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## Abstract
This manuscript reviews various experimental methods and mathematical approaches for nonlinear dynamics of paced cardiac tissue. A particular focus is on cardiac alternans. Several mapping models are introduced to predict alternans at the cellular level. Experimental observations and modeling approaches are introduced to understand mechanisms of alternans formation in extended heart tissue. In addition, potential bifurcation mechanisms of alternans and the underlying interplay between calcium and voltage dynamics are discussed.

## Keywords
- Alternans
- Action potential duration
- Restitution
- Bifurcations
Nonlinear dynamics of periodically paced cardiac tissue

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Received: 11 July 2011 / Accepted: 4 October 2011
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Abstract This manuscript reviews various experimental methods and mathematical approaches for nonlinear dynamics of paced cardiac tissue. A particular focus is on cardiac alternans. Several mapping models are introduced to predict alternans at the cellular level. Experimental observations and modeling approaches are introduced to understand mechanisms of alternans formation in extended heart tissue. In addition, potential bifurcation mechanisms of alternans and the underlying interplay between calcium and voltage dynamics are discussed.

Keywords Alternans · Action potential duration · Restitution · Bifurcations

1 Introduction

Sudden cardiac death is a major public health problem; it is one of the leading causes of mortality in the Western world [1–3]. Sudden cardiac death is caused primarily by ventricular fibrillation (VF). While it is generally agreed that the likeliest mechanism of VF is reentry, a major challenge in the field of cardiac electrophysiology is to understand how events at the cellular level translate into arrhythmic behavior in the whole organ. Under conditions of high-frequency excitation, the beat-to-beat alternation in the action potential duration (APD) which manifests itself on the ECG as T-wave alternans, may be a harbinger of VF in the whole heart [4–8].

The induction and maintenance of ventricular arrhythmias has been linked to single-cell dynamics [4, 9]. In response to an electrical stimulus, cardiac cells fire an action potential, 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). When the time interval between two consecutive stimuli, named the basic cycle length (BCL), is large enough, each stimulus gives rise to an identical action potential and thus elicits a normal 1:1 response (Fig. 1A). However, when the interval between stimuli decreases, the APD alternates between short and long values giving rise to electrical alternans [10, 11] (Fig. 1B).

Alternans was observed for the first time in animal experiments [12] and later reported in the clinic [13]. Recent experiments have established a causal link between alternans and the risk for ventricular arrhythmias, suggesting that the elimination of alternans may inhibit conduction block and, therefore, prevent the occurrence of fibrillation [14–16]. Thus, understanding the mechanism of alternans formation is a crucial
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Fig. 1 Action potential responses to periodic electrical stimuli during (A) 1:1 behavior and (B) alternans

step in the detection and prevention of fatal arrhythmias.

There are several numerical approaches to investigate and describe the dynamic behaviors of the heart: physiological ionic models, simplified models, and mapping models.

Ionic models describing the electrical activity of the cardiac cell [17–21] are becoming more and more complex. These models characterize the total current flowing through the membrane by combining various membrane currents obtained in voltage-clamp or patch-clamp experiments:

\[
C_m \frac{dV}{dt} = -(I_{ion} + I_{stim}) + \nabla \cdot (D \nabla V), \tag{1}
\]

where \(C_m\) is the cell membrane capacitance, \(I_{ion}\) is the current due to the different ions (mostly Na\(^+\), K\(^+\), and Ca\(^{2+}\)) flowing across the membrane, \(I_{stim}\) is a periodically applied stimulus current, and \(D\) is the effective diffusion coefficient in cardiac tissue. Much work has been done to develop physiologically accurate models for \(I_{ion}\), by fitting the kinetic properties of different ion currents. The development of physiological models of cardiac cell electrophysiology has expanded greatly in recent years due to the increased availability of experimental data. Several models now exist for the atria [20, 22] and ventricles [18, 19] of several species as well as for sinoatrial node and Purkinje cells [23]. These models incorporate varying degrees of complexity. For example, models may describe transmembrane currents using traditional Hodgkin–Huxley gating variables or Markov chains; intracellular calcium handling can be incorporated with the help of simple empirical functions or more biophysically detailed models of buffering and sarcoplasmic reticulum uptake and release of calcium; ion channel distribution in the cells can be uniform or imply spatial variations and associated gradients of ion concentrations within the cell, etc. [24]. Typically, these models might include several dozens of parameters, making them difficult for analysis and for two- and three-dimensional simulations.

Therefore, several attempts have been made to isolate the minimum key features necessary to characterize specific phenomena by using simplified models. However, it is important to keep in mind that some aspects of cardiac myocytes' dynamics might be lost during the reduction procedure. Simplified ionic models have been proposed to describe several aspects of cardiac dynamics using minimum sets of phenomenological currents [25–30]. These models represent a simplification of the more complex ionic models and they can reproduce quantitatively much of the behavior of the full model, including APD and conduction velocity (CV) restitutions. For instance, the Fenton–Karma model [27] contains three currents, loosely corresponding to sodium, calcium, and potassium. It is complex enough to exhibit many of the characteristics of cardiac cells, yet is simple enough that much of its behavior can be understood analytically. Analytical insight is important because, for example, it can guide the selection of many parameters that need to be adjusted in fitting the model to experiments.

