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A Class of Monte-Carlo-Based Statistical Algorithms for Efficient Detection of Repolarization Alternans

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Abstract

Cardiac repolarization alternans is an electrophysiologic condition identified by a beat-to-beat fluctuation in action potential waveform. It has been mechanistically linked to instances of T-wave alternans, a clinically defined ECG alternation in T-wave morphology, and associated with the onset of cardiac reentry and sudden cardiac death. Many alternans detection algorithms have been proposed in the past, but the majority have been designed specifically for use with T-wave alternans. Action potential duration (APD) signals obtained from experiments (especially those derived from optical mapping) possess unique characteristics, which requires the development and use of a more appropriate alternans detection method. In this paper, we present a new class of algorithms, based on the Monte Carlo method, for the detection and quantitative measurement of alternans. Specifically, we derive a set of algorithms (one an analytical and more efficient version of the other) and compare its performance with the standard spectral method and the generalized likelihood ratio test algorithm using synthetic APD sequences and optical mapping data obtained from an alternans control experiment. We demonstrate the benefits of the new algorithm in the presence of Gaussian and Laplacian noise and *frame-shift* errors. The proposed algorithms are well suited for experimental applications, and furthermore, have low complexity and are implementable using fixed-point arithmetic, enabling potential use with implantable cardiac devices.

Index Terms

Alternans; biomedical signal processing; medical signal detection; pacemakers

I. Introduction

T-WAVE alternans is a beat-to-beat oscillation in the amplitude or morphology of the T wave as seen on the surface and is typically induced at fast heart rates. Macroscopic T-wave alternans is rare, and as such, much attention has been dedicated to studying microscopic (i.e., microvolt) T-wave alternans (MTWA), which typically has an amplitude on the order

of a few microvolts. MTWA has been closely linked to instances of ventricular fibrillation (VF) and sudden cardiac death (SCD) in clinical [1]–[5] and experimental [6]–[8] studies, and recent studies have suggested that it could have added benefit for SCD risk stratification purposes [9]–[17].

The low amplitude nature of MTWA makes its detection in clinical and experimental settings difficult, as the presence of even the slightest amount of noise can mask and/or mimic an underlying alternating pattern. Because of this, there have been various T-wave detection algorithms proposed and utilized in the past that address this particular challenge [18]–[23] (see [24] for a review of different alternans detection methodologies).

T-wave alternans is a manifestation of underlying action potential duration (APD) alternans, which is a beat-to-beat alternation in APD and/or morphology expressed at the cellular level [20]. In fact, the potentially causal link between T-wave alternans and some episodes of VF/SCD has been posited to include cellular alternans-APD alternans has been shown to trigger reentrant electrical wave activity experimentally and computationally [25]–[27].

Because of the purported importance of APD (also known as repolarization) alternans within the context of fibrillation, there have been a number of studies that focus primarily on studying its dynamics in experimental settings. Some studies have focused on an approach to prevent and/or control cardiac alternans through the use of externally applied perturbations to the cardiac tissue [28]–[32].

Experimental research of this type is typically conducted using transmembrane potential recordings either through the use of microelectrodes [28], [29], [32], or voltage-sensitive fluorescent dyes (optical mapping) [27], [30]. The same issues that affect the detection of T-wave alternans are relevant in the study of APD alternans, namely, the ability for inherently noisy signals to mask and/or reproduce the characteristics of alternans.

However, algorithms intended for use in detecting MTWA have suboptimal performance when applied to cellular recordings [33]. One of the main reasons for this incompatibility relates to the recording lengths typically obtained for each. MTWA recordings are generally on the order of minutes (consisting of hundreds of beats) or longer, whereas cellular recordings (in particular those using optical mapping signals) are usually composed of much shorter segments (≈ 15 –30 beats).

Another problem that hinders the adoption of previously developed clinically oriented MTWA algorithms for use with transmembrane signals is the presence and usage of a threshold parameter. Such *ad hoc* parameters need extensive experimental validation, typically requiring the use of a large set of *normal* and *abnormal* subjects. As a result, use of these algorithms for novel signals (e.g., transmembrane potential recordings) would require an experimental validation step using a large dataset, which is not readily available. One potential solution is to use an algorithm with a solid theoretical basis for which the operational threshold translates into a well-defined statistical test.

In this paper, we present a class of alternans detection algorithms specifically targeted toward APD recordings. As one of our goals is to enable implantable devices (e.g., pacemakers and implantable defibrillators) to detect alternans *in situ* [34], our algorithms were made to be simple, have low time and space complexity, and be implementable using integer or fixed-point arithmetic.

