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Cross Approximate Entropy Analysis of Nocturnal Oximetry Signals in the Diagnosis of the Obstructive Sleep Apnea Syndrome

Daniel Álvarez*, Roberto Hornero, *Member*, *IEEE*, María García, Felix del Campo, Carlos Zamarrón, Miguel López, *Member*, *IEEE*

***Abstract* — This study is focused on the analysis of blood oxygen saturation (SaO_2) and heart rate (HR) from nocturnal oximetry using Cross Approximate Entropy (*Cross-ApEn*). We assessed its usefulness in screening obstructive sleep apnea (OSA) syndrome. We applied *Cross-ApEn*(*m*,*r*,*N*) to quantify the asynchrony between paired SaO_2 and HR records of 74 patients (44 with a positive OSA diagnosis and 30 with a negative OSA diagnosis). *Cross-ApEn* values were significantly lower in the OSA positive group compared with those obtained in the OSA negative group. A receiver operating characteristic (ROC) analysis showed that the best results, in terms of diagnostic accuracy, were achieved with $m = 2$ and $r = 0.6$. With these input parameters, the optimum decision threshold was found at 1.7, where we achieved 95.5% sensitivity, 73.3% specificity and 86.5% accuracy. Further analyses should be carried out with new and larger data sets to test the usefulness of our methodology prospectively.**

I. Introduction

THE Obstructive Sleep Apnea (OSA) syndrome is a major health problem, affecting 1 to 5% of adult men in western countries [1]. OSA is associated with conditions that are responsible for the most important causes of mortality in adults: hypertension and cardiovascular and cerebrovascular diseases. Moreover, subjects with OSA have an increased risk of being involved in road and work accidents [2]. OSA syndrome is now the most common respiratory referral to many sleep centers [3].

The standard diagnostic test for OSA is overnight polysomnography (PSG) [4], consisting in the recording of neurophysiological and cardiorespiratory signals subsequently used to analyze sleep and breathing. However, its high cost and complexity have arisen the need for alternative screening tools. Due to its simplicity and low cost, portable monitoring has been proposed as a substitute for PSG in the diagnostic assessment of patients with suspected sleep apnea [5].

Several quantitative indexes derived from nocturnal oximetry have been developed to diagnose OSA. The most widely used by physicians are the oxygen desaturation indexes (ODIs), which measure the number of dips in the blood oxygen saturation (SaO_2) signal below a certain threshold, and the cumulative time spent below a certain saturation level (CT) [6], [7]. However, there is not a consensus on their definition and use [7]. Furthermore, classical indexes like ODIs or CTs are defined exclusively for SaO_2. Although oximeters usually provide both SaO_2 and heart rate (HR), efforts have been mainly focused on oxygen saturation signals. Few studies have assessed the diagnostic accuracy of HR from nocturnal oximetry in screening OSA [8]–[10]. The study developed in [9] processed SaO_2 and HR independently, and shows that taking the results together improved those obtained individually. Other authors [10] processed both signals simultaneously, quantifying the relationship between oscillations in SaO_2 and HR by means of the frequency coherence function. In this study, we estimated the asynchrony between SaO_2 and HR from nocturnal oximetry using nonlinear methods. Nonlinear analysis of SaO_2 signals has demonstrated to be suitable in screening for OSA syndrome [11].

Similarities between time series are traditionally quantified with linear methods, usually coherency and spectral estimates. Coherency is a normalized measure of linear correlation as a function of frequency, widely applied to quantify functional interactions between different brain areas [12]. However, coherency estimates are not suitable to characterize nonstationary signals and only capture linear relations between time series [13], [14]. Moreover, standard spectral estimators can be inconsistent and badly biased, especially in the presence of outliers and nonstationarities [15]. A recently developed measure of asynchrony between time series, Cross Approximate Entropy (*Cross-ApEn*), has demonstrated to be complementary and often superior to both spectral and correlation-based methods [15]. Other entropy-based measures of asynchrony have been applied to cardiovascular variability signals, pointing out their advantages over the linear approach [14], [16].

