Review

A review on sample entropy applications for the non-invasive analysis of atrial fibrillation electrocardiograms

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ABSTRACT

The application of non-linear metrics to physiological signals is a valuable tool because “hidden information” related to underlying mechanisms can be obtained. In this respect, approximate entropy (ApEn) is the most popular non-linear regularity index that has been applied to physiological time series. However, ApEn presents some shortcomings, such as bias, relative inconsistency and dependence on the sample length. A modification of ApEn, named sample entropy (SampEn), was introduced to overcome these deficiencies. Recently, in the context of electrocardiography, SampEn has been applied to study non-invasively atrial fibrillation (AF), which is the most common arrhythmia encountered in clinical practice with unknown mechanisms provoking its onset and termination. Useful clinical information, that could help for a better understanding of AF mechanisms, has been obtained through the application of SampEn to electrocardiographic (ECG) recordings. This work reviews its application in the context of non-invasive analysis of AF. During this arrhythmia, atrial and ventricular components can be regarded as unsynchronized activities, whereby, the application of SampEn to the analysis of each component will be described separately. In first place, clinical challenges in which SampEn has been successfully applied to estimate AF organization from the atrial activity pattern are presented. The AF organization study can provide information on the number of active reentries, which can help to improve AF treatment and to take the appropriate decisions on its management. Next, the heart rate variability study via SampEn, to characterize ventricular response and predict AF onset, is described. Through the aforementioned applications it is remarked throughout this review that SampEn can be considered as a very promising and useful tool towards the non-invasive understanding of AF.

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1. Introduction

Non-linear analysis metrics are valuable in the assessment of physiological time series, because “hidden information” related to underlying mechanisms can be sometimes obtained [1, 2]. To this day, a high amount of non-linear complexity measures exists, such as dimensions, Lyapunov exponents and entropies. However, their computation is frequently compared with the problem of insufficient number of data points [3]. Additionally, most dimension and entropy definitions present application limitations associated to real world time series, since all recorded data are of limited duration and, to a certain degree, contaminated by noise. In this respect, a 2% noise is serious enough to prevent accurate estimation [4]. To solve the problems of short and noisy recordings in physiological signals, Pincus [5] presented approximate entropy (ApEn) as a measure of complexity that is applicable to noisy and medium-sized datasets. ApEn determines the conditional probability of similarity between a chosen data segment and the next set of segments of the same duration. The higher the probability, the smaller the ApEn value, indicating less irregularity of the data. This index has been successfully applied to analyze physiological signals in diverse applications. For instance, ApEn has been used to study intracranial hypertension episodes in pediatric patients with traumatic brain injury [6,7], to analyze temperature registers with the objective of predicting survival of critical patients [8,9], to analyze time series generated by schizophrenic patients [6], to study heart rate variability in disease and aging [10], etc.

Despite its popularity, ApEn has some known shortcomings, such as bias, relative inconsistency, and dependence on the sample length [2]. These shortcomings have led to the development of a related non-linear measure, sample entropy (SampEn) [2]. Theoretically, SampEn reduces the bias of ApEn by avoiding counting self-matches, it is independent of the time series length, and it is more consistent than ApEn. Additionally, SampEn is easier to compute than ApEn.

Thereby, this index has been also applied to analyze physiological signals in several recent studies. Some examples are the study of heart rate dynamics during episodes of mechanical ventilation and acute anoxia in rats [11], the analysis of heart rate variability in disease and aging [10], the electroencephalographic background activity characterization in Alzheimer's disease patients [12], the decision assessment of weaning from mechanical ventilation [13], the neonatal sepsis diagnosis improvement by evaluating reduced baseline variability and transient decelerations of heart rate [14], the exercise work load influence analysis on RR and QT time-series regularity [15], etc.

Moreover, a very recent application of SampEn has been the non-invasive study of atrial fibrillation (AF). This disease is a significant public health problem worldwide, affecting up to 1% of the general population and nearly 1 in 10 people over 80 years [16]. Despite its high prevalence, the physiological mechanisms provoking AF onset and termination are still unexplained and the current AF treatments are not completely satisfactory [17]. As a consequence, the study of AF has been considered as a challenge for researchers and a requirement for clinicians.

Within this context, useful clinical information that could improve the understanding of AF mechanisms and the existing treatments through the use of SampEn has been reported during the last years. The purpose of this article is to review the use of SampEn in the non-invasive analysis of AF. The manuscript describes initially the concept of AF and how the surface electrocardiographic (ECG) recordings were acquired. Next, a formal description of SampEn together with the most widely used parameters for its computation are introduced. Considering that the atrial activity (AA) can be viewed as uncoupled to the ventricular activity (VA) during AF [18], the applications of SampEn to AA and VA are described separately. Firstly, clinical challenges in which SampEn has been successfully applied to estimate AF organization from the AA patterns are presented. The AF organization study is a key aspect in the knowledge of the arrhythmia, because it provides information on the number of active reentries, which maintain and can perpetuate AF [19–22]. Secondly, different applications of SampEn to VA analysis are described. In this case, a non-invasive measure, such as the heart rate variability (HRV), has been used for the VA study. The HRV analysis is a valuable tool, because it allows to observe the heart’s regulation by the autonomic nervous system, which is believed to play an important role in the initiation of AF [23,24]. Finally, the concluding remarks will lead the paper to its end.

2. Short description of atrial fibrillation

Atrial fibrillation is the most commonly supra-ventricular tachy-arrhythmia encountered in the daily clinical practice [17], affecting roughly 2.2 million people in the US and 2 millions in Europe, with a prevalence that doubles with each advancing decade above 50 years and reaches almost 10% in octogenarians [25]. This arrhythmia may appear on three different forms, namely paroxysmal AF, i.e., self-terminating within 7 days, persistent AF, in which sinus rhythm cannot be restored or maintained [17].

