Chapter 8

The Contribution of Nonlinear Methods in the Understanding of Atrial Fibrillation

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1. Introduction

Analysis of cardiac time series by nonlinear metrics has recently gained great interest, because the latter observations suggest that the mechanisms involved in cardiovascular regulation likely interact with each other in a nonlinear way [1]. Furthermore, chaotic behavior can be appreciated in the diseased heart with atrial fibrillation (AF) at cellular level and atrial electrophysiological remodeling during this arrhythmia is a far-from-linear process [2]. Hence, the purpose of this chapter is to review the use of nonlinear methods in the analysis of AF, highlighting the clinically useful revealed information that can improve the understanding of this arrhythmia mechanisms and the existing treatments.

Considering that the atrial activity (AA) can be viewed as uncoupled to the ventricular activity (VA) during AF [3], the applications of nonlinear metrics to AA and VA are addressed separately. Regarding the AA study, different measures of irregularity, chaos and complexity of time series have provided a successful assessment of the fibrillatory (f) wave regularity from both single-lead invasive and surface recordings. This evaluation of temporal organization of AF has been directly associated with the number of active reentries wandering throughout the atrial tissue [4], which maintain and can perpetuate the arrhythmia [5, 6]. In agreement with this relation, nonlinear metrics have shown powerful prognostic information in the prediction of AF organization-dependent events, including spontaneous termination of paroxysmal AF, successful electrical cardioversion (ECV) of persistent AF patients, atrial remodeling time course during the arrhythmia or infusion effects of different drugs. In addition, these nonlinear analysis methods have also been applied to every signal collected by basked catheters, thus providing an estimation of spatial organization of AF by comparing different atrial sites. On the other hand, the application of nonlinear coupling approaches to intraatrial electrograms (EGMs) recorded simultaneously from different atrial places has reveal differences in the spatio-temporal organization of AF consistent with clinical studies [7]. Thus, differences between paroxysmal and persistent AF episodes and among patients with different organization degree, classified by following Wells' criteria [8], have been statistically detected. Moreover, patients successfully cardioverted making use of anti-arrhythmic drugs or ECV have been appropriately identified. Finally, with regard to the VA analysis, ventricular response has been widely characterized by quantifying nonlinear dynamics in interval series between successive R peaks, i.e., RR-interval series [9]. In this respect, multiple measures of fractal fluctuations, irregularity and geometric structure of time series have shown ability to evaluate the cardiovascular autonomic regulation before, during and after AF onset and characterize the main electrophysiological characteristics of the atrioventricular (AV) node.

2. Preprocessing of cardiac recordings

Prior to the application of nonlinear indices to surface ECG recordings and intraatrial EGMs, they requires at least the basic preprocessing described in the following subsections.

2.1. Surface ECG recording

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 [10]. 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 typically applied to the ECG for the reduction of noise sources, like baseline wandering, high frequency noise and powerline interference [11]. Thus, baseline wander is often removed making use of high-pass filtering (0.5 Hz cut-off frequency), high frequency noise with a low-pass filtering (70 Hz cut-off frequency) and powerline interference with an adaptive notch filtering.

Additionally, the f wave analysis from surface ECG recordings is complicated by the simultaneous presence of VA, which is of much higher amplitude. Thereby, the dissociation of atrial and ventricular components is mandatory [12]. 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, such as the method that solves the blind source separation problem [3] or the spatiotemporal QRST cancellation strategy [13]. 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 [12]. Recently, a variety of extensions for this method have been proposed [12, 14].

2.2. Intraatrial EGM

Nowadays, a variety of intraatrial recording modalities exists, such as bipolar and unipolar recordings from endocardial and epicardial electrodes, optical mapping and noncontact

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mapping [15]. Although recordings from each one of these modalities have their own characteristics, unipolar recordings are generally characterized by a substantial far-field contamination, such as VA, whereas bipolar recordings contains local atrial activations of the place in which the electrodes are located. Nonetheless, these recordings are also affected by ventricular interference, especially in recording sites closer to the ventricles, even if its effect is less evident than on unipolar EGMs and surface ECG recordings. Thereby, for the VA cancellation both from unipolar and bipolar recordings, an averaged ventricular interference complex, as in ABS, is usually computed and subtracted from each atrial signal [16, 17]. Only remark that the ventricular activations are habitually detected from a surface ECG recording simultaneously acquired for more accuracy.

On the other hand, given that atrial dynamics can be analyzed both from simple EGMs and local atrial period (LAP) series, i.e., the sequence of temporal distances between two consecutive local atrial activations, the appropriate identification of these points is a important task in this context. For this purpose, EGMs are habitually high-pass filtering (40–250 Hz) to remove baseline shifts and high-frequency noise [18]. The filtered signal is then rectified, introducing low-frequency components related to the amplitude of the high-frequency oscillations of the original signal. The modulus of the filtered signal is further low-pass filtered (cut-off at 20 Hz) to extract a waveform proportional to the amplitude of the components of occurring at 40–250 Hz. The atrial activations are then detected by threshold crossing and their occurrence time can be identified by different methods, including the local maximum peak, maximum slope of the atrial depolarization or their barycenter [19].

3. Nonlinear time series analysis

3.1. Fractal fluctuations quantification

The dynamics of a time series can be explored through its correlation properties, or in other words, the time ordering of the series. Fractal analysis is an appropriate method to characterize complex time series by focusing on the time-evolutionary properties on the data series and on their correlation properties. In this context, the *detrended fluctuation analysis* (DFA) method was developed specifically to distinguish between intrinsic fluctuations generated by complex systems and those caused by external or environmental stimuli acting on the system [20]. The DFA method can quantify the temporal organization of the fluctuations in a given non-stationary time series by a single scaling exponent α, a self-similarity parameter that represents the long-range power-law correlation properties of the signal. The scaling exponent α is obtained by computing the root-mean-square fluctuation $F(n)$ of integrated and detrended time series at different observation windows of size n and plotting $F(n)$ against n on a log-log scale. Fractal signals are characterized by a power law relation between the average magnitudes of the fluctuations $F(n)$ and the number of points n, $F(n) \sim n^{\alpha}$. The slope of the regression line relating $\log(F(n))$ to $\log(n)$ determines the scaling exponent α.

