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Chapter 7

Applications of Signal Analysis to Atrial Fibrillation

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Additional information is available at the end of the chapter

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1. Introduction

Currently, atrial fibrillation (AF) guidelines are intended to assist physicians in clinical decision making by describing a range of generally acceptable approaches for the diagnosis and management of AF. However, these guidelines provide no recommendations that takes into account other aspects of the arrhythmia related with its computational analysis. For example, the proper application of spectral analysis, how to quantify different AF patterns in terms of organization, or how to deal with ventricular contamination before AF analysis are some aspects that could provide an improved scenario to the physician in the search of useful clinical information [1].

Both in surface and invasive recordings of AF the presence of ventricular activity has to be considered as a contaminant signal which has to be removed. In this respect, the proper analysis and characterization of AF from ECG recordings requires the extraction or cancellation of the signal components associated to ventricular activity, that is, the QRS complex and the T wave. Unfortunately, a number of facts hinder this operation [2]. Firstly, the atrial activity presents in the ECG much lower amplitude, in some cases well under the noise level, than its ventricular counterpart. Additionally, both phenomena possess spectral distributions notably overlapped, rendering linear filtering solutions unsuccessful. Within this context, several methods have been proposed to deal with this problem during last years. They go from a simple average beat subtraction [3], to the most advanced adaptive methods based on multidimensional signal processing [4] that will be detailed Section § 2.

From a clinical point of view, the estimation of the dominant atrial frequency (DAF), i.e., the repetition rate of the fibrillatory waves, is an important goal in the analysis of ECG recordings in AF. By comparing endocardial electrograms with ECGs, it has been established that the ECG-based AF frequency estimate can be used as an index of the atrial cycle length [5].

AF recordings with low DAF are more likely to terminate spontaneously and to respond better to antiarrhythmic drugs or cardioversion, whereas high DAF is more often associated with persistence to therapy [6]. The likelihood of successful pharmacological cardioversion is higher when the DAF is below 6 Hz [7]. Moreover, the risk of early AF recurrence is higher for patients with higher DAF [8] and, therefore, the DAF may be taken into consideration when selecting candidates for cardioversion. Section § 3 will provide to the reader basic concepts and recent advances in DAF estimation, as well as more elaborated techniques like time-frequency analysis or spectral modeling.

On the other hand, organization deals with strategies to quantify the repetitiveness of the AF signal pattern, thus providing very useful clinical information on the arrhythmia state. This relevant concept will be addressed in Section § 4, where the most important methods will be described [9, 10]. AF organization has demonstrated its clinical usefulness because indices of organization have been related to the electrophysiological mechanisms sustaining AF, or may be useful in the evaluation of strategies for AF treatment, such as catheter ablation or electrical cardioversion [11].

2. Atrial activity extraction

This section describes the most widely used methods to separate atrial from ventricular activities, both on surface and invasive recordings, grouped by they core way of operation. Mathematical notation or equations have been avoided in the interest of readability. Anyway, the reader could find detailed explanations in the corresponding references. Firstly, the methods based on the generation of an average beat, able to represent approximately each individual beat, are detailed. Within these methods, the main idea is to subtract the average beat from every single beat. Next, other group of methods take profit of physiological observations such as atrial and ventricular activities being uncoupled and originated from independent electrical sources. This fact allows the application of signal separation methods to dissociate atrial from ventricular activities, that will be addressed later.

2.1. Average Beat Subtraction methods

The average beat subtraction (ABS) based method was firstly presented by Slocum et al. [3] and still remains as the most widely used on the surface ECG [12, 13]. The ABS methodology takes advantage of the lack of a fixed relationship between atrial and ventricular activities and the consistent morphology of the QRST complexes [3]. In this method, fiducial points from ventricular complexes are detected and aligned [14]. Next, an average beat is generated where the window length is determined by the minimum or mean R–R interval. The window was aligned such that 30% of it preceded the fiducial point and 70% followed it [15]. A template of average beats was constructed and subtracted from the original signal, resulting in the atrial activity with subtracted ventricular activity.

The use of an adaptive template in conjunction with the correct alignment of every QRS complex, both in time and space, has proven to be very effective through the spatiotemporal QRST cancellation [16]. Since ABS is performed in individual leads, it becomes sensitive to alterations in the electrical axis, which are manifested as large QRS-related residuals. However, the effect of such alterations can be suppressed by using the spatiotemporal QRST cancellation in which the average beats of adjacent leads are mathematically combined with

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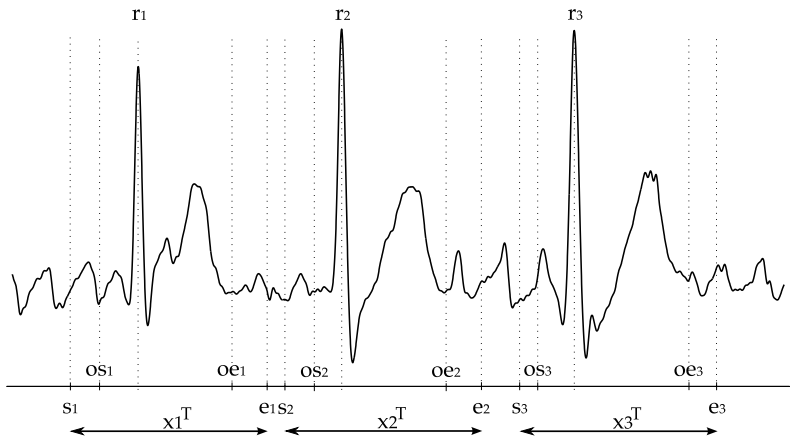

Figure 1. Relevant time instants used by the ASVC algorithm. The points s_i and e_i are the start and end points of the i-th QRST complex which is represented by $\mathbf{x}_i$, respectively. The points os_i and oe_i define the zones, at the beginning and the end of the i-th QRST complex, that will be processed to avoid sudden transitions after ventricular cancellation [13].

the average beat of the analyzed lead in order to optimize cancellation [16]. Other authors have proposed the idea of processing separately the QRS complex and the T wave [17]. This is because the depolarization waveform changes notably as a function of the heart rate, whereas the repolarization waveform remains almost unchanged.

Finally, the most recently ABS method is based on adaptive singular value cancellation (ASVC) of the ventricular activity [13]. Given that the ECG signal presents a high degree of temporal redundancy which could be exploited for ventricular activity cancellation, the ASVC method detected all the R waves making use of the Pan and Tompkins technique [14]. Next, the starting and ending points of each QRS complex were detected and the complexes were aligned using their R peak timing. Figure 1 depicts the fiducial points and relevant time instants described herein. Once all the beats were temporally aligned, their eigenvector sequence was obtained by singular value decomposition (SVD). In this way, the highest variance provided the eigenvector considered as the representative ventricular activity [13]. Thereby, this activity was used as the primary cancellation template. Next the template was adapted to each QRST width and height and was temporally aligned with each R peak in the ECG. Finally, the customized template for each beat was subtracted from every QRST complex and the atrial activity estimation inside the complex was obtained. This SVD–based method provided a more accurate ventricular activity representation adapted to each individual beat and, as a consequence, a higher quality AA extraction in a wide variety of AF recordings [13].

As an illustration on how the ABS-based methods can behave, Figure 2 plots the comparison between the simple ABS method introduced in [3] and the ASVC method presented in [13]. As can be observed, ventricular residua use to be present in the extracted AA, specially for the simple ABS method in (c). In fact, this is the main reason justifying the permanent optimization of atrial activity extraction methods during last years.

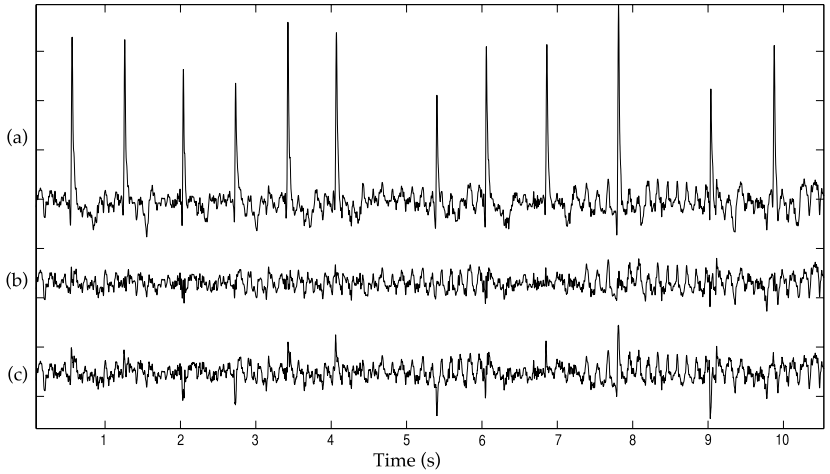

Figure 2. Example of a real ECG segment in AF with irregular QRST shape and the illustration on how the ABS-based method are able to cancel out ventricular activity. (a) ECG ready for ventricular activity cancellation. (b) Atrial activity signal provided by ASVC [13]. (c) Atrial activity signal provided by ABS [3].

2.2. Signal separation methods

Other recently proposed alternative consist of applying signal separation algorithms, which are able to use the multi-lead information provided by the ECG to obtain a unified atrial activity. They can be based on principal component analysis (PCA) [18] or blind source separation (BSS) [4]. These methodologies have been compared in a joint study proving their coincident results in the estimation of AF spectra on the surface ECG [19]. One common drawback to the ABS-based methods is that they are mainly thought to be applied over single lead ECGs. In other words, the application of ABS cancellation techniques to different ECG leads would involve the obtention of an equal number of different atrial activities as well. Consequently, they do not make use of the information included in every lead in an unified way. On the contrary, BSS techniques perform a multi-lead statistical analysis by exploiting the spatial diversity that multiple spatially-separated electrodes may introduce [4, 20].

