A Combinatorial Algorithm to Detect Higher-Order Dynamics in Cardiac Signals

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Abstract

Repolarization alternans is one of the mainstays of theoretical cardiac electrophysiology and provides a link between cellular dynamics and fibrillation. Action potential duration (APD) alternans is the simplest manifestation of repolarization dynamics. However, cardiac dynamics is complex and does not stop at period-2. Excitation-contraction coupling can generate higher-order periodicities that are precursors to chaotic rhythms. Higher-order periods have been experimentally elusive and only detected in a few cases.

We detect higher-order periods using a combinatorial algorithm. The key idea of the algorithm is to set up a weighted-directed graph, where the vertices correspond to the beats, and the links are assigned according to the distance metric function between the beats. The shortest path between the first and last beats in the graph determines the optimal periodicity of each beat.

We applied the algorithm to optical-mapping signals recorded using voltage-sensitive fluorescent dyes to six human heart transplantation recipients. We detected periods 4, 6, and 8, and higher (chaotic areas) with heterogeneous spatial distribution.

Our graph-based algorithm is a valuable tool to probe the complex dynamics of cardiac tissue by looking beyond classic alternans, especially at fast rates and before the transition to chaotic fibrillation.

1. Introduction

Malignant ventricular arrhythmias, including polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF), are the leading causes of sudden cardiac death [1]. However, the transition mechanisms from a regular rhythm to chaotic VF are still poorly understood. The concordant to discordant Action Potential Duration (APD) alternans pathway to VF initiation is one of the most extensively studied mechanisms of VF initiation [2].

The APD alternans is the beat-to-beat (period-2) oscillation in the APD and is one of the mainstays of theoretical cardiac electrophysiology. APD alternans is the simplest quantifier of repolarization dynamics. Classic alternans with period-2 results from the first bifurcation in a cascade of bifurcations with periods of 2, 4, 8, and higher powers-of-two. We anticipate that as the cycle length becomes shorter, higher-order periods appear until the system transitions to chaos and, hence, VF. The intermediate stages in the period-doubling cascade in cardiac tissue have been experimentally elusive and are reported in only a few animal models but not in human hearts.

Frequency analysis is the standard method to detect alternans and higher-order dynamics in long duration recordi. However, it is less effective for shorter duration recordings and in the presence of intermittent bursts of higher-order dynamics. In this study, we aim to develop a robust and practical algorithm for detecting higher-order periodicities in time series of cardiac signals composed of (typically) 50-150 beats.

2. Methods

2.1. Experimental Setup

We studied explanted human hearts obtained from recipients of heart transplantation at the time of surgery. Optical mapping using voltage-sensitive fluorescent dyes was performed [3]. Hearts were stimulated at an increasing rate until VF was induced. Signals from the right ventricle endocardial surface before induction of VF and in the presence of 1:1 conduction were processed to detect global and local repolarization dynamics.

2.2. The Algorithm

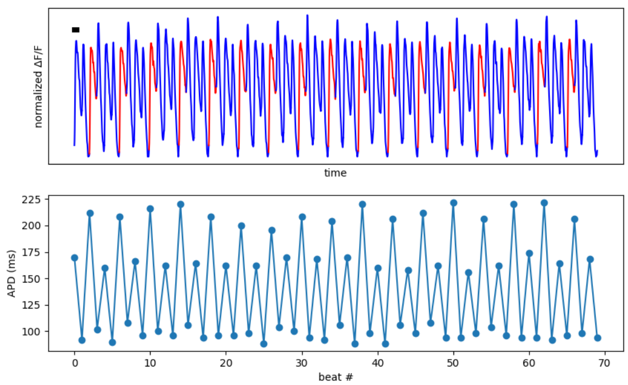


Figure 1. Example optical mapping signal and the corresponding APD trend from a human heart showing obvious period-4.

The combinatorial (graph-based) algorithm finds the optimal periodicity of each beat in each input sequence [4]. Figure 1 shows a representative optical mapping recording and the corresponding APD trend that shows obvious period-4.

For each pixel, the input to the algorithm is a sequence of n beats separated by the upstrokes of the action potential. Let $d(i,j)$ be a distance function that returns a non-negative real value, quantifying the difference between beats $i$and j. We assume that $d(i,j)$ satisfies the metric axioms, meaning that $d(i,i) = 0$, $d(i,j) = d(j,i)$, and $d(i,j) + d(j,k) \geq d(i,k)$. In this paper, we define the distance as the mean squared difference between beats. Figure 2 depicts the recurrence map for Figure 1, showing the pairwise similarity index (the inverse of the distance). We see the regular pattern formed because of period-4 with intermittent breaks in the pattern.