Our method is based on the generation of a random set of surrogate data derived from the random shuffling of the original input (a subtype of the general Monte Carlo simulation technique). In this way, the problem of alternans detection can be cast as a statistical test

comparing the original input and the surrogate dataset. A nonparametric version of the proposed surrogate-based test has been previously applied successfully for detection of MTWA [35]. In contrast, our method is parametric in nature, and allows for the estimation of the underlying alternans magnitude and noise level. As will be shown in *Algorithm 2*, we derived an analytical solution to the problem of surrogate generation, which significantly simplified the final algorithm and improved its time complexity.

We start by first presenting the method and developing the alternans detection framework. We discuss two algorithms—the first is a more basic algorithm, and is followed by a similar but more efficient version. Next, we apply the algorithm to simulated APD sequences amidst varying degrees of added realistic noise and sample sizes in an effort to probe the specificity (type I error rate) and sensitivity (“power”) of our method. We end by using the alternans detection method on experimental data obtained using fluorescence imaging (via optical mapping techniques).

II. Methods

Given a sequence $\mathbf{a}$ of n positive real numbers A_i representing APD, we define *average alternans magnitude* $\mu(\mathbf{a})$ as

$$\mu(\mathbf{a}) = \frac{\sum_{i=1}^{n-1} |A_{i+1} - A_i|}{n-1}. \quad (1)$$

Note that, for practical application purposes, the source is a time series of recorded signals, which needs to be first preprocessed before being reduced to a set of measurements suitable for inclusion in $\mathbf{a}$.

First, consider the trivial sequence, $\mathbf{b} = (L, L, \dots, L)$. This sequence does not exhibit any alternans; hence, $\mu(\mathbf{b}) = 0$. Now, compare this to the sequence $\mathbf{c} = (L, H, L, H, \dots)$, which represents an ideal alternating sequence (i.e., constant alternans and no noise), where $d = H - L$. Here, each term in the numerator of (1) is equal to d ; therefore, $\mu(\mathbf{c}) = d$.

However, true alternans is not the only factor that can affect the average alternans magnitude—random noise has a similar effect. Let us turn our attention to a realistic alternating sequence that is contaminated with noise. Let $\mathbf{d} = (L + \epsilon_1, H + \epsilon_2, L + \epsilon_3, H + \epsilon_4, \dots)$ be such a sequence. As earlier, we have $d = H - L$. It is similar to $\mathbf{c}$ with the addition of random Gaussian noise ϵ , with a mean of 0 and a standard deviation of $\sigma/\sqrt{2}$, i.e., $\epsilon \sim N(0, \sigma/\sqrt{2})$ (the use of $\sqrt{2}$ here simplifies the notation in the following).

The effect of the absolute value function is to reflect the negative part of the distribution (i.e., the collection of individual difference terms) over the y -axis. Hence, for sequence $\mathbf{d}$, each term in the numerator of (1) is from a *folded normal distribution* [36] [see Fig. 1(D)] with the probability density function, defined for $x \geq 0$, of

$$f(x; d, \sigma) = \frac{1}{\sigma \sqrt{2\pi}} \left(e^{-(-x-d)^2/(2\sigma^2)} + e^{-(x-d)^2/(2\sigma^2)} \right). \quad (2)$$

We now introduce the function $h(x, y)$ as

$$h(x, y) = y \sqrt{\frac{2}{\pi}} e^{-x^2/(2y^2)} + x \operatorname{erf}\left(\frac{x}{y\sqrt{2}}\right) \quad (3)$$

in which erf is the error function

$$\operatorname{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2} dt. \quad (4)$$

Integrating (2), we can show that the expected value of $\mu(\mathbf{d})$ is

$$E[\mu(\mathbf{d})] = \int_0^\infty x f(x; d, \sigma) dx \quad (5)$$

$$= h(d, \sigma). \quad (6)$$

The nonalternating sequence $\mathbf{e} = (L + \varepsilon_1, L + \varepsilon_2, \dots, L + \varepsilon_n)$ is a special case and forms a *half-normal distribution* [see Fig. 1(B)]. The expected value of $\mu(\mathbf{e})$ is calculated as

$$E[\mu(\mathbf{e})] = \int_0^\infty x f(x; 0, \sigma) dx \quad (7)$$

$$= h(0, \sigma) \quad (8)$$

$$= \sqrt{\frac{2}{\pi}} \sigma. \quad (9)$$

In this paper, our main goal is to describe a simple and robust method to estimate d and σ (either implicitly or explicitly), given an unknown sequence $\mathbf{x}$, and to determine whether the calculated d reaches statistical significance (i.e., is consistent with the existence of true underlying alternans). In particular, we seek a method that does not require finding an explicit solution to (3).

While a realistic sequence may not be exactly modeled as $\mathbf{d}$, it nevertheless provides a good starting point. One needs to calculate two parameters in order to estimate d and σ . The first is simply the average alternans magnitude of the original sequence, $\hat{\mu} = \mu(\mathbf{x})$. The second parameter is introduced as follows. The key to differentiating an alternating sequence from a sequence with added noise but no alternans is the observation that the apparent average alternans is dependent (independent) on the order of elements in the former (latter).

