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Discrimination of atrial rhythms by linear and non-linear methods

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Summary. - The discrimination among atrial rhythms is obtained through the analysis of linear and non-linear dynamics of atria electrograms and local atrial period (LAP) series. Linear and non-linear degree of coupling between atrial electrograms have been assessed using cross-correlation (CCI) and synchronization indexes. Dynamics of LAP series were investigated using level of predictability (LP) and regularity indexes. Atrial fibrillation (AF) episodes, classified according to Wells' criteria, were investigated. We found that metrics obtained from LAP series provide the best performance in the classification of AF rhythms. The LP index misclassified only 12 AF episodes over 87. Synchronization index was the most performing metric in the discrimination between organized and not-organized fibrillation: detection of organized rhythm; sensitivity (SE) > 95%; positive predictability (+P) > 95%. LP (SE: 89%; +P: 89%) and CCI (SE: 87%; +P: 83%) provide slightly lower performances.

Key words: atrial signal, linear predictability, regularity, non-linear dynamics, synchronization.

Riassunto *(Discriminazione di ritmi atriali mediante metodi lineari e non-lineari).* - L'individuazione di ritmi atriali è ottenuta attraverso l'analisi delle dinamiche lineari e non lineari tipiche degli elettrogrammi e delle serie di attivazione atriale locali (serie LAP). In particolare, il grado di accoppiamento lineare e non lineare è valutato mediante indici derivati dalla stima della funzione di cross-correlazione (CCI) e della misura della sincronizzazione tra elettrogrammi. La dinamica delle serie LAP è caratterizzata attraverso la stima del livello di predittività (LP) e mediante misure di regolarità. Sono stati analizzati differenti episodi di fibrillazione atriale (FA), classificati secondo i criteri di Wells. I risultati mostrano che le migliori prestazioni nella classificazione degli episodi di FA si ottengono dall'analisi delle serie LAP. L'indice LP, infatti, fallisce la classificazione solamente in 12 degli 87 episodi di FA considerati. L'indice di sincronizzazione fornisce le migliori prestazioni nella distinzione tra fibrillazione organizzata e non-organizzata: rilevazione di attività organizzata; sensibilità (SE) > 95%; predittività positiva (+P) > 95%. LP (SE: 89%; +P: 89%) e CCI (SE: 87%; +P: 83%) hanno prestazioni comparabili, ma leggermente inferiori.

Parole chiave: segnali atriali, predicibilità lineare, regolarità, dinamica non-lineare, sincronizzazione.

Introduction

Atrial fibrillation (AF) is not a totally random phenomenon [1]. Recent findings documented the presence of temporal and spatial organisation in the wavefront propagation along the atria during AF episodes. Botteron and Smith [2] demonstrated AF to be spatially cross-correlated, and derived an "activation space constant". Evidence of organisation have been assessed through spectral analysis [1], while the transient nature of the linking between atrial signals [3] have been assessed by spectral coherence [4] and linear prediction [5]. In addition the emerging of complex, non-linear patterns have been documented in single electrogram leads [6] and in atrial period time series [7].

The presence of linear and non-linear relationships between atrial signals and series, reveals the existence of some kind of underlying organization which creates, sustains and defines the number of circulating wavelets in the atria. According to Jalife *et al.* [1] there are only few "mother" wavelets originating in a finite number of atrial sites and propagating on both atria, where disturbance of impulse propagation and de-synchronization among atrial regions may encourage the genesis of secondary "daughter" wavelets. As the number of circulation wavelet has been associated to the spontaneous termination of AF [8, 9] and it was hypothesized to be related to a certain degree of synchrony among atrial electrical activity, the quantification of these interactions has relevant physiological and clinical impact. In

addition, the different characteristics of the relationships among atrial signals and series, and the capability to quantify it, may be employed for the developing of automatic, reliable algorithms for AF classification.

In this paper, we studied linear and non-linear indexes for the automatic discrimination of AF rhythms. We characterised atrial signals (AS) through linear parameters obtained from the estimation of the cross-correlation function (CCF) as well as by the synchronisation (S) metric based on the mutual corrected conditional entropy (MCCE) [10]. In addition, the dynamic characterisation of local activation period (LAP) series was obtained through the level of predictability (LP) index, computed through the identification of an autoregressive (AR) model, and the regularity (R) index [11], obtained through the estimation of the corrected conditional entropy (CCE). We have already described [12] the variations of these indexes during Wells' classes [14] of AF episodes. In this paper we will investigate these metrics in terms of their capability to detect and classify the AF episodes in humans. Both spontaneous and induced AF episodes will be considered.