Another tool for analyzing results obtained from numerical simulations of ionic models and for investigating the dynamics of cardiac myocytes analytically is to use finite difference equations or mapping models [31]. This allows a reduced description of the trajectory of the ordinary differential equation by a single number, the APD.

The aim of the manuscript is to review nonlinear dynamics of paced cardiac tissue from both experimental and theoretical perspectives. In Sect. 2, restitution properties of paced myocytes are introduced, and utilized in Sect. 3 to predict the formation of alternans at the cellular level. In Sect. 4, a review of alternans formation in extended tissue is given. Section 5 discusses bifurcations as a mechanism for alternans formation, and Sect. 6 includes an overview of voltage and calcium dynamics.

2 Restitution properties of periodically paced cardiac myocytes

One of the most fundamental characteristics of cardiac cells is the shortening of the APD as the heart rate in-
Nonlinear dynamics of periodically paced cardiac tissue

![Diagram](image)

**Fig. 2** (Adapted from [36].) (A) Restitution curves (RC) depend on the pacing protocol used to obtain it. A unique dynamic RC and several S1–S2 RCs are shown. (B) APD accommodation increases, a phenomenon known as electrical restitution. Restitution plays a vital role in heart function; for a given heart rate, a shorter APD allows for a longer diastolic interval (DI), thereby giving adequate time for the heart to refill with blood. Although important at moderate heart rates, at higher rates, restitution may result in life-threatening cardiac rhythms, VF in particular [1, 2, 32, 33].

Restitution curve, which is the nonlinear functional relation between the APD and the preceding DI, is one of the common techniques for studying the initiation and maintenance of alternans and other complex rhythms in periodically paced cardiac myocytes [10, 34]. Currently, several protocols are used to measure different types of individual restitution curves where the dynamic and S1–S2 restitution curves are the most common [29, 35, 36].

The dynamic restitution curve is obtained from a pacing protocol, in which steady state pairs (i.e., DI and APD) are measured at each BCL as the BCL is decreased. On the other hand, in the S1–S2 pacing protocol, a premature stimulus is applied at a coupling interval (S2) after a train of stimuli at a fixed BCL (S1). The full S1–S2 restitution curve can be obtained by changing the coupling interval. Figure 2A illustrates the traditional approach to investigate the dynamics of periodically paced cardiac myocytes. Here, a single dynamic restitution curve is shown together with two S1–S2 restitution curves (for different values of S1). While there is a unique dynamic restitution curve, there can be infinitely many different S1–S2 restitution curves corresponding to different values of S1. Note that these restitution curves have different slopes, but often, only one restitution curve is measured in experiments. Figure 2A clearly indicates that the dynamics of cardiac myocytes cannot be fully described by a single restitution curve. Instead, a variety of restitution curves have to be taken into account as it was shown that different restitution curves highlight different aspects of cardiac dynamics [37, 38].

It was proposed [10, 34] that the normal cardiac rhythm (1:1 response) becomes unstable when the magnitude of the slope of the restitution curve exceeds one, known as the restitution condition. This condition has been confirmed in some experiments [35] and has led to the restitution hypothesis, which states that flattening the restitution curve will help prevent fibrillation [39–42]. The restitution hypothesis is firmly engrained in the minds of many researchers and clinicians. However, recent experimental results have shown that this hypothesis is incorrect in many situations. For instance, stable 1:1 behavior is observed when the restitution curve is very steep [39–41], whereas the transition to alternans is observed in the presence of a shallow restitution curve [35, 42]. One of the main reasons why the restitution condition fails to accurately predict the onset of irregular cardiac rhythms is the presence of short-term memory in the cardiac myocytes [29, 43–50] which affects significantly the dynamics of responses. Short-term memory refers to the observation that APD is not only influenced by the previous DI but also depends on the pacing history. Short-term memory needs to be distinguished from cardiac memory, which may involve long-term (up to weeks) changes in protein regulation and/or gene expression [51]. In contrast, short-term memory affects the dynamics of periodically paced
cardiac myocytes over a much shorter time interval, up to several minutes [43, 46, 52].

The presence of short-term memory leads to two main consequences that need to be taken into account in order to understand the mechanisms of irregular cardiac rhythm formation: (i) the restitution curve depends on the pacing protocol used to obtain it, the phenomenon known as rate-dependent restitution (Fig. 2A); (ii) after a change in pacing rate, the APD needs a certain time (several minutes) to achieve a new steady-state, a phenomenon known as APD accommodation (Fig. 2B).

As a result of these consequences, the restitution condition might fail to predict the onset of irregular cardiac rhythms correctly. The memory-related phenomena have been studied in great detail by several laboratories [37, 43, 45, 49, 50] and short-term memory has been incorporated in several simple models describing the dynamics of cardiac myocytes [37, 43–45, 48, 50]. These studies emphasized, in particular, the importance of short-term memory for the initiation and maintenance of alternans and VF.

