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Multivariate Analysis of Blood Oxygen Saturation Recordings in Obstructive Sleep Apnea Diagnosis

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***Abstract*— This study focuses on the analysis of blood oxygen saturation (SaO_2) from nocturnal pulse oximetry (NPO) to help in the diagnosis of the obstructive sleep apnea (OSA) syndrome. A population of 148 patients suspected of suffering from OSA syndrome was studied. A wide set of 16 features was used to characterize changes in the SaO_2 profile during the night. Our feature set included common statistics in the time and frequency domains, conventional spectral characteristics from the power spectral density (PSD) function and nonlinear features. We performed feature selection by means of a step-forward logistic regression (LR) approach with leave-one-out cross-validation. Second and fourth order statistical moments in the time domain (*M2t* and *M4t*), the relative power in the 0.014 – 0.033 Hz frequency band (P_R) and the Lempel-Ziv complexity (*LZC*) were automatically selected. 92.0% sensitivity, 85.4% specificity and 89.7% accuracy were obtained. The optimum feature set significantly improved the diagnostic ability of each feature individually. Furthermore, our results outperformed classic oximetric indexes commonly used by physicians. We conclude that simultaneous analysis in the time and frequency domains by means of statistical moments, spectral and nonlinear features could provide complementary information from NPO to improve OSA diagnosis.**

***Index Terms* — Obstructive sleep apnea, nocturnal pulse oximetry, time domain analysis, frequency domain analysis, nonlinear analysis, logistic regression**

I. Introduction

OBSTRUCTIVE SLEEP APNEA (OSA) syndrome is a major sleep-related breathing disorder characterized by repetitive periods of reduced (hypopnea) or total cessation (apnea) of respiration caused by the partial or complete collapse of the upper airway, respectively [1]. Epidemiologic data consistently show a high prevalence of OSA in North America, Europe and Asia [2]. It is estimated that OSA affects 1 to 5% of adult men and 2% of women in western countries [3]. However, 90% of cases in men and 98% of cases in women may go undiagnosed for many years [4]. Several factors of OSA syndrome have contributed to its emergence as an important medical condition [2]. Recent studies link OSA to inflammatory and metabolic deregulation, atrial fibrillation, stroke, myocardial infarction and sudden cardiac death [2]. These consequences have augmented the interest of the medical community and the general population on OSA syndrome, exponentially increasing the number of patients for evaluation [5].

Overnight polysomnography (PSG) is the gold standard method for a definitive diagnosis of OSA [1]. The apnea hypopnea index (AHI) from the PSG is used to characterize its severity. It measures the average number of apnea and hypopnea events per hour of sleep [1]. However, the AHI is weakly correlated with sleepiness and daytime performance [6], [7]. Moreover, the relative high cost and complexity of PSG limit its capacity as a screening test [6]. Thus, further research on simplified and less expensive tools is encouraged [7], [5].

Nocturnal pulse oximetry (NPO) is a standard technique for monitoring the arterial blood oxygen saturation (SaO_2) [8]. NPO could provide relevant information on patients' sleep quality: SaO_2 tends to remain constant around 96% in normal subjects, whereas significant changes can be found in patients affected by OSA because of the recurrent apnea events [9]. Due to its simplicity and low cost, NPO has been proposed as an alternative for PSG [9]. Moreover, telemedicine systems based on oximetry alone could reduce referrals and waiting lists by identifying patients with strong suspicion of OSA [10]. NPO shows substantial accuracy as a screening test but important limitations decrease its value as a single diagnostic tool for OSA [9]. Thus, oximetry monitoring will not replace the gold standard of full PSG [10]. Our research was aimed to obtain further knowledge on SaO_2 dynamics to improve the diagnostic ability of NPO in OSA. Additionally, we should take into account that other pulmonary and cardiovascular diseases can also modify the SaO_2 profile during the night, which could influence the performance of oximetry monitoring [1]. Chronic obstructive pulmonary disease (COPD) is especially important because it is linked with deep nocturnal oxyhemoglobin desaturations [11]. The scope of the present study focused on patients with a clinical suspicion of sleep apnea regardless of additional respiratory disorders.

Oxygen desaturation indexes (ODIs) and cumulative time (CT) indexes from NPO are commonly used by physicians

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in OSA diagnosis [9], [12]–[14]. ODIs measure the number of dips in the SaO_2 signal below a certain threshold, whereas CT indexes compute the percentage of time spent below a specified saturation level. However, it is known that some patients show many hypopneas with small decrements in SaO_2, whereas others manifest relatively fewer but prolonged apneas [2]. Many limitations of classic indexes have been documented: CT indexes do not achieve high diagnostic accuracy [14], [15], there is not a standard definition for oxygen desaturation [9], [15], correlation with AHI is not high and their sensitivity and specificity greatly vary among studies [9], [14]. Thus, classic oximetric indexes based on the number and severity of desaturations could be insufficient to correctly diagnose OSA syndrome. The proposed methodology was aimed to characterize overall dynamics of SaO_2 recordings regardless of quantifying the number of desaturation events.

