# Spatio-temporal Wavefront Isolation an Approach to Quantify Fibrillation Complexity

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## Abstract

*Quantification of the complexity of fibrillatory processes may objectify the modifications induced by a therapy. However, its evaluation is usually restricted to a subjective visual inspection. The objective of this work is to classify isochronal maps attending to their organization into 3 types. An automatic classification method based on spatio-temporal isolation of activation wavefronts is presented. The method was tested on ventricular fibrillation recordings from 17 Langerdorff-perfused rabbit hearts using a 121 multielectrode with (N=9) and without (N=8) perfusion with propranolol. With the proposed method, changes in complexity caused by propranolol caused an increase in type I activations (21.2 vs. 49.9) and a decrease in type II (62.5 vs. 39.4) and type III (16.3 vs. 10.7), $p < 0.001$. The proposed method appears as a valuable tool for determining the complexity of multichannel recordings obtained during fibrillation in a fast, automatic and reproducible way.*

## 1. Introduction

Cardiac fibrillation is a complex arrhythmia whose mechanisms of onset, maintenance and interruption are not completely understood and thus they are still relevant subjects of research [1-2]. Analysis of the changes induced by drugs or maneuvers that alter the electrophysiological properties of the myocardium is of importance for understanding the mechanisms of maintenance of the arrhythmia and for developing better therapies. Moreover, the level of complexity of the arrhythmia is also relevant to estimate the probability of termination of the arrhythmia by the use of electrical therapies [3].

In order to quantify the complexity of isochronal maps during fibrillation a classification criterion and terminology was proposed by Konings [4], rating the complexity of isochronal maps according to a scale from type I to type III corresponding to increasing degrees of complexity. This classification criterion has been widely used in bibliography [5], but its main drawback is the need for an experienced observer to visually inspect the data, resulting in a very time-consuming task which additionally suffers from subjective variability.

This work describes implements and evaluates a methodology to completely automate the classification of epicardial maps based on Konings' criteria. To test the performance of our method, short-term reproducibility was assessed by comparing the results of analyzing consecutive fragments of 121-lead EGMs during induced ventricular fibrillation (VF) in eight isolated rabbit hearts, since long lasting VF remains stable while coronary perfusion is maintained [6]. Ability of our method to detect differences in complexity was also assessed by comparing complexity markers obtained for nine rabbit hearts perfused with propranolol, a drug which has the effect of making fibrillation less complex, to those obtained without drug infusion.

## 2. Materials and methods

### 2.1. Data analysis

EGM signals were processed in order to reduce noise content. Baseline removal was performed to each recording by using a high-pass filter (fc = 0.7 Hz) and a notch filter was used to eliminate power line interference (cutoff frequencies: 49.2 and 50.8 Hz).

Activation times (ATs) were automatically detected for each channel by identifying time instants corresponding to steep descents in the recording with spatio-temporal continuity [7]. In brief, the method of AT detection consists in (1) finding all time instants whose derivative is a negative local minimum, (2) discarding low amplitude ATs appearing within a window of 25 ms centered at higher amplitude ATs (3) discarding ATs which do not propagate to/from neighboring electrodes within a window of 5 ms.

An activated lapse of time was defined as a period of 20 ms starting at each AT. For any time instant each electrode was classified either as active or inactive

according to these activated lapses of time. These states (active/inactive) were used to construct a three-dimensional data structure where two of the dimensions corresponded with the spatial dimensions of the multielectrode and the third dimension represents time. Activation volumes are then constructed by connecting neighboring active points in this three-dimensional structure after filling gaps and holes by using a modified version of the closing algorithm used for imaging processing, adapted to 3D structures. Finally, volumes constituted by less than 70 points were removed.

In order to proceed with organization quantification, activation volumes constructed for the entire recording were split into activation periods (AP) with length comparable with the dominant cycle length (DCL). In order to obtain the DCL, Welch's periodogram was used to obtain the power spectral density of the signals recorded at each unipolar electrode, using a Hamming window of 1.25 s and 50% overlap. Frequency at which the power spectral density between 5 and 35 Hz showed a maximum value was obtained for each channel. Dominant frequency (DF) of the whole recording was defined as the mean value of F. Dominant cycle length (DCL) was defined as the inverse of DF.

APs were chosen to be periods with a length ranging from 0.8•DCL to 1.2•DCL beginning and ending at instants at which the number of points belonging to the active volume was minimal. Recordings were thus divided into consecutive APs.