Recently, several studies attempted to generalize the restitution hypothesis to include the influence of short-term memory [37, 38, 53]. It has been proposed that multiple restitution curves have to be measured simultaneously at the same pacing rate in order to predict the onset of alternans. As a result, a new protocol for measuring multiple aspects of cardiac dynamics simultaneously, rather than individual restitution properties, has been developed, leading to the concept of the restitution portrait of cardiac tissue [37, 38, 52].

The restitution portrait (Fig. 3A) is a much more powerful technique to represent and analyze restitution properties of periodically paced cardiac myocytes in the presence of short-term memory rather than individual restitution curves. It depicts multiple aspects of cardiac dynamics at each BCL, in contrast to traditional approaches (Fig. 2), which describe only individual aspects of dynamics. Specifically, the rate-dependent restitution is present in the restitution portrait as the difference between dynamic (blue) and local S1–S2 (red) restitution curves (Fig. 3). The APD accommodation, i.e., the slow change of APD in time (Fig. 3C), is shown in black. Several restitution portraits were recorded in different species: small bullfrog cardiac tissue [52], as well as myocytes isolated from the heart of rabbit and guinea-pig [54]. All of these restitution portraits are qualitatively similar and depict multiple aspects of cardiac dynamics, as shown in Fig. 3.

It has been recently demonstrated [55] that the restitution portrait can be used to quantify the amount of short-term memory that is present in cardiac myocytes. Specifically, the rate-dependent restitution can be measured as the difference (angle $\alpha$, Fig. 3B) between slopes of different restitution curves at the same value of BCL:

$$\alpha = S_{\text{dyn}}|_{BCL} - S_{12}|_{BCL}, \quad (2)$$

where $S_{\text{dyn}}$ and $S_{12}$ are slopes of the dynamic and local S1–S2 restitution curves, respectively. Equation (2) drastically differs from the previous attempts in quantifying short-term memory [43, 48, 50] because now the amount of short-term memory $\alpha$ can be directly measured both theoretically and experimentally. Moreover, this definition provides straightforward insights on several experimental and theoretical...
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Fig. 4 (Adapted from [55]) Rate-dependence of $S_{dyn}$, $S_{12}$ slopes and short term memory $\alpha$ in (A) the ionic model of rabbit action potential and (B) isolated cardiac myocytes.

Fig. 5 Cobweb diagram illustrating (A) 1:1 response where $|f'| < 1$ and (B) alternans where $|f'| = 1$.
strated that a model of this form could be derived analytically from an ionic model of the cardiac membrane [56]. This mapping model states that the APD depends not only on the preceding DI, but also on the preceding APD, so that

\[ A_{n+1} = F(D_n, A_n). \] (7)

Equation (7) is a two-variable, one-dimensional mapping model with one beat of memory. The explicit dependence of function \( F \) on both \( A_n \) and \( D_n \) allows the model to display rate-dependent restitution. The origin of rate-dependent restitution can be illustrated graphically for the mapping model (7) by taking \( A_n \) and \( D_n \) as independent variables and plotting \( F \) as a two-dimensional surface (blue), as shown in Fig. 6.

The dynamic restitution curve is shown in Fig. 6A as an intersection of the surface described by (7) and equation

\[ A_{n+1} = A_n \equiv A^* \] (8)

where \( A^* \) is the steady-state (fixed) point [37]. Equation (8) is coming from the definition of the dynamic restitution curve, which consists of steady-state responses only. Therefore, the dynamic protocol samples only a very limited region of the two-dimensional surface \( F \) because of the constraint imposed by (8).

Following the description of the S1–S2 protocol, the S1–S2 restitution curve can be obtained by noting that all APDs preceding the S2 stimulus are equal, so that

\[ A_n = A^*_{S1} \equiv \text{const} \] (9)

where \( A^*_{S1} \) is the steady-state APD at the pacing interval \( BCL = S1 \). Thus, the S1–S2 restitution curve is the intersection of the surface described by (7) with the vertical plane defined by (9) for a given value of \( S1 \), as shown in Fig. 6B.

A third restitution curve introduced in [50] describes the transient response of paced cardiac tissue for a constant BCL, as it approaches the equilibrium value following a change in BCL. In this situation, \( A_n \) and \( D_n \) are related through (5), so that the transient dynamics are given by the intersection of \( F \) and the vertical plane defined by (5), as shown in Fig. 6C for a certain value of BCL. This is the so-called constant-BCL restitution curve. The constant-BCL restitution curve consists of both the transients and the steady state of \( A_n \) and \( D_n \).

Note that the restitution curve is defined as the dependence of the APD on the preceding DI, so experimentally measured restitution curves consist of projections of Fig. 6D on the \((A_{n+1}, D_n)\) plane. Therefore,
in the presence of short-term memory, the combination of the slopes of different restitution curves at the point of their intersection has to be measured in order to predict the onset of alternans, but not their individual slopes.

A new restitution condition for the mapping model (7) was derived in [37] and predicts that alternans may exist when

\[ |F'| = \left| 1 - S_{12} - \frac{S_{12}}{S_{\text{dyn}}} \right| \geq 1, \quad (10) \]

where \( S_{12} \) and \( S_{\text{dyn}} \) are individual slopes of the S1–S2 and dynamic restitution curves, respectively, measured simultaneously at a given BCL.