The blind source separation consists in recovering a set of source signals from the observation of linear mixtures of the sources [21]. The term *blind* emphasizes that nothing is known about the source signals or the mixing structure, the only hypothesis being the source mutual independence [22]. To achieve the source separation, a linear transformation is sought such that the components of the output signal vector become statistically independent, thus representing an estimate of the sources except for (perhaps) scaling and permutation, which are considered as admissible indeterminacies [22]. Some authors have proposed the use of PCA to solve the mixing model between atrial and ventricular activity in AF [23]. However, it is important to remark that the success of PCA relies heavily on the orthogonality of the sources. But, in general, there is no reason why bioelectrical sources of the heart should be spatially orthogonal to one another in the ECG. This orthogonality condition can only be forced through appropriate electrode placement, as previously emphasized in the context of the fetal ECG extraction problem [24] and the cancellation of artifacts in the electroencephalogram [25].

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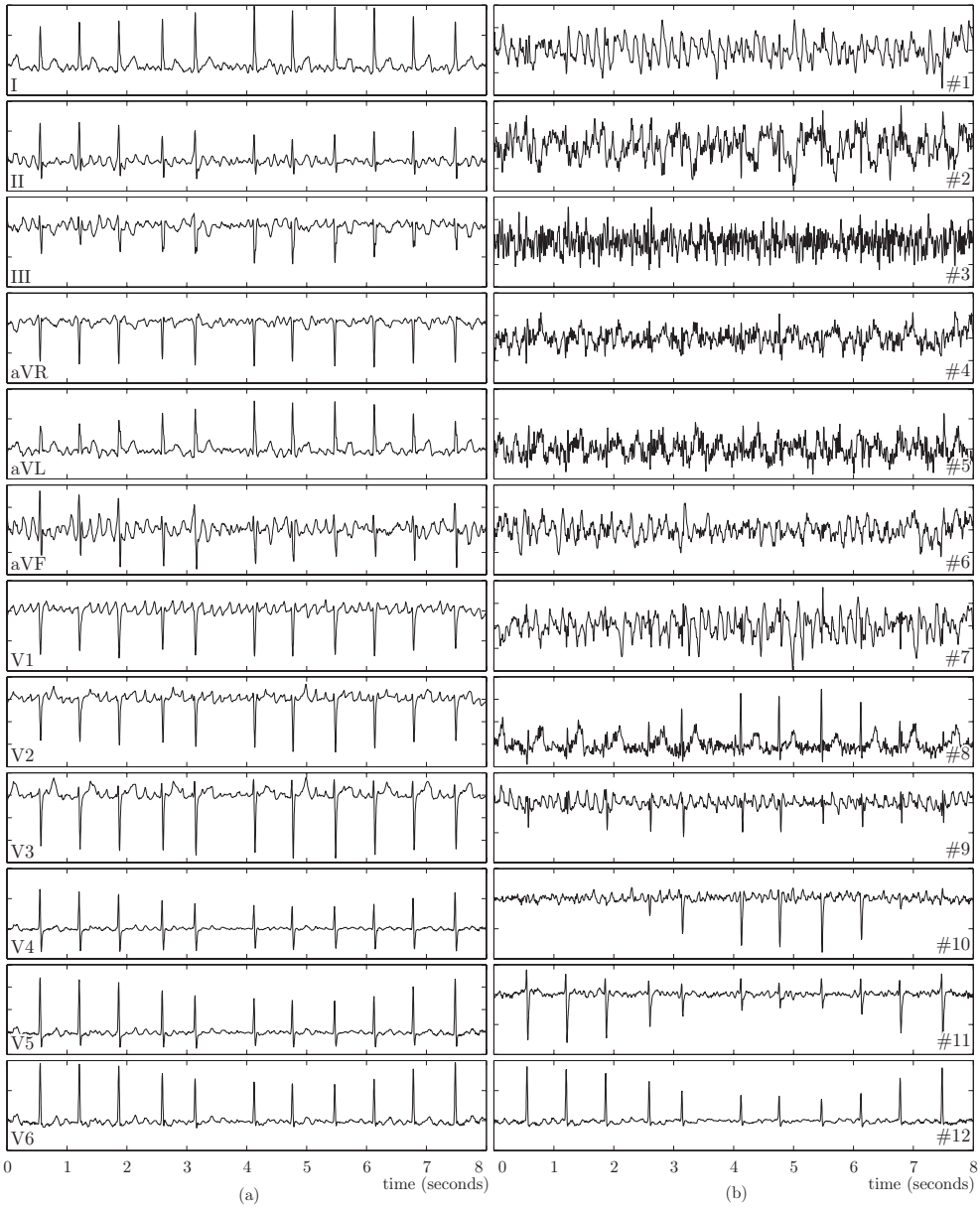

Figure 3. Input and result of the BSS separation process applied to an ECG of atrial fibrillation. (a) 12-lead ECG segment from a patient in AF. The multi-lead information will be used by BSS to yield a unified atrial activity. (b) Estimated sources obtained via BSS and reordered from lower to higher kurtosis value. The unified atrial activity is contained in source #1 [4].

When BSS is applied to an ECG in AF, a set of different sources can be observed as illustrated in Figure 3. Consequently a crucial step in BSS-based atrial activity extraction is to identify the sources(s) which contains atrial activity. The first algorithm proposed for this purpose made use of a kurtosis-based reordering of the components, relying on the assumption that sub-Gaussian sources are associated with atrial activity, approximately Gaussian ones with various types of noise and artifacts, whereas super-Gaussian sources are associated with ventricular activity [4]. Since information on kurtosis alone is insufficient for accurate identification of the atrial component, kurtosis reordering was combined with power spectral analysis of the sub-Gaussian components to detect when a dominant spectral peak, reflecting atrial rate, was present or not. It is commonly accepted that atrial rate is reflected by a peak whose frequency is confined to the interval 3–9 Hz [4]. In this respect Figure 4 shows the power spectral density associated to the separated sources with lower kurtosis in Figure 3. As can be appreciated, source #1 is the one representing the typical spectrum of an atrial activity.

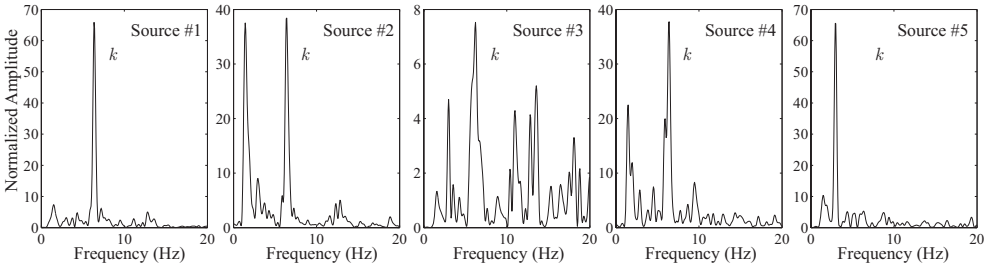

Figure 4. Power spectral densities from several BSS-estimated sources of Fig. 3. After kurtosis-based reordering only five sources have subgaussian kurtosis, and the one with lowest kurtosis (source #1) presents a power spectral density typically associated with the atrial activity in AF episodes [4].

Another approach to atrial component identification was later presented in [20], where kurtosis reordering and spectral analysis are supplemented with another technique with which ventricular components are excluded from further processing and only components with possible atrial activity are retained. Since the kurtosis of the ventricular components is usually very high, they can be excluded with a simple threshold test. It was found that a threshold of about 1.5 retained components with atrial activity, but excluded components with QRS complexes. The block diagram of this technique is represented in Figure 5.

The nonventricular components, i.e., atrial activity, noise, and artifacts, with kurtosis close to zero, are separated using second-order blind identification (SOBI). This technique aims at separating a mixture of uncorrelated sources with different spectral content through second-order statistical analysis which also takes into consideration the source temporal information [20].

2.3. Specific methods for invasive recordings

In the same way as with surface ECG recordings, other relevant point of view to understand the pathophysiological mechanisms of AF is the analysis and interpretation of atrial electrograms (AEG), which are recordings obtained on the atrial surface. More precise and successful therapies can be developed through this analysis, like guided radio-frequency ablation [26], analysis of antiarrhythmic drug effects [27] or performance improvement of

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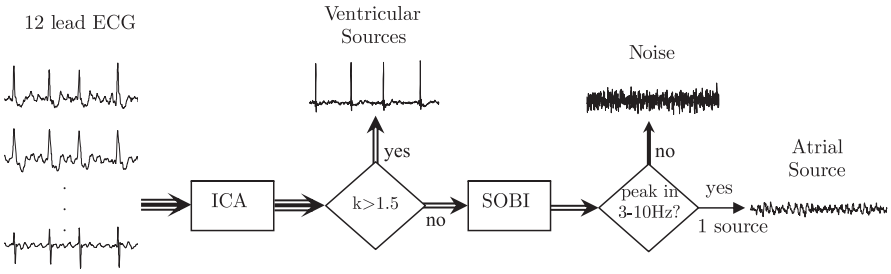

Figure 5. Block diagram of the BSS method, implemented by independent component analysis (ICA), and SOBI for atrial activity extraction in multi-lead ECGs of AF. It can be observed that components whose kurtosis exceed 1.5 are excluded from the SOBI stage [20].

atrial implantable cardioverter-defibrillators [28]. Within this context, ABS (or a similar methodology) has been applied to the AEG in order to discriminate sinus rhythm from AF [15], to measure AF organization [9] and synchronization [29] and to monitor the effects of ablation procedures and antiarrhythmic drugs [30].

However, ABS tends to distort the resulting atrial signal when the AEG under analysis corresponds to a well organized AF, as Figure 6 shows. Observe in Fig. 6.a that the atrial rhythm is well organized and uncoupled with the ventricular rhythm. The AEG shows ventricular depolarization contamination and the remaining three signals are the resultant atrial activity after applying ventricular reduction with the corresponding algorithm. Observe how ABS can modify the atrial waveform within the atrial segments. In contrast, Fig. 6.b shows a disorganized AF episode. In this case, thanks to the irregularity of the atrial signal, ABS performs better, preserving the atrial waveform and reducing ventricular peaks.

Because of the aforementioned problems with ABS, alternative methods have been introduced in the literature [31]. Firstly, adaptive ventricular cancellation (AVC) can be considered. This method is based on an adaptive filter that operates on the reference channel to produce an estimate of the interference, which is then subtracted from the main channel [32]. In this case the main channel was the recorded AEG containing both atrial and ventricular components. On the other hand, the reference channel was lead II from the standard surface ECG. The motivation to select this lead was based on the large ventricular amplitude that can be observed on it, and the precise time alignment existing between the QRS complex of lead II and the AEG [12, 33]. The resulting atrial activity provided by the AVC method can be observed in Figure 6 for two different types of AF recordings.

