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Editors

Advances in the Diagnosis and Treatment of Sleep Apnea

Filling the Gap Between Physicians and Engineers

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Preface

Sleep apnea is a sleep disorder with a very high prevalence and many health consequences. As such it is a major health burden (Benjafield et al., 2019). Sleep apnea has been systematically explored only a little more than 40 years now (Guilleminault & Dement, 1978). Major impacts of sleep apnea are sleepiness and associated risks for accidents (Bonsignore et al., 2021). Major health impacts are cardiovascular risk and pathophysiological traits, even if this is currently much debated when focusing on the apnea-hypopnea index as the measure for sleep apnea severity (Arnaud et al., 2020). Sleep apnea is a disorder which is a chronic condition and can be treated successfully.

The disorders of sleep-disordered breathing have largely supported the growth of sleep medicine in general from a small specialty field to a major spectrum of disorders in the arena of medical specialties. This activity helped to convert the niche field of sleep research into sleep medicine, a clinical discipline with its own departments, its own center certification, physician certification, dedicated conferences, journals, and research activities. The recognition and importance have grown so much that the new International Classification of Disorders by WHO in its 11th version, being launched in 2022, has added a new section on sleep and wake disorders with its own range of codes. This worldwide recognition will enable the growth of medical education on sleep physiology, sleep pathology, and specific sleep disorders.

The diagnostic field for sleep disorders, and for sleep apnea specifically, is strongly linked to the development of new and recent methods, which allow long-term recording and analysis of physiological functions during sleep. Sleep and sleep apnea are not just identified by taking a single blood sample or by a single measurement by a physician at a visit, but sleep recording requires the continuous recording of biosignals. This is comparable to monitoring of vital functions during anesthesia or intensive care. Because of this methodological challenge, biomedical engineering as well as new sensor and analysis technologies are closely linked to the development of sleep apnea diagnosis. New technologies helped to a large extent develop new diagnostic and treatment modalities for sleep-disordered breathing. Sleep apnea diagnostic research is now linked to the development of new wearables, nearables, and smartphone apps, and profits much from the ubiquitous development of photoplethysmography recording everywhere.

Artificial intelligence is playing a very important role in analyzing sleep recordings and, particularly, in automatizing several of the stages of sleep apnea diagnosis. Since the generalization of computerized analysis in the 1990s, automated processing of cardiorespiratory and neuromuscular signals from polysomnographic studies provided a number of indices able to assist sleep experts in the characterization of the disease (Shokoueinejad et al., 2017). Parameterization of the influence of apneic events on biological system dynamics has relied on widely known techniques from the engineering field, such as spectral and nonlinear analysis. Currently, there is a demand for novel alternative metrics able to overcome the limitations of the standard apnea-hypopnea index concerning its low association with patient symptoms and outcomes (Malhotra et al., 2021). In this regard, signal processing and pattern recognition are going to play a key role. In addition, machine learning has also shown its usefulness in the last decades (Uddin et al., 2018) and, like many other areas in our society, sleep apnea diagnosis is rapidly entering the deep learning era (Mostafa et al., 2019) and big data. These new analytical techniques, along with the advances in health device development, are the main hope for reaching a reliable diagnostic paradigm shift. One that finally could cope with the disease prevalence, personalized interventions, and runaway spending.

Beyond the widespread application of machine learning methods to automate polysomnography scoring and to provide sleep experts with tools for automated diagnosis, artificial intelligence has also the potential to significantly improve the management of sleep apnea treatment. Recent advances in the framework of big data together with remote monitoring capability of novel treatment devices are able to promote conventional sleep medicine towards a real personalized medicine. Identification of refined clinical phenotypes of patients will allow the development of precision interventions, enabling the quick identification of the treatment option that best fits the particular characteristics of a patient (Watson & Fernández., 2021). Similarly, machine learning is able to accurately model patient's adherence from usage data (pressure setting, residual respiratory events, mask leaks) derived from portable treatment devices, improving the efficacy of available therapies (Goldstein et al., 2020). Thus, artificial intelligence is going to significantly change the management of sleep apnea treatment in the short term.

This volume gives a basis of current knowledge on sleep research, sleep medicine, and sleep apnea, with a strong focus on new challenges and new research directions in the diagnosis of sleep apnea and its treatment. The volume contains three sections: the first one is on physiology and pathophysiology, the second one is on diagnostic advances, and the third one is on treatment advances. Each chapter author was asked to not only describe the state of the art but also develop visions for future research as seen from their special angle and viewpoint.

As editors, we think that the volume can serve as an introduction to the field of sleep-disordered breathing, can serve as a basis for educating in sleep-disordered breathing, and can immediately stimulate and trigger new research in physiology, clinical trials, and biomedical engineering for sensors and analysis methodologies.

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Oximetry Indices in the Management of Sleep Apnea: From Overnight Minimum Saturation to the Novel Hypoxemia Measures

Daniel Álvarez, Gonzalo C. Gutiérrez-Tobal, Fernando Vaquerizo-Villar, Fernando Moreno, Félix del Campo, and Roberto Hornero

Abstract

Obstructive sleep apnea (OSA) is a multidimensional disease often underdiagnosed due to the complexity and unavailability of its standard diagnostic method: the polysomnography. Among the alternative abbreviated tests searching for a compromise between simplicity and accurateness, oximetry is probably the most popular. The blood oxygen saturation (SpO_2) signal is characterized by a near-constant profile in healthy subjects breathing normally, while marked drops (desaturations) are linked to respiratory events. Parameterization of the desaturations has led to a great number of indices of severity assessment commonly used to assist in OSA diagnosis. In this chapter, the main methodologies used to characterize the overnight oximetry profile are reviewed, from visual inspection and simple statistics to complex measures involving signal processing and pattern recognition techniques. We focus on the individual performance of each approach, but also on the complementarity among the great amount of indices existing in the state of the art, looking for the most relevant oximetric feature subset. Finally, a quick overview of SpO_2-based deep learning applications for OSA management is carried out, where the raw oximetry signal is analyzed without previous parameterization. Our research allows us to conclude that all the methodologies (conventional, time, frequency, nonlinear, and hypoxemia-based) demonstrate high ability to provide relevant oximetric indices, but only a reduced set provide non-redundant complementary information leading to a significant performance increase. Finally, although oximetry is a robust

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tool, greater standardization and prospective validation of the measures derived from complex signal processing techniques are still needed to homogenize interpretation and increase generalizability.

Keywords

Apnea · Blood oxygen saturation · Deep learning · Desaturation · Hypopnea · Hypoxemia · Hypoxic burden · Nonlinear dynamics · Obstructive sleep apnea · Oximetry, oxygen desaturation index · Resaturation · Signal processing · Spectral analysis

13.1 Introduction

The blood oxygen saturation (SpO_2) signal from nocturnal oximetry is one of the most valuable tools in the framework of abbreviated diagnosis of obstructive sleep apnea (OSA). Overnight SpO_2 has shown to gather the relevant changes in the respiratory pattern linked to the presence and severity of OSA while being non-intrusive for patients, portable, and highly available (Del Campo et al., 2018; Terrill, 2020). Parameterization of the overnight oximetry profile focused the effort of many researchers, looking for indices able to characterize the number, duration, and severity of desaturations (Levy et al., 2021). The oxygen desaturation index (ODI) and the cumulative time (CT) below a certain saturation level have been traditionally used due to their simple computation and interpretation (Terrill, 2020). Indeed, many commercial oximeters provide the values of these indices in their summary reports, besides the mean and the minimum saturation values throughout the night (Otero et al., 2012).