A two-dimensional mapping model with memory was proposed in [45, 53], and it determines the APD as a function of the preceding APD and two preceding DIs

\[ A_{n+1} = \Phi(A_n, D_n, D_{n-1}). \quad (11) \]

This mapping model can be derived analytically from a two-current simplified ionic model that includes a concentration variable [30]. Visualization of the restitution curves in the mapping model (11) is more complex [38] as it requires plotting the function \( \Phi \), which belongs to 4-dimensional space.

A restitution condition for the mapping model (11) [53] predicts that alternans exists when

\[ \left| 1 - S_{12} - \frac{S_{12}}{S_{\text{dyn}}} + \frac{S_{12}(1 - S_{\text{dyn}})}{S_{\text{dyn}} - S_{12}} \times \left( 1 - S_{12} - \frac{S_{12}}{S_{\text{dyn}}} + S_{\text{bcl}} \right) \right| \geq 1, \quad (12) \]

where \( S_{\text{bcl}} \) is the slope of the constant-BCL restitution curve.

Note that the restitution conditions (10) and (12) were derived in the presence of short term memory and require knowledge of the slopes of different restitution curves measured at the same BCL. Thus, these restitution conditions may, in principle, explain experimental observations of both a stable 1:1 responses accompanied by a steep restitution curve and alternans accompanied by a shallow restitution curve. For instance, a validation of (10) is shown in Fig. 7, where the bifurcation diagram obtained from a numerical simulation of the mapping model (7) is shown in the case of alternans. One can see that at the onset of alternans (solid vertical lines) both \( S_{12} \) and \( S_{\text{dyn}} \) slopes are larger than one, but the combination of their slopes given by (10) is equal to one. Further numerical validation of (10) was given in [29] using a simplified ionic model, and the restitution condition (12) was checked in [53]. Although restitution conditions in the presence of short-term memory (10) and (12) were successfully confirmed theoretically, their experimental validation is still underway.

The dynamics of periodically paced cardiac myocytes described by three types of mapping models (4), (7), and (11) are different. For instance, the mapping model (4) reveals only one restitution curve independent on the pacing protocol used (Fig. 8A). The mapping model (7) allows for the demonstration of rate-dependent restitution, i.e., it distinguishes between S1–S2 and dynamic restitution curves (Fig. 8B). Finally, the mapping model (11) is capable of demonstrating the APD accommodation effect, in addition to the rate-dependent restitution (Fig. 8C). It has been demonstrated experimentally and by using numerical simulations of physiological models that the dynamics of periodically paced cardiac myocytes is qualitatively similar to the one described by a two-dimensional mapping model with memory, i.e. (11) [54, 55]. An attempt to quantitatively fit an experimental data leads to incorporation of calcium dynamics in the mapping model with memory [30]. On the other hand, it has been demonstrated that inclusion of an infinite number
The restitution hypothesis (i.e., the idea that the slope of the restitution curve can be used to determine the onset of alternans) was developed theoretically decades ago [10]. From an experimental standpoint, this hypothesis was very attractive because it allows complex cardiac rhythms to be predicted from the dynamical behavior of periodically paced cardiac tissue. However, the restitution hypothesis was compromised in several experimental studies due to the intrinsic complexity of the dynamical behavior of cardiac tissue. There are three major reasons for the failure of the restitution hypothesis, as discussed below.

First, the presence of short-term memory in cardiac tissue makes the restitution properties dependent on the pacing protocols applied, as have been discussed above. As a consequence, the restitution curves measured by different pacing protocols have different slopes and fail to predict the onset of irregular cardiac rhythms correctly. Researchers have made several attempts to reconsider the restitution hypothesis in the presence of short-term memory [37, 44, 45, 48, 50, 52], including the latest development of the restitution portrait concept [37, 38, 52]. However, while theoretical predictions from all these attempts provide promising results, an experimental confirmation of revised restitution hypothesis is still lacking [54].

The second major reason for the failure of the restitution hypothesis is the spatial complexity of the heart, the consequences of which are usually underestimated in experimental and clinical studies. Indeed, attempts to measure one or a few restitution curves for a given heart revealed that such restitution curves often represent average cardiac responses. Therefore, a single restitution curve measured in the heart does not reflect its spatiotemporal dynamics, and thus cannot correctly determine the onset of alternans. Various investigators have attempted to demonstrate the presence of spatial heterogeneity in the restitution properties of the heart using both individual restitution curves and restitution portraits [59, 101, 102], but a direct link between the onset of alternans in the heart and local restitution properties is still lacking.

Finally, the third major reason for the failure of the restitution hypothesis is the important role played by intracellular calcium cycling in the genesis of APD alternans [60]. This issue will be partially addressed in Sect. 6.

4 Alternans in extended cardiac tissue

The dynamics of periodically paced whole hearts are more complex, mainly due to the presence of cell-to-cell communication. Therefore, a single restitution curve measured in the heart does not reflect its spatiotemporal dynamics, and thus cannot correctly predict the onset of alternans. Several attempts have been made to demonstrate the spatial heterogeneity in restitution properties in the hearts, using both individual restitution curves and restitution portraits [58, 59]. Nevertheless, the direct link between the onset of al-
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Fig. 9 (Adapted from [60].) SCA (A) and SDA (B) in simulated 2D cardiac tissue. Top panels: action potentials from sites a and b both alternate in phase in A, and out-of-phase in B. Bottom panels: spatial APD distribution. The nodal line (white) with no APD alternans separates out-of-phase regions

ternans in the heart and local restitution properties is still missing.