The last approach introduced to deal with AA extraction from the AEG has been based also in BSS through the use of independent component analysis (ICA) [31]. This is because in the context of AF patients, atrial and ventricular activities can be considered as decoupled electrical processes that appear mixed at the electrode output [4]. Therefore, it should be possible to dissociate atrial from ventricular activity in one AEG lead by using the proper reference signal which, in this case, has been the surface standard lead II by the same reasons as with AVC. In this case, the dimension is 2×2 where the observations are composed of the AEG and lead II, and the sources are the atrial and ventricular components to be dissociated. The FastICA algorithm was preferred to perform the ICA process due to its fast convergence and robust performance, previously demonstrated in a variety of different applications [34].

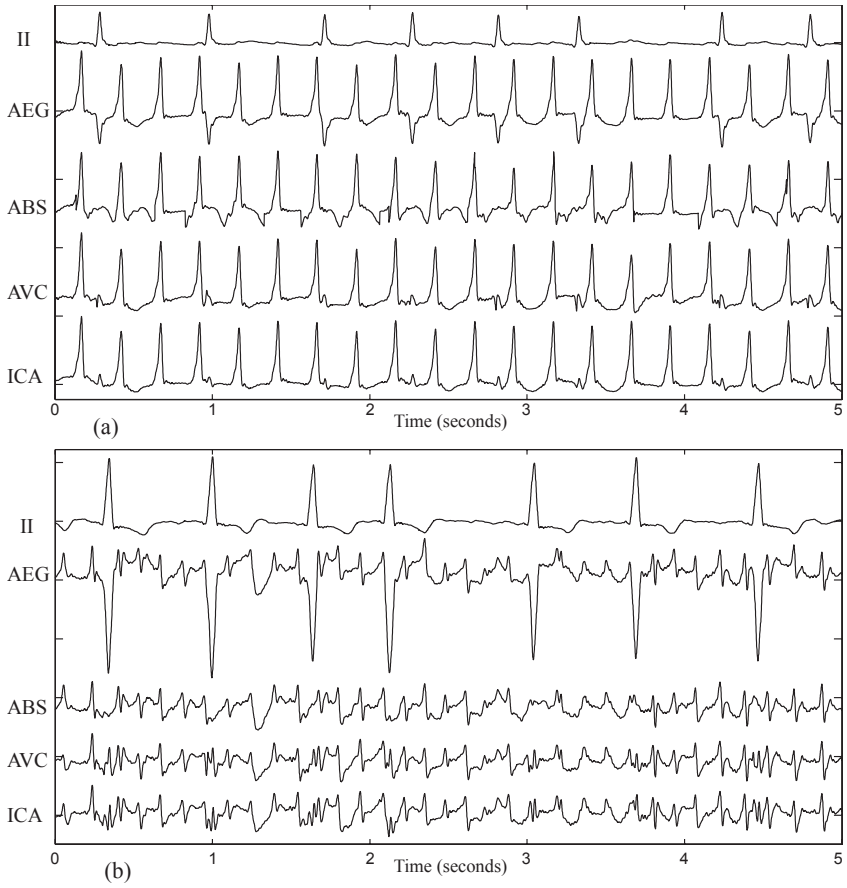

Figure 6. (a) From top to bottom, Lead II of an organized AF ECG shown for reference, the corresponding epicardial atrial electrogram (AEG), result of ventricular reduction with average beat subtraction (ABS), adaptive ventricular cancellation (AVC) and independent component analysis (ICA). (b) This panel plots the same information as panel (a) for a disorganized AF ECG. Note how ABS does not distort the resulting signal in this latter case [31].

The results provided by ICA in separating the atrial activity from ventricular contamination in AEGs are considered as better than those provided by ABS or AVC regarding how the atrial waveforms are preserved and the amount of ventricular residue removed [31], see Figure 6.

3. Frequency analysis of AF

When an atrial activity signal is available after QRST cancellation, the power spectral analysis door can be opened for the purpose of locating the dominant atrial frequency. This will be the first aspect to be addressed in this section. However, it is well known that the fibrillatory waves present time-dependent properties that may be blurred through a basic spectral analysis. As a consequence, when more detailed information and robust spectral estimation are needed, time-frequency analysis may be the way to go. In this respect, concepts like the

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spectral profile or the spectral modeling have proven to be efficient techniques that will be detailed by the end of this section.

3.1. Power spectral analysis

The computation of power spectral analysis on the atrial activity signal is the most common approach to determine the DAF [7]. Basically, the technique consist of locating the largest spectral peak within the power spectrum. The spectrum is usually defined as the discrete Fourier transform of the autocorrelation function of the signal. In this case, the signal is the atrial activity which is divided into shorter, overlapping segments, where each segment is subjected to proper windowing, e.g., using commonly the Welch's method [35]. Finally, the desired power spectrum is obtained by averaging the power spectra of the respective segments.

Primarily there exist two ways to compute the power spectral density of a discrete signal. First, estimate its autocorrelation function and then take its Fourier transform. Second, compute the Fourier transform of the signal and, next, square its magnitude to obtain the periodogram. Normally, the second way is the most commonly applied because of the great computational efficiency of the fast Fourier transform algorithm [36].

Depending on prior information about the signal, spectral estimation can be divided into two categories: nonparametric and parametric approaches. Nonparametric approaches explicitly estimate the autocorrelation function or the power spectral density of the process without any prior information. On the other hand, parametric approaches assume that the underlying random process has a certain structure, for example, an autoregressive (AR) model, which can be described using a small number of parameters and estimate the parameters of the model [37]. A widely used nonparametric estimation approach is the periodogram, which is based on the fast Fourier transform (FFT). A common parametric technique is maximum entropy spectral estimation, which involves fitting the observed signal to an AR model [36].

The raw periodogram is not a statistically stable spectral estimate since there is not much averaging on its computation. In fact, the periodogram is computed from a finite-length observed sequence that is sharply truncated. This sharp truncation effectively spreads the original signal spectrum into other frequencies, which is called spectral leakage [37]. The spectral leakage problem can be reduced by multiplying the finite sequence by a windowing function before the FFT computation, which reduces the sequence values gradually rather than abruptly. In order to reduce the periodogram variance, averaging can be applied. This modified algorithm is called Welch's method, which is the most widely used in nonparametric spectral estimation [35]. In order to increase the number of segments being averaged in a finite-length sequence, the sequence can be segmented with overlap; for example, 50% overlap can duplicate the number of segments of the same length [35]. Segment length can be considered as the most important parameter in AF spectral analysis since it determines the estimation accuracy of the DAF by restricting spectral resolution. It is advisable that the segment length is chosen to be at least a few seconds so as to produce an acceptable variance of the power spectrum [1, 2].

With respect to the surface ECG lead selection for AF power spectral analysis, this lead use to be V1. This is because lead V1 contains the fibrillatory waves with largest amplitude and, therefore, the associated DAF peak will be the largest in this lead [12]. As an example of

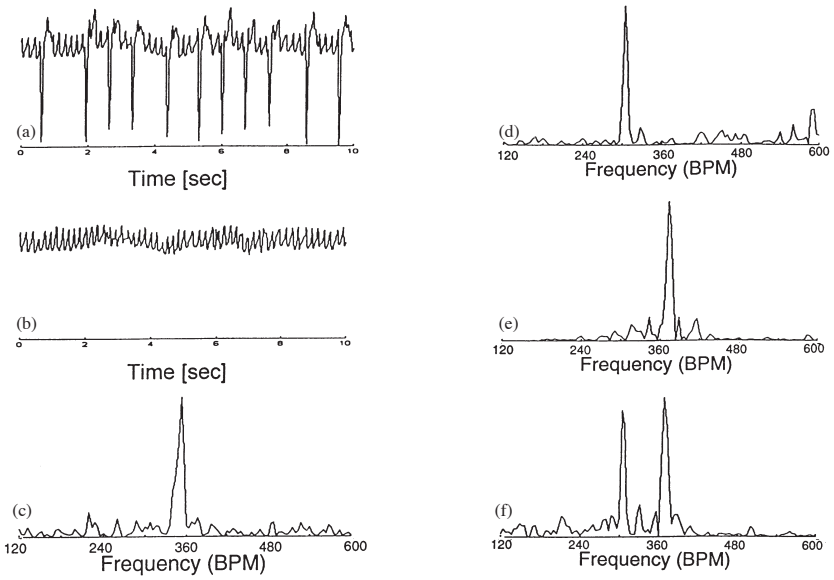

Figure 7. Example of AF power spectral analysis. (a) Surface ECG lead V1 from a patient in AF ready to be analyzed. (b) Atrial activity extracted from lead V1. (c) Atrial activity power spectral density. (d) and (e) Right and left atrium invasive recording PSDs of a different patient in which a notable frequency contrast between both atria was observed. (f) Surface lead V1 PSD of the patient in (d) and (e) proving how power spectral analysis can be useful in the study of AF [7].

power spectral analysis of AF, Figure 7 plots several situations related to this analysis. Firstly, the left panel shows the traditional procedure for AF spectral analysis, where the original ECG in AF is presented in Fig. 7.a. Next, the extracted atrial activity after QRST cancellation can be observed in Fig. 7.b. Finally, the power spectrum associated to that activity is shown in Fig. 7.c. In this example, the atrial activity signal was downsampled to 100Hz and processed with a Hamming window [38]. Next, a 1024-point FFT was applied and the PSD was displayed by computing the squared magnitude of each sample frequency. Remark that the frequency axis use to be traditionally expressed in Hz but, in some studies, clinicians prefer to express the fibrillatory frequencies in beats per minute (BPM). Furthermore, the right panel of Fig. 7 shows how AF power spectral analysis of the surface ECG is able to show the difference in the right and left atrial frequency. Hence, Fig. 7.d shows the right atrium invasive recording PSD, whereas Fig. 7.e plots the left atrium PSD. Finally, Fig. 7.f shows the PSD associated to the analysis of surface lead V1 from the same patient [1].