3.2. Chaos degree quantification

The principle of chaos analysis is to transform the properties of a time series into the topological properties of a geometrical object (attractor) constructed out of a time series, which is embedded in a *state/phase space*. The concept of phase space reconstruction is central to the analysis of nonlinear dynamics. A valid phase space is any vector space in which the state of the dynamical system can be unequivocally defined at any point [21]. The most used way of reconstructing the full dynamics of the system from scalar time measurements is based on the embedding theorem [21], which justifies the transformation of a time series into a m-dimensional multivariate time series. This is done by associating to each m successive samples distant a certain number τ of samples, a point in the phase space.

Several methods and algorithms are currently available to characterize a reconstructed phase space. Thus, two features widely used to emphasize the geometrical properties of the attractor are the *correlation dimension* (CD) and the *correlation entropy* (CorEn). The CD is a measure of the dimensionality of the attractor, i.e., of the organization of points in the phase space. Although there are several algorithms for its estimation, the CD can be computed by first calculating the correlation sum of the time series, which is defined as the number of points in the phase space that are closer than a certain threshold r [21]. Then, the CD is defined as the slope of the line fitting the log-log plot of the correlation sum as a function of the threshold. On the other hand, the CorEn is a measure of how fast the distance between two initially nearby states in phase space grows in time. This can be envisaged by taking a point in the reconstructed phase space, which corresponds to a segment in the time series. Another point in phase space located closely to the first one refers to a different segment in the time series. Thus, the CorEn is a measure of how fast these time segments loose their resemblance when both the segments are lengthened.

Lyapunov exponents (LEs) are also found habitually in the literature to enhance the dynamics of trajectories in the phase space. Precisely, these exponents quantify the exponential divergence or convergence of initially close phase space trajectories. LEs quantify also the amount of instability or predictability of the process. An m-dimensional dynamical system has m exponents but in most applications it is sufficient to compute only the largest LE (LLE), which can be computed as follows. First, a starting point is selected in the reconstructed phase space and all the points which are closer to this point than a predetermined distance, ϵ, are found. Then the average value of the distances between the trajectory of the initial point and the trajectories of the neighboring points are calculated as the system evolves. The slope of the line obtained by plotting the logarithms of these average values versus time gives the LLE. To remove the dependence of calculated values on the starting point, the procedure is repeated for different starting points and the LLE is taking as the average.

3.3. Information content quantification

Symbolic time series analysis involves the transformation of the original time series into a series of discrete symbols that are processed to extract useful information about the state of the system generating the process [20]. The first step of symbolic time series analysis is, hence, the transformation of the time series into a symbolic/binary sequence using a context-dependent symbolization procedure. After symbolization, the next step is the construction of words from the symbol series by collecting groups of symbols together in temporal order. This process typically involves definition of a finite word-length template that can be moved along the symbol series one step at a time, each step revealing a new sequence.

Quantitative measures of word sequence frequencies include statistics of words (word frequency or transition probabilities between words) and information theoretic based on entropy measures. Thus, a complexity measures widely used is the proposed by Lempel and Ziv [20], which will be referred to as *Lempel-Ziv complexity* (LZC). This metric provides a measure of complexity related to the number of distinct substrings and the rate of their occurrence along a given sequence, larger values of LZC corresponding to more complex series. Another metric habitually used is the *Shannon entropy* (ShEn) [21]. This index gives a number that characterize the probability that different words occur. Thus, counting the relative frequency of each word, the ShEn is estimated as the sum of the relative frequencies weighted by the logarithm of the inverse of the relative frequencies (i.e. when the frequency is low, the weight is high, and vice versa). For a very regular binary sequence, only a few distinct words occur. Hence, ShEn would be small because the probability for these patterns is high and only little information is contained in the whole sequence. For a random binary sequence, all possible words occur with the same probability and the ShEn is maximal.

3.4. Irregularity quantification

Approximate entropy (ApEn) provides a measure of the degree of irregularity or randomness within a series of data. ApEn assigns a non-negative number to a sequence or time series, with larger values corresponding to greater process randomness or serial irregularity, and smaller values corresponding to more instances of recognizable features or patterns in the data [21]. ApEn measures the logarithmic likelihood that runs of patterns that are close (within a tolerance window r) for length m continuous observations remain close (within the same tolerance r) on next incremental comparison. The input variables m and r must be fixed to calculate ApEn. The method can be applied to relatively short time series, but the amounts of data points has an influence on the value of ApEn. This is due to the fact that the algorithm counts each sequence as matching itself to avoid the occurrence of $\ln(0)$ in the calculations. The *sample entropy* (SampEn) algorithm excludes self-matches in the analysis and is less dependent of the length of data series [22].

On the other hand, the *multiscale entropy* (MSE) has been developed as a more robust measure of regularity of physiological time series which typically exhibit structure over multiple time scales [23]. For its computation, the sample mean inside each non-overlapping window of the original time series is calculated, thus constituting this set of sample means a new time series. Repeating the process N times with a set of window lengths starting from 1 to a certain length N, this will give a set of N time series of sample means. The MSE is obtained by computing any entropy measure (SampEn is suggested) for each time series, and displaying it as a function of the number of data points N inside the window (i.e. of the scale).