In cardiac tissue, APD alternans can be spatially concordant or spatially discordant [60], as shown in Fig. 9. Spatially concordant alternans implies that cells from different spatial locations (a and b in Fig. 9A) oscillate in phase, i.e., all cells display long–short sequences of APDs concurrently. In contrast, spatially discordant alternans appears when cells in different regions alternate out of phase (a and b in Fig. 9B), i.e., some cells display long–short sequences of APD while others display short–long sequences. The two spatial regions oscillating out-of-phase are separated by a nodal line, where no APD alternans is present.

It has been demonstrated previously [14] that spatially discordant alternans is a primary cause of T-wave alternans, a beat-to-beat change in the amplitude of the ECG that repeats once every other beat. T-wave alternans is recognized as a precursor of ventricular arrhythmias [13] since it was frequently observed in a wide variety of clinical and experimental conditions associated with such arrhythmias [61–65]. Thus, it is accepted that spatially discordant alternans desynchronizes depolarization, increases dispersion of refractoriness, and creates a substrate for VF [14, 66–69]. Although the arrhythmogenicity of discordant alternans is clear, the mechanisms underlying its formation are poorly understood.

In the literature, there are numerous theoretical and experimental studies on APD alternans [8, 14, 41, 60, 70–75] in the heart. However, surprisingly few studies address spatiotemporal formation of both concordant and discordant alternans. Recently, it has been demonstrated that the onset of spatially concordant APD alternans is a local phenomenon that is not only characterized by the value of BCL, but also by the percentage of the heart area occupied by the alternans as a function of the BCL. Note that spatially concordant alternans (blue) occurred locally at certain values of BCL and initially occupied a small percentage of the heart. As BCL decreased, the area of alternans increased and rapidly transformed into spatially discordant alternans (red). Figure 10B shows the spatial distribution of the spatially concordant alternans onset at different values of BCL. Note that alternans first appeared locally at BCL = 185 ms (green) and then occupied the entire surface of the heart as BCL decreased to 150 ms.

The transition from spatially concordant to spatially discordant alternans can occur via two different pathways [76]. First, as BCL decreases, the regions displaying spatially concordant alternans becomes larger, and the instantaneous transition to spatially discordant alternans occurs. Second, the transition to spatially discordant alternans occurs over time during APD adaptation. A representative example is shown in Fig. 11 where spatially discordant alternans (red) slowly developed over time from the spatially concordant alternans (blue) as BCL was decreased from 140 to 135 ms.

Two possible mechanisms have been proposed theoretically to explain the appearance of spatially discordant alternans. The first suggests that preexisting heterogeneities are required to be present, and that spatially discordant alternans can be formed via an appropriately timed stimulus or a change in the pacing rate [14, 70, 71]. Since alternans amplitude varies spatially in heterogeneous tissue, it is always possible to time a stimulus that reverses the alternans phase in one part of the tissue. Spatially discordant alternans will appear around locations of heterogeneity immediately as the pacing rate decreases from one value to another [72].

However, several numerical studies suggest that tissue heterogeneity is not essential, and the second mechanism for the formation of spatially discordant alternans is a steep CV restitution, i.e., when CV of a propagating wave has a steep dependence on the preceding DI [73, 74]. If CV restitution is sufficiently steep, a discordant pattern of APD alternans could form in which an alternans phase reverses across a point distal to the pacing site. This mechanism is purely dynamic and does not require heterogeneous
electrophysiological tissue substrates. Instead, the discordant alternans patterns are governed by the bulk properties of cardiac tissue, such as APD and CV restitution [78].

Some studies suggest that both tissue heterogeneity and steep CV restitution can be involved in the formation of spatially discordant alternans [41, 75]. This is because in the heart, unlike the numerical model, some ionic and/or anatomical heterogeneity is always present, and it has been difficult to distinguish between the two mechanisms.

Recently, Hayashi et al. [72] demonstrated that tissue heterogeneity and steep CV restitution mechanisms can be distinguished by the behavior of the nodal lines in spatially discordant alternans. This elegant numerical study predicted that if spatially discordant alternans develops through the first mechanism, i.e., heterogeneity, nodal lines will form at locations dictated by underlying tissue heterogeneities. Once a nodal line forms, it can (1) drift away from the pacing site on a beat to beat basis (in the case of the APD heterogeneity) or (2) remain pinned at the original position (heterogeneity of intracellular Ca^{2+} cycling). In contrast, if spatially discordant alternans develops through the second mechanism, i.e., steep CV restitution, nodal lines will move toward the pacing site as pacing rate increases.

The above predictions were tested experimentally by tracking the nodal lines formation during adaptation after changing the value of BCL in isolated rabbit heart. First, we investigated the temporal evolution of the nodal lines. A representative example of such behavior is shown in Fig. 12 when BCL was decreased from 140 to 135 ms. The results indicate that the nodal lines can behave according to the different scenarios.

