

Period-Doubling Bifurcation to Alternans in Paced Cardiac Tissue: Crossover from Smooth to Border-Collision Characteristics

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We investigate, both experimentally and theoretically, the period-doubling bifurcation to alternans in heart tissue. Previously, this phenomenon has been modeled with either smooth or border-collision dynamics. Using a modification of existing experimental techniques, we find a hybrid behavior: Very close to the bifurcation point, the dynamics is smooth, whereas further away it is border-collision-like. The essence of this behavior is captured by a model that exhibits what we call an unfolded border-collision bifurcation. This new model elucidates that, in an experiment, where only a limited number of data points can be measured, the smooth behavior of the bifurcation can easily be missed.

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Many nonlinear systems display a bifurcation, where the system's response changes qualitatively as an adjustable parameter is varied [1]. Nonlinear systems described by smooth differential equations or maps have been thoroughly investigated for many years. More recently, bifurcations occurring in *piecewise* smooth systems, such as a border-collision bifurcation, have come under investigation. Border-collision bifurcations, which display richer behaviors than smooth bifurcations [2], occur in a variety of systems, such as mechanical and electrical devices that involve sudden switching of a component.

The primary purpose of this Letter is to describe experimental observations and a theoretical model of the bifurcation to alternans (defined below) in paced bullfrog cardiac tissue. This bifurcation is important because it can initiate ventricular fibrillation [3–5], which often underlies sudden cardiac death, one of the leading causes of death in the United States [6]. Previous research has modeled the bifurcation as either the smooth or the border-collision type to describe the bifurcation to alternans. We find that neither model is adequate. Specifically, in investigating the system's sensitivity to perturbations, we find smoothlike behavior near the bifurcation point, while further away the behavior is border-collision-like. This apparently contradictory behavior can be understood qualitatively using a 1D mapping model that exhibits what we call an unfolded border-collision bifurcation.

Before describing our findings, we review the behavior of paced cardiac tissue. An applied electrical stimulus induces an action potential, which is the characteristic time course of the transmembrane voltage. In experiments, the dynamical state of the tissue is often described by measuring the action potential duration (APD). The pacing interval between stimuli, known as the basic cycle length (B), is the bifurcation parameter. If, under such periodic pacing, M stimuli elicit N unique action potentials, we

refer to the behavior as $M:N$ behavior. A transition from one response pattern to another under changes in B are mediated by bifurcation [1], and the bifurcation point is denoted by B_{bif} . For slow pacing, 1:1 behavior is observed, where each action potential duration is identical. As B is shortened, a bifurcation occurs, which can give rise to either a 2:2 or a 2:1 response [7]. The 2:2 behavior, where APD alternates in a long-short pattern, is called *alternans*. In their pioneering work, Nolasco and Dahlen [8] modeled the transition to alternans as a supercritical period-doubling bifurcation of a smooth mapping. More recently, Sun *et al.* [9] introduced a piecewise smooth mapping model for a cardiac conduction system that exhibits a border-collision period-doubling bifurcation [10,11]. Although they studied conduction times through the atrio-ventricular node to the bundle of His, their result implies that the bifurcation to alternans in paced cardiac tissue might be of the border-collision type.

In principle, smooth and border-collision period-doubling bifurcations can be distinguished based on their bifurcation diagrams, where the steady-state values of APD are plotted as a function of B . For a smooth period-doubling bifurcation, the two bifurcating curves meet at the bifurcation point to form a single smooth curve, as shown in Fig. 1(a). By contrast, for a border-collision bifurcation, the two branches generally meet at a sharp angle, as shown in Fig. 1(b). However, in experiments with cardiac tissue, it is difficult to obtain sufficient resolution in the bifurcation diagram to distinguish between these behaviors. For example, Figs. 1(a) and 1(b) show that the same set of discrete data (dots) is consistent with either type of model (lines). Attempts to gather more data close to the bifurcation are limited by the fact that the position of the bifurcation point is not known ahead of time. In addition, the response of excised cardiac tissue changes gradually over time, moving the bifurcation point.

