dynamics and can be readily applied to any dynamical systems.

The analysis based on simple dichotomy of smooth/border-collision bifurcation has limitations. Since it is assumed that a system either has well behaved derivatives or is discontinuous in first derivatives, the result is not directly applicable to the intermediate case, i.e., a system whose first derivatives are continuous but change rapidly. The model of unfolded border-collision bifurcation studied here serves to address the latter case.

Previous experimental findings [30, 31] suggest that modeling of cardiac dynamics should consider the rapid changes in the system’s properties, i.e., large variations over a narrow parameter interval. As one example, we study here the smoothed version of a border-collision model. We show that the smoothed map indeed unfolds the original border-collision period-doubling bifurcation to a smooth one. In addition, we carry out the analysis of the
unfolded map under alternate pacing. The result indicates that the unfolded border-collision model exhibits hybrid smooth/nonsmooth behaviors, which is in qualitative agreement with previous experimental observations on bullfrog hearts [30, 31]. We further illustrate that the unfolded border-collision model can more accurately describe alternans observed in an experiment on embryonic chick hearts [32]. The fact that hybrid behaviors are observed in different species indicates that this phenomenon may be prevalent in cardiac dynamics. It is worth noting that, besides the model studied here, the crossover between smooth and nonsmooth behaviors can also be captured by other types of maps. We choose the current model solely based on its simplicity and ease of analysis.

We note that many other physical systems also possess rapid changes in systems’ properties. To fully describe such rapid changes, one would need to use functions with highly localized properties. For convenience of analysis, these highly localized functions are often replaced by piecewise smooth functions, where each piece adopts a much simpler form. Perhaps, the simplest example is a bouncing ball, whose velocity changes rapidly before and after impacts and is often modeled by an instantaneous jump using the coefficient of restitution (see other examples in a recent special issue of the journal Nonlinear Dynamics on discontinuous dynamical systems [33]). Although this approach has proven to be useful in many problems in engineering and science, it brings up a more subtle question on the relation between the piecewise smooth bifurcation problem and the original smooth bifurcation problem. In [34], Dankowicz purposefully coarsened a smooth vector field with a piecewise smooth one and compared their bifurcation diagrams. The full potential and limitations of the idea of intentional nonsmoothing of a smooth function need to be explored in future research.

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Appendix: Alternate Pacing of a Border-Collision Map

In a previous paper [29], we have shown the general results of prebifurcation amplification for border-collision bifurcations using high-dimensional maps. Here, we briefly review the results using a one-dimensional map for simplicity. Consider a one-dimensional piecewise continuous map of $A$ with a bifurcation parameter $B$ as follows

$$A_{n+1} = \begin{cases} f_1 (A_n; B) , & \text{if } A_n > A_{\text{bif}} \\ f_2 (A_n; B) , & \text{if } A < A_{\text{bif}} \end{cases}$$

where $f_1 (A; B) = f_2 (A; B)$ when $A = A_{\text{bif}}$. Assume a border-collision bifurcation occurs at $B = B_{\text{bif}}$ and $A = A_{\text{bif}}$, as indicated in Fig. 2(b). Then the following conditions are satisfied
at the bifurcation point
\[
\partial_A f_2 < -1 < \partial_A f_1 < 1, \quad (41)
\]
\[
0 < \partial_B f_1 = \partial_B f_2 \equiv \partial_B f, \quad (42)
\]
where all derivatives are evaluated at the bifurcation point \((A_{\text{bif}}; B_{\text{bif}})\). For conditions on border-collision period-doubling bifurcations in multi-dimensional maps, see [21, 29]. Alternate pacing changes the map (40) to
\[
A_{n+1} = \begin{cases} 
  f_1 (A_n; B + (-1)^n \delta), & \text{if } A_n > A_{\text{bif}} \\
  f_2 (A_n; B + (-1)^n \delta), & \text{if } A_n < A_{\text{bif}}
\end{cases} \quad (43)
\]
Due to the alternating perturbation, the steady state of Eqn. (43) is a period-two solution, whose two branches can be written as
\[
A_n = \begin{cases} 
  A_{\text{odd}} (B, \delta), & \text{for odd } n \\
  A_{\text{even}} (B, \delta), & \text{for even } n
\end{cases}. \quad (44)
\]
Particularly,
\[
A_{\text{odd}} (B_{\text{bif}}, 0) = A_{\text{even}} (B_{\text{bif}}, 0) = A_{\text{bif}}. \quad (45)
\]
This solution consists of two different types: 1) in a unilateral solution, both branches are above the border, i.e., \(A_{\text{even}} > A_{\text{bif}}\) and \(A_{\text{odd}} > A_{\text{bif}}\); 2) in a bilateral solution, one branch is above and the other branch below the border, i.e., \((A_{\text{even}} - A_{\text{bif}}) \times (A_{\text{odd}} - A_{\text{bif}}) < 0\). In the following, we restrict attention to \(B \geq B_{\text{bif}}\) (prebifurcation condition) and deal with the two types of solutions, respectively.