Common statistics from time and frequency analyses of heart rate variability recordings have shown to be simple and accurate tools in the detection of sleep apnea [16], [17]. First to fourth order statistical moments (*M1 – M4*) could be very useful to characterize SaO_2 recordings. Spectral features from SaO_2 frequency analysis have been applied for diagnostic purposes [18]–[20]. Conventional characteristics such as the total signal power (P_T), the peak amplitude (*PA*) and the relative power (P_R) in the 0.014 – 0.033 Hz frequency band have been used to parameterize the SaO_2 spectrum. The median frequency (*MF*) and the spectral entropy (*SE*) are usually applied to obtain additional information from the frequency domain in other contexts, such as EEG analysis [21]–[23]. Thus, *MF* and *SE* could improve the usefulness of spectral analysis of oximetric signals in OSA detection. On the other hand, nonlinear analysis of SaO_2 has demonstrated to be a powerful tool in OSA diagnosis. Approximate entropy (*ApEn*) [24], central tendency measure (*CTM*) [25] and Lempel – Ziv complexity (*LZC*) [26] have been previously used to quantify irregularity, variability and complexity of SaO_2 recordings, respectively. Previous studies have shown that ApEn, CTM and LZC could improve the diagnostic accuracy of classic oximetric indexes [27]–[29]. An additional nonlinear measure of irregularity, sample entropy (*SampEn*), has been recently applied in the context of OSA diagnosis to characterize heart rate variability [30].

In the present research, we hypothesized that a large set of features from different approaches (time *vs.* spectral and linear *vs.* nonlinear) could be useful to characterize SaO_2 from NPO. Our analyses could provide essential and complementary information to improve the diagnostic ability of oximetric recordings in OSA detection. The following feature sets were included in our study:

1) Time domain statistics. First to fourth order statistical moments in the time domain (*M1t – M4t*).
2) Frequency domain statistics. First to fourth order statistical moments in the frequency domain (*M1f – M4f*), *MF* and *SE*.
3) Conventional spectral characteristics. P_T, *PA* and P_R.
4) Nonlinear characteristics. *SampEn*, *CTM* and *LZC*.

Our study was aimed to obtain an optimum feature set from SaO_2 signals, in order to provide simple and reliable OSA diagnosis. To achieve this goal, a step-forward logistic regression (LR) procedure with leave-one-out cross-validation was applied. Additionally, we evaluated whether the optimum feature set from the LR process could improve the diagnostic accuracy of classic oximetric indexes commonly used by physicians to diagnose OSA syndrome.

II. Population Set and Sleep Studies

The population under study consisted of 148 consecutive patients (115 males and 33 females) with a mean ± SD age of 52.9 ± 14.1 years and an average body mass index (BMI) of 29.8 ± 5.6 Kg/m^2. All subjects were derived to the Sleep Unit of the Hospital Universitario Pío del Río Hortega of Valladolid (Spain) reporting at least one of the following symptoms: daytime hypersomnolence, loud snoring, nocturnal choking and awakenings or apneic events. Patients suspected of having other sleep disorders, such as insomnia, parasomnia or narcolepsy, were excluded from the study. The Review Board on Human Studies approved the protocol and each subject gave his or her informed consent to participate in the study. Table I summarizes the demographic and clinical data of the population under study.

Overnight conventional PSGs were carried out from midnight to 08:00. Patients were continuously monitored using a polysomnograph (Alice 5, Respironics, Philips Healthcare, The Netherlands). Sleep was scored every 30 s epochs by a single scorer according to the standard criteria by Rechtschaffen and Kales. Apnea was defined as the absence of airflow for more than 10 s. Hypopnea was defined as a decrease in respiratory flow of at least 50%, accompanied by a greater than or equal to 3% decrease in the saturation of hemoglobin and/or an EEG arousal. Static (apneas) and dynamic (hypopneas) respiratory events were detected by means of a thermistor and a nasal cannula, respectively. An AHI ≥ 10 events per hour (e/h) from PSG was considered as diagnostic of OSA [31].

A positive diagnosis of OSA was confirmed in 100 patients (67.6%). They composed the OSA-positive group, with an average AHI of 40.9 ± 27.6 e/h. The remaining 48 subjects (32.4%) composed the OSA-negative group, with an average AHI of 4.1 ± 2.4 e/h. No significant differences between OSA-positive and OSA-negative groups were found in age, BMI and recording time. On the other hand, significant differences were found in the number of males (p-value < 0.01): the OSA-positive group had more males (83.0%) than the OSA-negative one (66.7%). This result agrees with the higher prevalence of the disease associated to the male gender [3]. Table I displays demographic and clinical characteristics for both groups.

