Nocturnal Pulse Oximetry Analysis in Sleep Medicine

Sónia Catarina da Costa Cardoso

Final Internship Report Presented to

Escola Superior de Tecnologia e Gestão

Instituto Politécnico de Bragança

To obtain the Master degree in

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INSCRIPTION

To my parents and grandparents for the love and unconditional support at all times of my life, especially in uncertain ones, teaching me to always have courage.

Without you nothing would be possible.

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ABSTRACT

Nowadays, as we are faced with an ageing society affected by stress and other risk factors, such as obesity, sleep disorders are more frequently observed. It is estimated that two thirds of the population experiences sleep related problems at one point in their lives. The oxygen desaturation (SpO_2) obtained through night pulse oxymetry is an important parameter in sleep medicine for diagnosing respiratory disturbances during sleep, especially for diagnosing Obstructive Sleep Apnea (OSAS)). Clinical interpretations are mostly based on the oxygen desaturation index (ODI). Several alternatives have been identified in this work, as well as their applicability for diagnosing OSAS in a sample of 83 people. These methods include approaches based on time (Delta index), non-linear analysis (Central tendency measure, Approximate entropy), and spectral methods (Welch transform, Wavelet transform). The analysis that was carried out includes sensibility, specificity, correlation coefficient and the threshold value (the value that differentiates between people suffering from OSAS and healthy people). An epidemiological analysis is also presented in this work, which links OSAS to being overweight. Finally, the role of pulmonary rehabilitation in sleep disorders, specifically OSAS, is also described.

Keywords: OSAS; Oxygen; Night pulse oxymetry; Sleep medicine.

RESUMO

Nos dias de hoje, e estando perante uma sociedade cada vez mais envelhecida e afetada pelo *stress* e outros fatores de risco tais como obesidade, são evidenciados com maior frequência casos de distúrbios ao nível do sono. Considera-se assim que cerca de dois terços da população apresenta problemas ao nível do sono durante algum momento da sua vida. A dessaturação de oxigénio (SpO_2) obtida através de oximetria de pulso noturna é um parâmetro indispensável em medicina do sono, para o diagnóstico de perturbações na respiração durante o sono, principalmente no diagnóstico da Síndrome da Apneia Obstrutiva do Sono (SAOS). Interpretações clínicas baseiam-se maioritariamente no índice de dessaturação de oxigénio (IDO). Neste trabalho foram estabelecidas várias alternativas e a sua aplicabilidade para o diagnóstico da SAOS, para uma amostra de 83 indivíduos. Os métodos estudados incluíram abordagens com base no tempo (Delta índex), análise não linear (Medida de Tendência Central, Entropia Aproximada), e métodos espectrais (Transformada de Welch, Transformada de Wavelet). Foram realizadas análises ao nível da sensibilidade, especificidade, coeficiente de correlação e o valor do *Threshold* (valor que distingue portadores de não portadores de SAOS). Neste trabalho é também apresentada uma análise epidemiológica que relaciona a SAOS e o excesso de peso. É ainda abordado o papel da reabilitação pulmonar nos distúrbios do sono, mais especificamente na SAOS.

Palavras-Chave: SAOS; Oxigénio; Oximetria de Pulso Noturna; Medicina do Sono.

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NOMENCLATURE

AASM	American Academy of Sleep Medicine
AHI	Apnea Hypopnea Index
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continue Positive Airway Pressure
CTM	Central tendency measurement
EEG	Electroencephalography
EnAp	Approximated Entropy
MATLAB	MATrix LABoratory
NREM	Non Rapid Eye Movement
NO	Nocturnal Oximetry
ODI	Oxygen Desaturation Index
OR	Odds Ratio
OSAS	Obstructive Sleep Apnea Syndrome
PSG	Polissonography
REM	Rapid Eye Movement
ROC	Receiver Operating Characteristic
RR	Relative Risk
RV	Likelihood ratio
RV^+	Positive Likelihood Ratio
RV^-	Negative Likelihood Ratio
SaO_2	Percentage of hemoglobin saturated with oxygen
SOA	Sleep Obstructive Apnea
TTR	Total Time of Recording
TTS	Total Time of Sleep
VPP	Predictive Value
VPP^+	Positive Predictive Value
VPP^-	Negative Predictive Value

CHAPTER 1

INTRODUCTION

1.1 Work Presentation

Obstructive sleep apnea (OSAS) is an important public health issue nowadays, which is often sub-diagnosed. This is worrisome because the pathology has a great impact on the quality of life of those who suffer from it.

Sleep disorders are considered to be disturbances in sleep patterns. Some of these disorders are serious enough to interfere with a person's emotional, physical and mental health.

Therefore, it is important to determine the size of the problem, considering that it involves risks not only for those suffering from the problem, but for third parties as well.

The oxygen desaturation (SpO2) obtained through night pulse oxymetry is an important parameter in sleep medicine, primarily for diagnosis related with respiratory disturbances during sleep. Obstructive sleep apnea syndrome (OSAS) is one of the most frequent disorders. It involves day-time symptoms caused by five or more obstructive events of the apnea or hypopnea type per hour of sleep (IAH $\geq$ 5/h)

In sleep medicine, digital oximetry is an essential tool for registering the rapid fluctuations in blood oxygen saturation, which are observed in patients suffering from sleep apnea and respiratory instability.

This work aims to study some of the more promising approaches for interpreting data obtained from night pulse oxymetry and it is organized in 6 chapters. The following paragraphs summarize what is covered in each of these chapters.

Chapter 2 shows the existing relationship between night pulse oximetry and sleep disorders, especially sleep apnea syndrome. The topics discussed include sleep, sleep disorders and pathologies, as well as obstructive sleep apnea, and how it relates to night pulse oximetry.

Chapter 3 describes a theoretical approach towards the mathematical processes used. Epidemiological fundaments of clinical validation are also addressed: sensitivity, specificity and predictive values. Another focus of this chapter is the assessment of the risk of disease. Some theoretical aspects related to linear correlation are addressed, as well as the relationship coefficient. It includes a theoretical approach of the methods used in the diagnosis of obstructive sleep apnea. Finally, this chapter analyses the mathematical codes, which were developed in MATLAB, as they are applied to the problem being studied.

In Chapter 4 the sample in the study is described based on the records obtained by night pulse oxymetry. It also shows how the mathematical models developed are applied to sleep medicine.

In Chapter 5 the role of pulmonary rehabilitation in chronic obstructive pulmonary disease is described, as well as the main non-invasive treatments for OSAS.

Finally, in Chapter 6, the final conclusions and perspectives are presented for suggested future research related to this work.

CHAPTER 2

OBSTRUCTIVE SLEEP APNEA SYNDROME

2.1 Introduction

The aim of this chapter is to show the relationship between night pulse oximetry and sleep disturbances, especially sleep apnea syndrome. In order to do so, it is first necessary to obtain basic knowledge related to sleep, sleep disorders and sleep pathologies in order to analyse sleep obstructive apnea in depth and how it relates to night pulse oximetry.

2.2 Sleep

Sleep is a reversible behavioural condition during which the individual loses consciousness of the environment in which he is, as well as any external and internal stimuli. The level of consciousness of the individual varies during this behavioural state. [1].

According to Briggs and Pope-Smith "*Sleep is important for recovering health in cases of disease, while the lack of sleep can affect cellular regeneration, as well as the total recovery of the immunitary function*" [1].

Although not all adults need the same number of hours of sleep, specialists believe that fewer than 7 hours of sleep every night, on a continuous basis, may have negative consequences for the body and the brain [1].

The brain activity during sleep is usually recorded by an electroencephalographic machine (EEG), as it's possible to observe in figure 2.1. During sleeping time there is an alternation between two different states: the NREM state (*Non Rapid Eye Movement*), during which sleep is synchronized, and the REM state (*Rapid Eye Movement*), desynchronized sleep. The EEG shows the basic patterns of activities for these two types of sleep [2].

Figure 2.1- Encephalogram [3].

2.2.1 NREM and REM Sleep

When a person sleeps, he/she goes into NREM sleep, during which their eyes do not move. This period can be divided into 4 stages of approximately 90 minutes. This sleep phase corresponds to 75% of the sleep time. The first stage, NREM, happens right when the person falls asleep and one might not even be aware that they've fallen asleep. In this first stage of sleep, NREM, there can be some muscular contractions, often accompanied by a feeling of losing balance, or sleep myoclonus. Sleep myoclonus occurs when the person is about to leave sleep, which can be observed due to a sensibility to stimuli or, in recurring cases, to more serious sleep disorders. During this type of sleep, brain activity is low, as well as the heart rate, and the body temperature decreases. [2].

The first stage of this phase is shown by the EEG to be identical to the stage of vigil, when the person is almost in a state of wakefulness. The data from the EEG shows that during this stage the alpha waves disappear (8-12 Hz), indicating a vigilant relaxation with closed eyes. The alpha waves, the neuronal oscillations, decrease with a state of sleepiness and with sleep [4]. This disappearance causes the appearance of theta cortical waves (4-7Hz), which tend to be related to the not very deep state of sleep [4].

The second stage lasts between 5 and 15 minutes. During this stage the person is already asleep, but not deeply. During this stage it is more difficult to wake up and there is the possibility of dreaming. The EEG shows the presence of sigma waves during this stage (12-14Hz), lasting at least 0, 5 seconds, representing a inhibition by the brain in order to

maintain a calm sleep. The appearance of the K complex also indicates the beginning of this stage 2 [5].

Finally, stages 3 and 4 are associated with deep sleep, characterized by the existence of slow sleep waves, delta waves. Rechtschaffen and Kales (1968) approached these two stages separately, which stopped making sense in 2008 when the American Academy of Sleep Medicine (AAMS) combined stages 3 and 4 into stage 3. This combined stage lasts approximately 30 seconds and consists of the presence of 20% or more of delta waves. During this phase the delta waves of 75 micro volts (0.5-2 Hz) predominate [5].

Figure 2.2 shows the results obtained by an EEG for the different stages of NREM sleep.

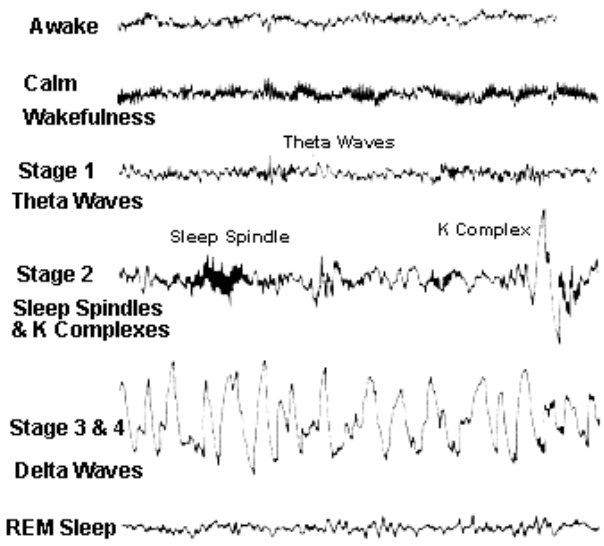

Figure 2.2- Results obtained from an EEG for the different stages of NREM sleep [3].

It is important to note that during the different phases of NREM sleep, what is observed in the EEG is a wave "retardation", or in other words, in the first stage of this type of sleep the wave frequency is higher than in the following stages. As these waves become slower, they also increase in amplitude [5].

REM sleep can be characterized by the muscular contractions of the eyes, causing them to move rapidly under the eyelids. Scientists see this movement as a sign of movement or activity during sleep [4 5].

Figure 2.3 shows the results obtained by the EEG during REM sleep.

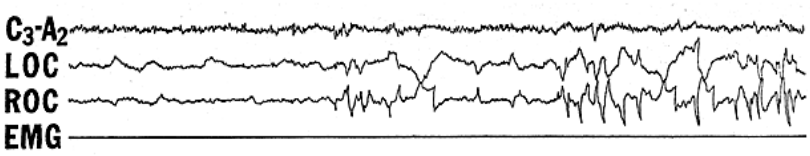

Figure 2.3- EEG results for REM sleep [3].

Where C3 is a derivation of the original signal and LOC and ROC represent the activity of the left and right eye respectively during REM sleep. During REM sleep, as opposed to NREM sleep the EEG shows low amplitude and high frequency waves, as well as rapid-eye movement. Therefore, the only way of distinguishing REM sleep from the state of vigil in the EEG is the observance of an intense muscular activity followed by temporary muscular paralysis in the REM sleep. The heart and pulmonary rates also increase. This phase of the sleep cycle is also known as the phase when dreams occur, normally dreams with strong emotional connections [6]. This phase represents 20 to 25% of the total sleep period and it usually lasts between 60 and 90 minutes [5]. This sleep time is essential for the physical and psychological well-being of the individual.

2.3 Risks Associated to Sleep Deprivation

In a society more and more focused on work, resting hours are often non-existent. The choice of "stealing" hours from sleep in order to carry out everyday chores leads to consequences that can be very harmful to both mental and physical health.

Sleep is essential to life and it is the basis of many physiological and psychological functions of the organism, such as the tissue repair, growth and preservation of memory and learning. Even though not all adults need the same number of hours of sleep, specialists believe that less than 7 hours a night, on a continuous basis, can have negative consequences for the body and the brain [7]. The term sleep deprivation refers to the number of hours of sleep the body lacks.

2.3.1 Types of Sleep Deprivation and Effects

Sleep deprivation can be acute, selective, partial or chronic. The acute lack of sleep can be observed when a person goes one night without sleep. The selective lack of sleep and the partial lack of sleep occur when a specific phase of sleep is missing. Chronic lack of sleep occurs when a person sleeps few hours during a prolonged period of time [8].

Sleep deprivation has recently been receiving more attention due to the harmful consequences for people's health and well. These consequences are related to metabolic dysfunctions, such as obesity, high blood pressure and cardiovascular problems [8].

When analysing the link between sleep and metabolism it is difficult to determine whether certain metabolic situations lead to sleep, or if the quality and duration of sleep is what stimulates the metabolism [2].

This type of situation represents a physiological stress to the organism, due to the high negative impact to several body systems, especially the cardiovascular system [8].

The ability to deal with sleep deprivation varies from person to person, as well as the factors responsible for this same deprivation.

An important factor is age, with the elderly suffering less as a result of sleep deprivation than young people. Personality is also a key factor which determines the ability to deal with sleep deprivation. People who suffer from mood swings due to sleep deprivation

can handle less time without sleep than people who feel euphoric with sleep deprivation [8].

A person's predisposition to developing sleep deprivation, such as insomnia, is also a factor which allows the person to handle sleep deprivation better [8].

2.3.2 Consequences of Sleep Deprivation

The effects of sleep deprivation are varied. Lack of sleep can lead to serious problems in the immunological system, making the person less resistant to diseases. Other consequences are disturbances in the digestive and circulatory system, short term memory and even the onset of cancer. The symptoms of sleep deprivation last a long time and affect different ages in different ways. For example, in older people sleep deprivation can cause senility, while in younger people this deprivation can affect growth and intellectual development [8].

Lack of sleep also affects daily activities such as work, driving, lack of energy, learning and concentration.

It is essential to sleep and sleep deprivation has a great impact over the most diverse aspects of life. Therefore, it is very important to correct and eliminate the erroneous information that individuals who suffer from sleep deprivation have about this subject and provide them with the information which can help them fight the fear of sleeping or dreaming, by overcoming their disorder. In certain cases, in order to do so it might be necessary to look for specialized help [8].

2.4 Testes and Devices used in Sleep Disorders

At some point in our lives everyone has experienced difficulties in sleeping and many sleepless hours in bed, which causes exhaustion and sleepiness during the day.

However, whenever the difficulties in sleeping are constant, to the point that they affect our daily activities, they can indicate a sleep disorder [9].

Sleep disorders are medical conditions which involve disorders in sleep patterns. Some can be serious enough to interfere with the person's emotional, physical and mental function. The assessment methods for this type of pathology range from subjective assessments, by using specific questionnaires, to day and night actigraphic or polysomnographic records. The most common medical test in night medicine used to determine the type of sleep disorder is the poliysomnograph (PSG) [9]. The equipment represented in figure 2.4 is a PSG device.

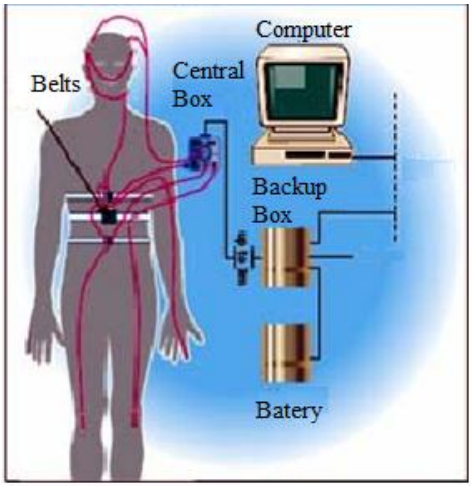

Figure 2.4- Polissonography [3].

This test quantitatively registers the changes that only occur during the night. Polysomnography is the monitoring of the patient's sleep in a calm and appropriate environment. The electroencephalogram, the electrooculogram, the electromyogram, oxygen saturation, the air flux, the respiratory effort and heart rate are all monitored. Due to the high cost of the above method, as well as its complexity and lack of availability, other variables with less sensibility and specificity have been used as diagnostic tools, as

well as the use of questionnaires, night oximetry and the ambulatory monitoring by portable machines [10].

2.4.1 Actigraphy

Actigraphy is a non-invasive method, which allows for the monitoring of the sleep/vigil cycle of a person during a 24-hour period. This assessment technique allows for the registration of the activity during sleep, which is digitalized and can then be transferred to a computer. This device can be observed in figure 2.5.

Figure 2.5- Actigraphy device [3].

The movements during sleep are different from those during the vigil state because there is no specific objective and the person is often not conscious of what's happening. This allows information to be obtained concerning total sleep time, total awake time, number of times a person awakens and sleep latencies [11].

When compared to the polysomnograph, the actigraph is 0,8 to 0,9 reliable, which is a cheaper method for providing information about the cycle of sleep/vigil, as well as being the cheapest method for providing information about the sleep/vigil cycle whenever it is necessary to record several days if needed [11].

It is particularly useful in the study of people who can't stand sleeping in labs, such as children and the elderly [11].

2.4.2 Polissonography

When a person experiences difficulty in sleeping he or she must see a doctor or a specialist in diagnosing this area in order to solve the problem. In order for an initial diagnosis to be confirmed, the person is submitted to a test in a specific clinic for sleep medicine studies, a test known as PSG. This test is recommended for cases with complex diagnosis, cases of behavioural changes during sleep, suspicion of epilepsy, among others. This test is an essential tool for diagnosing pathologies related to sleep medicine. [9].

PSG is a test which is based on measuring the cycles and stages of sleep, where several biological parameters are monitored and recorded. The biological parameters measured in this test during sleep are the following [10]:

- The levels of oxygen in the blood;
- Body position;
- Brain waves, by using an EEG;
- Respiratory rate;
- Electric activity of the muscles, by using an electromyogram (EMG);
- Eye movements through an electrooculogram (EOG);
- Movements of the lower members;
- Heart rate [11 12].

These parameters are not necessarily the best parameters, but it is through them that a definition of the sleep-vigil state is obtained [12].

When reading the PSG test, specialists must take into consideration the use of probe, which by its nature will alter a person's sleep in the study. This way, it is more difficult for doctors to find a balance between the precise estimates of the physiology of sleep with the least amount of interference [12].

In order to carry out the polysomnographic test, at least 11 wires/channels are needed with connections to the patient. Two channels are needed for the EEG, one or two channels or measuring the air flux, a channel for chin movements, one or more for leg movements, two for the eye movements (EOG), a channel for the heart rate, one for mediating oxygen saturation and one for each belt measuring the thoracic wall and the superior abdominal wall movement [11].

All these wires that allow for a person's biological signs to be read will converge into a central box, which is connected to a computer system that saves, stores and displays data [11].

During sleep, the computer monitor can display multiple channels continuously, as seen in figure 2.6.

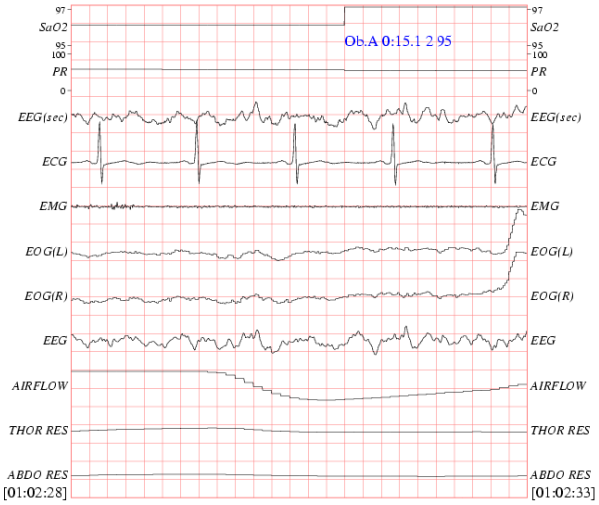

Figure 2.6- Polysomnogram [3].

The main data from a polysomnograph are the following:

- The total sleep time represented by TTS, vigil time and the total recorded time (TTR);
- Sleep efficiency time: TTS/TTR;
- Latency period for the beginning of sleep, latency for REM sleep and for the other stages of sleep;
- Duration in minutes and the proportion of the stages of sleep in TTS. These proportions vary according to age, with the slow wave sleep being physiologically lower among the elderly;
- Total number and the index of apneas and hypopneas (IAH) per hour of sleep;
- The saturation values and desaturation events of the oxyhemoglobin (drops > 3 or 4%, with a total time of 10 seconds);
- Total number and the index of periodic movements of the lower limbs per hour of sleep;

- Total number and the index of micro-awakenings per hour of sleep and how they relate to respiratory events or to leg movements;
- Heart rate and rhythm.

In addition to having physiological parameters monitored by a polysomnograph, the position of the body and the level of treatment are also factors described by technicians when carrying out this type of test. It is also standard practice in these situations to calibrate the amplifiers before the test itself. The impedance of the electrodes placed on the head is also checked before the recording. An ideal impedance ideal is higher than 5.000Ω, even though 10.000Ω or lower is considered to be acceptable. Electrodes with higher impedances need to be altered. A bio-calibration procedure is carried out, so the signs are obtained with the patient connected to the equipment. This procedure allows for the configuration of the amplification and integrity of the connections to the monitors and transductors to be checked [11].

