1. Introduction

Obstructive sleep apnea (OSA) is a common disorder with a prevalence of 2% and 4% in middle-aged women and men, respectively [Young et al, 2002]. Obstructive sleep apnea is characterized by the recurrent collapse of the pharyngeal airway during sleep, which generally requires arousal to reestablish airway patency and resumption of breathing. OSA first symptoms are decrease in oxygen saturation, snoring and frequent arousal during night leading to excessive daytime somnolence, poor concentration and irritability [Tarasiuk et al, 2006]. Moreover, untreated OSA is a major risk factor for cardiovascular disease, hypertension, and acute condition such as stroke, myocardial infarction, congestive heart failure and even sudden death [Tarasiuk et al, 2006]. OSA severity is defined by the number of obstructive apnea and hypopnea events per hour of sleep (apnea hypopnea index – AHI).

The gold standard for diagnosis of OSA is polysomnography (PSG). PSG requires a full night hospital stay connected to numerous physiologic electrodes and sensors which placed on the patient's body in order to record and analyze sleep disorders. The high cost of the in-sleep diagnosis, the limited number of available sleep laboratories, and the discomfort of the electrodes attached to the head and body of the patients, are the limitations of the PSG which leads to the desire of having an alternative method to diagnose OSA non-invasively, with greater comfort and at a lower cost.

Snoring is a common and earliest symptom of OSA, caused by the vibration of soft tissues due to turbulent airflow through a narrow oropharynx in the upper airway (UA) [Hofshtein, 1996]. Several studies have shown that OSA is associated with anatomical and functional abnormalities of the upper airway [Ayappa and Rapoport, 2003]. Patients with OSA commonly have narrower and more collapsible upper airways then subjects without OSA [Malhotra et al, 2002]. Similar to the vocal tract in speech production, the UA acts as a variable acoustic filter in the generation of snoring sounds [Abeyranthe, 2005]. Therefore, it is expected that the acoustic characterizations of snores from OSA patients and snores from benign snorers will be different.

However, Even though snoring is the most frequent and earliest symptom of OSA, snoring has not been properly exploited in the diagnosis. Literature describes few attempts for OSA detection using the snoring sounds. Sound intensity [Van Brunt et al, 1997], spectral [Fiz et al, 1996; Sola-Soler et al, 2003; Ng et al, 2007, 2009; Matsiki et al, 2007] and pitch [Sola-Soler et al, 2002; Abeyratne et al, 2005] related features was tested as a diffrentiative feature between benign and apneic snorers. However, none of these works, exhaustively analysed all the snoring episodes for the total sleep period. Understandably, one of the major difficulties in doing that is the huge amount of data generated in a 6-7 hours sleep, and the difficulties in manually extracting all the snoring events. Those studies investigated few manually isolated snores. More recently, Fiz et al [2010] used an automatic nocturnal snore detection that allows analysis of all-night acoustic signal acquired using a contact microphone. They concluded that

sound intensity and some snore frequency parameters may differentiate snorers according to OSA severity. However, the major weakness of the aforementioned studies is the limited number of analyzed subjects, and as consequences, no proper validation was done for the reported results.

Additionally, the majority of the previous mentioned studies have focused on intra-snore properties by analyzing snore-by-snore events. It is possible that the biological instability of the upper airway's formation during sleep [Malhotra et al, 2002] may lead to alterations in inter-snore properties (i.e. between snore events, between clusters of snores and across the night), mainly with relations to the proximity of obstructive apnea events per se. To the best of our knowledge, such perspective of analysis was not explored. Earlier study among 18 benign snorers and 12 apneic snorers analyzed sequential properties of snores across the night as a measure of inter-snore properties [Cavusoglu et al, 2008]. They found that OSA patients have higher variances of snores' durations, separations and average powers. However, authors did not mention any classification abilities and on top of that inconclusively findings were reported regard the prediction of AHI, mainly due to the small sample size of patients.

To date, there are no unifying hypotheses that incorporate inter- and intra- snore properties and jointly investigate their relations to OSA severity. In the current study, we developed snore detection algorithm, allows full-night acoustic analysis of snoring events. Various of inter and intra snore acoustic properties were extracted and investigated, and together, their relations to OSA severity was

explored and evaluated, i.e. a system was designed, able to either classify subjects into two or three degrees of severity, or direct estimate subject's AHI. We hypothesize that the acoustic snoring signal carries essential information that may assist discriminate between OSA patients and benign snorers.

Our preliminary results already presented and published on IEEE-EMBS proceeding (Buenos Aires, 2010): [Ben-Israel N, Tarasiuk A, Zigel Y. Nocturnal Sound Analysis for the Diagnosis of Obstructive Sleep Apnea. *Conf Proc IEEE Eng Med Biol Soc.* 2010, in press]. Additional paper is currently in peer-review, submitted to the European Respiratory Journal describing the bulk of this work.

The following document describes our work. The research objectives are the next to be presented. Chapter two presents basics of medical and engineering background needed for the understating of the applied methods. Chapter three specifies the study architecture, i.e. all the methods for data handling, starting from the acquisition process, through pre-processing, to all the applied and developed algorithms. Chapter four deals with the experimental setup, i.e. the acquisition system, what are the subjects' characteristics? how subjects were recruited and the steps they have been through. Chapter five extensively details the results in each of the steps towards the desired system. Chapter six discuss the results and consider the findings and other factors in the light of study limitations and current literature; and ends with conclusions. Chapter seven and last, considers further researches as future work.

1.1. Research Objectives

The overarching goal of this research is to assess whether a nocturnal snore sound signal can be used as a predictor for OSA Syndrome? and if so, does the analysis of this snoring signal has the potential to diagnose the disease severity?; the proposed research aim to develop a computer-based diagnostic and monitoring system for OSA which automatically classifies OSA snorers and benign snorers based on their snore sound signals.

Intermediate objectives are the creation and the organization of snoring signals database. A non contact condenser microphone, connected to an audio recording device, is placed above the patient's bad in the sleeping lab[1]. The acquired acoustic signal (approximately 6 hours) is stored in a computer database with the patient information. The next objective is to develop[2] an automatic snore detection tool aimed to segment sound events into snore, pure breath, silence and other background noises. Subsequently, analysis of the snore episodes should be done in order to identify acoustic features which best correlate with OSA severity and characterize the acoustic differences between apneic and benign snorers. Finally, incorporate the features in order to estimate OSA severity, either categorical using classifier, or AHI estimation using regression models.

As aforementioned, in the previous years, various researchers have been tried to find the acoustic features which will be able to classify OSA and benign snorers

1 Located in the sleep-wake disorder unit, Soroka university medical center.
2 Part of the algorithm was developed within the same framework by Dana Weiss.

using their snore sound signals. However, several factors differentiate our research from previous attempts: (1) Foremost, our method allows the whole nocturnal signal to be processed and analyzed. (2) We propose new acoustic features, which are related to the dynamics of the acoustic characteristics throughout the night. (3) We seek not only the snores, but the relative silence during an apnea event. (4) In addition, we use an adapted version of the mel frequency cepstral coefficients (MFCC), a common speech processing technique. (5) The number of subjects in the study currently stands at 85 subjects, making it one of the largest analyzed databases to date. (6) Unlike previous attempts, we will use accepted system validation techniques. Moreover, (7) the subjects were classified into three degrees of OSA severity (previous studies classify subjects only for two categories): comparison group - non OSA (AHI<10), mild to moderate OSA (10<AHI<30) and severe OSA (AHI>30), (8) on top of that, for the first time, using regression model, subject's AHI will be estimated. (9) And finally, the whole system designed to be fully automated.

The proposed approach for OSA’s diagnosis will reduce the expense and inconvenience convolved with the monitoring in the sleeping labs by "filtering" the healthy subjects and efficiently identifying the relevant patients. Furthermore, such system will able to shrink the long waiting list and economize the financial for the whole healthcare system. On top of that, OSA among patients, may be revealed at much earlier stages, and as consequence, the risk of future health implications will be diminished.

2. Background

The following chapter aim to give the reader all the essential background needed for understanding this paper and the applied methodologies; in addition, broaden literature review is given regards previous and current studies in the field of OSA diagnosis through snore acoustic signals - what has been done, pros and cons, and what we are proposing further.

2.1. Obstructive Sleep Apnea - Medical Background

Obstructive sleep apnea (OSA) is a common sleep disorder which became a worldwide health concern; a study done by Young et al [1993] on 602 US state employees found that it is have an incidence of 24% in men and 9% in women, aged 30-60; Whereas, the estimated averaged prevalence of elders suffer from OSA worldwide[3] is 2% in women and 4% in men [Vgontzas et al, 2001]. Furthermore, an interesting asseveration is that up to 93% of women and 82% of men with moderate to severe OSA remain undiagnosed [Pang et al, 2005]. It seems that the primary explanation for the immensely low rate of diagnosis is the lack of low-cost instruments which suitable for mass screening of the population.

2.1.1. OSA Basic Concepts

OSA is defined as repetitive pauses in respiration, corresponding to obstruction in the upper airways during sleep. An *apnea* event defined as an episode of

3 According to different studies the prevalence varied between countries; from 0.3% in England's males to 20-25% in Israel and Australia [Vgontzas et al, 2001; Young et al, 1993].

complete cessation of breathing, last for at least 10 seconds[4], with continuing inspiratory effort. A *hypopnea* occurs when continues inspiratory effort is accompanied by a reduction of at least 50% in airflow, resulting in either an arousal or oxygen de-saturation of at least 4% [American Thoracic Society, 1996].

Apnea patients may experience 30 to 300 such events per night [Cavasoglu et al, 2007]. A measure for the severity of the OSA is the apnea-hypopnea index (AHI), which expressed as the average number of apnea-hypopnea events per hour of sleep; AHI≤10 said to be normal physical condition, while greater AHI values, might indicate OSA syndrome. Accepted to claim that AHI > 20 indicate the need for CPAP therapy [bar et al, 2003]; AHI>30 indicate severe OSA.

OSA first symptoms are decrease in oxygen saturation, snoring and frequent arousal during night leading to excessive daytime somnolence, poor concentration and irritability [Malhorta and White, 2002]. Untreated OSA is a major risk factor for cardiovascular disease, hypertension, and acute condition such as stroke, myocardial infarction, congestive heart failure and even sudden death [Malhorta and White, 2002].

Several studies have shown that OSA is associated with anatomical and functional abnormalities of the upper airway [Ayappa and Rapaport, 2003; Lan et

[4] In young children, who normally breath at a much faster rate than adults, the pause may be many seconds shorter and still be considered apnea.

al, 2006]. Patients with OSA commonly have narrower and more collapsible upper airways then subjects without OSA.

The most common risk factor for OSA in general and even for snoring in particular are: (1) male gender, (2) obesity and large Neck circumference, (3) smoking, (4) alcohol consumption, (5) ingestion of tranquilizers or muscle relaxants and (5) as some studies argue, inheritance (family history) [Hoffstein, 1996].

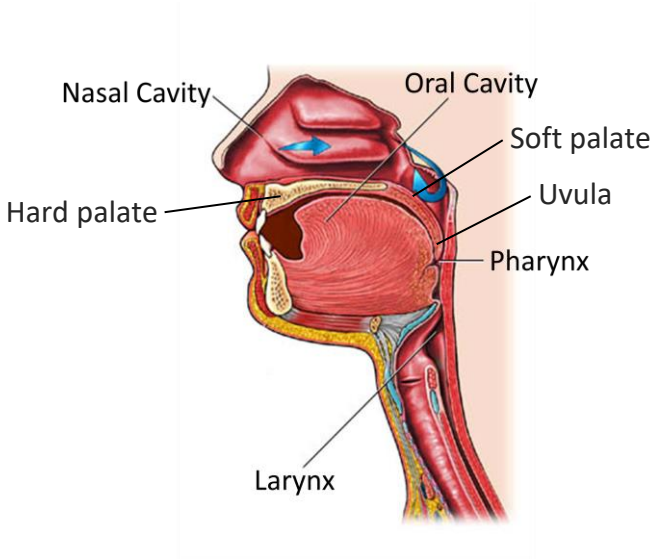

Figure 2.1: Upper airway anatomy

2.1.2. The Diagnosis Today

The gold standard for diagnosis of OSA is polysomnography (PSG). PSG test requires a full night hospital stay connected to numerous physiologic electrodes and sensors which placed on the patient's body and measure signals such as EEG (electroencephalography), ECG (electroencephalography), EOG (electrooculography), EMG (electromyography), airflow, respiratory effort, leg

movements and blood oxygen saturation; all those in order to analyze the sleep disorder [Abeyratne et al., 2005].

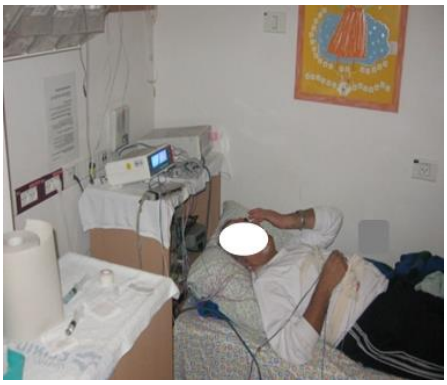

Figure 2.2: Patient during polysomnography test in the Sleep-Wake Disorders Unit, Soroka University Medical Centre.

The high cost of the in-sleep diagnosis and the limited number of available sleep laboratories, are some of the limitations of the PSG. Moreover, elderly or sick patients often find the PSG equipment too cumbersome, the electrodes attached to the head and body of the patients extremely discomforts and therefore may be reluctant to spend the night in the sleep laboratory.

The limited PSG facilities around the world resulted in long waiting lists, and as aforementioned, over 90% individuals with OSA currently remain undiagnosed [Flemons et al, 2003]. Thus, this leads to the desire of having an alternative and available method for diagnosis of OSA non-invasively, with greater comfort and at a lower cost.

Subjective Assessments tool, frequently used to study OSA and snoring is questionnaires, which founded to be useful as a predictor of sleep apnea,

although, myriad studies showed disadvantages and limitations. The main disadvantage described by Hoffstein [1996] as “most snorers are unaware of their snoring”; therefore, he argues that it should be answered by the bed-partners, which is later founded to be mostly uncorrelated with objective measurements.
Many researchers have attempted to search for other modalities to detect OSA, such as nasal pressure [Almeida et al, 2006], airflow [Nakano et al, 2007], and oxygen saturation [Hornero et al, 2007]; however, limitations such as: (1) specific expertise may be needed at the test site, (2) at least one cumbersome physical contact sensor is needed, (3) and sometimes uncertainty conclusions, are only few of the encountered.