We start the discussion by presenting the combinatorial algorithm to detect period-2 alternans. Our task is to classify each beat in the input sequence as one of two classes A and B. For example, A can be the long APD beats and B the short APD ones. A stable alternating sequence can be written as ABABAB. For such a sequence, we can simply assign A to the odd beats and B to the even beats. However, the input sequence may glitch (e.g., two adjacent beats are both short APD) such that the odd/even algorithm fails to work. This problem is especially relevant to higher-order periodicity, where glitches and frameshifts are the rules rather than the exception (Figure 2). The combinatorial algorithm is designed to overcome this shortcoming of simple periodicity detection algorithms.

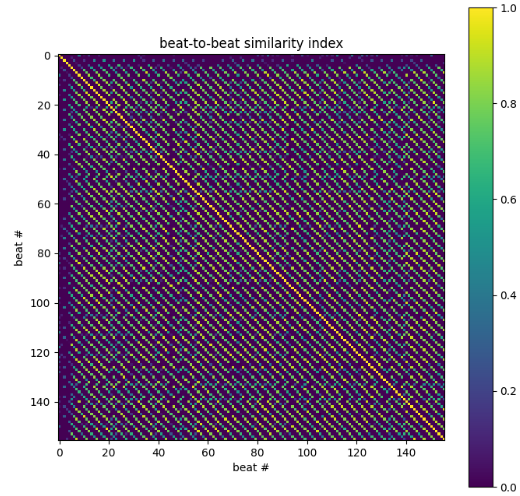


Figure 2. A recurrence graph showing the similarity index between the beats in Fig 1. A value of 1 means identical (the main diagonal) and a value of 0 means no significant similarity.

We find the optimal assignment by setting a weighted directed graph in such a way that the shortest path between the starting vertex (beat 1) and the last vertex (beat n) reveals the optimal assignment (Figure 3).

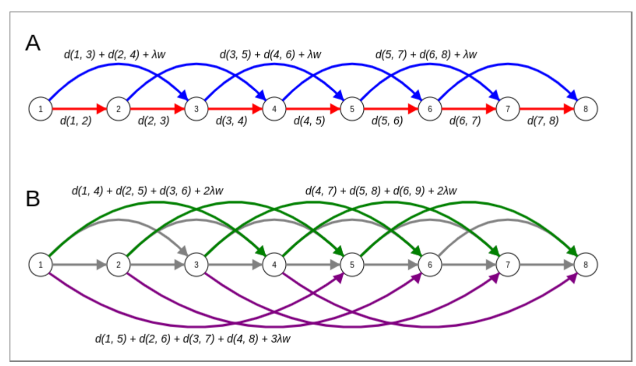


Figure 2. Schematics of the combinatorial algorithm for periodicity analysis.

Let $G = (V, E)$ be a graph composed of n vertices (corresponding to n beats) and $m > n$ edges. For the detection of period-2, we set up two edge types. An edge of the first type connects vertex i to vertex $i + 1$ with weight $d(i, i + 1)$. An edge of the second type connects i to $i + 2$ with weight $d(i, i + 2) + d(i + 1, i + 3) + \lambda w$, where w is the mean distance between two adjacent vertices and λ is a super-parameter. The second term is for regularization to prevent spurious high-order detection by favoring shorter periods. The optimal solution is found by assigning A to each vertex on the shortest path from 1 to n and B to the vertices not on the shortest path.

For detection of period-4, we expand the possible classes of assignment to {A,B,C,D}. Now, an ideal input sequence is ABCDABCDA. We can modify the algorithm above by adding edges of type $i \rightarrow i+3$ and $i \rightarrow i+4$ to detect periods up to 4.

Finally, we extend the algorithm to detect all periodicities up to a maximum p (Algorithm 1). In this paper, we set $p = 8$. We add p outgoing edges to each vertex i to the next p vertices with weights set as shown below. The formula for weights is designed in such a way that if the local periodicity in the vicinity of vertex i is, say q, then edge $i \rightarrow i+q$ falls on the shortest path from 1 to n. Therefore, by finding the shortest path, we can determine the local periodicities.

Algorithm 1. The Combinatorial Periodicity Detection Algorithm

Input: a sequence of n beats, a distance metric $d(i,j)$ between any two beats, and a maximum periodicity of p.
Output: a sequence of n integers in the range 1 to p, showing the best-fit periodicity for each beat.