Methods

Level of predictability

A discrete time-series *x(n)* can be modelled as the output of an autoregressive model of *p* order

$$x(n) = \sum_{k=1,p} a_k x(n - k) + w(n) \qquad (1)$$

where *n* is the discrete-time index, the a_k's are the model coefficients and *w(n)* is a Gaussian, zero-mean, white noise (WN) process of variance σ_w^2 feeding the model [15].

From the computation of the prediction error $e(n) = x(n)-\hat{x}(n)$ (i.e. the difference between the actual sample and its model prediction) an index of level of predictability (LP) may be defined as follows [16]:

$$LP = (1 - \sigma^2_e/\sigma^2_x) \qquad (2)$$

where σ^2_e is the variance of *e(n)* and σ^2_x is the variance of the process *x*. The index *LP* measures the percentage of power which may be predicted by the model. In the case of a purely random signal (σ^2_e is quite close to σ^2_x) the index tends to zero; in the case of a linearly predictable signal (σ^2_e tends to zero), *LP* tends to one and it remains between these two limits for intermediate processes.

Cross-correlation index

A measurement of the linear degree of coupling between two electrograms is obtained through the estimate of the cross-correlation function (CCF).

Normalised CCF was obtained by dividing the CCF value by the product of standard deviations of the two signals. The cross-correlation index was defined as the maximum absolute value of normalised CCF in a window (± 32 ms) centred around the zero-lag.

Regularity index

The evaluation of the regularity of a process *x* is based on the calculation of the conditional entropy (CE) over a normalized realization of *x* [11]. The CE_x function measures the amount of information carried by the most recent sample of *x* when its past L-1 samples are known: the more informative are the past samples to predict the future behavior, the smaller is CE_x. CE_x is a function of the number *(L)* of past samples used in the prediction and it is defined as:

$$CE_x(L) = - \sum_{L} p_L \log p_L + \sum_{L-1} p_{L-1} \log p_{L-1} \qquad (3)$$

where p_L is probability of the patterns of length *L* which may be extracted from *x*. Unfortunately, when *L* increases, eqn. 3 produces unreliable estimation of CE_x. To avoid this problem, it has been proposed [11] to add a corrective term, thus defining a new function (the corrected conditional entropy, CCE_x):

$$CCE_x(L) = CE_x(L) + perc(L) \cdot E(x) \qquad (4)$$

where *perc(L)* is the percentage of single points in the *L*-dimensional phase space and *E(x)*, is the Shannon Entropy of the process. When the CE_x estimate becomes unreliable, the corrective term forces the CE_x to increase and to tend to the CE pattern of a white noise with the same probability distribution of *x*. The minimum value of the CCE_x is taken as an index of complexity [11]: the larger the index, the more unpredictable and complex the series. To derive an index of complexity which is independent of the different probability distribution of the processes, the CCE_x is normalized by the Shannon entropy of the process [13], thus obtaining the normalized corrected conditional entropy *($NCCE_x$)*. Independently of the distribution of the process, the $NCCE_x$ ranges from 0 to 1. Therefore, the minimum of the $NCCE_x$ appears more useful than that of the CCE_x when processes with different probability distribution are analysed. In this case, the index of regularity of the process x is defined as

$$\rho = 1 - \min (NCCE_x(L)) \qquad (5)$$

Examples of the $NCCE_x$ functions calculated over simulated signals are shown in Fig.1. When a rigorously periodic pattern is considered, the $NCCE_x$ corresponds to the NCE_x (Fig. 1b) because the corrective term is null. In addition, as a result of the search of the $NCCE_x$ minimum, the zero NCE_x value can be detected as predicted by theory. When a white noise is considered,

the $NCCE_x$ is constant as predicted by the theory (Fig. 1d) because the corrective term is able to completely compensate the decrease to zero of the NCE_x estimate. When a second order autoregressive (AR(2)) process (pole modulus $\rho = 0.9$, pole phases $\varphi = \pm \pi/4$) is analysed, the $NCCE_x$ is characterised by a well-defined minimum (Fig. 1f) because the decrease of the NCE_x estimate is faster than the increase of the corrective term. The presence of a minimum shows that the process is neither completely deterministic nor fully unpredictable. Applications of the regularity index to cardiovascular variability series can be found in [13].