Since the introduction of the polysomnograph (PSG), in 1950, this diagnostic method has been considered to be an invaluable tool. It provides quantitative information about the time of sleep and the time of vigil. Even though PSG provides enough information related to the behaviour and physiology of sleep, this method has disadvantages as well, such as being very expensive and sometimes too invasive to be used in clinical studies where the main objective is the simple quantification of sleep time, vigil time or both [12 13]

2.5 Sleep Disorders

Nowadays, sleep and sleep disorders have gained importance in the medical field, privileged field of research, largely due to advances in neurophysiology. It is estimated that nowadays about two thirds of the population has some type of sleep-related disorder at one point in their lives [14].

In the clinical field, the constant complaints of insomnia or sleep quality tend to increase independently of age [14].

Sleep disorders are considered to be disturbances in the sleep pattern. Some of these sleep disturbances are serious enough to interfere with the person's emotional, physical and mental health.

According to the classification system of Mental and Developmental Disorders proposed by the American Association of Psychiatry, the primary sleep disorders can be divided into Dysomnias and Parasomnias. Dysomnia disorders are characterized by abnormalities in the amount, the quality or the time of sleep, while Parasomnias are described by behavioural and physiological events, and difficulty in sleeping. There are sleep disorders related to psychiatric imbalances [15].

As previously mentioned, the polysomnograph is the most complimentary diagnostic because it evaluates several phases of sleep as well as possible changes in its structure. The situations that determine sleep disorders are infinite and the diagnostic and therapeutic approach is usually multidisciplinary, involving many specialties.

- **Dysomnias**

Dysomnias are sleep disorders which affect a person's ability to fall asleep, stay asleep and can even cause excessive sleep. The symptoms can vary lightly, depending on the sleep disorder which is diagnosed. Some of these types of disorders can be considered hereditary. Other causes span many physical and psychological problems. [15].

There are several cause for Dysomnias. These can be either physical or psychological. Some of the physical reasons for these sleep disorders include sleepiness during the day, a lot of physical activity, ageing, among others. Stress, depression and many other mental factors can play a role in this disorder. For others still, the disorder is caused by a lack of sun during the day [15].

The most common types of Dysomnias are the following:

Primary Insomnia

Primary insomnia is the kind not attributed to a medical, psychiatric or environmental cause. Primary insomnia is a dissonance characterized by the difficulty in starting or maintaining sleep. From a polysomnographic point of view, it also shows changes in the induction, continuity and structure of sleep. It usually appears in the young adult, it is more common among women and it has a chronic development. Primary insomnia is

observed among 12, 5% and 22, 2% of patients who suffer from chronic insomnia, and only the insomnia of major depression is more frequent. In some cases, the treatment can be the administration of medication (sleep inducers or antidepressants in small doses), but the combination of treatments has provided better results. Alternative treatments to medication include appropriate hygiene for sleep, psychotherapy and relaxation techniques [15].

Primary Hypersomnia

According to the International Classification of Sleep Disorders, primary Hypersomnia is defined as a disorder of the central nervous system. It is associated to excessive sleepiness with episodes of prolonged NREM sleep. Primary hypersomnia can be classified as monosymptomatic when the excessive daytime sleep is not abnormal due to waking up at night or as polysymptomatic. In terms of the polysymptomatic aspect, this consists of an abnormally long night time sleep [16].

Narcolepsy

Narcolepsy is the term used for uncontrollable attacks of sleepiness, unintentional, inadequate, associated or not to cataplexy (a sudden reversible loss of muscular strength brought on by strong emotions), sleep paralysis or hallucinations which occur before sleeping. The symptoms of this pathology are typical of REM sleep, but they occur inappropriately during the day. The episodes can last 10 to 20 minutes, but can also last for several hours. This pathology is as common among men as it is among women. The beginning of the symptomatology occurs in the first years of life and 18% of children with this disorder are 10 or younger. This disorder has a high hereditary component. Narcolepsy has no cure, but the treatment consists of administering a stimulant to the nervous system [15].

Obstructive Apnea Syndrome

Sleep apnea literally means “respiratory stoppage”. It is characterized by a complete or partial closure of the upper respiratory tract during sleep. During an episode of apnea the diaphragm and the chest muscles undergo a great effort in order to open the obstructed respiratory tracts to allow air into the lungs. This effort results in respiratory pauses of 10 (s) or more, followed by desaturation of oxygen or not [17].

- **Parasomnias**

It is the name given to the strange manifestations and behaviours which occur during sleep. Parasomnias can occur when the person is falling asleep or at any time during the sleep cycle. They often involve vigorous sleep, fear-inducing nightmares. Parasomnias can be triggered by behavioural disorders, brain disorders, other sleep disorders, among others.

Other types of Parasomnias include the following:

Sleep-Walking

It is a disorder characterized by sudden and repeated episodes of complex motor activity during sleep. Sitting on the bed, talking and wandering are some of the observed behaviours. There are cases where the episodes finish when the person wakes up spontaneously after the episode and others where the person goes back to sleep until the morning. The memory of the events is practically null. This type of sleep disorder is commonly observed among children, usually starting between 6 and 12. These moments start during NREM sleep (stages 3 and 4), occurring during the first third of the night. Sleep-walking is equally found among both genders and usually disappears at the beginning of the teenage years. No treatment is needed for this type of sleep disorder [15].

Night Horrors

These are related to nightmares and the sudden awakenings that these can cause. During these episodes, the person can sometimes wake up sacred and with visible signs of anxiety, during the deep phase of NREM sleep. Night time horrors are associated with the male gender. Some of the factors that cause this behaviour are: sleep deprivation, changes in the times of the sleep-vigil cycle and physical and emotional stress [15].

Bruxism

Bruxism is a physical condition during which the individual clenches his or her teeth. People, who suffer from this disorder, clench or grind their teeth unconsciously during sleep [15].

This disorder does not normally require medical care, but severe cases and frequent grinding can lead to jaw disorders, headaches, damaged teeth, among other things [16].

Periodic Movement of the Limbs

It's a disorder that is related to the nervous system which affects the legs and causes the need to move them. Due to its capacity for interfering with sleep, this disorder is considered asleep pathology. It is characterized by repetitive rhythmic movements, generally described as spasms, which occur every 20 to 30 seconds. Some are small bending movements, varying in intensity. This pathology is related to the lower limbs, but in some people this type of movement is observed in the upper limbs. These movements cause frequent awakenings during the sleep cycle and can interfere with the onset of REM sleep [17].

2.6 Obstructive Sleep Apnea Syndrome (OSAS)

Obstructive sleep apnea (AOS) is a quite common disorder related to breathing during sleep. In order for this pathology to be correctly diagnosed it is important to consider certain concepts. By definition, breathing events during the night time must last at least 10s, and can be either obstructive or central apnea, or hypopenea [18].

Obstructive apnea is characterized by complete obstruction of the upper respiratory tracts. In this case, the air flux is interrupted, causing continuous respiratory strain. On the other hand, central apnea differs from obstructive apnea in the total lack of respiratory strain due to change in stimuli from the central nervous system. Finally, hypopenea involves a transitional and incomplete decrease in the air flux by at least 50% of the basal air flux. The latter can either be central or obstructive [18].

This study focuses exclusively on obstructive apnea, since central apneas are rarer, except among patients suffering from congestive heart failure.

Anatomic-structural and neuromuscular factors which constrain the pharynx are essential for the development of this type of pathology. The intermittent occlusion of the upper respiratory track leads to inefficient inspiration attempts, ventilator breaks, high blood pressure, changes to the arterial gases, among other things. These physical efforts cause the person to wake up frequently during sleep, leading to an increase in involuntary muscular spasms and adverse cardiovascular responses. These awakenings harm the cycle of sleep and hyper-sleepiness during the day [19].

The main characteristic of this pathology is the occurrence of inefficient inspiratory efforts, caused by the dynamic and repetitive occlusion of the pharynx during sleep, resulting in breathing pauses of less than 10 sec, accompanied or not by oxygen desaturation. Obstructive apnea is the most serious of a spectrum of obstructive disorders of the respiratory tracts during sleep. People who suffer from this pathology present symptoms such as noise (snoring) during sleep. The episodes of apnea fragment sleep, reduce the quality of life, increase the risk of automobile accidents and make the person susceptible to developing high blood pressure and, consequently, increase the risk of cardiovascular disease [20].

Obstructive sleep apnea syndrome (OSAS) is characterized by the presence of daytime symptoms produced by five or more obstructive events of the apnea type and hypopneia per hour of sleep (IAH $\geq$ 5/h), diagnosed by a polysomnograph or by the presence of an apnea+ hypopnea index higher or equal to 15 events per hour, which represents a more serious disorder [19 20].

Symptoms such as daytime hypersleepiness, fatigue, indisposition, lack of attention, reduced memory capacity, depression, lower reflexes and the sense of loss of organizational capacity are all common complaints which can help diagnose obstructive apneas when associated to complaints related to night time sleep. Some common complaints include pauses in breathing, snoring, asphyxia, expiratory moaning, restlessness in bed, short periods of noisy hyperpneia and jaw relaxation. The patient can also complain about waking up with a dry mouth or a sore throat [20].

Snoring is the nighttime symptom which is most characteristic of sleep apnea because it reflects the basic subjacent physiopathology of the disorder which is a critical narrowing of the upper respiratory tracts. Snoring is the most frequent symptom of OSAS, occurring in at least 95% of patients, but it has little predictive value due to the high prevalence of

snoring among the general population. This symptom helps identify the presence of the pathology, but it doesn't specify the seriousness of the disease [20 21].

Nigh time asphyxia is also one of the main symptoms of OSAS, many patients recount frightening episodes of lack of air which stops soon as they wake up. These episodes originate from the narrowing of the upper respiratory tracts which block the entrance of the air into the pulmonary system [20 21].

The most common day time symptom related to this pathology is excessive day time sleepiness. This symptom leads to OSAS, but it is not a symptom that allows differentiating between those who suffer from OSAS and those who are healthy or suffer from a different type of sleep disorder. It is also necessary to distinguish between excessive day time sleepiness from other symptoms of fatigue. Sleep apnea is related to many other symptoms of excessive daytime sleepiness, such as memory loss, changes in personality, morning headaches, automatic behaviour and depression [20 21].

Patients suffering from severe OSAS frequently present variations in coagulation which are classically related to a predisposition to cardiovascular disorders:

- An increase in platelet aggregation during the night phase has been identified among OSAS patients, which is related to high night time levels of catecholamine;
- An increase in the night time levels of fibrinogen;
- Increases in hematocrit and in blood viscosity are commonly associated with night time desaturation, which affects most people who suffer from obstructive apneas.

2.6.1 Physio-pathological and Epidemiological

Pharynx occlusion characteristic of AOS is a result of a strength imbalance between structural peripharyngeal and intrapharyngeal pressures, negative inspiratory pressure of the inside of the respiratory tracts and the complacency of the muscular walls of the pharynx. The complacency of the pharynx is expressed by the change in the dimensions of the transverse section of this organ by unit of pressure and which characteristically is enhanced by testosterone hormones, which possibly explains the fact that this pathology affects primarily males. Recent studies confirm that AOS cases are observed among post-menopausal [19 20].

Traditionally, obstructive sleep apnea episodes involve temporary, but repeated, physio-pathological changes during sleep. As previously stated, some of these changes are registered by a polysomnograph.

The observed changes can be of the following type:

- Progressive desaturation of oxyhemoglobin;
- Initial bradycardia;
- Subsequent restoration of the heart beat;
- An increase in CO2 in the blood;
- An exaggerated increase of the negative intra-thoracic pressure [20].

Pulmonary ventilation is controlled by two systems: an automatic one, located in the brainstem and another voluntary one located in the brain cortex. The central chemoreceptors are sensitive to variations in the pH; the increase in (CO2) reduces the pH, thus stimulating the chemoreceptors. The peripheral chemoreceptors are sensitive to the decrease of the partial oxygen pressure in the arterial blood and in the pH. These chemoreceptors stimulate the respiratory centres located in the brain stem, controlling ventilation in an automatic and metabolic way. A follow-up of interactions in the sympathetic and parasympathetic activities and of the chemoreceptors in pulmonary insufflations and high negative intra-thoracic pressure can cause a chaotic behaviour of the heart rate, mediated by the temporary disarray which occurs during obstructive apnea [21].

Several morphological and functional factors have been mentioned as being responsible for the Picture of obstructive sleep apnea, such as fat deposits in the cervical region, jaw or mandible hypoplasia, hypertrophy of the tonsils or adenoids and increased volume of respiratory secretions [21].

In terms of the epidemiology for this pathology, the real incidence of OSAS in the general population is unknown. It is believed that 4% of men in the workforce suffer from this syndrome. It is 8 to 10 times more common among women due to anatomical and hormonal factors, as previously mentioned.

OSAS can occur in any age group; however, the most affected group seems to be between 40 and 50 years old. Obesity is the main risk factor involved [21].

The incidence of this syndrome among the general population varies according to the age of the sample studied, as well as gender, country, methodology used and the criteria used for diagnosing [22].

It is estimated the 4% of adult men and 2% of adult women in the United States suffer from this type of sleep disorder. Specialists in the field have found a high incidence of this pathology (about 24%) among elderly volunteers over 65 years old in San Diego, California. However, in an Italian study with 1510 males there was an incidence of 2.7% and in Australia, in a study of 400 adults, this sleep disorder prevailed among 10% of the males and 7% of the females. All these studies carried out over population samples used the polysomnograph as a diagnostic tool or the ambulatory monitoring of sleep [22]. Tests carried out in the state of Rio Grande do Sul in Brazil, evaluated 1027 industrial workers. The incidence of obstructive sleep apnea was observed to be higher among males, about 1.2%, than among females, 0.4%. In spite of these numbers, it is known that this pathology is usually sub-diagnosed by doctors, a measure which is changing thanks to the proliferation of specialized centres in the study of sleep diseases. One of the factors which probably contribute to this sub-diagnosis is the lack of academic training in sleep pathologies in many medical schools. Failure to identify this disorder is worrisome, considering that it is associated with the risk of sudden death. Patients with high blood pressure are more susceptible to this disease, due to common risk factors, such as obesity, being male and snoring [22].

Recently, the analysis of obstructive sleep apnea syndrome has turned towards identifying it as an independent risk factor for the onset of other diseases. The disease which has been studied the most and been correlated with obstructive sleep apnea is high blood pressure. There is already sufficient data to consider obstructive sleep apnea as a cause for the onset of high blood pressure [20 21 22].

2.7 OSAS and Pulse Oximetry

One of the simplest methods used in night medicine for evaluating OSAS is the continuous recording of oxygen saturation (SpO2) during sleep. These studies are not based on periodicity, but on physiological changes. This type of method is adequate for an

ambulatory evaluation, considering that oxygen desaturation is usually observed in obstructive sleep apnea syndrome, where events associated with an increase in the resistance of the upper respiratory tracts is observed.

Therefore, it is possible to conclude that studies of nocturnal pulse oximetry are quite useful for severe cases of OSAS. The same is not observed in the case of less severe diseases, where another more detailed means of diagnosis is needed. Oximetry is a component of the polysomnograph, which is used to characterize the frequency and depth of oxygen desaturation [23].

In sleep medicine, digital oximetry is an essential tool for registering fast fluctuations in the arterial oxygen saturation, which are characteristic of patients with sleep apnea and breathing instability [24]. The digital oximeters monitor this saturation which reflects the percentage of oxygenated hemoglobin [25].

Pulse oximetry has been widely used in medicine and in different medical specializations because it is a non- invasive method, it is not expensive, and the patient-sensor interface provides easy availability [26]. Figure 2.7 shows a pulse oximeter.

Figure 2.7- Pulse Oximeter [3].

The literature has recently been debating the usefulness of oximetry in the study of patients with sleep disorders, but also the possibility of it substituting polysomnographs in certain pathological circumstances [25].

The main debate concerning the usefulness of oximetry as a diagnostic means happens in the British Thoracic Society [27] and the American Academy of Sleep Medicine, where the first one defends that there could be disadvantages to using nocturnal oximetry (NO) as an initial approach to patients with OSAS. This position goes against the American institution, which states that there are other diseases that can cause fluctuations in oxygen saturation; therefore, this method in itself is not sensitive enough to be clinically useful [28].

Studies which involve an isolated use of NO as a diagnostic method for detection of OSAS show divergent results [27]. In most studies there is a variation in sensibility, ranging between 31 and 98% and in specificity ranging between 41 and 100% [28]. The great amplitude in sensibility and specificity reveal some contradictory results, with some studies showing low sensibility and high specificity, while others show high sensibility for Obstructive Sleep Apnea Syndrome OSAS [29 30]. The differences in results have been a point of contention in terms of what caused them, primarily the proportion of patients with OSAS, the inconsistency in the proportion between light and severe forms of OSAS, in the many studies, or the variability in desaturation, the age group, the lung capacity and the degree of obesity[29 30].

In a study carried out in Portugal in 2007, it was possible to observe that the role of night pulse oximetry in the detection of OSAS is sufficient to aid in diagnosing OSAS. This can not only decrease the reliance on polysomnographs in countries with economic problems, because of their high cost, but also lead to a faster access to treatment by patients with suggestive clinical history and a significant oxygen desaturation. In terms of diagnostics, a positive night oximetry can suggest the existence of OSAS, while a negative OSAS cannot be used to exclude OSAS. Therefore, oximetry can be used as a fast and affordable detection method, whenever patients' complaints are compatible with OSAS and respiratory pathologies have been previously excluded, whether it is due to clinical history, objective exam or through any other diagnostic exam. Under these circumstances, whenever oxygen desaturation above 5% of total sleep time is observed, a diagnosis of OSAS can be reached and the patient can be sent to a centre specialized in sleep pathologies in order to start treatment [31 32].

Whenever oxygen desaturation under 5% of the total sleep time is observed, and as long as there is a suggestive clinical history, the patients must be directed to a specialized centre, in order to undergo a PSG test to obtain a definite diagnosis [31 32].

As seem above, there are two levels of diagnosis which can be established. The first one corresponds to the study of the patient, by using night pulse oximetry, while the second one resorts to a polysomnograph and constitutes a diagnosis which is more specific to sleep pathologies [31 32].

CHAPTER 3

MATHEMATICAL MODELS IN SLEEP MEDICINE

3.1 Introduction

A theoretical analysis of the mathematical processes used in this study is carried out throughout this chapter. The following epidemiological principles of clinical validity are considered: sensibility, specificity, prediction. Another focus of this chapter includes evaluating the risk of disease. Theoretical aspects related to linear correlation are also analysed, as well as the coefficient of relationship. In addition, this chapter includes a theoretical approach to the methods used in the diagnosis of OSAS. Finally, the chapter also includes the mathematical model (Matlab) developed for analysing the problem in the study.

3.2 Epidemiological Basics of Clinical Validation

In order to carry out clinical validation tests, it is necessary to include a population of patients suffering from a specific disease and patients who are not, to whom a certain diagnostic test has been given.
It is then possible to obtain a matrix, such as the one in table 3.1.

Table 3.1- Matrix for calculating the characteristics of the diagnostic methods [33].

	with ilness	without ilness
Test Positive	A	B
Test Negative	C	D

In this matrix, (A) corresponds to true positive values, (B) to false positives, (C) to false negatives and (D) to true negatives. Based on this relationship test-disease, it is possible to calculate the sensibility, specificity, the predictive sample value, among others.
The sensibility of a diagnostic test is the quotient between the number of patients who test positive and the total number of patients with the disease. The calculation of the sensibility can be done by using the following equation [33].

$$\text{Sensibility} = \frac{A}{(A+C)} \quad (1)$$

In terms of specificity, this is the quotient between those who don't have the disease and tested negative and the total of those who don't have the disease. This can be described by the following equation [33].

$$\text{Specificity} = \frac{\text{D}}{(\text{B+D})} \tag{2}$$

The predictive value (VPP) indicates the probability of a person being ill when the test is positive. The VPP is extremely important clinically and in planning scans because it provides the probability of an individual who tested positive being ill [33].

$$VPP = \frac{A}{(A+B)} \tag{3}$$

The concept of VPP, as defined, is rarely possible, considering that A comes from an unhealthy population while the value for B comes from a healthy population. However, this value can be easily calculated from two characteristics of the method, sensibility and specificity and of a characteristic of the disease, its prevalence [33].

The positive predictive value is equal to the true positive numbers divided by the sum of the true positives with the false positives. [33].

The problem in establishing discriminating values is that there is a compromise between the highest level, which maximizes the specificity and the VPP at the cost of the low sensibility and many false negatives. On the other hand there is also the compromise of the increase in sensibility at the cost of many false positives and the reduction of VPP [33].

A rule that must be taken into consideration is when the specificity is high in the presence of a positive test which is a strong indicator of the disease, since a negative test does not guarantee there is no disease. When the sensibility is high, a negative test is a strong indicator that the disease is absent, but a positive test might not be a great indicator of the presence of the disease [33].

The positive predictive value (VPP^{+}) is a proportion of the true positives among all people who are tested positive. It expresses the probability of a patient with a positive test having the disease and it is obtained through the following expression [34].

$$VPP^{+} = \frac{A}{(A+B)} \tag{4}$$

In terms of the negative predictive value (VPN) this is the proportion of true negatives among all people who are tested negative. It expresses the probability of a patient with a negative test not having the disease [34].

$$VPN = \frac{D}{(C+D)} \tag{5}$$

It can be said that the higher the sensibility, the better the negative predictive value will be, while the positive predictive value will be better the higher the specificity. [34].

The ratio between the probability of a certain result of a diagnostic test among carriers of the disease and the probability of the same result being observed among people without the disease is known as the likelihood ratio (RV). This can be positive (RV+), when it expresses the probability of finding a positive result among unhealthy people than among those who aren't. [34].

$$RV^{+} = \frac{Sensibility}{(1-Specificity)} \tag{6}$$

The negative likelihood ratio (RV^{-}) expresses the probability of having a negative result among unhealthy people than among those who aren't [34 35]

$$RV^{-} = \frac{1}{RV^{+}} \tag{7}$$

The ratio of the cross product or the *Odds Ratio (OR)*) expresses the number of times in which the presence of the factor being studied increases the probability of the disease occurring in relation to the lack of a factor [35].

$$OR = \frac{A*D}{C*B} \tag{8}$$

If the exposure frequency is higher among the cases, the OR will be higher than the unit, indicating an increased risk of the disease with exposure, Therefore, the higher the association between exposure and disease, the higher OR. Inversely, if the frequency of

exposure is lower among the cases, the OR will be lower than 1, indicating that the exposure is a protective factor in relation to the disease. [35]

The calculation of relative risk of illness (RR) allows for the expression of the associated force between two events. The RR expresses the excess of risk in a given injury among people exposed to risk factors, compared to those who aren't [35 36].

$$RR = \frac{A/(A+B)}{C/(C+D)} \tag{9}$$

Figure 3.1 shows the levels of risk associated to the disease being studied [34].