Data from the Framingham heart study show that a patient with AF has twice the risk of death than a healthy person [26,27], which may be due to the fact that AF is one of the main causes of embolic events, developing complications associated with cerebrovascular accidents in 75% of the cases [28]. In addition, AF may cause systemic thromboembolic complications, decrease exercise capacity, impair ventricular function, reduce quality of life and incur significant health care costs [27,29,30]. As a consequence, AF itself does not represent a life-threatening condition, but it considerably reduces the patients’ quality of life.

One normal cardiac cycle is started at the sinus node with the depolarization of the right atrium, and spreads towards the entire atria in a well-ordered manner. Atrial depolarization defines the P wave in the ECG, see Fig. 1(a). Next, the depolarization impulse reaches the ventricles and their fast contraction produces the QRS complex in the ECG. Finally, ventricular repolarization produces the T wave and concludes the cardiac cycle. The manifestation of AF is characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. AF occurs when the electrical activity in the atria degenerates from its usual organized pattern into a rapid chaotic pattern. This disruption results in an irregular and often rapid heartbeat that is classically described as “irregularly irregular” and is due to the unpredictable conduction of these disordered impulses across the atrioventricular node [17], see Fig. 1(b).

However, the physiological mechanisms provoking the onset and termination of AF episodes are still unexplained [17]. The most widely accepted theory to explain AF mechanisms is based on the continuous propagation of multiple wavelets wandering throughout the atria [17]. The fractionation of the wavefronts as they propagate results in self-perpetuating independent wavelets, called reentries. The number of simultaneous reentries depends on the refractory period, mass and conduction velocity along the atria, and these parameters present severe inhomogeneities in AF [17]. It has been also demonstrated that the number of propagating reentries into the atrial tissue is related to AF organization [19–22], therefore, a reliable organization estimation can provide very useful information on the arrhythmia. In this respect, when AF occurs, a notably disorganized atrial activity (AA) has been observed on internal recordings [20,21,31–33].
the atrial electrical activity with high degree of detail have been reached. Specially, the situations where the arrhythmia behaves with remarkable variations, like spontaneous AF onset and AF termination (spontaneous or induced by cardioversion), have been studied. In this respect, a progressive increase in the number of reentries during the first minutes after paroxysmal AF onset has been suggested in a recent work [34]. Additionally, it has been reported that the likelihood of spontaneous AF termination is inversely related to the number of wavefronts propagating throughout the atrial tissue [20]. In fact, several studies have demonstrated a decrease in the number of reentries prior to spontaneous AF termination, thus producing simpler wavefronts [31,32,35]. Regarding the forced termination of AF through electrical cardioversion (ECV), it has been shown that the higher the number of propagating wavelets, the larger the atrial volume that could support reentry propagation after the shock. As a consequence, a negative ECV outcome could be more likely for those patients [36].

An additional challenge in the understanding of AF should be to obtain non-invasively the aforesaid information, such as some authors have attempted [22]. Obviously, surface ECG recordings can be obtained easily and cheaply, which is essential from a clinical point of view. In addition, the risks for the patient associated to invasive procedures could be avoided thanks to the ECG [37]. Therefore, although the authors are conscious about the remarkable existing applications of SampEn to biomedical signals, this review is focused on a recent and challenging side of SampEn, such as its application to study AF from the surface ECG.

3. Surface ECG recordings

The surface ECG recording provides a widely used and non-invasive way to study AF. Some advantages of using the ECG include the ability to record data for a long period of time and the minimal costs and risks involved for the patient, in comparison with invasive procedures [37]. However, because of ECG represents the heart’s electrical activity recorded on the thorax’s surface, the signal is corrupted by different types of noise, which are picked up by the volume conductor constituting the human body. Thereby, in order to improve later analysis, these recordings need to be preprocessed. Filtering operations have been classically applied to the ECG for the reduction of noise sources like, i.e., baseline wandering, high frequency noise and powerline interference [38]. Concretely, in the studies that will be next described, baseline wander was removed making use of bidirectional zero-phase high-pass filtering with 0.5 Hz cut-off frequency [39], high frequency noise was reduced with an eight-order bidirectional zero-phase IIR Chebyshev low pass filtering, whose cut-off frequency was 70 Hz [40], and powerline interference was removed through adaptive notch filtering, which preserves the ECG spectral information [41].

As described before, the ECG in AF is characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves (f waves) that vary in size, shape, and timing [37], associated with an irregular ventricular response [17], see Fig. 1. The f waves analysis from surface ECG recordings is complicated by the simultaneous presence of ventricular activity, which is of much higher amplitude. Thereby, the dissociation of atrial and ventricular components is mandatory [42]. Nowadays, several methods to extract the AA signal from surface ECG recordings exist. The most powerful techniques are those that exploit the spatial diversity of the multilead ECG [43], such as the method that solves the blind source separation problem [18] or the spatiotemporal QRST cancellation strategy [44]. However, the performance of these techniques is seriously reduced when recordings are obtained from Holter systems for paroxysmal AF analysis. The reason is that, generally, Holter systems use no more than two or three leads, which are not enough to exploit the ECG spatial information. For single-lead applications the most widely used alternative to extract the AA is the averaged beat subtraction (ABS). This method relies on the assumption that the average beat can represent, approximately, each individual beat [42]. In the studies that will be next described, ABS or some variant [45] have been used to extract the AA from lead V1. This lead was chosen for analysis because it contains the highest AA amplitude [37]. Additionally, in those cases where the sampling frequency was originally low, the lead had to be upsampled to 1024 Hz to allow better alignment for QRST complex averaging and subtraction, as suggested in previous works [46].