Synchronization index

The concept of CE can be extended to measure synchronisation [10] between two normalized processes x and y. In this case, the CE is evaluated in order to measure the amount of information carried by a sample

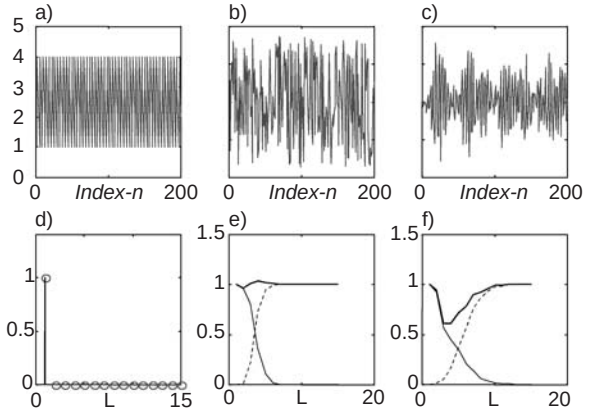

Fig. 1. - Examples of purely periodic (a), white noise (b) and second-order autoregressive (c) signals. (d)-(f) the estimated corrected conditional entropy functions (bold lines) is obtained as sum of conditional entropy term (thin lines) and corrective term (dotted lines).

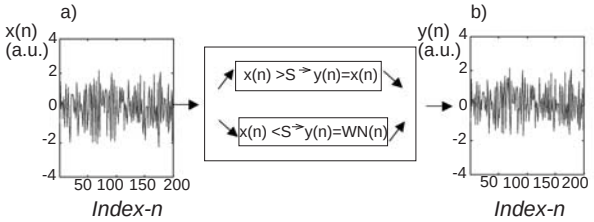

Fig. 2. - Build up of a mixed process. The signal $y(n)$ is obtained through a non-liner filtering procedure. The input signal x is compared with a threshold (S): values lower than S are substituted by WN, higher values come through the filter untouched.

of the signal x when L-1 past samples of the signal y are known $(CE_{x/y})$. $CE_{x/y}$ suffers the same limitation of CE_x: it decreases when L increases, independently of the type of coupling between x and y, as an effect of the shortness of the signals x and y. Therefore, when short segments of data are analysed, a corrected $CE_{x/y}$ $(CCE_{x/y})$ has to be utilised [10]. The $CCE_{x/y}$ is normalised $(NCCE_{x/y})$ by dividing by $E(x)$, thus avoiding the bias related to the shape of the probability distribution of x. Moreover, as no a priori knowledge about the causal relationships between x and y is usually given (it is unknown if y affects x or viceversa), the minimum between $NCCE_{x/y}$ and $NCCE_{y/x}$ is evaluated and the synchronisation index becomes:

$$S = 1 - \min\,(NCCE_{x/y}(L),\, NCCE_{y/x}\,(L)) \qquad (6)$$

As an example of the ability of the synchronisation index to capture the coupling between two processes, a simulation involving two mixed processes can be considered. Given an AR(2) process (pole modulus $\rho = 0.8$, pole phases $\varphi = \pm \pi/4$) with zero mean and unitary variance (Fig. 2a), a mixed process y (Fig. 2c) is obtained by substituting the samples of the AR(2) process x below the value $x_{min} + \eta \cdot (x_{max} - x_{min})$, where x_{min} and x_{max} represent the minimum and maximum values of x and η is a number ranging from 0 to 1, with independent identically distributed samples with zero mean and unitary variance. η modulates the amount of samples of the AR(2) process replaced by white noise samples (in Fig. 2 $\eta = 0.25$ in b and $\eta = 0.60$ in d), thus changing the coupling between x and y. When η is equal to 0, no sample of x is substituted (i.e. full coupling). On the contrary, when η is equal to 1 all the samples of x are replaced (i.e. no coupling). As expected, the minimum of Fig. 3a is deeper than the minimum of Fig. 3b. Comparison with cross-correlation function is also provided (Fig. 3 c,d). Applications of the synchronization index to cardiovascular variability series can be found in [13].

Experimental protocol

Forty informed subjects underwent an electrophysiological study. Twenty-two patients had chronic stable AF, in the remaining 18 patients AF episodes were electrically induced. Any drug that could interfer with atrial electrophysiological properties was suspended in due time before the beginning of the study.