Snoring is one of the primary symptoms of OSA and for long been viewed as the base for potential screening tool for apnea; although, it has not properly exploited in the diagnosis yet.

2.2. Snoring and OSA

Snoring is a common and earliest symptom of OSA. The odds for OSA are 3.2 times higher in snorers than in non-snorers [Wilson et al, 1999]. Snoring, caused by vibrating structures of the upper airway (UA). Any membranous part of the UA lacking cartilaginous support may vibrate, including soft palate, uvula, pharyngeal walls and the rest of the UA (almost to the level of vocal chords), due to turbulent airflow through the oropharynx. Recent studies of snoring sounds indicate that snoring occurs during inspiration and expiration[5] [Perez Padilla et al, 2003].

During sleep the tissues of the humans' body are relaxed. This tendency may cause constriction along the UA; accordingly, the breathing might "triggers" mechanical oscillations of tissues, such as those previously mentioned, around the constriction site. The snoring is the result of the tissues' oscillatory motion [Cavasoglu et al, 2007].

Theoretical analyses of snoring show that due to its instability, the repetitive oscillations of the walls may occur anywhere along the airway once the appropriate relationship between flow, airway elastanse and UA dimensions are satisfied. For each snorer, these parameters are unique, and therefore in different patient, the site of the sound production will vary. Moreover, results obtained by direct observations of the upper airway during sleep, show that even in the same patient, snoring may be generated in different sites [Skatvedt et al, 1993].

5 Rather than only during inspiration as was thought previously.

Although snoring is common and routinely been measured in sleep laboratories, little is known about acoustic characteristics of snores produced by OSA versus benign snorer. Earlier studies investigated various sound intensity [Van Brunt et al, 1997], spectral [Fiz et al, 1996; Abeyratne et al, 2001; Ng et al, 2007, 2009; Matsiki et al, 2007] and pitch [Sola-Soler et al, 2002] related features.

To further understand and discuss those attempts, some engineering background and explanations should be given regard acoustic analysis of snores.

2.2.1. Mathematical Model of Snore Production

Many authors suggest that snore and speech production share many similarities. They all [Abeyratne et al, 2005; Sola-Soler et al, 2003] ascribe to the upper airway same objective as to the vocal tract in speech processing theory; both act as an acoustic filter during the production of the sound. Mathematically, the recorded sleep sound signal, can be modelled as:

$$s(n) = s_{snore}(n) + s_{breath}(n) + b(n) \qquad (2.1)$$

Where $s(n)$ {n-sample number} is the recorded discrete signal, $s_{snore}(n)$ is the snore episode, $s_{breath}(n)$ is pure-breath and $b(n)$ represent the background noise (all unwanted acoustical and electrical noise coming from the environment and measuring instruments). Moreover, the snore episodes composed of voiced and unvoiced segments ($s_{snore}(n) = s_v(n) + s_{uv}(n)$) depends on the origin of the excitation. The snoring episode {$s_v(n)$, $s_{uv}(n)$} generated through the UA in a similar manner to the speech production:

$$s_{uv} = h_{uv}(n) * g_{uv}(n) \quad (2.2)$$

$$s_v = h_v(n) * g_v(n) \quad (2.3)$$

Where '*' denotes the linear convolution operator, the 'g' are the excitation sources and 'h' represent the UA which pretended to be an acoustic filter (also called *total airway responses - TAR*; slowly varying functions). Inspired by the speech analysis, the excitation sources can be considered a white noise process for unvoiced snores, and a pseudo periodic sequence, coming from the vibrated tissue, for the voiced segments (as the vibration of the vocal chords in speech analysis) [Sola-Soler et al, 2003].

To put it in order, voice segment generation modelled as vibration in the upper airways, represented as repetitive sound pulses of the type $\sum p(t - kT)$, filtered by the anatomic properties of the upper airway and surrounding tissue (*h(n)*). Then, neglecting the train finite duration, the produced signal can be expressed as $s(n) = w(t - kT)$, or in the frequency domain as:

$$X(f) = W(f) \sum \delta\left(f - \frac{k}{T}\right) \quad (2.5)$$

Regards the last expression: first, the fundamental frequency defined to be $f_0=1/T$ is the rate of the pulse repetition (the vibration frequency); second, *W(f)* is the spectral envelope contains knowledge about the filter, means carry information about the Upper airway anatomy [Abeyratne et al, 2005].

2.2.2. Concepts from Speech Processing

To understand the principles behind our methods, several explanations of common speech processing concepts are in order.

Liner Predictive Coding Model (auto regressive filter)

In speech processing theory, the spectral envelope originated from the vocal-tract contains information about the anatomical state. Most of the characteristics are hidden in the resonance frequencies. Well known method to extract the envelope of the acoustic filter frequency response is the linear predictive coding (LPC model) which simulates the acoustic filter to an auto regressive (AR) filter (also called all-pole filter). Fig 2.3 illustrates a *p*-order LPC model for the production of the sound signal.

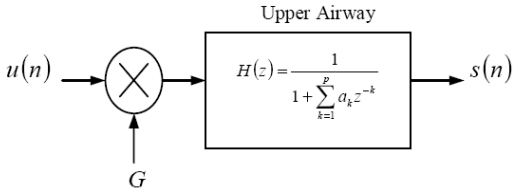

Figure 2.3: Speech signal production model adopted for snoring

The excitation source *u(n)* is modulated by the gain factor *G* and the scaled source is used as an input to the upper airway which is modelled to an AR filter (LPC); the *p* predictor coefficients, a_k, of the AR are computed using the auto-correlation method [Makhoul et al, 1975] guaranteeing all poles to be stability (inside the unit circle); To compute the coefficients for the auto correlation method, the Levinson-Durbin recursion is utilized aim to solve the Yule-Walker equations [Deller et al, 2000].

Cepstrum and mel-frequency-cepstrum

The cepstrum is a representation used in speech signal processing, to convert signals combined by convolution (such as the excitation and its filter) into sums of their cepstra, for linear separation. In particular, the power cepstrum is often used as a feature vector for representing the human voice. For these applications, the spectrum is usually first transformed using the mel-scale. The result is called the *mel-frequency cepstrum* or MFC (its coefficients are called mel-frequency cepstral coefficients or MFCCs). The cepstrum is useful in these applications because the low-frequency periodic excitation from the vocal cords and the formant filtering of the vocal tract, which convolve in the time domain and multiply in the frequency domain, and as such, are additive and in different regions in the quefrency domain. The mel-frequency cepstrum coefficients (MFCC) are computed as:

$$MFCC_i = \sum_{i=1}^{K} X_k \cos\left[i\left(k - \frac{1}{2} \right)\frac{\pi}{k} \right], \quad i = 1, 2....., M \tag{2.6}$$

Where M is the number of cepstrum coefficients, and X_k, k, = 1, 2,..., K, is the log energy output of the kth filter (K – Number of filters) [Deller et al, 2000].

Formants

The resonances of the vocal tract frequency response are known as formants, which are manifestation of energy maxima. Studies in speech analysis have shown that the firsts formants relate to the location and amount of constriction of The UA; more precisely, F1 (the first formant) associated with the degree of

constriction in the pharynx, F2 (the second formant) is related to the degree of advancement of the tongue relative to its neutral position while F3 corresponds to the length of the UA and the degree of the lip rounding [Deller, 2000]. Due to the similarities of the snore and speech productions; it can be assumable that the spectral envelope of the UA frequency response during snoring, expressed by the formants, contain vital information about OSA condition.

Pitch

As mentioned in the mathematical model of snore production, the excitation source in the production of the 'vocal' sound resembles an impulse train with frequency f_0. This frequency also called the pitch or the fundamental frequency. As we will see later, the pitch offered by authors [Sola soler et al, 2002; Abeyratne et al, 2005] as a differentiate feature between OSA and non-OSA snorers. There are plenty of approaches to extract the pitch from the recorded signal such as time domain methods (algorithm based on autocorrelation function and other event rate algorithms, phase based algorithm), frequency domain methods (cepstrum based methods, inverse LPC) and statistical domain method (based on neural networks) [Fukanaga, 2003]. For the purpose of our study, in order to extract the pitch we used the autocorrelation method [Deller, 2000].

2.2.3. Acoustic Analysis of Snoring for OSA assessment

Recently, much research has been dedicated to the analysis of snore signals in order to differentiate apneic patients from healthy patients. Amongst the attributes examined were acoustical characteristics such as sound intensity, spectral, pitch and time related features. However, in all of those researches, the conclusions were based on relatively small number of subjects, and they have usually investigated few and manually selected snoring events, and as such, essential information were not fully explored. On top of that, their results were limited and happen to contradict each other. In this section we will deepen on the key researches in the field.

Fiz et al [1996] studied the spectral patterns of snore sounds from simple snorers and OSA patients and reported that all seven simple snorers' snores and two of ten OSA patients' snores in their database were dominated by a harmonic spectral content, Furthermore, they indicated that the peak frequency in most of the OSA patients is lower compared to that of simple snorers. In contrast to their findings, Hara et al [2006] investigated the peak frequency (PF, the location of spectral peak) and found higher peak frequency values for OSA patients (in contrast to the findings of Fiz et al).

The research of Sola soler et al [2003], argues for larger variability between snores spectrums' patterns of the same OSA patient than the variability of the benign snorer; they explain it by the reduced stability of the upper airway in OSA

patients, closely related to its tendency to collapse. Their findings are the base for some of our proposed features.

Several groups study the relationship of the fundamental frequency of the OSA patients' snores. Sola-soler et al. [2002] analyzed few features related to the pitch: pitch mean value, pitch STD and pitch density, which is the fraction of the snoring time where the pitch is detectable over the total snoring time. Pitch mean and standard deviation values were analyzed in the plane (figure 2.4). The line *m=1.85s+0.69* was able to correctly classify 58.4% snores from benign snorers and 57.6% of apneic snores; Above the line (higher mean frequency and lower std) correspond to benign snorer and below, lower frequency and larger variance, for the apneic snores. Similar results and intensifications can be observed in the study of Abeyratne et al from 2005.

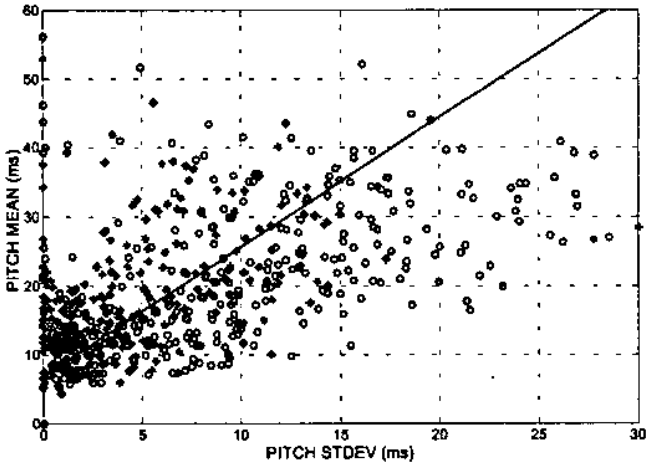

Figure 2.4: Pitch mean value against pitch std plot. The line obtained with linear discriminant analysis tries to separate values from simple snorers (hollow circles) and post-apneic snores (star '*'). [Morera el al, 2002]

It is known that in OSA, in many cases, there is oedema of the soft palate [Ryan et al, 1991]. Generally, vibrating structure emit a sound spectrum which is

related to their mass, in such a way that, the higher the mass, the lower the frequency. This fact can support the above classification.

In Miyazaki et al research [2002], the authors argue that sounds of snoring (particularly, the pitch frequency) can vary according to the production site. In their study, the patients were examined by PSG with simultaneous recordings of the intra-luminal pressure (four invasive sensors) of the UA and snoring sound. Based on the pressure's gradient between adjacent sensors, they devided all the snoeres into 4 types: soft palate type, tonsil/tongue type, combined type and larynx type. For each snorer, the fundamental frequency (F_0, or pitch) was estimated and classifiable values were found as shown in *table 2.1*. Note that in the tonsils type, F_0 was distributed with wider range and high average value; this is attributable to the variety of the physical contours of the obstructed sites: lingual tonsils, palatine tonsils, root of tongue, lateral pharyngeal wall and a combination of them. In contrast, the larynx type snores (which are rarer type as the author mentioned) had same pattern in all the presence.

Table 2.1: Site of obstruction and the pitch [Hz]. by Miyazaki et al, 1998.

Soft palate	Tonsil/tongue	Combined	Larynx
102.8+/-34.9Hz	331.7+/-144.8Hz	115.7+/-58.9Hz	~250Hz

The wide range of the pitch values (100-350Hz) in OSA patients, might put Sola-soler et al [2002] conclusions in question; whether the snorer's pitch mean values were affected due the obstruction site, rather then been generated by OSA patients.

The pitch density, reported in the same framework of Sola-soler [2002] founded to be more interesting and reliable; the authors claimed that high pitch density is a characteristic of very regular snores. Moreover, when they examine the pitch density against the OSA severity (AHI), a monotonic decrease founded. This indicates that a greater irregularity is present in snores from acuter OSA subject. Note that the analyzed snore of the OSA snorers in their research was the first three Post-apneic snores.

More recently, Fiz et al [2010] have used an automatic nocturnal snore detection that allows analysis of all-night acoustic signal acquired using a contact microphone. They concluded that sound intensity and some snore frequency parameters may differentiate snorers according to OSA severity. However, their conclusion was based, as well, on a small sample of patients (37), without sufficient validation (resubstitution method, i.e. optimistic evaluation), and reported limited performances (Patients were classified with thresholds AHI>5 with 87% sensitivity and 71% specificity). For comparison, we implemented their presented methodology, and evaluate it on our database. The results will be given later on this document.

Another earlier study among 18 benign snorers and 12 apneic snorers, analyzed sequential properties of snores across the night as a measure of inter-snore properties [Cavusoglu et al, 2008]. They found that OSA patients have greater variances of snore duration, separation, and average power. However,

inconclusive findings were reported regarding the prediction of AHI by these inter-snore measures, mainly due to the small sample size of patients.