Another index that can be used to quantity the regularity of a time series is the *conditional entropy* (CE) [24]. This index computed for a time series measures the amount of information carried by its most recent sample which is not explained by the knowledge of a predetermined conditioning vector containing information about the past of the observed multivariate process. The CE computation can be expressed as the difference between the ShEn calculated for the time series divided both in L and $L-1$ sample-length patterns. Thus, this index measures the amount of information obtained when the pattern length is augmented from $L-1$ to L. If a process is periodic (i.e. perfectly predictable) and has been observed for a sufficient time, it will be possible to predict the next samples. Therefore, there will be no increase of information by increasing the pattern length and CE will go to zero after a certain L. Nonetheless, this algorithm requires a corrective term to estimate accurately the CE. The correction is thought to counteract the bias toward a reduction of the CE which occurs increasing the size of the conditioning vectors and depends strongly on the length of the time series [24].

It is interesting to remark that a slightly modified version of the CE, such as *Cross-CE* (CCE), is able to assess the coupling degree between two time series [24]. Synchronization occurs when interactive dynamics between two signals are repetitive. In this line, this index computes the amount of information included in the most recent sample of a times series when the past L-sample-length pattern of the other series is given. Given that CCE suffers from the same limitation as CE, it has to be corrected in the same way.

Finally, other measure proposed to estimate coupling between time series is the *causal entropy* (CauEn) [25]. This index is an asymmetric, time-adaptive, event-based measure of the regularity of the phase- or time-lag with which point i fires after point j. It is calculated from two components: a non-parametric time-adaptive estimate of the probability density of spike time lag between two points i and j such that i follows j (and, independently, the distribution of j following i), and a cost function estimate of the spread and stability of the distribution. Although a variety of alternatives exists to compute this metric, CauEn can be easily estimated by choosing an event-normalized histogram as the time-adaptive density estimator and the ShEn as the cost function [25].

3.5. Geometric structure quantification

A *Recurrence plot* (RP) is a visual representation of all the possible distances between the points constituting the phase space of a time series [21]. Whenever the distance between two points is below a certain threshold, there is a recurrence in the dynamics: i.e. the dynamical system visited multiple times a certain area of the phase space. From this transformation, well suited for the study of short non-stationary signals, many geometric features can be extracted. In this sense, there are four main elements characterizing a RP: isolated points (reflecting stochasticity in the signal), diagonal lines (index of determinism) and horizontal/vertical lines (reflecting local stationarity in the signal). The combination of these elements creates large-scale and small-scale patterns from which is possible to compute several features, mainly based on the count of number of points within each element.

On the other hand, the *Poincaré plots* (PPs) are a particular case of phase space representation created selecting $m = 2$ and $\tau = 1$; that corresponds to displaying a generic sample n of the time series as a function of the sample $n - 1$ [21]. This is also known as a return map or a Lorenz plot. The main limitation of this technique is that assumes that a low dimensional representation of a dynamical attractor is enough to detect relevant features of the dynamics. Despite its simplicity, this transformation has been successfully employed also with high dimensional systems. The benefit is that, given the low dimensionality, it is possible to easily design and visualize several types of geometric features. These features are based on an ellipse fitted to the PP. These features can be seen as measures of nonlinear autocorrelation. If successive values in the time series are not linearly correlated, there will be a deviation from a line that is often properly modeled using an ellipse. The different features involve the centroid of the ellipse, the length of the two axes of the ellipse, the standard deviation in the direction of the identity line (called SD2) and the standard deviation in the direction orthogonal to the identity line (called SD1).

4. Atrial activity analysis

Although the mechanisms of AF still are unclear, several studies have demonstrated that this arrhythmia is associated with the propagation, throughout the atrial tissue, of multiple activation wavelets, resulting in complex ever-changing patterns of electrical activity [5]. As a consequence, the morphology of the registered f waves during AF changes constantly both in time and space showing different levels of organization, according to a definition of organization as repetitive wave morphologies in the AF signals [19]. Given that various morphologies reflect different activation patterns such as slow conduction, wave collision, and conduction blocks [26], AF organization analysis plays an important role to understand the mechanisms responsible for its induction and maintenance. In addition, the analysis of the degree of complexity characterizing the shape of the activation waves could provide useful information to improve AF treatment, which still is unsatisfactory, and contribute to take the appropriate decisions on its management [27].

Since a rigorous definition of organization does not exist, a variety of nonlinear indices have been applied to the AA signal extracted from both surface ECG recordings and intraatrial EGMs to quantify AF pattern dynamic and morphology. In the next subsections, the state of the art related to the AF organization estimation by using nonlinear methods is summarized.

4.1. Surface organization assessment

From a clinical point of view, the assessment of AF organization from the standard surface ECG is very interesting, because it can be easily and cheaply obtained [10]. Previous works have shown that structural changes into surface f waves reflect the intraatrial activity organization variation [28, 29]. Thus, it has been observed that ECGs acquired during intraatrial organized rhythms present f waves with well-defined and repetitive morphology and ECGs recorded during highly disorganized AA with fragmented activations contain surface f waves with very dissimilar morphologies [30]. Taking advantage of this finding, several nonlinear indices have been applied to single-lead ECG recordings to estimate the amount of repetitive patterns existing in their extracted AA signal. Leads V1 and II have been most often selected for this purpose, because the atrial signal is larger in these recordings [10].

The first proposed method to estimate non-invasively temporal organization of AF is based on the application of SampEn to the fundamental waveform of the AA signal, which have been named as main atrial wave (MAW) in the literature [4]. Note that SampEn computation directly from the AA has also been investigated, but an unsuccessful AF organization assessment has been reported by several authors [4]. The presence of ventricular residua and other nuisance signals together with the SampEn sensitivity to noise have been considered the main reasons for this poor result [4]. In contrast, the MAW-SampEn strategy has provided ability to reliably reflect the intraatrial fibrillatory activity dynamics [29] and has been validated by predicting successfully a variety of AF organization-dependent events. In this respect, the method has shown a high diagnostic accuracy in the paroxysmal AF termination prediction, presenting more regular f waves for terminating than non-terminating episodes [4]. This result is in agreement with the decrease in the number of reentries prior to sinus rhythm (SR) restoration observed in previous invasive studies, where AF termination was achieved by using different therapies [6]. In a similar way, according with the invasive observation that self-sustained AF is associated with more circulating wavelets that non-sustained AF [6], the method has noticed higher organization levels for paroxysmal than persistent AF episodes [31].