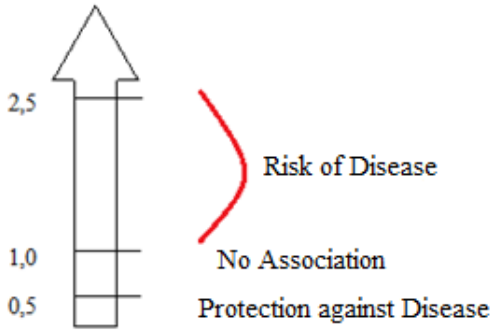

Figure 3.1- Levels of risk associated to the disease.

It can be said that based on image 3.1 that a relative risk equal to 1 indicates a health aggravation equal in both groups being compared. As such, exposure does not have a detectable effect, leading to the conclusion that there is no health risk, or that there is no association between cause and disease. A relatively higher risk than the unit reveals that the exposure constitutes a health risk factor. The more the values are distant from the unit, the higher the risk and the probability of the association being coincidental. A relative risk below 1 shows that the exposure is beneficial and constitutes a protective factor in terms of health [35].

3.3 Receiver Operating Characteristics Curves (ROC)

Most statistics methods applied to diagnostic medicine are directed towards classifying individuals into groups, the diagnostic test being the main example. These tests are considered to be theoretically adequate methods for determining the presence or absence of a certain disease [37]. A sensibility test is the probability of a diagnostic test producing a positive result, since the person is suffering from the disease, while the probability of the test producing a negative result, since the person is not suffering from the disease is called a specificity test [37].

The performance of one of these tests is usually described by the ROC curve (*receiver operating characteristic*). The ROC curve quantitatively describes the performance of a diagnostic test, the result of which can be treated as a continuous variable or as a binary [37].

The ROC curve was developed during World War II for the detection of electronic signals and radars, but it was in the 70s that this method propagated itself throughout the many branches of biomedical research. It served primarily as a tool for classifying people into healthy and not-healthy [37].

The ROC curve is a sensibility graph (true positives rate) versus the noise, the rate of false positives (1-specificity), as can be observed in figure 3.2.

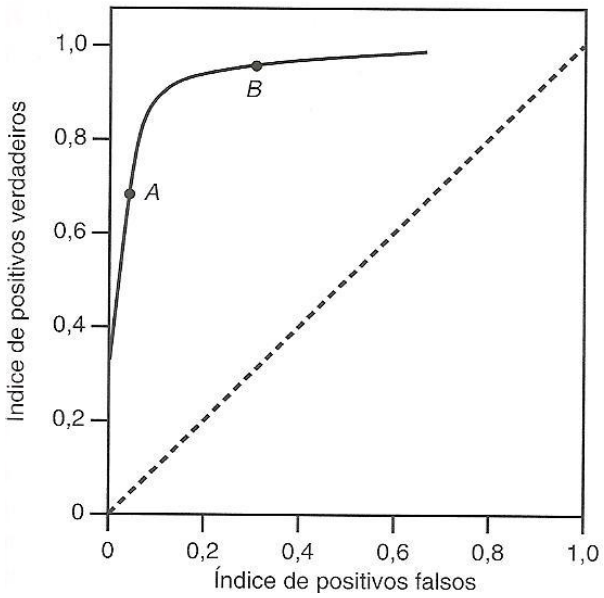

Figure 3.2- Graphic representation of the ROC curve [38].

The dotted diagonal line corresponds to an optional representation of a test that is randomly positive or negative. The ROC curve allows for the numbers for which there is a higher optimization of sensibility in relation to specificity to be highlighted, which corresponds to the point in which it is closest to the upper left hand corner of the diagram, since the index of true positives is 1 and that of the false positives is zero [38].

Each cut off point (point A and B) is associated to a pair (sensibility; 1-specificity) [38]. As a criteria for a positive test becomes more rigorous, the curve point corresponding to sensibility and 1-specificity (point A) moves downward and to the left (lower sensibility and higher specificity). If a less obvious criteria is chosen for identifying the positives, the curve point (point B) moves upward and to the right (higher sensibility, lower specificity) [38].

There is also the possibility of some healthy individuals being classified as positives, which means lower specificity. Therefore, choosing the best cut off point is often done based on the point where the sensibility and specificity are simultaneously higher [37 38].

The Pythagorean theorem is often used with the ROC curve because it provides information concerning the minimal distance between the cut off points in the curve and the maximum sensibility point (the positives index is 1 and the false positives is 0) figure 3.3.

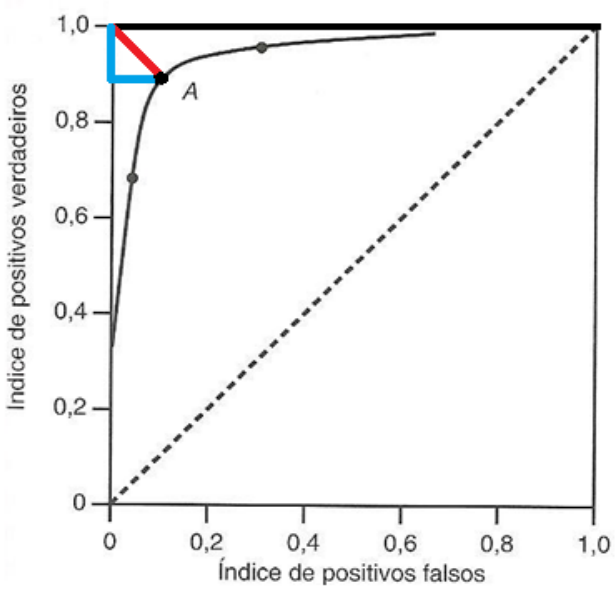

Figure 3.3- Representation of the application of the Pythagorean Theorem [38].

3.4 Linear Correlation

The correlation analysis is a statistical method used to study the degree of relationship among the variables. There is bidimensional statistical variable (X; Y) whenever two different characteristics are observed and studied for each element of the population, (X e Y). There is no differentiation between the cause and effect variables, meaning that the degree in combined variation between X is equal to the degree in combined variation in Y and X. The measure of the correlation strength of two variables is known as correlation coefficient. It can also be known as a measurement of association, interdependence, or the relationship among the variables [38].

There can be different types of correlation X and Y. The relationship between two variables will be linear when the value of one can be obtained by approximately half the equation of a straight line [38].

$$Y = \alpha + \beta X \tag{10}$$

Therefore, it is possible to adapt a straight line to the data. In this case, it is a simple linear correlation. However, whenever this is not observed, it does not mean there is no correlation between them. There might be a non-linear correlation between them. [39]

A simple way of checking the correlation type between two variables is through the graph known as “dispersion diagram”. The advantage of building a dispersion diagram is that it often makes observation easier, since through this aspect it is possible to obtain a good notion of how two variables relate to each other [39].

It consists of a graph which represents the pairs (Xi, Yi), where i = 1, 2,...,n, where n = the total number of observations [39]. In figures 4.4, 4.5, 4.6 and 4.7 it is possible to observe the different dispersion diagrams for the correlation analysis, which are the following: perfect linear correlation graph, null correlation, negative linear correlation and non-linear correlation [39].

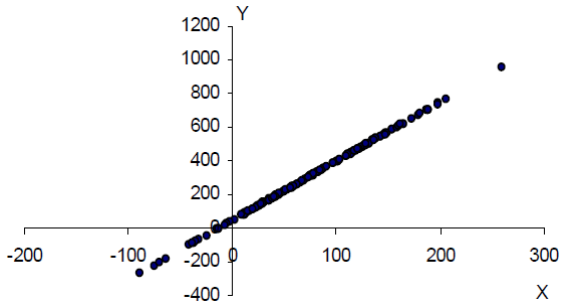

Figure 3.4- Positive linear correlation graph [39].

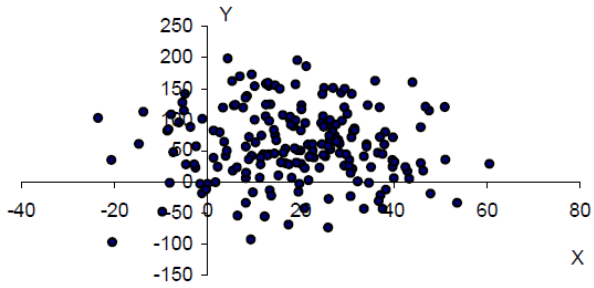

Figure 3.5- Null correlation graph [39].

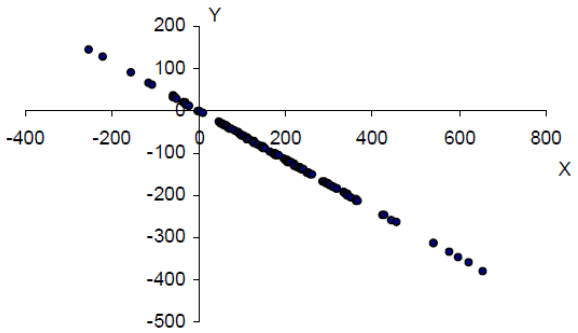

Figure 3.6- Negative linear correlation graph [39].

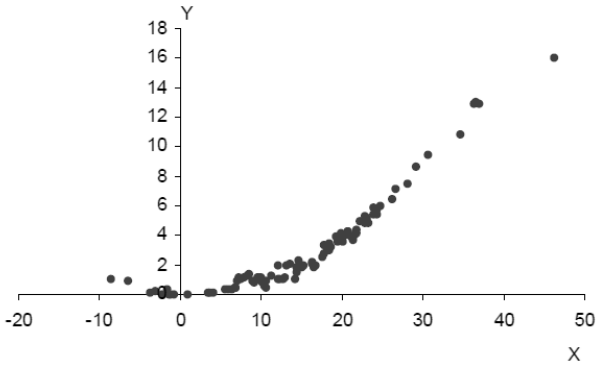

Figure 3.7- Non-linear correlation graph [39].

3.4.1 Correlation Coefficient

The common method for measuring the correlation between two variables is the Pearson Linear Correlation Coefficient. The correlation coefficient is a simple basic tool, though very efficient for estimating the linear relationship degree between the variables [39]. Behind the correlation coefficient lies another concept of statistics, called covariance. Covariance and variance are very similar concepts in theory. While covariance measures the relationship between two different variables, variance only depends on one variable. Unfortunately, covariance is not a concrete estimate of the relationship because it can assume values of less to more infinite, without a point of reference to differentiate a strong degree of relationship from a weak degree. Therefore, covariance does not allow for a strong or weak relationship to be defined. In order to solve this problem, covariance is divided by the product of the standard deviation of the samples from both variables (X e Y), creating a pattern for the expression. This new measure of relationship is what's called the correlation coefficient (ρ). The values for the correlation coefficient are always contained within the interval $[-1; +1]$ [40].

$$\rho = \frac{\sum(x_i-\bar{x})(y_i-\bar{y})}{\sqrt{(\sum(x_i-\bar{x})^2)(\sum(y_i-\bar{y})^2)}} \quad (11)$$

When the correlation coefficient is $0 < \rho < 1$ the relationship between the variables is positive, if it's 1 it's perfectly positive. When $-1 < \rho < 0$ the relationship is negative, if it takes the value -1 it's perfectly negative. In practice, these extreme values are not found in real world research, but they serve as points of reference. In this case, a value equal to zero means the absence of a linear relationship [40].

3.5 Mathematical Methods Used

The different methods demonstrated in this study provide additional information based not only on the periodicity, but also on changes on the level of the physiological series.

Nowadays, most clinical interpretations related to the diagnosis of obstructive sleep apnea syndrome are based primarily on the number of desaturation events per hour (oxygen

desaturation index, ODI). The methods being analysed serve as an alternative to the diagnosis of the syndrome [41]. The different methods include methods based on time (Delta *Index),* spectral methods (continuous Wavelet transform and Welch transform) and non-linear methods (central tendency measure and approximate entropy).

3.5.1 Delta Index

The idea of the Delta Index is to quantify the oxygen saturation oscillations related to apnea events. The Delta index was developed by Pépin J. (1991) and is calculated as the sum of the absolute variations between two successive points, divided by the number of intervals [41].

$$\Delta\ \text{índex} = \frac{1}{\mathrm{n}}\sum_{1}^{\mathrm{n}}\left|\frac{\delta(\mathrm{saO2_{min}})}{\delta(\mathrm{t})}\right| \qquad (12)$$

Where SaO_{2min} represents the minimum value of the interval in question and t represents the duration (s) of each interval [41].

The Delta *Index is n*ormally computerized with intervals of 12 (s) (Lévy et al.1996, Olson et al.1999, Magalang et al. 2003) but due to a frequency of samples provided, intervals of 14 (s) were used instead [42].

This parameter clearly does not detect and count apnea events; it is used to quantify the variability of oxygen saturation. As a result, it allows for patients suffering from the syndrome to be identified.

Because the Delta *Index* is influenced by artefacts, it should be previously treated.

3.5.2 *Welch* Transform

The *Welch* transform has been used in the night pulse oxymetry, as an alternative to the study of the number of oxygen desaturations per hour. Since the oxygen desaturation events reappear periodically, these affect the aspect of the potency spectrum, where the noise and other artifacts exert little or no influence [44]. Therefore, the *Welch* transform involves the sectioning of the signal and the normalization of the potency spectrum of the

respective sections [25]. The Welch transform can be applied through the MATLAB function.

[Pxx, W] = PWELCH (X, WINDOW, NOVERLAP, NFFT, Fs) (13)

Therefore, the potency spectrum of a varied length signal is ready to be compared to others [25]. The analysis of the spectral density of oxygen saturation using the fast Fourier transform. The potency spectrum leads to the maximum range and the band area. These calculations can be performed for two ranges, Schmittendorf Range (25-30s) and Zammarron Range (30-70s), these intervals are crucial in the study since testing pulse oximetry and heart rate tests abnormalities show up, this is present in a peak amplitude spectrum for patients with OSAS for this intervals. The same is not true for non-carriers of the disease.The maximum range becomes more susceptible for identifying periodic desaturations, while the band area reflects the number and severity of the apnea events [25]. This means the latter is a more significant parameter.

3.5.3 Wavelet Continuous Transform

The continuous *Wavelet* transform is usually used for measuring oxygen saturation through spectral data provided by an oxymeter.
The general formula for this transform is given by the following function [25]:

$$W(a,b) = \frac{1}{\sqrt{a}} \int_R f(t)\, \Psi\left(\frac{t-b}{a}\right) dt \quad (14)$$

The formula is based on the convulsion of a given function *f* with the Wavelet function [41]. Therefore, the specific Wavelet function Ψ is dilated by *a* and translated by *b*, which creates a matrix of coefficients representing the similarity between *f* and $\Psi(a,b)$ [41].
This transform was first used in oxygen saturation by Lee Y. (2004) without achieving good results [43]. Schultheiss B. (2011) proceeded to optimizing this parameter [41]. *"We reduced the complexity of the Wavelet matrix by estimating the normalized energy (...) as the mean of the sum of squared coefficients*".

3.5.4 Central Tendency Measurement (CTM)

The measure of central tendency (CTM), is defined by the number of points located within a given radius (ρ) (15) divided by the total number of points (16). For N points of the data series N-2 is the total number of points in the dispersion graph provided by (17).

$$[x(i+2)-x(i+1)]\ versus\ [x(i+1)-x(i)] \tag{15}$$

In order to computerize CTM, we have:

$$\mathrm{CTM} = \frac{1}{\mathrm{N}-2}\sum_{\mathrm{i}=1}^{\mathrm{N}-2}\delta_{\mathrm{i}} \tag{16}$$

Where,

$$\delta \mathrm{i} = \begin{cases} 1 \text{if} [\mathrm{x(i+2)} - \mathrm{x(i+1)})^2 + (\mathrm{x(i+1)} - \mathrm{x(i)})^2]^{\frac{1}{2}} < \rho \\ 0 \quad \text{otherwise} \end{cases} \tag{17}$$

For oxymetry signs, it is assumed that the points within the radius are associated with a noise, while the points outside this radius are associated to apnea events [25]. In order for this to be true, an optimization of the sample rate must be carried out [25].

According to Schultheiss B. (2011), in order to have a correct optimization *"... it is necessary to take into consideration the length of the vectors which go beyond the radius. It is necessary to first calculate the total length of the vectors (d) and divide them by the total number of points and then only calculate the length of the vectors which go beyond the radius (*dout*)"*.

Figure 3.8 demonstrates the length of the vectors *d and* dout.

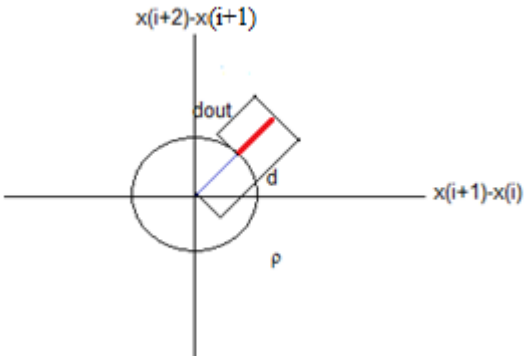

Figure 3.8- Representation of the radius and vectors d and dout.

3.5.5 Approximate Entropy (ApEn)

Approximate entropy (EnAp) aims to quantify the irregularities observed in sequences and temporal sequences, initially used in small signs and with a lot of noise [44]. The EnAp evaluates both dominant and subordinate patterns in the signal and discriminates data where recognizing characteristics is difficult [44]. Several properties make the EnAp a highly adequate tool for analysing biomedical series. EnAp is barely affected by low levels of noise, being a robust parameter, with an invariable scale and an independent model [44].

The algorithmic complex of EnAp is described by Pincus S. (2000) [45]. Through this method, an analysis which isn't very specific is made of the signal variation; while through the tolerance limits this method can be applied to signals which have noise, such as the case of signals emanating from oxymetries [46].

3.6 Programs Developed

MATLAB (MATrix LABoratory) is a programming environment where algorithms, data analysis, visualization and numeric calculations are developed [40].

The commands in MATLAB are very close to the way algebraic expressions are written, making them easier to use. Three different programs were created by using this *Software*.

The first program, Annex (A), represented in the flow chart of figure 3.9, presents a method in the domain of time (Delta Index), which aims to demonstrate its applicability in the quantification of the variation in oxygen saturation, in order to identify carriers of obstructive sleep apnea.

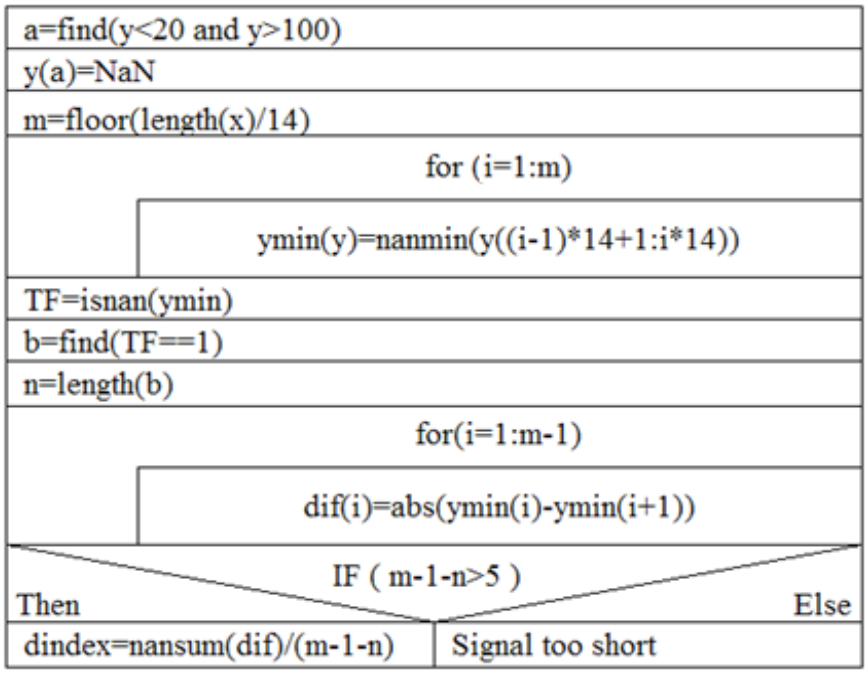

Figure 3.9- Flow chart of the Delta index program.

In this program the variable y is the reading obtained from the percentage of SpO2 where x is the variable of time (s). The length between intervals is 14 seconds. It was necessary to use only values of y between 20 and 100, considering that the values outsider of this interval are considered artefacts and become NaN. The cycle *for* finds the minimum value in each interval, an *array* TF of logistic values (1 NaN and 0 or not NaN values). This program calculates the number of intervals with a minimum NaN value, also calculating the difference between consecutive intervals of not NaN values (values within the normal parameters). If the number of intervals with normal values is superior to 5, then it is possible to calculate the Delta index. If this is not observed, the signal is very small for the calculation to be made.

The second program developed, Annex (B), figure 3.10, calculates sensibility and specificity.

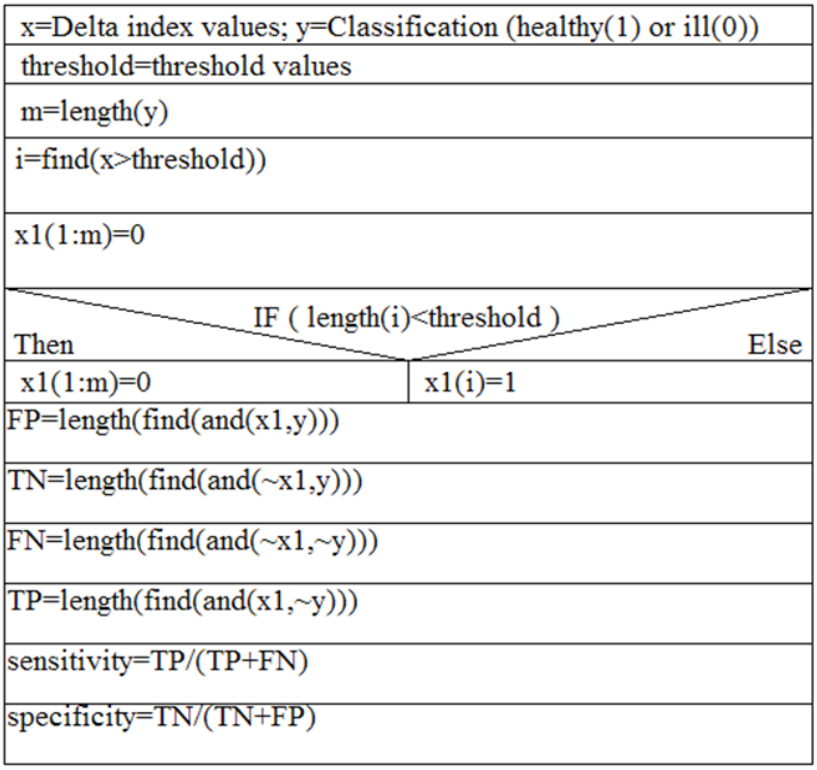

Figure 3.10- Flow chart for calculating sensibility and specificity.

