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Complexity and nonlinearities in cardiorespiratory signals in sleep and sleep apnea

Carolina Varon and Sabine Van Huffel

1 Introduction

This chapter is divided in two main parts. The first part focuses on the description and quantification of the different cardiac and respiratory dynamics during healthy sleep. Linear and nonlinear approaches that have been used to analyse the complexity of the cardiorespiratory system during different sleep stages are presented. For instance, the application of methods such as detrended fluctuation analysis, dynamic warping, correlation dimension, and entropy measures, on cardiac and respiratory signals during sleep are described. In addition, an overview of the cardiorespiratory interactions during sleep is provided, and different algorithms for sleep staging are compared.

The second part of this chapter discusses the effect that sleep apnea has on the cardiorespiratory dynamics and interactions, and special focus is put on how this effect has been quantified using linear and nonlinear techniques. The problem of sleep apnea detection is presented together with a comparison between the performances obtained using linear and nonlinear techniques.

2 Sleep Monitoring

Sleep is a complex process that plays a key role in maintaining homeostasis, well-being and overall health [1]. During a lifetime, humans normally spend up to one-third of the time sleeping, however, the current 24-hour society is reducing this time and keeping people from getting the necessary amount of sleep. In fact, sleep deprivation has been strongly associated with reductions of cognitive and behavioral performance, depression, memory loss, and cardiovascular diseases [2]. Not only society but also sleep disorders play a key role in the reduction of sleep quality. These disorders have been grouped in seven major categories: insomnia; sleep-related breathing disorders; central disorders of hypersomnolence; circadian rhythm sleep-wake disorders; sleep-related movement disorders; parasomnias; and other sleep disorders [2, 3], and they all have different effects on the human body. For instance, cardiorespiratory irregularities have been observed in patients suffering from circadian rhythm sleep disorder such as delayed sleep-phase syndrome, advanced sleep-phase syndrome and non-24-hour sleep-wake disorder, and in patients with obstructive sleep apnea (OSA) [2, 4, 1].

The gold standard in sleep monitoring and in the diagnosis of sleep disorders is the polysomnography (PSG), which is a sleep test usually recorded in a sleep laboratory [5, 6]. This test includes the overnight recording of, amongst others, the electrical activity of the brain using electroencephalography (EEG), the electrical activity of the heart using the electrocardiogram (ECG), airflow, respiratory effort measured on the chest and abdomen, and blood oxygen saturation (SaO_2). These signals are visually inspected by sleep experts in order to annotate the occurrence of different sleep stages [6], or events related to sleep disorders [5]. Although PSG is the most powerful tool in sleep medicine, it requires overnight hospitalization, costly sleep center facilities and sleep experts, and the use of instrumentation that might intervene with the normal sleep pattern. In order to overcome these limitations, many studies have focused on the development of non-intrusive technologies that can be used at home and that can monitor sleep during more than one single night. As a result, it is expected that the clinical practice of sleep medicine can be improved, and that early diagnosis of sleep disorders can be achieved with a non-intrusive screening tool[4]. One technology that has been considered for the development of such a tool is actigraphy. It can be recorded using wrist-worn devices and it has been proven to be useful in the monitoring of sleep in healthy adults [7]. However, its accuracy in the diagnosis of sleep disorders remains a challenge [8].

Apart from actigraphy, the changes in the cardiorespiratory signals during sleep have also been investigated and considered for the development of non-intrusive screening tools [4, 9, 10, 11, 12, 13]. The fact that cardiorespiratory activity changes with the sleep pattern (i.e. sleep stages) [14] has motivated many researchers to derive linear and nonlinear features from both the ECG and the respiratory signals. These features have then been used to detect either sleep stages, or events related to sleep disorders in particular to obstructive sleep apnea (OSA), or both simultaneously [11, 12, 15, 16]. Studies where both tasks are performed separately, namely sleep staging and OSA detection, have shown that promising results can be obtained using cardiorespiratory-based algorithms. However, their performance can be compromised when sleep staging is performed in the presence of OSA events [17]. All in all, a lot of improvements are still needed in the development of automatic sleep analysis before they can be accepted in sleep medicine [18].

3 Sleep Staging

Sleep is not just a *steady state*, instead it is a complex physiological process with an internal structure characterized by sleep stages [5]. These sleep stages were originally standardised by Rechtschaffen and Kales in 1968 [19] and later in 2007, they were redefined by the American Association of Sleep Medicine (AASM) [5]. The following five different sleep stages have been identified:

- Stage W (Wakefulness)
- Stage R (Rapid eye movement - REM)
- Stage N1 (non REM - NREM 1)
- Stage N2 (NREM 2)

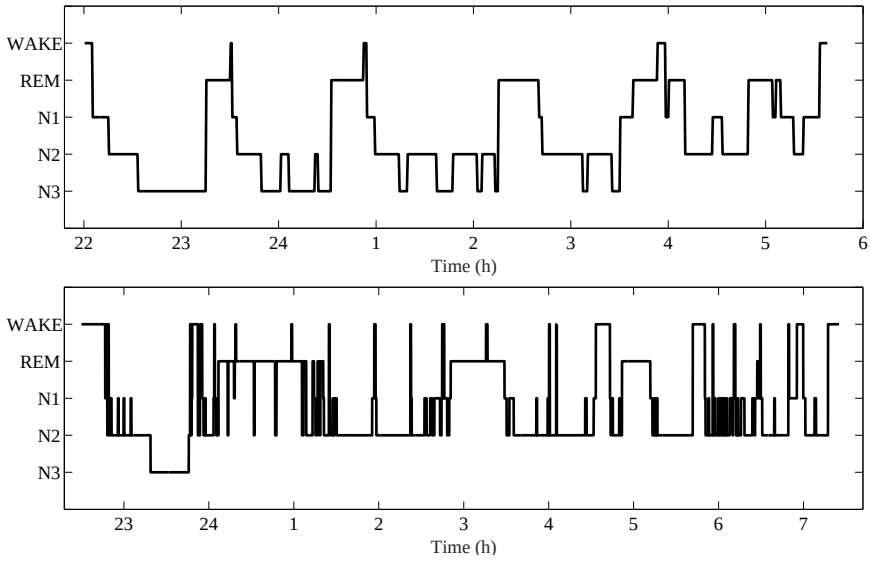


Figure 1: Exemplary hypnogram for a healthy sleep stage distribution (upper plot), and real hypnogram recorded from a patient suffering from sleep apnea (lower plot).

- Stage N3 (NREM 3)

The REM sleep stage can be subdivided into tonic REM and phasic REM [20]. In order to differentiate between them, wave characteristics in the electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG) have been clearly identified for each stage [5]. This differentiation is typically done using consecutive windows of 30 seconds, where one sleep stage is assigned to each window. As a result, a sleep profile, or so-called *hypnogram*, can be obtained for the entire night. Figure 1 shows an exemplary hypnogram of a healthy sleep stage distribution and a real hypnogram recorded from a patient suffering from sleep apnea.

A series of sleep cycles can be observed in the healthy distribution of sleep stages depicted in Figure 1. One sleep cycle typically lasts between 90 and 110 minutes, and it ideally follows a sequence that starts with wake followed by light sleep, namely N1 and N2, then a period of stage N3, which is also called deep sleep, and ends with REM sleep. From the lower plot of Figure 1 it is possible to observe that this sequence is destroyed in patients suffering from apnea. This particular example reveals an increased amount of time in light sleep (N1 and N2) and Wake, and it shows that deep sleep is only reached once during the entire night. These interruptions of the sleep cycle (i.e. sleep fragmentation) disrupt the restorative function of sleep and result in the multiple symptoms associated with sleep apnea. These symptoms will be discussed later in this chapter.

Sleep stages have a profound effect on the autonomic nervous system (ANS) [1]. During NREM, the activity of the parasympathetic nervous system (PNS) increases with respect to the one of the sympathetic nervous system (SNS), which is relatively low and stable. In tonic REM sleep, the latter is further reduced, while the PNS activity remains more or less unchanged. A different pattern is observed during phasic REM, where both the PNS and SNS activities increase with respect to the previous stages. At this point the activity of the SNS becomes variable and much

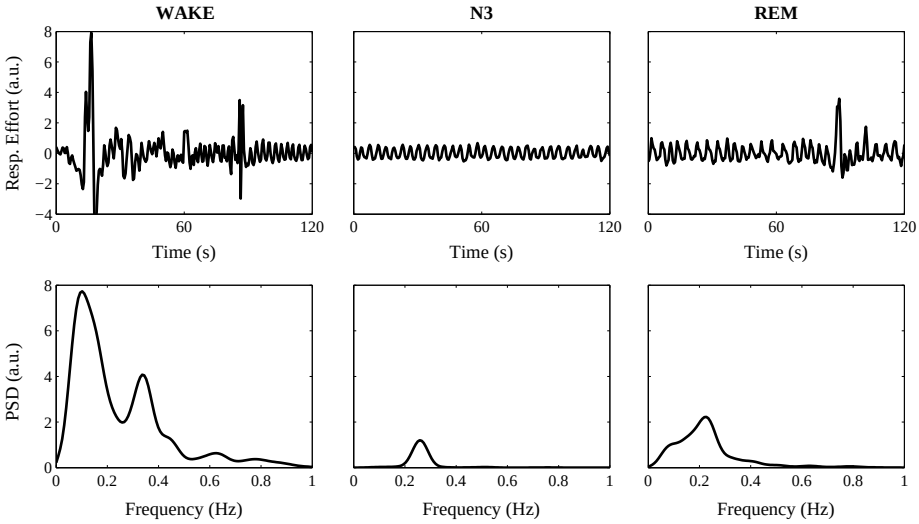


Figure 2: Two-minute segments of respiratory effort measured on the thorax (upper plots) and their corresponding PSD (lower plots). Note the clear regularity during deep sleep (N3), where a dominant respiratory frequency can be identified. In contrast, during both REM and Wake a wider respiratory bandwidth is observed.

higher than the PNS [14, 21]. Since the ANS is in charged of the unconscious control of both the heart and lungs, these variations are also reflected in the cardiac and respiratory activities.