Despite its widely known usefulness (Tsai et al., 2013; Dawson et al., 2015; Sharma et al., 2017), traditional measures just based on the number of events or the cumulative duration of the desaturations seem to be insufficient to completely characterize the severity of the disease, particularly in complex patients. In order to overcome this limitation, new measures have been proposed in the last years, aimed at quantifying the amount of hypoxemia involving the depth and duration of the events jointly (Kulkas et al., 2013a). Simultaneously, advanced signal processing techniques have provided clinicians with a number of automated oximetry indices during the past two decades, looking for a better characterization of oximetry dynamics in OSA patients (Zamarrón et al., 1999, 2003; Álvarez et al., 2006, 2010, 2012, 2013; Hornero et al., 2017; Terrill, 2020). Besides avoiding the problem of lack of standardization (as they are computed from well-known mathematical algorithms), these indices have demonstrated significant effectiveness in OSA diagnosis, though are sometimes difficult to interpret in terms of the physiopathology of the disease. Similarly, machine learning has been also applied to build oximetry-based models for decision support in the framework of OSA (Marcos et al., 2009; Álvarez et al., 2013; Uddin et al., 2018; Gutiérrez-Tobal et al., 2019). Additionally, the joint analysis of oximetric features by means of pattern recognition and artificial intelligence has allowed the detection of complementary (non-redundant) indices able to improve the diagnostic capability of oximetry (Álvarez et al., 2012, 2013). Concerning the usefulness of artificial intelligence, the raising of deep learning approaches has recently opened a new way to exhaustively analyze biomedical signals. Particularly, deep neural networks have been found appropriate tools to automatically learn discriminant features from the raw oximetry signal (Vaquerizo-Villar et al., 2021), potentially allowing to provide new oximetric indices if these new models (highly complex) are thoroughly interpreted.

Performance of oximetry-based methods for OSA diagnosis shows significant variability among studies (Uddin et al., 2018; Del Campo et al., 2018). In order to minimize this variability, it would be interesting to clarify some major points: search for the top-performance index; quantify the actual performance increase linked to the use of complex mathematical algorithms compared to the conventional ones (i.e., the complexity-effectiveness balance); or investigate the degree of complementarity among available indices, owing that they are all obtained from the same data source. The main goal of this chapter is to review and analyze the current knowledge concerning the diagnostic information derived from automatic processing of nocturnal oximetry recordings in the context of OSA management: from the conventional desaturation indices to the popular new measures of hypoxemia and the novel deep learning approaches. Accordingly, both individual (univariate) and joint (multivariate) performance of the most common characteristics found in the literature are assessed, which are categorized in the following groups: conventional indices, frequency-domain features, nonlinear measures, morphology-based parameters, and deep learning architectures. Furthermore, when possible, the performance increase concerning the inclusion of a particular set of features (statistical, spectral, nonlinear) is analyzed, in order to gain insight into the complementarity of the available oximetry indices.

13.2 Approaches for Parameterizing Changes in the Dynamics of the Oximetry Signal

A plethora of oximetric features derived from many different manual and automatic methodologies can be found in the literature. In order to facilitate its analysis throughout this chapter, oximetry measures are grouped in the following categories: (i) conventional measures (visual inspection, simple statistics, and the oxygen desaturation index); (ii) frequency-domain features (power spectral density, high-order spectra, wavelet); (iii) nonlinear measures (entropy, complexity, multiscale analysis); (iv) morphology-based parameters (hypoxic burden measures, characteristics of the desaturation curve); and (v) application of deep learning to the raw oximetry signal.

13.2.1 Conventional Approaches to Characterize the Overnight Oximetry Profile: Visual Inspection, Common Statistics, and the Oxygen Desaturation Index

Table 13.1 summarizes the main traditional methodologies applied for easy assessment and interpretation of the nocturnal oximetry profile. Visual inspection of the overnight SpO_2 tracing was predominantly used in the 1990s, in order to identify consecutive drops in the saturation value leading to the common "saw-tooth" pattern linked to the presence of OSA. The specificity of manual analysis is particularly high in severe OSA subjects. Subjectivity and complexity when analyzing long nocturnal profiles are major limitations even for trained sleep experts. Nevertheless, examination of overnight oximetry tracings is still used to perform preliminary OSA screening in especial patient groups, such as children (Brouillette et al., 2000; Velasco-Suarez et al., 2013; Tsai et al., 2013; Van Eyck et al., 2015) and those with concomitant respiratory comorbidities, such as chronic obstructive pulmonary disease (COPD) (Scott et al., 2014). In these studies, sensitivity ranges from 40.6% to 91.6%, while specificity varies between 40.6% and 98.9%.

Simple statistics derived from the data histogram of the nocturnal oximetry signal are also commonly used to characterize averages and trends potentially indicative of pathological states. Overall mean, variance, skewness (a measure of histogram asymmetry), and kurtosis (a measure of data concentration) have been proposed as an easy to obtain measures able to further complement more advanced automated features in numerous studies (Marcos et al., 2010a; Marcos et al., 2012; Álvarez et al., 2010, 2012, 2013, 2020; Gutiérrez-Tobal et al., 2019, 2021a). It is remarkable that at least one of these indexes is systematically included in the final optimum feature subset when a variable selection procedure is implemented,

Table 13.1 Visual inspection approaches and conventional oximetric parameters commonly used to characterize oximetry in the context of OSA diagnosis

Approach	Indices
Visual inspection Brouillette et al. (2000), Nixon et al. (2004), Velasco-Suarez et al. (2013), Tsai et al. (2013), Van Eyck et al. (2015), Scott et al. (2014), Villa et al. (2015)	• Recurrent drops in the SpO_2 profile along the night • Saw-tooth pattern • Clusters of desaturations (mainly in pediatric OSA)
SpO_2 data histogram and simple statistics Lévy et al. (1996), Olson et al. (1999), Magalang et al. (2003), Marcos et al. (2010a, 2012), Álvarez et al. (2010, 2012, 2013, 2017, 2018, 2020), Garde et al. (2014), Crespo et al. (2018), Vaquerizo-Villar et al. (2018c), Gutiérrez-Tobal et al. (2019, 2021a)	• Mean (central tendency), variance (dispersion), skewness (asymmetry), kurtosis (peakedness) • Median (central tendency), quantiles, and interquartile range (dispersion) are less used • Delta index (variability measure)
Intermittent hypoxemia Gyulay et al. (1993), Magalang et al. (2003), Rofail et al. (2010), Chung et al. (2012), Schlotthauer et al. (2014), Dawson et al. (2015), Kirk et al. (2003), Chang et al. (2013), Malbois et al. (2010), Ward et al. (2012), Aaronson et al. (2012), Mazière et al. (2014), Sharma et al. (2017)	• Oxygen desaturation index (ODI) of 2% (children) and 3% or 4% (adults)
Persistent hypoxemia Chaudhary et al. (1998), Golpe et al. (1999), Magalang et al. (2003)	• Overnight minimum saturation • Percentage of cumulative time (CT) spent with a saturation below a threshold: in the range 80–90% in adults and 95% in children

which highlights the importance and complementarity of the information provided by these simple measures. In the pediatric framework, the same behavior has been reported (Álvarez et al., 2017, 2018; Crespo et al., 2018; Vaquerizo-Villar et al., 2018c), showing significant complementarity among these common statistical moments and other techniques, such as spectral, wavelet, and nonlinear measures.

In addition to conventional standard deviation and variance, the delta index was also proposed to estimate the variability of the overnight SpO_2 recording (Lévy et al., 1996). It quantifies variation as the sum of the absolute differences between the saturation values corresponding to the upper and lower limits of each SpO_2 segment (commonly 12 s length with no overlap), normalized by the total number of intervals. Large imbalance in the sensitivity-specificity pair was shown, with high sensitivities ranging 88–98% and notably lower specificities ranging 40–59% (Lévy et al., 1996; Olson et al., 1999; Magalang et al., 2003).

