Slope Entropy as a Complexity Metric for the Characterization of Electrograms in Post-Ischemic Ventricular Tachycardia

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Abstract

Slope Entropy (SlopEn) has been recently introduced as a robust estimator of the complexity degree in physiological time series. Post-ischemic ventricular tachycardia (VT) patients exhibit highly fragmented and unstructured intracardiac electrograms (EGMs), called abnormal ventricular potentials (AVPs), referable to arrhythmogenic areas. This study aims to characterize VT EGMs, specifically physiological EGMs and AVPs, in terms of SlopEn metric, to support AVPs identification.

A dataset of 344 EGMs, (65% AVPs, 35% physiological EGM), was used to assess the impact of each parameter of SlopEn (i.e., the embedded dimension m, the vertical increment threshold γ, and the proximity-to-zero difference threshold δ) in terms of significant differences, by non-parametric statistical tests, in SlopEn values between physiological EGMs and AVPs.

This analysis allowed us to identify a good set of SlopEn parameters (i.e., m=3, δ=0.0003, and γ=0.0055) able to achieve a statistically significant difference ($p<0.0001$). According to these results, SlopEn effectively characterizes physiological and pathological EGMs in post-ischemic VT, and can be considered to support the identification of arrhythmogenic areas in VT electrophysiological studies.

1. Introduction

Since information entropy was introduced by Shannon in 1948 [1], many authors applied this concept to unravel information about physiological time series. In the cardiac electrophysiology field, Kolmogorov complexity has been used on coronary sinus atrial electrograms (EGMs) [2], while Shannon's entropy was evaluated on complex fractionated atrial EGMs to quantify their complexity [3].

Slope Entropy (SlopEn), introduced by Cuesta-Frau [4] in 2019, is a novel entropy measure based on a symbolic representation of signal patterns that accounts also for amplitude information, and as such it distinguishes itself from other, well-known entropy measures. Despite this advantage, to the best of the authors' knowledge, SlopEn has never been explored before in intracardiac EGMs. Patients with post-ischemic ventricular tachycardia (VT) present highly fragmented and unstructured intracardiac EGMs, hereafter called abnormal ventricular potentials (AVPs). These signals are associated with myocardial areas able to trigger and/or maintain the arrhythmia and are usually sought after by clinicians during electrophysiological studies to guide the VT ablation procedure. The scientific hypothesis behind this study is that SlopEn could be used to characterize the physiological EGMs and the AVP by revealing statistically significant differences in terms of this metric.

2. Slope Entropy

SlopEn exploits the symbolic representation of a time series by encoding the slope between two consecutive samples. Specifically, it computes the frequency of symbolic patterns associated with sub-sequences of the analyzed time series. Given the time series vector $x = \{x_0, x_1, \dots, x_{N-1}\}$, with N the number of total samples, all possible sub-sequences $x_j^m = \{x_j, x_{j+1}, \dots, x_{j+m-1}\}$ are sequentially extracted from x. In this latter formulation, j refers to the starting sample of the specific sub-sequence, being $0 < j < N - m + 1$, while m is the embedded dimension defining the length of each sub-sequence x_j^m.

By computing the difference between consecutive samples of these subsequences, new sequences with length $m - 1$ are derived. Their conversion into the symbolic series ψ is based on the following criteria:

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$$\psi_j^m = \begin{cases} +2, & x_i - x_{i-1} > \gamma \\ +1, & \delta < x_i - x_{i-1} \leq \gamma \\ 0, & |x_i - x_{i-1}| \leq \delta \\ -1, & -\gamma \leq x_i - x_{i-1} < -\delta \\ -2, & x_i - x_{i-1} < -\gamma \end{cases} \quad (1)$$

where i is used to enumerate the sub-sequence samples, and it ranges from $j \leq i \leq j + m - 1$, γ is the threshold set on the vertical increment, and δ is the proximity to 0-difference. A list of all the possible slope patterns is created and named Ψ, and the number of matches found in the analyzed series is stored. From this, the probability distribution p is computed, normalizing the number of matches for each pattern by the length of Ψ.