This preliminary study was aimed to assess whether a measure of asynchrony between SaO_2 and HR from nocturnal oximetry using *Cross-ApEn* could discriminate patients suffering OSA syndrome.

II. Material and Methods

A. Subjects and Signals

A total of 74 patients (56 males and 18 females) suspected of having OSA were studied. Patients have a mean ± standard deviation (SD) age of 58.3 ± 12.1 years and a body mass index (BMI) of 29.6 ± 5.7 kg/m^2. All subjects presented daytime hypersomnolence, loud snoring, nocturnal

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D. Álvarez, R. Hornero, M. García and M. López are with the E.T.S. Ingenieros de Telecomunicación, University of Valladolid, Camino del Cementerio s/n, 47011-Valladolid, Spain (phone: +34 983 423000, ext. 5589, fax: +34 983 423667; e-mails: dalvgon@ribera.tel.uva.es, {robhor, margar, miglop}@tel.uva.es).

F. del Campo is with the Hospital del Río Hortega, Valladolid, Spain.

C. Zamarrón is with the Hospital Clínico Universitario, Santiago de Compostela, Spain.

choking and awakenings, or apneic events (or all four symptoms) reported by the subject or a bed mate.

Sleep studies were carried out usually from midnight to 08:00 AM in the Sleep Unit of Hospital Clínico Universitario in Santiago de Compostela, Spain. The Review Board on Human Studies approved the protocol, and all subjects gave their informed consent to participate in the study. An overnight pulse oximetry analysis was carried out simultaneously with a conventional PSG study. All patients underwent overnight PSG (Ultrasom Network, Nicolet, Madison, WI, U.S.A.) which included EEG, ECG, electrooculogram, chin electromyogram, measurement of chest wall movement and air flow measurement (three-port thermistor). The PSG register was analyzed over periods of 30 s and during sleep phases I, II, III, IV and rapid eye movement, according to Rechtschaffen and Kales rules [17]. Apnea was defined as the cessation of airflow for more than 10 seconds and hypopnea as the reduction of respiratory flow for at least 10 seconds accompanied by a 4% or more decrease in the saturation of hemoglobin. The average apnea-hypopnea index (AHI) was calculated for hourly periods of sleep. Subjects with an AHI greater than or equal to 10 were diagnosed as suffering OSA. If the subject had less than 3 hours of total sleep, the sleep study was repeated.

The oximetry analysis was carried out using a Criticare 504 pulse oximeter (CSI, Waukesha, WI, U.S.A.). SaO_2 and HR signals were both simultaneously recorded using a dual wavelength-based finger probe with a sampling frequency of 0.2 Hz (one sample every 5 s), resulting from an average of the previous 16 R-R intervals. Oximetry signals were saved to separate files and processed off-line by means of *Cross-ApEn*. Table I summarizes the demographic and clinical data of the patient groups derived from the PSG diagnosis.

TABLE I
DEMOGRAPHIC AND CLINICAL FEATURES OF THE PATIENT GROUPS

	All Subjects	OSA Positive	OSA Negative
Subjects (n)	74	44 (59.5%)	30 (40.5%)
Age (years)	58.3 ± 12.1	56.73 ± 13.61	59.59 ± 10.19
Males (%)	75.7	79.55	70.00
BMI (kg/m^2)	29.6 ± 5.7	30.19 ± 5.09	28.93 ± 6.40
Time recorded (h)	8.2 ± 0.4	8.2 ± 0.5	8.3 ± 0.3
AHI (n/h)		38.11 ± 18.18	2.60 ± 2.51

Data are presented as mean ± SD or n (%). OSA Positive: patients with obstructive sleep apnea; OSA Negative: patients without obstructive sleep apnea; BMI: body mass index; AHI: apnea-hypopnea index.

B. Cross Approximate Entropy (Cross-ApEn)

Cross Approximate Entropy (*Cross-ApEn*) is a two parameter family of statistics introduced as a measure of asynchrony between two paired time series [18]. Its definition was proposed by Pincus as a method to compare correlated sequences, suggesting its application to physiological signals like HR and respiratory rate [19].