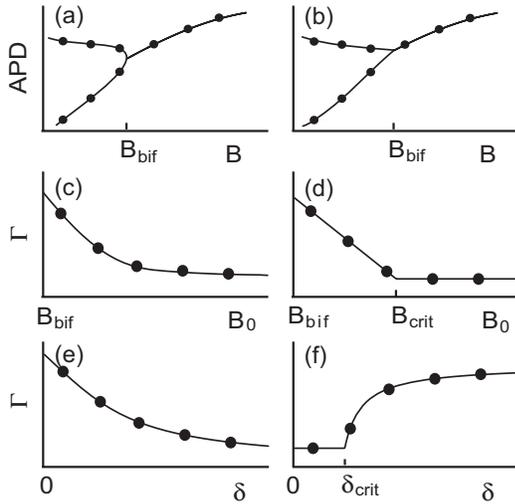


FIG. 1. Schematic bifurcation diagrams with discrete sampling. The sampled points (solid dots) are identical for the (a) smooth and (b) border-collision bifurcations. (c–f) Alternate pacing: The trend in Γ vs B is illustrated for (c) smooth and (d) border-collision bifurcations, and the trend in Γ vs δ is illustrated for (e) smooth and (f) border-collision bifurcations.

A more robust method of determining the type of the bifurcation is the alternate-pacing technique that was originally introduced by Heldstab *et al.* [12]. In the context of cardiac tissue, alternate pacing means perturbing the nominal pacing interval B_0 so that, for the n th stimulus,

$$B_n = B_0 + (-1)^n \delta, \quad (1)$$

where δ specifies the perturbation amplitude. As a result of such pacing, APD alternates in a long-short pattern, and we denote the corresponding steady-state values by APD_{long} and $\text{APD}_{\text{short}}$. To quantify the system's sensitivity to perturbations, we define a gain as

$$\Gamma = \frac{\text{APD}_{\text{long}} - \text{APD}_{\text{short}}}{2\delta}. \quad (2)$$

We emphasize that B_0 is in the 1:1 regime. It has been suggested that this protocol can determine the presence of alternans before its actual occurrence (cf. [13]).

In our previous work [14,15], we showed that studying Γ as a function of δ for fixed B_0 (close to the bifurcation point), rather than as a function of B_0 for a fixed (small) δ , permits a clearer distinction between a smooth and a border-collision bifurcation. The results of those papers are illustrated in Figs. 1(c)–1(f). Figures 1(c) and 1(d) show that the qualitative dependence of Γ on B_0 is similar for a smooth and border-collision bifurcation, especially when observed through discrete data points. In contrast, Figs. 1(e) and 1(f) show that the dependence of Γ on δ is very different for the two bifurcation types: In the case of the smooth bifurcation, Γ increase as δ decreases, and the opposite occurs in the case of a border-collision bifurcation. In particular, for a border-collision bifurcation and

finite $B_0 - B_{\text{bif}}$, perturbations are amplified only when δ is large enough to push the system over the border. However, because of the uniqueness in trends between a smooth model and a border-collision model, we are able to demonstrate that both models are inadequate for the case when both types of trends in Γ vs δ are present.

To understand how the trend in Γ vs δ is exhibited generically, consider the border-collision case shown in Fig. 1(b). Here APD is a piecewise smooth function of B , and, therefore, the derivative of the mapping has a discontinuity located at B_{bif} . Therefore, when δ is sufficiently large relative to $B_0 - B_{\text{bif}}$, the long and short responses due to alternate pacing lie on opposite sides of the surface across which the underlying mapping is nonsmooth; as a result, Γ exhibits a discontinuity in its derivative located at B_{crit} [Fig. 1(d)] and δ_{crit} [Fig. 1(f)]. On the other hand, since the mapping is continuous for the smooth supercritical period-doubling bifurcation case illustrated in Fig. 1(a), no critical values exist as Γ varies with respect to B_0 [Fig. 1(c)] and δ [Fig. 1(e)].

To investigate the bifurcation type experimentally, we perform the alternate-pacing protocol in 6 frog preparations. In these experiments, the heart is excised from an adult bullfrog (*Rana catesbeiana*) of either sex. After the pacemaker cells are cut away, the top half of the ventricle is removed and placed in a chamber that is superfused with a room-temperature, recirculated physiological solution [7]. A bipolar extracellular electrode applies 2-ms-long rectangular current pulses to the epicardial surface of the tissue [16]. The current, whose typical amplitude is twice the value needed to elicit a response for slow pacing, initiates a propagating wave of excitation. Transmembrane voltage is measured with a glass microelectrode filled with KCl conducting fluid. Before collecting any data, the tissue is paced at $B_0 = 1000$ ms for about 30 minutes. We collect data at a sampling rate of 4 kHz. The data are then processed using a custom-written MATLAB code [17].