Each AP may contain one or more activation volumes, which, in turn, may be constituted by a number of simple wavefronts (SW) or sub-volumes connected at every time instant. These SW may also arise from the fusion of multiple SWs not connected in previous time instants or result in a fractionation into multiple SW not connected in later time instants (see Fig. 1). Also, these SWs may originate outside or inside of the exploring electrode array, with the latter being defined as a breakthrough. SWs constituted by less than 15 points were discarded. Active volumes with at least 90% of their volume enclosed by one SW are defined as compact wavefronts (CW), and represent wavefronts without major fusions or fractionations.

Complexity of each AP was quantified according to the three types of maps during fibrillation proposed by Konings [4] based on the number of detected SWs and their volumes:

-Type I: presence of a CW representing at least 90% of the total active points in the AP.

-Type II: presence of either (1) a CW representing at least 70% of the total active points in the AP plus one SW or (2) an Active volume representing at least 85% of the total active points in the AP and constituted by three SWs, condition that will be found when one major fusion or fractionation occurs.

-Type III: all other cases.

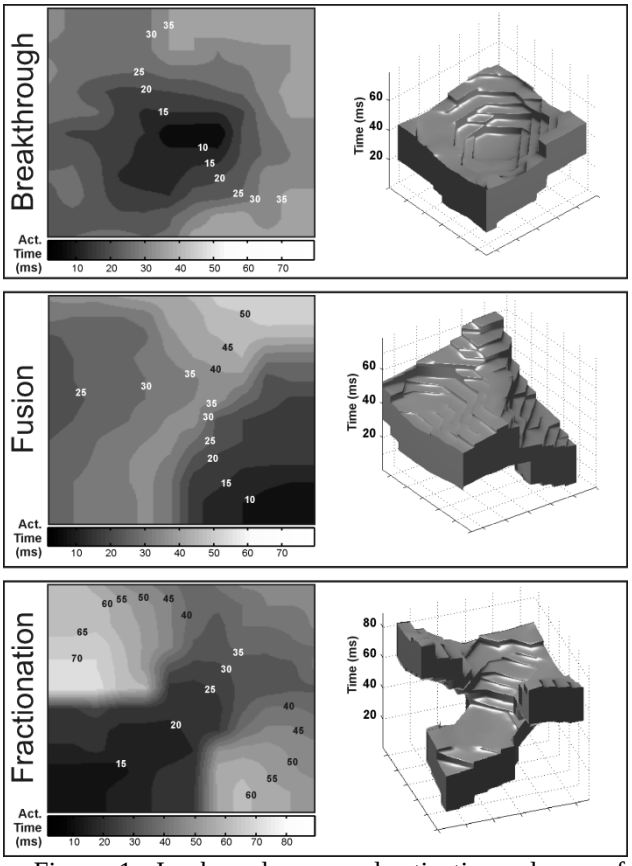


Figure. 1. Isochronal maps and activation volumes of breakthrough, fusion and fractionation. Left panels contain isochronal maps according to a gray scale: black represents early activations while white represents late activations. Right panels contain activation volumes of the same wavefronts. Top panel shows an example of a breakthrough, with a wavefront originated in the center of the multielectrode. Middle panel shows a fusion of two wavefronts. Bottom panel shows a fractionation of a wavefront into two wavefronts.

## 2.2. Performance analysis

Seventeen isolated and perfused rabbit hearts were used. After anesthesia with ketamine (25 mg/kg i.m.) and heparinization, animals were sacrificed, and their hearts were removed and immersed in cold (4ºC) Tyrode solution. Following isolation, the aorta was connected to a Langerdorff system for perfusing Tyrode solution at a pressure of 60 mmHg and a temperature of 37 ± 0.5ºC. The millimolar composition of the perfusion fluid was as follows: NaCl 130, NaHCO3 24.2, KCl 4.7, CaCl2 2.2, NaH2PO4 1.2, MgCl2 0.6 and glucose 12. Oxygenation was carried out with a mixture of 95% O2 and 5% CO2. The procedures employed in this study were in accordance with the guidelines for the care and use of animals of the US National Institutes of Health (NIH) and with the Institutional Animal Care and Use Committee.

In order to test the spatiotemporal wavefront isolation method presented, rabbit hearts were randomized either to a control group with no drug administration or to propranolol group with administration 1 μM of propranolol added to the Tyrode. Eight out of the seventeen hearts used for this study were randomized to the control group and nine were randomized to the propranolol group.