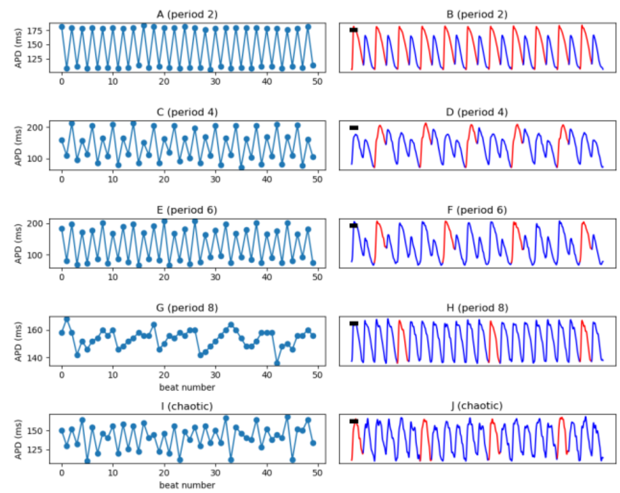
1. Setup a directed weighted graph $G = (V, E)$ with n vertices.
2. Add p outgoing edges from each vertex to the next p vertices. The weight of each edge is set as $W(i \rightarrow j) = \sum_{k=0}^{j-i-1} d(i+k, j+k) + (j-i-1)\lambda w$.
3. Find the *shortest path* from vertex 1 to vertex n.
4. The weights are assigned in such a way that the shortest path encodes the periodicity of each beat according to which outgoing edge is included in the shortest path.
5. Read the beat-wise periodicity from the shortest path!

3. Results

We applied the algorithm to optical-mapping signals recorded using voltage-sensitive fluorescent dyes to six human hearts obtained from heart transplantation recipients.

Frequency analysis revealed a prominent and statistically significant 1:4 peak (period-4) in three hearts. A borderline peak of uncertain significance was seen in another one. No 1:4 peak was present in two hearts. Figure 4 lists representative examples of period-2, period-4, period-6, period-8, and higher-order chaotic signals and the corresponding APD trends. Period-4 is stable, but higher-order periods are intermittent. Specifically, the period-8 signal is irregular but still has sufficient periodicity to be annotated period-8 by the local algorithm.

Figure 3: Representative APD alternans trends and optical mapping signals with periods 2, 4, 6, 8, and chaotic.



The distribution of areas with higher-order periodicity is heterogeneous in space and time and variable in different hearts. The spatial distribution of the dominant periodicity in four hearts is depicted in Figure 5. Period-4 regions are mainly circular and may anchor to anatomical structures, in contrast to period-6 and -8 regions that are spatially expanded and have a dynamical nature.

4. Conclusion

Our combinatorial (graph-based) algorithm is a valuable tool for probing the complex dynamics in cardiac electrophysiology. The algorithm is designed to detect higher-order periods in short segments of cardiac signal and in the presence of noise. Higher-order dynamics, beyond period-2 of classic alternans, occur commonly in diseased hearts. Our results suggest that the

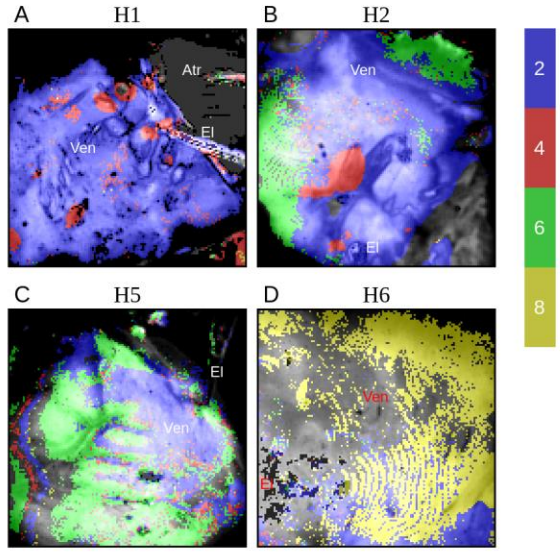


Figure 4. Spatial distribution of higher-order periodicities in four ex vivo human hearts.

period-doubling route to chaos may be one of the mechanisms of initiation of ventricular fibrillation. Detection and localization of higher-order dynamics may help with risk stratification and guide ablation of ventricular fibrillation.

Acknowledgments

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