Let $\pi_k(\mathbf{x})$ be a random permutation of $\mathbf{x}$, i.e., a sequence composed of the same values as $\mathbf{x}$ but in a random order. Assuming that $\mathbf{x}$ has the same dynamics as $\mathbf{d}$, on average each member L of $\pi_k(\mathbf{x})$ will be adjacent to one L and one H . Similarly, each H will be adjacent to one H and one L . Hence, the distribution of the random variable $X_i = |A_{i+1} - A_i|$ for $A_i \in \pi_k(\mathbf{x})$ exhibits a probability density function which is a combination of those derived from $\mathbf{e}$ and $\mathbf{d}$, i.e., $(f(x; 0, \sigma) + f(x; d, \sigma))/2$. Therefore

$$E[X] = \frac{h(0, \sigma) + h(d, \sigma)}{2}. \quad (10)$$

Let us now define

$$\mu_0 = \frac{1}{n!} \sum_k \mu(\pi_k(\mathbf{x})) \quad (11)$$

the summation of which occurs over all possible permutations of $\mathbf{x}$. Under this condition, we expect that μ_0 approaches $E[X]$. Accepting this assumption as valid and using (6) and (9), we can derive the following equation:

$$\sigma = \sqrt{\frac{\pi}{2}} (2\mu_0 - \hat{\mu}). \quad (12)$$

In this way, μ_0 provides the second parameter for estimating d (to be shown shortly hereafter in Section II-A) and σ . The basic idea for the detection algorithms discussed in the following is that if $\mathbf{x}$ is in fact alternating, then $\hat{\mu}$ will be significantly different from μ_0 . In order to test this, we define the null hypothesis as $H_0: \hat{\mu} = \mu_0$. We will derive the formula for the standard error of μ_0 in the discussion of Algorithm 2 and will show that $\sigma/\sqrt{n}$ is a good approximation. Hence, we can calculate the z -score as

$$z = \frac{\hat{\mu} - \mu_0}{\sigma/\sqrt{n}}. \quad (13)$$

The rejection of H_0 , based on a prechosen z -score cutoff, is indicative of alternans being present with the corresponding level of statistical significance.

A. Algorithm 1: Monte Carlo Simulation

The first algorithm is conceptually the simplest one; however, its time complexity is not optimal. The basic idea is to explicitly calculate μ_0 , starting from (11), but instead of generating all $n!$ permutations of the original sequence, we settle for a random subset of permutations. Specifically, for a given input sequence $\mathbf{a}$, we calculate the mean alternans magnitude $\hat{\mu} = \mu(\mathbf{a})$. Next, we generate m different random permutations (π_1 to (π_m)) of $\mathbf{a}$ and calculate the mean alternans magnitude for each permutation. In this way, we make the following assumption:

$$\mu_0 = \frac{1}{m} \sum_{i=1}^m \mu(\pi_i(\mathbf{a})). \quad (14)$$

We estimate the noise level and the z -score using (12) and (13), respectively, and alternans is detected in $\mathbf{a}$ if $z > z_0$, where z_0 is a preset cutoff value.

Moreover, we can estimate d by solving $\hat{\mu} = h(d, \sigma)$. One useful shortcut stems from the observation that $h(x, y) \approx \sqrt{x^2 + y^2}$. Hence

$$d \approx \sqrt{\hat{\mu}^2 - \sigma^2}. \quad (15)$$

Caution has to be practiced when generating random permutations of a sequence to avoid introducing bias into the process. An efficient and proven method, such as the Knuth–Fisher–Yates shuffling algorithm [37], ensures the randomness of the resulting sequences.

Algorithm 1 is simple to implement; however, its performance is suboptimal. Its time complexity is $O(nm)$, where n is the number of elements in $\mathbf{a}$ and $m = n!$ is the number of permutations generated. In general, calculating μ_0 accurately requires $m \gg n$. Fortunately, as described in the following, it is possible to improve this complexity by calculating μ_0 analytically in $O(n \cdot \log(n))$.

B. Algorithm 2: Analytic Monte Carlo (AMC)

The goal here is to improve on the time complexity of Algorithm 1 by deriving an analytical form for μ_0 . We define the rank $K(i)$ of an element A_i of the input sequence $\mathbf{a}$ equal to its index if $\mathbf{a}$ is sorted in a nondescending order. For example, if $\mathbf{a} = \{50, 55, 49, 54, 57, 52\}$, then $K(2) = 5$, since the index of the second element (55) in the sorted input sequence $\{49, 50, 52, 54, 55, 57\}$ is equal to 5. As shown in Appendix A, the closed form of μ_0 can be represented as

$$\mu_0 = \frac{2}{n(n-1)} \sum_{i=1}^n (2K(i) - n - 1) A_i. \quad (16)$$

This equation forms the basis for the AMC algorithm. Given $\mathbf{a}$, we first find $\hat{\mu} = \mu(\mathbf{a})$. Then, $\mathbf{a}$ is sorted to find the rank of each item. Next, (16) is used to calculate μ_0 . Finally, the algorithm continues similarly to Algorithm 1 by calculating the z-score and comparing it to the cutoff value. AMC has a time complexity of $O(n \cdot \log(n))$, resulting from the sorting stage.