3.1 Respiratory changes during sleep

In general, healthy adults tend to breath faster and shallower during sleep than during wakefulness, causing hypoventilation and hypoxia [22]. Nevertheless, clear differences in respiratory dynamics have been observed between sleep stages [22, 23]. In NREM sleep, the ventilation is reduced when compared to wakefulness, and the regularity of the respiration increases as the sleep goes from stage N1 to stage N3 [22]. On the other hand, during REM sleep the respiratory rate and depth tend to be very irregular [14, 22, 4], and the air volume tends to be similar [23] or even lower [22] than during NREM. In fact, the minute ventilation ($\dot{V}_E$)[1] can be reduced up to 84% of the values during wakefulness. This hypoventilation can be explained by a reduction in the ventilatory drive typical of REM [22]. Examples of these variations in the regularity and depth of the respiration are depicted in Figure 2. These segments of respiratory effort show that indeed there are morphological differences between sleep stages and that the bandwidth of the respiratory signal during deep sleep reveals a more regular breathing. All these changes suggest that the respiratory control during sleep can go from being entirely automatic during NREMS, to behavioral-based during REMS [14], where the metabolic control of respiratory drive is disturbed [23].

Different linear and nonlinear techniques have been used for the analysis of respiratory dynamics during sleep stages. From previous observations it is clear that simple features like the respi-

[1]Minute ventilation is the total air volume entering the lungs per minute

ratory frequency, the respiratory amplitude [22], and the power of respiration in the different frequency bands of HRV [4] clearly differ between sleep and wake. Although these features have a certain discriminative power, their accuracy is limited by the presence of artefacts and non-stationarities in physiological signals like the respiration. In addition, it is generally accepted that the respiratory signal is a nonlinear deterministic process, and that mathematical tools for the description of complex and chaotic processes are of great use in the analysis of respiratory signals during sleep [24].

Detrended fluctuation analysis on respiratory variability during sleep

Respiration can be seen as an integrative process, where each present breath is correlated with previous breaths [23]. Therefore, short- and long-term correlations are expected, and studies have shown that this is indeed the case. Long-term correlations were unveiled during REM sleep in healthy adults using detrended fluctuation analysis (DFA) [25]. This was done after applying DFA to breath-to-breath (BB) signals, which are computed as the time differences between consecutive peaks in the respiratory signal during deep sleep, REM sleep and Wake. In order to avoid transient influences caused by the transitions between sleep stages, 45s epochs at the beginning and at the end of each stage are often removed from the analysis [25, 23]. Linear and higher order polynomials were used in the fitting procedure of the DFA, resulting in DFA1, DF2, and DFAn, for linear, quadratic and order n polynomials, respectively. Figure 3 shows the log-log plot of the fluctuation function $F(L)$ against the time scale L, computed for a healthy adult during WAKE, N3, and REM sleep, using DFA1. This method allows to identify long-term correlations in the data when the scaling exponent is larger than 0.5 (i.e., $\alpha > 0.5$). In this particular example the results reported in [25] for sleep and in [26] for wakefulness were reproduced, where $\alpha = 0.94$ during REM sleep and $\alpha = 0.91$ during wakefulness confirm the long-term correlations in the breath-to-breath signals. In contrast, during deep sleep and light sleep, a loss of long-term correlations were observed. In [25] it was also shown that similar results can be found for different trends, namely using DFA2, DFA3, and higher polynomials. These results suggest that there is a difference between the autonomic regulation of respiration during REM and NREM sleep, and that the breath intervals are not completely independent from each other during REM sleep.

Apart from the long-term correlations discovered using DFA on the BB signal, short-term correlations have been found after applying DFA on drive and timing respiratory components [23]. Examples of these components are the minute ventilation ($\dot{V}_E$), tidal volume (V_T), respiratory drive ($[V_I/T_I]$) that is computed as the inspiratory volume (V_I) divided by the inspiratory time (T_I), and the respiratory time ($[T_I/T_{Tot}]$), which results after dividing T_I by the total time of the respiratory cycle (T_{Tot}). Two main scales were defined in [23] to analyze the correlations within the data. Scales between 7 and 14 breaths were taken for the analysis of short-term correlations (STC), and scales between 16 and (possibly larger than) 35 breaths were considered for long-term (LTC) correlations. After applying DFA2 on the different drive and timing respiratory components, the correlations indicated in Table 1 were found to be significant. The LTC indicate that even though the respiration becomes more irregular during REM, the respiratory pattern is not random, and the breath intervals are not independent from each other. These results are in agreement with those reported in [25]. The STC, on the other hand, suggest

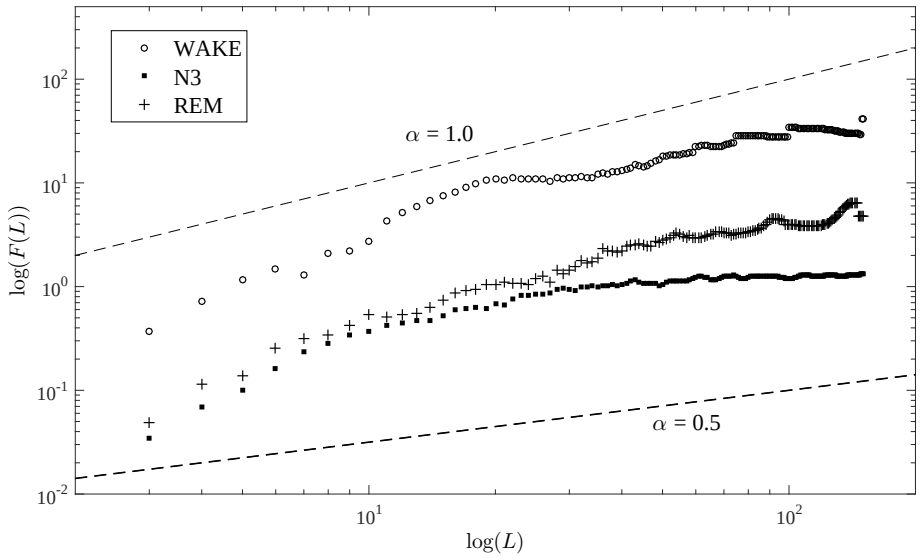


Figure 3: Detrended fluctuation analysis (DFA1) applied to breath-to-breath intervals of a healthy adult. Representative segments of 5 minutes were taken for each sleep stage in order to illustrate the findings reported in [25]. The scaling exponent α is equal to 0.91 in Wake, 0.55 during N3, and 0.94 during REM.

that the regulation of respiratory timing and drive are different, and that the latter remains unchanged during NREM and REM sleep. In other words, since the respiratory timing does not display STC, while the respiratory drive does, it is clear that timing and drive are regulated in a different way. One hypothesis is that the control of respiratory drive is done automatically and purely metabolic, in order to maintain blood gas homeostasis, while respiratory timing is more weakly and behavioural-based controlled to allow voluntary respiratory acts [27, 24].

Even though the mechanisms responsible for the respiratory regulation during sleep have not yet been fully understood, DFA has proven to be a powerful tool to identify regulatory differences between REM and NREM.

Table 1: Short- (STC) and long-term (LTC) correlations during REM and NREM sleep obtained using DFA2 in [23].

	STC	**LTC**
NREM	V_I/T_I V_T $\dot{V}_E$	NONE
REM	V_I/T_I V_T $\dot{V}_E$	T_I/T_{Tot} V_I/T_I $\dot{V}_E$ V_T

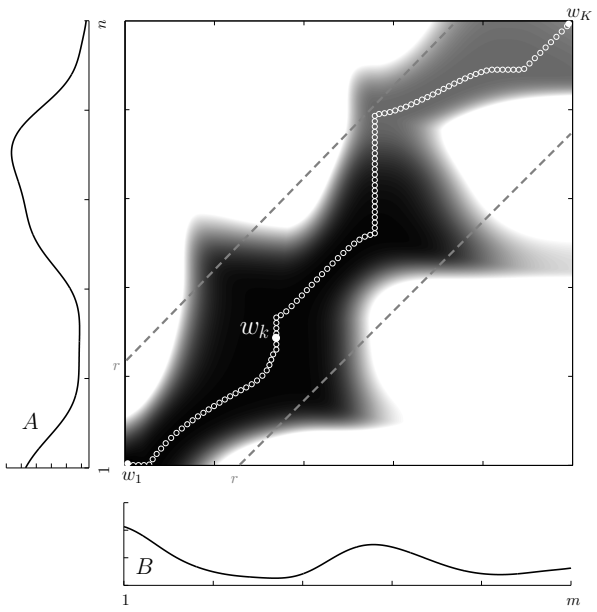


Figure 4: Dynamic time warping (DTW) between the time series A and B, which correspond to two respiratory segments of 5 seconds during deep sleep. The warping matrix D contains the distances between the series, with white indicating higher distances. The white circles depict the optimal path retrieved between the boundaries defined by r.

Dynamic warping on respiratory effort during sleep

Based on the increased regularity of the respiratory signal during sleep, a self-similarity function can be used to discriminate between wake and sleep segments. In [28, 29], this similarity was measured using dynamic warping (DW) in time and frequency domain [30]. Dynamic time warping (DTW) allows to assess the similarity between two time series by means of a non-linear mapping of one onto the other.