4. The concept of sample entropy

Sample entropy examines a time series for similar epochs and assigns a non-negative number to the sequence, with larger values corresponding to more irregularity in the data [2]. Two input parameters, a run length m and a tolerance window r, must be specified for SampEn to be computed. SampEn(m, r, N), being N the length of the time series, is the negative logarithm of the conditional probability that two sequences similar for m points remain similar at the next point, where self-matches are not included in calculating the probability. Thus, a lower value of SampEn also indicates more self-similarity in the time series [2].

Formally, given N data points from a time series \( \{x(n)\} = x(1), x(2), \ldots, x(N) \), SampEn can be defined as follows [2]:

1. Form vector sequences of size \( m \), \( x_m(m) \) = \( x(i), x(i+1), \ldots, x(i+m-1) \), \( 1 \leq i \leq N-m + 1 \), defined by \( x_m(i) = x(i), x(i+1), \ldots, x(i+m-1) \), \( 1 \leq i \leq N-m + 1 \). These vectors represent \( m \) consecutive \( v \) values, starting with the \( i \)th point.
2. Define the distance between vectors \( x_m(i) \) and \( x_m(j) \), \( d(x_m(i), x_m(j)) \), as the absolute maximum difference between their scalar components:
   \[
   d(x_m(i), x_m(j)) = \max_{k=0, \ldots, m-1} |x(i+k) - x(j+k)|.
   \] (1)
3. For a given \( x_m(i) \), count the number of \( j \) \( (1 \leq j \leq N-m, j \neq i) \), denoted as \( B_i \), such that the distance between \( x_m(i) \) and \( x_m(j) \) is less than or equal to \( r \). Then, for \( 1 \leq i \leq N-m \):
   \[
   B_i^m(r) = \frac{1}{N-m-1} B_i.
   \] (2)
Thus, for the application of SampEn to AF organization estimation results were achieved with within the range defined by Pincus were tested, but the optimal points, whereas SampEn which is estimated by the statistic (5) Increase the dimension to and calculate , as the number of within the Pincus’ range [13,15] or very close to it [3,23,52,53]. The use of this non-linear index is justified because non-linearity, as necessary condition for a chaotic behavior, is present in the diseased heart with AF at cellular level, and atrial electrical remodeling in AF is a far-from-linear process [58,59]. Electrical remodeling can be described as the progressive shortening of effective atrial refractory periods, thus increasing the number of simultaneous reentries and, as a consequence, the possibility of AF perpetuation [17]. In the next subsections, the state of the art related to the non-invasive AF organization estimation based on SampEn is summarized. These applications demonstrate how non-linear biomedical signal processing could contribute in the improvement of AF treatments.

5. Paroxysmal AF termination prediction

About 18% of paroxysmal AF degenerates into persistent AF in less than 4 years [60]. The associated risks of persistent AF are quite serious because it predisposes to thrombus formation within the atria that can cause stroke or any other thromboembolic events [28]. Therefore, the early prediction of paroxysmal AF maintenance is crucial, because appropriate interventions may terminate the arrhythmia and prevent AF chronification. In contrast, the prediction of spontaneous AF termination could avoid unnecessary therapy, reduce the associated clinical costs, and improve the patient’s quality of life.

In previous invasive studies where AF termination was achieved by using different therapies, a decrease in the number of reentries prior to AF termination was observed [21,31,32,35]. This decrease in the number of reentries produces simpler wavefronts into the atrial tissue and irregular waves evolve to regular P waves [37]. Therefore, the AA slightly evolves to a more organized pattern before AF termination. This feature has been used to predict paroxysmal AF termination.

In this sense, some authors applied non-linear regularity indexes to characterize AA organization from the surface ECG, but their results did not reveal significative differences between terminating and non-terminating paroxysmal AF episodes. The low signal to noise ratio of the AA was believed to be the main reason to this result [61,62]. In order to reduce the nuisance signals and enhance the AA, the application of two wavelet decomposition analyses to this atrial signal has been proposed [54], such as Fig. 2 shows. In the first analysis (block 1), the wavelet coefficient vector related to the scale containing the dominant atrial frequency (DAF), i.e., the frequency with the highest amplitude within the typical 3–9 Hz AF frequency range [63,64], was reconstructed back to the time-domain. As a result, nuisance signals were removed and the fundamental waveform associated to the AA, called main atrial wave (MAW), was obtained. In the second case (block 2), the same wavelet coefficient vector was linearly interpolated to obtain a vector with a number of samples equal to the original AA signal. Finally, the organization of the two provided time series was estimated via SampEn to obtain two different and independent classifications of paroxysmal AF into terminating and non-terminating episodes.

In order to validate this methodology, the database generated for the Computers in Cardiology Challenge 2004, which is available on Physionet [65], was used. This data set is composed by a learning set consisting of 20 paroxysmal AF recordings with known within the atria affects waves regularity, since it is directly related to the periodicity and repetitive morphology of the AA pattern, such as invasive recordings have reported [19–21]. Hence, given that the AA organization provides information on the number of active reentries, its non-invasive successful estimation could improve AF treatment, which still is unsatisfactory, and contribute to take the appropriate decisions on its management [22]. In this respect, very recent studies have applied SampEn to evaluate waves regularity as a successful non-invasive AF organization estimator [51,54,57]. The measurement of this non-linear index is justified because non-linearity, as necessary condition for a chaotic behavior, is present in the diseased heart with AF at cellular level, and atrial electrical remodeling in AF is a far-from-linear process [58,59]. Electrical remodeling can be described as the progressive shortening of effective atrial refractory periods, thus increasing the number of simultaneous reentries and, as a consequence, the possibility of AF perpetuation [17]. In the next subsections, the state of the art related to the non-invasive AF organization estimation based on SampEn is summarized. These applications demonstrate how non-linear biomedical signal processing could contribute in the improvement of AF treatments.