As seen in figure 3.10, *x* is the parameter for evaluation (in the case of the figure 3.10 it's represented Delta Index) and *y* s the classification of people in the study, 1 for non-carriers and 0 for carriers. The threshold value can take several values, where these values are "compared" with values of *x.* The vector *x1* takes values of 1 for carriers (values of *x*> threshold) and 0 for non-carriers (values of *x*< threshold). It is necessary to identify if they are false positives (FP) *x1*= 1 and *y*= 1, true negatives (TN) *x1*= 0 and y= 1, false negatives (FN) *x1*= 0 and *y*= 0 and true positives (TP) *x1*= 1 and *y*= 0. The sensibility and specificity calculation is obtained from the equation (1) and (2) respectively, for the different thresholds.

The third program, Annex (C), represented in figure 3.11 is used for an approach using the spectral field of variation in oxygen saturation. This method incorporates the Welch transform.

```
x=SpO2 values
w=2048
noverlap=1024
nfft=2048
[Pxx,W]=pwelch(x(n),w,noverlap,nfft,fs)
df=W(2)-W(1)
Pxx_t=Pxx*2
plot(W(5:length(Pxx_t)),Pxx_t(5:length(Pxx_t))*df)
```

Figure 3.11- Program for an approach using the spectral field, Welch transform.

Vector *x* was used for applying the Welch transform, which contains the values of SpO_2. For the size of the window (*w*) and for the value of Fourier transform (nfft, the value 2048 was used, a value which is usually used for biological signs. The number of samples of the signs is half the value of the window of the window, 1024, which prevents the loss of data and artefact (*aliasing* effect). The equation for the Welch transform is found in MATLAB, where the computational vector (*Pxx*) for the spectral density (Power *Spectral Density*) is given in units of energy according to frequency (fs=1). *W* is the frequencies of the spectral lines.

Each program was carried out in order to be applied to the sample in an individual way, where the data obtained from these were analysed by *Microsoft Excel* 2010.

CHAPTER 4

APPLICATIONS OF THE MODELS TO OSAS PATIENTS AND NOT OSAS PATIENTS

4.1 Introduction

This chapter describes the test sample, as well as the application of the mathematical models developed for the same sample.

4.2 Sample Characteristics

The test sample consists of 83 German adults (60 males and 23 females), who were submitted to night pulse oxymetry tests. The records were obtained by using a portable pulse oxymeter *Nonin WristOx 3100*, with a sampling rate of 1Hz. The factors considered in the study were age and anthropometric data's. It was calculated body mass index (BMI) through the division of the body mass of the individual (kg), for the square of the high (m) [45]. The table 4.1 shows the characterization of the sample in study.

Table 4.1- Average and Standard Deviation for the factors in the sample.

Characteristic	Average	Standard Deviation
Body Mass Index (BMI)	26.78	6.74
Body Mass (kg)	82.70	22.05
Age (years)	47.67	16.08

50 people in this sample suffer from obstructive sleep apnea syndrome (OSAS) while 33 do not. The clinical data for all those who suffer from the disease was obtained through polysomnographic tests carried out in a sleep medicine lab, as well as a diagnosis by a specialist in the field. The clinical data provided by the test include the average number of desaturations per hour (ODI), as well as the general diagnosis and the prescription for a continuous positive pressure treatment of the respiratory tracts (CPAP) adequate for OSA. The patients suffering from OSA were divided into 3 categories (light, moderate and severe), using heart rate variation analysis as a criteria, the oxygen desaturation index (ODI) and the minimum oxygen saturation values (Annex (D)).

Those with an inconclusive diagnosis or with a sleep time under 3 hours were not included in this study.

4.3 OSAS in The Sample in Study

4.3.1 Probability and Diagnostic Tests

As mentioned above, obstructive sleep apnea syndrome is associated with conventional risk factors, especially with obesity. It has been scientifically proven that the incidence of obstructive sleep syndrome increases with the degree of obesity and the age group of the population involved in the studies. The reason obesity contributes to the development of the syndrome is that obese people have more adipose tissue around the pharynx, causing respiratory problems [47]. Due to the role of obesity in contracting the syndrome and in its development, the sample was analysed in relation to this factor. In order to do so, the sample was divided into 2 categories according to body mass index l (BMI), for values above or equal to 25 and under 25. According to the World Health Organization, people with a BMI above or equal to 25 ranges from being overweight (25-29.9) to suffering from morbid obesity (≥ 40), as can be seen on table 4.2 [48].

Table 4.2- Classification of BMI in adults [48].

BMI Values	Risk Grade
< 18,5	Underweight
18,5-24,99	Normal Weight
25-29,99	Overweight
30-34,99	Obese Class I
35-39,99	Obese Class II
≥ 40	Obese Class III

The probability and diagnostic tests were carried out using this classification and taking the information from the sample into consideration, Annex (D).

4.3.2 Results of the Probability and Diagnostic Tests

In Table 4.3 it can be seen that 31 of those who suffer from the disease are either overweight or obese, while 4 of them are not. For those who don't suffer from the disease, 8 of them are overweight or obese, while 23 are under the overweight line. The study it's applied to 66 individual, because form the 83 of the sample only 66 had data for the calculation of BMI.

Table 4.3- Relationship between the test and the disease.

Results	With Disease	Without Dieses
BMI $\geq$ 25	31	8
BMI < 25	4	23

Table 4.4 shows the main conclusions about this study. The results that were obtained in the study of the sample of overweight people (BMI $\geq$ 25) and people with normal weight or (BMI < 25) show that there is a high percentage of people who suffer from the disease who are overweight (sensibility of 88.57%). When compared with BMI < 25 (sensibility 11.42%).

A specificity of 74.19% confirms a considerably high rate of healthy people with a BMI < 25, in. comparison with 25.80% for BMI $\geq$ 25.

The test for predictive value confirms that there are a high proportion of people with overweight who do not suffer from the disease 79.49%.

14.81% of the individuals with BMI < 25 are patients with OSAS. 85.19% represents the proportion of healthy individuals from the ones who have BMI < 25. 20.51% of the healthy individuals are overweight.

The prevalence (number of cases divided by the total number of individual in the sample) of the disease among the overweight people is 53.03% for a BMI $\geq$ 25 and 46.96% for a BMI < 25.

The test proves to be quite sensitive, considering that the false positives or the number of healthy people who are overweight is low, 25.81% for a BMI ≥ 25 and high for a BMI < 25, 74.2%.

The study of the likelihood ratio shows that a BMI ≥ 25 is 3.43 times more likely to happen among those suffering from obstructive sleep apnea syndrome than among healthy people (0.15 times).

An odds ratio is of 22.28 and the disease risk for BMI ≥ 25 is 5.37.

For a BMI < 25 the odds ratio is 0.04 and the disease risk is of 0.19.

A for a odds ratio of disease superior than 1, for BMI ≥ 25 means that for individuals with the disease, the group constituted for BMI ≥ 25 has greater proportions than the group with BMI < 25.

Table 4.4- Conclusion of the study.

Epidemiology	IMC ≥ 25	IMC < 25
Sensibility	88.57%	11.42%
Specificity	25.80%	74.19%
VPP^+	79.49%	14.81%
VPP^-	20.51%	85.19%
% False Positives	25.80%	74.19%
RV^+	3.43	0.15
RV^-	0.292	6.66
OR	22.28	0.04
RR	5.37	0.19

4.3.3 Application of the Delta Index

Oxygen desaturation index corresponds to the average oxygen desaturation per hour; there is a relation to the delta index. This relation can be seen in figure 4.1.

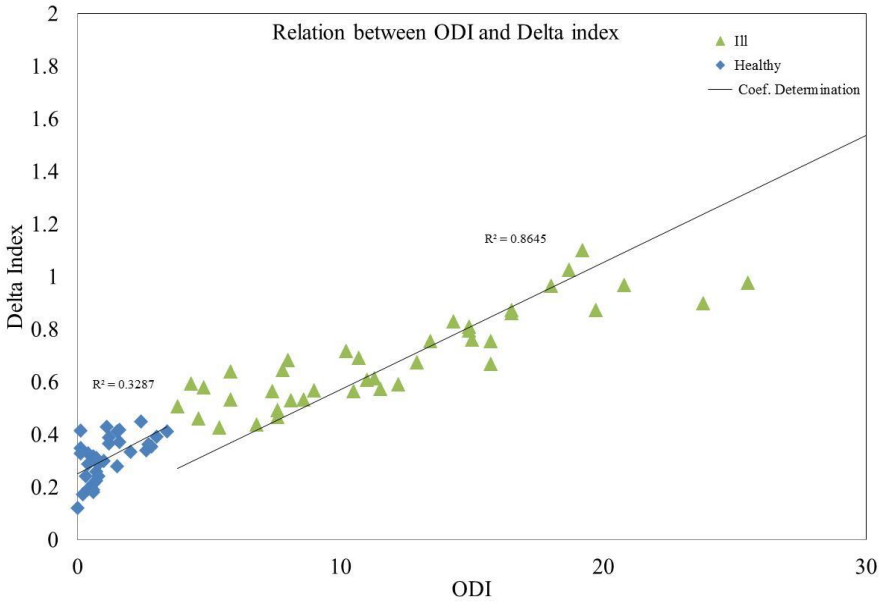

Figure 4.1- Correlation between the delta index and ODI on OSAS.

As can be seen in the graph of figure 4.1 the values for the coefficient of determination (R^2) are 0.8645 for patients suffering from the disease and 0.3287 for healthy ones. The coefficient of correlation can be calculated based on the coefficient of determination (R). It is the square root of the coefficient of determination. Therefore, the coefficient of correlation for patients suffering from the disease is 0.9297, while for the healthy ones it is 0.5733. There is a positive linear correlation between the oxygen desaturation index and the delta index.

By using the program shown in the flowchart in figure 3.10, quantitative descriptions can be obtained related to the delta index performance as a diagnostic test (sensibility and specificity). Different sensitivities and specificities are then obtained, depending on the threshold being tested, table 4.5.

The receiver operating characteristic (ROC) curves are analysed from the values obtained, since they highlight the values for which there is higher sensibility optimization in terms of specificity, figure 4.2.

Table 4.5- Threshold, Specificity, Sensibility for Delta Index

Sensibility	1-Specificity	Specificity	Threshold	Pythagoras T.
1.0000	1.0000	0.0000	0.1000	1.0000
1.0000	0.9697	0.0303	0.1500	0.9697
1.0000	0.8485	0.1515	0.2000	0.8485
1.0000	0.7273	0.2727	0.2500	0.7273
1.0000	0.5758	0.4242	0.3000	0.5758
1.0000	0.3636	0.6364	0.3500	0.3636
1.0000	0.2121	0.7879	0.3900	0.2121
1.0000	0.1818	0.8182	0.4000	0.1818
1.0000	0.1818	0.8182	0.4100	0.1818
1.0000	0.0606	0.9394	0.4200	0.0606
0.9800	0.0303	0.9697	0.4300	0.0363
0.9600	0.0303	0.9697	0.4400	0.0502
0.9600	0.0000	1.0000	0.4500	0.0400
0.9200	0.0000	1.0000	0.4800	0.0800
0.9000	0.0000	1.0000	0.5000	0.1000
0.8800	0.0000	1.0000	0.5200	0.1200
0.8200	0.0000	1.0000	0.5500	0.1800
0.6800	0.0000	1.0000	0.6000	0.3200

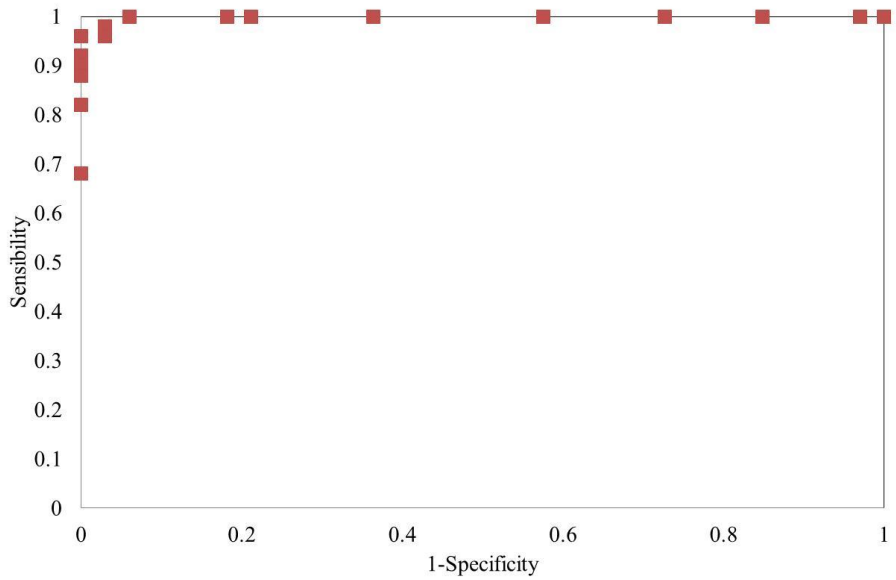

Figure 4.2- ROC curve for Delta Index.

The Pythagorean Theorem allows the point of greater sensibility optimization to be identified in terms of specificity, which corresponds to the closest point to the upper left hand corner of the diagram, since the true positives index is 1 and the false positives is zero. In order for this optimization to happen, it is necessary to calculate the ROC curve point which is found at the shortest distance from the point of greatest sensibility. The Pythagorean Theorem is then used, providing the graph in figure 4.3.

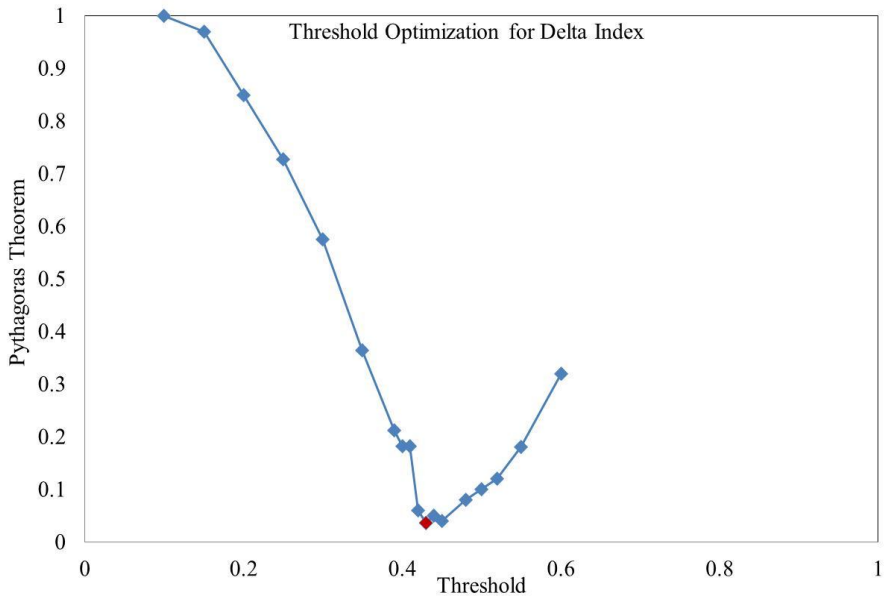

Figure 4.3- Threshold optimization for Delta Index, with Pythagoras Theorem.

In both tables 4.5 and figure 4.3, it can be seen that the curve point with the shortest distance (Pythagorean Theorem =0.0363) to the best sensibility optimization point in terms of specificity is the point (0.98; 0.9697). This point indicates a threshold value equal to 0.43. Therefore, 0.43 is the delta index reference point which separates patients suffering from the disease from healthy ones, which is associated to a high sensibility of 98% and a high specificity of 96.97% (1-specificity of 3.03%).

4.3.4 Power Spectral Density

A spectral study was also carried out in order to describe the behaviour of the signal energy and its frequency distribution. In order for this to be possible, it is necessary to use the *Fourier* transform, which can be seen in figure 3.11. The Power Spectral Density is given by the Welch transform, which involves the signal being divided into sections and the normalization of the potency spectrum of these sections. The power spectral density of the signals with variable lengths is comparable and can be used for calculating the threshold.

The Peak Amplitude and the Band Power were calculated from the power spectrum within a set time interval.

Two types of intervals were used for the band, *Schmittehdorf* Range (1/70-1/25 s or 0.0143-0.04Hz) and *Zamarrón* Range (1/70-1/30s or 0.0143-0.033(3)Hz). The program shown in the flowchart in figure 3.11 was applied to the sample and for each time interval identified by the spectral lines being studied. So, for *Schmittendorf*, the spectral line interval being studied is [30; 83] and for *Zamarrón* it is [30; 69], as can be observed in Annex (E).

- ***Schmittendorf Range (1/70-1/25s)***

The correlation with oxygen desaturation was also evaluated for the band power, the sum of the spectral lines in the study and for the peak amplitude, and the maximum value within the series of spectral lines. This can be seen in figure 4.4 and figure 4.5 for peak amplitude and for band power in terms of the *Schmittendorf* Range (54 spectral lines).

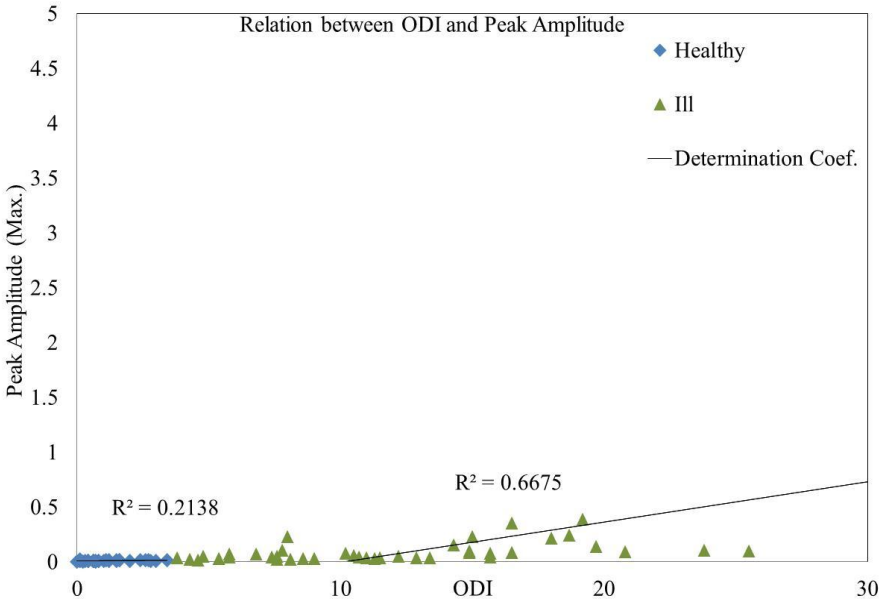

Figure 4.4- Linear correlation between the ODI and Welch method (Peak Amplitude).

This allows for the correlation coefficients to be obtained, which are 0.8170 for people suffering from the disease and 0.4625 for healthy people.

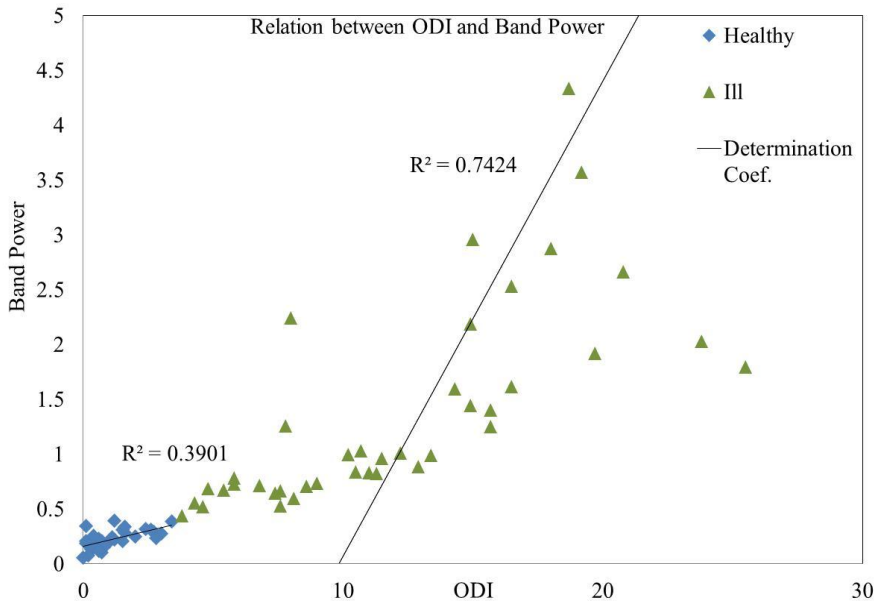

Figure 4.5- Linear correlation between the ODI and Welch method (Band Power).

For the band power in *Schmittendorf* the linear correlation coefficients are 0.8616 for the people suffering from the disease and 0.6246 for those who aren't.

For both the Maximum Amplitude of the Band, and the Band Power, the sensibility and specificity studies were used in order to optimize a threshold. The result was Table 4.6 for maximum amplitude, created by using the program shown in flowchart 3.10.

Table 4.6- Threshold, specificity, sensibility for Welch method (Peak Amplitude).

Sensibility	1-Specificity	Specificity	Threshold	Pythagoras T.
1.0000	0.5152	0.4848	0.0100	0.5152
1.0000	0.3030	0.6970	0.0130	0.3030
1.0000	0.1515	0.8485	0.0160	0.1515
0.9800	0.1212	0.8788	0.0180	0.1228
0.9800	0.0909	0.9091	0.0190	0.0931
0.9600	0.0303	0.9697	0.0200	0.0502
0.9600	0.0303	0.9697	0.0210	0.0502
0.9600	0.0000	1.0000	0.0220	0.0400
0.9400	0.0000	1.0000	0.0230	0.0600
0.9200	0.0000	1.0000	0.0260	0.0800
0.9000	0.0000	1.0000	0.0280	0.1000
0.8600	0.0000	1.0000	0.0300	0.1400
0.6600	0.0000	1.0000	0.0500	0.3400
0.5000	0.0000	1.0000	0.0800	0.5000
0.4600	0.0000	1.0000	0.0900	0.5400
0.4200	0.0000	1.0000	0.1000	0.5800

It is possible to observe in figure 4.6 the ROC curve obtained for Peak Amplitude.