Given the time series $A = \{a_i\}_{i=1}^{n}$ and $B = \{b_i\}_{j=1}^{m}$, a *warping matrix* $D \in \mathbb{R}^{n \times m}$ is constructed with entries d_{ij} defined as

$$d_{ij} = (a_i - b_j)^2. \tag{1}$$

In order to find the best alignment between the time series, an optimal path in D must be retrieved such that the cumulative distance between the series is minimized. This cumulative distance (DW) is defined as

$$DTW(A, B) = \left[\frac{1}{K} \sqrt{\sum_{k=1}^{K} w_k} \right], \tag{2}$$

with $w_k = (i, j)_k$ the k^{th} element of the path $W = \{w_k\}_{k=1}^{K}$, and K the total length of the path. This procedure is illustrated in Figure 4, where two real respiratory segments during sleep are used.

In principle, all the distance values in D could be taken into account for the computation of

the optimal path. However, the computational complexity of the algorithm increases with the length of the series, hence, in order to reduce the space search, five conditions can be used:

- *Monotonicity:* Guarantees that the indexes i and j are always increasing or remaining the same during the search, $i_l \geq i_{l-1}$ and $j_l \geq j_{l-1}$
- *Continuity:* The path takes indexes with one step at the time, $i_l - i_{l-1} \leq 1$ and $j_l - j_{l-1} \leq 1$
- *Boundary constraints:* $i_1 = 1$, $i_K = n$, $j_1 = 1$, and $j_K = m$
- *Warping window:* It is unlikely to find an optimal path far from the diagonal of D. This condition restricts the changes in i and j to a band of width r, such that $r > 0$ and $|i_l - j_l| \leq r$
- *Slope constraints:* $i_{l_p} - i_{l_0}/j_{l_p} - j_{l_0} \leq q$ and $j_{l_p} - j_{l_0}/i_{l_p} - i_{l_0} \leq p$, with $p, q \geq 0$, and p and q the number of steps in the horizontal direction and vertical direction, respectively.

This DTW procedure finds the minimum distance value between two time series, while dynamic frequency warping (DFW) computes the minimum distance between two PSDs.

Since respiration tends to be more regular during sleep, respiratory segments recorded during sleep are expected to be more self-similar than to segments recorded during wakefulness. In addition, the respiratory effort signal is known to be influenced by respiratory movements, as can be concluded from a correlation coefficient $r = 0.56$ with $p < 0.0001$ obtained between DTW features and parameters derived from actigraphy [29]. This suggests that body activity can be estimated from the respiratory effort. With this in mind, respiratory effort signals were recorded on the thorax of healthy volunteers, and different features such as time domain, frequency domain, and sample entropy were computed. A linear discriminant classifier was used and an accuracy of about 76% was reached for the discrimination between wake, REM, and NREM. A lower accuracy ($\approx 64\%$) was obtained when a discrimination between light and deep sleep was attempted. These performances can be improved by adding features computed from actigraphy as in [28]. In this case, DTW and DFW features were used together with actigraphy and a discrimination between wake and sleep was achieved with an accuracy of about 95%. Despite this improved performance, the discriminatory power of the respiratory effort and actigraphy is very limited for the classification of the different sleep stages. Nevertheless, this limitation can be overcome by the inclusion of cardiac and cardiorespiratory information into the classifier. This will be discussed further in this chapter.

Other nonlinear techniques applied to respiratory signals during sleep

Correlation dimension (CD) has also been used to analyze the complexity and nonlinearities of the respiratory signal during sleep stages. In [31], a population of healthy volunteers was used, and a differentiation between the correlation dimension during REM and NREM sleep was made. Correlation dimension was lower during deep sleep than during REM, which indicates once again that the respiration behaves in a more regular way during deep sleep, and that the complexity of the respiratory signal is higher during REM [24, 31]. In order to test for the

presence of nonlinearities in the respiratory signal, a comparison between the CD calculated from respiratory movements on the chest and the CD from surrogate data was performed. Significant differences were found between both CDs during REM and NREM, with much higher values during REM. This suggests that respiratory signals have nonlinear properties during sleep [24]. Similar results were also obtained in pre-term infants despite the fact that sleep dynamics are known to be completely different between both age groups [31].

A different measure of complexity that has been used for the analysis of respiratory signals during sleep is the *approximate entropy* (ApEn). In [24], the use of ApEn confirmed once again that an increased regularity in the respiratory signal can be found in deep sleep with respect to REM. Similarly, a surrogate data analysis was also performed using the ApEn, and again nonlinear dynamics in the respiratory signals were found during sleep. Finally, a comparison between the fundamental frequency of the respiratory signal obtained from the PSD, and the ApEn was performed for each sleep stage. A weak linear relationship between both parameters was found. However, no differentiation could be made between sleep stages using only the respiratory frequency despite the significant differences in ApEn. These results suggest that ApEn allows to extract more information about sleep stages than the classical spectral analysis.

3.2 Cardiac changes during sleep

Sleep stages deeply influence both the blood pressure (BP) and the heart rate (HR). For instance, NREMS are accompanied by bradycardia, hypotension and a reduction in cardiac output [21, 1, 14], effects which are more pronounced during deep sleep (N3). Bradycardias have been associated with an increase in parasympathetic activation, while hypotension results from vasodilation caused by a reduced sympathetic modulation [21]. During REMS, on the other hand, HR and BP can increase to levels similar to those recorded during wakefulness [21]. Nevertheless, it is important to differentiate between phasic REM, where there is rapid eye movement, and tonic REM, where there is not. Phasic REM is characterized by unstable HR and BP, and great transients in the cerebral blood flow [14]. Instead, during tonic REM, HR and BP can be reduced to values even lower than those recorded during NREMS. These variations in BP and HR during REM sleep, have been associated with potential cardiovascular risk for patients suffering from coronary and cerebrovascular diseases [1], and with myocardial ischemia [21].

It is clear that cardiac activity is influenced by the sleep stages, and this can be observed not only from the different values of HR but also from the *Heart Rate Variability* (HRV) [32]. This variability can be studied using the RR-interval time series, which is computed using the time differences between consecutive R-waves in the ECG. When looking at the RR-interval time series computed for a full night (see Figure 5), it is possible to observe changes in both the absolute value of the HR and the HRV during the different sleep stages. In fact, each sleep stage is characterized by a different pattern in the RR series. Figure 6 shows the RR series during 2 minutes of Wake, 2 minutes of deep sleep (N3), and 2 minutes of REM. As shown in the figure, the HR displays more regular oscillations during N3 than during Wake and REM. These oscillations are mainly modulated by the respiration through the well-known *respiratory sinus arrhythmia* (RSA). During Wake and REM, the RSA is attenuated by other sympathetic and parasympatethic modulators, which cause significant transient increases in HR, as can be seen in Figure 6. Spectral analysis of the RR-interval time series has shown an increase in the

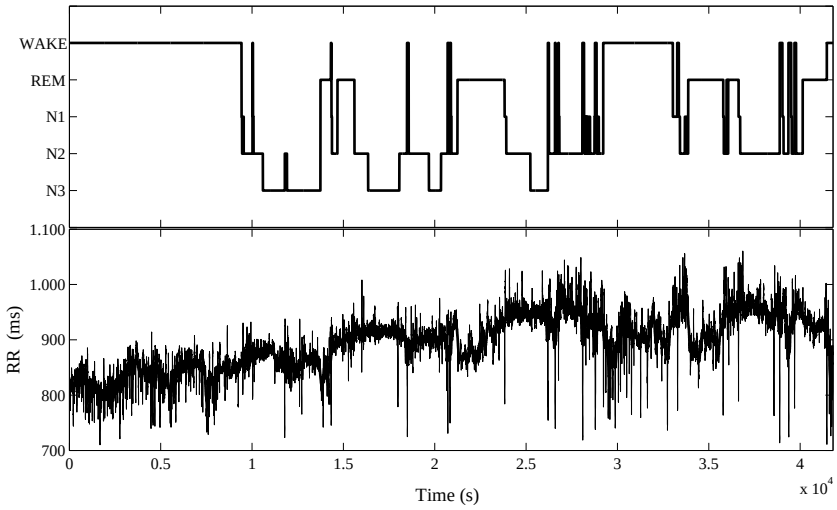


Figure 5: Hypnogram of a healthy subject (upper plot) and the progression of the RR-interval time series throughout the night (lower plot). Note the general trend towards a decreased HR (i.e. increase in RR-interval) during sleep, and the apparent changes in HRV during the different sleep stages.

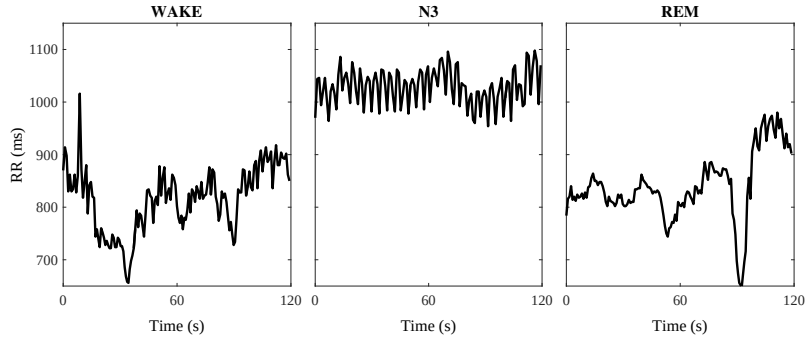


Figure 6: Segments of RR-interval time series of 2 minutes during WAKE, deep sleep (N3), and REM.

HF accompanied by a reduced LF component during NREM, and an opposite effect during wakefulness and REM sleep [33]. These results are in agreement with a higher sympathetic activation during REM and wakefulness. All these changes in autonomic control are influenced not only by the current sleep stage, but also by the preceding one and by the point in the sleep cycle [34]. For example, it has been observed that a period of REM sleep at the end of the night is accompanied by a larger sympathetic activation than a REM segment at the beginning of the night [35]. This again, can be associated with an increased risk of cardiovascular events during the early morning [35].