Equation (16) is also the basis for finding the standard error of μ_0 . Let $\mathbf{D} = \{\mathbf{d}_1, \mathbf{d}_2, \dots\}$ be a set of sequences generated according to the same dynamics as $\mathbf{d}$. Our goal is to find the standard deviation of a set whose elements are $\mu(\mathbf{d}_j)$, which is equal to the standard error of the estimation of $\mu(\mathbf{d})$. Under these conditions, we may assume that each A_i is an independent random variable with the same standard deviation as ε , i.e., $\sigma/\sqrt{2}$. Since $\text{Var}(\sum_i \alpha_i X_i) = \sum_i \alpha_i^2 \text{Var}(X_i)$ for independent random variables X_i and constant α_i , we have

$$\text{Var}(\mu_0) = \text{Var} \left(\frac{2}{n(n-1)} \sum_{i=1}^n (2K(i) - n - 1) A_i \right) \quad (17)$$

$$= \frac{4}{n^2(n-1)^2} \left(\sum_{i=1}^n (2K(i) - n - 1)^2 \text{Var}(A_i) \right) \quad (18)$$

$$= \frac{2\sigma^2}{n^2(n-1)^2} \sum_{i=1}^n (2i - n - 1)^2 \quad (19)$$

$$= \frac{2\sigma^2}{n^2(n-1)^2} \frac{n(n-1)(n+1)}{3} \quad (20)$$

$$= \frac{2(n+1)}{3n(n-1)} \sigma^2. \quad (21)$$

The transition from $\sum_{i=1}^n K(i)$ to $\sum_{i=1}^n i$ is valid because for $1 \leq i \leq n$, $\{K(i)\}$ is just a permutation of $\{1, \dots, n\}$. We can calculate the standard error as

$$\sigma(\mu_0) = \sigma \sqrt{\frac{2(n+1)}{3n(n-1)}} \quad (22)$$

$$\approx \sigma \sqrt{\frac{2}{3n}} \quad (23)$$

$$\leq \frac{\sigma}{\sqrt{n}} \quad \text{if } n \geq 5. \quad (24)$$

The last approximation is used in Algorithms 1 and 2. It is a conservative approximation that overestimates the true value of $\sigma(\mu_0)$ by a factor of $\sqrt{3/2} = 1.224745$.

The detailed derivation of (16) is presented in Appendix A. A sketch of the proof follows here. Assume that we generate all $n!$ different permutations of $\mathbf{a}$ and add the corresponding $\mu(\pi_k(\mathbf{a}))$, for $1 \leq k \leq n!$. The summation has $(n-1)n!$ terms of the form $|A_i - A_j|$ (note that the indices point to the position of each element in the original sequence $\mathbf{a}$). Now, we can convert $|A_i - A_j|$ to $A_i - A_j$ if $A_i > A_j$; otherwise, it can be converted to $A_j - A_i$. Each element A_j participates in $k = 2(n-1)!(n-1)$ terms. In each term, it has a plus sign if it is larger than A_j , which happens with a probability of $(K(j) - 1)/(n-1)$, and a minus sign if it is smaller than A_j with a probability of $(n - K(j))/(n-1)$. Hence, the coefficient of A_j in the final sum is proportional to $2K(j) - n + 1$. The rest of the proof deals with finding the correct normalization factor.

III. Results

In this section, we present the simulation-derived performance results of the AMC algorithm. First, we explore the response of the algorithm to pure noise input. Next, we compare the performance of the AMC algorithm to that of a standard spectral method (SM) widely used in practice [21] and a generalized likelihood ratio test (GLRT) method [38], [39].

Fig. 2 depicts a histogram showing the distribution of the noise estimation [i.e., σ in (12)] by the AMC algorithm when it is fed a nonalternating sequence with Gaussian noise, similar to sequence $\mathbf{e}$ with $\mathbf{e} = N(0, 1)$. As expected, the mean is $\approx \sqrt{2}$.

To implement SM, we applied a Hamming window to the input sequence followed by a fast Fourier Transform. The alternans ratio k was defined as the ratio of the spectral power at $0.5f$ to the mean noise power (measured in the $0.4f$ – $0.45f$ window). We implemented the

Laplacian noise-optimized variant of the GLRT algorithm (also called GLRT-L) [40]. For an input sequence $\mathbf{x} = \{X_1, X_2, \dots, X_n\}$, GLRT was calculated by de-trending the data and subtracting the mean, $Y_i = X_i - \bar{p}$, and then negating the values at the odd indices, $Z_i = (-1)^i Y_i$. Let $Z_0 = \text{median}_{i=1}^n(Z_i)$. The GLRT output parameter was calculated as $l = \sum_{i=1}^n (|Z_i| - |Z_i - Z_0|) / C$, where C is a constant proportional to the baseline noise.