First, nodal lines may remain at the same position after changing the BCL during pacing, as shown in Fig. 12 for the anterior (Ant) surface, i.e., display “stable” behavior. Further analysis [76] illustrates that CV restitution is steeper on the Ant surface, where the stable nodal lines are present, than on the posterior (Post) surface, where nodal lines exhibit unstable behavior, suggesting that steep CV restitution could be a possible mechanism of spatially discordant alternans formation for the case of stable nodal lines.

Second, in the same heart, nodal lines may also undergo temporal evolution, as shown in Fig. 12 for the Post surface, i.e., they display “unstable” behavior. In the latter case, the dynamics of the nodal lines is very complex and does not exhibit stable patterns. Nodal lines can drift in different directions, toward or away from the pacing site, suggesting that APD heterogeneity cannot be the underlying mechanism for unstable nodal lines. For the particular case of
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Fig. 12 (Adapted from [76].) Temporal evolution of the nodal lines on Ant and Post surfaces as BCL changes from 140 to 135 ms. Stimulus numbers are indicated on top of each map; asterisks represent the location of the pacing electrode; blue-arrows show the direction of nodal line drift.

Fig. 12, the two upper unstable nodal lines on the Post surface drift toward each other (see blue-arrows) and mutually annihilate over time (see steady state at BCL = 135 ms). The presence of unstable nodal lines suggests that short-term memory might be involved in the formation of spatially discordant alternans. It is well known [36, 43, 52] that one of the consequences of short-term memory is the slow APD accommodation (see Fig. 2B) upon a change in pacing rate. The time constant $\tau$ of APD accommodation was calculated for each pixel of the rabbit heart according to (3), and the results demonstrate that mean $\tau$ is significantly smaller for the Ant surface, where nodal lines are stable and CV restitution is deep, than for the Post surface, where nodal lines exhibit unstable behavior and CV restitution is shallow [76]. These results strongly suggest that the unstable behavior of the nodal lines is associated with the slow APD accommodation, i.e., short-term memory, in the absence of steep CV restitution.

5 Bifurcation to alternans

The transition from 1:1 response to alternans is through a period-doubling bifurcation. Historically, alternans has been modeled as a period-doubling bifurcation of a smooth system [9, 10, 34, 44]. However, recent experiments [82–84] have revealed nonsmooth features of alternans that can be approximated using piecewise smooth models (specifically, border-collision models [80, 81]). Berger et al. encountered evidence of a crossover between smooth and nonsmooth behaviors in alternans: very close to the bifurcation point, the dynamics is smooth, whereas further away it is border-collision-like [85].

Smooth and border-collision bifurcations have characteristic differences in their bifurcation diagrams, particularly near the bifurcation points. Note that in the context of cardiac dynamics, a bifurcation diagram can be generated by plotting the steady-state values of APD as a function of BCL. Thus, in principle, smooth and border-collision period-doubling bifurcations can be distinguished by closely examining their bifurcation diagrams. However, in experiments with cardiac tissue, it is difficult to obtain sufficient resolution in the bifurcation diagram to resolve the fine structure near the bifurcation point. Attempts to gather more data close to the bifurcation are limited by two factors: (i) the position of the bifurcation point is not known ahead of time; and (ii) the response of excised cardiac tissue changes gradually over time, moving the bifurcation point.

Utilizing the technique of alternate pacing, Zhao and associates developed a more robust method for determining the type of the bifurcation [85–88]. In the cardiac context, alternate pacing means that the $n$th and $(n + 1)$st stimuli are separated by alternating intervals

$$B_n = B_{av} + (-1)^n \delta$$

(13)

where $B_{av}$ is the base line BCL and $\delta$ is the magnitude of perturbation. As a result of such pacing, APD alternates in a $\delta$-short pattern, with the corresponding steady-state values defined as $A_{long}$ and $A_{short}$. To quantify the system’s sensitivity to perturbations, a gain can be introduced as

$$\Gamma = (A_{long} - A_{short})/2\delta.$$  

(14)

Note that since $B_{av}$ is greater than the bifurcation value $B_{bif}$ it follows that $\Gamma$ reflects pre-bifurcation amplification of the perturbation. Originally, it was proposed to study $\Gamma$ as a function of $B_{av}$ [89]. However, as shown in [85–87], determining $\Gamma$ as a function of $\delta$ for fixed $B_{av}$ (close to the bifurcation point) permits a much clearer distinction between a smooth and...
Fig. 13 (Adapted from [85].) Schematic bifurcation diagrams for (a) smooth (b) and border-collision bifurcations, during alternate pacing response. The gain $\Gamma$ as a function of BCL (c, d) and $\delta$ (e, f) is shown for smooth (c, e) and border-collision (d, f) bifurcations.

A border-collapse bifurcation. Specifically, in the case of the smooth bifurcation, $\Gamma$ increases as $\delta$ decreases (see Fig. 13a), and the opposite occurs in the case of a border-collapse bifurcation (see Fig. 13b). Thus, with a plot of just a few data points of $\Gamma$ versus $\delta$, the distinction between the two bifurcation types should be evident, even in the presence of experimental noise.