3.2. Time-frequency analysis

As demonstrated previously, power spectral analysis reflects the average signal behavior during the analyzed time interval, the robust location of the DAF being the main goal with clinical interest. However, this analysis may not be able to characterize temporal variations in the DAF. From an electrophysiological point of view, there are solid reasons to believe that the atrial fibrillatory waves have time-dependent properties, since they reflect complex patterns of electrical activation wavefronts. Therefore, it is advisable to employ time-frequency analysis in order to track variations in AF frequency when more detailed

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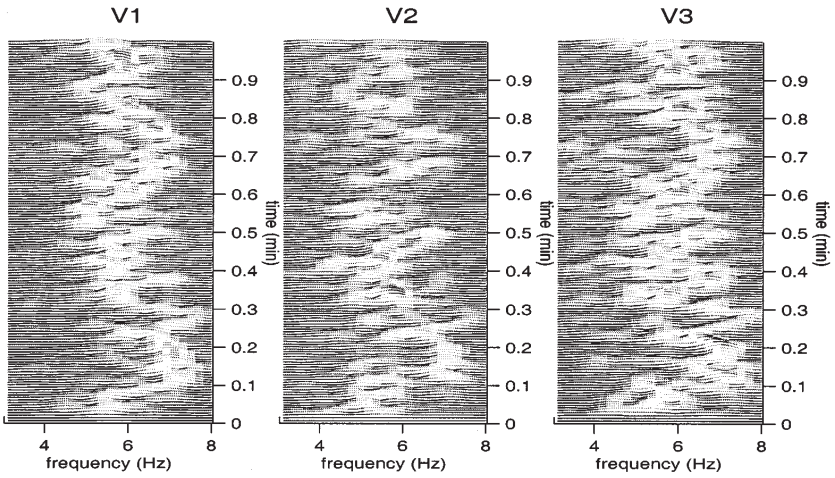

Figure 8. Spectrogram of a one minute atrial activity signal computed with a 128 point FFT using a 2.5 seconds window length. Surface leads V1 to V3 are shown for comparison [39].

information is needed [39]. The DAF is known to be influenced by autonomic modulation and its variations over time have been studied in terms of the effects of parasympathetic and sympathetic stimulation as well as with respect to circadian rhythm. It has been shown that AF frequency decreases during the night and increases in the morning [40].

The simplest way to apply time-frequency analysis to AF recordings consists of dividing the continuous-time atrial signal into short, consecutive and overlapping segments. Next, each of the segments will be subjected to spectral analysis. The resulting series of spectra reflects the time-varying nature of the signal [36, 39]. The most common approach to time-frequency analysis is the nonparametric, i.e., Fourier-based spectral analysis applied to each AF segment. This operation is known as the short-time Fourier transform (STFT) [41]. In this approach, the definition of the Fourier transform is modified so that a sliding time window defines each time segment to be analyzed. As a result, a two-dimensional function will be obtained in which the resolution in time and frequency will always have to be a trade-off compromise between both domains [37]. In the same way as with the periodogram, the spectrogram of a signal can be obtained by computing the squared magnitude of the STFT [41], thus making it possible to get a PSD representation of the signal in the time-frequency domain. An example on how an AF spectrogram looks like is shown in Figure 8, where three surface ECG leads are shown for comparison. As can be appreciated, the DAF trend presents great similarities but, also, some differences between leads. However, remark that the spectrogram frequency resolution cannot be better because of the time window length selected.

Because of the conflicting requirements between time and frequency resolution needed to be satisfied by the STFT, other techniques for time-frequency analysis have been proposed [42]. Basically, while the STFT depends linearly on the signal, these new techniques depend quadratically, thus providing much better resolution. One of the most successfully applied time-frequency distribution to AF recordings is the cross Wigner-Ville distribution (XWVD). Its selection was considered primarily because of its excellent noise performance for signals

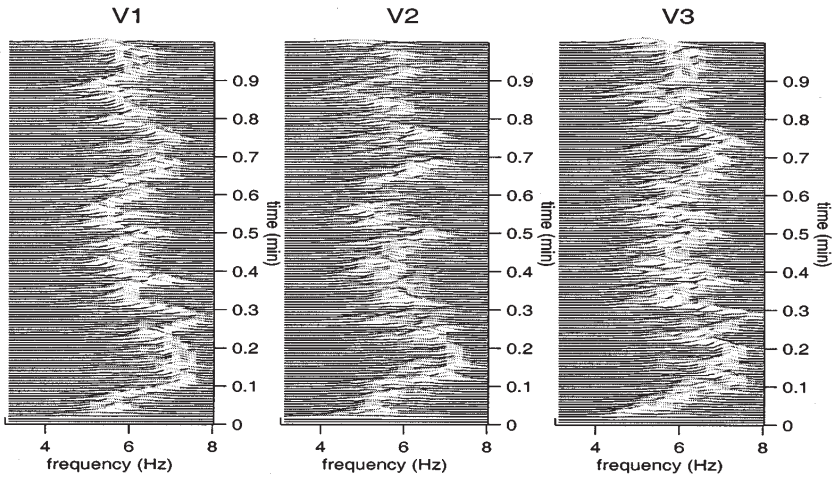

Figure 9. Cross Wigner-Ville distribution of the same atrial activity signal presented in Fig. 8. As shown, frequency resolution has been improved notably [39].

that are long compared to the window length [43], but also because it reflected precisely the variations in the DAF [39]. In order to illustrate how the XWVD is able to improve time-frequency analysis in AF, Figure 9 shows the same analyzed lead as in Fig. 8 but, this time, computed via the XWVD. As can be observed, frequency resolution has been improved notably, thus allowing to follow subtle changes in the DAF that would remain masked under STFT analysis [39].

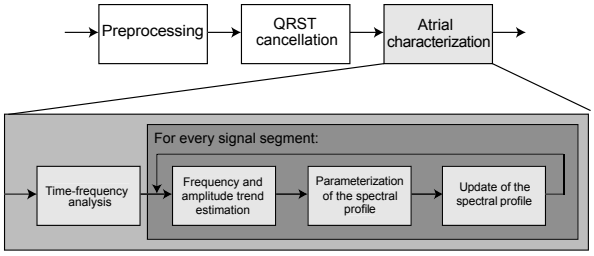

Figure 10. Block diagram of the spectral profile method for time-frequency analysis of atrial signals. Each new time slice, the time-frequency distribution is aligned to the spectral profile in order to find estimates of the frequency and amplitude. The spectral profile is then parameterized and updated [44].

3.3. The spectral profile

The aforementioned spectral analysis techniques had the limitation of only considering the fundamental spectral peak of the atrial activity, but its harmonics have not been put under consideration. However, harmonics could improve DAF estimation and, furthermore, their pattern may be of clinical interest [45]. To alleviate this problem the spectral profile has been proposed [44], its block diagram being depicted in Figure 10. Its main idea is to obtain a time-frequency distribution of successive short segments from the atrial signal. Next, the distribution is decomposed into a spectral profile and a number of parameters

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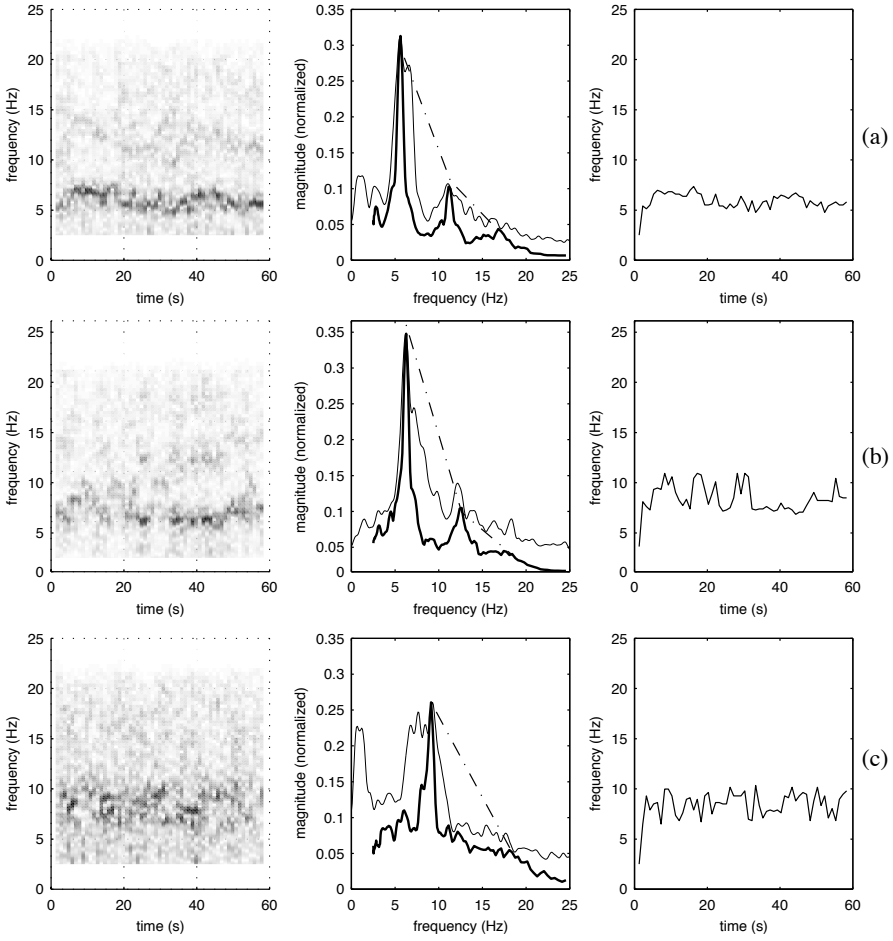

Figure 11. Illustration of the spectral profile technique for three one-minute recordings of atrial fibrillation. The left panel shows the logarithmic time-frequency distribution of the atrial signals. The middle panel shows the spectral profile in solid thick line, the conventional magnitude power spectrum in solid thin line and the fitted spectral line model in dashed line. Finally, the DAF trend is shown in the right panel.(a) Spectral profile for a rather organized AF. (b) Similar to (a) but with notably larger DAF variations. (c) A noisy case with a very high DAF together with a large trend variation [44].

able to describe variations in the DAF as well as in the fibrillatory waves morphology are extracted. Hence, each spectrum is modeled as a frequency-shifted and amplitude-scaled version of the spectral profile. The transformation to the frequency domain is performed by using a nonuniform discrete-time Fourier transform with a logarithmic frequency scale. This particular scale allows for two spectra to be matched by shifting, even though they have different fundamental frequencies and related harmonics [44].

