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Regularity analysis of nocturnal oximetry recordings to assist in the diagnosis of sleep apnoea syndrome

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ABSTRACT

The relationship between sleep apnoea–hypopnoea syndrome (SAHS) severity and the regularity of nocturnal oxygen saturation (SaO_2) recordings was analysed. Three different methods were proposed to quantify regularity: approximate entropy (AEn), sample entropy (SEn) and kernel entropy (KEn). A total of 240 subjects suspected of suffering from SAHS took part in the study. They were randomly divided into a training set (96 subjects) and a test set (144 subjects) for the adjustment and assessment of the proposed methods, respectively. According to the measurements provided by AEn, SEn and KEn, higher irregularity of oximetry signals is associated with SAHS-positive patients. Receiver operating characteristic (ROC) and Pearson correlation analyses showed that KEn was the most reliable predictor of SAHS. It provided an area under the ROC curve of 0.91 in two-class classification of subjects as SAHS-negative or SAHS-positive. Moreover, KEn measurements from oximetry data exhibited a linear dependence on the apnoea–hypopnoea index, as shown by a correlation coefficient of 0.87. Therefore, these measurements could be used for the development of simplified diagnostic techniques in order to reduce the demand for polysomnographies. Furthermore, KEn represents a convincing alternative to AEn and SEn for the diagnostic analysis of noisy biomedical signals.

1. Introduction

Regularity is defined as the consistency of subpattern recurrence in a time series [1]. It has shown to be a useful property of biomedical signals to discriminate those either generated by pathological systems or by the same system under different conditions [2]. Regular signals are characterised by a predictable behaviour, with recognizable patterns that repeat. Regularity is associated with the amount of information in a series, which, in a probabilistic sense, is a measure of the unexpectedness in the data [3]. Shannon [4] proposed the concept of entropy to evaluate the information (or uncertainty) in a message, which is modelled as a finite collection of random variables. In the context of infinite sequences or series, the entropy rate has been employed for the quantification of the amount of information [2]. Several metrics have been proposed to estimate the entropy rate of a series, with approximate entropy (AEn) [5] and sample entropy (SEn) [6] being the most common ones. A generalised entropy measure is given by the family of Renyi entropies (R_q), where q denotes the entropy order [7]. Lake [8] analysed the incorporation of the Renyi entropy into the entropy rate framework, showing that AEn and SEn approximate the differential Renyi entropy rate for $q = 1$ and $q = 2$, respectively.

AEn and SEn are based on the computation of probabilities by counting matches between signal subsequences of length m and $m + 1$. A match is found when the distance between two subsequences is lower or equal than a tolerance parameter r [6]. A different procedure to obtain the Renyi entropy rate of a series consists of substituting probability terms in AEn and SEn algorithms by the corresponding probability density functions [3,8]. Several advantages are found in this approach. It suppresses the need of predefined rules for the choice of the tolerance parameter r, which can be freely varied in order to obtain confident estimates of the density functions. In addition, entropy estimates made with different values of r measure the same inherent quantity and can be compared directly [8,9].

This approach requires the approximation of the (unknown) probability density function of the data, for which a finite set of samples extracted from the underlying series is initially available. Nonparametric kernel density estimation based on the Parzen window

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method has been suggested for this purpose [3,8]. Specifically, Gaussian kernels are of special interest since they result in a smooth and continuous profile of the approximated density [10]. Additionally, in the case of the quadratic entropy (R_2), i.e., the Renyi entropy of order $q = 2$, Gaussian kernels lead to the exact evaluation of the integral found in its definition [3]. In a preceding study, a kernel-based estimation of R_2 was adopted to assess the quadratic entropy rate of a time series [11]. The resulting measure, termed as kernel entropy (KEn), was proposed as an indicator of the irregularity of the series [11,12].

Entropy analysis has yield successful results in several applications involving time series processing such as earthquake forecasting [13], exchange rating [14] or fault detection [15]. Furthermore, entropy measures of biomedical signals have been widely used to assess physiological differences between subjects [16,17]. The present study focuses on this scenario. We explored the utility of entropy rate measurements of nocturnal oxygen saturation signals (SaO_2) in the context of sleep apnoea–hypopnoea syndrome (SAHS) diagnosis. Nowadays, a definitive diagnosis about SAHS is obtained from in-hospital evaluation of the patient's sleep through nocturnal polysomnography (PSG). This test enables the assessment of SAHS severity by means of the apnoea–hypopnoea index (AHI), which quantifies the number of apnoea and hypopnoea events per hour of sleep. To obtain the AHI of a patient, the sleep specialist must evaluate a large amount of clinical and physiological data that, in addition to SaO_2 series, include other signals such as the electrocardiogram (ECG), the electroencephalogram (EEG) or the respiratory airflow (AF) [18]. Therefore, PSG is a highly complex and time-consuming procedure.