Completely different approach proposed by Van Brunt et al [1997]. The main concept was seeking for the amount of acoustical signature events which defined as a loud sound proceeded by at least 10 second but no more than 90 second of silence. Such algorithms are very sensitive to background noises. Moreover, hypopnea for example, is not an absolute obstruction; therefore it may not be considered as an event. In their study, they define constant threshold of 50 µV for the detection of a sound event. It is clear that such threshold might results in numerous misdetections or false alarms, that because snoring sound intensity can vary meaningfully across night, between nights and between different patients; an adaptive threshold should be implemented in order to improve the robustness of the algorithm. Nevertheless, compared to the PSG test, their prediction was extremely satisfying as figure 2.5 exhibits.

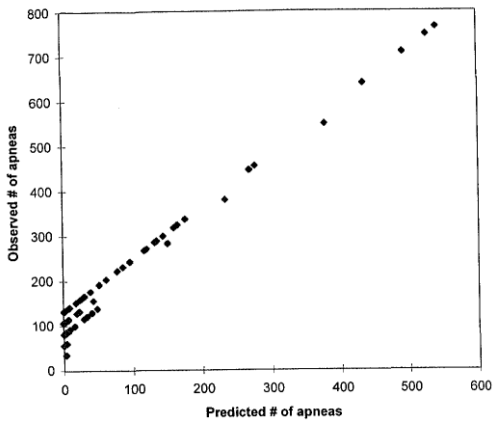

Figure 2.5: Relationship between the prediction of acoustical signature events and the results of polysomnography [Van Brunt et al, 1997].

Recently, few studies investigated non-linear and properties of snores for OSA detection. Abeyrante et al [2007] propose an algorithm based on higher-order-spectra (HOS) to jointly estimate a mixed-phased model for the total airway response (TAR), i.e. for the spectral envelope of the upper airway filter, aiming to further investigate the relation to OSA. Matsiki et al [2007], explore relationship between snoring analysis and apnea syndrome using wavelet transform. Andrew NG, 2009; ivestigates the feasibility of using nonlinear coupling between frequency modes in snore signals via wavelet bicoherence (WBC) analysis for screening of OSA. All of these methodologies based on the argument that classical linear models could not completely characterize snore signals, which are claimed to be nonlinear and non-Gaussian in nature. Moreover, unlike wavelet-driven algorithms, the commonly used Fourier-based approaches are limited to stationary signals, and thus, they are insensitive to capturing any form of transient, intermittent interactions in snore signals that are primarily nonstationary. However, despite the merit of the algorithms, none of the papers, presented substantial results, but only a primary results and a claim that further investigate should be done.

Not all of the previous reported studies, proposed any information regard the achieved ability to classify OSA snorer from benign snorer. For purpose of future comparison, table 2.2 present brief summary of those who specifically indicated their classification's performances.

Table 2.2: Previous Results

Name	Basic concept	Database	Validation Method	Performances (as reported)
Sola-soler 2002	Pitch Analysis	16 subjects. For OSA subjects, only post apneic snores were investigated.	Res.	60% correct detection
Abeyratne et al 2005	Pitch analysis	35 subjects.	Res.	OSA detection sensitivities of 86–100% while holding specificity at 50–80%
Ng et al 2006	Analysis of first formants	8 subjects. 10 snores from each subject.	Res.	sensitivity = 90%, specificity = 92%
Ng et al 2007	Formant analysis	34 patients. 40 snores were investigated per subject.	Res.	sensitivity of 88%, specificity of 82%
Cheng et al 2007	Sound intensity	10 OSA patients.	Holdout method	average sensitivity was 81.1% (range 62.2%–96.3%) and the average PPV was 73.3% (range 41.6%–93.6%) .
Sola-soler 2007	Pitch and frequency analysis	37 subjects.	Res. and cross validation (Leave one out)	sensitivity higher than 83% and a specificity between 73% and 88%
Ng et al 2009	Nonlinear Mode Interactions (wavelet becoherence)	30 apneic subjects. Few manually selected snores	Res.	sensitivity = 77.7–79.7%, specificity = 72.0–78.0%, $p<0.0001$)
Fiz et al 2010	Sound intensity and several snore frequency parameters.	37 subjects. full night analysis	Res.	sensitivity (specificity) of 87% (71%)

The majority of the previous mentioned studies have focused on intra-snore properties by analyzing snore-by-snore events. It is possible that the biological instability of the upper airway's formation during sleep may lead to alterations in inter-snore properties (i.e. between snore events, between clusters of snores and across the night), mainly with relations to the proximity of obstructive apnea events *per se*. To the best of our knowledge, such perspective of analysis was not

explored. Moreover, there is no unifying hypotheses that incorporate inter and intra snore properties and investigate their relations to OSA severity.

The aforementioned studies were focused in classification of subjects into two categories: healthy or apneic snorers (with different values of AHI thresholds). However, none of them tried to classify OSA subjects according to the severity of the syndrome, i.e. mild, moderate and severe OSA; on top of that, no attempt was made to estimate the AHI value itself. Such attitude should be further explored.

3. Methods

In the proposed research, subjects sleep sounds were recorded during nocturnal PSG study. In the following section I will describe all the data handling process, starting with pre-processing via all the signal analysis approaches and their evolutions.

Generally, the process consists of two major phases – design phase for system training and test phase for system evaluation. Both phases have similar data handling (figure 3.1); after pre-processing, an automatic snore detection algorithm was developed and applied in order to analyze the entire snores across the night; various acoustic features were extracted and investigated; Bayes classifier was designed according to the selected features and PSG results. Subjects were classified into categories of OSA severity, according to subject's AHI. In addition, AHI was estimated (i.e. AHI_{EST}) using multivariate regression model and was compared to the gold standard PSG result (i.e. AHI_{PSG}); System was evaluated using accepted performance evaluation methods (data was separated into design and test sets according to the evaluation method).

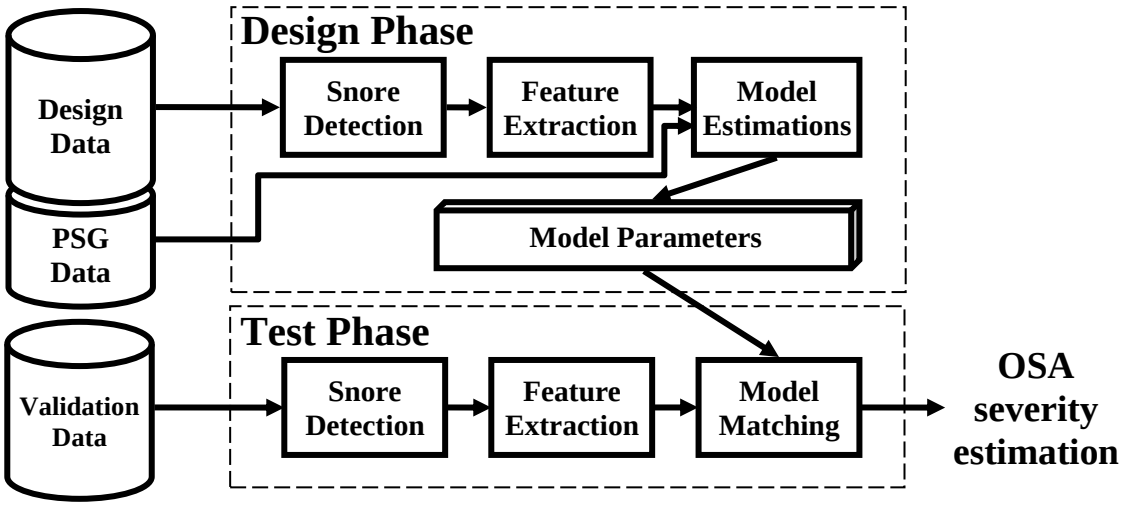

Figure 3.1: Block diagram of the audio-based OSA recognition system

All implementations and statistics in this work were done offline using MATLAB (R-2008a, The MathWorks, Inc., Natick, MA).

3.1. Pre-processing

Before signals were headed for analysis, each recorded signal (approximately 6 hours), was digitized (16bit, 44,100Hz), down sampled to 16 KHz and synchronized with PSG study onset (will be detailed in Section 3.1.1). The synchronization process is required because our recorder is independent with the PSG system and their inception time might be delayed for few seconds, or sometimes, even more (when laboratory staff forgets to turn it on simultaneously). Moreover, if needed, noise reduction methodologies were applied to overcome some noises ascribed to some electrical instruments as will be detailed in section 3.1.2.

3.1.1. Signal Synchronization

The synchronization of the recorded signal to PSG onset was done automatically using simple user interface (GUI), which require only the signal files paths (figure 3.2 exhibit typical screen shot of the GUI). The algorithm estimates the cross correlation function between the sound-level-meter channel of the PSG and our recordings and seeks its maxima. The maximum correlation indicates the exact time difference. At the beginning, first 5 minutes of the signal is analyzed; in the case when the correlation value is not high enough, better match will be searched in the next 5 minutes. Clapping hands in the beginning of the recording

facilitate the sync-process; the hand claps are relatively energetic and notable, and therefore, can reveal high cross-correlation values.

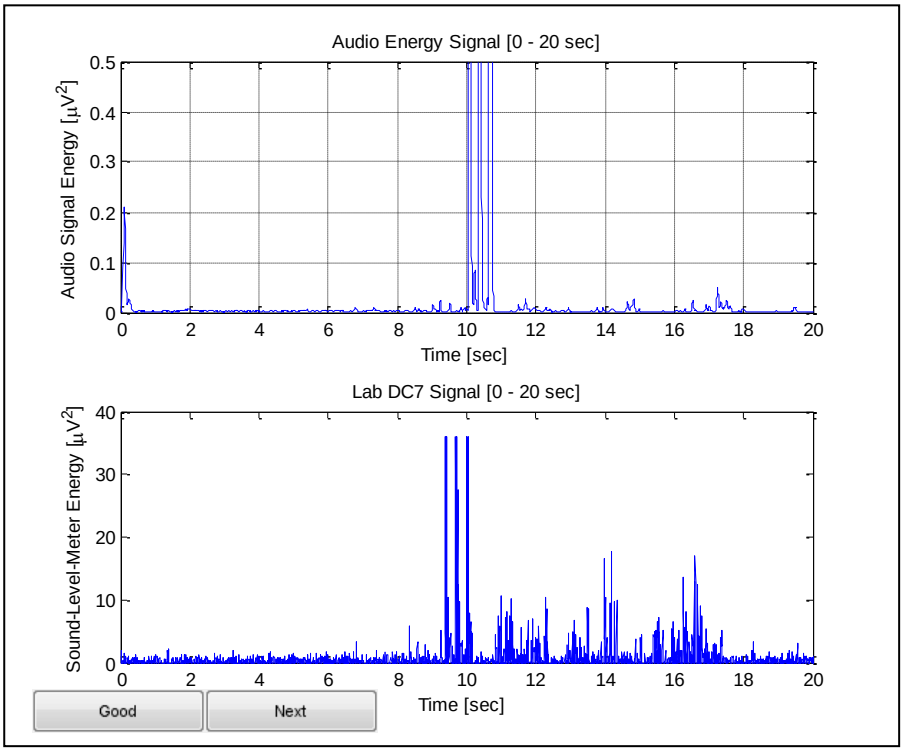

Figure 3.2: Screen-shot of graphical user interface designated for synchronization process. upper panel represent energy envelope of the acoustic recorded signal, and lower panel represent the sound level meter (channel DC7 of the PSG). The three energetic events in the middle of each panel are 3 handclaps. About 0.7 sec delay was obtained in this example.

3.1.2. Noise Reduction

The recorded snoring sounds might be corrupted with background noises, leading to inconsistencies in analysis. In this study, the data acquisition taken place in-laboratory setting, and prima facie, extraneous noises should be neglected. However, during the time, we encountered that several noises affect our signals significantly. In further research we found out that two main noise components should be taken care:

(1) Noise which is coming from the air condition adding a dominant 100Hz component which disturbs, inter alia, the pitch extraction algorithm (same frequency range). Therefore, in order to overcome this issue, first, the labour staff were asked to close the AC as long time as possible during night. Second, when necessary, simple 100Hz narrow IIR notch filter was applied (implemented using Matlab, filter design toolbox, The MathWorks, Inc., Natick, MA).

Figure 3.3: the air condition produces a 100Hz acoustic artefact.

(2) The respiratory belt's instrument is producing a sound artifact with varying frequency (around 2200Hz). Therefore, a simple filter, with a constant stop frequency, will not address the problem. Two approaches were applied to address the issue: first, an acoustic cover/box which is able to effectively filter acoustic noises above 500 Hz, was built and positioned as showed in figure 3.4. The positioning was done not before we had the approvement of the hospital's engineering unit (safety considerations such as heat resistance).

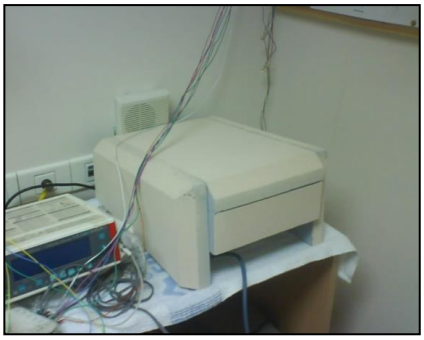

Figure 3.4: the acoustic cover (melamine sponge) placed over the respiratory instrument.

Second, an iterative algorithm which continuously finds the exact noise frequency and filters it was written. The algorithm is described clearly in the following flow chart, figure 3.5.