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termination properties and a test set of 30 recordings. The non-terminating paroxysmal AF episodes were observed to continue in AF for, at least, 1 h following the end of the excerpt (group \( N \)). In contrast, spontaneously terminating AF episodes terminated immediately after the end of the extracted segment (group \( T \)).

The independent application of each analysis block to the learning set allowed to obtain a predictive accuracy of 90% (18 out of 20) with 80% sensitivity (i.e., proportion of non-terminating episodes correctly classified) and 100% specificity (i.e., percentage of terminating episodes correctly discerned) for the first block and 85% (17 out of 20), with 100% sensitivity and 70% specificity, for the second block, see Fig. 3. The observation on these results in which non-terminating AF recordings that presented a high DAF, and terminating episodes having a low DAF, were incorrectly classified, suggested the combination of both blocks to obtain an improved classification strategy. Thus, when both blocks classified differently an AF episode and the DAF was lower than 5.5 Hz, the classification provided by block 1 was considered. On the contrary, if the DAF was higher than the mentioned threshold, the classification provided by block 2 was chosen. With this combined methodology, 100% (20 out of 20) and 93.33% (28 out of 30) of the learning and test recordings were correctly discriminated, respectively, with 93.75% sensitivity and 92.86% specificity for the test set.

Additionally, the results provided by block 1 showed that terminating episodes presented lower SampEn values and, consequently, higher AA organization, than non-terminating episodes, see Fig. 3(a). This observation was in agreement with the AA organization increase prior to AF termination reported through invasive recordings [21,31,32,35] which, at this moment, is clinically accepted [66]. As a consequence, it can be considered that the invasively observed increase in AF organization is reflected on the surface ECG when proper analysis tools are used.

Regarding a specific scale of block 2, the wavelet coefficient vector contained the similarity evolution along time between the analyzed signal and the scaled mother wavelet. A high regularity value in this time series indicated a constant waveform across the time period under analysis. On the contrary, low regularity implied variable waveforms that, for instance, may evolve to a more organized pattern. This fact was considered to justify the results obtained in block 2, where terminating paroxysmal AF episodes presented higher vector irregularity, see Fig. 3(b). Hence, the AA evolution from disorganized \( f \) waves to organized P waves, that
takes place in AF recordings prior to its termination [37], may cause the described behavior in the wavelet coefficient vector.

Finally, notice that several previous works have tried to predict the spontaneous AF termination from surface ECG recordings [67–70]. To this respect, Table 1 presents some of the most recently proposed methods. Most of them analyzed the DAF decrease, which was previously reported through invasive studies during catheter ablation [71]. However, in order to improve AF termination prediction, other parameters were analyzed and combined with the DAF. In this respect, Petrutiu et al. [72] studied the AA peak power evolution within the two last seconds of the recordings. This short studied time interval could limit seriously their method’s reliability, especially when other works did not find significative differences between the peak power of terminating and non-terminating AF episodes [67]. In Hayn et al. [73], an evolution of the averaged RR time interval was studied to correlate ventricular with atrial activities (represented by the DAF). In this method, two coefficients were empirically fitted to the analyzed signal set, but results were very variable, such as the poor outcomes obtained analyzing other databases have corroborated [68]. In addition, the relation between atrial and ventricular activities was also studied in other works, but lower predictive capacity than in the previous method was obtained [67]. In other studies, different time–frequency transforms were used to evaluate the AA time–frequency evolution [61,70,74]. However, the reported results did not reveal notable improvements in the prediction of AF termination. Parameters relative to the AA energy distribution, such as AA amplitude [70] or exponential decay [75], were also studied, but low significant differences between terminating and non-terminating AF episodes were obtained [76]. Therefore, the combined methodology described in this review could be considered as the most robust and reliable discrimination procedure, because it is completely based on AF physiological observations, which have been reported through invasive studies [20,21,31–33]. In addition, a predictive capacity higher than the majority of the indicated studies was obtained.

### 5.2. Paroxysmal AF organization time course

As previously described, the treatment of AF patients is still unsatisfactory, due to the progressing nature of this arrhythmia and its physiological mechanisms, making the onset and termination of AF episodes still unexplained [17]. Thus, the progressing evolution analysis of paroxysmal AF could help for a better understanding of its mechanisms. In this sense, as previously mentioned, recent invasive studies have evaluated AF organization time course during different episode parts. Concretely, the organization in the first minutes after AF onset has been evaluated by means of a cycle length beat-to-beat analysis and wave similarity [34]. On the other hand, organization before AF termination has been successfully evaluated by using different techniques [21,31,32,35].

From a non-invasive point of view, a very recent study has applied SampEn to the onset and offset of paroxysmal AF episodes to evaluate their organization time course [57]. In this work, for reducing noise, nuisance signals and enhancing the AA, the MAW was obtained through selective filtering of the AA by tracking its DAF, such as Fig. 4 shows. The MAW organization was estimated by
applying SampEn in non-overlapping segments of 2 s. Overlapping between segments was discarded in order to not benefit the organization assessment, to obtain more consistent results and to increase the proposed strategy reliability.