Parameterization of the desaturations by quantifying their number, duration, and depth, either manually or automated, has been traditionally used to characterize oximetry patterns in pathological patients. The number of desaturations from baseline greater than a threshold (usually 3% or 4%) per hour of sleep, i.e., the widely known oxygen desaturation index (ODI) (Gyulay et al., 1993; Magalang et al., 2003), and the overall minimum saturation value and the cumulative time (CT) with a saturation below a cutoff value (usually 90% for adults and 95% for children) relative to the total recording time (Chaudhary et al., 1998; Golpe et al., 1999) have been extensively used and commonly embedded in commercial pulse oximeters. Overall, the ODI has been found to remarkably outperform CT (Magalang et al., 2003). Individually, the ODI has demonstrated to be a high-performance oximetric feature for OSA detection, both in the adult (Rofail et al., 2010; Chung et al., 2012; Schlotthauer et al., 2014; Dawson et al., 2015) and the pediatric context (Kirk et al., 2003; Chang et al., 2013) and also even in the presence of comorbidities (Malbois et al., 2010; Ward et al., 2012; Aaronson et al., 2012; Mazière et al., 2014; Sharma et al., 2017). Reported sensitivities and specificities ranged 70.0–96.3% and 67.3–97.2% for adults, 59.26–70.59% and 60.0–86.0% for children, and 33.3–100% and 32.0–100% in the presence of comorbidities.

In addition, the ODI raised as an essential index in studies using multivariate approaches, being systematically selected to be part of the final optimum models, for both adult (Álvarez et al., 2020; Gutiérrez-Tobal et al., 2019, 2021a) and pediatric (Hornero et al., 2017; Crespo et al., 2017, 2018; Álvarez et al., 2017, 2018; Vaquerizo-Villar et al., 2018a, b, c) OSA automated detection. Similarly, the ODI has been combined with features from other biomedical signals in the context of pediatric sleep apnea diagnosis, showing significant correlation with novel spectral cardiac indices (Martín-Montero et al. 2021a, b) and remarkable complementarity with frequency/scale (power spectrum, bispectrum, and wavelet) and nonlinear (recurrence plots) characteristics from airflow recordings (Gutiérrez-Tobal et al., 2015; Barroso-García et al., 2020, 2021a, b; Jiménez-García et al., 2020). In the latter case, it is important to note that the ODI was selected 100% of times within the optimum feature subset. Interestingly, the studies by Barroso-García et al. (2020, 2021a, b) and Jiménez-García et al. (2020) design and assess their models with and without including the ODI, allowing to quantitatively measure the complementarity of this index in terms of the performance increase. In this regard, Jiménez-García et al. (2020) reported minor accuracy increments (from +0.77% to +1.28%) for the most restrictive cutoff for positive OSA (1 event/h) when the ODI is included in the analysis, while the increase was notably higher for larger cutoffs, particularly when the ODI is combined with airflow-derived measures (+19.23% for 5 events/h and + 11.29% for 10 events/h). Similarly, Barroso-García et al. (2020, 2021a, b) also reported higher performance increase when using cutoffs for detecting moderate-to-severe cases, achieving increments in the accuracy value ranging from +10.4% to +25.0%.

13.2.1.1 An Especial Oximetric Index in Childhood OSA: Clusters of Desaturations

This approach exploits the widely known recurrent behavior of desaturations, which tend to group in different time periods along the sleep time. This characteristic is closely related with the periodicity of desaturations and hence with the analysis of the signal in the frequency domain. However, while spectral analysis has been extensively applied regardless the context (either adult or pediatric), the characterization of the depth, number, and clustering of desaturations has been mostly used as a marker of childhood OSA. The intuition is that the larger the number of clusters, the larger the probability of OSA. However, there is not a clear definition of what a cluster is, and they are mainly detected by visual inspection (Nixon et al., 2004; Velasco-Suarez et al., 2013; Van Eyck et al., 2015; Villa et al., 2015). Recent reviews of the state of the art pointed out that this approach is particularly useful for the detection of moderate-to-severe OSA cases (Van Eyck & Verhulst, 2018).

Brouillette et al. (2000) firstly pointed out the screening ability of clusters of desaturations in children. They reported that the presence of three or more clusters showing falls greater than 4% from baseline and three or more falls in the saturation value below the threshold of 90% was predictive of pediatric OSA, though sensitivity was notably lower than specificity (42.9% vs. 97.8%, respectively). Based on this study, Nixon et al. (2004) defined the McGill oximetry score (MOS), reporting that the number and depth of the clusters could be used to estimate the severity of pediatric OSA, prioritize treatment, and schedule perioperative interventions. Similarly, Velasco-Suarez et al. (2013) reported higher and more balanced sensitivity and specificity values (86.6% vs. 98.9%) using a lower number of clusters (>2) and drops below 90% (>1) for positive OSA in children with adenotonsillar hypertrophy. Recently, Van Eyck et al. (2015) prospectively assessed the methods by Brouillette et al. (2000) and Velasco-Suarez et al. (2013) for childhood OSA detection based on the characterization of clusters of desaturations. Accuracies ranging 68–78% were reported using a conservative diagnostic threshold of 2 events/h for childhood OSA. Looking for a performance increase, Villa et al. (2015) combined the parameterization of clusters with data from the patient's clinical history, reaching 85.8% accuracy in the detection of this condition, while accurateness decreases to 69.4% for the detection of moderate-to-severe cases.

13.2.2 Analysis of Nocturnal Oximetry in the Frequency Domain

In addition to simple statistics and the ODI, one of the first attempts to automatically characterize the SpO_2 signal relied on the use of tools in the frequency domain. Nocturnal desaturations commonly present in the oximetry signal from OSA patients show a relative periodicity. The parameterization of the changes in the power spectrum of the signal linked to this pseudo-periodicity has been found to provide relevant and discriminative features able to discern OSA patients from healthy subjects.

In the framework of frequency analysis, a major decision is to define the spectral band of frequencies that is going to be analyzed. In this regard, standardized spectral bands exist in other biomedical signals, such as heart rate variability (HRV) or electroencephalogram (EEG). The low-frequency (LF: 0.04–0.15 Hz) and the high-frequency (HF: 0.15–0.40 Hz) bands were proposed many years ago to assess the influence of diseases in the cardiac autonomic function using the HRV signal as a surrogate of more intrusive techniques (Stein & Pu, 2012). Similarly, the power spectra in the classical EEG bands delta (0.1–3.5 Hz), theta (4–7.5 Hz), alpha (8–13 Hz), and beta (14–30 Hz) have been widely used to quantitatively measure the impact of diseases in the brain activity (Penttonen & Buzsáki, 2003). On the contrary, no standardized frequency bands are defined concerning the spectral analysis of the oximetry signal.