The spectral profile is dynamically updated from previous spectra, which are matched to each new spectrum using weighted least squares estimation. The frequency shift needed to achieve optimal matching then yields a measure on instantaneous fibrillatory rate and

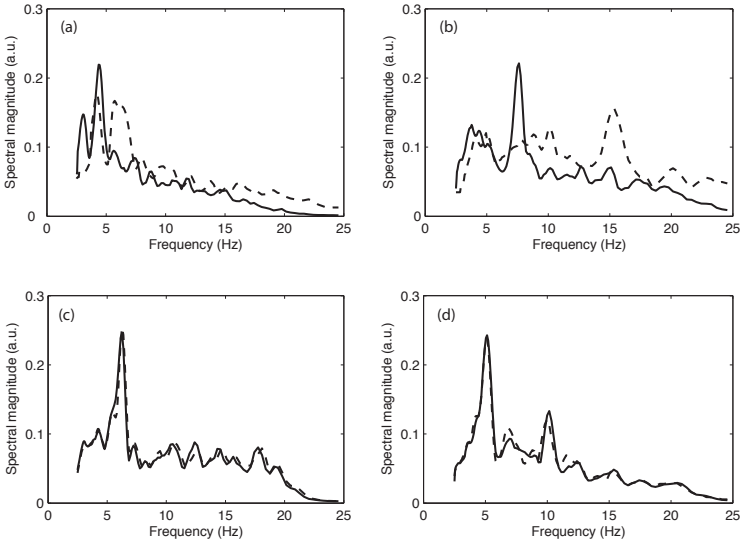

Figure 12. Spectral profile of different atrial signals (dashed line) and the corrected spectral profile obtained by spectral modeling applying the exclusion criteria (solid line). (a) and (b) atrial activity signals with a considerable amount of QRS residua. (c) and (d) atrial activities without noise contamination [46].

is trended as a function of time. An important feature of this approach is that, due to the alignment procedure, the peaks of the spectral profile become more prominent than the corresponding peaks of the conventional power spectrum. As a result, the spectral profile lends itself much better to analysis of the harmonics whose amplitudes reflect the shape of the fibrillatory waveforms and are related with AF organization [44].

Three different examples of the spectral profile technique are shown in Figure 11. Firstly, Fig. 11.a shows the results of a rather organized case of atrial fibrillation, with a DAF of about 6 Hz and a variation within 5–7 Hz. The high degree of organization in the signal is reflected in the presence of two harmonics in the spectral profile (thick solid line in the middle panel). Comparing the spectral profile to the magnitude spectrum (thin solid line), it is evident that the fundamental peak of the former spectrum is narrower and that its harmonics are much more easily discerned. Such a behavior is, of course, expected since the spectral profile represents an average of spectra from successive signal intervals where each individual spectrum, prior to averaging, has been shifted such that the fundamental is optimally aligned to the fundamental frequency of the spectral profile [44]. The example in Fig. 11.b has a DAF of about 7 Hz with a relatively large variation and one harmonic. Finally, Fig. 11.c presents a much more disorganized atrial activity, with a DAF around 8.5 Hz and lack of harmonic behavior. As can be appreciated in the three examples, the spectral profile notably improves DAF and harmonics estimation, specially in the presence of noisy signals.

3.4. Improved spectral estimation

A drawback of the spectral profile-based method is its lack of control of what goes into the spectral profile: a spectrum reflecting large QRS residuals is just as influential as a spectrum reflecting clear atrial activity. Although the spectral profile has a slow adaptation

rate, making it less sensitive to single noisy segments, a short sequence of bad segments causes the spectral profile to lose its structure, and thus, the frequency estimates become incorrect. Furthermore, once the spectral profile has lost its structure, the recovery time until the frequency estimates are valid again becomes unacceptably long, even if the segments have an harmonic structure.

Unfortunately, there are clinical situations in which sequences of noisy segments are common, e.g., during stress testing and ambulatory monitoring and, accordingly, the spectral profile is bound to become corrupt. Therefore, an improved spectral profile method has been proposed able to test the spectrum of each data segment before entering the spectral profile update [46]. A model defined by a superimposition of Gaussian functions, which represent the peaks of the fundamental and harmonics of the AF spectrum, has been proposed (see Fig. 12). These parameters are used to decide whether a new spectrum should be included in the spectral profile or not. The parameters are descriptors of the spectrum and designed so as to verify if a spectrum exhibits the typical harmonic pattern of AF, i.e., a fundamental component and, possibly, few harmonics [46].

Finally, a recently presented approach to improve AF spectral estimation is to use a hidden Markov model (HMM) to enhance noise robustness when tracking the DAF. With a HMM, short-time frequency estimates that differ significantly from the frequency trend can be detected and excluded or replaced by estimates based on adjacent frequencies [47]. A Markov model consists of a finite number of states with predefined state transition probabilities [48]. Based on the observed state sequence, the Viterbi algorithm retrieves the optimal sequence by exploiting the state transition matrix, incorporating knowledge of AF characteristics, and the observation matrix, incorporating knowledge of the frequency estimation method and signal-to-noise ratio [47].

4. Arrhythmia organization

During last years several methods to estimate the degree of AF organization have been presented. Primarily, organization estimation was introduced making use of invasive recordings, in which the atrial signal is of notably higher amplitude. However, in recent years, new methods have emerged in the estimation of organization from surface recordings, thus been able to provide clinical useful information through very cheap procedures. The next subsections will describe some of the most recent and extended methods to estimate atrial fibrillation organization.

4.1. Invasive organization methods

The observation that some degree of organization is present during AF has motivated many investigators to develop algorithms quantifying this degree of organization. Nevertheless, the term *organization* is ambiguous, because of the lack of a standard and common definition within the context of AF. As a consequence, several methods have been proposed to quantify different aspects of AF organization, which are related to different electrophysiological properties or AF mechanisms [49]. According to the number of endocardial recording places involved in the analysis, single-site measurements [50, 51] provide information on the local electrical activity of specific atrial areas, while multi-site algorithms [52–54] introduce the concept of spatial coordination between different regions.

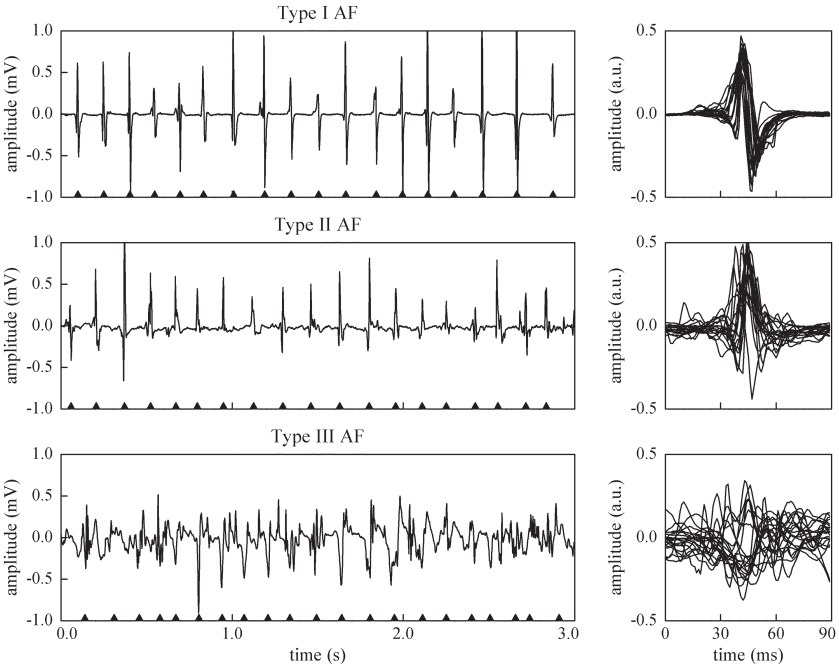

Figure 13. Analysis of the local activation waves for AF episodes with different complexity class. From top to bottom, bipolar electrograms of type I, type II, and type III AF following Wells classification. Filled triangles indicate the time of local activation waves detection. On the right panels, superposition of the normalized activation times obtained from the signals of the left panels [9].

Regarding single-site measurements, Wells et al. [55] published one of the earliest studies examining relative differences in atrial fibrillation electrograms. From right atrial bipolar electrograms after open-heart surgery, Wells classified atrial fibrillation recordings into four categories based on the discreteness of the electrograms and the stability of the baseline. However, the greatest weakness of this method is its subjectivity because it requires manual interpretation and over-reading of the epicardial recordings. Nonetheless, later works have implemented automated methods based on these criteria [56]. In this case, the method was based on comparing diverse features of the parameters describing the dynamic, morphological and spectral properties of intraatrial bipolar electrograms during AF. Next, by making use of that parameters an algorithm was designed for automated AF classification.

On the other hand, organization has also been used in the frequency domain. Given that the AF waveform can be effectively analyzed in the frequency domain, as described in Section § 3, some authors have hypothesized that analysis of the spectra of short segments of an interatrial electrogram during AF would show a correlation of the variance of the signal and the amplitude of harmonic peaks with defibrillation efficacy [51]. Furthermore, the same authors hypothesized that the spatiotemporal organization of AF would vary over time and tried to determine the optimal sampling window to optimize defibrillation predictability.

Nonlinear analysis has also been used to evaluate single-site AF electrograms. In this respect one of the first works specifically applied to atrial fibrillation electrograms was introduced by

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Hoekstra et al. [57]. They analyzed epicardial mapping data obtained from atrial fibrillation patients undergoing surgical correction of an accessory pathway. The nonlinear applied techniques were correlation dimension and correlation entropy on the epicardial signals. It was found that these measures discriminated between the various types of electrograms as defined by Wells, thus suggesting that nonlinear dynamics plays a relevant role in atrial fibrillation and can also be used to quantify AF organization.