Cross-ApEn is generally applied to compare sequences from two distinct yet intertwined variables in a network. It allows the assessment of system evolution characteristics such as feedback and control avoiding the requirement to model the underlying system [18]. *Cross-ApEn* evaluates subordinate as well as dominant patterns in data, quantifying changes in underlying episodic behavior that do not reflect in peak occurrences and amplitudes [20]. For two paired time series $u(i)$ and $v(i)$, *Cross-ApEn* measures, within tolerance r, the (conditional) regularity or frequency of v-patterns similar to a given u-pattern of window length m. Greater asynchrony indicates fewer instances of (sub)pattern matches, quantified by larger *Cross-ApEn* values [18].

Formally, given two length-N sequences $u = [u(1), u(2), \ldots, u(N)]$ and $v = [v(1), v(2), \ldots, v(N)]$, and fixed the input parameters m and r, *Cross-ApEn* could be computed as follows [18]:

1. Form the vector sequences $x(i) = [u(i), u(i+1), \ldots, u(i+m-1)]$ and $y(j) = [v(j), v(j+1), \ldots, v(j+m-1)]$. These vectors represent m consecutive u and v values respectively, commencing with the ith point.
2. Define the distance between $x(i)$ and $y(j)$, $d[x(i), y(j)]$, as the maximum absolute difference in their respective scalar components:

$$d[x(i),y(j)] = \max_{k=1,2,\ldots m} |u(i+k-1)-v(j+k-1)| \quad (1)$$

3. For each $x(i)$, count the number of j ($j = 1 \ldots N-m+1$) so that $d[x(i),y(j)] \le r$, denoted as $N_i^m(r)$. Then, for $i=1 \ldots N-m+1$, set

$$C_i^m(r)(v\|u) = N_i^m(r)/(N-m+1) \quad (2)$$

The $C_i^m(r)$ values measure within a tolerance r the regularity, or frequency, of (v–) patterns similar to a given (u–) pattern of window length m.

4. Compute the natural logarithm of each $C_i^m(r)$, and average it over i,

$$\phi^m(r)(v\|u) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1} \ln C_i^m(r)(v\|u) \quad (3)$$

5. Cross Approximate Entropy is defined by:

$$Cross\text{-}ApEn(m,r,N)(v\|u) = \phi^m(r)(v\|u) - \phi^{m+1}(r)(v\|u) \quad (4)$$

Typically, *Cross-ApEn* is applied to normalized $\{u^*(i), v^*(i)\}$ time series, where $u^*(i) = [u(i)-\text{mean}(u)]/\text{SD}(u)$ and $v^*(i) = [v(i)-\text{mean}(v)]/\text{SD}(v)$.

Two important issues must be taken into account in the calculation of *Cross-ApEn* [21]. First, $C_i^m(r)(v\|u)$ can be equal to 0, and there is no assurance that *Cross-ApEn*$(m,r,N)(v\|u)$ will be defined. Second, there is a direction dependence, and $\phi^m(r)(v\|u)$ will not be generally equal to $\phi^m(r)(u\|v)$. To ensure that *Cross-ApEn*$(m,r,N)(v\|u)$ will be always defined, we used two correction strategies proposed in [21]. Both corrections assign non zero values to the conditional probabilities $C_i^m(r)(v\|u)$ and $C_i^{m+1}(r)(v\|u)$ in the absence of any matches. The first one, called bias 0, sets the bias toward a *Cross-ApEn* value of zero by setting $C_i^m(r)(v\|u)$ and $C_i^{m+1}(r)(v\|u)$ equal to 1 if both were

originally zero, or $C_i^{m+1}(r)(v\|u)$ equal to $(N\text{-}m)^{-1}$ if $C_i^m(r)(v\|u) \neq 0$. The second correction, called bias max, sets the bias toward the highest observable value of *Cross-ApEn* by setting $C_i^m(r)(v\|u)$ equal to 1 when it would otherwise have been zero and $C_i^{m+1}(r)(v\|u)$ equal to $(N\text{-}m\text{+}1)^{-1}$. Both correction strategies were implemented. Furthermore, both *Cross-ApEn*(v||u) and *Cross-ApEn*(u||v) were estimated.