In the literature, different oximetry-based spectral bands have been proposed to characterize the severity of the disease. Table 13.2 summarizes the main spectral bands of interest used to assess the oximetry signal in the frequency domain. In the context of adult OSA, the frequency band 0.014–0.033 Hz has been predominantly used (Zamarrón et al., 2003; Chen-Liang et al., 2009; Álvarez et al., 2010, 2012, 2013). Shiomi et al. (1996) firstly identified a synchronization between decreased arterial oxygen satu-

Table 13.2 Most common spectral bands of interest of the oximetry signal in the frequency domain

Frequency bands for adults	Frequency bands for children
• 0.008–0.04 Hz (VLF) Shiomi et al. (1996) • 0.014–0.033 Hz (T_{30-70}) Zamarrón et al. (1999) • 0.017–0.1 Hz (T_{10-60}) Sánchez-Morillo and Gross (2013) • 0.017–0.05 Hz (T_{20-60}) Sánchez-Morillo and Gross (2013) • 0.013–0.1 Hz (T_{10-75}) Sánchez-Morillo and Gross (2013) • 0.013–0.05 Hz (T_{20-75}) Sánchez-Morillo and Gross (2013) • <0.2 Hz (artifact removal) Schlotthauer et al. (2014)	• ±0.02 around the peak in 0.005–0.1 Hz Garde et al. (2014) • 0.01755–0.03433 Hz (for AHI ≥1 event/h) Álvarez et al. (2017) • 0.02136–0.03967 Hz (for AHI ≥3 events/h) Álvarez et al. (2017) • 0.01755–0.03357 Hz (for AHI ≥5 events/h) Álvarez et al. (2017) • 0.02136–0.03357 Hz Álvarez et al. (2017) • 0.018–0.050 Hz Vaquerizo-Villar et al. (2018a, c) • 0.020–0.044 Hz Hornero et al. (2017) • 0.021–0.040 Hz Crespo et al. (2018)

ration and a power increase in the very-low-frequency components of the heart rate variability signal (VLF: 0.008–0.04 Hz). In this study, the authors laid the foundations of subsequent analysis of oximetry in the frequency domain, relating the upper and lower limits of the VLF band to the maximum and minimum durations of apneas, respectively: 120 s is stated as the maximum cycle length (i.e., 0.008 Hz), while 25 s is considered the minimum duration (i.e., 0.04 Hz), including the recovery (awakening response) after apnea episodes (Shiomi et al., 1996). Then, Zamarrón et al. (1999, 2003) thoroughly analyzed the spectral content of the oximetry signal within this band, reporting a characteristic and highly discriminative power increase in the period 30–70 s, i.e., the widely used 0.014–0.033 Hz band. Other authors used similar approaches, leading to slightly different bands. Sánchez-Morillo and Gross (2013) and Sánchez-Morillo et al. (2014) analyzed the histogram of the duration of the desaturations to determine the most common desaturation periods. They reported that 83.4% of the desaturations last between 10 and 60 s and that 90.5% between 10 and 75 s (Sánchez-Morillo and Gross, 2013). Accordingly, they defined the following periods of interest in order to parameterize the power spectrum of the oximetry signal: 10–60 s (i.e., 0.017–0.1 Hz), 20–60 s (i.e., 0.017–0.05 Hz), 10–75 s (0.013–0.1 Hz), and 20–75 s (0.013–0.05 Hz). Other authors used a more conservative approach when locating the spectral content of oximetry. In this regard, Schlotthauer et al. (2014) considered that desaturations linked to apneas have periods larger than 5 s, leading to relevant frequency components below 0.2 Hz.

In the framework of childhood OSA, there is a larger variability regarding the spectral band of interest of the oximetry signal compared to adults (see Table 13.2). Garde et al. (2014) used a frequency interval of 0.02 Hz centered around the peak amplitude of the power spectrum that they searched from 0.005 to 0.1 Hz. Álvarez et al. (2017) performed a statistical analysis searching for the frequencies leading to the highest discriminant ability between OSA groups. Accordingly, they identified three different bands of interest for pediatric OSA: 0.01755–0.03433 Hz for a cutoff of 1 event/h, 0.02136–0.03967 Hz for a cutoff of 3 events/h, and 0.01755–0.03357 Hz for 5 events/h. Finally, they proposed a single spectral frequency range as the broadest interval showing significant differences regardless the clinical threshold for positive OSA: 0.02136–0.03357 Hz. Similarly, Vaquerizo-Villar et al. (2018a, c) searched for a spectral band of interest able to maximize the differences between different OSA severity groups (AHI < 5 events/h, 5 ≤AHI < 10 events/h, and AHI ≥10 events/h), leading to the interval 0.018–0.050 Hz. Other authors used slight variations of these bands, such as Hornero et al. (2017) (0.020–0.044 Hz) and Crespo et al. (2018) (0.021–0.040 Hz).

Concerning the methodology used to inspect the frequency content of oximetry, different approaches have been assessed. The estimation of the power spectral density (PSD) using the non-parametric Welch method based on the fast Fourier transform has been predominantly used (Zamarrón et al., 1999, 2003; Chen-Liang et al., 2009; Álvarez et al., 2010, 2012, 2013, 2017; Hornero et al., 2017; Crespo et al., 2018). Alternatively, autoregressive methods were used by Sánchez-Morillo and Gross (2013) and Garde et al. (2014) to estimate the PSD. A number of measures have been used to parameterize the power spectrum (see Table 13.3), mainly based on amplitudes and total or relative power in the spectral band of interest. Additionally, common statistics, such as first-to-fourth statistical moments and the median frequency, as well as regularity measures as the Shannon spectral entropy have been also widely used to further characterize the spectral content of the signal. In this regard, peak amplitude, relative power, skewness, and spectral entropy have been found to jointly summarize oximetry dynamics in the frequency domain, for both adults (Álvarez et al., 2010, 2012, 2013, 2020; Sánchez-Morillo & Gross, 2013) and children (Garde et al., 2014; Hornero et al., 2017; Álvarez et al., 2017; Crespo et al., 2018).

On the other hand, novel and complementary approaches have been recently proposed to further assess the recurrent behavior of desatura-

Table 13.3 Measures commonly used to characterize the power spectrum of oximetry in the frequency domain

Method	Indices
Power spectral density (PSD) • Non-parametric fast Fourier transform (FFT)-based methods (Welch, Blackman-Tukey) Zamarrón et al. (1999, 2003), Chen-Liang et al. (2009), Álvarez et al. (2010, 2012, 2013, 2017), Hornero et al. (2017), Crespo et al. (2018) • Autoregressive methods (Yule-Walker) Sánchez-Morillo and Gross (2013), Garde et al. (2014)	• First-to-fourth statistical moments (mean, variance, skewness, kurtosis), median frequency • Shannon spectral entropy (SSE), mobility, Wootters' distance, Euclidean distance (measures of the concentration of the signal power) • Peak and minimum amplitudes, total power, relative power in the band of interest
Bispectrum (high-order spectra) Vaquerizo-Villar et al. (2018a)	• Mean amplitude • Sum of the logarithmic amplitudes of the whole bispectrum, sum of the logarithmic amplitudes in the main diagonal, first-order spectral moment of amplitudes in the main diagonal • Normalized bispectral entropy and normalized bispectral squared entropy • Phase entropy • Mean and variance of the bispectrum invariant
Wavelet transform Vaquerizo-Villar et al. (2018c), Poupard et al. (2012)	• First-to-fourth-order moments of the wavelet coefficients in the 9th detail band (D_9: 0.0244–0.0488 Hz) • Maximum amplitude of wavelet coefficients in D_9 • Energy of the coefficients in D_9 • Wavelet entropy • Ventilatory hypoxemic index

tions and to obtain complementary information to that provided by the PSD. In this regard, Vaquerizo-Villar et al. (2018a) used high-order spectra (HOS) to detect deviations from Gaussianity, linearity, and stationarity of the oximetry signal potentially linked to the apneic events. Particularly, they applied the bispectrum, a representation of the spectral decomposition of the third-order cumulant (skewness) of a signal over the frequency. In this study, two bispectral measures showed complementarity with PSD, the mean amplitude of the bispectrum and the mean of the bispectrum invariant, which account for magnitude differences and for phase coupling between spectral components, respectively. The authors reported a remarkable performance increase (+6.7% three-class accuracy) when including these bispectral features in a model for automated pediatric OSA diagnosis. Similarly, in a subsequent study in the same research line, Vaquerizo-Villar et al. (2018c) applied wavelet analysis in order to further characterize the spectral content of the signal, particularly in the very low frequencies owing that oximetry is characterized by very slow variations. In such low frequencies, traditional methods lack for appropriate spectral resolution, while the wavelet transform performs a multilevel analysis able to provide high frequency resolution at low frequencies and high time resolution at high frequencies. In the study by Vaquerizo-Villar et al. (2018c), the skewness and the energy of the coefficients in the level 9 detail signal (D_9, corresponding to the frequency range 0.0244–0.0488 Hz), as well as the overall wavelet energy, showed complementarity with conventional oximetric indices, including ODI, statistical moments, and features from the PSD.