Finally, one interesting work quantifying AF organization from single-site measurements was introduced by Faes et al. [9] and relied on wave morphology similarity. The algorithm quantified the regularity of an atrial electrogram by measuring the extent of repetitiveness over time of its consecutive activation waves. Since the analysis was focused on the shape of the waveforms occurring in correspondence to the local activations of the atrial tissue, the morphology of the atrial activations was the element by which the algorithm differentiated among various degrees of AF organization. As an example, Figure 13 plots the local activation waves associated to three different AF episodes with different complexity. As can be seen, the method is able to generate a pattern which, later, can be quantified following the organization criteria. The same team introduced an automatic organization estimation method based on features extraction, selection and classification of the AF patterns [58].

With respect to multi-site measurements, this viewpoint would imply that activity at one site should be judged in relation to the activity at another site. Furthermore, when distances between the recording sites are known, and especially when more than two sites are used to compute the organization, spatial organization concepts are also incorporated into these measures [11]. One interesting comparison of methods for estimating AF synchronization between two atrial sites was published by Sih et al. [53]. In this study, after filtering and scaling short segments (300 ms) of atrial fibrillation, the electrograms were passed through two parallel linear adaptive filters, as shown in Figure 14. One way of interpreting an adaptive filter is that it attempts to predict one electrogram through linear filtering of a second electrogram. If the two electrograms are linearly related, then the prediction process would theoretically be perfect. However, if there are non-linearities between the electrograms, the adaptive filter would yield a prediction error. This algorithm defines organization according to the prediction errors from the parallel adaptive filters. The algorithm was theoretically extensible to account for non-linear relationships between electrograms by simply altering the nature of the adaptive filters. This group used the algorithm to quantify organization differences between acute and chronic models of atrial fibrillation [59].

Other works have quantified AF organization between two different atrial sites making use of nonlinear techniques. In this way, Censi et al. [60] quantified the duration of stable recurrence patterns through the use of recurrent plots as well as a measure of entropy in the recurrence plots. The authors suggested that there may exist nonlinear relationships between electrograms from the right versus the left atrium that would otherwise be missed by algorithms relying on linear analyses.

Finally, cardiac mapping tools have brought a wealth of information to cardiac electrophysiology, where the concept of a combined spatial and temporal organization is most easily realized. Within this context, the concept of coupling between several endocardial signal has been introduced. In this respect a two-dimensional analysis by evaluating the simultaneous presence of morphological similarity in two endocardial signals, in order

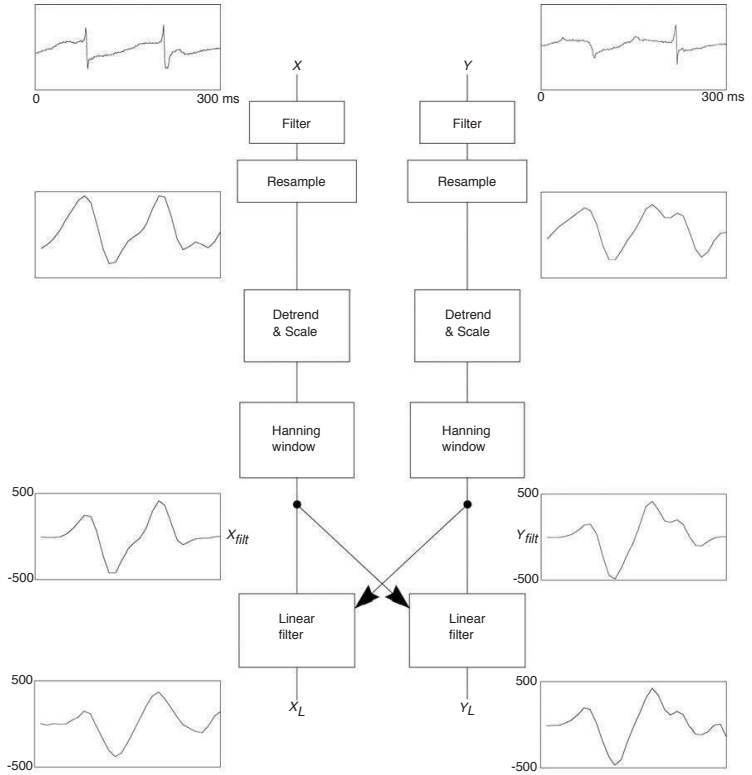

Figure 14. Example of a multi-site AF organization method based on the application of adaptive filtering to the electrograms under study. If there are nonlinearities between the two electrograms, the adaptive filters would yield a concrete prediction error, thus allowing to quantify the degree of synchronization between the electrograms [53].

to quantify their degree of coupling has been introduced [49]. The method considers the atrial activation times on every recording place and estimates the cross-probability of finding similar local activation waves between the considered recordings places, as shown in Figure 15. On the other hand, Mainardi et al. [54] introduced a comparative study for the analysis among atrial electrical activities in different sites during AF. They characterized the properties of pairs between atrial signals making use of a linear parameter obtained from the cross-correlation function and by a nonlinear association estimator. Furthermore, they also studied synchronization through the application of an index based on the corrected cross-conditional entropy [61]. The most recent advances in the study of propagation patterns in AF have been introduced by Richter and co-workers. They investigated propagation patterns in intracardiac signals using a approach based on partial directed coherence, which evaluated directional coupling between multiple signals in the frequency domain [62]. Furthermore, the same team recently presented an improvement in propagation pattern analysis based on sparse modeling through the use of the partial directed coherence function derived from fitting a multivariate autoregresive model to the observed signal [63].

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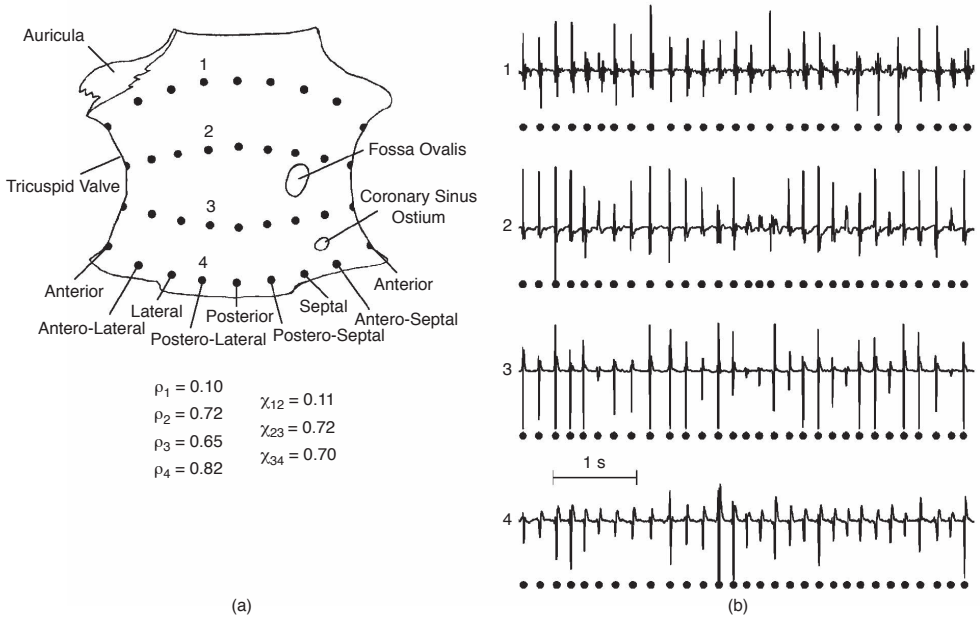

Figure 15. Example of regularity and coupling indices obtained for endocardial signals recorded by a multipolar basket catheter in the human right atrium during AF. (a) Schematic representation of the internal surface of the right atrium with the position of the sites of bipolar signal acquisition. (b) Endocardial recordings taken during AF, from the four electrodes placed in the postero-lateral wall along with the detected activation times (circles). The regularity index (ρ) associated with the four signals and the coupling (χ) between pairs of signals recorded on adjacent sites are indicated [49].

4.2. Surface organization methods

From a clinical point of view, the assessment of AF organization from the standard surface ECG would be very interesting, because it can be easily and cheaply obtained and could avoid the risks associated to invasive procedures [12]. However, only few indirect non-invasive AF organization estimates from this recording have been proposed in the literature. Firstly, the DAF, which has been described in Section § 3. Its inverse has been directly related to atrial refractoriness [64] and, hence, to atrial cycle length [5]. Moreover, it has been suggested that the DAF is directly related to the number of simultaneous wavelets [65]. On the other hand, the second way to get a non-invasive estimate of AF organization has been based on a nonlinear regularity index, such as sample entropy [66]. This index has been proposed to estimate the amount of repetitive patterns existing in the fibrillatory waves from the fundamental waveform of the atrial activity signal, which have been named as main atrial wave (MAW) in the literature. Through the application of sample entropy to the MAW, it has been possible to predict a number of AF-reated events. For example, the onset of paroxysmal AF, its spontaneous termination, its time course from the beginning up to the end of the episode or the outcome of electrical cardioversion in persistent AF [10].