With the described method, 25 ECG recordings continuously registered during the first 5 min following paroxysmal AF onset and available on Physionet [65] were studied. A progressive organization deterioration in the first 3 min after the onset takes place, as it can be observed in Fig. 5(a). This finding was in agreement with the conclusions reported from invasive recordings by several authors [34,77,78] and suggested that higher rates of success to revert the arrhythmia could be obtained through the early delivery of pacing, that is, when the episodes are more organized.

On the other hand, 20 ECGs, also available on Physionet [65], containing the last 2 min before spontaneous AF termination were also analyzed. In this case, the MAW organization analysis showed a progressive organization increase during the last minute, see Fig. 5(b). This organization variation was in agreement with the results presented for AF termination prediction in the previous subsection and those obtained by other authors, such as Takahashi et al [31] and Hoekstra et al [33], from invasive recordings.

5.3. Electrical cardioversion outcome prediction

When a patient is in persistent AF, it is a common practice to restore and maintain normal rhythm. In this respect, sinus rhythm restoration is required to reduce the risk of stroke and improve cardiac output [17]. This approach is based, in part, on data indicating that AF is a predictor of death in patients with heart failure and suggesting that the suppression of AF may favorably affect the outcome.

Generally, electrical cardioversion (ECV) is the most effective alternative to revert AF back to sinus rhythm [79]. However, because of the high risk of AF recurrence, especially during the first 2 weeks following the procedure [80], and because of potential collateral effects of ECV [79], it is clinically important to predict normal sinus rhythm (NSR) maintenance after ECV before it is attempted. With this objective, in a recent work [51], the AA organization was non-invasively estimated relying on the hypothesis that NSR maintenance would be more likelihood in patients who present a more organized AA. This assumption was based on the observation that the more disorganized the AA, the higher the number of propagating wavelets [20], and the larger the atrial volume that could support propagation of reentries after the shock [36].

As for paroxysmal AF termination prediction, in this work, a wavelet bidomain sample entropy methodology was used to reduce nuisance signals and enhance the AA [51]. In this case, however, when the classification result provided by blocks E1 and E2 in Fig. 2 was different, two indices indicating the closeness between the SampEn value of the analyzed signal and the optimum discrimination threshold for both time and wavelet domains were defined. Thus, only the result from the block presenting the highest index was considered.

Forty patients with persistent AF lasting for more than 30 days, undergoing the first attempt of ECV, were analyzed to validate the proposed method and to predict the ECV outcome. All the patients were under drug treatment with amiodarone and were followed during the first 4 weeks. The wavelet bidomain technique was applied to the 30 s length segment preceding the ECV of each patient. A diagnostic accuracy of 85.71% (30 out of 35) with 90.48% sensitivity (i.e., proportion of ECVs relapsing to AF correctly classified) and 78.57% specificity (i.e. percentage of ECVs resulting in NSR correctly discerned) was obtained for the first block, see Fig. 6(a). The accuracy for the second block was 82.86% (29 out of 35) with 80.95% sensitivity and 85.71% specificity, see Fig. 6(b). Finally, by combining both organization estimation strategies, an accuracy of 94.2% (33 out of 35), with 95.24% sensitivity and 92.86% specificity, was achieved.

Moreover, block 1 results showed that patients relapsing to AF presented higher SampEn values and, therefore, lower AA organization, than those resulting in NSR after 4 weeks, see Fig. 6(a). This observation was in agreement with findings reported by other works, such as the higher the AA organization, the higher the success rates in cardioversion of AF [19,20] and the lower the energy required for successful cardioversion [36]. Therefore, obtained results suggested that the higher the number of reentries wandering throughout the atrial tissue, the lower the probability of successful ECV. Regarding the block 2, the presence of a more stable AA waveform in organized atrial activities [37] was considered to justify that patients who relapsed to AF presented lower wavelet coefficient vector regularity than those who remained in NSR. In addition, it is noteworthy that five patients, in which NSR was not immediately restored after ECV, presented the lowest AA organization both in time and wavelet domains, thus increasing the obtained results consistency.
In previous works, some of which are summarized in Table 2, several clinical, electrophysiological and demographic features, such as AF duration, type of underlying disease, patient age, left atrium diameter, left ventricular function or continuation of therapy with antiarrhythmic drugs, were proposed as predictors of successful AF cardioversion and sinus rhythm maintenance. However, the predictive value of these parameters was far from optimal [81]. Regarding the explicit analysis of AF organization, Holmqvist et al. [82] evaluated a parameter obtained from time–frequency analysis of the atrial signals, such as harmonic decay. This parameter was designed to be an index of the waveform shape (and indirectly organization) of the atrial component in the ECG, but a low number of patients relapsing to AF were correctly identified (47%, 14 out of 30). In Berg et al.’s work [83], ventricular rhythm was analyzed using three-dimensional RR intervals plots, quantifying clustering of RR intervals. The authors speculated that RR intervals clustering represents a relatively high organization degree of atrial fibrillatory activity, and hypothesized that ECV would be more effective in patients with clustering. However, only 50% (11 out of 22) of patients who relapsed to AF during the first 4 weeks following ECV were correctly discerned. With respect to the use of advanced digital signal processing tools, Watson et al. [84] examined a variety of wavelet transform–based statistical markers as potential candidates to predict the post-cardioversion patient status after 1 month following ECV, and 88% (15 out of 17) sensitivity and 100% (13 out of 13) specificity were obtained. Zohar et al. [85] developed a non-deterministic model for predicting sinus rhythm maintenance after ECV, obtaining 71% (15 out of 21) sensitivity and 96% (22 out of 23) specificity when the patients were followed up during the first 3 months after ECV. Lombardi et al. [86] used spectral analysis of short-term heart rate variability (HRV) to evaluate the role of the autonomic nervous system after sinus rhythm restoration, and 76% (19 out of 25) sensitivity and 90% (61 out of 68) specificity were obtained after the first 2 weeks following ECV. Other works analyzed the DAF as a predictor of ECV outcome [87–89]. However, the results were conflicting and, therefore, inconclusive. The latest investigation suggested that the confounding effect of antiarrhythmic drug therapy could explain the differences among these results [88]; however, this aspect still remains unclear. Finally, a recent study showed that the amplitude of f waves had the ability of predicting ECV result with a sensitivity of 83.87% and a specificity of 72.73%, which could be improved with a discriminant model based on this amplitude and the DAF (83.87% sensitivity and 86.36% specificity) [90]. As a consequence, having all these methods and their outcomes in mind, the methodology based on AF organization estimation [51] was considered by the authors as a promising predictor of successful cardioversion and NSR maintenance following ECV of persistent AF patients, given that its diagnostic ability was higher than those provided by other presented methods.

Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Database</th>
<th>Database description</th>
<th>Short description of methods</th>
<th>Best results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcaraz and Riet [90]</td>
<td>Own database with 63 patients</td>
<td>31 relapsed to AF, 22 maintained NSR and 10 presented unsuccessful ECV</td>
<td>Discriminant model based on time and frequency parameters obtained from the AA</td>
<td>83.87% sensitivity, 86.36% specificity</td>
</tr>
<tr>
<td>Alcaraz and Riet [51]</td>
<td>Own database with 40 patients</td>
<td>21 relapsed to AF, 14 maintained NSR and 5 presented unsuccessful ECV</td>
<td>Regularity analysis via SampEn of time and wavelet domains of the AA</td>
<td>95% sensitivity, 93% specificity</td>
</tr>
<tr>
<td>Watson et al. [84]</td>
<td>Own database with 30 patients</td>
<td>17 relapsed to AF and 13 maintained NSR</td>
<td>Assessment of several wavelet transform–based statistical markers</td>
<td>88% sensitivity, 100% specificity</td>
</tr>
<tr>
<td>Holmqvist et al. [88]</td>
<td>Own database with 175 patients and 8 presented unsuccessful ECV</td>
<td>90 relapsed to AF, 77 maintained NSR</td>
<td>Analysis of atrial fibrillation rate (i.e., DAF multiplied by 60)</td>
<td>79% sensitivity, 80% specificity</td>
</tr>
<tr>
<td>Holmqvist et al. [82]</td>
<td>Own database with 54 patients</td>
<td>30 relapsed to AF and 24 maintained NSR</td>
<td>Assessment of the atrial harmonic decay with time–frequency analysis of the ECG</td>
<td>47% sensitivity, 92% specificity</td>
</tr>
<tr>
<td>Meurling et al. [89]</td>
<td>Own database with 37 patients</td>
<td>10 relapsed to AF, 22 maintained NSR and 5 presented unsuccessful ECV</td>
<td>Analysis of the dominant atrial cycle length and clinical characteristics</td>
<td>Non-significant differences between groups</td>
</tr>
<tr>
<td>Zohar et al. [85]</td>
<td>Own database with 44 patients</td>
<td>21 relapsed to AF and 23 maintained NSR</td>
<td>Non-deterministic model based on genetic programming</td>
<td>71% sensitivity, 96% specificity</td>
</tr>
<tr>
<td>Berg et al. [83]</td>
<td>Own database with 66 patients and 12 presented unsuccessful ECV</td>
<td>32 relapsed to AF, 22 maintained NSR and 13 presented unsuccessful ECV</td>
<td>Analysis of 3D RR intervals as a quantifier of AF organization</td>
<td>50% sensitivity, 56% specificity</td>
</tr>
<tr>
<td>Bollmann et al. [87]</td>
<td>Own database with 44 patients and 29 maintained NSR</td>
<td>13 relapsed to AF, 2 to atrial flutter and 29 maintained NSR</td>
<td>Experimental combination of atrial fibrillatory rate with the left atrium diameter</td>
<td>89% sensitivity, 78% specificity</td>
</tr>
<tr>
<td>Lombardi et al. [86]</td>
<td>Own database with 93 patients</td>
<td>25 relapsed to AF and 68 maintained NSR</td>
<td>Spectral analysis of short-term HRV</td>
<td>76% sensitivity and 90% specificity</td>
</tr>
</tbody>
</table>

$^a$ Sensitivity = proportion of patients who relapsed to AF correctly identified. Specificity = percentage of patients who resulted in NSR properly classified.