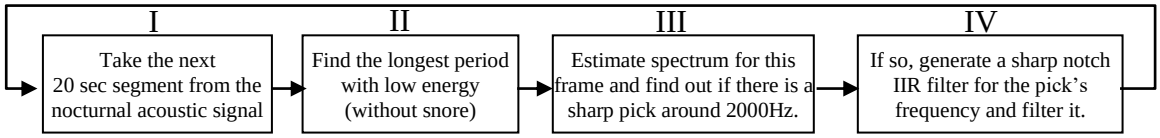

Figure 3.5 (A): Flow chart

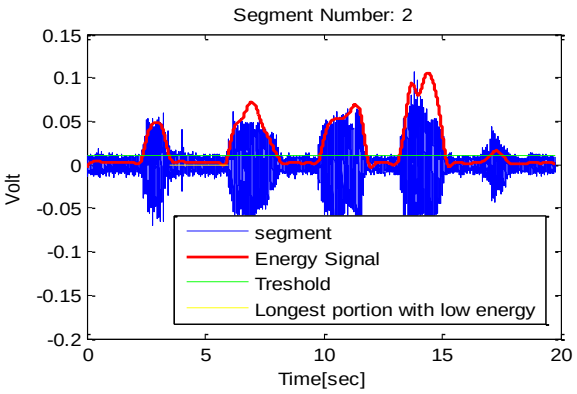

Figure 3.5 (B):

Steps I,II; finding the longest period within the segment which has low energy

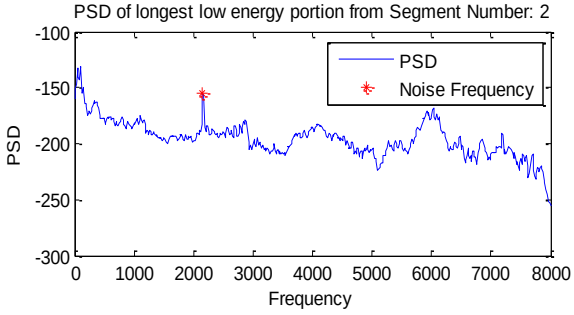

Figure 3.5 (C):

Steps III; Finding the noise frequency in the estimated spectrum.

3.2. Snore Detection Algorithm

The nocturnal signal consist of different types of background and transient noises such as speech, coughs, blanket sounds, body movements, etcetera; Isolating the snores from the entire extraneous noises will allow pure acoustic analysis. In order to isolate the snores, an automatic snore detection system was designed. It should be noted that most parts of this algorithm was developed in the same framework by Weiss Dana, after a depth investigation. The main concept of the algorithm is shown in the following block diagram (Figure 3.6).

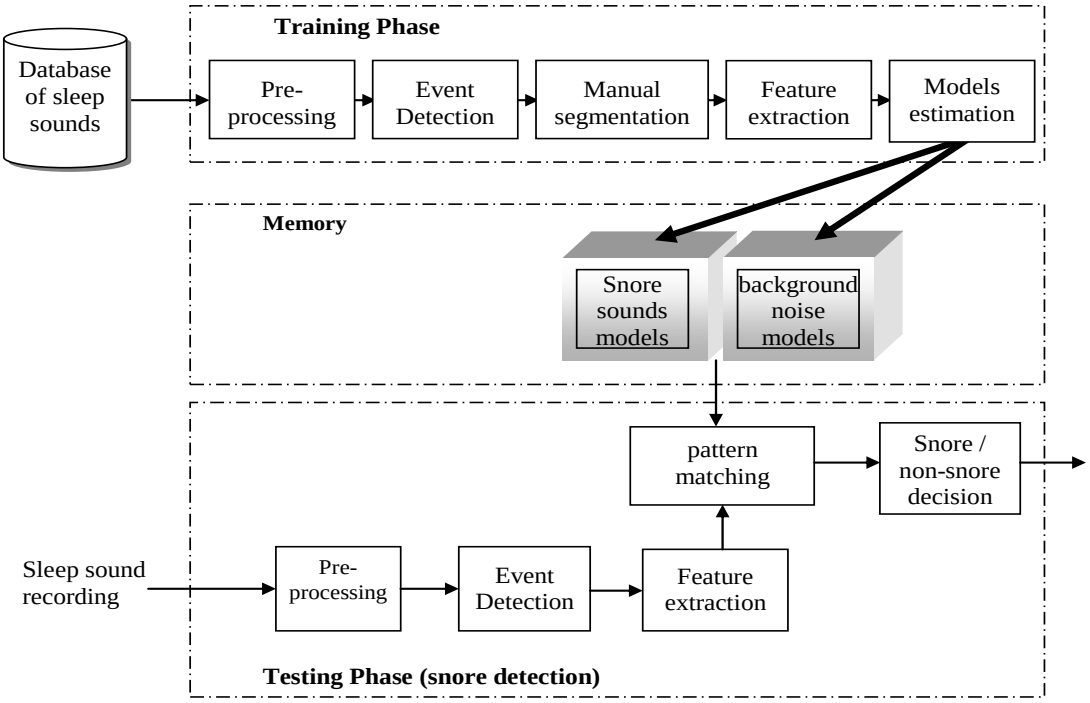

Figure 3.6: Block diagram of snore detection algorithm

After the aforementioned pre-processing, an event detection algorithm was implemented based on an adaptive energy threshold. Basically, the threshold is calculated from histogram of one minute moving window by evaluate 10% of the

histogram peak value; further adjustment is done, however, this isn't the scope of my work (can be found in Dana Weiss senior project) so I won't detail. These detected events are snore suspected events; they are relatively short and energetic.

Basically, the algorithm is subdivided into training and testing phases. In the training phases the detected events was manually classified as either snore or noise events using destined user interface (detailed in 3.2.1). Subsequently, the following features was extracted from each detected event: twelve linear predictive coefficients [Deller, 2000], average pitch value (calculated via autocorrelation method [Deller, 2000]), event duration, total energy, and the time from the beginning of the event to its highest peak. The manually annotated events, i.e. their features, were used to estimate parameters of Gaussian Mixture Models (GMMs) [Fukunaga, 1990]; one model for snore events (order 3), and one for different noise type events (order 10).

During test phase, the event detection algorithm was applied followed by the extraction of the same event feature set. Consequently, each of the events' feature set is matched to the designed models and ascribed as either snore or noise depend on the most likely model.

In order to validate the performance of the algorithm, we used the manually classified events as both for the design phase and for the test phase, and evaluate the detection rates using resubstitution (optimistic estimation) and 5-fold cross

validation methods(pessimistic estimation). The motivation of using both methods is to assess whether the complexity of the classifier is suitable for the amount of data, i.e. to have an indication for possible over-fitting.

Suggested amelioration to the algorithm was to combine sleep-wake information according to EEG and to assess whether it improve the algorithm performances. Such data is easy to obtain (without EEG signal) using simple actigraph.

3.2.1. Snore Manual Segmentation

An initial step towards automatic snore detection algorithm was the creation of an assistant graphical user interface (GUI) aim to manually classify events into snore\non snore events. Generally, in order to design snore detector, training data should be available, i.e. database of snores and database of different noise types. Those databases should be large enough if we desire a reliable model. Therefore, GUI as we developed is essential for efficient creation of such databases.

The following GUI gets as an input all the energetic sound events in the nocturnal signal, and allows the user to go over those events (listen) and decide whether it is a snore or a noise event. Finally the user annotation is saved into destined file.

In addition, this GUI helps with the quality assurance of the automatic snore detector, i.e. to test and evaluate the detector performance. Figure 3.7 exhibits a screenshot of the graphical interface.

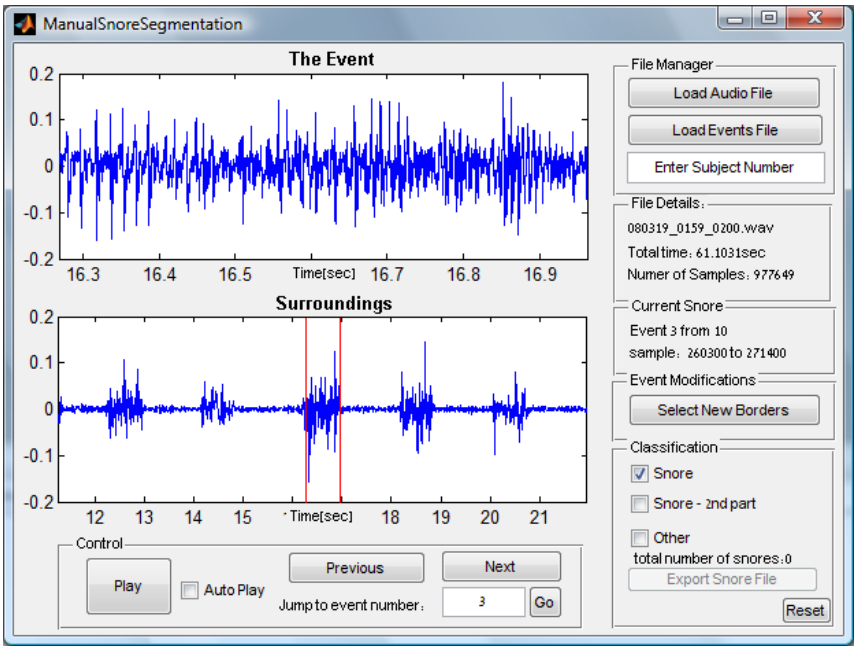

Figure 3.7: GUI for manual events classification. The GUI is able to exhibit the events, play it, change its boundaries and select its classification (snore/non-snore event)

3.3. Feature extraction

The bulk of my thesis, as we see it, summarized into this section. During the thesis numerous of acoustic features were examined, including both implementations of previously reported features, and exploring novel acoustic features. In case feature found to be correlated with OSA severity, we select this feature for our system; elsewhere, we checked weather the feature contribute to the classification ability of previously selected feature, and only if not, we abandoned it. Finally, five acoustic features which were best explain the relation to AHI, were chosen. Linear regressions were performed to determine the correlation between every selected feature values and the AHI. In case nonlinear transformation of the data improves the correlation we calculated linear regression to the transformed feature. In both case, r^2 will be calculated from the

linear line. In the following section the selected acoustic features will be extensively detailed.

3.3.1. Mel Cepstability

The name derived from 'mel frequency cepstrum coefficient stability', i.e., measures the entire night spectrum's stability, expressed using mel frequency cepstral coefficient (MFCC) [Deller, 2000] which is a representation of the short-term power spectrum, based on a cosine transform of a log power spectrum, on a mel-scale of frequencies. The Mel Cepstability feature for subject *j* was defined as the sum of variances of 12 MFCCs extracted from the highest energy frame (30 msec long) in each snore, normalized by mean of E_s (the total energy of the s^{th} snore) over all j^{th} subject snores:

$$MelCepstability(j) = \frac{\sum_{i=1}^{12} \mathrm{var}(\mathbf{c}_i)}{\frac{1}{S}\sum_{s=1}^{S} E_s} \qquad (3.1)$$

where $\boldsymbol{c_i}$ is a vector of the i^{th} MFCC of all the snores. *S* is the total number of snores of subject *j*. Due to the instability of the upper airway's muscle in OSA patients [Malhotra et al, 2002; Ayappa and Rapoport, 2003], which is represented by the spectral envelope [Abeyratne et al, 2005], lower variances of benign compared to apneic snorers are expected.

3.3.2. Running Variance

Overall analysis of the continuous nocturnal signal and previous sleep related studies [Cavasugolo et al, 2008, Fiz et al 2010] has claimed that the sleep pattern and its characteristics, including the acoustics, varied throughout the night.

In order to investigate the eventuation: (1) all the snores were clustered into groups of adjacent snores, i.e. a snore is ascribed to a group according to its distance from the closest snore in the group. In cases where the duration between the group and the snore is less than one minute, the snore is ascribed to the group. In addition, due to feature calculation matters, a group will not contain more than 20 snores. (2) Simultaneously, the total energy of each snore was extracted (3) and the within group feature variance was evaluated. (4) finally, for each patient, the global mean of running variances was calculated.

The motivation to use the running variance feature can be explain simply with the following illustration:

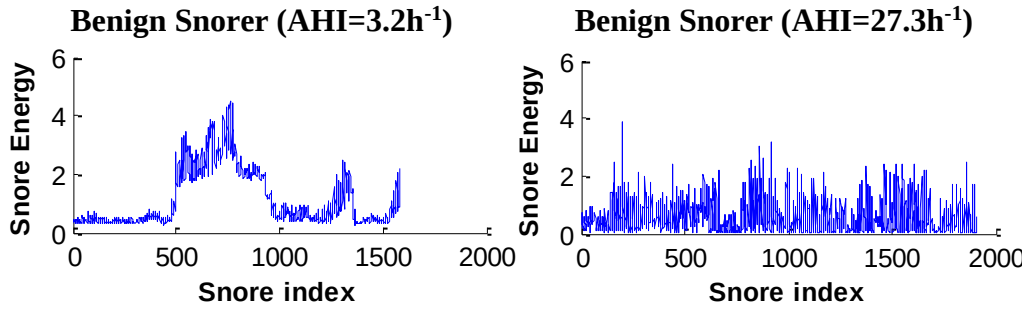

Figure 3.8: Illustration for better understanding of the running variance feature. left – benign snorer (AHI<3.2); right – apneic snorer (AHI=27.8).

The illustration presents time course of maximal snore energy of apneic (right) and benign (left) snorer. Calculating the total variance of the feature might indicate that the benign snorer persist higher variances. However, according to the illustration, every observer will argue that the apneic snorer tend to present higher variations. When using the running variance, or one can name it 'short time variance', the average within group variability will be higher for the apneic snorer.

3.3.3. Apneic Phase Ratio

Implementation of the aforementioned feature, raises a query: Do OSA and non-OSA subjects exhibit similar acoustic properties (feature variation) at portions of the night located distant to obstructive events? or in other words, whether the acoustic difference between benign and apneic snorers found expression mainly around those obstructive apnea events.

In order to investigate and address these queries, the acoustic data was synchronized with the PSG data to extract for each group of snores the distance to its closest apnea event. We define *benign phase* as the portion of sleep when no obstructive apnea occurs within a radius of 10 minutes. *Apneic phase* is defined as the portion of sleep, four minutes around each apnea event.

Indeed, we found interesting findings. Figure 3.9(a) and (b) show the histograms of the running variance features, for non-OSA and OSA subjects at benign phases and at apneic phases. For Both Subjects, variance histograms are similar. Figure 3.9(c) shows the difference of those histograms, when OSA and non-OSA subjects were merged.