Linear techniques such as the mean, standard deviation, autocorrelation, and spectral analysis have been used to study the HRV during sleep. They have shown that the HRV is, indeed, significantly higher during REM sleep than during NREM [32], however, they are not able

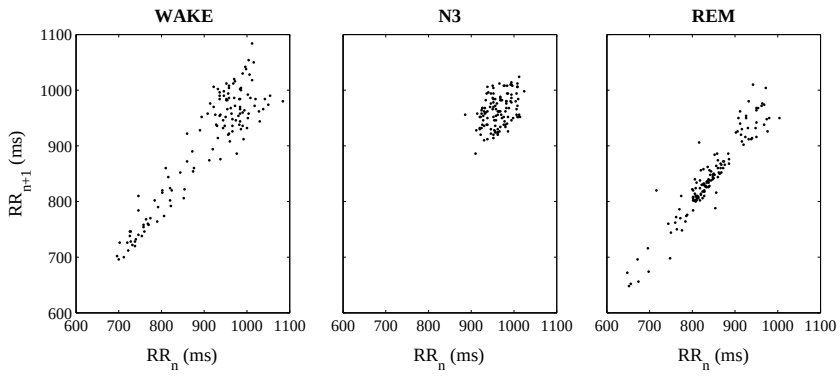


Figure 7: Poincaré plots of three RR-interval time series of 2 minutes during WAKE, deep sleep (N3), and REM.

to describe instantaneous changes in the control of the HR. Therefore, the use of nonlinear techniques is of paramount importance to assess the time-dependent behavior of the HR.

One way of analyzing the short- and long-term variability of the HR is by means of the Poincaré plot, where each RR-interval RR_n is plotted against the next interval RR_{n+1}. The scattering and the trajectory of the points describe the dynamics (depending on the extracted indices either linear and/ or nonlinear) of the HRV. The dispersion of the points along the y-axis for a given x indicates the beat-to-beat variability, while the total dispersion of the points in the x-axis describes the overall variation of the HR. Figure 7 shows three Poincaré plots obtained from RR-interval segments during wakefulness, deep sleep (N3), and REM sleep of a healthy adult. Here, the results presented in [32] are reproduced, and it is clear that high correlations exist between consecutive RR-intervals for the different sleep stages. The plots show that during N3 sleep, the overall variation of the HR is lower while the beat-to-beat variability is higher. This confirms that during this sleep stage the HR is more regular and mainly modulated by the RSA. In fact, these results can also be associated with a more regular respiratory signal during N3, as discussed in Section 3.1.

The reduced beat-to-beat variability during REM can be explained by a higher regulation of the short-term variability of the HR during REM [36]. In addition, the plots of Figure 7 confirm that the overall variability of the HR during REM is similar to the one recorded during wakefulness.

Different features can be extracted from the Poincaré plots. For instance, an ellipse can be fitted to the plot and the minor axis (SD1) can be associated with the beat-to-beat variability, and the major axis (SD2) with the long-term HRV. The ratio between the axes (SD1/SD2) indicates the relationship between short- and long-term variation of the HR [37]. These features were compared against typical linear and nonlinear measures of HRV in [38, 39], and high correlations were found between SD1 and HF and RMSSD. This is not a surprise, since the short-term variability is mainly vagally mediated. Similarly, SD2 was found to be highly correlated with SDNN, which is an indicator of the global HRV [38, 39]. A more interesting result was the high correlation obtained between SD1/SD2 and the short-term scaling exponent (α_1) computed using DFA [39]. More specifically, α_1 defined within the range of 4 and 11 heart beats. These findings suggest that nonlinear information of HRV might be described by the ratio SD1/SD2. However, these results need to be interpreted carefully, since other studies have shown that this

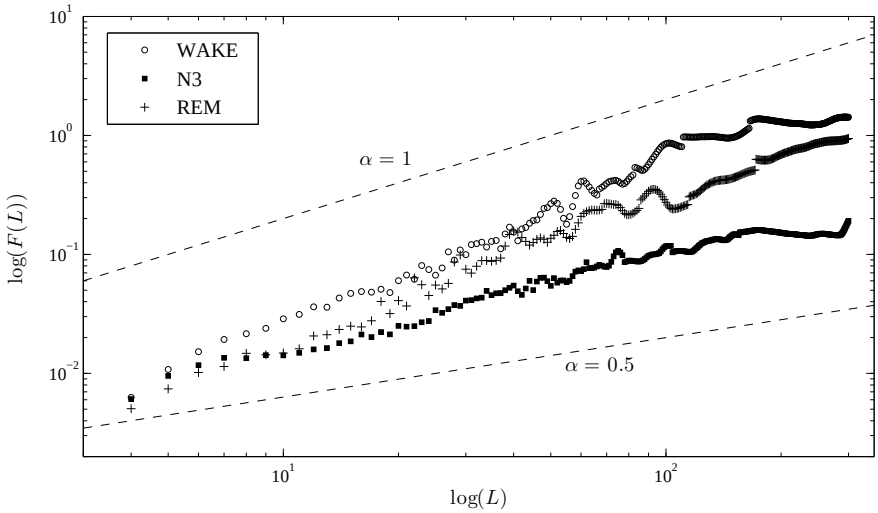


Figure 8: Second order detrended fluctuation analysis (DFA2) of 2 minute segments of RR-interval time series during wakefulness, REM, and deep sleep. For comparison, the dashed lines indicate uncorrelated ($\alpha = 0.5$) and correlated ($\alpha = 1$) behaviour.

ratio is only correlated with linear indices of HRV [38].

HRV analysis during sleep using detrended fluctuation analysis

Detrended fluctuation analysis (DFA) has been extensively used for the analysis of heart rate variability during sleep. Figure 8 shows the fluctuation curves ($F(L)$) for three different RR-interval segments recorded during wakefulness, deep sleep, and REM of a healthy adult. These curves were obtained using DFA2, where a second order polynomial was used in the detrending phase. The line with $\alpha = 0.5$ indicates uncorrelated behavior of the RR-intervals, while the line with $\alpha = 1$ indicates high correlations in the data. These results are consistent with the ones reported in [9, 40, 41], where quadratic and cubic polynomials were used in the analysis. Clear differences were found between sleep stages. In particular, the slope of the fluctuation function during N3 sleep is close to 1/2, which suggests a *loss* of long-term correlations, whereas some short-term correlations might be taking place during this stage. The latter are noticeable in the very small values of L, where it is clear that only after few heart beats in N3, the correlations are lost. In contrast, during REM and wakefulness clear long-term correlations can been identified. In [40], different degree polynomials were used for the detrending phase in order to evaluate the dependency of the results to the trends in the data. Again, the same results were found using a polynomial of up to a fourth degree. Furthermore, this analysis provided evidence that during deep sleep, the short-term correlations vanish after a time shorter than the breathing cycle time, which comprises few RR-intervals. This is, again, a strong indication of a higher cardiorespiratory coupling during N3.

The study of the different dynamics of the HRV during sleep stages is regularly performed using epochs of few minutes, where the transition periods between stages are eliminated [9, 40, 41].

Often, these periods are taken as the first and last 45s of each sleep stage. In [40], however, the RR-interval time series computed from the whole night were analyzed using DFA, without differentiating between sleep stages. As a result, a scaling exponent $\alpha = 0.85$ was obtained, which suggests the presence of long-term correlations in the beat-to-beat variability during the entire night. Moreover, the authors compared these results with those obtained after eliminating the transition periods and concatenating all the sleep stages together. The resultant fluctuation curve ($F(L)$) was similar to the one obtained during light sleep, with a lower scaling exponent. These results indicate that the long-term correlations identified during the entire night are caused by the transition periods between sleep stages.

One technique that can be used to analyze the whole night of recording without overestimating the long-term correlations, and without removing the transition periods, is *progressive* detrended fluctuation analysis (PDFA) [42]. The main difference between PDFA and DFA is that the integrated time series is no longer divided into non-overlapping windows of size L. Instead, PDFA analyzes partial sums of the total time series separately. The length p of these partial sums is increased progressively from 1 to the length of the series, i.e., $p = 1 \dots N$. Next, each partial sum is divided into non-overlapping epochs of fixed length L, which are then detrended as in DFA. As a result, a plot of the new fluctuation function against time can be obtained. This curve allows to identify the transition periods where the scaling exponent changes between one sleep stage to the other. In fact, the PDFA curves can be used to detect *ascending* transitions, namely, from deep sleep to either lighter sleep or wakefulness [43, 42], with more pronounced PDFA changes during the transitions to wakefulness. Conversely, *descending* transitions are not clearly identified from the PDFA curves. One possible explanation for this is the increased sympathetic tone experienced during the ascending transitions, and the fact that PDFA seems to be more sensitive to autonomic arousals [43]. Consequently, PDFA can be used to detect autonomic arousals and transitions to wake as demonstrated in [44].

Different studies have shown that DFA can be used to discriminate between sleep stages. For instance, Penzel et al. [41] compared the discrimination power of the scaling exponents against features derived from spectral analysis of HRV. Two different scaling parameters were computed, namely, α_1 defined in the range between 10 and 40 beats, and α_2 defined as the slope of the fluctuation curve between 70 and 300 beats. Furthermore, a discrimination between light sleep, deep sleep, REM, and wake was performed. The study showed that 78.4% of the RR-interval segments were correctly classified using only the DFA features, and after including the mean and standard deviation (SDNN) of the RR-intervals, this performance increased to 85%. In contrast, after using the classical spectral parameters of HRV, only 51.4% of the segments were assigned to the correct sleep stage. Finally, a combination of all DFA, spectral features, mean, and SDNN, resulted in 84% of correctly classified sleep segments. It is clear that the best discrimination could be done using DFA and time domain parameters of HRV.