Berger et al. [85] implemented the alternate pacing technique experimentally and found that the bifurcation to alternans exhibits both smooth and border-collapse behaviors, a so-called hybrid period-doubling bifurcation. Specifically, they found that the relation between the amplification gain $\Gamma$ and the perturbation size $\delta$ sometimes shows trends consistent with a smooth bifurcation, trends agreeing with a border-collapse bifurcation, and trends that cannot be classified into either category. These surprising observations suggest that both smooth and nonsmooth behaviors are present in cardiac alternans to some degree. Berger et al. showed a compelling evidence for the coexistence of both types of behaviors (see Fig. 14). Here, alternans are observed for $B_{av} \leq 750$ ms. Figure 14b shows smooth behavior when $B_{av} = 775$ ms but Fig. 14c shows border-collapse behavior when $B_{av} = 800$ ms. This experimental evidence of hybrid bifurcation demonstrates the need for research into new models and theories of alternans.

Berger et al. showed that the hybrid behavior in Fig. 14 can be interpreted using an unfolded border-collapse model. Specifically, they considered a piecewise smooth cardiac model (see [85, 88] for detailed derivations)

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

(15)

where $A_n$ and $D_n$ are connected through (5), i.e., $D_n = B - A_n$. It can be demonstrated [80] that under the following conditions:

$$-1 < \alpha + \beta < 1$$
$$-1 < \alpha^2 - \beta^2 < 1,$$

mapping model (15) possesses a border-collapse period-doubling bifurcation at

$$B_c = A_c + D_{th}. $$

(17)

To remove the nonsmoothness of mapping model (15), the singular term $\beta|D_n - D_{th}|$ can be unfolded as follows:

$$A_{n+1} = A_c + \alpha(D_n - D_{th}) + \beta\sqrt{(D_n - D_{th})^2 + D_{th}^2},$$

(18)
6 Interplay between voltage and calcium during alternans

It has been debated whether cardiac alternans is caused by instability in voltage dynamics or that in calcium dynamics. Interplay between the two mechanisms has been investigated by a few authors. Every contraction of the heart is triggered by a propagating action potential. Intracellular calcium (Ca) cycling plays a crucial role in excitation-contraction coupling in cardiac cells, and changes in Ca cycling and transmembrane voltage are intricately related \[90\]. The action potential triggers a calcium influx leading to a release of calcium from the sarcoplasmic reticulum resulting in contraction, whereas Ca affects the time course of transmembrane voltage \(V_m\) through various calcium-sensitive ionic currents. The review of the cellular mechanisms of alternans formation can be found in several recent publications \[60, 91, 92\].

Membrane voltage and Ca are bidirectionally coupled in cardiac tissue \[60\]. During an action potential, the elevation of \(V_m\) activates L-type calcium currents \(I_{Ca-L}\) and leads to the elevation of Ca, which in turn triggers calcium release from the sarcoplasmic reticulum \[93\]. The \(V_m \rightarrow Ca\) coupling satisfies graded release, where a larger DI leads to an increase in the calcium release at the following beat since it allows more time for L type calcium channels to recover. On the other hand, calcium release from the sarcoplasmic reticulum affects the APD in two folds: it can shorten the APD by enhancing the inactivation of \(I_{Ca-L}\) and it can prolong the APD by intensifying the \(Na^+ /Ca^{2+}\) exchange currents \(I_{NCX}\). Therefore, depending on the relative contributions of \(I_{Ca-L}\) and \(I_{NCX}\), an increase in calcium release may either shorten the APD (negative Ca \(\rightarrow V_m\) coupling) or lengthen the APD (positive Ca \(\rightarrow V_m\) coupling) \[94–96\].

There exist two main cellular mechanisms of alternans. First, alternans may be attributed to steep APD restitution \[10\], which is due to a period-doubling instability in the \(V_m\) dynamics. In this case, Ca transient alternans, as a slave variable, is induced because \(V_m\) regulates Ca via \(ICa-L\) and \(I_{NCX}\) currents. Secondly, alternans may be caused by a period-doubling instability in Ca cycling, which is associated with a steep relationship between the sarcoplasm reticulum release and load \[97, 98\]. In this case, APD alternans is a secondary effect via Ca \(\rightarrow V_m\) coupling. It is known that Ca alternans accompanies APD alternans giving rise to electromechanical alternans. This alternans can be electromechanically concordant (corresponding to positive Ca \(\rightarrow V_m\) coupling), and electromechanically discordant (corresponding to negative Ca \(\rightarrow V_m\) coupling). Up to now, it is unclear if APD alternans is driven by Ca\(\rightarrow\) alternans or vice versa \[97–99\].

Recently, Zhao carried out numerical and theoretical analyses to examine the differences between APD alternans and Ca alternans \[100\]. An interesting finding of this work is that Ca alternans leads to the coexistence of multiple spatiotemporal patterns of alternans, even when all parameters of the system are fixed. Which pattern occurs in the tissue is determined by the pacing history. As a result, the alternans pattern on a tissue becomes unpredictable from the system parameters alone. This is in vast contrast to the conventional understanding that the spatiotemporal pattern of alternans is uniquely determined by the given set of parameters \[78\].