In this study, we divided SaO_2 and HR signals in 200 sample epochs before *Cross-ApEn* was applied. The input parameters were fixed to m = 1 and 2, and r was varied from 0.1 to 1.0 in steps of 0.1 [21].

III. Results

Cross-ApEn was applied to both OSA positive and OSA negative groups with all possible combinations of m and r, with the two possible correction strategies bias 0 and bias max, and with the two possible directions (SaO_2||HR) and (HR||SaO_2). Student t-test was applied to check for significant differences between groups. A great difference exists between the directions (SaO_2||HR) and (HR||SaO_2). *Cross-ApEn*(m,r,N)(HR||SaO_2) achieved poor results with all combinations of m and r in terms of the p-value. This fits well with the nature of SaO_2 and HR signals. SaO_2 signals are more regular than HR in both OSA positive and OSA negative patients. Hence, $N_i^m(r)$ is better estimated comparing a fixed SaO_2 sample with all samples in a HR record than inversely. With respect to the correction strategies, no significant differences were found between bias 0 and bias max ($p > 0.05$).

Figure 1 depicts mean *Cross-ApEn*(m,r,N)(SaO_2||hr) values with bias 0 correction for each subject group with all suggested combinations of m and r [21]. We show that, for all equal m and r pairs, OSA negative group achieves higher values of *Cross-ApEn* than OSA positive group. Thus, we could say that OSA negative SaO_2 and HR paired records are more asynchronous than OSA positive oximetric records. In this preliminary study, we have also shown the relative consistency of *Cross-ApEn* for such kind of processes with r varying from 0.1 to 1.0 and m equal to 1 or 2 [22].

Finally, we evaluated the ability of *Cross-ApEn* to discriminate patients from OSA positive and negative groups using Receiver Operating Characteristics (ROC) plots. We used a computer program developed with Matlab® that calculated the sensitivity-specificity pair for different thresholds. The optimum threshold is selected by our program looking for a compromise between sensitivity and specificity. This value is graphically determined from the ROC curve as the closest point to the left top corner (100% sensitivity and 100% specificity). Table II shows the test results for the optimum threshold from ROC analysis for *Cross-ApEn*(m,r,N)(SaO_2||HR) with bias 0 correction. Best results in terms of diagnostic accuracy were achieved with m = 2 and r = 0.6. The optimum threshold was selected at 1.7, where we achieved 95.5% sensitivity, 73.3% specificity, 86.5% accuracy and an area under the ROC curve of 0.87.

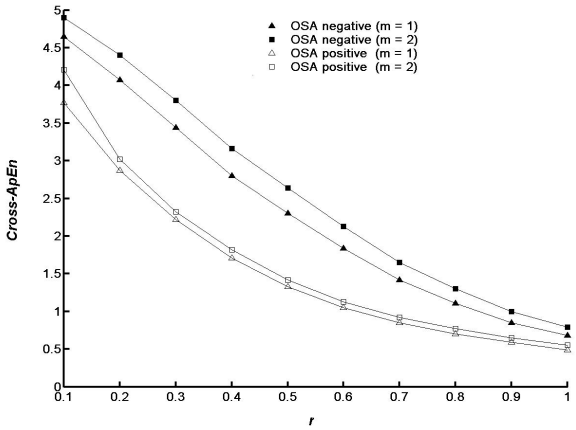

Fig. 1. Mean *Cross-ApEn* (SaO_2||HR) for both the OSA positive and OSA negative groups varying *Cross-ApEn* input parameters.