The polysomnograph equipment used in the present study included a Nonin PureSAT pulse oximeter (Nonin Medical Inc., Plymouth, MN, USA), with 3 s or faster averaging interval at a minimum heart rate of 60 beats per minute or

TABLE I
DEMOGRAPHIC AND CLINICAL FEATURES OF THE POPULATION SET

	All subjects	OSA positive	OSA negative	*p*-value
Subjects (n)	148	100	48	–
Age (years)	52.9 ± 14.1	55.2 ± 14.6	48.3 ± 11.8	NS
Males (n)	116	84	32	$p < 0.01$
BMI (kg/m^2)	29.8 ± 5.6	30.8 ± 5.0	27.3 ± 6.3	NS
Records (h)	7.2 ± 0.4	7.2 ± 0.4	7.2 ± 0.4	NS
AHI (e/h)		40.9 ± 27.6	4.1 ± 2.4	$p < 0.01$

Data are presented as mean ± SD or n; BMI: body mass index; AHI: apnea-hypopnea index; NS: no significant statistical differences

An AHI ≥ 10 (e/h) from PSG was considered as diagnostic of OSA

greater. The SaO_2 recordings from the overnight PSG were saved to separate files and processed offline. SaO_2 was recorded at a sampling rate of 1 Hz. A semi-automatic preprocessing stage was carried out. Firstly, we assessed each oximetric recording by visual inspection looking for artifacts. All SaO_2 signals presented drops to zero due to poor contact with the finger probe and/or patient movements. Finally, oximetric recordings were automatically scanned to remove zero samples.

III. METHODOLOGY

Our methodology was divided into three stages. Feature extraction was accomplished in the first stage. Oximetric recordings were analyzed using 16 characteristics from four different feature sets: time domain statistics, frequency domain statistics, conventional spectral characteristics and nonlinear measures. In the second stage, we carried out a feature selection process. A forward stepwise LR procedure was applied to obtain the optimum feature set. Finally, LR with leave-one-out cross-validation was used to assess the classification ability in the third stage. We evaluated the diagnostic performance of each single feature, the optimum model and the classic oximetric indexes from our data set.

A. Time domain statistics

The histogram from an overnight SaO_2 profile could show differences between OSA-positive patients (characterized by frequent desaturations) and OSA-negative subjects (showing slight variations). The amplitude (%) of the SaO_2 signal was used to compute the normalized histogram. First to fourth order statistical moments were computed as follows [32]:

$$M1 = E[x] = \mu = \frac{1}{N}\sum_{n=1}^{N} x_n , \quad (1)$$

$$M2 = E\left[(x-\mu)^2\right], \quad (2)$$

$$M3 = \frac{1}{\sigma^3} E\left[(x-\mu)^3\right], \quad (3)$$

$$M4 = \frac{1}{\sigma^4} E\left[(x-\mu)^4\right]. \quad (4)$$

Arithmetic mean (*M1t*), variance (*M2t*), skewness (*M3t*) and kurtosis (*M4t*) in the time domain were derived from each SaO_2 recording to quantify central tendency, amount of dispersion, asymmetry and peakedness, respectively. Each feature was computed dividing every SaO_2 signal in segments of 512 samples. Finally, we averaged over the total number of segments to obtain a single value per subject.

B. Frequency domain statistics

Spectral analysis was carried out to characterize the repetitive nature of apnea events. A power spectrum increase in the apnea interest frequency band (0.014–0.033 Hz) of SaO_2 recordings from OSA-positive patients has been previously reported [18], [19]. In this study, the PSD of each oximetric recording was computed applying the nonparametric Welch's method [33]. Firstly, the method divides the signal into M overlapping segments of length L, applies a smooth time weighting $w[n]$ and computes the modified periodogram of each windowed segment $v_L[n]$ by means of the discrete Fourier transform (DFT) $V[f]$ [33]:

$$\hat{P}[f] = \frac{|V[f]|^2}{f_s LU}, \quad (5)$$

where

$$V[f] = \sum_{n=0}^{N-1} v_L[n] e^{-j\frac{2\pi k}{N}n}, \quad (6)$$

and

$$U = \frac{1}{M}\sum_{n=0}^{M-1} |w(n)|^2 . \quad (7)$$

Finally, all DFTs are averaged to obtain the PSD function. 512-sample Hanning window with 50% overlap and 1024-points DFTs were used. These parameters ensured the performance of the PSD estimate. Next, six statistics not based on conventional spectral measures were computed.

1) First to fourth order moments in the frequency domain. The amplitude (W/Hz) of the PSD function at each single spectral component was used to obtain the normalized histogram in the frequency domain. Changes in the spectral content of SaO_2 signals due to recurrent apnea events could modify the shape of the histograms. Thus, mean, variance, skewness and kurtosis could provide useful information. First to fourth order moments in the frequency domain (*M1f–M4f*) were computed using (1)–(4).

2) Median frequency (MF). MF provides a simple means of summarizing the whole spectral content of the PSD. It is defined as the spectral component which comprises 50% of the total signal power [22]:

$$0.5\sum_{0Hz}^{0.5Hz} PSD(f) = \sum_{0Hz}^{MF} PSD(f) \cdot \quad (8)$$

Lower values of *MF* correspond to signals with spectral power comprised into small frequencies, whereas higher values correspond to signals with significant spectral components at higher frequencies.