In the context of adult OSA, the wavelet transform has been also applied to the oximetry signal to obtain a new measure of hypoxemia. Poupard et al. (2012) implemented a wavelet-aggregation procedure to quantify the overall absolute variations (both increases and decreases of amplitude) along the overnight oximetry recording. The ventilatory hypoxemic index (VHI) was defined as the cumulative time with absolute variations >4%, divided by the theoretical apnea cycle period, which was defined as the middle point in the interval 30–70 s identified by Zamarrón et al. (2003), i.e., 50 s. The VHI showed higher correlation with standard AHI than ODI (0.87 vs. 0.81), as well as lower bias (+5.7 vs. +13.5). In the same regard, VHI achieved more balanced sensitivity-specificity pair than the ODI for the common cutoffs for OSA (91–88% vs. 65–100%, AHI ≥5 events/h; 81–98% vs. 58–100%, AHI ≥15 events/h; 67–99% vs. 59–100%, AHI ≥30 events/h).

13.2.3 Methods Derived from Nonlinear Dynamics in the Oximetry Signal

Despite the usefulness shown by conventional oximetric indices, statistics, and frequency-domain methods, they are unable to completely explain all the dynamics of the oximetry signal. In addition to periodicities linked to the recurrent apneic events, there are also nonlinear changes typical of natural systems present in biomedical signals. In this regard, nonlinear methods derived from the chaos theory have demonstrated to provide relevant and complementary information in the automated diagnosis of OSA from oximetry. Table 13.4 shows the methods predominantly used to quantify nonlinear dynamics in the SpO_2 signal.

Approximate (ApEn) and sample (SampEn) entropies, central tendency measure (CTM), and Lempel-Ziv complexity (LZC) have been predominantly used. Individually, the quantification of irregularity in the overnight oximetry recording by means of ApEn shows remarkable performance in the detection of adult OSA (Del Campo et al., 2006; Hornero et al., 2007), reaching balanced sensitivity and specificity, as well as area under the ROC curve >0.90. In the same regard, CTM matches the behavior of ApEn, achieving accuracy values >87% with balanced sensitivity-specificity pair and area under the ROC curve >0.90 (Álvarez et al., 2006, 2007). Finally, LZC has shown slightly lower performance than single CTM or ApEn, although reaching notable accuracy (>82%) and area under the curve (>0.85) (Álvarez et al., 2006).

Concerning multivariate approaches, nonlinear measures have shown valuable complementarity with conventional oximetric indices for automated OSA diagnosis in both adults and children. In the adult context, nonlinear measures are systematically included in the final optimum subset from automated feature selection procedures. Particularly, the width of the Poincaré plot (SD_1) is complemented with different desaturation and resaturation indices as well as with spectral power (Sánchez-Morillo & Gross, 2013), LZC shows remarkable joint relevance with statistical moments in the time domain and the spectral power (Álvarez et al., 2010, 2013), and CTM fits with statistical moments in both the time and frequency domains and the peak spectral amplitude (Álvarez et al., 2012, 2013). Under a multiclass approach, SD_1, SampEn, CTM, and LZC all together combined with the ODI and a histogram-based index to discern between no-OSA and mild OSA individuals, whereas ApEn combined with histogram-based indexes, resaturation measures, and the ODI to classify moderate and severe OSA patients (Sánchez-Morillo et al., 2014). Without an appropriate feature selection stage, complementarity of nonlinear measures is not properly exploited, as shown in the study by Marcos et al. (2009), where the combination of nonlinear and spectral features did not significantly improve the accuracy reached with each individual approach (spectral vs. nonlinear). Alternatively, dimensionality reduction by means of principal component analysis showed a remarkable performance increase (+6.20% accuracy) when combining spectral and nonlinear features (Marcos et al., 2010b). Under a regression approach aimed at estimating the apnea-hypopnea index (AHI),

Table 13.4 Nonlinear methods commonly used to quantify changes in nonlinear dynamics of oximetry

Method	Indices
Irregularity or disorderliness measures by means of entropy del Campo et al. (2006), Hornero et al. (2007), Álvarez et al. (2006, 2010, 2012, 2013, 2017, 2020), Marcos et al. (2009, 2012); Marcos et al. (2010b), Sánchez-Morillo et al. (2014), Garde et al. (2014), Hornero et al. (2017), Crespo et al. (2018)	• Approximate entropyEntropies (ApEn) and cross-approximate entropy (cross-ApEn) • Sample entropy (SampEn) • Kernel entropy (KerEn)
Variability measures from scatter plots Álvarez et al. (2006, 2007, 2010, 2012, 2013, 2017, 2020), Marcos et al. (2009, 2012), Marcos et al. (2010b), Sánchez-Morillo and Gross (2013), Sánchez-Morillo et al. (2014), Garde et al. (2014), Hornero et al. (2017), Crespo et al. (2018)	• Length of the main (SD_1) and secondary (SD_2) axes of the ellipse that encloses the points in Poincaré plots • Central tendency measure (CTM) from second-order difference plots
Complexity measures Álvarez et al. (2006, 2010, 2012, 2013, 2020), Marcos et al. (2009, 2010b, 2012), Sánchez-Morillo et al. (2014), Hornero et al. (2017), Crespo et al. (2018)	• Lempel-Ziv complexity
Multiscale approaches Crespo et al. (2017), Vaquerizo-Villar et al. (2018a, b)	• Multiscale entropy (MSE): Individual entropy values in single scales; entropy value in the scale reaching the maximum margin between groups under study; slope of the MSE curve between a pair of scales; area enclosed under the MSE curve between a pair of scales; area enclosed between the first and the maximum margin scales; time scale where maximum entropy is reached • Detrended fluctuation analysis (DFA): slopes (scaling exponents) of the lines fitting the regions identified in the DFA curve; coordinates of the intersection of the line fitting these regions; value of the fluctuation function in the scale that maximizes its correlation with the AHI
Symbolic dynamics Álvarez et al. (2018)	• Probability of the words (particular sequence of symbols) representative of different states (high and low saturation values) and changes (desaturations and resaturations) of the signal • Forbidden words • Symbolic entropy

SampEn, CTM, and LZC from oximetry showed reliable completeness with statistical, spectral, and conventional oximetric indices (Marcos et al., 2012; Álvarez et al., 2020).

In the framework of pediatric OSA, the usefulness of traditional nonlinear indexes (SampEn, CTM, and LZC) from overnight oximetry has been less investigated, and their relevance seems to be slightly lower than in the adult context. The studies by Álvarez et al. (2017) and Crespo et al. (2018) include these measures in the beginning of a feature selection process, and only SampEn was found non-redundant and finally selected to be part of the optimum model for binary classification of children (non-OSA vs. OSA) using different cutoffs for the disease (1, 3, and 5 events/h). Additionally, Garde et al. (2014) and Hornero et al. (2017) also used nonlinear measures to characterize the nocturnal oximetry profile of children with suspicion of OSA, but no nonlinear index was included in the optimum model (binary classification and regression approaches) due to redundancy.