We implement the alternate-pacing protocol experimentally by carrying out the following steps: (i) We pace at B_0 for two minutes, during which we record the transient behavior of the APDs as they reach a steady state of either a 1:1 or a 2:2 rhythm; (ii) we perturb B_0 for 20 seconds at one value of δ and record the subsequent APDs; (iii) we repeat step (ii) three more times, each time with a new value of δ (for the majority of trials, δ sweeps from high to low, to include 20, 15, 10, and 5 ms; in one trial, we reverse the order); and (iv) the perturbations are turned off and pacing at B_0 is resumed for 20 seconds to confirm that the steady-state value of the APD does not drift. Steps (i)–(iv) are repeated for decreasing values of B_0 until persistent alternans over several B_0 's ensue or the tissue fails to respond to every applied stimuli. Twelve out of 51 trials exhibited a transition to alternans. Typically, B_0 is decreased in steps of 25 ms, which means that the last B_0 with a 1:1 response is within 25 ms of B_{bif} .

To analyze the results, we view the trend in Γ vs δ at each B_0 and determine the statistical significance of the

trend [17]. In six trials from four frogs, we find that Γ shows an *increasing* trend as δ decreases for B_0 closest to B_{bif} ; a typical example is shown in Fig. 2(a), which agrees with a smooth bifurcation [recall Fig. 1(e)]. However, three other trials from two frogs demonstrate a *decreasing* trend in Γ as δ decreases; a typical example is shown in Fig. 2(b), which agrees with a border-collision bifurcation [recall Fig. 1(f)]. In two other trials from two frogs, there are no significant variations in Γ for different δ 's, and, therefore, these trials cannot be classified into either category. These results call into question the assumption that the transition is either a smooth or a border-collision bifurcation; rather, it appears that both behaviors are present to some degree, and, therefore, the model describing the transition to alternans must include features of both types of behavior.

The remaining experimental trial provides the most compelling evidence for the coexistence of both types of behaviors. Specifically, we see a smooth behavior when $B_0 - B_{\text{bif}} \leq 25$ ms, but a border-collision behavior when $25 \text{ ms} \leq B_0 - B_{\text{bif}}$, as shown in Figs. 3(c) and 3(d), respectively. Figure 3(b) is a plot of steady-state APD vs the diastolic interval D , where $D = B_0 - \text{APD}$; the significance of Fig. 3(b) will be discussed in the limitations paragraph. Figure 3(a) shows Γ vs B_0 for different values of δ , where it is seen that these curves cross one another. This crossing is not consistent with either a smooth or border-collision period-doubling bifurcation. The presence of such a crossing is one of our most revealing experimental results.

Our experimental observations can be explained with a 1D mathematical model of the form

$$\text{APD}_{n+1} = f(D_n), \quad (3)$$

where n is the beat number. First, suppose that f is a piecewise linear function of the form

$$\text{APD}_{n+1} = A_0 + \alpha(D_n - D_{\text{th}}) + \beta|(D_n - D_{\text{th}})|, \quad (4)$$

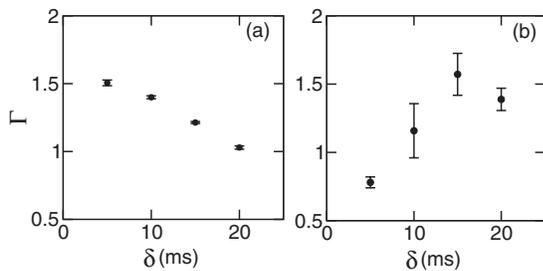


FIG. 2. Trials displaying two different trends in Γ vs δ as revealed by alternate pacing for two different frogs. The trend is consistent with (a) a smooth period-doubling bifurcation ($B_0 = 300$ ms, alternans observed at $B_0 = 275$ ms so that $275 \text{ ms} < B_{\text{bif}} < 300$ ms) and (b) a border-collision bifurcation ($B_0 = 700$ ms, alternans observed at $B_0 = 675$ ms so that $675 \text{ ms} < B_{\text{bif}} < 700$ ms). The error bars represent the statistical and systematic error in measuring APD; their variation is dominated by systematic errors.

where A_0 , D_{th} , α , and β are constants. The derivative of f is discontinuous when $D_n = D_{\text{th}}$, where $\text{APD}_n = A_0$. This map exhibits a border-collision period-doubling bifurcation under the condition $-1 < \alpha + \beta < 1 < \alpha - \beta$ and $-1 < \alpha^2 - \beta^2 < 1$. Now let us replace $|(D_n - D_{\text{th}})|$ in map (4) with $\sqrt{(D_n - D_{\text{th}})^2 + D_s^2}$, where D_s is a small parameter, so that

$$\text{APD}_{n+1} = A_0 + \alpha(D_n - D_{\text{th}}) + \beta\sqrt{(D_n - D_{\text{th}})^2 + D_s^2}. \quad (5)$$

We refer to map (5) as an *unfolding* [18] of map (4), which reduces to map (4) when $D_s = 0$. For any $D_s \neq 0$, the unfolded map (5) is smooth and exhibits what is technically a smooth period-doubling bifurcation. Nevertheless, the dynamics of maps (4) and (5) exhibit no significant differences except when $B - B_{\text{bif}}$ is less than or on the order of D_s .