TABLE II
TEST RESULTS FOR THE OPTIMUM DECISION THRESHOLD FROM ROC ANALYSIS

m	r	Th	S(%)	E(%)	A(%)	AROC
m=1	0.1	4.38	75.0	83.3	78.4	0.87
	0.2	3.74	84.1	80.0	82.4	0.89
	0.3	2.93	88.6	80.0	85.1	0.88
	0.4	2.18	86.4	80.0	83.8	0.87
	0.5	1.67	86.4	80.0	83.8	0.86
	0.6	1.40	93.2	73.3	85.1	0.85
	0.7	0.98	81.8	76.7	79.7	0.82
	0.8	0.82	84.1	73.3	79.7	0.81
	0.9	0.71	88.6	66.7	79.7	0.76
	1.0	0.57	84.1	66.7	77.0	0.77
m=2	0.1	4.85	79.6	76.7	78.4	0.84
	0.2	3.71	77.3	86.7	81.1	0.89
	0.3	3.29	88.6	80.0	85.1	0.89
	0.4	2.51	86.4	80.0	83.8	0.88
	0.5	1.65	81.8	83.3	82.4	0.87
	0.6	1.70	95.5	73.3	86.5	0.87
	0.7	1.10	81.8	76.7	79.7	0.83
	0.8	0.91	84.1	76.7	81.1	0.83
	0.9	0.79	90.9	66.7	81.1	0.79
	1.0	0.63	81.8	70.0	77.0	0.79

Th: Optimum threshold; S: Sensitivity; E: Specificity; A: Accuracy; AROC: Area under the ROC curve

IV. Discussion

In this preliminary study, a sample of 74 patients (44 with a positive diagnosis of OSA and 30 with a negative diagnosis of OSA) was studied. A nonlinear method called *Cross-ApEn* was applied to paired SaO_2 and HR signals from nocturnal oximetry to quantify their asynchrony. We found that the recurrent apnea events in OSA positive patients lead to a significant decrease in the *Cross-ApEn* values. A shorter value of *Cross-ApEn* indicates greater instances of (sub)pattern matches, so the sequences are more synchronous [18]. Oxygen desaturations associated with apnea events typical of OSA, cause coordinate fluctuations in both SaO_2 and HR signals, leading to low *Cross-ApEn* values. Furthermore, we found great direction dependence, *Cross-ApEn*(SaO_2||HR) is better estimated than *Cross-ApEn*(HR||SaO_2). On the other hand, no significant differences were found between correction strategies.

Previous studies assessed the relationship between

oscillations in SaO_2 and HR as a sign of periodic breathing [10], [23]. The study developed in [10] showed that the average level of SaO_2 and HR coherence in OSA positive patients was significantly higher than in OSA negative patients. These results fit well with those obtained in our study, indicating higher synchrony between oximetric signals from OSA subjects. According to diagnostic accuracy, best results were achieved with the input parameters $m = 2$ and $r = 0.6$. A sensitivity of 95.5%, a specificity of 73.3% and an accuracy of 86.5% were obtained for an optimum threshold of 1.7. An area under the ROC curve of 0.87 was achieved. Further work is needed to assess our methodology and to verify its advantages over the linear approaches.

We should take into account some limitations of our study. The sample size could be larger and OSA positive patients were predominantly studied. Further work is required to apply our methodology to a new and larger data set with a wide spectrum of sleep-related breathing disorders, as well as to study groups of especial interest, such as patients with lung diseases and young snorers. Moreover, a drawback in the applicability of our method should be mentioned. Oximetry signals were recorded simultaneously with PSG, eliminating potential confounders such as night to night variability of AHI, as well as ensuring that oximetry data were collected in exactly the same environment as the PSG data. Further analyses using unattended nocturnal oximetry in home are necessary. An additional difficulty lies in the estimation of the HR from the distal pulse obtained from pulse oximetry, instead of measuring the elapsed time between consecutive R waves. An overestimation of the high frequencies must be taken into account. Another limitation, related to the methodology applied, should be stated. Although relative consistency was found for values of r from 0.1 to 1.0 when applying *Cross-ApEn* to oximetric signals, further research is needed to really assess its validity.

In summary, we found that the recurrence of apnea events in patients with OSA determined a significant decrease in the *Cross-ApEn* values of the SaO_2 and HR signals. 95.5% sensitivity, 73.3% specificity and 86.5% accuracy were achieved using this method in screening OSA. However, we need to carry out this analysis with larger populations to verify prospectively whether this method may be an easy tool to use for diagnosis of OSA on an ambulatory basis.

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