The performance achieved using only spectral features of HRV is limited by the use of fixed LF and HF frequency bands. This is due to the time varying modulation of the ANS. In order to overcome this limitation, the boundaries of the HRV analysis can be adapted by means of time-frequency analysis. As a result, an accuracy of about 93% can be achieved in the classification of sleep and wake using only spectral features of HRV [45]. Note, however, that no differentiation can be made between the sleep stages using this approach.

Entropy measures of cardiac activity in healthy sleep

During sleep, several physiological mechanisms such as the baroreflex, central oscillations, sympathovagal balance, hormonal regulators, amongst others, play a key role in the regulation of the heart rate. This regulation, however, is strongly modified during sleep [21], and this can be clearly observed from the complexity of the HRV [46]. To measure this complexity during sleep, different entropy measures like Shannon entropy (SE), approximate entropy (ApE), sample entropy (SampEn), and conditional entropy (CE)[47] have been used, and the main findings will be described next.

Since REM sleep is characterized by an irregular HR and a higher autonomic activation that reaches values similar or even higher than those recorded during wakefulness, the complexity of the HRV during this sleep stage is expected to be higher [46]. However, opposite results have been reported on the behavior of entropy measures during REM sleep. In [48], for instance, SE and corrected conditional entropy (CCE) were studied in both young and old healthy subjects. No significant differences were found between the entropy values of different sleep stages in the young population. In contrast, older subjects displayed a significant reduction in complexity during wakefulness, light sleep and REM, with a more pronounced effect during the latter. This suggests that ageing causes a reduction in the complexity of the cardiovascular system, which in a long-term can be associated with less flexibility of the system to respond to stressful situations. Furthermore, this reduction in complexity is larger during REM, which again confirms that REM can be linked with a higher cardiovascular risk.

In a different study on healthy subjects, the SampEn was computed for different frequency components of the HRV, and then compared between sleep stages [49]. Five minute segments of RR-interval time series were first decomposed into three main components using a five-level wavelet decomposition. These components correspond to the very low frequency band (VLF: 0.0.0375 Hz), low frequency band (LF: 0.0375-0.15 Hz), and high frequency band (HF: >0.15Hz). Then, mean, standard deviation (SD), and SampEn were computed for each component and for each segment, after which a comparison between sleep stages was performed. The main results of this study are the increased SampEn values during deep sleep in the VLF band, and the increased SD during REM in all frequency bands. In fact, the SD during REM is significantly higher than during wakefulness, while no clear differences were found in SampEn values between these two stages. Even though the mechanisms responsible for the VLF variations of HRV are not yet fully understood, the results obtained during deep sleep can be associated with thermoregulatory changes, as suggested in [49]. The behavior observed during REM, on the other hand, is consistent to the one reported in [40], where a similar nonlinear behavior was observed during REM and Wake. A possible explanation for these results is that nonlinear HRV features describe the stability and the energy expenditure during each sleep stage. In particular, deep sleep is characterized by a regular HRV with a strong cardiorespiratory coupling, which results in a low energy expenditure, while REM sleep is accompanied by irregular HR and a high energy expenditure similar to wakefulness [49].

Other nonlinear measures of cardiac activity during sleep

A different way of quantifying the complexity of the cardiac activity during sleep was adopted in [50], and it used the entire ECG signal, instead of only the RR-interval time series. ECG segments of 2min44s were selected from a dataset recorded from 12 healthy adults during sleep, and different nonlinear features such as correlation dimension (D2), largest Lyapunov exponent (L1), and Kolmogorov entropy (K2), were computed. The main goal of the study was to identify possible differences between the ECG morphology during different sleep stages. Results indicate that D2 and K2 are the most discriminant features for the task of sleep staging, followed by L1. Moreover, L1 was found to be significantly larger and D2 significantly lower during REM sleep than during deep sleep. These findings reveal a lower complexity and a more chaotic behavior of the ECG during REM sleep.

With these results and those obtained using DFA and entropy-based features, it is possible to conclude that the increased HRV during REM sleep is associated with a less predictable ECG dynamics, and with a reduction of the RSA as a main modulator of the HR caused by a reduction of the parasympathetic modulation.

3.3 Cardiorespiratory changes during sleep

The analysis of linearities and nonlinearities of the heart rate and respiration showed that the effect of sleep stages was very similar in both [25]. As a result, it can be hypothesized that either both the cardiac and respiratory systems are affected in the same way, or that the cardiorespiratory coupling is modified during sleep.

Three different forms of cardiorespiratory coupling have been identified during sleep [51, 52], namely, respiratory sinus arrhythmia (RSA), cardiorespiratory phase synchronization (CRPS), and time delay stability (TDS). These different forms of coupling act in different time scales, and they all reflect different regulatory mechanisms. In [52], the HR and the respiratory signal recorded from 189 healthy adults were analysed, and it was shown that the RSA amplitude is highest during deep sleep, and lowest during REM and wakefulness. No clear differences between REM and wake were observed, but a tendency to lower RSA during wake was reported. These results are consistent with the different respiratory and cardiac findings discussed in previous sections. More interesting results were the clear differences in the strengths of the other two forms of cardiorespiratory coupling during sleep stages. The degree of CRPS, on the one hand, was highest during deep sleep and it significantly decreased during REM sleep to values even lower than those during wakefulness. An important finding is that compared to RSA, CRPS exhibits more pronounced changes between sleep stages. This behaviour of CRPS is consistent among all age groups as reported in [53], however, the degree of synchronization is reduced with age. This indicates that the effect of sleep on this form of cardiorespiratory coupling is maintained regardless of the age.

A comparison between RSA and CRPS revealed that they are two completely independent forms of coupling [52]. For example, it is known that RSA is a frequency dependent phenomenon, with a nonlinear response to changes in the respiratory frequency [54]. In contrast, the CRPS does

not display any dependency on the breathing frequency, in fact, different degrees of CRPS can be observed in a period of constant RSA.

The strength of the TDS, on the other hand, displays a completely different behaviour during REM and deep sleep than the one of RSA and CRPS [52]. TDS was much higher during wakefulness and light sleep, and lowest during REM and deep sleep. Furthermore, a remarkable difference was revealed between light and deep sleep, despite their similarities in the linear and nonlinear features of HRV. These results suggest that TDS reveals the effect of different regulation mechanisms of heart rate and respiration during sleep. In addition, TDS acts on a different time scale, namely, between 150 to 220 seconds, while CRPS is often observed within 20 to 45 seconds, and RSA comprises only few heart beats. The study of these three forms of coupling during sleep stages reveal that the autonomic regulation manifests itself in different ways and at different time scales. In effect, this is a step forward towards the understanding of the underlying autonomic control mechanisms of the cardiorespiratory system.

The results obtained with TDS can be explained by a different brain-heart connectivity during sleep stages. In [52], the coupling between different EEG channels with both the HR and the respiration was quantified using the TDS. This quantification revealed a different topology in the network during sleep stages. A higher connectivity was identified during light sleep and wake, a lower connectivity during REM sleep, and a loss of connectivity during deep sleep. Indeed, these results are very similar to those obtained using TDS on the HR and respiration, which suggests that TDS offers information about connectivity and network topology that the other forms of coupling cannot describe. Moreover, these results are also consistent with those reported in [55], where information dynamics was used to quantify the interactions between the frequency components of the EEG and the HRV in the HF band, during sleep. It was shown that information flow is bidirectional between brain and heart systems during sleep. In fact, the EEG β rhythms are the ones that appear to be sending most of the information to the heart. Furthermore, the links between brain and heart are stronger during light sleep, reduced during deep sleep, and partially or completely lost during REM. In other words, the brain components seem to be decoupled from the heart system during deep sleep and REM. This effect can be possibly explained by the changes in the dynamics of the heart occurring during sleep, which on their turn affect the coupling mechanisms with the brain and the respiration. Besides, it is also possible that the definition of the time scale limits the description of the network topology. Therefore, studies with different representations of the cardiac, respiratory, and brain activity need to be performed in order to enhance the understanding of this complex network. Methods that can be considered for this include the point process analysis presented in [56] and the instantaneous transfer entropy proposed in [57]. The advantage of these methodologies is that they can be used to analyze the whole night of recording without overestimating the long-term correlations, and without removing the transition periods between the different sleep stages.

3.4 Algorithms for sleep staging

It is clear that sleep stages affect the morphology of the ECG, the heart rate, the respiration, and the cardiorespiratory coupling. For this reason, heart rate and respiration have been extensively used in the development of algorithms for sleep staging. In fact, multiple algorithms have been proposed and they can be separated into three main groups according to the type of classification

they perform, namely, sleep-wake, wake-REM-NREM (WRN), and wake-REM-light sleep-deep sleep (WRLD). Typically, sleep staging algorithms attempt to generate a hypnogram with a 30s resolution [4, 17]. Nevertheless, in [58] a classification was made on 1 minute segments in order to match with the classical sleep apnea detection, which is often performed on a minute-by-minute basis.