Finally, SlopEn is computed as the Shannon entropy of the probabilities of the symbolic patterns, as:

$$SlopEn(\boldsymbol{x}, m, N, \gamma, \delta) = -\sum_{\forall k} p_k \log p_k \quad (2)$$

3. Materials and methods

For this study, we used a dataset composed of 119 physiological bipolar EGM signals and 225 AVPs from four post-ischemic VT patients in sinus rhythm who underwent electroanatomic (EA) mapping and radio-frequency catheter ablation. This retrospective study was approved by the Independent Ethical Committee of the ATS (Azienda Tutela Salute, Sardegna) and the enrolled participants provided their signed informed consent.

Each EGM signal, acquired using the CARTO®3 mapping system (Biosense Webster, Inc., Diamond Bar, California), is 2.5-s long and sampled at 1 kHz. Nonetheless, only the beat around a reference annotation provided by the CARTO on the 2000th sample is acquired during stable and effective contact of the electrode with the endocardium, and so under reliable acquisition conditions. Thus, only a window of 200 ms before and 300 ms after the reference point was used for the analyses.

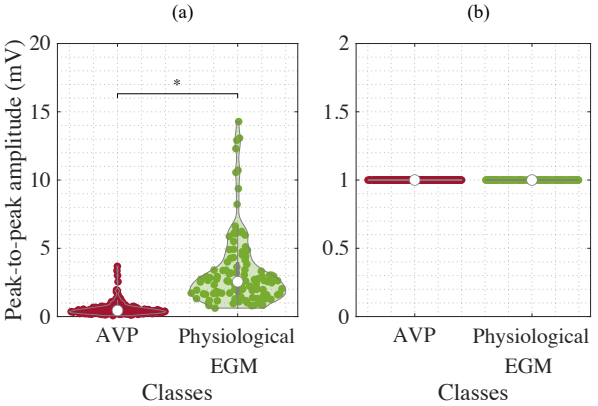

Figure 1. Distributions of the peak-to-peak amplitudes before (a) and after normalization (b) for AVPs (in red) and Physiological EGMs (in green).
$p < 0.0001$ are represented by *.

Initially, an undecimated wavelet denoising was performed, as reported in [5], to reduce the impact on the complexity metric computation of small-amplitude noise, such as the quantization errors. Specifically, the wavelet denoising was performed by using the Daubechies2 mother wavelet with a 2-level decomposition, the Universal threshold, and the soft-thresholding approach of the detail coefficients.

Then, the potential bias of the peak-to-peak amplitude (A_{pp}) in the distinction between physiological EGMs and AVPs was assessed. As shown in Fig. 1 (a), the two EGM types differ significantly, with physiological EGMs having a much higher A_{pp}. The A_{pp} bias was removed by normalizing each EGM with the min-max method and setting it to 1, as can be seen in Fig. 1 (b), and the normalized signals were then centered to be zero-mean.

As reported in Section 2, SlopEn depends on a set of three parameters (m, δ, and γ). To tune this parameters set to our post-ischemic VT dataset, we first set m equal to 3 as in [4] and started tuning γ and δ. Since these parameters correspond to thresholds on slopes (see Eq. 1), to select good values for them, we determined the slope distributions of both EGM types. To this aim, slopes were preliminarily computed as the difference between consecutive signal samples. The histogram of such values was then inspected to select a cut-off between physiological EGMs and AVP in terms of population density. Finally, a grid search was performed to identify a good set of parameters to characterize AVPs and physiological EGMs through SlopEn.

For each investigated set of parameters, the unpaired Mann-Whitney U test was performed, and the statistical significance was set at p-value < 0.05, after applying the Bonferroni correction.