Reliable indicators of SAHS severity automatically extracted from these data would enable an objective and simplified interpretation. Nocturnal oximetry recordings are of special interest as they reflect respiratory dynamics during sleep. Apnoeas and hypopnoeas are usually accompanied by hypoxaemia due to airflow reduction, which is reflected by a marked drop in the saturation value [19]. The diagnostic utility of oximetry signals has been previously evaluated through different methods. A straightforward approach is the use of oximetry parameters based on the computation of desaturation events or the time spent below a certain level of saturation [20,21]. In addition, complex signal processing and pattern recognition techniques like neural networks or genetic algorithms have been employed for the extraction of useful descriptors from SaO_2 data [22–24]. According to the reported results, a higher diagnostic accuracy can be obtained through the combination of different features including statistical, spectral and non-linear ones. Correct diagnostic rates close to 90% have been reported for screening algorithms based on this approach [22,25,26].

Among other features, SaO_2 irregularity measured by the entropy rate has been employed as a descriptor of the influence of SAHS severity on its dynamic behaviour [25,27]. The non-deterministic occurrence of apnoeic episodes tends to increase the uncertainty in the SaO_2 signal and, equivalently, its amount of information. As a result, signals from subjects suffering from SAHS are expected to have a higher entropy rate than those from control subjects. Previously, AEn has been employed to measure SaO_2 irregularity [27,28]. These preceding studies showed the relationship between higher irregularity of oximetry signals and SAHS severity, estimating that a correct diagnosis based on regularity analysis can be obtained for approximately 85% of the patients. However, AEn has proven to be a biased entropy estimator [6] and, thus, further analysis is required to extract robust conclusions on the relationship between SAHS severity and SaO_2 irregularity.

To this end, the present study proposes a comparative analysis between different entropy metrics. In addition to AEn, we suggest entropy analysis of SaO_2 series based on SEn and KEn, which provide two different approaches to estimate the quadratic entropy rate of a signal. The present study aims to determine to which extent the irregularity of SaO_2 data is related to SAHS severity, as well as the most accurate method to quantify this relationship.

We hypothesise that a more confident assessment of the entropy of SaO_2 recordings can be obtained by means of kernel-based approximations to probability density functions as implemented by KEn. This method represents a novel approach for entropy estimation with respect to conventional procedures like AEn and SEn. The framework implemented by KEn suitably adapts to oximetry analysis since SaO_2 samples can be interpreted as observations of a continuous variable. Thus, probability density functions may provide a more reliable description of their statistical behaviour. This hypothesis is evaluated through an exhaustive regularity analysis of SaO_2 data using AEn, SEn and KEn.

2. Materials and methods

2.1. Subjects and signals

A total of 240 subjects suspected of suffering from SAHS took part in the study. They underwent PSG in the Sleep Unit of Hospital Universitario Pío del Río Hortega, Valladolid, Spain. The Review Board on Human Studies approved the protocol and each subject gave their consent to participate in the study. To draw useful conclusions on the effect of SAHS on SaO_2 dynamics, subjects affected by any other relevant respiratory disorder were excluded. The selected patients were continuously monitored using a polysomnograph (Alice 5, Respironics, Philips Healthcare, The Netherlands). A medical expert analysed the PSG recordings according to the rules proposed by Rechtschaffen and Kales [29]. Once apnoeas and hypopnoeas were identified, the AHI was obtained as the total number of events (i.e., the sum of apnoeas and hypopnoeas) divided by the total sleep time. The resulting value is expressed as the number of events per hour of sleep [30]. A threshold given by AHI $= 10$ h^{-1} was used to determine a positive diagnosis of SAHS [31].

A Nonin PureSAT pulse oximeter (Nonin Medical Inc., USA) was used to record oximetry signals at a sampling frequency of 1 Hz. These signals were subsequently saved to separate files to be processed offline. A preprocessing stage was initially applied to remove artefacts like marked drops or zero samples due to a bad contact of the probe during sleep. The criteria suggested by Magalang et al. [32] were taken into account to perform signal preprocessing. According to these criteria, all changes greater than 4%/s between consecutive sampling intervals and any sample lower than 20% were removed.

Fig. 1 shows two oximetry recordings from our dataset once artefacts were removed. The signals correspond to a normal subject (AHI $= 0.5$ h^{-1}) and a subject with severe SAHS (AHI $= 32.1$ h^{-1}), respectively. In addition, a detailed view (12 min) of both recordings is provided (Fig. 1c,d). The differences between these signals reflect the influence of repeated apnoeas and hypopnoeas on SaO_2 dynamics. The signal from the normal subject is characterised by a near-constant saturation value along the night, with small fluctuations around the baseline level. This behaviour is confirmed when observed in detail, as it exhibits some variability without marked desaturation events. In contrast, the profile of the signal from the subject with severe SAHS reflects a significant instability as a consequence of repeated desaturations accompanying apnoeas and hypopnoeas. As is evident from the signals shown in Fig. 1(c, d) these desaturation events are more frequent when compared with the oximetry recording from the normal subject. Additionally, they are more pronounced and longer. Therefore, a distinct value of the entropy rate can be expected for these signals since they reflect different dynamics.

The hold-out method was used to prevent bias in the estimation of the performance of the three entropy metrics [10]. Therefore, the initial population was randomly divided into a training set with 96 subjects (40%) and a test set with 144 subjects (60%). The former was used to adjust user-dependent parameters in AEn, SEn and KEn