Algorithms based solely on the respiratory signal have achieved accuracies of up to 76% in WRN classification, and 63.8% in WRLD classification [29]. The algorithm proposed in [29] derives different features from the respiratory effort, such as, time and frequency parameters, non-linear features using dynamic time and frequency warping, and sample entropy. When only the features derived using dynamic warping were used, an accuracy of about 94% was achieved for sleep-wake classification. Algorithms based on the HR and HRV consist of either very simple rules as in [59], or of features derived using empirical mode decomposition, discrete wavelet transform, and linear and nonlinear dynamics features as in [60]. Even though these algorithms have proven to be good discriminators between sleep stages, mainly between sleep and wake stages, it is known that the fusion of features derived from the ECG and actigraphy allow for a better accuracy in sleep-wake classification [28]. In addition, the fusion between features derived from each modality separately and those quantifying cardiorespiratory coupling can achieve higher performances for the different classification tasks. Tables 2,3, and 4 summarize the results obtained with different algorithms, modalities, and for the three different classification tasks on healthy subjects. In the tables, Rs stands for respiratory signal, EDR is the ECG-derived respiration, Act stands for actigraphy, and EMD stands for empirical mode decomposition. After comparing the results, it is clear that nonlinear and complexity features have an added value in the different classification tasks.

Table 2: Performance of Sleep-Wake classification algorithms

Reference	**Signals**	**Features**	**Kappa**	**Acc.** (%)	
Redmond et al. 2007 [4]	HR, Rs, EDR	Time and Frequency domain	0.6	89	
Domingues et al. 2014 [61]	RR, Rs, Act	Frequency domain, CRPS	-	80.2	
Long et al. 2014 [45]	HR, Act	Frequency domain	0.64	95.8	
Long et al. 2014 [28]	Rs, Act	DTW, DFW	0.66	95.7	
Willemen et al. 2014 [13]	HR, Rs	Time and frequency domain	0.69	92	

Table 3: Performance of WRN classification algorithms

Reference	**Signals**	**Features**	**Kappa**	**Acc. (%)**	
Redmond et al. 2007 [4]	HR, Rs, EDR	Time and Frequency domain	0.46	76.1	
Ebrahimi et al. 2015 [62]	HR, Rs	Time and frequency domain, EMD, SampEn, DFA, SE, ApE	-	89.32	
Ebrahimi et al. 2013 [60]	HR	Time domain, Wavelet, DFA, ApE, SampEn SE, EMD	-	80.67	
Domingues et al. 2014 [61]	RR, Rs, Act	Frequency domain, CRPS	-	66.4	
Mendez et al. 2010 [63]	HR	Time-varying spectra	-	79.3	
Long et al. 2014 [29]	Rs	Time and frequency domain, DTW, DFW, SampEn	0.45	76.2	
Fonseca et al. 2015 [10]	HR, Rs	Time and frequency domain, DTW	0.56	80	
Willemen et al. 2014 [13]	HR, Rs	Time and frequency domain	0.62	81	
Kortelainen et al. 2010 [64]	HR, Act	Time-varying spectra	0.44	79	
Xiao et al. 2013 [65]	HR	Time and frequency domain, DFA, Multiscale entropy, Mutual Information	0.46	72.58	

Table 4: Performance of WRLD classification algorithms

Reference	**Signals**	**Features**	**Kappa**	**Acc. (%)**	
Isa et al. 2011 [66]	HR	Time and frequency domain	0.26	60	
Long et al. 2014 [29]	Rs	Time and frequency domain, DTW, DFW, SampEn	0.38	63.8	
Fonseca et al. 2015 [10]	HR, Rs	Time and frequency domain, DTW	0.49	69	
Willemen et al. 2014 [13]	HR, Rs	Time and frequency domain	0.56	69	

The performance of the different classifiers is determined using the annotations provided by the sleep experts. However, disagreement between scorers is known to play a key role in the reduction of this performance. In [67], a sleep stage agreement of 82.6% was found between more than 2500 scorers, with a higher agreement for the REM stage followed by N2 and wake. The agreement for N1 and N3 was 63% and 67.4%, respectively. These results suggest that there is room for improvement in the definition of the rules for sleep staging, and that an agreement of about 83% needs to be taken into account when comparing classification results.

4 Sleep apnea

Sleep apnea is an under-diagnosed sleep-related breathing disorder that affects up to 10% of middle-aged adults [68]. The reason for its under-diagnosis relies on the unawareness of the symptoms among the general population. Usually, people wait too long before seeking professional help, and they only do it when serious symptoms appear or when the disorder has reached an advanced stage. Clear symptoms of sleep apnea include excessive daytime sleepiness, fatigue, nocturia, irritability, depression, amongst others. In addition, sleep apnea is considered a risk factor for morbidity and mortality due to its long-term effect on the cardiovascular system [69]. This effect is linked with systemic hypertension and increased sympathetic modulation, which in a long-term compromise the well-functioning of the heart [70]. Not to mention the fact that hypertension is recognized as a common cause of cardiovascular and cerebrovascular diseases.

Sleep apnea is currently diagnosed using polysomnography (PSG), which is a sleep test that monitors different physiological signals such as heart rate and respiration. This test is typically performed in a hospital setting and it requires the supervision of a clinical expert, factors that make PSG an uncomfortable and costly procedure. For this reason, multiple studies have focussed on the development of less invasive devices for the diagnosis of sleep apnea. These devices are often designed using the heart rate and respiratory signals due to the clear effect that apnea has on the cardiorespiratory system [71, 11, 15, 12, 72].

Apneas and hypopneas are two types of respiratory events that are respectively characterized by a complete absence or reduction of airflow for at least 10s [73]. These events may occur up to hundreds of times per night, and they often last for 30-60s [9]. Apneas can be subdivided into three categories according to the respiratory effort: obstructive sleep apneas (OSA), central sleep apneas (CSA), and mixed apneas (MSA). During OSA events, the interruption of the respiratory flow is caused by an obstruction of the upper airways despite the respiratory effort, while in CSA events, this is caused by an absence of respiratory effort. MSA events are a combination of OSA and CSA and they typically start with a reduction of the respiratory effort that leads to an upper airway obstruction. Hypopneas, on the other hand, are characterized by a reduction of airflow, caused by either an obstruction or a reduced respiratory effort, that results in a drop of oxygen saturation. All apneas and hypopneas end with an arousal, which is a physiological state where the ANS restores the breathing regulation. The sympathetic tone increases as a consequence of these arousals and this on its turn causes an increase in heart rate. Figure 9 shows a segment of heart rate and respiratory effort before, during and after an OSA episode. Note the increase in respiratory effort followed by an increase in heart rate at the end of the apnea event. These arousals are responsible for the disruption of healthy sleep patterns,

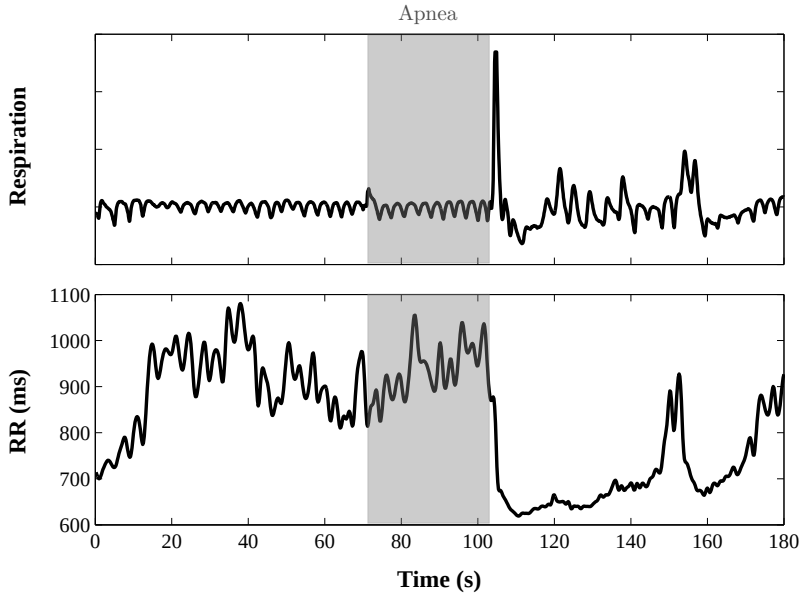


Figure 9: Respiration and heart rate during an OSA episode, which is indicated by the gray area.

as can be seen in Figure 1, which results in severe sleepiness during the day. The effects of sleep apnea on the dynamics of the cardiorespiratory system and on the "normal" sleep pattern will be described next.

4.1 Effect on respiratory dynamics

Sleep apnea is characterized by frequent discontinuations in the respiratory pattern, which result in breath-to-breath (BB) intervals larger than 10s [74]. This is, however, not the only effect that apnea has on the respiratory dynamics. The analysis of the distribution of BB signals recorded from patients suffering from sleep apnea, showed that the variability and regularity of the breathing pattern is affected during nonapneic periods [74]. In fact, an increased variability was reported in OSA patients when compared to the normal population, during all sleep stages. These changes in breathing variability could be associated with a higher upper-airway resistance typical in OSA patients.

Apart from BB variability, the respiratory movements appear to be random in OSA patients, according to the analysis of the largest Lyapunov exponent and correlation dimension performed in [75]. These results were later confirmed in [76], where the phase-space plots computed using respiratory effort signals during sleep periods of OSA patients, reveal the presence of random attractors. The latter study also attempted to analyze the correlation dimension, but its computation was not possible during sleep segments with apnea due to the lack of a plateau in the correlation integral curves. These results suggest an increase in complexity during these segments, however, further investigation is still needed to support these findings. In addition to segments with apnea, periods during wakefulness with eyes closed, and sleep with nasal continuous positive airway pressure (nCPAP) were also analyzed in [76]. The values of correlation

dimension derived from these segments were compared against surrogate data, and results indicate that respiratory movements display a nonlinear deterministic behavior. Furthermore, the values of correlation dimension were different for two pressure values in nCPAP, namely, 3 cm H_2O and 8 cm H_2O. As a result, correlation dimension could be considered as an index for titration of the CPAP treatment [76].