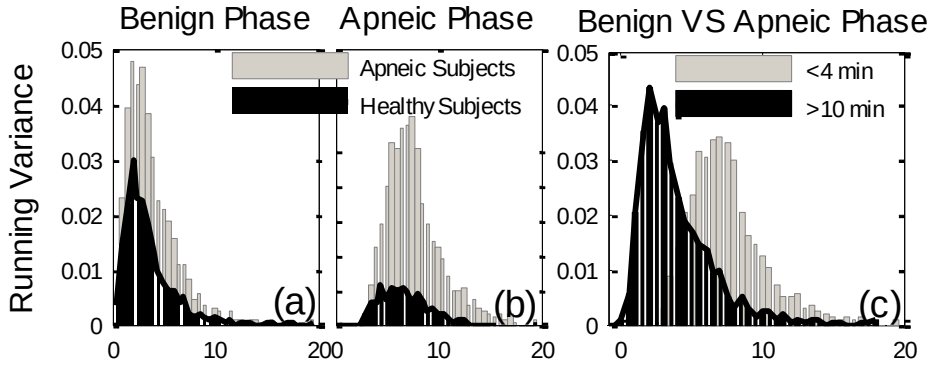

Fig. 3.9: (a,b) – Histogram of the running variance feature in benign and apneic phase, non-OSA vs OSA subjects. (c) – Histogram of OSA and non-OSA subjects together, separated by benign vs apneic phase.

Naturally, OSA patients have far more apneic phases. We assume that high feature variation within snore groups demonstrates apneic phase and low variance means benign phase. Figure 3.10A upper panel demonstrates ascension of the feature values around the apneic phase (marked with asterisk). Figure 3.10B represents typical benign phase and apneic phase. It is easy to see that in the apneic phase larger variability exist.

Therefore, we define *apneic phase ratio* feature as the relative number of snore groups with variance larger then ζ, i.e. it measures the quantity of apneic phase throughout the night. Basically, the choice of ζ was empirically, however, an adjustment is done for each patient, according to the total energy of the patient's acoustic nocturnal signal.

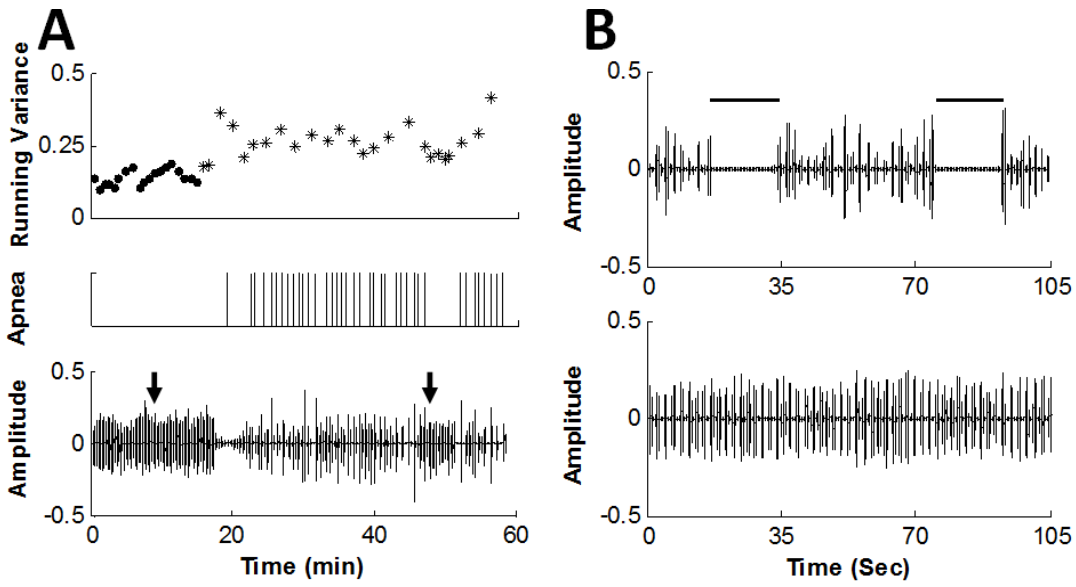

Figure 3.10: Benign and Apneic Snoring Phases. (A) Upper panel - time course of the running variance feature (arbitrary units); dots indicate benign snoring phase and asterisk – apneic phase. Middle panel – marking of obstructive apneas events (by PSG) by vertical lines. Lower panel - snore amplitude (arbitrary units). Note the ascension of the running variance values during apneic phase, i.e. around apnea events. (B) Upper panel demonstrate acoustic signal of typical apneic phase of the same subject taken from the time indicated by right arrow in A. Note the instability of the snores signal. Lower panel - typical benign phase, i.e at least 10 minute distant from obstructive apnea events. Note the differences in time base between A and B. Data was collected from 62 years man, BMI=28.7 (kg/m^2), AHI=33 (events/hr) about 2 hours after sleep onset.

3.3.4. Inter Event Silence

The acoustics of apnea event can be characterized through its pattern of silence in between two sound events (figure 3.11).

Correctly detecting and appraising of those suspicious intervals for a patient can lead to an accurate estimate of the real number of apnea occurrences.

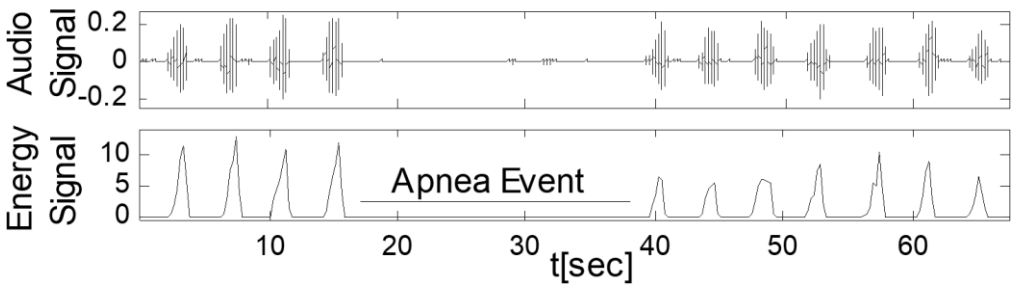

Figure 3.11: Typical pattern of apnea event. The acoustic audio signal (top) and the energy signal (bottom).

Only intervals of >10 up to 90 seconds were investigated. The reasons for these thresholds are as follows: 10 sec is formal definition of obstructive events in adults [American Thoracic Society, 1996]. Maximum of 1.5 minutes were chosen due to additional experiment, when we detect silent event according to PSG proven obstructive events, and plot histograms of the inter-event silence duration (figure 3.12). We set the maximum duration according to 95% of the silence durations.

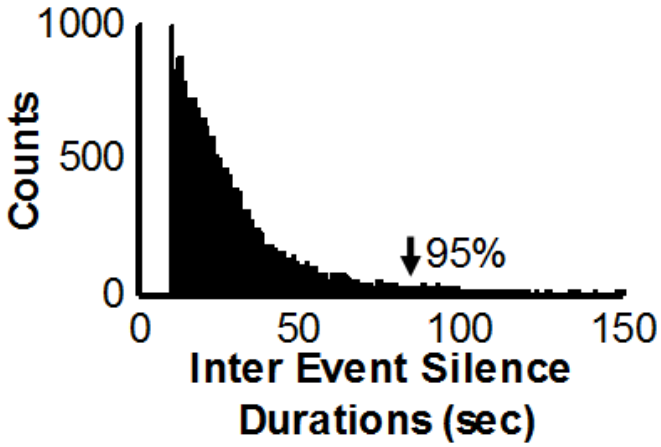

Figure 3.12: Distribution of Inter Event Silence durations. Histogram of silence durations that were marked as an obstructive events by PSG technician. Note that 95% of silence periods are ≤90 sec (arrow head). Threshold of ninety seconds was set to be the maximum length investigated when extracting the Inter-Event-Silence feature.

To extract those inter event silences: (1) first, we use the event detection results for defining optional intervals, suit the duration constraints; (2) Then, to ensure the subjects do not breath during "silence events", even slightly, a massive acoustic filtration was performed (using spectral subtraction method [Deller, 2000]). This procedure enabled detection of minimal breathing sounds that may be hidden by the background noise. An analogous apnea event detector already suggested [Van brunt et al, 1997] and will be discussed afterwards.

3.3.5. Pitch Density

[Sola-Soler et al, 2002], is a measure for the stability of the tissue's vibration frequency. Each snore event was subdivided into 30msec frames. For each frame, the autocorrelation function was estimated, and the value of the autocorrelation local maxima ($peak(R_{ii})$- a measure of the fundamental frequency's presence) was analyzed. The pitch density for each snore was calculated as the fraction of

the snoring time where the pitch is detectable ($peak(R_{ii})$ >0.5) over the total snoring time :

$$PitchDensity_s = \left(\sum_i^{N_s} bool\{peak(R_{ii}) > 0.5\}\right) / N_s \qquad (3.2)$$

where R_{ii} is the autocorrelation function of the i^{th} frame and N_s is the number of frames in the s^{th} snore. Actually, it is a measure for how long the vibration frequency (which is a factor in the snoring sound production) remains stable.

3.3.6. Preliminary attempts

In the following section I will present some preliminary attempts for features extractions which are very accepted in the field of sound processing; and reported by others as with potential ability to detect OSA using snoring; however, those features were "abandoned" due to poor performances on our database. The reason for given these within this section (and not within the results) is that we don't want to lead the reader into insignificant results that were not integrated in the general proposed system.

The features are the pitch frequency and the first three formant frequencies. Box-plots of those features, benign versus apneic patients are presented in figure 3.13. In every feature, both groups reveal similar behaviours, i.e. cannot be useful as discriminative features.

As mentioned in section 2.2.3, Sola-soler et al [2002] reported that apneic patients reviled lower pitch values and higher variance. Our results oppose their results and support Miyazaki et al [1998] saying that the pitch value is affected

by obstruction site, and therefore cannot differentiate benign and apneic snorer. Ng et al [2006, 2007] reported that formant frequencies are higher for apneic patients. Again, the presented results are contradictory. As we see it, the main reason for their inconclusive result is the limited validation; in those studies, only few snores of only few subjects were investigated.

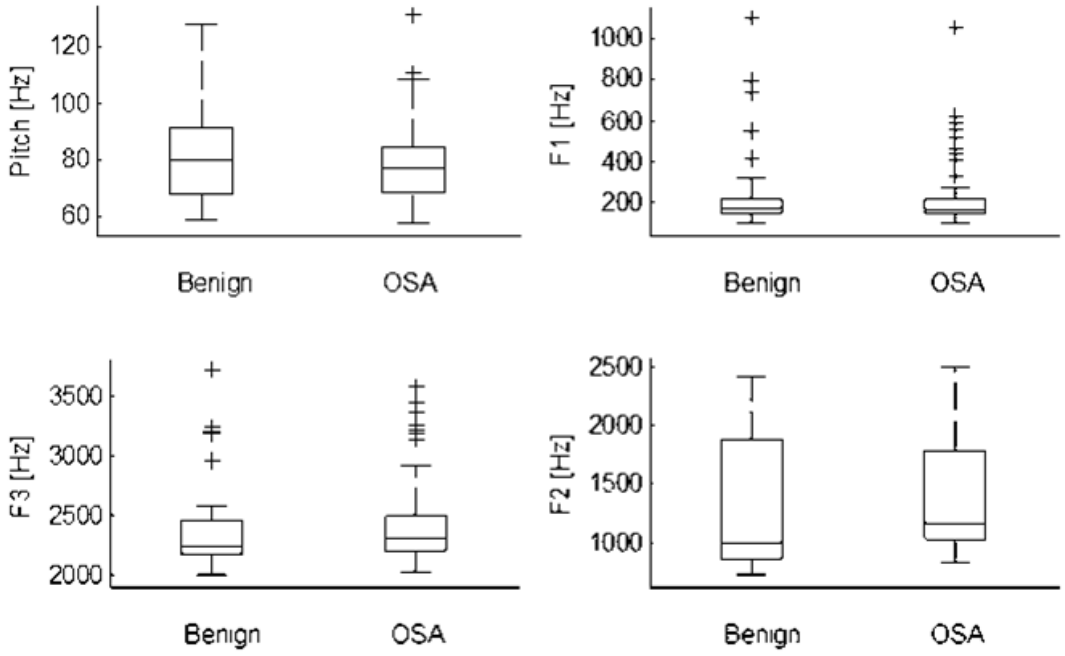

Figure 3.13: Formants and pitch frequency of benign versus apneic snorers (AHI threshold 10 h-1). Patient characteristics can be obtained in table 4.2.

3.4. OSA recognition

The following section describes the approaches taken in order to either classify a subject into two or three degrees of OSA severity, or to directly estimate subject's AHI. In addition, all the validation methods will be detailed.

3.4.1. OSA Classification

In our work we suggest two classification approaches. Both based on Bayes decision between Gaussian models.

First approach is classification into 2 categories – non OSA or OSA subjects, using thresholds of AHI>10 event/h, or AHI>20 event/h (which is a rule of thumb for CPAP treatment). Second approach is classification into three degrees of severities (non OSA – AHI<10; mild to moderate OSA – 10<AHI<30; and severe OSA – AHI>30).

The classifiers were fed by five-dimension feature vector $\boldsymbol{x}^{j}$ (j is the subject index) which was assigned to each subject, as detailed in the previous section. As initial step, the feature vector was normalized to obtain equal unitary variance in each dimension (every dimension were divided by its' standard deviation).

The classification performances were estimated using two main methods, the resubstitution method and the 5-fold cross validation method [Fukunaga, 1990]. Together, we have indication for possible over-fitting, i.e. whether the complexity of the classifier is suitable for the amount of data. Shortly, in resubstitution method, the system is validated with the same data set that trained the model, therefore it said to be optimistic estimation of the error. However, 5-

fold cross-validation is pessimistic estimation - the original sample is randomly partitioned into 5 subsamples. Of the 5 subsamples, a single subsample is retained as the validation data for testing the model, and the remaining 4 subsamples are used as training data. The cross-validation process is then repeated 5 times (the folds), with each of the 5 subsamples used exactly once as the validation data. The 5 results from the folds then can be combined to produce a single estimation.

In addition, we perform (3rd method) the holdout method, i.e. we separate the entire subjects to system-design dataset (n=55), and validation dataset (n=30), according to the PSG diagnosis date. This is another way to validate our results; this way is more acceptable with clinical experiments evaluation.

For two-class classification, sensitivity and specificity rates will be obtained, whereas for three class classification, a confusion matrix will be presented. The performance of the classifier for different working points will be obtained from a receiver operating curve (ROC) and the area under this curve (AUC) will be determined.