On the other hand, the MAW-SampEn method has also presented a high discriminant ability in the prediction of ECV result before the procedure is attempted. According with previous invasive findings [32], SampEn reported higher AF organization levels in those patients who maintained SR during the first month post-cardioversion [4]. In addition, analyzing SampEn after each needed electrical shock to restore SR, a relative entropy decrease was observed for the patients who finally reverted to SR, but the largest variation took place after the first attempt, thus indicating that this shock plays the most important role in the procedure [33]. Finally, remark that the method has also been used to assess the organization evolution along onward episodes of paroxysmal AF and within an specific episode. In the first case, the achieved results, in close agreement with previous findings obtained from invasive recordings [34], proved several relevant aspects of arial remodeling [35]. Thus, a progressive disorganization increase along onward episodes of AF was observed for 63% of the analyzed patients, whereas a stable AF organization degree was appreciated in the remaining 37%. Moreover, a positive correlation between episode duration and SampEn and a remarkable influence of the fibrillation-free interval, preceding each episode, on the corresponding level of AF organization at the onset of the subsequent AF episode were noticed. With respect to the application of the method to track organization variations within each specific episode [4], a decrease in the first minutes after AF onset and an increase within the last minute before spontaneous AF termination were revealed, in coherence with previous works [6].

It is interesting note that f waves regularity has also been assessed through the application of SampEn to the wavelet domain of the AA signal [4]. In this case, the proposed approach reached a slightly lower discriminant ability than the MAW-SampEn method both for paroxysmal AF termination and ECV outcome predictions. Nonetheless, both methodologies showed to provide complementary information, their combination allowing to improve the identification of AF organization time course [4]. A similar result has been recently observed when the variability of the wavelet coefficients computed from the AA signal has been quantified by the central tendency measure [36]. This nonlinear metric is the percentage of points which falls within a certain radius from the centre of the PP of the first difference of the original time series [21] and, in view of the provided results, can be considered as a successful non-invasive estimator of temporal organization of AF.

In addition to SampEn, other nonlinear indices have also been applied to the AA signal time domain. Thus, Kao et al [37] computed the CD, LLE and LZC from the AA signal extracted for the lead V1 in order to distinguish between atrial flutter and AF episodes. According to the expected AF disorganization levels, results showed that during AF, nonlinear parameters concentrated on higher values, which were lower at typical flutter and middle in atypical flutter. In addition, the combination of these parameters by using a neural network classification allowed the differentiation of these arrhythmias with a high diagnostic accuracy around 95%. On the other hand, Sun and Wang [38] have investigated the spontaneous termination of paroxysmal AF by quantifying the RP structure of the AA signal. More precisely, eleven features were extracted from the RP including, among others, the point recurrence rate, the patterns along the main diagonal, the patterns along the 135° diagonal and square-like patterns. Thereafter, a sequential forward search algorithm was utilized to select the feature subset which could predict the AF termination more effectively. Finally,

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a multilayer perceptron neural network was applied to predict the AF termination with an accuracy higher than 95%.

4.2. Intraatrial organization assessment

As an alternative to the use of surface recordings, AF organization can be quantified from single-lead atrial EGMs by analysis of the whole signal aimed to infer measures related to the dynamical complexity of the signal itself. As for surface ECG recordings, the presence of undisturbed portions of the signal or the repetitiveness over time of similar patterns, are indicative of high regularity, or low dynamical complexity, related to the temporal organization of the arrhythmia. Within this context, Wells et al [8] distinguished three types of AF. In type I AF, the EGMs showed discrete complexes of variable morphology separated by a clear isoelectric baseline. Type II AF EGMs were characterized by discrete atrial beat-to-beat complexes of variable morphology but, in contrast to type I AF, the baseline showed continuous perturbations of varying degrees. During type III AF, highly fragmented atrial EGMs could be observed with no discrete complexes or isoelectric intervals. An analysis looking at these characteristics in AF EGMs has a peculiar electrophysiological relevance, as it may reflect the propagation patterns underlying the maintenance of AF [6]. Indeed, the Wells' approach has been used in several clinical and experimental studies to identify organization patterns in paroxysmal and chronic AF and to support the ablative treatment of AF [39]. In addition, many authors have proposed to quantify automatically single-lead EGMs organization by using analysis of fractal fluctuations and entropy measures.

In this line, the study of Hoekstra et al [40] was the first exhaustive nonlinear analysis of AF in man. The authors estimated the CD and the CorEn of unipolar epicardial EGMs. Both indices were exploited to discriminate among EGMs during induced AF, revealing the presence of nonlinear dynamics in type I AF. In contrast, type II and type III AF did not appear to exhibit features of low-dimensional chaos. Both previous indices were also used to investigate the anti-fibrillatory properties of the class Ic agent cibenzoline in instrumented conscious goats in which sustained AF had been electrically induced [41]. Results showed that during drug administration the nonlinear parameters were not significantly different from control. Nonetheless, scaling regions in the correlation sum were observed after infusion of cibenzoline suggesting that the drug introduced low-dimensional features in the dynamics of AF, whereas SR recorded shortly after cardioversion was very regular. Hence, authors concluded that nonlinear analysis revealed that cibenzoline does not significantly alter the dynamics of sustained AF during pharmacological conversion other than a slowing down of the atrial activation and a somewhat increasing global organization of the atrial activation pattern.