4.2 Effect on cardiac dynamics

The cardiac effects of apnea have been widely investigated using several aproaches, such as linear and nonlinear techniques of HRV and morphological changes in the ECG [11, 77, 41, 78, 79, 80, 12]. For instance, spectral HRV analysis performed on apnea patients during wakefulness has revealed a possible autonomic dysfunction caused by sleep apnea [77]. This was concluded after observing lower HF values in patients than in controls, during free and controlled breathing periods. Similarly, a reduced vagal activation was also observed in apnea patients, during all sleep stages, and an increased sympathovagal balance was observed during wakefulness and N2 [41].

The complexity of the HRV signal in apnea patients was investigated in [78] by means of sample entropy. It was concluded that, similarly to the respiratory signal, the HRV pattern seems to be more regular in apnea patients. Therefore, a lower complexity of the HRV can be associated with the cyclic pattern consisting of bradycardia and tachycardia characteristic of apnea events.

The dynamics of the HRV signal during sleep stages in apnea patients have also been investigated using DFA [41, 9, 81]. In this context, a comparison between the long-term correlations described in Section 3.1 and those obtained in sleep apnea has been performed. This comparison is illustrated in Figure 10, where the results presented in [41] were reproduced using the HRV signal recorded from one sleep apnea patient of the sleep laboratory of the University Hospital Leuven (UZ Leuven), Belgium. Here, the DFA3 was used and the scaling parameter α was computed in the range $70 \leq t \leq 300$. The slopes of the fluctuation curves depicted in Figure 10, suggest that in the apnea patient the long-term correlations observed during REM sleep and wakefulness are maintained, while no long-term correlations are observed neither in deep nor in light sleep. These results are very similar to those obtained for the healthy population, which indicate that the long-term control mechanisms of the heart rate are only slightly affected by sleep apnea [81, 41].

4.3 Effect on cardiorespiratory interactions

Sleep apnea is associated with a reduced vagal activation during sleep, which might lead to changes in the way the respiration interacts with the heart rate through the RSA. This has been studied in [82], where the HR control during inhalation was found to be different than during exhalation. The increase in HR during inhalation is significantly affected during OSA events, while the HR decrease during exhalation seems to remain unchanged. The latter, however, disappears at the end of the event, possibly due to the arousal. These results suggest an inhibition of the vagal activation after the apnea event, which agrees with the increased sympathovagal

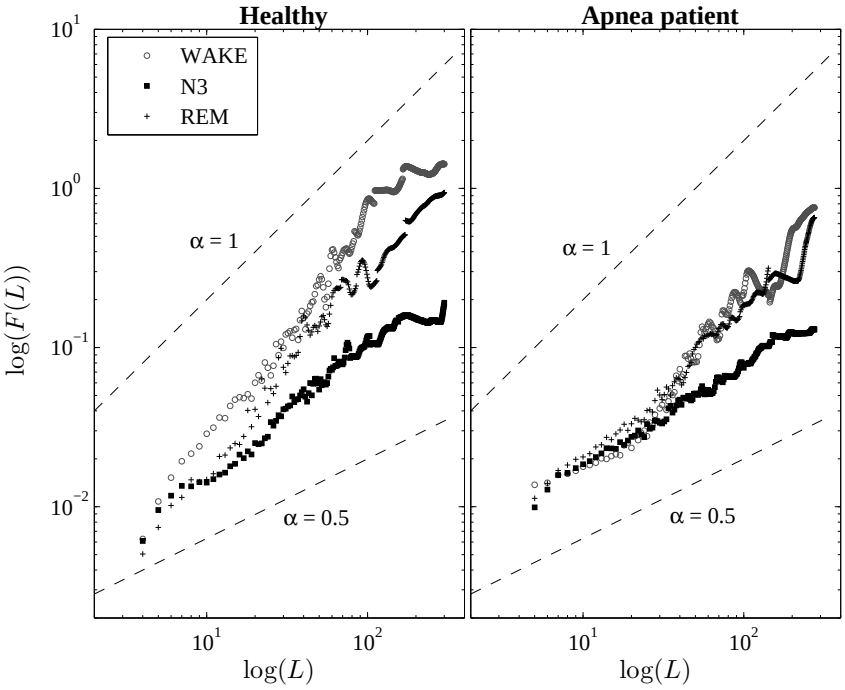


Figure 10: Third order detrended fluctuation analysis (DFA3) of 5 minute segments of RR-interval time series during wakefulness, REM and deep sleep of a healthy adult (same as in Figure 8) and an apnea patient. For comparison, the dashed lines indicate uncorrelated ($\alpha = 0.5$) and correlated ($\alpha = 1$) behaviour. The scaling parameters for the healthy subject and apnea patient were, respectively, 1.14 and 1.25 during wakefulness, 0.57 and 0.55 during N3, and 1.23 and 0.96 during REM.

balance used by many in sleep apnea detectors [79].

In [83], the cardiorespiratory coupling was analyzed using the cross-spectrum between the RR-interval time series and respiratory signal, in the LF (0.01-0.1 Hz) and HF (0.1-0.4 Hz) frequency bands. The study was based on the fact that there is a high-frequency coupling (HFC) related to the RSA, and a low-frequency coupling (LFC) associated with cyclic patterns in respiration of about 25-50 seconds. The LFC appears to be more accentuated in apnea patients, and it is directly associated with apnea episodes. Furthermore, it was demonstrated that OSA events display a broad band LFC, while CSA a narrow band LFC. These differences in the cardiorespiratory coupling could be used to differentiate between CSA and OSA, as proposed in [83].

Assessment of cardiorespiratory coupling using orthogonal subspace projections

The cardiorespiratory coupling was also investigated in [12], where orthogonal subspace projections (OSP) on the RR-interval time series and the ECG-derived respiratory signal (EDR) were used. This approach decomposes the HR signal into two different components, one containing all variations related to respiration, and one where all other modulators different from respiration

are described. The general procedure to perform this decomposition will be described next.

Given are two physiological signals, namely the RR-interval time series denoted by $\mathbf{X}$ and the EDR signal denoted by $\mathbf{Y}$. All the information contained in $\mathbf{X}$ that is linearly related to $\mathbf{Y}$, can be computed by projecting $\mathbf{X}$ onto a subspace $\mathbb{V}$ defined by variations in $\mathbf{Y}$. Once the basis $\mathbf{V}$ for the subspace $\mathbb{V}$ is computed, any signal $\mathbf{X}$ can be projected onto the subspace, by means of $\mathbf{X_Y} = \mathbf{PX}$, with $\mathbf{P}$ a projection matrix defined as $\mathbf{P} = \mathbf{V}(\mathbf{V}^T\mathbf{V})^{-1}\mathbf{V}$. Note that $\mathbf{X_Y}$ describes the dynamics of $\mathbf{X}$ related to $\mathbf{Y}$, and the part of $\mathbf{X}$ that is related to other mechanisms can be computed as $\mathbf{X_{Y^\perp}} = \mathbf{QX}$, with $\mathbf{Q} = I - \mathbf{P}$.

It is clear that the main result of this algorithm is the computation of a component of heart rate related to respiration denoted by $\mathbf{X_Y}$, and a component related to mechanisms other than respiration denoted by $\mathbf{X_{Y^\perp}}$.

The construction of the subspace $\mathbb{V}$ can be done using wavelet decomposition of the respiratory signal and selecting only the coefficients in a certain frequency band. In [12], this approach was used, and two main frequency bands were used, namely LF:$< 0.07Hz$ and HF:$0.07 - 0.6Hz$. As a result, the subspace related to respiration was constructed using the wavelet coefficients in those frequency bands and their delayed versions, using delays from 1 to m seconds. The relative power of each component was then computed as $F = (\mathbf{X_Y^T X_Y})/(\mathbf{X}^T\mathbf{X})$ for each subspace, or each frequency band. Figure 11 shows these power values for two different datasets: the Physionet Apnea-ECG dataset and a dataset collected in the sleep laboratory of UZ Leuven. For the latter, annotations of the different types of apnea were available, which allowed a differentiation between the cardiorespiratory interactions for each type. These results are again in agreement with the previous findings, where reduced interactions in the HF band were observed for apnea patients.

This approach takes into account only the linear cardiorespiratory interactions. In order to describe the nonlinear interactions, a nonlinear transformation is applied to both the HR signal and the respiratory signal as in [84]. Similar results were obtained, however, a better discrimination between normal and OSA events was achieved after taking nonlinearities into account. In particular, higher nonlinearities were found in the LF band, which lead to an improvement in the classification performance.

A different form of cardiorespiratory coupling, namely, CRPS also appears to be affected by sleep apnea, in particular by OSA [85]. This has been studied in [85, 86], where the phase of the heart rate and respiratory signals were calculated using the Hilbert transform. Then, the phase difference was used to estimate the phase-locking periods, which correspond to times where the phase difference remains the same or below a certain threshold. Results of these studies indicate that the phase-locking periods are reduced in OSA, and their reduction is more pronounced in severe OSA patients. These results can be associated with the reduced vagal activation and the elevated sympathovagal balance observed in apnea patients as discussed before. In other words, the cardiorespiratory control might also be influenced by the ANS, which on its turn is affected by the repetitive occurrence of apnea episodes.

Multiple techniques have been used to quantify the changes in the cardiorespiratory coupling, and they have been used for the classification of apnea episodes from the ECG. Some of these techniques will be discussed next.