In addition to these conventional nonlinear measures of irregularity, variability, and complexity, novel nonlinear methods have been recently applied to the oximetry signal in order to obtain as much information as possible from the recording. This is particularly important in the pediatric context, where pattern recognition and machine learning methods face a more challenging task compared to adults. In the study by Crespo et al. (2017), multiscale sample entropy (MSE) was applied to quantify entropy changes in the oximetry signal along larger time scales. Features derived from the MSE curve shown high performance (AUC 0.80) both individually and jointly. It is remarkable the complementarity of MSE variables and conventional oximetric indices (ODI, CT, minimum and average saturation), leading to a significant performance increase (+4.5% accuracy; +6% AUC) when properly combined using a stepwise approach. Similarly, Vaquerizo-Villar et al. (Vaquerizo-Villar et al., 2018b) applied detrended fluctuation analysis (DFA) to analyze changes in the correlation properties of the nocturnal oximetry profile for different ranges of scales. The slope in the first scaling region of the DFA curve showed high relevancy and complementarity with the ODI. Both were combined using a regression neural network aimed at estimating the AHI, reaching high agreement with actual AHI (0.891 intra-class correlation coefficient; 0.412 kappa) and notably outperforming the ODI alone (0.866 intra-class correlation coefficient; 0.355 kappa). Finally, Álvarez et al. (2018) analyzed nonlinearities present in the oximetry recording using a symbolic dynamics approach, which stablishes an alternative framework for investigating complex nonlinear systems. Features from the histogram of symbols reached the highest performance compared to conventional indexes, anthropometric measures, and common statistical moments. Moreover, symbolic dynamics features showed significant complementarity with these variable subsets, leading to a significant performance increase (+4.8% accuracy; +7% AUC) when used together after appropriate feature selection.

13.2.4 Quantifying the Morphology of Desaturation: Influence of the Area and the Velocity of Events

The conventional oxygen desaturation index has demonstrated to provide highly relevant information on the severity of OSA, reaching high performance when used individually as well as being systematically selected within the optimum feature subset under multivariate approaches. Nevertheless, the ODI is just based on counting the number of desaturations, regardless the total depth and length of these events. Hence, there is room for improvement if all these characteristics are put together in the same index. Table 13.5 shows several indices found in the literature aimed at parameterizing the morphology of the desaturation.

First attempts for joint characterization of both the length and depth of the desaturations were made by Chesson et al. (1993, 2001). They proposed the so-called saturation impairment time (SIT), an automated index aimed at quantifying cumulative nocturnal oxygen desaturation as a measure of hypoxemia in the context of respiratory-related breathing disorders. Contrary to traditional indices of hypoxemia just based on the percentage of time spent below a predetermined threshold (CTx%, being x% the cutoff), the SIT index integrates both time (length) and severity (depth) of the desaturations (Chesson et al., 1993). To measure the joint contribution of both characteristics, SIT is computed as the area enclosed under a fixed saturation value (similar to the threshold in CT indices) and the saturation curve. The authors reported good correlation

Table 13.5 Measures used to parameterize the morphology of the desaturation curve

Method	Indices
Severity of desaturations (quantification of the total or partial area of the desaturation) Chesson et al. (1993, 2001), Kulkas et al. (2013a, b, 2017), Muraja-Murro et al. (2014), Leppänen et al. (2017), Kainulainen et al. (2019, 2020), Linz et al. (2018), Khoshkish et al. (2018), Azarbarzin et al. (2019), Kim et al. (2020)	• Saturation impairment time (SIT) • Apnea severity, hypopnea severity, obstruction severity, and desaturation severity • Hypoxia load (HL) • Hypoxic burden
Parameterization of the sections of the desaturation Otero et al. (2012)	• Duration of the desaturation • Average and minimum (nadir) values of the saturation throughout the event • Elapsed time from the beginning of the event until the nadir point and from the nadir to the end of the desaturation • Overall drop in the saturation during the fall part of the event and overall increase in the rise section • Slope of both the fall and the rise parts of the event • Desaturation area

with CT ($r^2 > 0.8$) as well as complementarity with the respiratory disturbance index (RDI), i.e., patients with similar RDI showed variability in their SIT values. Accordingly, they concluded that the SIT index may provide additional and useful information in the characterization of desaturations during sleep.

The standard AHI from nocturnal PSG is commonly criticized due to its low correlation with physiological symptoms and consequences of OSA. In a similar way to the ODI, this problem is attributed to the own definition of the parameter, which is just based on counting the number of apneas and hypopneas throughout the time of sleep regardless their severity. Motivated by the increasing demand for alternatives to the standard AHI due to these limitations, different respiratory disturbance indices have been recently proposed aimed at gathering the severity of each individual event. These indices are commonly known as measures of "hypoxic burden." In 2013, Kulkas et al. (2013a) proposed a set of indices they named severity parameters, aimed at accounting for both the morphology and the duration of desaturations: *apnea severity*, *hypopnea severity*, *obstruction severity*, and *desaturation severity*. They are all based on the quantification of the *desaturation area* for each single event, which is the area enclosed between a saturation level determined by the starting point of the event and the oximetry curve until the minimum saturation value (nadir), i.e., the resaturation part of the event is not considered. The *desaturation severity* index is computed as the cumulative sum of the desaturation area of each single event and normalized by the total analyzed time. *Apnea severity*, *hypopnea severity*, and *obstruction severity* are based on the same definition, but the *desaturation area* is weighted by the duration of each kind of event, and only those events (apnea, obstructive, or hypopnea) followed by a desaturation event within the next 60 s are considered (Kulkas et al., 2013a). The authors reported moderate correlation of the novel severity indices with the standard AHI ($r^2 < 0.7$; $p < 0.001$) and with the ODI ($r^2 < 0.75$; $p < 0.001$) (Kulkas et al., 2013a), as well as remarkable variability for patients within the same AHI/severity range (Kulkas et al. 2013a, b), suggesting that the proposed severity parameters might provide complementary information on the assessment and management of the severity of OSA. In a subsequent study by the same group, Muraja-Murro et al. (2014) used the *obstruction severity* parameter to adjust the AHI. Interestingly, the adjusted AHI correlated better than standard AHI with mortality (both all-cause and cardiovascular) and non-fatal cardiovascular events, leading to significantly higher association (higher risk ratios) for these outcomes in the corrected moderate and severe groups. In addition, using the novel severity indices, Kulkas et al. (2017) and Leppänen et al. (2017) were able to gain insight into the differences among OSA patients concerning gender, while Kainulainen et al. (2019, 2020) found that severity of desaturations had a great impact on the level of daytime sleepiness and vigilance/reaction time in patients with OSA.

More recently, Linz et al. (2018) proposed a new measure for the quantification of the hypoxemic burden during sleep that they termed *hypoxia load*. The *hypoxia load* is defined as the integrated area of the desaturation curve to the theoretical maximal saturation, i.e., 100%. This way, the *hypoxia load* encompasses all the changes in the saturation signal linked to respiratory events (baseline saturation, number and length of desaturations, time below 90%, and minimum saturation value) regardless any threshold. This index is presented in the context of cardiovascular risk assessment in patients with sleep-disordered breathing (SDB). Linz et al. (2018) reported that the *hypoxia load* showed significant moderate correlation ($r^2 = 0.316$; $p < 0.05$) with epicardial fat volume, an established marker of cardiovascular risk, in patients with SDB after acute myocardial infarction. On the contrary, the AHI and conventional measures of hypoxemia did not show significant association. Additionally, Khoshkish et al. (2018) reported significant correlation ($r^2 \approx 0.1$; $p < 0.05$) between hypoxia load and pulse pressure during both the day and the night, while standard AHI did not. These findings led the authors to suggest that the new measures of hypoxic burden could be used to predict blood pressure patterns and help in the management of hypertensive patients.