We simulate the alternate-pacing protocol with map (5) using the parameters $\alpha = 0.79$, $\beta = -0.69$, $A_0 = 621$ ms, $D_{\text{th}} = 164$ ms, and $D_s = 10$ ms. The parameter D_s sets the scale for the size of the window of smoothlike behavior in the unfolded border-collision model. Figure 4(a) shows Γ vs B_0 for different values of δ . These curves cross one another in the region $775 \text{ ms} < B_0 < 800$ ms as shown in Fig. 4(a), similar to our experimental results shown in Fig. 3(a). In Fig. 4(c), Γ vs δ for $B_0 = 775$ ms displays a trend consistent with a smooth bifurcation [comparable to Fig. 3(c)]. On the other hand, in Fig. 4(d), Γ vs δ for $B_0 = 800$ ms shows a trend consistent with a border-collision bifurcation, also comparable to our experimental results shown in Fig. 3(d). To summarize, the

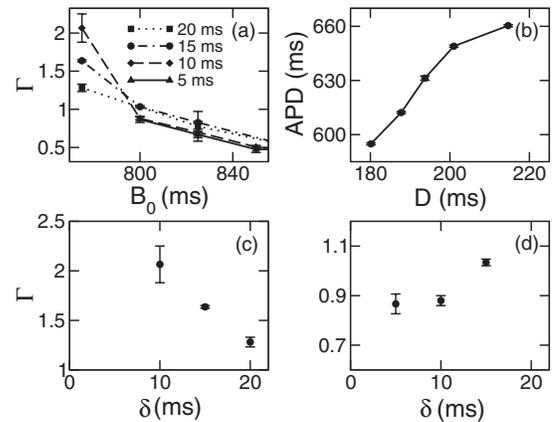


FIG. 3. Experimental evidence consistent with both a smooth and a border-collision bifurcation in a single trial. (a) The trend in Γ vs B_0 for four different values of δ (legend). We observe alternans at $B_0 = 750$ ms so that $750 \text{ ms} < B_{\text{bif}} < 775$ ms. (b) The corresponding dynamic restitution curve (see text for details). Some of the data from this trial are replotted in (c) and (d) as Γ vs δ for $B_0 = 775$ ms and $B_0 = 800$ ms, respectively. The behavior in (c) for $B_0 = 775$ ms is consistent with a smooth bifurcation and in (d) for $B_0 = 800$ ms is consistent with a border-collision bifurcation.

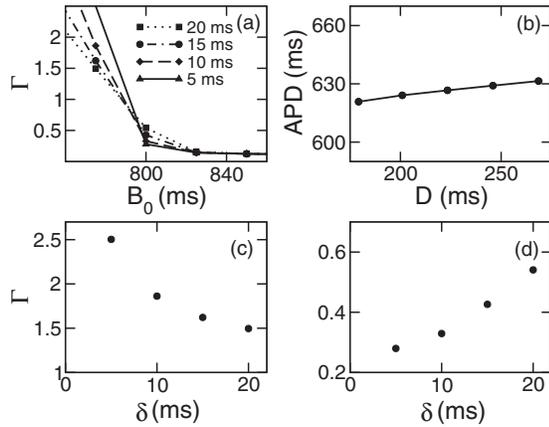


FIG. 4. Theoretically predicted behavior of the unfolded border-collision bifurcation [map (5)]. (a) The trend in Γ vs B_0 for four different values of δ (legend). Alternans occurs at $B_{\text{bif}} = 750$ ms. Some of the data from this simulation are replotted in (c) and (d) as Γ vs δ for $B_0 = 775$ ms and $B_0 = 800$ ms, respectively. The trend in Γ vs δ is consistent with a smooth bifurcation in (c) and a border-collision bifurcation in (d). (b) shows the dynamic restitution curve as an illustration of the steady-state behavior for the range of B_0 's in (a).

period-doubling bifurcation of map (5) is smooth, but the effects of this smoothness can be seen only in a narrow range of B_0 , when $B_0 - B_{\text{bif}}$ is on the order of D_s , exactly the behavior observed experimentally. Furthermore, in different experimental trials, the precise location of B_{bif} varies so that smooth behavior is not always easy to capture. Thus, our experimental results presented in Fig. 2 are elucidated.