6. Ventricular activity analysis

The second part of this review summarizes the applications of SampEn, focused on the ventricular activity, to the surface ECG in AF. In this respect, ventricular response has been widely characterized making use of the heart rate variability (HRV) analysis, since the state of the autonomic nervous system, and related diseases, can be investigated non-invasively using relatively basic signal processing techniques [91]. Thus, in recent years, numerous measures have been suggested to characterize HRV. In this sense, several time domain metrics, which quantify the correlation between different RR intervals, have been proposed. However, the exclusion of non-normal RR intervals, provoked by false detection of R peaks, is an important step to obtain more reliable outcomes [92]. The resulting interval series is commonly referred as the normal–to-normal intervals (NN intervals), see Fig. 7(a). Thus, some metrics commonly obtained from this series have been the standard deviation of NN intervals (SDNN), the number of successive pairs of NN intervals that differ more than 50 ms (pNN50) and the root mean square of the differences between consecutive NN intervals (RMSSD) [92]. More advanced measures are those based on spectral analysis of the heart rhythm, since oscillations embedded in the rhythm, for example, due to respiratory activity or variations in blood pressure, can be quantified from the corresponding peaks in the estimated power spectrum [93]. The oscillations are characterized by low-frequency components, which typically are located in the interval below 0.5 Hz, see Fig. 7(b). Unfortunately, the oscillations are sometimes poorly pronounced. This problem is commonly alleviated by quantifying, instead, the power of low-frequency (LF) and high-frequency (HF) components in the intervals 0.04–0.15 Hz and...
0.15–0.40 Hz, respectively [93]. The spectral power measured in these two intervals has been closely associated with autonomic balance. An increase in sympathetic activity is related to an increase of the LF power, whereas an increase in parasympathetic or vagal activity is primarily related to an increase of the HF power [93,94]. Hence, the ratio between these two spectral power measures has been considered as an index of autonomic balance [86]. However, in an increasing number of recent papers, controversial opinions on the role of vagal and sympathetic systems in AF have been reported [94,95]. Thereby, to obtain relevant clinical information and a better understanding of the underlying mechanisms of HRV, several non-linear complexity metrics have been studied in recent works. Moreover, relationships with the classical time and frequency domains linear measures have been also found out [15,94]. The application of non-linear metrics for HRV analysis is justified given that non-linear processes are involved in the genesis of heart rate modulation [96,97]. Within the aforementioned context, the next subsection summarizes how SampEn has been applied to HRV analysis in an attempt to predict the onset of paroxysmal AF.

### 6.1. Paroxysmal AF onset prediction

The prediction of spontaneous AF onset is clinically important because the possibility of electrically stabilizing and preventing the onset of atrial arrhythmias with different atrial pacing techniques increases notably. Dual chamber atrial pacing may reduce the heterogeneity of atrial refractoriness, manifested by P wave duration changes on the surface ECG recording. Preliminary studies by Prakash et al. [98] have indicated that acute suppression of paroxysmal AF is possible in selected patients with dual-site right atrial pacing from the coronary sinus ostium and high right atrium. The advances in anti-arrhythmia pacing and drug management may be applied to prevent the acute onset of paroxysmal AF prior to the loss of sinus rhythm. The maintenance of sinus rhythm can lead to decreased symptoms, improved hemodynamics and, possibly, a decrease in the atrial remodeling that causes increased susceptibility to future episodes of paroxysmal AF [99]. In addition, a reduction in the risk of thromboembolic events can also be remarkable.

The mechanisms leading to the initiation of AF have been under intensive investigation within the last decade. It has been proposed that the autonomic nervous system might have a role in the initiation of this arrhythmia. Concretely, increased vagal tone can predispose to the development of AF [23]. Thereby, in several works, SampEn has been applied to study the HRV complexity evolution in the minutes preceding spontaneous AF onset. In this sense, Tuzcu et al. [23] studied the HRV complexity of 30 min

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**Fig. 6.** Classification into ECVs resulting in NSR and relapsing to AF after 4 weeks following the procedure obtained with the organization analysis of (a) block 1 (time-domain) and (b) block 2 (wavelet-domain) showed in Fig. 2[51]. SampEn values obtained for all the analyzed signals together with the mean and standard deviation for each group are displayed. Optimal thresholds are represented with a dashed line.

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**Fig. 7.** For the analysis of HRV time series, the exclusion of non-normal RR intervals, provoked by false detection of R peaks, is crucial in the outcomes [92]. The resulting interval series is referred as the normal-to-normal intervals, which are presented in (a) acquired during AF conditions. On the other hand, the power spectrum of the previous series is plotted in (b).
length segments containing the ECG immediately preceding a paroxysmal AF episode (pre-AF) and 30 min length segments of ECG during a period distant, at least 45 min, from any episode of AF (AFd). This data set was available on Physionet [65] and called unedited data. SampEn of the HRV was found to be significantly reduced in the segments preceding AF compared with those distant from any AF occurrence, see Fig. 8(a). The same study was repeated, but premature atrial complexes were previously removed. In this case, the data set was called edited data and a less pronounced difference was provided, such as Fig. 8(b) shows. The authors considered that decreased heart rate complexity, for both edited and unedited data, reflects a change in cardiovascular autonomic regulation that preconditions AF onset.

Additionally, the segments preceding AF onset were divided into three successive 10 min periods and analyzed with SampEn in order to show the presence of a possible trend. A decreasing trend towards the onset of AF in the unedited data was observed, see Fig. 9(a). After the removal of ectopic beats, a similar decrease in entropy towards AF onset was also noticed, but it was less pronounced, such as Fig. 9(b) shows. According to the authors, the decrease in SampEn before the onset of AF resulted mainly from
Table 3

Comparison between some of the most recent studies presented to predict AF onset.