In 2019, Azarbarzin et al. (2019) defined a similar index of OSA-related hypoxemia, the *hypoxic burden*, which was presented as a potential predictor of cardiovascular disease (CVD)-related mortality. The *hypoxic burden* index aims to characterize just intermittent hypoxemia typical of OSA and not persistent hypoxemia commonly present in other respiratory diseases. Accordingly, it was defined as the area under the oxygen saturation curve only in the desaturations associated with apneas or hypopneas. A subject-specific search window is defined by segmenting, overlapping using a common synchronization point at the end of each event, and finally averaging all the oximetry segments linked to annotated respiratory events of the individual (i.e., apneas and hypopneas both obstructive and central, regardless their association to a desaturation or an arousal). Finally, the total *hypoxic burden* is computed as the cumulative sum of individual areas normalized by the total sleep time. The authors found that the *hypoxic burden* index was a strong predictor of CVD mortality in different populations (Osteoporotic Fractures in Men Sleep Study, hazard ratio 2.73, 95%CI 1.71–4.36; Sleep Heart Health Study, hazard ratio 1.96, 95%CI 1.11–3.43) independent of the AHI/ODI and traditional measures of hypoxemia (CT90, minimum saturation). In a subsequent study, Kim et al. (2020) found a significant association between an increment (1 SD increment in a log-transformed space) in the *hypoxic burden* index and the increase in blood pressure (1.1% increase in systolic blood pressure, 95%CI 0.1–2.1%; 1.9% increase in diastolic blood pressure, 95%CI 1.0–2.8%) in patients not using hypertensive medication.

Concerning the morphology of events, Otero et al. (2012) proposed a set of indices aimed at parameterizing additional features of desaturations that are not usually considered in the diagnosis and characterization of OSA severity. These indices include not only measures of duration and depth but also features related to the velocity of both the fall and rise parts of the desaturation. The following measures were defined: (i) duration of the desaturation; (ii) average and minimum (i.e., nadir point) values of the saturation throughout the whole event; (iii) elapsed time from the beginning of the event until the nadir point is reached as well as from the nadir to the end of the desaturation; (iv) overall drop in the saturation during the fall part of the event and overall increase in the rise section; (v) slope of both the fall and the rise parts of the event; and

(vi) the desaturation area, measured as the area enclosed between the straight line joining the starting and ending points on the event and the saturation curve. In addition, these oximetry-based measures were computed to characterize the whole overnight oximetric recording: (i) mean saturation throughout the recording; (ii) basal saturation; (iii) difference between the basal value and the mean value; (iv) percentage of the sleep time while the patient is in hypoxemia; and (v) area between a straight line set to the basal saturation value and the oximetry curve.

When assessing the relevance of these indices in the context of OSA diagnosis, the authors found that the most common oximetry features (duration of the desaturation, average, and minimum values) were not selected using a battery of automated feature selection processes. The most relevant oximetry indices were the following: (i) percentage of time in hypoxemia; (ii) difference between basal and average values; (iii) area between basal level and the oximetry profile; (iv) saturation increase during the rise part of the desaturation associated with apnea events; and (v) saturation drop during the fall section of the desaturation associated with apnea events. Individually, the performance of these morphology-related desaturation indices in the detection of OSA ranged 81–90.9% accuracy (86.5–95.7% sensitivity; 47.8–76.1% specificity).

13.2.5 Oximetry and Deep Learning Approaches

Deep learning is changing the paradigm of both image and signal processing in the field of medicine. Traditional machine learning methods rely on the so-called feature engineering, where models are fed with features previously derived from the signals based on the knowledge of the problem under study. Thus, this is a human-driven approach, and so it is highly dependent on the skills of the researchers to compose a relevant feature set. On the contrary, deep learning is able to learn hidden complex patterns directly from the raw signal (Faust et al., 2018), avoiding the bias linked to an a priori known limited set of indices. To do that, deep learning techniques use architectures with multiple levels of representation or data abstraction (Goodfellow et al., 2016), commonly different types of neural networks, such as convolutional or recurrent deep neural networks.

In the context of OSA, deep neural networks have been used in the last years for automated decision-making (Mostafa et al., 2019). Table 13.6 summarizes the main goals of deep learning approaches in the framework of OSA involving the oximetry signal. Main tasks focus on abbreviated OSA diagnosis and automated sleep staging. Nikkonen et al. (2019) applied a fully connected deep neural network to estimate the AHI directly from overnight oximetry (10-

Table 13.6 Techniques and approaches involving deep learning and oximetry in the management of OSA

Goals	Methods
Automated diagnosis Classification of segments (normal vs. apneic) and subsequent estimation of the AHI (short segments: 1- to 5-min length epochs, with or without overlapping) Mostafa et al. (2020a, b), Bernardini et al. (2021) Direct regression of the AHI (larger segments: 10- to 20-minute length epochs, with or without overlapping) Nikkonen et al. (2019), Leino et al. (2021), Vaquerizo-Villar et al. (2021)	Dense fully connected neural networks Convolutional neural networks (CNN) Recurrent neural networks (RNN) Long short-term memory (LSTM) Convolutional + dense (CNN+ dense) Convolutional + recurrent (CNN + RNN)
Sleep staging (short segments: 30 s epochs) Casal et al. (2021) 2-class categorization (wake vs. sleep) 3 class (wake vs. NREM (N1/N2/N3) vs. REM) 4-class (wake vs. light sleep (N1/N2) vs. deep sleep (N3) vs. REM) 5-class (wake vs. N1 vs. N2 vs. N3 vs. REM)	Recurrent neural networks (RNN) Long short-term memory (LSTM) Gated recurrent unit (GRU) Convolutional + recurrent (CNN+ RNN)

min epochs with 98% overlap were used), achieving 0.96 intra-class correlation coefficient (ICC) with actual AHI. Using the estimated AHI, 90.9% of patients were classified in the correct OSA severity group. On a subsequent study by this research group, Leino et al. (2021) proposed a convolutional neural network instead, in order to estimate the rate of respiratory events overnight using single-channel oximetry (10-min epochs with 98% overlap). They obtained 0.97 ICC and 88.3% overall four-class accuracy in a test set composed of patients commonly referred to the sleep unit due to suspicion of OSA, while 0.97 ICC and 77.9% four-class accuracy were reached in a test set of patients with acute cardiovascular disease. Similarly, Vaquerizo-Villar et al. (2021) implemented a convolutional neural network aimed at estimating the AHI from oximetry alone (20-minute segments with no overlapping), reaching ICC values ranging 0.58–0.96 in different extensive test datasets. Using the estimated AHI, the overall three-class accuracy varies between 60.2% and 72.8%.