Sequences of APD values were simulated with a known “true” alternans magnitude (i.e., d) and three different types of added noise. First, we tested sequences with varying amounts of added random Gaussian white noise (with rms power of $\sigma / \sqrt{2}$). The signal-to-noise ratio (SNR) was defined as d / σ . For each SNR, 5000 sequences were generated and subjected to the AMC, SM, and GLRT algorithms. For each algorithm, a receiver operating characteristic (ROC) curve was derived by varying a threshold parameter and finding the detection rate for the given threshold among the 5000 generated sequences (sensitivity) and among a matched set of 5000 generated sequences with no alternans (1-specificity). For a given threshold t , the detection rate was the ratio of sequences with the output parameter (z for AMC, k for SM, and l for GLRT) greater than t . Fig. 3(A) includes the ROC results for SNR = 1. In this case, AMC and SM were similar, while GLRT had a better performance. Here, the performance was defined as the area under the ROC curve (AUC).

The second type of noise was Laplacian (with a double exponential probability distribution), which has been proposed as a more realistic model of ECG noise [39]. Fig. 3(B) shows the ROC curve for the three algorithms applied to random alternating sequences with added Laplacian noise (SNR = 1). As earlier, AMC and SM were similar, whereas GLRT outperformed both, albeit to a greater extent. This result is consistent with the fact that the GLRT method is based on a maximum likelihood estimator that assumes Laplacian noise.

The third type of added noise relates to *frame-shift* errors, which occur commonly in real signals. Some possible causes for frame-shift errors are alternans phase reversal, transient episodes of alternans in the same sequence, ectopic beats, and spurious beat detection. For example, given an alternating sequence $\{L, H, L, H, \dots\}$, a frame-shift error can result in a sequence of the form $(\dots, L, H, H, L, \dots)$ or $(\dots, H, L, L, H, \dots)$. For an input sequence $\mathbf{x}$, the shift probability p_s is defined as the probability of a frame shift for any two consecutive elements, X_i, X_{i+1} .

Fig. 3(C) and (D) compares the performance of the three algorithms applied to sequences with a 0.1 frame shift probability (C: with added Gaussian noise, SNR = 1; D: with added Laplacian noise, SNR = 1). Particularly, under Gaussian noise conditions, the GLRT algorithm was very sensitive to frame shift noise and its performance degraded with even a small shift probability. The AMC method was mostly resistant to frame-shift errors, while SM performance was in the middle.

Fig. 4 shows ROC comparisons amongst the AMC, SM, and GLRT algorithms for a range of sequence lengths, Laplacian noise, and the expected numbers of frame-shift errors in a given sequence np_s where n is the sequence length and p_s is the shift probability. For each data point, we determined the best algorithm based on the AUC calculated from 20 000 generated sequences. Fig. 4 shows that GLRT was the optimal algorithm for low SNR/low frame shift points, whereas AMC performed better for points with higher SNR and larger frame shift numbers. SM performance was generally in the middle and not optimal for any point; hence, no SM region is shown in the graph.

In order to further probe the functionality of each algorithm under frame shift noise, we tested sequences of different lengths (2^r , for $4 \leq r \leq 8$) and added random Gaussian white

noise ($\text{SNR} = 3$). As earlier, for each set of parameters, 5000 sequences were generated and subjected to AMC, SM, and GLRT. A *detection rate* was calculated in each case [see Fig. 5(A)–(C)]. The detection rate was the probability that the target algorithm returned *true*. For AMC, a positive detection was defined as $z > 2$; for SM, positive detection corresponded to $k > 3$ (according to standard practice); similarly, for GLRT, positive detection corresponded to $l > 3$.

As expected, for all three algorithms, the detection rate increased for longer sequences. For short sequences ($n \approx 16$), all three algorithms showed great sensitivity to frame-shift errors. For longer sequences, the detection rate of SM and GLRT improved slightly and approached a limiting curve [see Fig. 5(B) and (C)], whereas AMC showed continuing improvement [see Fig. 5(A)].