Thirty minutes after positioning the heart in the Langerdorff system, VF was induced by pacing at increasing frequencies from 4 to 20 Hz, and coronary perfusion was maintained during the arrhythmia. Pacing was performed using a bipolar electrode (diameter = 0.125 mm, interelectrode distance = 1 mm) located in the upper zone of the multiple electrode. Pacing was carried out using a GRASS S88 (Grass Instruments Inc., Quincy, MA, USA) stimulator equipped with a stimulus isolation unit (SIU5). Stimuli were rectangular pulses of 2 msec duration and intensity twice the diastolic threshold. VF was identified by visual inspection of the electrograms. Once induction of VF was achieved, pacing was stopped.

Five minutes after VF induction, unipolar electrograms (EGMs) were recorded using a multiple electrode composed of 121 unipolar stainless steel electrodes (square distribution: 11x11; diameter = 0.125 mm, interelectrode distance = 1 mm) positioned at the epicardial surface of the free wall of the left ventricle. The reference electrode was a 4 mm x 6 mm silver plaque located over the cannulated aorta.

Ten-second long recordings were obtained with a cardiac electrical activity mapping system (MAPTECH, Waalre, The Netherlands) during VF. The electrograms were amplified with a gain of 100–300, broad-band (1–400 Hz) filtered, and multiplexed. The sampling rate of each channel was 1 kHz.

In order to check the reproducibility of our algorithm, each 10 seconds control recording was divided into 2 second segments and each segment was analyzed. Measurements obtained for each segment were compared to those obtained for the following segment. Measurements include DCL, number of breakthroughs, fusions and fractionations per AP and percentage of type I, II and III APs.

With the purpose of testing the ability of our method at discriminating among different degrees of VF organization, organization was quantified both for control and propranolol groups, chosen because of the well-known regularizating effect of this drug on VF [5]. Same measurements described above were obtained for the entire recording (10 seconds) of all hearts in control group and compared to propranolol group.

Data are presented as the mean ± standard deviation (SD). Comparisons between two sets of data were performed by using Student's t-test for paired data corresponding to the reproducibility or drug assessment respectively. Differences between qualitative variables were analyzed by the $\chi 2$-test. Differences were considered significant for $p < 0.05$.

Table 1. Reproducibility Assessement

| | Sec 1-2 | Sec 3-4 | Sec 5-6 | Sec 7-8 | Sec 9- 10 |
|---|---|---|---|---|---|
| DCL | 68.2 ± 9.9 | 67.0 ± 9.6 | 68.8 ± 9.7 | 67.5 ± 11.0 | 67.6 ± 9.6 |
| BrTh | 0.36 ± 0.16 | 0.36 ±0.16 | 0.45 ± 0.32 | 0.28 ± 0.10 | 0.32 ± 0.12 |
| Fus | 0.89 ± 0.27 | 1.18 ±0.59 | 1.37 ± 0.68 | 0.90 ± 0.18 | 1.04 ± 0.42 |
| Frac | 1.13 ±0.24 | 1.45 ± 0.81 | 1.52 ± 0.55 | 1.27 ± 0.28 | 1.29 ± 0.48 |

Mean ± SD of dominant cycle length (DCL) in ms, number of breakthroughs (BrTh) per activation period (AP), number of fusions per AP (Fus), number of fractionations per AP (Frac) for consecutive 2-second segments are given.

## 3. Tables and figures

Table 1 summarizes measurements obtained for the reproducibility test. No significant differences were found between measurements from consecutive segments.

In Fig. 2 results of VF organization measurements in the reproducibility test are depicted. Classification of APs did not differ significantly between consecutive segments, obtaining variations in the percentage of type I APs in the range [18.0 ± 9.3, 27.4 ± 9.6], type II APs in the range [66.4 ± 10.3, 57.2 ± 6.7] and type III APs in [16.5 ± 12.5, 10.9 ± 7.2].

Table 2 summarizes measurements obtained for the drug effect test. Significant increasing of the DCL was found when using propranolol. Significant reductions of the rate of breakthroughs, fusions and fractionations per AP were also found during the use of the drug.

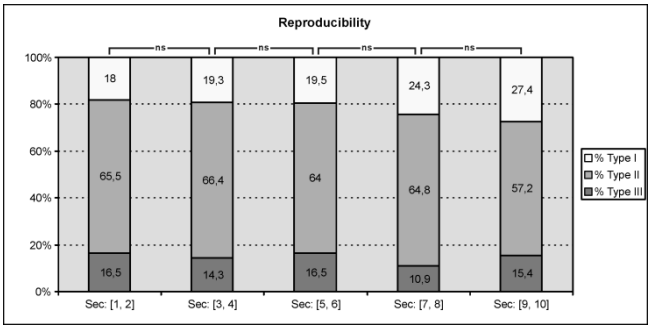


Figure 2. Organization measurements for the reproducibility test. Percentage of type I, II and III activation periods for consecutive 2-second segments are depicted. No significant differences were found between consecutive segments.