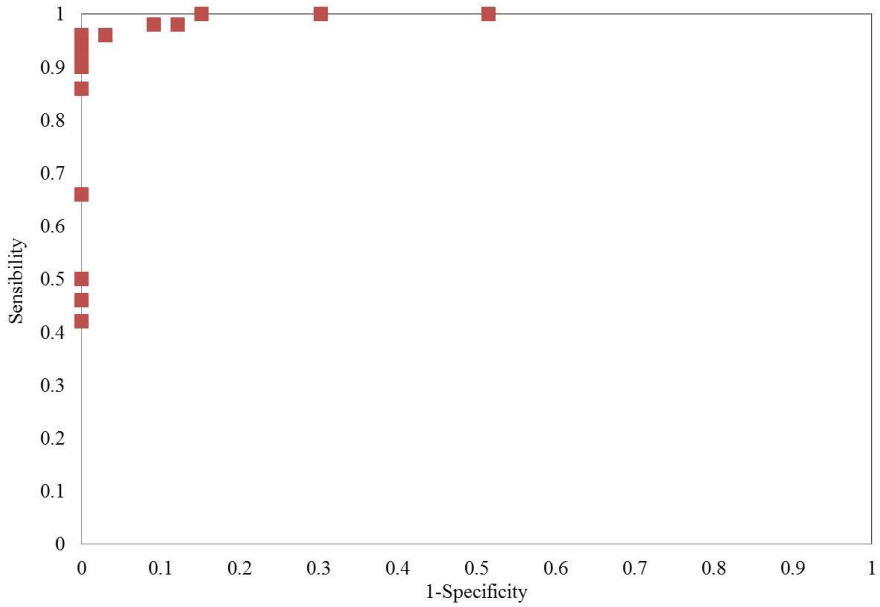

Figure 4.6- ROC curve of the method of Welch (Peak Amplitude).

As shows table 4.6, Pythagoras Theorem allows the threshold optimization. That optimization can be seen in figure 4.7.

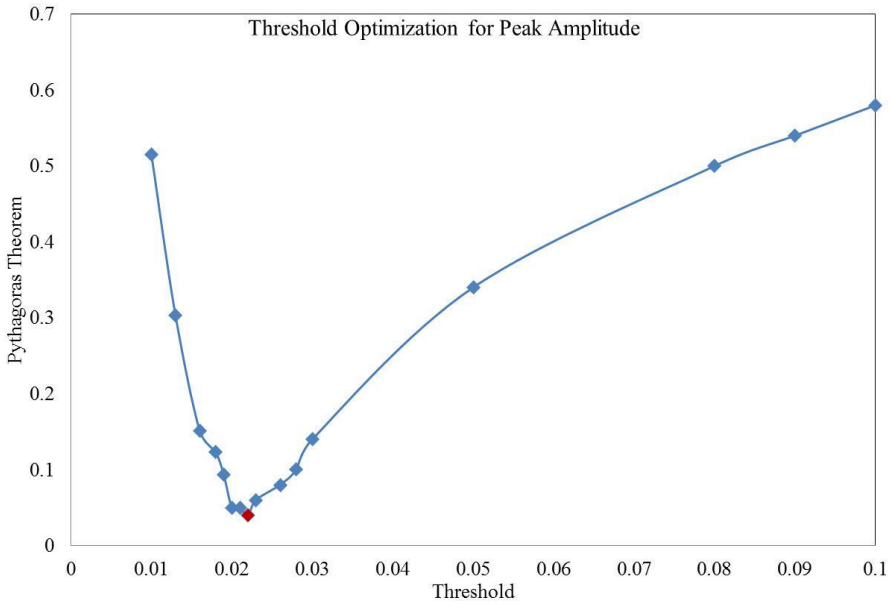

Figure 4.7- Threshold optimization for the method of Welch.

The best observed value for the threshold is 0.022 where represented in the ROC curve at the point (0; 0.96). The sensibility is 96 % and specificity 100%. The same was observed for the Band Power, where table 4.7 represents the values of sensibility, specificity, threshold values and the optimization obtained from the Pythagorean Theorem.

Table 4.7- Threshold, specificity and sensibility, method of Welch (Band Power).

Sensibility	1-Specificity	Specificity	Threshold	Pythagoras T.
1.0000	0.9697	0.0303	0.0650	0.9697
1.0000	0.9394	0.0606	0.0900	0.9394
1.0000	0.9394	0.0606	0.1000	0.9394
1.0000	0.8788	0.1212	0.1200	0.8788
1.0000	0.7273	0.2727	0.1600	0.7273
1.0000	0.6970	0.3030	0.1800	0.6970
1.0000	0.6061	0.3939	0.2000	0.6061
1.0000	0.3636	0.6364	0.2500	0.3636
1.0000	0.2727	0.7273	0.2800	0.2727
1.0000	0.2121	0.7879	0.3000	0.2121
1.0000	0.1212	0.8788	0.3200	0.1212
1.0000	0.1212	0.8788	0.3300	0.1212
1.0000	0.0909	0.9091	0.3400	0.0909
1.0000	0.0606	0.9394	0.3500	0.0606
1.0000	0.0606	0.9394	0.3600	0.0606
1.0000	0.0606	0.9394	0.3800	0.0606
1.0000	0.0000	1.0000	0.4000	0.0000
1.0000	0.0000	1.0000	0.4100	0.0000
1.0000	0.0000	1.0000	0.4300	0.0000
0.9800	0.0000	1.0000	0.4400	0.0200
0.9000	0.0000	1.0000	0.6000	0.1000

The ROC curve can be drawn in figure 4.8 based on the values shown in table 4.7 and the threshold optimization graph from the Pythagorean Theorem in figure 4.9.

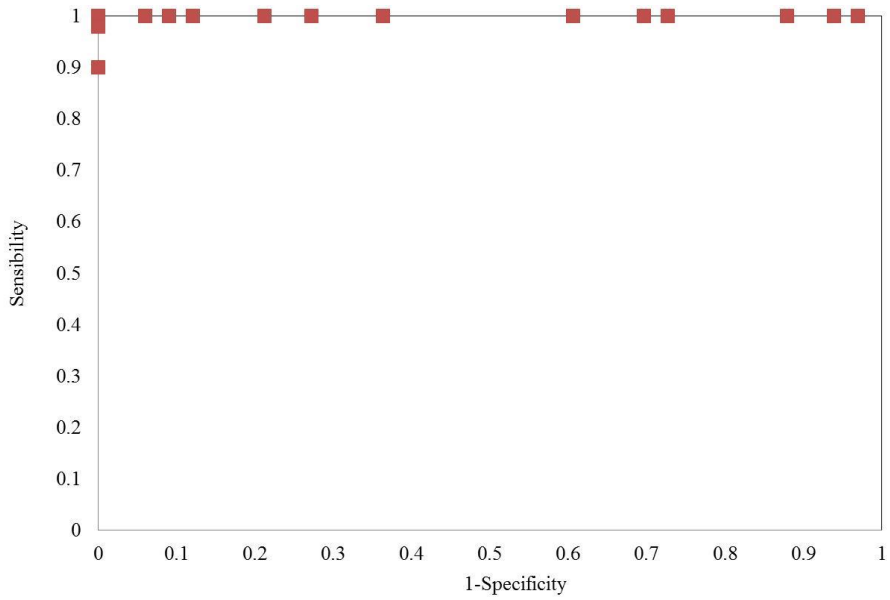

Figure 4.8- ROC curve for Welch method (Band Power).

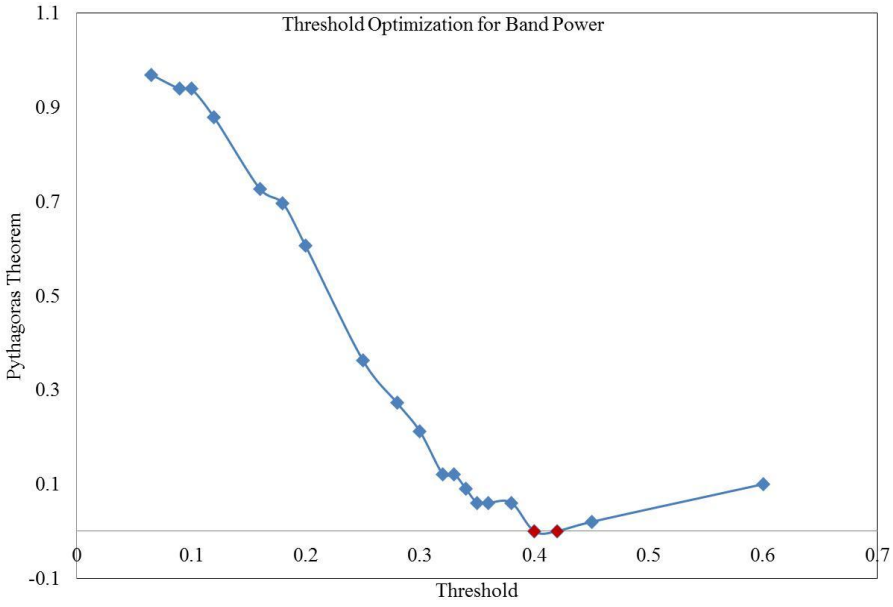

Figure 4.9- Threshold optimization for method of Welch.

As can be seen in both table 4.7 and figure 4.9 the threshold value obtained for the band power is found in the interval 0.4-0.43. Within the ROC curve with the coordinates (0; 1), this being the point of highest sensibility and specificity (both with 100%).

- ***Zamarrón Range (1/70-1/30s)***

The same type of assessment was carried out using the *Zamarrón Range* where the interval of spectral lines (40 lines) is shorter in relation to the number of spectral lines *Schmittendorf* (54 lines).

For the band power, the sum of the spectral lines being studied and the peak amplitude, the maximum value within the spectral lines series were used to evaluate the existing correlation with the oxygen desaturation index (ODI). This can be seen in figures 4.10 and 4.11 for the peak amplitude and for the band power respectively *Zamarrón Range*, where the values obtained are found in table in the Annex (F).

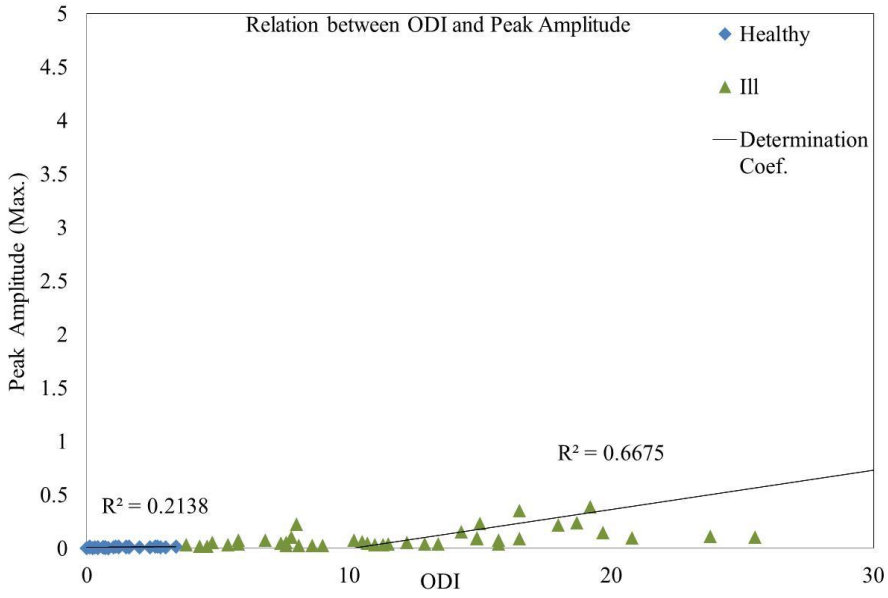

Figure 4.10- Linear correlation between the ODI and Welch method (Peak Amplitude).

It is also possible to obtain the coefficients of correlation, where 0.817 is for patients suffering from the disease and 0.4625 for the healthy ones.

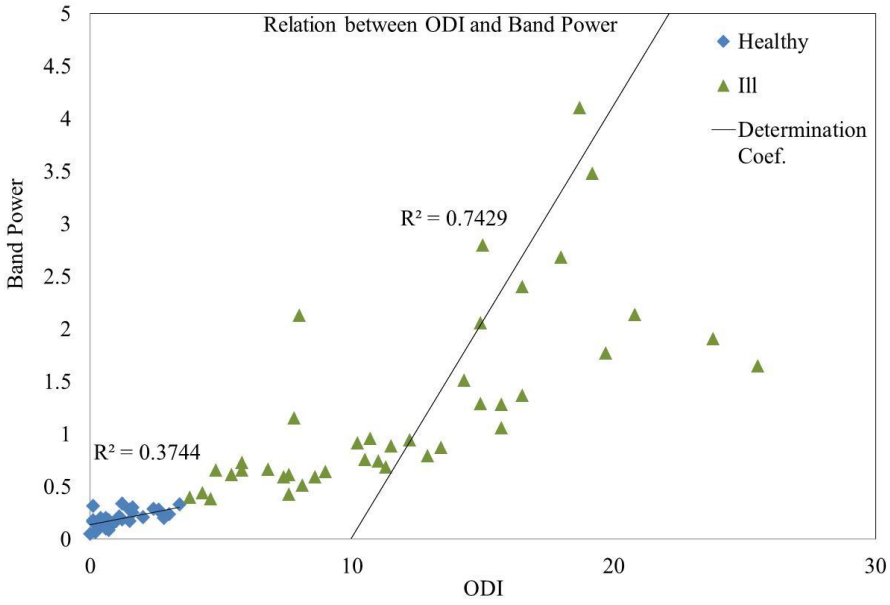

Figure 4.11- Correlation between the ODI and Welch method (Band Power).

For the band power in Zamarrón, the coefficients obtained for the correlation were 0.8619 for patients suffering from the disease and 0.6119 for the healthy ones.

The study of the sensibility and specificity were used for both the maximum amplitude of the band and the band power in order to optimize a threshold. This is represented in table 4.8 using the program shown in the flow chart 3.10.

Table 4.8- Threshold, specificity and sensibility for Welch method (Peak Amplitude).

Sensibility	1-Specificity	Specificity	Threshold	Pythagoras T.
1.0000	0.5152	0.4848	0.0100	0.5152
1.0000	0.3030	0.6970	0.0130	0.3030
1.0000	0.1515	0.8485	0.0160	0.1515
0.9800	0.1212	0.8788	0.0180	0.1228
0.9800	0.0909	0.9091	0.0190	0.0931
0.9600	0.0303	0.9697	0.0200	0.0502
0.9600	0.0303	0.9697	0.0210	0.0502
0.9600	0.0000	1.0000	0.0220	0.0400
0.9400	0.0000	1.0000	0.0230	0.0600
0.9200	0.0000	1.0000	0.0260	0.0800
0.9000	0.0000	1.0000	0.0280	0.1000
0.8600	0.0000	1.0000	0.0300	0.1400
0.6600	0.0000	1.0000	0.0500	0.3400
0.5000	0.0000	1.0000	0.0800	0.5000
0.4600	0.0000	1.0000	0.0900	0.5400
0.4200	0.0000	1.0000	0.1000	0.5800
0.3600	0.0000	1.0000	0.1200	0.6400
0.3600	0.0000	1.0000	0.1300	0.6400
0.3600	0.0000	1.0000	0.1400	0.6400
0.3400	0.0000	1.0000	0.1500	0.6600
0.3200	0.0000	1.0000	0.1600	0.6800
0.3200	0.0000	1.0000	0.1800	0.6800
0.3000	0.0000	1.0000	0.2000	0.7000
0.3400	0.0000	1.0000	0.2400	0.6600
0.2200	0.0000	1.0000	0.2600	0.7800
0.2200	0.0000	1.0000	0.2800	0.7800
0.2200	0.0000	1.0000	0.3000	0.7800
0.2200	0.0000	1.0000	0.3500	0.7800
0.1600	0.0000	1.0000	0.4000	0.8400
0.1400	0.0000	1.0000	0.4500	0.8600
0.1200	0.0000	1.0000	0.5000	0.8800

Based on the table above, a ROC curve can be drawn for the maximal power, figure 4.12 and the threshold optimization by using the Pythagorean Theorem in figure 4.13.

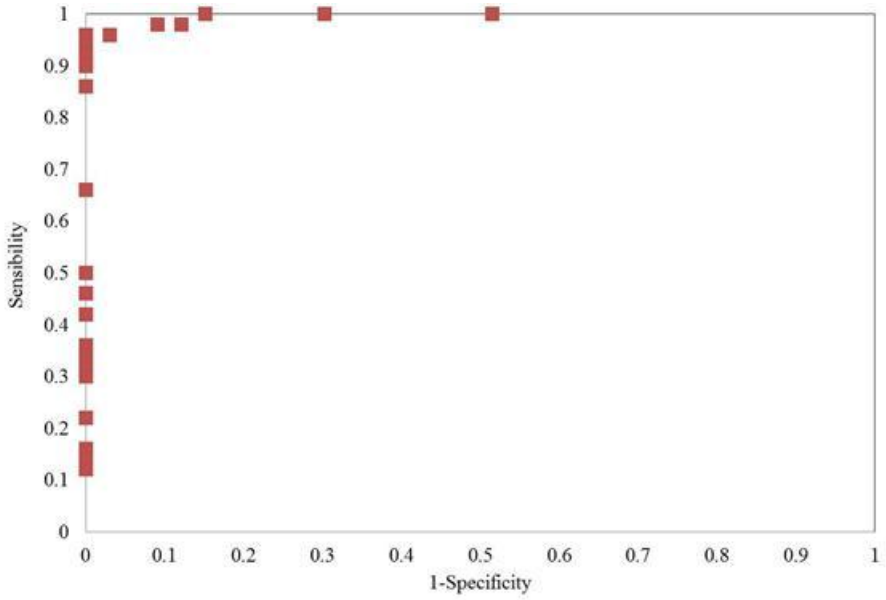

Figure 4.12- ROC curve for method of Welch (Peak Amplitude.

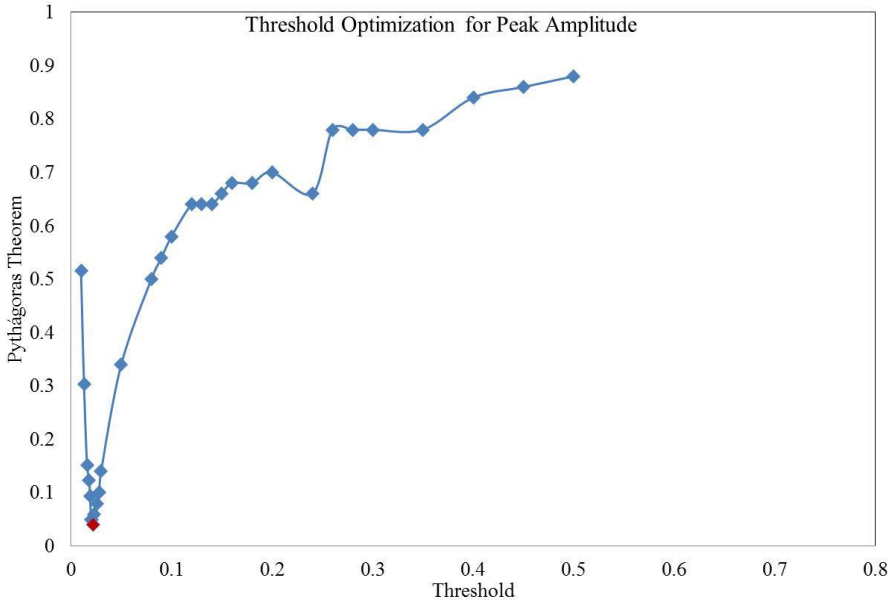

Figure 4.13- Threshold optimization for Welch method (Peak Amplitude).

As observed, the best threshold value is 0.022, a value which is represented in the ROC curve at the point (0; 0.96). The sensibility is 96 % and specificity is 100% (1-specificity 0%).

The same was observed for the Band Power, where table 4.9 represents the sensibility and specificity values, threshold values and the optimization obtained from the Pythagorean Theorem in *Zammarron Range*.

Table 4.9- Threshold, specificity and sensibility for method of Welch (Band Power).

Sensibility	1-Specificity	Specificidade	Threshold	Pythagoras T.
1.0000	0.9394	0.0606	0.0650	0.9394
1.0000	0.9091	0.0909	0.0900	0.9091
1.0000	0.9091	0.0909	0.1000	0.9091
1.0000	0.8485	0.1515	0.1200	0.8485
1.0000	0.6670	0.3330	0.1600	0.6670
1.0000	0.5152	0.4848	0.1800	0.5152
1.0000	0.4545	0.5455	0.2000	0.4545
1.0000	0.2727	0.7273	0.2500	0.2727
1.0000	0.1818	0.8182	0.2800	0.1818
1.0000	0.1212	0.8788	0.3000	0.1212
1.0000	0.0606	0.9394	0.3200	0.0606
1.0000	0.0606	0.9394	0.3300	0.0606
1.0000	0.0000	1.0000	0.3400	0.0000
1.0000	0.0000	1.0000	0.3500	0.0000
1.0000	0.0000	1.0000	0.3600	0.0000
1.0000	0.0000	1.0000	0.3800	0.0000
0.9800	0.0000	1.0000	0.3900	0.0200
0.9600	0.0000	1.0000	0.4000	0.0400
0.9600	0.0000	1.0000	0.4200	0.0400
0.9200	0.0000	1.0000	0.4500	0.0800
0.8600	0.0000	1.0000	0.6000	0.1400
0.8200	0.0000	1.0000	0.6200	0.1800
0.8000	0.0000	1.0000	0.6500	0.2000
0.7200	0.0000	1.0000	0.7000	0.2800
0.6400	0.0000	1.0000	0.8000	0.3600

Considering the values shown in table 4.9, it is possible to trace a ROC curve shown in figure 4.14, as well as obtain an optimization graph of the threshold optimization for the Pythagorean Theorem figure 4.15.