3) Spectral entropy (SE). SE is a disorder quantifier related to the flatness of the spectral content. Its definition is based on the Shannon's entropy [23]:

$$SE = -\sum_j p_j \ln(p_j), \quad (9)$$

where p_j is the normalized value of the PSD at each spectral component, with a bin width of one spectral unit [21]. High *SE* implies a flat PSD with a broad spectral content (or higher irregularity in the time domain), whereas low *SE* implies a PSD with all the power condensed into a single frequency band (oscillatory behavior in the time domain).

C. Conventional spectral characteristics

Conventional frequency analysis was also included in our study. The following spectral features were derived from each PSD estimate [18], [19]:

1) Total spectral power (P_T). It is computed as the total area under the PSD function.
2) Peak amplitude (PA) in the apnea frequency band. It is the local maximum of the SaO_2 spectral content in the apnea frequency range, from 0.014 to 0.033 Hz.
3) Relative power (P_R) in the apnea frequency band. It is the ratio of the area enclosed under the PSD function in the apnea frequency band to the total signal power.

D. Nonlinear feature set

1) Sample entropy (SampEn). *SampEn* is a family of statistics defined to quantify the irregularity of time series, with larger values corresponding to more irregular data [21], [30], [34]. $SampEn(m, r, N)$ is defined as the negative logarithm of the conditional probability that two sequences that are similar (within the tolerance width r) for m contiguous points remain similar when the run length increases to m+1 [34]:

$$SampEn(m,r,N) = -\ln\left[\frac{A^m(r)}{B^m(r)}\right]. \quad (10)$$

A^m and B^m are the average number of (m)-length and (m+1)-length segments $X_m(i)$ ($1 \le i \le N\text{-}m\text{+}1$) with $d[X_m(i),X_m(j)] \le r$ ($1 \le j \le N\text{-}m, j \ne i$), respectively, where

$$d[X_m(i),X_m(j)] = \max_{k=0,\ldots,m-1}(|x(i+k)-x(j+k)|). \quad (11)$$

In order to measure irregularity by means of *SampEn*, we used the recommended input parameters m = 1 and r = 0.25 times the SD of the signal under analysis [27].

2) Central tendency measure (CTM). *CTM* provides a variability measure from second order difference plots, assigning larger values to lower variability [25], [28], [29]. *CTM* is computed selecting a circular region of radius ρ around the origin, counting the number of points that fall inside, and dividing by the total number of points [25]:

$$CTM = \frac{1}{N-2}\sum_{i=1}^{N-2}\delta(d_i), \quad (12)$$

where

$$\delta(d_i) = \begin{cases} 1 & \text{if } \left[(x(i+2)-x(i+1))^2 + (x(i+1)-x(i))^2\right]^{1/2} < \rho \\ 0 & \text{otherwise} \end{cases}. \quad (13)$$

In the present study, we applied the recommended radius ρ = 1 to compute *CTM* [29].

3) Lempel – Ziv complexity (LZC). *LZC* is a nonparametric measure of complexity, with larger values corresponding to high complexity data [26], [28], [35]. To compute *LZC*, the original signal is firstly converted into a binary sequence comparing each sample with a predefined threshold T_d. Next, a complexity counter $c(n)$ is increased every time a new subsequence is encountered [35]. Finally, $c(n)$ is normalized:

$$LZC = c(n)/b(n), \quad (14)$$

where

$$b(n) \equiv n/\log_2(n). \quad (15)$$

Two symbols ('0' and '1') were used to obtain binary sequences from the original SaO_2 signals. In this study, the median value was used as threshold T_d [28].

We estimated *SampEn*, *CTM* and *LZC* for all 512-sample segments within each SaO_2 signal. Finally, we averaged these values to obtain a single irregularity, variability and complexity measure per subject.

E. Classic oximetric indexes

The cumulative time spent below a saturation of 90% (CT90) and ODIs over 2% (ODI2), 3% (ODI3) and 4% (ODI4) were computed offline from SaO_2 recordings. The definition of a desaturation event was based on the study by Magalang *et al.* [15]: a decrease in SaO_2 greater than or equal to the set amount (2%, 3% or 4%) from baseline for at least 10 s and at a rate >0.1%/s, returning within 60 s to a 1%-interval of the initial value. Baseline was set as the mean saturation in the previous minute [12]. The mean level in the first 3 min of recording was used to initialize its value.

F. Statistical analysis

Statistical tests with no prior assumptions about the probability distribution of the data were applied. Statistical differences were evaluated by means of the nonparametric Mann-Whitney U test, whereas LR was used to investigate group classification. Additionally, the Dickey-Fuller unit root test was applied to assess stationarity.

Forward stepwise LR was applied to perform feature selection. The procedure selected the strongest variables in the data set in terms of statistical significant differences: iterative binary LR processes were applied to describe the relationship between a dichotomous dependent variable (OSA-negative vs. OSA-positive) and the 16 independent variables included in the study. At each iteration, the stepwise method performs a test for backward elimination followed by a forward selection procedure [36].