**Unilateral Solution**

Because \(A_{\text{even}} > A_{\text{bif}}\) and \(A_{\text{odd}} > A_{\text{bif}}\), it follows from Eqn. (43) that
\[
A_{\text{even}} = f_1 (A_{\text{odd}}; B - \delta), \quad (46)
\]
\[
A_{\text{odd}} = f_1 (A_{\text{even}}; B + \delta). \quad (47)
\]
To leading order, the solution of Eqs. (46) and (47) is
\[
A_{\text{even}} = A_{\text{bif}} + \frac{\partial_B f}{1 - \partial_A f_1} (B - B_{\text{bif}}) - \frac{\partial_B f}{1 + \partial_A f_1} \delta, \quad (48)
\]
\[
A_{\text{odd}} = A_{\text{bif}} + \frac{\partial_B f}{1 - \partial_A f_1} (B - B_{\text{bif}}) + \frac{\partial_B f}{1 + \partial_A f_1} \delta. \quad (49)
\]
Recalling the conditions in Eqs. (41) and (42), it follows that \(A_{\text{odd}} > A_{\text{even}}\). Moreover, it follows from Eqn. (48) that the unilateral solution is valid as long as
\[
B - B_{\text{bif}} > \rho_{\text{crit}} \delta, \quad (50)
\]
where
\[
\rho_{\text{crit}} = \frac{1 - \partial_A f_1}{1 + \partial_A f_1} > 0. \quad (51)
\]
Bilateral Solution

The bilateral solution occurs in the region $B - B_{\text{bif}} < \rho_{\text{crit}} \delta$. By continuity, the solution in this region satisfies $A_{\text{odd}} > A_{\text{bif}} > A_{\text{even}}$. It follows from Eqn. (43) that

$$A_{\text{even}} = f_1(A_{\text{odd}}; B - \delta),$$  \hfill (52) \\
$$A_{\text{odd}} = f_2(A_{\text{even}}; B + \delta).$$  \hfill (53)

Linearizing Eqns. (52) and (53) around $A = A_{\text{bif}}$ and $B = B_{\text{bif}}$ yields

$$A_{\text{even}} = A_{\text{bif}} + \partial A f_1 (A_{\text{odd}} - A_{\text{bif}}) + \partial_B f (B - B_{\text{bif}} - \delta),$$  \hfill (54) \\
$$A_{\text{odd}} = A_{\text{bif}} + \partial A f_2 (A_{\text{even}} - A_{\text{bif}}) + \partial_B f (B - B_{\text{bif}} + \delta),$$  \hfill (55)

where the derivatives are evaluated at $(A_{\text{bif}}; B_{\text{bif}})$. Solving the above equations yields the leading-order solution for $A_{\text{even}}$ and $A_{\text{odd}}$ as

$$A_{\text{even}} = A_{\text{bif}} + \frac{1 + \partial A f_1 (B - B_{\text{bif}}) - (1 - \partial_A f_1) \delta}{1 - \partial_A f_2 \partial A f_1} \partial_B f,$$  \hfill (56) \\
$$A_{\text{odd}} = A_{\text{bif}} + \frac{1 + \partial_A f_2 (B - B_{\text{bif}}) + (1 - \partial_A f_2) \delta}{1 - \partial_A f_2 \partial A f_1} \partial_B f.$$  \hfill (57)

Prebifurcation Gain

When $B - B_{\text{bif}} > \rho_{\text{crit}} \delta$, it follows from Eqs. (48) and (49) that the gain is

$$\Gamma = \frac{A_{\text{odd}} - A_{\text{even}}}{2 \delta} = \frac{\partial_B f}{1 + \partial_A f_1} \equiv \Gamma_{\text{const}},$$  \hfill (58)

When $B - B_{\text{bif}} < \rho_{\text{crit}} \delta$, it follows from Eqs. (56) and (57) that the gain is

$$\Gamma = \frac{A_{\text{odd}} - A_{\text{even}}}{2 \delta} = \Gamma_{\text{const}} - \gamma \left( \frac{B - B_{\text{bif}}}{\delta} - \rho_{\text{crit}} \right),$$  \hfill (59)

where

$$\gamma = \frac{\partial_A f_1 - \partial_A f_2}{2 (1 - \partial_A f_2 \partial A f_1)} \partial_B f > 0.$$  \hfill (60)

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