Obviously, the drawback of non-invasive organization estimation is the lack of strict accuracy in the process, given that both sample entropy and DAF are only able to assess fibrillatory waves regularity indirectly. However they have been recently validated by comparison with

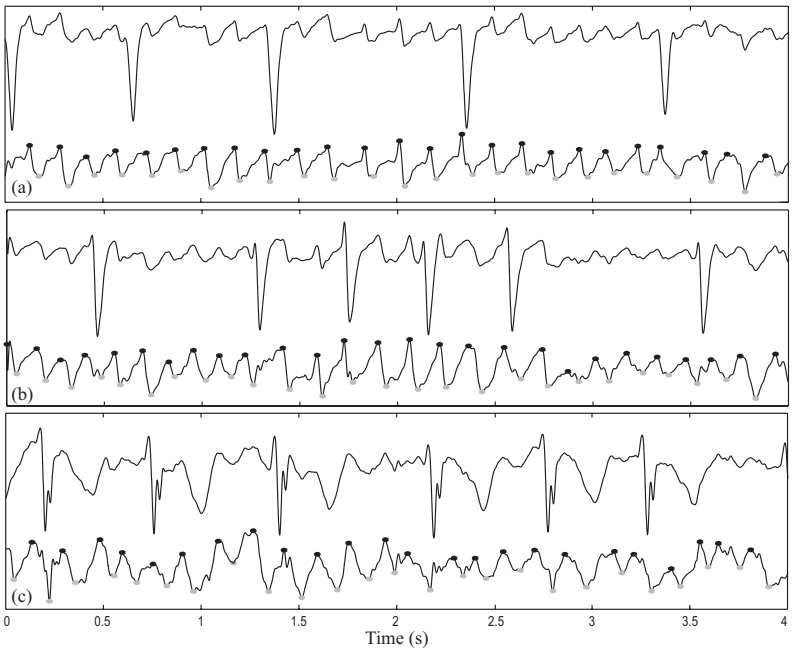

Figure 16. Delineation of the fibrillatory waves for typical 4 second segments corresponding to (a) type I, (b) type II and (c) type III AF episodes, respectively. For each segment, the ECG and atrial activity, after QRST cancellation, are displayed. The upper black circles mark the maximum associated to each activation, whereas lower gray circles indicate their boundaries [70].

invasive recordings [67]. On the other hand, an additional disadvantage of these estimators is that the proper DAF identification in the AA spectral content, computed via the fast Fourier transform, depends significantly on the analyzed segment length, because it determines the spectral resolution [68]. It is advisable that segment length is chosen to be, at least, several seconds for an appropriate DAF identification and to produce an acceptable variance of the frequency estimate [69]. On the other hand, although AF organization could be successfully estimated by analyzing a segment as short as 1 second with sample entropy, the proper MAW obtention depends on an adequate DAF computation [10]. Thereby, it could be considered that the two aforesaid estimators can only yield an average AF organization assessment, thus blurring the possible information carried by each single activation.

One solution to the aforementioned limitations has been recently proposed which is able to quantify directly and in short-time AF organization from the surface ECG. The method quantifies every single fibrillatory wave regularity by measuring how repetitive its morphology is along onward atrial activations [70]. Basically, the atrial activity was delineated through mathematical morphology operators [71]. A combination of erosion and dilation operations was applied to the atrial activity with two structuring elements. The first one was adapted to the fibrillatory waves by an even triangular shape with duration proportional to the DAF. The second was designed as a rectangular shape of length larger to the DAF to suppress the drift between atrial cycles [70]. Finally, the resulting impulsive signal was used to extract atrial activations by peak detection [70]. An example of the potential applications offered by this method, able to work from the surface ECG, is shown

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in Figure 16 where several recordings and the corresponding delineation result have been plotted. As can be observed, the method is able to provide precise and automatic fibrillatory waves delineation, making it possible to quantify non-invasively AF organization in short time.

5. Conclusions

The recent advances in signal analysis and processing have provided powerful solutions for the improved knowledge of atrial fibrillation. In this respect, intensive research has been carried out to separate atrial activity from ventricular activity in the ECG and invasive recordings. Furthermore, the proper extraction of an atrial signal has opened the possibilities of developing advanced analysis techniques to gain as much information as possible on the fibrillatory waves. Within this context, relevant information, like the atrial fibrillatory frequency or arrhythmia organization, have been reliably assessed from surface and invasive recordings using digital signal processing methods.

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References

[1] Andreas Bollmann, Daniela Husser, Luca Mainardi, Federico Lombardi, Philip Langley, Alan Murray, José Joaquín Rieta, José Millet, S. Bertil Olsson, Martin Stridh, and Leif Sörnmo. Analysis of surface electrocardiograms in atrial fibrillation: Techniques, research, and clinical applications. *Europace*, 8(11):911–926, Nov 2006.

[2] Leif Sörnmo, Martin Stridh, Daniela Husser, Andreas Bollmann, and S Bertil Olsson. Analysis of atrial fibrillation: from electrocardiogram signal processing to clinical management. *Philos Transact A Math Phys Eng Sci*, 367(1887):235–53, Jan 2009.

[3] J Slocum, E Byrom, L McCarthy, A Sahakian, and S Swiryn. Computer detection of atrioventricular dissociation from surface electrocardiograms during wide qrs complex tachycardias. *Circulation*, 72(5):1028–1036, 1985.

[4] José Joaquín Rieta, Francisco Castells, César Sánchez, Vicente Zarzoso, and José Millet. Atrial activity extraction for atrial fibrillation analysis using blind source separation. *IEEE Trans Biomed Eng*, 51(7):1176–1186, Jul 2004.

[5] M. Holm, S. Pehrson, M. Ingemansson, L. Sörnmo, R. Johansson, L. Sandhall, M. Sunemark, B. Smideberg, C. Olsson, and S. B. Olsson. Non-invasive assessment of the atrial cycle length during atrial fibrillation in man: Introducing, validating and illustrating a new ECG method. *Cardiovasc Res*, 38(1):69–81, Apr 1998.

[6] Shinichi Niwano, Takeshi Sasaki, Sayaka Kurokawa, Michiro Kiryu, Hidehira Fukaya, Yuko Hatakeyama, Hiroe Niwano, Akira Fujiki, and Tohru Izumi. Predicting the efficacy of antiarrhythmic agents for interrupting persistent atrial fibrillation according to spectral analysis of the fibrillation waves on the surface ecg. *Circ J*, 73(7):1210–8, Jul 2009.

[7] A. Bollmann, N. K. Kanuru, K. K. McTeague, P. F. Walter, D. B. DeLurgio, and J. J. Langberg. Frequency analysis of human atrial fibrillation using the surface electrocardiogram and its response to ibutilide. *Am J Cardiol*, 81(12):1439–1445, Jun 1998.

[8] J J Langberg, J C Burnette, and K K McTeague. Spectral analysis of the electrocardiogram predicts recurrence of atrial fibrillation after cardioversion. *J Electrocardiol*, 31 Suppl:80–4, 1998.

[9] Luca Faes, Giandomenico Nollo, Renzo Antolini, Fiorenzo Gaita, and Flavia Ravelli. A method for quantifying atrial fibrillation organization based on wave-morphology similarity. *IEEE Trans Biomed Eng*, 49(12 Pt 2):1504–1513, Dec 2002.

[10] Raul Alcaraz and Jose Joaquin Rieta. A review on sample entropy applications for the non-invasive analysis of atrial fibrillation electrocardiograms. *Biomed Signal Process Control*, 5:1–14, 2010.

[11] HJ Sih. Measures of organization during atrial fibrillation. *Annali dell'Istituto superiore di sanità*, 37(3):361–9, 01 2001.

[12] Simona Petrutiu, Jason Ng, Grace M Nijm, Haitham Al-Angari, Steven Swiryn, and Alan V Sahakian. Atrial fibrillation and waveform characterization. A time domain perspective in the surface ECG. *IEEE Eng Med Biol Mag*, 25(6):24–30, 2006.

[13] Raúl Alcaraz and José Joaquín Rieta. Adaptive singular value cancellation of ventricular activity in single-lead atrial fibrillation electrocardiograms. *Physiol Meas*, 29(12):1351–1369, Oct 2008.

[14] J. Pan and W. J. Tompkins. A real-time QRS detection algorithm. *IEEE Trans Biomed Eng*, 32(3):230–236, Mar 1985.

[15] S. Shkurovich, A. V. Sahakian, and S. Swiryn. Detection of atrial activity from high-voltage leads of implantable ventricular defibrillators using a cancellation technique. *IEEE Trans Biomed Eng*, 45(2):229–234, Feb 1998.

[16] M. Stridh and L. Sörnmo. Spatiotemporal QRST cancellation techniques for analysis of atrial fibrillation. *IEEE Trans Biomed Eng*, 48(1):105–111, Jan 2001.

[17] Mathieu Lemay, Jean-Marc Vesin, Adriaan van Oosterom, Vincent Jacquemet, and Lukas Kappenberger. Cancellation of ventricular activity in the ECG: Evaluation of novel and existing methods. *IEEE Trans Biomed Eng*, 54(3):542–546, Mar 2007.

[18] D. Raine, P. Langley, A. Murray, S. S. Furniss, and J. P. Bourke. Surface atrial frequency analysis in patients with atrial fibrillation: Assessing the effects of linear left atrial ablation. *Journal of Cardiovascular Electrophysiology*, 16(8):838–844, 2005.

[19] Philip Langley, José Joaquín Rieta, Martin Stridh, José Millet, Leif Sörnmo, and Alan Murray. Comparison of atrial signal extraction algorithms in 12-lead ECGs with atrial fibrillation. *IEEE Trans Biomed Eng*, 53(2):343–346, Feb 2006.

[20] F Castells, J J Rieta, J Millet, and V Zarzoso. Spatiotemporal blind source separation approach to atrial activity estimation in atrial tachyarrhythmias. *IEEE Transactions on Biomedical Engineering*, 52(2):258–267, 2005.

[21] P. Comon. Independent component analysis, a new concept? *Signal Processing*, 36(3):287–314, 1994.

[22] J. F. Cardoso. Blind signal separation: Statistical principles. *Proceedings of the IEEE*, 86(10):2009–2025, 1998.

[23] P. Langley, J. P. Bourke, and A. Murray. Frequency analysis of atrial fibrillation. In *Conf Proc IEEE Comput Cardiol*, volume 27, pages 65–68, Los Alamitos, CA, 2000. IEEE.

[24] V. Zarzoso and A. K. Nandi. Noninvasive fetal electrocardiogram extraction: blind separation versus adaptive noise cancellation. *IEEE Trans. Biomed. Eng*, 48(1):12–18, 2001.

[25] T. P. Jung, S. Makeig, C. Humphries, T. W. Lee, M. J. McKeown, V. Iragui, and T. J. Sejnowski. Removing electroencephalographic artifacts by blind source separation. *Psychophysiology*, 37(2):163–178, 2000.

[26] K Nademanee, J McKenzie, E Kosar, M Schwab, B Sunsaneewitayakul, T Vasavakul, C Khunnawat, and T Ngarmukos. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol*, 43(11):2054–2056, 2004.

[27] Z Shan, PH Van Der Voort, Y Blaauw, M Duytschaever, and MA Allessie. Fractionation of electrograms and linking of activation during pharmacologic cardioversion of persistent atrial fibrillation in the goat. *J. Cardiovasc. Electrophysiol.*, 15(5):572–580, 2004.