More recently, Mainardi et al [24] have developed a regularity index based on the corrected CE for single-site atrial EGMs and LAP series, which has provided ability to discriminate among different atrial rhythms and, particularly within different AF complexity classes according to Wells' criteria [24, 42]. In a similar way, the index has been able to capture subtle changes due to isoproterenol infusion both during SR and AF [43]. On the other hand, ShEn has been tested as a measure of EGMs complexity for distinguishing complex fractionated atrial electrograms (CFAE) from non-CFAE signals [44]. Given that CFAE have been identified as targets for AF ablation, the development of robust automatic algorithms to objectively classify these signals is clinically relevant. An index of fractional intervals (FI) has been traditionally used and validated as a semiautomatic algorithm to identify CFAE [45]. This measure takes the average interval between deflections of an EGM signal during AF. In contrast, ShEn computation requires each EGM amplitude sample to be classified into bins of defined amplitude ranges. After quantifying EGMs with a bin with of 0.125 their with a bin width of 0.125 times their standard deviation, ShEn provided comparable results to the index of FI in distinguishing CFAE from non-CFAE without requiring user input for threshold levels. Hence, authors claimed that ShEn can be a useful tool in the study of AF pathophysiology as well as help in the classification of CFAE, although its use for EGM-guided approaches in AF ablation requires further validation.

It is interesting note that approaches of nonlinear analysis have also been applied to each one of the bipolar signals collected by basked catheters, thus providing estimates of spatial organization of AF. In this respect, Pitschner et al [46] calculated the CD of the depolarization wavefronts on signals measured during paroxysmal AF and found that the area anterior to the tricuspid valve showed the most pronounced chaotic activity. Later, Berkowitsch et al [47] proposed a combination of symbolic dynamics and adaptive power estimation to compute the normalized algorithmic complexity of single-site bipolar EGMs. The algorithm produces a measure of the ″redundancies″ in patterns of the AF EGM so that the complexity is inversely related to the number of redundancies found in the analyzed signal. The method was used to show heterogeneous complexity among different atrial regions and complexity changes after drug administration [48]. In a similar way, Cervigón et al [49] analyzed the regularity differences in EGMs captured both from right (RA) and left (LA) atria after propofol administration. Global regularity from each atrium was estimated by applying both MSE and ShEn to each registered single EGM and averaging all the recordings acquired from each atrium. Results revealed differences between the MSE profiles in basal and propofol states and that EGMs at basal condition were sightly less irregular in RA than in LA. In addition, an irregularity decrease in EGMs was noticed, through the MSE, for RA during the proposal infusion. Note that this behavior was observed for all time scales, although MSE decreased on small scales and gradually increases indicating the reduction of complexity on the larger scales. The application of ShEn showed the same upward trend in the LA during propofol infusion, and downward trend in the RA in the anaesthesic state.

In a similar way, both MSE and ShEn have also been used to assess regional organization differences between paroxysmal and persistent AF episodes [50]. In this case, both for paroxysmal and persistent AF patients, no significant differences were found in an intra-atrial analysis (i.e. between the EGMs within the same atrium) in any atria. However, in an inter-atrial analysis, entropy values were higher at the LA than at the RA; i.e. the atrial activations were generally more organized at the RA than at the LA. However, compared with persistent AF, results from the analysis of paroxysmal AF demonstrated larger differences between the atrial chambers. Therefore, a regional gradient from the LA to RA in the organization degree of the atrial electrical activity was found in paroxysmal AF patients, whereas no gradient was found in persistent AF patients.

4.3. Intraatrial synchronization assessment

Spatio-temporal organization of AF has been investigated from mutual analysis of pairs of EGMs simultaneously collected during different atrial rhythms. In this case, measuring organization implies judging the electrical activity at one site in relation to the activity of another. Measures derived in such a way emphasize the concepts of relative temporal behavior and spatial coordination between electrical activations occurring at different sizes. With respect to approaches developed for single-site EGMs, the introduction of algorithms involving two (or more) signals provide complementary information. For instance, synchronization measures have been exploited to investigate the preferential directions of waveforms propagation during arrhythmias, or to reflect the spatial dispersion of electrophysiological parameters such as conduction velocity and refractory period.

To capture and quantify nonlinear interactions among EGMs, some entropy measures have been adapted to the analysis of endocardial signals. Indeed, the studies of Censi et al [51] and Mainardi et al [24] estimated the degree of nonlinear coupling between pairs of bipolar EGMs acquired by decapolar catheters by performing specific multivariate embedding procedures. In particular, Censi et al [51] assessed the organization of the LAP series during AF by means of two indices, namely independence of complexity and independence of predictability. These indices were computed on the basis of a multivariate embedding procedure for the estimation of CD and CorEn. Significant degrees of nonlinear coupling were found in segments belonging to types I and II, while type III EGMs turned out to be only weakly coupled. On the other hand, Mainardi et al [24] estimated spatio-temporal organization in the atria by means of a synchronization index assessing the coupling level between EGMs by means of the corrected CCE. Although this index is sensitive to various signal coupling mechanisms (linear or not), it provides superior performance when compared to linear indices derived from the cross-correlation function, as evidenced in many applications [24]. Thus, it was found to be the best discriminator between organized (sinus rhythm and AF I, classified according to Wells' criteria) and non-organized (AF II and AF III) rhythms [24], showing sensitivity and positive predictability higher than 95%. The index also provided ability to capture subtle changes in atrial dynamics, thus improving the understand the effect of the sympathetic nervous system activity during SR and AF in patients suffering from paroxysmal and persistent AF [43]. In a similar way, the synchronization index showed to be able to underline the effect of the adrenergic stimulation, highlighting variations related to the distance between recording sites [7]. These variations were not detected with the same level of detail by any other linear and nonlinear parameter. Finally, a reduction in the synchronization among EGMs was evidenced by using this index during isoproterenol infusion in both SR and paroxysmal AF episodes [52].