3.4.2. Apnea Hypopnea Index estimation

Using multivariate regression model, fed by the entire set of features, we able to estimate the OSA severity (AHI_{EST}), i.e. we estimate an equation which binds the proposed features (independent variables) to AHI_{EST} (dependent variable):

$$\mathrm{AHI}_{\mathrm{EST}} = [a_0 \quad \dots \quad a_5] \cdot [1 \quad Feat_1 \quad \dots \quad Feat_5]^T \qquad (3.3)$$

Where $a_{0...5}$ are the regression coefficient, and $Feat_{1...5}$ are the proposed five features.

Altman Blend plot [Bland et al, 1986] was used to determine agreement between gold standard AHI_{PSG} and AHI_{EST}, in this analysis we compute the limits of agreement that specified as bias ± 1.96 STD (average difference ± 1.96 standard deviation of the difference). The *diagnostic agreement* approach [White et al, 1995] was used to assess the accuracy of our system in OSA prediction. *Diagnostic agreement* is defined when: AHI>30 on both assessments[6] or, if AHI_{PSG}<30 and AHI_{EST} was within10 events/h; *Overestimate* is defined when AHI_{EST} was 10events/h greater than AHI_{PSG} (both<30/hour); *Underestimate* is defined when AHI_{EST} was 10events/h less then AHI_{PSG} (both<30/hour). Shortly, the motivation of using such approach is that there are no well-defined "cut-off" which above or below sleep apnea syndrome diagnosed or rejected, moreover, tiny changes in AHI between our system and the PSG might be clinically unimportant, whereas, regular threshold analysis might interpret it as miss-classification.

[6] Originally, White et al define this threshold at 1995 to be $40h^{-1}$ but according to nowadays conventions we modify the threshold to be $30h^{-1}$.

4. Experimental Setup

The Institutional Review Committee of the Soroka Medical Center (Helsinki Committee) approved the study protocol.

4.1. Subjects

Between January 2008 and August 2010 we recruited ninety three adult subjects , 57 males and 36 females, age 53±13 year, BMI=31.7±5.1 kg/m^2 (Table 4.1), with “typical” symptoms of OSA [Tarasiuk et al, 2006] (Table 4.1), that were referred for PSG evaluation by otolaryngology (ENT) surgeons or pulmonologists. Eight patients (2 males and 6 females, AHI=8.7±3.9) did not snore and therefore were excluded from statistics; further detail regard those patient and how we "treat" them can be found in the discussion. Patients with facial abnormalities, subjects undergoing CPAP treatment, or subjects who have previously performed PSG, were excluded.

Table 4.1 represents in addition, the characteristics of system-design and validation group separately (the groups for the holdout methods for evaluation of the system performance). There were no significant differences between the groups in terms of AHI, age, BMI, sleep assessments or co-morbidities (student t-test, p values are presented in the table).

Table 4.2 will exhibit essential patient characteristics according to three categories of OSA severities.

Table 4.1: Subject Characteristics and main co-morbidities.

	All	System Design	Validation	P value
N	85	55	30	
Age (years)	53.2±13.5	51.6±12.9	56.1±14.1	0.16
Gender (M/F)	55/30	35/20	20/10	
BMI (kg/m^2)	31.7±5.0	31.8±4.9	31.6±5.3	0.88
ESS (score)	9.33±5.6	9.0±6.0	9.7±4.9	0.63
Reported Snoring (yes)	92%	89.5%	96%	0.25
Tobacco Smoking (yes)	59.7%	61.2%	57.1%	0.15
TST (min)	335±52	331±52	344±52	0.28
Sleep efficiency (%)	80.4±11.4	80.9±11.2	79.4±11.7	0.55
WASO (minutes)	47±35	46±35	49±35	0.72
Ar + Aw index (events/hr)	32.1±21.2	31.0±20.8	34.1±21.9	0.53
S1 (%)	2.7±3.9	2.2±3.5	3.5±4.5	0.17
S2 (%)	72.2±11.7	73.3±11.1	70.3±12.5	0.28
S3+4 (%)	9.8±7.8	9.9±7.7	9.7±8.0	0.91
REM (%)	15.4±9.9	14.8±10.7	16.5±8.4	0.43
AHI (events/hr)	20.8±18.9	19.4±18.1	23.4±20.0	0.37
Mean wake SaO2 (%)	96.6±1.6	96.5±1.7	96.8±1.3	0.31
Nadir SaO2 (%)	82.4±8.5	81.9±9.0	83.3±7.3	0.44
T90 (%)	8.4±13.9	9.0±15.3	7.5±11.2	0.62
DI (events/hr)	19.2±17.3	17.4±15.8	22.5±19.3	0.23
Detected Snores (number)	1195±945	1257±1111	1147±870	0.59
Co morbidities (% of subjects)				
HTN	54	50	61.5	0.34
CVD	60.5	60	61.5	0.63
Diabetes	29.3	26.5	34.6	0.48

AHI – apnea hypopnea index; Ar + Aw index – number of arousal and awakening events per hour of sleep; TST – Total sleep time; WASO – wake after sleep onset; DI – desaturation index; HTN – Hypertension; CVD – Cardiovascular disease (include hypertension, ischemic heart disease, and/or stroke); Prevalence values are related to past or present diagnosis.

Table 4.2: Subject Characteristics separated according to OSA severity

	Number (Male/Female)	**Age**	**BMI**	**AHI**	**analyzed snores per subject (#)**
Non OSA AHI<10	13/18	50.9±13.4	30.6±5.4	5.7±2.6	1241±987
Mild OSA 10<AHI<30	27/8	52.7±13.9	31.2±4.3	17.9±5.8	1186±1019
Severe OSA AHI>30	16/3	57.6±12.5	33.2±5.7	50.5±15.4	1136±760

AHI – apnea hypopnea index (event/h); BMI – body mass index (kg/m²)

4.2. Standard OSA evaluation

Patients were referred to sleep laboratory for standard OSA evaluation procedure:

Questionnaires: Subjects completed a validated self-administered sleep questionnaire. [Rotem et al, 2003 ; Tarasiuk et al, 2006] The Epworth sleepiness scale was used to evaluate daytime sleepiness [Johns et al, 1991].

Polysomnography (PSG): Subjects underwent PSG as previously described [Rotem et al, 2003]. They reported to the laboratory at 8:30 PM and were discharged at the following morning. Subjects were encouraged to maintain their usual daily routine and to avoid any caffeine and/or alcohol intake on the day of the study. Shift workers did not perform the PSG study in the week following shift duty. Overnight PSG included recordings (Viasys, SomnoStar Pro, Yorba Linda, CA, USA) of EEG (C3/A2, C4/A1, and O2/A1, O1/A2), electrooculogram (right and left outer canthus), electromyogram, and electrocardiogram. Airflow (pressure transducer, Pro Tech Monitoring Inc, USA), Chest and abdominal efforts (inductive plethysmography, Respitrace Ambulatory Monitoring) and arterial oxyhemoglobin saturation (Respironix

Movametrix, USA) were recorded. Nocturnal sleep/wake and sleep stages were scored in accordance with the Rechtschaffen and Kales criteria [Rechtschaffen et al, 1968]. Arousals and awakenings were scored according to the American Sleep Disorders Association task force recommendation [Sleep Disorders Atlas Task Force, 1992]. Obstructive apnea was defined as paradoxical breathing for at least two respiratory cycles with complete cessation of nasal airflow. A hypopnea was scored when the paradoxical breathing was accompanied by a reduction of at least 50% in airflow, resulting in either an arousal or in oxygen desaturation of at least 4% [American Thoracic Society, 1996]. Apnea Hypopnea Index (AHI) was calculated as the number of respiratory events per hour of sleep.

4.3. Data acquisition

A non-contact directional condenser microphone (RØDE®, NTG-1) with a 20–20,000 Hz frequency range was placed 1m above the patient's bed (figure 4.1). The microphone was connected to an audio recording device (Edirol R-4 Pro portable recorder) which includes a pre amplifier, A/D converter and internal 80G Hard-Disk. The recorded data was transferred to our lab for further analysis. The synchronization of the recorded signal to PSG onset was done offline using designated algorithm (detailed in section 3.1.1). To facilitate the sync-process we guided the sleep-lab staff to clap hands toward the microphones right after lights off.

During the dissertation period, we attended the sleeping lab repetitively and guided the lab's staff through our needs.

Figure 4.1: Left - The R-4 Pro 4 channel recorder located in the sleep laboratory's control room; Right - a Patient during PSG test. Our microphone is located 1m above the bed.

4.3.1. Database Organization

Characterizations of the database index which is easy to retrieve and maintain had an utmost importance for the success of the research. The generated database contains the audio signals, the patient details (the medical secrecy constituted a main issue in the data organization) and the PSG data (contains all the PSG channels, i.e. sleep stages, the times of the apnoea\hypopnoea events etcetera). Special care was given to maintain data backups.

5. Results

This chapter focuses on the results, step by step; snore detection, acoustic features and OSA recognition.

5.1. Snore Detection

The snore detection algorithm based on GMMs for snore and for noise events were trained and tested using the manually labelled events of the first fifty five recruited subjects. In total, 121400 snoring events and 77400 of noise events were manually segmented.

Very good performance rates of 87-92% correct snore detection and 6-10% false positive was achieved using resubstitution and cross validation methods. The number of detected snoring events was 1195±945 per subjects (range 127-4030, table 4.1), and as such is sufficient for reliable statistics, and large relative to previous studies.

Additional information such as sleep-wake data, according to EEG, did not improve detection rates of the algorithm.

5.2. Feature Extraction

Scatter-plots with regression lines of the five acoustic features versus AHI are presented in Figure 5.1. All selected features significantly correlate with AHI, i.e. as alone, has the ability to predict OSA severity. The open circle and close circles corresponded system-design (first 55 recruited subjects) and validation (extra 30 subjects) groups respectively (hold out validation). For the regressions, Similar coefficients were observed for both groups (student t-test on the coefficient

between groups reveal all p values as larger than 0.3). Therefore, one regression was performed for the all 85 subjects.

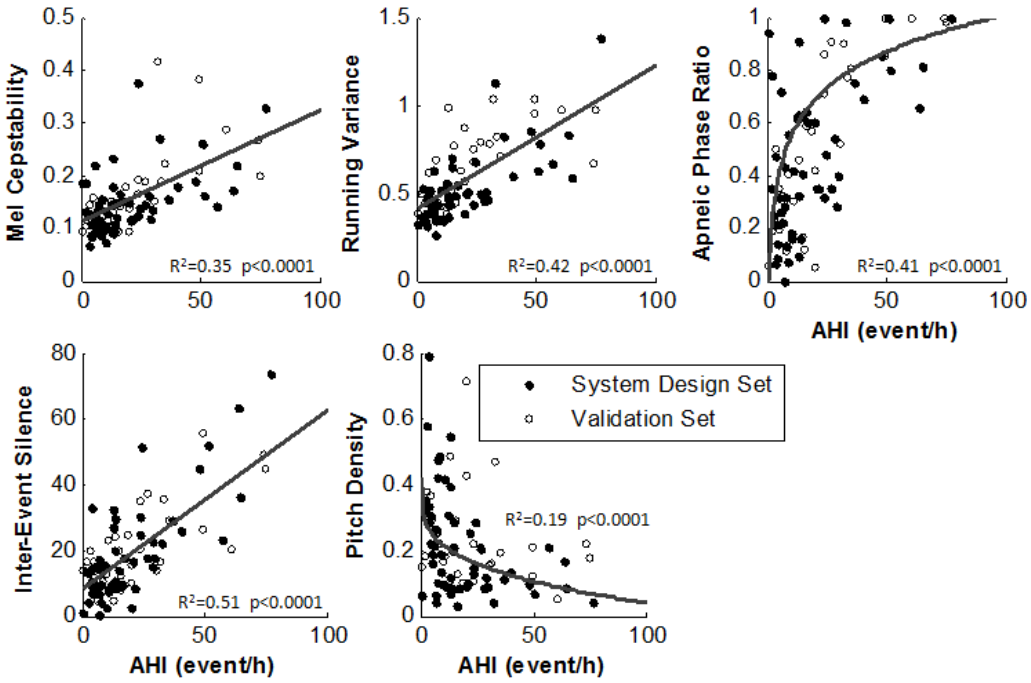

Figure 5.1: Acoustic Features Analysis. All selected acoustic features correlate with AHI (events/hr). Closed and open circles correspond to system design and validation group, respectively. Mel-Cepstability, running variance, and inter-event silence features were fitted using a linear regression model (*ax+b*). Apneic Phase Ratio was fitted after a nonlinear transformation of log-regression model (*ln(ax)+b*); and Pitch Density using a power regression model(ax^b+c). Y axes represent features values (arbitrary units). All r^2 values were calculated using the linear regression.

5.3. OSA recognition

The following section described the results of the recognition process. Note that the merits of our research found expressions in the ability to classify subjects into 3 categories of OSA severity and on top of that, to estimate subject's apnea-hypopnea index.

5.3.1. Non-OSA \ OSA classification

Using the Bayes classifier, we classified the subjects into two groups using threshold of AHI>10 (events/hr). The obtain detection rates were 87-91% (CV-resubstitution) sensitivity and 86-87% specificity (Table 5.1). The small gap

between resubstitution and cross validation can assure that the complexity of the classifier is suitable for the amount of data used for training.

As for the holdout method, in the study design and validation study, the detection rates were ranged about 84-96%. Further details are presented in table 5.1. Results for threshold AHI >20 events/hr are shown as well.

Table 5.1: System Performance. non-OSA \ OSA Classification.

	All subjects (n=85)		System Design (n=55)		Validation (n=30)
AHI>10 Detection Ratio (False Positive ratio)	Res.	0.913 (0.856)	Res.	0.963 (0.857)	0.842 (0.909)
	CV	0.870 (0.871)	CV	0.889 (0.821)	
AHI>20 Detection Ratio (False Positive ratio)	Res.	0.969 (0.807)	Res.	1.000 (0.939)	0.917 (0.900)
	CV	0.878 (0.865)	CV	0.890 (0.842)	

ROC curves corresponded to AHI>10, AHI>20 for resubstitution and cross validation are presented in figure 5.2. The AUC are presented on graph, showing high sensitivity and specificity in screening for OSA. As for the holdout method, plot are not shown due to redundancy, the obtained AUC were all above 0.9.