As shown in \[100\], the difference in APD alternans and Ca alternans can be analyzed using a simple mapping model:

\[
\begin{align*}
A_{n+1} &= -F(D_n, C_n), \\
C_{n+1} &= -G(D_n, C_n),
\end{align*}
\] (19)

where \(C_n\) represents the value of intracellular calcium concentration at the end of \(n\)th action potential. The function \(F\) describes a general dependence of APD on DI and \(C_a\) in the previous beat. The function \(G\) accounts for excitation-contraction coupling. Under periodic stimulation at basic cycle length \(B\), it follows from (5) that \(D_n = B - A_n\). One can show that the eigenvalues of this mapping model satisfy the following equation:

\[
(\lambda + F_A)(\lambda + G_C) - F_C G_A = 0,
\] (20)

where subscripts denote the derivatives with respect to the corresponding variable. It is easy to see that
the system may lose stability through an increasing magnitude of $F_A$ (voltage-driven alternans) or an increasing magnitude of $G_C$ (calcium-driven alternans). Moreover, when the variation of $F_A$ and $G_C$ collectively lead to instability, it corresponds to the so-called intermediate alternans, which may lead to a quasiperiodic response for negative $C_{\text{d}} \to V_m$ coupling [94]. The three different mechanisms of alternans are schematically represented in Fig. 15.

To illustrate the influences of different alternans mechanisms in cardiac tissue, we consider a short fiber on which the conduction time is negligible since the conduction time is an order of magnitude less than the APD. On such a fiber, the APD values in all cells are identical due to fast diffusion of sodium ions whereas the values of $C_{\text{d}}$ in different cells are different because calcium ions diffuse slowly. Denote the number of cells by $M$ and the position of cell $i$ by $x_i$. The effect of electrotonic coupling can be taken into account by using a weighted averaging algorithm, as proposed in Fox et al. [74]. Then the mapping model (19) can be rewritten in terms of APD and calcium concentration as follows:

$$A_{n+1} = \frac{1}{M} \sum_{i=1}^{M} F(A_n, C_n(x_i)), \quad C_{n+1}(x_1) = -G(A_n, C_n(x_1)), \quad \ldots \quad C_{n+1}(x_M) = -G(A_n, C_n(x_M)). \quad (21)$$

Note that the APD value is identical for all cells and $C_n(x_i)$ represents the $C_{\text{d}}$ peak concentration for the $i$th beat in the cell located at $x_i$. Consider a 1:1 solution in the fiber, i.e., a fixed point solution of the coupled-mapping model. One can write the Jacobian corresponding to the fixed point as

$$\begin{bmatrix}
- F_A & -\frac{1}{M} F_C & -\frac{1}{M} F_C & \ldots & -\frac{1}{M} F_C \\
- G_A & -G_C & 0 & \ldots & 0 \\
- G_A & 0 & -G_C & \ldots & 0 \\
- G_A & 0 & 0 & \ldots & -G_C \\
- G_A & 0 & 0 & \ldots & -G_C
\end{bmatrix} \quad (22)$$

It follows that the characteristic polynomial of the Jacobian satisfies

$$(\lambda + G_C)^{M-1}(\lambda + F_A)(\lambda + G_C) - FCG_A) = 0. \quad (23)$$

Note that the second parenthesis on the left-hand side is exactly the same as the characteristic polynomial for the single-cell case. Recall that the bifurcation resulted from an increasing $F_A$ leads to voltage-driven alternans whereas the bifurcation from an increasing $G_C$ leads to calcium-driven alternans. Since there are $M - 1$ eigenvalues equal to $-G_C$, calcium-driven alternans will lead to multiple unstable modes, and thus multiple patterns of alternans. On the other hand, voltage-driven alternans will not cause such a phenomenon of multiple unstable modes. This simple example exhibits phenomena similar to previous numerical observations in [100].

The influences of different alternans mechanisms on cardiac tissue probably can be most clearly manifested using an example of two coupled cells (see Fig. 16). Here, it is clear that calcium induced alternans and intermediate alternans may lead to the coexistence of multiple spatiotemporal patterns because multiple unstable boundaries may be crossed under variation of the bifurcation parameter.

![Fig. 15](image-url) Three different mechanisms of alternans in a single cell: voltage-induced alternans (v), calcium induced alternans (c), and intermediate alternans (i). Curves represent stability boundaries in the single cell model (19), where solid curves represent the primary bifurcations and dashed curves represent secondary bifurcations. The dotted curve (red) represents quasiperiodic bifurcation. In (a), $FCGA > 0$, corresponding to positive voltage-calcium coupling. In (b), $FCGA < 0$, corresponding to negative voltage-calcium coupling.

![Fig. 16](image-url) Three different mechanisms of alternans in (a) in two coupled cells. Notations are similar to Fig. 15. Note the presence of additional boundaries in compare to Fig. 15.
Nonlinear dynamics of periodically paced cardiac tissue

Acknowledgements  This work was supported by National Science Foundation grants PHY0957468 (E.G.T) and 0845753 (XZ).

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