Fig. 6 demonstrates how the algorithm can be used to detect alternans in experimental data (in this case, transmembrane fluorescence optical mapping recordings were used). The experimental setup was described previously [30]. In brief, arterially perfused canine right ventricular preparations were stained with a voltage-sensitive fluorescent dye. Linear high spatial resolution optical mapping images were obtained from the endocardial surface by a line-scan charge-coupled device camera. After realtime processing, the data were reduced to 128 channels. A span of the recording line ≈ 2.75 cm in length is depicted in Fig. 6(A) and (B). The channel located at 0 was fed to a real-time control system implementing the adaptive diastolic interval algorithm [31], which modulated the timing of the pacemaker spikes to suppress alternans. Three sequential recordings were processed using AMC [see Fig. 6(A) and (B)]. The first recording (blue trace) shows how static (control-off) pacing induced alternans. A segment of the recorded signal at the control channel and the measured APDs is shown in Fig. 6(C). There was clear alternans, both visually, and as detected by AMC. Note that discordant alternans was induced in this example, hence the presence of areas of reduced alternans (*nodes*). In the second recording (green trace), an alternans control pulse sequence was successfully applied at the proximal end of the tissue and eliminated alternans as was reflected in the spatially extended z-score computed. Example three (red trace) shows the reversion back to alternans when static pacing was resumed.

IV. Discussion

In this paper, we present a new class of algorithms for the detection and measurement of alternans in generic sequences. We further provide an analytical solution (AMC) that negated the need to explicitly generate a large number of random test sequences and one which poses near-optimal time complexity. Additionally, we tested the noise (Gaussian, Laplacian, and frame shift) and sequence length sensitivity of the algorithm and compared its performance with that of the SM and GLRT methods. Finally, we applied our algorithm to actual signals obtained during optical mapping, and in doing so showed their applicability in real experiments.

Over the last 25 years, many different algorithms and methods have been proposed for alternans detection [24], so many that one may wonder what the incentive for the development of yet another algorithm might be. It should be noted that various algorithms for alternans detection cannot be simply ranked on an absolute scale as better or worse—each algorithm has specific advantages and disadvantages.

In choosing a particular algorithm for a given detection task, one should take into consideration the specific nature of the input signal, including the expected alternans amplitude, the type and magnitude of the noise, availability of multiple correlated input channels,¹ and the duration of the input signal in addition to computational constraints

(processor speed, available memory, presence of a hardware floating point unit, online versus offline computation).

Most alternans detection algorithms have been designed and validated for the detection of MTWA; thus, they are geared toward relatively low SNR signals and long sequences that are primarily contaminated with Gaussian or Laplacian noise. On the other hand, our primary motivation in developing this new class of algorithms was the detection of alternans in optically recorded signals. The particular characteristics of optical signals are relatively large SNR (> 1), short sequence lengths (≈ 15 – 30 beats), and the additional presence of non-Gaussian noise (i.e., frame-shift errors). In addition, as was shown in Section III, these new algorithms have near-optimal performance for this class of signals.

The source of frame shift or phase errors depends on the particular type of the input signal. For detection of MTWA in surface ECG signals, premature ventricular beats or runs of ventricular tachycardia introduce frame-shift error. Typically, input signals with even a modest burden of premature beats are excluded from MTWA analysis. The use of a method that is (partially) resistant to frame-shift errors expands the range of acceptable inputs. In this paper, our experimental focus was on optically recorded transmembrane potentials, for which mis-detection of action potentials may result in frame-shift error. Another source of phase error is the presence of two or more intervals of transient alternans in the input signal, which can occur in both surface and intracardiac signals.

A secondary motivation was the development of an algorithm that can be easily implemented in an implanted device like a pacemaker or an implantable cardioverter-defibrillator, which imposes severe constraints on the time and space complexity allowable. AMC fulfills this condition because not only does it possess favorable time and space complexity, but also it is numerically stable and can be implemented using fixed-point arithmetic.

Another advantage of the presented algorithms is that its output is expressed in terms of a z -score, which can then be tested and understood using standard statistical methodology. This feature is particularly useful in the case of novel signals, such as optical recordings, for which the algorithm is not validated formally.

The ability to detect and quantify experimentally observed alternans is particularly useful when trying to better understand the dynamics of alternans and its relationship with reentrant wave formation and VF initiation. Although recent studies have aimed to uncover the dynamics of alternans initiation, the mechanisms(s) are not completely understood (especially for discordant alternans initiation). Subtle changes in pacing rate [42], ectopic beat activity [43], and conduction-velocity/APD restitution [44] interactions may all play a role. These dynamical transitions often occur very close to the system's bifurcation instability point, during periods of small alternans magnitude, and given the inherently imperfect nature of transmembrane voltage measurements (of which optical mapping is a prime example), these conditions can be difficult to analyze. Moreover, many of these phenomena are transient and require the ability to detect alternans, given a short segment of the data. Experiment-tailored statistical tools could also aid in better understanding the dynamics of wave propagation conduction block [26], [27], [42]–[44] and the genesis of spiral waves (and wavelets) [45], [46].

¹The alternans detection algorithm can include multiple input channels in its analysis to enhance the accuracy of detection (*multilead analysis*) [41].