Coupling between atrial EGMs can also be assessed by quantifying the temporal synchronism between activation times in two sites. In this context, researches have focused their attention to either the LAP series or the activation time sequences. Thus, Censi et al [53] exploited RPs to show that a certain degree of organization during AF can be detected as spatio-temporal recurrent patterns of the coupling between the atrial depolarization periods at two atrial sites. They demonstrated a deterministic mechanism underlying the apparently random activation processes during AF. Other approach for the same purpose was proposed by Masé et al [54] who characterized the synchronization between two atrial signals through a measure of the properties of the time delay distribution by the ShEn. Specifically, the values of the propagation delay were quantized into severals bins and the entropy of their distribution was estimated. After introducing a corrective term to reduce the systematic underestimation of ShEn due to the approximation of the probabilities with the corresponding sample frequency, the index was validated with a computer model of atrial arrhythmias. It was shown to discriminate among different AF types and to elicit spatial heterogeneities in the synchronization between different atrial sites. Moreover, a comparison of the real data with simulation results linked the different shapes of the time delay distribution, and thus the proposed index, to different underlying electrophysiological propagation patterns.

Finally, CauEn has been recently used to monitor coupling between temporal variations from two atrial EGMs for paroxysmal and persistent AF episodes [50]. Results showed differences between both atrial chambers with a higher disorganization in the LA than RA in paroxysmal AF patients and a more homogenous behavior along the atria in persistent AF patients. These findings were in strong agreement with the hypothesis that high-frequency periodic sources located in the LA drive AF [55]. Nonetheless, the result may also support the multiple wavelet hypothesis, which have a random movement throughout the atria [5].

5. Ventricular activity analysis

Ventricular response during AF has been widely characterized making use of the heart rate variability (HRV) analysis. Although how the autonomic nervous system exactly modulates the heart rate remains an open question, HRV can be used to quantify several aspects of the autonomic heart rate modulation [56]. Standard time and frequency domain methods of HRV are well described by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [57], but they fail to show the dynamic properties of the fluctuations. Therefore, nonlinear methods have been typically applied to the HRV for assessing its variability, scaling and correlation properties, thus providing complementary information to the standard HRV metrics [9]. Within this context, the next subsections summarize how nonlinear indices has been applied to HRV analysis in an attempt to understand cardiovascular autonomic regulation before, during and after AF onset and behavior of the AV node during the arrhythmia.

5.1. HRV analysis during SR

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. Precisely, increased vagal tone can predispose to the development of AF [58]. Thereby, several measures of entropy, such as SampEn and ApEn, together with the DFA have been applied to study the HRV complexity evolution in the minutes preceding spontaneous paroxysmal AF onset. To this respect, Vikman et al [59] studied the DFA and ApEn in 20-minutes intervals before 92 episodes of paroxysmal AF in 22 patients without structural heart disease. A progressive decrease in complexity was observed by both indices before the AF episodes. In addition, they also noticed lower complexity values before the onset of AF compared with values obtained from matched healthy control subjects. In a similar way, Tuzcu et al [58] studied via SampEn the HRV complexity of 30 minutes-length segments containing the ECG immediately preceding a paroxysmal AF episode and 30 minutes-length segments of ECG during a period distant, at least 45 minutes, from any episode of AF. Complexity of the HRV was found to be significantly reduced in the segments preceding AF compared with those distant from any AF occurrence. The same study was repeated, but premature atrial complexes were previously removed. In this case, a less pronounced difference was provided. The authors considered that decreased heart rate complexity, for both cases, reflects a change in cardiovascular autonomic regulation that preconditions AF onset. Additionally, the segments preceding AF onset were divided into three successive 10 minutes periods and analyzed with SampEn in order to show the presence of a possible trend. A decreasing complexity trend towards the onset of AF was observed independently on the presence or absence of ectopics, although in the later case the tendency was less pronounced. According to the authors, the decrease in complexity via SampEn before the onset of AF resulted mainly from atrial ectopy. Moreover, the decrease was in consistent agreement with the observed ectopic firing significance, that serves as a trigger of paroxysmal AF, in subjects without evidence of other structural cardiac abnormalities [60].

On the other hand, because of paroxysmal AF has been classified into vagally-mediated and sympathetically-mediated types, based on the autonomic profile and the clinical history, Shin et al [61] analyzed the HRV complexity in these types of AF. In this study, for 44 episodes, divided in three subgroups (vagal, sympathetic and non-related types), the 60 minutes segment of normal sinus rhythm preceding AF onset was divided into 6 periods of 10 minutes. The DFA showed a poor tendency to decrease before the onset of AF and the change of this parameter was divergent according to the AF type. In contrast, ApEn and SampEn revealed a linear decrease of complexity irrespective of AF type. In addition, this result in both ApEn and SampEn before AF onset was not affected whether excluding the ectopic beats or not. In the authors' opinion, the meaning of this progressive entropy reduction before the start of AF was that the heart rate became more orderly before AF; that is, there is a loss of normal "healthy" complexity, thus leading to a cardiac environment vulnerable to the occurrence of AF.

It is interesting note that although nonlinear indices, especially SampEn, have provided to be better predictors than standard HRV measures, their diagnostic ability in paroxysmal AF prediction is far from clinically optimal. Thus, in order to improve their discriminant capability, these nonlinear indices have been combined with other HRV metrics making use of different classification approaches. In this respect, Chesnokov [62] analyzed the combination of spectral features, SampEn and MSE of the HRV by using different artificial intelligent methods. More recently, Mohebbi and Ghassemian have proposed two different combinations of parameters to reach a diagnostic accuracy higher than 95%. Thus, in a first way, they computed a RP of the RR-interval series together with five statistically significant features: recurrence rate, length of longest diagonal segments, average length of the diagonal lines, entropy and trapping time. These parameters were combined making use of a support vector machine (SVM)-based classifier [63]. In the second alternative, a SVM-based classifier was also used to combine spectrum and bispectrum features with SampEn and PP-extracted parameters from the HRV [64].