The confusion matrices for classification into 3 categories of severities are shown in Table 5.2. The algorithm achieves 81% and 76.5% correct detection in resubstitution and cross-validation methods, respectively.

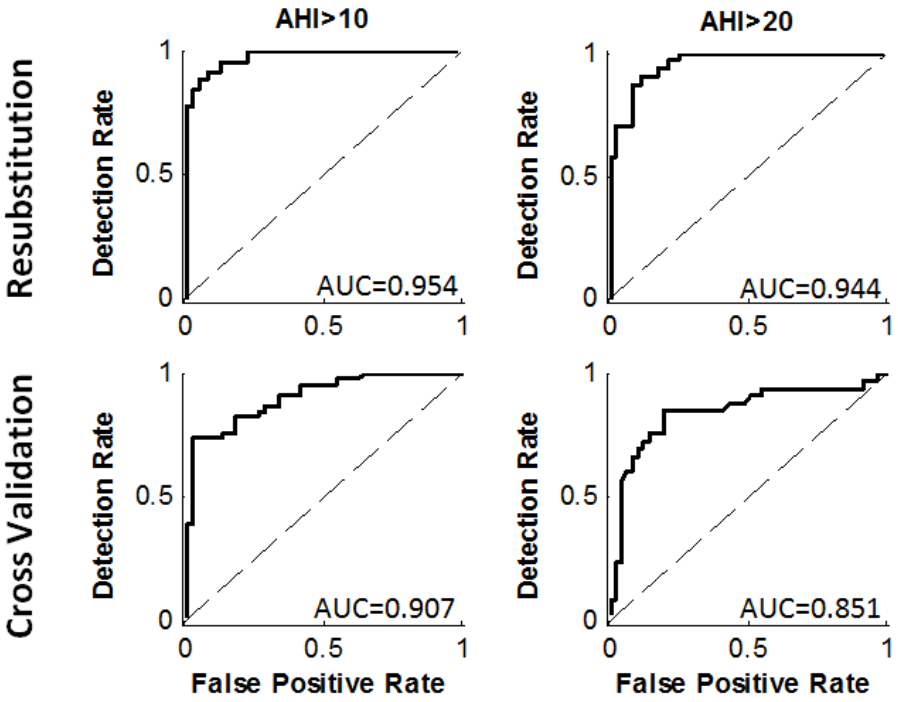

Figure 5.2: Receiver operating characteristic (ROC) curve. ROC curves of two AHI cutoff points, i.e., AHI >10 (left), >20 (right) (events/hr). Upper panel Resubstitution method, and lower panel, 5-fold cross validation method. AUC – Area under ROC curve.

Table 5.2: System Performance – three category classification.

Confusion Matrices	Resubstitution			Cross Validation		
PSG \ Est.	Non	Mild	Severe	Non	Mild	Severe
Non OSA (n=39) (AHI<10)	0.85	0.13	0.03	0.87	0.10	0.03
Mild OSA (n=27) (10<AHI<30)	0.15	0.67	0.19	0.22	0.56	0.22
Severe OSA (n=19) (AHI<30)	0	0.11	0.89	0.05	0.11	0.84

AHI – apnea hypopnea index (event/h); Est. – estimated severity;

5.3.2. Apnea-Hypopnea Index Estimation (AHI_{EST})

AHI_{EST} was estimated by multivariate linear regression model, fed by the five features as the independent variables. Figure 5.3 present scatter plots of AHI determined by PSG (AHI_{PSG}) versus estimated AHI, i.e. AHI_{EST}. High and

statistically significant correlation (r^2=0.71, p<0.001) were obtained. Note that 79 of 85 subjects are within the 95% confidence interval.

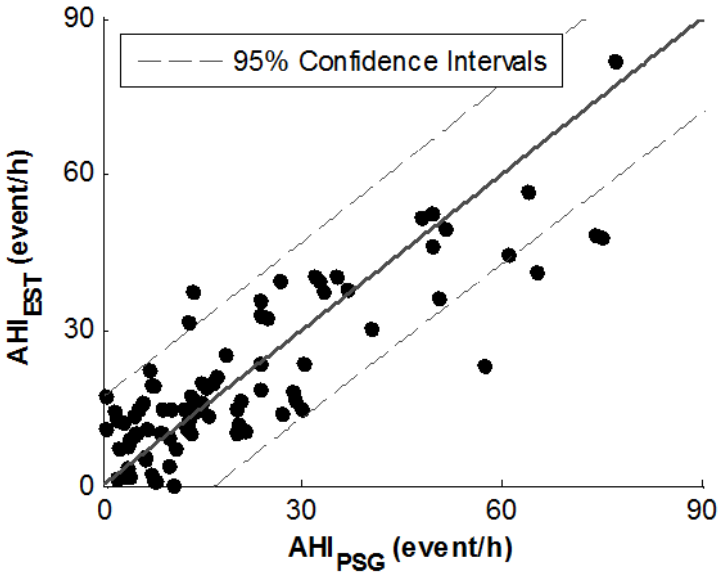

Figure 5.3: Scatter plots of estimated AHI (i.e., AHI_{EST}) versus gold standard AHI determined by polysomnography (AHI_{PSG}). The identity line and 95% confidence interval were added.

Bland-Altman-plot is presented in Figure 5.4. Again, Only 5 of 85 subjects (5.9%) fall outside the two standard deviations lines. Moreover, the estimation was unbiased (mean of differences was 0.12 event/h^{-1}). It should be noted that 4 of those outliers (miss-agreements) correspond to severe OSA subjects which our system underestimates their AHI, however, their diagnosis remains moderate to severe OSA (AHI>23).

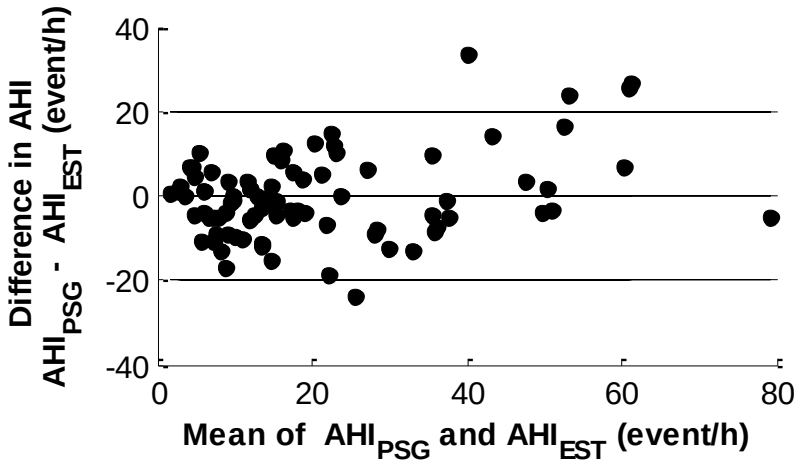

Figure 5.4: Bland-Altman-plot. Lines indicate the average difference and 2 standard deviations. very good agreement with the gold standard AHI_{PSG} is obtained.

Finally, using the diagnostic agreement approach [White et al, 1995] we found eighty percent of diagnostic agreements with PSG (Table 5.3); results for hold-out method are presented as well.

Table 5.3: Diagnostic Agreement

	All Subjects (n=85)	System Design (n=55)	Validation (n=30)
Agreement	0.80	0.76	0.87
Under-Estimate	0.08	0.12	0.03
Over-Estimate	0.12	0.12	0.10

6. Discussion and Conclusions

An innovative algorithm for monitoring sleep apnea based on acoustic nocturnal signal was proposed and validated. Snore analysis, based on the proposed snore acoustic properties, which demonstrate the nocturnal instability of upper airways in OSA patients, allows differentiation of apneic and benign snorers. All the features found to be correlated, by themselves, with the AHI and when incorporated into OSA recognition system, subject's AHI (i.e. AHI_{EST}) can be estimated. AHI_{EST} was found to be an accurate and reliable approach for the detection of OSA and demonstrated very good agreement with AHI_{PSG}. Further studies are required to determine the cost-effectiveness of the proposed approach. The following discussion considers these findings and other factors in the light of limitations of the study and current literature.

One of the merits of this study is the ability to estimate AHI solely on snoring signal (AHI_{EST}). Across a wide range of OSA severities, the AHI_{EST} highly correlated with the AHI_{PSG}. To our knowledge, none of the previous reports proposed estimation of AHI by snoring analysis. Van Brunt et al [1997], however, sought for an acoustical signature event, defined as a loud sound preceded by silence period, and quantify apneas events accordingly. A major limitation of their approach was the high sensitivity to artefact noises and the need for process automatization that was not performed and is essential for across-night snoring analysis. Our study provides ameliorations to Van Brunt’s approach by applying an event detection algorithm and trace for other indicators for obstructive events,

such as transient ascension of variances. Taken together, the proposed method to evaluate AHI_{EST} is a relatively accurate and reliable approach for the detection of OSA having very good agreement with AHI_{PSG}.

In the current study we analyzed snoring signals collected from eighty-five adults with typical symptoms of OSA [Tarasiuk et al, 2006] undergoing in-laboratory PSG diagnosis. To the best of our knowledge, this is the largest study sample exploring acoustic properties of snoring signals across the night. Earlier studies investigated various snoring properties; however, their conclusions were based on relatively small number of subjects. In their papers, Sola-soler et al, evaluated 6 subjects and 36 subjects [2002, 2007]; Fiz et al. used 17 subjects and 37 subjects [1996,2010]; Ng et al, recruited 16 and 40 subjects [2007, 2009]; and Abeyratne et al, used 45 subjects [2005]. Moreover, the majority of the previously mentioned research based their analyses on few and manually selected snoring events, and as such, essential information such as inter-snore properties (between snore events and/or across time) was not explored.

It should be noticed that the subjects we studied did not include patients with central sleep apnea. However, given the very low prevalence of central apnea among the referred population to diagnostic in sleep laboratories and the fact that the treatment of choice is usually the same, we do not consider this to be a major disadvantage.

Our approach is based solely on the analysis of acoustic snoring signals. Snoring is a primary symptom of OSA [Hoffstein 1996]. However, absence of snores does not indicate that the subject does not have OSA. In our study 9% of the subjects did not manifest habitual snoring and were excluded from statistics; those patient were significantly with lower AHI. Characterization of patients suitable for our diagnosis must be considered. It can be said that our system suitable only for subject who habitually snore. However, it should be noted that our system can 'say' that the subject so not snore and therefore no decision was made.

Our data show greater variances in snore characteristics among patients with AHI >10, both in frequency domain (Mel-Cepstability) and across the night (Running Variance). These findings support the thought that OSA is associated with functional abnormalities of the upper airways indicating collapsibility [Malhotra et al, 2002; Ayappa and Rapoport, 2003]. All the aforementioned studies explored jointly all the snores of a subject, without any reference to snore timeline across the night. Our study shows for the first time transient variations in the acoustic signal in adjacent to obstructive events (Figure 2). Such a perspective found expression in the Apneic Phase Ratio feature, which quantifies temporary accessions of feature variation around obstructive events, caused, probably, due to biological alterations of the airway patency during efforts to restore ventilation [Jordan et al, 2007].

The feature, which best describe the relation to AHI (R^2=0.51) is the *Inter Events Silence*, which is the most intuitive features, as it seek for the typical acoustic pattern of the apnea events itselves. However, OSA assessment is a combination of hypopnea events as well, which acoustically comes into expression by the sounds of breathing efforts. Those noises might mislead the silence detection, and as consequences, the estimated AHI of patients who mostly manifest hypopnea instead of full apnea, might be lower, i.e. consider as underestimation (due to the fact that only apneas can be detected by this feature).

Acoustic analysis of snore signals in order to monitor sleep apnea is widely reported in the literature. Type of used sensor, is one of the ways to differ between methods. In general, two types of microphones are utilized – non-contact microphone and contact microphone (attached to the patient body). In our study we choose to use a directional non-contact condenser microphone. However, each type has its own superiority. Attached microphones are less sensitive to surround noises; however those noises usually came from other medical equipments and have constant properties which are easier to overcome. Oppositely, frequent blanket\body movements badly affect those microphones. On top of that, it is clear that non contact microphones are more convenient for the patient and as alone, might supply more natural sleep, i.e. like-home sleep. It should be noted that, as widely reported, Body posture during sleep may also affect acoustic characteristics (snoring intensity) of snores and OSA severity [Oksenberg et al, 1998]. The use of a contact microphone might mimic this affect [Fiz et al, 2010]. Therefore, when using ambient microphone, as we do, it is

important to use features which are less sensitive to changes in sound intensities (affected by sleep positions). The entire feature we used designed to be robust: Mel-Cepstability based on the cepstrum coefficient [Deller, 2000] which not effected at all; Inter-Event-Silent based on the event detection which has an adaptive energy threshold; Pitch Density based on the autocorrelation function and as such not affected; and the Running Variance and Apneic Phase Ratio are robust because the changes in the sleep position is relatively not frequent and as such, the calculated local variance will not be affected. In order to check the robustness of our features, a secondary experiment was conducted. We took ten signals of different patients, randomly magnify their amplitudes by random factors and when investigate their results compared to those the original signals yielded, similar conclusions were obtained.

When comparing our ability to classify OSA subjects (threshold of AHI>10h^{-1}) with more than 88% sensitivity and more than 86% specificity, to previous reported results (Table 2.2), our performance is superior. Fiz et al [2010] were the first to incorporate different features into a classifier for the detection of OSA. As aforementioned they investigated snore number, average intensity, and power spectral density parameters and used a logistic regression model for the assessment. In order to better compare our performances, we implemented their methodology, as they describe it in their paper and perform a validation using our database (on the first 55 subjects). A sensitivity of 71% and specificity of 68% were achieved using resubstitution method (they reported 87% and 71% respectively using only 37 subjects). The differences in the achieved results can

be explained by the following: (1) due to the relatively small database, there is possible under-fitting of their classifier; (2) they used tracheal-contact microphone which might result in different acoustic properties, and therefore these feature might not suit our settings; (3) it is also possible that extraneous noises, which more affect our type of microphone, influence our signals and therefore might mislead the feature extraction results. To conclude considering our relatively large database our result is similar or event better than previous reported attempts.

Snoring analysis as we propose is not likely to replace the conventional diagnosis procedure of OSA through a polysomnographic study and a complete clinical evaluation, but it can significantly improve the management of this pathology. Automatic snoring analysis could also be helpful for the follow-up of snorers without OSA before and after application of medical and surgical therapies.