Mostafa et al. (2020a) used shorter epochs (1, 3, and 5 min with 1-minute overlap) to implement an event-based approach (detection of apneas) using different architectures of convolutional neural networks, achieving accuracies ranging 84.8–94.2%. In a subsequent study (Mostafa et al., 2020b), the same group implemented a new convolutional neural network architecture based in the same approach, reporting patient-based accuracies of 95.7% and 100% in different test datasets. In a recent study by Bernardini et al. (2021), oximetry (2.5-minute epochs) is analyzed under a deep learning approach both alone (using a recurrent neural network) and together with ECG (combining convolutional and recurrent neural networks). A long short-term memory (LSTM) neural network (a kind of recurrent deep neural network) reached 67.6% and 63.3% accuracies under per-second and per-patient classification approaches, respectively. Using ECG segments as inputs to a deep learning architecture that combines convolutional and recurrent blocks, 76.9% and 73.3% accuracies were reported for the same performance assessment schemes. Interestingly, when both ECG and oximetry were analyzed jointly (2D input), the network achieved 81.5% and 93.3% accuracies for per-second and per-patient classification, respectively, i.e., +4.6% and +20.0% increase compared to the use of ECG alone.

In automatic sleep staging, only one study has used the raw oximetry signal (Casal et al., 2021). In this work, recurrent neural networks are used to discern wakefulness from sleep (binary classification) using blood oxygen saturation and heart rate from pulse oximetry (30-sec epochs), reporting 90.1% accuracy and 0.74 Cohen's kappa. Similar approaches exist using the photoplethysmogram (PPG) signal from pulse oximetry instead of the blood oxygen saturation or pulse rate times series, achieving promising performance (84.2% accuracy) in a two-class classification problem (Malik et al., 2018), while the accuracy decreases to 80.1%, 68.5%, and 64.1% for three-, four-, and five-stage classification tasks, respectively (Korkalainen et al., 2020).

13.3 Discussion and Conclusions

The great amount of indices derived from the oximetry signal existing in the literature (Del Campo et al., 2018; Terrill, 2020; Levy et al., 2021) is representative of the high relevance of this biomedical recording in the framework of OSA. Recent reviews and meta-analyses summarizing all the research made around oximetry during the last years confirm this intuition. In a systematic review by Uddin et al. (2018), single-channel oximetry raises as an effective biomedical signal to implement binary expert systems for automated OSA detection (OSA positive vs. OSA negative). Similarly, in the recent meta-analysis by Wu et al. (2020), oximetry is found to yield remarkable specificity in the detection of all OSA severity groups. In the context of pediatric OSA, the meta-analysis by Gutiérrez-Tobal et al. (2021b) revealed that top performance methodologies were those involving oximetry, particularly for the detection of moderate and severe cases, showing also less variability among studies. Beyond its diagnostic ability, nocturnal oximetry dynamics have been also found to be associated with clinical and epidemiological outcomes (Suen et al., 2019; Terrill, 2020), increasing its usefulness as essential tool for integrated management of OSA.

Since first attempts to characterize changes in overnight oximetry by means of the minimum saturation value, ODIs, and CTs, different approaches have been applied to obtain as much information as possible from the recording, including characterization of the data histogram using different statistics, analysis in the frequency domain with different methods of power spectral density estimation, nonlinear analysis, parameterization of the parts of the desaturation, quantification of the area enclosed within each desaturation, and, recently, deep learning. All these methodologies have yielded relevant indices in the characterization of OSA severity. Despite being one of the first measures developed for that aim, usually used as benchmark for comparison purposes, the ODI stands out for its great individual accuracy, rarely outperformed by univariate approaches. Moreover, the ODI has been found as an essential predictor under multivariate schemes, being systematically selected within the final optimum feature subsets. In the same regard, statistical, spectral, and nonlinear variables, as well as the novel hypoxic burden measures, have shown major complementarity, leading to a significant performance increase when input features are properly selected via automated variable selection procedures (Álvarez et al., 2010, 2012, 2013). Additionally, oximetry in general, and particularly ODI, has also shown significant complementarity with other cardiorespiratory signals related to OSA, such as pulse rate (Álvarez et al., 2009; Garde et al., 2014) and airflow (Gutiérrez-Tobal et al., 2015; Álvarez et al., 2020; Barroso-García et al., 2021b) in both adults and children.

Besides the nonlinear methods based on traditional entropy and complexity measures, novel nonlinear methods, such as multiscale entropy, detrended fluctuation analysis, and symbolic dynamics, recently demonstrated major efficiency when applied to the oximetry signal. Nevertheless, ApEn, SampEn, CTM, and LZC are predominantly used under multivariate approaches instead of MSE scales, DFA slopes, and symbolic entropy. Although these methods are computationally demanding, it would be important to promote their use to prospectively validate their accuracy and to include them in the available toolboxes for automated signal processing of oximetry.

Concerning the novel measures of hypoxemia named hypoxic burden indices (saturation impairment time, desaturation severity, hypoxia load, and hypoxic burden), they have been found to provide complementary data to the AHI/ODI and conventional hypoxemia measures (CT90, minimum saturation). This suggests that not only the recurrence but also the morphology (depth and duration) of the events have jointly a significant impact on the characteristics of respiratory-related diseases and associated comorbidities. Nevertheless, this "information gain" has not become a significant performance increase regarding automated detection of OSA from oximetry. Thus, further research is encouraged to exploit all the diagnostic capability available in these indices. On the other hand, hypoxic burden measures have demonstrated to be robust predictors of cardiovascular status and mortality due to the intermittent hypoxemia typical of OSA (Muraja-Murro et al., 2014; Khoshkish et al., 2018; Azarbarzin et al., 2019; Kim et al., 2020). These novel hypoxemia measures seem to outperform conventional indices (overnight minimum saturation, CT90, and ODIs), which performed modestly as predictors of cardiovascular events (stroke, heart failure) and related mortality (Kendzerska et al., 2014; Stone et al., 2016; Gellen et al., 2016). Nonetheless, due to the dissimilarities in the computation of these new parameters, thorough research and prospective validation are still needed to fully understand the link between each particular index and patient outcomes.

In regard to the usefulness of artificial intelligence, relevant recent reports highlight its potential to boost sleep medicine (Goldstein et al., 2020; Watson & Fernandez, 2021; Malhotra et al., 2021). Concerning the oximetry signal, a number of automated expert systems have been developed for OSA diagnosis, mostly using feature engineering and traditional machine learning models for both binary and multiclass classification of patients, as well as regression of the AHI. Nevertheless, deep learning approaches recently raised as valuable tool able to boost the diagnostic ability of oximetry, mainly when applied to categorize segments (apneic vs. normal) and predict the AHI using oximetry alone. The next step (individual indices, multivariate analysis, artificial intelligence, deep learning) should be the application of eXplainable Artificial Intelligence (XAI) techniques to thoroughly interpret the particularly complex models derived from deep learning. XAI methods are able to identify which parts of the oximetry signal mainly contribute to the final decision. Thus, XAI might be used to confirm the relevance of sections of the desaturation event highlighted in some studies, whose widespread application is commonly hindered by more popular indices. For example, higher saturation values and resaturations have shown significant relevancy and complementarity (Sánchez-Morillo & Gross, 2013; Sánchez-Morillo et al., 2014; Álvarez et al., 2018), although they have been marginally used in multivariate subsequent studies. Furthermore, XAI approaches have the potential to provide clinicians with new oximetric features with the upmost diagnostic capability hidden until now in the raw oximetry signal.

During the last two decades, the oximetry signal has been found to provide high-performance indices in the framework of OSA management. With the improvement of medical technology in terms of portability, autonomy, and computational capability, and taking into account the simplicity, low cost, and high availability of oximeters, peripheral blood oxygen saturation raises as a key signal in the development of simple as well as accurate diagnostic tests for OSA. Moreover, oximetry could be an essential tool to foster sleep medicine toward the concept of precision and personalized medicine. However, both greater standardization in the definition of available indices and extensive validation of the novel measures derived from the signal processing theory are still needed to increase generalizability of overnight oximetry as an alternative abbreviated test for OSA.

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