Finally, several studies have applied nonlinear indices to the HRV after coronary artery bypass graft surgery, i.e. before the onset of AF. Thus, Hogue et al [65] showed that patients who developed AF presented reduced heart rate complexity through ApEn and that standard measures of HRV did not distinguish between these two groups. Logistic regression analysis indicated that only lower complexity via ApEn and higher heart rate were independently associated with AF. In addition, ApEn did not correlate with any other HRV variable, so that the data provide little evidence for a direct relationship between the magnitude of ApEn and the level of autonomic modulation of heart rate. In a similar way, Chamchad et al showed that ApEn provides little complexity in predicting AF after off-pump coronary artery bypass graft surgery [66] and that the CD was independently associated with AF after coronary artery bypass graft surgery, larger values of HRV complexity being associated with the development of post-surgery AF [67].

5.2. HRV analysis during AF

In order to characterize the chaos degree in the ventricular response during AF, Stein et al. [68] implemented an algorithm that uses nonlinear predictive forecasting for the RR-interval series, predicting its future behavior for a few beats by observing other sufficiently similar trajectories in the phase space [69]. Thus, given a RR-interval, the next interval is predicted as the weighed mean of the RR intervals following the three nearest neighbors (found according to Euclidean distance). Results showed that some patients had RR interval series during AF significantly (although weakly) predictable on very short-term scale. This weak predictability, according to the authors, may represent the effect of cyclic oscillations in vagal and/or sympathetic tone at the level of the AV node.

The aforementioned regularity index presented by Mainardi et al [24] has also been applied to the evaluation of exercise effect on ECG recordings from patients with persistent AF [70]. As the autonomic nervous system plays an important role among the factors influencing ventricular response by modulating refractoriness of the AV node, that is mainly dependent on vagal tone, the purpose of the study was to characterize ventricular response during AF to changes of the autonomic balance induced by exercise. The index, reflecting nonlinear series predictability, tended to increase during exercise. It was found that regularity values were very low compared to SR [71], thus the predictability degree of ventricular response is very small during AF. Nevertheless, taking linear and nonlinear dynamics into account, the index succeeded in underlining the increased predictability of ventricular response during exercise. The results highlighted the relevant activity played by the autonomic nervous system in patients with AF, as time domain parameters decreased and predictability indices increased. On the other hand, note that the same regularity index has also been used in order to assess different characteristics in spontaneous paroxysmal AF termination [71]. Thus, the index tried to discriminate between paroxysmal AF episodes that terminate immediately (within 1 second) and others that were not observed to terminate for the duration of the long-term recording, at least for an hour. Results showed higher regularity values for non-terminating than terminating paroxysmal AF episodes, suggesting in agreement with aforementioned works a decrease in the HRV complexity prior to the SR restoration [58, 59, 61].

Sun and Wang have also presented two different alternatives from the HRV analysis to predict spontaneous termination of paroxysmal AF. Thus, in a first way [72], they characterized RR-interval series and its PP extracting eleven features from statistical and geometric viewpoints, respectively. A sequential forward search algorithm was utilized for feature selection and a fuzzy SVM was applied for AF termination prediction. The second alternative [73] was based on the sign sequence of differences of RR intervals. More precisely, this sequence of differences was transformed into the sign sequence based on a threshold. Next, the complexity of the sign sequence and ShEn of probability distribution of substring length were taken as the features of AF signals. Finally, a fuzzy SVM was used to predict AF termination. Although a notably high diagnostic accuracy was reached by both algorithms, the complex combination of multiple parameters in both cases makes difficult the clinical interpretation of the results. In this sense, clinical meaning of each individual parameter is blurred within the classification approach.

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On the other hand, Yamada et al [74] analyzed the prognostic significance of ApEn by quantifying intrinsic unpredictability of the RR patterns and found reduced entropy of beat-to-beat fluctuations being predictive of cardiac mortality after adjustment for left ventricular ejection fraction and ischemic etiology of AF. In a similar way, Platonov et al [75] examined the regularity via ApEn of the RR-interval series during AF using short ECG tracings in a subgroup of patients enrolled in the MADIT-II study. However, contrary to the previously mentioned work, ApEn was not predictive of clinical outcome in the MADIT-II subgroup. Nonetheless, there were important differences in the clinical profile of the ischemic patients with congestive heart failure enrolled in the MADIT-II study and the patients with permanent AF with mostly preserved left ventricular ejection fraction studied by Yamada et al [74].

Finally, PPs were used to determine the ventricular response to AF and quinidine-induced changes in its variability in an in vivo study in horses [76]. Results showed a distinct shape in the RR-interval series distribution, suggesting that each RR-interval is determined by the previous one. This, together with the demonstration that there was a negative correlation between consecutive RR intervals and that the standard deviation of the mean of RR intervals was reduced as the AF frequency decreases in the course of quinidine administration, supported the suggestion that, although in the long-term the ventricular response may seem unpredictable, in the short term, the beat-to-beat changes in RR intervals follow deterministic laws established by the frequency-dependent conduction properties of the AV node. On the other hand, by adding the number of occurrences of RR-interval pairs, a 3-D PP can be constructed in which clusters of RR intervals can be identified. Interestingly, in AF patients with clustering of RR intervals, ECV was more effective to restore SR, and, of greater clinical interest, SR persisted for a longer period than in patients without clustering [77].