Summary

An algorithm for monitoring OSA based on acoustic snoring signal analysis is proposed. We believe that this study shows that the snoring analysis can be simple, adequate and reliable method for screening OSA. Our approach may address the growing needs for OSA screening diagnosis tools.

7. Future Work

In the following section I will describe, by some key points, issues that should be further investigated. It should be noted that this study will be continued by other students in the Biological Signal Processing Lab, under the supervision of Dr. Yaniv Zigel.

a) Snore detection algorithm – although the relatively good obtained performance. There are several ameliorations that should be considered. (1) First, normal breathing sound might contain additional information about the airway patency and flow limitation [Kulkas, 2010]. Therefore, isolate the breathing as well might able this analysis as well. (2) More modern classification approaches, such as Hidden Markov Model, might improve classification results. This approach gives additional significance to the timeline. For instance, it is clear that long sequence of snores might indicate that next event will be snore as well or at least increase the probability to be a snore event. (3) As for now, the algorithm is very time consuming. The effectiveness of the algorithm in sense of operation time should be handled.

b) Feature extraction – Recently, as aforementioned, few studies proposed, without a validation, some "sophisticated" acoustical properties such as higher order spectra, wavelets, nonlinear interactions etcetera. Such perspectives should be further investigated.

c) Super Snore – Without any sufficient basis, special analysis of pre- or post-apneic snores might reveal novel properties. These snores seem to be unique; usually shorter and more energetic.

d) Sleep Positions – It is said that sleep position might affect acoustic properties of the snore. Further investigation should explore these affects on our features.

e) Sleep Stages - Moreover, sleep stages and their affect on snore acoustics, should be investigated in order to deepen our knowledge regard snore acoustics. Penzel et al [2001] study the relationship between sleep stages and the collapsibility of the upper airways. They showed that it is not mediated by sleep stages. However, contrary to Penzel's results, few researchers [Hoffstein, 1996; Perez-Padilla et al, 1987], suggested that because airway elastance depends on the muscle tone, determined by the neural output to upper airway muscles and the sympathetic activity, it is expected that the presence of snoring will be different during REM and non-REM sleep.

   A preliminary trail can be observed in figure 7.1. The first 3 AR coefficients were extracted from each snore of a random selected subject (AHI=7.6h^{-1}). These coefficients were plotted, while all the snores from NREM sleep (larger asterisk, blue) were separated from the ones occur during REM sleep. We can clearly see the affect of sleep stages on this subject, whereas, this isn't the situation for all the subjects. Further research is required.

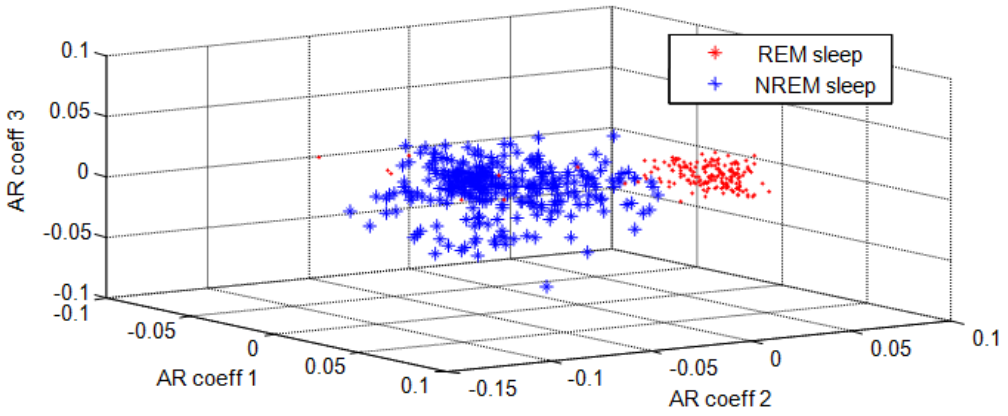

Figure 7.1: the effect of REM sleep on the snore spectrum (which represented by the AR coefficients) for randomly selected subject (AHI 7.6h^{-1}).

f) Children – To the best of my knowledge, there is no literature regard snore acoustics for the diagnosis of apnea among children. Such research might be revolutionary.

g) At home re-test – Sound base analysis is vulnerable by extraneous noises. However, those are well controlled in our laboratory settings. Further studies should explore reproducibility of the results by comparing in-laboratory and at-home environments. In addition - care should be given to overcome different noises in other settings.

h) Classification – In our study we used simple Bayes classifier for the OSA detection. Testing different classifiers might improve the performance. One possibility is to examine support vector machine (SVM) [Fan et al, 2005].

8. References

[1] Abeyratne UR, Wakwella AS, Hukins C. Pitch jump probability measures for the analysis of snoring sounds in apnea. *Physiol Meas* 2005; 22: 779-798.

[2] Almeida SR, Ayas NT, Utsuka R, Hamilton P, Ryan FC, Lowe AA. Nasal pressure recordings to detect obstructive sleep apnea. *sleep & breathing* 2006; 10(2): 62-69.

[3] American Thoracic Society: Standards and indications for cardiopulmonary sleep studies in children. The official statement of the American Thoracic Society. *Am J Respir Crit Care Med* 1996; 153: 866-878.

[4] Ayappa I, Rapoport DM. The upper airway in sleep: physiology of the pharynx. *Sleep Med Rev* 2003; 7(1): 9-33.

[5] Bar A, Pillar G, Dvir I, Sheffy J, Schnall RP, Lavie P. Evaluation of a portable device based on peripheral arterial tone for unattended home sleep studies. *Chest* 2003;123(3): 695-703.

[6] Ben-Israel N, Tarasiuk A, Zigel Y. Nocturnal Sound Analysis for the Diagnosis of Obstructive Sleep Apnea. *Conf Proc IEEE Eng Med Biol Soc*. 2010 in press.

[7] Bland J, Altman DJ. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; i: 307-310.

[8] Cavusoglu M, Kamasak M, Erogul O, Ciloglu T, Akcam T, Serinagaoglu Y. An efficient method for snore/nonsnore classification of sleep sounds. *Physiol Meas* 2002; 28: 841-853.

[9] Cavusoglu M, Ciloglu T, Serinagaoglu Y, Kamasak M, Erogul O, Akcam T. Investigation of sequential properties of snoring episodes for obstructive sleep apnoea identification. *Physiol Meas* 2008; 29(8): 879-898.

[10] Croft CB, Pringle M. Sleep nasendoscopy: a technique of assessment in snoring and OSA. *Clin Otolaryngol* 2001; 16: 504-509.

[11] Deller JR, Hansen JHL, Proakis JL. Discrete-time processing of speech signals. 2nd ed. New York; Institute of Electrical and Electronics Engineers Press: 2000.

[12] Fan RE, Chen PH, Lin CJ. Working Set Selection Using Second Order Information for Training Support Vector Machines. *J Machine Learning Research* 2005; 6: 1889–1918.

[13] Fiz J, Abad J, Jane R, Riera M, Manhanas MA, Caminal P, Rodenstein D, Morer J. Acoustic analysis of snoring sound in patients with simple snoring and obstructive sleep apnoea. *Eur Respir J* 1996; 9: 2365-2370.

[14] Fiz JA, Jané R, Solà-Soler J, Abad J, García MA, Morera J. Continuous analysis and monitoring of snores and their relationship to the apnea-hypopnea index. *Laryngoscope* 2010; 120(4): 854-862.

[15] Flemons WW, Rowely JA, Anderson WM, McEvoy RD. Home diagnosis of sleep apnea: a systematic review of literature. *Chest* 2003; 124(4), 1543-1579.

[16] Fukunaga K. Introduction to Statistical Pattern Recognition. 2nd ed. Academic Press, London; 1990.

[17] Hara H, Murakami N, Miyauchi Y, Yamashita H. Acoustic analysis of snoring sounds by a multidimensional voice program. *Laryngoscope* 2006; 116(3): 379-81.

[18] Hoffstein V. Snoring. *Chest* 1996; 109; 201-222.

[19] Hornero R, Alvarez D, Abásolo D, del Campo F, Zamarrón C. Utility of approximate entropy from overnight pulse oximetry data in the diagnosis of the obstructive sleep apnea syndrome. *IEEE Trans Biomed Eng* 2007; 54(1):107-13.

[20] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540-554.

[21] Jordan AS, Wellman A, Heinzer RC, Lo YL, Schory K, Dover L, Gautam S, Malhotra A, White DP. Mechanisms used to restore ventilation after partial upper airway collapse during sleep in humans. *Thorax* 2007; 62(10): 861-867.

[22] Kulkas A, Huupponen E, Virkkala J, Saastamoinen A, Rauhala E, Tenhunen M,Himanen SL. Tracheal sound parameters of respiratory cycle phases show differences between flow-limited and normal breathing during sleep. *Physiol Meas* 2010; 31(3): 427-38

[23] Malhotra A, White D. Seminar: obstructive sleep apnoea. *Lancet* 2002; 360: 237-245.

[24] Matsiki D, Deligianni X, Vlachogianni-Daskalopoulou E, Hadjileontiadis LJ. Wavelet-based analysis of nocturnal snoring in apneic patients undergoing polysomnography. *Conf Proc IEEE Eng Med Biol Soc*; 2007: 912-915.

[25] Miyazaki S, Yoshiaki I, Kazuo I, Kiyoshi T. Acoustic analysis of snoring and the site of airway obstruction in sleep related respiratory disorders. *Acta Otolaryngol* 1998 (Skotch); 537: 47-51.

[26] Morrera J, Fiz JA, Abad J. Acoustic analysis of snoring sound in patients with simple snoring and OSA. *Eur Respir J* 1996; 6: 531-5.

[27] Nakano H, Tanigawa T, Furokawa T Nishima S. Automatic detection of sleep-disordered from a single channel airflow record. *Eur Respir J* 2007; 29: 728-736.

[28] Ng KA, Koh TS, Puvanendean K. Speech-like analysis of snore signals for the detection of obstructive sleep apnea. *Conf Proc IEEE ICBPE*; 2006.

[29] Ng KA, Koh TS. Could formant frequencies of snore signals be an alternative means for the diagnosis of obstructive sleep apnoea? *Sleep Med* 2007; 1: S49-S66.

[30] Ng KA, Koh TS, Abeyratne U, Puvanendran K. Investigation of obstructive sleep apnea using nonlinear mode interactions in nonstationary snore signals. *Ann Biomed Eng* 2009; 37(9): 1796-1806.

[31] Oksenberg A, Silverberg DS. The effect of body posture on sleep-related breathing disorders: facts and therapeutic implications. *Sleep Med Rev* 1998; 2(3): 139-162.

[32] Pang D, Terris D. Screening for obstructive sleep apnea: an evidence-based analysis. *Am J of Otolaryngology* 2005.27(2): 112-118.

[33] Penzel T, Moller M, Heinrich F, Lennart K, Jorg-Hermann P. Effect of sleep position and sleep stage on the collapsibility of the upper airway in patient with sleep apnea. *Sleep* 2001; 24(1): 90-95.

[34] Perez-Padilla, Slawinski E, Difrancesco LM. Characteristics of the snoring noise in patients with and without OSA. *Am Rev Respir Dis* 1993; 147: 634-644.

[35] Ryan CF, Lowe AA, Li D, Fleetham JA. Three-dimensional upper airway computed tomography in obstructive sleep apnea. A prospective study in patients treated by uvulopalatopharyngoplasty. *Am Rev Respir Dis* 1991; 144(2): 428-32.

[36] Rechtschaffen A, Kales A. A manual of standardized terminology: techniques and scoring system for sleep stages of human subjects. US Public Health Service, Washington, DC; 1968.

[37] Rotem AY, Sperber AD, Krugliak P, Tarasiuk A. Polysomnography and actigraphy evidence of sleep fragmentation in irritable bowel syndrome. *Sleep* 2003; 26: 746-752.

[38] Skatvedt O. Localization of site of obstructive sleep apnea: a comparison of fiberoptic nasopharyngoscopy and pressure. *Acta Otolaryngol* 1993 (Skotch); 113: 206-209.

[39] Sleep Disorders Atlas Task Force. EEG arousals: scoring rules and examples. *Sleep* 1992; 15: 173-184.

[40] Solà-Soler J, Jane R, Fiz JA, Morrera J. Pitch analysis in snoring signals from simple snorers and patients with obstructive sleep apnea. *Conf Proc IEEE Eng Med Biol Soc*; 2002(2): 1527-8.

[41] Solà-Soler J, Jane R, Fiz JA, Morrera J. Spectral envelope analysis in snoring signals from simple snorers and patients with OSA. *Conf Proc IEEE Eng Med Biol Soc*; 2005.

[42] Solà-Soler J, Jané R, Fiz JA, Morera J. Automatic classification of subjects with and without sleep apnea through snoring analysis. *Conf Proc IEEE Eng Med Biol Soc*; 2007: 6094-6097.

[43] Tarasiuk A, Dotan SG, Simon T, Tal T, Oksenberg A, Reuveni H. Low socioeconomic status is a risk factor for cardiovascular disease among adult obstructive sleep apnea patients requiring treatment. *Chest* 2006; 130: 766-773.

[44] Van Brunt DL, Lichstein KL, Noe SL, Aguillard RN, Lester KW. Intensity pattern of snoring sounds as a predictor for sleep-disordered breathing. *Sleep* 1997; 20:1151-1156.

[45] Vgontzas A, Bixler E, Lin H, Rein J, Lin H, Kales A. Prevalence of sleep-disordered breathing in women. *Am J Respir Crit Care Med* 2001; 163: 613-618.

[46] White DP, Gibb TJ, Wall JM, Westbrook PR. Assessment of accuracy and analysis time of a novel device to monitor sleep and breathing in the home. *Sleep* 1995; 18(2):115-126.

[47] Wilson K, Stoohs RA, Mulrooney TF, Johnson LJ, Guilleminault C, Huang Z. The snoring spectrum. Acoustic assessment of snoring sound intensity in 1,139 individuals undergoing polysomnography. *Chest* 1999; 115: 762-770.

[48] Young T, Peppard PE, Gottlieb DG. Epidemiology of obstructive sleep apnea. *Am J Resp Crit Care Med* 2002; 165: 1217-1239.