A leave-one-out cross-validation process was carried out to ensure the statistical validity of classification results. A LR classifier was applied along 148 iterations, so that all subjects within our population set were used for both training and testing the methodology. At each iteration, a subset composed of 147 subjects was used to compute the logistic model, which was subsequently tested using the remaining subject. A different subject was left out at each iteration. Finally, sensitivity (OSA-positive patients correctly classified), specificity (OSA-negative subjects rightly classified) and accuracy (the total percentage of subjects correctly classified) were computed taking into account the total number of cases from the testing process. Additionally, the area under the receiver operating characteristics curve (AROC) was computed.

IV. Results

A. Single feature assessment

Fig. 1 (a) displays the overnight oximetric recordings from a common OSA-negative subject, showing minor changes in the SaO_2 profile, and a common OSA-positive patient, with deep desaturations due to apnea events. Fig. 1 (b) displays the PSD functions of these recordings, showing a power increase in the apnea interest frequency band corresponding to the OSA-positive patient. Figs. 1 (c) and (d) plot the normalized histogram envelopes of the data for both subjects in the time and frequency domains, respectively. The Dickey-Fuller unit root test showed that 95.2% and 97.9% of all 512-sample segments from OSA-negative and OSA-positive subjects were stationary, with a significance level of 0.05 and correction for serial correlation of the residuals. In addition, Table II summarizes the average (mean ± SD) values of each feature included in the study for both groups. SaO_2 profiles from OSA-negative subjects had significantly higher mean and lower variance than OSA-positive patients. Additionally, the OSA-negative group also showed significantly higher skewness and kurtosis than the OSA-negative one. This agrees with Fig. 1 (c), where the envelope of the histogram from the OSA-negative subject shows higher symmetry and peakedness. In the frequency domain, OSA-positive patients had significantly higher mean and variance than OSA-negative subjects. On the other hand, non-OSA subjects showed higher positive skewness and kurtosis than OSA-positive patients, i.e. lower symmetry and higher peakedness. This agrees with Fig. 1 (d), where almost all the spectral power in the OSA-negative subject is comprised in the very low frequency components. On the other hand, Fig. 1 (b) shows a broader spectral content in the normalized PSD function of the OSA-positive patient due to the power increase in the apnea frequency band. Thus, OSA-positive patients presented significantly higher *MF* and *SE* than OSA-negative subjects. Conventional spectral features also achieved essential information. According to Fig. 1 (b), patients in the OSA-positive group showed significantly higher *PA*, P_T and P_R than non-OSA subjects, due to the repetition of apnea events during the night. Finally, OSA-positive patients had higher average *SampEn*, lower *CTM* and higher *LZC* than non-OSA subjects due to the apnea events, i.e. higher irregularity, variability and complexity. The SaO_2 profiles in Fig. 1 (a) illustrate these results.

Table III summarizes the classification ability of each single feature using LR with leave-one-out cross-validation. On average, classical spectral features reached the highest diagnostic accuracies. 86.0% sensitivity, 77.1% specificity and 83.1% accuracy were reached with *PA*. In the nonlinear feature set, *CTM* equaled the highest accuracy (81.0% sensitivity, 87.5% specificity and 83.1% accuracy), slightly improving the AROC (0.918). *SE* achieved the highest accuracy (87.0% sensitivity, 54.2% specificity, 76.4% accuracy, 0.835 AROC) and *MF* achieved the highest AROC (76.0% sensitivity, 75.0% specificity, 75.7% accuracy, 0.864 AROC) within the frequency domain statistics feature set. Finally, *M2t* reached the highest accuracy and AROC within the time domain statistics feature set (86.0% sensitivity, 70.8% specificity, 81.1% accuracy, 0.891 AROC).

B. Forward Stepwise LR procedure

Four features were automatically selected from the whole data set: two common statistics in the time domain (*M2t* and *M4t*), one classical spectral feature (P_R) and one nonlinear measure (*LZC*). Table IV summarizes the classification statistics at each step in the LR procedure with leave-one-out cross-validation. The diagnostic accuracy increased from 79.7% to 89.7% at the end of the process. Additionally, the

