

Applying Cross Approximate Entropy to Blood Oxygen Saturation and Heart Rate from Nocturnal Oximetry in Screening for Obstructive Sleep Apnea

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INTRODUCTION

Obstructive sleep apnea (OSA) syndrome is a major sleep-related breathing disorder, affecting 1% to 5% of adult men in western countries (Young, Peppard, & Gottlieb, 2002). This disease is now the most common respiratory referral to many sleep units (Douglas 2002). OSA syndrome is associated with excessive daytime sleepiness, neurocognitive deficits, and psychological problems. A significant number of patients with suspicion of OSA present mild to severe symptoms of depression (Schwartz, Kohler, & Karatinos, 2005). OSA syndrome is also a risk factor for cardiovascular disease morbidity and mortality (Leung and Bradley 2001). People with OSA have higher risk of sudden death due to cardiac causes during sleep than the general population (Gami, Howard, Olson, & Somers, 2005). Furthermore, subjects with OSA present an increased risk of being involved in traffic and work accidents (Barbé, Pericas, Muñoz, Findley, Anto, & Agustí, 1998).

The recommended diagnostic test for OSA is overnight polysomnography (PSG) (Polysomnography Task Force, 1997), which records neurophysiological and cardiorespiratory signals to analyze sleep and breath-

ing. However, its relative high cost and complexity, along with the large number of people suspected of having this disease, limit its capacity as a diagnostic test for OSA (Whitelaw, Brant, & Flemons, 2005). Due to its simplicity and low cost, *portable monitoring* has been proposed as an alternative method to PSG in the diagnostic assessment of patients with suspected sleep apnea (Flemons & Littner, 2003).

Nocturnal oximetry provides different quantitative indexes commonly used by physicians in screening for OSA. Oxygen desaturation indexes (ODIs), which measure the number of dips in the oxygen saturation signal below a certain threshold, and the cumulative time (CT) spent below a certain saturation level, are the most widely used (Chaudhary, Dasti, Park, Brown, Davis, & Akhtar, 1998; Netzer, Eliasson, Netzer, & Kristo, 2001). However, their diagnostic sensitivity and specificity vary in a wide range between different studies and there is not a consensus on their definition (Netzer et al., 2001). Although oximeters usually provide both blood oxygen saturation (SaO_2) and heart rate (HR), classical indexes like ODIs or CTs are defined exclusively for SaO_2 . Few studies have assessed the diagnostic accuracy of HR from nocturnal oximetry to diagnose OSA (Zamarrón, Gude, Barcala, Rodríguez,

& Romero, 2003; Zamarrón, Pichel, & Romero, 2005; Zamarrón, Romero, Gude, Amaro, & Rodríguez, 2001). The study developed by Zamarrón et al. (2003) showed that frequency characteristics from HR signals improved results obtained processing SaO₂ individually. In a later research by Zamarrón et al. (2005), both signals were processed together to quantify the relationship between oscillations in SaO₂ and HR by means of the frequency coherence function. In the present study, we estimate the *asynchrony* between SaO₂ and HR from nocturnal oximetry by means of a nonlinear measure called *cross approximate entropy (cross-ApEn)*. Previous studies have demonstrated the usefulness of nonlinear analysis in the diagnosis of OSA syndrome (Álvarez, Hornero, Abásolo, del Campo, & Zamarrón, 2006; Hornero, Álvarez, Abásolo, del Campo, & Zamarrón, 2007).

BACKGROUND

Similarities between two signals or variables have been traditionally quantified by means of linear methods, like the cross-correlation function or spectral estimates based on cross-spectrum, especially *coherency*. The magnitude squared coherence is a normalized cross-spectral density function that gives a measure of the degree of linear correlation between each of the individual frequency components of two signals (Hampson & Mallen, 2006). It has been widely applied to quantify functional interactions between different brain areas (Nunez et al., 1997). However, these classical estimates are often inadequate to satisfactorily identify visually apparent instances of significant association or correspondence between paired series (Liu, Pincus, Keenan, Roelfsema, & Veldhuis, 2005). Statistical estimation methods are nontrivial and their interpretation could be problematic. Moreover, standard spectral estimators can be inconsistent and biased, especially in the presence of outliers and nonstationarities (Pincus, 2000). Particularly, coherency estimates are not suitable to characterize nonstationary signals and only capture linear relations between time series (Porta, Baselli, Lombardi, Montano, Malliani, & Cerutti, 1999; Stam & van Dijk, 2002).

A recently developed measure of asynchrony between time series, the *cross-ApEn*, has demonstrated to be complementary and often superior to both spectral and correlation based methods (Pincus, 2000). *Cross-ApEn* provides substantially more general or robust

measures of feature persistence than both correlation and spectral based methods (Pincus, Mulligan, Iranmanesh, Gheorghiu, Godschalk, & Veldhuis, 1996). Cross-ApEn is a family of statistics proposed by Steven M. Pincus, suggesting its application to physiological signals like HR and respiratory rate (Pincus & Singer, 1996). It has been mainly applied to study hormone time series dynamics, like luteinizing and follicle-stimulating hormones (Veldhuis, Iranmanesh, Mulligan, & Pincus, 1999), luteinizing hormone and testosterone (Veldhuis, Pincus, García-Rudaz, Ropelato, Escobar, & Barontini, 2001), or adrenocorticotrophic hormone and cortisol (Liu et al., 2005). Other entropy-based measures of asynchrony have been also applied to cardiovascular variability signals, pointing out their advantages over the linear approach (Porta et al., 1999; Porta et al., 2000).

This study was aimed to assess whether a measure of asynchrony between SaO₂ and HR from nocturnal oximetry using *cross-ApEn* could help in the diagnosis of OSA syndrome.

CROSS APPROXIMATE ENTROPY ANALYSIS TO HELP IN THE OSA DIAGNOSIS

Polysomnography and Oximetry Studies

A total of 187 patients with suspicion of OSA syndrome were studied. Sleep studies were carried out 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. A nocturnal oximetry study (pulse oximeter Criticare 504, CSI, Waukesha, WI, USA) was performed simultaneously with a conventional PSG (Polygraph Ultrasom Network, Nicolet, Madison, WI, USA). If a subject had less than 3 hours of total sleep, the sleep study was repeated.

The PSG register was analyzed according to Rechtschaffen and Kales rules (Rechtschaffen & Kales, 1968). An *apnea event* was defined as a cessation of airflow for more than 10 seconds, whereas hypopnea was defined as the reduction of respiratory flow for at least 10 seconds accompanied by a 4% or more decrease in the saturation of hemoglobin. An average apnea-hypopnea index (AHI) derived from the PSG study was

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