Table 2.Drug Effecty Assessement

| | Control | Propranolol | Difference |
|---|---|---|---|
| DCL | 68.6 ± 10.4 | 85.8 ± 4.3 | * |
| BrTh | 0.31 ± 0.09 | 0.18 ± 0.10 | * |
| Fus | 0.93 ± 0.19 | 0.43 ± 0.32 | * |
| Frac | 1.17 ± 0.25 | 0.49 ± 0.29 | * |

Mean ± SD of the dominant cycle length (DCL) in ms, number of breakthoughs (BrTh) per activation period (AP), number of fusions per AP (Fus) and number of fractionations per AP (Frac) for control and propranolol groups are given. (*: $p < 0.005$).

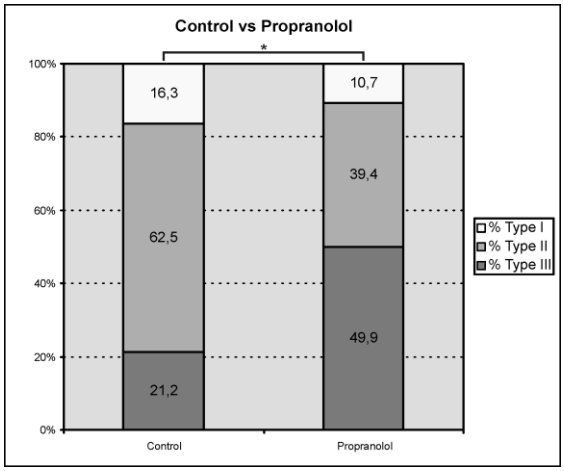

Figure. 3. Organization measurements for the drug effect test. Percentage of type I, II and III activation periods for control and propranolol are given. (* $p < 0.001$)

In Fig 3. results of VF organization measurements during the drug test are presented. Classification of APs for control and propranolol groups significantly differed in the percentage of type I APs (21.2 ± 9.4 vs. 49.9 ± 25.8), type II APs (62.5 ± 4.8 vs. 39.4 ± 19.5) and type III APs (16.3 ± 8.7 vs. 10.7 ± 9.2), $p < 0.001$. The increase of type I APs and the decrease of type II and III shows a reduction of the FV complexity when using propranolol.

## 4. Discussion

This work presents a methodology developed with the aim of automating the quantification of complexity of isochronal maps during fibrillation in an objective, fast and reproducible way. The method is based on a three-dimensional representation of the activation patterns, and subsequent decomposition of the fibrillation rhythm into its constituent activation wavefronts. Data structure is then segmented into activation periods with a length related to the frequency of the fibrillation which enables us to make an analysis of the complexity independently of the frequency of the signal, desirable since acceleration of the activity is not necessary related with more complex activation patterns. Wavefronts can then be quantified in terms of their internal fractionations, fusions and volume, and classified according to its complexity using Konings' criteria [4], widely used for the analysis of the complexity of fibrillatory processes [5-6].

Our method showed reproducible results in the analysis of stable fibrillation and has demonstrated to be able to discriminate among different degrees of VF complexity, as those observed with and without perfusion with propranolol. Decreased complexity was reflected in a lower rate of breakthroughs, fusions and fractionations consistent with an increase in the percentage of type I APs together with a decrease in type II and III APs.

VF occurs in a three-dimensional volume and is, therefore, a three-dimensional process. The method proposed for quantifying VF complexity is based on recording the electrical activity of a two dimensional surface of 1 cm2 approximately, which represents 5~10% of the total surface of the ventricular epicardium. Although this method has shown to be valuable for studying variations in complexity with minor electrophysiological modifications, accurate conclusions of the whole fibrillatory process cannot be extracted. More accurate recording systems employ up to 80 needles with several sensing sites introduced into the myocardial tissue, but this procedure has a high risk of injuring the cardiac tissue and thus modify the electrophysiological properties of the myocardium. In either case, the proposed method could be adapted to different electrode configurations.

## Acknowledgements

This work was supported by Spanish Ministry of Education and Science under TEC2009-13939.

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