In general, successful alternans detection requires careful attention to the characteristics of the input signal, the external constraints of the system, and the nature of the desired output. The algorithms described in this paper, especially the implicit form formulated in AMC, provide investigators with an additional tool to perform this task and may in fact be optimal for a certain class of input signals.

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Appendix A. Proof of the Correctness of Algorithm 2

In this appendix, we prove (16), which is

$$\mu_0 = \overline{\mu(\mathbf{a})} = \frac{2}{n(n-1)} \sum_{i=1}^n (2K(i) - n - 1) A_i \quad (25)$$

where $\mathbf{a}$ is the input sequence of n elements and $K(j)$ is the rank function defined in *Algorithm 2*. The starting point is the definition of the absolute value function

$$|A_i - A_j| = \beta_{ij}(A_i - A_j) \quad (26)$$

where

$$\beta_{ij} = \begin{cases} +1 & \text{if } A_i > A_j \text{ or } (A_i = A_j \text{ and } i > j) \\ -1 & \text{if } A_i < A_j \text{ or } (A_i = A_j \text{ and } i < j). \end{cases} \quad (27)$$

The reason for assigning $\beta = 1$ or $\beta = -1$ instead of $\beta = 0$ in the equal cases is to enforce a strict ordering on A_i to simplify the following discussion (see in the following). Substituting (26) into (1)

$$\mu(\mathbf{a}) = \frac{1}{n-1} \sum_{i=1}^{n-1} |A_i - A_j| \quad (28)$$

$$= \frac{1}{n-1} \left(-\beta_{21} A_1 + \beta_{n,n-1} + \sum_{i=2}^{n-1} (\beta_{i,i-1} - \beta_{i+1,i}) A_i \right) \quad (29)$$

$$= \frac{1}{n-1} \sum_{i=1}^n \alpha_i A_i \quad (30)$$

where α_i is an integer between -2 to $+2$, depending only on whether A_j is smaller or larger than its neighbor(s).

In Algorithm 1, we generated m distinct permutations of $\mathbf{a}$. Here, we consider all $m!$ possible permutations. We can write

$$\overline{\mu(\mathbf{a})} = \frac{1}{n-1} \sum_{i=1}^n \overline{\alpha_i} A_i. \quad (31)$$

Here, $\overline{\alpha_i}$ is the average value of α_i over all the permutations. Let us define l_i and r_i

$$l_i = \text{ord}\{A_j | A_j < A_i\} \quad (32)$$

and

$$r_i = \text{ord}\{A_j | A_j > A_i\}. \quad (33)$$

In other words, l_i is the number of items in $\mathbf{a}$ which are smaller than A_i , whereas r_i is the number of items which are larger. Now, considering all the permutations, the probability that A_j is at one end of a permutation is $2/n$, and the probability that A_j is larger than its neighbor is $l_i/(n-1)$; hence,

$$P(\alpha_i = +1) = \frac{2l_i}{n(n-1)} \quad (34)$$

where $P(S)$ stands for the probability of the statement S being true. Similarly

$$P(\alpha_i = -1) = \frac{2r_i}{n(n-1)} \quad (35)$$

To find the probability of $\alpha_i = +2$, we multiply the probability that A_i is not at one end of the permutation $(n-2)/n$ by the probability of A_i being larger than or equal to its two neighbors

$\frac{l_i(l_i-1)}{(n-1)(n-2)}$ to obtain

$$P(\alpha_i = +2) = \frac{l_i(l_i-1)}{n(n-1)}. \quad (36)$$

Again

$$P(\alpha_i = -2) = \frac{r_i(r_i-1)}{n(n-1)}. \quad (37)$$

The probability that $\alpha_i = 0$ is $1 - P(\alpha = +1) - P(\alpha = -1) - P(\alpha = +2) - P(\alpha = -2)$. In summary

$$P(\alpha_i = x) = \begin{cases} \frac{2l_i}{n(n-1)} & x = +1 \\ \frac{2r_i}{n(n-1)} & x = -1 \\ \frac{l_i(l_i-1)}{n(n-1)} & x = +2 \\ \frac{r_i(r_i-1)}{n(n-1)} & x = -2 \\ \frac{n(n-1) - l_i(l_i+1) - r_i(r_i+1)}{n(n-1)} & x = 0. \end{cases} \quad (38)$$

By definition, we have

$$\overline{\alpha_i} = P(\alpha_i = +1) - P(\alpha_i = -1) + 2P(\alpha_i = +2) - 2P(\alpha_i = -2). \quad (39)$$

Simplifying

$$\overline{\alpha_i} = \frac{2(l_i - r_i)}{n}. \quad (40)$$

Note that we used $l_i + r_i = n - 1$ in simplification. Substituting back into (31) we obtain the equation to calculate $\overline{\mu(\mathbf{a})}$

$$\overline{\mu(\mathbf{a})} = \frac{2}{n(n-1)} \sum_{i=1}^n (l_i - r_i) A_i. \quad (41)$$

We have $l_i = K(i) - 1$ and $r_i = n - K(i)$ (see the definition of $K(i)$ in Algorithm 2). Because of the strict ordering enforced by (26), these equations remain valid even if multiple elements of $\mathbf{a}$ have the same numerical value. Replacing l_i and r_i , we obtain (25).