[28] DJ Dosdall and RE Ideker. Intracardiac atrial defibrillation. *Heart Rhythm*, 4(3):S51–56, 2007.

[29] M. Mase, L. Faes, R. Antolini, M. Scaglione, and F. Ravelli. Quantification of synchronization during atrial fibrillation by shannon entropy: validation in patients and computer model of atrial arrhythmias. *Physiological Measurement*, 26(6):911–923, Dec 2005.

[30] RP Houben and MA Allessie. Processing of intracardiac electrograms in atrial fibrillation. diagnosis of electropathological substrate of af. *IEEE Engineering in Medicine and Biology Magazine*, 25(6):40–51, 2006.

[31] Jose Joaquin Rieta and Fernando Hornero. Comparative study of methods for ventricular activity cancellation in atrial electrograms of atrial fibrillation. *Physiol Meas*, 28(8):925–936, 2007.

[32] B. Widrow, J. R. Glover, J. M. McCool, and et al. Adaptive noise cancelling: Principles and applications. *Proceedings of the IEEE*, 63(12):1692–1716, 1975.

[33] J. Malmivuo and R. Plonsey. *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields*. Oxford University Press, 1995.

[34] A. Hyvarinen, J. Karhunen, and E. Oja. *Independent Component Analysis*. John Wiley & Sons, Inc., 2001.

[35] P. D. Welch. Use of Fast Fourier Transform for estimation of power spectra: A method based on time averaging over short modified periodograms. *IEEE Trans. Audio and Electroacustics*, 15(2):70–73, 1967.

[36] Dimitris G Manolakis, Vinay K Ingle, and Stephen M Kogon. *Statistical and adaptive signal processing: spectral estimation, signal modeling, adaptive filtering, and array processing*. Artech House, Boston, 2005.

[37] Mohamed Najim. *Modeling, estimation and optimal filtering in signal processing*. Digital signal and image processing series. J. Wiley & Sons, London, 2008.

[38] R. W Hamming. *Digital filters*. Prentice-Hall signal processing series. Prentice-Hall, Englewood Cliffs, N.J., 1977.

[39] M. Stridh, L. Sörnmo, C. J. Meurling, and S. B. Olsson. Characterization of atrial fibrillation using the surface ECG: Time-dependent spectral properties. *IEEE Trans Biomed Eng*, 48(1):19–27, Jan 2001.

[40] Frida Sandberg, Andreas Bollmann, Daniela Husser, Martin Stridh, and Leif Sörnmo. Circadian variation in dominant atrial fibrillation frequency in persistent atrial fibrillation. *Physiol Meas*, 31(4):531–42, Apr 2010.

[41] Antonia Papandreou-Suppappola. *Applications in time-frequency signal processing*. CRC Press, Boca Raton, 2003.

[42] Leon Cohen. *Time-frequency analysis*. Prentice Hall PTR, Englewood Cliffs, N.J, 1995.

[43] B. Boashash. Estimating and interpreting the instantaneous frequency of a signal. ii. algorithms and applications. *Proceedings of the IEEE*, 80(4):540 –568, apr 1992.

[44] Martin Stridh, Leif Sörnmo, Carl J Meurling, and S. Bertil Olsson. Sequential characterization of atrial tachyarrhythmias based on ECG time-frequency analysis. *IEEE Trans Biomed Eng*, 51(1):100–114, Jan 2004.

[45] T H Everett, 4th, J R Moorman, L C Kok, J G Akar, and D E Haines. Assessment of global atrial fibrillation organization to optimize timing of atrial defibrillation. *Circulation*, 103(23):2857–61, Jun 2001.

[46] Valentina D A Corino, Luca T Mainardi, Martin Stridh, and Leif Sörnmo. Improved time–frequency analysis of atrial fibrillation signals using spectral modeling. *IEEE Trans Biomed Eng*, 55(12):2723–30, Dec 2008.

[47] Frida Sandberg, Martin Stridh, and Leif Sörnmo. Frequency tracking of atrial fibrillation using hidden markov models. *IEEE Trans Biomed Eng*, 55(2 Pt 1):502–11, Feb 2008.

[48] Benjamin Schuster-Böckler and Alex Bateman. An introduction to hidden markov models. *Curr Protoc Bioinformatics*, Appendix 3:Appendix 3A, Jun 2007.

[49] L Faes and F Ravelli. A morphology-based approach to the evaluation of atrial fibrillation organization. *Engineering in Medicine and Biology Magazine, IEEE*, 26(4):59–67, 2007.

[50] V Barbaro, P Bartolini, G Calcagnini, F Censi, S Morelli, and A Michelucci. Mapping the organization of atrial fibrillation with basket catheters. part i: Validation of a real-time algorithm. *Pacing and clinical electrophysiology : PACE*, 24(7):1082–8, 07 2001.

[51] T H Everett, 4th, L C Kok, R H Vaughn, J R Moorman, and D E Haines. Frequency domain algorithm for quantifying atrial fibrillation organization to increase defibrillation efficacy. *IEEE Trans Biomed Eng*, 48(9):969–78, Sep 2001.

[52] GW Botteron and JM Smith. A technique for measurement of the extent of spatial organization of atrial activation during atrial fibrillation in the intact human heart. *IEEE transactions on bio-medical engineering*, 42(6):579–86, 06 1995.

[53] H. J. Sih, D. P. Zipes, E. J. Berbari, and J. E. Olgin. A high-temporal resolution algorithm for quantifying organization during atrial fibrillation. *IEEE Trans Biomed Eng*, 46(4):440–450, Apr 1999.

[54] Luca T Mainardi, Valentina D A Corino, Leonida Lombardi, Claudio Tondo, Massimo Mantica, Federico Lombardi, and Sergio Cerutti. Linear and nonlinear coupling between atrial signals. Three methods for the analysis of the relationships among atrial electrical activities in different sites. *IEEE Eng Med Biol Mag*, 25(6):63–70, 2006.

[55] J.L. Wells, R.B. Karp, N.T. Kouchoukos, WA MacLean, TN James, and AL Waldo. Characterization of atrial fibrillation in man: studies following open heart surgery. *Pacing and Clinical Electrophysiology (PACE)*, 1(4):426–438, 1978.

[56] V Barbaro, P Bartolini, G Calcagnini, S Morelli, A Michelucci, and G Gensini. Automated classification of human atrial fibrillation from intraatrial electrograms. *Pacing and clinical electrophysiology : PACE*, 23(2):192–202, 02 2000.

[57] B P Hoekstra, C G Diks, M A Allessie, and J DeGoede. Nonlinear analysis of epicardial atrial electrograms of electrically induced atrial fibrillation in man. *J Cardiovasc Electrophysiol*, 6(6):419–40, Jun 1995.

[58] G Nollo, M Marconcini, L Faes, F Bovolo, F Ravelli, and L Bruzzone. An automatic system for the analysis and classification of human atrial fibrillation patterns from intracardiac electrograms. *IEEE Transactions on Biomedical Engineering*, 55(9):2275, 2008.

[59] H. J. Sih, D. P. Zipes, E. J. Berbari, D. E. Adams, and J. E. Olgin. Differences in organization between acute and chronic atrial fibrillation in dogs. *J Am Coll Cardiol*, 36(3):924–931, Sep 2000.

[60] F Censi, V Barbaro, P Bartolini, G Calcagnini, A Michelucci, G F Gensini, and S Cerutti. Recurrent patterns of atrial depolarization during atrial fibrillation assessed by recurrence plot quantification. *Ann Biomed Eng*, 28(1):61–70, Jan 2000.

[61] L T Mainardi, A Porta, G Calcagnini, P Bartolini, A Michelucci, and S Cerutti. Linear and non-linear analysis of atrial signals and local activation period series during atrial-fibrillation episodes. *Med Biol Eng Comput*, 39(2):249–54, Mar 2001.

[62] U Richter, L Faes, A Cristoforetti, M Masè, F Ravelli, M Stridh, and L Sornmo. A novel approach to propagation pattern analysis in intracardiac atrial fibrillation signals. *Annals of biomedical engineering*, 08 2010.

[63] U Richter, L Faes, F Ravelli, and L Sornmo. Propagation pattern analysis during atrial fibrillation based on sparse modeling. *IEEE transactions on bio-medical engineering*, 59(5):1319–28, 05 2012.

[64] A. Capucci, M. Biffi, G. Boriani, F. Ravelli, G. Nollo, P. Sabbatani, C. Orsi, and B. Magnani. Dynamic electrophysiological behavior of human atria during paroxysmal atrial fibrillation. *Circulation*, 92(5):1193–1202, Sep 1995.

[65] A. Bollmann, K. Sonne, H. D. Esperer, I. Toepffer, J. J. Langberg, and H. U. Klein. Non-invasive assessment of fibrillatory activity in patients with paroxysmal and persistent atrial fibrillation using the holter ECG. *Cardiovasc Res*, 44(1):60–66, Oct 1999.

[66] J. S. Richman and J. R. Moorman. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol*, 278(6):H2039–H2049, Jun 2000.

[67] Raúl Alcaraz, Fernando Hornero, and José J Rieta. Assessment of non-invasive time and frequency atrial fibrillation organization markers with unipolar atrial electrograms. *Physiol Meas*, 32(1):99–114, Jan 2011.

[68] Jason Ng and Jeffrey J Goldberger. Understanding and interpreting dominant frequency analysis of AF electrograms. *J Cardiovasc Electrophysiol*, 18(6):680–5, Jun 2007.

[69] Jason Ng, Alan H Kadish, and Jeffrey J Goldberger. Technical considerations for dominant frequency analysis. *J Cardiovasc Electrophysiol*, 18(7):757–64, Jul 2007.

[70] Raúl Alcaraz, Fernando Hornero, Arturo Martínez, and José J Rieta. Short-time regularity assessment of fibrillatory waves from the surface ecg in atrial fibrillation. *Physiol Meas*, 33(6):969–84, Jun 2012.

[71] P Maragos. Morphological filters–part I: Their set-theoretic analysis and relations to linear shift-invariant filters. *IEEE Transactions on Acoustics, Speech and Signal Processing*, 35(8):1153 – 1169, 1987.