5.3. HRV analysis to distinguish between AF and SR

Automated detection of AF in heart beat interval time series is useful in patients with cardiac implantable electronic devices that record only from the ventricle. To this respect, PPs have been widely applied to the RR-interval series. Thus, Kikillus et al [78] estimated density of points in each segment of PP and calculated an indicator of AF from standard deviation of temporal differences of the consecutive inter-beat intervals. Thuraisingham [79] used a wavelet method to obtain a filtered time series from the input ECG. He calculated the standard deviation of the time series and the standard deviation of successive differences, and the length of the ellipse that characterized the PP. These indicators were used to discriminate AF from SR. Esperer et al [80] analyzed PP of 2700 patients with atrial and/or ventricular tachyarrhythmias and 200 controls with pure SR. Each plot obtained was categorized according to its shape and basic geometric parameters. Thus, results provided that different shapes were associated with AF and SR, both rhythms being accurately distinguished. Finally, Park et al [81] extracted three measures from PP characterizing AF and SR: the number of clusters, mean stepping increment of inter-beat intervals and dispersion of the points around a diagonal line in the plot. They divided distribution of the number of clusters into two, calculated mean value of the lower part by *k*-means clustering method and classified data whose number of clusters was more than one and less than this mean value as SR data. In the other case, they tried to discriminate AF from SR using SVM with the other feature measures: the mean stepping increment and dispersion of the points in the PP.

Although previous algorithms reached a high classification ability in long heart rate records, their performance was notably reduced for sort data sets. Similar behavior was appreciated for MSE measures [23]. Thus, in long RR time series, when matches abound, entropy metrics can distinguish AF well from SR [23]. However, there is a challenge, though, in assuring a sufficient number of matches when the data sets are short [82]. Thereby, Lake and Moorman [82] optimized the SampEn, developing general methods for the rational selection of the template length m and the tolerance matching r. The major innovation was to allow r to vary so that sufficient matches are found for confident entropy estimation, with conversion of the final probability to a density by dividing by the matching region volume, $2r^m$. The optimized SampEn estimate and the mean heart beat interval each contributed to accurate detection of AF in as few as 12 heartbeats. The final algorithm, called the coefficient of SampEn (COSEn), provided high degrees of accuracy in distinguishing AF from SR in 12-beat calculations performed hourly. The most common errors were atrial or ventricular ectopy, which increased entropy despite SR, and atrial flutter, which can have low or high entropy states depending on dynamics of atrioventricular conduction.

Finally, Segerson et al [83] showed that measures of short-term HRV during SR correlate with measures of cycle length entropy during paroxysms of AF. More precisely, two measures of short-term HRV in SR, such as the root mean square of the differences between consecutive normal intervals (RMSSD) and the inter-beat correlation coefficient (ICC), correlated with well-established measurements of entropy during AF, such as ShEn and ApEn. Recognizing that RMSSD and ICC are known measures of parasympathetic function in SR, authors' claimed that their results suggest a role for vagal regulation of cycle length entropy during AF.

5.4. HRV analysis to characterize the AV node

During AF, the fibrillatory impulses continuously bombard and penetrate the AV node to varying degrees (concealed conduction), creating appreciable variability on the AV nodal refractoriness [84]. Since the AV node is the structure responsible for the conduction of atrial impulses to the ventricles, the strategy of rate control during AF deals with efforts to utilize and adjust the propagation properties of the node [84]. Characteristics of AV conduction have been widely investigated during the last years by using different techniques and, especially, PP analysis. In this graph, it is possible to identify the lower envelope, which have been used to characterize the functional refractory period and the rate dependence of AV node conduction [85, 86]. In addition, the degree of scatter of the PP, calculated as the root mean square difference of each RR-interval and the lower envelope, has been presented as a measure of concealed conduction in the AV node [86].

By applying PP analysis to 24-h Holter recordings of 48 patients with chronic AF, it was suggested that both AV node refractoriness and the degree of concealed AV conduction during AF may show a circadian rhythm, but also that circadian rhythms may be attenuated in patients with heart failure [86]. These findings point to the possibility of obtaining information concerning altered autonomic control of the RR intervals in patients with AF (and heart failure or other disease) with this simple technique.

On the other hand, Oka et al [87] showed that for some PPs computed from 24-h recordings exhibited two separate sectors of RR intervals. When this occurred, the RR-interval histogram disclosed a bimodal distribution in approximately 40% of patients. It should be noted, however, that these RR-interval histograms were not stratified for different average heart rates. Nonetheless, authors suggest that PPs with two sectors could hold information of the functional refractory periods of each of the two conduction routes that can present the AV node [87]. Interestingly, the circadian variability of the fast pathway functional refractoriness was more pronounced than that of the slow pathway. More recently, Climent et at [88] have presented a method to automatically detect and quantify preferential clusters of RR-intervals. This method, named Poincaré surface profile (PSP), uses the information of histographic PPs to filter part of the AV node memory effects. PSP detected all RR populations present in RR interval histograms in 55 patients with persistent AF and also 67% additional RR populations. In addition, a reduction of beat-to-beat dependencies allowed a more accurate location of RR populations. This novel PP-based analysis also allowed monitoring of short-term variations of preferential conductions, which was illustrated by evaluating the effects of rate control drugs on each preferential conduction.

6. Conclusions

Different pathophysiologic processes control heart's behavior during AF in opposite directions, making difficult the understanding of the mechanisms provoking onset, maintenance and termination of this arrhythmia. Nonetheless, the state of the art summarized in the present work suggests that the use of modern methods of nonlinear analysis can facilitate the understanding of cardiovascular function during AF, in a complementary way to the traditional linear techniques. Thus, nonlinear indices have provided robust estimates of AF organization able to reveal information about several aspects of the arrhythmia. In this respect, clinically relevant information related to the arrhythmia state and its progression after pharmacological and electrical cardioversion has been shown by different researches. In addition, nonlinear analysis has shown to play an important role in the analysis of the ventricular response provoked by the arrhythmia, thus being able to reflect cardiovascular autonomic regulation changes before, during and after AF onset.

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