4. Results and discussions

The histograms of the slopes of the EGMs (see Fig. 2) revealed that most of the samples exhibit low slope values in both groups, overall. However, for signal slope values between ±0.0003, it is evident that the percentages of observations (i.e., probability) for the physiological EGMs become higher than the AVPs' one. Conversely, the probability that consecutive samples coming from physiological signals may assume slope values outside the range defined by ±0.0003 becomes lower than for AVPs. In the light of these histogram findings, δ and γ parameters were investigated for values approaching 0.0003.

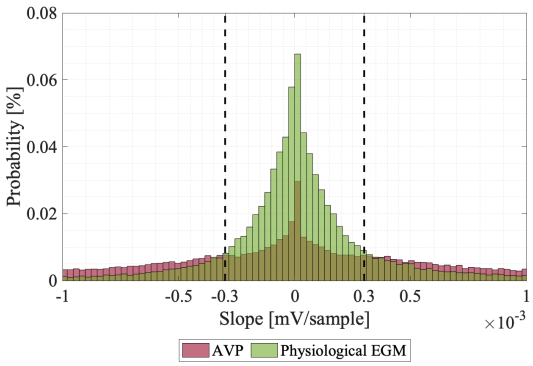

Figure 2. Zoomed central section of histograms showing the signal slope values for Physiological EGMs (in green) and AVPs (in red). The dashed black line indicates the threshold value of 0.0003.

By definition, γ must be greater than δ, hence the value 0.0003 was used to set δ and, consequently, higher values for γ were explored. To define the upper limit for γ, the maximum slope of the overall samples (both EGM types), i.e., 0.9, was considered. Therefore, at first, SlopEn was evaluated considering $m = 3$, $\delta = 0.0003$, and γ ranging from 0.0005 up to 0.9, in 0.005 steps. Figure 3 (a) shows the results of this first grid search in terms of median and interquartile range (IQR). The two curves exhibit a good separation for low values of γ (i.e., from 0.0005 to 0.0805). As γ increases, the medians of the two distributions approached each other until they completely overlap. It is noteworthy that, as γ approaches its maximum value, the number of slopes that exceeds this threshold decreases, generating small variations in the list of patterns. Indeed, SlopEn shows a plateau from $\gamma = 0.4405$ onwards, a value that is exceeded in magnitude only by a small percentage for both Physiological EGMs (i.e., 0.04%) and AVPs (i.e., 0.02%). According to this first assessment, the best results were obtained with $\gamma = 0.0055$, with a p-value < 0.0001.

Then, γ was set to 0.0003, and δ ranged from 0 up to 0.0003 in 0.00001 steps. As displayed in Fig. 3 (b), in this second grid search, the two curves exhibit a similar pattern, with a notable overlap in the IQRs and a minimal difference between the medians. An exception is observed for $\delta = 0.0003$, i.e., when both parameters have the same value, for which a higher difference between the medians is obtained. Also from a statistical perspective, this parameter configuration leads to the optimal result in this scenario, with a p-value < 0.0001. Making the δ and γ threshold equal implies a reduction in the number of thresholds involved in the symbolic representation, which in turn leads to a decreased variability in the resulting patterns. Nevertheless, the best results obtained in this second analysis are still less statistically significant compared to those obtained in the first scenario: as such, the best set of parameters was found to be $\delta = 0.0003$ and $\gamma = 0.0055$.