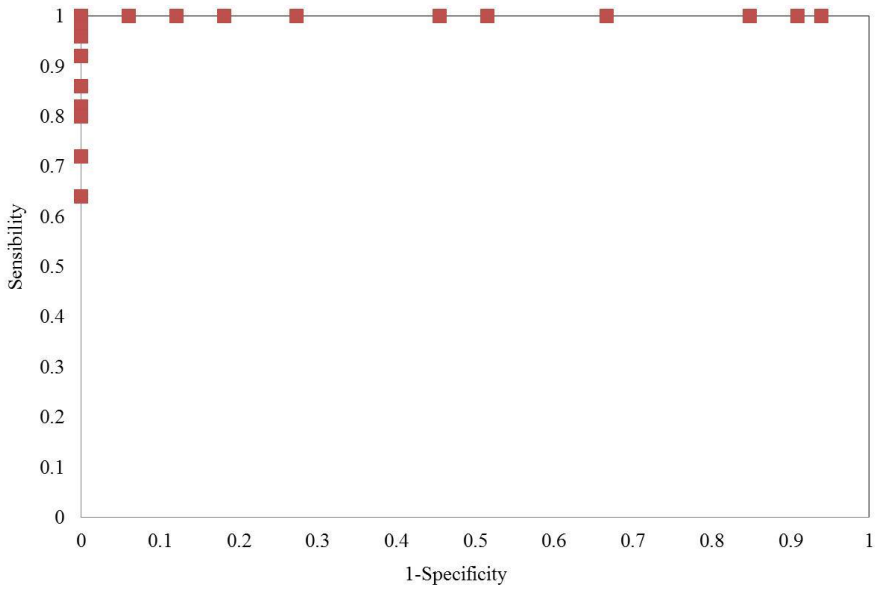

Figure 4.14- ROC curve for method of Welch (Band Power).

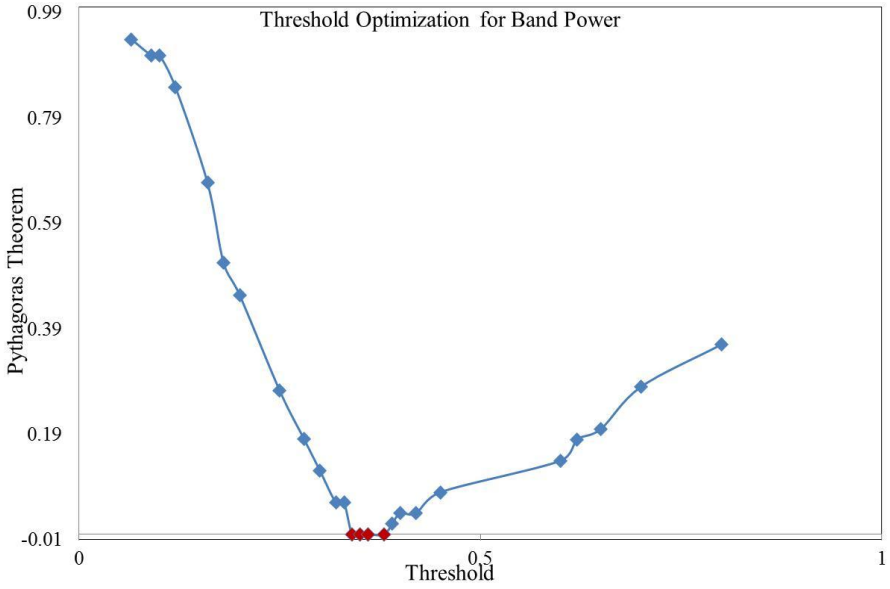

Figure 4.15- Threshold optimization for Welch method.

In both table 4.9 and figure 4.15 it can be seen that the threshold value obtained for the band power is found within the interval 0.34-0.38. The interval points are located on the ROC curve with the coordinates (0; 1), which is also the point of highest sensibility and specificity (both with 100%).

4.3.5 Other parameters analysed in the sample

Considering the data provided by the Annex (G), the same type of analysis described above can be applied to different parameters. These parameters are divided in two categories, non-linear analysis parameters and spectral parameter. The central tendency measure and the approximate entropy are found within the non-linear analysis parameters, while the Wavelet transform is found within the spectral parameter.

These parameters were previously developed by a Jade University lab and only the results they obtained were made available to me, Annex (G).

4.3.5.1 Central Tendency Measurement (CTM)

Non-linear parameters, such as the central tendency, are proven to be appropriate for problems related to events associated with obstructive sleep apnea syndrome. In the analysis that was carried out, the CTM was used to measure the number of points within a given radius, where values close to 1 are expected for healthy people and values close to zero for those suffering from the disease.

A negative linear correlation graph is obtained by relating the CTM results with the oxygen desaturation index, figure 4.16.

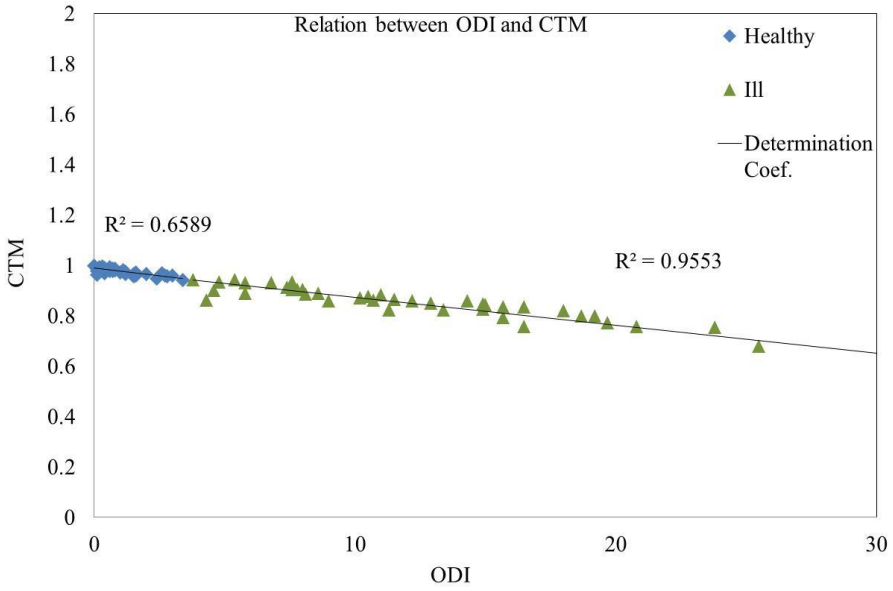

Figure 4.16- Negative linear correlation between CTM and ODI.

The linear correlation coefficients obtained were -0.9774 for patients suffering from the disease and -0.8117 for the healthy ones. The correlation observed for CTM is a negative linear correlation. This correlation obtained for CTM is due to the nature of the method, which attributes low values to cases with higher variability (SaO_2) and vice-versa. The healthy people are those with a lower variability in the percentage of oxygen in the blood (SaO_2) while the patients suffering from the disease have a higher SaO_2 variation.

When resorting to the program of Annex (B) for CTM, the CTM method substitutes the signal in order to differentiate patients from healthy people. For this method then, the CTM values above the threshold value represents healthy people and values under this value represents patients suffering from the disease.

By using the change to the program, this parameter can be evaluated in terms of its sensibility and specificity, as shown in table 4.10.

Table 4.10- Threshold, specificity and sensibility for CTM.

Sensibility	1-Specificity	Specificity	Threshold	Pythagoras T.
0.1400	0.0000	1.0000	0.5000	0.8600
0.1800	0.0000	1.0000	0.6000	0.8200
0.2200	0.0000	1.0000	0.7000	0.7800
0.3600	0.0000	1.0000	0.8000	0.6400
0.5400	0.0000	1.0000	0.8500	0.4600
0.8000	0.0000	1.0000	0.9000	0.2000
0.8600	0.0000	1.0000	0.9100	0.1400
0.9200	0.0000	1.0000	0.9300	0.0800
0.9600	0.0000	1.0000	0.9400	0.0400
0.9600	0.0000	1.0000	0.9420	0.0400
0.9800	0.0303	0.9697	0.9430	0.0363
1.0000	0.0303	0.9697	0.9440	0.0303
1.0000	0.0303	0.9697	0.9450	0.0303
1.0000	0.0303	0.9697	0.9490	0.0303
1.0000	0.0606	0.9394	0.9500	0.0606

From the data provided by table 4.10 it is possible to obtain a ROC curve for CTM, figure 4.17, as well as a threshold optimization using the Pythagorean Theorem, figure 4.18.

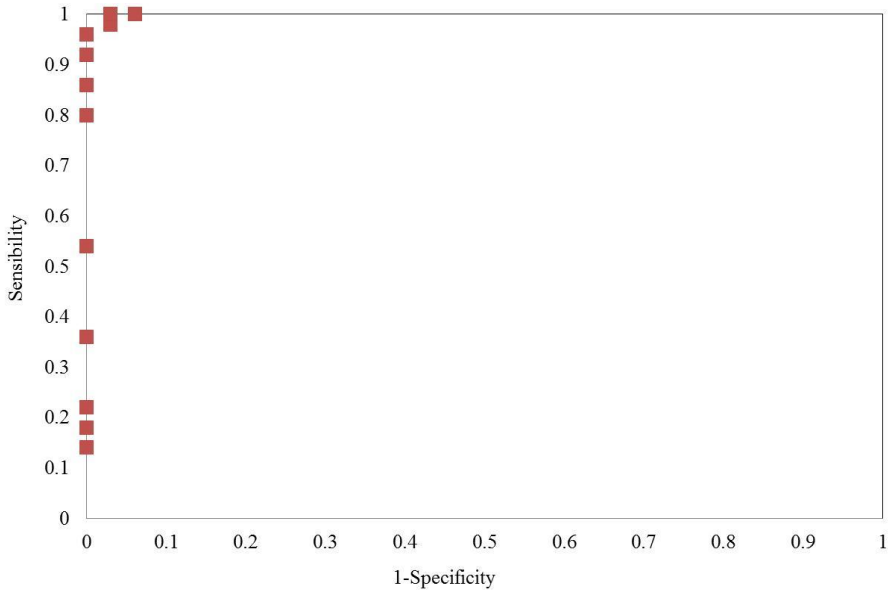

Figure 4.17- ROC curve for Central Tendency Measurement (CTM).

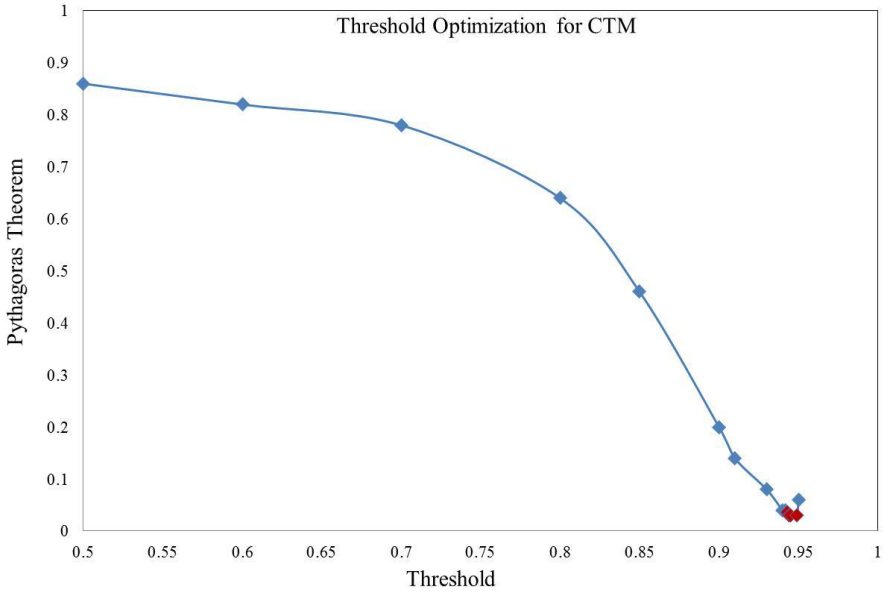

Figure 4.18- Threshold optimization for CTM.

As can be seen, the best threshold value is in the interval 0.944-0.949, which is represented in the ROC curve at the point (0.0303; 1). The sensibility is 100% and the specificity is 96.97% (1-specificity 0.0303%).

Another type of MTC was also analysed, the CTM dout, a method developed by the University of Jade, in Germany.

This is an optimization of the previous method using the length of the vectors outside a given radius, for which the values outside the radius are associated to apnea events, while the values within the radius are considered noise. Therefore, it is possible to statistically consider the quality of the oxygen desaturations. In contrast with the previous method the greater variability of oxygen desaturation corresponds to people suffering from the disease, while a lower variation corresponds to healthy people. A relationship between CTM dout and the oxygen desaturation index was observed, figure 4.19.

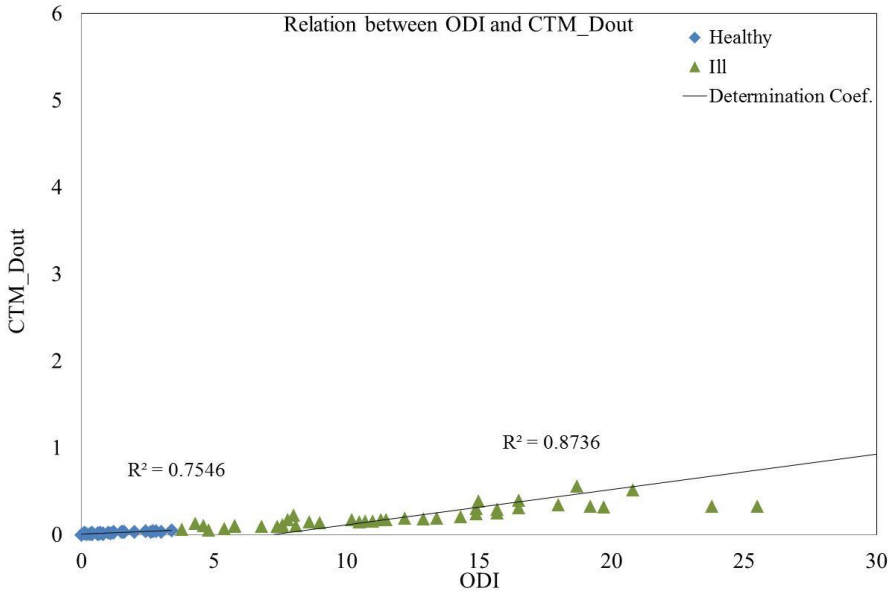

Figure 4.19- Positive linear correlation between the CTM dout and ODI.

There is a positive linear correlation between the CTM dout and the oxygen desaturation index (ODI), where the correlation coefficient for patients suffering from the disease is 0.9347 and for healthy people it is 0.8687.

For this CTM optimization there is no change needed in the program shown in the flowchart of the Annex (B). Table 4.11 is obtained by applying this program to that parameter.

Table 4.11- Threshold, sensibility and specificity for CTM dout.

Sensibility	1-Specificity	Specificity	Threshold	Pythagoras T.
1.0000	0.7576	0.2424	0.0100	0.7576
1.0000	0.6667	0.3333	0.0130	0.6667
1.0000	0.5455	0.4545	0.0160	0.5455
1.0000	0.5152	0.4848	0.0180	0.5152
1.0000	0.5152	0.4848	0.0190	0.5152
1.0000	0.4848	0.5152	0.0200	0.4848
1.0000	0.4848	0.5152	0.0210	0.4848
1.0000	0.4545	0.5455	0.0220	0.4545
1.0000	0.4242	0.5758	0.0230	0.4242
1.0000	0.3636	0.6364	0.0260	0.3636
1.0000	0.3636	0.6364	0.0280	0.3636
1.0000	0.3333	0.6667	0.0300	0.3333
1.0000	0.0909	0.9091	0.0400	0.0909
1.0000	0.0303	0.9697	0.0450	0.0303
1.0000	0.0303	0.9697	0.0480	0.0303
1.0000	0.0000	1.0000	0.0500	0.0000
1.0000	0.0000	1.0000	0.0510	0.0000
0.9800	0.0000	1.0000	0.0520	0.0200
0.9600	0.0000	1.0000	0.0600	0.0400
0.9400	0.0000	1.0000	0.0650	0.0600
0.9400	0.0000	1.0000	0.0700	0.0600
0.9400	0.0000	1.0000	0.0750	0.0600

It is possible to trace the ROC curve for the CTM dout, figure 4.20, as well as the threshold optimization using the Pythagorean Theorem figure 4.21.

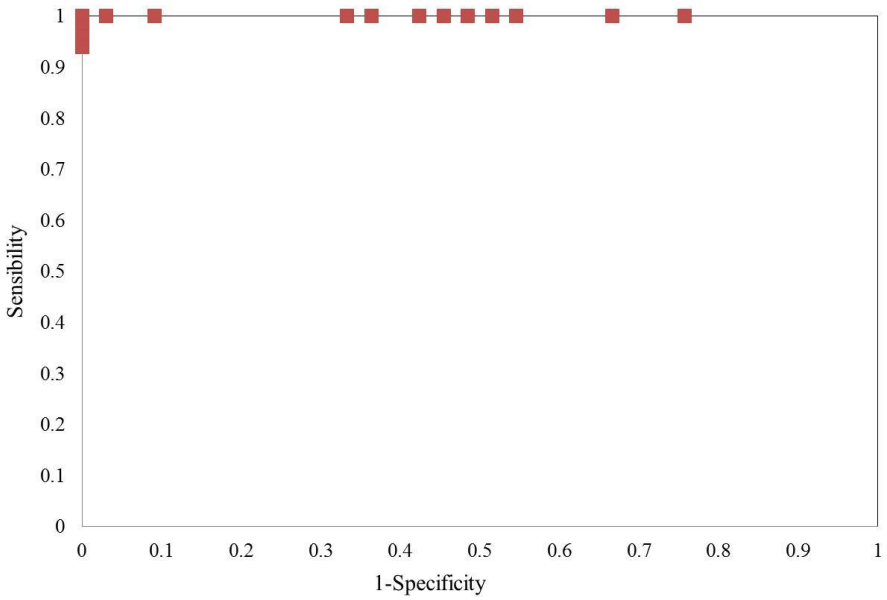

Figure 4.20- ROC curve for CTM dout.

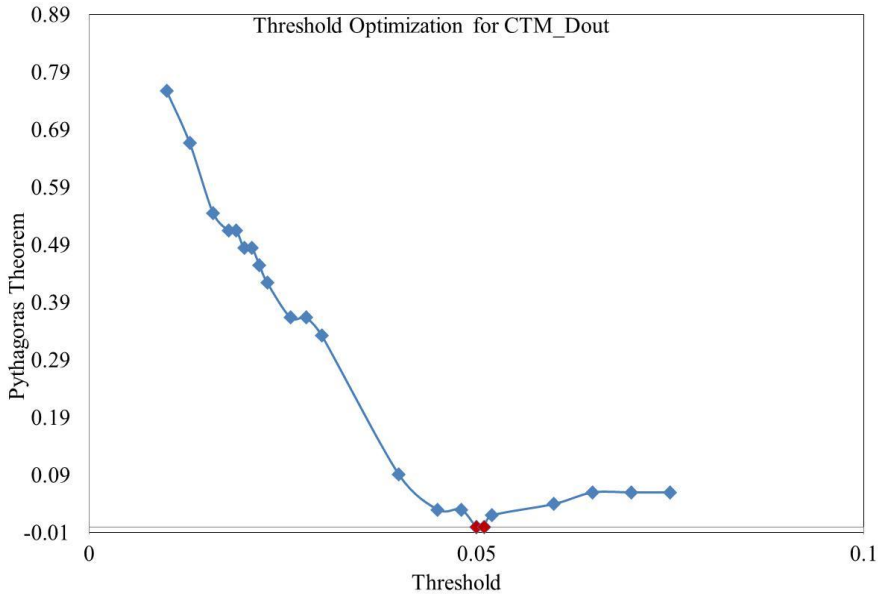

Figure 4.21- Threshold optimization of CTM dout.

As can be seen, the best value for the threshold is found within the interval 0.05-0.051 and both values are represented in the ROC curve at the point (0; 1). The sensibility and specificity are 100%.

4.3.5.2 Approximate Entropy(AnEp)

Approximate entropy (EnAp) is a statistical method known as a form of quantifying irregularities found in sequences and given temporal series. A regular data series results in a low EnAp. When this method is applied to night oxymetry, the irregularities caused by apnea events result in increases in the EnAp values for the SaO2 signal. This method was also approached differently by the University of Jade lab, in Germany. The EnAp approach was changed in terms of the optimization of the vector length, the sequence length, and the tolerance limit.

The EnAp values seen in the Annex (G), represent the average EnAp value for each patient during the night.

The relationship between EnAp and the oxygen desaturation index is represented in figure 4.22.

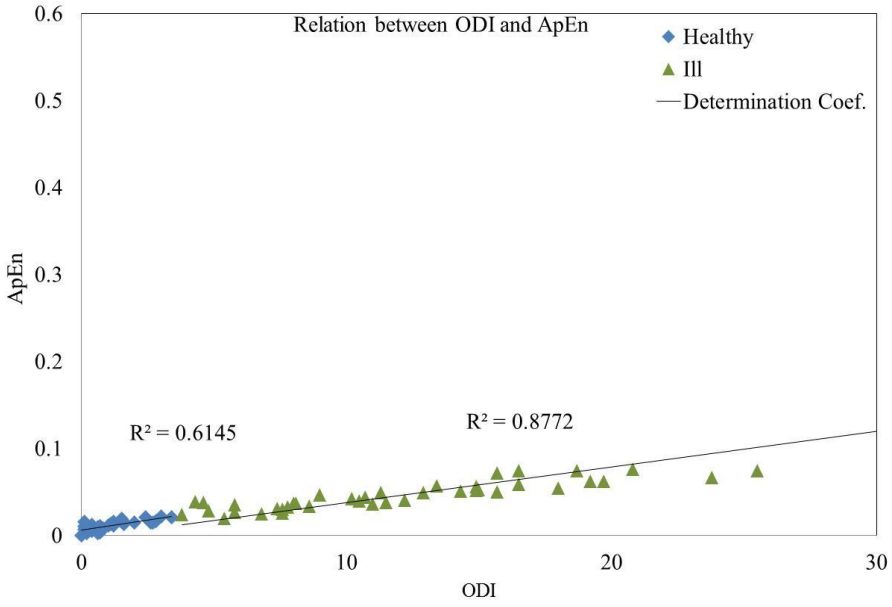

Figure 4.22- Positive linear correlation between the ApEn and ODI.

There is a positive linear correlation between ApEn and the oxygen desaturation index (ODI), where the coefficient of correlation for people suffering from the disease is 0.9366 and for the healthy ones it is 0.7839.

Table 4.12 is obtained by applying the program represented in the flow chart found in figure 3.10.

Table 4.12- Threshold, specificity and sensibility for ApEn.