Appendix B. Algorithm Code

Algorithm 1

Require: $\mathbf{a} = \{A_1, A_2, \dots, A_n\}$ is the input sequence and z_0 is the preset cutoff

$\hat{\mu} \leftarrow \mu(\mathbf{a})$

$\mu_0 \leftarrow 0$

for $\pi_i \in \{\pi_1, \pi_2, \dots, \pi_m\}$ **do**

$\mu_0 \leftarrow \mu_0 + \mu(\pi_i(\mathbf{a}))/m$

end for

$\sigma \leftarrow \sqrt{\pi/2}(2\mu_0 - \hat{\mu})$

$z \leftarrow (\hat{\mu} - \mu_0) \sqrt{n}/\sigma$

if $z > z_0$ **then**

return true {Alternans is detected}

else

return false {No alternans is detected}

end if

Algorithm 2

Require: $\mathbf{a} = \{A_1, A_2, \dots, A_n\}$ is the input sequence and z_0 is the preset cutoff

$\hat{\mu} \leftarrow \mu(\mathbf{a})$

$\mu_0 \leftarrow 0$

sort $\mathbf{a}$ in non-descending order

for $i = 1 \rightarrow n$ **do**

$\mu_0 \leftarrow \mu_0 + 2A_i(2i - n - 1)/(n(n - 1))$

end for

$\sigma \leftarrow \sqrt{\pi/2}(2\mu_0 - \hat{\mu})$

$z \leftarrow (\hat{\mu} - \mu_0) \sqrt{n}/\sigma$

if $z > z_0$ **then**

return true {Alternans is detected}

else

return false {No alternans is detected}

end if

Fig. 1. Half-normal and folded normal distributions. (A) Probability density function of the $A_{i+1} - A_i$ terms derived from a nonalternating sequence with added Gaussian noise. (B) Half-normal distribution (a special case of the folded normal distribution) is formed by taking the absolute value of each $A_{i+1} - A_i$ term derived from (A). (C) One half of the probability density function of the $A_{i+1} - A_i$ terms derived from an alternating sequence with added Gaussian noise (half of the bimodal distribution is shown for clarity purposes). (D) Folded normal distribution is formed by taking the absolute value of each $A_{i+1} - A_i$ term derived from (C) (and from the other half of the bimodal distribution).

Fig. 2. Histogram showing the noise estimation of the AMC algorithm in response to pure Gaussian noise inputs ($N(0, 1)$). A total 50 000 input sequences of length $n=64$ were fed into the algorithm and the noise was estimated using (12). The mean is $\sigma=1.4136 \approx \sqrt{2}$. The standard deviation of the distribution is $\approx \sigma / \sqrt{n}$.

Fig. 3. AMC, SM, and GLRT ROC curves under (A) and (C) Gaussian and (B) and (D) Laplacian noise (sequence length = 32, SNR = 1). A–B: absence of frame shift noise; C–D: frame shift noise probability = 0.1.

Fig. 4.

ROC contours (Laplacian noise) comparing AMC, SM, and GLRT algorithms for a range of SNR and the expected frame shift numbers. The red curve is for a sequence length of $n=24$, green is for $n=32$, and blue is for $n=48$. Contour lines denote equivalence between AMC and GLRT algorithms (in term of AUC equivalence). Each area is marked by the algorithm which has superior performance therein (as measured by AUC). SM algorithm was not superior in any point and has no designated area in this figure.

Fig. 5. AMC, SM, and GLRT detection rates, given varying levels of frame shift probability and varying sequence lengths (SNR = 3; Gaussian noise). Varying amounts of frame shift noise were added to sequences ($L = 16, 32, 64, 128$, and 256) of synthetic APD alternans data. The detection rate is how often (A) AMC, (B) SM, and the (C) GLRT method identified the resulting sequence as one with underlying alternans (5000 sequences were simulated for each data point).

Fig. 6. Alternans detection applied to optical mapping data. AMC and (15) were used on action potential sequences (22 APDs) derived from a 2.75 cm region of cardiac tissue during an alternans control experiment. The alternans control sequence was off(blue)–on(green)–off(red), and the resulting (A) z-scores and (B) d-values (i.e., estimated underlying alternans magnitude) that were calculated at each point are shown. (z -score >2 indicates alternans is

present). (C) Transmembrane fluorescence signal from the site of electrode stimulation and the resulting APD values shown above [data used in that of the blue trace in (A) and (B)].

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