<table>
<thead>
<tr>
<th>Study</th>
<th>Database description</th>
<th>Short description of methods</th>
<th>Best results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chesnokov [52]</td>
<td>Some segments extracted from the episodes of Cinc/Challenge 2001 database [65]</td>
<td>Neural network based on spectral and non-linear features obtained from HRV</td>
<td>76.19% sensitivity, 93.75% specificity</td>
</tr>
<tr>
<td>Hayn et al. [68]</td>
<td>Episodes selected from Cinc/Challenge 2001 and MIT-BIH</td>
<td>Morphology analysis of the P waves of premature heart beats</td>
<td>77% sensitivity, 72% specificity</td>
</tr>
<tr>
<td>Budeus et al. [107]</td>
<td>Atrial Fibrillation databases [65]</td>
<td>Assessment of pathological chemoreflexsensitivity and atrial late potentials</td>
<td>Classification results not provided</td>
</tr>
<tr>
<td>Tuzcu et al. [23]</td>
<td>Learning episodes of Cinc/Challenge 2001 database [65]</td>
<td>Analysis of HRV complexity through SampEn</td>
<td>Classification results not provided</td>
</tr>
<tr>
<td>Shin et al. [55]</td>
<td>Own database with 44 episodes preceding AF onset</td>
<td>Evaluation of linear and non-linear parameters from HRV</td>
<td>Classification results not provided</td>
</tr>
<tr>
<td>Thong et al. [111]</td>
<td>All the episodes of Cinc/Challenge 2001 database [65]</td>
<td>Analysis of isolated premature atrial complexes not followed by a regular RR interval</td>
<td>89% sensitivity, 91% specificity for test set</td>
</tr>
<tr>
<td>Hickey et al. [112]</td>
<td>Episodes selected from several databases. Some are available on Physionet [65]</td>
<td>Discriminant model based on HRV spectral parameters and the number of atrial premature complexes</td>
<td>81.1% sensitivity and 85.1% specificity</td>
</tr>
<tr>
<td>Ros et al. [113]</td>
<td>Learning episodes of Cinc/Challenge 2001 database [65]</td>
<td>Modular classification algorithm based on the nearest K-neighbors and parameters related to both P wave and QRS complex</td>
<td>96% sensitivity, 88% specificity</td>
</tr>
<tr>
<td>Andrikopoulos et al. [106]</td>
<td>Own database with 110 episodes</td>
<td>Evaluation of P wave duration variance</td>
<td>88% sensitivity, 75% specificity</td>
</tr>
<tr>
<td>Vikman et al. [109]</td>
<td>Own database with 92 episodes preceding AF onset</td>
<td>Multivariate analysis of non-linear parameters from HRV</td>
<td>Classification results not provided</td>
</tr>
<tr>
<td>Dilaveris et al. [104]</td>
<td>Own database with 100 episodes</td>
<td>Analysis of the maximum P wave duration and its dispersion</td>
<td>83% sensitivity and 85% specificity</td>
</tr>
</tbody>
</table>

* Sensitivity = proportion of episodes preceding AF onset correctly identified. Specificity = percentage of episodes distant from AF onset properly classified.
premature atrial complexes not followed by a regular R–R interval reached a sensitivity of 89% and specificity of 91%.

Finally, some works considered the possible relationship between AA and VA prior to AF onset [112]. To this respect, a proposed method was based on a combination of techniques which assess autonomic tone (through HRV) and atrial ectopic beat occurrence. Depending on whether there is a significant correlation between observed low-frequency and high-frequency spectral power in the RR power spectral density, HRV or premature atrial complexes analysis was considered. Precisely, if there is high correlation, a discriminant analysis based on spectral features of HRV was used to predict AF onset, whereas in the low-correlation case, atrial premature contractions are also added to the discriminant model. However, this method was characterized by a notably low sensitivity, although it was robust in the presence of no episodes. Other work presented a modular classification algorithm based on the nearest K-neighbors and parameters no episodes. Other work presented a modular classification discriminant model. However, this method was characterized by a high correlation, a discriminant analysis based on spectral features of HRV was used to predict AF onset, whereas in the low-correlation case, atrial premature contractions are also added to the discriminant model. However, this method was characterized by a notably low sensitivity, although it was robust in the presence of no episodes.

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The present review has shown the applications of sample entropy to the electrocardiogram of atrial fibrillation. Regarding atrial activity, SampEn has demonstrated to be a robust organization estimator able to provide information about several aspects of the arrhythmia. In this respect, clinical relevant information related to spontaneous AF termination, to the organization time course variation in the onset and termination of AF and to sinus rhythm maintenance after electrical cardioversion, are some of its applications. On the other hand, SampEn can also play an important role in the ventricular activity analysis of AF, thus, being able to reflect cardiovascular autonomic regulatory changes in the instants preceding AF onset. The studies summarized in the present work suggest that sample entropy can be considered as a useful non-linear metric to quantify accurately atrial and ventricular cardiac dynamics from the surface ECG in atrial fibrillation.

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References


Recently, the use of non-linear metrics to quantify atrial activity, SampEn has demonstrated to be a robust organization estimator able to provide information about several aspects of the arrhythmia. In this respect, clinical relevant information related to spontaneous AF termination, to the organization time course variation in the onset and termination of AF and to sinus rhythm maintenance after electrical cardioversion, are some of its applications. On the other hand, SampEn can also play an important role in the ventricular activity analysis of AF, thus, being able to reflect cardiovascular autonomic regulatory changes in the instants preceding AF onset. The studies summarized in the present work suggest that sample entropy can be considered as a useful non-linear metric to quantify accurately atrial and ventricular cardiac dynamics from the surface ECG in atrial fibrillation.

7. Conclusions

The present review has shown the applications of sample entropy to the electrocardiogram of atrial fibrillation. Regarding atrial activity, SampEn has demonstrated to be a robust organization estimator able to provide information about several aspects of the arrhythmia. In this respect, clinical relevant information related to spontaneous AF termination, to the organization time course variation in the onset and termination of AF and to sinus rhythm maintenance after electrical cardioversion, are some of its applications. On the other hand, SampEn can also play an important role in the ventricular activity analysis of AF, thus, being able to reflect cardiovascular autonomic regulatory changes in the instants preceding AF onset. The studies summarized in the present work suggest that sample entropy can be considered as a useful non-linear metric to quantify accurately atrial and ventricular cardiac dynamics from the surface ECG in atrial fibrillation.

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