Sensibility	1-Specificity	Specificity	Threshold	Pythagoras T.
1.0000	0.7576	0.2424	0.0070	0.7576
1.0000	0.6364	0.3636	0.0095	0.6364
1.0000	0.6061	0.3939	0.0100	0.6061
1.0000	0.3939	0.6061	0.0130	0.3939
1.0000	0.1515	0.8485	0.0160	0.1515
1.0000	0.1212	0.8788	0.0180	0.1212
1.0000	0.1212	0.8788	0.0190	0.1212
0.9800	0.0909	0.9091	0.0200	0.0931
0.9800	0.0606	0.9394	0.0210	0.0638
0.9800	0.0000	1.0000	0.0220	0.0200
0.9800	0.0000	1.0000	0.0230	0.0200
0.9796	0.0000	1.0000	0.0240	0.0204
0.8800	0.0000	1.0000	0.0280	0.1200
0.8600	0.0000	1.0000	0.0300	0.1400
0.6200	0.0000	1.0000	0.0400	0.3800
0.5000	0.0000	1.0000	0.0500	0.5000

The ROC curve in figure 4.23 can be obtained by using the statistical values in table 4.12 and by optimizing the threshold through the Pythagorean Theorem in figure 4.24.

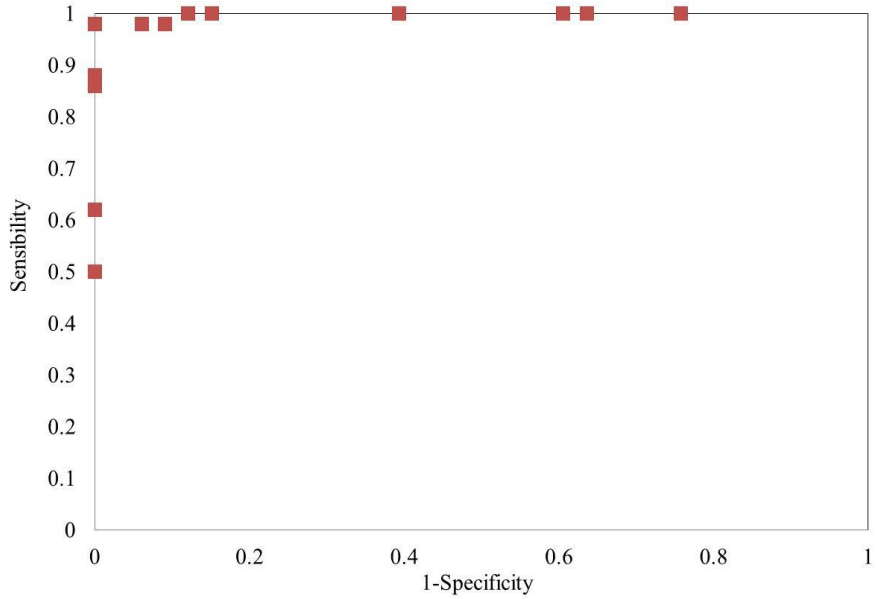

Figure 4.23- ROC curve for ApEn.

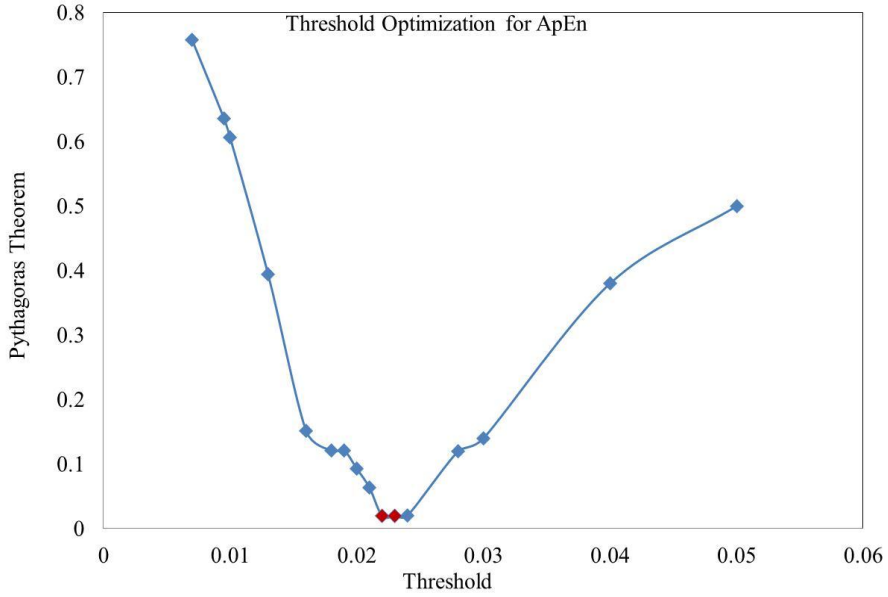

Figure 4.24- Threshold optimization for ApEn.

The best threshold value is found within the interval 0.022-0.023. Both values are shown in the ROC curve at the point (0; 0.98). Sensibility is 98% and specificity is 100%.

4.3.5.3 Continuous Wavelet Transform

The Wavelet continuous transform was applied to the oxymetry studies because it works with any type of scale and it preserves all the information present in the signal [41]. The Wavelet continuous transform is normally used for measuring oxygen saturation through spectral data provided by the oxymeter (the photoplethysmogram measures the variation in the absorbed light) [41]. Since apnea events are stationary events, the Wavelet continuous transform proves to be an appropriate method.

Figure 4.25 shows the relationship between the Wavelet continuous transform and the oxygen desaturation index (ODI).

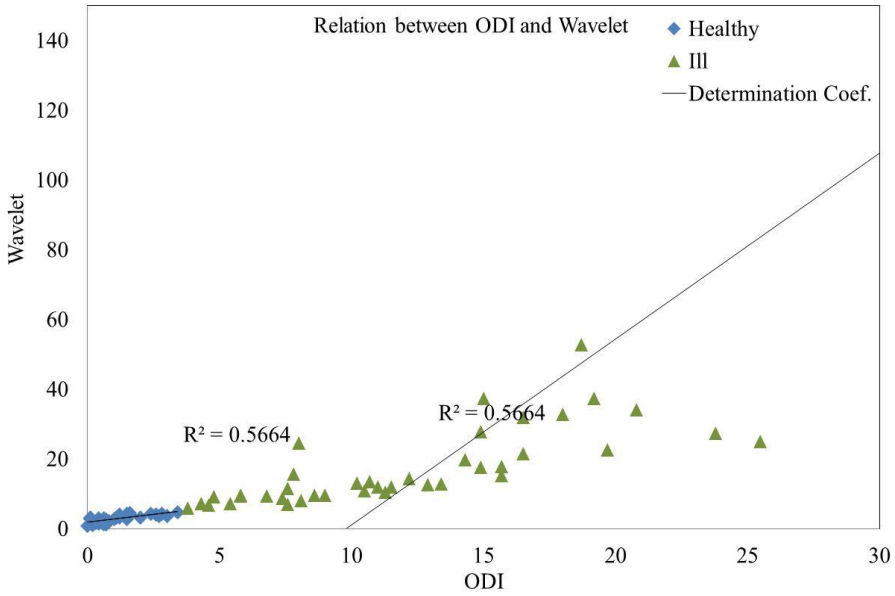

Figure 4.25- Positive linear correlation between the Wavelet transform and ODI.

There is a positive linear correlation between the Wavelet transform and the oxygen desaturation index (ODI), where the correlation coefficient for patients suffering from the disease is 0.8663 and for healthy ones it is 0.7525.

Table 4.13 is obtained by applying the program shown in the flow chart in figure 3.10 to the Wavelet continuous transform.

Table 4.13- Threshold, specificity and sensibility for Wavelet transform.

Sensibility	1-Specificity	Specificity	Threshold	Pythagoras T.
1.0000	0.9697	0.0303	1.0000	0.9697
1.0000	0.8788	0.1212	1.5000	0.8788
1.0000	0.7576	0.2424	2.0000	0.7576
1.0000	0.6667	0.3333	2.5000	0.6667
1.0000	0.5152	0.4848	3.0000	0.5152
1.0000	0.3030	0.6970	3.5000	0.3030
1.0000	0.2424	0.7576	4.0000	0.2424
1.0000	0.2121	0.7879	4.1000	0.2121
1.0000	0.1515	0.8485	4.2000	0.1515
1.0000	0.0909	0.9091	4.3000	0.0909
1.0000	0.0909	0.9091	4.4000	0.0909
1.0000	0.0303	0.9697	4.5000	0.0303
1.0000	0.0303	0.9697	4.8000	0.0303
1.0000	0.0000	1.0000	4.9000	0.0000
1.0000	0.0000	1.0000	5.8000	0.0000
0.9800	0.0000	1.0000	5.9000	0.0200
0.9800	0.0000	1.0000	6.0000	0.0200
0.9400	0.0000	1.0000	7.0000	0.0600

The data from table 4.13 can be used for tracing the ROC curve for the Wavelet continuous transform, figure 4.26, as well as an optimization threshold using the Pythagorean Theorem, figure 4.27.

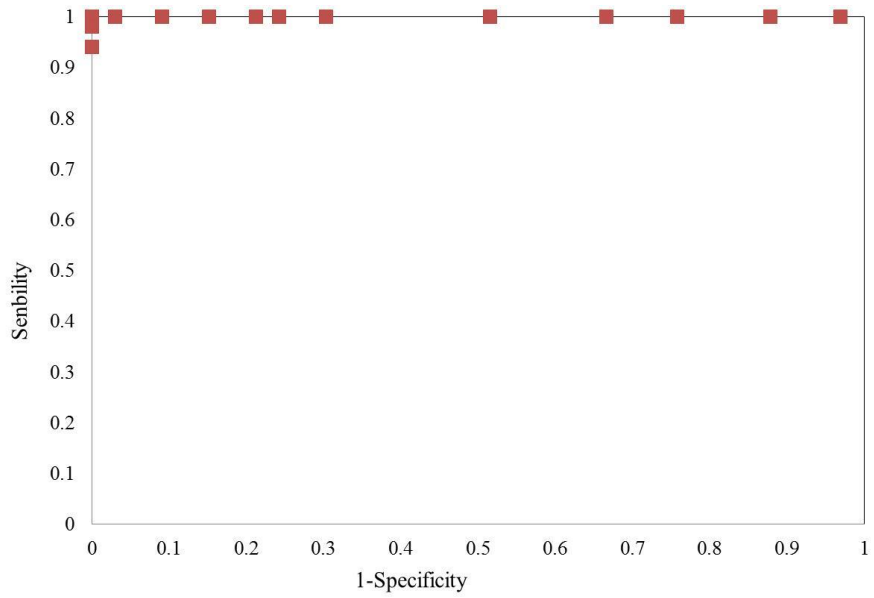

Figure 4.26- ROC curve for Wavelet transform.

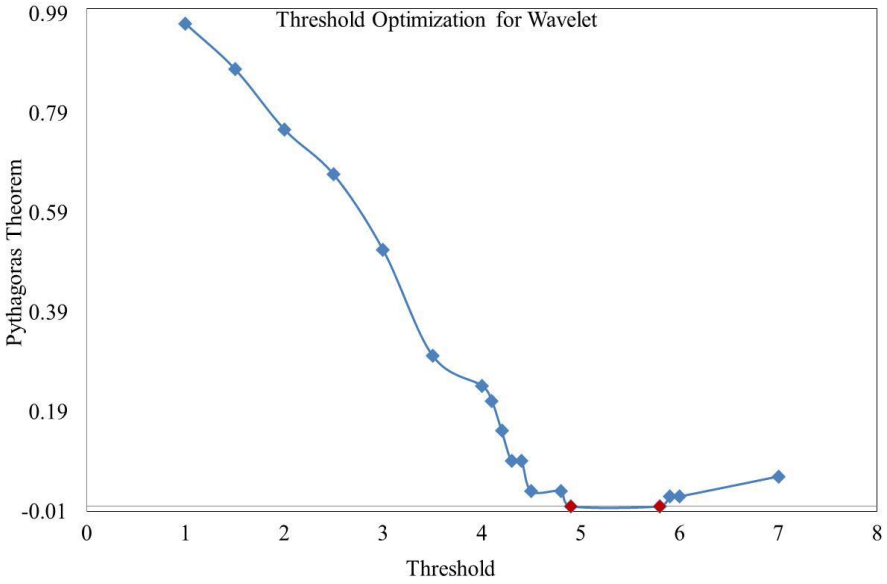

Figure 4.27- Threshold optimization for Wavelet transform.

As can be seen, the best threshold value for the threshold is found within the interval 4.9-5.8, both values being shown on the graph by the ROC curve at the point (0; 1). Sensibility is 100% and specificity is 100%.

4.4 Results of the Mathematical Models

The methods used to separate the patients are shown in table 4.14, which are the results in terms of sensibility, specificity, threshold and correlation coefficient between the respective method and the oxygen desaturation index.

Table 4.14- Applied Methods.

	Delta Index	Schmittendorf		Zamarrón		CTM	CTMdout	ApEn	Wavelet
		Peak Amp.	Band Power	Peak Amp.	Band Power				
Sensibility [%]	98.00	96.00	100	96.00	100	100	100	98.00	100
Specificity [%]	96.97	100	100	100	100	96.97	100	100	100
Healthy Correlation Coef.	0.929	0.817	0.862	0.817	0.862	-0.977	0.935	0.937	0.866
Ill Correlation Coef.	0.573	0.462	0.625	0.463	0.612	-0.812	0.869	0.784	0.753
Threshold	0.430	0.022	0.400 a 0.430	0.022	0.340 a 0.380	0.944 a 0.949	0.050 a 0.051	0.022 a 0.023	4.90 a 5.80

The data obtained shows that all the alternative methods had a high sensibility and specificity, as well as a high correlation coefficient. In all cases, the correlation coefficient between each of the methods and the oxygen desaturation index was higher than 0 ($0 < \rho < 1$), showing the relationship between the variables to be positive. As for all the methods the correlation coefficient is close to the unit, so it can be said it's a strong positive linear correlation, with exception for the Peak Amplitude for the different ranges, where the correlation with ODI for ill patients is lower.

As can be seen, the study of the Band Power for the different intervals had more sensibility (100%) than the Peak Amplitude (96%). This is because the Peak Amplitude becomes more susceptible to identifying periodic desaturations, while the Band Power reflects the number and severity of the apnea events.

Even though all the methods show good applicability, the ones the stand out are the CTM dout, the band power for the different intervals and the Wavelet transform. These methods show excellent values in terms of sensibility and specificity, which indicates a strong detection of people suffering from the disease and healthy people, thus avoiding false

positives. The greater the sensibility and the specificity, the better the result of the applied test is obtained.

The threshold obtained for the different methods does not allow for a comparison between them. For those which obtained a higher value interval for the threshold, the value to take into consideration must be the lowest one in the interval. This assures the correct identification of people suffering from the disease, avoiding the risk of an incorrect diagnosis.

4.5 General Analyze of the Results

The epidemiological analysis applied to the study sample shows the relationship between the OSAS and being overweight. This analysis is quite sensitive, providing information about risk of disease for overweight patients and for patients with a normal BMI number or below it, as well as the probability of the disease happening in relation to this risk factor.

In spite of the vast amount of information obtained, this information is very generalized because it is based on one sample. Consequently, more specific tests should be used.

The analysis done through the mathematical models becomes more specific as it deals with patients on an individual basis, providing additional information based not only on periodicity, but also on physiological changes related to oxygen desaturation. The methods analysed serve as an alternative for the diagnosis of the syndrome.

It can be concluded that both types of analysis complement each other, both in terms of the information they provide, as well as in terms of studying the main risk factors responsible for the disease.

CHAPTER 5

PULMONARY REAHBILITATION IN PATIENTS WITH OSAS

5.1 Introduction

Obstructive Sleep Apnea Syndrome occurs when respiration temporarily stops during sleep. This happens due to muscular collapse and soft tissue in the throat and neck [46].

One of the clinically observed factors leading to the aggravation of the clinical history of this syndrome is morbid obesity (around 50-60% of the morbidly obese suffer from sleep apnea syndrome). The more overweight the person is, the more fat there is pressuring the chest and the lungs, making breathing difficult [49].

The most frequent sleep disorders are insomnia and obstructive sleep apnea syndrome (sleep breathing disorder). Respiratory problems are the most common causes of the inability to carry out routine tasks [49].

Pulmonary rehabilitation returns patients suffering from a respiratory disorder to as normal and independent a life as possible. Pulmonary rehabilitation programs provide a decrease in physical and psychological disabilities caused by respiratory diseases through the improvement of physical and mental aptitudes and, consequently, patient performance, providing maximum social integration of the patient with the lowest possible incapacity [50].

5.2 Pulmonary Rehabilitation

Pulmonary rehabilitation is a multidisciplinary field which provides care for patients suffering from chronic respiratory alterations, combining primary diagnosis of the disease; pharmacological, nutritional and physiotherapy treatment; physical reconditioning, psychosocial support and education. This field adapts itself to the individual needs of each patient in order to maximize their autonomy, as well as their physical and social performance [51].

Chronic obstructive pulmonary disease (DPOC) refers to the chronic limitation of the air flux, which is not completely reversible after the use of a bronchodilator [52].

Patients with DPOC show a change in the pulmonary function, as well as dyspnoea. Another change that can be verified in these patients is the atrophy of the peripheral skeletal muscles [52 53].

Atrophy on the muscular level can lead to an intolerance of physical exercise which affects the fitness level in a way that can limit everyday activities, often causing social isolation, anxiety, depression and dependence. These patients often show changes in weight and body mass, which not only aggravate their lives on a psychological and physical level, but also lead to the progression of their DPOC. There is no pulmonary function test which is considered to be sufficient criteria for the inclusion or exclusion of a patient classified as a patient suffering from DPOC or not [53].

Based on scientific evidence it can be stated that pulmonary rehabilitation improves the individual's ability to do exercise and reduces the sensation of shortness of breath [48 51].

5.2.1 Pulmonary Rehabilitation and the COPD Patients

Several treatment methods are used in order to correct or minimize the dysfunctions triggered by COPD, to limit the advance of the disease, improve physical capacity and quality of life, while reducing the psychological impact. Some of these treatment methods are the exclusion of risk factors, such as to stop smoking, pharmacological treatments, oxygen-therapy, ventilator support and pulmonary rehabilitation. The latter promotes the improvement of the functional capacity for exercise and of the quality of life, at the same time as it reduces apnea and the frequency and duration of hospital admissions [54].

In terms of psychological gains, pulmonary rehabilitation aims to boost self-esteem, reduce the state of anxiety and depression and overcome the notion of incapacity [48].

All patients who have any type of physical limitation caused by a respiratory disease are advised to undergo pulmonary rehabilitation, while those suffering from COPD show changes in their pulmonary function, dyspnoea and peripheral skeletal muscle atrophy. Therefore, people who find themselves in any stage of COPD can benefit from some form of pulmonary rehabilitation [51 54].

The usual procedure is for the patient to be subject to this type of program in a very advanced phase of the disease. The groups specialized in rehabilitation have been making an effort to change this attitude by encouraging doctors and other medical professionals to direct patients in less advanced phases of the disease [51 54].

5.2.2 Physical and Psychological tests in Pulmonary Rehabilitation

Once the patient is selected, he or she must be submitted to a stress test to assess the tolerance and the patient's limiting causes towards exercise [55].

Normally a stress test uses a 6 to 12 minute walk. The test can be progressive or constant, meaning that the charge is increased according to pre-determined intervals up to the maximum charge or the limit. Ideally, a 10 to 15 min walk is used [55].

The monitoring exams of the stress test are endless and each service adopts the ones which are better suited to the patient. One of them is the spyrometry, a non-invasive and painless exam to the lungs, which allows for various air volumes and air fluxes to be registered; oximetry, CO_2 diffusion capacity test, blood gasometry test, ECG, blood pressure and the visual analogical scale (VAS) of dyspnoea and fatigue, which consists of a vertical or horizontal line, usually 10 cm, where one extreme represents the total absence of dyspnoea , while the other extreme represents the worst sensation of dyspnoea ever felt by the patient [55].

Other scales for measuring apnea can be used, but the most common is shown in figure 5.1.

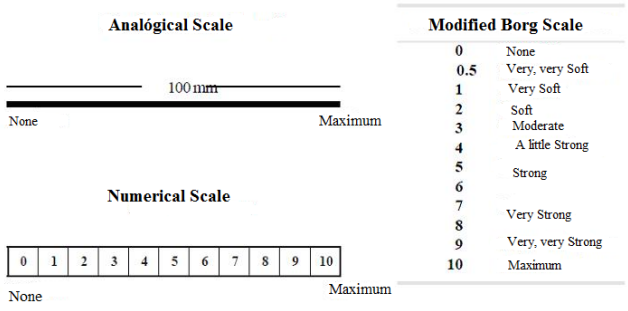

Figure 5.1- Scales for measuring the degree of dyspnoea [55].

The assessment of dyspnoea is important in pulmonary rehabilitation because it has been clinically proven to be directly associated with the mortality of patients suffering from DPOC. In addition, the degree of apnea can be a guide for indicating and evaluating the progress of rehabilitation [51 55].

After carrying out the stress test and analysing the monitoring exams, the next step is to create a personalized plan for physical fitness.

Another important factor to consider is the psychological one. It is important to carry out a previous assessment of the psychological state of the patient, considering that a great percentage of these tend to be anxious and depressed. This assessment indicates how much the disease bothers the patient psychologically and it can reflect the degree of effort that the patient might put into the rehabilitation program. The psychological approaches attempt to actively involve the patient in the decision-making process, as well as changing the patient's attitude towards their disease [48 52]

5.2.3 Equipment Related

Concerning the essential equipment for this procedure, these must include portable sources of oxygen, pulse oximetries, chronometers, weights, and a large enough room for group physical activity. Other equipment which can be used includes treadmills and/or ergonometric bicycles and cyclo-ergometric ones for the upper limbs, heart monitors (to be used exclusively for tests), spyrometers and physiotherapy equipment. A defibrillator is highly recommended, as well as professionals who are trained to use it, though incidents with patients in pulmonary programs are not common [51 55].
Figure 5.2 shows the pulmonary function device.

Figure 5.2- Pulmonary function test device [3].

5.3 Non Invasive Treatment for OSAS

Most sleep apnea cases are not easily solved, such as adopting a new position while sleeping, losing weight or doing certain types of physical exercise. To avoid the discomfort and the health risks caused by this type of sleep disorder, diagnosed patients need to undergo treatment. The treatment for OSAS consists of many aspects, such as an intense weight loss program, positional therapy, a systemic high blood pressure control, an endocrine treatment in case of hypothyroidism, specific surgeries and positive pressure treatments [55].

One of the most efficient and scientifically approved non-surgical alternatives for obstructive sleep apnea syndrome is the use of continuous positive pressure in the respiratory tracts (CPAP), which is responsible for maintaining the respiratory tracts open, avoiding apnea events and night time hypopnea, which are common to the syndrome [53].