Since the unfolded border-collision bifurcation model fits the data obtained through alternate pacing, this indicated that existing ionic models may need to be adjusted to include elements of nonsmooth behavior. Modifications to models may involve tracking a mechanism that becomes activated when a threshold in state space is crossed. For example, a piecewise smooth model [19], which was used recently to capture calcium cycling dynamics, could contribute to the mechanism that gives rise to the hybrid behavior.

We note that map (5) faces some limitations. For example, it is known that the dynamic restitution behavior of cardiac tissue (how steady-state values of APD depend on D) cannot be adequately described by a simple 1D map [20]. Not surprisingly, although map (5) fits the gain under alternate pacing rather well, it cannot capture all of the restitution phenomena. For example, comparing Fig. 3(b) to Fig. 4(b), we see that the agreement between the two dynamic restitution curves is poor. Nevertheless, map (5) suggests that existing models should be modified to include nonsmooth features.

Finally, our results suggest that the proposed clinical use of alternate pacing [13] may not be successful. In applying alternate pacing to a map that exhibits a smooth bifurca-

tion, one expects large Γ for $B_0 \gg B_{\text{bif}}$. As a result, in the clinic, the propensity for alternans could be revealed using pacing rates that are slow enough to avoid inducing a life-threatening arrhythmia. However, we find that Γ remains small until the pacing rates are decreased to a value very close to the bifurcation, greatly diminishing the diagnostic value of such a procedure.

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- [1] S.H. Strogatz, *Nonlinear Dynamics and Chaos* (Westview Press, Cambridge, 1994), Chap. 3.
- [2] Z.T. Zhusubaliyev and E. Mosekilde, *Bifurcations and Chaos in Piecewise-smooth Dynamical Systems* (World Scientific, Singapore, 2003).
- [3] A. Karma, *Chaos* **4**, 461 (1994).
- [4] J.M. Pastore *et al.*, *Circulation* **99**, 1385 (1999).
- [5] D.S. Rosenbaum *et al.*, *New Engl. J. Med.* **330**, 235 (1994).
- [6] T. Thom *et al.*, *Circulation* **113**, e85 (2006).
- [7] G.M. Hall, S. Bahar, and D.J. Gauthier, *Phys. Rev. Lett.* **82**, 2995 (1999).
- [8] J.B. Nolasco and R.W. Dahlen, *J. Appl. Physiol.* **25**, 191 (1968).
- [9] J. Sun, F. Amellal, L. Glass, and J. Billette, *J. Theor. Biol.* **173**, 79 (1995).
- [10] D.S. Chen, H.O. Wang, and W. Chin, in *Proceedings of the 1998 IEEE International Symposium on Circuits and Systems* (IEEE, New York, 1998), Vol. 3, p. 635.
- [11] M.A. Hassouneh and E.H. Abed, *Int. J. Bifurcation Chaos Appl. Sci. Eng.* **14**, 3303 (2004).
- [12] J. Heldstab, H. Thomas, T. Geisel, and G. Rands, *Z. Phys. B* **50**, 141 (1983).
- [13] A. Karma and Y. Shiferaw, *Heart Rhythm* **1**, S290 (2004).
- [14] X. Zhao, D.G. Schaeffer, C.M. Berger, and D.J. Gauthier, *Nonlinear Dynamics* **48**, 381 (2007).
- [15] X. Zhao and D.G. Schaeffer, *Nonlinear Dynamics* doi:10.1007/s11071-006-9174-1 (2007) (<http://www.springerlink.com/content/136278068v467u8w/>).
- [16] All procedures are approved by the Duke University Institutional Animal Care and Use Committee.
- [17] See EPAPS Document No. E-PRLTAO-99-043732 for additional data to support the claims made in this Letter. Specifically, we explain our data processing technique and give a full presentation of all of our data. For more information on EPAPS, see <http://www.aip.org/pubservs/epaps.html>.
- [18] M. Golubitsky and D. Schaeffer, *Singularities and Groups in Bifurcation Theory* (Springer, Berlin, 1985).
- [19] Y. Shiferaw, D. Sato, and A. Karma, *Phys. Rev. E* **71**, 021903 (2005).
- [20] S.S. Kalb *et al.*, *J. Cardiovasc. Electrophysiol.* **15**, 698 (2004).