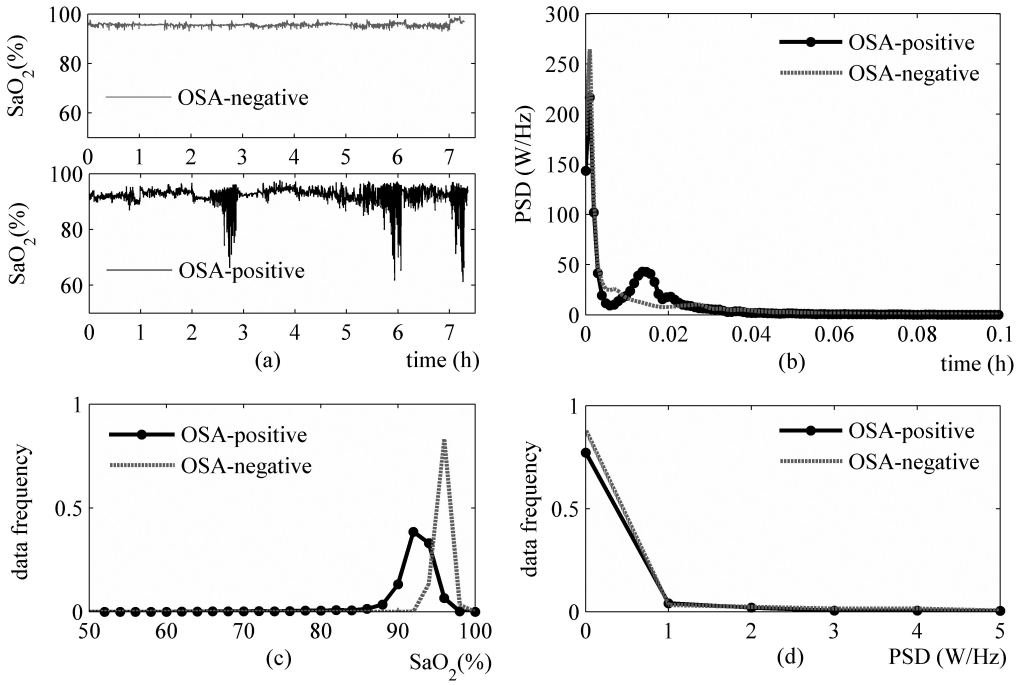

Fig. 1. Overnight SaO_2 profiles for a common OSA-negative subject and a common OSA-positive patient (a) in the time domain and (b) in the frequency domain. Normalized histogram envelopes for both typical recordings (c) in the time domain and (d) in the frequency domain.

TABLE II
AVERAGE VALUE OF EACH FEATURE FROM THE GROUPS UNDER STUDY

	OSA negative	OSA positive
M1t	94.44 ± 2.39	92.67 ± 3.94
M2t	0.70 ± 0.31	2.02 ± 1.79
M3t	0.03 ± 0.47	-0.22 ± 0.31
M4t	4.62 ± 1.12	3.67 ± 0.71
M1f	3.90 ± 6.15	27.74 ± 64.46
M2f	36.47 ± 71.29	177.91 ± 542.27
M3f	13.55 ± 1.15	10.34 ± 2.89
M4f	205.65 ± 27.17	137.32 ± 61.77
MF	0.002 ± 0.002	0.010 ± 0.007
SE	0.45 ± 0.08	0.54 ± 0.06
PA	18.68 ± 19.54	473.68 ± 1107.37
P_T	1.74 ± 2.66	12.92 ± 29.27
P_R	0.15 ± 0.06	0.32 ± 0.13
SampEn	0.31 ± 0.05	0.33 ± 0.06
CTM	0.997 ± 0.004	0.922 ± 0.116
LZC	0.24 ± 0.02	0.26 ± 0.03

Data are presented as mean ± SD.

TABLE III
DIAGNOSTIC ASSESSMENT OF EACH SINGLE FEATURE

	TP	TN	FP	FN	Se	Sp	Ac	AROC
M1t	98	3	45	2	98.0	6.3	68.2	0.712
M2t	86	34	14	14	86.0	70.8	81.1	0.891
M3t	93	13	35	7	93.0	27.1	71.6	0.687
M4t	91	19	29	9	91.0	39.6	74.3	0.777
M1f	100	2	46	0	100	4.2	68.7	0.829
M2f	100	0	48	0	100	0	67.6	0.744
M3f	78	26	22	22	78.0	54.2	70.3	0.828
M4f	78	25	23	22	78.0	52.1	69.9	0.822
MF	76	36	12	24	76.0	75.0	75.7	0.864
SE	87	26	22	13	87.0	54.2	76.4	0.835
PA	86	37	11	14	86.0	77.1	83.1	0.913
P_T	98	9	39	2	98.0	18.8	72.3	0.837
P_R	85	33	15	15	85.0	68.8	79.7	0.891
SampEn	93	2	46	7	93.0	4.2	64.2	0.648
CTM	81	42	6	19	81.0	87.5	83.1	0.918
LZC	91	15	33	9	91.0	31.3	71.6	0.731

TP: True Positives; TN: True Negatives; FP: False Positives; FN: False Negatives; Se: Sensitivity (%); Sp: Specificity (%); Ac: Accuracy (%); AROC: Area under the ROC curve.

AROC increased from 0.891 to 0.967.

Finally, we assessed the diagnostic ability of classic oximetric indexes. LR with leave-one-out cross-validation was applied to test each single parameter. Table V summarizes the classification statistics. ODI2 obtained the best results in terms of diagnostic accuracy and AROC (85.0% sensitivity, 87.5% specificity, 85.8% accuracy and 0.943 AROC).