The CPAP treatment is an intrinsic mechanism which absorbs the air from the environment, filters it and sends it to the patient through a flexible tube. The continuous air flow (40 a 60 l/min) released by the machine is transported to a mask adapted for the patient's nose [55 56]. Figure 5.2 shows a CPAP device.

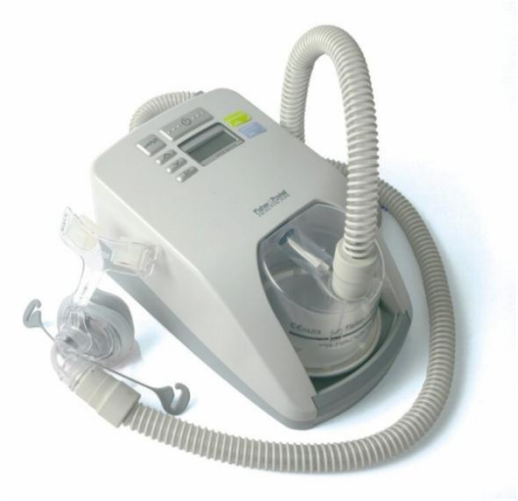

Figure 5.3- CPAP device [3].

Before starting the CPPRT treatment the machine needs to be adjusted during a polysomnographic test. The continuous use of the device during sleep time reduces, and in some cases, can even solve the OSAS. If this treatment is administered correctly, it can eliminate the risk of cardiovascular problems, improve snoring and high blood pressure [56].

The main inconvenience of this treatment is the discomfort it can cause the patient during sleep. This negative aspect is not very significant when compared to the positive aspects which come from using it. Some of these benefits include an improvement in daily function, regulation of the chemo-receptors, an improvement in cardiovascular and pulmonary functions and an improvement in expiratory volumes during physical activity [55 56]. This equipment clearly plays an important role as a main treatment for OSAS, as well as a rehabilitating tool for several pulmonary diseases.

CHAPTER 6

CONCLUSION AND FUTURE STUDIES

6.1 Conclusion

The effects of sleep deprivation are varied. It can lead to severe immunological problems, causing the patient to be less resistant to other diseases. Sleep and sleep deprivation have come to play a key role in current Medicine, becoming an important research field.

Obstructive sleep apnea syndrome (OSAS) is a common disorder associated to breathing during sleep. The main characteristic of this pathology is the occurrence of inefficient inspiratory efforts, caused by the dynamic and repetitive occlusion of the pharynx during sleep, resulting in respiratory pauses of at least 10 seconds, followed or not by oxygen desaturation. OSAS is the most serious condition in a spectrum of obstructive disorders associated to the respiratory tracts during sleep.

In sleep medicine, digital oxymetry is an important tool for registering the rapid fluctuations in blood oxygen saturation, commonly found in patients suffering from sleep apnea and respiratory instability.

This study describes different approaches to diagnosing OSAS, by using night pulse oxymetry. It shows that a quantitative analysis of night pulse oxymetry can help in the selection of OSAS patients. In moderate OSAS cases, the diagnosis can be done by using the analysis from the night pulse oxymetry. However, none of the analysis obtained from night pulse oxymetry can substitute polysomnography. Just one polysomnographic test can confirm the OSAS diagnosis. Nonetheless, this possibility allows for the reduction in the number of polysomnographs in developing countries, as well as for a faster access to treatment in patients with a suggestive clinical history and significant O_2 desaturation in the oxymetry. Therefore, oximetry can be used as a fast and accessible screening method whenever there are patients whose complaints match the symptoms of OSAS.

Sleep disorders exert a significant impact on diverse aspects of everyday life, affecting people both physically and emotionally. Pulmonary rehabilitation can restore a normal life, as well as independence, as much as it is possible to those suffering from sleep disorders which involve respiratory problems. In addition to weight loss and a plan with adequate physical exercise, the most efficient and best scientifically proven treatment for obstructive sleep apnea is the use of continuous positive pressure on the respiratory tracts (PCAP). This treatment aims to prevent the occurrence of apneic events.

The main aim of the pulmonary rehabilitation programs is to reduce physical and psychological incapacitation caused by respiratory diseases through the improvement of physical and mental ability. It aims to consequently also improve the patients'

performance, providing them with a maximum level of social reintegration with the lowest possible level of incapacity.

The results of this study demonstrate a complementarity between the epidemiological study and the study of mathematical models. Since the analysis by means of mathematical models becomes more specific, as it approaches the patients individually, providing additional information not only in frequency but also based on changes in the physiological level, related to the oxygen desaturation. The methods studied provided good results for the identification of patients of OSAS, thus serving as an option for the diagnosis of the syndrome.

6.2 Future Studies

Based on the mathematical models developed for analysing obstructive sleep apnea syndrome, it would be interesting in the future to broaden the study sample to other nationalities. The analysis of results could also be completed by including the patients' professions.

As an example, it would be interesting to carry out a night pulse oximetric assessment of a sample of professional bus/lorry and taxi drivers, as well as pilots, among other professions Because they provide a public service, it could ensure their own well-being, as well the well-being of the users of these services, thus avoiding accidents which are directly or indirectly caused by sleep disorders.

Another topic for future studies would be to use a sample of OSAS patients including some anemic patients, suffering from iron deficiency. A comparison between anemic and non-anemic patients could analyze if this factor has possible worsening effects on the OSAS or not.

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ANNEXES

ANNEX (A)

Calculation of Delta Index, with x as the vector of recording time (s) and y as the vector of values obtained for SpO2.

```
%delta index: This index measures the variation between successive data
at
%constant time intervals of 14 seconds each

y=SpO2 values
x=Recording time[s]




a=find(y<20 | y>100)
y(a)=NaN

m=floor(length(x)/14)



for i=1:m

   ymin(i)=nanmin(y((i-1)*14+1:i*14));
end
TF=isnan(ymin)
 b=find(TF==1)
 n=length(b)

for i=1:m-1;
   dif(i)=abs(ymin(i)-ymin(i+1))

end
 if m-1-n>5
 dindex=nansum(dif)/(m-1-n)
 else
 disp('Signal too Short')
 end
```

Delta Index Function

With x as the vector of recording time (s) and y as the vector of values obtained for SpO2.

```
function dindex=delta_ind(x,y)

a=find(y<20 | y>100)
y(a)=NaN

m=floor(length(x)/14)

for i=1:m
   ymin(i)=nanmin(y((i-1)*14+1:i*14));
end

TF=isnan(ymin)
 b=find(TF==1)
 n=length(b)
for i=1:m-1;
   dif(i)=abs(ymin(i)-ymin(i+1))

 end
 if m-1-n>5
 dindex=nansum(dif)/(m-1-n)
 else
 disp('Signal too Short')
 end
```

ANNEX (B)

Function that calculates the sensitivity and specificity, where x is the vector of the parameter to evaluate (Delta Index, IDO MTC) eyo vector classification (y = 1 and y = 0 noncarriers patients with OSA) is a threshold value assigned within the range observed

```
function [sensibility,specificity]=OptmTff_f(x,y,threshold)

m=length(y);
i=find(gt(x,threshold));
x1(1:m)=0;
if length(i)<threshold;
x1(1:m)=0;
else x1(i)=1;
end

FP=length(find(and(x1,y)));
TN=length(find(and(~x1,y)));
FN=length(find(and(~x1,~y)));
TP=length(find(and(x1,~y)));

sensibility=TP/(TP+FN)
specificity=TN/(TN+FP)
```

CTM function:

The function calculates the sensibility and specificity, where *x* is the CTM parameter and *y* it's the classification vector (1 for healthy and 0 for ill).

```
function [sensitivity,specificity]=CTMTff_f(x,y,threshold)
m=length(y);
i=find(lt(x,threshold));
x1(1:m)=0;
if length(i)>threshold;
x1(i)=1;
else
x1(1:m)=0;
```

```
end

FP=length(find(and(x1,y)));
TN=length(find(and(~x1,y)));
FN=length(find(and(~x1,~y)));
TP=length(find(and(x1,~y)));

sensitivity=TP/(TP+FN)
specificity=TN/(TN+FP)
```

ANNEX (C)

Welch Method:

```
n=find( x<101);
w=2048;
noverlap=1024;
nfft=2048;
fs=1;
figure
[Pxx,W]=pwelch(x(n),w,noverlap,nfft,fs);
df=W(2)-W(1);
Pxx_t=Pxx*2;
plot(W(5:length(Pxx_t)),Pxx_t(5:length(Pxx_t))*df)
title('Test-Graphic')
xlabel('Frequency')
ylabel('Power')
```

Welch method function:

```
function [Pxx_t1,W]=test_welchT(x)
n= x<101;
plot(n)
figure
w=2048;
noverlap=1024;
nfft=2048;
fs=1;
figure
[Pxx,W]=pwelch(x(n),w,noverlap,nfft,fs);
df=W(2)-W(1);
Pxx_t=Pxx*2;
Pxx_t1=Pxx_t*df;
plot(W(5:length(Pxx_t)),Pxx_t1(5:length(Pxx_t)),'b')
title('Test-Graphic')
xlabel('Frequency')
ylabel('Power')
```

ANNEX (D)

Sample table of data provided for 50 patients with OSAS:

PatID	MessID	Date of Measurement	Body Mass Index	ODI	Delta Index
531	r084	14.08.2010	29.20	11.30	0.6127
532	r085	17.08.2010	23.70	18.00	0.9655
564	r117	23.09.2010	49.60	15.70	0.7544
565	r118	25.09.2010	31.50	4.60	0.4615
574	r127	06.10.2010	26.00	10.20	0.7177
391	i057	08.03.2006	33.46	13.40	0.7562
335	i001	23.06.2006	30.10	14.90	0.8092
449	i115	05.08.2006	27.13	36.80	1.9491
529	r082	12.08.2010	23.90	8.00	0.6822
598	r151	01.12.2010	30.00	7.60	0.4943
362	i028	11.02.2006	42.52	60.10	2.8345
550	r103	07.09.2010	36.50	52.70	1.7064
…					
461	i127	21.09.2006	24.16	5.80	0.6391

Sample table of data provided for 33 non-carriers of OSAS:

PatID	MessID	Date of Measurement	BMI	ODI	Delta index
579	r132	02.11.2010	22.90	1.50	0.2805
498	r051	08.07.2010	23.03	0.70	0.2241
310	f004	25.10.2007	23.20	0.60	0.2141
311	f010	29.05.2008	26.50	1.20	0.3672
312	f016	01.12.2007	19.00	0.60	0.3186
313	f020	01.01.2001	20.80	1.60	0.3720
313	f024	18.03.2008	21.00	0.80	0.2878
314	f028	17.02.2008	22.80	0.10	0.3496
317	f032	31.03.2008	27.70	2.60	0.3405
320	f036	04.04.2008	21.60	0.20	0.1737
324	f042	28.04.2008	20.80	2.40	0.4498
…					
328	f048	26.07.2008	23.00	0.40	0.1934

ANNEX (E)

Tables obtained for 40 spectral lines in patients with OSAS for Zamarron Range (1/70-1/30s).

Number of Spectral lines	i001	i012	i013	i021	i025	i028	i050	i055
30	0.04825	0.01354	0.01449	0.02813	0.02551	0.1631	0.04533	0.14907
31	0.06404	0.02419	0.00945	0.02103	0.02182	0.44443	0.0537	0.13392
32	0.08576	0.01279	0.01095	0.01174	0.01509	0.76343	0.03987	0.17924
33	0.06104	0.01698	0.01036	0.01538	0.01229	0.71381	0.02856	0.24528
34	0.05427	0.01696	0.01374	0.01256	0.01788	0.26286	0.05702	0.30068
35	0.05775	0.01678	0.01825	0.00989	0.02388	0.26556	0.06364	0.30621
36	0.04001	0.02479	0.0343	0.01067	0.01901	0.32572	0.06313	0.26684
37	0.03457	0.01577	0.02052	0.01218	0.02551	0.48339	0.0463	0.51661
38	0.04013	0.01142	0.02219	0.01107	0.03847	0.66967	0.04366	0.44259
39	0.0375	0.01411	0.02041	0.01108	0.02892	0.32911	0.05649	0.48908
40	0.05196	0.01271	0.02078	0.01634	0.01261	0.7325	0.06028	1.33313
...								
69	0.01467	0.00494	0.00443	0.01458	0.00776	0.04977	0.02147	0.03024
Max.	0.08576	0.02479	0.0343	0.02813	0.03847	0.76343	0.06364	1.33313
Sum	0.58995	0.18496	0.19987	0.17466	0.24874	5.20334	0.57945	4.39289

Tables obtained for 54 spectral lines in patients with OSAS for Schmittendorf Range (1/70-1/25s).

Number of Spectral lines	i001	i012	i013	i021	i025	i028	i050	i055
30	0.04825	0.01354	0.01449	0.02813	0.02551	0.1631	0.04533	0.14907
31	0.06404	0.02419	0.00945	0.02103	0.02182	0.44443	0.0537	0.13392
32	0.08576	0.01279	0.01095	0.01174	0.01509	0.76343	0.03987	0.17924
33	0.06104	0.01698	0.01036	0.01538	0.01229	0.71381	0.02856	0.24528
34	0.05427	0.01696	0.01374	0.01256	0.01788	0.26286	0.05702	0.30068
35	0.05775	0.01678	0.01825	0.00989	0.02388	0.26556	0.06364	0.30621
36	0.04001	0.02479	0.0343	0.01067	0.01901	0.32572	0.06313	0.26684
37	0.03457	0.01577	0.02052	0.01218	0.02551	0.48339	0.0463	0.51661
38	0.04013	0.01142	0.02219	0.01107	0.03847	0.66967	0.04366	0.44259
…								
82	0.01009	0.00428	0.00201	0.0068	0.00331	0.04303	0.0088	0.04524
83	0.00841	0.00681	0.00244	0.00508	0.00352	0.04881	0.00991	0.0255
Max.	0.08576	0.02479	0.0343	0.02813	0.03847	0.76343	0.06364	0.51661
Sum	0.50431	0.1643	0.15871	0.14455	0.20628	4.1838	0.45991	2.61119

Tables obtained for 40 spectral lines in non-carriers of OSAS for Zamarron Renge (1/70-1/30s).

Number of spectrel line	f001	f004	f007	f009	f010	f011	f015	f016
30	0.00383	0.00578	0.00764	0.00442	0.01437	0.00943	0.0107	0.01127
31	0.00517	0.00643	0.00658	0.00675	0.01354	0.01318	0.01149	0.01043
32	0.00363	0.00636	0.00506	0.00621	0.01692	0.01045	0.01018	0.00756
33	0.00738	0.00517	0.00523	0.00525	0.01591	0.00996	0.00837	0.00735
34	0.00842	0.00448	0.00574	0.01088	0.01154	0.00803	0.00693	0.00516
35	0.0092	0.00405	0.00571	0.00651	0.00947	0.0077	0.00869	0.0053
36	0.00519	0.00843	0.00623	0.00357	0.01308	0.01553	0.00891	0.00711
37	0.00244	0.00728	0.00688	0.00343	0.00938	0.01253	0.00838	0.00689
38	0.00355	0.00429	0.00558	0.0038	0.00991	0.00723	0.00802	0.00596
39	0.00083	0.00638	0.00632	0.00352	0.01017	0.00527	0.00624	0.00815
...								
69	0.00158	0.00101	0.0032	0.00086	0.00613	0.00219	0.00242	0.00194
Max.	0.0092	0.00843	0.00764	0.01088	0.01692	0.01553	0.01149	0.01127
Sum	0.05123	0.05965	0.06417	0.0552	0.13041	0.1015	0.09033	0.07712

Tables obtained for 54 spectral lines in non-carriers with OSAS for Schmittendorf Range (1/70-1/25s).

Number of spectrel line	f001	f004	f007	f009	f010	f011	f015
30	0.00383	0.00578	0.00764	0.00442	0.01437	0.00943	0.0107
31	0.00517	0.00643	0.00658	0.00675	0.01354	0.01318	0.01149
32	0.00363	0.00636	0.00506	0.00621	0.01692	0.01045	0.01018
33	0.00738	0.00517	0.00523	0.00525	0.01591	0.00996	0.00837
34	0.00842	0.00448	0.00574	0.01088	0.01154	0.00803	0.00693
35	0.0092	0.00405	0.00571	0.00651	0.00947	0.0077	0.00869
36	0.00519	0.00843	0.00623	0.00357	0.01308	0.01553	0.00891
37	0.00244	0.00728	0.00688	0.00343	0.00938	0.01253	0.00838
38	0.00355	0.00429	0.00558	0.0038	0.00991	0.00723	0.00802
39	0.00083	0.00638	0.00632	0.00352	0.01017	0.00527	0.00624
…							
83	0.00062	0.00082	0.00133	0.00053	0.00354	0.00129	0.00204
Max.	0.0092	0.00843	0.00764	0.01088	0.01692	0.01553	0.01149
Sum	0.05452	0.06453	0.06917	0.05716	0.1365	0.11156	0.09606

ANNEX (F)

Tables of 83 data for example the Band Power (Sum. Values) and Peak Amplitude (Max. Values) in the range of Zamarron for non-carriers of OSAS.

ID	ODI values	Max. Values	Sum values
f001	0.6	0.009195636	0.136289
f004	0.6	0.009052237	0.159266
f007	1	0.007638691	0.173763
f009	0.3	0.010880456	0.116277
f010	1.2	0.016917623	0.338016
f011	2.7	0.015528127	0.251847
f015	3	0.011486029	0.241137
f016	0.6	0.01127317	0.206352
f020	1.6	0.014489409	0.256349
f021	1.2	0.01211839	0.190962
f024	0.8	0.006525058	0.134197
f025	0.4	0.006525058	0.134197
…			
f029	1.5	0.019169536	0.283224

Tables of 83 data for example the Band Power (Sum. Values) and Peak Amplitude (Max. Values) in the range of Zamarron for carriers of OSAS.

ID	ODI values	Max. Values	Sum values
i001	14.9	0.085763294	1.289343
i012	8.1	0.024794193	0.512276
i013	3.8	0.034300667	0.39643
i021	8.6	0.028134147	0.591376
i025	12.2	0.052104676	0.943277
i028	60.1	1.325780345	16.53428
i050	31.4	0.198068263	2.901844
i055	41.5	1.974754107	11.17746
i056	23.8	0.108101595	1.906761
i057	13.4	0.039549217	0.873131
i069	10.5	0.057340083	0.759232
i090	7.4	0.043544032	0.594019
…	7.6	0.022131715	0.422454
i115	36.8	1.080669483	8.475931

Tables of 83 data for example the Band Power (Sum. Values) and Peak Amplitude (Max. Values) in the range of Schmittendorf for non-carriers of OSAS.

ID	ODI values	Max. Values	Sum values
f001	0.6	0.009195636	0.149824
f004	0.6	0.009052237	0.181057
f007	1	0.007638691	0.20346
f009	0.3	0.010880456	0.131227
f010	1.2	0.016917623	0.398062
f011	2.7	0.015528127	0.288188
f015	3	0.011486029	0.278066
f016	0.6	0.01127317	0.231317
f020	1.6	0.014489409	0.283867
f021	1.2	0.01211839	0.222084
f024	0.8	0.006525058	0.152849
f025	0.4	0.006525058	0.152849
…			
f029	1.5	0.019169536	0.314828

Tables of 83 data for example the Band Power (Sum. Values) and Peak Amplitude (Max. Values) in the range of Schmittendorf for carriers of OSAS.

ID	ODI values	Max. Values	Sum values
i001	14.9	0.085763294	1.443947
i012	8.1	0.024794193	0.591177
i013	3.8	0.034300667	0.435413
i021	8.6	0.028134147	0.706468
i025	12.2	0.052104676	1.006305
i028	60.1	1.325780345	17.17688
i050	31.4	0.198068263	3.128102
i055	41.5	1.974754107	11.82534
i056	23.8	0.108101595	2.029653
i057	13.4	0.039549217	0.988677
i069	10.5	0.057340083	0.833336
i090	7.4	0.043544032	0.644051
i101			
i115	36.8	1.080669483	8.699786

ANNEX (G)

Sample table of 83 data provided for other mathematical models for carriers of OSAS.

ID	Date of Measurement	ODI	CTM	CTM_dout	ApEn	Wavelet
r005	21.04.2010	5.40	0.9426	0.0621	0.0193	7.0951
i013	02.02.2006	3.80	0.9433	0.0592	0.024	5.8866369
i069	17.03.2006	10.50	0.8766	0.1436	0.0392	10.740941
r034	02.06.2010	9.00	0.8578	0.135	0.0462	9.4775622
r040	25.06.2010	5.80	0.929	0.0873	0.0264	9.4619839
r063	27.07.2010	11.00	0.8814	0.148	0.0358	11.900874
r046	01.07.2010	6.80	0.9293	0.0913	0.0243	9.3294632
r071	03.08.2010	10.70	0.8604	0.1529	0.0437	13.370748
k004	03.11.2007	15.00	0.8444	0.3825	0.0521	37.296338
i101	10.07.2006	7.60	0.9049	0.1049	0.0293	6.8583483
r044	30.06.2010	14.30	0.8571	0.2048	0.0509	19.759225
r084	14.08.2010	11.30	0.8228	0.1719	0.0492	10.447957
…						
r117	23.09.2010	15.70	0.7931	0.2882	0.0713	15.239922

Sample table of 83 data provided for other mathematical models for non-carriers of OSAS.

ID	Date of Measurement	ODI	CTM	CTM_dout	ApEn	Wavelet
r132	02.11.2010	1.50	0.9655	0.0343	0.0155	2.7154809
r017	05.05.2010	0.40	0.9706	0.0211	0.0122	3.0758724
r051	08.07.2010	0.70	0.9861	0.0118	0.004	1.3624828
f004	25.10.2007	0.60	0.9824	0.0153	0.0078	2.4067157
f010	29.05.2008	1.20	0.9677	0.0317	0.0154	4.1150495
f016	01.12.2007	0.60	0.9796	0.0161	0.0099	3.0126575
f020	01.01.2001	1.60	0.9715	0.0298	0.0135	4.0299422
f024	18.03.2008	0.80	0.9872	0.0092	0.0078	2.0492283
f028	17.02.2008	0.10	0.9877	0.0118	0.0071	3.0689231
f032	31.03.2008	2.60	0.9683	0.0316	0.0149	4.1606719
f036	04.04.2008	0.20	0.9942	0.0062	0.003	1.0303361
f042	28.04.2008	2.40	0.9499	0.0409	0.0206	4.2322077
…						
f048	26.07.2008	0.40	0.9915	0.006	0.0051	1.6207093