Endocardial electrical activity was recorded through a 6F, 5-mm spaced, decapolar catheter. It was advanced from the right femoral vein and placed in the right atrium with the distal electrodes in proximity of the sinus node. The stability of the catheter was assessed by fluoroscopy each minute. Bipolar electrograms were obtained by combining electrodes 1-2 (high atrium), 4-5 (mid atrium) and 9-10 (low atrium), simultaneously recorded and real-

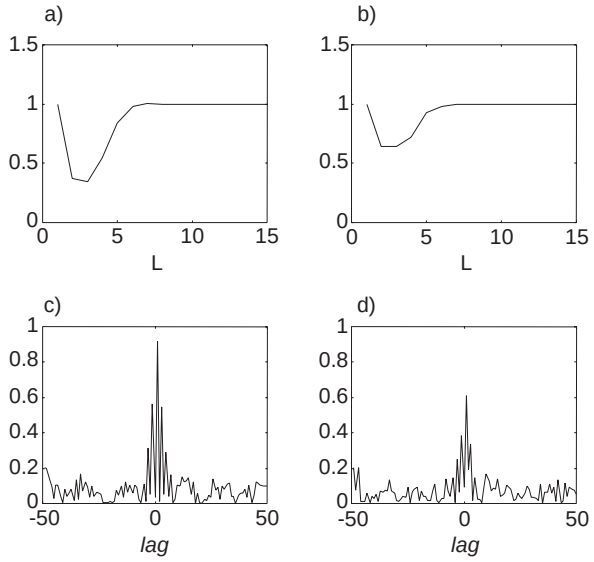

Fig. 3. - Estimated corrected conditional entropy functions (a)-(b) and cross-correlation function (c)-(d) for two normalized process *x* and *y*. Two *y* processes are obtained by setting the threshold equal to 0.25 and 0.6 times the range of input *x* process (see also Fig. 2 for details).

time digitized. A 6 Fr 1-cm spaced quadripolar electrode catheter was also used to record His bundle deflection or for sensing and pacing the right ventricle during endocavitary electrical cardioversion. Data were collected inside the national project of the Istituto Superiore di Sanità "Function replacements, artificial organs and organ transplantations". More details can be found in [17].

Intra-atrial traces were inspected by expert cardiologists and the different AF epochs were classified according to Wells' criteria [14]: normal sinus rhythm, AF of types I, II, III and IV.

Several episodes of AF were extracted and grouped in two sets of data. The training set (Table 1) and the test set (Table 2). The training set included 150 electrograms segments, 6 seconds each, and 98 LAP series, 300 activation intervals each. The test group included a smaller number of episodes: in details, 138 electrograms segments and 87 LAP series. Both groups included various examples of normal sinus rhythm and AF rhythms. No AF-IV episodes were included.

Detailed description of electrograms pre-processing used in the extraction of the LAP series and in the computation of the proposed indexes may be found in [12].

Results

Fig. 4 shows the estimated values of the proposed metrics as obtained for the training set. Data are plotted as a function of atrial rhythms. The synchronisation and cross-correlation indexes (Fig. 4a,b), measuring the degree of coupling between two electrograms, show a progressive decrease passing from NSR to AF-III. However, several overlapping values among atrial rhythms do exist. It is worth noting that the S index experienced a marked separation between organised (AF-I) and not-organised (AF-II+AF-III) rhythms (Fig. 4a).

Indexes extracted for LAP series show a better capability to discriminate among different atrial rhythms as evidences in Fig. 4c,d. Both indexes show a marked reduction passing from NSR to AF-II and a small number of overlapping values between fibrillation types.

Performances of the proposed metrics in the classification of AF episodes of the test set are shown in Tables 3 and 4. Two cases are considered: a) in Table 3, the capability of the LAP indexes to discriminate among atrial rhythms is evaluated; b) in Table 4 the capability of electrograms indexes to discriminate among organised and not-organised rhythms is considered. Among the analysed metrics, the LP is the best classifier of atrial rhythms: only 12 case over 87 were mis-classified (13%). AF-I segments were the most difficult to be classified: in 7 cases over 32 (21%) classification was incorrect. None of AF-II episode was classified as NSR and vice-versa.

The synchronisation index was the best parameter able to discriminate between organised and not-organised rhythms: in the considered population, sensitivity (SE) and positive predictability (+P) were higher than 95%. Slightly lower performances were obtained from the LP index (detection of organised rhythm SE: 89%; +P:

Table 1. - Training set: number of segments for each atrial rhythm

Rhythms	Electrograms (number)	LAP series (number)
NSR	30	35
AF-I	47	33
AF-II	47	30
AF-III	26	-
Total	150	98

LAP: local activation period; NSR: normal sinus rhythm; AF: atrial fibrillation.