V. DISCUSSION AND CONCLUSIONS

In the present research, we exhaustively analyzed SaO_2 recordings, in order to improve diagnostic ability of NPO to help in OSA detection. *M2t* and *M4t* time domain statistics, P_R from the classical spectral feature set and *LZC* from the nonlinear set, were automatically selected.

On average, conventional features from spectral analysis (*PA*, P_T and P_R) achieved higher diagnostic accuracy and AROC than other approaches. Frequency-based measures could improve the detection of OSA-positive subjects with small but frequent desaturations. Frequency domain statistics (*M1f* – *M4f*, *MF* and *SE*) achieved lower performance. Differences between OSA-positive and OSA-negative patients decreased because these features take into account all the frequency components within the whole spectrum, whereas *PA* and P_R focused on the apnea frequency band. On the other hand, statistics from the histogram in the time domain outperformed the diagnostic ability of statistical moments in the frequency domain. The variance (*M2t*) and the peakedness (*M4t*) of the SaO_2 amplitude distribution could differentiate OSA patients with few but deep desaturations from non-OSA subjects better than other features based on the number or periodicity of the desaturations. Finally, *CTM* from the nonlinear analysis was better able to differentiate OSA-negative subjects than other parameters. *CTM* is a variability measure based on differences between delayed versions of the time series, which improves the detection of non-OSA subjects with just low basal SaO_2.

TABLE IV
RESULTS FROM THE DIAGNOSTIC ASSESSMENT OF EACH ITERATION INTO THE FORWARD STEPWISE LR PROCESS

	TP	TN	FP	FN	Se	Sp	Ac	AROC
LR (P_R)	85	33	15	15	85.0	68.8	79.7	0.891
LR (P_R, *M4t*)	89	37	11	11	89.0	77.1	85.1	0.935
LR (P_R, *M4t*, *LZC*)	90	39	9	10	90.0	81.3	87.2	0.948
LR (P_R, *M4t*, *LZC*, *M2t*)	92	41	7	8	92.0	85.4	89.7	0.967

TABLE V
DIAGNOSTIC ASSESSMENT OF CONVENTIONAL OXIMETRIC INDEXES

	TP	TN	FP	FN	Se	Sp	Ac	AROC
CT90	100	0	48	0	100	0	67.6	0.794
ODI2	85	42	6	15	85.0	87.5	85.8	0.943
ODI3	86	41	7	14	86.0	85.4	85.8	0.932
ODI4	85	42	6	15	85.0	87.5	85.8	0.922

The optimum model from the LR process summarized the main characteristics of apneic events: frequency and variability. P_R quantifies the repetitive behavior of desaturations due to apnea episodes. On the other hand, *M2t*, *M4t* and *LZC* take into account the variability and complexity of the overnight SaO_2 profile in OSA-positive patients. Our results suggest that a well-balanced model from multivariate analysis could distinguish OSA-negative and OSA-positive subjects showing different overnight SaO_2 profiles better than conventional single approaches.

A sensitivity of 92.0%, specificity of 85.4% and an accuracy of 89.7% were reached. The recurrent apnea events during the night in OSA-positive subjects could be not completely explained by measures from a single approach. The optimum feature set significantly outperformed the diagnostic ability of each single parameter. Features within the model did not achieve the highest accuracies individually. However, they maximized statistical differences between OSA-positive and OSA-negative subjects jointly. Thus, variability, peakedness, frequency and complexity measures from *M2t*, *M4t*, P_R and *LZC*, respectively, could provide complementary information in the context of OSA diagnosis. Furthermore, our methodology significantly improved classification statistics

of classic oximetric indexes commonly used by physicians.

The utility of SaO_2 recordings from NPO in OSA diagnosis has been widely studied during the last years [9]. Unbalanced sensitivity *vs.* specificity pairs (31% vs. 100% and 91% vs. 69%) were obtained by visual inspection of the SaO_2 profile [37], [38]. In the same way, the presence of a peak in the power spectrum of SaO_2 signals achieved 78% sensitivity and 89% specificity [18]. Automated analysis of oximetric recordings improved the diagnostic ability of NPO. A sensitivity of 89.7% and a specificity of 57.8% were reached computing CT90 and the average SaO_2 [39]. The saturation impairment time, which combines time and severity of desaturations, provided additional information to that obtained with CT indexes [40]. Higher diagnostic accuracies were reached using ODIs [12], [14], [41]. Sensitivities ranged from 32% to 98.0% and specificities from 88.0% to 97.0%. These studies presented two important limitations: the threshold used to diagnose OSA varies among the studies (from 5 to 15 e/h) and there was not a consensus in the definition of desaturation [9], [15].