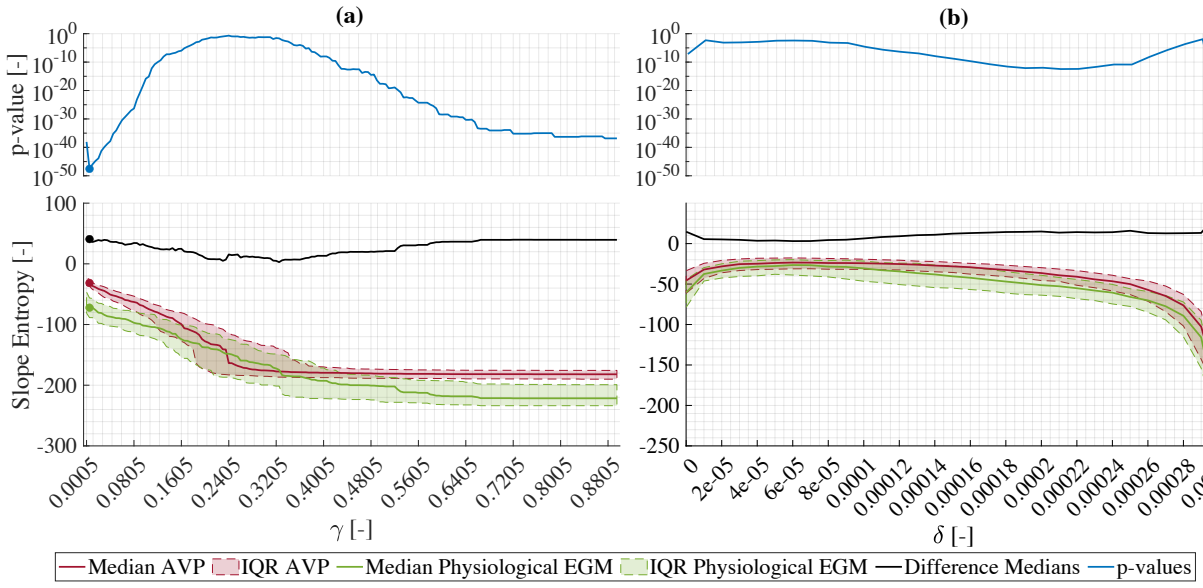

Figure 3. Graphs showing p-values for different γ (a) and δ (b) values, on the top panel, and the SlopEn curves for the two EGM types, in terms of interquartile (IQR) range and median values for the two grid searches on the bottom panel. The best result in each graph is identified by the marker (●).

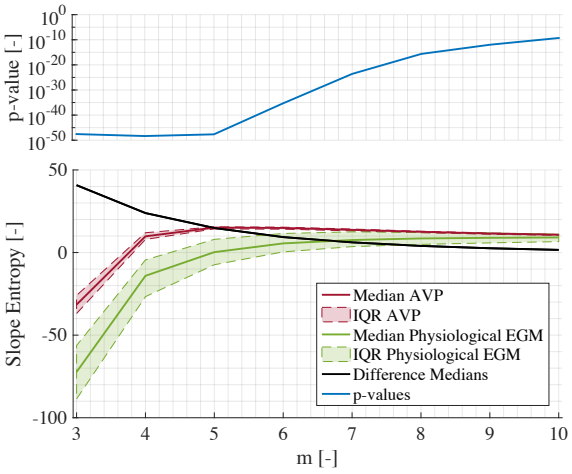

Figure 4. From top to bottom, the graphs showing p-values for different values of m, and the corresponding SlopEn trend for the two EGM types.

Finally, to investigate the role of m, the two optimal parameters were fixed (i.e., $\delta = 0.0003$ and $\gamma = 0.0055$), while different values for the embedded dimension were tested, specifically ranging from 3 up to 10. In terms of statistical significance, the results obtained with $m = 3$ and $m = 4$ were comparable, with a slightly better performance for $m = 4$. However, with $m = 3$ there was a larger difference between the median of the two distributions, as shown in Fig. 4.

5. Conclusions

In this work, SlopEn was preliminarily assessed as a tool to characterize ventricular EGMs in post-ischemic patients with VT, in sinus rhythm. As expected, this complexity metric assumes significantly different values for physiological EGMs and AVPs. Even though the parameterizations and their granularity might have influenced the statistical findings, the results highlight that physiological EGMs always presented lower SlopEn values than AVPs, at least when a statistically significant difference was observed, in line with the assumption that AVPs are characterized by highly fragmented and unstructured morphologies.

These results pave the way to the study and adoption of complexity metrics to support ablation procedures by complementing the current substrate representations in electrophysiology procedures for post-ischemic VT.

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