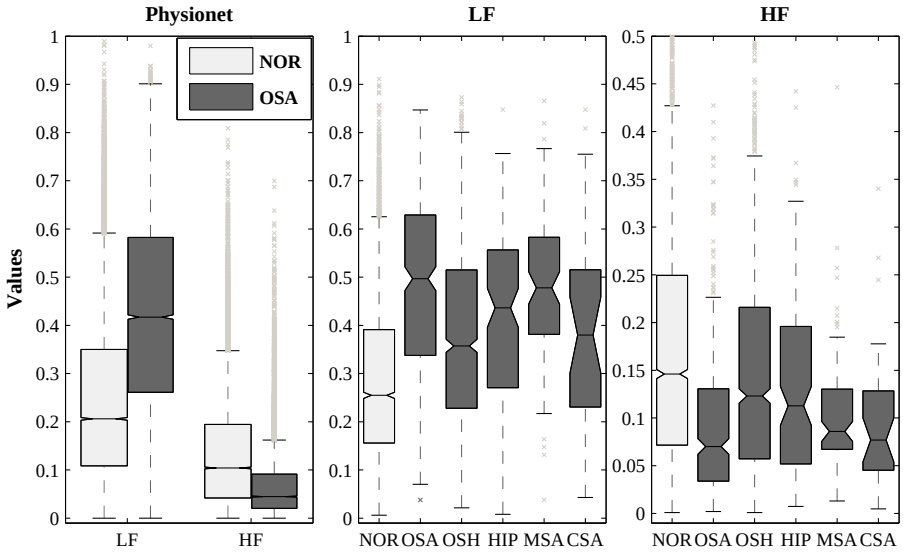


Figure 11: Relative power of HR projected onto the respiration in the LF and HF bands. The middle and right plot show the values for the dataset recorded in UZ Leuven. Normal segments: NOR; Obstructive apneas: OSA; obstructive hypopneas: OSH; hypopneas: HPA; central apneas: CSA; and mixed apneas: MSA, are indicated.

4.4 Sleep apnea detection

The clear changes in respiration, heart rate, and cardiorespiratory coupling during apnea episodes have motivated the development of detection algorithms using as few signals as possible. For example, [71, 11, 15, 87, 12] proposed to derive several features from the electrocardiographic (ECG) signal to detect sleep apnea. Moreover, instead of measuring the respiratory signal, those algorithms first compute the so-called ECG-derived respiration (EDR), and then derive a set of features that can later be used for the discrimination of apneas. Algorithms to compute the EDR include the R-peak amplitude [88], principal component analysis (PCA) [89], and kernel PCA [90].

The performance of the sleep apnea algorithms is typically evaluated on the *Apnea-ECG* dataset, publicly available in Physionet. However, many algorithms are tested on private datasets. Hence, the interscorer disagreement reported in [91] must be considered when comparing algorithms. An overall agreement of 93.9% for scoring respiratory events was reported, with an agreement for OSA segments, hypopnea segments, and CSA segments of 77.1%, 65.4%, and 52.4%, respectively. These results reinforce the fact that the detection of hypopneas and central apneas constitute a big challenge in sleep apnea detection. Hypopneas, for instance, appear very similar to normal segments in the ECG, which makes them very difficult to identify using only this signal. Obstructive sleep apnea, on the other hand, is much easier to detect from the ECG, and many algorithms have been proposed to solve this problem. In [79] a summary of the results of the Physionet challenge of 2000 is presented, and the algorithm with the best performance that uses a fully automated approach is described in [11]. This algorithm uses the time and frequency features of HRV, and it achieves an accuracy of 89.4% for the detection of sleep apnea on

a minute-by-minute basis. A different fully automated algorithm was recently proposed in [12], and it uses features derived by means of OSP and features describing the changes in morphology of the ECG. An accuracy of 84.74% was reached by this algorithm on the Physionet dataset. Mendez et al., 2010 reported accuracies of 89% and 85% using empirical mode decomposition and wavelet analysis of the HRV, respectively, on the same dataset [92]. However, these last results were achieved after manually correcting the position of the Rpeaks in the ECG.

On a different (private) dataset, the spectral features of HRV achieved an accuracy of 70.4%, and together with values of sample entropy, an accuracy of 72.9% was reached [78]. In a different study, the time domain features, namely, the mean and the standard deviation of the RR-interval series, together with the scaling parameters derived using DFA2, achieved an accuracy of 74.4% in the discrimination of apnea cases [41].

The detection of CSA has been tackled in different studies. For instance, in [87] features derived from the recurrent plots obtained from the EDR signal achieved a positive predictive value of 60% and a sensitivity of 84%. In [83], on the other hand, a PPV of 58% and a sensitivity of 81% were obtained using features derived from the cross spectral power between the RR-interval time series and the EDR.

As can be seen, the sleep apnea algorithms that use linear techniques have outperformed those based on nonlinear approaches for the detection of sleep apnea. Nevertheless, complexity measures might be useful for the detection of central sleep apnea. The detection of hypopneas, however, from the cardiac and respiratory signals remains an open problem.

The aforementioned methodologies focused on the minute-by-minute classification, which might be later used to assess the severity of the disease in each particular patient. Other methodologies have focused on the assessment of the severity of OSA for each patient, without looking into each particular event. An example of such a methodology is the one presented in [93], where symbolic dynamics applied to HRV was used together with clinical data, such as age, neck circumference, daytime sleepiness, and intensity of snoring, to classify patients with high probability of OSA. This algorithm reached an area under the ROC curve of 94.1% in a private dataset. Even though this algorithm integrates clinical information with physiological variables, other algorithms, like those described in [94, 95, 96], which are based solely on the linear dynamics of HRV still reach an accuracy of 100% on the detection of OSA patients. These results suggest that linear dynamics of HRV might be enough to detect patients suffering from obstructive sleep apnea. However, it is important to note that these studies have not included patients with heart disorders, which are known to be closely related to the sleep apnea syndrome [69]. Hence, the question of whether nonlinear dynamics can improve the classification of sleep apnea in the general population remains open.

5 Public datasets for sleep staging and sleep apnea detection

The following list summarizes the public datasets that are available for the analysis of the dynamics of HRV and/or respiration during sleep and sleep apnea.

- The Apnea-ECG database [71] is commonly used to test ECG-based algorithms for sleep apnea detection. It contains 70 ECG recordings, of which 8 are accompanied by signals of respiratory effort, oro-nasal airflow, and blood oxygen saturation.
- The MIT-BIH Polysomnographic Database [97] is regularly used for the analysis of sleep stages, and it might be used for the study of chronic obstructive sleep apnea syndrome. The dataset includes, amongst other signals, 16 ECG recordings accompanied by respiratory signals, which were either measured with a nasal thermistor or derived from inductance plethysmography.
- Sleep recordings and hypnograms in European data format (EDF) [98]. This dataset contains 61 PSGs, which contain oro-nasal respiratory signals that can be used for the analysis of respiration during different sleep stages.
- The CAP Sleep Database [99] consists of 108 PSGs that include the ECG signal, airflow, and respiratory effort recorded on both the abdomen and the thorax. This dataset is useful for the analysis of HRV and respiratory dynamics during sleep stages. The data includes recordings from healthy subjects and patients diagnosed with either nocturnal frontal lobe epilepsy, REM behavior disorder, periodic leg movements, insomnia, narcolepsy, sleep-disordered breathing, or bruxism.
- The Sleep Heart Health Study (SHHS) [100, 101, 102] can be used to analyse the impact of sleep-disordered breathing on the cardiovascular system. In this dataset more than 9000 PSGs are included, which contain, among other signals, the ECG, the respiratory effort on both the abdomen and thorax, and the airflow.
- The DREAMS Apnea Database [103] consists of 12 PSGs of patients suffering from sleep apnea. It contains ECG recordings, respiratory effort on both the abdomen and thorax, and nasal airflow. Annotations of sleep apnea events and sleep stages are available, which allow to use this dataset for both tasks described in this chapter.
- The St Vincent's University Hospital/University College Dublin sleep apnea database [104] contains 25 PSGs from adults suffering from sleep-disordered breathing. The recordings include the ECG signals, respiratory efforts, and oro-nasal airflow, among others. Both sleep stages and respiratory events are annotated in the dataset.

6 Conclusions

This chapter focused on the cardiorespiratory changes during sleep, and on how they are affected by sleep apnea. Special attention was on the complexity of the heart rate and respiratory signals during different sleep stages and on how their complexity is reduced due to the occurrence of sleep apnea events. In addition, the use of different nonlinear techniques for the assessment of cardiorespiratory dynamics was discussed in the framework of sleep staging and sleep apnea detection. For the sleep staging problem it was shown that a slight increase in performance could be obtained by including nonlinear features of HRV. However, for sleep apnea detection this has not been the case yet. The best algorithms in literature are based on features derived from the HRV and EDR signal using linear techniques, in particular, the classical time and frequency domain features of HRV. This can be seen as an advantage, since the clinical interpretability

of linear methods is often simpler than that of the nonlinear counterparts. As a consequence, linear methods might be more easily accepted in a clinical setting.

Despite the good performance of the algorithms describing linear dynamics, it is important to keep in mind two main considerations. On the one hand, most of the public and private datasets on sleep apnea that have been used in the literature, do not include patients suffering from a cardiovascular disease. This can be seen as a limitation, since it is well-known that sleep apnea has a long-term effect on the cardiovascular system. Therefore, the effect of the nonlinear behaviour of HRV on the classification performance is still unknown in this type of patients.

On the other hand, it is essential to consider the assumptions and limitations of the nonlinear methodologies that have been used for the detection of sleep apnea before concluding that nonlinearities are not useful for this task. For instance, the accurate computation of some nonlinear features (e.g. DFA and Lyapunov exponent) can only be done on long time series. Moreover, some approaches assume either stationarity (e.g. Sample entropy, orthogonal subspace projections) or a certain joint probability distribution between heart rate and respiration, not to mention the bias induced by artefacts in the time series. As can be seen, non-linear methods, with different assumptions, might still contribute to the improvement of sleep apnea detection in the general population.

All in all, the influence of nonlinearities of heart rate and respiration during sleep and sleep apnea is not yet fully understood. Further research is needed to assess how nonlinear approaches can improve the understanding of the physiology during sleep.

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