Other researchers quantify the variability of the SaO_2 profile independently of the definition of desaturation. 90.0% sensitivity and 75.0% specificity were reached using the delta index (*Δ index*) [42]. The repetition of apnea episodes has been also studied [18], [19]. Common spectral features based on the peak amplitude and the relative power achieved high sensitivities (94% and 91%) but small specificities (65% and 67%) [18]. In the same way, the negative slope of the PSD in the high frequency band (0.1 – 0.5 Hz) reached 78% sensitivity and 80% specificity [20]. On the other hand, a recent study found that ODIs showed higher ability in predicting OSA severity than conventional spectral features. However, this study focused on moderate (AHI ≥ 15) and severe (AHI ≥ 30) OSA patients [43]. Recent studies by our own group applied nonlinear methods to quantify regularity, variability and complexity of SaO_2 recordings [27]–[29], [44]. Accuracies of 84.1% (82.1% sensitivity and 86.9% specificity), 87.2% (90.1% sensitivity and 82.9% specificity) and 82.9% (86.5% sensitivity and 77.6% specificity) were reached with *ApEn*, *CTM* and *LZC*, respectively. Our results outperformed the diagnostic accuracy reported in previous studies. We would like to emphasize that classic indexes and new measures from NPO were computed using the same data base. Additionally, we developed a common methodology based on LR with leave-one-out cross-validation to properly assess each parameter.

Previous studies applied multivariate analysis to improve OSA diagnosis from NPO recordings. A sensitivity of 88% and a specificity of 70% were reached applying stepwise linear regression [45], whereas 90% sensitivity and 70% specificity were obtained with adaptive regression splines [15], both using classical indexes and the *Δ index*. 82% sensitivity and 84% specificity were obtained applying LR and spectral features [20]. A preliminary study by our own group assessed the usefulness of different classifiers in OSA diagnosis. The highest diagnostic performance (91.1% sensitivity, 82.6% specificity, 87.6% accuracy and 0.925 AROC) was obtained using a reduced set of spectral features from NPO as inputs to a linear discriminant classifier [46]. The classification ability of the classifier decreased when nonlinear features were included in the study. Other researches have assessed multivariate analysis to classify patients with OSA from ECG. A wide set of time and spectral features from RR-interval time series were used to assess linear and quadratic discriminant classifiers. An accuracy of 100% was reported using quadratic discriminant analysis when borderline patients were removed from the study [17]. 74.4% accuracy was reached using discriminant analysis to characterize the apnea severity from time statistics and scale features in a similar study [47]. In our research, we obtained an optimum feature set from a forward stepwise LR procedure. To our knowledge, this is the first study where a wide set of features from four different approaches are combined to obtain an optimum model of SaO_2 dynamics using forward stepwise LR with leave-one-out cross-validation. Our methodology had some advantages over previous studies: no assumptions about the data probability distribution are needed when applying LR and the stepwise process automatically selects the features that best fit the model.

Limitations of the study. We should take into account some drawbacks that limit the generalization of our results. The population under study could be larger and OSA-positive patients were predominant. An important limitation should also be pointed out. Desaturations in the overnight SaO_2 profile could not be exclusively due to apnea events typical of OSA. Patients with different respiratory or sleep-related breathing disorders may exhibit significant desaturations during the night, which could influence our results. The severity of OSA could be overestimated if COPD coexists since individuals with both diseases have more and worse sleep desaturations than they would have with only one condition [48]. On the other hand, patients with COPD alone could increase the number of OSA-false positive cases. Thus, our findings should only be applied to patients without significant pulmonary or cardiac comorbidity. Additionally, patients under study were derived to the Sleep Unit due to prior symptoms of suffering from OSA, which limits the general application of our methodology. Oximetry alone has demonstrated to achieve high sensitivity and specificity in populations showing moderate to high risk of OSA [49]. However, a control group composed of normal subjects without suspicion of sleep-related breathing disorders could provide significant information about the consistence of our methodology. Moreover, further work is required to test the performance of our methodology when oximetric recordings are carried out from ambulatory portable monitoring at patient's home.

Another limitation of the study should be taken into account regarding the oximetry equipment setting, i.e. sampling frequency and averaging time. A different equipment setting could influence our results. We would like to point out that our methodology could be less dependent on changes in SaO_2 resolution than conventional approaches based on the detection and quantification of desaturations, such as ODIs. Nevertheless, the performance of our methodology should be assessed using different oximetry monitors, with different sampling frequencies and time

averaging intervals. Additionally, although our methodology reached high diagnostic accuracy, we should take into account that a definitive diagnosis must be done on the basis of additional information. The American Academy of Sleep Medicine recommends that OSA diagnosis should be performed using portable monitoring together with a comprehensive sleep evaluation [49].

In summary, we found that diagnostic ability of NPO in OSA diagnosis could be enhanced combining features from different approaches. Conventional oximetric indexes are insufficient to completely characterize changes in the SaO_2 profile during the night. Time, frequency and nonlinear analyses provide additional and complementary information that could be used to better characterize SaO_2 dynamics. Additionally, stepwise LR has shown to be a powerful tool to obtain an optimum model from oximetric recordings. The automatically selected optimum feature set significantly improved the diagnostic accuracy of conventional indexes commonly used by physicians. Thus, this new model could enhance the performance of NPO to help in the diagnostic assessment of OSA syndrome.

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