Table 2. - Test set: number of segments for each atrial rhythm

Rhythms	Electrograms (number)	LAP series (number)
NSR	24	30
AF-I	47	32
AF-II	41	25
AF-III	26	-
Total	138	87

LAP: local activation period; NSR: normal sinus rhythm; AF: atrial fibrillation.

89%), cross-correlation index (detection of organised rhythm SE: 87%; +P: 83%) and regularity (detection of organised rhythm SE: 75%, +P: 85%).

Discussion and conclusions

In this paper we assessed the performances of linear and non-linear parameters, extracted from intra-atrial electrograms signals and local activation period series, in the automatic classification of Wells type, AF episodes. The proposed parameters capture different characteristics of atrial signals and LAP series: level of predictability and the regularity index measure the degree of predictability of atrial activation sequence; the cross-correlation and synchronisation indexes infer the level of atrial organization through the quantification of the linear and non-linear degree of coupling between electrograms.

Selection of these metrics was supported by the current knowledge about AF mechanisms. In fact, presence of linear and non-linear [7] dynamics in the sequence of local atrial activation have been documented [3], in agreement with the observation that a reduced level of predictability characterizes the LAP series during different Wells type of AF [12]. In addition, electrograms recording were found to be spatially cross-correlated during AF [2], and significant reduction of degree of coupling has been observed during AF episodes [12]. These findings supported the idea to employ measurements of predictability and coupling as classifier of AF episodes, classified according to Wells' criteria.

Among the considered metrics, the analysis of predictability of atrial activation sequences provides the most relevant information for the discrimination among fibrillation rhythms. In particular linear predictability (LP index) performed better than regularity index, suggesting that quantification of the non-linear dynamics of LAP series may not be relevant for the classification of atrial rhythms. Conversely, when the interest is in the discrimination between organized and not-organized rhythms, the use of a parameter, such as the synchronization which accounts for a both linear and non-linear patterns, yielded the best results. Thus synchronization is able to capture evidences of atrial organization, even where other methods fail, because it may account for a wide range of coupling mechanisms [10]. This aspect leads to a more correct detection of atrial organization.

Finally, it worth noting that the presented metrics are simple and easy-to-compute. In particular, the non-liner index need lower computation time and shorter data sequences than most of the non-linear metrics presented in literature. This makes the parameters particularly suitable for both the description of short-time links between atrial signals and for their implementation on portable, real-time devices. It is worth noting that quantification of the dynamics of the activation sequences required a longer data sequence (i.e 1-2 minutes) than indexes obtained from electrograms analysis (i.e. 6 seconds). Thus the latter indexes are more suitable when transient, sort duration relationships need to be addressed [3, 18].

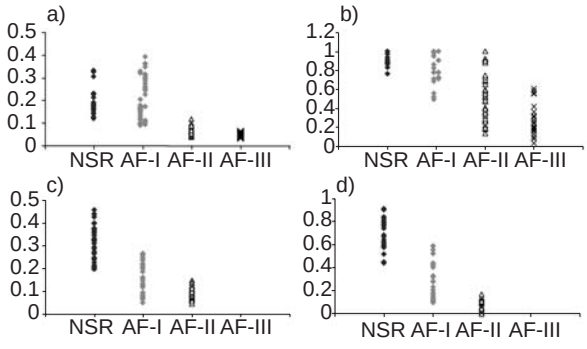

Fig. 4. - Values of the proposed metrics obtained on the test data sets. (a) synchronization index; (b) cross-correlation index; (c) regularity and (d) level of predictability.

Table 3. - Performances of LAP series indexes

Rhythms	Regularity			Level of predictability		
	NSR	AF-I	AF-II	NSR	AF-I	AF-II
NSR	23	7	0	28	2	0
AF-I	0	24	8	4	25	3
AF-II	0	4	21	0	3	22

LAP: local activation period; NSR: normal sinus rhythm; AF: atrial fibrillation.

Table 4. - Performances of electrograms indexes

Rhythms	Synchronization		Cross-correlation index	
	AF-I	AF-II/ AF-IIII	AF-I	AF-II/ AF-IIII
AF-I	45	2	41	6
AF-II/ AF-IIII	2	65	8	59

AF: atrial fibrillation.

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